

Healthcare resource utilisation, common mental health problems, and infections in people with inflammatory bowel disease (IBD)

NCT number: Not available at submission

Document date: 6th Dec 2018

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The research is supported by Momentum Data Ltd



Abstract

Background

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory conditions collectively termed inflammatory bowel disease (IBD). Both conditions are chronic and involve a lifetime of treatment. Current treatment strategies for IBD focus on the use of immune modulating medications, which have the potential to increase the risk of common infections. An understanding of the healthcare resource utilisation and overall infection risk in IBD is therefore important. Despite increasing treatment options, quality of life is significantly reduced in people with IBD and a high prevalence of mental health disorders has been reported. However, the magnitude of any potential association between IBD and mental illness in adults has not yet been fully explored.

Objective

We aim to provide an accurate and contemporary measurement of the current healthcare resource utilisation in people with IBD. We also aim to provide estimates of infection incidence in this population and the prevalence of common mental health conditions. We will also

Method

We will identify UC and CD using algorithms validated for accurately identifying these conditions from primary care records in the UK. We will identify a prevalent cohort of adults with IBD with the RCGP RSC network over the last decade. We will identify a matched cohort of people without IBD; matched on age, gender and primary care practice. Across these cohorts we will compare healthcare resource utilisation (primary care attendances, number of primary care prescriptions for antidepressant and anxiolytic medications, number of primary care prescriptions for medications used in IBD, recorded secondary care attendances, and issue of statements of fitness for work), incident infections (any common infection, any viral infection, or any gastrointestinal infection), and common mental health conditions (depression, anxiety, and attention deficit hyperactivity disorder).

Lay Summary

Ulcerative colitis and Crohn's disease are the commonest types of inflammatory bowel disease (IBD). Both conditions range in severity from no symptoms to being potentially fatal. Both conditions are treated with medications which suppress the immune system. It is not known whether this increases the risk for infections in these conditions. It is also recognised by healthcare professionals that these conditions cause a considerable amount of psychological distress. However, this has never been measured in a large population sample.

These studies will investigate any associations with treatment and new onset infections. They will also examine the relationship between IBD and common mental health problems (specifically, depression and anxiety) and the impact that these have on the healthcare use (including number of GP appointments, hospital attendances, and medication prescriptions). Combined, these studies should provide a better understanding of the impact of IBD on affected people and provide evidence to support the correct allocation of healthcare resources.

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory conditions collectively termed inflammatory bowel disease (IBD).¹ In both conditions there is a spectrum of disease ranging from a quiescent state with few or no symptoms to potentially fatal disease. Both conditions commonly require extensive medical intervention over many decades of disease and may also require substantial surgical treatment.^{2, 3} With the global burden of IBD rising, calls have been made for improved treatment options,⁴ and these been met with the development of a range of biologic therapies.¹

Current treatment strategies for UC focus on the use of immune modulating medications. Whilst frequently effective for disease control, these treatments have the potential to increase the risk of common infections,^{5, 6} which includes both common and atypical pathogens.⁶ An understanding of the infection risk in a community-based population with UC is therefore important. However, the existing literature on infection rates in people with UC has focused almost exclusively on secondary care populations. It therefore remains unclear what the total burden of infectious disease is in a population-based cohort with UC and how this compares to those without UC.

Despite increasing treatment options, quality of life is significantly reduced in people with IBD⁷ and the prevalence of mental health disorders has been reported to be higher in children with IBD.⁸ However the magnitude of any potential association between IBD and mental illness in adults has not yet been fully explored.

Given the prolonged course of medical treatment in IBD, it is important for payers to have a good understanding of the total healthcare utilisation of people with IBD. Again, in this area, existing studies have focussed on secondary care based cohorts. Little is known about healthcare resource utilisation in primary care, in people with IBD, in the UK.

Aims

1. We aim to describe the incidence of common infections in a population of individuals with IBD, compared to a matched control population without IBD. We will explore all common infections and also focus on viral and gastrointestinal infections.
2. We will explore how incidence of infection varies by age, and other factors associated with risk of infection in IBD including medication use.
3. We aim to describe the prevalence of common mental health conditions (anxiety, depressive episodes, and recurrent depressive disorder) in people with IBD when compared to an age and gender matched cohort.
4. We aim to explore healthcare utilisation in individuals with IBD with and without common mental health problems.

Methods

Study design

We aim to perform a retrospective matched cohort study. We will match people with UC and CD, to people without IBD. A history of common mental health conditions was assessed at baseline (matching date) in both cohorts, and compared. Both cohorts will be followed-up (retrospectively) from the matching date for incident infections, and healthcare resource utilisation.

Data source

We aim to use the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database. This database contains the pseudonymised primary care records of the registered population all from a network of GP practices which provide a representative sample of the UK population.⁹ The RCGP RSC database contains complete data on all events and clinical entities coded in UK primary care. These include demographic information, clinical diagnoses, laboratory test results, primary care issued prescriptions, process of care codes (e.g. specialist referrals), and anthropometric measurements (e.g., body mass index; BMI), and are coded using the Read coding system.¹⁰

UK general practice records provide several advantages for this study type;^{11, 12} UK primary care is a registration-based system (a patient can only register with a single GP), records have been computerised since the 1990s, and pay-for-performance targets (introduced in 2004 through The Quality and Outcomes Framework; QOF) have resulted in consistent high-quality clinical data entry about chronic disease. Studies using the RCGP RSC data have been published across a range of chronic diseases.¹³⁻¹⁵ RCGP RSC practices get feedback on their data quality, including using a dashboard. A particular emphasis of this feedback is “episode typing” – designating cases first, new, or ongoing – which helps differentiate incidence from prevalence.¹⁶

Study population and outcome measures

All adults (aged ≥ 18) registered with a GP practice contributing to the RCGP RCS at the time of data extraction will be eligible for inclusion.

Definition of the IBD cohort

All individuals with one or more diagnostic codes for UC or CD prior to the study start date were eligible for inclusion in the IBD cohort. The use of diagnostic codes to identify IBD from UK primary care records has been validated and shown to be accurate and to correctly differentiate between UC and CD.^{17, 18} The Read codes used to identify UC and CD were based on the codes list used by Abrahami et al.,¹⁸ and mapped to both Read code versions used within the RCGP RSC network (Appendix 1). The use of diagnostic codes to identify IBD has also been shown to have good validity in US claims databases.¹⁹

Definition of the matched cohort

The matched unexposed cohort will be identified by matching individuals with IBD to people without IBD. Matching will be performed on age and gender as a minimum. Follow-up for each matched individual will begin at the same baseline date as those with IBD.

Infections outcomes

Infections outcomes will comprise:

1. The time to first recorded presentation with a new episode of any common infection during the study period; a composite of upper respiratory tract infections, pneumonia, bronchitis, influenza-like illness, skin infections, genital infections, urinary tract infections and gastrointestinal infections.
2. The time to first recorded presentation with a new episode of any viral infection.
3. The time to first recorded presentation with a new episode of any episode of gastrointestinal infection.

The Read codes used to identify infections will be adapted from the validated indicators used in routine surveillance by the RCGP RSC. The chosen infections in the composite infections outcomes were selected principally as they represent the majority of the primary care adult infectious disease burden, and include a mixture of viral, bacterial and fungal infections. First or new episodes of an infection are coded accordingly in the database, enabling differentiation from chronic infections or follow-up visits for the same episode. If available, we will also explore type and pathogens contributing to the incident infections.

Mental health outcomes

The presence of common mental health conditions at baseline will be determined for the case and control cohorts. We will examine three groups of common mental illness as defined by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10) classification;²⁰ depressive episodes (F32), recurrent depressive disorder (F33), and non-phobia related anxiety disorders (F41). These conditions are chosen as they represent the most common mental health conditions presenting to primary care.²¹ These conditions will be identified using algorithms validated in UK primary care.²² We selected the algorithms used here (Appendix 2) to optimise the positive predictive value. In brief, we will use a concurrent diagnosis and treatment code to identify acute episodes (depressive episodes and anxiety episodes) and for recurrent depression either a historical code for any depression and current treatment or a recurrent

depression specific diagnosis code (Appendix 2). As a secondary analysis we will also explore the prevalence of attention deficit hyperactivity disorder (ADHD) in the case and control cohorts.

Healthcare utilisation outcomes

The components of healthcare utilisation to be examined comprise; number and duration of primary care attendances, number of primary care prescriptions for antidepressant and anxiolytic medications, number of primary care prescriptions for medications used in IBD, recorded secondary care attendances, and issue of statements of fitness for work (also termed fit notes or sick notes).

Antidepressant medication classes to be examined comprise, selective serotonin reuptake inhibitors (SSRIs) and related medications (serotonin and norepinephrine reuptake inhibitors; SNRIs), tricyclic antidepressants (TCAs) and related medications (tetracyclic antidepressant TeCAs), and monoamine oxidase inhibitors (MOAIs). Anxiolytic medications to be examined comprise all benzodiazepines and other related medications indicated for use in anxiety states (Appendix 3). Medications used for the treatment of IBD to be examined will comprise; topical 5-aminosalicylic acid (5-ASA) medications, topical glucocorticoids, oral 5-ASA medications, oral glucocorticoids, non-biologic immunosuppressant medications (cyclosporine, azathioprine, mercaptopurine, methotrexate), and biologic therapies (Appendix 3).

Other baseline measures

Socioeconomic status will be defined using the official national measure; the index of multiple deprivation (IMD).²³ This is calculated at the point of data extraction, using patient postcode, with the resultant scores stratified by deprivation quintile. Ethnicity will be extracted from the primary care record and grouped into major ethnic groups; white, black, Asian, mixed, and others.²⁴ BMI will be defined as the most recently recorded measurement prior to the study start date. Smoking status will be defined using the most recently recorded data prior to the study start date. Diagnosis codes will be used to define the presence of comorbidities at baseline; diabetes, hypertension, atrial fibrillation, angina, myocardial infarction, congestive heart failure, stroke, transient ischaemic attack, chronic kidney disease (stages 3–5), dementia, rheumatoid arthritis, chronic liver disease, asthma and chronic obstructive pulmonary disease (COPD).

Statistical Analyses

Comparison of the prevalence of mental health conditions

We will compare the prevalence of the three common mental health conditions in people with IBD and matched controls prior to the baseline date (January 1, 2015). We will stratify groups by age, and gender, and for those with IBD by condition (UC or CD) and duration of disease, and other important baseline factors. We will evaluate differences in baseline characteristics between the cohorts using the χ^2 test for categorical variables and the unpaired t-test for continuous data. Other statistical tests may be used if appropriate, depending on the data type and distribution.

Comparison of healthcare utilisation

We will compare the measures of healthcare utilisation between people with IBD and matched cohorts over a follow-up period. Follow-up will end at the earliest of; the study end-date (data extraction date), the date of patient transfer from an included practice, or date of death. All individuals contributing at least 1 day of follow-up will be included for analysis. We will stratify and compare healthcare utilisation in people with IBD by age and gender, condition (UC or CD), duration of disease, the presence of mental health conditions, and other important

confounders. All utilisation outcomes will be adjusted for the duration of follow-up and reported as event rates.

Where sample size allows we will examine factors associated with increased healthcare utilisation. We will use regression analyses to assess potential associations between healthcare utilisation outcome measures and important patient and treatment factors.

Comparison of infections

Infection incidence rates will be calculated as the number of events divided by the total person-years of follow-up and expressed as the number per 1000 person-years. We will estimate the risk of infection in people with and without IBD using Cox proportional hazards models, and report estimated hazard ratios for associations with 95% confidence intervals. We will evaluate factors associated with an increased risk of infection. Factors assessed will include age, gender, socioeconomic status, household size (if available), comorbidities, and UC medications.

All statistical analyses will be performed in the R statistical package.

Ethical approval

Study approval will be requested from the Research Committee of the RCGP RSC. The study does not meet the requirements for formal ethics board review as defined using the NHS Health Research Authority research decision tool (<http://www.hra-decisiontools.org.uk/research/>).

Contributors

Research support for this project in several areas including data analysis, literature searching, and medication writing will be provided by Momentum Data. John Dennis and Andrew McGovern of Momentum Data have contributed to the writing of this protocol and to the study design. Funding for these studies has been provided by Pfizer UK.

Scientific rigor and study registration

The team ethos at Momentum Data is to support the highest quality research, for patient benefit, with rigorous scientific standards. Publication bias remains an issue in observational studies. Therefore, if approval is granted the protocol will be registered as an observational study with ClinicalTrials.gov and made publicly available prior to the commencement of data analysis. Any protocol amendments will be published alongside this public record of the study and will be noted in any final publication with the rationale for the modification. Any changes will be assessed for the need for ethics approval and further RCGP RSC study approval; these will be sought if required.

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Appendices

Appendix 1

Ulcerative colitis		
Read V2 Code	Term ID	Description
J41..	All	Ulcerative colitis and/or proctitis
J410.	All	Ulcerative proctocolitis
J4100	All	Ulcerative ileocolitis
J4101	All	Ulcerative colitis
J4102	All	Ulcerative rectosigmoiditis
J4103	All	Ulcerative proctitis
J4104	All	Exacerbation of ulcerative colitis
J410z	All	Ulcerative proctocolitis NOS
J411.	All	Ulcerative (chronic) enterocolitis
J412.	All	Ulcerative (chronic) ileocolitis
J413.	All	Ulcerative pancolitis
N0454	All	Juvenile arthritis in ulcerative colitis
N0310	All	Arthropathy in ulcerative colitis
Read CTV3 Code	Term ID	Description
XE0ag	All	Ulcerative colitis
XaZ2j	All	Left sided ulcerative colitis
XaYzX	All	Ulcerative pancolitis
XaK6E	All	Exacerbation of ulcerative colitis
J410.	All	Ulcerative proctocolitis
J4100	All	Ulcerative ileocolitis
J410z	All	Ulcerative proctocolitis NOS
Jyu41	All	[X]Other ulcerative colitis
Crohn's disease		
Read V2 Code	Term ID	Description
J40..	All	Regional enteritis- Crohn's disease
J400.	All	Regional enteritis of the small bowel
J4002	All	Crohn's disease of the terminal ileum
J4003	All	Crohn's disease of the ileum unspecified
J4004	All	Crohn's disease of the ileum NOS
J4005	All	Exacerbation of Crohn's disease of small intestine
J400z	All	Crohn's disease of the small bowel NOS
J40..	All	Crohn's disease
J4012	All	Exacerbation of Crohn's disease of large intestine
J401z	All	Crohn's disease of the large bowel NOS
J402.	All	Regional ileocolitis
J40z.	All	Crohn's disease NOS

Read CTV3 Code	Term ID	Description
XE2QL	All	Crohn's disease
Xa0lh	All	Regional enteritis
X302r	All	Crohn's jejunitis
X302t	All	Crohn's ileitis
J4003	All	Crohn's disease of the ileum unspecified
J4004	All	Crohn's disease of the ileum NOS
J4002	All	Crohn's disease of terminal ileum
J400.	All	Regional enteritis of small bowel
XaK6C	All	Exacerbation of Crohn's disease of small intestine
J400z	All	Crohn's disease of the small bowel NOS
J401.	All	Regional enteritis of the large bowel
XE0af	All	Crohn's disease of the large bowel NOS
XaK6D	All	Exacerbation of Crohn's disease of large intestine
J40z.	All	Regional enteritis NOS
J4010	All	Crohn's colitis
J4011	All	Crohn's proctitis
X3050	All	Perianal Crohn's disease
Jyu40	All	[X]Other Crohn's disease

Supplementary table S1. Read codes used to identify inflammatory bowel disease

Appendix 2

Clinical entity	ICD 10 code	Definition
Anxiety	F41	Any coded anxiety episode AND concurrent treatment for anxiety
Depressive episode	F32	Any coded depressive episode AND concurrent treatment for depression
Recurrent depressive disorder	F33	(Any historical code* for a depressive episode AND current treatment for depression) OR Any code for recurrent depressive disorder
Anxiety treatments	NA	SSRIs, anxiolytics, counselling, CBT, and psychotherapy
Depression treatments	NA	SSRIs, TCAs, MAOIs, counselling, CBT, and psychotherapy

Supplementary table S2. Algorithms used to identify anxiety episodes, depression episodes, and recurrent major depression. Expressions in capitals equate to Boolean expressions. *More than 1 year ago. SSRIs = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressants, MAOI = monoamine oxidase inhibitors, CBT = cognitive behavioural therapy.

Read V2 Code	Term ID	Description
E200.	All	Anxiety states
E2000	All	Anxiety state unspecified
E2001	All	Panic disorder
E2002	All	Generalised anxiety disorder
E2003	All	Anxiety with depression
E2004	All	Chronic anxiety
E2005	All	Recurrent anxiety
E200z	All	Anxiety state NOS
Eu41.	All	[X]Other anxiety disorders
Eu410	All	[X]Panic disorder [episodic paroxysmal anxiety]
Eu411	All	[X]Generalized anxiety disorder
Eu412	All	[X]Mixed anxiety and depressive disorder
Eu413	All	[X]Other mixed anxiety disorders
Eu41y	All	[X]Other specified anxiety disorders
Eu41z	All	[X]Anxiety disorder, unspecified
Read CTV3 Code	Term ID	Description
E200.	All	Anxiety disorder
XE1Y7	All	Panic disorder
Eu410	All	[X]Panic disorder [episodic paroxysmal anxiety]
E2002	All	Generalised anxiety disorder
X00Sb	All	Mixed anxiety and depressive disorder
X00RP	All	Organic anxiety disorder
E2004	All	Chronic anxiety
E2005	All	Recurrent anxiety
E200z	All	Anxiety state NOS
X00Sc	All	Anxiety hysteria
Eu41.	All	[X]Other anxiety disorders
Eu413	All	[X]Other mixed anxiety disorders
Eu41z	All	[X]Anxiety disorder, unspecified
XE1Zj	All	[X]Other specified anxiety disorders

Supplementary table S3. Read codes used to identify anxiety episodes.

Read V2 Code	Term ID	Description
E0013	All	Presenile dementia with depression
E0021	All	Senile dementia with depression
E112.	All	Single major depressive episode
E1120	All	Single major depressive episode, unspecified
E1121	All	Single major depressive episode, mild
E1122	All	Single major depressive episode, moderate
E1123	All	Single major depressive episode, severe, without mention of psychosis
E1124	All	Single major depressive episode, severe, with psychosis
E1125	All	Single major depressive episode, in partial or unspecified remission
E1126	All	Single major depressive episode, in full remission
E112z	All	Single major depressive episode NOS
E113.	All	Recurrent major depressive episode
E1130	All	Recurrent major depressive episodes, unspecified
E1131	All	Recurrent major depressive episodes, mild
E1132	All	Recurrent major depressive episodes, moderate
E1133	All	Recurrent major depressive episodes, severe, without mention of psychosis
E1134	All	Recurrent major depressive episodes, severe, with psychosis
E1137	All	Recurrent depression
E113z	All	Recurrent major depressive episode NOS
E118.	All	Seasonal affective disorder
E11y2	All	Atypical depressive disorder
E11z2	All	Masked depression
E130.	All	Reactive depressive psychosis
E135.	All	Agitated depression
E2003	All	Anxiety with depression
E291.	All	Prolonged depressive reaction
E2B..	All	Depressive disorder NEC
E2B1.	All	Chronic depression
E2B0.	All	Postviral depression
Eu204	All	[X]Post-schizophrenic depression
Eu251	All	[X]Schizoaffective disorder, depressive type
Eu32.	All	[X]Depressive episode
Eu320	All	[X]Mild depressive episode
Eu321	All	[X]Moderate depressive episode
Eu322	All	[X]Severe depressive episode without psychotic symptoms
Eu323	All	[X]Severe depressive episode with psychotic symptoms
Eu324	All	[X]Mild depression
Eu325	All	[X]Major depression, mild
Eu326	All	[X]Major depression, moderately severe
Eu327	All	[X]Major depression, severe without psychotic symptoms
Eu328	All	[X]Major depression, severe with psychotic symptoms

Eu32y	All	[X]Other depressive episodes
Eu32z	All	[X]Depressive episode, unspecified
Eu33.	All	[X]Recurrent depressive disorder
Eu330	All	[X]Recurrent depressive disorder, current episode mild
Eu331	All	[X]Recurrent depressive disorder, current episode moderate
Eu332	All	[X]Recurrent depressive disorder, current episode severe without psychotic symptoms
Eu333	All	[X]Recurrent depressive disorder, current episode severe with psychotic symptoms
Eu334	All	[X]Recurrent depressive disorder, currently in remission
Eu33y	All	[X]Other recurrent depressive disorders
Eu33z	All	[X]Recurrent depressive disorder, unspecified
Eu412	All	[X]Mixed anxiety and depressive disorder
Read CTV3 Code	Term ID	Description
X00Sb	All	Mixed anxiety and depressive disorder
X00SO	All	Depressive disorder
X761L	All	Seasonal affective disorder
Xa0wV	All	Recurrent brief depressive disorder
X00SQ	All	Agitated depression
XE1YC	All	Reactive depression
X00SR	All	Endogenous depression
X00SS	All	Endogenous depression first episode
XE1Y0	All	Single major depressive episode
E1120	All	Single major depressive episode, unspecified
E1120	All	Single major depressive episode, unspecified
E1121	All	Single major depressive episode, mild
E1122	All	Single major depressive episode, moderate
E1123	All	Single major depressive episode, severe, without mention of psychosis
E1124	All	Single major depressive episode, severe, with psychosis
XaX53	All	Single major depressive episode, severe, with psychosis, psychosis in remission
E1125	All	Single major depressive episode, in partial or unspecified remission
E1126	All	Single major depressive episode, in full remission
E112z	All	Single major depressive episode NOS
XM1GC	All	Endogenous depression - recurrent
E1130	All	Recurrent major depressive episodes, unspecified
E1131	All	Recurrent major depressive episodes, mild
E1132	All	Recurrent major depressive episodes, moderate
E1133	All	Recurrent major depressive episodes, severe, without mention of psychosis
E1134	All	Recurrent major depressive episodes, severe, with psychosis
E1135	All	Recurrent major depressive episodes, in partial or unspecified remission
E1136	All	Recurrent major depressive episodes, in full remission
E113z	All	Recurrent major depressive episode NOS

X00SU	All	Masked depression
E11y2	All	Atypical depressive disorder
X00S8	All	Post-schizophrenic depression
XSEGJ	All	Major depressive disorder
XSKr7	All	Cotard syndrome
XSGol	All	Moderate major depression
XSGok	All	Mild major depression
XSGom	All	Severe major depression without psychotic features
XSGon	All	Severe major depression with psychotic features
E1137	All	Recurrent depression
E130.	All	Reactive depressive psychosis
E2B..	All	Depressive disorder NEC
E2B0.	All	Postviral depression
E2B1.	All	Chronic depression
Eu320	All	[X]Mild depressive episode
Eu321	All	[X]Moderate depressive episode
Eu331	All	[X]Recurrent depressive disorder, current episode moderate
XE1Y1	All	Recurrent major depressive episodes
XE1ZY	All	[X]Severe depressive episode without psychotic symptoms
XE1ZZ	All	[X]Severe depressive episode with psychotic symptoms
XE1Za	All	[X]Other depressive episodes
XE1Zb	All	[X]Depressive episode, unspecified
XE1Zd	All	[X]Recurrent depressive disorder, current episode severe without psychotic symptoms
XE1Ze	All	[X]Recurrent depressive disorder, current episode severe with psychotic symptoms
XE1Zf	All	[X]Recurrent depressive disorder, unspecified
XaB9J	All	Depression NOS
XaCHr	All	[X] Single episode agitated depression without psychotic symptoms
XaCHs	All	[X] Single episode major depression without psychotic symptoms
XaCIs	All	Mild depression
XaCIt	All	Moderate depression
XaCIu	All	Severe depression
E0013	All	Presenile dementia with depression
E0021	All	Senile dementia with depression

Supplementary table S4. Read codes used to identify, depression episodes.

Read V2 Code	Term ID	Description
E113.	All	Recurrent major depressive episode
E1130	All	Recurrent major depressive episodes, unspecified
E1131	All	Recurrent major depressive episodes, mild
E1132	All	Recurrent major depressive episodes, moderate
E1133	All	Recurrent major depressive episodes, severe, without mention of psychosis
E1134	All	Recurrent major depressive episodes, severe, with psychosis
E1135	All	Recurrent major depressive episodes, in partial or unspecified remission
E1136	All	Recurrent major depressive episodes, in full remission
E1137	All	Recurrent depression
E113z	All	Recurrent major depressive episode NOS
E2B1.	All	Chronic depression
Eu32A	All	[X]Recurrent major depressive episodes, severe, with psychosis, psychosis in remission
Eu33.	All	[X]Recurrent depressive disorder
Eu330	All	[X]Recurrent depressive disorder, current episode mild
Eu331	All	[X]Recurrent depressive disorder, current episode moderate
Eu332	All	[X]Recurrent depressive disorder, current episode severe without psychotic symptoms
Eu333	All	[X]Recurrent depressive disorder, current episode severe with psychotic symptoms
Eu334	All	[X]Recurrent depressive disorder, currently in remission
Eu33y	All	[X]Other recurrent depressive disorders
Eu33z	All	[X]Recurrent depressive disorder, unspecified
Read CTV3 Code	Term ID	Description
Xa0wV	All	Recurrent brief depressive disorder
XM1GC	All	Endogenous depression - recurrent
E1130	All	Recurrent major depressive episodes, unspecified
E1131	All	Recurrent major depressive episodes, mild
E1132	All	Recurrent major depressive episodes, moderate
E1133	All	Recurrent major depressive episodes, severe, without mention of psychosis
E1134	All	Recurrent major depressive episodes, severe, with psychosis
XaX54	All	Recurrent major depressive episodes, severe, with psychosis, psychosis in remission
E1135	All	Recurrent major depressive episodes, in partial or unspecified remission
E1136	All	Recurrent major depressive episodes, in full remission
E113z	All	Recurrent major depressive episode NOS
E1137	All	Recurrent depression
E2B1.	All	Chronic depression
Eu331	All	[X]Recurrent depressive disorder, current episode moderate
XE1Y1	All	Recurrent major depressive episodes

XE1Zd	All	[X]Recurrent depressive disorder, current episode severe without psychotic symptoms
XE1Ze	All	[X]Recurrent depressive disorder, current episode severe with psychotic symptoms
XE1Zf	All	[X]Recurrent depressive disorder, unspecified

Supplementary table S5. Read codes used to identify a diagnosis of recurrent major depression.

Counselling		
Read V2 Code	Term ID	Description
67...	11	Counselling/health education
671..	All	Counselling - general
6712.	All	Counselling offered
6714.	All	Counselling carried out
6715.	All	Counselling by other agency
6716.	All	Counselling of benefit
6717.	All	Counselling of no benefit
671Z.	All	Counselling - general NOS
672..	All	Person counselled
6721.	All	Patient counselled
6722.	All	Family counselled
673..	All	Person counselled by
6731.	All	Counselled by a doctor
6732.	All	Counselled by a nurse
6733.	All	Counselled by a health visitor
6735.	All	Counselled by a social worker
6736.	All	Counselled by a counsellor
6737.	All	Counselled by a vol. worker
673Z.	All	Counselled by person NOS
8M8..	All	Counselling requested
9NJ1.	All	In-house counselling
9NJR.	All	In-house counselling first appointment
9NJT.	All	In-house counselling follow-up appointment
Read CTV3 Code	Term ID	Description
X71Ec	All	Counselling
X71Ep	All	Coping strategy counselling
XaEC1	All	Phobia counselling
XaD27	All	Family counselling
6779.	All	Psychological counselling
XaECG	All	Anxiety counselling
XaECF	All	Self-esteem counselling
XaI8j	All	Stress counselling
672..	All	Person counselled
6721.	All	Patient counselled
6722.	All	Family counselled
XE1TI	All	Person counselled by
6715.	All	Counselling by other agency
6731.	All	Counselled by a doctor
6732.	All	Counselled by a nurse
6733.	All	Counselled by a health visitor
6735.	All	Counselled by a social worker

6736.	All	Counselled by a counsellor
6737.	All	Counselled by voluntary worker
673Z.	All	Counselled by person NOS
Xa07L	All	Counselled by member of primary health care team
9N2B.	All	Seen by counsellor
XaAS4	All	Seen by mental health counsellor
XaBT1	All	Refer to counsellor
XaAfj	All	Referral to mental health counsellor
9NJ1.	All	In-house counselling
XaLnp	All	In-house counselling first appointment
XaLnr	All	In-house counselling follow-up appointment
671..	All	Counselling - general
6712.	All	Counselling offered
6714.	All	Counselling carried out
6716.	All	Counselling of benefit
6717.	All	Counselling of no benefit
671Z.	All	Counselling - general NOS
XaAOd	All	Under care of counsellor
XaAOh	All	Under care of mental health counsellor
Cognitive Behavioural Therapy		
Read V2 Code	Term ID	Description
8G13.	All	Cognitive-behaviour therapy
8G130	All	Cognitive behavioural therapy parenting programme
8G131	All	CBTp - cognitive behavioural therapy for psychosis
7L1a.	All	Cognitive behavioural therapy
7L1a0	All	Cognitive behavioural therapy by unidisciplinary team
7L1a1	All	Cognitive behavioural therapy by multidisciplinary team
7L1ay	All	Other specified cognitive behavioural therapy
7L1az	All	Cognitive behavioural therapy NOS
8G510	All	Group cognitive behavioural therapy
8G15.	All	Computerised cognitive behavioural therapy
8HLK.	All	Referral for cognitive behavioural therapy
Read CTV3 Code	Term ID	Description
Ub0qp	All	Cognitive and behavioural therapy
XaABO	All	Cognitive - behaviour therapy
Xad6J	All	Cognitive behavioural therapy for psychosis
Xaaa6	All	Cognitive behavioural therapy parenting programme
XaQC0	All	Guided self help cognitive behavioural therapy
XaKzQ	All	Computerised cognitive behavioural therapy
Xa8I9	All	Generic cognitive behavioural therapy
XaM2I	All	Cognitive behavioural therapy by unidisciplinary team
XaM2J	All	Cognitive behavioural therapy by multidisciplinary team
XaM2K	All	Other specified cognitive behavioural therapy

XaM2L	All	Cognitive behavioural therapy NOS
XaR2j	All	Referral to cognitive behavioural therapist
XaR5D	All	Referral for cognitive behavioural therapy
XaYgB	All	Referral for high intensity cognitive behavioural therapy
Psychotherapy		
Read V2 Code	Term ID	Description
8G...	All	Psychotherapy
8G1..	All	General psychotherapy
8G10.	All	Psychotherapy - behavioural
8G100	All	Behavioural activation therapy
8G101	All	Dialectical behaviour therapy
8G102	All	Behavioural parent training
8G11.	All	Psychotherapy - cognitive
8G12.	All	Psychotherapy - psychodynamic
8G120	All	Short-term psychodynamic therapy
8G121	All	Dynamic interpersonal therapy
8G122	All	Focal psychodynamic therapy
8G14.	All	Cognitive analytic therapy
8G15.	All	Computerised cognitive behavioural therapy
8G16.	All	Interpersonal psychotherapy
8G18.	All	Cognitive stimulation therapy
9NIK.	All	Seen by psychotherapist
9NIK0	All	Seen by trainee psychotherapist
8HHT.	All	Referral to psychotherapist
ZV57D	All	[V]Psychotherapy, not elsewhere classified
ZV673	All	[V]Psychotherapy or other treatment for mental disorder follow-up
8G9Z.	All	Other psychotherapy NOS
8G9..	All	Other psychotherapy
Read CTV3 Code	Term ID	Description
X71bp	All	Psychotherapy
XaaU0	All	Cognitive rehabilitation therapy
XaItc	All	Brief solution focused psychotherapy
Xa8IG	All	Psychoanalytic and psychodynamic therapy
Xa8IJ	All	Long-term exploratory psychotherapy
3841.	All	Psychoanalysis
XaA8V	All	Generic psychoanalysis
XaA8W	All	Independent psychoanalysis
XaA8T	All	Kleinian psychoanalysis
XaA8U	All	Bion-based group psychoanalysis
XaA8X	All	Classical psychoanalysis
XaA8Y	All	Lacanian psychoanalysis
XaA8g	All	Group psychoanalysis
XaA8U	All	Bion-based group psychoanalysis

384Z.	All	Psychological analysis NOS
Xa8IM	All	Jungian-based therapy
Xa8IN	All	Generic Jungian-based therapy
Xa8IP	All	Analytical psychology
Xa8IR	All	Long-term psychodynamic psychotherapy
XaA8Z	All	Developmental psychodynamic psychotherapy
XaA8c	All	Supportive expressive psychodynamic psychotherapy
XaA8d	All	Psychodynamic-interpersonal psychotherapy
XaEVq	All	Psychodynamic psychotherapy
Xad7C	All	Focal psychodynamic therapy
Xa8IR	All	Long-term psychodynamic psychotherapy
XaA8Z	All	Developmental psychodynamic psychotherapy
XaA8c	All	Supportive expressive psychodynamic psychotherapy
XaA8d	All	Psychodynamic-interpersonal psychotherapy
Xa8II	All	Short-term psychodynamic therapy
XaXuc	All	Dynamic interpersonal therapy
XaA9g	All	Specific task orientated psychotherapy
XE0iL	All	Psychotherapy/sociotherapy
8G9Z.	All	Other psychotherapy NOS
8G9..	All	Other psychotherapy

Supplementary table S6. Read codes used to identify non-medication based treatments for depression or anxiety.

Appendix 3

Medication class	Medications
Medications for mental health conditions	
SSRIs and related medication	Venlafaxine, Bupropion, Duloxetine, Naltrexone, Citalopram, Dapoxetine, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
TCA's	Amitriptyline, Clomipramine, Dosulepin, Doxepin, Mianserin, Trazodone, Trimipramine, Imipramine, Lofepamine, Nortriptyline
MAOIs	Tranlycypromine, Phenelzine, Isocarboxazid, Moclobemide
Anxiolytic medications	Alprazolam, Chlordiazepoxide, Clobazam, Clonazepam, Diazepam, Lorazepam, Oxazepam, Buspirone, Meprobamate, Clomipramine, Clomethiazole
Medication for IBD	
Topical 5-ASA	Mesalazine, Sulfasalazine
Topical glucocorticoids	Budesonide, Hydrocortisone, Prednisolone
Oral 5-ASA	Balsalazide, Mesalazine, Olsalazine, Sulfasalazine
Oral glucocorticoids	Prednisolone, Cortisone, Dexamethasone, Methylprednisolone, Beclomethasone, Betamethasone, Budesonide, Deflazacort
Antimetabolites	Azathioprine, Mercaptopurine, Methotrexate
Biologic therapies	Adalimumab, Golimumab, Infliximab, Vedolizumab

Supplementary table S7. Medications analysed by medication class. SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressants, MAOI = monoamine oxidase inhibitors, 5ASA = 5-aminosalicylic acid.