Antidepressant medication use in Inflammatory Bowel Disease: a nationally representative population-based cohort study

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Ethical approval

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Contributorship

The POP-IBD study group is collaboration between St George's University of London, Imperial College London, University College London, and King's College London, conducting population-based studies in the field of

Inflammatory Bowel Disease. NJ and JB contributed equally to this project and are joint first authors. NJ, JB, SS, AB, IP, HC, MH & RP conceived and designed this study. NJ and JB prepared the data and carried out statistical analysis overseen by IP and AB. All authors contributed to the development of the analysis, interpreting data and preparing the manuscript. RP will act as the guarantor for the article.

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None declared

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Conflict of interest

None declared.

ABSTRACT

Background

Despite high rates of depression and anxiety, little is known about the use of antidepressants amongst individuals diagnosed with inflammatory bowel disease (IBD).

Aims

To evaluate temporal trends in the use of antidepressants; rates of antidepressant initiation and adherence of antidepressant use to international guidelines among individuals with IBD.

Methods

This is a cohort study of 14,525 incident IBD cases from 2004-2016 compared with 58,027 controls matched 1:4 for age and sex from the Clinical Practice Research Datalink. After excluding tricyclic antidepressants, we performed a Cox regression analysis to determine the risk associated with antidepressant use and logistic regression analysis to determine risk associated with antidepressant undertreatment.

Results

Antidepressant use among individuals with IBD increased by 51% during the 12-year study period, who were 34% more likely to initiate antidepressants in the year after IBD diagnosis compared with controls (aHR:1.34, 95% CI 1.21-1.49). In those with IBD starting antidepressants, 67% received treatment lasting less than the duration recommended in international guidelines, of which 34% were treated for one month or less.

18–24-year-olds were twice as likely to discontinue treatment within 1 month compared with those aged 40-60 years (aHR:2.03, 95% CI 1.40-2.95). Socioeconomic deprivation was also associated with early treatment discontinuation (aHR:1.40, 95% CI 1.07-1.83).

Conclusions

In the year following IBD diagnosis individuals are significantly more likely to start antidepressants compared with controls, but treatment duration fell short of recommendations in the majority. Better integration of services may benefit individuals with IBD and psychiatric comorbidity.

Key words

Inflammatory Bowel Disease, Crohn's disease, Ulcerative Colitis, incidence, antidepressant medication, antidepressants, depression, anxiety, and Clinical Practice Research Datalink.

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INTRODUCTION

Depression and anxiety are approximately twice as common among individuals living with inflammatory bowel disease (IBD) relative to the general population, and these conditions may often go undetected or undertreated.[1–3] The importance of this mental health burden has been starkly highlighted by a recent findings indicating an excess risk of suicide in the IBD population.[4] In its active state, IBD manifests with symptoms of abdominal pain, weight loss, diarrhoea, and rectal bleeding, which may result in reduced quality of life, social functioning and mental well-being.[5] Conversely, individuals with IBD who suffer from depression and anxiety are more likely to have adverse IBD outcomes and increased contact with healthcare providers.[6–8]

Depression and anxiety are the most common comorbid psychiatric disorders diagnosed among individuals with IBD.[4] Antidepressant medications (ADM) are most frequently used to treat these conditions.[9] However, data regarding their use among individuals with coexistent IBD is lacking. In order for antidepressants to maintain remission and reduce the risk of relapse of depression and anxiety, international guidelines indicate a treatment course should continue for at least six months following symptom resolution.[10–14] Despite these recommendations, no previous studies have examined whether antidepressants are prescribed for an appropriate duration amongst IBD patients. Research is needed to identify risk factors predicting undertreatment with antidepressant medication in order to guide the development of appropriately targeted integrated care pathways.

We therefore aimed to: (1) compare rates of antidepressant initiation following IBD diagnosis with a matched control cohort without IBD; (2) determine the duration of antidepressant treatment and assess adherence to international guidelines; (3) examine risk factors

associated with sub-optimal antidepressant treatment duration; and (4) examine temporal trends in antidepressant prescribing in line with guidelines.

METHODS

Design and data source

We obtained ethical and scientific approval for the use of the Clinical Practice Research Datalink (CPRD) for a comparison cohort study from the Independent Scientific Advisory Committee [ISAC Protocol number: 15_018R].

We analysed routinely collected primary care data from electronic health records from general practices that contributed to the CPRD, the largest validated primary care research database in the world.[15] It contains longitudinal, patient-level, anonymised electronic health records of 18 million patients from more than 700 general practices and is broadly representative of the UK population. The median follow-up for individuals registered on CPRD is 9.4 years, allowing the study of long-term outcomes. Primary care physicians use clinical codes to record symptoms, diagnoses, and prescriptions. Participating practices need to achieve and maintain 'up to standard' status to continue contributing to the dataset. The coding system has been previously validated for use in IBD and mental health disorders.[16,17]

Selection of IBD (Crohn's Disease and Ulcerative Colitis) and control cohorts

We defined incident cases of IBD, using a previously validated and published methodology, as individuals who had a first diagnostic Read code for either Crohn's disease (CD) or Ulcerative colitis (UC) at least one year after registering with an 'Up To Standard' practice between 1st of January 2004 and 31st of December 2015.[17]

We excluded individuals if they had codes for both CD and UC, or indeterminate codes such as 'non-specific colitis'. We matched the IBD cohort by age and sex with four randomly selected controls without a record of IBD at any stage of their follow-up to form a control

cohort. Members of the control cohort were assigned the IBD diagnosis date of their matched IBD case termed as 'pseudo-diagnosis date'.

Individuals were followed forward from an index date two years prior to their recorded date of IBD diagnosis in CPRD. Our recent study demonstrated a significant excess of depression in the two years prior to diagnosis of IBD.[17] Therefore we considered the index date as two years prior to the IBD diagnosis/pseudo-diagnosis date, in order to also capture incident psychiatric morbidity that develops in the peri-diagnostic period requiring treatment with antidepressant medication. Follow-up time started and continued from the index date up to the first recorded date of antidepressant use, when an individual left the practice or died, if these occurred before that time, or at the study end date. All individuals regardless of whether they had a record for a psychiatric comorbidity prior to the study index date were included in the cohort, in order to ensure that the entire at-risk population was considered.

Outcome definition

Our main outcomes were incidence of antidepressant use following the index date in relation to diagnosis or pseudo-diagnosis with IBD and the proportion of antidepressant episodes which had a duration of 7 months or more as recommended in guidelines. Excluding tricyclic antidepressants, we examined temporal trends in the rates of initiation of seven most commonly prescribed antidepressants accounting for over 99% of the total antidepressant prescriptions in 2012.[18,19] We excluded tricyclic antidepressants from our main analysis, since we previously found they are primarily prescribed at low dose for indications other than anxiety and depression.[19] The incidence of tricyclic antidepressant use were considered in a separate sub-group analyses.

We defined incident antidepressant use as the first recorded prescription for an antidepressant medication following the index date in relation to diagnosis or pseudo-diagnosis with IBD (**Supplemental appendix F - ADM Code List**). Individuals were excluded from the incident antidepressant cohort if they had a prior record of antidepressant use at any time before the study index date.

We used the term "antidepressant episode" to describe the period from initiating to discontinuing an antidepressant. We determined the proportion of antidepressant episodes lasting at least seven months, as this is the minimum recommended duration of antidepressant treatment.[10–14] This duration is based on international guidance that a course of antidepressant medication should continue for at least six months after full symptom resolution, which normally takes at least one month, irrespective of the presence of comorbid chronic medical conditions, including IBD.[10–14]

We calculated the duration of an "antidepressant episode" as any period of continuous antidepressant use with less than 90 days between antidepressant prescriptions. We chose the cut-off of 90 days since we found the majority of individuals received prescriptions every 2 months. The cut-off allowed for late collection of prescriptions without being considered to have discontinued treatment.

We determined the rate of new antidepressant prescriptions by individual drug, to explore antidepressant prescribing trends between 2004 and 2015. In this analysis we considered prescribing episodes involving two or more prescriptions.

We determined the incidence of depression and anxiety following the index date in relation to diagnosis or pseudo-diagnosis with IBD. We defined incident depression and anxiety as

individuals with a first ever record of depression, anxiety, or those with symptoms of depression or anxiety (**Supplemental appendix G - Depression and Anxiety Code List**). Individuals were excluded from the incident depression and anxiety cohort if they had a record for these conditions at any time before their index date.

Covariates

To identify risk factors associated with antidepressant medication undertreatment a priori, we identified relevant variables based on clinical knowledge and published literature as previously described.[19,20] We explored potential risk factors for undertreatment with antidepressant medication and adjusted for the following covariates: sex, age at IBD diagnosis (under 18, 18-24, 25-39, 40-59, over 60 years), socio-economic deprivation (SED), smoking status, corticosteroid use and era of IBD diagnosis.

We used the Index of Multiple Deprivation (IMD), a postcode-linked measure of socio-economic deprivation, to assign individuals to 1 of 5 groups defined using IMD quintile cut-off points, from IMD group 1 (least deprived) to 5 (most deprived).

We defined individuals as ‘smokers’, ‘ex-smokers’ or ‘non-smokers’ based on codes for smoking status preceding diagnosis. Individuals whose most recent code indicated active smoking were classed as ‘smokers’ and those with codes indicating previous but not current smoking were classed as ‘ex-smokers’; individuals with only ‘non-smoker’ codes were classed as ‘non-smokers’.

We defined corticosteroid use by identifying individuals who were prescribed at least one episode of corticosteroids at any point after the study index date. To examine changes in

antidepressant prescribing practice over the study period, we adjusted for era of IBD diagnosis (Era 1: 2004-2007; Era 2: 2008-2011; Era 3: 2012-2015).

STATISTICAL ANALYSIS

Baseline characteristics of the cohort were summarised using frequencies and percentages. We used t-tests and the one-way analysis of variance (ANOVA) to determine differences between groups of continuous data, and Chi- squared test for comparisons of categorical data. We calculated crude incidence rates of antidepressant use amongst the IBD and control cohort. We first used a univariable Cox proportional hazards model to calculate hazard ratios (HR) for the risk of incident antidepressant use followed by a multivariable regression analysis adjusting for sex, age at IBD diagnosis, socioeconomic deprivation, smoking status, corticosteroid use and era of IBD diagnosis. We also adjusted for clustering by general practice to account for variation in diagnosis, prescribing and coding by practice. We then calculated the proportion of antidepressant medication episodes which lasted the recommended minimum duration of 7 months. We used simple and multiple ordered logistic regression analysis to identify risk factors associated with antidepressant medication undertreatment. We conducted a further analysis to examine the risk of discontinuing an antidepressant medication following a single prescription, to gain an understanding of the proportion of the IBD cohort who were considered to have a psychiatric comorbidity severe enough to warrant treatment but did not continue treatment beyond 28 days. We calculated the rate of new antidepressant prescriptions per 100-person years at risk by each drug during each year of the study period.

We calculated the crude and adjusted incidence rates of depression and anxiety from the study index date, amongst the IBD and control cohort. We developed a Cox regression model for a multivariable regression analysis to determine risk factors for the incidence of depression and anxiety amongst individuals diagnosed with IBD adjusting for sex, age at IBD

diagnosis, socioeconomic deprivation, smoking status, corticosteroid use and era of IBD diagnosis. We conducted a sensitivity analysis where individuals with a record for depression, anxiety, and antidepressant use prior to the index date were included in order to obtain estimates of the proportion of the IBD population who experienced depression, anxiety, or antidepressant use in the period either side of the study index date (**Supplemental appendix A**). All analyses were performed using STATA 16 (Statacorp LP, College Station, TX, USA).

RESULTS

We identified 14,525 incident cases of IBD diagnosed between January 1st, 2004, and December 31st, 2015. Of these, 4,436 had CD and 10,089 had UC. We identified 58,100 age and sex matched controls. Following the initial matching process, 73 individuals of the control cohort (<0.001%) were later diagnosed with IBD during the study follow up period and were therefore excluded from the study, leaving a control cohort of 58,027 individuals (**Table 1**).

Antidepressant use in IBD versus control cohort

During a median follow up of 7.7 years we found the incidence rate of antidepressant use was 19.54 versus 16.94/1000 person-years amongst individuals with IBD and the control cohort without IBD, respectively. The highest risk of incident antidepressant use was observed during the first year after IBD diagnosis (aHR = 1.34, 95% CI, 1.21 - 1.49). The excess risk persisted for 10 years after diagnosis (aHR = 1.11, 95% CI, 1.04 - 1.17) **(Table 2).** The incidence rate of tricyclic antidepressant use, considered separately, was 17.76 versus 8.41/1000 person-years amongst individuals with IBD and the control cohort without IBD, respectively. Similarly, the highest risk of incident tricyclic antidepressant use was observed during the first year after IBD diagnosis (aHR = 1.59, 95% CI, 1.42 - 1.77) (**Supplemental appendix B**).

Antidepressant episode duration and predictors of undertreatment

The median duration of an antidepressant prescribing episode was 98 days (Interquartile range: 28 - 317 days; total range 28 - 4977 days). Among individuals with IBD started on an antidepressant medication, two-thirds (67%) received treatment for less than the recommended minimum duration of 7 months. Individuals aged 18 - 24 years at IBD diagnosis were twice as likely to discontinue antidepressant treatment early compared with individuals aged between 40 and 60 years at diagnosis (aHR = 2.03; 95% CI, 1.40 - 2.95). Amongst

individuals initiating an antidepressant, 78% of 18-24-year-olds received an antidepressant treatment course lasting less than recommended guidance compared with 61% of 40-60-year-olds (**Table 3**).

One in three (34%) individuals started on an antidepressant medication received only a single prescription in their first treatment episode, meaning they received treatment for 28 days or less (**Supplemental appendix E**). Of these, only 7% went on to receive a further antidepressant course lasting 7 months duration or longer. Amongst individuals starting antidepressant treatment, we found 11% switched to an alternative antidepressant class within their first treatment episode.

Individuals aged 18 - 24 years at IBD diagnosis were significantly more likely to discontinue treatment after just one prescription than older individuals aged between 40 and 60 years (aHR = 2.03, 95% CI, 1.44 - 2.84). Those living in areas of greater socioeconomic deprivation were also more likely to discontinue treatment after a single prescription (IMD 4-5 vs IMD 1-3: aHR = 1.40; 95% CI, 1.07 - 1.83) **(Table 3)**.

Trends in antidepressant prescribing in the IBD population

Antidepressant use increased for individuals diagnosed with IBD between the two era 2004 - 2007 and 2012 - 2015 (aHR = 1.51, 95% CI, 1.33 - 1.71) (**Table 5**). There were temporal changes in the prescription rates of each antidepressant medication (**Figure 1**). Overall, the most frequent antidepressant used was citalopram. The incidence of citalopram prescribing, decreased from 2.1 per 100-person years to 1.6 (95% CI 1.4 - 2.8); whereas the rate of sertraline initiation increased steadily from 0.5 to 1.4 (95% CI, 1.2 - 2.2) between 2004 and 2015.

New onset depression and anxiety in IBD

In tandem with the differences observed for antidepressant use, we found the incidence rate of depression was 14.81 and 11.99/1000 person-years in the IBD cohort and matched control cohort respectively. Likewise, the incidence rate of anxiety was 12.99 and 10.30/1000 person-years in the IBD cohort and matched control cohort respectively. In keeping with our findings with respect to incident antidepressant use, we found the highest risk of incident depression and anxiety was observed during the first year after IBD diagnosis (Depression aHR = 1.26, 95% CI, 1.13 - 1.40: Anxiety aHR = 1.36, 95% CI, 1.21 - 1.52) (**Table 4**). The close relationship between antidepressant use and depression or anxiety is underscored when inter-relations were reported as conditional frequencies **(Supplemental appendix D).**

DISCUSSION

Main findings

The risk of antidepressant use among individuals with IBD increased by more than half during the twelve-year study period. In the year following IBD diagnosis individuals are 34% more likely to initiate an antidepressant compared with the general population. Two-thirds of individuals who started an antidepressant did not receive the adequate duration of treatment recommended by international guidelines. Moreover, a third of individuals with IBD who initiated an antidepressant received just a single prescription. Individuals diagnosed with IBD between the ages of 18 and 24 years and those living in areas of higher socioeconomic deprivation were at greatest risk of treatment duration falling short of recommendations.

Findings in relation to previous studies

Our study demonstrates individuals diagnosed with IBD are significantly more likely to initiate an antidepressant medication compared with matched controls. This is the first nationally representative study to report the incidence of antidepressant use in IBD. A Finish and a Canadian study have reported the prevalence of antidepressant use amongst individuals with IBD but these studies preceded the introduction of international guidelines and the more recent wider use of selective serotonin reuptake inhibitors (SSRIs).[21,22]

We found the greatest frequency of antidepressant use occurred in the first year following IBD diagnosis, and the likelihood of initiating an antidepressant in the years following IBD diagnosis increased by 51% between 2004 and 2015. This is consistent with findings that report the highest risk of common psychiatric morbidity occurs in the first year after IBD diagnosis.[4]

Our study is the first to examine the duration of antidepressant treatment and adherence to published recommendations in IBD. International guidelines indicate antidepressant should be continued for a minimum of 6 months after symptom resolution of depression or anxiety, which takes a minimum of one month to achieve.[10–14] We found two thirds of antidepressant treatment courses prescribed fell short of this duration, leaving individuals inadequately treated. This is important since treatment of depression and anxiety lasting less than 6 months following symptom resolution carries a high risk of relapse.[22,23] Meta-analysis indicates continuing antidepressants for at least 6 months after successful treatment of depression is associated with a significantly lower rate of relapse.[23] In turn, untreated psychiatric co-morbidity may adversely impact the disease course of IBD.[6,7,24,25] However, it is important to stress our analysis could not adjust for either non-response to treatment or potential drug-related adverse events, which may necessitate appropriate treatment discontinuation.

Our study found those living in areas of greater socioeconomic deprivation and younger individuals, at IBD diagnosis were at particular risk of antidepressant undertreatment. Young adults frequently relocate in pursuit of education and employment, and the absence of a consistent point of health care contact may be a contributing factor. Furthermore, the affordability of prescriptions has been reported as a barrier to obtaining medications for those on lower incomes.[26]

We found a third of individuals with IBD that started an antidepressant received only a single prescription, consistent with findings in the general popullation.[20] Reasons for early discontinuation are likely to be varied and include: resolution of precipitating stressors; lack of timely response; side effects and concerns about dependency. Whilst there is good

evidence for the efficacy of antidepressant in treating comorbid mood disorders in people with other physical illnesses, in IBD, despite their common use, evidence is limited.[27] We found amongst individuals with IBD who were prescribed a single course of antidepressants, 83% had a record for either a diagnosis or symptoms of depression or anxiety following treatment. Three small trials have been conducted exploring the efficacy of antidepressants in the treatment of comorbid depression and anxiety in IBD.[28–30] Whilst Tianeptine and Duloxetine reduced symptoms of depression and anxiety in comparison with placebo, fluoxetine had no effect. Our study demonstrated temporal shifts in the choice of antidepressant used during the 12 year study period, changes consistent with that in the general population.[20] We found SSRIs made up the majority of antidepressant prescriptions with a switch from citalopram to sertraline among IBD patients in recent years.

Strengths and Limitations

Our study used data from a large, nationally representative primary care research database, using previously validated methodology to establish the duration of an antidepressant episode.[20] CPRD data is collected at the time of consultation or prescription and is independent of referral centre, recall or participant selection bias. We used validated diagnostic codes for depression and anxiety. In common with other observational studies using routinely collected data, inaccuracies in coding and completeness may occur. Previous studies suggest depression and anxiety may not always be detected in primary care and thus our findings may underestimate their occurence.[31]

The CPRD dataset does not record the indication for antidepressant prescriptions, therefore we cannot be certain that antidepressants were prescribed for a diagnoses or symptoms of depression or anxiety. However, we observed a strong inter-relationship between

antidepressant use and mood disorders. Previous studies report three quarters of antidepressant prescriptions are for either depression or anxiety, and still greater for SSRIs, which comprised the majority of antidepressant prescriptions in our study.[9] We acknowledge individuals may start antidepressant treatment in primary care when they present with distress, which may then resolve quickly, accounting for some early discontinuation.

Unlike previous studies we excluded the use of tricyclic antidepressant prescriptions from our main analysis, since they are primarily prescribed at low dose for disorders of brain-gut axis, functional syndromes, chronic pain, and a number of other conditions.

Antidepressant prescriptions may be initiated in secondary care but, in the UK, prescriptions are then continue to be issued in the primary care setting.[32] We were unable to determine the severity of depression or anxiety using a standardised psychiatric tool, since these are not routinely used in primary care. Neither were we able to ascertain associations with IBD phenotype or severity, which may have influenced the risk of psychiatric co-morbidity. Nor were we able to evaluate the rate of initiation of psychological therapy since these episodes are not coded in the dataset.[33] Corticosteroid use has been associated with an increased risk of psychiatric morbidity.[34] For this reason we identified and adjusted for the occurrence of corticosteroids prescribing. We were unable to adjust for anti-TNF use or other biologics since these are not coded in the dataset.

Implications

Despite the heavy burden of depression and anxiety amongst individuals diagnosed with IBD the duration of antidepressant treatment falls short of recommended international guidance in more than two thirds. This raises concern, since individuals discontinuing antidepressant treatment continue to have a risk of relapse even when continued longterm.[35] Some evidence

suggests comorbid depression in the context of other chronic conditions may be less likely to respond to antidepressants .[36,37] Early referral for psychological therapy may offer a better alternative but access to such services is often limited.[38,39] 'The IBD Benchmarking Exercise' reported that only 2% of adult IBD units in the UK meet the benchmark for adequate access to psychological and psychiatric support.[39] Moreover, only a quarter of 10,000 IBD patients surveyed reported being asked about their mental health or emotional wellbeing in the clinic. In order to improve antidepressant adherence, psychological well-being and IBD outcomes there is a need for better integration of IBD and mental health services at the point of diagnosis and beyond.[40,41]

Conclusion

In the year following IBD diagnosis individuals are significantly more likely to initiate an antidepressant medication compared with controls. Two-thirds of individuals with IBD who initiate antidepressant treatment do not complete an adequate course. Better integration of services may benefit individuals with IBD and psychiatric comorbidity.

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Data availability statement

Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. Data were obtained from CPRD GOLD.

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FIGURE LEGENDS

Figure 1. Rate of new antidepressant medication prescribing by drug amongst individuals diagnosed with IBD.

RESULTS TABLES AND FIGURES

Table 1: Baseline characteristics of study population

IBD Status	Crohn's Disease	Ulcerative Colitis	Controls	P value
	4,436	**10,089**	**58,027**	
Demographics				
Men: n (%)	2,096 (47)	5,396 (53)	29,930 (52)	P = 0.99
Age at diagnosis: n (%)				
< 18 years	492 (12)	372 (4)	3,452 (6)	P = 0.99
18 < 25 years	504 (12)	553(6)	4,226 (8)	P = 0.98
25 < 40 years	1,092 (26)	2,377 (24)	13,866 (25)	P = 0.97
40 < 60 years	1,216 (29)	3,267(34)	17,910 (32)	P = 0.99
≥60 years	958 (22)	3,204(33)	16,617 (30)	P = 0.96
Social deprivation: n (%)				
IMD* 1-3	1,614 (37)	4,131 (41)	21,337 (37)	P < 0.0001
IMD 4-5	918 (21)	1,780 (18)	12,151 (21)	P < 0.0001
Unknown	1,904 (42)	4,178 (41)	24,539 (42)	P < 0.0001
Smoking status n (%)				
Smoker	1,110 (25)	1,044 (10)	5,506 (9)	P < 0.0001
Ex-smoker	1,037 (23)	3,752 (37)	6,591 (11)	P < 0.0001
Never	1,198 (27)	2,895 (29)	22,458 (38)	P < 0.0001
Missing	1,091 (25	2,398 (24)	23,472 (40)	P < 0.0001

***IMD – Index of Multiple Deprivation; IMD 1 represents the least deprived and IMD 5 the most deprived. Data available only for individual's resident in England**

Table 2: Risk of first ADM use in the first year and ten years following diagnosis amongst individuals with IBD compared with the control cohort

	First year		Ten years	
Outcome	**Unadjusted HR (95% CI; P value)**	**Adjusted* HR (95% CI; P value)**	**Unadjusted HR (95% CI; P value)**	**Adjusted* HR (95% CI; P value)**
Cohort				
Matched Controls	1 (-)	1 (-)	1 (-)	1 (-)
IBD	**1.49 (1.34 - 1.64; 0.000)**	**1.34 (1.21 - 1.49; 0.000)**	**1.20 (1.13 - 1.27; 0.000)**	**1.11 (1.04 - 1.18; 0.001)**
Sex				
Male	1 (-)	1 (-)	1 (-)	1 (-)
Female	**1.46 (1.32 - 1.61; 0.000)**	**1.43 (1.29 - 1.58; 0.000)**	**1.44 (1.37 – 1.52; 0.000)**	**1.45 (1.38 - 1.53; 0.000)**
Age at diagnosis (years)				
< 18	**0.14 (0.09 - 0.24; 0.000)**	**0.24 (0.15 - 0.41; 0.000)**	**0.56 (0.49 - 0.65; 0.000)**	**0.67 (0.57 - 0.78; 0.000)**
18 < 25	**1.29 (1.08 - 1.53; 0.007)**	**1.42 (1.19 - 1.70; 0.000)**	**1.57 (1.44 - 1.72; 0.000)**	**1.67 (1.52 - 1.84; 0.000)**
25 < 40	**1.22 (1.08 - 1.39; 0.002)**	**1.25 (1.10 - 1.42; 0.000)**	**1.29 (1.20 - 1.38; 0.000)**	**1.29 (1.21 - 1.39; 0.000)**
40 < 60	1 (-)	1 (-)	1 (-)	1 (-)
≥60	0.90 (0.79 - 1.02; 0.103)	0.91 (0.80 - 1.04; 0.162)	0.95 (0.89 - 1.02; 0.192)	0.97 (0.91 - 1.04; 0.437)
Social deprivation				
IMD 1-3	1 (-)	1 (-)	1 (-)	1 (-)
IMD 4-5	**1.18 (1.02 - 1.35; 0.018)**	1.09 (0.95 - 1.25; 0.214)	**1.19 (1.10 - 1.28; 0.000)**	**1.12 (1.04 - 1.21; 0002)**
Unknown	1.04 (0.93 - 1.68; 0.442)	1.02 (0.91 - 1.14; 0.735)	1.06 (0.99 - 1.12; 0.067)	1.00 (0.95 - 1.07; 0.815)
Era of IBD diagnosis				
Era 1 2004 - 2007	1 (-)	1 (-)	1 (-)	1 (-)
Era 2 2008 - 2011	**1.13 (1.00 - 1.28; 0.045)**	1.02 (0.90 - 1.15; 0.772)	**1.30 (1.22 - 1.38; 0.000)**	**1.27 (1.19 - 1.35; 0.000)**
Era 3 2012 - 2015	**1.56 (1.39 - 1.77; 0.000)**	**1.35 (1.19 - 1.53; 0.000)**	**1.82 (1.69 - 1.97; 0.000)**	**1.76 (1.63 - 1.91; 0.000)**
Smoking status n (%)				
Never	1 (-)	1 (-)	1 (-)	1 (-)
Smoker	**2.02 (1.77 - 2.30; 0.000)**	**1.94 (1.70 - 2.21; 0.000)**	**1.74 (1.62 - 1.89; 0.000)**	**1.71 (1.58 - 1.84; 0.000)**
Ex-smoker	**1.25 (1.10 - 1.42; 0.001)**	**1.26 (1.10 - 1.45; 0.001)**	**1.17 (1.08 - 1.26; 0.000)**	**1.24 (1.15 - 1.34; 0.000)**
Missing	**0.46 (0.39 - 0.54; 0.000)**	**0.53 (0.45 - 0.63; 0.000)**	**0.89 (0.84 - 0.96; 0.003)**	0.99 (0.92 - 1.07; 0.797)
Corticosteroid use				
No	1 (-)	1(-)	1 (-)	1 (-)
Yes	0.83 (0.57- 1.21; 0.328)	1.11 (0.76 - 1.64; 0.585)	**0.78 (0.63 - 0.94; 0.010)**	0.89 (0.73 - 1.10; 0.260)

All covariates in the table were included within the adjusted analysis. Abbreviations: ADM (Antidepressant medication); HR (Hazard Ratio); CI (Confidence Interval) * IBD (Inflammatory Bowel Disease) *IMD – Index of Multiple Deprivation; IMD 1 represents the least deprived and IMD 5 the most deprived.

IMD - Data available only for individual's resident in England

Table 3: Predictors of first ADM episode duration amongst the IBD population

	ADM episode lasting < 6 months		ADM episode lasting ≤ 28 days	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
	OR (95% CI)	**OR (95% CI; P value)**	**OR (95% CI)**	**OR (95% CI; P value)**
IBD Cohort				
UC	1 (-)	1 (-)	1 (-)	1 (-)
CD	1.06 (0.87 - 1.29)	0.95 (0.77 - 1.17; 0.621)	1.05 (0.87 - 1.29)	1.42 (0.81 - 1.25; 0.950)
Sex				
Male	1 (-)	1 (-)	1 (-)	1 (-)
Female	0.96 (0.79 - 1.16)	0.97 (0.80 - 1.17; 0.747)	0.91 (0.75 - 1.11)	0.92 (0.76 – 1.11; 0.393)
Age at diagnosis (years)				
<18	1.32 (0.77 - 2.24)	1.42 (0.81 - 2.47; 0.220)	1.20 (0.70 - 2.06)	1.27 (0.73 - 2.21; 0.413)
18 <25	**2.15 (1.52 - 3.04)**	**2.03 (1.40 - 2.95; 0.000)**	**1.91 (1.39 - 2.60)**	**2.03 (1.44 - 2.84; 0.000)**
25 <40	1.10 (0.86 - 1.39)	1.12 (0.88 - 1.41; 0.349)	1.11 (0.88 - 1.43)	1.12 (0.87 - 1.43; 0.375)
40 <60	1 (-)	1 (-)	1 (-)	1 (-)
≥60	**1.38 (1.07 - 1.79)**	**1.40 (1.07 - 1.82; 0.012)**	**1.50 (1.16 - 1.94)**	**1.47 (1.13 - 1.92; 0.004)**
Social deprivation				
IMD 1-3	1 (-)	1 (-)	1 (-)	1 (-)
IMD 4-5	**1.07 (1.01 - 1.40)**	1.05 (0.80 - 1.38; 0.739)	**1.40 (1.07 - 1.82)**	**1.40 (1.07 - 1.83; 0.013)**
Unknown	0.81 (0.65 - 0.99)	0.79 (0.64 - 0.98; 0.033)	0.98 (0.75 - 1.15)	0.94 (0.76 - 1.17; 0.576)
Era of IBD diagnosis				
Era 1 2004-2007	1 (-)	1 (-)	1 (-)	1 (-)
Era 2 2008-2011	1.06 (0.86 - 1.32)	1.07 (0.86 - 1.33; 0.533)	1.06 (0.85 - 1.31)	1.04 (0.83 - 1.30; 0.744)
Era 3 2012-2015	1.10 (0.84 - 1.37)	1.07 (0.84 - 1.37; 0.584)	0.97 (0.76 - 1.24)	0.96 (0.75 - 1.24; 0.762)
Smoking status				
Never	1 (-)	1 (-)	1 (-)	1 (-)
Smoker	1.81 (0.62 - 1.06)	1.06 (0.80 - 1.41; 0.654)	1.14 (0.92 - 1.42)	1.17 (0.88 - 1.55; 0.229)
Ex-smoker	0.98 (0.74 - 1.29)	0.85 (0.66 - 1.09; 0.214)	1.21 (0.92 - 1.59)	1.19 (0.90 - 1.57; 0.891)
Missing	0.80 (0.59 - 1.07)	**0.86 (0.65 - 1.14; 0.311)**	0.91 (0.67 - 1.24)	0.96 (0.70 - 1.32; 0.151)
Corticosteroid use				
No	1 (-)	1 (-)	1 (-)	1 (-)
Yes	1.24 (0.83 - 1.85)	1.19 (0.79 - 1.78; 0.409)	1.00 (0.66 - 1.51)	0.96 (0.63 - 1.46; 0.874)

All covariates described were included within the adjusted analysis. Abbreviations: HR (Hazard Ratio); CI (Confidence Interval); * IBD (Inflammatory Bowel Disease) *IMD – Index of Multiple Deprivation; IMD 1 represents the least deprived and IMD 5 the most deprived. IMD - Data available only for individual's resident in England

Table 4: Risk of incident depression and anxiety in the first year following diagnosis amongst individuals with IBD compared with the control cohort

	DEPRESSION		ANXIETY	
Outcome	**Unadjusted HR (95% CI; P value)**	**Adjusted* HR (95% CI; P value)**	**Unadjusted HR (95% CI; P value)**	**Adjusted* HR (95% CI; P value)**
Cohort				
Matched Controls	1 (-)	1 (-)	1 (-)	1 (-)
IBD	**1.37 (1.23 - 1.52; 0.000)**	**1.26 (1.13 - 1.40; 0.000)**	**1.50 (1.35- 1.68; 0.000)**	**1.36 (1.21 - 1.52; 0.000)**
Sex				
Male	1 (-)	1 (-)	1 (-)	1 (-)
Female	**1.80 (1.61 – 2.00; 0.000)**	**1.77 (1.59 - 1.97; 0.000)**	**1.68 (1.50 - 1.87; 0.000)**	**1.67 (1.49 - 1.86; 0.000)**
Age at diagnosis (years)				
< 18	**0.36 (0.25 - 0.50; 0.000)**	0.59 (0.42 - 0.83; 0.003)	**0.39 (0.28 - 0.55; 0.000)**	**0.55 (0.38 - 0.77; 0.001)**
18 < 25	**1.23 (1.02 - 1.47; 0.028)**	**1.37 (1.14 - 1.64; 0.001)**	**1.20 (0.99 - 1.46; 0.094)**	**1.30 (1.06 - 1.58; 0.011)**
25 < 40	**1.17 (1.02 - 1.32; 0.019)**	**1.19 (1.04 - 1.35; 0.010)**	**1.16 (1.01 - 1.33; 0.028)**	**1.18 (1.03 - 1.35; 0.019)**
40 < 60	1 (-)	1 (-)	1 (-)	1 (-)
≥60	**0.77 (0.67 - 0.90; 0.000)**	**0.79 (0.69 - 0.91; 0.001)**	0.83 (0.72 - 0.98; 0.008	**0.82 (0.71 - 0.95; 0.007)**
Social deprivation				
IMD 1-3	1 (-)	1 (-)	1 (-)	1 (-)
IMD 4-5	**1.24 (1.07 - 1.42; 0.002)**	**1.14 (0.99 - 1.31; 0.056)**	1.07 (0.92 - 1.24; 0.380)	1.02 (0.88 - 1.18; 0.787)
Unknown	1.06 (0.94 - 1.19; 0.335)	1.06 (0.93 - 1.19; 0.333)	1.12 (0.99 - 1.25; 0.068)	1.11 (0.98 - 1.25; 0.098)
Era of IBD diagnosis				
Era 1 2004-2007	1 (-)	1 (-)	1 (-)	1 (-)
Era 2 2008-2011	**1.21 (1.07 - 1.36; 0.002)**	**1.11 (1.02 - 1.29; 0.102)**	**1.02 (0.90 - 1.16; 0.809)**	0.95 (0.86 - 1.12; 0.470)
Era 3 2012-2015	**1.23 (1.08 - 1.40; 0.002)**	**1.08 (1.00 - 1.31; 0.230)**	**1.41 (1.24 - 1.61; 0.000)**	**1.27 (1.12 - 1.46 ; 0.000)**
Smoking status n (%)				
Never	1 (-)	1 (-)	1 (-)	1 (-)
Smoker	**2.03 (1.77 - 2.32; 0.000)**	**1.96 (1.71 - 2.24; 0.000)**	**1.65 (1.41 - 1.91; 0.000)**	**1.60 (1.37 - 1.86; 0.000)**
Ex-smoker	**1.23 (1.08 - 1.41; 0.002)**	**1.32 (1.15 - 1.51; 0.000)**	**1.32 (1.15 - 1.53; 0.000)**	**1.37 (1.18 - 1.58; 0.000)**
Missing	0.57 (0.48 - 0.66; 0.000)	**0.61 (0.52 - 0.72; 0.000)**	0.70 (0.60 - 0.82; **0.000**)	0.78 (0.67 - 0.92; 0.003)
Corticosteroid use				
No	1 (-)	1(-)	1(-)	1(-)
Yes	0.89 (0.59 - 1.32; 0.564)	1.14 (0.76 - 1.72; 0.525)	0.63 (0.44 - 0.91; 0.013)	0.84 (0.58 - 1.22; 0.367)

***All covariates in the table were included within the adjusted analysis. Abbreviations: * ADM (Antidepressant Medication); * OR (Odds Ratio); *CI (Confidence Interval); * IBD (Inflammatory Bowel Disease) *CD (Crohn's Disease) *UC (Ulcerative Colitis) *IMD – Index of Multiple Deprivation; IMD 1 represents the least deprived and IMD 5 the most deprived. IMD - Data available only for individual's resident in England * Depression (depression diagnostic and/or depressive symptom code) * Anxiety (anxiety diagnostic and/or anxiety symptom code)**

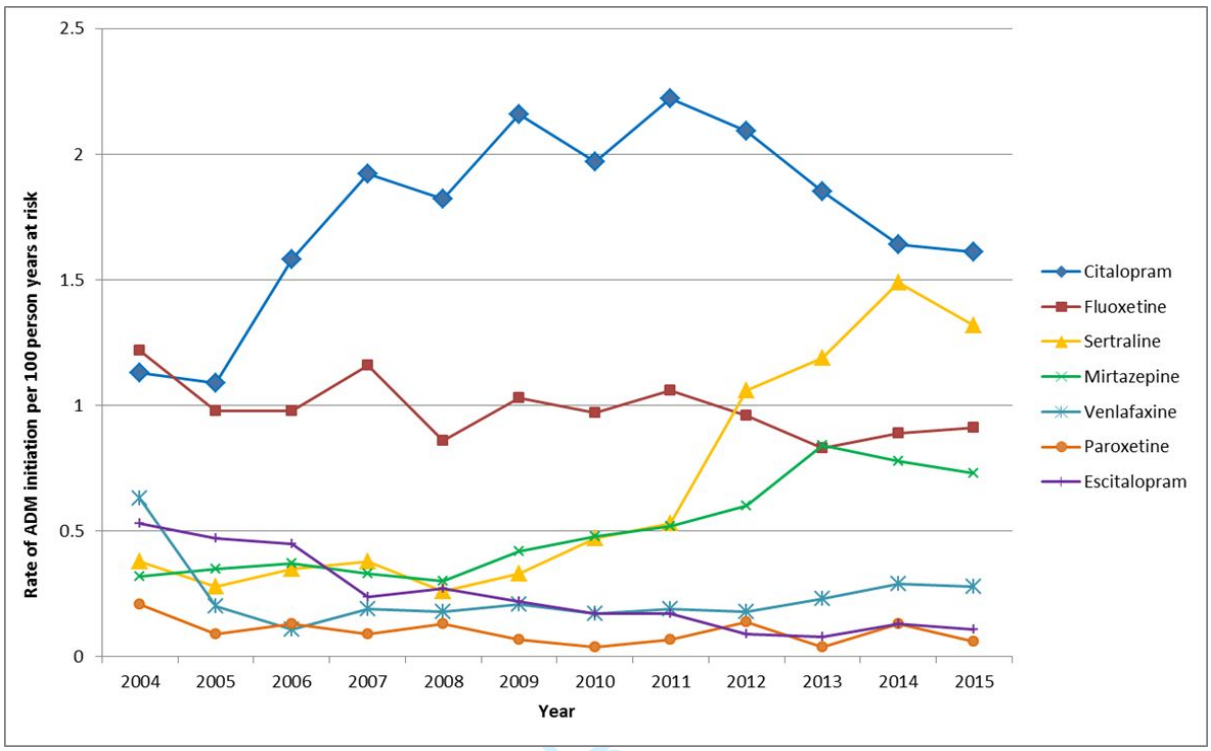
Table 5: Predictors of incident depression, anxiety, and ADM use amongst the IBD population

	DEPRESSION		ANXIETY		ADM	
	Unadjusted HR (95% CI)	**Adjusted HR (95% CI; P value)**	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI; P value)**	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI; P value)**
IBD Cohort						
UC	1 (-)	1 (-)	1 (-)	1 (-)	1 (-)	1 (-)
CD	**1.29 (1.16 - 1.44)**	1.10 (0.98 - 1.24; 0.116)	**1.15 (1.02 - 1.29)**	1.04 (0.91 - 1.17; 0.570)	**1.19 (1.08 - 1.32)**	1.05 (0.95 - 1.17; 0.299)
Sex						
Male	1 (-)	1 (-)	1 (-)	1 (-)	1 (-)	1 (-)
Female	**1.54 (1.39 - 1.71)**	**1.51 (1.36 - 1.68; 0.000)**	**1.53 (1.37 - 1.71)**	**1.52 (1.36 – 1.70; 0.000)**	**1.34 (1.22 - 1.47)**	**1.31 (1.19 - 1.43; 0.000)**
Age at diagnosis (yea						
<18	0.93 (0.73 - 1.19)	1.21 (0.94 - 1.56; 0.140)	0.88 (0.67 - 1.15)	0.98 (0.74 - 1.31; 0.916)	**0.55 (0.42 - 0.73)**	**0.68 (0.51 - 0.90; 0.007)**
18 < 25	**1.76 (1.49 - 2.08)**	**1.80 (1.49 - 2.16; 0.000)**	**1.61 (1.34 - 1.94)**	**1.69 (1.37 - 2.07; 0.000)**	**1.79 (1.54 - 2.08)**	**1.78 (1.50 - 2.09; 0.000)**
25 < 40	**1.28 (1.1 - 1.46)**	**1.27 (1.11 - 1.45; 0.000)**	**1.40 (1.21 - 1.61)**	**1.39 (1.21 - 1.60; 0.000)**	**1.40 (1.24 - 1.57)**	**1.38 (1.23 - 1.55; 0.000)**
40 < 60	1 (-)	1 (-)	**1 (-)**	1 (-)	1 (-)	1 (-)
≥ 60	**0.78 (0.68 - 0.91)**	**0.81 (0.70 - 0.93; 0.004)**	**0.78 (0.68 - 0.89)**	**0.79 (0.67 - 0.92; 0.003)**	0.89 (0.79 - 1.01)	0.92 (0.81 - 1.04; 0.192)
Social deprivation						
IMD 1-3**	1 (-)	1 (-)	1 (-)	1 (-)	1 (-)	1 (-)
IMD 4-5	**1.18 (1.02 - 1.36)**	1.10 (0.95 - 1.27; 0.200)	1.04 (0.88 - 1.22)	0.98 (0.85 - 1.17; 0.845)	**1.18 (1.03 - 1.34)**	1.09 (0.97 - 1.21; 0.179)
Unknown	1.02 (0.91 - 1.15)	0.99 (0.88 – 1.11; 0.850)	**1.21 (1.06 - 1.36)**	**1.18 (1.04 - 1.34; 0.008)**	1.07 (0.97 - 1.19)	1.01 (0.91 - 1.12; 0.926)
Era of IBD diagnosis						
Era 1 2004-2007	1 (-)	1 (-)	1 (-)	1 (-)	1 (-)	1 (-)
Era 2 2008-2011	0.91 (0.81 - 1.02)	0.88 (0.84 - 1.31; 0.143)	0.98 (0.86 - 1.12)	0.97 (0.85 - 1.10; 0.652)	1.11 (0.99 - 1.24)	1.11 (0.99 - 1.24; 0.140)
Era 3 2012-2015	0.99 (0.86 - 1.15)	0.97 (0.76 - 1.25; 0.644)	**1.22 (1.05 - 1.42)**	**1.19 (1.01 - 1.38; 0.026)**	**1.56 (1.36 - 1.75)**	**1.51 (1.33 - 1.71; 0.000)**
Smoking status						
Never	1 (-)	1 (-)	1 (-)	1 (-)	1 (-)	1 (-)
Smoker	**1.54 (1.34 - 1.78)**	**1.47 (1.27 - 1.71; 0.000)**	**1.25 (1.05 - 1.48)**	**1.21 (1.02 - 1.44; 0.029)**	**1.45 (1.28 - 1.66)**	**1.44 (1.26 - 1.65; 0.000)**
Ex-smoker	0.94 (0.82 - 1.08)	1.12 (0.96 - 1.27; 0.116)	1.01 (0.88 - 1.17)	**1.19 (1.02 - 1.37; 0.024)**	0.96 (0.85 - 1.08)	1.06 (1.02 - 1.27; 0.523)
Missing	0.74 (0.64 - 0.87)	0.77 (0.66 - 0.90; 0.002)	0.92 (0.79 - 1.08)	0.99 (0.84 - 1.17; 0.913)	0.69 (0.60 - 0.79)	**0.78 (0.68 - 0.90; 0.001**)
Corticosteroid use	0.98 (0.77 - 1.24)	1.03 (0.81 - 1.31; 0.747)	0.84 (0.66 - 1.07)	0.88 (0.69 - 1.12; 0.289)	0.86 (0.70 - 1.05)	0.90 (0.74 - 1.10; 0.349)

***All covariates in the table were included within the adjusted analysis. Abbreviations: *HR (Hazard ratio); *CI (Confidence Interval); * IBD (Inflammatory Bowel Disease); *CD (Crohn's Disease) *UC (Ulcerative Colitis); * Depression (depression diagnostic and/or depressive symptom code); * Anxiety (anxiety diagnostic and/or anxiety symptom code); * ADM (Antidepressant Medication).*IMD – Index of Multiple Deprivation; IMD 1 represents the least deprived and IMD 5 the most deprived. IMD data available only for individual's resident in England**

FIGURES

Figure 1: Rate of ADM initiation by drug type following IBD diagnosis



Antidepressant medication use in Inflammatory Bowel Disease: a nationally representative population-based cohort study

Supplementary appendices, figures, and tables

Supplementary appendix A: Figure 1a: Cumulative combined risk of incident depression, anxiety, or ADM use amongst the IBD and general population. Figure 1b: Cumulative combined risk of depression, anxiety, or ADM use amongst the IBD and general population including individuals with records prior to study index date

Figure 1a

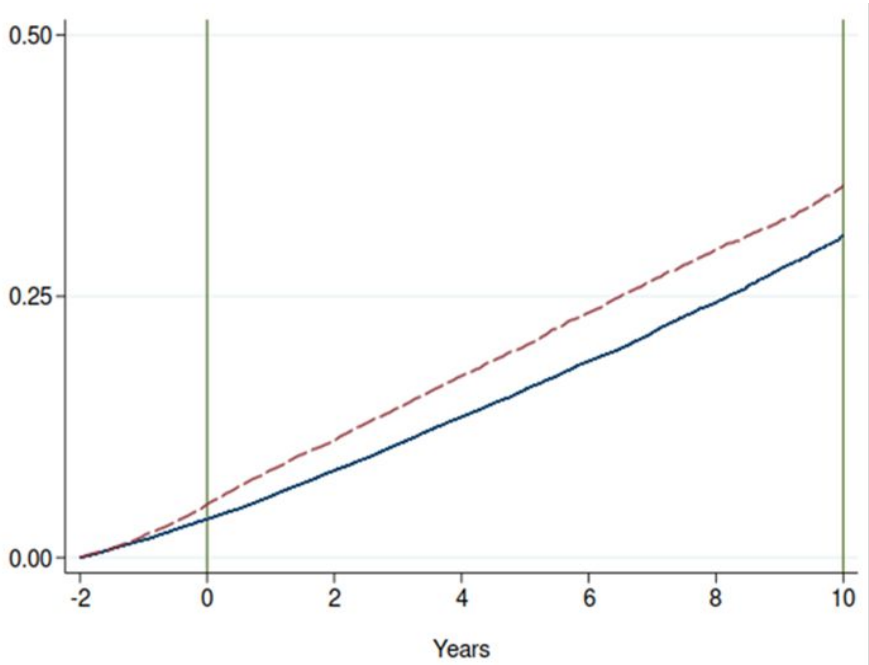
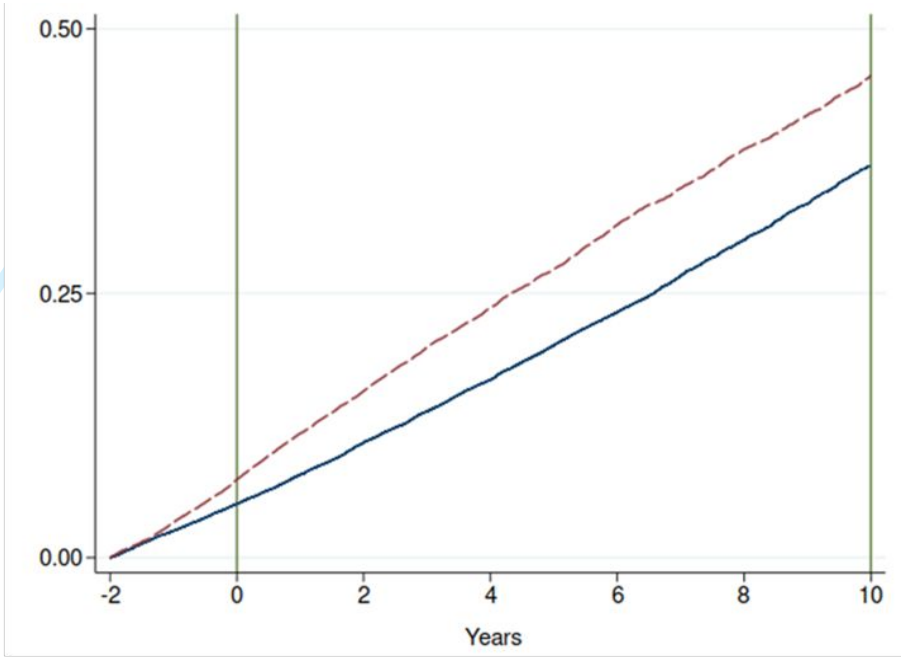


Figure 1b



Abbreviations: * IBD (Inflammatory Bowel Disease); * Depression (depression diagnostic and/or depressive symptom code); * Anxiety (anxiety diagnostic and/or anxiety symptom code); * ADM (Antidepressant Medication). IBD diagnosis date marked with first vertical green line (Year 0); second vertical line denotes 10 years following IBD diagnosis/pseudo diagnosis date.

Supplementary appendix B: Risk of first TCA use in the first year and ten years following diagnosis amongst individuals with IBD compared with the control cohort

	First year		Ten years	
Outcome	**Unadjusted HR (95% CI)**	**Adjusted* HR (95% CI)**	**Unadjusted HR (95% CI)**	**Adjusted* HR (95% CI)**
Cohort				
Matched Controls	1 (-)	1 (-)	1 (-)	1 (-)
IBD	**1.74 (1.56 - 1.93)**	**1.59 (1.42 - 1.77)**	**1.51 (1.42 - 1.61)**	**1.38 (1.30 - 1.48)**
Sex				
Male	1 (-)	1 (-)	1 (-)	1 (-)
Female	**1.52 (1.36 - 1.69)**	**1.50 (1.35 - 1.68)**	**1.55 (1.46 - 1.65)**	**1.55 (1.47 - 1.65)**
Age at diagnosis (years)				
< 18	**0.17 (0.10 - 0.28)**	**0.29 (0.18 - 0.49)**	**0.26 (0.21 - 0.32)**	**0.35 (0.30 - 0.43)**
18 < 25	**0.60 (0.47 - 0.77)**	**0.67 (0.52 - 0.87)**	**0.59 (0.51 - 0.68)**	**0.65 (0.56 - 0.75)**
25 < 40	**0.81 (0.70 - 0.94)**	**0.84 (0.72 - 0.97)**	**0.77 (0.72 - 0.84)**	**0.79 (0.72 - 0.86)**
40 < 60	1 (-)	1 (-)	1 (-)	1 (-)
≥60	1.19 (1.05 - 1.35)	**1.17 (1.03 - 1.33)**	**1.15 (1.07 - 1.23)**	**1.15 (1.07 - 1.23)**
Social deprivation				
IMD 1-3	1 (-)	1 (-)	1 (-)	1 (-)
IMD 4-5	**1.18 (1.02 - 1.35)**	1.05 (0.91 - 1.22)	**1.19 (1.10 - 1.28)**	**1.13 (1.04 - 1.23)**
Unknown	1.04 (0.93 - 1.68)	0.99 (0.88 - 1.13)	1.06 (0.99 - 1.12)	0.99 (0.92 - 1.06)
Era of IBD diagnosis				
Era 1 2004 - 2007	1 (-)	1 (-)	1 (-)	1 (-)
Era 2 2008 - 2011	**1.49 (1.31 - 1.70)**	**1.34 (1.17 - 1.53)**	**1.38 (1.29 - 1.48)**	**1.30 (1.21 - 1.39)**
Era 3 2012 - 2015	**1.56 (1.65 – 2.18)**	**1.63 (1.42 - 1.87)**	**1.77 (1.63 - 1.94)**	**1.64 (1.51 - 1.80)**
Smoking status n (%)				
Never	1 (-)	1 (-)	1 (-)	1 (-)
Smoker	**1.36 (2.39 - 3.03)**	**1.36 (1.17 - 1.59)**	**1.44 (1.32 - 1.57)**	**1.46 (1.33 - 1.59)**
Ex-smoker	**1.36 (1.48 - 1.89)**	**1.18 (1.02 - 1.35)**	**1.38 (1.28 - 1.49)**	**1.25 (1.16 - 1.35)**
Missing	**0.33 (0.27 - 1.39)**	**0.42 (0.34 - 0.51)**	**0.60 (0.55 - 0.65)**	**0.76 (0.70 - 0.83)**
Corticosteroids use				
No	1 (-)	1(-)	1 (-)	1 (-)
Yes	1.01 (0.64- 1.58)	1.44 (0.91 - 2.27)	**0.77 (0.55 - 0.65)**	0.99 (0.79 - 1.24)

All covariates in the table were included within the adjusted analysis. Abbreviations: TCA; Tricyclic antidepressant; HR (Hazard Ratio); CI (Confidence Interval); IMD (Index of Multiple Deprivation) IMD – Index of Multiple Deprivation; IMD 1 represents the least deprived and IMD 5 the most deprived. IMD - Data available only for individual's resident in England

Supplementary appendix C: Ten-year risk of incident depression and anxiety amongst individuals diagnosed with IBD compared with the control cohort

	DEPRESSION		ANXIETY	
	Unadjusted HR (95% CI)	**Adjusted* HR (95% CI)**	**Unadjusted HR (95% CI)**	**Adjusted* HR (95% CI)**
Cohort				
Matched Controls	1 (-)	1 (-)	1 (-)	1 (-)
IBD	**1.24 (1.16 - 1.33)**	**1.17 (1.09 - 1.25)**	**1.29 (1.20 - 1.38)**	**1.20 (1.11 - 1.28)**
Sex				
Male	1 (-)	1 (-)	1 (-)	1 (-)
Female	**1.60 (1.50 - 1.70)**	**1.62 (1.52 - 1.72)**	**1.61 (1.50 - 1.72)**	**1.62 (1.51 - 1.73)**
Age at diagnosis (years)				
< 18	0.88 (0.77 - 1.01)	1.11 (0.96 - 1.28)	0.86 (0.74 - 1.00)	1.03 (0.88 - 1.19)
18 < 25	**1.60 (1.45 - 1.77)**	**1.76 (1.60 - 1.97)**	**1.62 (1.46 - 1.80)**	**1.73 (1.34 - 1.94)**
25 < 40	**1.27 (1.17 - 1.37)**	**1.28 (1.18 - 1.38)**	**1.31 (1.20 - 1.42)**	**1.33 (1.22 - 1.44)**
40 < 60	1 (-)	1 (-)	1 (-)	1 (-)
≥60	**0.76 (0.70 - 0.83)**	**0.77 (0.71 - 0.84)**	**0.74 (0.67 - 0.81)**	**0.73 (0.67 - 0.81)**
Social deprivation				
IMD 1-3	1 (-)	1 (-)	1 (-)	1 (-)
IMD 4-5	**1.23 (1.13 - 1.34)**	**1.32 (1.15 - 1.50)**	**1.14 (1.04 - 1.25)**	**1.06 (0.97 - 1.17)**
Unknown	1.05 (0.98 - 1.21)	1.08 (0.97 - 1.20)	**1.11 (1.03 - 1.20)**	1.08 (1.00 - 1.16)
Era of IBD diagnosis				
Era 1 2004- 2007	1 (-)	1 (-)	1 (-)	1 (-)
Era 2 2008-2011	1.07 (0.99 - 1.15)	1.03 (0.96 - 1.10)	**1.10 (1.01 - 1.19)**	1.06 (0.98 - 1.15)
Era 3 2012-2015	**1.16 (1.06 - 1.27)**	1.09 (0.99 - 1.20)	**1.44 (1.31 - 1.58)**	**1.36 (1.28 - 1.49)**
Smoking status n (%)				
Never	1 (-)	1 (-)	1 (-)	1 (-)
Smoker	**1.78 (1.62 - 1.93)**	**1.70 (1.56 - 1.85)**	**1.50 (1.36 - 1.65)**	**1.44 (1.31 - 1.59)**
Ex-smoker	**1.23 (1.04 - 1.24)**	**1.28 (1.18 - 1.40)**	**1.13 (1.03 - 1.24)**	**1.28 (1.16 - 1.41)**
Missing	0.85 (0.78 - 0.92)	**0.81 (0.74 - 0.89)**	**0.89 (0.81 – 0.97)**	**0.89 (0.81 - 0.97)**
Corticosteroid use				
No	1 (-)	1 (-)	1 (-)	1 (-)
Yes	0.84 (0.67 - 1.07)	1.00 (0.79 - 1.28)	**0.71 (0.56 - 0.90)**	0.87 (0.68 - 1.10)

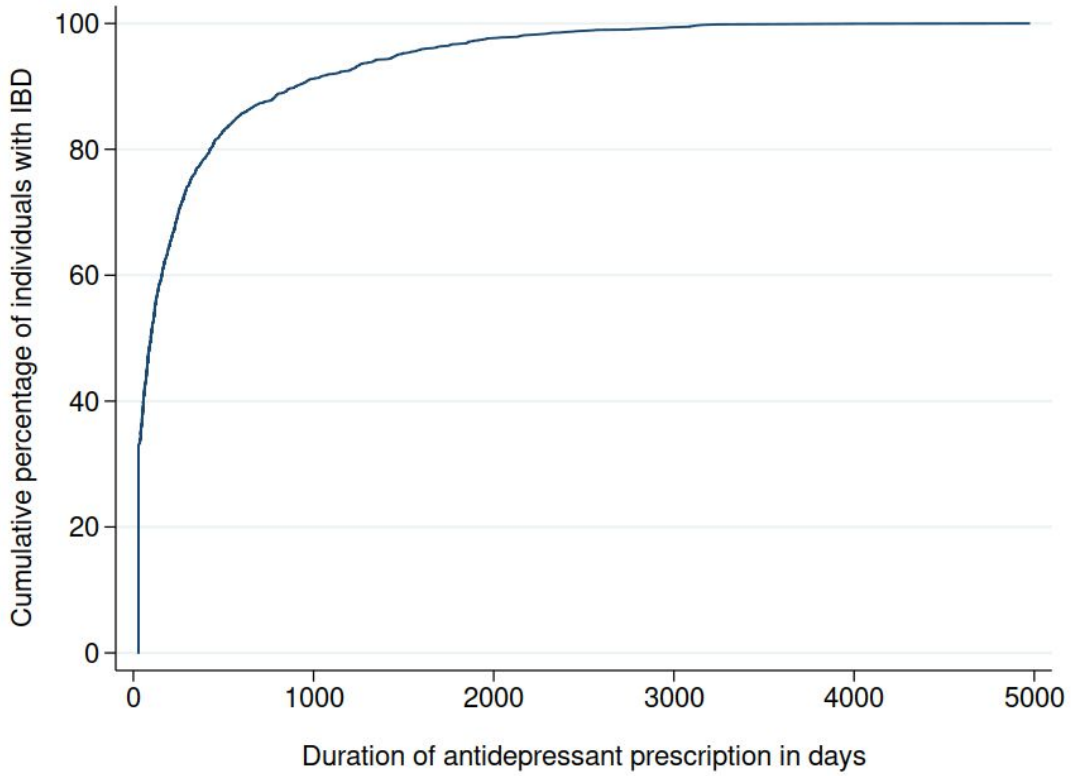
All covariates in the table were included within the adjusted analysis. Abbreviations: HR (Hazard Ratio); CI (Confidence Interval); IMD (Index of Multiple Deprivation) IMD – Index of Multiple Deprivation; IMD 1 represents the least deprived and IMD 5 the most deprived. IMD - Data available only for individual's resident in England

Supplementary appendix D: Conditional frequency of incident depression, anxiety, and ADM records f (X=1|Y=1) [%]

D DIAG	44	63	15	24
18	D SYMP	54	14	19
19	39	ADM	19	20
12	27	52	A DIAG	30
13	26	38	20	A SYMP

Conditional frequency of records given that one has the condition on the y-axis, what is the frequency of having the condition on the x-axis * D DIAG - Diagnosis of depression * D SYMP - Depressive symptoms * A DIAG - Diagnosis of anxiety * A SYMP - Anxiety symptoms * ADM – Antidepressant Medication. Of those with a depression diagnosis 44% also had a record for depressive symptoms and of those with an anxiety diagnosis 30% also had a record for symptoms of anxiety. 18% of those who had depressive symptoms had a diagnosis of depression and 20% of those with who had symptoms of anxiety had a diagnosis of anxiety. Sixty three percent of individuals with a diagnosis of depression and 54% with depressive symptoms also had a record for a newly initiated ADM; whilst 52% of individuals with a diagnosis of anxiety and 38% of individuals with symptoms of anxiety had a record for a newly started an ADM following study index date.

Supplementary appendix E: Cumulative percentage of individuals diagnosed with IBD by duration of antidepressant episode



Supplementary appendix F: 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. 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 main analyses.

Citalopram	**Prodcode**
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) 26016Citalopram 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 (Prodcode)

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 (Prodcode)

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
Felicium 20mg capsules (Opus Pharmaceuticals Ltd)	33071
Oxactin 20mg capsules (Discovery Pharmaceuticals Ltd)	14740

Mirtazepine (Prodcode)

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 (Prodcode)

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 (Prodcode)

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 (Prodcode)

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
Rodomel XL 150mg capsules (Teva UK Ltd)	41314
Rodomel 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

Supplementary appendix G: Depression and Anxiety code list

Depression

Agitated depression	1055
Postnatal depression	2639
H/O: depression	2716
[X]Depressive episode, unspecified	2970
[X]Recurrent depressive disorder	3292
Chronic depression	4323
[X]Depressive episode	4639
Recurrent depression	6482
[X]Other depressive episodes	6854
Endogenous depression first episode	6950
Single major depressive episode NOS	7011
[X]Neurotic depression	7737
Masked depression	9183
[X]Moderate depressive episode	9211
[X]Severe depressive episode without psychotic symptoms	9667
Single major depressive episode	10610
[X]Mild depression	10667
[X]Mild depressive episode	11717
[X]Severe depressive episode with psychotic symptoms	12099
Recurrent major depressive episodes, moderate	14709
Single major depressive episode, moderate	15155
Single major depressive episode, severe, without psychosis	15219
Single major depressive episode, mild	16506
Psychotic reactive depression	17770
[X]Recurrent depressive disorder, currently in remission	22116
Recurrent major depressive episode NOS	25563
Recurrent major depressive episodes, severe, no psychosis	25697
Recurrent major depressive episodes, mild	29342
[X]Recurrent depressive disorder, current episode moderate	29520
[X]Recurrent depressive disorder, current episode mild	29784
Single major depressive episode, severe, with psychosis	32159
[X]Recurr depress disorder cur epi severe without psyc sympt	33469
Single major depressive episode, unspecified	34390
Recurrent major depressive episodes, unspecified	35671
Single major depressive episode, partial or unspec remission	43324
[X]Recurrent depressive disorder, unspecified	44300
[X]Recurrent depress disorder cur epi severe with psyc symp	47009
[X]Other recurrent depressive disorders	47731
Recurrent major depressive episodes, in full remission	55384

Single major depressive episode, in full remission	57409
[X]Major depression, moderately severe	98252
[X]Major depression, mild	98346
[X]Major depression, severe without psychotic symptoms	98414
[X]Recurr major depr ep, severe with psych, psych in remiss	101153
Recurrent major depressive episodes, unspecified	35671
Single major depressive episode, partial or unspec remission	43324
[X]Recurrent depressive disorder, unspecified	44300
[X]Recurrent depress disorder cur epi severe with psyc symp	47009
[X]Other recurrent depressive disorders	47731
Recurrent major depressive episodes, in full remission	55384
Single major depressive episode, in full remission	57409
[X]Major depression, moderately severe	98252
[X]Major depression, mild	98346
[X]Major depression, severe without psychotic symptoms	98414
[X]Recurr major depr ep, severe with psych, psych in remiss	101153
Depressed	1996
C/O - feeling depressed	4824
Low mood	8928
Symptoms of depression	9796
Depressed mood	10015
Depressive symptoms	10438
Loss of capacity for enjoyment	25435
Loss of hope for the future	53148
Health of the Nation Outcome Scale item 7 - depressed mood	96038
Feeling low or worried	101422

Anxiety

Anxiety with depression	655
[X]Anxiety neurosis	962
Chronic anxiety	1758
Phobic disorders	1907
H/O: anxiety state	3407
Panic disorder	4069
Anxiety state NOS	4534
Recurrent anxiety	4634
Generalised anxiety disorder	4659
Neurotic disorders	5249
[X]Other anxiety disorders	5385
Separation anxiety disorder	6221
Anxiety state unspecified	6939
[X]Mild anxiety depression	7749

Anxiety counselling	7999
[X]Panic disorder [episodic paroxysmal anxiety]	8205
[X]Anxious [avoidant] personality disorder	8424
[X]Phobic anxiety disorders	9386
Phobic anxiety	9944
[X]Generalized anxiety disorder	10344
[X]Mixed anxiety and depressive disorder	11913
Neurotic disorder NOS	14780
[X]Persistent anxiety depression	15220
Social phobic disorders	16638
[X]Dream anxiety disorder	17687
[X]Separation anxiety disorder of childhood	18032
Psychoneurotic personality disorder	21077
[X]Anxiety disorder, unspecified	23838
[X]Other specified anxiety disorders	24066
[X]Phobic anxiety disorder of childhood	24351
[X]Anxiety NOS	25638
Reducing anxiety	26295
[X]Anxiety hysteria	28167
Neurotic personality disorder	28227
Alleviating anxiety	28381
[X]Social anxiety disorder of childhood	29907
[X]Phobic anxiety disorder, unspecified	34064
Other neurotic disorders	42000
Other neurotic disorder NOS	43050
[X]Other mixed anxiety disorders	44321
[X]Other specified neurotic disorders	44331
[X]Neurotic disorder, unspecified	49628
[X]Anxiety state	50191
[X]Psychoneurotic personality disorder	50348
[V]Personal history of neurosis	51613
[X]Childhood overanxious disorder	61430
Anxiousness	131
Panic attack	462
Tension - nervous	514
Nervous breakdown	791
Hypochondriasis	966
Cancer phobia	1510
Nervous exhaustion	1582
Claustrophobia	1723
Obsessional neurosis	2030
Phobia unspecified	2300

[D]Nervousness	2509
Worried	2524
[X]Agoraphobia	2571
Tenseness - symptom	2585
Neurotic personality	2729
Agoraphobia with panic attacks	3076
General nervous symptoms	3328
'Nerves'	3586
[X]Panic state	4081
Fear of flying	4167
Poor insight into neurotic condition	5274
Fear	5347
Compulsive neurosis	5678
Anxiousness - symptom	5902
Fear of pregnancy	6071
[X]Phobia NOS	7222
O/E - nervous	8725
Anxiety management training	9125
Neurotic, personality, and other nonpsychotic disorders	9686
[X]Specific (isolated) phobias	9785
Fear of death	10390
[D]Nervous tension	10723
[X]Hypochondriasis	10870
[X]Claustrophobia	11280
[X]Occupational neurosis,	11339
[X]Social phobias	11602
C/O - panic attack	11890
Acute panic state due to acute stress reaction	11940
[X]Needle phobia	12508
[X]Simple phobia	12635
Agoraphobia without mention of panic attacks	12838
O/E - anxious	13124
Phobic disorder NOS	14729
[X]panic disorder with agoraphobia	14890
Cardiac neurosis	15292
Somatization disorder	15321
Neurotic condition, insight present	15811
Social phobia, fear of eating in public	16199
[X]Agoraphobia without history of panic disorder	16729
[X]Animal phobias	18248
Social phobia, fear of public washing	18603
Specific fear	18672
Fear of getting cancer	18967
O/E - panic attack	19000

General nervous symptom NOS	20089
Apprehension	20163
[V]'Worried well'	20375
[X]Organic anxiety disorder	20773
[X]Neurosis NOS	21431
[X]Obsessive-compulsive neurosis	21836
Acknowledging anxiety	22159
[X]Neurotic, stress	23808
[X]Anankastic neurosis	24251
[X]Hypochondriacal neurosis	24264
[X]Somatization disorder	24439
Nervous syst/mental state NOS	25213
O/E - fearful mood	26331
[X]Other neurotic disorders	28090
Acrophobia	28106
Examination fear	28129
Worried well	28408
Referral for guided self-help for anxiety	28925
Animal phobia	28938
Tenseness	29569
'Nerves' - nervousness	29608
Disturbance of anxiety and fearfulness childhood/adolescent	31522
Fear of crowds	31672
Social phobia, fear of public speaking	31957
[X]Traumatic neurosis	32182
Disturbance anxiety and fearfulness childhood/adolescent NOS	35594
Childhood and adolescent over anxiousness disturbance	35619
[X]Anxiety reaction	35825
O/E - afraid	38155
Other occupational neurosis	39518
Cries easily	40431
Neuroses or other mental disorder NOS	42410
[X]Social neurosis	42788
[X]Cardiac neurosis	44269
Anancastic neurosis	47365
[X]Enduring personality change after catastrophic experience	48232
Other specified neuroses or other mental disorders	50106
Encounter for fear	53067
Childhood and adolescent fearfulness disturbance	56026
Adjustment reaction with anxious mood	56924
[X]Character neurosis NOS	57567
Recognising anxiety	62935
[X]Gastric neurosis	63259
[X]Phobic state NOS	67898
[X]Acrophobia	67965

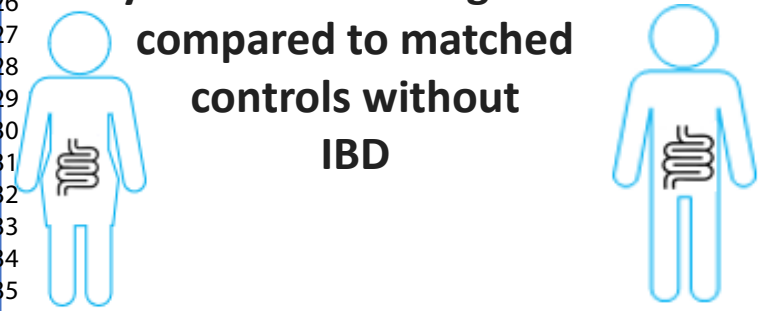
Psychasthenic neurosis	72171
[X]Psychasthenia neurosis	90597
Anxious	93401
Feeling low or worried	101422
Anxiety about breathlessness	107410

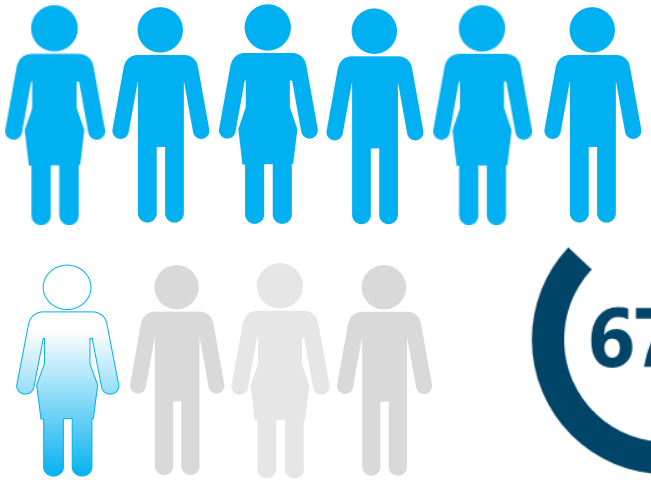
Antidepressant medication use in Inflammatory Bowel Disease: A nationally representative population-based cohort study

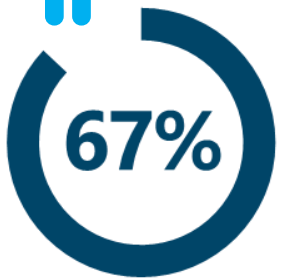
Individuals diagnosed with Inflammatory Bowel Disease are

34%

more likely to start antidepressants in the year after IBD diagnosis compared to matched controls without IBD

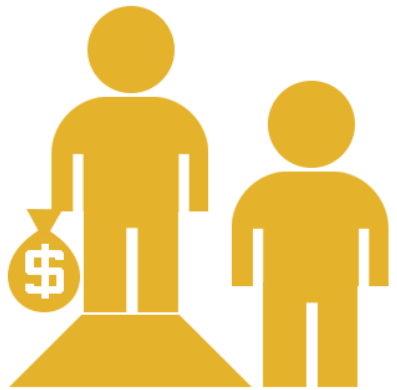






Only a third of IBD patients received antidepressant treatment lasting more than 7 months which is the minimum recommended in international guidelines

Young adults diagnosed with IBD aged between 18 and 24 years and socioeconomic deprivation is associated with a risk of early antidepressant discontinuation



Jayasooriya N, Blackwell J, Saxena S, Bottle A, Petersen I, Creese H, Hotopf M, Pollok R C G, POP-IBD study group

STROBE Statement—Checklist of items in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **(Page 1 and Page 4)**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **(Page 4)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **(Page 7)**
Objectives	3	State specific objectives, including any prespecified hypotheses **(Pages 7 and 8)**
Methods		
Study design	4	Present key elements of study design early in the paper **(Page 9)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **(Pages 9 and 10)**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **(Pages 9 to 12)**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **(Pages 9 and 10)**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **(Pages 9 to 12)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **(Pages 11 and 12)**
Bias	9	Describe any efforts to address potential sources of bias **(Pages 9 and 10)**
Study size	10	Explain how the study size was arrived at **(Pages 9 and 10)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **(Pages 11 and 12)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **(Pages 13 and 14)**
		(*b*) Describe any methods used to examine subgroups and interactions **(Pages 13 and 14)**
		(*c*) Explain how missing data were addressed **(Pages 13 and 14)**
		(*d*) If applicable, explain how loss to follow-up was addressed **(Pages 13 and 14)**
		(*e*) Describe any sensitivity analyses **(Pages 13 and 14)**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **(Page 15)**

		(b) Give reasons for non-participation at each stage **(Page 15)**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders **(Page 30)**
		(b) Indicate number of participants with missing data for each variable of interest **(Page 30)**
		(c) Summarise follow-up time (eg, average and total amount) **(Pages 15 and 16)**
Outcome data	15*	Report numbers of outcome events or summary measures over time **(Pages 15 and 16)**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **(Pages 15,16,31-34)**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **(Page 12)**
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses **(Page 16 and Supplementary appendix C)**
Discussion		
Key results	18	Summarise key results with reference to study objectives **(Page 17)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **(Pages 19 and 20)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **(Pages 20 and 21)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **(Pages 20 and 21)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **(Page 22)**

*Give information separately for exposed and unexposed groups.