Investigating age at onset in bipolar disorder

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Abstract

Bipolar disorder (BD) is a complex mental health disorder with a heterogenous clinical course, diagnostic delays, high relapse rates, and sub-optimal treatment outcomes. Age at onset (AAO) has been proposed as a useful specifier for defining more homogeneous BD subgroups that can inform clinical course and symptom profiles. This thesis aimed to investigate the utility of AAO as a clinical specifier by defining and validating AAO subgroups; identifying predictive factors for BD AAO; investigating the relationship between premorbid factors, AAO, and functional outcomes; and examining the association between AAO and mood instability.

Using mixed methods across four experimental chapters, this thesis provides novel insights into the role of AAO in BD. Chapter 2 presents a systematic review of AAO distributions in BD and provides a recommended AAO definition. Chapter 3 uses machine learning approaches to explore predictive factors for BD AAO. Chapter 4 investigates the potential pathways between premorbid factors, BD AAO, and functional outcomes using prospective data. Chapter 5 examines the association between AAO and mood instability using longitudinal mood monitoring data. Findings reveal a trimodal distribution of AAO in BD, with distinct early-life risk factors, which may represent potential causal pathways to clinical outcomes. Additionally, mood instability is identified as a promising target for intervention in the clinical trajectory of BD. These results have important theoretical and practical implications, informing early intervention strategies and providing further evidence for the distinctiveness of AAO subgroups.

The thesis concludes with a general discussion of the findings and implications for future research. Overall, this thesis provides valuable insights into the role of AAO in BD, highlights the importance of identifying more homogeneous subgroups to improve diagnosis and treatment outcomes, and underscores the need for continued research in this area.

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Declarations

This thesis was completed between October 2018 and April 2023, supervised by Professor John Geddes and Dr Kate Saunders. The work is my own and has not been submitted for any other degree, in this or any other university or learning institute. Some parts of the thesis have been published, and details are given in the relevant chapters. In accordance with the guidelines, the body of this thesis does not exceed 50,000 words (excluding references, appendices, figures, and tables) and contains fewer than 150 figures.

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List of Abbreviations

AAO	Age at Onset
ADHD	Attention Deficit Hyperactivity Disorder
AIC	Akaike Information Criterion
ALSPAC	Avon Longitudinal Study of Parents and Children
ANOVA	Analysis of Variance
BD	Bipolar Disorder
BD-NOS	Bipolar Disorder Not Otherwise Specified
BD-SA	Bipolar Disorder Schizoaffective type
BDI	Bipolar Disorder type I
BDII	Bipolar Disorder type II
BDNF	Brain-Derived Neurotrophic Factor
BDRN	Bipolar Disorder Research Network
BIC	Bayesian Information Criterion
BIOSIS	Biosciences Information Service
BLEQ	Brief Life Events Questionnaire
CADM2	Cell Adhesion Molecule 2
CBT	Cognitive Behavioural Therapy
CECA	Childhood Experiences of Care and Abuse
CENTRAL	Cochrane Central Register of Controlled Trials
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CI	Confidence Interval
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CLEQ	Childhood Life Events Questionnaire
CRAN	Comprehensive R Archival Network
CRIS	Clinical Record Interactive Search
CV	Cross-validation
DAST	Drug Abuse Screening Test
DBT	Dialectical Behaviour Therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
EAS	Emotionality–Activity–Sociability
EI	Early Intervention
EIP	Early Intervention in Psychosis
EMBLEM	European Mania in Bipolar Longitudinal Evaluation of Medication
EMDR	Eye Movement Desensitisation Reprocessing
EPIMAN	Epidemiology of Mania
EPQ-R	Eysenck Personality Questionnaire Revised
GAF	Global Assessment of Functioning
GWAS	Genome-Wide Association Study
HPA	Hypothalamic-Pituitary-Adrenal
ICD	International Classification of Diseases

KSQ	Kings Schizotypy Questionnaire
LASSO	Least Absolute Shrinkage and Selection Operator
LEQ	Life Event Questionnaire
LL	Log-likelihood
LOESS	Locally Weighted Regression
LOOCV	Leave One Out Cross Validation
MAE	Mean Absolute Error
MAR	Missing At Random
MBCT	Mindfulness-Based Cognitive Therapy
MCAR	Missing Completely at Random
MCMC	Markov Chain Monte Carlo
MD	Major Depression
MEDLINE	Medical Literature Analysis and Retrieval System Online
MI	Mood Instability
MICE	Multiple imputation using chained equations
ML	Maximum Likelihood
MLR	Robust Maximum Likelihood
MNAR	Missing Not at Random
MREC	Multicentre Research Ethics Committee
MSSD	Mean of the Squared Successive Differences
NHS	National Health Service
NIMH	National Institute of Mental Health
OCD	Obsessive Compulsive Disorder
OLS	Ordinary Least Squares
OPCRIT	Operational Criteria Checklist for Psychotic Illness and Affective Illness
OS	Operating System
OSF	Open Science Framework
PMM	Predictive Mean Matching
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
PTSD	Post-traumatic stress disorder
QIDS	Quick Inventory of Depressive Symptomatology
RCT	Randomised Control Trial
RDC	Research Diagnostic Criteria
REML	Restricted Maximum Likelihood
RMSE	Root Mean Squared Error
RMSEA	Root Mean Square Error of Approximation
RSE	Residual Standard Error
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SCID	Structured Clinical Interview for DSM-IV
SD	Standard Deviation
SE	Standard Error
SEM	Structural Equation Modelling

SES	Socio-economic Status
SRMR	Standardized Root Mean Square Residual
SSRI	Selective Serotonin Reuptake Inhibitor
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
TEMPS-A	Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-Questionnaire
TFCBT	Trauma-Focused Cognitive–Behavioural Therapy
TLI	Tucker-Lewis Index
TRIPOD	Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis
tRMSSD	Time-Adjusted Root Mean Squared of The Successive Differences
VIF	Variance Inflation Factor

Chapter 1. Introduction

1.1 Introduction

Bipolar Disorder (BD) is a chronic mental health disorder with a population prevalence of 1-4% (Merikangas et al., 2011; Pini et al., 2005). It can be considered a developmental disorder presenting with nonspecific prodromal symptoms early in life, which subsequently crystallise into pathological symptoms later in life (Duffy, 2007; Geoffroy et al., 2013). The disorder is characterised by recurring episodes of depression and mania or hypomania. These mood episodes alternate or co-occur (mixed state), and are interspersed with periods of stable mood, known as euthymia (Grande et al., 2016). BD exhibits a capricious and heterogenous clinical course which makes accurate diagnosis and treatment challenging. Patients experience diagnostic delays of up to a decade (Fritz et al., 2017), and even after a confirmed diagnosis and subsequent treatment, relapse rates are as high as 80% and daily functioning often remains impaired (Anderson et al., 2012; Gignac et al., 2015; Gitlin & Miklowitz, 2017; Judd et al., 2002). It is therefore broadly accepted that current approaches to defining, diagnosing, and treating BD are sub-optimal, and addressing this has become a priority for clinical research and practice.

Accordingly, the field has increasingly aimed to better understand the biopsychosocial basis of BD pathology and how this gives rise to a heterogenous clinical presentation. Advancing knowledge in this way has the potential to move beyond existing nosological frameworks to demarcate more aetiologically and phenotypically homogenous groups of BD individuals (Duffy, Goodday, et al., 2017). The hope is that identifying relevant BD subgroups will allow early detection and diagnosis, and that subgroup stratification will help shape interventions to ameliorate a pernicious clinical course. Surmounting evidence suggests that 'age-at-onset' (AAO) of BD may be a key variable in demarcating more uniform subgroups (Leboyer et al., 2005). Thus, AAO may be

a useful BD group specifier that can give patients and clinicians a roadmap for expected clinical course and likely symptom profiles. Equally, elucidating why some individuals are more likely to develop BD at a younger age than others can inform early intervention and preventative strategies; the goal of which is to improve illness outcome and reduce disease burden.

This thesis therefore aims to examine the role of BD age-at-onset in delineating more homogenous clinical groups. Specifically, the goal is to investigate whether there are meaningful differences between individuals based on their age-at-onset and how this may inform clinical course. The current Introduction Chapter (Chapter 1) provides context for the aims of this thesis. To begin, the existing classification of BD is outlined, the heterogenous prognosis is discussed, and the current evidence-based treatment approaches are summarised. This background information provides a springboard for the discussion of why the current framework in which research and clinical decision making is conducted is less than optimal. As a possible solution, evidence regarding the role of age-at-onset as a clinical specifier is then considered. Finally, the implications and pitfalls of employing BD age-at-onset as a subgroup specifier are evaluated, and the ensuing aims and corresponding experimental chapters of this thesis are outlined.

1.2 Bipolar Disorder

1.2.1 Current Nosology

BD is commonly diagnosed and classified using two major diagnostic systems: the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (American Psychiatric Association, 2013) and the 11th revision of the International Classification of Diseases (ICD-11) (World Health Organization, 2022).

DSM-V subcategorises BD based on the severity of manic symptoms into: Bipolar I Disorder (BD-I), defined by manic episodes; Bipolar II Disorder (BD-II), distinguished by episodes of hypomania;

and Bipolar Disorder Not-Otherwise-Specified (BD-NOS), which includes disorders with bipolar features that do not meet the criteria for BD-I or BD-II (American Psychiatric Association, 2013). A manic episode is defined as a period of elevated or irritable mood, lasting at least one week, that causes significant impairment to normal functioning and may require hospitalisation. It is marked by symptoms including grandiosity, decreased need for sleep, talkativeness, racing thoughts, extreme disinhibition, risk-taking behaviour, and psychomotor agitation. Up to 75% of individuals experiencing a manic episode will also present with psychotic features, such as hallucinations, delusions, and disturbed thoughts (Goodwin & Jamison, 2007). In contrast, while hypomania shares the same core symptoms as mania, episodes last less than a week and are not severe enough to cause marked impairment in functioning, hospitalisation, or psychotic features.

According to the ICD-11, BD is subcategorised as bipolar affective disorder, which can be further classified as BDI , BDII, and other specified bipolar and related disorders (World Health Organization, 2022). A manic episode is defined as a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy lasting for at least seven days (or any duration if hospitalisation is required). The symptoms during a manic episode are similar to those described in the DSM-V. Hypomania is defined as a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy lasting for at least four consecutive days. However, unlike the DSM-V, the ICD-11 does not require that the episode cause marked impairment in social or occupational functioning.

Both the DSM-V and ICD-11 require the presence of a depressive episode for the diagnosis of BD. The criteria for a depressive episode are similar in both systems, with symptoms that persist for two weeks or more including low mood, loss of interest or pleasure in daily activities, changes in

weight and appetite, sleep disturbances, lethargy, problems concentrating, and suicidal ideation (American Psychiatric Association, 2013).

It can be argued, however, that these current classification systems for BD are based on phenomenology – i.e., the observable course of illness – rather than a bottom-up approach that establishes relevant biomarkers and grounds classification in aetiology (Benazzi, 2009). Grouping in this top-down way may explain why inter-individual clinical trajectory is highly variable, with evidence indicating that these phenomenological groups may not be aetiologically related (Leboyer et al., 2005; Merikangas et al., 2002). Moreover, current research and clinical practice is somewhat limited by virtue of being couched within the framework of this classification system. This framework makes it challenging to move beyond observable symptoms profiles when it comes to classifying individuals for research and treatment innovation. In clinical settings in particular, little weight is given to biomarkers and emerging illness course, which constrains early intervention and preventative strategies.

1.2.2 Diagnosis and Prognosis

Establishing an aetiologically meaningful and clinically useful framework for delineating and classifying BD is especially important seeing that the clinical trajectory of BD is highly variable, with phenomenological and biological heterogeneity contributing to differences in illness course and prognosis (Soreca et al., 2009). This makes accurate and timely diagnosis challenging, with patients reporting an average diagnostic delay of almost a decade (Fritz et al., 2017). This delay is associated with poorer prognosis, including greater symptom severity and increased suicidality (Drancourt et al., 2013; Post et al., 2010). A major reason for this diagnostic delay is that up to 70% of individuals are misdiagnosed, primarily with unipolar depression (Fajutrao et al., 2009; Stiles et al., 2018). In part, this is due to individuals being more likely to present to services during a depressive episode, with manic or hypomanic symptoms being missed, misinterpreted, or yet

to manifest (Hirschfeld et al., 2003). Furthermore, the prevalence of depressive symptoms tends to be greater across the illness course, with (hypo)manic symptoms being reported as little as 1% of the overall time spent symptomatic (Judd et al., 2003). This is further complicated by mixed states obscuring the detection of (hypo)mania (Phillips & Kupfer, 2013). As a result, individuals may receive inappropriate treatment such as antidepressant monotherapy, which has been prospectively associated with an increased risk of developing mania and subsequent accelerated cycling between mood states (Carvalho et al., 2020; Goldberg & Truman, 2003). This highlights why greater emphasis should be placed on early illness course and premorbid markers. Gaining a better understanding of early-life factors that may contribute to illness manifestation can help reduce diagnostic delays and correspondingly guide appropriate treatment.

Appropriate diagnosis and treatment are especially important given the significant mortality and morbidity seen in BD (Crump et al., 2013; Hawton et al., 2005; Laursen et al., 2014). Research has suggested that life expectancy is between 8 to 20 years shorter in individuals with BD compared to the general population (Crump et al., 2013; Laursen et al., 2013; Miller & Bauer, 2014), with a 2-fold risk of cardiovascular-related-mortality, and a 30- to 60-fold risk of suicide attempts – the highest rate of any affective disorder (Dong et al., 2019; Gonda et al., 2012; Miller & Black, 2020; Plans et al., 2019).

Concomitant with increased mortality, individuals with BD also experience high levels of psychiatric and medical comorbidities, with a lifetime prevalence of approximately 90% (Carvalho et al., 2020; McIntyre et al., 2020). Meta-analytic results indicate that BD is most commonly comorbid with anxiety disorders, with an estimated 40.5% of BD individuals diagnosed with a concurrent anxiety disorder across their lifetime (Yapici Eser et al., 2018). Additionally, substance and alcohol misuse, attention deficit hyperactivity disorder (ADHD), and personality disorder are highly comorbid with BD (Messer et al., 2017; Nery et al., 2014). Chronic medical conditions are

also more common in BD than the general population, including obesity, circulatory disorders, type 2 diabetes mellitus, neurological disorders (e.g., migraine), and respiratory disorders (Fornaro & Stubbs, 2015; Krishnan, 2005; McIntyre et al., 2007; Vancampfort et al., 2016; Wang et al., 2022). The high rate of comorbidities in BD increases the illness burden, worsens prognosis, and complicates treatment and diagnosis.

1.2.3 Treatment

This diverse clinical picture in BD underlies differences in treatment approaches. Therapeutic strategies can differ considerably depending on an individual's current mood state (depression, hypomania, mania, euthymia), medical and psychiatric comorbidities, prior treatment response, and willingness to comply with treatment (Grande et al., 2016). Once a BD diagnosis is confirmed and a comprehensive clinical picture has been gathered, the two main treatment goals are (1) acute stabilisation and (2) long-term maintenance, traditionally via pharmacotherapeutic approaches (Geddes & Miklowitz, 2013).

1.2.3.1 Acute Treatment

The aim of acute treatment is to stabilise the individual's mood, from either a depressive or manic episode, to a euthymic (stable) state. Mood stabilisers and antipsychotics are a principal component of acute management for both manic and depressive symptoms. Meta-analytic results indicate that antipsychotic drugs are significantly more effective than mood stabilisers: with risperidone, olanzapine, and haloperidol considered most efficacious and tolerable in the treatment of manic episodes (Cipriani et al., 2011). In contrast, evidence for the use of pharmacotherapy in the acute treatment of bipolar depression is less robust. There is limited evidence to support the use of antidepressants in the treatment of bipolar depression (Sidor & MacQueen, 2012), with antidepressant monotherapy often resulting in a switch to a manic state (Geddes & Miklowitz, 2013). However, a recent network-meta-analysis suggests that several

antipsychotics (e.g., quetiapine, olanzapine, cariprazine, lurasidone) and antiepileptics (e.g., lamotrigine, divalproex), as well as adjunct antidepressant use (e.g., olanzapine-fluoxetine combination), may be effective and well-tolerated in treating bipolar depression, whilst being no more likely to trigger a treatment-emergent manic switch compared to placebo (Bahji et al., 2020).

1.2.3.2 Long-term Management

Given the recurrent and remitting course of BD, long-term management focuses on preventing relapse, reducing subthreshold symptoms, and strengthening social and occupational functioning through the combination of pharmacological, psychological, and behavioural approaches (Geddes & Miklowitz, 2013; Grande et al., 2016). For over 60 years, lithium has been the first-line treatment option for the long-term management of BD, with pooled results demonstrating its efficacy in preventing relapse for both depressive and manic episodes (Alda, 2015; Miura et al., 2014). However, the use of lithium is limited by its toxicity profile, which necessitates routine monitoring of serum concentrations to mitigate adverse events including a decline in renal function, hypothyroidism, and hyperglycaemia (McKnight et al., 2012). Combining pharmacotherapy with psychosocial interventions can bolster the prophylactic effects of medication by increasing treatment adherence, teaching patients about illness-management and coping skills, and enhancing interpersonal functioning and family relationships (Colom et al., 1998; Miklowitz & Scott, 2009; Scott et al., 2007). Evidence-based psychosocial approaches include cognitive-behavioural therapy (CBT), family-focused therapy, interpersonal and social rhythm therapy, and group psychoeducation (Lam et al., 2009; Miklowitz, 2008). A recent systematic review and network meta-analysis of 39 randomised clinical trials of adjunctive psychotherapy found that psychosocial interventions reduced episode recurrence and stabilised residual symptoms compared to treatment as usual (i.e., pharmacotherapy with routine monitoring visits) (Miklowitz et al., 2021).

1.2.4 Early intervention

The extant literature surrounding the treatment and management of BD focuses almost exclusively on tertiary prevention, which refers to the treatment of individuals after they have received a diagnosis (Malhi et al., 2014; Vieta et al., 2018). In contrast, very little attention has been paid to early intervention and preventative strategies. In the context of BD, early intervention (EI) refers to approaches that involve identifying and treating high-risk groups, along with early detection and treatment of an index mood episode. While early intervention in psychosis (EIP) has been extensively studied and dedicated clinical EIP programmes have been implemented around the world, there remains a paucity of research investigating EI in BD (Post, 2018). This is partly attributable to difficulties in defining what constitutes a 'high-risk' state for the development of BD, and, in contrast to psychosis, the prodromal phases of the disorder are less well defined. For instance, the prodromes in BD often present as nonspecific symptoms, such as sleep disturbances, subsyndromal anxiety, and mood alterations (Duffy et al., 2010). Additionally, while uncommon, not all individuals will experience a prodromal period and instead exhibit a precipitous onset of BD (Malhi et al., 2014).

Despite a lack of clarity surrounding the definition of the bipolar prodrome, the development and evaluation of EI approaches is essential given that BD has a progressive nature. Evidence indicates that allostatic load from cumulative episodes results in neurocognitive 'wear and tear' which reduces resilience and increases treatment resistance over time (Kapczinski et al., 2008). A recent systematic review investigating EI approaches in BD suggests that psychological and pharmacological treatments may improve mood, anxiety, sleep symptoms, and daily functioning in high-risk groups (Saraf et al., 2021). However, the authors note that their conclusions are limited by the lack of biologically homogenous high-risk groups. This limitation makes it hard to determine if prodromal symptoms improved due to the specific utility of EI strategies, or whether

this change was reflective of intra-group differences in aetiology. This further reinforces the need for the identification of homogenous BD groups that share psychosocial and biological risk markers.

1.3 Delineating more homogenous bipolar subgroups

The evidence outlined thus far highlights that the clinical presentation of BD is extremely heterogenous. Bipolar individuals experience a highly variable illness trajectory – which both contributes to, and is worsened by, a significant delay in diagnosis (Passos et al., 2016) – and endure residual symptoms and reduced functioning for almost a third of their lives (Anderson et al., 2012; Judd et al., 2002). Yet, the available pharmacological and psychosocial treatment approaches remain sub-optimal. Even with treatment, evidence indicates that up to 50% of BD patients will relapse within two-years, and between 60-80% within four to seven years (Gignac et al., 2015; Perlis et al., 2006; Wittchen et al., 2003). While treatments can help individuals recover from BD symptoms, research suggests that daily functioning remains significantly impaired (despite syndromal recovery) and may never return to pre-morbid levels (Gitlin & Miklowitz, 2017). Moreover, clinical decision making is based on current frameworks (e.g., DSM-V) which are defined by phenomenology rather than aetiology. This constrains the efficacy of current treatment approaches and overlooks opportunities for early intervention and primary prevention.

A key tenet of bipolar research, therefore, is to better understand the psychopathology behind this heterogenous clinical presentation (Duffy, Goodday, et al., 2017). In doing so, the goal is to identify and define aetiologically homogenous BD subtypes (Wu et al., 2017). In line with the aims of precision psychiatry, reducing heterogeneity in this way has the potential to aid earlier diagnosis thereby streamlining treatment approaches and improving illness outcomes (Fernandes et al., 2017).

1.4 Age at onset as a clinical specifier

Currently the field commonly uses the classic nosologically-defined groups – i.e., BD-I, BD-II, BD-NOS – as specifiers to delineate BD clusters (see Section 1.2.1). While these specifiers are phenomenologically and clinically relevant (Karanti et al., 2020), increasing evidence indicates that they're not reliably associated with biomarkers, suggesting that these groups may not be aetiologically related (Benazzi, 2009; Merikangas et al., 2002). Research has therefore aimed to move beyond traditional classifications to identify phenotypic markers that give rise to distinct BD subgroups that are aetiologically similar (Leboyer et al., 2005). A burgeoning body of research has demonstrated that age at onset (AAO) is likely a key variable in demarcating more homogeneous subgroups of BD individuals, with evidence suggesting that the clinical trajectory of BD differs according to AAO (Geoffroy et al., 2013; Holtzman et al., 2015; Schürhoff et al., 2000).

Given its potential aetiological and clinical relevance, grouping individuals according to their AAO of BD should be a priority for current and future research. However, there are various challenges associated with studying AAO. Most notably, there is (i) no established definition for 'onset' in BD and (ii) no consensus regarding what is meant by 'early' versus 'late' onset. To establish the utility of AAO as a clinical specifier, these challenges must be addressed to lay the foundations for valid and reliable research.

1.4.1 Defining age at onset

There is currently no consistent definition for 'onset' in BD (Carlson & Pataki, 2016; Duffy & Malhi, 2017). Studies varyingly define AAO as the age at: (i) onset of mood symptoms (Baldessarini et al., 2012); (ii) first episode of depression or mania meeting diagnostic criteria (Coryell et al., 2013; Etain et al., 2012; Nowrouzi et al., 2016); (iii) first treatment; or (iv) first

hospitalisation (Bellivier et al., 2001). Each of these definitions have their pitfalls, and it is important to note that within the current classification system a definable (hypo)manic episode is required for a confirmed diagnosis of BD, even though depressive episodes and non-specific, subsyndromal symptoms may develop prior to (hypo)mania (Ratheesh et al., 2017).

AAO definitions based on 'the onset of mood symptoms' reference subsyndromal symptoms that do not meet diagnostic criteria. Only in retrospect, post-diagnosis, can a decision be made as to whether these early features were related to incipient BD, or a normal part of development (Jones, 2013). Retrospectively deciding what constitutes pathology is limited by the fact that possible symptoms are viewed through the lens of an adult diagnosis, despite subsyndromal symptoms being inherently equivocal. Consequently, potential symptoms may be misattributed, under-detected, and underreported, leading to error or bias in recall (Simon & Vonkorff, 1995). In turn, pinpointing the exact time of onset of non-specific, subsyndromal symptoms is unrealistic, further distorting the reported AAO (Akiskal & Benazzi, 2005). Thus, determining AAO from the 'first episode of depression or mania meeting diagnostic criteria' is a more reliable approach, as the event is clearly defined in time compared to generalised alterations in mood. Limitations of recall bias may be mitigated by referring to case notes and interviews with family members rather than relying solely on self-report. However, individuals with BD may be more likely to recall depressive compared to manic episodes or even fail to recognise hypomanic episodes pre-diagnosis as pathological (de Assis da Silva et al., 2014; Gazalle et al., 2007). Definitions referring to 'age at first treatment or first hospitalisation' are even more clearly delineated in time, and patient self-report can be accurately corroborated by medical records. This definition seems robust as it can be assumed that most individuals with BD will eventually come to the attention of clinical services and receive treatment (Kessler et al., 2007). However, this definition precludes relevant episodes of depression and mania prior to treatment and/or hospitalisation, which is relevant due to the substantial delay between onset of mood symptoms

and subsequent diagnosis and treatment (Kessler et al., 2005; Leboyer et al., 2005; Vaingankar et al., 2012).

As a gold-standard therefore, research investigating AAO in BD should aim to employ prospective longitudinal methodologies using the age at 'first affective episode meeting diagnostic criteria' as the standardised definition for the point of disease onset (Goodwin & Jamison, 2007). Prospective approaches can overcome the limitations of error and bias associated with retrospective recall. To date, however, almost no known research has investigated AAO prospectively.

1.4.2 What is early onset?

Not only is there no reliable definition of AAO, but there is also a dearth of research validating AAO subgroups, with no consensus regarding what is meant by 'early' vs. 'late' onset (Bellivier et al., 2001; Geoffroy et al., 2013).

In recent years, it has been acknowledged that AAO in BD is not a simple unimodal distribution but can better be explained by a mixture of distributions. Evidence suggests that BD aggregates either into a bimodal distribution with two subgroups (early vs. late AAO), or a trimodal distribution with three subgroups (early vs. mid vs. late AAO) (Bauer et al., 2010; Bellivier et al., 2003; Coryell et al., 2013; Hamshere et al., 2009; Joslyn et al., 2016; Leboyer et al., 2005). However, it is not known which of these distribution modalities are most reliable and consistent. Discrepancies in findings likely arise from methodological differences and variances in the populations being studied. For instance, methodologies differ by study type and location (e.g., Europe vs. USA), recruitment setting (e.g., outpatient clinic vs. hospital vs. community vs. registry data) and the definition used to operationalise AAO.

Notably, it has been suggested that diagnostic rates of 'early-onset' BD are significantly higher in the United States compared to Europe, Australia, and New Zealand (Blader & Carlson, 2007; Clacey et al., 2015; James et al., 2014). This difference in rates of childhood BD is present when looking at administrative prevalence – i.e., the rate of diagnoses made by health care professionals in a particular location, during a specified time (Joslyn et al., 2016; Stringaris & Youngstrom, 2014) – but disappears when examining 'true' epidemiological prevalence (van Meter et al., 2019). Thus, the difference is likely driven by variances in diagnostic practices and patient expectations. For example, a focus on non-specific symptoms as a core feature of paediatric BD – such as chronic irritability – may lead to rates of over-diagnosis (Dubicka et al., 2008; James et al., 2014), despite guidelines indicating that irritability without elation or grandiosity is not a developmental presentation of mania (Stringaris, 2019; Stringaris et al., 2018). The high prevalence of 'early-onset' BD may be influenced by the US medical system incentivising early diagnosis and prescription more than other countries, as clinicians receive higher reimbursement rates for pharmacological compared to psychosocial interventions (Stringaris & Youngstrom, 2014). These factors are often overlooked when investigating rates of childhood-onset BD.

The distribution of AAO in BD samples will also diverge according to sample characteristics including reported diagnosis (BDI vs. BDII vs. BD-NOS); method of obtaining diagnosis (e.g., ICD vs. DSM, clinician administered vs. not); treatment seeking vs. not treatment seeking; acute mood state (depressed, manic, hypomanic, mixed, or euthymic); presence of psychotic features; polarity of index episode; and age at assessment. These factors introduce high levels of variability when trying to form a consensus regarding AAO groupings in BD. To further complicate the picture, several studies investigating AAO in BD use pre-defined cut-offs to define AAO groups, which are arbitrarily chosen and not based on the distribution observed in the sample. This is an inherently biased approach, as it relies on the studies authors' preconceptions rather than

allowing the data to inform the outcome. One of the most popular data-driven analysis approaches for determining AAO groups from a given dataset is admixture analysis. This approach assumes that the data is a mixture of distinct Gaussian distributions – one for each underlying subgroup – and thus explores the theoretical model that best fits the observed distribution, weighting each subset by its prevalence in the sample (Montlahuc et al., 2017). The field would therefore benefit from a synthesis of studies that use a data-driven approach, such as admixture analysis, to define AAO groups.

1.4.3 Evidence for distinct subgroups

These challenges notwithstanding, interest in AAO as a clinical specifier for BD continues to grow. There is a plethora of emerging evidence indicating that BD individuals aggregate into distinct AAO groups with phenotypic and biological similarities within groups, and differences between groups. The extant evidence spans clinical characteristics, neurobiology, genetics, and environmental factors. Pertinently, AAO has the potential to be especially useful as a group specifier as it is a variable that is defined in time, meaning that it lends itself well to predictive modelling. In turn, this expands the opportunities for innovation in early intervention and prevention, with the potential to delay or halt neuro-progression and improve long-term outcomes.

1.4.3.1 Clinical characteristics

The notion that there are distinct AAO subgroups in BD is supported by evidence demonstrating that clinical characteristics and prognostic outcomes appear to vary according to AAO. Meta-analytic results suggest that 'early-onset' follows a more pernicious course than 'later-onset': with longer delays to treatment, greater severity of depressive symptoms, increased rates of suicide attempts, and higher levels of comorbid anxiety and substance abuse (Joslyn et al., 2016). Early- compared to late-onset has also been associated with high levels of mood instability

(Henry et al., 2008), characterised as “rapid oscillations of intense affect, with a difficulty in regulating these oscillations or their behavioural consequences”(Broome, Saunders, et al., 2015; Marwaha et al., 2014).

However, research to date often overlooks the intercorrelation between clinical characteristics, such as duration of illness, making it difficult to separate out the risk associated with such factors compared to the specific risk conferred by early-onset. The precise relationship between earlier onset and clinical course therefore remains unclear. It may be that ‘early’ onset is a causal risk factor that confers a more severe clinical course by disrupting the developing brain at a critical period, thus tiggering a cascade of maladaptive behaviours and coping strategies. Alternatively, early-onset may simply be a risk marker – i.e., a factor that is associated with an outcome but is not necessarily its cause (Feinleib, 2001). For instance, increased risk of suicide attempts may be an artefact of a longer duration of illness, or factors such as substance abuse may precipitate an early-onset and worsen symptom severity. Disentangling these relationships has implications for therapeutic strategies and early intervention.

1.4.3.2 Genetics and neurobiology

Beyond clinical characteristics, there is evidence to suggest that heritability and neurobiological factors differ by AAO group. According to estimates from twin studies, BD is the most heritable of all psychiatric and behavioural disorders, with heritability estimates as high as 90% (Bienvenu et al., 2011; Merikangas & Yu, 2002). It is thought that early-onset BD may be more heritable than late-onset, with studies demonstrating differences in transmission patterns and more pronounced familial aggregation in early- compared to late-onset BD (Geoffroy et al., 2013; Grigoroiu-Serbanescu et al., 2001; Hamshere et al., 2009; Köhler-Forsberg et al., 2020; Leboyer et al., 2005; Post et al., 2016; Preisig et al., 2016; Priebe, Degenhardt, Herms, Haenisch, Mattheisen, Nieratschker, Weingarten, Witt, Breuer, Paul, Alblas, Moebus, Lathrop, Leboyer,

Schreiber, Grigoroiu-Serbanescu, Maier, Propping, Rietschel, Nöthen, et al., 2012). Over the past two decades, studies have investigated genetic loci responsible for early-onset BD. Whilst most findings have not been replicated and remain inconclusive (Belmonte Mahon et al., 2011; Kalman et al., 2021), a recent a genome-wide association study (GWAS) suggested that a specific locus in the *CADM2* gene is associated with early-onset BD and may also exert an effect on clinical expression (Wu et al., 2021). GWAS have their limitations, however, and AAO is likely influenced by many genes of smaller effect sizes as well as rare variants (Belmonte Mahon et al., 2011; Toma et al., 2018).

Nonetheless, susceptibility loci (such as those on *CADM2*) are thought to interact with environmental and neurobiological factors to influence the AAO of BD (Nassan et al., 2020). For example, it is thought that exposure to childhood trauma interacts with genes that are involved in pathways relating to neuroplasticity, inflammation, circadian rhythm, and calcium signalling to influence AAO (Aas et al., 2016; Anand et al., 2015; Benedetti et al., 2014; Etain et al., 2015; Oliveira et al., 2015). A 2013 study by Miller et al. demonstrated that the brain-derived neurotrophic factor (BDNF) val66met polymorphism interacted with the presence of childhood sexual abuse to influence the AAO of BD; only individuals with the Met allele (vs. non-Met allele carriers) with a history of childhood abuse had an earlier AAO of BD (Miller et al., 2013). In this way, epigenetic modifications in gene function may play an important role in the mechanism underlying the relationship between environmental factors present in early life and a younger AAO of BD (Aas, Haukvik, et al., 2014; Duffy, Goodday, et al., 2019; Oliveira et al., 2015; Perroud et al., 2016; Petronis, 2003; Roth et al., 2009).

1.4.3.3 Environment

Childhood maltreatment is one of the most studied environmental risk correlates in BD, encompassing physical, verbal, sexual, and emotional abuse, and physical and emotional neglect

(Etain et al., 2008). A large body of research has found maltreatment in childhood to be more common in individuals with BD compared to healthy controls (Daruy-Filho et al., 2011), and that it is associated with an earlier AAO (Agnew-Blais & Danese, 2016; Etain et al., 2013). It has been hypothesised that abuse in childhood may lead to structural and functional brain alterations – such as changes in hippocampal and amygdala volumes and white matter integrity (Frodl et al., 2010; Janiri et al., 2017; Stevelink et al., 2018) – that expedite the onset of BD (Post et al., 2015). These alternations may reduce an individual's neurobiological (and corresponding behavioural) resilience, thus precipitating early onset. This parallels the kindling/sensitisation hypothesis (Post, 2007). This postulates that individuals who experience severe early adversity become more sensitive to later adversity, and therefore relapse following lower levels of stress than those with mild or no early adversity (Dienes et al., 2006; Subramanian et al., 2017); this could help explain the recurring and remitting course seen in early-onset BD. Additionally, a high frequency of stressful life events is thought to contribute to an early AAO (Grandin et al., 2007; Hays et al., 1998), along with other environmental factors including substance abuse, socioeconomic status, sleep disturbances and comorbid vascular conditions (Geoffroy et al., 2013; Ritter et al., 2015; Strakowski, 2000). Unlike childhood trauma, however, these factors are not unique to early-life and therefore may also contribute to the manifestation of later-life BD.

1.5 Implications

Taken together, evidence from phenomenological, genetic, neurobiological, and environmental studies suggests that AAO may indeed be a useful specifier for identifying more homogenous BD subgroups. Research indicates that AAO subgroups share clinical characteristics and may be aetiologically homogenous. The aim of identifying these congruent subgroups is twofold: firstly, to facilitate a better understanding of the biopsychosocial mechanisms underlying BD, and secondly, as a corollary, to help inform clinical decision making. The goal, therefore, is to use AAO

subgroup information to (i) predict who might get sick and when, and (ii) help predict illness course. This has the potential to tailor and enhance treatment and early intervention.

1.5.1 Predicting age at onset: early intervention

As evidence suggests that there are distinct AAO groups, it would be helpful to identify premorbid factors that denote which AAO group an individual is likely to belong to. In this way, individuals can be stratified to ascertain those who are most likely to develop BD at a younger (versus older) age. This can then inform early intervention approaches. Additionally, identifying differences in premorbid features between AAO groups would provide further evidence to bolster the idea that these groups are meaningfully different and are likely aetiologically distinct. However, despite the apparent distinction between 'early' and 'late' onset BD, no know research has systematically investigated what psychosocial factors may predict BD AAO (Baldessarini et al., 2012; Coryell et al., 2013; Etain et al., 2012; Schürhoff et al., 2000).

While the evidence outlined thus far suggests that there are genetic, environmental, and clinical factors associated with early onset, these studies almost exclusively rely on retrospective reports. Retrospective reports are subject to recall bias and corresponding inaccuracies and cannot provide a reliable insight into nonspecific symptoms or life events pre-onset. Indeed, the vast amount of literature examining AAO in BD – with the exclusion of genetic studies – focuses on associations between AAO and characteristics that are not exclusively premorbid. For instance, comorbid substance abuse and anxiety disorders may be present both pre- and post-onset. Yet, it is unclear whether this is a cause of a consequence of early-onset BD, and the extant literature has not disentangled this association. Given that the field broadly acknowledges that an early AAO is a more severe phenotype than late AAO, it is perhaps surprising that more attention has not been paid to examining a range of modifiable premorbid factors that may predict AAO. The gold-standard for identifying reliable predictive factors is phenotypically detailed prospective

follow-up of high-risk youth cohorts. The hope is that this will allow the detection of risk factors that can be targeted in preventative strategies and early intervention. Detailed stratification of high-risk groups can thus help inform illness course and guide treatment provision.

1.5.2 Illness course: putative mechanisms

As highlighted, a key objective of identifying features that may predict AAO is to inform appropriate junctures for early intervention. By the same token, predicting likely AAO groupings can provide a roadmap for expected clinical course, as it has been demonstrated that 'earlier-onset' follows a more pernicious course than 'later-onset'. In early-onset BD, longer delays to treatment, greater severity of depressive symptoms, increased rates of suicide attempts, and higher levels of comorbidities worsen illness burden and increase treatment resistance (Joslyn et al., 2016). Thus, likely illness trajectory can be anticipated from AAO information. This then provides a platform for clinicians to think about upcoming treatment options and discuss these in conjunction with patients and carers. In turn, this is likely to empower patients and family members by educating them about possible upcoming challenges and corresponding ameliorative approaches at an early stage.

Beyond guiding treatment however, identifying predictive factors for the onset of BD has the potential to clarify putative mechanisms underpinning the association between AAO and prognosis. For instance, initial evidence suggests that childhood abuse predicts both an early AAO and an adverse course in BD (Leverich & Post, 2006; Post et al., 2015). Yet the nature of this relationship has not been investigated. It may be that a risk factor, such as childhood abuse, precipitates an early AAO during a developmentally critical period, and this disruption to typical development results in poor long-term outcomes. In this instance, it is specifically 'early AAO' that confers a poor prognosis. Alternatively, childhood abuse (or any other risk factor) may be the driving force behind a poor clinical course, whilst independently associating with AAO.

Disentangling this relationship has implications for therapeutic strategies and early intervention, although research to date has been constrained by a lack of prospective data to determine possible causal relationships.

1.5.2.1 Mood instability

Although retrospective in nature, emerging evidence suggests that increased mood instability is present in individuals with an early AAO and might mediate the relationship between negative early-life factors and adverse clinical outcomes (Marwaha et al., 2020). Mood instability has been defined as "rapid oscillations of intense affect, with a difficulty in regulating these oscillations or their behavioural consequences" (Broome, Saunders, et al., 2015). High levels of mood instability are associated with more severe symptoms, including increased symptom severity in adult community samples with depression (Thompson et al., 2011), and children and adolescents with ADHD (Sobanski et al., 2010). Offspring at high genetic risk of BD, as well as newly diagnosed patients, self-report high levels of mood instability (Duffy, Keown-Stoneman, et al., 2019; Stanislaus et al., 2020), suggesting that mood instability may play a role in the development and onset of BD.

Consistent with this assertion, increasing evidence implicates mood instability in the development and trajectory of psychiatric disorders in general, and BD in particular (Patel et al., 2015). This is perhaps unsurprising given that fluctuations in affect (between depression and mania) are the hallmark of BD. In fact, evidence suggests that inter-episode euthymic periods are characterised by elevated mood instability (Harrison et al., 2016), and that BD is better viewed as a disorder of chronic mood instability rather than an episodic disorder with inter-episodic periods of 'wellness' (McKnight et al., 2017). Mood instability in bipolar offspring is a risk factor for the subsequent onset of BD (Hafeman et al., 2016), and is present in the prodromal phases of the disorder (Malhi et al., 2014). Notably, greater levels of mood instability have been associated

with an earlier BD AAO (Henry et al., 2008; Miklowitz et al., 2022). Younger individuals and those who have experienced childhood maltreatment are reported to experience greater mood instability than older individuals and those with no history of childhood abuse (McKnight et al., 2017; Teicher et al., 2015). Evidence also suggests that mood instability is correlated with poorer long-term outcomes such as longer duration and increased severity of mood episodes, shorter time to recurrence of episodes, decreased psychosocial functioning, increased reliance on healthcare services, and elevated use of psychotropic medications including antipsychotics and mood stabilisers (Miklowitz et al., 2022; O'Donnell et al., 2018; Patel et al., 2015; Perlis et al., 2006; Stanislaus et al., 2020). This closely parallels the picture seen in the prognosis of early-onset BD. Mood instability may therefore be of potential mechanistic relevance to the expression and clinical course of early-onset BD. To date however, no known research has specifically investigated differences in mood instability over time according to AAO subgroups. This could provide a useful insight into illness course and signal that more intensive mood-stabilising therapies may be required in individuals with early-onset.

1.6 Aims of the thesis

There is growing demand to improve treatment outcomes and intervention approaches in BD by moving beyond current nosology to define and validate more homogenous subgroups. As outlined in the current chapter, evidence suggests that AAO in BD may be a key variable used to demarcate aetiologically and phenomenologically similar subgroups. Yet, the reliability and validity of this evidence is constrained by the lack of a consistent definition for AAO, as well as the absence of clearly defined AAO groups, with no consensus of what constitutes early versus late onset in BD. These limitations must be addressed to reliably establish the utility of AAO as a clinical specifier. Consequently, the first aim of this thesis is as follows:

What is the age at onset distribution in bipolar disorder, and what constitutes early age at onset?

Accordingly, Chapter 2 is the first of four experimental chapters, and investigates if AAO in BD can be consistently divided into distinct subgroups based on the extant literature. This chapter is a systematic review examining the AAO distributions in BD and correspondingly what age range constitutes an early age-at-onset.

With a clearer foundation regarding the definition and distribution of AAO in BD, it is apt to identify premorbid factors that may predict which AAO group an individual is likely to belong to. Identifying predictive factors for BD AAO can inform early intervention and provide further evidence that these AAO groups are meaningfully distinct. Thus, the second aim of this thesis is to investigate:

What factors are associated with and predict bipolar disorder age-at-onset?

Chapter 3 employs a machine learning approach to explore what premorbid features may predict BD AAO in a well-characterised longitudinal dataset.

While Chapter 3 gives us a better understanding of what factors may predict AAO, it is yet unclear why earlier onset confers a worse clinical course. This gives rise to the following aim:

What is the relationship between early-life factors, age at onset and functional outcome in high-risk BD offspring?

Thus, Chapter 4 aims to better understand the association between premorbid features, BD AAO, and functional outcomes through mediation analysis. Prospective data from the Flourish Canadian high-risk cohort are used to disentangle this relationship, with functional outcome operationalised by global assessment of functioning scores.

Mood instability may be of possible mechanistic relevance to early onset BD and contribute to a worsened illness course. No known evidence to date has investigated differences in mood instability according to AAO. Results can provide a useful insight into the mechanisms underpinning illness course and inform the use of mood-stabilising treatment. Accordingly, Chapter 5 uses longitudinal mood monitoring data to investigate the final aim of this thesis:

To what extent is age-at-onset associated with mania and depression instability and severity in BD?

Finally, Chapter 6 provides a general discussion, where the findings of this thesis are summarised, implications discussed, and suggestions for further work are proposed.

Chapter 2. Distribution of Age at Onset in Bipolar Disorder

This chapter has been adapted from the following paper:

Bolton, S., Warner, J., Harriss, E., Geddes, J., & Saunders, K. E. (2021). Bipolar disorder: Trimodal age-at-onset distribution. Bipolar disorders, 23(4), 341-356. https://doi.org/10.1111/bdi.13016

2.1 Introduction

2.1.1 Rationale

AAO in BD has been recognised as being important in the clinical course and outcome of the disorder. Meta-analyses suggest that an early (compared to late) AAO in BD is associated with longer delays to treatment, greater severity of depression, and increased comorbidities, including anxiety and substance abuse (Agnew-Blais & Danese, 2016; Joslyn et al., 2016). Research also indicates that early-onset BD may have a stronger genetic component than late-onset BD (Geoffroy et al., 2013; Grigoroiu-Serbanescu et al., 2001; Hamshere et al., 2009; Köhler-Forsberg et al., 2020; Leboyer et al., 2005; Post et al., 2016; Preisig et al., 2016; Priebe, Degenhardt, Herms, Haenisch, Mattheisen, Nieratschker, Weingarten, Witt, Breuer, Paul, Alblas, Moebus, Lathrop, Leboyer, Schreiber, Grigoroiu-Serbanescu, Maier, Propping, Rietschel, Nöthen, et al., 2012). Given the differing clinical trajectory between early versus late onset BD, along with the likely biological variability underpinning this divergent phenotype (Geoffroy et al., 2013), it has been proposed that AAO may be a key variable in delineating more homogeneous subgroups of BD patients (Leboyer et al., 2005).

To date however, no research has systematically validated what the various AAO subgroups should be, and there is no concurrence across studies regarding what is meant by 'early onset' (Bellivier et al., 2001; Geoffroy et al., 2013). Moreover, there is no standardised definition for

AAO, with studies varyingly defining AAO as the age at: (i) onset of mood symptoms (Baldessarini et al., 2012); (ii) first episode of depression or mania meeting diagnostic criteria (Coryell et al., 2013; Etain et al., 2012; Nowrouzi et al., 2016); (iii) first treatment; or (iv) first hospitalisation (Bellivier et al., 2001).

Traditionally, AAO in BD has been conceptualised as a unimodal gaussian distribution, which parallels findings from other severe mental health disorders. Recent meta-analytic studies have found unimodal AAO distributions for schizophrenia-spectrum and other primary psychotic disorders, as well as personality disorders, with a peak AAO at 20.5 years with nearly 50% of individuals experiencing onset before the age of 25 (Solmi et al., 2022). Similar findings were reported for BD AAO, with a peak at 20.5 years and 32% of individuals experiencing onset by 25 years (Solmi et al., 2022). However, it is worth noting that the meta-analysis combined BD with other mood disorders, which raises questions about the accuracy of these results when examining BD on its own.

Indeed, evidence indicates that BD AAO can better be explained by a mixture of more than one distribution. Evidence has suggested that BD aggregates either into a bimodal distribution with two subgroups (early vs. late AAO), or a trimodal distribution with three subgroups (early vs. mid vs. late AAO) (Bauer et al., 2010; Bellivier et al., 2003; Coryell et al., 2013; Hamshere et al., 2009; Joslyn et al., 2016; Leboyer et al., 2005). However, it is not known which of these distribution modalities are more reliable and consistent, and much of the extant literature surrounding AAO in BD uses pre-defined age groupings based on the authors' judgement rather than data-driven approaches. It thus remains unclear what age range constitutes 'early-onset'. A better understanding of the distribution of age at onset in BD has the potential to anticipate disease trajectory both between and within AAO groups, provide an insight into the biopsychosocial mechanisms of illness, and guide appropriate timeframes for primary and secondary prevention

(Jones, 2013). Understanding the age at onset distribution of bipolar disorder over the life course can also inform and streamline the conduct of clinical and epidemiological research, and health service provision and planning.

2.1.2 Objective

The aim of this systematic review was to investigate AAO distributions in bipolar disorder, and correspondingly what constitutes an early age at onset. Only studies that use a data-driven approach to define AAO groups were included in data synthesis, as segregating BD into AAO groups using pre-defined cut-offs is an inherently biased approach. One of the most popular analysis approaches for determining AAO groups is admixture analysis, as it explores the theoretical model that best fits the observed distribution of a continuous variable. Based on the evidence outlined above, it is expected that BD AAO will not be a unimodal gaussian distribution but instead be made up of a mixture of distributions, the number of which may depend on the studies' diagnostic criteria and location.

2.2 Methods

2.2.1 Eligibility Criteria

This study was pre-registered via PROSPERO (https://bit.ly/333fs2V). All studies had to meet four criteria: 1) include participants who were recruited with a primary diagnosis of BD I, II or not-otherwise-specified (NOS); 2) report on the distribution of bipolar disorder AAO using a data-driven analysis approach (e.g. admixture analysis); 3) be an original article including epidemiological, cohort, longitudinal, cross sectional, survey, or observational studies; 4) be an English-language article. Animal research, single case studies, duplicates, conference abstracts or articles with unobtainable missing data were excluded.

2.2.2 Search Strategy

Searches of the following databases were carried out in February 2019: Cochrane Central Register of Controlled Trials (CENTRAL; Wiley interface), PsycINFO, MEDLINE (OVID interface, 1948 onwards), Embase (OVID interface, 1980 onwards), Cumulative Index of Nursing and Allied Health Literature (CINAHL), and Scopus. Grey literature was also searched via Proquest Dissertations and Theses, BIOSIS Previews, and Google Scholar.

Search strategies were developed using medical subject headings (MeSH) and text words related to bipolar disorder, age at onset, and study type. The full search strategy is detailed in Appendix A.1. The syntax and subject headings of the search strategies were adapted for each database, and Boolean operators and truncation were used to extend the search terms (Appendix A.2.). No date limits were imposed on the searches.

2.2.3 Study selection

The web-based systematic review software, DistillerSR (Evidence Partners, 2014) was used to complete screening and data extraction. Two reviewers (SB, JW) independently screened titles and abstracts. A third reviewer (KS) resolved any eligibility conflicts. Following title and abstract screening, a full text review of eligible articles was conducted. Where necessary, additional information from study authors was sought to resolve questions about eligibility and obtain missing data. Included studies were not quality assessed, as accepted standards of quality assessing non-randomised studies are lacking (Mueller et al., 2018), and the included articles employed a broad range of study designs with diverging methodologies and reporting standards.

2.2.4 Data analysis

Data from eligible studies was extracted using a standardised data extraction form. This included data on diagnoses, recruitment strategies, demographics, and details of age at onset groups,

including means, standard deviations (SDs) and age ranges. Summary statistics were computed from the extracted data for each study describing participant characteristics (sample size, age range and gender ratio); diagnostic criteria used; age at onset definition; recruitment settings (clinic, community, hospital); and study locations. Two studies (Javaid et al., 2011; Nowrouzi et al., 2016) recruited mixed samples which included participants with schizoaffective disorder; where possible, only participants with a BD diagnosis were included in analyses and samples with schizoaffective disorder participants were excluded.

Studies were separated into those reporting a trimodal AAO distribution, a bimodal distribution, and those investigating cohort effects on AAO. For each study, the average AAO per subgroup was extracted – for those studies reporting a trimodal AAO distribution the mean and SD for the early-, mid- and late-onset groups were extracted, and for those studies reporting a bimodal AAO distribution means and SDs for the early- and late-onset groups were extracted. These averages were used to plot probability density functions and boxplots for each AAO group in studies reporting a trimodal versus bimodal AAO distribution. This was done using the ggplot2 (Wickham, 2016) data visualisation package in RStudio (version 1.2.1335) (RStudio Team, 2018) – the analysis code can be found on the Open Science Framework (OSF) (https://osf.io/5c89s/). Data are also openly available via the OSF (Bolton, 2020).

2.3 Results

The search produced 14129 results. After duplicates were removed, the titles and abstracts of 9454 articles were screened for relevance and 74 articles were considered eligible for full text review (PRISMA Diagram Figure 1); see Appendix A.3. for a reference list of studies excluded at full-text review. Twenty-four articles met full-text eligibility criteria, and 21 articles were included in data synthesis. Three of the 24 eligible studies were excluded (Holtzman et al., 2016; Manchia

et al., 2010; Massat et al., 2007) due to missing data, which were unobtainable after contacting the authors.

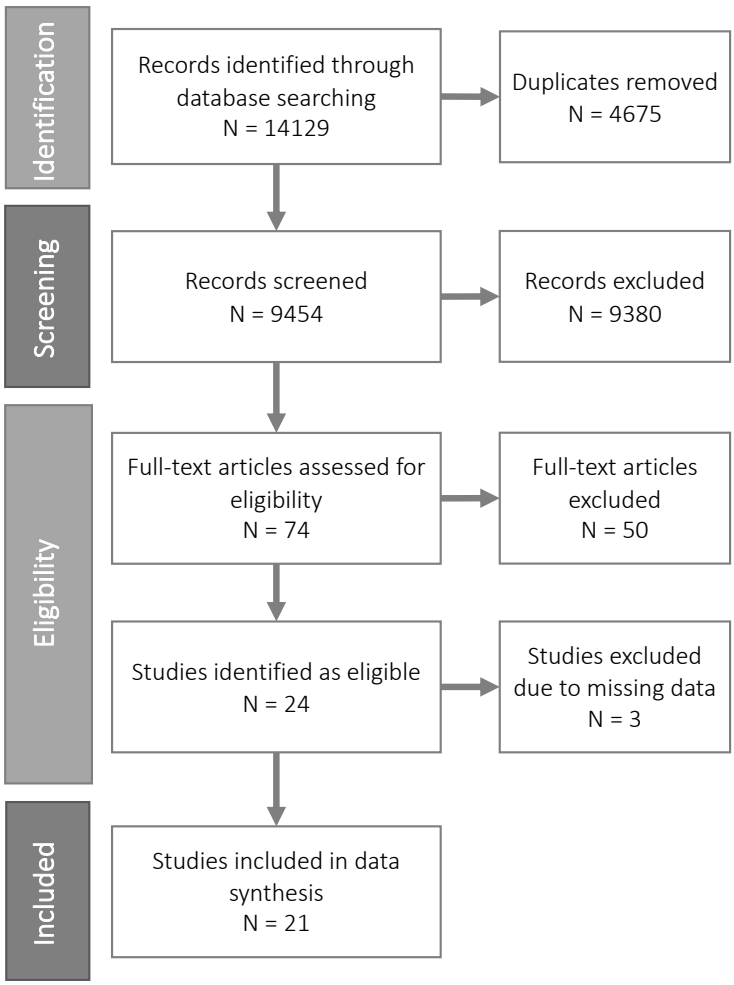

Figure 1. PRISMA flowchart of included studies.

2.3.1 Study Characteristics

All included studies were conducted from 2001-2017, with the majority (n = 15, 71%) published from 2009 onwards.

2.3.2 Participants

Across all studies there were a total of 22904 bipolar disorder participants, with an average sample size of 1094 participants per study. In total there were 22165 (96.78% of total) participants with a diagnosis of BDI, 653 (2.85%) with BDII, 12 (0.05%) with BD-NOS and 74

(0.32%) with schizoaffective disorder. There were more female than male participants, with an average of 59.9% female participants across all studies.

2.3.2.1 Age of participants at study entry

Fifteen studies reported age ranges or average age of their samples; with an overall average age of 43.2 years.

2.3.2.2 Diagnostic Criteria

Thirteen studies (62%, n = 13) used DSM-IV criteria alone to determine a bipolar disorder diagnosis (Azorin et al., 2013; Bauer et al., 2010, 2015; Bellivier et al., 2001, 2003, 2014; Biffin et al., 2009; González Pinto et al., 2009; Grigoroiu-Serbanescu et al., 2014; Hamshere et al., 2009; Javaid et al., 2011; Kennedy et al., 2005; Manchia et al., 2017). Two studies used DSM-IV or ICD-10 criteria (Golmard et al., 2016; Tozzi et al., 2011), one used DSM-IV or Research Diagnostic Criteria (RDC) (Ortiz et al., 2011), one used DSM-IV or DSM-III-R criteria (Nowrouzi et al., 2016), one used both DSM-III-R and RDC (Lin et al., 2006), two used RDC only (Manchia et al., 2008; Severino et al., 2009), and one used case records only (Lehmann & Rabins, 2006).

2.3.3 Age at Onset Definitions

Heterogeneous definitions of AAO were used across studies including: age at which diagnostic criteria for an affective episode were first met according to medial case-notes, interviews, or self-report (Azorin et al., 2013; Bauer et al., 2010, 2015; Bellivier et al., 2001, 2003, 2014; Biffin et al., 2009; Grigoroiu-Serbanescu et al., 2014; Lin et al., 2006; Manchia et al., 2008, 2017; Ortiz et al., 2011; Severino et al., 2009; Tozzi et al., 2011); age at first impairment due to an affective episode according to self-report (Hamshere et al., 2009); age at first contact with psychiatric services for symptoms of mania (Javaid et al., 2011; Kennedy et al., 2005); age at first treatment for an affective disorder (González Pinto et al., 2009); and age at first psychiatric hospitalisation

(Lehmann & Rabins, 2006). Across all studies, AAO was determined retrospectively using information gathered from medical records and/or interviews with participants and their relatives.

2.3.4 Recruitment Setting

Seven studies recruited patients from a clinic setting only (Bauer et al., 2010; Biffin et al., 2009; Grigoroiu-Serbanescu et al., 2014; Manchia et al., 2008, 2017; Nowrouzi et al., 2016; Severino et al., 2009), two from community settings only (Hamshere et al., 2009; Ortiz et al., 2011), and two from inpatient hospital settings only (Azorin et al., 2013; Lehmann & Rabins, 2006). Three studies recruited from both the clinic and the community (Bauer et al., 2015; Golmard et al., 2016; Tozzi et al., 2011), three from both the clinic and hospital setting (Bellivier et al., 2001; González Pinto et al., 2009; Lin et al., 2006), and four studies recruited from the hospital, clinic and the community (Bellivier et al., 2003, 2014; Javaid et al., 2011; Kennedy et al., 2005).

2.3.5 Study Locations

The largest of the included studies collected data on 4037 bipolar patients across 36 collection sites in 23 countries throughout Asia, Africa, Europe, North and South America, and Australia (Bauer et al., 2015). Of the remaining studies, eleven were conducted in Europe (Azorin et al., 2013; Bellivier et al., 2001, 2003; Golmard et al., 2016; González Pinto et al., 2009; Grigoroiu-Serbanescu et al., 2014; Hamshere et al., 2009; Kennedy et al., 2005; Manchia et al., 2008, 2017; Severino et al., 2009), six in North America (Bauer et al., 2010; Javaid et al., 2011; Lehmann & Rabins, 2006; Lin et al., 2006; Nowrouzi et al., 2016; Ortiz et al., 2011), one in Australia (Biffin et al., 2009), and two articles combined data from collection sites in both North America and Europe (Bellivier et al., 2014; Tozzi et al., 2011).

2.3.6 Age at Onset Distributions

There were three separate types of distributions found for bipolar disorder age-at-onset across the 21 articles. Fourteen studies showed a trimodal distribution (Azorin et al., 2013; Bellivier et al., 2001, 2003, 2014; Biffin et al., 2009; González Pinto et al., 2009; Grigoroiu-Serbanescu et al., 2014; Hamshere et al., 2009; Lin et al., 2006; Manchia et al., 2008; Nowrouzi et al., 2016; Ortiz et al., 2011; Severino et al., 2009; Tozzi et al., 2011), five a bimodal distribution (Bauer et al., 2010; Javaid et al., 2011; Kennedy et al., 2005; Lehmann & Rabins, 2006; Manchia et al., 2017), and two studies examined cohort effects on AAO (Bauer et al., 2015; Golmard et al., 2016).

2.3.6.1 Trimodal Age at Onset Distribution

Fourteen (67%) of the included 21 articles, including 59% (n = 13549) of all participants, reported a trimodal age-at-onset distribution with three subgroups: early-onset, mid-onset, and late-onset (Table 1, Page 50). Eight of these studies were conducted in Europe, three in America, two in both North America and Europe, and one in Australia. Of the fourteen studies, nine included participants with a diagnosis of BDI only, three with a diagnosis of BDI, BDII or BD-NOS, and two with a diagnosis of BDI, BDII or schizoaffective disorder.

Of the two studies including schizoaffective disorder patients (Javaid et al., 2011; Severino et al., 2009), Javaid et al. (2011) report their findings including and excluding participants with schizoaffective disorder. The results of the 'bipolar only' sample was used in analyses.

Two of these fourteen studies had a partial overlap in their samples (Manchia et al., 2008; Severino et al., 2009) (Table 1). Manchia et al. (2008) recruited 181 BDI participants from the Lithium Clinic of the Clinical Psychopharmacology Centre, University of Cagliari, Italy. Severino et al. (2009) used these same BDI participants, and additionally recruited 45 participants with BDII and 74 participants with a diagnosis of schizoaffective disorder. To account for this sample

overlap and the inclusion of participants with schizoaffective disorder, these papers were excluded one by one from analyses. Excluding these studies did not make a significant difference to results (Appendix A.4.).

Across these fourteen studies the average age of early-, mid- and late-onset was: 17.3 years (SD = 1.19); 26.0 years (SD = 1.72); and 41.9 years (SD = 6.16). Results suggest that most BD cases occurred in the early-onset range, with an average of 45% out of a total 13626 participants displaying early-onset, compared to 35% mid-onset and 20% late-onset (Figure 2).

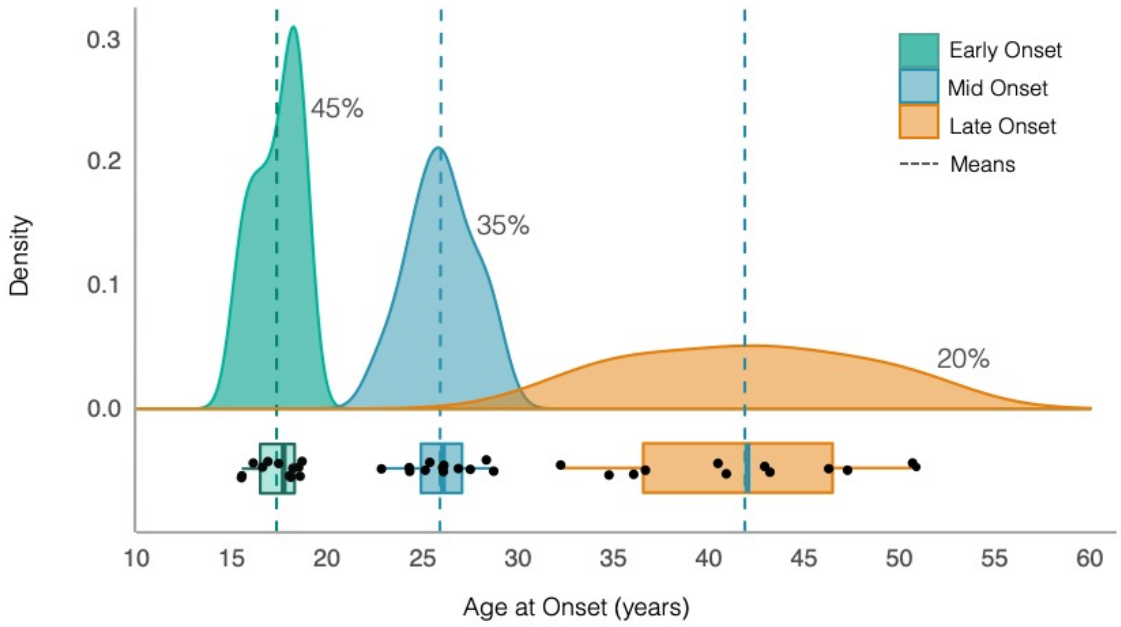

Figure 2. Trimodal age-at-onset (AAO) distribution in bipolar disorder. This figure displays the density function for each AAO group across all 14 studies, with the mean AAO per group depicted as dashed vertical lines. Under each density plot, boxplots display interquartile ranges (coloured boxes), medians (solid vertical lines), and the minima and maxima (whiskers: coloured horizontal lines).

2.3.6.2 Bimodal Age at Onset Distribution

Five studies (24%), representing 6% (n = 1422) of all participants, described a bimodal age at onset distribution with two subgroups: early-onset and late-onset (Table 2). Two of these studies

were conducted in Europe and three in North America. Three of the studies included participants with a diagnosis of BDI only, and two included those with a diagnosis of BDI, BDII or BD-NOS.

Across these five studies the average age of early-onset was 22.5 years (SD = 7.32) and late-onset was 40.8 years (SD = 16.89). Results indicated that an average of 63% out of a total of 1422 participants across the five studies displayed early-onset, compared to 37% late-onset (Figure 3).

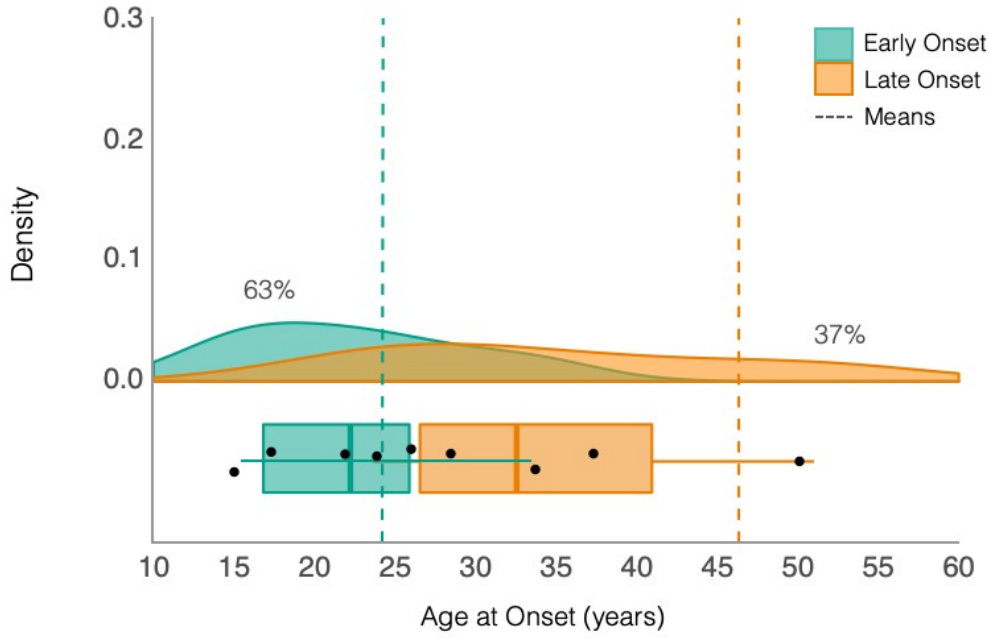

Figure 3. Bimodal age-at-onset (AAO) distribution in bipolar disorder. This figure displays the density function for each AAO group across all 5 studies, with the mean AAO per group depicted as dashed vertical lines. Under each density plot, boxplots display interquartile ranges (coloured boxes), medians (solid vertical lines), and the minima and maxima (whiskers: coloured horizontal lines).

2.3.6.3 Effect of Birth Cohort

The remaining two of the 21 included articles examined cohort effects on AAO (Table 3). Both studies examined the effect of birth cohorts on age-at-onset in samples of BDI patients (total n = 7933) recruited from clinical and community settings.

When the effect of birth cohort was not modelled, both studies found a trimodal bipolar disorder AAO distribution. When birth cohort was adjusted for, both studies reported that a

bimodal distribution fit the data better. Across all cohorts in both studies, the overall mean ages for early-, mid- and late- onset were 18.7 (SD = 1.52), 25.5 (SD = 1.47), and 29.4 (SD = 2.21) years, representing an average of 48.5%, 12.0% and 39.5% respectively.

Table 1. Details of the studies which report a trimodal age-at-onset distribution in bipolar disorder. Age bounds for the subgroups are provided. Numbers reported to one decimal place.

Study	N	Country	Diagnosis	Recruitment	Definition of age-at-onset	Method of determining AAO	Mean age of sample at study entry (SD)	Early-onset		Mid-onset		Late-onset	
								Upper age limit	Mean (SD), %	Lower and upper age limits	Mean (SD), %	Lower age limit	Mean (SD), %
Azorin et al. (2013)	1082	France	DSM-IV BDI	The EPIMAN II Mille study, a multi-centre naturalistic study conducted in 19 French medical centres	Age at which the patient first met the Research Diagnostic Criteria for an affective episode	Medical records. Structured interviews with patients and relatives.	42.9 (13.7)	20	18.6 (2.1), 19%	21-29	24.3 (5.3), 38.9%	30	36.7 (10.8), 42%
Bellivier et al. (2001)	211	France	DSM-IV BDI	Consecutive inpatients and outpatients in France	Age at which DSM-IV criteria for an affective episode were first met	Medical records. Diagnostic Interview for Genetic Studies	42.4 (14.8)		16.9 (2.7), 41.4%		26.9 (5.0), 41.8%		46.2 (8.0), 16.6%
Bellivier et al. (2003)	579	France, Switzerland Germany Ireland	DSM-IV BDI	Inpatients and outpatients across four countries	Age at which DSM-IV criteria for an affective episode were first met	Medical records. Diagnostic Interview for Genetic Studies	Not reported		17.4 (2.3), 27.9%		25.1 (6.2), 50.1%		40.4 (11.3), 21.9%

Bellivier et al. (2014)	5891	Europe and USA	DSM-IV BDI	Recruited for genetic, pharmacological and observational studies across 18 sites in Europe (N = 3616, incl. participants from the EMBLEM study) and from the Stanley Centre Bipolar Registry in the USA (N = 2275)	Age at which DSM-IV criteria for an affective episode were first met	Semi-structured interview	44.0 (13.2) 40.8 (11.7)	Europe USA	19 (2.7), 24.8% 14.5 (4.9), 63.0%	27.2 (6.3), 50.7% 26.5 (7.6), 28.5%	41.8 (10.7), 24.5% 39.5 (12.5), 8.5%
Biffin et al. (2009)	162	Australia	DSM-IV BDI	Recruited as part of the Bipolar Comprehensive Outcome Study (BCOS) in Melbourne, Australia	Self-reported age at which episode of mania or depression first met diagnostic criteria	Questionnaire developed by the research team	Early:38.7 (12.6) Mid: 43.7 (12.6) Late: 58.9 (11.5)		15.5 (2.7), 44.4%	26.1 (4.8) 48.1%	50.6 (9.0), 7.4%
González Pinto et al. (2009)	169	Spain	DSM-IV BDI	Inpatients and outpatients who were receiving treatment in Alava, a Spanish province.	The age at first treatment for an affective disorder	Medical records. Semi-structured SCID-P interview. Emergency service records. Interviews with relatives.	46.0 (16.0)		18.2 (2.0), 34.0%	26.1 (5.5), 44.0%	50.9 (9.1), 22.0%

Hamshere et al. (2009)	1369	UK	DSM-IV BDI	Large-scale genetic epidemiological study. Recruited via community mental health teams, general practitioner surgeries, and patient support organisations across the UK.	Age at first impairment due to an affective episode according to self-report	Medical records. Schedules for Clinical Assessment in Neuropsychiatry (SCAN).	Age range: 6 to 73 years	22	18.7 (3.7), 47.1%	25-37	28.3 (5.5), 38.8%	40	43.3 (9.1), 14.3%
Lin et al. (2006)	211	USA	DSM-III-R BD-I	NIMH Genetics Initiative for Bipolar Disorder (McInnis et al., 2003)	Self-reported age at which episode of (hypo)mania or depression first met diagnostic criteria	Medical records. Diagnostic Interview for Genetic Studies.	Age range: 0 to >61 years	21	16.6 (5.1), 79.7%	22-28	26.0 (1.4), 7.2%	28	34.7 (6.6), 13.1%
Manchia et al. (2008)	181	Sardinia	RDC-BDI	Recruited from the Lithium Clinic of the Clinical Psychopharmacology Centre, University of Cagliari, Italy	Age at first reliably diagnosed (hypo)manic or depressive episode	Medical records. Semi-structured interview	42.8 (14.8)	20	18.1 (2.3), 36.0%	21-33	24.3 (5.3), 39.0%	34	41.0 (11.5), 25.0%
Nowrouzi et al. (2016)	194	Canada	DSM-III-R or DSM-IV BDI BDII	Recruited from four clinical sites across Ontario, Alberta and British Columbia, Canada	Unknown	Unknown	25.2 (9.51), range 14-65 years		18.0 (2.9), 69.0%		28.7 (3.5), 22.0%		47.3 (7.8), 9.0%

Ortiz et al. (2011)	379	Canada	DSM-IV or RDC BDI BDII	Recruited through the Maritime Bipolar Registry, a community-based project in the Maritime Provinces of Canada (Hajek et al., 2005)	Age at which DSM-IV criteria for an affective episode were first met (according to medial case-notes and interviews)	Medical records. Schedule for Affective Disorders and Schizophrenia, Lifetime version	50.1 (12.7)	19	15.5 (2.0), 29.0%	20-31	22.8 (4.6), 37.1%	32	36.1 (10.1), 33.4%
Severino et al. (2009)	300	Italy	RDC BDI BDII Schizo-affective bipolar manic type	Outpatients at the Lithium Clinic of the Clinical Psychopharmacology Centre, University of Cagliari, Italy	Age at first reliably diagnosed (hypo)mania or depression according to RDC criteria (using medical records)	Medical records. Semi-structured interview	42.9 (14.8)	22	18.5 (2.6), 43.0%	23-37	27.5 (6.1), 42.0%	38	43.0 (10.8), 15.0%
Tozzi et al. (2011)	964	UK and Canada	DSM-IV or ICD-10 BD-I BD-II	Recruited across three sites: Toronto (Canada) at the Centre for Addiction and Mental Health, London (UK) at the Institute of Psychiatry, and Dundee (UK) at the University of Dundee	Self-reported age at which episode of mania or depression first met diagnostic criteria	Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview	47.2 (12.1), range 18-84 years	24	16.1 (4.2), 64.0%	25	25.4 (2.5), 6.0%	26	32.2 (9.5), 30.0%

							43.4 (13.4)	Romania			
								17.6 (3.2), 43.0%	N/A	20-21	29.9 (8.2), 57.0%
								17.3 (2.8) 33.0%	25.6 (6.3), 46.0%		40.9 (5.3), 21.0%
Grigoroiu-Serbanescu et al. (2014)[†]	1857	Germany Poland Romania	DSM-IV BDI	Consecutive inpatients recruited at three sites:	Age at which DSM-IV criteria for an affective episode were first met	Medical records. Semi-structured interview with patients and relatives	44.0 (13.4)	Germany			
								20.7 (6.0), 67.0%	N/A	25	38.4 (6.5), 33.0%
								19.3 (5.5), 46.0%	28.5 (7.1), 41.0%		45.4 (4.7) 13.0%
							45.0 (14.1)	Poland			
								20.47 (3.91), 65%	N/A	24-25	33.57 (9.12), 35%
								20.7 (3.7), 44.0%	33.0 (6.1), 45.0%		49.0 (5.3), 11.0%

[†] Two component and three component models fitted the data equally well.

Table 2. Details of the studies reporting a bimodal age-at-onset distributions in bipolar disorder. Age bounds for the subgroups are provided. Numbers reported to one decimal place.

Study	N	Country	Diagnosis	Recruitment	Definition of age-at-onset	Method of determining AAO	Mean age of sample at study entry (SD)	Early-onset		Late-onset
								Upper age limit	Mean (SD), %	Mean (SD), %
Bauer et al. (2010)	270	USA	DSM-IV BDI BDII	Consecutive outpatients recruited from US clinics	Age at which episode of (hypo)mania or depression first occurred	Semi-structured interview	Age range: ≤12 to ≥30 years		15.1 (4.7), 68.1%	27.5 (10.2), 31.9%
Javaid et al. (2011)	353	Canada	DSM-IV BD or schizoaffective disorder	Recruited through newspaper advertisements and hospital clinic referrals from the Toronto region.	Age at first diagnosis of a major mood episode or mood-related psychotic symptoms	Medical records. Structured Clinical Interview. Interviews with relatives	Whole sample: Males: 35 (10.7) Females: 36 (10.7)	22	Incl. schizoaffective disorder (n = 353) 16.9 (3.6) Bipolar only (n = 318) 16.5 (3.1)	24.4 (9.2) 23.7 (8.9)
Kennedy et al. (2005)	246	UK	DSM-IV BDI, first manic episode	Inpatient and outpatient cases of first-episode mania presenting to psychiatric services in Camberwell, southeast London, between 1965 and 1999 were identified	Age at which first contact with psychiatric services was sought for mania	Medical records	Age range: 16 to ≥76	40	25.6 (6.0), 78.0%	51.0 (16.3), 22.0%

Lehmann & Rabins (2006)	73	USA	BDI	Inpatients aged >65 admitted to Johns Hopkins Hospital psychiatric service, 1990-1995	Age at first psychiatric hospitalisation	Medical records	≥65	45	33.2 (7.4), 52.0%	64.4 (10.8), 48.0%
Manchia et al. (2017)	515	Italy	DSM-IV BDI BDII BD-NOS	Recruited at two sites in Italy: Anxiety and Mood Disorders Unit, University of Turin, and at the Department of Psychiatry, University of Naples	Age at which DSM-IV criteria for an affective episode were first met	Medical records. Semi-structured interviews with patients and first-degree relatives	47.2 (13.0)	32 28 30	BDI 22.6 (4.8), 67% BDII 20.9 (4.1), 44.0% Whole Sample 21.9 (4.6), 55.0%	35.1 (10.1), 33.0% 38.2 (11.8), 56.0% 37.6 (11.5), 45.0%

Table 3. Details of the studies investigating cohort effects on age-at-onset distributions in bipolar disorder. Numbers reported to one decimal place.

Study	N	Country	Diagnosis	Recruitment	Definition of age-at-onset	Method of determining AAO	Mean age of sample at study entry (SD)	Cohort	Early-onset Mean (SD), %	Mid-onset Mean (SD), %	Late-onset Mean (SD), %
Bauer et al. (2015)	4037	23 countries across Asia, Africa, Australia, Europe, North and South America	DSMI-IV BDI	Data obtained retrospectively from 36 collection sites for a study of the impact of solar insolation on the age of onset of bipolar disorder	Age at first episode of depression, mania or hypomania meeting DSM-IV criteria (according to medical case notes and interviews).	Medical records and semi-structured interviews	48.1 (14.5)	Whole sample without birth cohorts (n = 4037) With birth cohorts incl. in model (n = 4037): born <1940, 1940-1959, >1959 Youngest cohort, born >1959 (n = 2550)	17.2 (3.2), 41.7% 20.7 (5.8), 62.1% 18.1 (3.7), 56.9%	23.9 (5.1), 24.7% N/A N/A	32.20 (12.0), 33.6% 30.1 (10.4), 37.9% 25.8 (8.4), 43.1%
Golmard et al., 2016)	3896	Belgium Denmark Finland France Germany Greece Ireland	DSM-IV or ICD-10 BDI	Inpatients and outpatients recruited for participant in genetic studies, and patients recruited for	Age at which DSM-IV criteria for an affective episode were first	Medical records. And semi-structured clinical interviews	44.0 (13.3)	Whole sample born >1960 Whole sample born ≤1960	20.6 (3.7), 65%	26.8 (1.7), 26% 25.9 (1.8), 32.8%	29.8 (0.5), 9% 29.8 (0.5), 17.6%

	Italy The Netherlands Norway Portugal Spain Switzerland and the UK	the EMBLEM study, a multicentre study conducted in 14 different European countries between 1993 to 2008	met (according to medial case-notes and interviews)	Matched for age at interview (n=125): Born >1960 Born ≤1960	19.3 (3.0), 49.7% 18.2 (2.5), 48% 16.9 (0.9), 16%	30.9 (5.3), 52% 27.1 (6.9), 84%

2.3.7 Age at onset distributions by study location and diagnostic criteria

Prior research has suggested that study location and BD diagnosis may influence AAO distributions (Dell'Osso et al., 2016; Dubicka et al., 2008; Duffy, 2007; James et al., 2014; Post et al., 2017; Schürhoff et al., 2000).

2.3.7.1 Location

Of the eleven studies conducted in Europe, eight found a trimodal AAO distribution, two found a bimodal distribution and one reported cohort effects. There was an even split between studies reporting bi- and tri-modal distributions (3 vs. 3) in North American samples. Studies conducted in both Europe and North America found a trimodal AAO distribution. The one study conducted in Australia reported a trimodal distribution.

2.3.7.2 Diagnosis

Two thirds of studies included participants with a diagnosis of BDI only (n = 14, 67%). Nine of these studies (64%) found a trimodal AAO distribution, compared to three reporting a bimodal distribution (21%). Five studies (25%) recruited samples with BDI, BDII and BD-NOS. Three of these studies reported a trimodal distribution and two a bimodal distribution. Two studies included schizoaffective disorder as a diagnostic category, and both studies reported a trimodal AAO distribution.

There was no significant effect of study location or diagnostic category on the reported AAO distribution (bimodal or trimodal) (see Table 4). The Freeman-Halton extension of the Fisher exact probability test was carried out to examine this. Both tests were non-significant (Location: two-tailed Fisher's exact test, P = 0.497; Diagnosis: two-tailed fishers exact test, P = 0.598)

Table 4. Age-at-onset distributions according to location in which the study was conducted and diagnostic category.

Location	Number of studies	AAO Distributions		
		Bimodal	Trimodal	Birth Cohort
Europe	11	2	8	1
North America	6	3	3	0
Australia	1	0	1	0
Europe and North America	2	0	2	0
Worldwide	1	0	0	1
Total	21	5	14	2
Diagnostic Category				
BDI	14	3	9	2
BDI and BDII	5	2	3	0
BDI, BDII and Schizoaffective Disorder	2	0	2	0
Total	21	5	14	2

2.4 Discussion

This is the first systematic review of age at onset (AAO) in bipolar disorder. The aim of this review was to provide a more reliable understanding of the AAO distribution in BD, including how 'early-onset' should be defined. Results demonstrate that a trimodal AAO distribution (early-, mid- and late-onset subgroups), compared to a bimodal distribution (early- versus late-onset), is found across a broader range of bipolar disorder diagnoses (BDI, BDII and schizoaffective disorder) and a greater number of patients (59% vs. 6% of all participants – excluding cohort studies). This provides compelling evidence to suggest that bipolar disorder onsets during early, mid, or late life, with the majority (45%) of participants displaying an average age at onset of 17.3 years (SD = 1.91).

2.4.1 Defining early-onset

These findings offer a more robust understanding of when bipolar disorder is likely to manifest across the life course, and correspondingly provide a benchmark for what can be considered 'early-onset' bipolar. In accordance with the present results, it is appropriate to propose that a distinction should be made between 'early-life onset' and 'early-onset'. The results of this systematic review indicate that the majority of BD cases onset in early life, from the ages of 14-21 years, with an average onset of 17.3 years. As it is customarily used, the term 'early-onset' implies an 'earlier than expected AAO', whereas throughout the included studies the 'early-onset' group is the most common age range for the onset of BD. Therefore, the term early-onset should be reconceptualised to represent life-stage rather than as a comparator. 'Early-onset' in the sense it is traditionally referred to is thus best described as onset before the age of 14 years. This distinction has the potential to aid the interpretation of existing treatment guidelines, which currently offer recommendations for treating 'early-onset and early-stage' BD without providing corresponding definitions (Chia et al., 2019).

The diagnosis of pre-pubertal BD, which is prevalent in North America (Duffy, 2007; Wozniak, 2003), has long been viewed as contentious due to high rates of comorbidities and elevated levels of symptom overlap with other juvenile psychiatric disorders (Serra et al., 2017; Youngstrom et al., 2008). The current findings do not directly refute the diagnosis of paediatric BD, but they do suggest that prepubertal onset is rare. This assertion is strengthened as the included studies used samples from both Europe and North America and is concordant with a recent meta-analysis reporting no differences in rates of youth BD between North American and European samples (van Meter et al., 2019). The lack of support for childhood onset may reflect the low diagnostic stability associated with very-early-onset BD. Evidence from longitudinal studies of high-risk offspring suggests that manic-like symptoms in very young children without a confirmed history of BD are not predictive of a later BD diagnosis (Duffy, Vandeleur, et al., 2017).

Additionally, epidemiological findings indicate that individuals diagnosed with BD-NOS in childhood do not go on to receive an adult BD diagnosis (Parry et al., 2018; Stringaris et al., 2010). As the included studies assessed AAO retrospectively in adult samples with a confirmed BD diagnosis, any individuals that received a diagnosis of childhood BD which did not persist into adulthood will have been overlooked.

A corollary to forming a more robust definition of 'early-onset' BD is that clinical trajectory can be better anticipated, as early-life-onset is thought to confer a more severe and remitting course (Agnew-Blais & Danese, 2016; Joslyn et al., 2016). For instance, early-onset BD is associated with comorbid anxiety disorders and substance abuse (Agnew-Blais & Danese, 2016; Larsson et al., 2013); clinicians should be mindful of this when assessing and treating early-onset patients. Demarcating these AAO groups thus has implications for treatment provision, with the potential to guide appropriate junctures for intervention across the lifespan.

2.4.2 Mid and Late-life-onset

While 45% of cases onset in the 'early' group, the second most common AAO group was the 'mid-onset' subgroup, with 35% of cases onsetting from an age range of early 20s to early 30s, exhibiting an average AAO of 26 years. In contrast, only 20% of cases were deemed 'late-life-onset' of over 40 years of age (Figure 2). This indicates that the 'late-onset' subgroup may be an aetiologically distinct form of the same disorder, as suggested by prior research (Schouws et al., 2009; Schürhoff et al., 2000). However, late-onset BD may have been underreported in the included studies as there was a sizeable skew towards younger samples (with an average age at study entry of 43.2 years). Additionally, a BD diagnosis in older age may be masked or missed in favour of more prevalent later-life disorders with psychiatric symptoms (e.g., frontotemporal dementia), thus obscuring the true rate of late-onset BD.

2.4.3 Putative Mechanisms

The current results indicate that a three-component model (early-, mid-, late-onset) best describes the AAO distribution of BD. As with most psychiatric disorders, the interaction between genes and environment is likely to underpin the manifestation of this trimodal distribution in bipolar disorder AAO.

There is strong evidence for a genetic predisposition in BD, with heritability estimates ranging from 60 to 85%, but the influence of genetics on AAO in bipolar is comparatively under-studied and results remain inconclusive (Burmeister et al., 2008; Priebe, Degenhardt, Herms, Haenisch, Mattheisen, Nieratschker, Weingarten, Witt, Breuer, Paul, Alblas, Moebus, Lathrop, Leboyer, Schreiber, Grigoroiu-Serbanescu, Maier, Propping, Rietschel, Nöthen, et al., 2012). Initial evidence suggests that there is genetic homogeneity within AAO subgroups and heterogeneity between groups (Etain et al., 2006; Grigoroiu-Serbanescu et al., 2001; Mathieu et al., 2010). It has been proposed that early-onset BD may be a more heritable form of the disorder. For instance, studies demonstrate that familial risk is higher for relatives of those with early-onset, early-onset probands have more early-onset relatives, and there are differences in transmission patterns between early- and late-onset groups (Baron et al., 1981; Geoffroy et al., 2013; Grigoroiu-Serbanescu et al., 2001; Hamshere et al., 2009; Leboyer et al., 2005;Post et al., 2016; Priebe, Degenhardt, Herms, Haenisch, Mattheisen, Nieratschker, Weingarten, Witt, Breuer, Paul, Alblas, Moebus, Lathrop, Leboyer, Schreiber, Grigoroiu-Serbanescu, Maier, Propping, Rietschel, Nöthen, et al., 2012).

Genetics do not explain the whole picture however, and there are environmental and neurobiological factors that are thought to interact with various susceptibility genes to influence the AAO of BD (Nassan et al., 2020). For instance, exposure to childhood trauma is thought to play a role in early-onset. Evidence indicates that the presence of childhood trauma interacts

with genes that are involved in pathways relating to neuroplasticity, serotonergic neurotransmission, inflammation, calcium signalling and circadian rhythms to decrease AAO (Anand et al., 2015; Benedetti et al., 2008, 2014; Etain et al., 2015; Oliveira et al., 2015). While still understudied, it is also thought that exposure to childhood trauma may affect the hypothalamic-pituitary-adrenal (HPA) axis via epigenetic changes to stress regulatory genes, and that such epigenetic effects may play a role in the mechanism underlying early AAO in BD (Aas et al., 2014, 2016; Duffy, Goodday, et al., 2019; Klengel et al., 2013; Miller et al., 2013; Perroud et al., 2016; Petronis, 2003; Roth et al., 2009). Childhood trauma is also associated with AAO independent of these genetic factors. Evidence suggests a dose effect of exposure to childhood trauma on the AAO of BD, with physical and sexual abuse, as well as verbal abuse, family conflict and emotional and physical neglect being significantly associated with an earlier AAO (Agnew-Blais & Danese, 2016; Daruy-Filho et al., 2011; Larsson et al., 2013; Maniglio, 2013; Post et al., 2015).

Other candidate environmental risk factors for the subsequent onset of BD include substance abuse, decreased socioeconomic status, sleep disturbances and comorbid vascular conditions (Geoffroy et al., 2013; Ritter et al., 2015; Strakowski, 2000). These factors, unlike childhood trauma, are not unique to early-life and therefore may be expressly involved in the aetiology and manifestation of mid- and late-onset groups. Perhaps most relevant to the mid-onset subgroup (onset in 20s to early 30s) is the phenomenon of post-partum BD. During this time women are at increased risk for mood episodes compared with non-postpartum periods, and childbirth has been reported as one of the most potent triggers for mania or hypomania (Jones & Craddock, 2005; Tsuchiya et al., 2003). It is not yet understood why childbirth is a specific trigger for manic onset, but it has been suggested that immune system dysregulation, puerperal hormones and genetic factors may activate disease pathways (Bergink, 2016; Jones & Craddock, 2005). Late-onset bipolar disorder is associated with increased rates of cerebrovascular disease, more

medical and psychiatric comorbidities, and a weaker family history of psychiatric problems (Cassidy & Carroll, 2002; Hays et al., 1998). However, without employing detailed prospective longitudinal methodologies, it is unclear whether all these environmental factors are a cause or consequence (or both) of incipient BD.

2.4.4 Strengths and Limitations

This is the only known systematic review investigating age at onset in bipolar disorder. To ensure all relevant studies on BD AAO were captured a search strategy with broad criteria was used and several different databases and grey literature searches were included. Risk of bias was unable to be assessed due to the broad range of reporting standards and methodologies used in the included studies.

Several limitations must be considered when interpreting the findings. It has been suggested that admixture analysis is sensitive to the sample size and the characteristics of the data (Montlahuc et al., 2017) a bimodal AAO distribution had smaller sample sizes on average compared to those reporting a trimodal AAO distribution. Interestingly, both cohort studies found a bimodal AAO distribution when they included birth cohorts in their models, but a trimodal AAO distribution when analysing the whole sample. This may be because including birth cohorts in AAO analysis can artificially truncate the data, making the results of admixture analysis unreliable.

Inter-study differences in findings may further be attributed to the inconsistency in the definitions used for AAO of BD, as research has suggested that admixture analysis is further sensitive to the criterion used to define groups (Montlahuc et al., 2017). It has been proposed that the most valid definition for bipolar disorder AAO is the 'first affective episode meeting diagnostic criteria', as it does not preclude relevant episodes of depression prior to manic onset

(Leboyer et al., 2005). However, this does not overcome the limitation of recall bias, which was mitigated in some of the included studies by referring to case notes and interviews with family members rather than relying solely on self-report. Yet, BD patients may be more likely to recall depressive compared to manic episodes or even fail to recognise hypomanic episodes pre-diagnosis as pathological (de Assis da Silva et al., 2014; Gazalle et al., 2007). Deciding what constitutes pathology in retrospective studies is further distorted by the fact that potential symptoms in youth are viewed retroactively once an adult diagnosis has been received. As a gold-standard therefore, future research investigating AAO in bipolar disorder should aim to employ prospective longitudinal methodologies, using the age at 'first affective episode meeting diagnostic criteria' as the standardised definition for the point of disease onset.

Results will also have been influenced by factors including inter- and intra-country differences in diagnostic practices, evolving diagnostic criteria, varying degrees of stigma surrounding mental illness, and availability of healthcare provision. Yet, the fact that most studies displayed a trimodal AAO despite this heterogeneity suggests that it can be considered a robust finding.

2.4.5 Theoretical Considerations

As well as various methodological limitations, there are also theoretical limitations that should be considered. Related to the problem of establishing a standardised definition, it's important to note that non-specific prodromal symptoms will occur at ages younger than those reported as first onset. This raises questions regarding what should be viewed as initial age at onset. There is merit in the view that initial onset should be defined as the age at which prodromal symptoms first appear, as arguably this is the true start of illness manifestation. However, using prospective methodologies it is unclear what behaviour and experiences should be deemed part of normal developmental stages, and what can be viewed as pathological. Deciding what constitutes pathology in retrospective studies is distorted by the fact that possible prodromal, non-specific

nascent symptoms are framed by an existing adult diagnosis, and therefore may be misinterpreted. Furthermore, using retrospective accounts of age at onset from cohorts of treated individuals may miss bipolar disorder patients who have not been picked up by services due to, for example, less disabling symptoms (Jones, 2013). Considering prodromes as the true age at onset complicates the decision as to *when* early intervention is likely to be most useful and appropriate. It may therefore be most suitable to manage non-specific early-life symptoms in a more generalised and dimensional way, without looking towards distinct diagnostic categories. However, the field must be careful not to partition the study and treatment of bipolar disorder into 'child and adolescent', 'adult' and 'late-life' domains. This approach would undermine emerging research that focuses on 'staging' models in BD, which place an emphasis on the developmental stages of BD and change across the lifespan. Furthermore, it would ignore the fact that AAO groups are overlapping and represent different modes of a single distribution rather than being clearly demarcated groups.

2.4.6 Future Directions

Notably, one of the largest international BD cohorts - the Systematic Treatment Enhancement Program for Bipolar Disorder cohort (STEP-BD) (Sachs et al., 2003) – was not included in this systematic review. This is because the STEP-BD articles identified by the search strategy used pre-defined cut-offs to define AAO groups (e.g., <13, 13-18, >18 years old) and therefore did not meet eligibility criteria. The field would benefit from a data-driven approach (such as admixture analysis) to defining BD AAO in this well-characterised cohort. Similar analyses in other large, phenotypically detailed cohorts should also be prioritised in future research (e.g., the Flourish Canadian prospective high-risk offspring cohort; Duffy et al., 2007). Furthermore, future research projects should strive to implement the recommendations from the current study when defining AAO, to enhance understanding of the precise relationship between AAO and clinical outcomes in BD. The BrainWaves (https://brainwaveshub.org/) program, a collaborative research initiative

between the University of Oxford, Swansea University, and The Day newspaper, presents a promising opportunity to incorporate the latest research into its planning and development. The program aims to establish a rolling cohort of children and young adults from secondary schools in the UK. The development of this cohort offers the ability to incorporate current advancements in AAO research into the cohort's methodological design and measurements, thus enabling detailed prospective analysis. Additionally, the cohort's size provides the potential for the necessary statistical power to conduct appropriate analyses for investigating the complexities of BD AAO. This emerging resource presents a unique opportunity to advance the understanding of mental health in young individuals. As a result, this cohort will likely be a valuable resource for furthering understanding of the development of BD.

2.5 Conclusions

The results of this systematic review indicate that bipolar disorder has a trimodal age at onset distribution, segregating into early-, mid- and late-onset subgroups with the most common average age at onset being 17.3 years. The field should move towards a conceptualisation of these subgroups as referring broadly to life-stage and move towards a consistent definition of bipolar AAO as 'the first affective episode meeting diagnostic criteria'. Providing valid evidence for three AAO subgroups in BD will help to delineate more homogeneous subgroups of BD. Demarcating bipolar disorder AAO groups in this way can provide a framework for future research to continue to investigate potential mechanisms and thus inform treatment targets.

Chapter 3. Psychosocial markers of age at onset in bipolar disorder: a machine learning approach

This chapter has been adapted from the following paper:

Bolton, S., Joyce, D. W., Gordon-Smith, K., Jones, L., Jones, I., Geddes, J., & Saunders, K. E. A. (2022). Psychosocial markers of age at onset in bipolar disorder: a machine learning approach. BJPsych Open, 8(e133), 1–9. https://doi.org/10.1192/bjo.2022.536.

3.1 Introduction

3.1.1 Rationale

The clinical course of BD is characterised by significant variability, which is attributed to both phenotypic and biological heterogeneity (Soreca et al., 2009). This heterogeneity poses a challenge for accurate and timely diagnosis, with patients reporting an average diagnostic delay of almost a decade (Fritz et al., 2017). This delay is associated with poorer prognosis, including greater symptom severity and increased suicidality (Drancourt et al., 2013; Post et al., 2010). Recent research has sought to reduce clinical heterogeneity by demarcating more homogenous subgroups of BD patients, with the aim of improving diagnostic accuracy and refining appropriate treatment options (Duffy, Vandeleur, et al., 2017). AAO has emerged as a key variable in demarcating these subgroups (Leboyer et al., 2005). Meta-analytic results indicate a differing clinical trajectory according to AAO, with an early AAO associated with a more pernicious course of illness and longer delays to treatment (Agnew-Blais & Danese, 2016; Joslyn et al., 2016). Furthermore, evidence suggests that there is genetic homogeneity within AAO subgroups and heterogeneity between groups (Etain et al., 2006; Grigoroiu-Serbanescu et al., 2001; Mathieu et al., 2010). Collectively, these findings suggest that an individual's AAO may play a role in their illness course and treatment response.

Despite this, no known research has comprehensively investigated potential psychosocial predictors of AAO (Baldessarini et al., 2012; Etain et al., 2012). For instance, research that has aimed to identify psychosocial predictors for BD AAO has tended to focus on predictors in isolation, rather than examining a range of factors collectively. Identifying the risk factors that likely interact with various susceptibility genes to influence BD AAO has the potential to inform diagnosis and targeted approaches for early intervention.

3.1.2 Objective

To address this gap in the extant literature, the aim of the current Chapter was to build a model examining which psychosocial factors are individually and collectively associated with BD AAO. To achieve this, a supervised machine learning approach was employed (detailed below Section 3.1.3). Potential predictors were selected based on their availability in the dataset and possible relevance to BD AAO based on prior research. As the data was retrospective, only variables that could be reasonably considered as present 'pre-onset' were selected. These included: family history of suicide, psychiatric, and/or affective disorders (Hamshere et al., 2009; Post et al., 2016); alcohol use (Holtzman et al., 2015; Javaid et al., 2011); drug use (Lagerberg et al., 2011; Lin et al., 2006); poor premorbid social and work adjustment (Baldessarini et al., 2012; Hafeman et al., 2017; Tsuchiya et al., 2003); low educational attainment (Tsuchiya et al., 2003); personality traits and temperament (Akiskal et al., 2003; Hafeman et al., 2016; Oedegaard et al., 2009); childhood trauma or abuse (Agnew-Blais & Danese, 2016; Daruy-Filho et al., 2011; Garno et al., 2005; Leverich & Post, 2006; Post et al., 2015); and stressful life events (Hosang, Korszun, et al., 2012; Post et al., 2013). It is expected that increased scores on these factors will be associated with an earlier AAO.

3.1.3 Choice of modelling approach

3.1.3.1 Practical and theoretical considerations

Deciding on the most appropriate modelling approach to investigate the relationship of these predictor variables with AAO was an iterative process. The starting point was firstly, (i) the research objective, which was to identify psychosocial predictors of AAO, and secondly, (ii) the available data, which comprised a mixture of continuous and categorical predictor variables with AAO as the outcome variable. Given points (i) and (ii), a classical approach would be to conduct all-subsets multiple regression using linear least squares methods, such as Ordinary Least Squares (OLS), to build a model that minimises error to best predict the outcome variable. However, consideration number three, (iii) was that the systematic review from Chapter 2 indicated that BD AAO does not follow a normal distribution but has a trimodal distribution comprised of three distinct AAO groups (early-, mid- and late-onset). To preserve this finding, a form of generalised linear modelling could be employed to account for the three-group structure of AAO (Gueorguieva, 2017). Logistic regression is the foremost method that allows the prediction of groups – in this case AAO subgroup: early-, mid-, and late-onset. Although this approach would preserve the underlying trimodal structure of AAO, it would require 'binning' participants into one of three groups rather than keeping AAO as a continuous variable. In this way, logistic regression would lose a lot of information and thus undermine the predictive validity of the resulting model. For example, binning AAO onset into three groups would not account for the overlapping tails of the trimodal distribution, with the subgroups being artificially truncated. It was therefore decided that AAO should be modelled as a continuous outcome using multiple regression methods.

3.1.3.2 Regression methods: least squares vs. regularisation techniques

When choosing a regression method, OLS is the classical approach used for linear regression problems (Gang Su, 2009; R. A. Gordon, 2015). OLS methods are often chosen because they are

simple to implement and require little computational power, making them a convenient and efficient choice for smaller datasets or simpler models. OLS methods also allow for straightforward interpretation of estimated coefficients and enable the calculation of standard errors, confidence intervals, and hypothesis tests for these coefficients, which is important for model inference.

However, the present study includes a fairly large number of candidate predictor variables (28 in total; see Section 3.2.1.3). With many predictor variables, the OLS approach is prone to overfitting as there is no penalty for adding extra predictors to the model (Babyak, 2004; Hawkins, 2004). Overfitting means that while the model may perform well on the sample data from which it was trained, it has limited generalisability when applied to other samples (McNeish, 2015). This lack of generalisability can be explained by the bias-variance trade-off, which is a fundamental concept in machine learning and statistical modelling and refers to the trade-off between the complexity of the model and its ability to generalise to new or unseen data. In this context, a model fitted using OLS methods will be unbiased (i.e., minimise the prediction error) in the sample used to fit the model, but have huge variance across samples, introducing high prediction error rates on unseen data (Briscoe & Feldman, 2011). As OLS methods are liable to overfitting in this way, 'unnecessary' predictor variables may be included in the model, which harms interpretability and violates Occam's razor – the principle of parsimony – which holds that the simplest explanation is often the best (Gamberger & LavraČ, 1997; Hawkins, 2004). Occam's Razor is a guiding principle for model selection and hypothesis testing, with a preference for simpler models that are more likely to generalise well to new data and avoid overfitting.

Therefore, rather than using OLS methods, it is more appropriate to employ a regression method that can help select the most important predictor variables for a parsimonious model (McNeish, 2015).

Regularisation methods are a set of techniques used to help address overfitting by adding a penalty term to the model that discourages complexity (Friedman et al., 2010, 2015; Tibshirani, 1996). Ridge regression and Least Absolute Shrinkage and Selection Operator (LASSO) regression are two common types of regularisation methods (Friedman et al., 2010; Hoerl & Kennard, 1970; Tibshirani, 1996). Ridge regularisation can be useful when all of the predictor variables are expected to be relevant and contribute to the outcome. In this case, ridge regression can help to reduce overfitting by shrinking the coefficients towards zero, without setting them to exactly zero. On the other hand, LASSO regularisation can be particularly useful when there are many predictor variables, and some of them are likely to be irrelevant. The LASSO method encourages sparse models (i.e., models with few parameters), as the LASSO uses regularisation techniques to allow coefficient weights to be shrunk to exactly zero; automatically performing variable selection (Ambler et al., 2012; Tibshirani, 2011). This can improve the interpretability of the model and minimise overfitting by reducing model complexity.

Consequently, as the goal was to fit an interpretable model that doesn't use all available predictors, LASSO regression was chosen (Tibshirani, 1996). To date, no known study has used this modelling approach to investigate predictors of AAO in BD. This is perhaps because one of the drawbacks of LASSO is that, unlike OLS methods, it does not produce standard errors and confidence intervals for estimated model parameters, making model inference more challenging. To address this, bootstrap resampling with k-fold cross-validation was performed 1000 times to aid inferential analysis (Chatterjee & Lahiri, 2012; Hesterberg, 2011; Kohavi, 1995; Liu et al., 2017; Liu & Yu, 2017). This approach involves randomly sampling the original dataset with replacement to create 1000 new bootstrap datasets, which are then used to fit LASSO regression models. K-fold cross-validation is used to partition each of these bootstrapped samples into k equal parts (10 in the current study), using k-1 parts to fit the model and the remaining part to test its performance (Mosteller & Tukey, 1968; Stone, 1974). This process is repeated k times,

with each part of the dataset used as the testing set once (Gueorguieva, 2017). By combining bootstrapping and k-fold cross validation methods, more accurate estimates of the LASSO coefficients can be obtained, and their stability can be evaluated across multiple resamples (Kohavi, 1995). In the present study, the chosen final model included only predictor variables present on >90% of resampling runs, and density plots were derived for each 'stable' predictor to visualise uncertainty estimates. This approach can provide robust estimates of the LASSO coefficients and their standard errors and help identify the most important predictor variables while avoiding overfitting. Further details on the LASSO, and the procedure used for inferential analysis, are given in Section 3.2.2.

3.2 Methods

This study used data from the UK Bipolar Disorder Research Network cohort (BDRN; www.bdrn.org) which is an on-going programme of research into the genetic and non-genetic determinants of BD and related mood disorders. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by a Heath Research Authority NHS Research Ethics Committee (MREC/97/7/01) and all participating NHS Trusts and Health Boards. Written informed consent was obtained from all participants. The data used in the current analysis was accrued from February 2002 to June 2015 and analysed in 2021.

Participants were recruited throughout the UK via NHS services and advertisements through patient support organisations. Inclusion criteria were: (i) aged 18 years or over, (ii) able to provide written informed consent, (iii) met DSM-IV criteria (American Psychiatric Association, 2000) for BD, and (iv) onset of mood symptoms before the age of 65 years. Individuals were

excluded if they experienced affective illness only because of substance use or medical illness or were biologically related to another study participant.

3.2.1 Measures

3.2.1.1 Diagnosis

Best-estimate main lifetime diagnosis was made according to DSM-IV criteria based on in-depth interview using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990), and review of psychiatric and primary care case-notes where available.

3.2.1.2 Outcome Measure

The primary outcome variable was AAO of BD, defined as the age at first clinically significant impairment due to manic or depressive symptoms. Signs of clinically significant impairment included: arguments and/or fights; missed work and/or job loss; treatment referral; the use of Lithium or neuroleptics for treatment of manic symptoms; disrupted work or social life; police involvement; family breakdown; and psychotic features.

3.2.1.3 Candidate Predictors

Twenty-eight predictors were considered – detailed below. These were selected based on availability in the present dataset and potential relevance to BD AAO based on prior research.

3.2.1.3.1 Psychiatric Family History

Participants were asked if they had a family history of (i) affective disorders, (ii) psychiatric disorders, and/or (iii) suicide. Answers were scored as ‘yes’, ‘no’ and ‘unknown’ for each of these three variables.

3.2.1.3.2 Childhood Abuse

The Childhood Life Events Questionnaire (CLEQ; (Upthegrove et al., 2015) was used to determine the presence of any known sexual and/or physical and/or emotional childhood abuse occurring before the age of 16 years. Answers were scored as 'no known childhood physical, sexual or emotional abuse' or 'yes: experienced sexual, physical and or/emotional abuse before the age of 16'.

3.2.1.3.3 Alcohol units per week in year before onset

Participants were asked to enter the average number of units of alcohol they drank per week in the year before BD onset. If unknown, or if the participant did not use alcohol regularly, this was recorded as 'NA'.

3.2.1.3.4 Drug Use

Participants were asked if they had ever regularly used cannabinoids or unspecified non-prescription drugs. 'Regularly' was defined as 'persistently for one month, or at least once a week for >6 months of the year'. If participants answered 'yes' then they were asked if they cannabinoids or unspecified non-prescription drugs in the year before BD onset: yes, no, and unknown.

3.2.1.3.5 Education

Highest level of educational attainment was recorded. Responses were grouped into 'yes' attained higher education (degree or post-graduate degree), 'no' higher-education, and 'unknown'.

3.2.1.3.6 Work and Social Adjustment

The Modified OPCRIT Symptom Checklist Details and History questionnaire (Azevedo et al., 1999; Brittain et al., 2013) was used to assess work and social adjustment prior to illness onset:

i. Poor premorbid work adjustment refers to work history before onset of illness. Scored as 'yes' if the participant was unable to keep a job for >6 months; had a history of frequent job changes; couldn't sustain a job expected by their educational level or training; persistently had a very poor standard of housework (housewives); failed to keep up with studies (students). Otherwise scored as 'no', 'not applicable' or 'unknown'.

ii. Poor premorbid social adjustment refers to social adjustment before onset of illness. Scored as 'yes' if the participant found difficulty entering or maintaining normal social relationships; showed persistent social isolation, withdrawal or maintained solitary interests prior to onset of symptoms; or participant having had no friends at school or only one casual friend. Participants who had several casual friends or good friends were scored as 'no'. Otherwise, scores were 'not applicable' or 'unknown'.

3.2.1.3.7 Trait Measures

Trait neuroticism, schizotypal personality traits, and five aspects of temperament were assessed as follows:

i. Trait neuroticism. Assessed using the Neuroticism subscale of the Eysenck Personality Questionnaire Revised (EPQ-R; (Eysenck & Eysenck, 1991). Scores range from 0 to 23, with higher total scores denoting higher levels of trait neuroticism.

ii. Schizotypal personality traits. Assessed using the self-report Kings Schizotypy Questionnaire (KSQ; (L. A. Jones et al., 2000). This is a 63-item forced-choice (yes/no) questionnaire with seven subscales assessing schizotypy: recurrent illusions (2x subscales), social isolation, social anxiety, magical thinking, paranoid ideation, and ideas of reference. Higher total scores indicate higher levels of schizotypal personality traits.

iii. Temperament. Evaluated using the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Auto-questionnaire (TEMPS-A). This self-report questionnaire uses five subscales to assess cyclothymic, depressive, irritable, hyperthymic, and anxious

temperament (Akiskal et al., 2005). Higher scores on each subscale indicate a greater number of features of the corresponding temperament.

3.2.1.3.8 Life Events

Eleven questions from the Brief Life Events questionnaire (BLEQ) – Table 5 below – were included as potential predictors (Brugha et al., 1985; Brugha & Cragg, 1990). These self-report questions referred to the six months before BD onset. Three items from the BLEQ were excluded from analysis. Item number seven – 'In the 6 months prior to your illness onset, were you made redundant or sacked from your job?' - was not included as the goal was to identify predictors of AAO, and not all participants were of legal working age at the time of their reported age at BD onset. Item 13 – 'Do you think that anything happened which contributed to you becoming unwell? If yes, what was it?' - and item 14 – 'Do you think that there is anything that happened to you during your life which contributed to you becoming unwell? If yes, what was it?' - were not included as these were free text answers and coding these into categories for quantitive analysis was beyond the scope of the current study.

Table 5. Questions from the BLEQ included as potential predictors in modelling.

Question (yes vs. no response)
Did you suffer from a serious illness, injury, or assault?
Did a close relative suffer a serious illness, injury, or assault?
Did a parent, spouse/partner, child, or sibling of yours die?
Did a close family friend or relative die?
Did you have a separation due to marital difficulties or break off a steady relationship?
Did you have a serious problem with a close friend, neighbour or relative?
Were you seeking work without success for more than one month?
Did you have a major financial crisis such as losing the equivalent of three months' income?
Did you have problems with the police involving a court appearance?
Was something you valued lost or stolen?
Did you or your wife/partner give birth to a child?

3.2.1.4 Demographics

Age at interview and individuals' highest level of occupation were recorded. These were not considered as potential predictor variables as they did not specifically relate to pre-BD onset. For individuals' highest occupation, responses were grouped into 'professional', 'non-professional', 'never worked', 'student', and 'unknown'.

3.2.2 Statistical Analysis

The R code used for data pre-processing and analysis is openly available via the Open Science Framework.

3.2.2.1 Data Pre-processing

Analysis was conducted in R version 4.0.3 (2020-10-10) (R Core Team, 2020) for Mac OS using the 'glmnet' package version 4.1.1 for the main analysis (Friedman et al., 2010, 2015) along with multiple helper packages (listed in Appendix B.1. with references), while figures were produced

using the 'ggplot2' package version 3.3.5 (Wickham, 2016). Missing variables were removed using the listwise-deletion method, with analysis conducted on this dataset. The datasets with versus without missing data removed were not statistically significantly different from one another (Appendix B.2.). Pre-processing steps for the full sample included: (i) log transforming the outcome variable, AAO, so that age was correctly modelled as a positive number in analyses (Steyerberg, 2009) (Appendix B.3.), (ii) filtering out data collected pre-2008 as not all questionnaires were administered prior to this date, (iii) dummy coding all categorical variables (with *K*-1 levels per variable), and (iv) scaling numeric dependent variables using z-score standardization. The correlations between all 28 predictor variables were examined. Pearson's correlation coefficients ranged from small (+/- 0.21) to moderate (0.68) effect sizes according to Cohen's Rule of Thumb (Appendix B.4.). The variables that were most highly correlated were those relating to dimensions of personality and temperament, which are known to be traits that cluster. Accordingly, as these traits cannot be considered in isolation, they were retained in the model building process to preserve ecological validity.

Sociodemographic characteristics of the sample were described with mean and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. The full sample was randomised into a model development (70%, N = 717 of total sample) and a held-out validation set (30% of sample, N = 305). This 70:30 split ensured a sufficiently large training set for the purposes of model development, while maintaining an adequately large sample size for out-of-sample model evaluation.

3.2.2.2 Model Building

Model development and evaluation followed the recommendations from the TRIPOD statement (Collins et al., 2015). Model development was performed with a supervised machine-learning method, the LASSO. With many predictors (n = 28), this approach is computationally more

efficient than more 'classical' model selection methods such as subset selection, which use least squares to fit a linear model that contains a subset of the predictors (James et al., 2013). In contrast, LASSO is a penalised regression analysis method that can fit a model containing all predictors and then perform regularisation and variable selection. Regularisation involves shrinking the sum of the absolute values of the regression coefficients; thus, LASSO (unlike other shrinkage methods such as ridge regression) can effectively exclude predictors from the final model by shrinking their coefficients to zero – i.e., performs variable selection (Ambler et al., 2012). This regularisation approach helps mitigate over-fitting and allows for a more parsimonious, interpretable, and replicable model (Tibshirani, 1996).

3.2.2.3 Internal Model Validation

LASSO methods require the shrinkage hyper-parameter (lambda) to be optimised for the data and model. In contrast to model parameter estimation methods in classical regression, LASSO algorithms do not yield standard errors and uncertainty intervals for estimated model parameters. For this reason, the following procedure was applied:

1. Resample (with replacement) the model development data set (N = 717) to generate a sample, *S*.
2. Execute the LASSO procedure with 10-fold cross-validation on *S* to locate the optimal lambda parameter that yields the minimum mean squared error between predicted and actual AAO outcomes.
3. Extract the model parameters given the optimal lambda parameter.
4. Repeat from Step 1 one thousand times.

The 'cv.glmnet' function from the R package 'glmnet' version 4.1-1 (Friedman et al., 2010) was used for steps two and three. After 1000 resample-fitting procedures, all parameter estimates (coefficients) were collated to examine which predictor variables were consistently retained and

estimated the variability in these coefficients. These non-exponentiated coefficients are reported as histograms, showing their distributions over 1000 resamples of the training set (Appendix B.7.).

For inferential analysis, the number of times a predictor was included on each of the 1000 resampling runs / model fits was ranked. The predictors that were included on >90% of these runs were then selected. A 90% cut-off point was chosen pre-analysis as a limit that was sufficiently high enough to ensure predictors were reliably present in each model refit. Once a selected set of predictors had been identified, to display effect sizes, density plots were derived for each predictor from the coefficients generated across the 1000 resamples (Figure 4). The most common (modal) coefficient value was reported for each of the predictors present on >90% of reruns (Table 8).

3.2.2.4 Model Evaluation

In an exploratory internal validation, the selected model was applied to the held-out validation set (N = 305). The model generated predictions for bipolar disorder AAO for each case in the validation set. Model predictive performance was assessed using a calibration curve. Calibration refers to the agreement between observed AAO values in the validation set and predictions from the model and can be represented graphically with predictions on the x-axis, observed outcome on the y-axis, and a 45° line representing perfect calibration (Steyerberg et al., 2010). A non-parametric locally weighted scatter plot smoothing algorithm (LOESS) was employed to produce a calibration plot. LOESS is a form of regression that uses a weighted, sliding window (passing along the x-axis) average to calculate a line of best fit. The span parameter – which is the size of the sliding window – determines the amount of smoothing and was set to 0.3 (Austin & Steyerberg, 2014). Plotting the smoothed regression line allows us to examine calibration across the full range of predicted values.

3.3 Results

3.3.1 Sociodemographic and Clinical Characteristics of the Sample

There were a total of 1022 participants. The sample is described with mean, standard deviation, and range for continuous variables (Table 6), and absolute and relative frequencies for categorical variables (Table 7).

Table 6. Means, standard deviations (SD) and ranges for continuous measures in the total sample (n = 1022).

Variable	Mean (SD, range)
Age at BD onset	23.0 (9.86, 5-68)
Age at interview	45.5 (12.1, 18-83)
Alcohol units consumed per week in the year before BD onset	14.5 (30.4, 0-350)
Trait Neuroticism	15.7 (5.40, 0-23)
Schizotypal personality traits	20.8 (12.1, 1-58)
Cyclothymic Temperament	7.08 (3.88, 0-12)
Depressive Temperament	2.55 (2.31, 0-8)
Irritable Temperament	2.62 (2.24, 0-8)
Hyperthymic Temperament	3.63 (2.35, 0-8)
Anxious Temperament	1.30 (1.14, 0-3)

Table 7. Absolute (n) and relative (%) frequencies for categorical variables in the total sample (n = 1022).

Variable		n	%
Diagnosis	BDI	630	61.6
	BDII	346	33.9
	BD Schizoaffective	26	2.5
	BD NOS	20	2.0
Family history of affective disorders	No	177	17.3
	Yes	845	82.7
Family history of psychiatric disorders (other than affective disorders)	No	640	62.6
	Yes	382	37.4
Family history of suicide	No	837	81.9
	Yes	185	18.1
Education	Higher education	493	48.2
	No higher education	529	51.8
Highest occupation	Professional	556	54.0
	Non-professional	449	43.5
	Never worked	7	0.7
	Student	18	1.8
Childhood physical, sexual or emotional abuse	No	802	78.5
	Unknown	25	2.4
	Yes	195	19.1
Regular use of cannabinoids in the year before onset	No	914	89.4
	Yes	108	10.6
Regular use of non-prescription drugs (other than cannabinoids) in the year before onset	No	979	95.8
	Yes	43	4.2
Poor premorbid work adjustment	No	1018	99.6
	Yes	4	0.4

Poor premorbid social adjustment	No	1009	98.7
	Yes	13	1.3
Life Events 6-months prior to BD onset:			
A serious illness, injury, or assault	No	871	85.2
	Yes	151	14.8
Close relative suffered serious illness, injury, or assault	No	893	87.4
	Yes	129	12.6
Death of parent, partner, child, or sibling	No	956	93·5
	Yes	66	6.5
Death of close family friend or relative	No	902	88.3
	Yes	120	11.7
Separation from or break-up with partner	No	841	82.3
	Yes	181	17.7
A serious problem with a close friend, neighbour, or relative	No	781	76.4
	Yes	241	23.6
Seeking work without success for one month or more	No	954	93.3
	Yes	68	6.7
Major financial crisis	No	926	90.6
	Yes	96	9.4
Problems with the police involving a court appearance	No	999	97.7
	Yes	23	2.3
Something of value was lost or stolen	No	970	94.9
	Yes	50	5.1
Birth of child	No	930	91.0
	Yes	92	9.0

3.3.2 Predictors of BD AAO

3.3.2.1 Model Development

For >90% of the resampling runs, the cross-validated LASSO regression analysis (mean λ = 0.0182, SD = 0.00727) consistently selected eleven variables as predictors of AAO (Figure 4). Of these eleven variables, the following six were associated with an earlier AAO: 1) childhood abuse; 2) regular cannabis use in the year before onset; 3) death of a close family friend or relative in the six months prior to onset; 4) family history of suicide; 5) schizotypal personality traits; and 6) irritable temperament. Five variables were associated with a later AAO: 1) the average number of alcohol units consumed per week in the year before onset; 2) birth of a child in the six months prior to onset; 3) death of parent, partner, child, or sibling in the six months prior to onset; 4) seeking work without success for one month or more in the six months prior to onset; and 5) a major financial crisis in the six months prior to onset. Of these 11 variables, some had partial correlation with one another as well as with non-chosen predictor variables, with effect sizes ranging small (+/- 0.21) to moderate (0.68) (see Appendix B.4.). The non-exponentiated modal coefficients for these eleven predictors are shown in Table 8. The full model with all predictors' coefficients (not just those selected on >90% of resampling runs) can be found in Appendix B.5. and Appendix B.6.

3.3.2.2 Model Internal Validation on Held Out Samples

The model showed reasonable calibration when validated on the held-out test set with R^2 = 0.237 and exponentiated Mean Absolute Error (MAE) = 2.004. Exponentiated MAE was chosen as the most appropriate metric for model accuracy as it is on the same scale as the outcome measure, AAO. Thus, the average absolute difference between the observed AAO and the predicted AAO values was approximately 2 years. This reasonable calibration can also be judged visually - as shown in Figure 5 the predicted and observed AAO are similar, with approximately 90% of the model's confidence interval lying close to the 45° line.

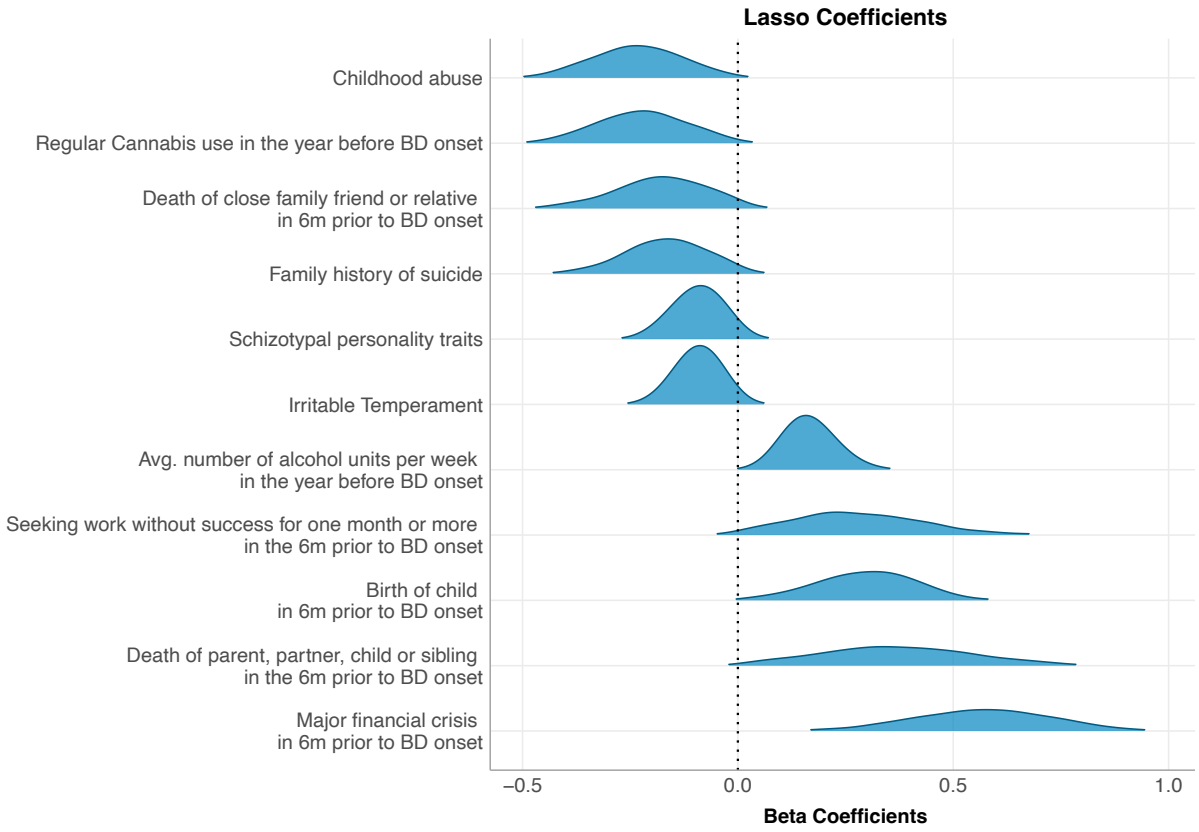

Figure 4. Density plots for the eleven predictors selected by cross-validated LASSO regression model on >90% of the 1000 resampling runs. Negative beta coefficients indicate an association with an earlier AAO, while positive coefficients represent an association with a later AAO.

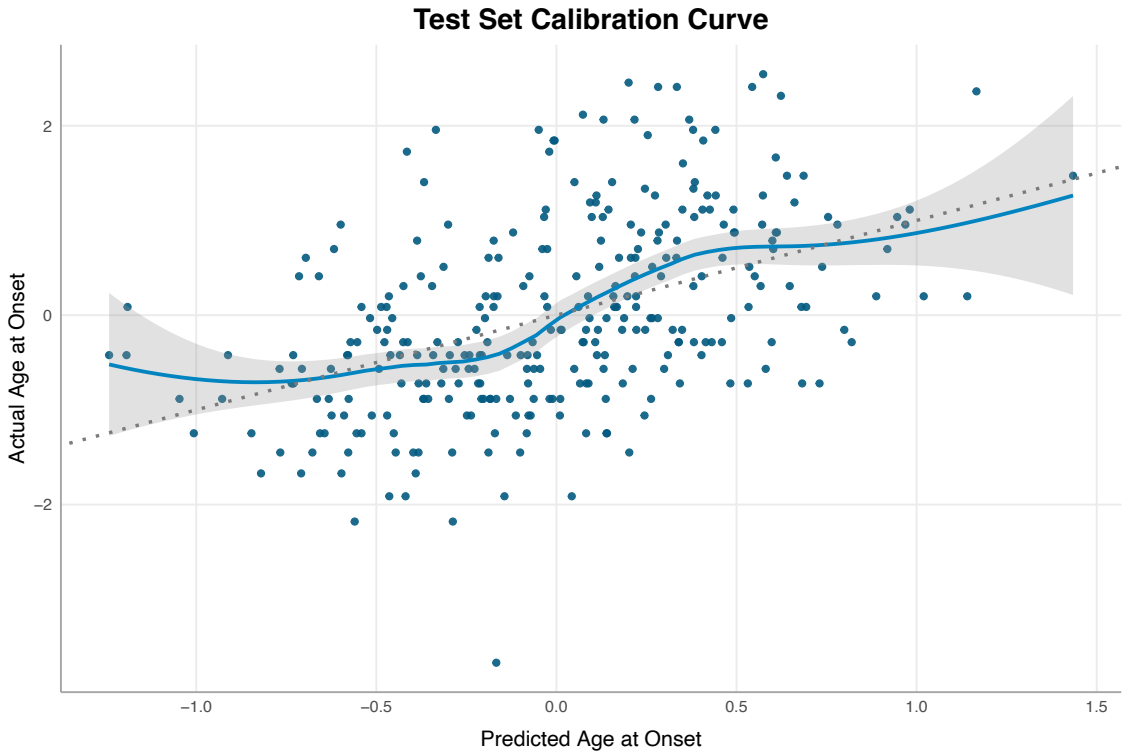

Figure 5. Calibration curve showing the agreement between observed outcomes and predictions using the test set data. The dotted line represents 'perfect model calibration'; the blue line is the calibration curve generated by the model using a LOESS smoother with 95% confidence intervals (grey); the blue scatter points are the observed data. N.B. observed and predicted AAO is shown on a natural logarithm scale.

Table 8. Non-exponentiated modal coefficients for each of the eleven predictors selected by the LASSO regression model on >90% of resampling runs.

Predictors	Modal Coefficients
Childhood abuse	-0.2855
Regular Cannabis use in the year before BD onset	-0.2765
Death of close family friend or relative in 6 months prior to BD onset	-0.2435
Family history of suicide	-0.1385
Schizotypal personality traits	-0.1055
Irritable Temperament	-0.0685
Average number of alcohol units per week in the year before BD onset	0.1385
Birth of child in 6 months prior to BD onset	0.2755
Death of parent, partner, child, or sibling in the 6 months prior to BD onset	0.3125
Seeking work without success for one month or more in the 6 months prior to BD onset	0.3505
Major financial crisis in 6 months prior to BD onset	0.4575

3.3.3 Post-hoc Analysis

Post-hoc, to ensure the model was reliable, the full model building procedure was re-run (using the cv. glmnet' package) employing ridge regression ($\alpha = 0$) and elastic net penalised regression ($\alpha = 0.5$) which employs L1 and L2 regularisation, rather than LASSO which uses L1 regularisation. The elastic net model selected the same eleven predictors as the LASSO regression, indicating that these features were stable across models, and showed comparable prediction accuracy. Ridge regression resulted in a less parsimonious model with all 29 predictors included. Table 9 below compares these models.

Table 9. Accuracy metrics for LASSO, Elastic Net and Ridge models.

Model	Root Mean Squared Error	R-squared
LASSO	0.881	0.237
Elastic Net	0.874	0.258
Ridge	0.881	0.251

3.4 Discussion

This is the first known study to comprehensively investigate a range of psychosocial predictors for BD age-at-onset. Eleven variables were reliably associated with BD AAO. Six predicted an earlier AAO: 1) childhood abuse; 2) regular cannabis use in the year before onset; 3) death of a close family friend or relative in the six months prior to onset; 4) family history of suicide; 5) schizotypal personality traits; and 6) irritable temperament. While five were associated with a later AAO: 1) the average number of alcohol units consumed per week in the year before onset; 2) birth of a child in the six months prior to onset; 3) death of parent, partner, child, or sibling in the six months prior to onset; 4) seeking work without success for one month or more in the six months prior to onset; and 5) a major financial crisis in the six months prior to onset. These findings are discussed in the context of previous research, along with their implications for diagnosis, treatment, and early intervention.

3.4.1 Childhood abuse and individual level characteristics

The variable that was associated with the earliest AAO was childhood abuse. This aligns with a large body of evidence indicating that maltreatment in childhood is associated with an earlier AAO (Agnew-Blais & Danese, 2016) and is more common in individuals with BD compared to healthy controls (Daruy-Filho et al., 2011). As suggested by prior research, the trauma of childhood abuse may expedite the AAO of BD (Daruy-Filho et al., 2011; Geoffroy et al., 2013). For instance, recent research (which has partial sample overlap with the current study) found that the path between childhood abuse and an earlier AAO was selectively explained by individuals' mood instability (Marwaha et al., 2020). The authors suggest that mood instability – defined as rapid and intense fluctuations in affect – may bring forward illness onset in children who are vulnerable because of abuse, with increased mood instability developing into episodes of mania or depression (Berk et al., 2017; Broome, Saunders, et al., 2015). However, the causal nature of this relationship is yet unclear. It may be that behavioural difficulties and emotional dysfunction

resulting from an early BD AAO confer greater social and emotional vulnerability, which in turn has been identified as a major risk factor for childhood abuse (Fleming et al., 1997; Sheikh, 2018). Thus, there may be a bi-directional relationship between mood instability and childhood abuse, with increased mood lability reducing an individual's resilience to childhood abuse, and/or vice versa, with childhood abuse increasing the likelihood for mood instability. Prospective longitudinal studies are needed to elucidate the precise nature of the relationship between mood instability, childhood abuse and how it relates to early-onset BD.

The mediating effect of mood instability on the relationship between trauma and early-onset BD parallels the finding that irritable temperament was associated with an earlier AAO. Irritable temperament has been positively associated with mood instability, borderline symptoms, impulsivity, and grandiosity (Walsh et al., 2012), while also predicting manic symptoms (Iasevoli et al., 2013). It has been suggested that irritable temperament forms part of a broader BD spectrum and represents a prodromal phase of the disorder (Duffy et al., 2016), and, as with mood instability, may accelerate the onset of manic or depressive episodes meeting diagnostic criteria. Indeed, the association between high levels of trait irritability and an earlier AAO may be an artifact of the increased likelihood of these individuals manifesting behavioural problems that are brought to the attention of psychiatric services, in turn making it more likely to receive an early (or timely) diagnosis. Indeed, the diagnosis of pre-pubertal bipolar disorder, which is prevalent in North America, requires irritability (not mania) as a core symptom for diagnosis (Duffy, 2007; Wozniak, 2003).

Irritability is not the only trait measure that appears to be predictive of an earlier AAO. Greater endorsement of schizotypal personality traits – including magical thinking, paranoid ideation, ideas of reference, and social isolation or anxiety – was also associated with an earlier AAO in the current model. As with irritability, it is thought that schizotypy represents a dimensional trait that

indexes the genetic liability to BD and forms part of the BD spectrum (Mahon et al., 2013). While this is the first known study to specifically investigate schizotypal personality traits in relation to BD AAO, previous research indicates that schizotypal traits are elevated in those with BD and predict future hypomanic episodes (Joyce et al., 2004; Schürhoff et al., 2005). There is a growing body of evidence demonstrating that genes (e.g., variants of the catechol-o-methyltransferase gene) may interact with environmental factors, such as childhood abuse, to contribute to elevated levels of schizotypal traits in BD (Savitz et al., 2010). Additionally, greater genetic liability for schizophrenia in individuals with BD has been associated with increased schizotypy scores (Hori et al., 2012). As the current findings show a link between increased schizotypal traits and early AAO, this lends support to the idea that earlier- vs. later-onset BD may differ in genetic aetiology and highlights the importance of recognising the role of genetic interactions with the psychosocial predictors in the model. Of note however, schizotypal traits and irritable temperament were partially correlated with other personality traits not included in the final model (e.g., trait neuroticism, cyclothymic temperament, depressive temperament). These correlated but not included temperament traits may also be of predictive relevance. As dimensions of personality are known to be traits that cluster, this should be considered when interpreting the impact of personality traits on AAO (Iasevoli et al., 2013).

3.4.2 Life Experiences and Familial Risk

Pertinent to the discussion of gene-environment interactions, 'family history of suicide' was predictive of an earlier AAO, which is in line prior research (Chen et al., 2014; Post et al., 2016). A family history of suicide confers a stronger familial/genetic loading for suicidality and corresponding psychiatric disorders, which supports the view that genetics contribute to an increased vulnerability for an earlier AAO in BD. This is consistent with evidence suggesting that early-onset may be a more heritable form of BD than late-onset, with studies demonstrating differences in transmission patterns and more pronounced familial aggregation in early-

compared to late-onset BD (Etain et al., 2006; Geoffroy et al., 2013; Mathieu et al., 2010; Priebe, Degenhardt, Herms, Haenisch, Mattheisen, Nieratschker, Weingarten, Witt, Breuer, Paul, Alblas, Moebus, Lathrop, Leboyer, Schreiber, Grigoroiu-Serbanescu, Maier, Propping, Rietschel, Nothen, et al., 2012). Beyond specific genetic influences, a family history of suicide can convey increased transgenerational risk based on intra-familial behavioural interactions and their associated stressors (Post et al., 2016; Serretti et al., 2013). This in turn influences family environment and reciprocal offspring resilience (Miklowitz et al., 1996), hinting that epigenetic mechanisms may be at play in BD AAO (Agnew-Blais & Danese, 2016; Daruy-Filho et al., 2011; Post et al., 2015).

Looking beyond childhood abuse and family suicide, the current model also suggests that other negative early-life experiences may catalyse disorder onset. Namely, 'the death of a close family friend or relative in the six months prior to BD onset' correlated with an earlier AAO. Within the psychological framework of the diathesis-stress model, it is thought that early negative life events interact with predisposed vulnerability to precipitate disorder onset (Brietzke et al., 2012; Horesh et al., 2011). Accordingly, evidence suggests a dose effect of exposure to stressful life events on the AAO of BD, with a greater number of early stressors being significantly associated with an earlier AAO (Hosang, Korszun, et al., 2012; Post et al., 2013). In contrast to this however, results indicated that the following life events were associated with a later AAO: birth of a child, major financial crisis, and/or death of parent, partner, child, or sibling in the six months prior to BD onset; as well as seeking work without success for one month pre-onset. Yet, the direction of these relationships is unclear. For instance, these are all life events that become more common with increasing age, which therefore confounds the direction of these associations with a later AAO. In support of this, Figure 4 shows that the coefficient variability of these four variables is greater than the others (i.e., 'flatter' density plots), which suggests that the relationship between these life events and AAO may be less reliable than the other predictors in the model and is likely weakened by age being a possible confound. Equally, there were small numbers of participants

reporting these negative life events which could have weakened the strength of their relationship to AAO. This slightly less robust association may also be partially attributed to the finding that the effect of life events on the emergence of BD diminishes with age (Hillegers et al., 2004), perhaps due to the development of appropriate coping strategies or the presence of other neutralising life events.

3.4.3 Substance Use

The presence of stressful life events has also been associated with alcohol use (Paulino et al., 2017), which was identified as a significant predictor in the present model. The model suggests that alcohol use correlates with a slightly later AAO. Previous research has found mixed results, with some studies demonstrating that premorbid alcohol use is significantly associated with an earlier AAO (Azorin et al., 2013; Holtzman et al., 2015; Lin et al., 2006), while others have found an association with a later AAO (Lagerberg et al., 2011; Strakowski et al., 2005). Similar to the age-dependent life events discussed above, the relationship between alcohol use and an early BD onset may be confounded by age restrictions on purchasing and accessing alcohol. Equally however, it may be that increases in alcohol use masks the true AAO of BD, with it being unclear if mood and behavioural disturbances are a consequence of incipient BD or directly related to heavy alcohol use (Berk et al., 2017). Thus, individuals may not recognise their first incidence of impairment as specifically related to BD, artificially inflating their reported AAO. Early prodromal symptoms, such as sleep disturbances and anxiety symptoms may be attributed to alcohol use rather than recognised as part of the clinical trajectory of early-stage BD (Stein & Friedmann, 2008). Indeed, anxiety symptoms have been found to be both a cause and a consequence of heavy alcohol use, as well as a clinical precursor in BD (Duffy, 2014; Duffy et al., 2014; Kushner et al., 2000). This highlights that the relationship between alcohol consumption and BD AAO is likely non-linear, and so the present findings must be interpreted with caution.

Despite previously mixed findings regarding the relationship between AAO and alcohol use, the finding that alcohol use was associated with a later AAO while cannabis use was associated with an earlier AAO, directly corroborates previous research which controlled for age as a potential confound (Lagerberg et al., 2011). Furthermore, evidence from systematic reviews and meta-analyses points towards a significant association between cannabis use and an earlier AAO in BD (Bally et al., 2014; Leite et al., 2015; Sideli et al., 2019), with results suggesting that cannabis use may trigger the onset of mania (M. Aas, Etain, et al., 2014; Bally et al., 2014; S. M. Strakowski et al., 2007). The mechanism behind this effect is unclear, but it has been hypothesised that the principal ingredients in cannabis (tetrahydrocannabinol and cannabidiol) effect mood via their interaction with the endocannabinoid, dopamine, and serotonin neurotransmitter systems (Chadwick et al., 2013; Gibbs et al., 2014). In contrast, alcohol use is thought to increase the risk for depressive, rather than manic symptoms (Baethge et al., 2008; Sideli et al., 2019). This may help explain why increased alcohol use was not associated with an earlier AAO, as the presence of a manic episode is needed before a clinical diagnosis of BD can be made.

3.4.4 Strengths and Limitations

This is the only known study which models a wide range of psychosocial markers of AAO in a large, well-characterised sample of BD participants. A novel machine-learning approach was used, not previously employed when investigating BD AAO, employing bootstrapping, k-fold cross-validation and a held-out validation set to ensure model robustness and reduce overfitting. The final model showed good calibration, indicating a high level of confidence in its predictive validity.

There are however several methodological limitations that must be considered. Relating to model validation, there was no independent sample available for external validation. While a held-out test set was used, this was a subsample of the original dataset and therefore subject to

the same limitations as the data used for model building. The most notable of these limitations is the cross-sectional retrospective nature of the study, and the cohorts' limited generalisability. As the analyses are not based on prospective data, the direction of causality in the current model cannot be established, and it is unclear whether the predictors should be conceptualised as causal risks factors or as risk markers - i.e., a factor that is associated with an outcome but is not necessarily its cause (Feinleib, 2001). Although, as with many psychiatric illnesses, it is likely that the relationships are bidirectional and symbiotic. Retrospective studies are also subject to recall bias, which undermines the reliability of self-reported AAO. This was mitigated by referring to medical case notes rather than relying solely on self-report. Yet, it has been suggested that people with BD may be more likely to recall depressive compared to manic episodes or even fail to recognise hypomanic episodes pre-diagnosis as pathological (de Assis da Silva et al., 2014; Gazalle et al., 2007). This introduces biases into individuals' recall of their bipolar AAO. Additionally, as the sample was skewed towards a younger age at study entry (average age of 46 years), late-onset BD may have been underreported, thus weakening the reliability of the current model. Moreover, a BD diagnosis in older age may be masked or missed in favour of more prevalent later-life disorders with psychiatric symptoms (e.g., frontotemporal dementia), further obscuring the true rate of late-onset BD. As a gold-standard therefore, future research investigating BD AAO should aim to employ prospective longitudinal methodologies.

Furthermore, the included personality trait predictors had partial correlation with other personality variables not chosen in the final model. Thus, schizotypal personality traits and irritable temperament may not be the most valuable personality predictors per se, but rather represent the predictive importance of a clustering of other personality variables, such as high trait neuroticism, and cyclothymic, depressive, and anxious temperaments. Additionally, there are other theoretically driven potential psychosocial predictors that would have been interesting to include in modelling. This includes information on pre-onset smoking and suicide attempts, as

well as sleep and circadian rhythms, mood lability, and premorbid anxiety, which are known to be important in the manifestation and prodromal stages of BD (Duffy, 2009; Ritter et al., 2015). Additionally, given the likely role of gene-environment interactions, including genetic data in future analyses would help to elucidate aetiological mechanisms.

3.5 Conclusions

The present study sheds light on the importance of several psychosocial markers for bipolar disorder age-at-onset. Identifying these predictors provides is a further step towards understanding key processes in the aetiology of this heterogeneous psychiatric disorder. The findings suggest that age at onset of BD is likely catalysed via an interplay of genetic susceptibility, individual-level personality traits and exposure to negative life events and trauma in childhood. The identified predictor variables can be used to stratify individuals already at high-risk for bipolar disorder (e.g., offspring of bipolar parents) into likely age-at-onset groups. Defining these AAO subgroups can help guide treatment provision and streamline approaches to early intervention. Future research should aim to externally validate the current model in prospective, phenotypically detailed cohorts.

Chapter 4. Disentangling the relationship between early-life factors, age at onset and functional outcomes in high-risk BD offspring

4.1 Introduction

4.1.1 Rationale

As outlined in previous chapters, age at onset (AAO) has been identified as a factor that influences the clinical trajectory of BD. Early-onset BD has been associated with more severe and chronic illness outcomes compared to late-onset BD (Agnew-Blais & Danese, 2016; Joslyn et al., 2016), but the specific mechanisms underlying this link remain poorly understood. Previous research has suggested that early-life factors such as childhood trauma, family history of mood disorders, stressful life events and pre-morbid drug and alcohol use may contribute to the development and course of BD (Daruy-Filho et al., 2011; Hamshere et al., 2009; Hosang, Uher, et al., 2012; Ortiz et al., 2011; Post et al., 2014, 2016). Indeed, the results of the previous chapter identified several variables that were associated with an earlier AAO including drug and alcohol use, childhood abuse, and adverse life events (Bolton et al., 2022). However, the precise relationship between these factors, AAO, and functional outcomes in BD remains unclear.

To address this gap in knowledge, this chapter aims to build upon the results of Chapter 3 (Bolton et al., 2022) by investigating the potential causal pathways underlying the relationship between early-life factors and AAO, and how these associations relate to functional outcome in BD. The goals of the current chapter are threefold: first, to validate the results of Chapter 3 using prospective longitudinal data; second, to investigate early-life psychosocial factors' relationship with functioning in BD; and third, to disentangle how these relationships are affected by AAO.

To investigate this, the chapter will use data from the Flourish high-risk cohort, which is comprised of children of parents with BD (Goodday et al., 2018). This high-risk cohort provides a unique opportunity to study early-life factors that may contribute to the development and course of BD. Importantly, using this high-risk cohort allows for the collection of data prior to the onset of illness. This prospective data provides an opportunity to examine factors that are present pre-illness, such as childhood trauma, temperament, parent attachment, and pre-morbid drug and alcohol use. Studying these factors over time allows us to gain a deeper understanding of how they may contribute to the onset and progression of illness.

In order to disentangle the relationship between AAO, early-life factors, and functional outcome, this chapter describes an approach using path analysis. Path analysis is a statistical method that is commonly used to investigate the complex relationships between variables (Hoyle, 2011; Nachtigall et al., 2003). In the context of the current study, path analysis will be used to examine the direct and indirect effects of early-life factors on global functioning, while accounting for the influence of AAO. Results from the machine learning analysis in Chapter 3 will inform model development by taking the variables that were significantly associated with AAO (see Chapter 3) and investigating how these relate to global functioning while accounting for the mediating effect of AAO.

By identifying the mechanisms linking early-life factors, AAO, and functional outcomes, this study may help develop more targeted and effective treatments for BD patients. However, working with prospective longitudinal data presents challenges, and using modelling techniques such as path analysis requires careful consideration of model building to ensure valid and reliable results.

4.1.2 Analysis Approaches

4.1.2.1 Dealing with missing data

One of the most significant challenges associated with the analysis of prospective longitudinal data, such as the Flourish dataset, is the presence of missing observations. Missing data can arise for various reasons, including drop-out, data collection errors, or participants refusing to answer certain questions. Missingness can be classified into three types: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR) (Rubin, 1976). MCAR occurs when the probability of a data point being missing is unrelated to any other variables in the dataset. MAR occurs when the probability of missingness depends on observed variables, whereas MNAR occurs when the probability of missingness depends on unobserved variables. Missing data can lead to biased estimates, reduced statistical power, and decreased generalisability of findings. It is therefore important to consider the missing data mechanism and use appropriate statistical techniques to address the issue of missing data in prospective longitudinal datasets.

4.1.2.1.1 Multiple Imputation

Multiple imputation is a statistical technique used to deal with missing data, which involves creating imputed values for the missing data points based on the available observed data (Campion & Rubin, 1989; Rubin, 1976, 1996; Schafer, 1999). It is accepted as the best general method to deal with incomplete data as it can handle all types of missingness, including MCAR, MAR, and MNAR (van Buuren, 2018). The basic principle is to estimate missing data multiple times to create a set of plausible imputed values that can be used for analysis. The multiple imputation process is carried out in three stages: first, the missing values are imputed 'm' times to create 'm' complete datasets; second, the complete datasets are analysed separately; lastly, the results are combined to provide one set of estimates, test statistics and inferences (Gueorguieva, 2017).

Multiple imputation using chained equations (MICE) is a commonly used statistical method for imputation. The approach involves iteratively creating multiple imputations, one variable at a time, using regression models that are conditional on all other variables in the imputation model (Lee & Carlin, 2017; Raghunathan & Siscovick, 1996; Van Buuren et al., 1999). This process generates several complete datasets that can be used for analysis (Little & Rubin, 2014). MICE is based on the concept of joint probability distributions, which refers to the probability distribution of all the variables in the dataset, including the missing data points (van Buuren, 2018). By estimating the missing data points using a series of regression models that capture the relationships between the variables, MICE can impute missing values.

The computational method employed in MICE is Markov Chain Monte Carlo (MCMC) (Brooks et al., 2011; Schafer, 1997). MCMC is used to simulate values for the missing data points by generating samples from the joint probability distribution of the variables in the dataset, where the samples are correlated with each other. MCMC is based on the concept of a Markov chain, which is a stochastic process where the probability of moving from one state to another depends only on the current state and not on the previous states (Brooks et al., 2011). In MCMC, the Markov chain is constructed such that the stationary distribution of the chain is the desired probability distribution (Brooks, 1998). This means that if the chain is run for a long time, the samples generated will be representative of the desired distribution (Spade, 2020).

The MCMC algorithm involves generating a sequence of samples from the target distribution by iteratively proposing a new sample and accepting or rejecting it based on the probability of the proposed sample relative to the current sample (van Ravenzwaaij et al., 2018). Bayesian statistics provides the theoretical framework for MCMC methods, where probability distributions are used to model uncertainty, with prior distributions representing the uncertainty in the model

parameters before the data are observed, and the posterior distribution capturing the updated probability distribution after the data have been observed (Casella & George, 1992; Gelfand & Smith, 1990; van Ravenzwaaij et al., 2018).

Thus, MICE is a powerful technique for imputing missing data in longitudinal datasets. It can handle various types of missingness and provides a flexible and robust way to address missing data, which helps obtain more accurate and reliable model estimates. In the current study, MICE will be used to impute the missing data and provide a complete dataset for analysis.

4.1.2.2 Exploring relationships: Structural equation modelling

To elucidate the relationships between early-life factors, AAO, and functional outcomes, path analysis was employed using structural equation modelling (SEM). SEM is a statistical technique that allows for the estimation of complex relationships between variables in a single model (Gueorguieva, 2017). SEM is a combination of two modelling approaches: confirmatory factor analysis (CFA) and path analysis (Fan et al., 2016). The purpose of CFA is to estimate 'latent' variables (Kline, 2011). These latent variables are not directly measured but are inferred from observed variables in the available data, which are believed to be indicators of the latent variable (Grace, 2006; Hoyle, 2011; Kline, 2011). For example, in the current context, a latent variable might be 'BD severity', which is inferred from observed indicators such as 'symptom severity' and 'functional impairment'. On the other hand, path analysis aims to represent causal relationships between variables (Fan et al., 2016; Ullman & Bentler, 2012). An important feature of path analysis is mediation, which assumes that a variable can influence an outcome directly and indirectly through another variable. By combining these two statistical approaches – CFA and path analysis – SEM can provide valuable insights into the underlying mechanisms that contribute to a particular outcome.

The SEM model consists of two components: the measurement model and the structural model. The measurement model specifies the relationships between the latent variables and their observed indicators, while the structural model specifies the relationships between the latent and observed variables themselves, based on path analysis (Nachtigall et al., 2003).

The default method for estimating SEM models is maximum likelihood, which involves finding the parameter estimates that maximize the likelihood of the observed data given the model (Hoyle, 2011; Kline, 2011). However, there are various assumptions that must be met for estimation using maximum likelihood approaches, including (i) no skewness or kurtosis in the joint distribution of the variables (e.g., multivariate normality); (ii) variables are continuous; and (iii) the proportion of missing data is low (Fan et al., 2009; Hoyle, 2011; Kline, 2011; Lee & Carlin, 2017). In practice however, longitudinal multivariate data rarely confirm to all these assumptions.

The fit of the model to the data can be evaluated using various goodness-of-fit indices, such as the chi-square test, the Comparative Fit Index, and the Root Mean Square Error of Approximation (Fan et al., 1999; Schreiber, 2017). These indices provide information about how well the model fits the data, and whether it is a good representation of the underlying relationships between variables.

One of the key advantages of SEM is its ability to estimate both the direct and indirect effects of variables on each other. This allows identification of potential mediating variables that may explain the relationship between two other variables. For example, childhood abuse may have a direct effect on BD severity, but it may also have an indirect effect on BD severity through its impact on AAO. By including all these paths in the model, we can gain a more comprehensive understanding of the pathways involved in the onset and maintenance of BD.

4.1.3 Objectives

In summary, the current chapter aimed to investigate the relationship between age at onset (AAO) and functional outcome in BD, with a focus on the role of early-life factors. Based on prior research and the results of Chapter 3, it was anticipated that greater scores on negative early-life factors (e.g., presence of childhood abuse, high levels of drug use) would be associated with decreased future functioning, and that these relationships may be mediated by AAO. By utilising the Flourish high-risk cohort, which collected data prior to the onset of illness, the study described in the current chapter used SEM, a statistical method used to investigate complex relationships between variables. The challenge of missing data was addressed using multiple imputation. The current study represents an essential step towards a better understanding of the complex relationship between AAO and clinical trajectory in BD. By building upon previous research and using advanced statistical methods, this study has the potential to significantly improve understanding of the mechanisms underlying the association between AAO and functional outcomes in BD.

4.2 Methods

4.2.1 Participants

The Flourish Canadian high-risk study is a prospective cohort study that began in 1996, aimed at investigating the risk of mood disorders in high-risk families. The study focused on bipolar parents and later expanded to include adult siblings and high-risk offspring. Families were identified through mood disorder subspecialty clinical programs in Ottawa and the Maritimes. The study used semi-structured interviews and consensus reviews by independent research psychiatrists to establish diagnoses of BDI or BDII in the probands. Offspring from eligible families within the age range of 5-25 years completed annual research assessments using validated measures, and clinically significant sub-threshold symptoms were based on operationalised

definitions using all available research and clinical information. The data used in the current study relates to the high-risk offspring of BD parents.

4.2.2 Measures

The Flourish data has over 100 different measures spanning several years, including information on socioeconomic status, life events, parent-offspring relationships, symptom severity, and trait measures such as self-esteem and aspects of temperament. As the model specified in the current study is based on findings from the BDRN model in Chapter 3, the following five questionnaires are focused on for use in the present analysis:

4.2.2.1 Global Assessment of Functioning (GAF)

The GAF is a standardised rating scale used to evaluate an individual's overall functioning in social, occupational, and psychological domains. The GAF score ranges from 0 to 100 and is divided into ten levels, with higher scores indicating better functioning (Aas, 2011; Hall, 1995). The GAF has excellent inter-rater reliability and concurrent validity (Startup et al., 2002).

4.2.2.2 Drug Abuse Screening Test (DAST-20)

The DAST-20 is a self-administered questionnaire that assesses an individual's drug use, abuse, and dependence (Skinner, 1982). It covers a range of drugs, including alcohol, marijuana, cocaine, and prescription drugs. The DAST-20 score ranges from 0 to 20, with higher scores indicating a greater likelihood of drug abuse or addiction. The DAST-20 demonstrates overall good validity and reliability (Cronbach's $\alpha > .80$) (Villalobos-Gallegos et al., 2015).

4.2.2.3 Childhood Experiences of Care and Abuse (CECA)

The CECA questionnaire is a semi-structured interview used to assess childhood experiences of care and abuse in ages 12 and above (Brown & Harris, 1994). The CECA consists of four key scales including: (a) neglect - this refers to parent's disinterest in material care (feeding and clothing),

health, schoolwork, and friendships, and is assessed for each parent or surrogate with whom the child lived for at least 12 months prior to age 17; (b) antipathy, which is defined as hostility, coldness, or rejection shown to the child by parents or surrogate parents; (c) physical abuse – defined as hitting by parents or other older household members; and (d) sexual abuse, which involves contact of a sexual nature by any adult to the child but excludes willing sexual contact with peers. The CECA questionnaire shows satisfactory reliability and validity as a self-report measure for adverse childhood experience (Bifulco et al., 2005). For the purposes of analysis, physical and sexual abuse were combined into one category – 'yes' vs. 'no' for 'ever experienced physical or sexual abuse'.

4.2.2.4 Early Adolescent Emotionality–Activity–Sociability (EAS) Temperament Scale

This 20-item questionnaire is used to assess temperament dimensions of children during early adolescence (Buss & Plomin, 1984). It covers temperament dimensions, including: (a) emotionality - the tendency to become aroused easily and intensely; (b) activity – preferred levels of activity and speed of action; (c) sociability – the tendency to prefer the presence of others to being alone; and (d) shyness – the tendency to be in inhibited in new social situations. These sub-scales are scored from 1 to 5, with higher scores indicating greater levels of temperament. Responses are given by either a parent (for children under 13 years of age) or the offspring themselves. This questionnaire has been extensively studied in children and adolescents and has shown itself to be a reliable and valid measure of temperament (Buss & Plomin, 1984; Mathiesen & Tambs, 1999; Wamboldt & Chipuer, 1990).

4.2.2.5 Life Events Questionnaire – Adapted, Ages 13+

Life events and friendship difficulties occurring in the previous 12 months were assessed using a semi-structured interview procedure adapted from Goodyer et al. (Goodyer et al., 1990, 1997). The questionnaire consisted of 13 items covering a range of events, such as moving house, death

of a loved one, starting a new school, loss of a pet, and hospitalisation. Significant events were recorded and rated by the offspring in terms of negative impact on a 5-point scale from very pleasant to very unpleasant. For the purposes of analysis, responses were coded as 'yes' versus 'no' for having experienced one of the 13 negative life events.

4.2.2.6 Other measures

The Flourish data also includes variables on interview ages, sex, parent and offspring socioeconomic status, primary mood diagnoses, age at diagnosis, lithium response, proband age at onset and proband mood diagnosis.

4.2.3 Statistical Analysis

Data analysis was conducted in R version 4.2.3 (2023-03-15) for Mac OS. The R code used for data pre-processing and analysis is openly available via the Open Science Framework.

4.2.3.1 Pre-Processing

Prior to performing multiple imputation, the raw data underwent pre-processing. This involved several steps to ensure that the data was cleaned, organised, and in a suitable format for analysis. Data cleaning was the first step in the pre-processing procedure, which involved removing any missing or erroneous data points and addressing inconsistencies. Variables with over 90% missing data were eliminated during this stage. Next, data wrangling was performed to convert the data into a structured format that could be more easily analysed. This involved transforming variables and recoding categorical data into numerical formats as necessary. As the study aimed to investigate the mediating effect of AAO on functioning, filtering was applied so that only variables that were recorded pre-AAO were included in the dataset. Finally, data integration was performed to combine multiple datasets into a single, cohesive data frame for analysis. The combined dataset was further assessed for missingness, and variables with over

90% missing values were dropped. Although variables with significant missing data were already eliminated, this additional step was necessary because new variables were created during data wrangling, such as composite scores and separating out component questions for questionnaire variables. Overall, this pre-processing was essential to ensure that the data used in the multiple imputation analysis was accurate, complete, and in a suitable format.

4.2.3.2 Multiple Imputation

Multiple imputation was conducted using the 'mice' package version 3.15.0 in R (van Buuren & Groothuis-Oudshoorn, 2011), which provides a flexible interface for implementing the MICE algorithm for imputing missing data.

4.2.3.2.1 Checks prior to imputation

To ensure accurate and reliable imputations using the MICE algorithm, evaluation of the missing data was conducted beforehand. The amount, pattern, and type of missing data in the dataset were identified through missingness plots, and Little's test was performed to determine whether the missing data were MCAR or not (p-values <.05 indicate the data are not MCAR) (Li, 2013). Data with >90% missing values had already been removed, which reduces imputation uncertainty, thereby increasing the reliability of subsequent analyses.

Data distribution plots were inspected for potential outliers and/or skewness that may have impacted imputation. Multivariate normality tests were carried out to test whether the data are consistent with a multivariate distribution. The 'MVN' package version 5.9 (Korkmaz et al., 2014) was used to run Henze-Zirkler's and Mardia's tests for normality.

To determine the appropriate imputation method for each variable, variable types were explicitly specified within the code. For numerical columns, 'mice' used predictive mean matching (PMM)

to impute missing values, selecting the k-nearest neighbours, and weighting their values based on their correlation with the variable being imputed. PMM is a non-parametric method for imputing missing values in MICE, and therefore is robust to violations of normality. Logistic regression was used for factor columns with two categories, polynomial regression for columns with unordered factors, and proportional odds logistic regression for columns with ordered factors with more than two categories. By selecting appropriate imputation methods based on the data and variable types, the MICE algorithm was able to provide valid imputations for subsequent analyses.

To ensure maximum efficiency and minimal bias, all variables in the dataset were included in the imputation process, helping to make the imputations more valid and reliable(van Buuren, 2018).

4.2.3.2.2 Convergence of imputation chains

After multiple imputation was performed, imputation diagnostics were examined. This included inspection of convergence rates to assess whether the imputations were reliable and accurate. The convergence of the MICE algorithm refers to the point at which the imputation chains have reached a stable posterior distribution, indicating that the algorithm has produced a satisfactory set of imputed values. Trace plots are used to assess convergence by examining the predicted means of the imputed values over each iteration of the algorithm. Convergence occurs when the predicted means reach a stationary phase and the variability between different chains is similar to the variability within each chain. In other words, convergence is achieved when the imputed values are consistent across multiple imputation chains and there is no evidence of significant changes in the predicted values over time. If convergence has not been reached, then the trace plot may show that the predicted values continue to change substantially with each iteration, or that the variability between chains is much larger than the variability within each chain. Trace plots were plotted using 'ggplot2' version 3.4.1 (Wickham, 2016) to assess convergence.

4.2.3.3 Structural Equation Modelling

A structural equation model was employed to investigate the hypothesised direct and indirect relationships between GAF scores (the outcome measure), AAO (the mediator) and the following eight variables: childhood abuse, childhood neglect, drug abuse, frequency of drug use, death of a family member or close relative, and three temperament dimensions: emotional, active, and shy. Not all of the variables from Chapter 3 were able to be matched with the Flourish variables due to methodological differences between the two datasets, but those listed here are those that had available data and have been included in modelling.

4.2.3.3.1 Model Specification

The SEM model included a measurement model and a structural model. The measurement model comprised a latent variable, Childhood Neglect, which was operationalized by the CECA Neglect scores reported by both the mother and father.

The structural model specified the relationships between several predictor variables and global functioning (GAF). To capture the direct effect of AAO on total GAF scores, a path from 'AAO' to 'GAF Total' was specified. The model also included direct paths from seven observed variables – childhood abuse, drug abuse, frequency of drug use, death of a family member or close relative (LEQ8), and temperament dimensions (emotional, shy, active and social) – and one specified latent variable, childhood neglect, to total GAF scores. To investigate the indirect effects of these variables on GAF scores, paths were specified from each of these variables to AAO. The code specified that these predictor variables affect the mediator variable, AAO, which, in turn, affected the outcome variable, GAF scores. Collectively, these indirect effects are the mediation effect.

The model also included several variances and covariances between the predictor variables. For clarity, these are detailed in Table 10. The table can be read as, for example, in the first row: "drug abuse was allowed to covary with drug frequency".

Table 10. Details of user specified variances and covariances between variables in the SEM model. The 'operator' term refers to the syntax used to specify covariance in the R lavaan package.

Left Hand Side	Operator	Right Hand Side
Drug Abuse (Total)	~~	Drug Frequency
	~~	Emotional Temp + Shy Temp + Active Temp + Social Temp
Drug Frequency	~~	Emotional Temp + Shy Temp + Active Temp + Social Temp
Childhood Abuse	~~	Drug Abuse
	~~	Drug Frequency
	~~	Emotional Temp + Shy Temp + Active Temp + Social Temp
Childhood Neglect	~~	Drug Abuse
	~~	Drug Frequency
	~~	Childhood Abuse
	~~	Death of family member or close friend
	~~	Emotional Temp + Shy Temp + Active Temp + Social Temp
Emotional Temperament	~~	Shy Temp + Active Temp + Social Temp
Shy Temperament	~~	Active Temp + Social Temp
Active Temperament	~~	Social Temp

4.2.3.3.2 Model Estimation

The 'semtools' (version 0.5.6.917) package was used to estimate the SEM model, iterating through each of the imputed datasets. The following parameters were specified: the model, the imputed dataset, the "sem" function to estimate the model, the estimator set to robust maximum likelihood, the "mice" package as the imputation method, and the number of imputations as 5. A seed value of 1993 was also specified for replicability.

4.2.3.3.3 Model Summary

The summary() function was used to summarize the results of the SEM analysis. The output of this included goodness-of-fit statistics, and standardised coefficients. The resulting summary provided information about the fit of the model, as well as the estimated coefficients and their standard errors, t-values, and p-values.

4.2.3.3.4 Model Visualisation

Finally, the 'lavaan plot' (version 0.6.2) package was used to visualize the SEM model with path analysis. The resulting plot displayed the observed variables, latent variables, and their relationships. The plot provided a visual representation of the model and its path coefficients, making it easier to interpret the results of the SEM analysis.

4.3 Results

4.3.1 Demographics

There was a total of 308 participants; sociodemographic and clinical characteristics are described in Table 11 and Table 12 below.

Table 11. Means, s.d. and ranges for continuous measures and absolute (n) and relative (%) frequencies for categorical variables in the total sample (n = 308).

Variables		
Sex	Male	126 (41%)
	Female	182 (59%)
Primary Mood Diagnosis AAO	Age in years	19.61 (5.12)
	Unknown Age	174
Primary Mood Diagnostic Categories	Cyclothymia	1 (0.3%)
	Dysthymia	2 (0.6%)
	Mood NOS	4 (1.3%)
	Schizoaffective	7 (2.3%)
	BDI	12 (3.9%)
	BDII	14 (4.5%)
	BD NOS	14 (4.5%
	Depression NOS	14 (4.5%)
	MD Single	30 (9.7%)
	MD Recurrent	36 (11.7%)
	Missing	174 (56.5%)
Proband Mood Diagnosis	Depression NOS	1 (0.3%)
	MD Recurrent	2 (0.6%)
	Schizoaffective	9 (2.9%)
	BDI	131 (42.5%)
	BDII	130 (42.2%)
	BD NOS	11 (3.6%)
	Missing	24 (7.8%)
Interview Age	First	16.68 (7.01)
	Last	24.07 (8.89)
	Unknown	1
CECA Neglect by Mother		11.18 (3.50)
	Unknown	117
CECA Neglect by Father		14.4 (5.43)
	Unknown	122
CECA Childhood Physical or Sexual Abuse	No	272 (88%)
	Yes	36 (12%)
	Missing	0 (0%)
SES Parent (n = 306)	1 = low	1 (0.3%)
	2	7 (2.3%)
	3	32 (10%)
	4	108 (35%)
	5 = high	158 (52%)
	Unknown	2
SES Offspring (n = 146)	1 = low	4 (2.7%)
	2	9 (6.2%)
	3	23 (16%)
	4	63 (43%)
	5 = high	47 (32%)
	Unknown	162

Table 12. Mean (s.d.) for continuous measures and absolute (n) and relative (%) frequencies for categorical variables in the total sample (n = 308) over each time point.

Variable		Time									
		1	2	3	4	5	6	7	8	9	10
GAF	Total	82.29 (10)	81.64 (10)	81.08 (11)	81.32 (10)	81.56 (10)	82.27 (11)	81.16 (10)	79.05 (12)	81.52 (9)	79.59 (11)
	Missing	7	87	128	159	192	208	225	247	264	274
Life Event Questionnaire (LEQ)	Age	18.66 (8)	20.74 (7)	22.52 (8)	23.39 (7)	23.52 (7)	23.50 (6.1)	23.2 (5.6)	NA	NA	NA
	Missing	29 (9.4%)	93 (30%)	142 (46%)	175 (57%)	203 (66%)	233 (76%)	256 (83%)	NA	NA	NA
LEQ1: Changed schools	No	194 (63%)	74 (24%)	117 (38%)	93 (30%)	64 (21%)	46 (15%)	36 (12%)	NA	NA	NA
	Yes	85 (28%)	141 (46%)	49 (16%)	40 (13%)	41 (13%)	29 (9.4%)	16 (5.2%)	NA	NA	NA
LEQ2: Household number changed	No	159 (52%)	113 (37%)	105 (34%)	68 (22%)	57 (19%)	43 (14%)	28 (9.1%)	NA	NA	NA
	Yes	120 (39%)	102 (33%)	61 (20%)	65 (21%)	48 (16%)	32 (10%)	24 (7.8%)	NA	NA	NA
LEQ3: Moved house	No	200 (65%)	138 (45%)	120 (39%)	94 (31%)	62 (20%)	52 (17%)	31 (10%)	NA	NA	NA
	Yes	79 (26%)	77 (25%)	46 (15%)	39 (13%)	43 (14%)	23 (7.5%)	21 (6.8%)	NA	NA	NA
LEQ4: Disaster at home	No	261 (85%)	195 (63%)	151 (49%)	121 (39%)	99 (32%)	68 (22%)	49 (16%)	NA	NA	NA
	Yes	18 (5.8%)	20 (6.5%)	15 (4.9%)	12 (3.9%)	6 (1.9%)	7 (2.3%)	3 (1.0%)	NA	NA	NA
LEQ5: Anything successful or enjoyable outside school/college	No	122 (40%)	85 (28%)	73 (24%)	59 (19%)	43 (14%)	29 (9.4%)	19 (6.2%)	NA	NA	NA
	Yes	157 (51%)	130 (42%)	93 (30%)	74 (24%)	62 (20%)	46 (15%)	33 (11%)	NA	NA	NA

LEQ6: Family or close friend had serious illness or accident	No	174 (56%)	133 (43%)	107 (35%)	84 (27%)	65 (21%)	43 (14%)	34 (11%)	NA	NA	NA
	Yes	104 (34%)	82 (27%)	59 (19%)	49 (16%)	40 (13%)	32 (10%)	18 (5.8%)	NA	NA	NA
LEQ7: You or family or close friend spent time in hospital	No	161 (52%)	127 (41%)	102 (33%)	82 (27%)	50 (16%)	42 (14%)	33 (11%)	NA	NA	NA
	Yes	118 (38%)	88 (29%)	64 (21%)	51 (17%)	55 (18%)	33 (11%)	19 (6.2%)	NA	NA	NA
LEQ8: Family or close friends died	No	213 (69%)	177 (57%)	133 (43%)	99 (32%)	80 (26%)	57 (19%)	43 (14%)	NA	NA	NA
	Yes	66 (21%)	38 (12%)	33 (11%)	34 (11%)	25 (8.1%)	18 (5.8%)	9 (2.9%)	NA	NA	NA
LEQ9: Loss of a pet	No	217 (70%)	177 (57%)	141 (46%)	111 (36%)	87 (28%)	64 (21%)	45 (15%)	NA	NA	NA
	Yes	62 (20%)	38 (12%)	25 (8.1%)	22 (7.1%)	18 (5.8%)	11 (3.6%)	7 (2.3%)	NA	NA	NA
LEQ10: Lost touch with friends	No	183 (59%)	137 (44%)	108 (35%)	84 (27%)	70 (23%)	46 (15%)	37 (12%)	NA	NA	NA
	Yes	96 (31%)	78 (25%)	58 (19%)	49 (16%)	35 (11%)	29 (9.4%)	15 (4.9%)	NA	NA	NA
LEQ11: Difficulties with friends	No	193 (63%)	157 (51%)	129 (42%)	99 (32%)	75 (24%)	53 (17%)	37 (12%)	NA	NA	NA
	Yes	85 (28%)	58 (19%)	37 (12%)	34 (11%)	30 (9.7%)	22 (7.1%)	15 (4.9%)	NA	NA	NA
LEQ12: Bullied or teased	No	237 (77%)	197 (64%)	144 (47%)	125 (41%)	97 (31%)	74 (24%)	49 (16%)	NA	NA	NA
	Yes	42 (14%)	18 (5.8%)	22 (7.1%)	8 (2.6%)	8 (2.6%)	1 (0.3%)	3 (1.0%)	NA	NA	NA
LEQ13: Other significant life events	No	199 (65%)	144 (47%)	115 (37%)	103 (33%)	83 (27%)	60 (19%)	38 (12%)	NA	NA	NA
	Yes	80 (26%)	71 (23%)	51 (17%)	30 (9.7%)	22 (7.1%)	15 (4.9%)	14 (4.5%)	NA	NA	NA

Temperament	Shy	2.44 (0.88)	2.55 (0.93)	2.64 (0.88)	2.59 (0.83)	2.64 (0.88)	2.76 (0.85)	NA	NA	NA	NA
	Social	3.35 (0.74)	3.22 (0.80)	3.17 (0.71)	3.14 (0.73)	3.04 (0.65)	2.89 (0.72)	NA	NA	NA	NA
	Emotional	2.45 (0.88)	2.35 (0.88)	2.40 (0.91)	2.39 (0.90)	2.44 (0.88)	2.53 (0.90)	NA	NA	NA	NA
	Active	3.49 (0.73)	3.44 (0.78)	3.37 (0.74)	3.46 (0.70)	3.33 (0.77)	3.31 (0.73)	NA	NA	NA	NA
	Unknown	55	134	191	225	254	276	NA	NA	NA	NA
Drug Abuse	Total	1.40 (2.56)	1.02 (1.66)	1.04 (1.55)	1.16 (1.88)	NA	NA	NA	NA	NA	NA
	Unknown	135	195	235	265	NA	NA	NA	NA	NA	NA
Drug Frequency	Yearly	33 (11%)	18 (5.8%)	NA	NA	NA	NA	NA	NA	NA	NA
	Monthly	9 (2.9%)	7 (2.3%)	NA	NA	NA	NA	NA	NA	NA	NA
	Weekly	15 (4.9%)	16 (5.2%)	NA	NA	NA	NA	NA	NA	NA	NA
	Daily	10 (3.2%)	2 (0.6%)	NA	NA	NA	NA	NA	NA	NA	NA
	Never	0 (0%)	0 (0%)	NA	NA	NA	NA	NA	NA	NA	NA
	Unknown	241 (78%)	265 (86%)	NA	NA	NA	NA	NA	NA	NA	NA

4.3.2 Multiple Imputation

4.3.2.1 Data distributions and missingness patterns

The distribution of all categorical and continuous variables in the full data frame were inspected prior to imputation (see Appendix C.1. and Appendix C.2.). Both Henze-Zirkler's (H-Z) and Mardia's multivariate normality tests indicated that the continuous variables in the data were significantly non-normal: H-Z = 1.08, p <.001; Mardia skewness = 2234.74, p<.001; Mardia kurtosis = 5.61, p <.001. Additionally, missingness was plotted for both the full data (Appendix C.4. and for the variables used in analysis (Figure 6). This permitted an overall view of how much data was missing and what the missingness pattern was – e.g., MAR, MCAR, MNAR.

Non-normality and high levels of missingness was dealt with by using the non-parametric method PMM for numerical variables in the dataset. Logistic regression was used for factor columns with two categories, polynomial regression for columns with unordered factors, and proportional odds logistic regression for columns with ordered factors with more than two categories.

4.3.2.2 Imputation

Missing data were handled using multiple imputation technique implemented in the 'mice' package in R. As multiple imputation is computationally demanding, only 10 iterations were run initially to ensure that the method was functioning properly and to troubleshoot any problems. One the algorithm was confirmed to be working as intended, the procedure was re-run using 30 iterations, since more iterations are generally considered better for achieving convergence.
A total of 30 iterations were performed, and five imputed datasets were generated. The imputation process involved using all available variables, including the outcome variable, as predictors.

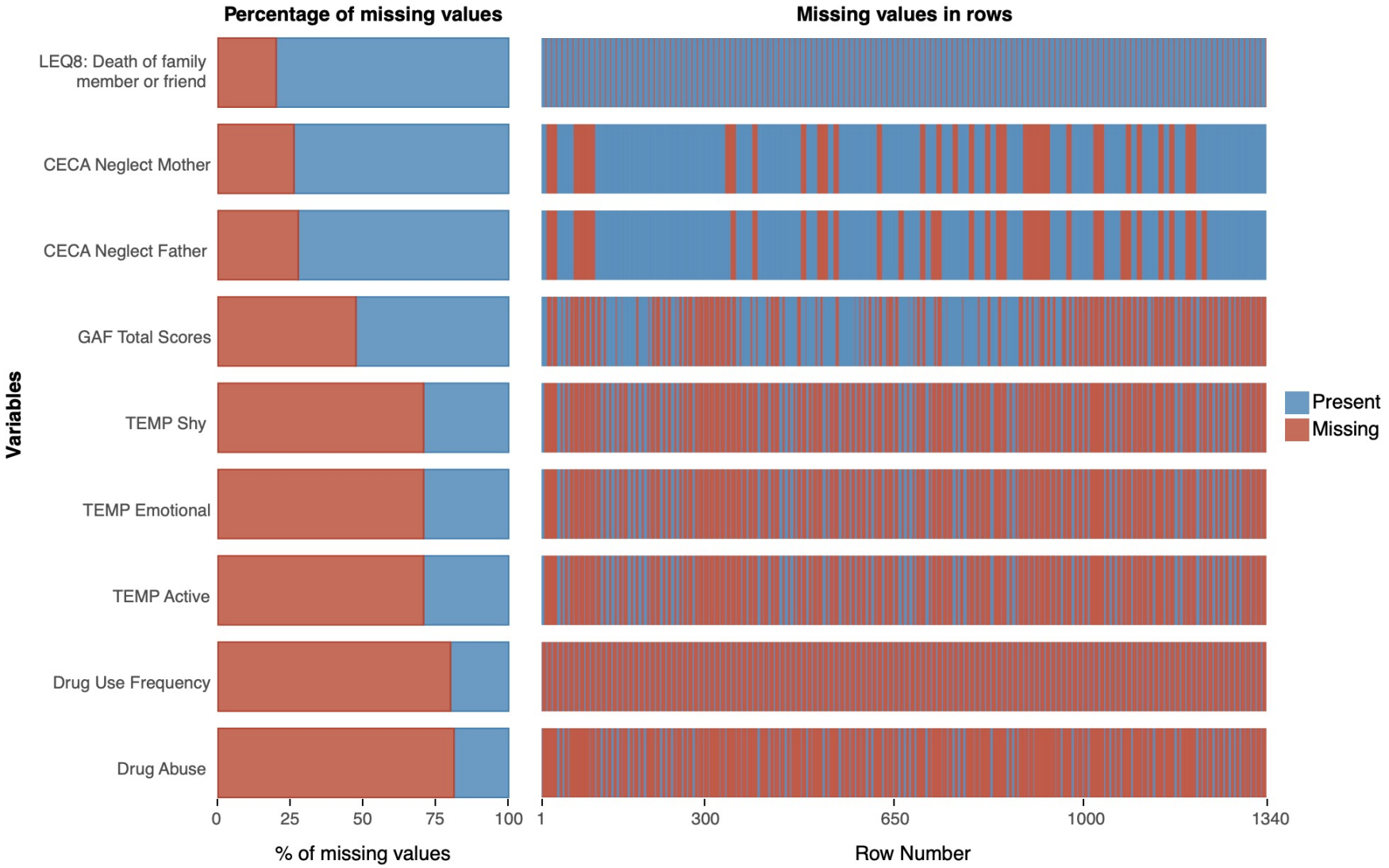

Figure 6. Left hand side: bar plot displaying percentage of missing variables across all time points (n = 308); right hand side: missing values per rows (data stored in long format so there are several rows per participant corresponding to Time1, Time2 etc. per variable).

4.3.2.3 Convergence

Trace plots were used to visually assess the convergence of the imputation chains (Appendix C.3.) . The results showed that the imputation chains had converged, as the variance between chains was similar to the variance within each chain over 30 iterations, indicating healthy convergence (van Buuren, 2018).

4.3.3 Model Summary

To account for non-normality in the data, the robust maximum likelihood (MLR) estimator was when fitting the model. The MLR estimator provides robustness to non-normality by using robust (Huber-White) standard errors and a scaled test statistic. This allowed for more reliable estimates of the model parameters and standard errors, even when the distributional assumptions of traditional maximum likelihood estimation were violated. Several metrics for assessing model fit are examined. The indices' details, as well as the 'general rule for acceptance' (taken from Schreiber, 2008, 2017), are displayed in Table 13 below.

4.3.3.1 Model fit

Table 13. Fit indices and related information.

Fit Indices	Abbreviation	Value	General rule for acceptance
Comparative Fit Index	CFI	0.969	≥ 0.95
Tucker-Lewis Index	TLI	1.00	≥ 0.95
Root Mean Square Error of Approximation	RMSEA	0.073 90% CI: .068 - .078	<.05 with confidence interval .00 - .08
Standardized Root Mean Square Residual	SRMR	0.030	≤ 0.08

The model converged on all five imputed datasets. Rubin's (1987) rules were used to pool point and standard error estimates across the five imputed datasets and to calculate degrees of freedom for each parameter's t-test and confidence interval. Robust corrections were made by

pooling the naive chi-squared statistic, then applying the average (across imputations) scaling factor to the pooled value.

The model fit was evaluated using a chi-squared test, which indicated that the user-specified model fitted the data significantly better than the baseline model, $\chi^2(16) = 598.66$, $p < 0.001$. The scaling correction factor was 0.982, indicating that the model may be slightly underfitting the data. Therefore, additional fit indices were examined to provide a more accurate assessment of the model fit. The Robust CFI value was 0.969 and the Robust TLI value was 1.000, indicating an excellent model fit. The Robust RMSEA was used to assess absolute model fit, with a value of 0.073 (confidence interval: 0.068 - 0.078), suggesting a reasonable fit. The SRMR value was 0.030, indicating an acceptable fit.

4.3.3.2 Direct and indirect effects

The standardised regression coefficients were estimated using the Sandwich estimator for standard errors. A visual summary of the results can be found in Figure 7 and Figure 8.

4.3.3.2.1 Direct Effects

Results showed that the latent variable 'childhood neglect' was significantly negatively associated with GAF scores ($\beta = -0.038$, $p = .003$). There were significant positive relationships between GAF scores and: emotional temperament ($\beta = 0.132$, $p < .001$); shy temperament ($\beta = 0.153$, $p < .001$); and social temperament ($\beta = 0.298$, $p < .001$. There were significant negative associations with GAF scores and: childhood abuse (CECA scores) ($\beta = -0.069$, $p < .001$), drug abuse scores ($\beta = -0.048$, $p < .001$), and active temperament ($\beta = -0.186$, $p < .001$). No significant relationships were found between AAO ($\beta = 0.001$, $p = .899$), drug frequency ($\beta = -0.013$, $p = .213$), or death of a family member or close friend ($\beta = -0.009$, $p = 0.384$) and GAF scores.

The following variables were all significantly positively associated with AAO: childhood abuse (β = 0.094, p <.001), death of a family member or close friend (β = 0.097, p<.001), frequency of drug use (β = 0.051, p <.001), emotional temperament (β = 0.155, p < .001), shy temperament (β = 0.077, p < .001), active temperament (β = 0.222, p < .00.1), and social temperament (β = 0.050, p < .001). Drug abuse scores were significantly negatively related to AAO (β = -0.034, p = .010). There was no significant association between AAO and childhood neglect (β = -0.018, p = .175).

4.3.3.2.2 Indirect effects

No significant indirect effects were found, with p-values across all indirect effects ranging from 0.815 to 0.817.

4.3.4 Post-hoc Analysis

Modification indices were run to assess the impact of modifying the structure of the model. Modification indices can indicate how much the model fit would improve if a particular path was added or a model constraint freed. The 'modindices.mi' function from the semTools package (version 0.5.6.917) (Jorgensen et al., 2023) was used to run modification indices. This function employed a method which involves pooling the gradient and information matrices across imputed data sets (Mansolf et al., 2020), which is a method analogous to the "D1" Wald test that uses an adjusted estimate of parameters' variance to account for additional variability introduced by imputation (Li et al., 1991). While results indicated that changing the structure of the model may improve fit, the suggested changes were not theoretically appropriate. For example, the results suggested a direct effect of variables measured at a later time on variables at an earlier time point, which is not theoretically plausible.

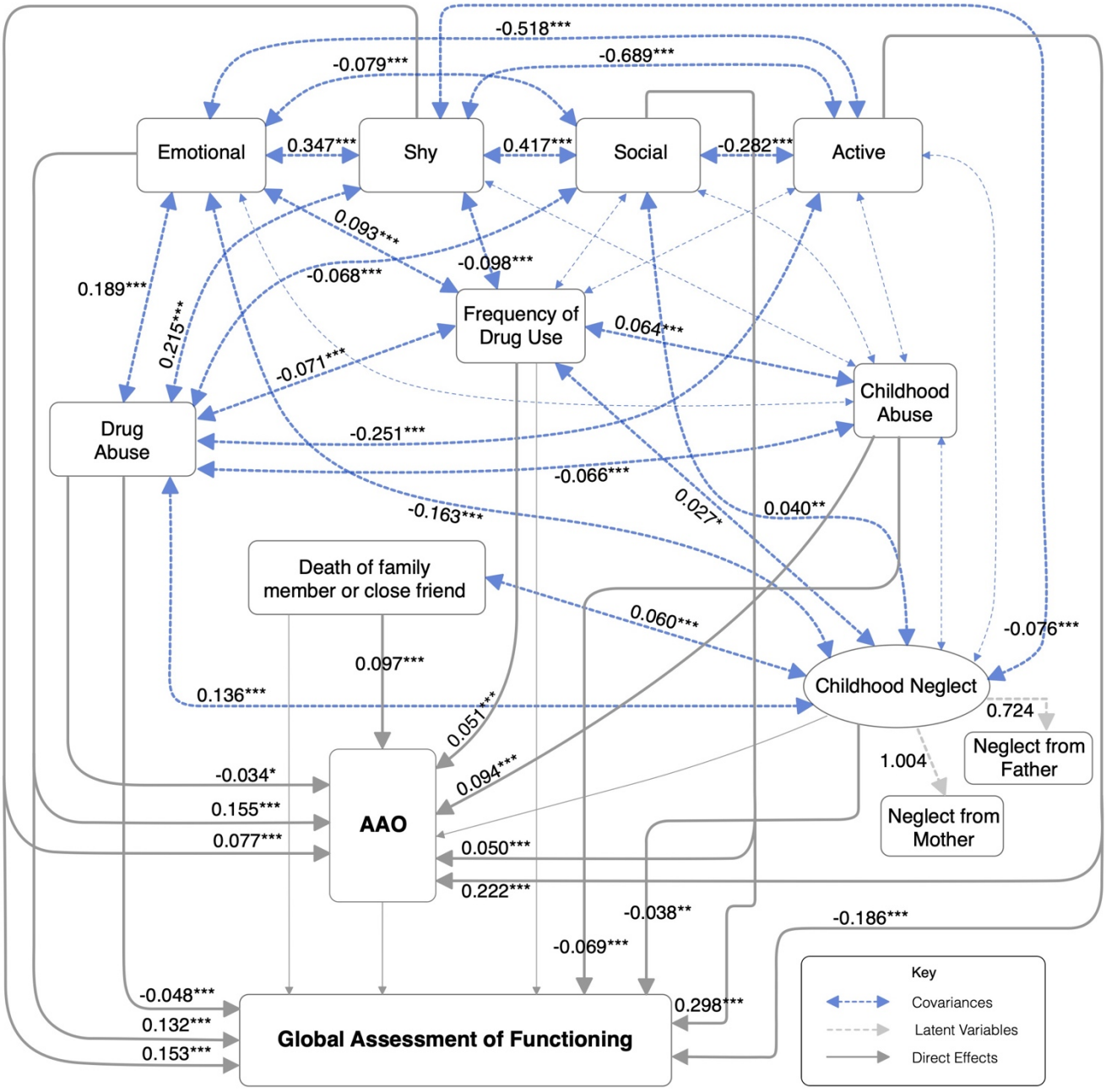

Figure 7. Full SEM analysis diagram including the pathways between AAO, global function and the following variables: four aspects of temperament (emotional, shy, social, active), drug abuse, drug frequency, childhood abuse, childhood neglect, and death of a family member or friend. Covariances between independent variables are represented by blue dotted arrows.

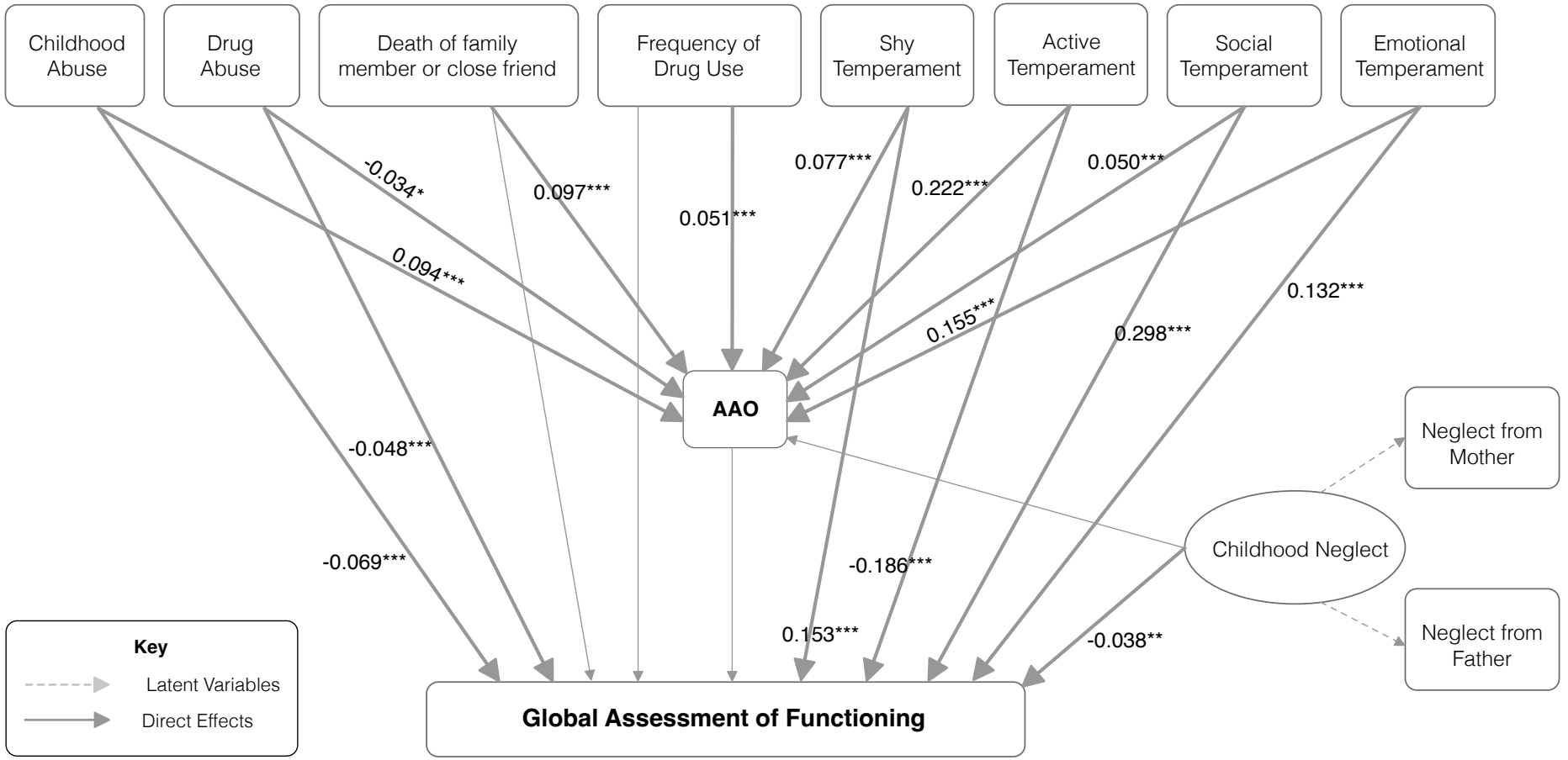

Figure 8. Simplified path diagram showing only significant direct and indirect effects and omitting the covariances between independent variables.

4.4 Discussion

The current chapter uses prospective data from 308 high-risk offspring of BD probands to investigate the role of early-life factors on subsequent AAO of mood disorder and functional outcomes. This is the only known study to investigate these relationships by employing multiple imputation with SEM using prospective longitudinal data. The goal was to examine potential mechanistic pathways between early-life factors and global functioning, considering the potential mediating role of AAO. Analyses were performed on five multiply imputed datasets to identify significant direct and indirect relationships between variables and results were pooled. The findings have implications for understanding the causal pathways between risk correlates, early AAO and functioning in BD, and can thus inform treatment and intervention.

4.4.1 Main findings

Findings showed that the latent variable childhood neglect was negatively associated with GAF scores, indicating that childhood neglect decreased future global functioning. The presence of childhood physical and/or sexual abuse, increased levels of drug abuse, and a greater endorsement of 'active temperament' traits were also related to a decrease in global functioning. In contrast, emotional, social, and shy temperaments were associated with increased global function. No significant relationships were found between global functioning scores and AAO, drug frequency, or death of a family member or close friend.

The following variables were significantly associated with an increase in AAO: childhood abuse, death of a family member or close friend, increased frequency of drug use, and greater endorsement of emotional, shy, active, and social temperament traits. In contrast, increased drug abuse scores were significantly related to a younger AAO. There was no significant association between AAO and childhood neglect. Importantly, no significant mediating effect of AAO was found. The following discussion assesses the extant literature to contextualise these

findings, and implications for understanding aetiological mechanisms and improving interventions are examined.

4.4.2 Childhood abuse and neglect

The current results indicate that the presence of childhood abuse was associated with an increase in AAO, while analysis did not show a significant relationship between neglect and AAO. These findings directly contradict a large body of previous research, including the results of Chapter 3 (Agnew-Blais & Danese, 2016; Bolton et al., 2022; Daruy-Filho et al., 2011). However, results from a 2013 study by Miller et al. demonstrated that the Val66Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene interacted with the presence of childhood sexual abuse to influence the AAO of BD. Specifically, BD individuals with the Met allele (i.e., Val/Met or Met/Met genotype) and a history of childhood sexual abuse had an earlier AAO of BD, while this effect was not observed in non-Met allele carriers (Val/Val genotype) (Miller et al., 2013). These findings suggest that the presence of the Met allele in combination with childhood sexual abuse may contribute to the development of BD at an earlier age. Consequently, the absence of a relationship between childhood abuse and decreased age at onset in the current sample may be due to a lower frequency of Met allele carriers, and therefore a lack of this epigenetic effect. Notably, the Val66Met polymorphism is a less common variant of the BDNF gene, occurring in around 30% of the U.S. population, compared to the Val/Val variant which occurs in 50-70% of the U.S. population (Shimizu et al., 2004).

However, as genetic information was not included in the present study, the validity of this claim cannot be confirmed. Therefore, it is crucial to contextualise the results within the broader scope of family dynamics when interpreting this finding. For instance, prior research indicates that childhood abuse is related to a decrease in family functioning, including increased parental stress and high family conflict (Scully et al., 2020). In turn, it is posited that decreased family functioning

results in parents being less able to understand and reflect on the needs of their child (Fonagy & Steele, 1991; Fonagy & Target, 2008; Scully et al., 2020). Given that the present study operationalises AAO as 'age at receiving a diagnosis', attenuated understanding of and reflection on a child's needs by their parents may lead to a delay in recognising pathological symptoms and seeking a diagnosis. This therefore may have confounded the associations in the current study. To clarify this relationship, future research would benefit from including family and parent functioning in models examining the pathways from childhood abuse to BD AAO.

The idea that childhood abuse was associated with an increased AAO due to diagnostic delay is indirectly supported by the finding that both childhood abuse and neglect were associated with decreased global functioning. This indicates that childhood abuse does indeed have a negative impact on outcome, even if this is not observed as a decrease in AAO. This finding is corroborated by previous research demonstrating that high-risk offspring of BD parents who were exposed to childhood abuse and/or neglect had significantly lower GAF scores, IQ, poorer cognitive performance, and diminished executive functioning compared to those who had not experienced abuse or neglect (Berthelot et al., 2015; Savitz et al., 2008). A history of childhood abuse in BD has further been associated with increases in rapid cycling, suicide attempts, frequency of mood episodes, comorbidities, and psychotic features (Etain et al., 2008). More generally, childhood abuse correlates with impairments in psychological well-being and functioning in adulthood, including decreased life satisfaction, struggles with intimate relationships, problems parenting, and job and financial difficulties (Anda & Felitti, 2004; Colman & Widom, 2004; DiLillo, 2001; Friedmann et al., 2020; Grilo et al., 1999; Hughes et al., 2016). This tallies with the current finding that abuse and neglect in childhood is related to subsequent worse global functioning.

Given these findings, it is important to consider how the negative effects of childhood abuse can be mitigated in treatment approaches and early intervention strategies. In terms of psychological interventions, trauma-based therapy such as trauma-focused cognitive–behavioural therapy (TFCBT) and eye movement desensitisation reprocessing (EMDR) have been shown to be effective in the treatment of post-traumatic stress disorder (PTSD), according to the results of a Cochrane systematic review (Bisson et al., 2013). Additionally, both TFCBT and EMDR have been shown to be effective treatments for children and adolescents (Lewey et al., 2018), making them appropriate candidates for early intervention approaches. These therapies may therefore be a promising therapeutic avenue for BD individuals with a history of childhood abuse.

Furthermore, treatments targeting affective instability have been proposed as a key focus for prevention and management in BD (Hett et al., 2022). Evidence suggests that the impact of childhood abuse on clinical outcomes in BD is mediated by mood instability (Marwaha et al., 2020), and therefore therapies that include strategies for affect regulation warrant further investigation to determine their efficacy (Hett et al., 2022). Existing treatments that have components targeting affect regulation include mindfulness-based cognitive therapy (MBCT) and dialectical behaviour therapy (DBT). Preliminary evidence indicates that MBCT and DBT for BD can improve symptoms and lead to increased psychological well-being and decreased emotional reactivity (Eisner et al., 2017; Lovas & Schuman-Olivier, 2018). However, further research is needed to confirm these effects and to establish these therapies' utility in BD individuals with a history of childhood abuse.

4.4.3 Drug use

Beyond childhood physical, sexual, and emotional abuse, the present results further indicate that an increase in drug abuse, including alcohol abuse, is associated with a decline in global functioning. This is confirmed by previous research, with the deleterious impact of drug and/or

alcohol use on functioning in psychiatric disorders being well-studied (Messer et al., 2017). Findings have demonstrated high rates of comorbid substance abuse in BD, which is accompanied by increased symptom severity (Cassidy et al., 2001; Nesvåg et al., 2015; Nolen et al., 2004; Ringen et al., 2008). Directly corroborating the present findings, BD individuals with substance use problems have been shown to have lower occupational status, educational attainment, and GAF-scores compared to the general population (Lagerberg et al., 2010). A trend towards higher rates of suicidality and decreased medication compliance was also found in this group of BD individuals (Lagerberg et al., 2010).

Importantly, the association of drug use with functioning in BD is likely multifaceted, as environmental factors in childhood and adolescence likely influence both premorbid functioning and susceptibility to later drug use. For instance, results have shown that greater lifetime prevalence of childhood physical and/or sexual abuse, conduct disorder, and PTSD are significantly correlated with higher rates of substance misuse (Goldstein et al., 2008). Moreover, results from cross-sectional and longitudinal research indicate that both impulsivity and mood instability are related to problems with alcohol, but not the frequency of use, and that heavy drinking predicts subsequent increases in affective lability (Atkinson et al., 2019; Simons, 2003; Simons et al., 2009; Simons & Carey, 2006; Veilleux et al., 2014). This, coupled with evidence that that the path between childhood abuse and drug misuse in BD may be mediated by increased impulsivity (Marwaha et al., 2020), underscores the likely importance of mood instability and impulsivity in the development and maintenance of drug use problems. BD individuals may thus benefit from therapeutic approaches such as CBT, MBCT, and DBT, either alone or in combination with medication, to target mood lability and impulsivity to achieve and maintain recovery from substance use disorders.

The current analyses indicated that higher frequency of drug use in high-risk offspring was linked to a later AAO, which substantiates the results from Chapter 3. Yet, previous research on the association between drug use, particularly alcohol use, and the age of onset of BD has yielded mixed results. Some studies show that pre-existing alcohol use is significantly associated with an earlier AAO (Azorin et al., 2013; Holtzman et al., 2015; Lin et al., 2006), while others have found the opposite association (Lagerberg et al., 2011; Strakowski et al., 2005). It is possible that age restrictions on purchasing and accessing alcohol may confound the relationship between alcohol use and early onset BD. It is also important to draw the distinction between drug frequency and drug abuse in the present study. Increased drug frequency does not always mean increased abuse – indeed, increased age means that the frequency of consuming non-illicit drugs such as alcohol will undoubtedly increase, but this increase does not have to be accompanied by problems with alcohol use. In this context, the association between drug frequency and increased AAO can be understood. Having said this, it is important to consider that the effect of frequent drug and alcohol use may mean that individuals do not recognise their first incidence of impairment as related to BD and instead attribute it to substance use, artificially inflating their reported age of onset (Berk et al., 2017; Goldberg, 2001). Early prodromal symptoms, such as sleep disturbances and anxiety symptoms, may also be attributed to drug use rather than recognised as part of the clinical trajectory of early-stage BD (Stein & Friedmann, 2008). Anxiety symptoms have been found to be both a cause and a consequence of heavy alcohol use, as well as a clinical precursor in BD (Duffy, 2014; Duffy et al., 2014; Kushner et al., 2000). Furthermore, alcohol use is believed to increase the risk of depressive, rather than manic symptoms (Baethge et al., 2008; Sideli et al., 2019), which may explain why increased alcohol use is not associated with an earlier age of onset of BD, as a manic episode is required for a clinical diagnosis of BD.

4.4.4 Temperament

Results indicated that social, shy, and emotional temperaments improved global functioning. Previous research on personality traits in high-risk and BD individuals has mainly focused on affective temperaments – i.e., anxious, irritable, cyclothymic, hyperthymic, and depressive temperaments – which differ from the temperament domains examined in the present study. However, given that personality traits cluster, it's likely that the temperaments studied in this research share some underlying characteristics with those examined in previous studies. Thus, despite differences in the exact temperament dimensions studied, the current results can be viewed in the context of prior research.

For instance, while the finding that emotional temperament improves global functioning may appear counterintuitive, research has demonstrated that in BD higher ratings of cyclothymia and irritability (which are traits associated with emotionality) were associated with better processing speed, working memory, reasoning, and problem-solving (Russo et al., 2014). The reverse relationship was true in healthy controls (Russo et al., 2014). It's possible that better performance in these cognitive areas could contribute to the overall enhancement of functioning observed in the current study, which includes social, psychological, and occupational domains. Notably, further research has shown that BD is associated with higher IQ scores and excellent school performance in childhood (Koenen et al., 2009; MacCabe et al., 2010). Additionally, mood instability (which parallels increased endorsement of emotional traits) in BD individuals has been associated with increased set-shifting abilities – the ability to shift attention and cognitive strategies from one task or mental set to another – compared to healthy controls (Aminoff et al., 2012). These results highlight that it may not be that increased scores on emotional, shy, and social temperaments are the reason for increased functioning per se. Rather, these traits may index cognitive flexibility and efficiency which is then associated with higher IQ and academic performance.

It is important to note that the results of the current study pertain to the offspring of BD parents, meaning that while these individuals are at elevated risk for developing BD, not all of them have received a BD diagnosis. To avoid an underpowered sample however, the present study was not able to control for diagnosis-type in analysis. Interestingly, evidence suggests that individuals who are at high risk for BD but do not meet the threshold for a diagnosis, may demonstrate adaptive traits compared to healthy controls (Greenwood, 2016; Higier et al., 2014). For instance, a 2014 study by Higier et al. investigated neurocognitive functioning and temperament in twins discordant for BD – where one twin had a BD diagnosis while the other did not. Results showed that BD co-twins had elevated scores on a 'positivity' temperament scale, indicating traits of social ease, confidence, and assertiveness, as well as superior neurocognitive performance on tests of verbal learning and fluency relative to demographically matched healthy control twins (Higier et al., 2014). This aligns with the current finding that social temperament was associated with increased global functioning. Additionally, a considerable amount of research has shown a link between BD and enhanced creativity, with studies indicating that creative professions have an overrepresentation of BD individuals, and that unaffected first-degree relatives exhibit high levels of success and creativity in artistic occupations (Andreasen, 1987; Greenwood, 2016; Jamison, 1989; Ludwig, 1992; Post, 1994). This suggests that certain aspects of the bipolar spectrum may confer advantages, while severe expressions of symptoms may negatively influence achievement (Greenwood, 2016). Indeed, elevated scores for shy, social, and emotional temperaments parallels stereotypes of the 'artistic temperament' (Greenwood, 2016; Kyaga et al., 2011; Motto & Clark, 1992), and may help to explain why these traits were associated with increased global functioning, which includes occupational domains.

While emotional, shy, and social temperaments appear to be correlated with improved outcomes, the current findings indicate that active temperament was related to a decrease in

global functioning. Active temperament was operationalised using items concerning 'speed of movement', energy, and being 'always on the go'. Higher scores on these traits have been found to be predictive of subsequent hyperactive and impulsive behaviour (Frick et al., 2018), and children with ADHD have been shown to exhibit significantly higher scores on active temperament dimensions (Foley et al., 2008). This suggest that increased active temperament in the current sample may overlap with ADHD traits and subsequent diagnosis. In turn, ADHD individuals have been found to exhibit deficits in executive function including poorer working memory, planning, and inhibition compared to controls (Krieger et al., 2019; Nigg et al., 2010; Sergeant et al., 2002). Significant impairment in social and academic functioning has also been shown in children with ADHD (Heiligenstein et al., 2010; Ros & Graziano, 2017). Taken together, these findings can help explain why increased active temperament was associated with decreased global functioning in the present study.

Another important consideration with regards temperament measures is that there was no corresponding information on the time of assessment. It is therefore not possible to determine whether temperament ratings were conducted pre- or post-scoring for global functioning and AAO. Thus, the temporal direction of the relationship between emotional, shy, social, and active temperaments and functioning cannot be determined. This is an important consideration as prior research has demonstrated that BD individuals exhibit continuously varying temperament and personality traits (Qiu et al., 2017), suggesting that these characteristics may not be stable over time, as is the case with healthy individuals. Consequently, the relationship between global functioning and these temperament domains may be constantly changing, and so the strength of these relationships should be interpreted with caution.

It is further important to consider the temporal course of these variables when evaluating the finding that all aspects of temperament are associated with a later AAO. If temperament is

assessed after the onset of BD, symptoms may have influenced scores. For example, if an individual experienced a manic episode before being assessed for their temperament, they may score higher on measures of activity or energy, even if these traits were not as prominent before the onset of the disorder. Conversely, if temperament scores were assessed before the onset of bipolar disorder, they may reflect more stable traits that are less likely to be influenced by the disorder itself, providing more confidence in the validity of the current results. Therefore, future research should aim to control for the timing of temperament assessments and use appropriate statistical methods to account for potential confounds.

This is especially important given that some findings contradict those of the present study, with research suggesting increased emotional temperament predicted an earlier AAO (Oedegaard et al., 2009), while other studies have found that increased depressive temperament predicted a later AAO (Azorin et al., 2013). Although the reasons for the associations in the current study remain speculative, one possible explanation is that these temperamental traits may help individuals cope with the symptoms of BD and delay the onset of the disorder. For example, individuals who are more emotionally expressive may be better able to regulate their emotions and cope with mood swings, while individuals who are more socially connected may have better social support networks to help them manage the disorder. Similarly, individuals who are more active and energetic may be better able to cope with the high-energy states (mania or hypomania) that are characteristic of BD. Conversely, individuals with a shy or introverted temperament may be less likely to engage in risky or impulsive behaviours, which are often associated with BD. This could also contribute to a later recognition of BD symptoms and thus a delay in AAO. Of course, it is also important to place temperament in the context of the other variables in the study when looking at its relationship with AAO. For example, all aspects of temperament shared significant variance with drug abuse. Increased drug use may thus

confound the relationship by masking the true AAO of BD, with symptoms being incorrectly attributed to substance use.

Overall, temperament is an important factor to consider when evaluating functioning and AAO in BD. However, the temporal course of temperament assessment should be carefully controlled to ensure accurate results, and further research is necessary to determine underlying mechanisms and potential confounding factors. Understanding the relationship between temperament and AAO may contribute to the development of more effective prevention and intervention strategies for BD. This may involve attitudinal-focused interventions, with research promoting the use of schema-focused cognitive therapy which aims to increase acceptance of, and adaptability to, illness by targeting self-related schema including temperament dimensions, developmental experiences, and cognitive vulnerabilities (Ball et al., 2003).

4.4.5 Life events

In contrast to previous research, including findings from Chapter 3 (Bolton et al., 2022), the current study found that exposure to 'death of a close friend or relative' was linked to an increased AAO. This goes against the expected direction of the relationship, which suggests that negative early-life experiences interact with a person's predisposed vulnerability to trigger disorder onset (Brietzke et al., 2012; Horesh et al., 2011). However, research has indicated that childhood trauma, including negative life events such as the death of a close friend, was significantly associated with greater mood instability only in BDI, while no such association was found for individuals with BDII or major depression (Marwaha et al., 2016). It follows that increased levels of mood instability may confer an earlier AAO, as greater lability in mood states may be more likely to be identified as pathological. In the present study, it may be that the mix of diagnostic categories in the current sample masked this association. Furthermore, evidence suggests that the negative impact of life events on the development of BD lessens with age

(Hillegers et al., 2004), possibly due to the acquisition of effective coping mechanisms or the occurrence of other neutralising life events. These findings suggest that the relationship between life events and AAO in BD may be more complex than previously thought. While negative life events are often considered a risk factor for an earlier onset of BD, the timing and nature of these events may play a role in determining their impact on AAO. Further research is needed to clarify these relationships and to identify potential protective factors that may mitigate the impact of negative life events on AAO in BD.

4.4.6 Insights into causality

The present study offers an important extension from Chapter 3, as it uses SEM to investigate theoretical causal pathways. While it was expected that there would be a significant mediating effect of AAO on the relationship of early-life variable on global functioning, no such associations were found. It may be that AAO does however show a mediating effect on other variables not included in the present analysis. The Flourish cohort has an extensive number of measures that were not specifically investigated in the current study, as the primary aim was to build upon model results from Chapter 3. While post-hoc analysis could have been conducted to include other theoretically relevant variables in the path model, is it important to avoid over-specifying models in SEM. Over-specification refers to the situation where the model includes more parameters than necessary to adequately describe the data. Over-specification can result in several problems, including decreased statistical power, overfitting, and increased complexity, making the results less reliable and reducing the practical use of the model in terms of informing treatment approaches and communicating the findings. As the model fit indices for the current model indicated a good fit to the data, adding in more paths to analysis may have results in over-specification.

Future research would benefit from employing prospective longitudinal data, such as the Flourish dataset, to examine whether the AAO mediates the relationship between other potential risk factors, including other life events, medication use, comorbidities, and various aspects of personality and functioning such as self-esteem, and depression and mania ratings. This would provide a more comprehensive understanding of the causal pathways involved in the onset and progression of BD and inform the development of effective interventions.

Currently, the precise relationship between earlier onset and clinical course remains unclear, but the present results suggest that early-onset may be a risk marker (Feinleib, 2001), rather than a direct cause of worse functional outcomes. In other words, early-onset is a factor that is associated with poorer clinical outcomes, but other factors may be more important in determining the course of the disorder. For example, factors such as childhood abuse, childhood parental neglect, and premorbid drug abuse may play a more significant role in the causal pathways of poor clinical and functional outcomes in BD. Despite this, AAO can still be a useful indicator for healthcare providers to identify individuals who are at increased risk of developing more severe symptoms.

4.4.7 Strengths and Limitations

The present study used prospective data from a large sample of high-risk offspring of BD parents to explore the relationship between early-life factors, AAO, and global functioning. This is the first known study to investigate these relationships using multiple imputation with SEM, a powerful statistical method that allowed the examination of potential mechanistic pathways between early-life factors and global functioning while accounting for missing data. Furthermore, the use of longitudinal data allowed us to examine temporal relationships between variables and increase the confidence in the direction of causality. By employing multiple imputation with SEM

on five datasets, significant direct and indirect relationships were identified between variables with a high degree of precision, and results were pooled to improve statistical power.

Despite the strengths of the study, several limitations must be considered when interpreting the results. Notably, the sample was predominantly White and from middle-class backgrounds and consisted of high-risk offspring of BD probands, which may limit the generalisability of the findings to other populations. Importantly, not all the sample had received a diagnosis of BD, with most participants not having received a mood-related diagnosis at all. For those that had, recurrent major depression was the most common diagnostic category. Furthermore, the study relied on self-reported measures of childhood abuse, neglect, and life events, which may be subject to recall bias and limit the accuracy of the results.

In terms of analysis approaches, although multiple imputation with SEM is a powerful statistical method, it is not immune to bias, and the results should be interpreted with caution. Additionally, the study did not account for potential confounding variables, such as comorbid mental health conditions or medication use, which may have influenced the results. Deficits in global functioning could be related to medication effects, but this was not able to be controlled for in analysis. Due to a limited sample size, which is part and parcel of working with detailed prospective data, it was not possible to differentiate between the types of mood disorder (e.g., BDI vs. BDII) in analyses. This is important as they may have different aetiologies and treatment implications. Also, the study did not assess the severity or duration of childhood neglect and abuse, which may be important factors to consider when examining their impact on global functioning and AAO. It would be additionally helpful to include not just stressful life events but also examine the impact of positive events, as BD individuals have been shown to exhibit increased manic symptoms in response to goal-striving events (Nusslock et al., 2007). Finally, the

study did not include measures of genetic factors or gene-environment interactions, which may play a significant role in the development of BD.

4.4.8 Conclusions

In conclusion, the present study utilised multiple imputation with SEM to investigate the relationship between early-life factors, AAO, and global functioning in a large sample of high-risk offspring of BD probands. While the expected significant mediating effect of AAO on the relationship between early-life variables and global functioning was not found, the study's findings have important implications for understanding the causal pathways between risk correlates, AAO, and functioning in BD, and can inform treatment and intervention strategies aimed at improving functional outcomes in individuals with BD.

The results of the present study highlight the potential importance of mood instability as a marker underlying the relationships between the identified variables and global functioning and AAO in individuals with BD. Specifically, mood instability emerged as a potential common thread among the variables found to be significantly related to these outcomes. These findings suggest that mood instability may represent a critical target for interventions aimed at improving functional outcomes in individuals with BD. Future research should further explore the role of mood instability as an illness marker in BD and other psychiatric disorders, which may inform the development of more effective and targeted interventions. Consistent with this assertion, increasing evidence implicates mood instability in the development and trajectory of psychiatric disorders in general, and BD in particular (Patel et al., 2015). Notably, greater levels of mood instability have been associated with an earlier BD AAO (Henry et al., 2008; Miklowitz et al., 2022), and evidence suggests that mood instability is correlated with poorer long-term outcomes such as longer duration and increased severity of mood episodes, shorter time to recurrence of episodes, decreased psychosocial functioning, increased reliance on healthcare services, and

elevated use of psychotropic medications including antipsychotics and mood stabilisers (Miklowitz et al., 2022; O'Donnell et al., 2018; Patel et al., 2015; Perlis et al., 2006; Stanislaus et al., 2020). This closely parallels the picture seen in the prognosis of early-onset BD. Mood instability may therefore be of potential mechanistic relevance to the expression and clinical course of early-onset BD.

Overall, by identifying specific early-life factors that are associated with a later onset of BD and increased global functioning, this study can contribute to the development of targeted interventions aimed at improving functional outcomes in individuals with BD. Nonetheless, the study's limitations must be considered when interpreting the results, and future research should aim to address these limitations and replicate the findings in other populations.

Chapter 5. What factors are associated with mania and depression instability and severity in BD?

5.1 Introduction

Mood instability is a relatively common experience in the general population, with prevalence estimates of 13.9% (Marwaha, Parsons, Flanagan, et al., 2013). Mood instability (MI) can be defined as "rapid oscillations of intense affect, with a difficulty in regulating these oscillations or their behavioural consequences" (Marwaha et al., 2014). It is a prominent transdiagnostic feature of several psychiatric disorders, with MI being documented in 12.1% of adults (n = 27704) who presented to a UK mental healthcare service (Patel et al., 2015). MI was most frequently reported in individuals with BD (22.6%) and was associated with more adverse outcomes, including greater number of days spent in hospital, greater frequency of hospital admissions, and an increased likelihood of prescription of antipsychotics or non-antipsychotic mood stabilisers (Patel et al., 2015).

Increasing evidence implicates MI in the development and trajectory of psychiatric disorders in general, and BD in particular (Patel et al., 2015). Self-reported MI has been observed in offspring at high genetic risk of BD, as well as newly diagnosed patients (Birmaher & Axelson, 2005; Duffy, Keown-Stoneman, et al., 2019; Stanislaus et al., 2020). Evidence indicates that elevated levels of MI are a risk factor for the subsequent onset of BD (Hafeman et al., 2016), and are present in the prodromal phases of the disorder (Malhi et al., 2014). This is perhaps unsurprising given that mood fluctuations between episodes of depression and mania are the hallmark of BD. However, beyond the switch in polarity of mood episodes, evidence suggests that inter-episode euthymic periods are characterised by elevated MI (Harrison et al., 2016; Henry et al., 2008). This suggests that BD is better viewed as a disorder of chronic MI rather than an episodic disorder with inter-episodic periods of 'wellness' (McKnight et al., 2017).

Notably, greater levels of MI have been associated with an earlier AAO (Henry et al., 2008; Miklowitz et al., 2022). Younger patients and those who have experienced childhood maltreatment are reported to experience greater MI than older patients and those with no history of childhood abuse (McKnight et al., 2017; Teicher et al., 2015). Evidence also suggests that MI in BD is correlated with poorer long-term outcomes such as longer duration of mood episodes, shorter time to recurrence of episodes, decreased psychosocial functioning, increased reliance on healthcare services, and elevated use of psychotropic medications including antipsychotics and mood stabilisers (Miklowitz et al., 2022; O'Donnell et al., 2018; Patel et al., 2015; Perlis et al., 2006; Stanislaus et al., 2020). This clinical picture closely parallels that seen in the prognosis of early-onset BD (see Chapter 1 Section 1.4.3.1), and suggests that MI may contribute to the onset and progression of BD.

However, the mechanisms underlying these relationships remain unclear. It is proposed that MI is comprised of three core dimensions: lability, intensity, and capacity to regulate these changes in mood (Henry et al., 2008; Marwaha et al., 2014). Mood intensity denotes the magnitude at which positive or negative emotions are experienced, whereas mood lability relates to the frequency of observed fluctuations in mood. Evidence suggests that mood lability and mood intensity can differentiate between diagnostic groups. Both borderline personality disorder and ADHD are associated with higher affective intensity scores compared to those with BD, while BD individuals show greater lability than those with ADHD and other personality disorders (Henry et al., 2001).

While the way in which these dimensions of MI are operationalised and measured varies between studies (Marwaha et al., 2014), previous research has used self-report questionnaires such as the Affective Lability Scale (Harvey et al., 1989) or the Affect Intensity Measure (Larsen et

al., 1986). However, these one-off measures used in isolation do not adequately capture the key features of MI (Marwaha et al., 2014). More recent research has therefore employed remote-capture methods to monitor mood lability and intensity more accurately in individuals with BD. A 2019 study by Faurholt-Jepsen et al. used a daily smartphone-based self-monitoring system to measure changes in MI in individuals with BDI and BDII over a nine-month period. Results indicated that individuals with BDII, compared to BDI, had higher inter-episodic MI for depression (Faurholt-Jepsen, Frost, et al., 2019). Taken together, this growing body of evidence suggests that MI may play a key role in differentiating both between diagnostic groups, as well as within groups of BD individuals. This in turn suggests that MI may hold mechanistic importance in the development and course of psychiatric disorders.

Despite increasing evidence highlighting the potential phenotypic and mechanistic importance of MI in BD, no known research has specifically focused on the relationship between MI and AAO. Investigating this relationship could provide valuable insights into the clinical presentation of BD and guide more effective treatment strategies. For example, if MI is found to be more severe or persistent in individuals with early-onset BD, this would suggest that more intensive treatment strategies, such as combination therapy with multiple mood stabilisers, may be necessary to achieve optimal outcomes. Thus, this chapter presents an exploratory study to investigate the relationship between MI and AAO in BD.

5.1.1 Objectives

Investigating the relationship between dimensions of MI and AAO in BD is an important area of research with significant clinical implications. By providing a better understanding of MI in relation to AAO this research can shed light on potential early-intervention approaches and lead to more effective treatments for BD individuals. This study therefore aimed to investigate how severity and instability scores in depression and mania are influenced by demographic and illness

variables, with a focus on AAO. Data from a symptom monitoring platform, True Colours, was used to measure MI over time in BD. As the True Colours system does not specifically allow for ratings of subjective mood intensity or instability, the present study follows the lead of prior research (Faurholt-Jepsen, Frost, et al., 2019) and uses depression and mania severity scores over time to gain an insight into intensity, with greater severity being used as a proxy for increased intensity. As well as using severity scores over time, MI was summarised using a metric (tRMSSD – see Section 5.1.2.1.2 Mood Instability) which accounts for both amplitude changes and the temporal dependency between mood scores (Tsanas et al., 2016). While the study is exploratory in nature, a working hypothesis was that an earlier AAO would be associated with increased severity and instability for both depression and mania.

5.1.2 Modelling Approaches

A-priori, several different analysis approaches were considered for modelling the current data. The data structure is a mixed design, whereby mood scores are a repeated-measures variable with individual participants reporting their depression and mania scores longitudinally, while other descriptive variables are collected at one time point and are predominantly retrospective in nature (e.g., psychiatric history). Although the current study aims to place particular focus on the relationship between AAO and mood, AAO is not set as the dependent variable with mood as a predictor variable as the data are not prospective, and therefore directionality would be difficult to interpret. Thus, mood scores are the dependent variables of interest.

As the objective of the study is to look at (i) severity and (ii) instability these two metrics need to be treated differently. For instance, severity can either be looked at in terms of computing a summary measure (e.g., mean severity scores per participant across time), or else preserving the underlying data structure and including all data in the model. In contrast, instability is given by a summary metric, the time-adjusted root mean squared of the successive differences (tRMSSD)

between mood scores (see Section 5.2.1.2.2 below for further details). The choice of metric influences the analysis approach.

5.1.2.1 Appropriate analysis techniques

5.1.2.1.1 Mood Severity

In terms of modelling mood severity, including all data rather than simply a summary metric is preferable as this provides a more fine-grained approach which can better capture nuances in the data. The best analysis approach is therefore a mixed-effects model, as this is considered the gold standard for analysis of repeated measures data (Gueorguieva, 2017). Mixed models are a generalisation of ordinary-least-squares approaches that explicitly capture the dependency among data points – in this case, due to observations coming from the same individual – via random effects parameters (Singmann & Kellen, 2019). There are several advantages of mixed-effects models over traditional approaches such as Analysis of Variance (ANOVA). For instance, mixed-effects models (a) can include all available data on participants (rather than a summary measure); (b) don't assume that data points are independent or that residuals are identically distributed; (c) can deal with missing data without having to perform listwise-deletion or imputation; and (d) are flexible in accounting for unbalanced designs – e.g. where there are unequal sample sizes across groups or incomplete measurements (Field et al., 2012; Gueorguieva, 2017; Singmann & Kellen, 2019).

The use of mixed models has historically been limited due to the computational power required to run them, and it is only in the last few years that they have become accessible due to the increased computational efficiency of modern computers (Singmann & Kellen, 2019). The relatively recent emergence of mixed-effects models in the medical sciences field means that the optimal approach to formulating, building, and interpreting these models is not always straightforward, compared to more traditional methods. Consequently, researchers often

suggest different optimal methods for model building (e.g., simplest model first vs. most complex model first, all parameters as random effects vs. only those of theoretical interest) and therefore different interpretations may be reached using different mixed models on the same dataset (Field et al., 2012; Gueorguieva, 2017). Nonetheless, compared to traditional approaches, mixed models provide more generalisable and accurate effects estimates, improved statistical power, and non-inflated Type I errors (i.e., false positives) (Singmann & Kellen, 2019). This study therefore uses mixed effects modelling to assess the relationship between mood severity and demographic and illness-characteristic variables.

5.1.2.1.2 Mood Instability

Participants' mood ratings over time were used to calculate a summary measure for MI per participant: tRMSSD. As this is a continuous variable, and there are several independent variables which are a mix of continuous and categorical data, this lends itself to multiple regression analysis with tRMSSD as the outcome variable. To enhance the robustness of this modelling approach, a supervised machine-learning technique – k-fold cross-validation – is applied. K-fold cross validation is a resampling method that allows model performance to be evaluated. It is termed a resampling method as it involves fitting the same statistical learning procedure (in this case, multiple regression) several times using different subsets of the data (Kassambara, 2017). Broadly, cross validation approaches work by partitioning the dataset into 'training' and 'test' subsets. Models are built using the training data, and their accuracy is tested on the previously unseen, held-out test data. For k-fold cross validation specifically (Kassambara, 2017):

1. The data is portioned into 'k' subsets (or folds) of approximately equal size.
2. One of these subsets is held out to be used as the test set, and the other subsets are used to train the model.
3. The fitted model is tested on the held-out test subset and the prediction error (i.e., how accurately the model predicts the outcome variable) is recorded.

4. Steps one to three are repeated until each 'k' subset has served successively as the test set.
5. The average prediction error across k-subsets is calculated. This is called the cross-validation error as it serves as the performance metric for the final model.

This cross-validation approach overcomes the problem of not having an independent dataset on which to test model performance, and therefore allows information to be obtained that would not be available from fitting the model only once using the original dataset alone (James et al., 2013). K-fold cross-validation is chosen over other cross-validation approaches such as leave-one-out cross-validation, as it is more computationally efficient and can often give more accurate estimates of the prediction error rate (James et al., 2013; Kassambara, 2017). Thus, the current study employs multiple regression analysis with k-fold cross-validation to establish the relationship between MI and demographic and illness-characteristic variables.

5.2 Methods

The study used data from the UK Bipolar Disorder Research Network cohort (BDRN; www.bdrn.org) which is an on-going programme of research into the genetic and non-genetic determinants of BD and related mood disorders. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by a Heath Research Authority NHS Research Ethics Committee (MREC/97/7/01) and all participating NHS Trusts and Health Boards. Written informed consent was obtained from all participants. The data used in the current study was accrued in two stages: baseline measures and demographic data were gathered from March 2001 to May 2018, and mood data was recorded from March 2015 to August 2021. Data analysis was conducted in 2022.

Participants were recruited throughout the UK via NHS services and advertisements through patient support organisations. Inclusion criteria were: (i) aged 18 years or over, (ii) able to provide written informed consent, (iii) met Diagnostic and Statistical Manual-IV (DSM) criteria (American Psychiatric Association, 2000) for BD, and (iv) onset of mood symptoms before the age of 65 years. Individuals were excluded if they experienced affective illness only because of substance use or medical illness or were biologically related to another study participant.

5.2.1 Measures

5.2.1.1 Diagnosis

Best-estimate main lifetime diagnosis was made according to DSM-IV criteria based on in-depth interview using the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990), and review of psychiatric and primary care case-notes where available.

5.2.1.2 Dependent Variables

5.2.1.2.1 Total Mood Scores

Longitudinal prospective ratings of (hypo)mania and depression were collected via True Colours, which is a symptom monitoring platform that prompts participants, via text message or email, to self-rate their mood. Participants were able to tailor the frequency of these prompts, with the default being once per week. The presence and severity of manic or hypomanic symptoms was assessed using the 5-item Altman Self-Rating Mania Scale (Altman et al., 1997). The 16-item Quick Inventory of Depressive Symptomatology (Rush et al., 2003) was used to self-report depressive symptom severity.

From this mood data was derived (i) total ratings for mania and depression per participant over time (i.e., repeated measures per participant) and (ii) instability in mania and depression ratings over time (i.e., one summary metric per participant).

5.2.1.2.2 Mood Instability

The overall instability in mania and depression scores per participant was calculated. Instability in mood ratings over time can be quantified using the mean of the squared successive differences (MSSD), which is a common metric for estimating variance in successive data points (Carr et al., 2018; Faurholt-Jepsen, Geddes, et al., 2019). Taking the square-root of MSSD scores (referred to as RMSSD) normalises the inherent positive skew of MSSD data for parametric analyses. The standard formula for calculating RMSSD is:

$$RMSSD = \sqrt{\frac{1}{N}\sum_{i=1}^{N-1}(x_{i+1} - x_i)^2}$$

Where N is the total number of data points in the timeseries and x_i indicates the ith data point in the timeseries, with $\mathrm{i} + 1$ indicating successive data points.

However, the conventional RMSSD metric assumes that successive data points are equally separated in time, which is not always the case as participants engaged with the study for different durations, and/or may have missing data (Taquet et al., 2023). Therefore, to account for time differences between data points, the RMSSD is generalised by calculating the average squared slope (referred to as tRMSSD) with the formula:

$$tRMSSD = \sqrt{\frac{1}{N}\sum_{i=1}^{N-1}\left(\frac{x_{i+1} - x_i}{t_{i+1} - t_i}\right)^2}$$

Where N is the total number of data points in the timeseries, x_i indicates the ith data point in the timeseries, t_i indicates the ith timestamp at which the datapoint was submitted and $i + 1$ and $t + 1$ indicating successive data points and timestamps, respectively (Taquet et al., 2023).

5.2.1.3 Independent Variables

A total of 18 independent variables were used in modelling, these are listed in Table 14. Predictors were chosen based on their availability in the dataset and their expected influence on mood symptoms as indicated by previous research (Agnew-Blais & Danese, 2016; Baek et al., 2011; Birmaher et al., 2009; Joslyn et al., 2016; Kupka et al., 2005; Severus et al., 2018).

Table 14. Descriptions of the 18 candidate predictor variables used in the modelling of mood data.

Variable	Definition
Age at onset	Age in years at first clinically significant impairment due to manic or depressive symptoms. Signs of clinically significant impairment included: arguments and/or fights; missed work and/or job loss; treatment referral; the use of Lithium or neuroleptics for treatment of manic symptoms; disrupted work or social life; police involvement; family breakdown; and psychotic features.
Age at interview	Age at interview in years
Diagnosis	BDI, BDII, BD-NOS or BD-Schizoaffective
Lithium Response	'Yes' – defined as either (i) subjective good response; (ii) objective evidence for beneficial response, i.e., clear reduction in number and/or severity of episodes following introduction of lithium prophylaxis; or (iii) objective evidence for excellent response to lithium prophylaxis, i.e., frequency of episodes reduced to <10% of frequency after lithium prophylaxis and/or 2 or more episodes of illness occurring within weeks of cessation of lithium. 'No' – no evidence of response Never taken
Rapid Cycling	'Yes' – pertains to a 'lifetime ever rapid cycling diagnosis' which is considered as either (i) the occurrence of 4 or more episodes (mania or depression) in a 12-month period or (ii) rapid cycling predominates course of illness and has been present for at least 5 years during the total course of the illness 'No' – was defined as Rapid cycling is not present or suspected despite a duration of illness of at least 7 years (since onset), and at least 3 episodes of mood disorder during this time.
Psychiatric History	ADHD Autism Depression OCD Schizophrenia Anxiety disorder diagnosis including anxiety, agoraphobia, panic disorder or specific phobias Eating disorder diagnosis including anorexia or bulimia Alcohol abuse or other substance abuse
Medication ever taken	Including antidepressants, anxiolytics, depot injections, hypnotics, mood stabilisers, antipsychotics, electroconvulsive therapy
Therapy ever undergone	Including CBT or another talking therapy

5.2.2 Statistical analysis

The R code used for data pre-processing and analysis is openly available via the Open Science Framework.

5.2.2.1 Data Pre-processing

Analysis was conducted in R version 4.2.1 (2022-06-23) (R Core Team, 2022) for Mac OS. The 'nmle' package (version 3.1.157; Pinheiro et al., 2022; Pinheiro & Bates, 2000), the 'lme4' package (version 1.1.30; Bates et al., 2015) and 'lmerTest' package (version 3.1.3; Kuznetsova et al., 2017) were used for mixed effects modelling of total mood scores. The 'lm' function from the 'stats' package (version 4.2.1; R Core Team, 2022) was used for the main analysis of MI data. Multiple other helper packages were also used (listed in Appendix D with references), while figures were produced using the 'ggplot2' package version 3.3.6 (Wickham, 2016). Missing variables were removed using the listwise-deletion method, rather than imputed, with analysis conducted on this full dataset.

To compute the instability (tRMSSD) for mania and depression scores per participant, missing variables were removed and only cases where participants recorded >1 mood rating were included (to compute change over time). For mixed effects models, only cases where >5 mood ratings were recorded were included, as mixed effects models are sensitive to the number of levels in the random intercept term (Gelman & Hill, 2006). This filtering resulted in different sample sizes for each mania and depression model (see Results). The dataset contains 20 variables including eighteen predictor variables (categorical and continuous) and mood scores for depression and mania (continuous). For all analyses, numeric dependent variables were centred and scaled with z-score standardisation, and categorical predictors were dummy coded with K-1 levels per variable.

5.2.2.2 Modelling Total Mood Scores

The aim of this first analysis pipeline was to investigate the severity of mood scores per participant over time, while accounting for the effect of AAO and including covariate measures. Linear mixed effects models, which are considered the gold standard for analysing repeated measured data, were run with (i) total mania scores and (ii) total depression scores as the outcome variables. Separate models were run for these outcome measures as these variables were highly correlated.

5.2.2.2.1 Assessing the need for a multilevel model

For each outcome variable, two different models were initially run, fit using maximum likelihood estimation using the 'gls' and 'lme' functions from the 'nlme' package (version 3.1.157; Pinheiro et al., 2022; Pinheiro & Bates, 2000):

i) Model A: Null model, with only an intercept term.

ii) Model B: Adding participant ID as a random intercept.

These two models were compared using Analysis of Variance (ANOVA) and the resulting likelihood ratio, Akaike Information Criterion (AIC) and Schwarz's Bayesian Information Criterion (BIC) were examined. The likelihood ratio is a standard statistical test for comparing the goodness of fit of two nested models. This test consists of the ratio of the maximum likelihoods of the models being compared. The test statistic of the likelihood ratio test follows a chi-squared distribution with degrees of freedom equal to the difference in number of parameters between models (Vuong, 1989; Welham & Thompson, 1997).

If Model B had a lower AIC and BIC than Model A, and the log-likelihood ratio was significant, it was concluded that a multilevel model was appropriate as the variability in intercepts should be modelled, with participant ID as a random effect. This means that the model allows intercepts to vary by participant. Here, the random effects approach is more appropriate than a covariance-

pattern approach to account for correlations between repeated measures as individuals are not observed at the same time points (Gueorguieva, 2017).

5.2.2.2.2 Model Building

Once it was confirmed that a multilevel model was appropriate for the repeated measures data, a model was built including all fixed effects (Table 14), and the random effects' structure was specified.

It has been suggested that all fixed effects of theoretical interest should be modelled as random slopes, which can help reduce Type I error (Barr et al., 2013), but the added value of their inclusion should be tested more formally using a likelihood ratio test, which will minimise Type II error (Bates et al., 2014). AAO is the fixed effect of interest as *a priori* evidence suggests that mood scores may differ according to AAO (Henry et al., 2008; Miklowitz et al., 2022). This difference can be modelled by an AAO-specific random slope; resulting in an overall model for mood where participants have different baselines (accounted for as a random intercept for participant ID), and that this relationship can vary by AAO (modelled as a random slope for AAO). This model can be represented by the general equation (Claeskens & Hjort, 2008; Field et al., 2012):

$$\Upsilon_{i,j} = \left(b_0 + u_{0j}\right) + \left(b_1 + u_{1j}\right)\mathrm{X}_{ij} + \varepsilon_{ij}$$

Where Υ is the value of the outcome for the ith participant of the jth observation, X is a predictor, and ε the error. The coefficients b_0 and b_1 represent the fixed intercept and slope of the overall model, while u_{0j} and u_{1j} are the random intercepts and slopes.

To formally test the added value of an AAO-specific random slope, and to determine whether the random effects should be specified as correlated or uncorrelated, the following models were run:

i) Model 1: All fixed effects, random intercept (participant ID)

ii) Model 2: All fixed effects, random intercept (participant ID), and *uncorrelated* random slope (AAO)

iii) Model 3: All fixed effects, random intercept (participant ID), and *correlated* random slope (AAO)

Building the models in this way – by starting with all fixed effects and then adding random effects – is recommended to identify the best random effects' structure (Raudenbush & Bryk, 2002; Twisk, 2006). This also means that the likelihood ratio test can be used for model selection as the fixed effects remain constant across models. The likelihood ratio test takes the likelihood value for each model and compares their goodness-of-fit. All three models were fit using maximum likelihood (ML) estimation. ML estimation was chosen over restricted maximum likelihood (REML) estimation – which produces unbiased estimators of the variance components – as ML is necessary for model comparison and yields more accurate estimates for fixed regression parameters compared to REML (Twisk, 2006). These three models were then compared using ANOVA. To select a 'winning model', the values of AIC, BIC and the significance of the likelihood ratio test were examined. It has been suggested that the AIC should be used when the goal is to find a good model for the population and identify fixed effect parameters of importance (Vaida & Blanchard, 2005). While the AIC favours models with more parameters, the BIC tends to be more conservative by favouring more parsimonious models. Taking both these metrics into account during model selection, along with the likelihood ratio test, allows explanatory power to be balanced with parsimony.

Once these models were compared and a winning model identified, this best model was refitted using REML estimation, as model comparison is no longer necessary and REML produces an unbiased estimator. Model assumptions were then tested and if the model satisfied these assumptions, results were presented for inference.

5.2.2.2.3 Testing Assumptions

In mixed-effects models, as in other model classes, the residuals can be examined to assess whether model assumptions are satisfied. Model assumptions are similar to those of regression, thus for the best-fitting or 'winning' model, residual plots were used to assess normality, the presence of potential outliers, and whether residual variance is constant across observations – i.e., 'homoscedastic' variance (Gueorguieva, 2017; Kutner, 2005). The 'performance' package version 0.10.1 (Lüdecke et al., 2021) was used to formally test these assumptions. Firstly, a composite outlier score obtained via the joint application of multiple outlier detection algorithms – e.g., Cook's distance and leverage values – was used to detect the presence of possible outliers. Cook's distance estimates variations in model coefficients after removing each observation in turn (Cook, 1977). Since Cook's distance has an F distribution with p and n-p degrees of freedom, the median point of the quantile distribution can be used as a cut-off for determining outlier values (Bollen & Jackman, 1985). The Shapiro-Wilk test and the Breusch-Pagan test were used to assess normality and homoscedasticity in studentised residual errors respectively. If these assumptions were violated, a 'sandwich' covariance estimator was employed to correct for this, as it is robust to non-constant variance in a model's residuals (Hardin, 2003; Kauermann & Carroll, 2001). When using the 'standard' ordinary-least-squared (OLS) method to obtain standard errors for estimated model coefficients, the conditional variance of the outcome variable is treated as constant and independent. In contrast, the 'sandwich' method uses the *squared* value of the observed residuals as a plug-in estimate of the variance of each component, which can vary between observations, and is thus robust to heteroscedasticity. As an alternative approach to correct for heteroscedastic standard errors, the bootstrap was employed. This approach resamples with replacement and re-estimates the standard error from the standard deviation of the coefficient estimates across resampling runs (Efron, 1979, 1988; Efron & Tibshirani, 1993).

5.2.2.3 Modelling Mood Instability

The aim of this second analysis pipeline was to examine what factors were associated with MI. Two models were run (i) using depression tRMSSD and (ii) using mania tRMSSD as the outcome variable. Eighteen predictor variables were entered into both models (Table 14). All-subsets regression was run for both outcome variables. To find the 'best' model k-fold cross validation (with k = 10) was employed. K-fold cross-validation (CV) consists of dividing the data into k subsets. Each subset serves successively as a test data set and the remaining subsets act as training data. The cross-validation error is computed as the average of the k prediction errors and serves as a performance metric for each model (Kassambara, 2017). The model that minimised the cross-validation error was selected as the 'winning' model.

5.2.2.3.1 Testing Assumptions

After the winning model had been defined, model assumptions were tested including examining the size of residuals, and the values of Cook's Distance, leverage, the covariance ratio, and the variance inflation factor. The 'car' package (version 3.1.0) was used to conduct outlier tests, which reported Bonferroni p-values for testing if each observation was a mean-shift outlier. To visually assess whether the assumptions of random errors and homoscedasticity were met, studentised residuals were plotted against the values fitted by each model. To assess whether the model residuals deviated from a normal distribution histograms and Q-Q plots of the studentised residuals were plotted. These assumptions were also formally tested: the Shapiro-Wilk test (from the 'stats' package version 4.2.1; (R Core Team, 2021) was used to assess normality of the outcome variables, and the studentized Breusch-Pagan test (from the 'lmtest' package, version 0.9.40; Hothorn & Zeileis, 2011) was used to assess homoscedasticity in residual errors. If heteroscedasticity was present, a 'sandwich' covariance estimator was employed to

correct for this (Hardin, 2003; Kauermann & Carroll, 2001), as well as bootstrap resampling (Efron, 1979, 1988; Efron & Tibshirani, 1993).

5.2.2.3.2 Model Accuracy

To assess goodness-of-fit, each model's residual standard error (RSE), R-Squared, adjusted R-squared and F-statistic were reported. The prediction error rate was obtained by dividing the RSE by the mean value of the outcome variable. It was not possible to evaluate the predictive accuracy of the models on held-out test sets, as splitting the data into test and training sets would result in insufficient power to detect medium effect sizes (determined using G*Power 3.1; Erdfelder et al., 2009).

5.3 Results

5.3.1 Demographics

There was a total of 322 participants; sociodemographic and clinical characteristics are described in Table 15 below.

Table 15. Means, s.d. and ranges for continuous measures and absolute (n) and relative (%) frequencies for categorical variables in the total sample (n = 322).

Continuous Variables		Mean	SD, Range
Interview Age		46.50	11.68, 18-78
Age at Onset		22.56	9.46, 6-69
Categorical Variables		**n**	**%**
Diagnosis	BDI	197	61.2
	BDII	108	33.5
	BD-SA	7	2.2
	BD-NOS	10	3.1
Lithium Response	No	6	1.9
	Yes	165	51.2
	Never taken	151	46.9
ADHD	No	314	97.5
	Yes	8	2.5
Autism	No	318	98.8
	Yes	4	1.2
Depression	No	40	12.4
	Yes	282	87.6
OCD	No	292	90.7
	Yes	30	9.3
Schizophrenia	No	312	96.9
	Yes	10	3.1
Rapid Cycling	No	213	66.1
	Yes	109	33.9
Anxiety Disorder	No	105	32.6
	Yes	217	67.4
Eating Disorder	No	313	97.2
	Yes	9	2.8
Substance Abuse	No	282	87.6
	Yes	40	12.4
Medication ever taken	No	28	8.7
	Yes	294	91.3
Therapy undertaken	No	157	48.8
	Yes	165	51.2

5.3.2 Total Mood Scores

5.3.2.1 Mania Severity

Analysis was run on data from 297 participants. To determine whether a mixed effects analysis was appropriate, the null model with an intercept only term was compared to a model including participant ID as a random intercept term. For mania severity, there was significant variance in intercepts across participants, SD = 0.631 (95% CI: 0.581, 0.688), X^2 = 15364, p<.0001 (Table 16), indicating that adding a random intercept term significantly improves model fit, and therefore running a mixed effects analysis is appropriate.

Table 16. Assessing the need for a multilevel model for total mania severity by comparing a null model (Model A) to one including a random intercept (Model B). Degrees of freedom (df), AIC, BIC, log-likelihood (LL), LL ratio and the p-value for the test statistic are reported.

	Model	df	AIC	BIC	LL	LL ratio	p-value
A	Intercept Only	2	109320.86	109337.98	-54658.43		
B	Random Intercept	3	93958.49	93984.17	46976.24	15364.37	<.0001

Next, three models were compared which included all fixed effects and either a random intercept only (participant ID), or a random intercept with either an uncorrelated or correlated random slope (AAO).

Table 17 indicates that a model with uncorrelated random intercepts and slopes (Model 2) was the winning model. Model comparison showed that adding the random slope of AAO uncorrelated with the random intercept of participant ID leads to a significant improvement in model fit, SD = 0.277 (95% CI: 0.099, 0.437), X^2 = 5.54, p<.05, while the addition of correlation between the slope and intercept (Model 3), while better than an intercept only term (Model 1), did not lead to a significantly better model fit than Model 2, SD = 0.355 (95% CI: 0.194, 0.483), X^2 = 3.02 p = .082.

Table 17. Model fit criteria for total mania severity. Models include all fixed effects but vary by random effects.

	Model	Random Effects	Fixed Effects	AIC	BIC	Loglikelihood	Test	Likelihood ratio	P-value
1	Random intercept	Intercept	All	93948	94127	- 46953			
2	Uncorrelated random intercepts and slopes	Intercept and slope (uncorrelated)	All	93944	94132	- 46950	Model 1 vs. 2	X2(2) = 5.544	0.019*
3	Correlated random intercepts and slopes	Intercept and slope (correlated)	All	93943	94140	- 46949	Model 2 vs. 3	X2(1) = 3.023	0.082

The winning model (Model 2) was refit using REML estimation. Table 18 shows that 'rapid cycling' was the only fixed effect that was significantly related to mania scores, $\beta = 0.304$, $t(265) = 3.724$, $p<.0001$.

5.3.2.1.1 Testing Assumptions

Plots of the model's residuals were examined to assess whether assumptions were met (Appendix D.2.). It appeared that there were departures from normality and heteroscedasticity may be present. This was tested formally. Examination of Cook's distance values (threshold of 0.97) for the whole model indicated that no datapoints were classified as outliers. The Shapiro-Wilk normality test was significant, $p< .001$, indicating that the data were non-normal. The studentized Breusch-Pagan test was also significant, $p < .001$, indicating that heteroscedasticity was present in the model. To adjust for these violations in assumptions, a robust sandwich estimator from the 'parameters' package version 0.20.0 (Lüdecke et al., 2020) was employed, as well as bootstrap resampling with 1000 replications using the bootstrap function from 'lmeresampler' package version 0.2.2 (Loy et al., 2022). Confidence intervals for the beta coefficients of each variable in the standard model, the model with a robust sandwich estimator,

and the bootstrap model were plotted (Figure 9). The sandwich and bootstrap models produced the same results as the standard model, although with slightly wider confidence intervals for some variables.

Table 18. Results from the winning models for mania and depression severity. Coefficient estimates (β), standard errors (SE), t-statistics and corresponding p-values and 2.5- 97.5% confidence intervals (CI) are reported.

Variables		Mania Model					Depression Model				
		β Estimate	SE	Statistic	P-value	2.5% CI	β Estimate	SE	Statistic	P-value	2.5% CI
AAO		0.048	0.049	t(105) = 0.976	.331	-0.049 0.145	-0.07	0.074	t(153) = -0.943	.347	-0.216 0.076
Interview Age		-0.035	0.038	t(254) = -0.931	.353	-0.11 0.039	-0.012	0.067	t(155) = -0.177	.86	-0.143 0.12
Diagnosis	BDII	0.108	0.081	t(261) = 1.327	.186	-0.052 0.269	0.054	0.138	t(154) = 0.39	.697	-0.218 0.325
	SA	-0.014	0.248	t(202) = -0.057	.955	-0.503 0.475	0.568	0.337	t(153) = 1.687	.094	-0.097 1.234
	NOS	0.202	0.209	t(271) = 0.969	.333	-0.209 0.614	-0.398	0.37	t(150) = -1.077	.283	-1.129 0.333
Lithium Response	Yes	0.248	0.257	t(257) = 0.964	.336	-0.258 0.754	-0.533	0.434	t(154) = -1.228	.221	-1.39 0.325
	Never Taken	0.443	0.259	t(257) = 1.71	.089	-0.067 0.954	-0.396	0.427	t(154) = -0.927	.356	-1.241 0.448
Rapid Cycling		**0.304**	**0.082**	**t(265) = 3.724**	**<.000*** ***	**0.143 0.464**	**0.551**	**0.141**	**t(154) = 3.899**	**<.000*** ***	**0.272 0.83**
ADHD		0.22	0.238	t(285) = 0.925	.356	-0.249 0.689	0.145	0.377	t(155) = 0.385	.700	-0.599 0.89

Autism		-0.187	0.327	t(262) = -0.571	.568	-0.83 0.457	0.739	0.42	t(147) = 1.757	.081	-0.092 1.57
Depression		0.064	0.14	t(269) = 0.456	.649	-0.212 0.339	-0.156	0.218	t(152) = -0.716	.475	-0.587 0.275
OCD		0.158	0.132	t(272) = 1.199	.232	-0.101 0.417	**0.627**	**0.237**	**t(153) = 2.643**	**<.01****	**0.158 1.096**
Schizophrenia		0.173	0.204	t(208) = 0.847	.398	-0.229 0.575	-0.449	0.421	t(147) = -1.068	.287	-1.28 0.382
Anxiety Disorder		-0.066	0.085	t(263) = -0.769	.443	-0.233 0.102	-0.098	0.143	t(155) = -0.689	.492	-0.381 0.184
Eating Disorder		0.158	0.209	t(243) = 0.757	.450	-0.253 0.569	-0.013	0.454	t(152) = -0.029	.977	-0.911 0.884
Substance Abuse		0.027	0.112	t(275) = 0.239	.811	-0.194 0.248	0.035	0.193	t(154) = 0.182	.856	-0.347 0.417
Medication ever	Yes	-0.179	0.148	t(231) = -1.206	.229	-0.471 0.113	0.335	0.228	t(154) = 1.47	.144	-0.115 0.786
Therapy ever	Yes	-0.016	0.074	t(259) = -0.212	.832	-0.162 0.125	0.166	0.123	t(154) = 1.343	.181	-0.078 0.41

*p ≤ .05, **p ≤ .01, ***p ≤ .001, ****p ≤ .0001

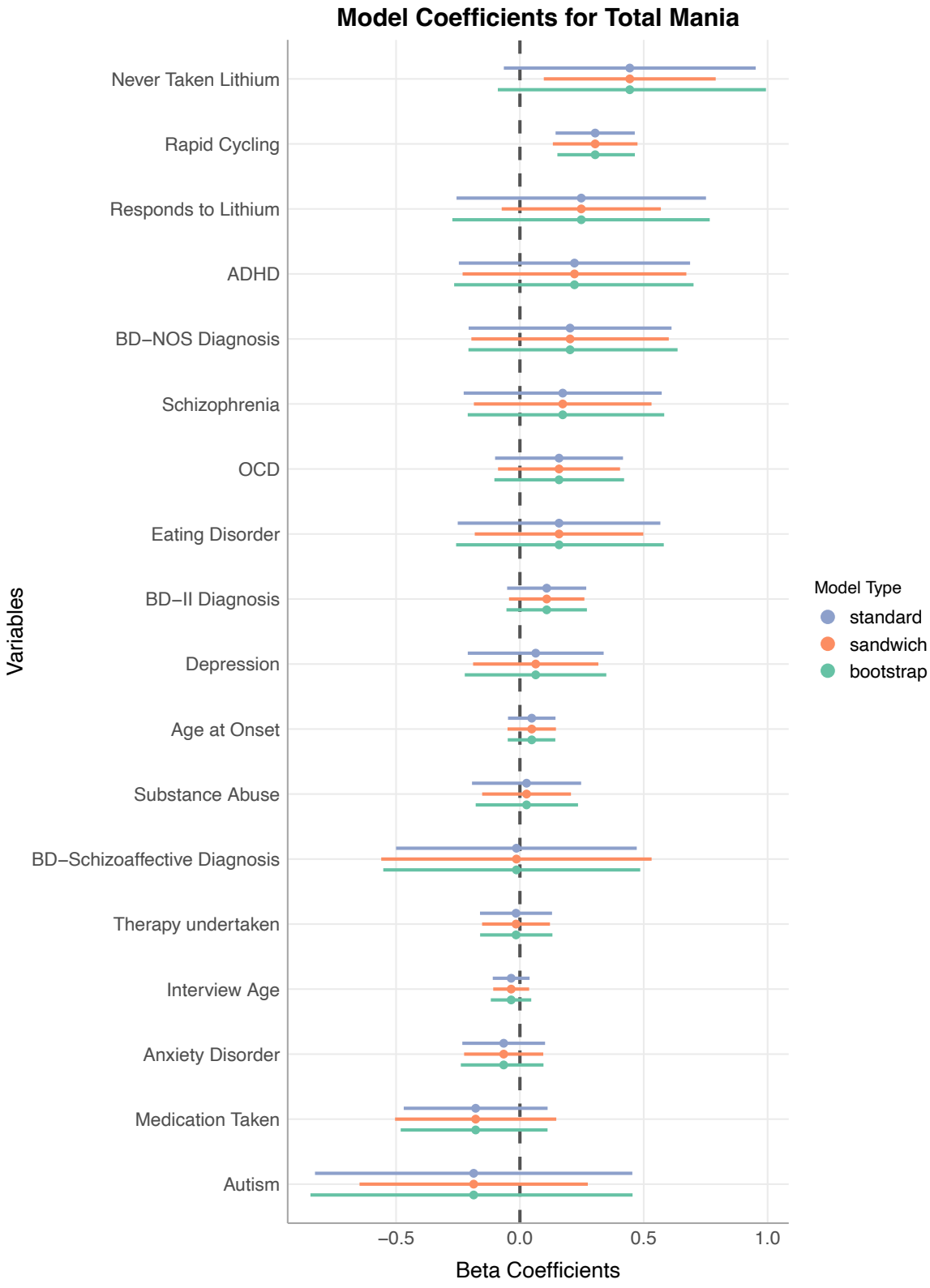

Figure 9. Caterpillar plot for model comparison displaying confidence intervals (CIs) for the 18 predictors entered as fixed effects into the 'mania severity' model. CIs that cross the zero line are not significantly related to mania severity. The bootstrap and sandwich models adjust for the violations of model assumptions.

5.3.2.2 Depression Severity

Analysis was run on data from 172 participants. To determine whether a mixed effects analysis was appropriate, the null model with an intercept only term was compared to a model including participant ID as a random intercept term. For mania severity, there was significant variance in intercepts across participants, SD = 0.825 (95% CI: 0.738, 0.922), X^2 = 10852, p<.0001 (Table 19), indicating that adding a random intercept term significantly improves model fit, and therefore running a mixed effects analysis is appropriate.

Table 19. Assessing the need for a multilevel model for total depression severity by comparing a null model (Model A) to one including a random intercept (Model B). Degrees of freedom (df), AIC, BIC, log-likelihood (LL), log-likelihood ratio and the p-value for the test statistic are reported.

	Model	df	AIC	BIC	LL	LL ratio	p-value
A	Intercept Only	2	36387.42	36402.34	-18191.71		
B	Random Intercept	3	25537.22	25559.60	-12765.61	10852.2	<.0001

Three models were compared which included all fixed effects and either a random intercept only (participant ID), or uncorrelated and correlated random slopes (AAO). Table 20 indicates that Model 1 was the winning model. Model comparison showed that adding the random slope of AAO uncorrelated with the random intercept (Model 2) did not significantly improve model fit, SD = 0.217 (95% CI: 0.000, 0.576), X^2 = 0.398, p = .528, and the addition of correlation between the slope and intercept (Model 3) also did not lead to a significantly better model fit than Model 1, SD = 0.163 (95% CI: 0.000, 0.560), X^2 = 0.296 p = .586.

Table 20. Model fit criteria for total depression severity. Models include all fixed effects but vary by random effects.

	Model	Random Effects	Fixed Effects	AIC	BIC	Loglikelihood	Test	Likelihood ratio	P-value
1	Random intercept	Intercept	All	25521	25677	- 12739			
2	Uncorrelated random intercepts and slopes	Intercept and slope (uncorrelated)	All	25522	25686	- 12739	Model 1 vs. 2	$X^2(2)$ = 0.398	0.528
3	Correlated random intercepts and slopes	Intercept and slope (correlated)	All	25524	25695	- 12739	Model 2 vs. 3	$X^2(1)$ = 0.296	0.586

The winning model (Model 1) was refit using REML estimation. Table 18 shows that the fixed effects 'rapid cycling', β = 0.551, t(12800) = 3.899, p<.001, and 'psychiatric history of OCD', β = 0.627, t(12800) = 2.643, p<.01 were significantly related to depression scores.

5.3.2.2.1 Testing Assumptions

To visually assess model assumptions, the plots of residuals were evaluated (Appendix D.2.), which indicated that there may be some departures from normality and heteroscedasticity may be present. This was tested formally: The Shapiro-Wilk normality test was significant, p< .001, indicating that the data were non-normal. The studentized Breusch-Pagan test was also significant, p < .001, indicating that heteroscedasticity was present in the model. Examination of Cook's distance values (threshold of 0.97) for the whole model indicated that no datapoints were classified as outliers. To adjust for the violations of normality and homoscedasticity, a robust sandwich estimator from the 'parameters' package version 0.20.0 (Lüdecke et al., 2020) was employed, as well as bootstrap resampling with 1000 replications using the bootstrap function from 'lmeresampler' package version 0.2.2 (Loy et al., 2022). Confidence intervals for the standard model, the model with a robust sandwich estimator, and the bootstrap model were

plotted (Figure 10). The sandwich and bootstrap models produced the same results as the standard model, although with slightly wider confidence intervals for some variables.

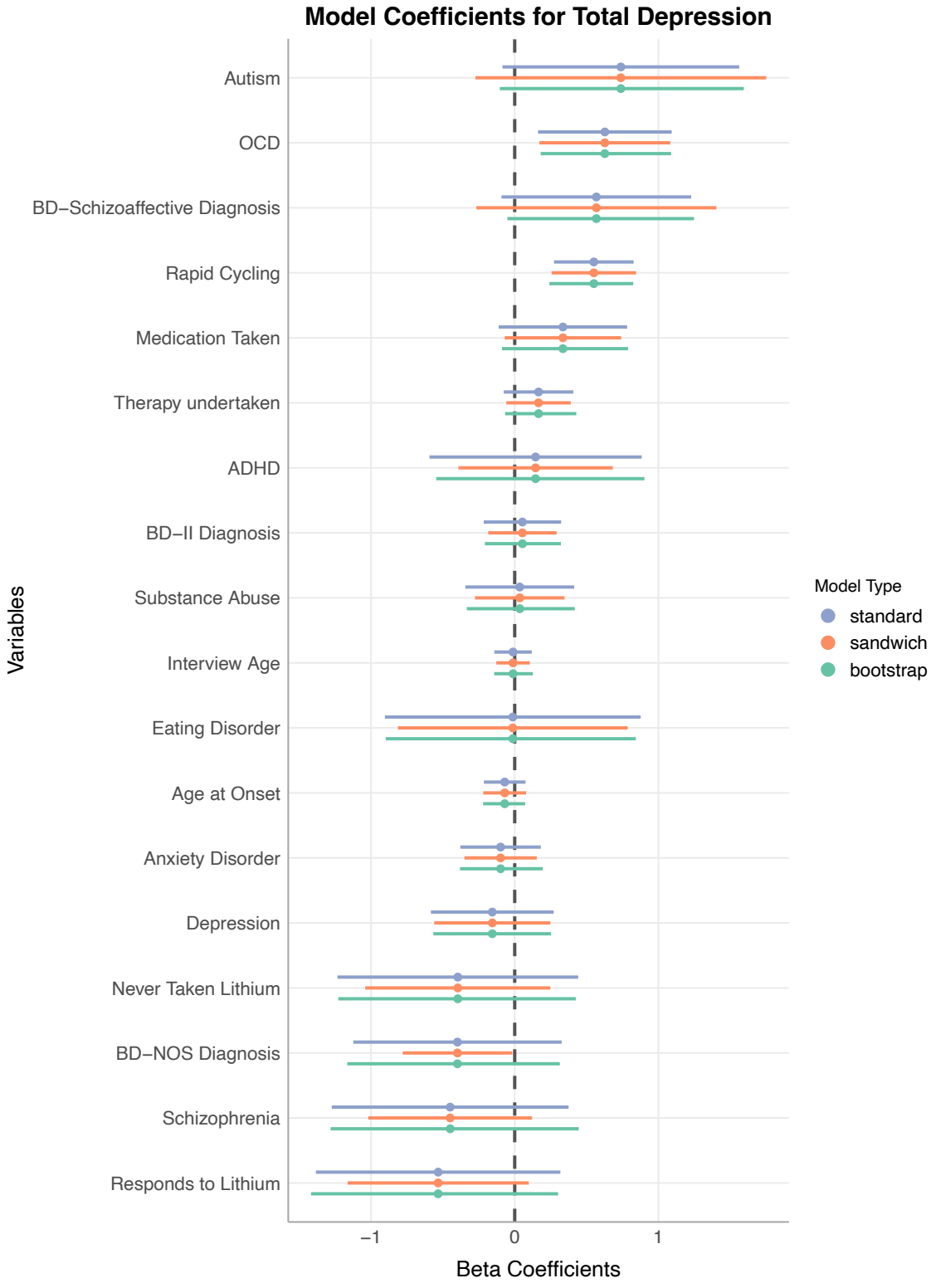

Figure 10. Caterpillar plot for model comparison displaying confidence intervals (CIs) for the 18 predictors entered as fixed effects into the 'depression severity' model. CIs that cross the zero line are not significantly related to depression severity. The bootstrap and sandwich models adjust for the violations of model assumptions.

5.3.3 Mood Instability

5.3.3.1 Mania Instability

For mania instability, tRMSSD was calculated using a median number of 67 ratings per participant (range: 2-333, mean = 107).

5.3.3.1.1 Modelling

All-subsets regression was run with 10-fold cross validation on data from 322 participants. The model that minimised the cross-validated error was statistically significant ($F(3,318) = 21.61$, $p < .000$, $R2 = 0.17$, adjusted $R2 = 0.16$) and included three variables that were significantly associated with mania instability: never haven taken lithium ($\beta = 0.284$, $p < .001$), positive psychiatric history of OCD ($\beta = 0.$ 0.639, $p < .000$) and presence of rapid cycling ($\beta = 0.611$, $p < .000$).

5.3.3.1.2 Testing Assumptions

Eight cases (2.5% of the total dataset) appeared to have large residuals with absolute values above 2.5. All eight cases were within accepted limits for Cook's Distance and leverage values, but two observations had covariance ratios below the calculated accepted lower bound of 0.823. The outlier test from the 'car' package (Fox & Weisberg, 2019) indicated that these two observations may be outliers (with Bonferroni $p < .01$). After inspecting the data, it was decided to retain these cases in modelling as the values did not appear to be mis-recorded and were in-line with the participants' other data. Collinearity was not present in the data according to variance inflation factor (VIF) diagnostics. The VIF for each predictor variable was <10 (range: 1.02 to 1.04) (Steinhorst & Myers, 1988), the average VIF was 1.03 which is not substantially greater than 1.0, (Bowerman & O'Connell, 1992) and there was no tolerance value ≤ 0.2 (Menard, 2010). To visually assess normality and homoscedasticity of the model residuals, the residual plots were evaluated (Appendix D.3.). Visual inspection indicated that there may be some departures from normality, and heteroscedasticity may be present. This was tested

formally using the Shapiro-Wilk and Breusch-Pagan Tests. The Shapiro-Wilk normality test was significant, W = 0.90095, p< .000, indicating that the data were non-normal. The studentized Breusch-Pagan test was also significant, BD = 20.069, df = 3, p < .000, indicating that heteroscedasticity was present in the model. To account for heteroscedasticity, a robust sandwich estimator from the sandwich package version 3.0.2 (Zeileis, 2006) was employed, as well as bootstrap resampling with 1000 replications (Efron, 1979, 1988; Efron & Tibshirani, 1993). Confidence intervals for the ordinary-least-squared model, the model with a robust sandwich estimator, and the bootstrap model were plotted (Figure 11).

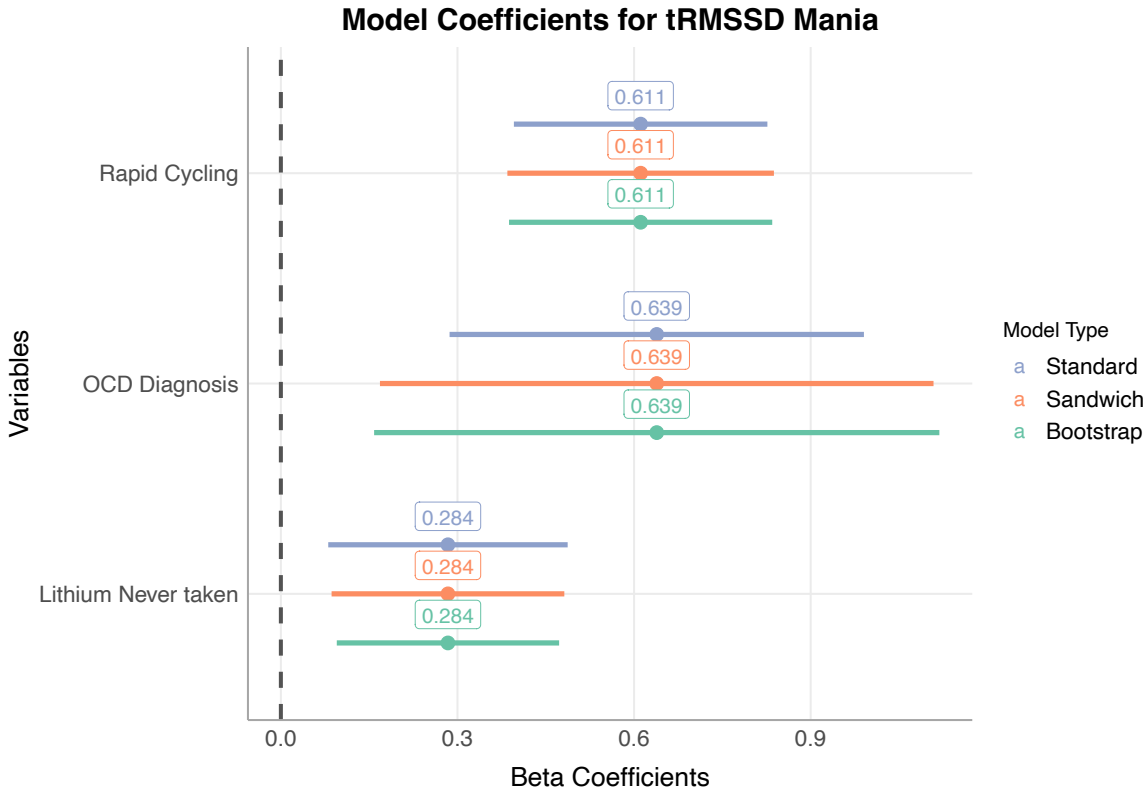

Figure 11. Caterpillar plot for model comparison displaying coefficient values and confidence intervals for the winning model for 'mania instability'. The bootstrap and sandwich models adjust for the violations of model assumptions.

The models adjusting for heteroscedasticity were compared with the standard OLS model. Confidence intervals were similar across models, and the three predictor variables remained significantly associated with mania instability (Table 21 and Figure 11).

Table 21. Comparison of 'mania instability' models adjusting for heteroscedastic standard errors. Coefficient estimates are given followed by their standard errors, denoted as '(SE)' and confidence intervals shown as '[lower CI, upper CI]'.

	Standard OLS Model	Sandwich Estimator Model	Bootstrap Model
Constant Term (Intercept)	-0.399 (0.077) ***	-0.399 (0.068) ***	-0.399 (0.066) ***
	[-0.552, -0.247]	[-0.534, -0.265]	[-0.530, -0.269]
Psychiatric History of OCD	0.639 (0.179) ***	0.639 (0.248) *	0.639 (0.245) **
	[0.287, 0.990]	[0.151, 1.126]	[0.156, 1.121]
Never taken Lithium	0.284 (0.103) **	0.284 (0.102) **	0.284 (0.100) **
	[0.080, 0.487]	[0.083, 0.484]	[0.088, 0.480]
Presence of Rapid Cycling	0.611 (0.109) ***	0.611 (0.117) ***	0.611 (0.113) ***
	[0.396, 0.826]	[0.381, 0.841]	[0.389, 0.833]
Number of Observations	322	322	322
AIC	1489.0	1489.0	1489.0
BIC	2689.4	2689.4	2689.4
R2	0.17	0.17	0.17
Adjusted R2	0.16	0.16	0.16
RSE	0.92	0.92	0.92
*=.05, **=.01, ***=0.001			

5.3.3.2 Depression Instability

For depression instability, tRMSSD was calculated using a median number of 16 ratings per participant (range: 2-326, mean = 53).

5.3.3.2.1 Modelling

All-subsets regression was run with 10-fold cross validation on data from 235 participants. The model that minimised the cross-validated error was statistically significant ($F(2,232) = 11.40$, $p < .000$, $R2 = 0.09$, adjusted $R2 = 0.08$) and included an intercept term (($\beta = -0.14$, $SE = 0.08$, $p < .001$) and two variables that were significantly associated with depression instability: interview age ($\beta = -0.20$, $SE = 0.06$, $p < .001$), and presence of rapid cycling ($\beta = 0.42$, $SE = 0.13$, $p < .001$).

5.3.3.2.2 Testing Assumptions

Two cases had large residuals with absolute values greater than 2.5 (standardised residuals of 8.41 and 2.81). One of these cases was identified as an outlier, with a large studentised residual value of 10.06, Bonferroni $p < .000$. This outlier was removed as the value did not appear to be a feasible recording (see Appendix D.3. – highlighted outlier in orange), and the modelling process was re-run on data from 234 participants.

5.3.3.2.3 Model Updating

Once the outlier was removed, the fitted model that minimised the cross-validated error was statistically significant ($F(3,230) = 10.11$, $p < .000$, $R2 = 0.12$, adjusted $R2 = 0.11$) and included an intercept term ($\beta = -0.16$, $SE = 0.06$, $p < .02$) and three variables that were significantly associated with depression instability: interview age ($\beta = -0.19$, $SE = 0.05$, $p < .001$), positive psychiatric history of OCD ($\beta = 0.43$, $SE = 0.20$, $p < .05$) and presence of rapid cycling ($\beta = 0.27$, $SE = 0.11$, $p < .02$).

Model assumptions were re-tested on the updated model with the outlier removed. Fewer than 1% of total cases had large residuals, and none of these observations violated assumptions of Cook's distance, leverage, or covariance ratio. No outliers were identified, as the outlier test from the car package was non-significant (studentised residual = 3.478, Bonferroni p = 0.142). Collinearity was not present in the data: the VIF for each predictor variable was <10 (range: 1.02 to 1.04) (Steinhorst & Myers, 1988), the average VIF was 1.04 which is not substantially greater than 1.0, (Bowerman & O'Connell, 1992) and there was no tolerance value ≤ 0.2 (Menard, 2010). Normality and homoscedasticity were assessed by evaluating plots of the residuals (Appendix D.3.), as well as running the Shapiro-Wilk and Breusch-Pagan Tests. The data was non-normal, according to the Shapiro-Wilk test, W = 0.925, p < .000., and heteroscedasticity was present, studentized Breusch-Pagan test = 24.986, df = 3, p-value < .000. Therefore, a robust sandwich estimator was used to obtain heteroscedasticity-consistent standard errors using the sandwich package (Zeileis, 2006). The Bootstrap, with 1000 resample runs, was also employed to deal with the bias in standard errors. Confidence intervals for the three selected predictors were compared for the ordinary-least-squared model, the model with a robust sandwich estimator, and the bootstrap model (Figure 12).

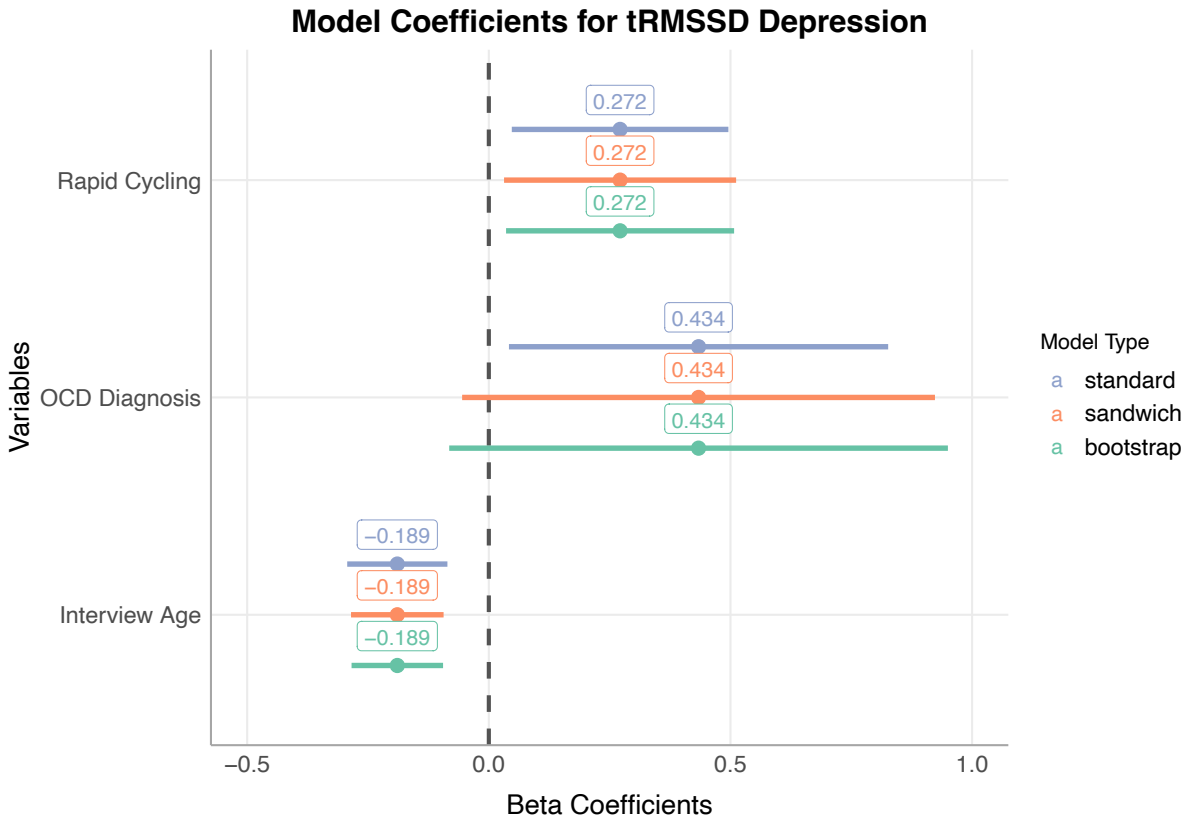

Figure 12. Caterpillar plot for model comparison displaying coefficient values and confidence intervals (CIs) for the winning model for 'depression instability'. The bootstrap and sandwich models adjust for the violations of model assumptions.

The models adjusting for heteroscedasticity were compared with the standard OLS model. Confidence intervals were similar across models. However, while 'rapid cycling' and 'interview age' remained significant predictors of depression instability, a 'psychiatric history of OCD' was no longer a significant predictor when adjusting for heteroscedasticity (Figure 12 and Table 22).

Table 22. Comparison of 'depression instability' models adjusting for heteroscedastic standard errors. Coefficient estimates are given followed by their standard errors, denoted as '(SE)' and confidence intervals shown as '[lower CI, upper CI]'.

	Standard OLS Model	Sandwich Estimator Model	Bootstrap Model

Constant Term (Intercept)	-0.156 (0.064) *	-0.156 (0.056) **	-0.156 (0.055) **
	[-0.282, -0.030]	[-0.266, -0.046]	[-0.264, -0.048]
Age at Interview	-0.189 (0.053) ***	-0.189 (0.050) ***	-0.189 (0.049) ***
	[-0.293, -0.086]	[-0.287, -0.091]	[-0.286, -0.093]
Psychiatric History of OCD	0.434 (0.199) *	0.434 (0.263)	0.434 (0.262)
	[0.042, 0.826]	[-0.085, 0.953]	[-0.083, 0.951]
Presence of Rapid Cycling	0.272 (0.114) *	0.272 (0.124) *	0.272 (0.123) *
	[0.048, 0.496]	[0.026, 0.517]	[0.030, 0.513]
Number of Observations	234	234	234
AIC	1012.3	1012.3	1012.3
BIC	1807.0	1807.0	1807.0
R2	0.09	0.09	0.09
Adjusted R2	0.08	0.08	0.08
RSE	0.79	0.79	0.79
*=.05, **=.01, ***=0.001			

5.3.4 Post-hoc analysis

Post-hoc, for MI, analyses were re-run using 'leave one out cross validation' (LOOCV) rather than k-fold CV. LOOCV splits the dataset into a training set and a testing set using n - 1 observations for the training set, thus reducing potential bias. Using LOOCV produced the same 'winning' models as k-fold CV. The best models (those with the lowest RMSE) contained the same variables as significant predictors of mania instability and depression instability when using LOOCV and k-fold CV. Indeed, k-fold CV often gives more accurate estimates of the test error rate than does LOOCV (James et al. 2014).

Correlations between all predictor variables were examined (see Appendix D.4.) Correlation coefficients ranged from moderate (0.49) to large (-0.96) effect sizes according to Cohen's Rule of Thumb. The variables that were most highly correlated related to diagnostic categories (e.g., a diagnosis of BDI was negatively correlated with a diagnosis of BDII, as expected) and lithium response (positive response to lithium was negatively correlated with never having taken lithium). Accordingly, as these are variables that are inherently related and cannot be considered in isolation, they were retained in the model building process to preserve ecological validity.

5.4 Discussion

This study integrates mixed modelling approaches to investigate which factors are associated with mood severity and instability in BD, with a focus on AAO. No known studies in the extant literature have used these statistical approaches to explore this relationship. Findings are combined from the results of mixed effects models and regression analyses employing supervised machine learning techniques, including bootstrapping and k-fold cross-validation. Analyses were partitioned into two streams: (i) mood severity and (ii) mood instability (MI) for both mania and depression. Findings are discussed for both severity and instability in the context of previous research, along with implications for treatment decisions and hypothesised aetiological mechanisms.

5.4.1 Summary of findings

The winning model identified for mania severity specified participant ID and AAO as random effects. Presence of rapid cycling as a diagnostic specifier was the only fixed effect that was significantly related to total mania scores in this model; with rapid cycling being associated with increased mania scores over time. For depression severity, the winning model included participant ID as a random effect but, unlike mania severity, did not include AAO. The fixed effect terms of rapid cycling and psychiatric history of OCD were both significantly related to an increase in total depression scores. Positive psychiatric history of OCD and presence of rapid cycling were also significantly associated with both increased depression and mania instability. Increased mania instability was further linked to never having taken lithium, while decreased depression instability was correlated with an increased age at interview.

5.4.2 Rapid Cycling

Together, results indicate that rapid cycling (RC) is associated both with greater total severity and instability in mania and depression scores across participants over time. This is perhaps

unsurprising given that the DSM-IV criteria for a RC specifier requires at least four distinct mood episodes per year meeting the criteria for (hypo)mania or depression (American Psychiatric Association, 2013). This higher rate of switching between mood states is, by virtue of its definition, more instable, and the higher frequency of episodes confers a greater probability of experiencing increased symptom severity. Not only are mood episodes more frequent in RC compared to other BD subtypes, but a recent systematic review and meta-analysis emphasised that RC individuals also have poorer treatment response, with manic symptoms being particularly treatment refractory (Strawbridge et al., 2022). This poor treatment response is compounded by the finding that antidepressant use may trigger an increase in RC (Carvalho et al., 2014). Thus, the frequency of recurring mood episodes and lack of treatment efficacy can help explain why RC is associated with increased severity and instability of mood symptoms in the current study.

This association between RC and mood may also provide a partial mechanistic account for the increased risk of serious suicide attempts and completions, along with increased numbers of hospitalisations and poorer psychological functioning, that is observed in individuals with RC BD compared to those without a RC specifier (Bronisch et al., 2005; Carvalho et al., 2014; Coryell et al., 2003). Indeed, in line with the current findings, Coryell et al. (2003) found that across an average of 14 years follow-up, RC individuals were depressed for a significantly greater proportion of time compared to non-RC BD. They posit that this predominant depressive symptomatology, together with the abrupt transitions from mania or hypomania to depression that is characteristic of RC, may further predispose to suicidality (Coryell et al., 2003). Moreover, a burgeoning body of research indicates that MI is perhaps the single most important factor in explaining suicidal thoughts (Anvar et al., 2022; Bowen, Balbuena, Peters, et al., 2015; Palmier-Claus et al., 2012), even over and above suicidal ideation's demonstrable association with high levels of impulsivity, PTSD, and depression (Marwaha, Parsons, & Broome, 2013; Peters et al.,

2016). This suggests that the relationship between increased MI, severity, and suicidal ideation and/or suicide attempts should be explored more thoroughly.

5.4.3 Psychiatric history of OCD

5.4.3.1 Mood Severity

The current findings further indicate that increased depression severity, but not mania severity, was associated with a psychiatric history of OCD. This is consistent with evidence suggesting that BD individuals with comorbid OCD, compared to those without, experience a greater number of depressive episodes overall, with depressive rather than manic symptoms dominating the course of illness (Amerio, Odone, Liapis, et al., 2014; Mahasuar et al., 2011). As the predictor variables in the present study were recorded at one timepoint and are therefore cross-sectional in nature, the casual direction of the relationship between OCD history and increase depression severity cannot be expounded. However, the present results parallel prior research demonstrating that BD individuals with comorbid OCD showed obsessive-compulsive symptom improvement during hypomania/mania but greater severity during depressive spells (A. Gordon & Rasmussen, 1988; Kendell & Discipio, 1970; Zutshi et al., 2007). In fact, evidence indicates that obsessive-compulsive symptoms sometimes emerge exclusively in combination with depressive episodes and may often remit entirely during (hypo)manic episodes (Amerio, Odone, Liapis, et al., 2014). In part, this may be due to the anxiolytic effects of some antimanic agents, as well as the antimanic effect of certain anxiolytic medications such as the anticonvulsant gabapentin and benzodiazepines, including lorazepam and clonazepam (Freeman et al., 2002; Perugi et al., 2002; Vázquez et al., 2014). However, as the present findings relate to a psychiatric history of OCD, we cannot be certain whether individuals (a) ever used specific anxiolytic medication for OCD symptoms, or (b) were continuing using anxiolytics at the time of data collection. Results from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) indicates that comorbid conditions in BD are often under-treated, with limited use of comorbidity-specific

pharmacotherapy (Simon et al., 2004). Thus, the current interpretations about medication use influencing the purported relationship between OCD and manic symptoms are only tentative. Nonetheless, the current results together with previous findings indicate that there is a probable bi-directional relationship between depressive and obsessive-compulsive symptoms in BD. Yet, as the current data pertaining to psychiatric comorbidities is cross-sectional and retrospective, the directionality of this relationship remains unclear; a history of OCD symptoms may contribute to a worsening in depressive symptomatology over time, or vice versa. While the mechanistic underpinnings of the relationship between bipolarity and anxiety disorders have not yet been elucidated, previous evidence suggests a complex interplay of neurobiological and psychosocial factors, which are in turn influenced by pharmacological and psychological treatment approaches (Freeman et al., 2002; Mitchell, 2015; Pavlova et al., 2015).

5.4.3.2 Mood Instability

As well as being associated with greater depression severity, psychiatric history of OCD was further associated with increased MI for both depression and mania. There is a relative paucity of literature examining the relationship between OCD traits and/or comorbidity and MI in BD, and so interpretation of this finding is speculative. One important point to consider is that high-dose SSRIs are the first line treatment for comorbid OCD in BD, but they have been shown to induce manic switch and MI, especially when maintained for a long time and even in conjunction with concomitant mood stabilisers (Amerio et al., 2019; Amerio, Odone, Marchesi, et al., 2014; Kazhungil & Mohandas, 2016; Keck et al., 2006; Math & Janardhan Reddy, 2007). Conversely, when OCD symptoms are not the primary clinical concern – as is likely the case in the current study, with findings referring to a historical OCD diagnosis – obsessive-compulsive symptoms may not be treated adequately by medication typically used for BD. For instance, second-generation antipsychotics, usually clozapine, have been shown to trigger and exacerbate obsessive-compulsive symptoms in individuals with schizophrenia (Lim et al., 2007; Schirmbeck & Zink,

2013). More recent research similarly suggests that use of second-generation antipsychotics can provoke previously absent OCD symptoms in BD, and that these symptoms worsen during depressive episodes (Jeon et al., 2018).

Beyond the role that pharmacotherapy plays, there is likely a significant association between increased MI and OCD as they share certain phenomenological characteristics and may have overlapping pathophysiology. For example, OCD can be considered as closely related to other anxiety disorders: historically sharing a diagnostic group under the umbrella of "neurotic conditions" in previous classification schemes, including DSM-IV (American Psychiatric Association, 1994) and the International Classification of Disease 10th Revision (ICD-10; (World Health Organization, 1993). Pertinently, MI has emerged as a core component of neuroticism. Research examining the factor structure of neuroticism indicated that MI was most strongly associated with neuroticism over and above dimensions of anxiety and low mood, and that MI most strongly predicted worse psychological distress up to seven years later (Bowen et al., 2012). This association with neuroticism indirectly reinforces the hypothesis that MI and OCD may share underlying pathological mechanisms.

Moreover, unpredictable, recurring, and abrupt changes in mood – the hallmark of high MI – could lead to heightened threat-vigilance and an associated fearful and anxious attitude, which may further help to explain the association between MI and OCD (Bowen, Balbuena, Baetz, et al., 2015; Marwaha, Parsons, Flanagan, et al., 2013). Indeed, intolerance of uncertainty has been specifically linked with subsequent OCD symptomatology (Gentes & Ruscio, 2011). On the other hand, it may be that OCD traits and/or symptomatology increases an individuals' vigilance to their internal mood states, and thus increase reporting rates. For instance, anxious individuals display a heightened tendency to self-monitor body sensations, to detect and respond to possible perceived threats (Olatunji et al., 2007). The same may therefore be true for monitoring

of internal mood-states, especially as mood-states can be linked to physiological changes, and vice versa. In further support of the idea that MI and OCD may be underpinned by shared neurobiological mechanisms, diffusor tensor imaging studies provide evidence for increased white matter abnormalities in OCD individuals, as well as abnormal connections between the amygdala and pre-frontal cortex, which may account for unstable neuro-connectivity that relates to the expression of MI (Bora et al., 2011; Bowen, Balbuena, Baetz, et al., 2015; Broome, He, et al., 2015).

5.4.4 Further associations

5.4.4.1 Age at Onset

While both models for mania and depression severity included participant ID as a significant random effect – indicating that the intercepts for mood scores varies significantly across participants – only the mania model included AAO as a random effect. Further, AAO was not found to be a significant predictor in the models for MI. Existing research indicates that individuals with a younger AAO of BD are more likely to experience RC (Ernst & Goldberg, 2004; Geller & Luby, 1997; Schulze et al., 2002); the present results corroborate this as RC was included as a fixed effect in the model for total mania severity, with AAO as a random effect. While previous findings are mixed, some studies suggest that the association between AAO and RC is accompanied by a greater frequency of manic rather than depressive episodes, which is concordant with the present evidence (Geller et al., 1995). However, findings from nearly 2,000 individuals with BD, recruited as part of the STEP-BD study, indicated that AAO was not significantly related to rapid cycling when baseline illness severity and recent history of rapid cycling were accounted for (Schneck et al., 2008). As the predictor variables in the current study were not measured longitudinally, this relationship cannot be tested. Future research would benefit from using prospective longitudinal data to conduct path analyses; this would help elucidate whether there may be an indirect association of AAO with mood which the current

analyses did not investigate. For example, a younger AAO may elicit a developmental vulnerability to rapid cycling or OCD, and therefore AAO may be the important factor driving the indicated association, but this association may be masked in the present study. In turn, this would help to elucidate causal mechanisms which is important not only for understanding aetiology but also for informing treatment approaches.

5.4.4.2 Lithium Response

Increased mania instability was linked to never having taken lithium. While there was no significant association between 'responding to lithium' and a decrease in manic instability, this finding indirectly implies that taking lithium protects against greater instability of manic symptoms. This aligns with well-established evidence demonstrating that lithium is an effective treatment for acute mania (Bowden, 2004). Results from a 2019 Cochrane systematic review indicate that lithium is superior compared to placebo – as well as some other active treatments, including antipsychotics and mood stabilisers – at reducing manic symptoms and achieving remission (McKnight et al., 2019). For treating BD depressive episodes though, a systematic review of RCTs and meta-analyses indicated that lithium is only efficacious when combined with other agents, such as lamotrigine or an antidepressant, and not as a monotherapy (Fountoulakis et al., 2022). Similarly, results suggest that when RC or concomitant OCD is present lithium's efficacy is only evident when administered in combination. For instance, in comorbid OCD, lithium is only effective when combined with an antipsychotic such as aripiprazole or the glutamate receptor antagonist memantine (Fountoulakis et al., 2022). The present study did not find a significant association between 'no response to lithium' and manic symptoms, which is likely due to the very low numbers (n = 6) in the 'no response' group. Furthermore, 'response to lithium' was not significantly associated with decreased mania. This could be due to the naturalistic study design, as individuals may be on lithium prior to beginning their mood ratings

and remain using it for the duration of their mood scoring; thus, there is no 'without lithium' baseline to detect a decrease in mania severity.

5.4.4.3 Age at Interview

Lastly, decreased depression instability was correlated with an increased age at interview; suggesting that older participants exhibited less depression instability. In concordance with this, research suggests that symptom severity in BD may decrease over time, with relapse and psychiatric hospitalization diminishing with age (Kessing et al., 2004; Sajatovic et al., 2015). This is paralleled by research in healthy individuals without a BD diagnosis that indicates emotion regulation improves with age (Brummer et al., 2014), and that older adults self-report better control of their emotions compared to younger adults (Schirda et al., 2016). It is thought that this may be due to older adults having a greater knowledge of emotion regulation strategies and being better at perceiving, understanding, and suppressing their emotions without accompanying psychological distress (Brummer et al., 2014; Livingstone & Isaacowitz, 2021).

Additionally, research across the lifespan suggests that the number and frequency of traumatic and stressful life events decreases with age (Hatch & Dohrenwend, 2007); which means a decline in triggering events that may exacerbate mood symptoms and MI. This may also help explain why the current findings pertain specifically to depression instability and not mania instability, as negative life events have been shown to trigger depressive rather than manic episodes (Gershon et al., 2013; Johnson, 2005). Furthermore, it has been demonstrated that the presence of fewer negative life events is associated with increased treatment adherence in BD (Corréard et al., 2017), and that older individuals with BD show greater adherence to antipsychotic medications compared to younger individuals (Sajatovic et al., 2007). Increased medication adherence has further been shown to be related to decreased self-stigma and greater illness understanding in older BD adults (Savaş et al., 2011; Smilowitz et al., 2019). Overall, discussion on age related

changes in life events, emotional regulation and processing, and medication adherence in both BD and non-BD individuals underscores the importance of a lifespan perspective in research and clinical care.

5.4.5 Strengths and Limitations

This is the first known study investigating the relationship between prospectively observed mood severity and instability in BD with AAO and other various sociodemographic variables. Gold-standard modelling approaches were used to disentangle this relationship. Mixed-effects models were employed to investigate mood severity, and multiple regression with k-fold cross-validation was applied to investigate MI; both analyses approaches employed robust covariance estimation using sandwich estimators and bootstrapping to adjust for heteroscedasticity.

Despite these strengths, there are certain limitations that must be considered when interpreting the results. Firstly, there was no independent sample available for external model validation. While cross-validation approaches go some way to mitigating this, cross-validation methods only use subsamples of the original dataset and are therefore subject to the same limitations as the data used for model building. For instance, analyses were constrained by the retrospective and cross-sectional nature of the independent variables, making it impossible to establish the direction of associations and corresponding causal inference. Regarding causality, future studies should aim to use path analysis or mediation approaches to better understand the precise and perhaps bi-directional nature of the relationship between predictor variables, AAO, and prospective mood ratings. For instance, AAO may have exerted a moderating or mediating effect on the relationship of significant variables, such as rapid cycling and history of OCD, with mood outcomes, however the modelling approaches employed in the present analysis were not able to test this hypothesis.

Furthermore, retrospective data are subject to recall bias, which undermines the reliability of self-reported demographic variables including AAO and psychiatric history. This was partially mitigated by referring to medical case notes rather than relying solely on self-report. Yet, the reliability of AAO remains under question as it has been suggested that people with BD may be more likely to recall depressive compared to manic episodes or fail to recognise hypomanic episodes pre-diagnosis as pathological (de Assis da Silva et al., 2014; Gazalle et al., 2007).

In addition to the potential impact of recall bias on the reliability of the data, it is important to acknowledge that engaging in mood monitoring is an active process that may affect reported mood states. Mood monitoring is often used clinically to help individuals with mood disorders track and manage their mood, and is believed to facilitate self-awareness and reflection, which can be valuable for maintaining wellness (Goodday et al., 2020; Jonathan et al., 2021). Therefore, it is possible that participating in mood monitoring via the True Colours platform may have had a therapeutic effect, potentially reducing reported levels of MI in the current study. Moreover, it should be noted that individuals with BD may have difficulty accurately identifying their mood states, particularly during (hypo)manic phases (Ghaemi & Rosenquist, 2004).

Additionally, the sample of BD individuals used in the current study may not be representative of the larger BD population as they are generally highly educated, technologically inclined, and motivated to participate in research. The current sample represents only about 8% of the total 4080 individuals in the BDRN cohort who were invited to use the True Colours system. Of those participants who signed up to use TC, those with a diagnosis of BDII were more likely to register to use the platform (Goodday et al., 2020). It is therefore possible that this motivated and engaged sub-sample may have been more likely to complete mood assessments and follow the study protocol compared to individuals that chose not to participate in using the TC platform. Caution should therefore be taken when generalising the present findings.

Lastly, while the datasets were relatively large, model fitting would benefit from increased numbers of data points covering a wider representation of participants to increase generalisability. As a gold-standard therefore, future research investigating mood in BD with psychosocial variables should aim to employ fully prospective longitudinal methodologies across a variety of cohorts.

5.4.6 Conclusions

While the final models must be interpreted with caution, current findings both corroborate and advance the extant literature. This study helps deepen the understanding of the relationship between sociodemographic and illness characteristics with mood in BD. Findings underscore the association of a rapid cycling specifier and history of OCD as factors that may increase subsequent mood severity and instability. More tentative results highlight the role of AAO and lithium use in increased mood severity and instability respectively, while increasing chronological age appears to help stabilise mood. These results can help given clinicians and BD individuals a better understanding of illness course, and thus have the potential to inform treatment approaches and medication choices. In particular, the importance of treating concomitant OCD and mood symptoms has been highlighted, along with the prophylactic benefits of lithium use for reducing manic instability. Future research would greatly benefit from using prospective longitudinal data to disentangle the causal relationship between these variables.

Chapter 6. General Discussion

The central aim of this thesis was to investigate the potential of age at onset (AAO) as a clinical specifier in bipolar disorder (BD) to identify aetiologically and phenomenologically similar subgroups. By establishing the utility of AAO as a variable that demarcates more homogeneous BD subgroups, the thesis aimed to provide an evidence-based foundation for improving treatment outcomes and intervention approaches. The investigation of AAO as a potential clinical specifier in BD was motivated by the limitations of current nosology, which fails to define and validate clinically and aetiologically uniform BD subgroups, resulting in sub-optimal treatment efficacy and a lack of early intervention approaches. It is hoped that the results from this thesis can contribute to ongoing efforts to enhance the understanding and management of BD by assessing the reliability and validity of AAO as a clinical specifier.

6.1 Summary of findings

Chapter 2 presents the first known systematic review of AAO in BD. The results of this systematic review indicated that BD has a trimodal AAO distribution, segregating into early-, mid- and late-onset subgroups with the most common average AAO being 17.3 years. Having established that there are distinct subgroups according to AAO, Chapter 3 went on to employ a novel combination of machine learning techniques to investigate psychosocial predictors of BD AAO in the Bipolar Disorder Research Network (BDRN) cohort. Eleven variables were found to be associated with BD AAO, with six predicting an earlier AAO, including childhood abuse, regular cannabis use prior to onset, death of a close family friend or relative, family history of suicide, schizotypal personality traits, and irritable temperament. Five variables predicted a later AAO, including alcohol consumption, birth of a child, death of a family member, unemployment, and major financial crisis. These findings suggested that BD AAO was likely influenced by a complex

interplay of genetic susceptibility, individual-level personality traits, exposure to negative life events and trauma in childhood.

Building upon the results of Chapter 3, Chapter 4 used prospective data from 308 high-risk offspring of BD probands to investigate the potential causal pathways underlying the relationship between early-life psychosocial factors, AAO, and functional outcomes. While the expected mediating effect of AAO on the relationship between early-life variables and global functioning was not observed, several significant direct pathways between premorbid factors, AAO, and functioning were identified. Childhood neglect and abuse, drug abuse, and an active temperament, were associated with decreased global functioning, while emotional, social, and shy temperaments were linked to increased global functioning. Furthermore, childhood abuse, frequency of drug and alcohol use, and death of a family member or friend, along with temperament traits (emotional, shy, active, and social) were associated with a later AAO, whereas increased drug abuse was related to a younger AAO. Prior research suggested that some of these relationships may be moderated by mood instability.

Chapter 5 integrated mixed modelling approaches to investigate which factors were associated with mood severity and instability in BD, with a focus on AAO. Results indicated that rapid cycling was significantly related to increased mania scores, while rapid cycling and OCD history were associated with increased depression scores and instability for both depression and mania. Never having taken lithium was linked to increased mania instability, and increased age at interview was related to decreased depression instability. These findings likely have important implications for treatment decisions.

6.2 Implications

Overall, there are three inter-related key points that can be taken from the results of this thesis: (1) that AAO in BD has a trimodal distribution spanning the life course, (2) differing AAO is associated with distinct early-life risk factors, which may represent part of a causal pathway to clinical outcome, and (3) mood instability is a promising targetable factor in the clinical trajectory of BD. These findings extend the extant literature and hold important theoretical and practical implications. The implications of these findings are discussed alongside other insights gained during the course of this thesis.

6.2.1 Theoretical Implications

6.2.1.1 Defining AAO

One of the central findings of this thesis is that AAO in BD has a three-group distribution; early-, mid- and late-onset. This is not often acknowledged in prior research, with studies investigating associations with AAO using analysis techniques that do not permit modelling of this trimodal structure. This lack of acknowledgement may be partly influenced by the preponderance of unimodal AAO distributions in other mental health disorders, including schizophrenia, personality disorders, depressive disorders, and eating disorders (Solmi et al., 2022). Indeed, the studies conducted in the present thesis are also subject to this limitation as they were constrained by a lack of accessible statistical approaches to model outcome variables with a non-normal distribution, without resorting to 'binning' methods (e.g., logistic regression) thus losing the level of detail given by continuous measurements. The field would therefore benefit from the use of more advanced statistical approaches to investigate predictors of AAO preserving its trimodal structure. Beyond this limitation however, the systematic review findings highlight that the field should move towards a conceptualisation of these AAO subgroups as referring broadly to life-stage and establish a consistent definition of bipolar AAO as 'the first affective episode meeting diagnostic criteria'. This can provide a solid basis on which to conduct future research.

Furthermore, the identification of early-, mid-, and late-onset subgroups highlights the importance of considering developmental stages when studying BD, as the underlying mechanisms and risk factors may differ across the lifespan.

6.2.1.2 Putative mechanisms

The importance of adopting a lifespan perspective in understanding risk factors for BD is supported by the results of Chapters 3 and 4. These findings highlight the interplay of individual-level characteristics, premorbid substance use, exposure to negative life events, and trauma in childhood, in the onset of BD. Exposure to varying types of negative life events will differ across the life course, however it is important to acknowledge the role that genetic vulnerability may play in contributing to early adversities through gene-environment correlation. Childhood trauma, for example, may interact with a child's genetic vulnerability to predispose them to develop symptoms of depression and anxiety. This can then impact the child's environment, leading to social isolation and decreased support, thus reinforcing their symptoms and genetic vulnerability over time. Therefore, an integrative model that considers the complex interaction between genetics, environmental factors, individual traits, and family setting is necessary for a nuanced understanding of the aetiology of BD.

With regards the role of AAO in the clinical course of BD, results from Chapter 4 suggest that AAO in BD may be better viewed as a risk marker rather than a risk factor, as there was no significant mediating effect of AAO on functional outcome. Rather, premorbid factors prior to onset directly influenced future functioning. The idea that AAO may be a risk marker means that it is not necessarily a younger AAO that leads to a more deleterious clinical course. It has been hypothesised that an earlier AAO disrupts typical development at a critical stage, and correspondingly precipitates a cascade of maladaptive biopsychosocial mechanisms which contribute to poorer long-term outcomes (Leboyer et al., 2005). However, the results of this

thesis suggest that early-life factors may instead be the driving force between early-onset and worse outcomes, with results indicating direct pathways between these premorbid factors and both an early AAO and decreased functioning. These results have promising implications for the development of early intervention strategies aimed at identifying and addressing these risk factors.

6.2.1.3 Delineating homogenous subgroups

The findings of the current thesis have implications for the delineation of homogenous subgroups in BD. Although AAO may be a valuable clinical specifier for defining subgroups with unique clinical and psychosocial characteristics, the lack of consistent associations between AAO and mood instability in Chapter 5 challenges the utility of this approach. The current findings suggest that early-life factors may be a more important determinant of illness course and functional outcomes than AAO, which indicates a potential advantage of a more comprehensive framework for categorising individuals with BD. In addition, the psychosocial factors associated with AAO require further validation to determine their uniqueness to specific AAO groups. A more comprehensive understanding of the relationship between AAO, early-life factors, and functional outcomes may enable the validation of more homogenous groups and corresponding development of targeted and effective interventions. However, more research is needed to fully understand the complex interactions between these variables, as well as other factors that may contribute to the heterogeneity of BD.

6.2.1.4 Integrative analysis approaches

The findings presented in this thesis highlight the importance of integrating different analytical approaches in psychiatric research to gain a comprehensive understanding of complex disorders such as BD. The use of systematic reviews, machine learning techniques, prospective data, and mixed modelling demonstrates the value of using diverse methods to investigate complex

questions. However, through the development of this thesis is has become apparent that traditional statistical approaches in the domains of psychology and psychiatry are not always optimal when presented with complex outcome measures and interrelated variables. It is vital therefore that psychiatric research continues to benefit from collaboration between bioinformaticians, mathematicians, statisticians, and data scientists, for more advanced modelling methodologies to become commonplace in the analysis of complex mental health data. Such interdisciplinary approaches, together with the use of large-scale datasets, biomarkers, and computational modelling, can aid in the identification of new subtypes of psychiatric disorders, the development of more targeted interventions, and a better understanding of the underlying mechanisms of these conditions. Ultimately, this may lead to more personalised and effective treatments for individuals with mental health disorders.

6.2.2 Clinical Implications

The findings of this thesis also have important practical and clinical implications for the diagnosis and treatment of BD. It is hoped that the identification of subgroups based on AAO and psychosocial factors may lead to earlier diagnoses and more personalised treatment approaches. For instance, results indicate that BD is most likely to onset in early life from the ages of 14-21 years, with the most common average AAO being 17.3 years. This suggests that clinicians should be more vigilant to the development of symptoms during this life-stage, especially in high-risk individuals such as those with a close relative with BD. In this way, a better understanding of when BD onsets across the life course can help facilitate more accurate and timely diagnoses.

6.2.2.1 Preventative strategies and early intervention

Awareness of the BD AAO distribution can further be used to tailor interventions according to developmental stage. For instance, the 'early-onset' subgroup overlaps with the age range for secondary school, which represents a critical developmental period. Thus, school-based

educational campaigns that promote greater awareness and recognition of possible prodromal symptoms, both within individuals and their peers, may represent a simple yet effective first step towards early intervention.

Such approaches could include raising awareness about the specific risk factors that may exacerbate the development and progression of BD, as well as educating individuals about potential mitigating strategies that could help improve trajectory or potentially help delay the onset of the disorder. For instance, given that the present findings highlight that greater levels of drug and alcohol use may confer a high-risk sate for the development of BD, educating individuals to the potential deleterious effects of substance use is likely valuable. Promisingly, a synthesis of systematic review evidence indicates that school-based prevention programs, family-based interventions addressing family functioning, community-based programs, and digital media campaigns have all been shown to reduce and even prevent smoking, alcohol consumption, and drug use in adolescents (Das et al., 2016). Such educational strategies may be additionally useful since one of the limitations discussed in this thesis is that substance use may mask the true onset of BD, with symptoms being attributed to substance use rather than the expression of the bipolar prodrome. Avoiding or reducing drug and alcohol consumption would provide a more accurate clinical picture regarding disorder onset, and thus facilitate more timely diagnoses, corresponding appropriate treatment, and a better clinical outcome.

Furthermore, given the role of childhood abuse in the likely aitiology and trajectory of BD, providing safe spaces and support groups within school and community settings, as well as raising awareness, may help with prevention. For example, research suggests that protective factors for childhood abuse include the presence of caring and informed adults and peers, a positive school and community environment, social connectedness, parental resilience and competence, shared responsibility within the community, and raised awareness to support the

development of safe environments (Roygardner et al., 2021). However, these approaches require significant further development and involvement from public health services in collaboration with clinicians and researchers. In terms of existing strategies, a systematic review of randomised control trials highlighted the efficacy of home visits, both from nurses and non-professional lay visitors, in decreasing the rate of child abuse in high-risk families (Levey et al., 2017).

To complement this general 'catch-all' approach, targeted interventions aimed at high-risk groups could offer a more streamlined strategy for early intervention. High-risk individuals could be identified through comprehensive assessment of those who have a family history of BD or a personal history of mood or behavioural symptoms that are consistent with BD. The results of this thesis indicate that individuals who experience early life stressors or trauma, exhibit high levels of mood instability, or have a history of frequent substance use, may be at increased risk for BD. Future studies validating these findings hold the potential to extend prior work in precision psychiatry. For example, the identified potential risk factors could be used to improve risk calculators that aim to predict BD onset, such as the one developed by Hafeman et al. (2017). This person-level risk calculator used factors such as dimensional mood and anxiety symptoms, general psychosocial functioning, and parental age at mood disorder onset to discriminate between those who developed BD within a 5-year follow-up period and those who did not. Taking this further, future research should aim to integrate biomarkers, such as genetic testing or brain imaging, which may also provide useful information in identifying high-risk individuals. By using a combination of these approaches, mental health professionals could then offer personalised interventions to prevent or delay the onset of this disorder. In this way, precision medicine offers a promising way to guide early intervention strategies and improve outcomes for individuals at high risk for BD.

Taken together, there is merit both in precision medicine as well as a more holistic approach to intervention and treatment. A holistic approach offers a way of addressing non-specific risk-factors within a family, community, and society-wide setting. In contrast, precision medicine aims to provide personalised interventions and treatment plans that are specific to an individual's genetic, environmental, and clinical characteristics. While each approach has its strengths, a combination of both could offer the most effective way to prevent and treat BD. Regardless of the approach used, the present findings underscore the importance of mental health professionals screening for risk factors, such as childhood abuse, regular drug and alcohol use, and family history of psychiatric disorders and suicide, when assessing an individual's risk for developing BD. Early detection of symptoms can guide interventions that may help mitigate the negative impact of these risk factors on functional outcomes and improve the long-term prognosis of individuals with BD. Overall, a balanced approach that considers both the holistic and personalised aspects of care can help optimise outcomes for individuals with BD.

6.2.2.2 Improving clinical outcomes

Beyond targeting early-life factors with the goal of prevention and early-intervention, findings from this thesis also have implications for the acute and long-term management of BD symptoms. For instance, results pertaining to mood severity and instability in BD have implications for treatment decisions, such as the use of lithium for individuals with increased mania instability and the importance of addressing rapid cycling and comorbid obsessive-compulsive disorder (OCD) in individuals with increased depression instability. Additionally, considering age when developing treatment plans for individuals with BD is crucial, as the finding that increased age at interview was related to decreased depression instability indicates that treatment plans should be tailored to the individual's developmental stage. These results underscore the importance of personalised treatment approaches in BD and the need for

clinicians to consider a range of factors beyond symptom presentation when making treatment decisions.

In summary, the findings presented in this thesis have important theoretical and practical implications for the field of BD research. The identification of subgroups based on AAO and psychosocial factors may lead to more personalised diagnosis and treatment approaches, improving clinical outcomes. Moving forward, further research is needed to fully understand the complex interplay between genetic, environmental, and developmental factors in the onset and progression of BD and to develop more effective treatments for individuals with this disorder.

6.3 Limitations

Specific limitations of each study have been discussed in the corresponding chapters. However, there are some general limitations that should be considered when interpreting the results of this thesis. One of the main limitations is that the thesis relies on the analysis of secondary data. While the use of secondary data can be extremely powerful by providing access to large longitudinal and prospective datasets that are not feasible to collect within the course of a DPhil, it also has several limitations. One of these limitations is that the measures have not been collected with the current research aims in mind. This means that not all relevant data will have been recorded, which can impact the validity and reliability of the results. For example, not all variables used in analysis had time markers associated with them, which is important to consider when investigating AAO, especially when the temporal direction of associations is of interest. This limitation further contributes to the difficulty in establishing causality in observational studies. While the thesis found significant associations between certain psychosocial factors and AAO, it is difficult to establish a causal relationship between these factors and AAO.

Furthermore, results may not be generalisable to other populations or settings. For example, the samples used in analyses may not be representative of the larger population of individuals with BD as they comprised predominantly middle-class participants from Western countries and of European ancestry. There may be other factors, such as biological or environmental factors that are unique to different ethnic or cultural groups, that were not included in analysis. These limitations may therefore constraint the external validity of the current findings. It is also worth noting that much of the data used in this thesis come from self-report measures of psychosocial factors, which are subject to various biases. For example, childhood abuse may be underreported, or individuals may have difficulty accurately recalling childhood experiences. This could impact the validity of the results if these self-report measures are not accurate or comprehensive.

Another inherent problem of working with large observational datasets is that there is often a substantial amount of missing data (Faurholt-Jepsen, Geddes, et al., 2019). While Chapter 4 aimed to account for missingness by using multiple imputation, this is not a perfect fix as it is restricted by the same limitations as the original dataset. Researchers therefore need to consider more sophisticated ways to mitigate the impact of missing data on the results. Indeed, emerging evidence demonstrates that missingness itself can be informative when studying psychiatric disorders. Research examining longitudinal self-reported mood ratings has demonstrated that building a model which includes missing data as its own signal is able to achieve superior accuracy in differentiating between diagnostic groups (BD, borderline personality disorder, and healthy controls) than models that do not include a missingness signal (Wu et al., 2022). The finding that missingness can serve as a valuable indicator of illness course is understandable in the context of BD, as participants experiencing episodes of mania or depression are unlikely to be motivated to catalogue their mood states or have insight into their symptoms. To mitigate this limitation, future research should consider using proxy measures of mood states, such as

actigraphy, to improve the accuracy of mood assessment. These measures could provide more accurate and comprehensive data that could help to overcome some of the limitations of the current datasets used in this thesis.

6.4 Future Directions

Considering the limitations of this thesis, several directions for future research are proposed. As a logical next step, future research should aim to validate and extend the findings of the current thesis by using other available datasets to investigate the association of early-life factors with AAO and functional outcomes. Using other available data sources such as the Avon Longitudinal Study of Parents and Children (ALSPAC), UK Biobank, more recent data from the BDRN cohort, population-based registries (e.g., the Swedish national population register), and electronic clinical records such as UK Clinical Record Interactive Search (CRIS), could provide valuable data with which to assess the reliability and validity of the present findings. Despite the potential benefits of utilising these various data sources, it is important to acknowledge the associated limitations. In fact, many of these limitations overlap with those outlined for the datasets used in the current thesis, which may result in inconsistent findings and inhibit the ability to extract meaningful information from the data. One such limitation in investigating predictors of AAO in BD is the lack of appropriate or easily accessible statistical methods that can preserve the trimodal AAO distribution. While there are available statistical approaches that can be useful for examining predictors and associations in BD, none of them are optimal for this specific purpose, as highlighted by the current thesis. To address this challenge, continued integration of expertise from statisticians, mathematicians, and engineers together with psychiatrists and psychologists is recommended. The development and refinement of a modelling approach that allows the assessment of predictors and paths leading to a trimodal AAO distribution while maintaining AAO as a continuous variable would be of great value in validating and extending current research in BD.

The lack of appropriate statistical methods to preserve the trimodal distribution of AAO in BD highlights a broader challenge in mental health research. Namely, that the field lacks large-scale prospective longitudinal data sources designed specifically for mental health outcomes. This limits the extent to which causal mechanisms in psychiatric disorders can be established, thus constraining advancements in prevention and treatment. Harnessing big data and remote monitoring approaches, such as smartwatches, may offer a promising opportunity to curate valuable longitudinal mental health databases. By collecting continuous data on mood, behaviour, and physiological markers, these technologies could provide a more comprehensive understanding of illness trajectories over time. This could lead to earlier identification of at-risk individuals and more personalised treatment approaches. However, there are challenges to consider, such as data privacy and security, the need for appropriate algorithms and data analytics, and potential biases in the data. Additionally, it is important to ensure that such approaches do not exacerbate health disparities or further marginalise vulnerable populations who may not have access to these technologies. Nevertheless, by leveraging the power of big data and remote monitoring, there is potential to transform BD research and care in innovative ways, and allow for a more comprehensive understanding of the causal pathways underpinning the development and progression of BD.

Another important direction for future research would be to focus on the development and evaluation of preventative and early intervention strategies for BD. Given the high burden of the disorder on individuals and society, identifying individuals at high risk for developing BD and providing targeted interventions to prevent or delay the onset of symptoms would be a valuable approach. As discussed, targeted interventions aimed at high-risk groups, identified through comprehensive assessment of potential risk factors, could complement a general approach to early intervention for BD. By combining precision medicine, such as risk calculators and

biomarkers, with a more holistic approach, mental health professionals can offer personalised interventions to prevent or delay the onset of this disorder, ultimately improving outcomes for individuals at high risk for BD. Furthermore, given the highlighted significance of mood instability in BD, future research could explore the benefits of specifically targeting this transdiagnostic feature in treatment approaches. As BD is often comorbid with other psychiatric disorders, targeting shared mechanisms across different disorders could help to improve treatment effectiveness and reduce the burden of comorbidities. Transdiagnostic methods are in line with the dimensional model of mental health disorders and often include approaches such as cognitive remediation, emotion regulation, and mindfulness-based interventions (McHugh & Barlow, 2010; Newby et al., 2015). These have demonstrated promising results in ameliorating symptoms and could be further explored in future BD research (Carlucci et al., 2021).

Overall, future research that employs novel and existing longitudinal designs, develops appropriate statistical methodologies, evaluates prevention and early intervention strategies, and considers genetics and transdiagnostic approaches, can improve the understanding and treatment of BD.

6.5 Conclusions

This thesis underscores the importance of adopting a multidimensional approach to studying BD, acknowledging the complexity and heterogeneity of the disorder. Although AAO shows promise as a clinical specifier for identifying subgroups of BD with similar aetiology and phenomenology, there are limitations that must be addressed in future research. These include the reliance on retrospective reports, as well as the need for large, longitudinal datasets that capture the dynamic nature of psychiatric disorders. While access to such datasets presents a challenge, investing in their development has the potential to revolutionise our understanding of BD and improve treatment approaches. It is important to recognise that AAO is a complex construct that

may be influenced by multiple factors, such as genetic susceptibility, personality traits, and exposure to negative life events and trauma. Further research is necessary to validate the findings presented in this thesis and determine the clinical utility of AAO as a specifier for BD. Ultimately, a nuanced and comprehensive understanding of BD is necessary for improving treatment outcomes and developing more effective interventions.

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Appendix A

Appendix A relates to Chapter 2

Appendix A.1. Summary of Search Results

Database	Number of search results
CENTRAL (searched 04/02/19)	926 trials
CINAHL via EBSCO (searched 01/02/19)	860
Scopus (searched 01/02/19)	3386
ProQuest Dissertations and Theses - Global (searched 01/02/19)	2
BIOSIS Citation Index (searched 01/02/19)	1087
Ovid Medline (searched 04/02/19)	2251
Ovid Embase (searched 04/02/19)	4325
Ovid PsycINFO (searched 04/02/19)	1292
Total	14,129
Total after deduplication	9454

Appendix A.2. Search strategies used for each database

MEDLINE – Ovid Interface

Searched 04/02/19	
Database: Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present Search Strategy:	

1	bipolar disorder/ (38056)
2	((bipolar or "bi polar") adj5 (disorder* or depress*)).ti,ab. (31404)
3	((cyclothymi* or rapid or ultradian) adj5 cycl*).ti,ab. (6008)
4	(BD or BD1 or BD2 or BDi or BDii).ti,ab. (25884)
5	(hypomani* or mania* or manic* or "mixed episode*" or rcbd).ti,ab. (19488)
6	1 or 2 or 3 or 4 or 5 (79693)
7	"age of onset"/ (35352)
8	(age adj3 onset).ti,ab. (39126)
9	AAO.ti,ab. (1658)
10	((first or initial or 1st or index or pediatric* or paediatric* or child*) adj2 (onset* or treat* or hospital* or diagnos* or symptom* or episode*)).ti,ab. (277157)
11	7 or 8 or 9 or 10 (335861)
12	6 and 11 (5146)
13	Epidemiology/ (12133)
14	exp epidemiologic studies/ (2261235)
15	observational study/ (57456)
16	epidemiolog*.ti,ab. (343434)
17	"case control".ti,ab. (113015)
18	cohort*.ti,ab. (496219)
19	"follow up stud*".ti,ab. (46369)
20	longitudinal*.ti,ab. (231040)
21	retrospective*.ti,ab. (639823)
22	"cross section*".ti,ab. (334118)
23	observational*.ti,ab. (147343)
24	((admixture or mixture) adj3 analys*).ti,ab. (2122)
25	survey*.ti,ab. (572951)
26	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (3586707)
27	6 and 11 and 26 (2383)
28	27 (2383)
29	limit 28 to english language (2251)

Embase

Searched 04/02/19	
Database: Embase 1974 to present Search Strategy:	

1	bipolar disorder/ (47736)
2	((bipolar or "bi polar") adj5 (disorder* or depress*)).ti,ab. (47508)
3	((cyclothymi* or rapid or ultradian) adj5 cycl*).ti,ab. (7535)
4	(BD or BD1 or BD2 or BDi or BDii).ti,ab. (45251)
5	(hypomani* or mania* or manic* or "mixed episode*" or rcbd).ti,ab. (26379)

6	1 or 2 or 3 or 4 or 5 (117727)
7	onset age/ (75599)
8	(age adj3 onset).ti,ab. (62544)
9	AAO.ti,ab. (1989)
10	((first or initial or 1st or index or pediatric* or paediatric* or child*) adj2 (onset* or treat* or hospital* or diagnos* or symptom* or episode*)).ti,ab. (430619)
11	7 or 8 or 9 or 10 (523962)
12	exp epidemiology/ (3043419)
13	epidemiolog*.ti,ab. (429254)
14	"case control".ti,ab. (145828)
15	cohort*.ti,ab. (830828)
16	"follow up stud*".ti,ab. (58958)
17	longitudinal*.ti,ab. (305473)
18	retrospective*.ti,ab. (1046991)
19	"cross section*".ti,ab. (422696)
20	observational*.ti,ab. (229646)
21	((admixture or mixture) adj3 analys*).ti,ab. (2453)
22	survey*.ti,ab. (723157)
23	observational study/ (159721)
24	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (5292815)
25	6 and 11 and 24 (4545)
26	25 (4545)
27	limit 26 to english language (4325)

PsycINFO

Searched 04/02/19	
Database: PsycINFO 1806 to present	
Search Strategy:	

1	exp bipolar disorder/ (25506)
2	((bipolar or "bi polar") adj5 (disorder* or depress*)).ti,ab. (30151)
3	((cyclothymi* or rapid or ultradian) adj5 cycl*).ti,ab. (2453)
4	(BD or BD1 or BD2 or BDi or BDii).ti,ab. (11700)
5	(hypomani* or mania* or manic* or "mixed episode*" or rcbd).ti,ab. (20752)
6	1 or 2 or 3 or 4 or 5 (51786)
7	"onset (disorders)"/ (12142)
8	(age adj3 onset).ti,ab. (13291)
9	AAO.ti,ab. (171)
10	((first or initial or 1st or index or pediatric* or paediatric* or child*) adj2 (onset* or treat* or hospital* or diagnos* or symptom* or episode*)).ti,ab. (59200)
11	7 or 8 or 9 or 10 (77912)
12	exp epidemiology/ (47714)
13	epidemiolog*.ti,ab. (43138)
14	"case control".ti,ab. (9961)
15	cohort*.ti,ab. (68739)
16	"follow up stud*".ti,ab. (12043)
17	longitudinal*.ti,ab. (105777)
18	retrospective*.ti,ab. (39544)
19	"cross section*".ti,ab. (71755)

20	observational*.ti,ab. (24642)
21	((admixture or mixture) adj3 analys*).ti,ab. (428)
22	survey*.ti,ab. (273755)
23	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (566394)
24	6 and 11 and 23 (1408)
25	24 (1408)
26	limit 25 to english language (1292)

Cochrane Central Register of Controlled Trials

Searched 04/02/19, 17:28:20		
Issue 2 of 12, February 2019		
#1	MeSH descriptor: [Bipolar Disorder] explode all trees	(2326)
#2	((bipolar or "bi polar") near/5 (disorder* or depress*))	(5248)
#3	((cyclothymi* or rapid or ultradian) near/5 cycl*)	(377)
#4	BD or BD1 or BD2 or BDi or BDii	(8125)
#5	hypomani* or mania* or manic* or "mixed episode*" or rcbd	(3033)
#6	#1 or #2 or #3 or #4 or #5	(13997)
#7	MeSH descriptor: [Age of Onset] explode all trees	(599)
#8	age near/3 onset	(2269)
#9	AAO	(268)
#10	((first or initial or 1st or index or pediatric* or paediatric* or child*) near/2 (onset* or treat* or hospital* or diagnos* or symptom* or episode*))	(54719)
#11	#7 or #8 or #9 or #10	(56649)
#12	#6 and #11	(1346)
= 926 trials		

CINAHL

Searched 01/02/19 12:55:31 PM				
#	Query	Limiters/Expanders	Last Run Via	Results
S26	S6 AND S11 AND S24	Narrow by Language: - english Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	860
S25	S6 AND S11 AND S24	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	868
S24	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	1,080,269
S23	TI survey* OR AB survey*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced	211,381

			Search Database - CINAHL	
S22	TI (((admixture or mixture) adj3 analys*) OR AB (((admixture or mixture) adj3 analys*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	0
S21	TI observational* OR AB observational*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	53,233
S20	TI "cross section*" OR AB "cross section*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	113,142
S19	TI retrospective* OR AB retrospective*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	154,943
S18	TI longitudinal* OR AB longitudinal*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	71,682
S17	TI "follow up stud*" OR AB "follow up stud*"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	9,852
S16	TI cohort* OR AB cohort*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	165,411
S15	TI "case control" OR AB "case control"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	27,199
S14	TI epidemiolog* OR AB epidemiolog*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	62,438
S13	(MH "Epidemiological Research+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced	27,303

			Search Database - CINAHL	
S12	(MH "Epidemiology+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	588,665
S11	S7 OR S8 OR S9 OR S10	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	103,930
S10	TI (((first or initial or 1st or index or pediatric* or paediatric* or child*) n2 (onset* or treat* or hospital* or diagnos* or symptom* or episode*))) OR AB (((first or initial or 1st or index or pediatric* or paediatric* or child*) n2 (onset* or treat* or hospital* or diagnos* or symptom* or episode*)))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	90,217
S9	TI AAO OR AB AAO	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	649
S8	TI age n3 onset OR AB age n3 onset	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	7,407
S7	(MH "Age of Onset")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	9,981
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	17,699

S5	TI (hypomani* or mania* or manic* or "mixed episode*" or rcbd) OR AB (hypomani* or mania* or manic* or "mixed episode*" or rcbd)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	3,284
S4	TI (BD or BD1 or BD2 or BDi or BDii) OR AB (BD or BD1 or BD2 or BDi or BDii)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	4,838
S3	TI (((cyclothymi* or rapid or ultradian) n5 cycl*)) OR AB (((cyclothymi* or rapid or ultradian) n5 cycl*))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	511
S2	TI (((bipolar or "bi polar") n5 (disorder* or depress*))) OR AB (((bipolar or "bi polar") n5 (disorder* or depress*)))	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	8,871
S1	(MH "Bipolar Disorder+")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	10,050

Scopus

Searched 01/02/19
((TITLE-ABS-KEY (((bipolar OR "bi polar") W/5 (disorder* OR depress*)))) OR (TITLE-ABS-KEY (((cyclothymi* OR rapid OR ultradian) W/5 cycl*))) OR (TITLE-ABS-KEY (bd OR bd1 OR bd2 OR bdi OR bdii)) OR (TITLE-ABS-KEY ((hypomani* OR mania* OR manic* OR "mixed episode*" OR rcbd)))) AND ((TITLE-ABS-KEY (age W/3 onset)) OR (TITLE-ABS-KEY (aao)) OR (TITLE-ABS-KEY (((first OR initial OR 1st OR index OR pediatric* OR paediatric* OR child*) W/2 (onset* OR treat* OR hospital* OR diagnos* OR symptom* OR episode*))))) AND ((TITLE-ABS-KEY (epidemiolog* OR "case control" OR cohort* OR "follow up stud*" OR longitudinal* OR retrospective* OR "cross section*" OR observational* OR survey*)) OR (TITLE-ABS-KEY (((admixture OR mixture) W/3 analys*)))) AND (LIMIT-TO (LANGUAGE , "English"))

ProQuest Dissertations and Theses – Global

Searched 01/02/19

((ti((bipolar OR "bi polar") NEAR/5 (disorder* OR depress*)) OR ab((bipolar OR "bi polar") NEAR/5 (disorder* OR depress*))) OR (ti((cyclothymi* OR rapid OR ultradian) NEAR/5 cycl*) OR ab((cyclothymi* OR rapid OR ultradian) NEAR/5 cycl*)) OR (ti(bd OR bd1 OR bd2 OR bdi OR bdii) OR ab(bd OR bd1 OR bd2 OR bdi OR bdii)) OR (ti(hypomani* OR mania* OR manic* OR "mixed episode*" OR rcbd) OR ab(hypomani* OR mania* OR manic* OR "mixed episode*" OR rcbd))) AND (ti((admixture OR mixture) near/3 analys*) OR ab((admixture OR mixture) near/3 analys*)) AND ((ti(epidemiolog* OR "case control" OR cohort* OR "follow up stud*" OR longitudinal* OR retrospective* OR "cross section*" OR observational* OR survey*) OR ab(epidemiolog* OR "case control" OR cohort* OR "follow up stud*" OR longitudinal* OR retrospective* OR "cross section*" OR observational* OR survey*)) OR (ti((admixture OR mixture) near/3 analys*) OR ab((admixture OR mixture) near/3 analys*)))

BIOSIS Citation Index via Web of Science Core Collection

Searched 01/02/19		
# 1	TOPIC: ((bipolar OR "bi polar") near/5 (disorder* OR depress*)) Indexes=BCI Timespan=All years	28,534
# 2	TOPIC: ((cyclothymi* OR rapid OR ultradian) near/5 cycl*) Indexes=BCI Timespan=All years	6,169
# 3	TOPIC: (bd OR bd1 OR bd2 OR bdi OR bdii) Indexes=BCI Timespan=All years	19,963
# 4	TOPIC: (hypomani* OR mania* OR manic* OR "mixed episode*" OR rcbd) Indexes=BCI Timespan=All years	18,432
# 5	#4 OR #3 OR #2 OR #1 Indexes=BCI Timespan=All years	61,740
# 6	TOPIC: (age near/3 onset) Indexes=BCI Timespan=All years	29,646
# 7	TOPIC: (AAO) Indexes=BCI Timespan=All years	815
# 8	TOPIC: ((first OR initial OR 1st OR index OR pediatric* OR paediatric* OR child*) near/2 (onset* OR treat* OR hospital* OR diagnos* OR symptom* OR episode*)) Indexes=BCI Timespan=All years	206,624
# 9	#8 OR #7 OR #6 Indexes=BCI Timespan=All years	233,226
# 10	TOPIC: (epidemiolog* OR "case control" OR cohort* OR "follow up stud*" OR longitudinal* OR retrospective* OR "cross section*" OR observational* OR survey*) Indexes=BCI Timespan=All years	1,955,702
# 11	TOPIC: ((admixture OR mixture) near/3 analys*) Indexes=BCI Timespan=All years	5,570
# 12	#11 OR #10 Indexes=BCI Timespan=All years	1,960,951
# 13	#12 AND #9 AND #5 Indexes=BCI Timespan=All years	1,113
# 14	#12 AND #9 AND #5 Refined by: LANGUAGES: (ENGLISH) Indexes=BCI Timespan=All years	1,087

Google Scholar

Screened the first 10 pages of results for each of the following (sorted by relevance):
("bipolar disorder"|"bi polar disorder"|"bipolar depress*"|"bi polar depress*"|"cyclothymi* cycl*"|"rapid cycl*"|"ultradian cycl*"|bd|bd1|bd2|bdi|bdii|hypomani*|mania*|manic*|"mixed episode*"|rcbd)("age of onset"|"onset age"|AAO|"first diagno*")
https://scholar.google.co.uk/scholar?hl=en&as_sdt=0%2C5&q=%28%22bipolar+disorder%22%7C%22bi+polar+disorder%22%7C%22bipolar+depress*%22%7C%22bi+polar+depress*%22%7C%22cyclothymi*+cycl*%22%7C%22rapid+cycl*%22%7C%22ultradian+cycl*%22%7Cbd%7Cbd1%7Cbd2%7Cbdi%7Cbdii%7Chypomani*%7Cmania*%7Cmanic*%7C%22mixed+episode*%22%7Crcbd%29%28%22age+of+onset%22%7C%22onset+age%22%7CAAO%7C%22first+diagno*%22%29&btnG
("bipolar disorder"|"bi polar disorder"|"bipolar depress*"|"bi polar depress*"|"cyclothymi* cycl*"|"rapid cycl*"|"ultradian cycl*"|bd|bd1|bd2|bdi|bdii|hypomani*|mania*|manic*|"mixed episode*"|rcbd)("first symptom*"|"first epidsode*"|"first onset*"|"first treat*"|"first hospital*)
https://scholar.google.co.uk/scholar?hl=en&as_sdt=0%2C5&q=%28%22bipolar+disorder%22%7C%22bi+polar+disorder%22%7C%22bipolar+depress*%22%7C%22bi+polar+depress*%22%7C%22cyclothymi*+cycl*%22%7C%22rapid+cycl*%22%7C%22ultradian+cycl*%22%7Cbd%7Cbd1%7Cbd2%7Cbdi%7Cbdii%7Chypomani*%7Cmania*%7Cmanic*%7C%22mixed+episode*%22%7Crcbd%29%28%22first+symptom*%22%7C%22first+epidsode*%22%7C%22first+onset*%22%7C%22first+treat*%22%7C%22first+hospital*%29&btnG
("bipolar disorder"|"bi polar disorder"|"bipolar depress*"|"bi polar depress*"|"cyclothymi* cycl*"|"rapid cycl*"|"ultradian cycl*"|bd|bd1|bd2|bdi|bdii|hypomani*|mania*|manic*|"mixed episode*"|rcbd)("initial onset*"|"initial treat*"|"initial hospital*")
https://scholar.google.co.uk/scholar?hl=en&as_sdt=0%2C5&q=(%22bipolar+disorder%22%7C%22bi+polar+disorder%22%7C%22bipolar+depress*%22%7C%22bi+polar+depress*%22%7C%22cyclothymi*+cycl*%22%7C%22rapid+cycl*%22%7C%22ultradian+cycl*%22%7Cbd%7Cbd1%7Cbd2%7Cbdi%7Cbdii%7Chypomani*%7Cmania*%7Cmanic*%7C%22mixed+episode*%22%7Crcbd)(%22initial+onset*%22%7C%22initial+treat*%22%7C%22initial+hospital*%22)&btnG
("bipolar disorder"|"bi polar disorder"|"bipolar depress*"|"bi polar depress*"|"cyclothymi* cycl*"|"rapid cycl*"|"ultradian cycl*"|bd|bd1|bd2|bdi|bdii|hypomani*|mania*|manic*|"mixed episode*"|rcbd)("initial diagnos*"|"initial symptom*"|"initial episode*")
https://scholar.google.co.uk/scholar?hl=en&as_sdt=0%2C5&q=%28%22bipolar+disorder%22%7C%22bi+polar+disorder%22%7C%22bipolar+depress*%22%7C%22bi+polar+depress*%22%7C%22cyclothymi*+cycl*%22%7C%22rapid+cycl*%22%7C%22ultradian+cycl*%22%7Cbd%7Cbd1%7Cbd2%7Cbdi%7Cbdii%7Chypomani*%7Cmania*%7Cmanic*%7C%22mixed+episode*%22%7Crcbd%29%28%22initial+diagnos*%22%7C%22initial+symptom*%22%7C%22initial+episode*%22%29&btnG

Appendix A.3. List of papers excluded at full-text review

#	Reference
1	Alda, M. (2013). Does age at onset define a subtype of bipolar disorder? *Bipolar Disorders*, *15*(SUPPL.1), 28. https://doi.org/http://dx.doi.org/10.1111/bdi.12079
2	Alda, M., Grof, P., Ravindran, L., Cavazzoni, P., Duffy, A., Grof, E., … Wilson, J. (2000). Anticipation in bipolar affective disorder: is age at onset a valid criterion?. *American Journal of Medical Genetics*, *96*(6), 804–807.
3	Azorin, J.-M., Belzeaux, R., & Adida, M. (2015). Age-at-onset and comorbidity may separate depressive disorder subtypes along a descending gradient of bipolar propensity. *Behavioural Brain Research*, *282*, 185–193. https://doi.org/https://dx.doi.org/10.1016/j.bbr.2015.01.014
4	Baldessarini, R. J., Bolzani, L., Cruz, N., Jones, P. B., Lai, M., Lepri, B., … Vieta, E. (2010). Onset-age of bipolar disorders at six international sites. *Journal of Affective Disorders*, *121*(1–2), 143–146. https://doi.org/https://dx.doi.org/10.1016/j.jad.2009.05.030
5	Bauer, M. (2012). Factors associated with age at onset of bipolar disorder. *Bipolar Disorders*, *14*(SUPPL. 1), 33–34. https://doi.org/http://dx.doi.org/10.1111/j.1399-5618.2012.00977.x
6	Bauer, M., Glenn, T., Alda, M., Aleksandrovich, M. A., Andreassen, O. A., Angelopoulos, E., … Whybrow, P. C. (2017). Solar insolation in springtime influences age of onset of bipolar I disorder. *Acta Psychiatrica Scandinavica*, *136*(6), 571–582. https://doi.org/https://dx.doi.org/10.1111/acps.12772
7	Bellivier, F. (n.d.). Time trends of age at onset of bipolar I disorder. *Bipolar Disorders*, *15*(SUPPL.1), 28–29. https://doi.org/http://dx.doi.org/10.1111/bdi.12079
8	Benazzi, F. (1998). Late-life depression in private practice depressed outpatients: a 203-case study. *International Journal of Geriatric Psychiatry*, *13*(3), 145–148.
9	Benazzi, F. (2009). Classifying mood disorders by age-at-onset instead of polarity. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *33*(1), 86–93. https://doi.org/10.1016/j.pnpbp.2008.10.007
10	Benazzi, Franco. (2007). Does age at onset support a dimensional relationship between Bipolar II disorder and major depressive disorder?. *The World Journal of Biological Psychiatry : The Official Journal of the World Federation of Societies of Biological Psychiatry*, *8*(2), 105–111.
11	Bogren, M., Mattisson, C., Isberg, P.-E., Munk-Jorgensen, P., & Nettelbladt, P. (2010). Incidence of psychotic disorders in the 50 year follow up of the Lundby population. *Australian and New Zealand Journal of Psychiatry*, *44*(1), 31–39. https://doi.org/http://dx.doi.org/10.3109/00048670903393647
12	Burke, K. C., Burke, J. D. J., Rae, D. S., & Regier, D. A. (1991). Comparing age at onset of major depression and other psychiatric disorders by birth cohorts in five US community populations. *Archives of General Psychiatry*, *48*(9), 789–795.
13	Burke, K. C., Burke, J. D. J., Regier, D. A., & Rae, D. S. (1990). Age at onset of selected mental disorders in five community populations. *Archives of General Psychiatry*, *47*(6), 511–518.
14	Chengappa, K. N. R., Kupfer, D. J., Frank, E., Houck, P. R., Grochocinski, V. J., Cluss, P. A., & Stapf, D. A. (2003). Relationship of birth cohort and early age at onset of illness in a bipolar disorder case registry. *The American Journal of Psychiatry*, *160*(9), 1636–1642.

15	Coryell, W., Fiedorowicz, J., Leon, A. C., Endicott, J., & Keller, M. B. (2013). Age of onset and the prospectively observed course of illness in bipolar disorder. *Journal of Affective Disorders*, *146*(1), 34–38. https://doi.org/https://dx.doi.org/10.1016/j.jad.2012.08.031
16	Da Silva Magalhães, P. V, Gomes, F. A., Kunz, M., & Kapczinski, F. (2009). Birth-cohort and dual diagnosis effects on age-at-onset in Brazilian patients with bipolar i disorder. *Acta Psychiatrica Scandinavica*, *120*(6), 492–495. https://doi.org/10.1111/j.1600-0447.2009.01426.x
17	Dell'Osso, B., Buoli, M., Riundi, R., D'Urso, N., Pozzoli, S., Bassetti, R., … Altamura, A. C. (2009). Clinical characteristics and long-term response to mood stabilizers in patients with bipolar disorder and different age at onset. *Neuropsychiatric Disease and Treatment*, *5*, 399–404.
18	De Luca, V. (2015). Age at onset in first episode bipolar disorder: Effect of recall bias and cultural influences. *Bipolar Disorders*, *17*(SUPPL. 1), 121. https://doi.org/http://dx.doi.org/10.1111/bdi.12309
19	Depp, C. A., Jin, H., Mohamed, S., Kaskow, J., Moore, D. J., & Jeste, D. V. (2004). Bipolar disorder in middle-aged and elderly adults: is age of onset important?. *The Journal of Nervous and Mental Disease*, *192*(11), 796–799.
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21	Fogarty, F., Russell, J. M., Newman, S. C., & Bland, R. C. (1994). Epidemiology of psychiatric disorders in Edmonton: Phenomenology and comorbidity: Mania. *Acta Psychiatrica Scandinavica*, *89*(SUPPL. 376), 16–23. https://doi.org/10.1111/j.1600-0447.1994.tb05787.x
22	Goldberg, J. F., & Garno, J. L. (2009). Age at onset of bipolar disorder and risk for comorbid borderline personality disorder. *Bipolar Disorders*, *11*(2), 205–208. https://doi.org/10.1111/j.1399-5618.2008.00653.x
23	Golmard, J.-L., Etain, B., Scott, J., Malafosse, A., Henry, C., Jamain, S., … Bellivier, F. (2011). Birth Cohort and Period Effects on Age at Onset in Bipolar I Affective Disorder. *Biological Psychiatry*, *69*(9, Suppl. S), 55S.
24	Golmard, J.-L., Scott, J., Etain, B., Malafosse, A., Henry, C., Jamain, S., … Bellivier, F. (2013). Birth Cohort Effect on Age at Onset of Bipolar I Disorder : Are We Entering the Age of Mania? *Biological Psychiatry*, *73*(9, Suppl. S), 171S.
25	Grande, I., Magalhaes, P. V, Chendo, I., Stertz, L., Panizutti, B., Colpo, G. D., … Vieta, E. (2014). Staging bipolar disorder: clinical, biochemical, and functional correlates. *Acta Psychiatrica Scandinavica*, *129*(6), 437–444. https://doi.org/https://dx.doi.org/10.1111/acps.12268
26	Grigoroiu-Serbanescu, M., Nothen, M. M., Ohlraun, S., Propping, P., Maier, W., Wickramaratne, P., … Rietschel, M. (2005). Family history influences age of onset in bipolar I disorder in females but not in males. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics : The Official Publication of the International Society of Psychiatric Genetics*, *133B*(1), 6–11.

27	Haouala, B., Amamou, B., Allegue, M., & Zaafrane, F. (2016). Age at onset of bipolar disorders: Clinical implication and prognosis of early and late onset. *European Neuropsychopharmacology*, *26*(Supplement 2), S429.
28	Holtzman, J. N., Miller, S., Hooshmand, F., Wang, P. W., Chang, K. D., Hill, S. J., … Ketter, T. A. (2015). Childhood-compared to adolescent-onset bipolar disorder has more statistically significant clinical correlates. *Journal of Affective Disorders*, *179*, 114–120. https://doi.org/10.1016/j.jad.2015.03.019
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30	Kroon, J. S., Wohlfarth, T. D., Dieleman, J., Sutterland, A. L., Storosum, J. G., Denys, D., & de Haan, L. (2013). Incidence rates and risk factors of bipolar disorder in the general population: A population-based cohort study. *Bipolar Disorders*, *15*(3), 306–313. https://doi.org/http://dx.doi.org/10.1111/bdi.12058
31	Larsson, S., Lorentzen, S., Mork, E., Barrett, E. A., Steen, N. E., Lagerberg, T. V., … Andreassen, O. A. (2010). Age at onset of bipolar disorder in a Norwegian catchment area sample. *Journal of Affective Disorders*, *124*(1–2), 174–177. https://doi.org/https://dx.doi.org/10.1016/j.jad.2009.10.031
32	Manchia, M., Lampus, S. F., Margiani, S., Chillotti, C., Ardau, R., Severino, G., & Del Zompo, M. (2006). Bipolar disorder in Sardinian population: Age at onset as an endophenotype? *American Journal of Medical Genetics*, *141B*(7), 776.
33	Marchand, W., Wirth, L., & Simon, C. (2004). Delayed diagnosis of pediatric bipolar disorder in a community sample. *Journal of Affective Disorders*, *78*(Supplement 1), S60–S61.
34	Masi, G., Perugi, G., Millepiedi, S., Mucci, M., Toni, C., Bertini, N., … Pari, C. (2006). Developmental differences according to age at onset in juvenile bipolar disorder. *Journal of Child and Adolescent Psychopharmacology*, *16*(6), 679–685.
35	Matteo, P., & Stefano, P. (2015). Age at onset in a sample of bipolar patients: clinical features and psychiatric comorbidity. *European Neuropsychopharmacology*, *25*(Suppl. 2), S388. https://doi.org/10.1016/s0924-977x(15)30507-1
36	Mérette, C., Roy-Gagnon, M. H., Ghazzali, N., Savard, F., Boutin, P., Roy, M. A., & Maziade, M. (2000). Anticipation in schizophrenia and bipolar disorder controlling for an information bias. *American Journal of Medical Genetics - Neuropsychiatric Genetics*, *96*(1), 61–68. https://doi.org/10.1002/(SICI)1096-8628(20000207)96:1<61::AID-AJMG13>3.0.CO;2-W
37	Moorhead, S. R. J., & Young, A. H. (2003). Evidence for a late onset bipolar-I disorder sub-group from 50 years. *Journal of Affective Disorders*, *73*(3), 271–277.
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41	Post, R. M., Altshuler, L. L., Kupka, R., McElroy, S. L., Frye, M. A., Rowe, M., … Nolen, W. A. (2016). Age of onset of bipolar disorder: Combined effect of childhood adversity and familial loading of psychiatric disorders. *Journal of Psychiatric Research*, *81*, 63–70. https://doi.org/https://dx.doi.org/10.1016/j.jpsychires.2016.06.008
42	Post, R. M., & Kowatch, R. A. (2006). The health care crisis of childhood-onset bipolar illness: some recommendations for its amelioration. *The Journal of Clinical Psychiatry*, *67*(1), 115–125.
43	Post, R. M., Kupka, R., Keck, P. E. J., McElroy, S., Altshuler, L., Frye, M., … Nolen, W. (2015). Evidence for a cohort effect: A child network for assessing naturalistic treatment in the community. *Bipolar Disorders*, *17*(SUPPL. 1), 106. https://doi.org/http://dx.doi.org/10.1111/bdi.12309
44	Roy-Byrne, P., Post, R. M., Uhde, T. W., Porcu, T., & Davis, D. (1985). THE LONGITUDINAL COURSE OF RECURRENT AFFECTIVE ILLNESS LIFE CHART DATA FROM RESEARCH PATIENTS AT THE NATIONAL INSTITUTE OF MENTAL HEALTH. *Acta Psychiatrica Scandinavica Supplementum*, *71*(317), 1–34. https://doi.org/10.1111/j.1600-0447.1985.tb10510.x
45	Scott, J., Etain, B., Azorin, J. M., & Bellivier, F. (2018). Secular trends in the age at onset of bipolar I disorder - Support for birth cohort effects from interational, multi-centre clinical observational studies. *European Psychiatry : The Journal of the Association of European Psychiatrists*, *52*, 61–67.
46	Singh, N., MacMohan, H., Bilderbeck, A., Reed, Z. E., Tunbridge, E., & Churchill, G. C. (2016). Plasma glutathione as a marker of oxidative stress in bipolar disorder. *European Neuropsychopharmacology*, *26*(Supplement 2), S421–S422.
47	Smeraldi, E., Gasperini, M., Macciardi, F., Bussoleni, C., & Morabito, A. (n.d.). Factors affecting the distribution of age at onset in patients with affective disorders. *Journal of Psychiatric Research*, *17*(3), 309–317.
48	Smeraldi, E., Macciardi, F., Holmgren, S., Perris, H., von Knorring, L., & Perris, C. (1987). Age at onset of affective disorders in Italian and Swedish patients. *Acta Psychiatrica Scandinavica*, *75*(4), 352–357.
49	Tillman, R., Geller, B., Bolhofner, K., Craney, J. L., Williams, M., & Zimerman, B. (2003). Ages of onset and rates of syndromal and subsyndromal comorbid DSM-IV diagnoses in a prepubertal and early adolescent bipolar disorder phenotype. *Journal of the American Academy of Child and Adolescent Psychiatry*, *42*(12), 1486–1493.
50	Vaingankar, J. A., Rekhi, G., Subramaniam, M., Abdin, E., & Chong, S. A. (2013). Age of onset of life-time mental disorders and treatment contact. *Social Psychiatry and Psychiatric Epidemiology*, *48*(5), 835–843. https://doi.org/https://dx.doi.org/10.1007/s00127-012-0601-y

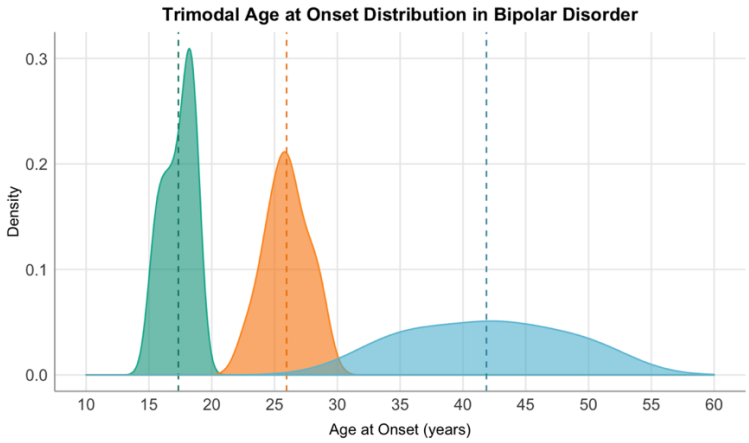
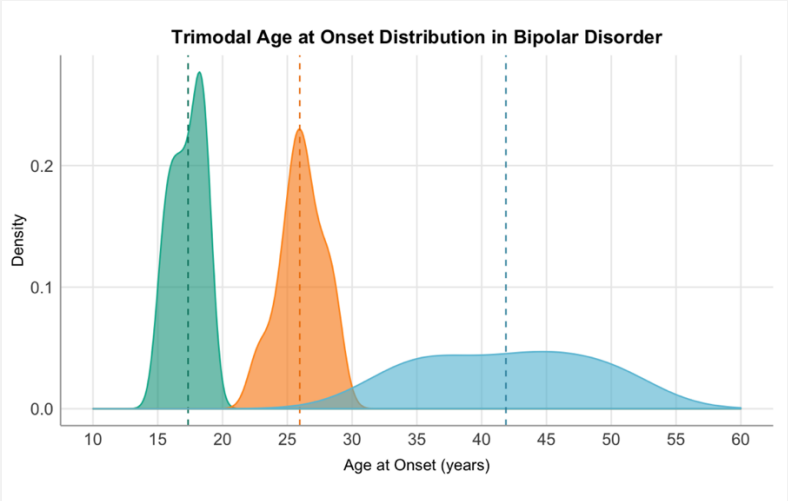
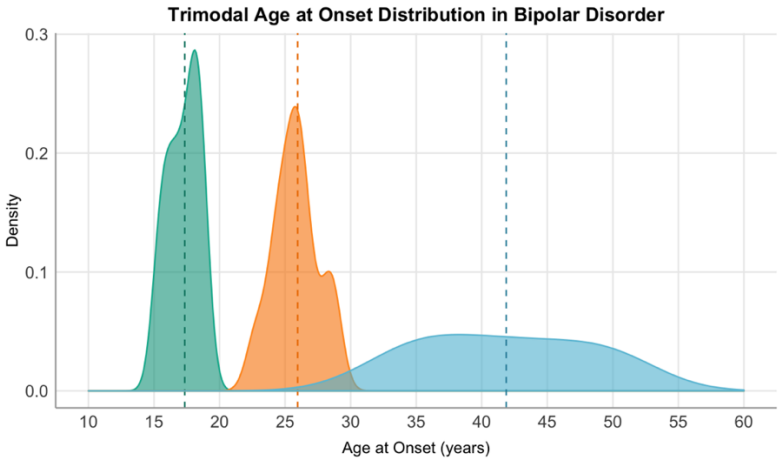
Appendix A.4. Overlapping Samples: Trimodal Age at Onset Distribution

Manchia et al. (2008) and Severino et al. (2009) both use an overlapping sample of 181 BDI participants recruited from the Lithium Clinic of the Clinical Psychopharmacology Centre, University of Cagliari, Italy. The later 2009 Severino et al. paper additionally includes 74 participants with a diagnosis of schizoaffective disorder and 45 participants with BDII. Analyses were repeated excluding first the Manchia et al. (2008) paper, and then the Severino et al. (2009) paper. This does not make a significant difference to the overall means (and SDs) per AAO group, or to the proportion of participants in each AAO group:

Descriptive stats excluding Manchia et al. (2008) and Severino et al. (2009).

	Currently reported in Chapter 2		Excluding Manchia et al. (2008)		Excluding Severino et al. (2009)	
	Mean (SD)	Proportion of pps per group	Mean (SD)	Proportion of pps per group	Mean (SD)	Proportion of pps per group
Early onset	17.34 (1.19)	44.54%	17.27 (1.22)	45.32%	17.23 (1.89)	44.68%
Mid onset	25.96 (1.73)	34.51%	26.11 (1.72)	34.10%	25.82 (1.74)	33.83%
Late onset	41.87 (6.16)	20.81%	41.95 (6.45)	20.43%	41.76 (6.45)	21.33%

Additionally, removing these studies did not make a substantial difference when plotting our final model, as can be seen from the following three figures. As the exclusion of the papers does not significantly alter our findings and interpretation of the data, we have chosen to include both studies.

Graphs of AAO distributions with / without the specified studies	
As currently reported. Not excluding Manchia et al. (2008) or Severino et al. (2009)	
Excluding Manchia et al. (2008)	
Excluding Severino et al. (2009)	

Appendix B

Appendix B relates to Chapter 3

Appendix B.1. R packages used in analysis

Package Name	Author(s)	Version	URL
BSDA	Arnholt & Evans (2017)	1.2.0	https://CRAN.R-project.org/package=BSDA
car	Fox & Weisberg (2019)	3.0-11	https://cran.r-project.org/web/packages/car/index.html
caret	Kuhn (2019)	6.0-84	https://CRAN.R-project.org/package=caret
dplyr	Wickham et al. (2020)	1.0.2	https://CRAN.R-project.org/package=dplyr
feather	Wickham (2019)	0.3.5	https://CRAN.R-project.org/package=feather
forcats	Wickham (2020)	0.5.0	https://CRAN.R-project.org/package=forcats
ggforce	Pedersen (2021)	0.3.3	https://CRAN.R-project.org/package=ggforce
ggplot2	(Wickham, 2016)	3.3.2	https://ggplot2.tidyverse.org
glmnet	Friedman et al. (2010)	4.1-1	https://glmnet.stanford.edu
ggridges	Claus O. Wilke (2021)	0.5.3	https://CRAN.R-project.org/package=ggridges
HDCI	Liu et al. (2017)	1.0-2	https://cran.r-project.org/package=HDCI
Hmisc	Harrell (2020)	4.4-1	https://CRAN.R-project.org/package=Hmisc
magrittr	Bache & Wickham (2020)	2.0.1	https://CRAN.R-project.org/package=magrittr
MASS	Venables & Ripley (2002)	7.3-54	https://CRAN.R-project.org/package=MASS
moments	Komsta & Novomestky (2015)	0.14	https://CRAN.R-project.org/package=moment
naniar	Tierney et al. (2020)	0.6.1	https://CRAN.R-project.org/package=naniar
plyr	Wickham (2011)	1.8.6	https://CRAN.R-project.org/package=plyr
questionr	Barnier et al. (2020)	0.7.4	https://CRAN.R-project.org/package=questionr
rcompanion	Mangiafico (2021)	2.4.1	https://CRAN.R-project.org/package=rcompanion
readr	Wickham & Hester (2020)	1.4.0	https://CRAN.R-project.org/package=readr
recipes	Kuhn & Wickham (2020)	0.1.15	https://CRAN.R-project.org/package=recipes
tidyverse	Wickham et al. (2019)	1.3.0	http://tidyverse.tidyverse.org

Appendix B.2. Missingness Comparing samples with vs. without missing variables removed

We compared the demographic and clinical characteristics of the dataset with and without missing values removed using X^2 tests; Fisher exact test; and unpaired, 2-tailed t tests.

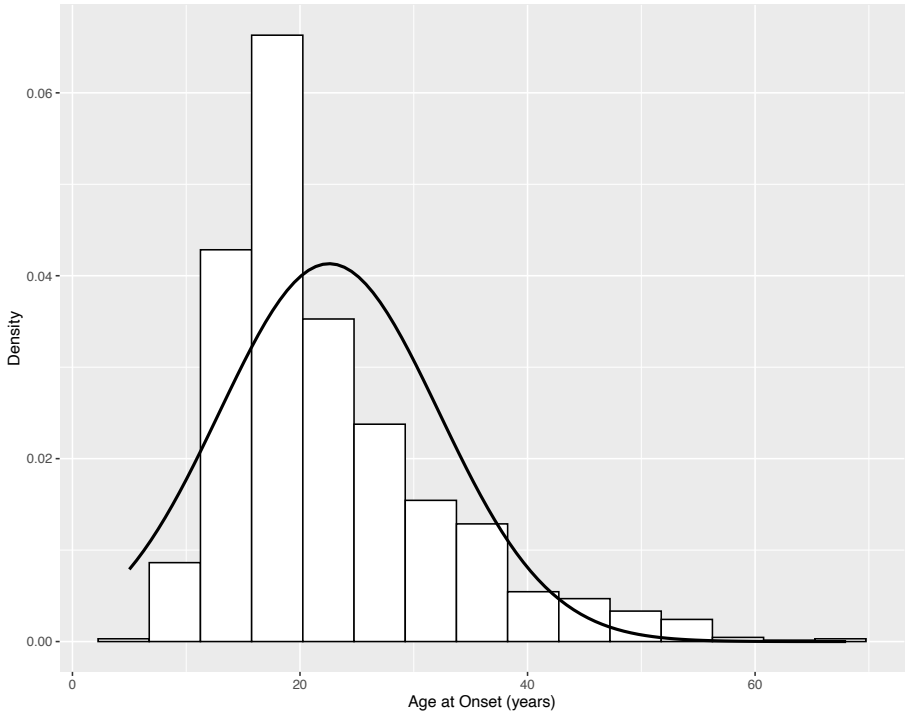
Variables		Main Sample (Missing Removed) N = 1084		Full Sample N = 1468		X^2		
		n	% of total sample	n	% of total sample	Test Statistic	df	p-value
Diagnosis	BDI	630	61.6	889	60.6	2.362	9	0.9844
	BDII	346	33.9	494	33.7			
	BD Schizoaffective	26	2.5	45	3.1			
	BD NOS	20	2.0	40	2.7			
Family History of Affective Disorders	No	177	17.3	238	16.2	0.576	3	0.902
	Yes	845	82.7	1230	83.8			
Family History of Psychiatric Disorders	No	640	62.6	898	61.2	0.583	3	0.900
	Yes	382	37.4	570	38.8			
Family History of Suicide	No	837	81.9	1189	81.0	0.352	3	0.950
	Yes	185	18.1	279	19.0			
Education	Higher education	493	48.2	793	54.0	1.339	3	0.720
	No higher education	529	51.8	675	46.0			
Occupation	Professional	552	54.0	761	51.8	1.529	9	0.997

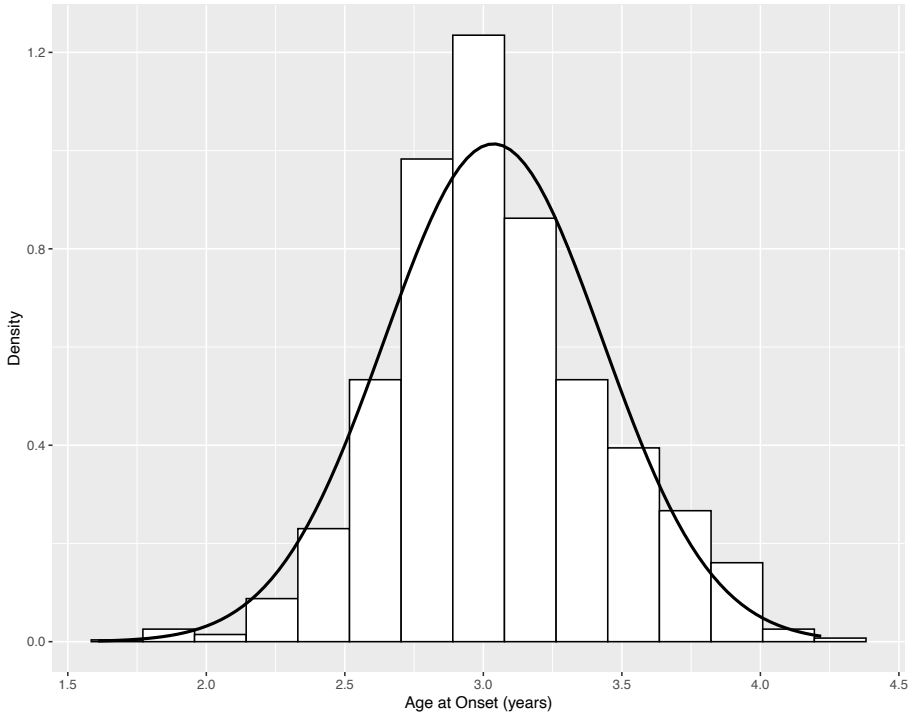
	Non-professional	445	43.5	669	45.6			
	Never worked	7	0.7	13	0.9			
	Student	18	1.8	25	1.7			
Regular use of cannabinoids in the year before onset	No	914	89.4	1308	89.1	0.075	3	0.995
	Yes	108	10.6	160	10.9			
Regular use of non-prescription drugs in the year before onset	No	979	95.8	1394	95.0	1.016	3	0.798
	Yes	43	4.2	74	5.0			
Poor premorbid work adjustment	No	1018	99.6	1462	99.6	0.005	3	0.999
	Yes	4	0.4	6	0.4			
Poor premorbid social adjustment	No	1009	98.7	1442	98.2	1.059	3	0.787
	Yes	13	1.3	26	1.8			

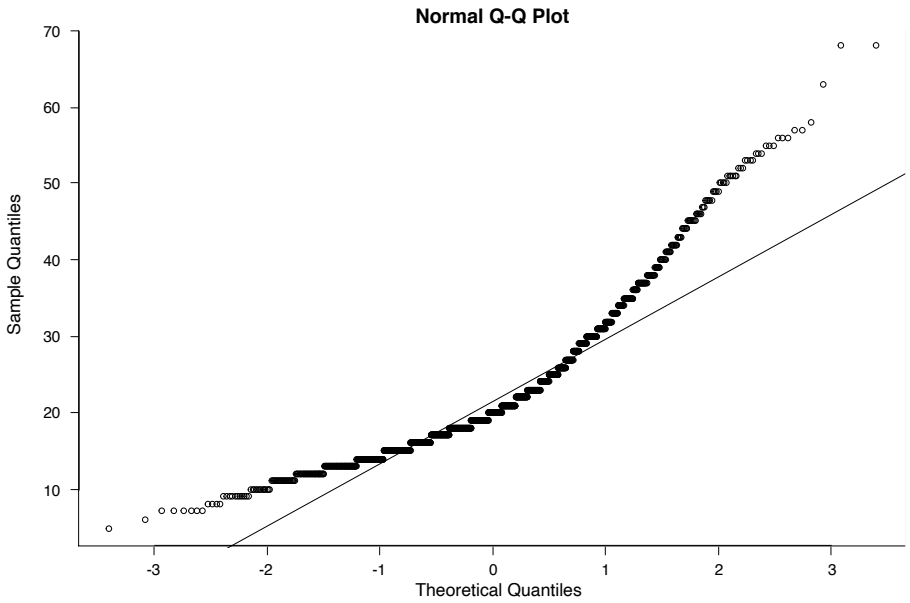
Variables					Welch Modified Two-Sample t-Test		
	Mean (SD)	Range	Mean (SD)	Range	Test Statistic	df	p-value
Age at Onset	23.0 (9.86)	5-68			0.157	27.383	0.876
Age at Interview	45.5 (12.1)	18-83			0.084	26.39	0.934
Alcohol Consumption	14.5 (30.4)	0-350			-0.154	24.126	0.879

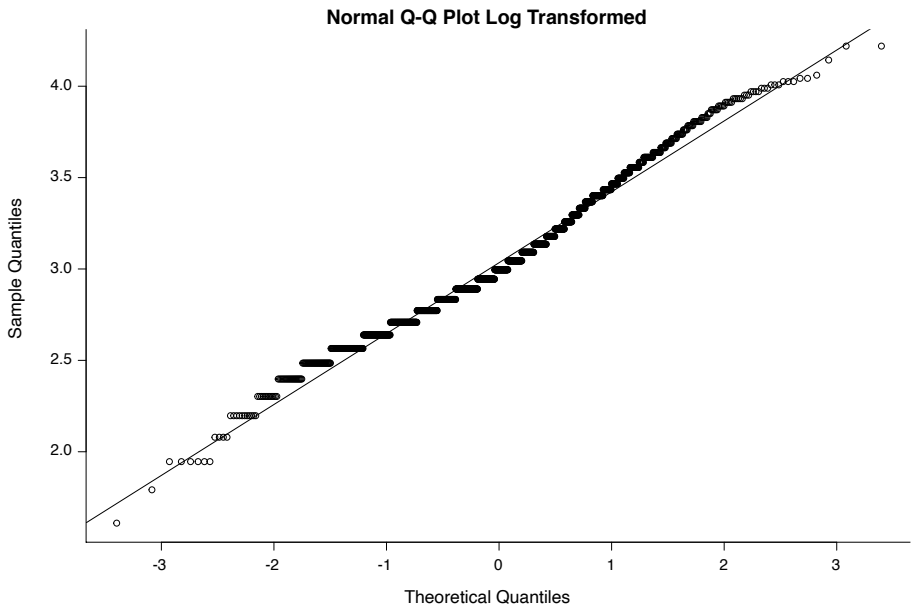
Appendix B.3. Data Transformation

Our outcome variable Age at Onset (AAO) must be a positive real value, therefore we log-transformed the data such that log(AAO) has a mean of 3.0 and symmetric variance. Additionally, AAO was positively skewed (skewness = 1.34) and significantly non-normal (Shapiro-Wilk normality test W = 0.89172, p-value < 2.2e-16). Log transformation helped correct for non-normality as shown in the Figures below. (reduced skewness: 0.29).



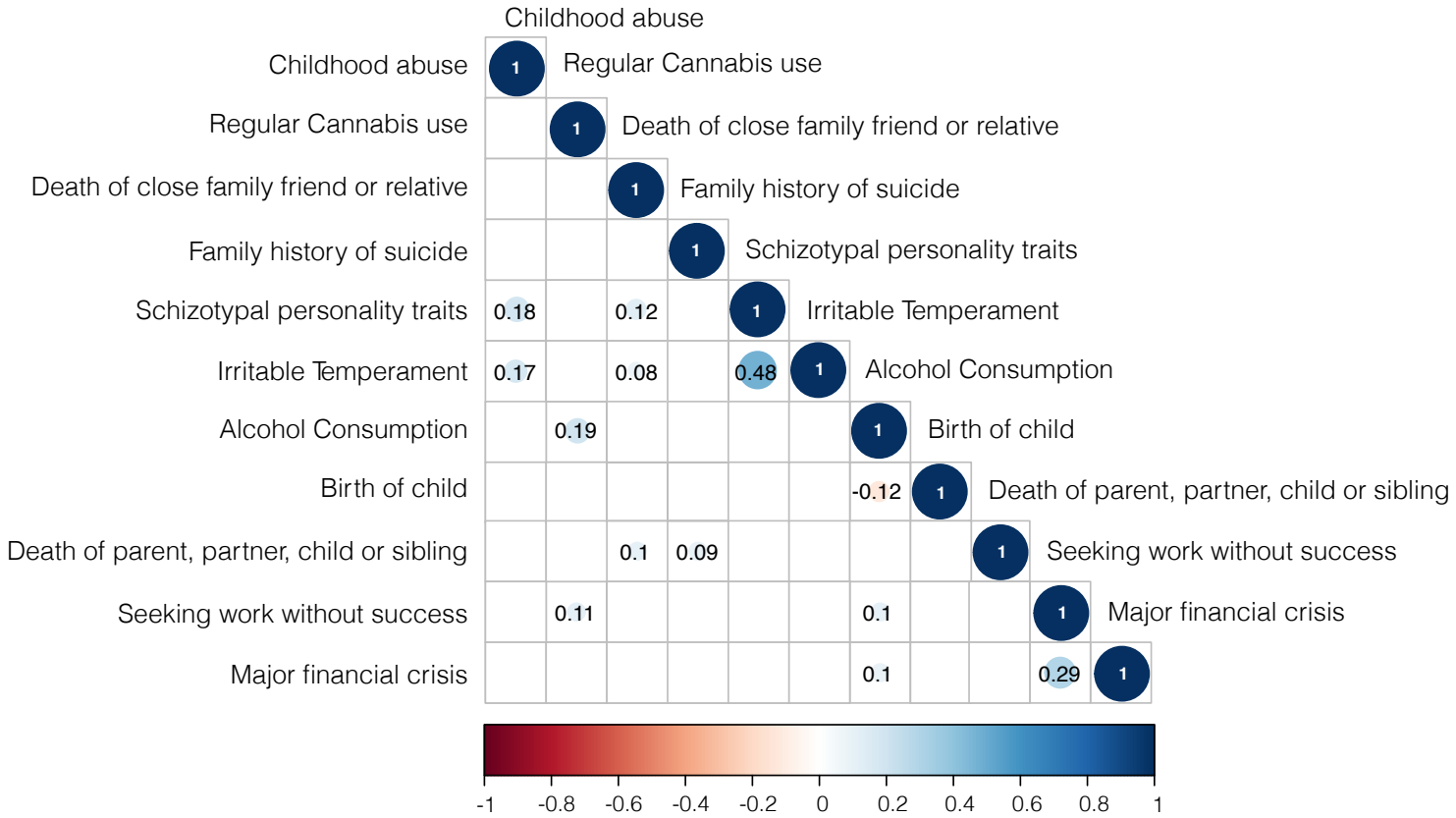


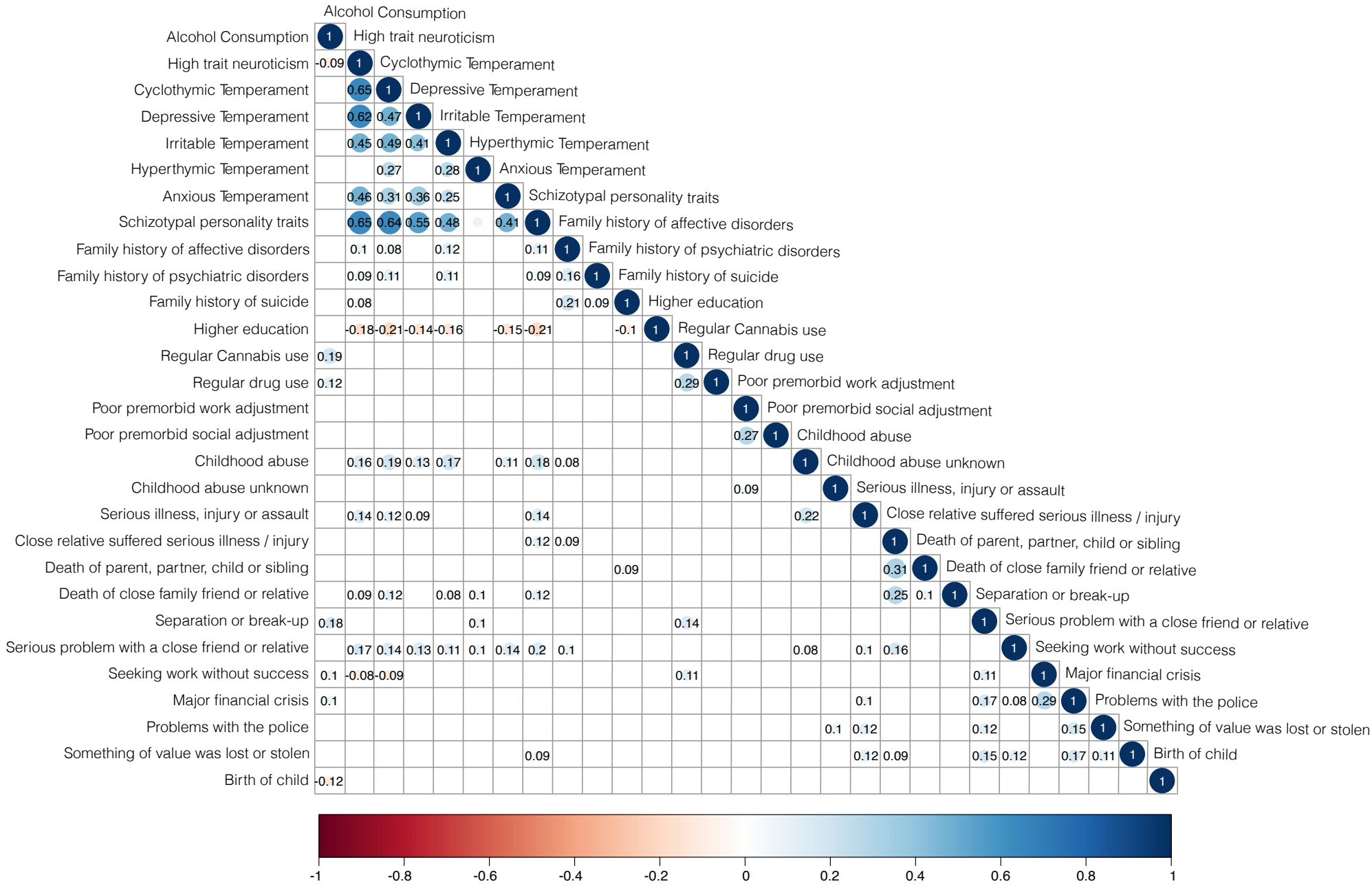

Normal Q-Q Plot
Sample Quantiles
Theoretical Quantiles
70
60
50
40
30
20
10
-3
-2
-1
0
1
2
3


Normal Q-Q Plot Log Transformed
Sample Quantiles
Theoretical Quantiles
4.0
3.5
3.0
2.5
2.0
-3
-2
-1
0
1
2
3

Appendix B.4. Variable Correlation

To address variable correlation, we computed two correlation matrices: one including all 28 predictor variables, and one for the 11 'most important' variables included in our final model.




Alcohol Consumption
Alcohol Consumption
High trait neuroticism
Cyclothymic Temperament
Depressive Temperament
Irritable Temperament
Hyperthymic Temperament
Anxious Temperament
Schizotypal personality traits
Family history of affective disorders
Family history of psychiatric disorders
Family history of suicide
Higher education
Regular Cannabis use
Regular drug use
Poor premorbid work adjustment
Poor premorbid social adjustment
Childhood abuse
Childhood abuse unknown
Serious illness, injury or assault
Close relative suffered serious illness / injury
Death of parent, partner, child or sibling
Death of close family friend or relative
Separation or break-up
Serious problem with a close friend or relative
Seeking work without success
Major financial crisis
Problems with the police
Something of value was lost or stolen
Birth of child
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1

Appendix B.5. Predictors included on resampling runs

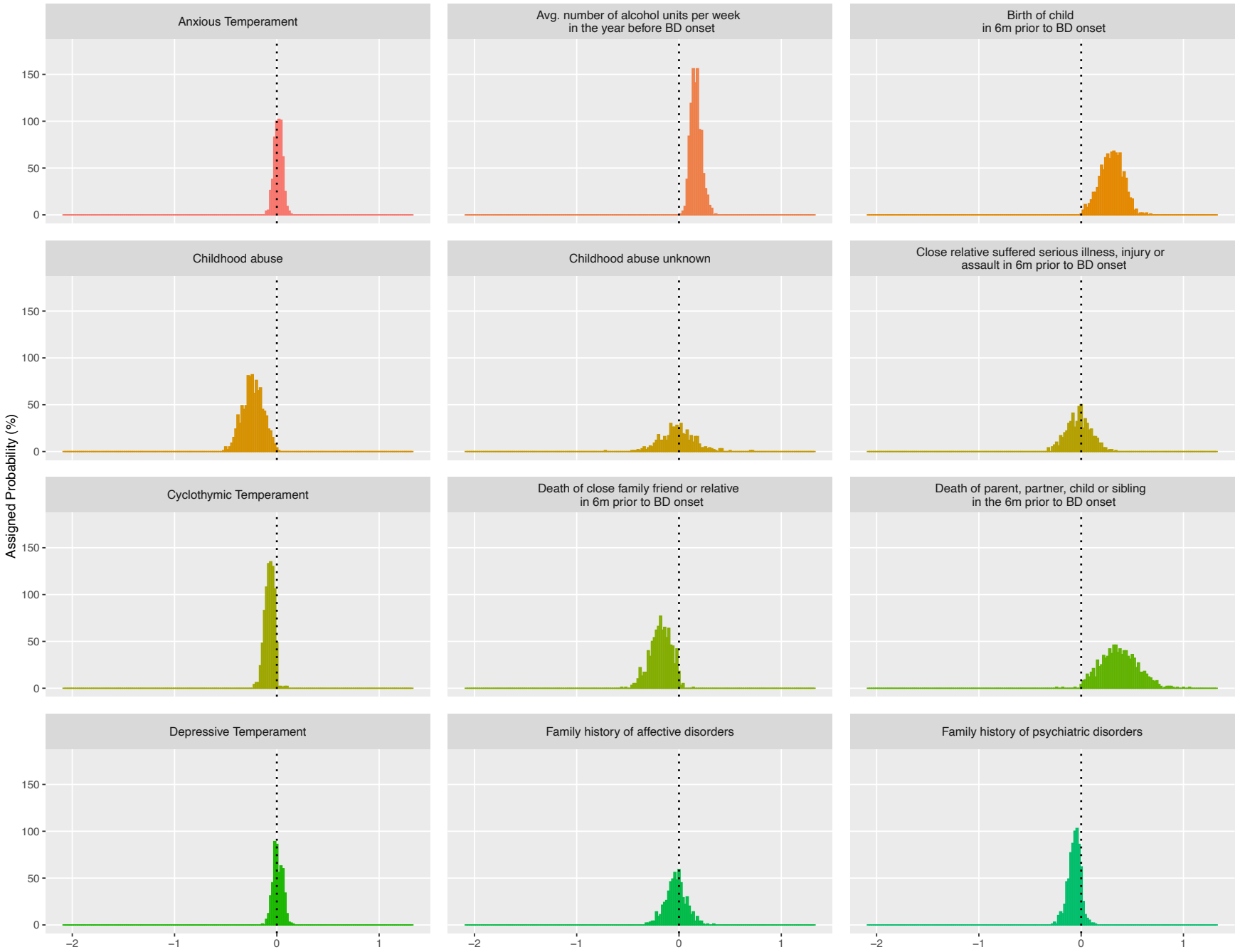
Predictors	N Resampling Runs
Avg. number of alcohol units per week in the year before BD onset	1000
Major financial crisis in 6m prior to BD onset	999
Birth of child in 6m prior to BD onset	992
Childhood abuse	987
Irritable Temperament	965
Regular Cannabis use in the year before BD onset	960
Death of parent, partner, child, or sibling in the 6m prior to BD onset	959
Schizotypal personality traits	948
Family history of suicide	943
Seeking work without success for one month or more in the 6m prior to BD onset	937
Death of close family friend or relative in 6m prior to BD onset	908
Problems with the police involving a court appearance in 6m prior to BD onset	885
High trait neuroticism	861
Poor premorbid social adjustment	853
Cyclothymic Temperament	841
Hyperthymic Temperament	835
Family history of psychiatric disorders	726
Serious problem with a close friend, neighbour or relative in 6m prior to BD onset	717
Separation from or break-up with partner in 6m prior to BD onset	694
Regular drug use in the year before BD onset	666
Serious illness, injury, or assault in 6m prior to BD onset	633
Family history of affective disorders	609
Higher education	607
Close relative suffered serious illness, injury, or assault in 6m prior to BD onset	580
Something of value was lost or stolen in 6m prior to BD onset	570
Anxious Temperament	560
Depressive Temperament	501
Childhood abuse unknown	479
Poor premorbid work adjustment	409

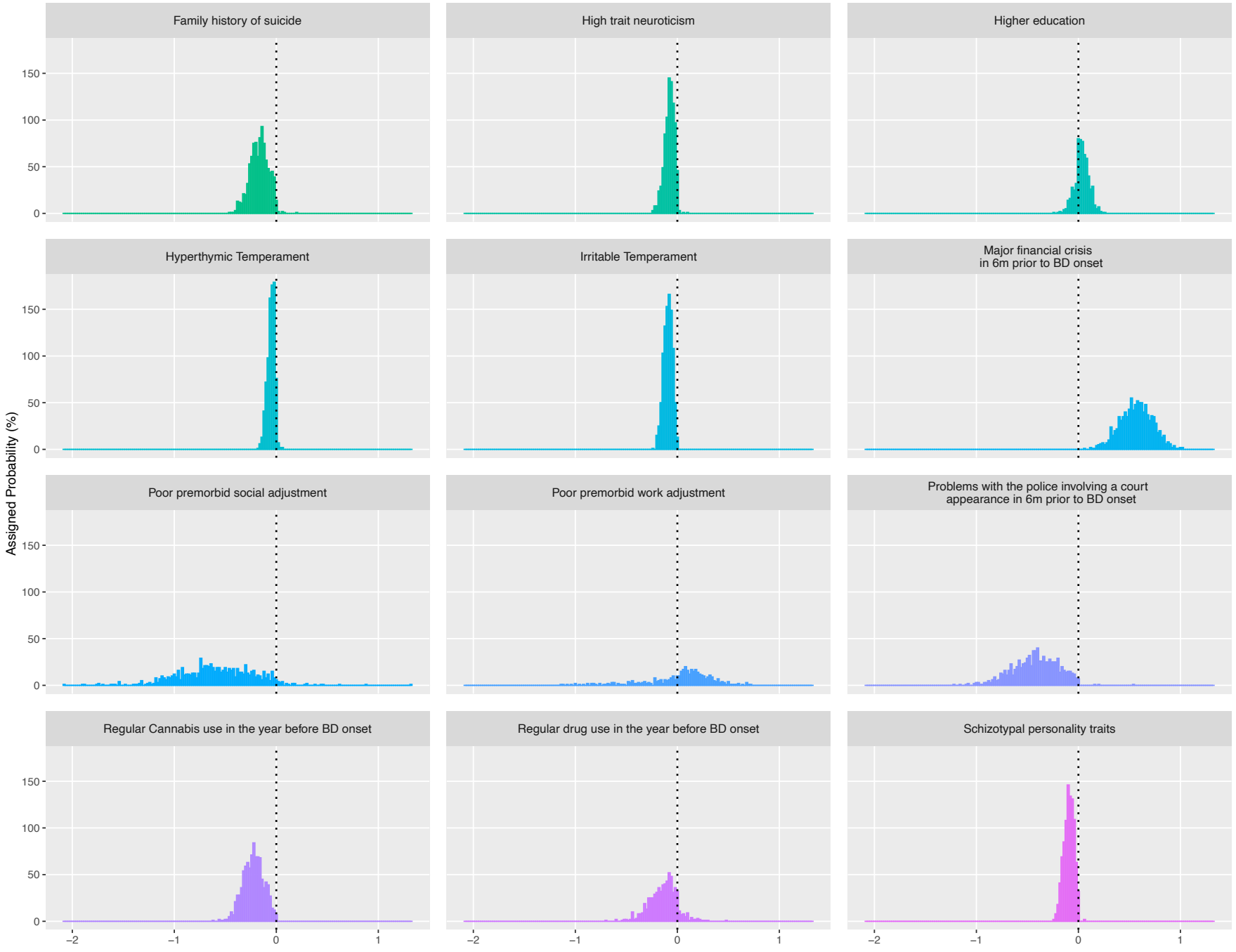
Appendix B.6. Modal Coefficient Values for all predictors

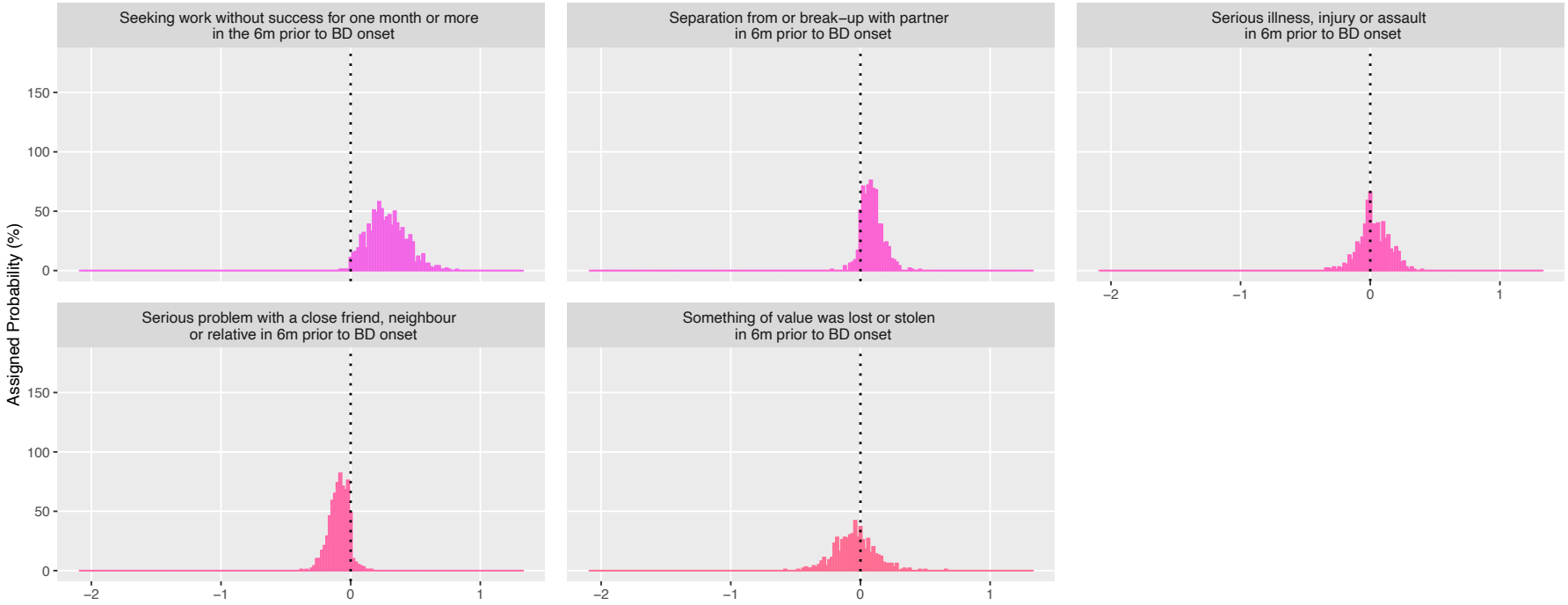
Predictors	Modal Coefficients
(Intercept)	0.0855
Avg. number of alcohol units per week in the year before BD onset	0.1385
High trait neuroticism	- 0.0835
Cyclothymic Temperament	- 0.0835
Depressive Temperament	- 0.0285
Irritable Temperament	- 0.0685
Hyperthymic Temperament	-0.0455
Anxious Temperament	0.0435
Schizotypal personality traits	- 0.1055
Family history of affective disorders	- 0.0215
Family history of psychiatric disorders	- 0.0225
Family history of suicide	- 0.1385
Higher education	0.0115
Regular Cannabis use in the year before BD onset	- 0.2765
Regular drug use in the year before BD onset	- 0.0705
Poor premorbid work adjustment	- 0.1695
Poor premorbid social adjustment	- 0.7495
Childhood abuse	- 0.2855
Childhood abuse unknown	- 0.0745
Serious illness, injury, or assault in 6m prior to BD onset	- 0.0085
Close relative suffered serious illness, injury, or assault in 6m prior to BD onset	- 0.1155
Death of parent, partner, child, or sibling in the 6m prior to BD onset	0.3125
Death of close family friend or relative in 6m prior to BD onset	- 0.2435
Separation from or break-up with partner in 6m prior to BD onset	0.0525
Serious problem with a close friend, neighbour or relative in 6m prior to BD onset	- 0.0845
Seeking work without success for one month or more in the 6m prior to BD onset	0.3505
Major financial crisis in 6m prior to BD onset	0.4575
Problems with the police involving a court appearance in 6m prior to BD onset	- 0.2945
Something of value was lost or stolen in 6m prior to BD onset	0.0065
Birth of child in 6m prior to BD onset	0.2755

Appendix B.7. Histograms of non-exponentiated coefficients

All parameter estimates (coefficients) were collated to examine which predictor variables are consistently retained and estimated the variability in these coefficients. These non-exponentiated coefficients are reported as histograms, showing their distributions over 1000 resamples of the training set.


Anxious Temperament
Avg. number of alcohol units per week in the year before BD onset
Birth of child in 6m prior to BD onset
Childhood abuse
Childhood abuse unknown
Close relative suffered serious illness, injury or assault in 6m prior to BD onset
Cyclothymic Temperament
Death of close family friend or relative in 6m prior to BD onset
Death of parent, partner, child or sibling in the 6m prior to BD onset
Depressive Temperament
Family history of affective disorders
Family history of psychiatric disorders
Assigned Probability (%)
0
50
100
150
−2
−1
0
1


Family history of suicide
High trait neuroticism
Higher education
Hyperthymic Temperament
Irritable Temperament
Major financial crisis
in 6m prior to BD onset
Poor premorbid social adjustment
Poor premorbid work adjustment
Problems with the police involving a court
appearance in 6m prior to BD onset
Regular Cannabis use in the year before BD onset
Regular drug use in the year before BD onset
Schizotypal personality traits
Assigned Probability (%)
0
50
100
150
−2
−1
0
1

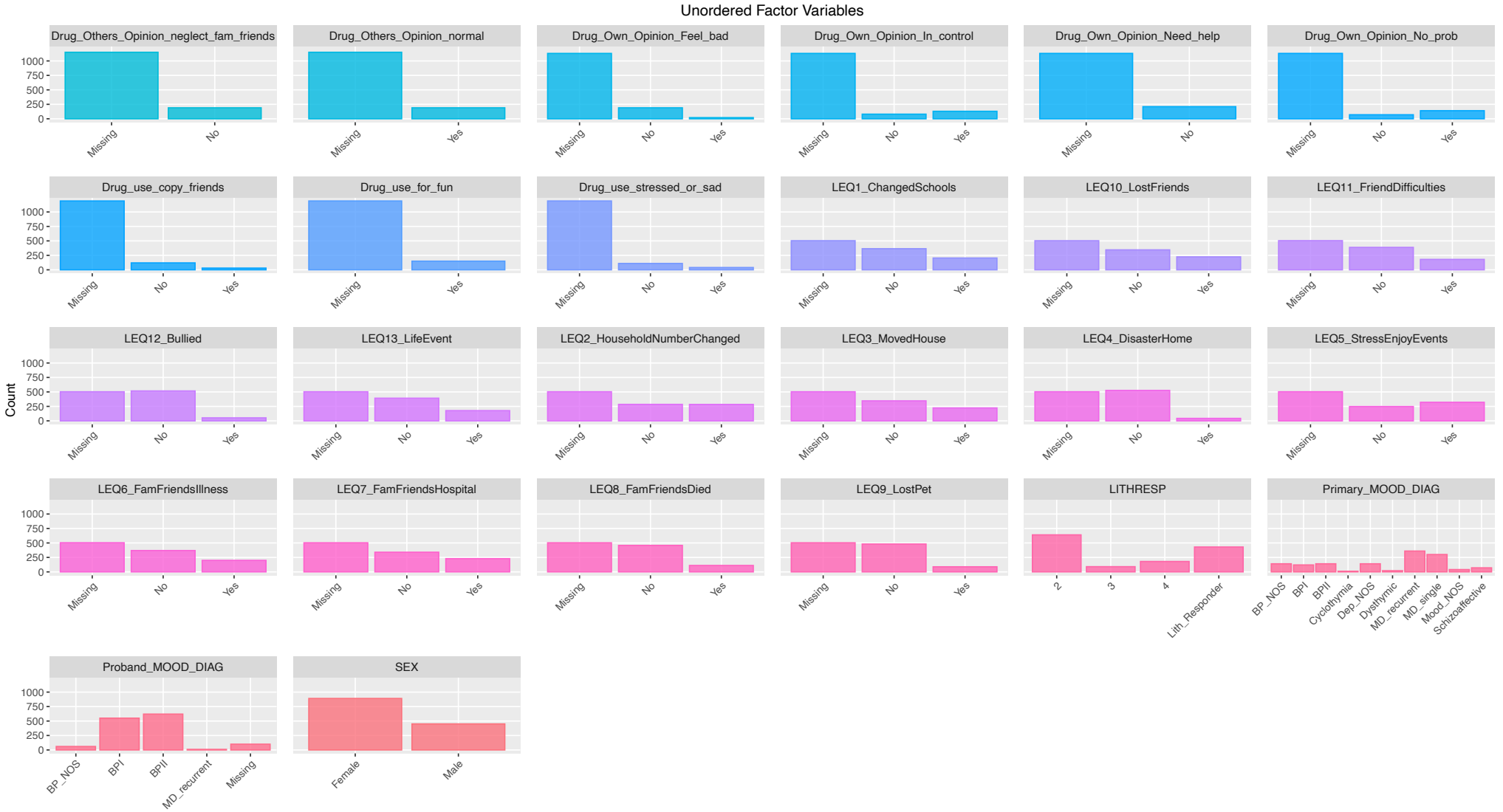

Seeking work without success for one month or more in the 6m prior to BD onset
Separation from or break−up with partner in 6m prior to BD onset
Serious illness, injury or assault in 6m prior to BD onset
Serious problem with a close friend, neighbour or relative in 6m prior to BD onset
Something of value was lost or stolen in 6m prior to BD onset
Assigned Probability (%)
150
100
50
0
−2
−1
0
1

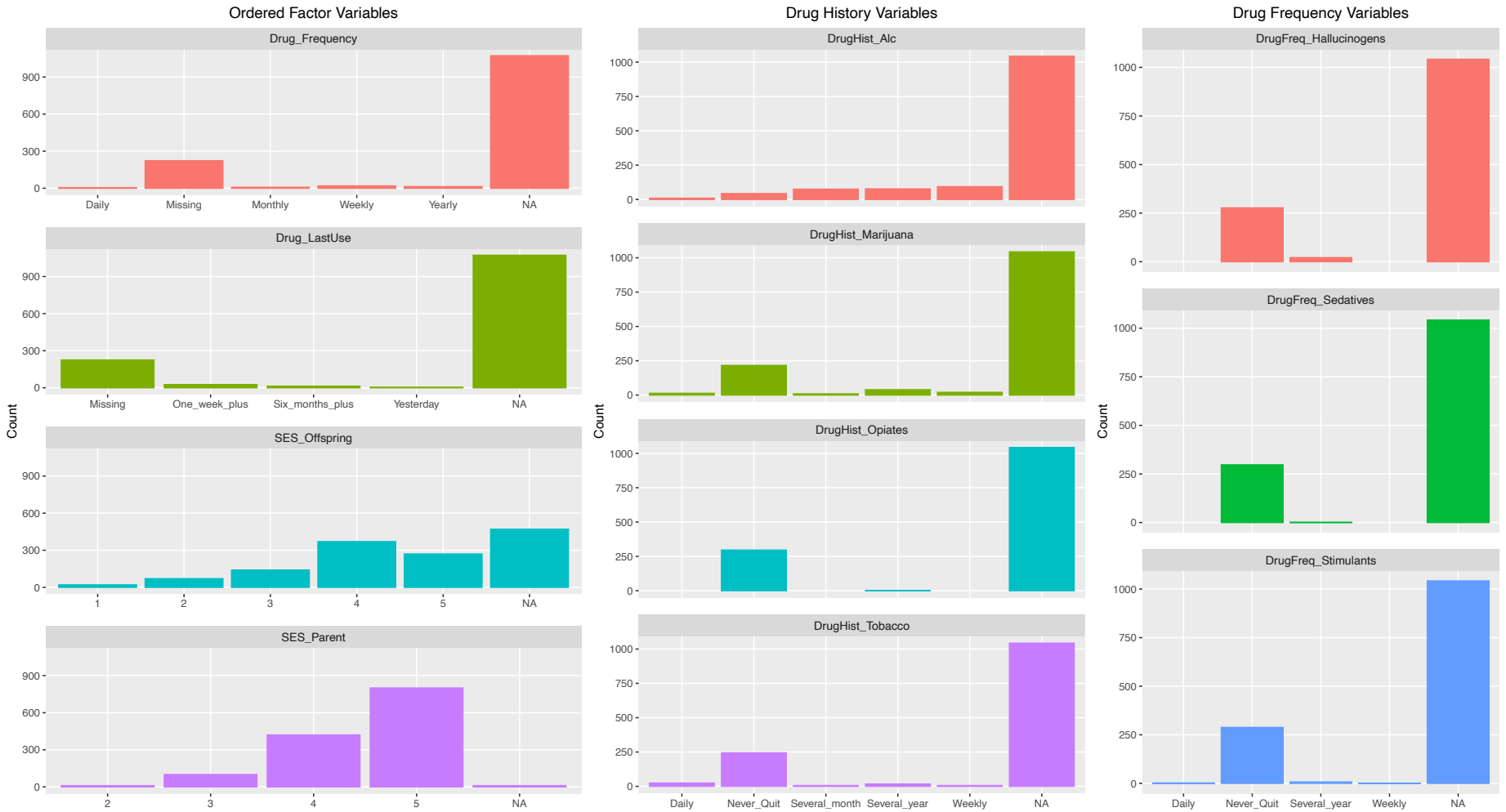
Appendix C

Appendix C relates to Chapter 4

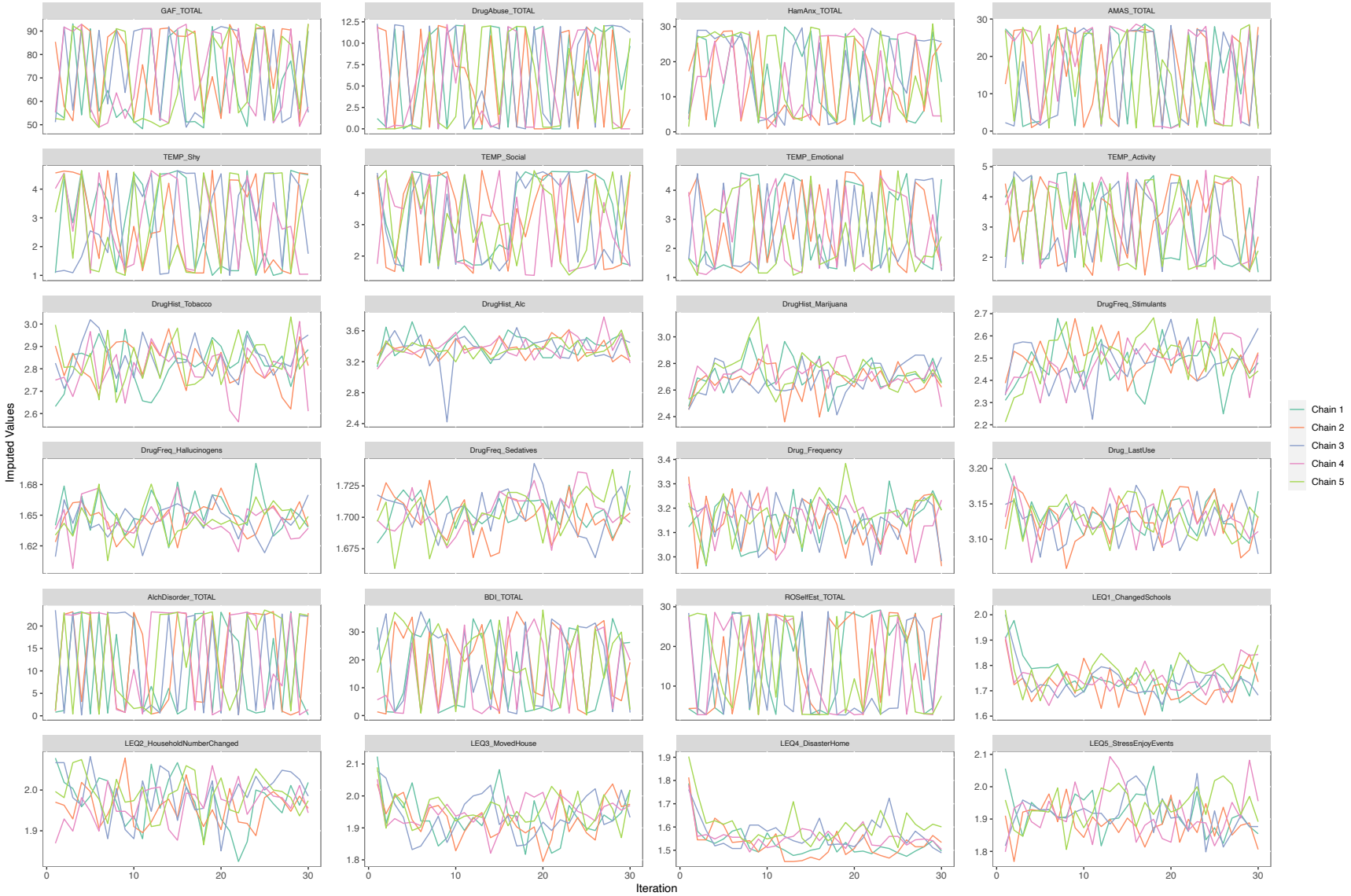
Appendix C.1. Data Distributions: Histograms of Numeric variables:

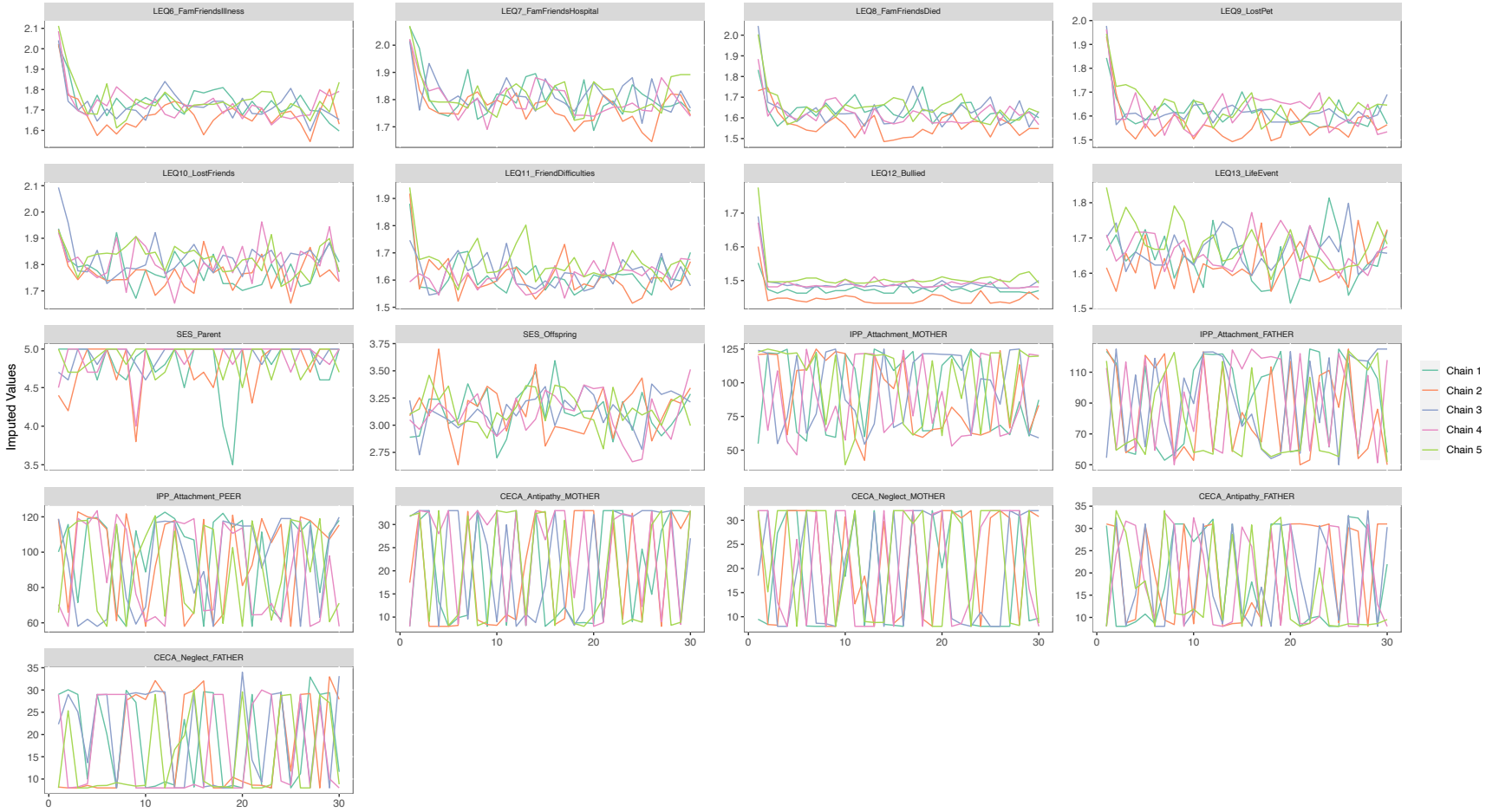
Appendix C.2. Bar charts of categorical variables:


Unordered Factor Variables
Count
Drug_Others_Opinion_neglect_fam_friends
Drug_Others_Opinion_normal
Drug_Own_Opinion_Feel_bad
Drug_Own_Opinion_In_control
Drug_Own_Opinion_Need_help
Drug_Own_Opinion_No_prob
Drug_use_copy_friends
Drug_use_for_fun
Drug_use_stressed_or_sad
LEQ1_ChangedSchools
LEQ10_LostFriends
LEQ11_FriendDifficulties
LEQ12_Bullied
LEQ13_LifeEvent
LEQ2_HouseholdNumberChanged
LEQ3_MovedHouse
LEQ4_DisasterHome
LEQ5_StressEnjoyEvents
LEQ6_FamFriendsIllness
LEQ7_FamFriendsHospital
LEQ8_FamFriendsDied
LEQ9_LostPet
LITHRESP
Primary_MOOD_DIAG
Proband_MOOD_DIAG
SEX
0
250
500
750
1000
Missing
No
Yes
2
3
4
Lith_Responder
BP_NOS
BPI
BPII
Cyclothymia
Dep_NOS
Dysthymic
MD_recurrent
MD_single
Mood_NOS
Schizoaffective
MD_recurrent
Female
Male


Ordered Factor Variables
Drug History Variables
Drug Frequency Variables
Drug_Frequency
Daily
Missing
Monthly
Weekly
Yearly
NA
Drug_LastUse
Missing
One_week_plus
Six_months_plus
Yesterday
NA
SES_Offspring
1
2
3
4
5
NA
SES_Parent
2
3
4
5
NA
DrugHist_Alc
DrugHist_Marijuana
DrugHist_Opiates
DrugHist_Tobacco
Daily
Never_Quit
Several_month
Several_year
Weekly
NA
DrugFreq_Hallucinogens
DrugFreq_Sedatives
DrugFreq_Stimulants
Daily
Never_Quit
Several_year
Weekly
NA
Count
0
300
600
900
250
500
750
1000

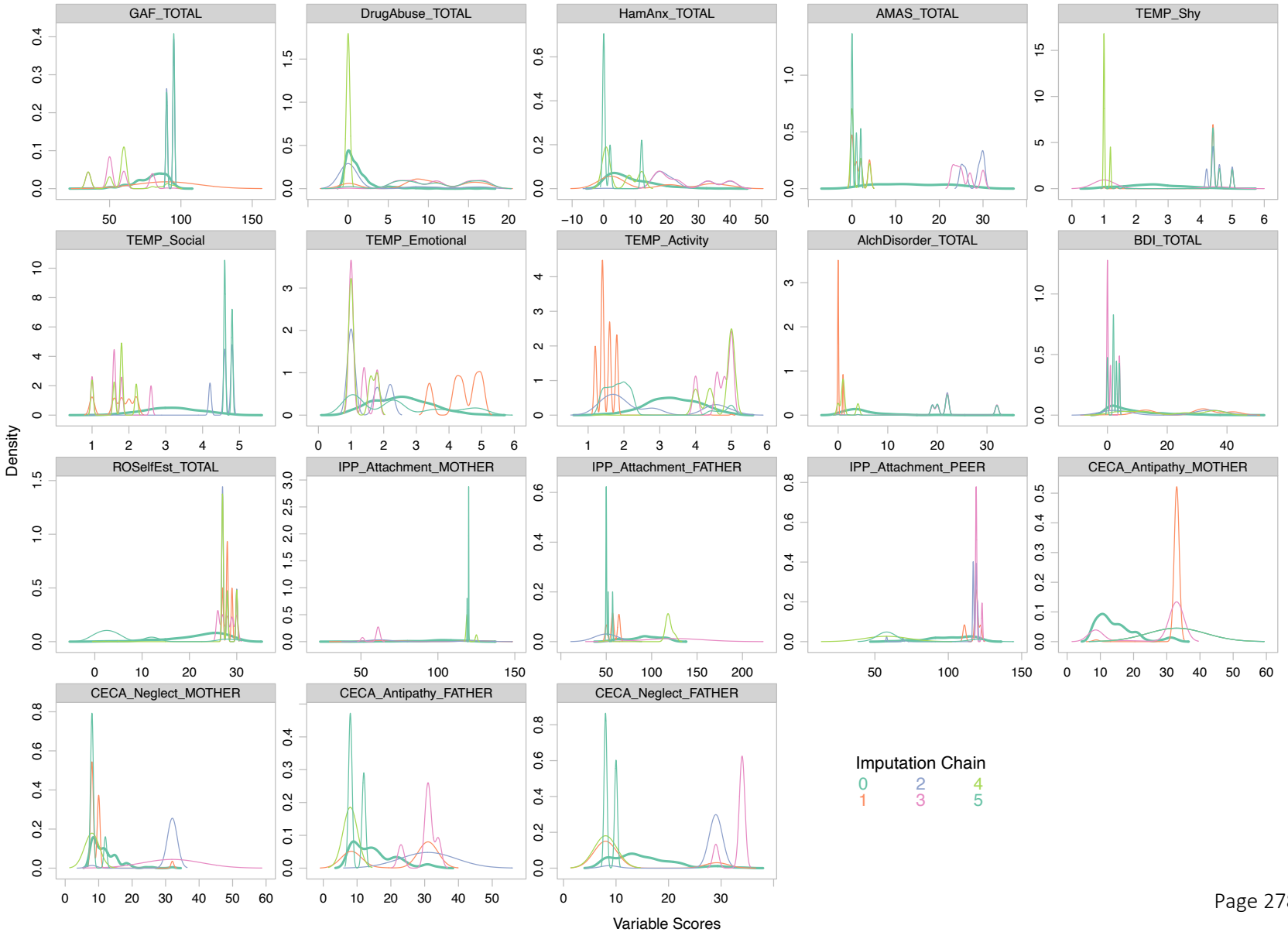
Appendix C.3. Multiple Imputation Convergence

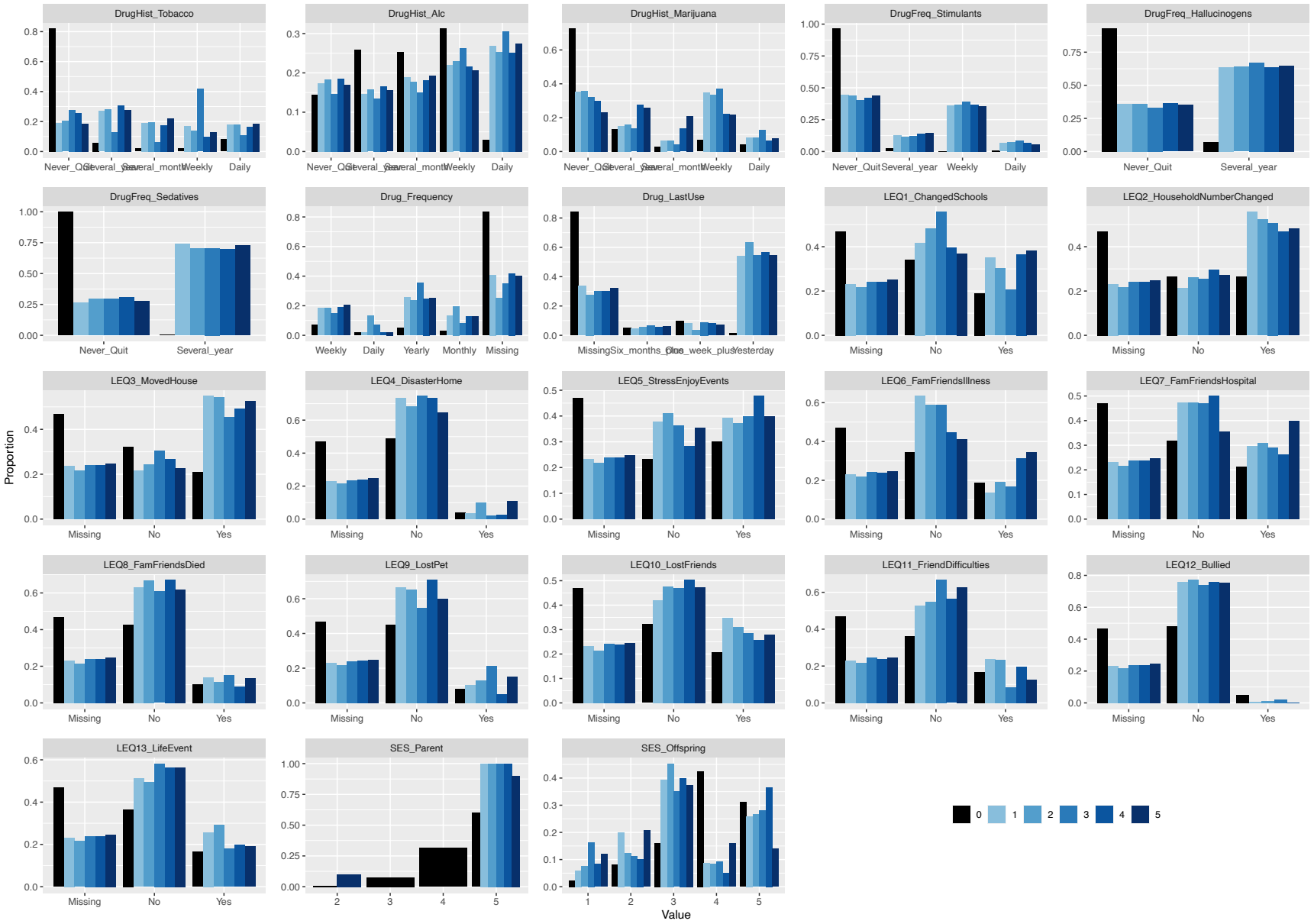



LEQ6_FamFriendsIllness
LEQ7_FamFriendsHospital
LEQ8_FamFriendsDied
LEQ9_LostPet
LEQ10_LostFriends
LEQ11_FriendDifficulties
LEQ12_Bullied
LEQ13_LifeEvent
SES_Parent
SES_Offspring
IPP_Attachment_MOTHER
IPP_Attachment_FATHER
IPP_Attachment_PEER
CECA_Antipathy_MOTHER
CECA_Neglect_MOTHER
CECA_Antipathy_FATHER
CECA_Neglect_FATHER
Imputed Values
Chain 1
Chain 2
Chain 3
Chain 4
Chain 5

Appendix C.4. Missingness

Appendix C.5. Variable scores across imputation chains




DrugHist_Tobacco
DrugHist_Alc
DrugHist_Marijuana
DrugFreq_Stimulants
DrugFreq_Hallucinogens
DrugFreq_Sedatives
Drug_Frequency
Drug_LastUse
LEQ1_ChangedSchools
LEQ2_HouseholdNumberChanged
LEQ3_MovedHouse
LEQ4_DisasterHome
LEQ5_StressEnjoyEvents
LEQ6_FamFriendsIllness
LEQ7_FamFriendsHospital
LEQ8_FamFriendsDied
LEQ9_LostPet
LEQ10_LostFriends
LEQ11_FriendDifficulties
LEQ12_Bullied
LEQ13_LifeEvent
SES_Parent
SES_Offspring
Proportion
Value
Never_Quit
Several_year
Several_month
Weekly
Daily
Missing
Six_months_plus
Yesterday
No
Yes
Monthly
Yearly
0
1
2
3
4
5

Appendix C.6. Details of R helper packages

Package	Title	Maintainer	Version	Date of Publication
car	Companion to Applied Regression	John Fox <jfox@mcmaster.ca>	3.1-1	2022-10-19
DiagrammeRsvg	Export DiagrammeR Graphviz Graphs as SVG	Richard Iannone <riannone@me.com>	0.1	2016-02-04
dplyr	A Grammar of Data Manipulation	Hadley Wickham <hadley@posit.co>	1.1.0	2023-01-29
ggforce	Accelerating 'ggplot2'	Thomas Lin Pedersen <thomasp85@gmail.com>	0.4.1	2022-10-04
ggmice	Visualizations for 'mice' with 'ggplot2'	Hanne Oberman <h.i.oberman@uu.nl>	0.0.1	2022-03-17
ggplot2	Create Elegant Data Visualisations Using the Grammar of Graphics	Thomas Lin Pedersen <thomas.pedersen@posit.co>	3.4.1	2023-02-10
gridExtra	Miscellaneous Functions for "Grid" Graphics	Baptiste Auguie <baptiste.auguie@gmail.com>	2.3	2017-09-09
htmlTable	Advanced Tables for Markdown/HTML	Max Gordon <max@gforge.se>	2.4.1	2022-07-07
kableExtra	Construct Complex Table with 'kable' and Pipe Syntax	Hao Zhu <haozhu233@gmail.com>	1.3.4	2021-02-20
lattice	Trellis Graphics for R	Deepayan Sarkar <deepayan.sarkar@r-project.org>	0.20-45	2021-09-22
lavaan	Latent Variable Analysis	Yves Rosseel <Yves.Rosseel@UGent.be>	0.6-15	2023-03-14
lavaanPlot	Path Diagrams for 'Lavaan' Models via 'DiagrammeR'	Alex Lishinski <alexlishinski@gmail.com>	0.6.2	2021-08-13
magrittr	A Forward-Pipe Operator for R	Lionel Henry <lionel@rstudio.com>	2.0.3	2022-03-30

mice	Multivariate Imputation by Chained Equations	Stef van Buuren <stef.vanbuuren@tno.nl>	3.15.0	2022-11-19
naniar	Data Structures, Summaries, and Visualisations for Missing Data	Nicholas Tierney <nicholas.tierney@gmail.com>	1.0.0	2023-02-02
officer	Manipulation of Microsoft Word and PowerPoint Documents	David Gohel <david.gohel@ardata.fr>	0.6.1	2023-03-08
patchwork	The Composer of Plots	Thomas Lin Pedersen <thomasp85@gmail.com>	1.1.2	2022-08-19
readr	Read Rectangular Text Data	Jennifer Bryan <jenny@posit.co>	2.1.4	2023-02-10
reshape2	Flexibly Reshape Data: A Reboot of the Reshape Package	Hadley Wickham <h.wickham@gmail.com>	1.4.4	2020-04-09
semPlot	Path Diagrams and Visual Analysis of Various SEM Packages' Output	Sacha Epskamp <mail@sachaepskamp.com>	1.1.6	2022-08-10
semTools	Useful Tools for Structural Equation Modeling	Terrence D. Jorgensen <TJorgensen314@gmail.com>	0.5-6	2022-05-10
stringr	Simple, Consistent Wrappers for Common String Operations	Hadley Wickham <hadley@rstudio.com>	1.5.0	2022-12-02
tidySEM	Tidy Structural Equation Modeling	Caspar J. van Lissa <c.j.vanlissa@uu.nl>	0.2.3	2022-04-14
tidyverse	Easily Install and Load the 'Tidyverse'	Hadley Wickham <hadley@rstudio.com>	2.0.0	2023-02-22
viridis	Colorblind-Friendly Color Maps for R	Simon Garnier <garnier@njit.edu>	0.6.2	2021-10-13

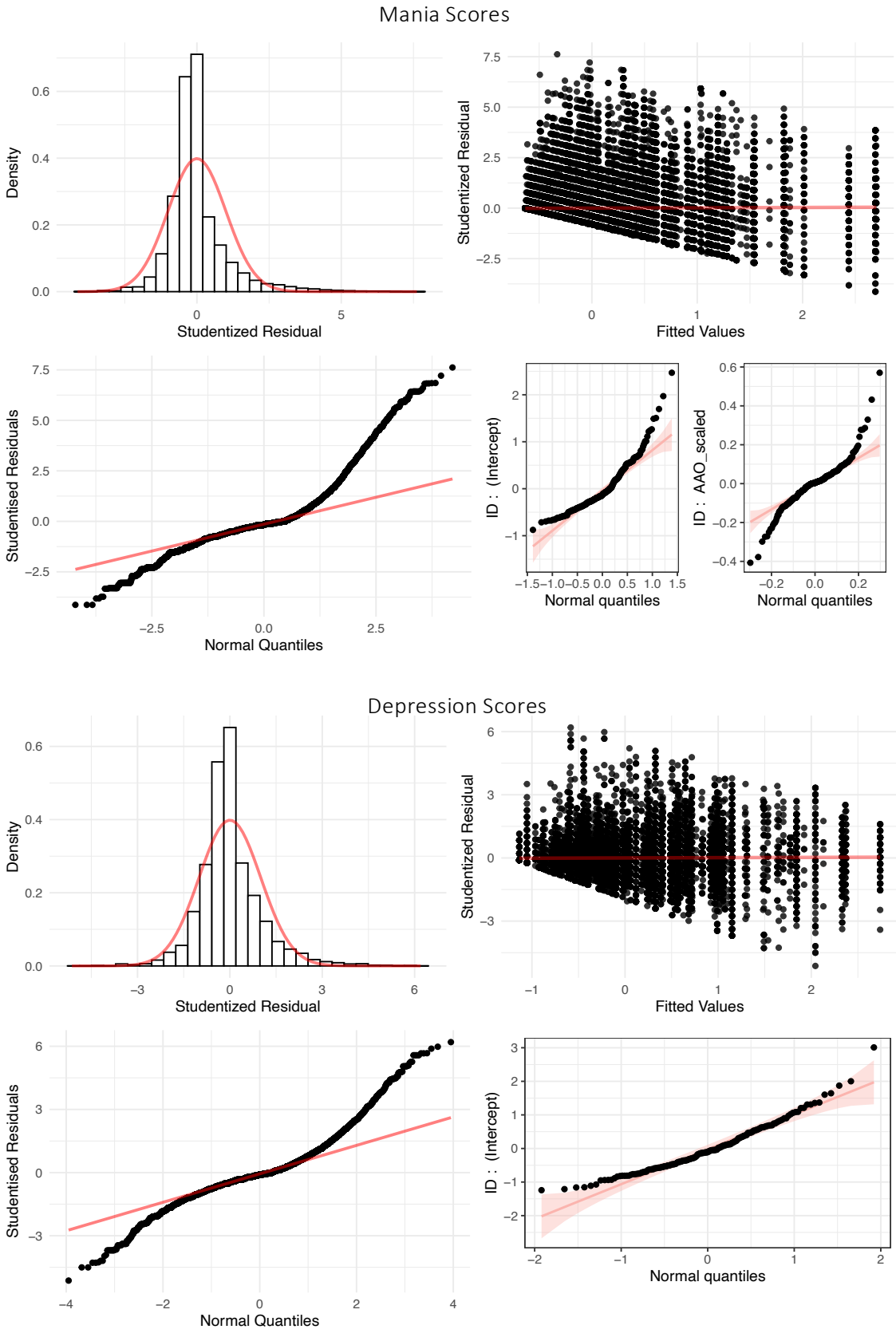
Appendix D

Appendix D relates to Chapter 5

Appendix D.1. R helper packages

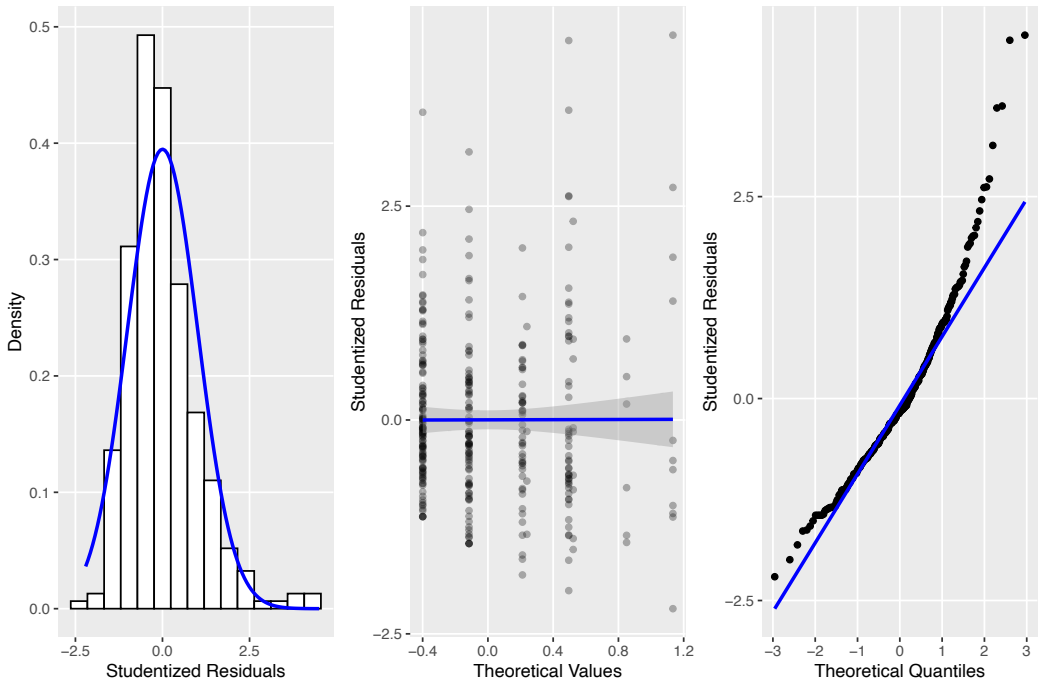
Package Name	Author(s)	Version	URL
car	Fox & Weisberg (2019)	3.0-11	https://cran.r-project.org/web/packages/car/index.html
dplyr	Wickham et al. (2020)	1.0.2	https://CRAN.R-project.org/package=dplyr
forcats	Wickham (2020)	0.5.0	https://CRAN.R-project.org/package=forcats
ggplot2	(Wickham, 2016)	3.3.2	https://ggplot2.tidyverse.org
glmnet	Friedman et al. (2010)	4.1-1	https://glmnet.stanford.edu
Hmisc	Harrell (2020)	4.4-1	https://CRAN.R-project.org/package=Hmisc
magrittr	Bache & Wickham (2020)	2.0.1	https://CRAN.R-project.org/package=magrittr
MASS	Venables & Ripley (2002)	7.3-54	https://CRAN.R-project.org/package=MASS
plyr	Wickham (2011)	1.8.6	https://CRAN.R-project.org/package=plyr
readr	Wickham & Hester (2020)	1.4.0	https://CRAN.R-project.org/package=readr
recipes	Kuhn & Wickham (2020)	0.1.15	https://CRAN.R-project.org/package=recipes
tidyverse	Wickham et al. (2019)	1.3.0	http://tidyverse.tidyverse.org

Appendix D.2. Residual plots for assessing mixed-model assumptions

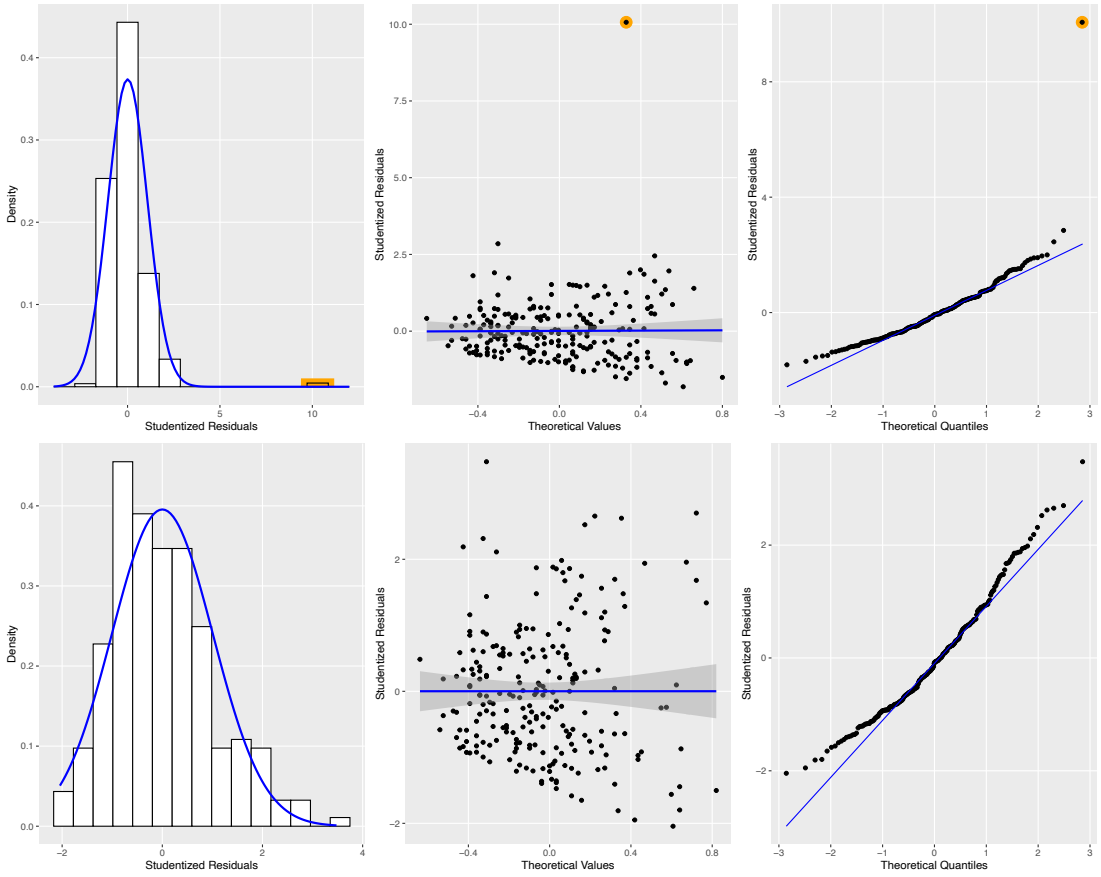


Appendix D.3. Residual plots for assessing regression model assumptions

Mania:



Depression:



Appendix D.4. Correlation plot of variables