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Identifying prior signals of bipolar disorder using primary care electronic health records

Catharine Morgan
PhD
Research Fellow
Faculty of Biology, Medicine and Health
Manchester Academic Health Science Centre
NIHR Greater Manchester Patient Safety Research Collaboration
The University of Manchester
Williamson Building, Oxford Road
Manchester, M13 9PL, UK
ORCID ID: 0000-0001-9033-1986

Darren M Ashcroft
PhD
Professor of Pharmacoepidemiology
Centre for Pharmacoepidemiology and Drug Safety
Faculty of Biology, Medicine and Health
Manchester Academic Health Science Centre
NIHR Greater Manchester Patient Safety Research Collaboration
NIHR School for Primary Care Research
The University of Manchester
Stopford Building, Oxford Road
Manchester, M13 9PT, UK
ORCID ID: 0000-0002-2958-915X

Carolyn A Chew-Graham
MD
Professor of General Practice Research
School of Medicine
Keele University
Staffordshire, ST5 5BG, UK
ORCID ID: 0000-0002-9722-9981

Matthew Sperrin
PhD
Senior Lecturer
School of Health Sciences
Division of Informatics, Imaging & Data Sciences
Faculty of Biology, Medicine and Health
Manchester Academic Health Sciences Centre
The University of Manchester
Vaughan House
ORCID ID: 0000-0002-5351-9960

Roger T Webb
PhD
Professor of Mental Health Epidemiology
Centre for Mental Health & Risk
Faculty of Biology, Medicine and Health
Manchester Academic Health Science Centre
NIHR Greater Manchester Patient Safety Research Collaboration
The University of Manchester  
Jean McFarlane Building, Oxford Road  
Manchester, M13 9PL, UK  
ORCID ID: 0000-0001-8532-2647

Anya Francis  
Honorary Research Assistant  
The University of Manchester  
Stopford Building, Oxford Road  
Manchester, M13 9PT, UK  
ORCID ID: 0000-0002-1026-7265

Jan Scott  
Professor of Psychiatry, Institute of Neuroscience, Newcastle University UK;  
NTNU, Trondheim, Norway;  
Universite de Paris, Paris, France;  
Brain and Mind Centre, University of Sydney, Australia.  
ORCID ID: 0000-0002-7203-8601

Alison R Yung  
Professor of Psychiatry and NHMRC Principal Research Fellow, Institute for Mental and Physical Health and Research Translation, Deakin University  
Emeritus Professor of Psychiatry, Centre for Psychology and Mental Health, School of Health Sciences, University of Manchester  
ORCID ID: 0000-0002-0401-9791

Corresponding author:  
Catharine Morgan  
Email: Cathy.Morgan@manchester.ac.uk

Word count 3174
Abstract (249 words)

Background: Bipolar disorders (BD) are serious mental illnesses yet evidence suggests that the diagnosis and treatment of BD can be delayed by around 6 years.

Aim: To identify signals of undiagnosed BD using routinely collected electronic health records.

Design and setting: A nested case-control study conducted using the UK Clinical Practice Research Datalink (CPRD) GOLD dataset, an anonymised electronic primary care patient database linked with hospital records. Cases were adult patients with incident BD diagnoses between 1st January 2010 and 31st July 2017.

Method: Cases were matched by age, sex, and registered general practice to 20 controls without recorded BD. Annual episode incidence rates were estimated and odds ratios from conditional logistic regression models were reported for recorded health events prior to index (diagnosis) date.

Results: There were 2,366 patients with incident BD diagnoses and 47,138 matched control patients (median age 40 years; 60.5% females). Compared with controls, BD cases had higher incidence of diagnosed depressive, psychotic, anxiety and personality disorders recorded and escalating self-harm, up to 10 years before BD diagnosis. Sleep disturbance, substance misuse and mood swings were more frequent among cases than controls. Cases had more frequent face-to-face consultations and were more likely to miss multiple scheduled appointments and prescribed three different psychotropic medication classes in a given year.

Conclusion: Psychiatric diagnoses, psychotropic prescriptions and health service use patterns might be signals of unreported BD. Recognising these signals could prompt further investigation for undiagnosed significant psychopathology, leading to timely referral, assessment and initiation of appropriate treatments.

Keywords (MeSH: Primary health care; Bipolar disorder; Electronic health records; Case-control studies; Incidence; Signs and symptoms; Prodromal symptoms

How this fits in: Four short sentences (previously known, what research adds, relevance to clinicians)

- Delayed diagnosis and treatment of BD of between 6-10 years leads to adverse patient outcomes.
- No published studies examine the timings of early signals of BD in a primary care setting and/or use electronic health records.
- Routinely collected data identified early signals of undiagnosed BD: previous depressive episodes, sleep disturbance, substance misuse, those receiving 3 or more different psychotropic medication classes in a year, escalating self-harm, twice as many face-to-face consultations and missing scheduled appointments.
- Awareness of collective early signals can be used to prompt consideration of BD and offer timelier referral for specialist assessment of a BD diagnosis and initiation of appropriate treatment.
Introduction

Bipolar disorders (BD) are serious mental illnesses characterised by instability in mood and rest-activity rhythms. The lifetime prevalence of BD (which comprise BD-I, II and spectrum disorders) is between 1.0 and 3.7%\(^1,2\) and the peak age range for onset is 15 to 25 years.\(^2\) Despite the clinical, social and economic burden of BD\(^4\), there is a delay between the early manifestations of BD and its diagnosis and/or treatment of about 6 years.\(^3\) In a study of individuals with unipolar depression attending primary care services, at least one in 30 were identified as having undiagnosed BD.\(^4\) In a recent UK study, 10% of 233 individuals prescribed antidepressants in primary care were found to have previously undiagnosed BD.\(^5\) Similar results of under-diagnosis of BD in primary care were found in a meta-analysis using structured clinical interview and screening tools for identification.\(^6\)

Delayed diagnosis of BD is associated with poor social adjustment, multiple hospital admissions\(^7\), elevated risk of self-harm, suicide and interpersonal violence\(^8\) and greatly raised prevalence of cardiovascular, endocrine/metabolic and neurological conditions.\(^9\) Missed or delayed diagnosis of BD might also result in inappropriate prescribing, such as the use of antidepressant monotherapy, which in turn might increase the risk of drug-induced hypo/hypomania,\(^10\) or trigger rapid cycling.\(^11\)

Despite the poor outcomes related to delayed diagnosis, screening tools such as Hypomania Checklist,\(^12\) and Mood Disorder Questionnaire\(^13\) are found to have varied performance within different healthcare settings, with high false positive rates.\(^14,15\) Furthermore one of the best predictors of developing BD, family history of BD (especially in first degree relatives), is not routinely entered in patients’ primary care records.

Retrospective studies indicate that individuals diagnosed with BD might experience a range of antecedent psychopathology, including childhood anxiety and adolescent depression. In addition, personality disorders, psychotic symptoms and/or a subthreshold psychotic episode might occur prior to BD diagnosis.\(^7,16-19\) In summary, there are currently no screening instruments or risk calculators that can assist general practitioners in making a timely BD diagnosis. However, this does not mean that it is impossible to identify individuals who have characteristics that could indicate the presence of unrecognised BD and who might benefit from referral for a diagnostic assessment. As such, the purpose of this descriptive study was to identify potential signals of BD from primary care electronic health records among individuals who were subsequently diagnosed with BD, and to compare them with persons who did not receive a BD diagnosis during this time. In addition, utilisation of a large cohort of primary care electronic health records with a long historic observation period, enabled descriptive exploration of signals over time to facilitate operationalising them prior to bipolar disorder diagnosis.

Methods

Data sources

The Clinical Practice Research Datalink (CPRD) GOLD dataset holds information from general practices in all regions of the UK. It covers approximately 7 percent of all persons registered with a general practice and is broadly representative of the national population in terms of age, sex and ethnicity.\(^20\) The primary care electronic health records hold routinely collected information and patient-GP interactions pertaining to symptoms, diagnoses, prescribed medication and referrals to secondary care services. For a subset of English practices participating in the CPRD linkage scheme, which included 56.7% (cases) and 52.4% (controls) of eligible patients for linkage, secondary care clinical data were obtained through linkage to Hospital Episode Statistics (HES), including ICD-10 diagnostic coding of inpatient episodes and emergency department attendance. Interlinkage of primary and secondary data sources enhanced ascertainment of incident BD cases (Figure 1) and
events related to antecedent signals of BD. The area-level Index of Multiple Deprivation (IMD 2015) was obtained as a deprivation measure derived from a combination of socioeconomic indicators based on practice postcode.

Following a review of the literature, input from clinical experts and members of our Lived Experience Advisory Panel (LEAP), a list of candidate symptoms and signals that might precede BD onset was considered and specified according to primary care Read codes (CPRD) and secondary care ICD-10 codes (HES - including emergency department attendance). Complete information on medication prescribed in general practice was extracted from patient records held in the CPRD. Health events of interest included indications of: 1) mental health or recorded diagnosis of: depression (and related symptoms), anxiety disorders, psychotic disorders including schizophrenia, personality disorders, suicidal ideation and self-harm; drug and alcohol misuse, anger and aggression, mood swings and sleep disturbance; 2) prescribed medication: antidepressants, antipsychotics, benzodiazepines, Z-drugs, gabapentoids, mood stabilisers, strong opioids and the number of psychotropic medication classes prescribed during each year of observation; 3) health service interactions: consultations with a GP or practice nurse, non-attendance at scheduled appointments, referral to mental health services, emergency department attendances and subsequent admissions.

**Study design**

We implemented a case-control study design. The first BD event recorded in the electronic health record was identified either through a relevant primary care Read code (CPRD data) or ICD-10 codes (F30-F31 inclusive) from hospital admission records, whichever code was dated earliest. All adults aged 16 years and older with an incident diagnosis between 1st January 2010 and 31st July 2017 were included. The definition of BD included manic episodes, and the classification was subject to clinical review by a senior researcher with expertise in general practice (CC-G) and independently by a senior academic psychiatrist (ARY). The date pertaining to the incident diagnostic code was set as the index date and cases were then matched by age, sex and registered general practice with up to 20 controls without a recorded diagnosis of BD on the index date of the corresponding matched case. Matching on registered general practice ensured balance between case and control patients on numerous unmeasured practice-level and other system-level factors. This effectively removed such influences from our investigation, thereby enabling us to examine patient-specific factors independent of these extraneous factors. Figure 1 shows the study flowchart, including cohort recruitment and derivation of first bipolar disorder diagnosis date from both CPRD and HES data sources.
Figure 1: Flowchart summarising the derivation and delineation of the study cohort from interlinked CPRD GOLD and HES datasets.

CPRD: Clinical Practice Research Datalink; ONS: Office of National Statistics; IMD: Index of Multiple Deprivation; HES: Hospital Episode Statistics;
**Analysis**

For each health event examined, the annual episode incidence rate per 1000 person years (and its 95% confidence interval) was estimated over time for each year prior to index date for individuals with BD and their matched controls. The signals were presented as binary indicator variables and counted as being ‘present’ or ‘absent’ once only in each year period prior to the index date from the date the individual registered with their general practice for at least a year (Supplementary Table S1). Odds ratios (and their 95% CIs) were calculated for symptoms and signals, measuring the association between each health event and having a recorded bipolar disorder diagnosis. The odds ratio indicates, for patients with a recorded BD code (cases), how many more times their odds were of having the prior symptom or signal of interest versus those without a BD diagnosis (controls). Odds ratios were presented in year ranges of less than 1 year, at 1 and less than 3 years, at 3 years and less than 5 years and at 5 and less than 10 years prior to index date. Each dichotomous event variable was entered into their own model for each year range using conditional logistic regression, thereby accounting for the matched design. The number of classes of psychotropic medication within a given year, non-attendance at scheduled appointments, referrals to mental health services, and emergency department attendance were aggregated annually prior to index date and analysed as count data within each year. Face-to face patient-GP consultations were presented as median counts and interquartile ranges.

All code lists applied in this study are published online https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/201/. All analyses were conducted using Stata/SE 14.2. Details of Stata analysis code can be found in Supplementary S1.
Results

A total of 2,366 persons diagnosed with BD and 47,138 matched control patients were included in the analysis (60.4% Female). The median age at the date of index diagnosis was 40 (IQR 23) years.

Mental health, self-harm and addiction
As early as 10 years prior to BD diagnosis there was an incidence of 240 per 1,000 person years of recorded diagnosis of depression and depressive symptoms among cases. As shown in Figure 2a, depressive episodes and symptoms increased from 6 years prior to index date. Those diagnosed with BD were more likely to have had a record of anxiety disorders, with an increased incidence 5 years prior to index date, albeit to a less degree than for recorded diagnosis of depression (Figure 2b). The odds of someone with a BD diagnosis also having a prior record of personality disorder diagnosis was 28-times larger than the odds for someone without a BD diagnosis; the odds were 26-times larger for a prior diagnosis of schizophrenia and related disorders. (Table 1 & Figure 2c & 2d).

Self-harm and suicidal ideation episodes increased in frequency in the period leading up to a BD diagnosis. They were noted as early as 10 years before the index diagnosis. Those diagnosed with BD were 8 times more likely to have harmed themselves or had suicidal thoughts recorded in their notes than those without a BD diagnosis (Table 1 and Figure 3a). Mood swings also occurred more frequently prior to BD diagnosis, with a marked increase 2 years before the index date (Figure 3b). Sleep disturbance showed a pattern of rising incidence over a long time period (of at least 10 years) prior to the index diagnosis (Figure 3c).

Drug and alcohol misuse were also more frequently recorded for individuals subsequently diagnosed with BD compared with controls (Figure 3d & 3e). Higher drug and alcohol misuse rates were present 10 years prior to diagnosis. In the one year before index diagnosis date, those diagnosed with BD were over 7 and 5 times more likely to experience drug or alcohol misuse, respectively, than those without a BD diagnosis recorded (Table 1). The pattern of coding for anger and aggression was similar (Figure 3f). In the one year before diagnosis, those with a BD diagnosis than those without were over 15 times more likely to have anger or aggression issues recorded.

Psychotropic medication prescribing
Antidepressants and antipsychotics were much more widely prescribed than any other psychotropic medication type (Figures 4a & 4b). In particular, antidepressants were more frequently prescribed in individuals who were later diagnosed with BD compared to controls (for at least 10 years prior to diagnosis); these prescriptions increased from 6 years prior to index BD diagnosis date. At 5 years prior to index date, those receiving a BD diagnosis were 8 times more likely to be prescribed an antidepressant (Table 1) and 4 times and 6 times more likely to be prescribed a benzodiazepine or a Z-drug, respectively than those without a BD diagnosis recorded (Supplementary Figure S1).

Differences were also seen in number of psychotropic medication classes prescribed. Comparing those with a BD diagnosis and those without, BD cases were 8 times more likely to be prescribed three or more different classes of psychotropic medication during the same year compared to those prescribed two or less different classes of psychotropic medication (OR 8.4; 95% CI 6.8, 10.6; p<0.001) (Figure 4c). This high likelihood was seen in the 2 years prior to diagnosis but also evident across the preceding 6 year period.

Health service use
Statistically significant differences were observed between persons diagnosed with BD and control patients in median number of consultations per year prior to index date, although large variability around the median was observed (Supplementary Figure S2). At 5 years before diagnosis date the median number of consultations was 8 (IQR 15) for BD patients versus 4 (IQR 19) for controls (Mann-Whitney test, p<0.001) (Table 2). At this time, those with a recorded BD diagnosis were 4 times more
likely to have missed 6 or more scheduled appointments compared to those missing fewer appointments for any reason in a year, than those not having BD (Table 2).

Figure 2: Annual episode incidence of a) depression, b) anxiety disorders, c) personality disorders, d) Schizophrenia and related disorders - in patients with BD (cases) and without BD (controls) from 10 years prior to when the BD diagnosis was made.
Figure 3: Annual episode incidence of a) Self-harm and suicidal ideation, b) mood swings, c) sleep disturbance, d) alcohol misuse, e) drug misuse, f) anger or aggression - in patients with BD (cases) and without BD (controls) from 10 years prior to when the BD diagnosis was made.
*Includes antidepressants, antipsychotics, benzodiazepines, Z-drugs, mood stabilisers, gabapentin, pregabalin and strong opioids

†One prescription in each medication category counted only once per annum

Figure 4: Annual episode incidence of prescribing† an antidepressant and antipsychotic medication and prescribed three or more psychotropic medications in patients with BD (cases) and without BD (controls) from 10 years prior to when the BD diagnosis was made
<table>
<thead>
<tr>
<th>Illnesses, symptoms &amp; behaviours</th>
<th>Up to 1 year</th>
<th>≥1 to 3 years</th>
<th>≥3 to 5 years</th>
<th>≥5 to 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression &amp;/or depressive symptoms</td>
<td>13.2 (12.0, 14.6)</td>
<td>8.5 (7.8, 9.3)</td>
<td>6.9 (6.2, 7.7)</td>
<td>6.3 (5.6, 7.1)</td>
</tr>
<tr>
<td>Personality disorders</td>
<td>51.8 (32.4, 82.9)</td>
<td>31.9 (21.0, 48.3)</td>
<td>28.1 (14.1, 55.9)</td>
<td>13.4 (7.7, 23.2)</td>
</tr>
<tr>
<td>Schizophrenia and related disorders</td>
<td>77.6 (54.1, 111.4)</td>
<td>25.2 (19.5, 32.6)</td>
<td>26.1 (18.4, 36.9)</td>
<td>24.1 (17.2, 33.7)</td>
</tr>
<tr>
<td>Depression &amp;/or depressive symptoms</td>
<td>13.2 (12.0, 14.6)</td>
<td>8.5 (7.8, 9.3)</td>
<td>6.9 (6.2, 7.7)</td>
<td>6.3 (5.6, 7.1)</td>
</tr>
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<td>31.9 (21.0, 48.3)</td>
<td>28.1 (14.1, 55.9)</td>
<td>13.4 (7.7, 23.2)</td>
</tr>
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<td>77.6 (54.1, 111.4)</td>
<td>25.2 (19.5, 32.6)</td>
<td>26.1 (18.4, 36.9)</td>
<td>24.1 (17.2, 33.7)</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>7.4 (6.6, 8.4)</td>
<td>5.34 (4.8, 6.0)</td>
<td>4.0 (3.5, 4.5)</td>
<td>4.1 (3.6, 4.7)</td>
</tr>
<tr>
<td>Mood swings</td>
<td>45.2 (33.4, 61.2)</td>
<td>14.4 (10.6, 19.6)</td>
<td>6.3 (4.0, 9.7)</td>
<td>6.1 (4.2, 8.7)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>5.5 (4.5, 6.5)</td>
<td>4.5 (3.9, 5.2)</td>
<td>3.5 (2.9, 4.2)</td>
<td>3.2 (2.7, 3.8)</td>
</tr>
<tr>
<td>Self-harm and suicidal ideation</td>
<td>28.2 (22.5, 35.2)</td>
<td>11.7 (9.6, 14.3)</td>
<td>8.4 (6.5, 11.0)</td>
<td>8.8 (7.0, 11.1)</td>
</tr>
<tr>
<td>Drug misuse</td>
<td>7.8 (5.7, 10.8)</td>
<td>4.6 (3.4, 6.3)</td>
<td>6.4 (4.5, 9.0)</td>
<td>4.3 (3.0, 6.0)</td>
</tr>
<tr>
<td>Alcohol misuse</td>
<td>5.8 (4.4, 7.5)</td>
<td>4.1 (3.3, 5.2)</td>
<td>4.5 (3.3, 6.2)</td>
<td>4.3 (3.3, 6.1)</td>
</tr>
<tr>
<td>Anger or aggression</td>
<td>15.7 (11.4, 21.7)</td>
<td>7.7 (5.8, 10.3)</td>
<td>6.6 (4.6, 9.5)</td>
<td>4.5 (3.3, 6.1)</td>
</tr>
<tr>
<td>Prescribed medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>14.4 (13.1, 15.8)</td>
<td>10.2 (9.3, 11.2)</td>
<td>8.3 (7.5, 9.2)</td>
<td>6.0 (5.4, 6.8)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>23.1 (20.7, 25.8)</td>
<td>11.0 (9.9, 12.3)</td>
<td>7.5 (6.6, 8.6)</td>
<td>5.2 (4.5, 5.9)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>9.1 (8.1, 10.1)</td>
<td>5.2 (4.7, 5.8)</td>
<td>4.04 (3.5, 4.6)</td>
<td>3.4 (2.9, 3.8)</td>
</tr>
<tr>
<td>Z-drugs</td>
<td>11.6 (10.2, 13.1)</td>
<td>6.6 (5.8, 7.5)</td>
<td>6.4 (5.5, 7.43)</td>
<td>4.6 (3.9, 5.4)</td>
</tr>
<tr>
<td>Mood stabilisers (excl. Lithium)†</td>
<td>16.9 (14.6, 19.7)</td>
<td>9.0 (7.6, 10.7)</td>
<td>6.3 (5.1, 7.8)</td>
<td>4.4 (3.4, 5.7)</td>
</tr>
<tr>
<td>Gabapentinoids</td>
<td>3.6 (3.0, 4.5)</td>
<td>2.94 (2.4, 3.7)</td>
<td>2.5 (1.8, 3.4)</td>
<td>2.1 (1.4, 3.1)</td>
</tr>
<tr>
<td>Strong opioids</td>
<td>2.6 (2.2, 3.1)</td>
<td>2.3 (2.0, 2.7)</td>
<td>2.0 (1.7, 2.4)</td>
<td>1.7 (1.4, 2.1)</td>
</tr>
</tbody>
</table>

†Assumption of lithium prescription was an indication of BD diagnosis and therefore excluded

**Table 1**: Odds ratios for persons diagnosed with BD cases (vs. controls) having an additional psychiatric illness diagnosis, symptom or behaviour signal or prescribed psychotropic medication recorded before index date
<table>
<thead>
<tr>
<th>No. of years prior to bipolar disorder diagnosis date</th>
<th>In year 1</th>
<th>In year 3</th>
<th>In year 5</th>
<th>In year 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of face-face consultations:</td>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar disorder patients</td>
<td>21 (12-32)</td>
<td>12 (5-22)</td>
<td>8 (2-17)</td>
<td>2 (0-8)</td>
</tr>
<tr>
<td>Matched control patients</td>
<td>6 (2-13)</td>
<td>5 (2-12)</td>
<td>4 (1-10)</td>
<td>1 (0-5)</td>
</tr>
<tr>
<td>Number of missed appointments*</td>
<td>Odds ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.09 (1.89, 2.31)</td>
<td>1.89 (1.69, 2.11)</td>
<td>1.70 (1.50, 1.94)</td>
<td>1.42 (1.16, 1.72)</td>
</tr>
<tr>
<td>2-3</td>
<td>4.34 (3.86, 4.89)</td>
<td>2.83 (2.43, 3.29)</td>
<td>2.50 (2.07, 3.02)</td>
<td>2.04 (1.49, 2.80)</td>
</tr>
<tr>
<td>4-5</td>
<td>7.29 (5.87, 9.04)</td>
<td>3.91 (2.90, 5.27)</td>
<td>5.36 (3.70, 7.75)</td>
<td>4.39 (2.13, 9.03)</td>
</tr>
<tr>
<td>6+</td>
<td>12.63 (9.28, 17.19)</td>
<td>7.38 (4.79, 11.35)</td>
<td>4.42 (2.41, 8.11)</td>
<td>3.64 (0.81, 16.40)</td>
</tr>
<tr>
<td>Number of ED attendances†</td>
<td>Odds ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.11 (1.82, 2.46)</td>
<td>1.60 (1.36, 1.89)</td>
<td>1.26 (1.05, 1.51)</td>
<td>-</td>
</tr>
<tr>
<td>2-3</td>
<td>3.89 (3.23, 4.68)</td>
<td>2.40 (1.92, 3.00)</td>
<td>2.77 (2.22, 3.48)</td>
<td>-</td>
</tr>
<tr>
<td>4+</td>
<td>5.98 (4.30, 8.33)</td>
<td>2.99 (1.81, 4.93)</td>
<td>1.71 (0.86, 3.38)</td>
<td>-</td>
</tr>
</tbody>
</table>

*AE HES data source from April 2007 and therefore too few individuals with more than 10 years of data to calculate odds ratio for ED attendance at 10 years

Table 2: Service interaction prior to index date among patients with BD (cases) and without BD (controls): including median number of face-to-face consultations and odds ratios for persons diagnosed with BD (vs. controls) not attending a scheduled appointment and emergency department (ED) attendance prior to index date
Discussion

Summary
This study examined information that was routinely recorded in patients’ primary care electronic health records to identify the frequency and timing of potentially important and detectable signals of undiagnosed BD. Depressive episodes and lifetime diagnoses of personality disorder and schizophrenia were frequently reported in the years prior to BD diagnosis. Furthermore, several clinical characteristics showed an escalating pattern in the period proximal to BD recognition. Self-harm and suicidal ideation, whilst elevated at least 10 years before diagnosis, were markedly higher in the 2 years immediately preceding BD diagnosis. Sleep disturbance was present for many years prior to diagnosis, while mood swings appeared to be a later phenomenon, recorded more frequently 1-2 years prior to diagnosis. Drug or alcohol misuse and anger or aggression also occurred more commonly (than controls) among individuals who were later diagnosed with BD. Another potential indicator of undiagnosed BD was psychotropic medication polypharmacy. Antidepressants, antipsychotics and more than three psychotropic prescriptions within the same year were all more likely to be recorded in undiagnosed BD patients compared with controls. Multiple GP consultations in one year and increasing frequency of not attending scheduled appointments for any reason also signalled undiagnosed BD.

Strengths and limitations
Identification of signals from information that is routinely entered in electronic health records is a major strength of this study. These datasets enabled investigation of a variety of potential signals including patterns of medication prescribing and patients’ interactions with health services as well prior symptoms and diagnoses. Furthermore, we could implement a nested case-control design, sampled from a very large cohort of BD cases and controls.

The study does, however, have some limitations. Researchers using electronic health care records are reliant on the Read codes applied in the course of clinical care or by practice administrators. These might not capture the rich contextual information useful for researchers. In addition, misclassification might occur due to code inputting and a degree of inconsistency in GP coding choices. Furthermore, the timing of BD diagnosis is difficult to establish using only information that is contained in primary care records. However, by identifying relevant diagnostic codes from both primary care and linked secondary care records, we were able to more accurately ascertain and date incident BD diagnoses. Likely incomplete capture of family history of mental disorders, as one of the strongest risk factors for early onset of BD, was an important limitation GPs will more often report these details using free text, potential patient identifier information, which is not held by CPRD and therefore cannot be accessed for CPRD studies. Highlighting this limitation provides the opportunity to improve GP coding of family history within the electronic health record. Finally, use of a case-control design, although appropriate for our study’s purpose and research question, increased the likelihood of spurious association and selection bias. Therefore, the signals that we have reported should be validated in a cohort study to enable more conclusive clinical interpretation.

Comparison with existing literature
As previously reported, individuals who develop BD experience a range of lifetime psychiatric comorbidities, especially antecedent anxiety disorders and depression. The raised incidence of depressive symptoms prior to BD diagnosis was consistent with previous literature indicating that more than a quarter of patients with a previous diagnosis of unipolar major depressive disorder progress to BD. However, it is difficult to determine whether the antecedent depression is part of the natural evolution of BD (i.e., where depression is the first manifestation and hypo/mania occurs some years later) or whether evidence of hypo/manic symptoms or episodes have been missed or indeed the individual has only sought help during long periods of depression. Thus, it is important
to increase GP inquiries about periods of elation or increased activity levels in anyone seeking help for depression.

Antipsychotic medication prescription and diagnostic coding of schizophrenia and related disorders noted in patient records prior to BD diagnosis is suggestive of the individual experiencing psychotic symptoms. Previous studies report psychotic experiences often precede a diagnosis of BD. Indeed their presence increases the likelihood that individuals receive specialist assessments. Misdiagnosis as a condition other than BD or missed diagnosis of BD will lead to inappropriate clinical management. Overuse of antidepressants, especially without co-prescription of a mood stabiliser, might exacerbate affective symptoms thereby increasing the risk of drug-induced mania, switching between mania and hypomanic states, and emergence of rapid-cycling, whereby the disorder accelerates with more mood shifts in a given timeframe.

Although sleep disturbances are not unique to BD, this was evident for many years prior to BD diagnosis. Previous studies showing sleep and circadian rhythm disturbances are common in patients with BD, including during euthymia (i.e., when the individual does not have an acute mood episode). Drug or alcohol misuse were also evident and escalated prior to BD diagnosis. It is reported, between 40-70% of individuals diagnosed with bipolar disorder experience substance misuse. Self-harm and suicidal ideation episodes, although elevated at least 10 years before diagnosis, were much more common in the 2 years before diagnosis. Previous studies have reported that delayed diagnosis or misdiagnosis are major contributors to elevated risk of dying by suicide among BD patients.

Implications for research and/or practice

For a person diagnosed with BD, receiving the diagnosis earlier could reduce or prevent many harmful outcomes including antidepressant induced rapid cycling, non-fatal self-harm and suicide, substance misuse and interpersonal violence. Raising awareness among GPs, many of who might lack understanding of BD course and associated signals, will improve recognition. Using the electronic health record as a prompt to process the signals cumulatively and highlight a probable BD diagnosis to trigger further assessment when continuity of care is not always possible would, therefore, be a helpful resource. It might also provide a useful addition to present screening tools to further enhance diagnostic specificity to BD.

In addition, the GP would have evidence from a patients’ electronic health record to support a referral to specialist care, where the diagnosis of BD is made. Secondary mental health services, however, need to be responsive and willing to rapidly assess patients referred by GPs. National Institute for Health and Care Excellence (NICE) guidance CG185 outlines the recognition of BD in primary care for consideration of referral when patients present with depression along with previous periods of “over activity of disinhibited behaviour” lasting 4 or more days. In practice, however, this often does not occur due to high thresholds for acceptance to a Community Mental Health Team. Optimising the service pathway to improve the interface between primary and secondary care is essential. The roll-out of the Mental Health Implementation Plan in April 2021 offers a more integrated approach of primary and secondary care. It is also an opportunity to reduce barriers with more flexible care and to reassess the referral criteria threshold for possible BD.

Conclusion

We have identified potentially important signals within the primary care record that might prompt a GP to consider a diagnosis of BD, and support referral to secondary care. Additional work is needed to establish the specificity of these signals collectively, the sequential and concurrent nature of the
signals and the practical and acceptable use to both patients and GP in primary care. This proactive approach could ensure that individuals receive a timelier referral, intervention and effective treatment to prevent harmful impacts on their mental and physical health.

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Clinical Approval

This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. Hospital Episode Data and the ONS Data Copyright © (2017), are re-used with the permission of The Health & Social Care Information Centre. All rights reserved. The study was approved by the independent scientific advisory committee for Clinical Practice Research Datalink research (protocol No. 18_048R). The interpretation and conclusions contained in this study are those of the authors alone.

Authors contributions

CM completed the literature search. ARY, AF, CAC-G, CM, DMA, RTW, MS designed the study and data analysis plan. CM performed the data analysis. ARY, AF, CAC-G, CM, DMA, RTW, JS, MS interpreted the results. ARY and CAC-G agreed on the final clinical Read code lists. CM and ARY drafted initial manuscripts. All authors critically reviewed the manuscript and approved the final version.

Declaration of interests

ARY, CM, JS, CAC-G, RTW, AF, MS and DMA have no known conflicts of interest in relation to the submitted work.

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