Preliminary results from the Australian Genetics of Bipolar Disorder Study: A nation-wide cohort

Running title: Australian Genetics of Bipolar Disorder Study

Authors

Penelope A Lind[1,2,3], Dan J. Siskind[3,4], Ian B. Hickie[5], Lucía Colodro-Conde[1], Simone Cross[1], Richard Parker[1], Nicholas G. Martin[6], and Sarah E Medland[1,3,7]

Affiliations

[1]Psychiatric Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Australia

[2]School of Biomedical Sciences, Queensland University of Technology, Brisbane, Australia

[3]Faculty of Medicine, University of Queensland, Brisbane, Australia

[4]Metro South Addiction and Mental Health Service, Brisbane, Australia

[5]Brain and Mind Centre, University of Sydney, Camperdown NSW Australia

[6]Genetic Epidemiology, QIMR Berghofer Medical Research Institute, Brisbane, Australia

[7]School of Psychology, University of Queensland, Brisbane, Australia

Corresponding author: Penelope A. Lind, Psychiatric Genetics, QIMR Berghofer Medical Research Institute, 300 Herston Road, Herston, QLD 4006, Australia; Email: penelope.lind@qimrberghofer.edu.au.

ORCID iDs

Penelope A Lind: https://orcid.org/0000-0002-3887-2598

Dan J. Siskind: https://orcid.org/0000-0002-2072-9216

Ian B. Hickie: https://orcid.org/000-0001-8832-9895

Lucía Colodro-Conde: https://orcid.org/0000-0002-9004-364X

Richard Parker: https://orcid.org/0000-0003-1451-5622

Nicholas G. Martin: https://orcid.org/0000-0003-4069-8020

Sarah E Medland: https://orcid.org/0000-0003-1382-380X

Acknowledgments

We thank the participants for giving their time and support for this project. We acknowledge and thank M. Steffens for her generous donations in loving memory of J. Banks.

Funding Information

Data collection was funded and data analysis was supported by the Australian National Health and Medical Research Council (No. APP1138514) to SEM. DJS is supported by a National Health and Medical Research Council Investigator Grant (No. APP1194635). NGM is supported by a National Health and Medical Research Council Investigator Grant (No. APP 1172990). SEM is supported by a National Health and Medical Research Council Investigator Grant (No. APP1172917).

Declaration of Conflicting Interests

IBH is the Co-Director of Health and Policy at the Brain and Mind Centre (BMC) University of Sydney. The BMC operates an early-intervention youth services at Camperdown under contract to

Headspace. He is the Chief Scientific Advisor to, and a 3.2% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the $30 M Australian Government-funded Project Synergy (2017-20; a three-year program for the transformation of mental health services) and to lead transformation of mental health services internationally through the use of innovative technologies. PAL, DJS, LC-C, SC, RP, NGM, and SEM declare that there are no conflicts of interest with respect to the research, authorship and/or publication of this article.

ABSTRACT

Objective: The Australian **G**enetics of **Bip**olar Disorder (GBP) Study is a nation-wide cohort of adults living with Bipolar disorder (BD). The study aims to detect the relationships between genetic risk, symptom severity, and the lifetime prevalence of BD, treatment-response and medication side-effects, and patterns and costs of health care usage.

Methods: A total of 6,682 participants (68.3% female; aged 44.8±13.6 years [range 18–90]) were recruited in three waves; a nation-wide media campaign, a mail-out based on prescriptions for lithium carbonate, and through the Australian Genetics of Depression Study. Participants completed a self-report questionnaire. A total of 4,706 (70%) participants provided a saliva sample and were genotyped and 5,506 (82%) consented to record linkage of their Pharmaceutical and Medicare Benefits Schedule data.

Results: Most participants were living with Bipolar I disorder (n=4,068) while 1,622 participants were living with Bipolar II disorder and 992 with sub-threshold BD. The mean age of BD diagnosis was 32.7±11.6 years but was earlier in Bipolar I (P=2.0E-26) and females (P=5.7E-23). Excluding depression with onset prior to BD diagnosis, 64.5% of participants reported one or more co-occurring psychiatric disorders; most commonly Generalised anxiety disorder (43.5%) and Posttraumatic stress disorder (20.7%). Adverse drug reactions were common and resulted in discontinuation rates ranging from 33.4% for lithium to 63.0% for carbamazepine.

Conclusion: Individuals with lived experience of BD, particularly Bipolar I disorder, psychotic-like experiences and use of lithium carbonate and antipsychotics are motivated to participate in genetically-focused research into risk, treatment experiences and health care utilisation.

Keywords: Bipolar disorder, Australia, Adverse drug reactions, Comorbidity

1. INTRODUCTION

Bipolar disorder (BD) is a severe and typically relapsing mental illness that is classified as Bipolar I disorder (BD-I) when it is characterised by episodes of mania (which are typically interspersed with major depression) and Bipolar II disorder (BD-II) when characterised by episodes of hypomania that alternate with periods of major depression[1]. BD is highly heritable with twin-based studies estimating that 60-85% of the risk of developing BD can be explained by genetic factors[2,3] while the largest genome-wide association study of BD to date estimated that 18.6% of the phenotypic variance in BD could be explained by common genetic variation[4].

In 2020-21, there were approximately 744,800 Australians with lived experience of BD[5] and in 2010 it was estimated that 100,666 Australians lived with severe BD[6]. The lifetime and 12-month prevalence rates for BD in the 2020-21 Australian National Survey of Mental Health and Wellbeing were 3.8% and 2.2% respectively[5]. A systematic review by Clemente et al.[7] reported a similar lifetime prevalence of BD (1.06% for BD-I and 1.57% for BD-II). However, the Australian prevalence rates are higher than those reported in the World Mental Health Survey Initiative which reported lifetime prevalence rates of BD-I, BD-II, and subthreshold BD from the pooled sample of 11 countries were 0.6%, 0.4%, and 1.4%, respectively[8].

Critically, BD is associated with significant economic burden, mortality, and morbidity. In Australia, combined excess health sector and individual costs of BD in Australia were estimated to be $3.97–$4.95 billion using health utilisation data and morbidity indicators from the 2004 South Australian Health Omnibus Survey, with mean annual costs per person living with BD

estimated to be $9,877 of which $8,553 (86.6%) were attributed to costs paid by individuals and their families[9]. Overall, hospital inpatient services accounted for 69.6% of all health sector excess costs while 'days unable to work' and 'days of reduced work' accounted for 60.2% and 39.3% of all individual costs[9].

A meta-analysis[10] of 19 international studies reporting mortality among people living with BD found that all-cause mortality was elevated and estimated the relative risk of death was 2.00 (95% CI, 1.70-2.34). Furthermore, BD was associated with substantially reduced life expectancy; a recent meta-analysis of years of potential life lost (YPLL) in BD reported a weighted average of 12.89 years (95% CI, 12.72-13.07)[11]. Of note, estimates of YPLL owing to natural causes was higher in women than men (6.88 *vs* 5.14) while unnatural-cause YPLL estimates were almost twice as high in men compared to women (5.10 *vs* 2.68)[11]. A substantial cause of unnatural deaths among individuals living with BD was suicide; compared to the general population, the suicide rate is 20-30-fold higher among individuals living with BD[12].

While there has been progress in identifying genetic variants influencing BD and response to lithium treatment, there is also relatively little currently know about how genetic risk influences health care use and costs and response to treatment of other medications. To address these questions, we established a nation-wide cohort of 6,682 individuals living with BD in Australia. The Australian **G**enetics of **B**i**p**olar Disorder (GBP) Study has three main aims to identify genetic risk factors influencing BD as well as medication treatment-response and adverse drug reactions (ADRs), to characterise the patterns and costs of health care usage in BD, and to examine the relationship with genetic risk and symptom severity. This article describes the design of the GBP

Study, characteristics of the sample, and summarises phenotypic data collected on BD, psychiatric comorbidities, and medication use.

2. METHODS

2.1 Study Design

The GBP Study started recruitment in November 2018. Participants were recruited using three approaches and while the study continues to accept new participants no further recruitments are planned. The data presented in this paper were collected between November 20, 2018 and February 11, 2021

The first wave of recruitment (n=1,524) of participants to the GBP Study was via a nation-wide media publicity campaign managed by a Sydney-based public relations company (VIVA! Communications). The media campaign focused on recruiting volunteers from the general public who had been diagnosed with or treated for BD at some stage in their lives. The campaign comprised a physical media launch on November 20, 2018 with follow-up via television, radio, print and online interviews and a sequence of social media posts. Potential participants were directed to the study website (https://www.geneticsofbipolar.org.au) where more detailed information was provided.

A second wave of recruitment (n=3,576) used the mail-out service of *Services Australia* who identified prospective participants based on PBS prescription records retained by the Australian Government using a query with the following selection criteria: individuals aged between 18 years

and 65 years at time of mail-out who had two or more dispensed prescriptions within the last 4.5 years for lithium carbonate (PBS Item Codes 3059B and 8290H). Exclusion criteria applied were New South Wales residents born before 1960 (due to another BD study that was being conducted within this State), and Medicare/PBS addresses corresponding to healthcare (e.g. hospital), correctional or aged-care facilities.

We requested study invitation letters describing the study to be sent to 50,000 individuals on March 29, 2019 by *Services Australia*. The letter explained that the recipient was being contacted by *Services Australia* on behalf of researchers at QIMR Berghofer to invite them to participate in a study on the genetics of Bipolar disorder and that their personal details had not been released to the researchers. The letter also described the purpose of the study and asked willing individuals to visit our URL link for the study website (https://www.geneticsofbipolar.org.au).

The Participant Information and Consent Form on the study website contained contact details for the project coordinator and QIMR Berghofer Human Research Ethics Committee (HREC). Individuals recruited in the first two recruitment waves who were willing to participate were asked to confirm that they had read and understood the information sheet and then asked to complete the online consent form to enrol in the study and to indicate whether they would be willing to provide a saliva sample so that DNA could be extracted and genotyped. Participants then entered their details onto an online form securely hosted on QIMR Berghofer servers and were assigned a unique link to an online questionnaire hosted on the *Qualtrics* website. The unique link was also emailed to the participant so that they did not need to complete the questionnaire immediately or in one session.

A third wave of data collection (n=1,582) started on April 27, 2020 as part of a follow-up survey of the Australian Genetics of Depression Study (AGDS)[13]. The AGDS cohort (n=23,814) was recruited between 2017 and 2020. A total of 2,059 (8.6%) participants self-reported a diagnosis of BD and 1,457 (6.1%) reported that they had taken lithium carbonate in their lifetime. During the AGDS follow-up survey, participants were presented with the content from core module of the GBP Study survey (see Table S1 for measures collected).

2.2 Ethics

All participants provided informed consent for the study. Ethics approval for all aspects of the project was obtained from the QIMR Berghofer Medical Research Institute HREC for the GBD (P3408) and AGDS (P2118) studies. The External Request Evaluation Committee of *Services Australia* approved the study mail-out and the consenting process for linkage to participant Medicare Benefits Schedule (MBS) and PBS data (EREC reference number MI10846).

2.3 Online Survey

A total of 6,682 participants provided self-reported responses including 102 participants who requested to be mailed an abridged paper-based version of the questionnaire. The GBP Study online survey was designed to overlap with the content of the AGDS online questionnaire[13]. Participants completed a core module which included demographic questions, self-report mental health diagnostic history, BD diagnosis history, and a BD screen using the Mood Disorder Questionnaire (MDQ)[14] and additional items corresponding to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[1] BD diagnostic criteria.

The MDQ is a self-administered BD screening instrument comprising three parts; 13 yes/no response items reflecting DSM-IV criteria[15] and clinical experiences to identify a lifetime history of hypomanic or manic episodes; a question assessing the symptoms were experienced in the same period (*yes, no*); and a 4-point scale question (*no problem*, *minor problem*, *moderate problem*, *serious problem*) assessing the level of functional impairment resulting from the symptoms. A positive screen was defined as the endorsement of 7 or more items in part 1, plus indication that the symptoms occurred simultaneously and caused at least moderate impairment[14]. A 2015 meta-analysis of 21 studies reported a summary sensitivity of 0.62 and summary specificity of 0.85 for the detection of BD[16].

In addition to the MDQ, items included in the online survey to determine BD diagnosis assessed: the duration of the manic or hypomanic episode (*less than 4 days*, *less than a week [4-7 days]*, *less than a fortnight [8-14 days]*, *less than a month [15-30 days]*, *more than a month [30+ days]*), whether the respondent felt this way most, if not all, of the day (*yes, no*), whether the respondent was hospitalised during one of those periods (*yes, no*), whether the respondent thought their episodes ever occurred as the result of physical causes such as physical illness or injury or the use of medication, drugs, or alcohol (*yes, no*), and items corresponding to DSM-5 diagnostic criteria for Major Depressive Disorder (MDD).

The core module also included screens for suicidality, anxiety, and phobias and a checklist of six psychotic-like experiences (PLEs) including auditory hallucinations and delusions of persecution

and control. Participants responded (*yes*, *no*) whether they had ever experienced the PLE when they were not dreaming, half-asleep or under the influence of alcohol or drugs.

After completing the core module, participants were invited to complete two additional modules (completed by 3,103 and 2,553 participants respectively) containing questions relating to general physical health and health care, work and sleep, life events, migraines, substance use, and gambling. Figure 1 provides an overview of the GBP Study and Tables S1 and S2 (available online) summarise the instruments included, and data collected in the survey.

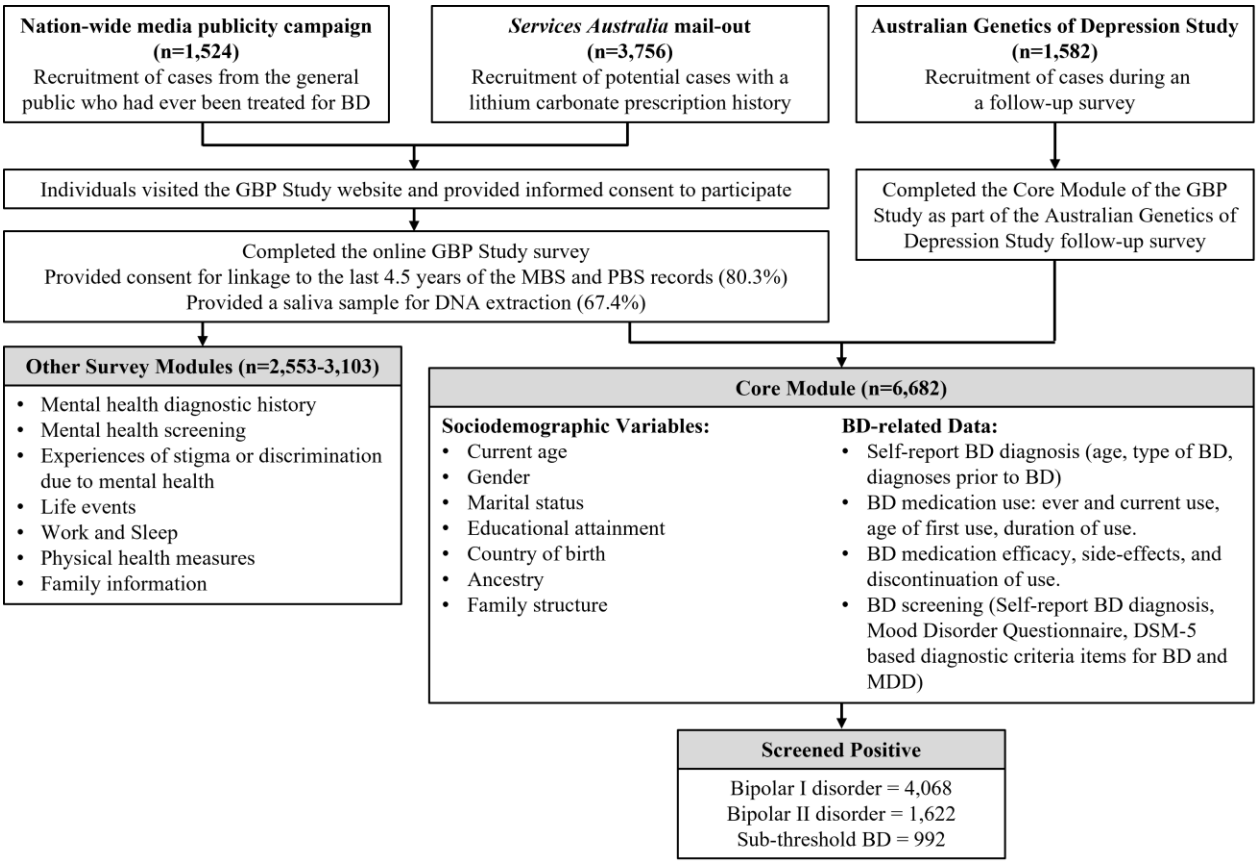

Figure 1. Overview of the Australian Genetics of Bipolar Disorder Study recruitment strategy and data collected. Abbreviations: GBP: Australian Genetics of Bipolar Disorder; AGDS: Australian

Genetics of Depression Study; BD: Bipolar disorder; DSM-5: Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders; MBS: Medicare Benefits Schedule; MDD: Major depressive disorder; PBS: Pharmaceutical Benefits Scheme

2.4 Record linkage

Participants were asked to consent to allow the study to access their PBS and MBS records for the previous 4.5 years to directly assess prescription dispensing history sand health service usage and costs. PBS data contain records of pharmacy transactions for all drugs listed on the PBS schedule and dispensed to eligible Medicare card holders. MBS data contains records of health services, Medicare service provider identifiers, diagnostic procedures and tests provided outside of hospitals. Neither PBS nor MBS records contain diagnosis or indication information. Consent for PBS and MBS data linkage was provided by 80.3% of Wave 1 and 2 participants (n=4,093) and 89.3% of Wave 3 participants. Consent forms were sent to *Services Australia* in August 2022 to request approval to link the participant's electronic PBS and MBS records. The window for data extraction was from 30/06/2014 to 30/06/2019 (5 years).

2.5 Saliva Collection and Genotyping

Participants from the first two recruitment waves that were willing to provide a saliva sample for DNA extraction and genotyping were sent an Isohelix GeneFix GFX-02 2 mL Saliva Collection Device via mail; saliva samples were returned to the Sample Processing laboratory at QIMR Berghofer via prepaid Australia Post. Following DNA extraction, genotyping was conducted using the Illumina Global Screening Array V.2.0 and is available for 3,437 (67.4%) Wave 1 and 2 participants and 1,269 (80.2%) of Wave 3 (AGDS) participants. Overall, there are 3,020 genotyped

participants living with BD-I, 1,069 with BD-II and 617 who did not meet full criteria for BD (sub-threshold BD).

2.6 Statistical analyses

Basic statistical analysis, including descriptive statistics analysis, and data quality control were conducted using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Significance of differential responses between participants was assessed using chi-square tests, Student *t*-tests and one-way analysis of variance tests.

3. RESULTS

3.1 Overall sample description

As of February 11, 2021, 6,682 participants had completed the online survey. The majority of participants were female (68.2%) and participants were aged between 18 and 90 years old (on average 44.7±13.7 years old) (Table 1). When answering the question "Are you male or female? Note: This question refers to biological sex, not gender", 21 participants chose the option "Unspecified" (n=13) or "Prefer not to answer" (n=8). To reduce potential identifiability of these participants, their data were not aggregated in Table 1.

Half of the participants were married or in a de facto relationship. More than 40% of participants were in paid work or in an apprenticeship, 6.4% were studying, 13.6% were receiving sickness allowance or disability support pension, and 4.3% were unemployed or looking for work. The ethnicity/ethnicities among 5,851 participants (87.6%) who provided data were 93.0% Caucasian, 3.3% Australian Aboriginal and/or Torres Strait Islander peoples, 2.9% Eastern or South Eastern

Asian, 1.6% Māori or Pacific Islander, 1.6% South Asian ethnicity, 1.4% Middle Eastern, 1.1% African, and 0.5% American First Nations, Native American, Inuit or Métis descent. At the time of interview, 98.2% of participants resided in Australia, with 29.0% living in regional or rural communities and 1.5% living in remote or very remote communities based on the 2019 Modified Monash Model[17]. Importantly, the *Services Australia* mail-out enabled the recruitment of a higher proportion of participants from these communities (1.8%) than the nation-wide media publicity campaign (1.0%). Educational attainment levels among participants who responded (74.9% with a post-school qualification) were higher than that observed in 2018-19 (63% of Australians aged 15-64)[18] and more recently in May 2021 (62% of Australians aged 15-74 years)[19], indicating that people with higher education levels were more likely to participate in the study. When comparing education attainment levels with those reported in the 2016 Australian Census (where 56% of persons aged 15 and over had post-school qualifications)[20], higher levels were observed among GBP participants across all 5-year age groups, and the difference was highest for the 20-24 year group where 70.3% of participants reported obtaining a post-school qualification compared to 46.4% in the 2016 Census[20].

3.2 Bipolar disorder diagnosis

We used MDQ and DSM-5 BD data to determine BD-I and BD-II diagnosis. For those individuals with missing MDQ and DSM-5 BD data, we used the participant's self-reported BD-I or BD-II diagnosis. A total of 3,747 participants met criteria for BD-I and 976 participants met criteria for BD-II. Additionally, 321 participants with missing data self-reported a diagnosis of BD-I and 646 a diagnosis of BD-II. Finally, almost 15% of participants (n=992) self-reported a diagnosis of BD but did not meet DSM-5 criteria for BD and we will refer to these participants as living with sub-

threshold BD. Participants living with sub-threshold self-reported experiencing, an average, 1.3±2.0 of the seven DSM-5 BD symptoms (range 0–7). Overall, the GBP cohort includes 4,068 participants living with BD-I, 1,622 with BD-II, and 992 sub-threshold BD. BD diagnoses differed significantly between men and women (P=7.2E-14), with women more likely (26.6% *vs* 19.2%) diagnosed with BD-II.

3.3 Age of Bipolar disorder diagnosis

Self-reported age at BD diagnosis significantly differed between BD subtypes, $F(2, 5861)=59.8$, P=1.9E-26, where participants living with BD-I reported earlier diagnoses ($\bar{x}$=31.6 years old, s=11.0) compared to participants living with BD-II ($\bar{x}$=33.4 years old, s=11.6) and sub-threshold BD ($\bar{x}$=36.2 years, s=12.6) (Table 2). A bimodal distribution of age of BD diagnosis was observed particularly among male participants living with BD-I and BD-II (Figure 2). Almost 5% of participants living with BD-I or BD-II reported that they received a BD diagnosis during adolescence or childhood.

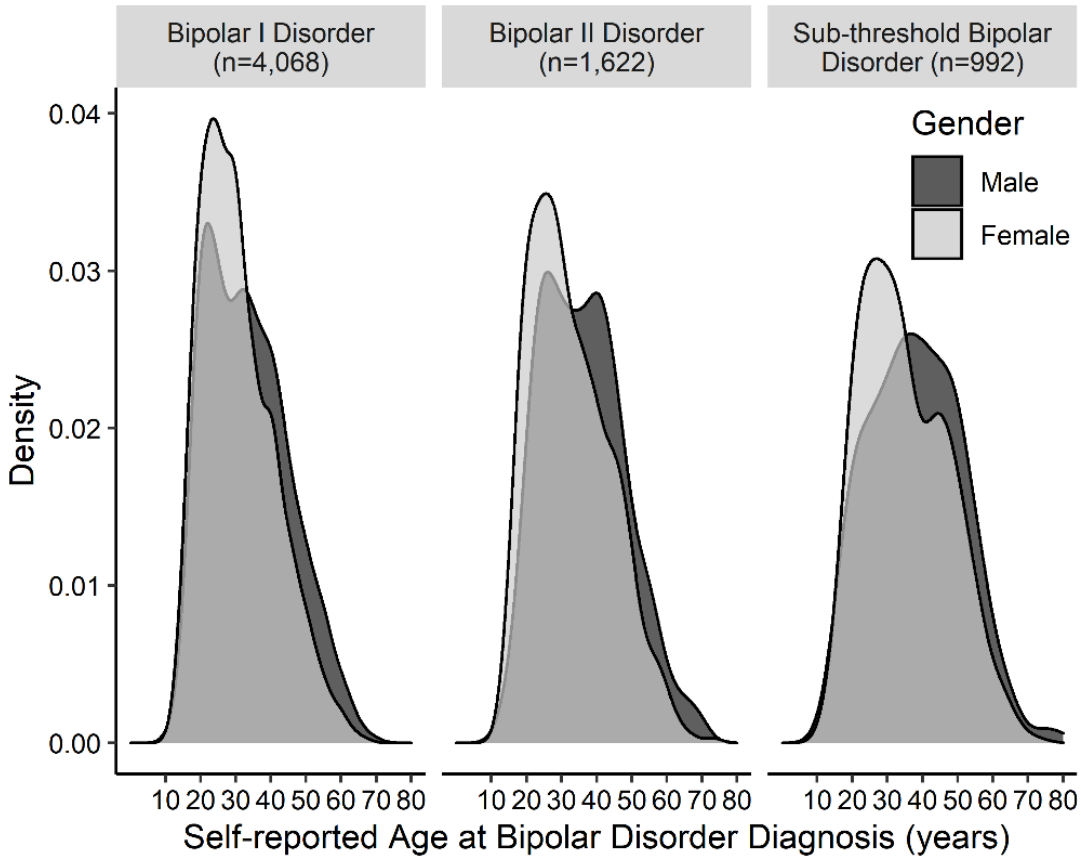

Figure 2. Distribution of self-reported age at diagnosis by sex and type of Bipolar disorder.

The average age of BD diagnosis reported among female participants with lived experience of BD-I or BD-II (31.3±10.8 years) was significantly lower, t(4976)=8.668, P=5.9E-18, than that reported by males (34.3±11.8 years). Female participants were 1.6-times more likely to be diagnosed with BD before the age of 20 (odds ratio [OR]=1.64, 95% confidence interval [CI]=1.33–2.02, P=3.0E-06). Among the 4,854 participants living with BD-I or BD-II who reported the number of professionals they spoke to about their symptoms before they were diagnosed with BD, 42.5% reported speaking to 3-5 professionals while more than one-quarter spoke to six or more professionals.

3.4 Manic episodes and hospitalisations

Among the 4,681 participants who reported when they experienced their first manic episode lasting four days or longer, 11.3% had not started high school and 29.5% were in high school. The average age of first manic episode was 22 years old. Among 2,548 participants who reported being hospitalised due to BD, the majority (91.6%) were living with BD-I (Table 2). The average number of hospitalisations across all participants was 4.6±8.5; almost 1 in 2 participants were hospitalised once or twice (48.0%) and 27.7% reported being hospitalised five or more times.

3.5 Mental health comorbidity

Approximately 1 in 6 participants (16.3%) reported a first degree relative (parent, sibling or child) with a lifetime history of BD, while only Depression (32.5%) and Generalised anxiety disorder (GAD; 17.7%) were reported at higher frequencies among first-degree relatives. Overall, 2,668 (39.6%) of participants reported a first degree relative with any mood or anxiety disorder. The frequency of all self-reported diagnoses is provided in Table 2.

More than two-thirds of participants (64.5%) reported being diagnosed with Depression prior to their BD diagnosis. The next most commonly reported psychiatric diagnoses received prior to BD diagnosis were GAD (26.9%) and Posttraumatic stress disorder (PTSD; 9.1%). Excluding depression with onset prior to BD diagnosis, 65.1% of participants reported one or more co-occurring psychiatric disorders. The most common comorbid diagnoses were GAD (43.5%), PTSD (20.7%) and Personality disorders (12.2%). Following multiple testing correction for the number of psychiatric disorders participants were asked about ($P<0.05/18$), the type of BD diagnosis was significantly associated with lifetime diagnoses of PTSD ($\chi^2(2)=34.9$, P=2.6E-08)

and GAD ($\chi^2(2)=16.4$, P=2.8E-04); participants living with sub-threshold BD reported lower rates of PTSD and GAD (16.6% and 38.4% respectively) compared to BD-I (23.0% and 43.6%) and BD-II (17.3% and 46.5%).

Compared to females, males were significantly more likely to report being diagnosed with Schizophrenia (OR=1.8, 95% CI=1.4–2.3, P=2.0E-06), and ADHD (OR=1.4, 95% CI=1.2–1.7, P=4.6E-04). However, males were less likely to report diagnoses of Anorexia (OR=0.09, 95%CI=0.05–0.16, P=2.1E-16), Bulimia (OR=0.11, 95% CI=0.06–0.19, P=3.7E-14), Personality disorders (OR=0.43, 95% CI=0.36–0.52, P=1.7E-18), Agoraphobia (OR=0.48, 95% CI=0.33–0.69, P=9.9E-05), Specific Phobia (OR=0.48, 95% CI=0.36–0.65, P=9.4E-07), PTSD (OR=0.49, 95% CI=0.43–0.57, P=9.4E-23), GAD (OR=0.53, 95% CI=0.48–0.59, P=1.3E-30), Panic Disorder (OR=0.60, 95% CI=0.49–0.73, P=2.3E-07), and Obsessive compulsive disorder (OCD; OR=0.60, 95% CI=0.50–0.74, P=7.2E-07).

History of psychiatric diagnoses was also influenced by the age of BD diagnosis among participants living with BD-I or BD-II. Compared to participants who reported receiving a BD diagnosis aged 20 years or older, those who received a BD diagnosis before the age of 20 were significantly more likely to report a lifetime history of ADHD (OR=2.1, 95% CI=1.6–2.7, P=5.0E-09), ASD (OR=3.0, 95% CI=2.0–4.5, P=1.4E-07), Anorexia (OR=2.1, 95% CI=1.5–3.0, P=4.1E-05), or GAD (OR=1.4, 95% CI=1.1–1.6, P=0.001).

Finally, 47.1% (n=3149) of participants reported experiencing one or more psychotic-like experiences in their lifetime (Table 2). While no significant sex differences were observed, the

prevalence of PLEs differed significantly between BD diagnoses ($\chi^2(2)=234.7$, P=1.1E-51), with participants living with BD-I reporting higher rates of PLEs (57.1%) compared to BD-II (40.1%) and sub-threshold BD (17.6%). Of note, 3.5% of participants (n=201) living with BD-I or BD-II also self-reported a diagnosis of Schizophrenia, suggesting a diagnosis of Schizoaffective disorder rather than BD. Compared to participants without a diagnosis of Schizophrenia, these individuals were much more likely to likely to have reported PLEs (OR=3.3, 95% CI=2.3–4.6, P=3.9E-12).

3.6 Medication usage and adverse drug reactions

Participants were asked to indicate which medications they had ever taken from a list of mood stabilisers, antipsychotics, and antidepressants. These included the mood stabilisers: lithium, carbamazepine, lamotrigine, valproate, topiramate; antipsychotics asenapine, clozapine, lurasidone, ziprasidone, amisulpride, aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, haloperidol, Fluanxol Depot [or Clopixol Depot], Largactil [or Modecate, or Stelazine or Neulactil]); and antidepressants: selective serotonin reuptake inhibitors (SSRI; sertraline, citalopram, escitalopram, paroxitine, fluoxetine), serotonin-norepinephrine reuptake inhibitors (SNRI; venlafaxine, desvenlafaxine, duloxetine) and two other antidepressant medications (amitriptyline, mirtazapine). Current use and presence of adverse drug reactions (ADRs) associated with specific medications was asked regarding the five mood stabilisers and four antipsychotics (asenapine, clozapine, lurasidone, ziprasidone).

A total of 5,774 (86.4%) participants reported ever taking one or more of the five mood stabilisers and 13 antipsychotics (Table 3). For the medications for which current use data was available 4,506 participants (67.4%) reported current use of one or more medication. Among participants

living with sub-threshold BD, 83.8% reported ever using a listed medication and 57.2% reported current use. The most commonly prescribed class of listed medications was mood stabilisers; lithium, valproate, and lamotrigine had been taken by 72.9%, 38.8%, and 34.0% of participants respectively. Approximately 54% of participants had ever taken one or more of the listed antipsychotic medications, with quetiapine (34.8%) and olanzapine (20.5%) the most taken. Of the 908 participants who reported never taking a listed mood stabiliser or antipsychotic, almost 90% had been prescribed one or more antidepressant medication, most commonly sertraline.

Participants reported experiences of 29 adverse drug reactions (ADRs) for each of the listed medications (mood stabilisers and antipsychotics) they had ever taken. The ADRS were agitation, bloating, blurred vision, constipation, diarrhoea, difficulty getting to sleep, dizziness, drowsiness, dry mouth, fatigue or weakness, feeling mentally slow/fuzzy headed, headache, increased anxiety, increased blood sugar/diabetes, increased heat/sun sensitivity, metallic taste, muscle pain, nausea, rash, reduced sexual desire, runny nose, shaking or tremor, attempted suicide, suicidal thoughts, sweating, thirst, vomiting, weight gain, and weight loss. The five most commonly experienced ADRs were weight gain (42.1%), dry mouth (38.5%), shaking or tremor (36.6%), thirst (31.9%), and feeling mentally slow or fuzzy headed (31.4%) (Figure 3).

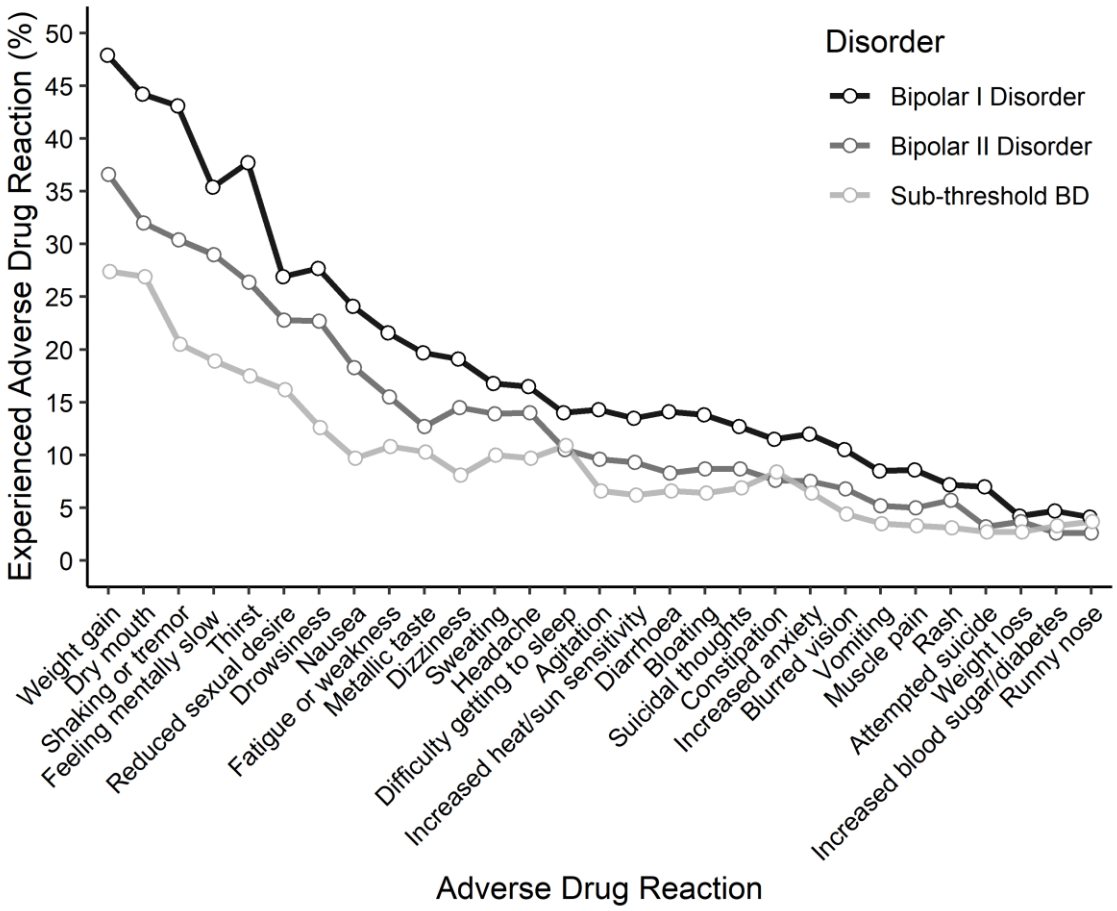

Figure 3. Frequency of reported adverse drug reactions (ADRs)[†] by type of Bipolar disorder. [†]ADR data were available for five mood stabilisers (lithium, carbamazepine, lamotrigine, valproate, topiramate) and four antipsychotics (asenapine, clozapine, lurasidone, ziprasidone).

Overall, participants who had taken lithium reported the highest number of ADRs (3.8±4.2). However, 84.1% of users perceived that lithium worked moderately or very well and only one-third of users stopped taking lithium due to the ADRs. For the other medications, participants experienced an average of 2.1–2.8 ADRs. The highest rates of medication discontinuation (60% and over) due to ADRs were reported for carbamazepine and use of any antipsychotic.

4 DISCUSSION

A total of 6,682 participants aged 18–90 years old provided phenotypically rich information about their experiences with BD, their mental health and medication use. The majority of participants also provided a saliva sample for genotyping and consented to PBS and MBS record linkage, providing their Medicare card number, name and address.

The mean age of BD diagnosis was 32.7 years in the GBP Study. Consistent with the lifetime trajectory of bipolar disorder, more than two-thirds of participants living with BD-I and BD-II (68.5%) were originally diagnosed with Depression prior to their first hypomanic or manic episode. While we did not collect data on the length of time it took to receive a BD diagnosis, more than half of the participants reported speaking to three or more professionals about their symptoms before they were diagnosed, with 12.3% reporting they spoke with six or more professionals. This is consistent with other research reporting a large time interval (5-10 years[21 22 23 24]) between the onset of symptoms and the diagnosis and treatment of BD.

Overall, 42% of participants reported that a first-degree relative (parent, brother, sister or child) had been diagnosed with one or more mental health disorders. Approximately 16% of participants reported a family history of BD reflecting the moderate to high heritability of BD[2,3]. Excluding Depression, almost two-thirds of participants reported one or more diagnoses of another psychiatric disorder with GAD (20.5%) or PTSD (18.9%) the most reported. Overall, 62.7% of participants reported a diagnosis of any anxiety disorder. This level of psychiatric comorbidity is consistent with that found in the World Mental Health Survey Initiative where three-quarters of participants living with BD met criteria for one or more other disorders[8]. While the rate of co-

occuring anxiety disorders in our cohort was similar (62.7% vs 52.0%) to that observed among participants living with BD in the 1997 Australian National Survey of Mental Health and Well-Being[25], our levels of GAD and PTSD were approximately double those reported in that study.

Higher lifetime rates of self-reported PLEs among participants living with BD-I (57.1%) compared to those living with BD-II (40.1%) has been previously observed in the Jorvi Bipolar Study where almost half of the 191 BD patients reported psychotic symptoms and the rate was twice as common among patients living with BD-I (67.8%) than BD-II (33.7%)[26].

Most participants (84.7%) reported taking the prescribed mood stabilisers we asked about while 54.3% had taken one or more of the 13 antipsychotic medications. Overall, more than half of participants reported having taken three or more of the 18 BD medications we asked about. Preliminary analysis of medication usage data suggested that while most participants were experiencing considerable benefits from their medications, ADRs were common and resulted in medication discontinuation rates ranging from 33.4% for lithium to 63.0% for carbamazepine. As might be expected, medications perceived to be working moderately or very well were least likely to be discontinued due to ADRs experienced. Of note, ADRs (in particular weight gain, tremors, cognitive impairment, and sedation) are a frequent reason reported for non-adherence of mood stabilisers by 20-40% of patients living with BD[27]. Medication discontinuation due to ADRs is an important clinical issue because they can substantially contribute to poorer outcomes and treatment failure such as manic episode recurrences and increased risk of hospitalisations and suicide[28].

A major strength of the study is its sample size, as it is the largest population-based studies of adults living with BD in Australia. Importantly, we were able to recruit participants from across Australia, including remote communities, and ethnicity data indicates that participants are representative of the Australian population. Another strength is that 80.3% of Wave 1 and 2 participants consented to link the questionnaire data with their electronic PBS and MBS records. When the PBS records become available, we will be able to validate self-report medication use and discontinuation data during the previous 5 years. Finally, the high proportion of participants that met criteria for BD-I and the high rates of self-reported PLEs and family history of BD suggests that we have recruited a more severely ill cohort of adults living with BD than would be observed in the Australian population—while this might make the sample less representative it is a strength for genetic studies.

This study also has some limitations. First, the sampling frame for our medication-based recruitment strategy only included adults with two or more dispensed prescriptions of lithium carbonate. This may have resulted in patterns of BD medication treatment that do not generalise to the majority of Australians living with BD. Second, the relatively low participation rate (7.2%) from the 50,000 adults sent study invitation letters by *Services Australia* means that selection bias cannot be excluded and this is likely reflected in the higher levels of educational achievement in our sample as compared to the general population.

In conclusion, our study demonstrates that Australian residents with lived experience of BD, particularly BD-I, psychotic-like experiences and use of lithium carbonate and antipsychotics, are motivated to participate in genetically-focused research studies if given the opportunity and

provided with avenues to participate. Compared to our media-based recruitment, our medication-based strategy reached more participants living in remote areas of Australia. Furthermore, the immediacy of participation is important and internet-based research potentially lowers barriers to participation. Importantly, future analyses of PBS and MBS data will allow us to clarify the relationship between BD subtypes, pharmacotherapy treatment response, cost of illness, and health service usage within an Australian context.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: Fifth Edition*. American Psychiatric Association; 2013.

2. Smoller JW, Finn CT. Family, twin, and adoption studies of bipolar disorder. *Am J Med Genet C Semin Med Genet*. Nov 15 2003;123c(1):48-58. doi:10.1002/ajmg.c.20013

3. Johansson V, Kuja-Halkola R, Cannon TD, Hultman CM, Hedman AM. A population-based heritability estimate of bipolar disorder – In a Swedish twin sample. *Psychiatry Res*. 2019/08/01/ 2019;278:180-187. doi:10.1016/j.psychres.2019.06.010

4. Mullins N, Forstner AJ, O'Connell KS, et al. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat Genet*. 2021/06/01 2021;53(6):817-829. doi:10.1038/s41588-021-00857-4

5. Australian Bureau of Statistics. National Survey of Mental Health and Wellbeing: Summary of Results. 2022. Accessed 2 September, 2022. https://www.abs.gov.au/statistics/health/mental-health/national-study-mental-health-and-wellbeing/latest-release

6. The Royal Australian and New Zealand College of Psychiatrists. The Economic Cost of Serious Mental Illness and Comorbidities in Australia and New Zealand. Royal Australian and New Zealand College of Psychiatrists (RANZCP); 2016. Accessed July 5, 2022. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwji6KT2wPX5AhXNSWwGHR-FD9sQFnoECA4QAQ&url=https%3A%2F%2Fwww.ranzcp.org%2Ffiles%2Fresources%2Freports%2Franzcp-serious-mental-illness.aspx&usg=AOvVaw1PT4VaD6fl-quLXxMSZ8AM

7. Clemente AS, Diniz BS, Nicolato R, et al. Bipolar disorder prevalence: a systematic review and meta-analysis of the literature. *Braz J Psychiatry*. Apr-Jun 2015;37(2):155-61. doi:10.1590/1516-4446-2012-1693

8. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry*. Mar 2011;68(3):241-51. doi:10.1001/archgenpsychiatry.2011.12

9. Fisher LJ, Goldney RD, Dal Grande E, Taylor AW, Hawthorne G. Bipolar disorders in Australia. A population-based study of excess costs. *Soc Psychiatry Psychiatr Epidemiol*. Feb 2007;42(2):105-9. doi:10.1007/s00127-006-0133-4

10. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry*. Apr 2015;72(4):334-41. doi:10.1001/jamapsychiatry.2014.2502

11. Chan JKN, Tong CHY, Wong CSM, Chen EYH, Chang WC. Life expectancy and years of potential life lost in bipolar disorder: systematic review and meta-analysis. *Br J Psychiatry*. Feb 21 2022:1-10. doi:10.1192/bjp.2022.19

12. Plans L, Barrot C, Nieto E, et al. Association between completed suicide and bipolar disorder: A systematic review of the literature. *J Affect Disord*. Jan 1 2019;242:111-122. doi:10.1016/j.jad.2018.08.054

13. Byrne EM, Kirk KM, Medland SE, et al. Cohort profile: the Australian genetics of depression study. *BMJ Open*. May 26 2020;10(5):e032580. doi:10.1136/bmjopen-2019-032580

14. Hirschfeld RM, Williams JB, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *Am J Psychiatry*. Nov 2000;157(11):1873-5. doi:10.1176/appi.ajp.157.11.1873

15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition*. American Psychiatric Association; 1994.

16. Wang HR, Woo YS, Ahn HS, Ahn IM, Kim HJ, Bahk WM. The Validity of the Mood Disorder Questionnaire for Screening Bipolar Disorder: A Meta-Analysis. *Depress Anxiety*. Jul 2015;32(7):527-38. doi:10.1002/da.22374

17. Australian Government Department of Health. Modified Monash Model. Accessed 2 September, 2021, https://www.health.gov.au/health-topics/rural-health-workforce/classifications/mmm

18. Australian Bureau of Statistics. Qualifications and work. Australian Bureau of Statistics. Accessed 5 September, 2022, https://www.abs.gov.au/statistics/people/education/qualifications-and-work/2018-19#data-download

19. Australian Bureau of Statistics. Education and Work, Australia. Australian Bureau of Statistics. Accessed 5 September, 2022, https://www.abs.gov.au/statistics/people/education/education-and-work-australia/latest-release#data-download

20. Australian Bureau of Statistics. 2071.0 - Census of Population and Housing: Reflecting Australia - Stories from the Census, 2016 Australian Bureau of Statistics. Accessed 5 September, 2022, https://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/2071.0Main+Features100012016?OpenDocument

21. Dagani J, Signorini G, Nielssen O, et al. Meta-analysis of the Interval between the Onset and Management of Bipolar Disorder. *Can J Psychiatry*. Apr 2017;62(4):247-258. doi:10.1177/0706743716656607

22. Keramatian K, Pinto JV, Schaffer A, et al. Clinical and demographic factors associated with delayed diagnosis of bipolar disorder: Data from Health Outcomes and Patient Evaluations in Bipolar Disorder (HOPE-BD) study. *J Affect Disord*. Jan 1 2022;296:506-513. doi:10.1016/j.jad.2021.09.094

23. Medici CR, Videbech P, Gustafsson LN, Munk-Jorgensen P. Mortality and secular trend in the incidence of bipolar disorder. *J Affect Disord*. Sep 1 2015;183:39-44. doi:10.1016/j.jad.2015.04.032

24. Drancourt N, Etain B, Lajnef M, et al. Duration of untreated bipolar disorder: missed opportunities on the long road to optimal treatment. *Acta Psychiatr Scand*. Feb 2013;127(2):136-44. doi:10.1111/j.1600-0447.2012.01917.x

25. Mitchell PB, Slade T, Andrews G. Twelve-month prevalence and disability of DSM-IV bipolar disorder in an Australian general population survey. *Psychol Med*. Jul 2004;34(5):777-85. doi:10.1017/s0033291703001636

26. Mantere O, Suominen K, Leppamaki S, Valtonen H, Arvilommi P, Isometsa E. The clinical characteristics of DSM-IV bipolar I and II disorders: baseline findings from the Jorvi Bipolar Study (JoBS). *Bipolar Disord*. Oct 2004;6(5):395-405. doi:10.1111/j.1399-5618.2004.00140.x

27. Mago R, Borra D, Mahajan R. Role of adverse effects in medication nonadherence in bipolar disorder. *Harv Rev Psychiatry*. Nov-Dec 2014;22(6):363-6. doi:10.1097/HRP.0000000000000017

28. Pompili M, Serafini G, Del Casale A, et al. Improving adherence in mood disorders: the struggle against relapse, recurrence and suicide risk. *Expert Rev Neurother*. 2009/07/01 2009;9(7):985-1004. doi:10.1586/ern.09.62

29. Australian Bureau of Statistics. National, state and territory population. 2021. Accessed June 2, 2022. https://www.abs.gov.au/ausstats/abs@.nsf/Previousproducts/6227.0Media%20Release1May%202015?opendocument&tabname=Summary&prodno=6227.0&issue=May%202015&num=&view=

TABLES

Table 1. Basic demographics and Bipolar disorder history of participants by gender.

Characteristic	Male	Female	Total
Participants, n (%)	2,118 (31.8)	4,543 (68.2)	6,661 (100.0)
Age at survey, y			
Mean (SD)	48.3 (13.3)	43.1 (13.5)	44.7 (13.7)
Range (Minimum – Maximum)	18 – 84	18 – 90	18 – 90
BD diagnosis, n (%)[†]			
Bipolar I disorder	1322 (62.4)	2732 (60.1)	4054 (60.9)
Bipolar II disorder	406 (19.2)	1210 (26.6)	1616 (24.3)
Sub-threshold BD	390 (18.4)	601 (13.2)	991 (14.9)
Completed Survey, n (%)			
Core module only	1177 (55.6)	2381 (52.4)	3558 (53.4)
Core module and Module 2	176 (8.3)	374 (8.2)	550 (8.3)
Core module, Module 2 and Module 3	765 (36.1)	1788 (39.4)	2553 (38.3)
Marital Status, n (%)			
Married	887 (41.9)	1628 (35.8)	2515 (37.8)
Separated or divorced	375 (17.7)	793 (17.5)	1168 (17.5)
Widowed	18 (0.8)	76 (1.7)	94 (1.4)
De facto relationship	474 (22.4)	1024 (22.5)	1498 (22.5)
Never married	227 (10.7)	629 (13.8)	856 (12.9)
Chose not to answer	137 (6.5)	393 (8.7)	530 (8.0)
Highest level of education, n (%)			
No formal education	6 (0.3)	7 (0.2)	13 (0.2)
Primary school	6 (0.3)	8 (0.2)	14 (0.2)
Middle high school	128 (6.0)	240 (5.3)	368 (5.5)

Senior high school	175 (8.3)	286 (6.3)	461 (6.9)
Certificate or diploma	410 (19.4)	810 (17.8)	1220 (18.3)
Undergraduate degree	482 (22.8)	1070 (23.6)	1552 (23.3)
Postgraduate degree, doctorate, or PhD	426 (20.1)	943 (20.8)	1369 (20.6)
Don't know	137 (6.5)	395 (8.7)	532 (8.0)
Chose not to answer	348 (16.4)	784 (17.3)	1132 (17.0)
Current main activity, n (%)			
Student attending school	6 (0.3)	12 (0.3)	18 (0.3)
Student attending university, TAFE or other education	75 (3.5)	333 (7.3)	408 (6.1)
Full-time paid work (≥30 hours/week)	721 (34.0)	1144 (25.2)	1865 (28.0)
Part-time paid work (<30 hours/week)	174 (8.2)	699 (15.4)	873 (13.1)
Volunteer work	43 (2.0)	91 (2.0)	134 (2.0)
Unemployed/looking for work	118 (5.6)	169 (3.7)	287 (4.3)
Apprenticeship/Traineeship	3 (0.1)	10 (0.2)	13 (0.2)
Home duties	32 (1.5)	349 (7.7)	381 (5.7)
Not working due to illness, vacation, etc	31 (1.5)	74 (1.6)	105 (1.6)
Currently receiving sickness allowance or disability support pension	323 (15.3)	586 (12.9)	909 (13.6)
Other	236 (11.1)	419 (9.2)	655 (9.8)
Chose not to answer	356 (16.8)	657 (14.5)	1013 (15.2)
Australian State or Territory, n (%)[‡]			
New South Wales (31.8%)	633 (29.9)	1260 (27.7)	1893 (28.4)
Queensland (20.3%)	474 (22.4)	1064 (23.4)	1538 (23.1)
Victoria (25.9%)	452 (21.3)	1003 (22.1)	1455 (21.8)
Western Australia (10.4%)	232 (11.0)	490 (10.8)	722 (10.8)
South Australia (6.9%)	144 (6.8)	282 (6.2)	426 (6.4)
Tasmania (2.1%)	83 (3.9)	153 (3.4)	236 (3.5)

Australian Capital Territory (1.7%)	53 (2.5)	161 (3.5)	214 (3.2)
Northern Territory (1.0%)	11 (0.5)	27 (0.6)	38 (0.6)
Unknown	36 (1.7)	103 (2.3)	139 (2.1)
Modified Monash Model 2019, n (%)			
Metropolitan	1417 (66.9)	3059 (67.3)	4476 (67.2)
Regional or rural	634 (29.9)	1301 (28.6)	1935 (29.0)
Remote or very remote	25 (1.2)	73 (1.6)	98 (1.5)
Unknown	42 (2.0)	141 (3.1)	183 (2.7)

†Determined either using the Mood Disorder Questionnaire[14] with additional items corresponding to the fifth edition of the DSM-5 BD diagnostic criteria[1], or self-reported BD diagnosis.

‡The percentage of the Australian population by State or Territory at 30 March 202[29] is provided in brackets.

Abbreviations: BD, Bipolar disorder; SD, standard deviation.

Table 2. Participant diagnosis history and impact of Bipolar disorder and psychiatric comorbidities reported by type of Bipolar disorder.

Characteristic	Bipolar I disorder[†]	Bipolar II disorder[†]	Sub-threshold BD[†]	Total
Participants, n (%)	4068 (60.5)	1622 (24.1)	992 (14.8)	6682 (100)
Gender, n (%)				
Female	2732 (67.2)	1210 (74.6)	601 (60.6)	4543 (68.0)
Male	1322 (32.5)	406 (25.0)	390 (39.3)	2118 (31.7)
Unspecified	9 (0.2)	4 (0.2)	0	13 (0.2)
Prefer not to answer	5 (0.1)	2 (0.1)	1 (0.1)	8 (0.1)
Diagnosed with BD, n (%)	3435 (84.4)	1621 (99.9)	992 (100.0)	6048 (90.5)
Self-reported BD diagnosis, n (%)				
Bipolar I disorder	1676 (41.2)	0	0	1676 (25.1)
Bipolar II disorder	1031 (25.3)	1521 (93.8)	0	2552 (38.2)
Another type	85 (2.1)	17 (1.0)	106 (10.7)	208 (3.1)
Don't know	646 (15.9)	84 (5.2)	781 (78.7)	1511 (22.6)
Chose not to answer	630 (15.5)	0	105 (10.6)	735 (11.0)
Age at BD diagnosis, y				
Mean (SD)	31.6 (11.0)	33.4 (11.6)	36.2 (12.6)	32.7 (11.6)
Childhood diagnosis, n (%)	7 (0.2)	4 (0.2)	6 (0.6)	17 (0.3)
Adolescence diagnosis, n (%)	190 (4.7)	71 (4.4)	33 (3.3)	294 (4.4)
Adulthood diagnosis, n (%)	3209 (78.9)	1526 (94.1)	833 (84.0)	5568 (83.3)
Chose not to answer, n (%)	662 (16.3)	21 (1.3)	120 (12.1)	803 (12.0)
Number of professionals talked to about symptoms before diagnosed with BD, n (%)				
1-2	1447 (35.6)	515 (31.8)	290 (29.2)	2252 (33.7)
3-5	1080 (26.5)	330 (20.3)	144 (14.5)	1554 (23.3)
6-10	329 (8.1)	85 (5.2)	46 (4.6)	460 (6.9)
More than 10	258 (6.3)	63 (3.9)	37 (3.7)	358 (5.4)
Chose not to answer	954 (23.5)	629 (38.8)	475 (47.9)	2058 (30.8)
Psychiatric disorder diagnoses prior to BD diagnosis, n (%)				
Depression	2516 (61.8)	1379 (85.0)	639 (64.4)	4534 (67.9)
Generalised anxiety disorder	984 (24.2)	553 (34.1)	259 (26.1)	1796 (26.9)
Another disorder	592 (14.6)	220 (13.6)	119 (12.0)	931 (13.9)

Posttraumatic stress disorder	361 (8.9)	151 (9.3)	95 (9.6)	607 (9.1)
Schizophrenia	213 (5.2)	34 (2.1)	71 (7.2)	318 (4.8)
Attention-deficit/hyperactivity disorder	192 (4.7)	87 (5.4)	36 (3.6)	315 (4.7)
Autism spectrum disorder	34 (0.8)	14 (0.9)	11 (1.1)	59 (0.9)
Hospitalised due to BD, n (%)				
No	1385 (34.0)	874 (53.9)	267 (26.9)	2526 (37.8)
Yes	2335 (57.4)	78 (4.8)	135 (13.6)	2548 (38.1)
Chose not to answer	348 (8.6)	670 (41.3)	590 (59.5)	1608 (24.1)
Number of times hospitalised, Mean (SD)	4.7 (8.5)	4.3 (5.9)	4.3 (9.5)	4.6 (8.5)
Longest number of days hospitalised, Mean (SD)	41.4 (55.5)	52.6 (62.3)	41 (45.1)	41.7 (55.3)
Age when had first manic episode lasting 4 days or longer, n (%)				
Age, y, Mean (SD)	22.6 (10.3)	22.4 (10.7)	26.6 (13)	22.9 (10.7)
Before starting high school	362 (8.9)	103 (6.4)	63 (6.4)	528 (7.9)
While in high school	952 (23.4)	312 (19.2)	118 (11.9)	1382 (20.7)
After finished high school	1849 (45.5)	587 (36.2)	335 (33.8)	2771 (41.5)
Chose not to answer	905 (22.2)	620 (38.2)	476 (48.0)	2001 (29.9)
Number of manic episodes that lasted 1 or more weeks, n (%)				
1-2	992 (24.4)	529 (32.6)	238 (24.0)	1759 (26.3)
3-5	833 (20.5)	194 (12.0)	101 (10.2)	1128 (16.9)
6-10	467 (11.5)	85 (5.2)	38 (3.8)	590 (8.8)
More than 10	787 (19.3)	137 (8.4)	94 (9.5)	1018 (15.2)
Chose not to answer	989 (24.3)	677 (41.7)	521 (52.5)	2187 (32.7)
Lifetime presence of psychotic-like experiences, n (%)[‡]				
Reported any psychotic-like experience	2324 (57.1)	650 (40.1)	175 (17.6)	3149 (47.1)
Age of first psychotic-like experience, Mean (SD)	23.4 (11.4)	22.8 (11.8)	25.5 (13.4)	23.6 (11.7)
Number of lifetime psychiatric diagnoses excluding BD and Depression[§]				
Mean (SD)	1.6 (1.8)	1.5 (1.6)	1.4 (1.7)	1.5 (1.7)
Range	0 – 12	0 – 11	0 – 10	0 – 12
Other mental health disorder diagnoses, n (%)[§]				
Generalised anxiety disorder	1772 (43.6)	754 (46.5)	381 (38.4)	2907 (43.5)
Post-traumatic stress disorder	936 (23.0)	280 (17.3)	165 (16.6)	1381 (20.7)
Personality disorder	521 (12.8)	180 (11.1)	115 (11.6)	816 (12.2)
Social Anxiety disorder	463 (11.4)	210 (12.9)	107 (10.8)	780 (11.7)
Panic disorder	392 (9.6)	130 (8.0)	109 (11.0)	631 (9.4)
Obsessive compulsive disorder	380 (9.3)	140 (8.6)	78 (7.9)	598 (8.9)

Attention-deficit/hyperactivity disorder	340 (8.4)	148 (9.1)	69 (7.0)	557 (8.3)
Substance use disorder	296 (7.3)	94 (5.8)	49 (4.9)	439 (6.6)
Specific phobia	207 (5.1)	59 (3.6)	43 (4.3)	309 (4.6)
Seasonal Affective disorder	189 (4.6)	76 (4.7)	35 (3.5)	300 (4.5)
Anorexia nervosa	183 (4.5)	64 (3.9)	42 (4.2)	289 (4.3)
Schizophrenia	177 (4.4)	24 (1.5)	84 (8.5)	285 (4.3)
Bulimia	163 (4.0)	60 (3.7)	22 (2.2)	245 (3.7)
Agoraphobia	117 (2.9)	46 (2.8)	26 (2.6)	189 (2.8)
Autism spectrum disorder	98 (2.4)	47 (2.9)	26 (2.6)	171 (2.6)
Hoarding disorder	28 (0.7)	12 (0.7)	9 (0.9)	49 (0.7)
Tourette's disorder	11 (0.3)	3 (0.2)	0 (0.0)	14 (0.2)
First-degree relative has a mental health disorder diagnosis, n (%)				
No	945 (23.2)	359 (22.1)	217 (21.9)	1521 (22.8)
Yes	1784 (43.9)	730 (45.0)	317 (32.0)	2831 (42.4)
Chose not to answer	1339 (32.9)	533 (32.9)	458 (46.2)	2330 (34.9)
Mental health disorder in first-degree relatives, n (%)				
Depression	1345 (33.1)	584 (36.0)	240 (24.2)	2169 (32.5)
Generalised anxiety Disorder	730 (17.9)	330 (20.3)	122 (12.3)	1182 (17.7)
Bipolar disorder	706 (17.4)	252 (15.5)	132 (13.3)	1090 (16.3)
Substance use disorder	248 (6.1)	84 (5.2)	37 (3.7)	369 (5.5)
Schizophrenia	209 (5.1)	64 (3.9)	45 (4.5)	318 (4.8)
Attention-deficit/hyperactivity disorder	178 (4.4)	98 (6.0)	39 (3.9)	315 (4.7)
Personality disorder	165 (4.1)	75 (4.6)	33 (3.3)	273 (4.1)
Autism spectrum disorder	158 (3.9)	57 (3.5)	24 (2.4)	239 (3.6)
Obsessive compulsive disorder	131 (3.2)	57 (3.5)	29 (2.9)	217 (3.2)

[†]Determined either using the Mood Disorder Questionnaire[14] with additional items corresponding to the fifth edition of the DSM-5 BD diagnostic criteria[1], or self-reported BD diagnosis.

[‡]The checklist of six psychotic-like experiences included auditory hallucinations and delusions of persecution and control.

[§]Selected from a checklist of 19 psychiatric disorders.

Abbreviations: BD, Bipolar disorder; SD, standard deviation.

Table 3. Medication use and adverse drug reactions reported by type of Bipolar disorder.

Characteristic	Bipolar I disorder†	Bipolar II disorder†	Sub-threshold BD†	Total
Number of Participants, n (%)	4068 (60.5)	1622 (24.1)	992 (14.8)	6682 (100)
Ever prescribed a listed medication, n (%)‡	3412 (83.9)	1531 (94.4)	831 (83.8)	5774 (86.4)
Lithium	3135 (77.1)	1104 (68.1)	634 (63.9)	4873 (72.9)
Any antipsychotic	2321 (57.1)	892 (55.0)	415 (41.8)	3628 (54.3)
Valproate	1706 (41.9)	593 (36.6)	295 (29.7)	2594 (38.8)
Lamotrigine	1322 (32.5)	777 (47.9)	175 (17.6)	2274 (34.0)
Carbamazepine	487 (12.0)	128 (7.9)	74 (7.5)	689 (10.3)
Topiramate	319 (7.8)	128 (7.9)	46 (4.6)	493 (7.4)
Total number of listed medications ever prescribed, n (%)‡				
Mean (SD)	3.0 (2.5)	2.7 (1.9)	2.0 (1.8)	2.8 (2.3)
Range	0 – 18	0 – 15	0 – 12	0 – 18
0	656 (16.1)	91 (5.6)	161 (16.2)	908 (13.6)

1	587 (14.4)	399 (24.6)	312 (31.5)	1298 (19.4)
2	707 (17.4)	418 (25.8)	225 (22.7)	1350 (20.2)
3	640 (15.7)	295 (18.2)	134 (13.5)	1069 (16.0)
4	517 (12.7)	175 (10.8)	73 (7.4)	765 (11.4)
5+	961 (23.6)	244 (15.0)	87 (8.7)	1292 (19.4)
Currently prescribed a listed medication, n (%)‡				
Lithium	2056 (50.5)	711 (43.8)	418 (42.1)	3185 (47.7)
Lamotrigine	732 (18.0)	487 (30.0)	108 (10.9)	1327 (19.9)
Valproate	457 (11.2)	157 (9.7)	104 (10.5)	718 (10.7)
Any antipsychotic	299 (7.4)	78 (4.8)	38 (3.8)	415 (6.2)
Topiramate	73 (1.8)	40 (2.5)	17 (1.7)	130 (1.9)
Carbamazepine	70 (1.7)	27 (1.7)	13 (1.3)	110 (1.6)
Total number of listed medications currently prescribed, n (%)‡				
Mean (SD)	0.91 (0.79)	0.93 (0.71)	0.70 (0.71)	0.88 (0.76)
Range	0 – 7	0 – 4	0 – 3	0 – 7

0	1317 (32.4)	434 (26.8)	425 (42.8)	2176 (32.6)
1	1934 (47.5)	917 (56.5)	450 (45.4)	3301 (49.4)
2	703 (17.3)	230 (14.2)	103 (10.4)	1036 (15.5)
3+	114 (2.8)	41 (2.6)	14 (1.4)	169 (2.5)
Currently prescribed a listed antidepressant medication, n (%)[‡]				
Selective serotonin reuptake inhibitor (SSRI)	3103 (76.3)	1324 (81.6)	675 (68.0)	5102 (76.4)
Serotonin-norepinephrine reuptake inhibitors (SNRI)	722 (17.7)	355 (21.9)	208 (21.0)	1285 (19.2)
Other	312 (7.7)	117 (7.2)	91 (9.2)	520 (7.8)
Listed medication worked moderately or very well, n (%)[§]				
Lithium	2527 (84.1)	830 (83.3)	432 (85.2)	3789 (84.1)
Lamotrigine	905 (73.8)	544 (77.4)	100 (73.0)	1549 (74.9)
Valproate	928 (58.6)	317 (60.8)	148 (67.3)	1393 (59.9)
Any antipsychotic	477 (57.4)	129 (47.1)	47 (46.5)	653 (54.1)
Topiramate	110 (39.3)	60 (56.6)	18 (52.9)	188 (44.8)
Carbamazepine	178 (41.2)	39 (36.8)	22 (46.8)	239 (40.9)

Total number of 29 ADRs ever experienced, Mean (SD)[§]				
Lithium	4.2 (4.4)	3.3 (3.9)	2.4 (3.7)	3.8 (4.2)
Any antipsychotic	3.2 (4.8)	2.5 (3.9)	1.8 (3.0)	2.8 (4.5)
Topiramate	2.4 (3.4)	2.2 (3.8)	2.5 (4.1)	2.3 (3.6)
Valproate	2.7 (3.7)	2.2 (3.2)	1.8 (3.2)	2.5 (3.5)
Carbamazepine	2.5 (3.5)	2.2 (3.4)	1.6 (3.1)	2.3 (3.5)
Lamotrigine	2.3 (3.3)	1.9 (3.0)	1.7 (3.1)	2.1 (3.2)
Stopped taking a listed medication due to ADRs, n (%)[§]				
Carbamazepine	181 (64.0)	40 (64.5)	12 (48.0)	233 (63.0)
Any antipsychotic	354 (61.2)	97 (59.1)	31 (51.7)	482 (60.1)
Topiramate	106 (61.3)	35 (52.2)	9 (39.1)	150 (57.0)
Valproate	552 (52.5)	149 (47.2)	54 (46.2)	755 (50.8)
Lamotrigine	275 (36.7)	126 (30.7)	30 (37.5)	431 (34.8)
Lithium	816 (34.9)	214 (29.7)	93 (30.8)	1123 (33.4)

†Determined either using the Mood Disorder Questionnaire[14] with additional items corresponding to the fifth edition of the DSM-5 BD diagnostic criteria[1], or self-reported BD diagnosis..

‡The 'ever use' medication checklist included five mood stablilisers (lithium, carbamazepine, lamotrigine, valproate. topiramate) and thirteen antipsychotics (asenapine, clozapine, lurasidone, ziprasidone, amisulpride, aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, haloperidol, Fluanxol Depot [or Clopixol Depot], Largactil [or Modecate, or Stelazine or Neulactil]). The 'current use' medication checklist included five mood stablilisers (lithium, carbamazepine, lamotrigine, valproate, topirimate) and four antipsychotics (asenapine, clozapine, ziprazidone, lurasidone). The antidepressant medication checklist included five selective serotonin reuptake inhibitors (sertraline, citalopram, escitalopram, paroxitine, fluoxetine), three serotonin-norepinephrine reuptake inhibitors (venlafaxine, desvenlafaxine, duloxetine), and two other medications (amitriptyline, mirtazapine). Lithium and asenapine ever use data collected in the Australian Genetics of Depression Study baseline survey[13] from the 1,582 Australian Genetics of Depression Study participants was included.

§Percent, means and standard deviations are calculated from responses only. The medication checklist included four mood stablilisers (lithium, carbamazepine, lamotrigine, valproate), four antipsychotics (asenapine, clozapine, ziprazidone, lurasidone) and topirimate.

Abbreviations: ADR, adverse drug reaction; BD, Bipolar disorder; SD, Standard deviation.

FIGURE LEGENDS

Figure 1. Overview of the Australian Genetics of Bipolar Disorder Study recruitment strategy and data collected.

Abbreviations: AGDS: Australian Genetics of Depression Study; BD: Bipolar disorder; DSM-5: Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders; GBP: Australian Genetics of Bipolar Disorder; MBS: Medicare Benefits Schedule; MDD: Major depressive disorder; PBS: Pharmaceutical Benefits Scheme.

Figure 2. Distribution of self-reported age of diagnosis by sex and type of Bipolar disorder.

Figure 3. Frequency of reported adverse drug reactions (ADRs)[†] by type of Bipolar disorder. [†]ADR data was available for five mood stabilisers (lithium, carbamazepine, lamotrigine, valproate, topiramate) and four antipsychotics (asenapine, clozapine, lurasidone, ziprasidone).