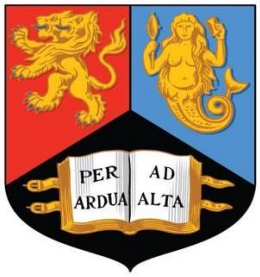

UNDERSTANDING THE DEVELOPMENTAL PATHWAYS TO BIPOLAR DISORDER

by

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Dedication

This PhD thesis is dedicated to my dad, Metin Durdurak and mom, Aysegul Durdurak. You are both my heroes. If it wasn't for you, I wouldn't have had the opportunity to follow my dreams. And I know you did everything you could to provide the life you wish you had for me. This PhD is dedicated to you.

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Abstract

Bipolar Disorder (BD) is a multifactorial condition, with a diversity of trajectories. Existing evidence indicates the presence of significant psychopathology preceding the onset of BD, such as Borderline Personality Disorder (BPD), Attention Deficit Hyperactivity Disorder (ADHD) and depression. However, a more nuanced understanding of these developmental risk trajectories and their relationship to BD are lacking and remain essential to disentangle risks and links.

The overarching aim of this thesis is to develop new knowledge of the developmental pathways to BD, so that people who are vulnerable to developing BD can be more clearly identified so that ultimately targeted interventions can be developed for this group. In doing so the thesis will also review gaps in current knowledge and provide directions for future research.

Three studies were conducted to answer the research aim via examining developmental trajectories of BPD, ADHD, and depression to BD. Firstly, factors that are associated with the early course of BD and BPD symptoms, features, or onset were examined in a priori literature to be able to understand the differences and similarities in developmental pathways to these disorders were examined. To address this aim and take advantage of the recent surge in publications, I conducted a meta-review of systematic reviews evaluating prospective studies investigating these factors. Secondly, the associations between ADHD symptom trajectories (including its subtypes) through childhood and adolescence with clinically significant hypomanic symptoms at age 21-23 years were examined, using data from the Avon Longitudinal Study of Parents and Children (ALSPAC). Thirdly, the association between trajectories of depressive

symptoms in adolescence and the risk of subsequent clinically significant hypomanic symptoms at 21-23 years and whether atypical depression features and psychotic symptoms potentially mediate any association were investigated, using data from the same UK birth cohort ALSPAC. Findings from the meta-review of reviews demonstrated that family history of psychopathology, affective instability, ADHD, anxiety disorders, depression, sleep disturbances, substance abuse, psychotic symptoms, suicidality, childhood adversity and temperament were common predisposing factors/trajectories across both disorders. Since the detected risk trajectories are non-specific and overlapping, results can advance the field of defining progressive stages in transdiagnostic clinical staging models in youth mental health.

Results from the second study showed that individuals with persistently high and increasing levels of ADHD symptoms had increased odds of hypomanic symptoms compared to persistently low and remitting classes. In separate analyses, persistently high levels of hyperactivity, and increasing levels of inattentive symptoms were also independently associated with hypomanic symptoms. These trajectories in childhood and adolescence may represent distinct phenotypic risk profiles for subsequently developing BD and be clinically significant targets for prevention and treatment of BD.

Results from the third study indicated that adolescents with increasing levels of depression symptoms were more likely to develop clinically significant hypomanic symptoms at 21-23 years, compared to adolescents with persistently low depression symptoms. Both atypical depression features and psychotic symptoms partially mediated the association of increasing depression levels with hypomanic symptoms.

The collective implications and limitations of the findings arising from these three studies, along with future directions are discussed in the final chapter. Overall, these studies advance our

understanding and differentiation of emerging trajectories in BD by taking a developmental prospective approach and encouraging early recognition and treatment of emerging syndromal illnesses in youth mental health.

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Chapter 2: Durdurak, B. B., Altaweel, N., Upthegrove, R., & Marwaha, S. (2022). Understanding the development of bipolar disorder and borderline personality disorder in young people: a meta-review of systematic reviews. *Psychological Medicine, 52*(16), 3769-3782.

Chapter 4: Durdurak, B. B., Muñoz, I. M., Hosang, G. M., & Marwaha, S. ADHD symptom trajectories across childhood and early adolescence and risk for hypomanic symptoms in young adulthood. European Psychiatry, 1-29.

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Chapter 5: Durdurak, B. B., Morales-Muñoz, I., Ratheesh, A., Berk, M., & Marwaha, S. (2024). Depression symptom trajectories across adolescence and risk of hypomanic symptoms in young adulthood: A UK Birth Cohort Study. Under Review in *European Neuropsychopharmacology*. Submitted on 26/09/2024.

Additional publications to which I have contributed throughout my PhD

Durdurak BB, Williams B, Zhigalov A, et al. Factors associated with chronic depressive symptoms across adolescence and young adulthood: a UK birth cohort study. Epidemiology and Psychiatric Sciences. 2024;33:e32. doi:10.1017/S2045796024000350

Altaweel, N., Upthegrove, R., Surtees, A., Durdurak, B., & Marwaha, S. (2023). Personality traits as risk factors for relapse or recurrence in major depression: a systematic review. *Frontiers in Psychiatry*, *14*, 1176355.

Hett, D., Morales-Muñoz, I., Durdurak, B. B., Carlish, M., & Marwaha, S. (2023). Rates and associations of relapse over 5 years of 2649 people with bipolar disorder: a retrospective UK cohort study. *International journal of bipolar disorders, 11*(1), 23.

Morales-Muñoz, I., Durdurak, B. B., Bilgin, A., Marwaha, S., & Winsper, C. (2021). Understanding the relationship between sleep problems in early childhood and borderline personality disorder: A narrative review. *Nature and science of sleep*, 2175-2202.

Chapter 1

Introduction

Chapter Overview

The overarching aim of this thesis is to understand the developmental pathways to Bipolar Disorder (BD). This introductory chapter provides an overview of BD's epidemiology, current diagnostic challenges, clinical staging, and the importance of prospective studies for understanding the aetiological pathways to BD. It then goes on to discuss the developmental trajectories to Borderline Personality Disorder (BPD), Attention Deficit and Hyperactivity Disorder (ADHD) and depression and their link to BD. The chapter concludes with a summary of the key points and the specific aims of the thesis.

1.1. Bipolar Disorder

Bipolar Disorder (BD) is a debilitating mental health disorder characterized by episodes of intense mood swings, cognitive impairments, immunological and physiological alterations, and disruptions in daily functioning (Grande et al., 2016), with onset usually before the age of 25 years. It ranks among the primary causes of disability globally and is linked to elevated rates of premature death, attributable to both suicide and medical conditions such as cardiovascular diseases (McIntyre et al., 2020).

1.2. History of Bipolar Disorder

Origins of BD has its roots in the work of ancient Greco-Roman writings of physician-scholars on syndromes designated as mania and melancholia (López-Muñoz et al., 2018). Hippocrates was the first who systematically described mania and melancholia (Angst & Marneros, 2001). He assumed a biological basis, namely disturbances or damages of the brain for depression and mania but also for psychosis and anxiety (Angst & Sellaro, 2000). Later work by Aretaeus of

Cappadocia linked these two states of mania and melancholia and indicated that melancholia and mania have the same aetiology coming from brain dysfunction (Mason et al., 2016).

During middle 19th century, somaticist movements began to emerge in the psychiatry field and BD was seen as an entity of its own (López-Muñoz et al., 2018). This conclusion was stated first by Jean-Pierre Falret (López-Muñoz et al., 2018). In his statement in 1851, Falret introduced a distinct mental disorder he called 'folie circulaire,' characterized by a continual cycle of depression, mania, and varying lengths of symptom-free periods (Angst & Marneros, 2001). After Faltret's publication on 'folie circulaire', in 1854 Jules Baillarger published his concept of 'foliea` double forme', drawing a conclusion very different from Faltret's (Mason et al., 2016). Baillarger identified a type of illness where mania and melancholia transition into one another, with the interval between episodes deemed irrelevant (Angst & Marneros, 2001). Conversely, Falret emphasized the significance of the interval between manic and melancholic episodes in his concept (Angst & Marneros, 2001).

There was a significant progress after Jean-Pierre Falret's concept of 'folie circulaire' (Angst & Marneros, 2001). In 1899, Emil Kraeplin created the concept of "manic depressive insanity", dissociating it from schizophrenia (Angst & Sellaro, 2000; Marneros, 2001). However, Kraepelin's idea of unifying of all affective disorders under the concept of manic-depressive illness met with significant opposition by many such as Carl Wernicke and Karl Kleist (Angst & Marneros, 2001). According to Wernicke, manic-depressive illness should be understood strictly as described by Falret (folie circulaire) or by Baillarger (folie à double forme; Angst & Sellaro, 2000). Karl Kleist, too, opposed Kraepelin's concept of manic- depressive insanity and differentiated unipolar and bipolar affective disorders (Angst & Sellaro, 2000; Marneros, 2001). Wernicke and Kleist's concepts were further developed by Karl Leonhard (Angst & Marneros,

2001), who classified the “phasic psychoses” into “pure phasic psychoses” (such as “pure melancholia”, “pure mania”, etc.) and “polymorphous phasic disorders”. Both Karl Kleist and Karl Leonhard gathered many clinical and family history data to support the distinction between “unipolar” and “bipolar” (Marneros, 2001). Although their opinions had no relevant influence on international psychiatry for a long time, in 1966, the work of many others confirmed some fundamental assumptions of Wernicke, Kleist and Leonhard (Angst & Marneros, 2001).

1.3. Aetiology of Bipolar Disorder

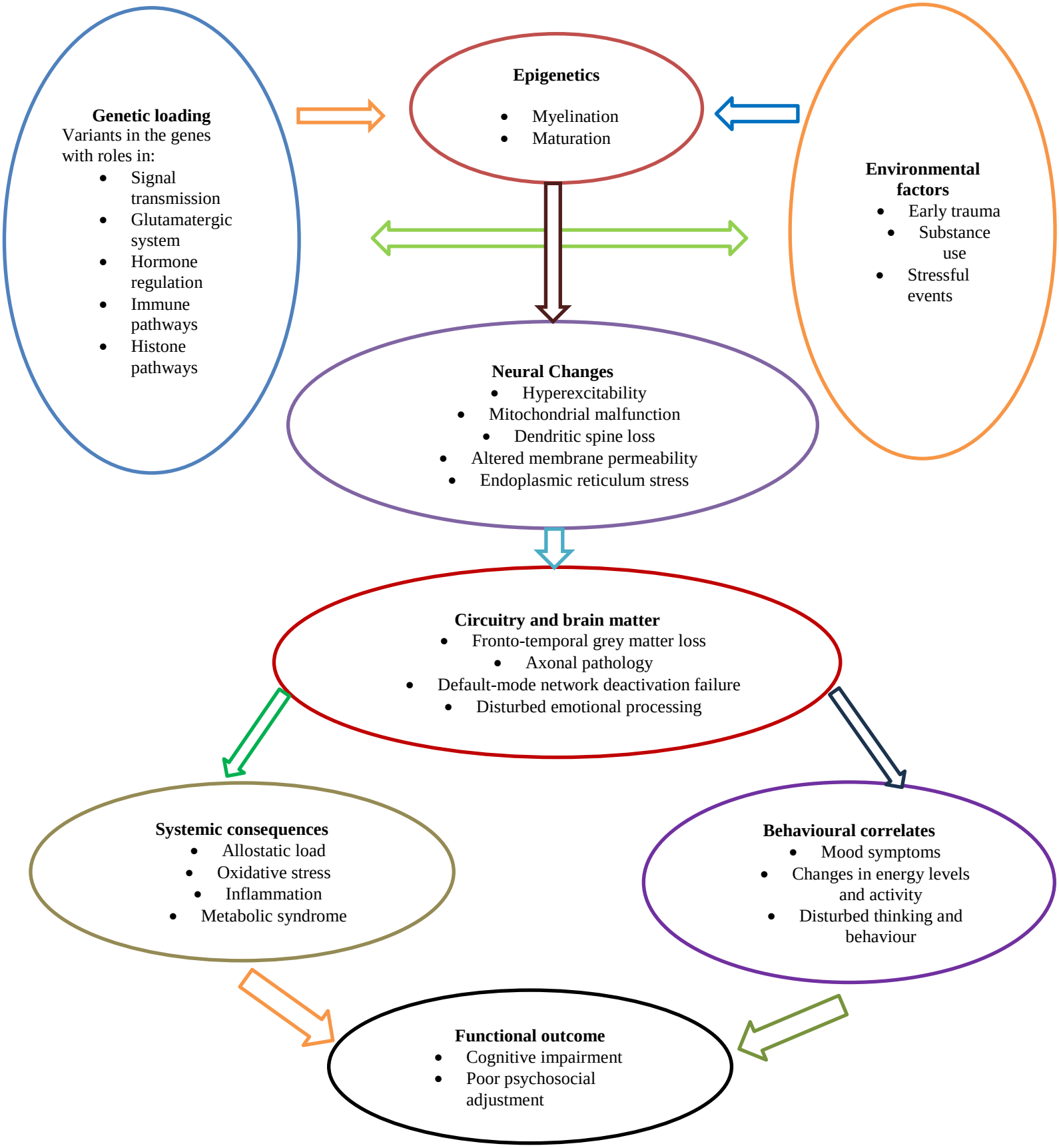
BD has a complex aetiology and is highly heritable (McIntyre et al., 2020; Young & Juruena, 2021). It is suggested that BD may arise from the interplay between genetic factors that increase susceptibility and risk factors that predispose, precipitate, and perpetuate the condition (McIntyre et al., 2020; see Figure 1 adapted from Vieta et al., 2018). That is why, there has been increasing interest and emerging evidence regarding the genetics of BD, risk factors, gene-environment interactions, and the potential characteristics of the bipolar prodrome prior to the onset of an episode of (hypo)mania or depression (Rowland & Marwaha, 2018a).

As stated, the aetiology of BD is multifactorial, but this PhD thesis will be focusing mainly on potentially relevant childhood and adolescence psychopathology as risk factors in the risk of developing BD, to help inform early intervention and prevention strategies. However, the introductory part of the thesis will also briefly review other potential underlying mechanisms such as genetics, neurobiology, and biomarkers.

1.4. Epidemiology of Bipolar Disorder

BD is a chronic and recurrent disorder that affect >1% of the global population (Vieta et al., 2018). More specifically, BD-I has an estimated global lifetime prevalence of 0·6–1·0% and BD-II has an estimated global lifetime prevalence of 0·4–1·1% (K. R. Merikangas et al., 2011). Regarding the sex differences in prevalence rates, the latest World Mental Health survey

Figure 1. Multifactorial model of Bipolar Disorder. Adapted from Vieta et al. (2018).



between 2001 and 2022 involving 156,331 respondents across 29 countries showed a lifetime BD prevalence of 2.5% in men and 2.3% in women (McGrath et al., 2023). More specifically, Bipolar II and other bipolar-spectrum disorders, including cyclothymic disorder, are more prevalent in females, while bipolar I is equally prevalent in males and females (Loftus et al., 2020a). BD is also prevalent in primary care practices and patients receiving care for unipolar depression in primary care practices may have an unrecognized BD (Daveney et al., 2019). One of the limitations of the current prevalence estimates is that they have largely been derived from studies of high-income countries (McIntyre et al., 2020). The lifetime prevalence of BD has been variably reported in low- and middle-income countries (McIntyre et al., 2020). For example, rates from Africa and Asia are less than half of those from North and South America (Moreira et al., 2017). More specifically, the lifetime prevalence of BD is approximately 0·1–1·8% in Ethiopia and Nigeria, and 3·0–4·0% in South Africa (Godman et al., 2019; Steel et al., 2014a). Further, a systematic review and meta-analysis showed a 0.11% lifetime prevalence rate for BD in China (Zhang et al., 2017). The reason for international variations in the estimates of BD is not entirely clear, and ethnicity, cultural factors, variations in diagnostic criteria and study methodology may each have an impact (Rowland & Marwaha, 2018). Further studies from non-Western countries are needed to refine understanding of international prevalence.

BD often emerge during adolescence and young adulthood and is estimated to affect 0.003%–3.9% of the child and adolescent population (Fahrendorff et al., 2023). However, although BD emerge in youth, misdiagnosis and lack of diagnosis are common (Van Meter et al., 2021). While the peak age range for onset of BD is 15–25 years old, diagnosis and the initiation of appropriate care and treatment are likely to be delayed until age 25–35 years (Scott et al., 2022). Delays in treatment have significant consequences both for the short- and long-term outcomes

(Kessing et al., 2021; Van Meter et al., 2021). For example, delayed treatment has been associated with an increased number of suicide attempts (Altamura et al., 2010).

Approximately 6 to 7% of individuals with BD commit suicide (Carvalho et al., 2020). However, like prevalence rates, there is also discrepancy in suicide attempt rates across regions. For instance, a systematic review and meta-analysis found that the lifetime rate of suicide attempt is significantly higher in high and middle-income countries compared to low-income countries (Dong et al., 2019).

Estimates of the global burden of disease have shown that 5 of the top 20 causes of disability are due to mental illnesses and BD is the 17th leading cause of global burden of disease (Vigo et al., 2016). Cost estimates of BD in the United Kingdom amounted to £5.1 billion for the year 2010–2011 (2018–2019: £6.4 billion), resulting in £1.6 billion (2018–2019: £2.0 billion) costs directly related to the health care sector (Simon et al., 2021).

BD also often leads to functional impairment and reduced quality of life (Oldis et al., 2016) which also put a burden on family members and economically active population as high costs to society are incurred in terms of direct health-care costs and the costs of disability (Gardner et al., 2006; Macneil et al., 2011; Vieta et al., 2018). This impact is likely greatest in younger individuals, as BD disrupt the attainment of developmental, relational, educational and occupational aspects (Vieta et al., 2018).

1.4.1. Potential Underlying Mechanisms/pathophysiology in BD

1.4.1.1. Genetics

Family Genetic studies

BD is a highly heritable disease (O'Connell & Coombes, 2021), with heritability estimated between 60% and 90% by twin studies (Craddock & Sklar, 2013; K. Merikangas & Yu, 2002; Smoller & Finn, 2003). However, there are worries that the traditional twin study design might

overestimate heritability in certain situations where model assumptions are not met (Zuk et al., 2012). These assumptions include unbiased participant selection, equal environments for monozygotic and dizygotic twins, and potential gene-environment correlations (Gordovez & McMahon, 2020). Additionally, despite the strong and consistent evidence in favour of a genetic aetiology, BD does not follow a Mendelian inheritance pattern, and linkage studies have not pinpointed any individual genes with a strong association with the disorder (Badner et al., 2012), due to the fact that linkage methods do not work well in the face of complex patterns of inheritance (Gordovez & McMahon, 2020; Prathikanti & McMahon, 2001).

Findings from Genome-wide association studies

Genome-wide association studies (GWAS), which involve testing large numbers of genetic markers across the genome for their association with a trait, typically using large case-control samples, have proven to be a successful strategy thus far for identifying genetic variants associated with BD (Gordovez & McMahon, 2020). A GWAS study has identified about 30 common genetic variants significantly associated with BD, of which 20 had not previously been recognised (Stahl et al., 2019). These susceptibility loci offer indirect insights into the underlying mechanisms of BD (McIntyre et al., 2020).

Shared Genetic Correlations with Other Mental Health Disorders

BD shows strong genetic correlations with schizophrenia (Stahl et al., 2019), major depressive disorder (Huang et al., 2010; Middeldorp et al., 2011; Stahl et al., 2019), attention deficit hyperactivity disorder (ADHD; (Weber et al., 2011), and BPD (Witt et al., 2017). Recent studies have also revealed small yet meaningful genetic connections between BD and educational attainment (Stahl et al., 2019), creativity (Greenwood, 2020), and leadership (Kyaga et al., 2015). These findings led researchers to suggest that BD may exist on a spectrum of genetic

vulnerability, where quantitative differences in genetic factors contribute to a variety of mood, perception, and cognitive disorders rather than distinct categorical differences (Gordovez & McMahon, 2020). The observed genetic overlap between BD and the other mental health disorders may also suggest many variants likely influence multiple phenotypes which may be differentiated by phenotype-specific effect size distributions among the shared influencing variants (Mullins et al., 2021).

Notwithstanding the genetic basis, genetic testing with utility for the diagnosis of BD or its treatment is not currently validated or recommended and, instead, diagnosis remains a clinical endeavour as BD continues to be descriptive syndrome (McIntyre et al., 2020). However, genome-wide approaches may help navigate through the complex genetic landscape in an unbiased manner (Gordovez & McMahon, 2020). What emerges from the findings of genetic studies in BD are that BD is a heterogenous group of illness and that there are common genetic risk factors with schizophrenia and major depression and also with ADHD and BPD (Gordovez & McMahon, 2020). While high-risk alleles do exist, they are rare and nonspecific, and there is currently no evidence for monogenic forms of BD (Gordovez & McMahon, 2020). With the growing capability of GWAS studies to identify polymorphisms that confer a very small increased risk, it is essential to further investigate how these genes interact with environmental factors to trigger BD (Rowland & Marwaha, 2018). Incorporating ancestrally diverse samples in these studies could also enable improved identification of causal variants for the disorder (O'Connell et al., 2021).

1.4.1.2. Neurobiological Mechanisms

Functional and structural imaging studies of BD have revealed fronto-limbic functional abnormalities (Chen et al., 2011; Strakowski et al., 2005, 2012) and structural changes, such as lateral ventricle enlargement (Arnone et al., 2009; Kempton et al., 2009; McDonald et al., 2006).

Other studies also show small but robust differences in the volumes of some brain structures, notably decreases in hippocampus, amygdala and thalamus, white matter decrements, reduced cortical thickness (Hibar et al., 2016, 2018; Pezzoli et al., 2018; Wise et al., 2017), decreased glial density in the subgenual anterior cingulate cortex and calbindin-positive neuron density (Kloiber et al., 2020). A meta-analysis found deficits across set-shifting, inhibition, planning, verbal fluency, working memory, and sustained attention in euthymic BD patients compared to controls (Dickinson et al., 2017). Another meta-analysis looking at functional and structural magnetic resonance imaging studies investigating unaffected relatives and healthy controls demonstrated that increased brain volume and activation are present in unaffected relatives suggesting that these may represent intermediate phenotypes for BD (Cattarinussi et al., 2019). However, there is still no neuropathological correlates of BD of sufficient robustness, magnitude, and specificity, to be of clinical or diagnostic value (Harrison et al., 2020).

1.4.1.3. Environmental Risk Factors

Although BD have high heritability, there is evidence for environmental factors that can modify the onset and course of BD (Vieta et al., 2018). The literature on the role of environmental factors in BD is limited, but several environmental risk factors have been identified such as prenatal and perinatal risk factors, childhood adversity, and substance abuse.

Prenatal and perinatal risk factors

Whilst the hypothesis that prenatal and perinatal (i.e., time from pregnancy until 1 year after giving birth) factors could contribute to a later onset of BD is debated in the literature (Buoli et al., 2017), a recent meta-analysis has found four prenatal and perinatal factors that made individuals more likely to meet DSM (American Psychiatric Association) or ICD (World Health Organisation) criteria for a later BD diagnosis: peripartum asphyxia (i.e., peripartum deficiency in brain oxygenation), low birth weight (less than 2500 g),

maternal stress during pregnancy, and obstetric complications (Shintani et al., 2023). Exposure to substance use, perinatal infections (e.g., influenza and toxoplasma gondii), smoking during pregnancy, hormonal factors, perinatal exposure to oxytocin (Kloiber et al., 2020), and paternal age at birth (A. M. Rodriguez et al., 2018) are other suggested risk factors for BD but the results are inconsistent.

Childhood Adversity

In individuals suffering from severe mental disorders, childhood trauma is reported at a much higher rate (Aas et al., 2016). In relation to BD, individuals with BD are 2.6 times more likely to report having experienced childhood adversity when compared with a non-clinical control group (J. E. Palmier-Claus et al., 2016). Childhood maltreatment also predicts unfavourable clinical features and course of illness in BD such as greater mania severity, greater depression severity, greater psychosis severity, higher risk of comorbidity, earlier age at onset, higher risk of rapid cycling, greater number of manic episodes, greater number of depressive episodes, higher risk of suicide attempt (Agnew-Blais & Danese, 2016) and higher affective instability (Marwaha et al., 2016; Palmier-Claus et al., 2024)compared with those with BD without childhood maltreatment (Agnew-Blais & Danese, 2016). Additionally, a study showed that any form of childhood maltreatment (i.e., child abuse or child neglect) was significantly related to the diagnosis of at least one medical illness in BD but not unipolar depression (Hosang et al., 2018). Further, maltreatment in childhood may have implications for neurodevelopment in BD such as hippocampal subfield volumes (Janiri et al., 2019), estimated intellectual functioning (Martins et al., 2019), amygdala volume, prefrontal-limbic functional connectivity and uncinate fractional anisotropy (Souza-Queiroz et al., 2016), and lower integrity of white matter microstructure (Stevelink et al., 2018). Childhood physical abuse might also be involved in a poor future

response to lithium prophylaxis in BD (Etain et al., 2017). It is also found that less genetic risk may be needed to develop a more unstable form of BD when exposed to childhood maltreatment (Aas et al., 2020). Given the fact that childhood maltreatment is a well-known risk factor for developing more severe and complex form of BD (Marwaha et al., 2020), it is suggested that a coherent and comprehensive pathogenetic model of BD must also integrate the impact of trauma on the risk and course of BD (McIntyre et al., 2020).

Substance Misuse

Substance use disorders (SUDs) are present in up to 70% of patients BD and contribute to high rates of disability, morbidity, and treatment non-adherence (Gold et al., 2018). For instance, individuals with substance misuse have three times increased risk to develop BD (Rodriguez et al., 2021). Regarding the impact in terms of the type of substance, a recent systematic review found that cannabis use, nonmedical use of prescription medications, nicotine, and alcohol use were all risk factors for BD (Lalli et al., 2021). There is increasing evidence that cannabis use can act as a risk factor for the development of bipolar as well as psychotic disorders. A systematic review (Gibbs et al., 2015) identified several studies supporting a link between cannabis use and subsequent relapse of manic symptoms. Further, adolescent cannabis use may also be an independent risk factor for future hypomania (Marwaha et al., 2018).

1.5. Comorbidity in BD

The lifetime prevalence of psychiatric and medical comorbidities in adults with BD is estimated to be around 90% (Merikangas et al., 2007). Additionally, about 50% of individuals with BD experience polymorbidity, meaning that they have three or more comorbid conditions (Sylvia et al., 2015). Comorbidity in BD is linked to an earlier onset and a more complex presentation of the disorder, higher rates of suicidality, and a less favourable response to treatment (McIntyre et al., 2020).

1.5.1. Comorbid Psychiatric Illness in BD

Among BD comorbidities, anxiety disorders are one of the commonly encountered psychiatric comorbidity (Yapici Eser et al., 2018). According to a meta-analysis, any lifetime anxiety disorder comorbidity in BD was 40.5%, followed by panic disorder (18.1%), generalized anxiety

disorder (13.3%), social anxiety disorder (13.5%) and obsessive-compulsive disorder (9.7%; Yapici-Eser et al., 2018). However, a recent study looking at persistent anxiety symptoms across childhood and adolescence in a large community cohort did not find significant associations between persistent anxiety and hypomanic symptoms in young adulthood (Morales-Muñoz et al., 2023).

In addition to anxiety disorders, about 30–50% of adults with BD have either substance use disorder or alcohol use disorder (Messer et al., 2017). Behavioural addictions (e.g., pathological gambling, compulsive buying, sexual and work addictions) are also reported to be several folds more common in individuals with BD compared to controls (Di Nicola et al., 2010). Additionally, a systematic review looking at comorbidity between BD and BPD found that over a fifth of subjects showed comorbidity between BPD and BD (Frías et al., 2016).

Eating disorders are prevalent among people with BD as well, with binge eating disorder (BED) occurring in 12.5% of BD, Bulimia Nervosa (BN) in 7.4% of people with BD, and Anorexia Nervosa (AN) in 3.8% of people with BDs (Fornaro et al., 2021). Finally, regarding sex differences, women with BD have higher rates of anxiety and eating disorders than men, whereas men with BD are more likely to have simultaneous substance use disorders and alcohol misuse than women (Loftus et al., 2020).

1.5.2. Comorbid Neurodevelopmental Disorders

ADHD and BD are also highly comorbid; a recent systematic review and meta-analysis found that 1 in 13 patients with ADHD had BD and nearly 1 in 6 patients with BD were diagnosed with ADHD (Schiweck et al., 2021). There is also evidence for BD being highly prevalent in people diagnosed with autism (Kirsch et al., 2020); according to a recent meta-analysis, the pooled prevalence of BD in adults with autism is 7.5 % (Varcin et al., 2022).

1.5.3. Physical Health Problems

BD is linked to substantial morbidity and mortality (Kessing, Vradi, & Andersen, 2015), leading to an estimated reduction in life expectancy of 12–20 years for men and 11–17 years for women compared to the general population (Laursen et al., 2013). While individuals with BD have an

elevated risk of suicide (Plans et al., 2019), the primary factor contributing to their reduced life expectancy is the high incidence of medical comorbidities, particularly cardiovascular disease (Coello et al., 2019; Kessing et al., 2015). Other medical conditions that have been associated with risk of BD in addition to cardiovascular diseases are multiple sclerosis, stroke, systemic lupus erythematosus and endocrine disorders (Steel et al., 2014), subthreshold hypothyroidism (Mcintyre et al., 2004), autoimmune disorders, obesity, diabetes (Sayuri Yamagata et al., 2017).

1.6. Differential Diagnosis and Diagnostic Challenges in BD

Modern classifications of mental disorders still assume a categorical model which may be helpful in terms of reliability and communication among clinicians and researchers, but this approach raises serious concerns about diagnostic validity and boundaries between entities (Vieta & Phillips, 2007). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) and International Classification of Diseases, Eleventh Edition (ICD-11) are the most widely used classification systems in psychiatry representing a categorical understanding of mental health disorders. The DSM-5-TR and ICD-11 criteria for BD require at least one lifetime manic episode, whilst bipolar II disorder is defined by the presence of at least one hypomanic episode and one depressive episode (see Table 1). Mania is characterized by an elevated, expansive, or irritable mood such as mood elevation, grandiosity, impulsivity, risk-taking behaviour, restlessness, racing thoughts, reduced need for sleep, increased productivity, inflated self-confidence, impaired judgment, irritability, and agitation.

The differential diagnosis of BD includes other mental disorders characterised by impulsivity, affective instability, anxiety, irritability, cognitive disorganisation (e.g., inattention, distraction), depression, and psychosis (McIntyre et al., 2020). For example, although depression is usually the index presentation of BD (McIntyre et al., 2020), differentiating BD from major depressive

Table 1. Diagnostic criteria for Bipolar Disorder

Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision Criteria	**International Classification of Diseases, 11th Criteria**
Bipolar I disorder Criteria met for at least 1 manic episode, which might have been preceded or followed by a hypomanic episode or major depressive disorder; depressive episodes or psychosis do not have to be present for a diagnosis.	*Bipolar disorder* Characterised by two or more episodes in which the patient's mood and activity levels are considerably disturbed (i.e., elevation of mood and increased energy and activity [hypomania or mania] or lowering of mood and decreased energy and activity [depression]). Repeated episodes of hypomania or mania only are classified as bipolar.
Bipolar II disorder Criteria met for at least 1 current or past hypomanic episode and a major depressive episode.	*Cyclothymic disorder* Persistent instability of mood involving numerous periods of depression and mild elation that are not sufficiently severe or prolonged to satisfy a diagnosis of bipolar affective disorder or recurrent depressive disorder.
Cyclothymic disorder Hypomanic symptoms that do not meet the criteria for hypomania and depressive symptoms that do not meet the criteria for major depressive episodes in numerous periods (at least half of the time) for at least 2 years (1 year in those <18 years); criteria for major depressive, manic, or hypomanic episodes never met.	*Bipolar affective disorder, current episode hypomanic* The patient is currently hypomanic, and has had at least one other affective episode (hypomanic, manic, depressive, or mixed) in the past.

Other specified bipolar disorder Bipolar-spectrum phenomena that do not satisfy the criteria for bipolar I disorder, bipolar II disorder, or cyclothymic disorder (i.e., short-duration or low severity of hypomanic episodes, hypomanic episodes without a previous major depressive episode)	*Bipolar affective disorder, current episode manic without psychotic symptoms* The patient is currently manic, without psychotic symptoms, and has had at least one other affective episode (hypomanic, manic, depressive, or mixed) in the past.
Unspecified bipolar and related disorder Symptoms in the bipolar spectrum that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, but do not meet the full criteria for any of the disorders in the bipolar and related disorders diagnostic class	*Bipolar affective disorder, current episode manic with psychotic symptoms* The patient is currently manic, with psychotic symptoms, and has had at least one other affective episode (hypomanic, manic, depressive, or mixed) in the past.
	Bipolar affective disorder, current episode mild or moderate depression The patient is currently depressed, as in a depressive episode of either mild or moderate severity, and has had at least one authenticated hypomanic, manic, or mixed affective episode in the past.
	Bipolar affective disorder, current episode severe depression without psychotic symptoms The patient is currently depressed, as in severe depressive episode without psychotic symptoms, and has

	had at least one authenticated hypomanic, manic, or mixed affective episode in the past.
	Bipolar affective disorder, current episode severe depression with psychotic symptoms The patient is currently depressed, as in severe depressive episode with psychotic symptoms, and has had at least one authenticated hypomanic, manic, or mixed affective episode in the past.
	Bipolar affective disorder, current episode mixed The patient has had at least one authenticated hypomanic, manic, depressive, or mixed affective episode in the past, and currently exhibits either a mixture or a rapid alteration of manic and depressive symptoms. Excluding:single mixed affective episode
	Bipolar affective disorder, currently in remission The patient has had at least one authenticated hypomanic, manic, or mixed affective episode in the past, and at least one other affective episode (hypomanic, manic, depressive, or mixed) in addition, but is not currently suffering from any significant mood disturbance, and has not done so for several months.
	Other bipolar affective disorders

	Bipolar II disorder Recurrent manic episodes NOS *Bipolar affective disorder, unspecified* Manic depression NOS

disorder is one of the most common clinical challenges for most clinicians (McIntyre & Calabrese, 2019). Mania, and even more so hypomania, can be missed, as it is often not associated with subjective distress like depression and easily misinterpreted or misattributed by individuals (Berk et al., 2017). Other differential diagnoses to consider in people with possible BD are ADHD and BPD (McIntyre et al., 2019b). In fact, a recent study deployed 3 online surveys to gain an understanding of how clinicians are currently conducting a differential diagnosis in BD (McIntyre et al., 2019b). The poll respondents chose BPD as the most difficult to differentiate from BP-I, followed by unipolar depression and ADHD.

BPD is a mental health disorder characterized by extreme sensitivity to perceived interpersonal slights, inconsistent identity, intense and volatile emotionality and impulsive behaviours that are often self-destructive (Bohus et al., 2021; Gunderson et al., 2018). The DSM-5 outlines the following diagnostic criteria, requiring at least five of the following symptoms: emotional dysregulation, intense mood swings lasting a few hours to a few days, impulsivity, fear of abandonment, unstable relationships, chronic feelings of emptiness, inappropriate anger or difficulty controlling anger and paranoia or dissociative symptoms. Similarly, the ICD-11 classifies BPD under "Emotionally Unstable Personality Disorder (EUPD)", with two main subtypes: impulsive and borderline. The borderline subtype is characterized by intense and unstable interpersonal relationships, self-image instability, and self-destructive behaviour. BPD frequently co-occurs with BD, with significant symptom overlap (e.g., mood instability, impulsivity), making differential diagnosis complex (Chanen et al., 2016).

ADHD is a common neurodevelopmental disorder affecting between 5 and 8% of children (Asherson et al., 2016; Faraone et al., 2015; Faraone et al., 2021). Up to 65 % of patients continue to experience impairing symptoms into adulthood (Faraone et al., 2006). According to the DSM-5, the diagnosis requires: the presence of developmentally inappropriate levels of

hyperactive-impulsive and/or inattentive symptoms for at least 6 months; symptoms occurring in different settings (e.g., home and school); symptoms interfere with, or reduce the quality of, social, school, or work functioning; and no other disorder better explains the symptoms. The ICD-11 classifies ADHD as "Attention-Deficit Hyperactivity Disorder", with similar subtypes. Like BPD, ADHD frequently co-occurs with BD and have substantial symptom overlap (e.g., inattention, impulsivity, irritability).

Some research suggests that the diagnoses of ADHD and BPD are potentially comorbid and additional rather than diagnoses of exclusion (McIntyre et al., 2020; Perugi et al., 2016). However, it is also suggested that the high prevalence of psychiatric comorbidity in BD might, in some cases, reflect overlapping pathogenesis (McIntyre et al., 2020). In other words, what appears to be comorbidity in childhood, manifesting as ADHD, anxiety disorders, or both, might in fact be phenotypic

variant of BD rather than a discrete comorbid condition (i.e., heterotypic continuity; Mcintyre & Correll, 2014). For example, brain regions implicated in affective instability and cognitive function in BD are also implicated in ADHD and anxiety disorders (McIntyre et al., 2020). Additionally, there is genetic overlap between ADHD and BD (van Hulzen et al., 2017) and BPD and BD (Witt et al., 2017). Previous epidemiological research indicated that individuals with BD often have a history of psychopathology in childhood and adolescence that is broader than just having unipolar depression (Duffy et al., 2010). Lastly, ADHD and BPD in childhood have been associated with a greater risk for developing BD (Hosang et al., 2019; Meier et al., 2018; Winsper et al., 2020).

1.7. At-risk Mental Health States: Moving from Static to Dynamic Models of the Onset of Mental Disorders

Emerging evidence highlights the need for a developmental approach to BD. BD is potentially a neuroprogressive condition, resulting in treatment resistance and neuropsychological deficits (Kloiber et al., 2020; Yatham et al., 2024). Additionally, several studies indicate the existence of a prodromal stage before the onset of the illness (Duffy et al., 2019; Ratheesh et al., 2023). To integrate a longitudinal dimensional perspective into the diagnostic process, which would encompass the earliest phases of BD and inform treatment and prognosis, some researchers have proposed incorporating the staging model in psychiatry (Salagre et al., 2018).

Severe forms of mental disorders are typically preceded by a relatively non-specific period of symptoms, which are subthreshold in nature and of insufficient severity and clarity to justify a diagnosis (McGorry et al., 2018). Additionally, psychopathology is highly dynamic and changeable in nature; symptoms can vary substantially over time on a micro level (momentary and day-to- day) and a macro level (months and years; Nelson et al., 2017). The symptoms may

defy diagnostic boundaries, and these patterns of symptom development can differ substantially between individuals (Nelson et al., 2017). That is why, predictions based on single baseline assessments (i.e., static models of prediction) may not be fit for purpose (Nelson et al., 2017).

Despite the challenges posed by the current diagnostic classification systems of mental illness, researchers have made a significant step toward pre-emptive psychiatry and early intervention by developing the ultra-high risk (UHR) criteria (Hartmann et al., 2021). The UHR aims to identify young individuals at risk of experiencing a first episode of psychosis through a combination of attenuated or short-lived psychotic symptoms and/or trait vulnerability, independent of the thresholds established by DSM or ICD (Hartmann et al., 2021). The idea behind the UHR was that psychotic disorders typically have a precursor phase characterized by developing milder symptoms and subsequent functional decline, rather than emerging all of a sudden (Destrée et al., 2024). “Sub-threshold” versions of mental disorders which are not considered by psychiatric diagnostic systems, frequently precede later full syndrome disorders (McGorry et al., 2018). This development laid the groundwork for a clinical staging model, and numerous studies have demonstrated the relevance of these criteria not just for psychosis, but also for a range of other persistent and incident psychiatric disorders including BD, BPD, and unipolar depression (Hartmann et al., 2021). The results arising from these studies suggested that there is a possibility of a shared early pathway or what is called “pluripotent at-risk state” for psychiatric disorders; the early stages are non-specific, but the later stages of different mental illnesses can have divergent course and outcomes (McGorry et al., 2018).

Table 2. Comparison of complementary staging models of BD as proposed by Berk et al. (2007), Kapczinski et al. (2009) and Duffy (2014)

Stage	Berk et al. staging model	Stage	Kapczinski et al. staging model	Stage	Duffy et al. staging model
0	Increased risk of severe mood disorder (e.g., family history, abuse, substance use) No specific symptoms currently	Latent	Increased risk of bipolar disorder	0	Confirmed familial risk
1a	Mild or non-specific symptoms of mood disorder		Mood or anxiety symptoms without criteria for threshold BD	Stage 1	Positive family history + non-specific disorders and symptoms
1b	Prodromal features: ultra high risk				
2	First-episode threshold mood disorder	I	Well-defined periods of euthymia without overt psychiatric symptoms	Stage 2	Positive family history + minor mood disorder and/or clinically significant mood symptoms
3a	Recurrence of sub-threshold mood symptoms			Stage 3	Positive family history + major depressive disorder, single, or recurrent
3b	First threshold relapse	II	Symptoms in interepisode periods related to comorbidities		

3c	Multiple relapses	III	Marked impairment in cognition and functioning		
4	Persistent unremitting illness	IV	Unable to live autonomously owing to cognitive and functional impairment	Stage 4	A – Classical episodic bipolar disorder (BDI, II, NOS) with or without psychotic features in episodes and good quality of remission B – Bipolar disorder with residual symptoms: Reflecting burden of illness effects (addiction, medical comorbidity, non-optimal treatment) or A- Non-classical bipolar disorder (cyclic mania, mixed mania, BDI, II, NOS) typically not fully remitting and often attenuated psychotic symptoms B- Psychotic spectrum bipolar

					disorders (schizoaffective: poorly remitting) chronic fluctuating and cognitive and functional decline

1.8. The Importance of Prospective Studies to Identify Robust Risk Factors

To achieve prevention, it is necessary to predict those who might develop the disorder (Ratheesh et al., 2023). Similar to the idea of McGorry and colleagues' (McGorry et al., 2006), three traceable prognostic staging models for BD has been proposed due to the fact that there is growing evidence for a prodromal state and a progressive and deteriorating course for BD (see Table 1; Berk et al., 2007). These three models address staging from different perspectives and examine the BD phenomenon in different populations studied during different phases and viewed as complementary (Kupka et al., 2021). This variation also reflects the heterogeneity inherent in illness progression in BD (Kupka et al., 2021). The overall cumulative incidence of conversion from a prodromal stage to Bipolar Disorder can also highly vary. For example, a study looking at predictors of diagnostic conversion from unipolar depression to BD found a rate of 8.7% in females and 7.7% in males (Musliner & Østergaard et al., 2018).

Although different staging models have been proposed in BD, they still need to be better operationalized and validated by empirical research (Vieta et al., 2011) because there is still no consensus on what constitutes a high-risk state for developing BD (Saraf et al., 2021). To be able enhance the early intervention prospects in BD, there is a need to identify individuals displaying the earliest signs of sub-threshold presentations or other risk factors of BD (Geoffroy & Scott, 2017), which might precede more typical, adult forms of BD (Faedda et al., 2019). The results arising from these studies will also ultimately help refine current staging models. That is why, information about homotypic (i.e., symptom expressions overlapping with the diagnostic criteria for BD), heterotypic (i.e., symptom expressions not directly overlapping with the diagnostic criteria for BD) and other risk factors for BD (e.g., perinatal), derived from prospective studies are crucial and still needed (Marangoni et al., 2018).

Evidence indicates that many of the individuals who eventually meet diagnostic criteria for BD have had a variety of homotypic symptoms including mood lability, subsyndromal depression or

episodes of major depression, combination of subclinical hypomania with subclinical psychosis, cyclothymia, symptoms of elation or irritability, and especially their combination in youth as well as nonspecific heterotypic psychopathology, including anxiety, substance abuse, childhood ADHD and behavioural difficulties, or sleep disturbances (Berk et al., 2017; Faedda et al., 2019). In many of these prospective at-risk studies, subthreshold (hypo)manic symptoms have emerged as a key predictor of the development of (hypo)mania in community, clinical high-risk, and familial at-risk studies (Vieta et al., 2018). That is why, investigating hypomanic symptoms (i.e., symptoms that do not meet diagnostic criteria for hypomanic/manic episodes) in youth can aid early identification of individuals at high risk of BD (Hosang et al., 2019). This approach holds great promise because hypomanic and manic episodes are BD's defining feature (Hosang et al., 2022).

1.8.1. Limitations that need to be addressed

Most of these prospective at-risk studies looked at risk factors for BD through recruiting the offspring of BD parents. Notwithstanding the usefulness of these studies since BD is highly heritable (Duffy et al., 2019), these studies cannot always help clinicians in day-to-day practice (Geoffroy & Scott, 2017). This is because most youth presenting with BD seen in general settings do not have a parent or other close family member with BD (Geoffroy & Scott, 2017). Further, not all individuals with a positive family history convert to BD (Merikangas et al., 2014; Saraf et al., 2021). Additionally, as indicated previously, there is substantial variability in severity and clinical course of these symptoms, in the emergent course of BD and mental illness in general. That is why, psychiatric research may benefit from approaching psychopathology as a system rather than as a category, identifying dynamics of symptom change and variability and assessing symptomatology on a continuum (Nelson et al., 2017). Assessing symptomatology on

a continuum via examining the developmental variability in symptom levels prospectively, can help capture the complexities of emerging pathways and early illness course in BD better.

1.9. Evaluating Trajectories of BPD to BD

As stated previously, distinguishing BPD from BD is considered diagnostically difficult (Bayes & Parker, 2020). Differential diagnosis problems mainly emerge from overlapping symptoms such as dysphoric mood states, impulsivity, affective lability, self-harm and suicidality. Additionally, the two disorders share a genetic overlap (Witt et al., 2017) and there is substantial comorbidity between them (Zimmerman et al., 2021). Studies have therefore compared BD and BPD to identify key distinguishing features to aid differential diagnosis, describing the relationship between the two disorders in terms of their phenomenology, rather than their aetiology or pathogenesis (Chanen et al., 2016). Instead, investigating the early signs and symptoms in leading to the development of BD and BPD could be beneficial to clarify which symptoms are the most sensitive and specific markers of these disorders in young people.

Both BPD and BD become clinically prominent from puberty through to young adulthood (Chanen et al., 2016). Many of the risk factors associated with BPD are also risk factors for a later diagnosis of BD such as ADHD, depression, irritability, mood lability, disruptive behaviour disorders, substance abuse, impulsivity, and history of childhood trauma in childhood and adolescence (Chanen et al., 2016). However, despite various prospective studies, including systematic reviews and meta-analyses, looking at the developmental trajectories of BPD and BD onset, there were no existing meta-review of reviews collating evidence to understand the aetiology of BD and BPD. Understanding the developmental trajectories to BD and BPD can also help clinical staging models for BD and BPD become more sophisticated, leading to novel early intervention strategies (Chanen et al., 2016) and guide pathoaetiological research

(McGorry & Mei, 2021). This can also help identifying trans-diagnostic targets for intervention that are particularly relevant in youth mental health (Shah et al., 2020).

1.10. Evaluating Trajectories of ADHD to BD

As indicated previously, comorbidity of BD and ADHD is common (Bartoli et al., 2023). In fact, a meta-analysis found that ADHD is 1.7 times more common in people with BD compared to people with MDD (Sandstrom et al., 2021). Further, differential diagnosis between ADHD and BD remains a challenge (Marangoni et al., 2015). This is due to considerable overlap in the diagnostic criteria and associated features between the two disorders such as impulsivity, poor sleep, irritability, mood lability (Comparelli et al., 2022; Faraone & Larsson, 2019) and cognitive impairments (e.g., inattention, distractibility and task-related dorsal prefrontal hypo-frontality; Rubia, 2018; Zarp Petersen et al., 2022). The differential diagnosis is further complicated by the inter-episode cognitive deficits in BD as well as common subsyndromal mood states and phenomena such as mixed episodes and rapid cycling (Schiweck et al., 2021). The two disorders not only share symptomatic overlap but there is also shared genetic grounds between both disorders (O'Connell & Coombes, 2021; van Hulzen et al., 2017; Zhao et al., 2018). In addition to the genetic overlap, there is also a strong familial association which advocates in favour of a more systematic screening. In fact, ADHD is one of the most frequent non-bipolar conditions diagnosed in high-risk BD offspring samples (Lau et al., 2018). A recent meta-analysis also found that relatives of ADHD patients had an increased risk of BD and offspring of individuals with BD had a higher risk for ADHD (Khoury et al., 2023). Further, abnormal dopamine signalling likely plays a role in the cognitive impairments evident across BD and ADHD (Miskowiak et al., 2017). Considering all these, greater attention should be paid to trajectories of ADHD and their relationship to BD. However, since findings across studies looking at ADHD as a risk trajectory for developing BD are inconsistent (e.g., Arnold et al.,

2020; Brancati et al., 2021), further prospective studies are needed to elucidate this association particularly in large community cohorts with different statistical approaches that can capture developmental course of mental illness.

1.11. Evaluating Trajectories of Depression to BD

Examining trajectories of depression and their relationship to BD is also of particular interest for several reasons. As stated previously, bipolar depression is initially considered or misdiagnosed as MDD, and misdiagnosis is especially likely early in the illness course (Baldessarini et al., 2020). Further, bipolar depression is the leading cause of morbidity in patients with BD (McIntyre & Calabrese, 2019). Therefore, it is clinically very important to be able to detect bipolar depression and discriminate between it and unipolar depression.

As usually the index presentation of BD is depressive episodes with hypomania and mania presenting later (McIntyre et al., 2020; Vieta et al., 2018), longitudinal studies have also assessed the presence of symptoms of conversion from unipolar depression to BD. Meta-analyses looking at prospective follow-up studies which identified rates and characteristics predictive of transition to BD in people with MDD found that family history of BD, earlier age at onset of depression, presence of psychotic symptoms, gender, number of depressive episodes, treatment resistance to antidepressants, the prevalence of chronic depression, atypical features and severity of depression were predictive of transition to BD (Kessing et al., 2017; Ratheesh et al., 2017). However, the authors added that it was not possible to identify risk factors that were consistently or mainly confirmed to predict conversion across studies. Additionally, these prospective studies have been limited by measuring depressive symptomatology, using a binary classification (i.e., a snapshot of clinical state) and providing mainly diagnostic proportions or reporting mean symptom levels. Taken together, further prospective studies are needed to explore the phenomenology of depression and their relationship to BD.

1.12. Summary and rationale

As the above overview reveals, BD is highly heritable, disabling, and functionally impairing psychiatric disorder associated with substantial morbidity and mortality (McIntyre et al., 2020; Saraf et al., 2021). Aetiological pathways are still not clear, and the course of the disorder is highly heterogeneous between and within individuals throughout the developmental trajectory (McIntyre et al., 2022). The duration of untreated illness is high (Scott et al., 2022) and the disorder is often initially misdiagnosed, more often with unipolar depression, BPD and ADHD (McIntyre et al., 2019b).

Taken together, early intervention and prevention strategies are urgently needed, particularly because people with BD usually start to manifest mood symptoms in adolescence or young adulthood, making BD an ideal candidate for early intervention strategies (Vieta et al., 2018). To achieve this goal, several attempts have been made to define BD at-risk groups and to better understand and characterize the psychopathological conditions/risk trajectories arising in youth, which precede and lead to the development of BD (Faedda et al., 2019).

Prospective studies assessed potential risk phenotypes, implicated in the development of BD, mostly by following high-risk offspring of BD parents longitudinally. However, although BD offspring are at elevated risk for BD, a large proportion of people who develop BD do not have an affected first-degree relative (Van Meter et al., 2021b). Additionally, most of these prospective studies simply reported the mean symptom levels or diagnostic proportions for the sample at various follow-up times, which cannot capture the highly heterogeneous course of BD or mental health disorders in general. In order to advance current knowledge, further prospective studies in population-based community samples utilising more fine-grained approaches that can capture the long-term heterogenous course of emerging psychopathology across a developmental period and examine the association between these risk trajectories and BD are needed.

Lastly, due to the multidimensional nature of mental health problems (Scott et al., 2024), the current nosological system presents diagnostic, prognostic, and treatment challenges to clinicians. As stated before, aetiological pathways are not clear in BD and given the overlaps in the phenomenology and evolution of BD compared with BPD, there is a further need to understand systematically the common and differentiating developmental pathways in at-risk stages in both disorders.

1.13. Overall Aim and Objectives of the Thesis

The overarching aim of this PhD is to elucidate the developmental pathways to BD. The thesis comprises three studies to achieve this aim. Specific aims of each of the research studies are described below.

In order to achieve these three aims, two main methodologies were utilised; a) synthesising the available evidence in systematic reviews and meta-analyses pertaining to developmental risk trajectories associated with the risk of developing BD and comparing and contrasting these with the developmental risk trajectories associated with the risk of developing BPD; b) utilising a longitudinal population sample to examine whether and which ADHD and depression symptoms trajectories in childhood and adolescence confer risk for developing clinically significant hypomanic symptoms in young adulthood.

Study one: Understanding the development of bipolar disorder and borderline personality disorder in young people: a meta-review of systematic reviews (Chapter 2)

There are many systematic reviews and meta-analyses looking at risk factors related to emerging BD and BPD (e.g. Ratheesh et al., 2017; Stepp et al., 2016). However, none of them have compared BD and BPD at-risk populations concurrently. To be able to make this comparison, a meta-review of reviews to synthesize the available evidence was conducted. Findings from the

review also informed the aims, objectives, and outcomes for the subsequent chapters (Chapter 4 and 5) of the PhD.

Aim: To understand the differences and similarities in developmental pathways to these disorders.

Research Questions:

- Which developmental risk trajectories are associated with the early course of *BD* symptoms, features, or onset?
- Which developmental risk trajectories are associated with the early course of *BPD* symptoms, features, or onset?
- Which developmental risk trajectories are common between the two disorders?
- Which developmental risk trajectories are distinct between the two disorders?

This paper has been published in *Psychological Medicine.*

Study two: ADHD symptom trajectories across childhood and early adolescence and risk for hypomanic symptoms in young adulthood (Chapter 4)

Evidence suggests that ADHD precedes BD (Hosang et al., 2019). However, most studies have measured ADHD symptoms at only one time point, or provided one-off sampling of cross-sectional data (i.e., a snapshot of clinical state), not capturing the highly dynamic changes evident in ADHD presentation.

Primary Aim: To characterize ADHD symptom trajectories across childhood and adolescence from age 8 to 13 in ALSPAC, and to describe their prospective associated risk for subsequent clinically significant hypomanic symptoms assessed between 21-23 years old.

Secondary Aim: To distinguish inattention from hyperactivity to further examine the origins of the ADHD-BD overlap and investigate the prospective relationship between subtypes of ADHD (hyperactivity and inattentive symptoms) and clinically significant hypomanic symptoms

Research Questions:

- Are different trajectories of ADHD symptoms in childhood and early adolescence associated with risk of clinically significant hypomanic symptoms?
- Are different trajectories of inattentive symptoms in childhood and early adolescence associated with risk of clinically significant hypomanic symptoms?
- Are different trajectories of hyperactivity symptoms in childhood and early adolescence associated with risk of clinically significant hypomanic symptoms?

This paper is under review in *European Psychiatry.* Submitted on 29/09/2024.

Study three: Depression symptom trajectories across adolescence and risk of hypomanic symptoms in young adulthood: A UK Birth Cohort Study (Chapter 5)

Depression has been identified as a risk factor for BD (Kessing et al., 2017; Ratheesh et al., 2017). However, most studies have measured depressive symptoms at either only one time point or provided either mean symptom levels or diagnostic percentages. Parsing the heterogeneity in the course of depression and identifying which course trajectories are associated with clinically hypomanic symptoms have the potential to change how we understand the phenomenology of bipolar depression. Further, potential underlying mechanisms of these associations should be investigated.

Primary Aim: To investigate heterogeneity in trajectories of depression symptoms in adolescence in ALSPAC cohort, from age 10.5 until 16.5 years and examine the relationship

between different depression course trajectories and the risk for subsequent clinically significant hypomanic symptoms in young adulthood.

Secondary Aim: To explore the potential mediating role of atypical depression features and psychotic symptoms on the prospective associations between observed depressive symptom trajectories and risk of hypomanic symptoms.

Research Questions:

- Which trajectories of depression symptoms in adolescence are associated with risk of hypomanic symptoms in young adulthood?
- Do atypical depression symptoms mediate these associations?
- Do psychotic symptoms mediate these associations?

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Chapter 2

Understanding the development of Bipolar Disorder and Borderline Personality Disorder in young people: A meta-review of systematic reviews

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Abstract

Background: There is ongoing debate on the nosological position of Bipolar Disorder (BD) and Borderline Personality Disorder (BPD). Identifying the unique and shared risks, developmental pathways, and symptoms in emerging BD and BPD could help the field refine aetiological hypotheses and improve the prediction of the onset of these disorders. This study aimed to: a] systematically synthesise the available evidence from systematic reviews and meta-analyses concerning environmental, psychosocial, biological, and clinical factors leading to the emergence of BD and BPD ; b] identify the main differences and common features between the two disorders to characterise their complex interplay and, c] highlight remaining evidence gaps.

Methods: Data sources were; PubMed, PsychINFO, Embase, Cochrane, CINAHL, Medline, ISI Web of Science. Overlap of included SRs/MAs was assessed using the corrected covered area process. The methodological quality of each included SR and MA was assessed using the AMSTAR.

Results: 22 systematic reviews (SRs) and meta-analyses (MAs) involving 249 prospective studies met eligibility criteria. Results demonstrated that family history of psychopathology, affective instability, attention deficit hyperactivity disorder, anxiety disorders, depression, sleep disturbances, substance abuse, psychotic symptoms, suicidality, childhood adversity and temperament were common predisposing factors across both disorders. There are also distinct factors specific to emerging BD or BPD.

Conclusions: Prospective studies are required to increase our understanding of the development of BD and BPD onset and their complex interplay by concurrently examining multiple measures in BD and BPD at-risk populations.

2.1. Introduction

Differential diagnosis between Bipolar Disorder (BD) and Borderline Personality Disorder (BPD) is often difficult due to the high frequency of comorbidity and overlap of symptoms between the two disorders (Baryshnikov et al., 2015). The prevalence of BD and BPD was 21.6%; and 18.5% respectively (Fornaro et al.,2016). There is an ongoing debate over whether BPD should be considered as part of the spectrum of BD disorders (Akiskal, 2004; Benazzi, 2006; Deltito et al., 2001; McGlashan, 1983; Zimmerman, Ruggero, & Young, 2009) or not (Bassett et al., 2017; Paris & Black, 2015).

Although BD and BPD are defined as distinct psychopathologies in Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) and International Classification of Diseases (ICD; World Health Organisation, 2015), there are many common features between these disorders that contribute to diagnostic confusion. The common features that are frequently stated in the literature are affective instability (AI), impulsivity, troubled relationships, distractibility, irritability, suicidality, flight of thoughts and childhood adversity (John & Sharma, 2009). The clinical evidence against for the existence of a "bipolar-borderline continuum" argue that although there are common symptoms between the two, they present these traits differently (e.g., Henry et al., 2001; Renaud, Corbalan, & Beaulieu, 2012). However, in practical terms these distinctions are far from clear, particularly when there is no history of manic episodes (Sanches, 2019). For instance, differences in intensity or frequency might exist when comparing the two conditions for AI, but it is also unclear whether the anger and anxiety that BPD patients experience are distinct in nature than the mood experienced in a dysphoric or irritable manic state (MacKinnon & Pies, 2006). A concern that has compounded these issues is the increasing recognition that mood can be highly variable in people with bipolar

disorder outside of frank manic or depressive episodes, a move away from the traditional view of euthymia in bipolar disorder (Bonsall, Wallace-Hadrill, Geddes, Goodwin, & Holmes, 2012).

There is also ambiguity of the relationship between impulsiveness and the diagnostic syndromes between BD and BPD. Impulsivity is considered to be a stable symptom of BPD diagnosis like AI (Wilson & Stanley, 2007). However, Zanarini, Frankenburg, Hennen, Reich, and Silk (2005) in their longitudinal study found that impulsive traits were likely to remit in the future in BPD patients. On the contrary, although impulsivity is considered to be episodic in nature in BD, Swann, Pazzaglia, Nicholls, Dougherty, and Moeller (2003) found that impulsivity had both state and trait related aspects in BD patients.

Practitioners are facing challenges when they attempt to classify the symptoms of these disorders based on the DSM's and ICD's classifications because these disorders sometimes do not fall clearly into state- and trait- like categories resulting in under, over or misdiagnoses (Ruggero, Zimmerman, Chelminski, & Young, 2010; Wilson & Stanley, 2007; Zimmerman, Ruggero, Chelminski, & Young, 2008). Investigating the early signs and symptoms in leading to the development of BD and BPD could be beneficial to clarify which symptoms are the most sensitive and specific markers of these disorders in young people. Whilst these studies will help determine their pathogenesis, they could also let us understand whether they are distinct clinical entities. Additionally, young people's affinity to impulsive and self-harming behaviour places them at-risk for adverse health outcomes (Kaess, Brunner, & Chanen, 2014). Both BD and BPD are associated with severe impairment in psychosocial functioning and a high suicide rate (Zimmerman et al., 2014). The risk for suicide among individuals diagnosed with BD are up to 20-30 times greater than that for the general population (Pompili et al., 2013) while the lifetime suicide rate for BPD is estimated to be 8% (Pompili, Girardi, Ruberto, & Tatarelli, 2005). Thus, it is critically important

to synthesise and evaluate the current evidence which examine the interaction between environmental, biological, sociocultural, and clinical precursor signs and symptoms and their relationship to onset of BPD and BD diagnosis.

Many studies, including systematic reviews (SRs) and meta-analyses (MAs), have examined factors related to emerging BD and BPD (e.g., Ratheesh et al., 2017; Stepp, Lazarus, & Byrd, 2016). However, none of them compared BD and BPD at-risk populations concurrently, probably because there is still no consensus around BD prodrome and emerging BPD traits (Berk et al., 2007; Chanen & Kaess, 2011; Skjelstad, Malt, & Holte, 2010). Thus, a meta review of reviews approach to synthesising this evidence was adopted to be able to make this comparison. By synthesising the evidence now, future studies can investigate these common and distinct features cross-diagnostically in at-risk BD and BPD populations to provide better clinical diagnosis and treatment.

The aim of this review is to systematically assess SRs and MAs from prospective studies on factors that are associated with the early course of BD and BPD symptoms, features, or onset to be able to understand the differences and similarities in developmental pathways to these disorders and to determine whether they are two distinct clinical entities or belong on a continuum within the affective spectrum.

2.2. Methods

Protocol and registration

The protocol was registered with PROSPERO in January 2021 (registration no. CRD42021235193).

Search Strategy

The most current version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting systematic reviews Moher et al.'s (2015)

guidelines were used as a framework (Page et al., 2021). An extensive search of papers catalogued in Embase, PsychINFO, PubMed, CINAHL, COCHRANE, ISI Web of Science, Medline databases was conducted in January 2021. Search terms were agreed by the authors following a scoping search. The terms were then modified following advice from a librarian and field experts. The search was conducted by combining six groups of terms using medical subject headings (MeSH) and text words (see Supplementary) relating to; Borderline Personality Disorder (e.g., 'borderline personality'), Bipolar Disorder (e.g., 'bipolar disorder'), risk factors/onset (e.g., 'develop*' OR risk*), longitudinal studies (e.g., 'prospective study'), youth (e.g., 'young adult') and systematic reviews/meta-analyses (e.g., 'systematic review'). In addition, we hand searched 10 specialty journals and reference lists. We also examined the first 30 pages in Google Scholar using the terms 'bipolar AND borderline personality AND systematic review'. The search was updated in February 2022.

Eligibility criteria

Inclusion criteria were:

1) SRs or MAs containing at least one relevant prospective study with at least 2 structured clinical assessments and diagnostic outcome at follow-up of BD or BPD onset, prodrome, features or symptoms
2) Measure the precursor and/or vulnerability factor related to the BD/BPD outcomes prior to the outcome assessment of BD or BPD
3) Include a clinical, high-risk or community population
4) Include studies that assess BD or BPD through fully, semi-, or unstructured interviews administered by mental health professionals, symptom checklists, self-reports, interviews, or self-reported questionnaires that are based on standard classification systems such as,

the International Classification of Diseases (ICD; World Health Organisation, 2015) or the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013)

5) Include studies reporting group comparisons between participants with BD or BPD and healthy or clinical control on any factor related to the BD or BPD outcome

Exclusion criteria were:

1) Reviews including only intervention, cross-sectional, or other studies where the exposure was collected retrospectively and no relevant prospective study

2) Dissertation papers, books, book chapters, editorials, letters, or conference proceedings

3) Reviews including studies that were not reporting precursors of transitions or symptoms/features

4) Genetic studies

5) Full text of the manuscript is not available

Study selection and data management

A bespoke data extraction form was developed in Microsoft Excel prior manuscript review. Two independent authors (BD, NA) performed all the initial screening steps on the pre-defined eligibility criteria, and disagreements were solved through discussion with a third reviewer (SM). No publication or language restrictions were applied. Title and abstract screening were conducted using the Endnote X9 reference management tool for full text retrieval. Authors independently searched the full-text articles for inclusion in the review. BD and NA managed and extracted relevant data in duplicate from each eligible study on the extraction form relating to relevant study information (e.g., sample characteristics, aims, number of databases sourced and searched, type of

factor studied and outcomes) and risk of bias quality assessment. The results of the extracted data were then cross-checked.

Risk of Bias Assessment

Two authors (BD, NA) independently assessed the methodological quality of each included SR and MA using the Assessment of Multiple Systematic Reviews (AMSTAR; Shea et al., 2007).

Data synthesis and analysis

Data were qualitatively synthesized within the review as the data were not suitable for quantitative synthesis due to the high heterogeneity among reviews

Overlapping Data

Overlap of included SRs/MAs was assessed using the corrected covered area (CCA; Pieper, Antoine, Mathes, Neugebauer, & Eikermann, (2014). Pieper et al.'s (2014) protocol according to $CCA = \frac{N-r}{rc-r}$ was followed, where N is the total number of included studies in SRs/MAs (including double counting), r is the number of primary studies, and c is the number of SRs/MAs. Overlap thresholds were used for interpretations of overlapping data; 0–5%—slight, 6–10%—moderate, 11–15%—high, >15%—very high (Pieper et al., 2014). For each disorder, a citation matrix and pairwise CCA tables were provided to address the overlap.

2.3. Results

Description of studies

As shown in the PRISMA flow chart (Figure 1), the literature search yielded 1485 records, 1073 were screened after duplication and 89 retrieved in full text. 66 articles were subsequently excluded with reasons (see Supplementary Table S5) leaving 22 SRs and MAs to be synthesised in this systematic review of reviews.

Supplementary Table S1 and Table S2 summarise the main characteristics of the 22 eligible SRs/MAs. The studies were published between 2011 and 2022. Nine studies are SRs and MAs, ten studies conducted systematic review of the literature with narrative syntheses of the results, and three performed meta-analyses. The 22 reviews varied by population and outcomes.

In BD at-risk studies, three reviews studied individuals with depression who later showed (hypo)manic symptoms, six reviews studied individuals who developed BD at follow-up or at-risk for BD, six reviews studied high-risk offspring of BD and two reviews studied BD cohort with a recent first episode of mania. Three studies examined multiple factors, one examined suicidality, one examined cannabis use, one examined aberrancy in white matter, one examined grey matter changes, one examined childhood adversity, four examined sleep alterations, one examined development of BD in patients with ADHD and three examined family history of BD.

In BPD at-risk studies, two studied individuals who showed BPD symptoms or features or diagnosed with BPD at follow-up and three studied individuals diagnosed with BPD at baseline or showed BPD features, symptoms or diagnosed with BPD at follow-up. Three studies examined several factors related to BPD outcomes, one examined neurobiological correlates and one examined sleep profile.

Primary Studies

Within the 22 systematic reviews, there were 678 primary studies of which 249 met the eligibility criteria for this systematic review of reviews (see Supplementary Table S1 and Table S2 for the number of relevant prospective studies synthesised for each study). The other 428 primary studies were excluded mostly because they were not prospective studies, or the participants had a full-syndromal diagnosis at the first intake. In BD studies, there were 2418329 participants across all included primary studies, of whom 127706 were included in this review.

BPD studies included 125406 participants in total, of whom 82015 were eligible to include in this review. The methodology applied here is in line with Prousali et al.'s (2019) overview of reviews.

Overlapping Data for BD and BPD Studies

The 17 included SRs and MAs for BD comprised 250 overlapping individual studies, of which 145 were unique. Five included SRs and MAs for BPD comprised 74 overlapping individual studies, of which 64 were unique. A citation matrix presenting all the included SRs and MAs on BD and BPD in columns and index publications in rows and pairwise CCA tables are provided in Supplementary Table S8, Table S9, Figure S1 and Figure S2.

$$\text{CCA} = \frac{\text{N}-\text{r}}{\text{rc}-\text{r}} = \frac{(250-145)}{(145\times22-145)} = \sim 0.03\ \%$$ Slight Overlap for BD studies

$$\text{CCA} = \frac{\text{N}-\text{r}}{\text{rc}-\text{r}} = \frac{(74-64)}{(64\times5-64)} = \sim 0.04\ \%$$ Slight Overlap for BPD studies

As CCA is estimated at %0.03 for BD studies and 0.04 for BPD studies, the overlap is in the low range reflecting a low risk of skewed reporting (Pieper et al., 2014).

Assessment of methodological quality

Based on the findings from AMSTAR ratings that were performed to evaluate the methodological quality of the included SRs/MAs, the majority of the reviews were deemed to be high quality (see Supplementary Table S1 and Table S2, full assessments provided in Supplementary Table S6 and Table S7).

Synthesis of results

Supplementary Table S3 and Table S4 summarises the findings of SRs/MAs, respectively. A summary of the shared factors in emerging BD and BPD can be seen in Table 2. The evidence for developmental precursors that are prospectively related to BD and BPD outcomes are presented below except for the vulnerability factors which can be found in the Supplementary.

Here we define the precursors (e.g., clinical symptoms, signs or syndromes, prodromes, biomarkers) and vulnerability risk factors (e.g., gender, family history of psychopathology, childhood adversity) as prospectively identified variables that increase the odds of later BD onset, BPD onset or features.

At-risk BD reviews differed in how they defined at-risk BD; the participants were either at familial (e.g., offspring of BD) and/or clinical risk (e.g., youth with subthreshold mania) for BD stages either at 0, 1a, 1b, or 2 (see Table S1). At-risk BPD reviews did not define an at-risk state for BPD but examined papers which included community or clinical samples who had BPD symptoms, features, or diagnosis at follow-up assessment (see Table S2).

Biological Factors

Three reviews reported data regarding differences in the white matter in a high-risk population (Hu, Stavish, Leibenluft, & Linke, 2020), neural reward circuit dysfunction (Bart, Titone, NG, Nusslock, & Alloy, 2021) and longitudinal grey matter changes following first episode mania (Cahn, Keramatian, Frysch, Yatham, & Chakrabarty, 2021) compared to healthy controls. Hu et al. (2020) indicated that the trajectory of fractional anisotropy reduction did not differ significantly between high-risk young adults and controls. Cahn et al. (2021) found that adolescents with mania fail to exhibit normal increases in amygdala volume. No comparable studies were available for BPD. According to Bart et al.'s (2021) findings, lower right ventral striatum–left caudal anterior cingulate functional connectivity to loss and greater right pars orbitalis–orbitofrontal cortex functional connectivity to reward may be trait-level neural markers that may reflect risk for BD in at-risk youth. Additionally, lower parietal cortical thickness may lead to lower executive functioning and emotional regulation capacity and predispose to higher future mixed/mania and irritability.

Clinical Factors

Suicidality

Two reviews provided evidence for the association between suicidality and transition to BD (Cardoso, Mondin, Azevedo, Toralles, & de Mattos Souza, 2018; Ratheesh et al., 2017). Both reviews reported inconsistent results for the association between suicidality and later BD onset; out of seven individual studies they included, only four found a significant association between suicidality and later BD.

For BPD, two reviews assessed this association. Stepp et al. (2016) found consistent prospective associations between suicidality and later BPD symptoms, whereas Winsper et al. (2016a) found suicidal ideation in adolescence was not stable after post-hospitalisation.

Affective Instability

Data regarding the effect of AI on risk for BD was provided by three reviews (Faedda et al., 2015; Keramatian, Chakrabarty, Saraf, & Yatham, 2021; Ratheesh et al., 2017). All three studies found that AI predicted BD onset.

For BPD, both Stepp et al. (2016) and Skabeikyte and Barkauskiene (2021) found that AI and other negative affectivity symptoms such as emotionality and aggressiveness/tantrums predicted increases in mean levels of BPD features through adolescence.

Depression

Three reviews studied the relationship between depression and BD (Faedda et al., 2015; Ratheesh et al., 2017; Keramatian et al., 2021). They found that major depressive episodes, unipolar depression, depressive disorders NOS, mild depressive episodes, early onset of depression, longer and higher number of depressive episodes, greater loading of depressive symptoms, and higher recurrence rates, severity of depression, guilt, psychomotor retardation

and AI coexistent with MDD predicted transition to BD. There was also a significant association between age of onset of depression and later BD. The associations for recurrent MDD, chronicity of depression, atypical feature, hypersomnic-retarded depression, and conversion to BD was inconsistent.

For BPD, two reviews found significant association between depression and later BPD (Stepp et al., 2016; Skabeikyte & Barkauskiesne, 2021). Additionally, decreases in depression severity predicted faster declines in average levels of BPD symptoms.

Subsyndromal Hypomania

Evidence regarding hypomanic symptoms was available from three reviews for BD (Faedda et al., 2015; Keramatian et al., 2021; Ratheesh et al., 2017). They found that higher scores on Hypomanic Personality Scale (HPS), lifetime subsyndromal hypomanic symptoms and the combination of subclinical mania with subclinical psychosis at baseline significantly predicted transition to BD. Keramatian et al. (2021) also reported association between antidepressant associated subthreshold hypomanic episodes and transition to BD. No comparable studies were available for BPD.

Cyclothymia and Bipolar NOS

Faedda et al. (2015) and Keramatian et al. (2021) indicated earlier onset Bipolar NOS predicted conversion to BD. Similarly, cyclothymic disorder and hyperthymic temperaments significantly predicted diagnoses of BD. No comparable studies were available for BPD.

Psychosis and Psychotic Symptoms

Two reviews assessed the associations between psychotic symptoms and later BD (Faedda et al., 2015; Ratheesh et al., 2017). They demonstrated that psychotic features significantly predicted conversion to BD. Higher conversion rates to BD were also found in people with

psychosis NOS, schizotypal features, and schizophrenia nuclear symptoms but the results were inconsistent.

Only one review indicated significant associations between psychotic symptoms and later BPD (Stepp et al., 2016).

Substance Use

Three reviews investigated the association between SUD and conversion to BD (Gibbs et al., 2015; Keramatian et al., 2021; Ratheesh et al., 2017). Gibbs et al. (2015) and Keramatian et al. (2021) reported consistent significant associations between cannabis use and hypo/sub-threshold mania symptoms. The magnitude of this relationship was small to medium. Ratheesh et al. (2017), on the other hand, reported inconsistent results among studies examining the association between SUD and later BD.

Three reviews assessed the associations between SUD and later BPD symptoms (Stepp et al., 2016; Winsper et al., 2016a; Skabeikyte & Barkauskiene, 2021). Skabeikyte and Barkauskiene (2021) indicated that SUD was predictive of changes in BPD features during adolescence whereas, Stepp et al. (2006) and Winsper et al. (2016a) found significant associations.

Antidepressant Use

The association between antidepressant use and later BD was examined in two reviews; while Ratheesh et al. (2017) reported a non-significant relationship, Keramatian et al. (2021) found that exposure to antidepressants during follow-up was associated with increased risk of conversion. However, the evidence was available from only one primary study. No comparable studies were available for BPD.

Comorbidity with Internalising and Externalising disorders

Data regarding the association between comorbid disorders and later BD was available from three reviews (Brancati, Perugi, Milone, Masi, & Sesso, 2021; Keramatian et al., 2021; Ratheesh et al., 2017). Ratheesh et al. (2017) found comorbid social phobia and comorbid attention deficit hyperactivity disorder (ADHD) significantly predicted later BD onset. Results for comorbid generalised anxiety disorder and comorbid anxiety disorders as a group were inconsistent. Brancati et al. (2021) indicated a significantly greater risk of BD occurrence in ADHD patients versus healthy controls. Keramatian et al. (2021) found that anxiety disorders predicted conversion to BD in youth.

Evidence concerning the comorbidity with other mental health illnesses and later BPD symptoms were examined in three reviews (Skabeikyte & Barkauskiene, 2021; Stepp et al., 2016; Winsper et al., 2016a). They indicated childhood inattention, oppositional behaviour, anxiety symptoms, ADHD, somatisation significantly predicted the new onset of BPD and BPD symptom changes. They also reported significant associations between dissociation, conduct disorder, oppositional defiant disorder, depression, and later BPD symptoms. Individual social and physical aggression in childhood and comorbid obsessive compulsive disorder, on the contrary, did not predict BPD symptom changes.

Temperament/Personality Traits

Evidence regarding temperament in BD at-risk populations was available from one review (Keramatian et al., 2021). They found key symptoms to identify children with BD from well children in cohort samples; sensitivity, hyper alertness, anxiety/worry, somatic complaints, bold/intrusive, excessive talking, talking too loudly, decreased sleep, and impaired role in school.

Two reviews assessed the association between temperament/personality and later BPD (Skabeikyte & Barkauskine, 2021; Stepp et al., 2016). Low levels of sociability, high levels of

emotionality, activity and shyness in childhood, poor self-control, experiential avoidance, and disturbances in self-representation predicted later BPD symptoms.

Attachment

One review reported associations between attachment style and later BPD symptoms (Stepp et al., 2016). They indicated that disorganised/controlling behaviour in childhood and insecure attachment in peer relationships predicted BPD symptoms in adolescence. The results for attachment disorganisation and security in infancy and toddlerhood and later BPD symptoms were inconsistent. No comparable data were available for BD.

Impulsivity

Two reviews reported associations between impulsivity and later BPD symptoms (Skabeikyte & Barkauskine, 2021; Stepp et al., 2016). They demonstrated that impulsivity (e.g., effortful control, low self- control, and low constraint) was predictive of BPD symptoms and new onset of BPD in adolescence. No comparable evidence was available for BD.

Sleep Disturbances

Evidence regarding the association between sleep disorders and the risk of developing BD were available from five reviews (Keramatian et al., 2021; Pancheri et al., 2019; Ritter, Marx, Bauer, Lepold, & Pfennig, 2011; Scott, Kallestad, Vedaa, Sivertsen, & Etain, 2021; Scott et al., 2022). Pancheri et al. (2019) and Ritter et al. (2011) indicated that the offspring of patients with BD had sleep problems more frequently compared to not-at-risk offspring with a 30-fold increased risk to develop. The high-risk offspring with poor sleep were also more likely to develop BD. Keramatian et al. (2021), Scott et al. (2021), and Scott et al. (2022) found that individuals with a history of any type of sleep disturbance had an increased odds of developing BD.

Only one review reported associations between sleep problems and later BPD (Winsper et al., 2017). They found that chronic nightmares and chronic sleep disturbances were significantly associated with later BPD.

Disruptive Behaviour Disorders (DBD)

DBD was associated with subsequent manic, mixed, or hypomanic episodes in one BD at-risk review (Keramatian et al., 2021). No comparable studies were available for BPD at-risk.

2.4. Discussion

To the best of our knowledge, this is the first meta review of reviews aiming to understand the developmental pathways of BD and BPD, disorders that share some phenotypic features that could imply an overlap of aetiological mechanisms. 22 eligible reviews provided significant data about the factors which might contribute to the onset of BD or BPD. The current meta-review demonstrates that there are many "distinct" clinical, environmental, psychosocial, and biological variables that can be found early in the course of BD and BPD, even in at-risk stages, but the disorders share a variety of clinical and vulnerability factors too. However, since these "distinct" variables are evident only either in BD or BPD at-risk reviews, their distinctive value is speculative until further systematic longitudinal studies examine these factors in both disorders.

A notable and critical limitation of the literature is there were no studies comparing BD and BPD at-risk populations at the same time, compounding the difficulty of understanding specific BD or BPD developmental trajectory. Additionally, the neurobiological data from the BD at-risk studies are currently limited and there are no comparing studies done in BPD at-risk populations. This is why despite many previous commentary pieces on this issue (Bassett, 2012; Bayes et al., 2015; Deltito et al., 2001; Massó Rodriguez et al., 2021; Paris, 2004; Sanches, 2019;

Smith, Muir, & Blackwood, 2004; Stone, 2006; Zimmerman & Morgan, 2013a; Zimmerman & Morgan, 2013b), in reality at the current time it is not possible to answer whether these disorders should be on the same affective continuum, or they should be regarded as separate nosological conditions.

Gender, differences in the white matter, changes in the amygdala, neural reward circuit dysfunctions, DBD, subsyndromal hypomania, cyclothymia or bipolar NOS, frequency and loading of affective symptoms, and antidepressant use were factors examined only in BD studies. Only changes in the amygdala, neural reward circuit dysfunctions, subdyndromal hypomania, cyclothymia or bipolar NOS, frequency and loading of affective symptoms consistently predicted BD transition. Interestingly there was no data available for emerging BPD for cyclothymia although previous research comparing participants with BD and BPD found that participants with BPD too show similar or even higher levels of abnormal cyclothymic temperament (Eich et al., 2014; Nilsson, Jørgensen, Straarup, & Licht, 2010). Previous evidence also shows that hypomanic days were reported frequently in both the BD and BPD subcohort (Socada, Söderholm, Rosenström, Ekelund, & Isometsä, 2021). However, based on our findings while hypomanic symptoms predicted BD onset (Faedda et al., 2015), there was no data pertaining to BPD onset. Likewise, accumulated evidence shows BD patients demonstrated enlarged amygdala (Soares & Young, 2016) while BPD patients showed decreased amygdala volumes (Perez-Rodriguez et al., 2018). Our results are not in accordance with these results because according to Cahn et al.'s (2021) findings, adolescents with mania failed to exhibit normal increases in amygdala volume. It is interesting that studies of people who are at-risk of developing BD has showed decreased in amygdala volumes while previous studies with BPD populations have also showed the same results. However, since there was no data on amygdala

changes or hypomania symptoms in participants with BPD features, it is not possible to conclude at the moment whether both at-risk populations fail to exhibit normal increases in amygdala or hypomania is a shared feature.

Hu et al. (2020) indicated that differences in white matter integrity between high-risk individuals and control could occur in earlier childhood. This is consistent with a systematic review (Serafini et al., 2014) which found reduced corpus collosum volume and increased rates of deep white matter hyperintensities were more specific to paediatric BD in comparison to unipolar depression. There is however a need to replicate these findings with future longitudinal follow-up studies in both at-risk populations.

Amongst the factors examined in relation to transition to BD, the greatest amount of evidence was for family history of BD. Although inconsistencies in results were present in family history of BD studies (Keramatian et al., 2021; Lau et al., 2017; Narayan, Allen, Cullen, & Klimnes-Dougan, 2013; Rasic, Hajek, Alda, & Uher, 2013; Ratheesh et al., 2017), some studies suggest that there might be a relative specificity of family history of BD to predicting later BD in MDD samples (Ratheesh et al., 2017; Vandeleur, Merikangas, Strippoli, Castelao, & Preisig, 2013). Likewise, the evidence in the current review was also inconsistent as some of the individual studies found a significant relationship between a family history of other mental illnesses (i.e., affective disorder or depression) and later BD conversion while the others did not. This is not surprising because although high-risk studies can be informative about transition to BD (DelBello & Geller, 2001; Duffy et al., 2011; McGuffin et al., 2003), these studies still have not supported the validity of the pre-pubertal BD phenotype and not all children of parents with BD develop BD or a mood disorder (Duffy, Carlson, Dubicka, & Hillegers, 2020; Malhi, Moore, & McGuffin, 2000; Malhi, Morris, Hamilton, Outhred, & Mannie, 2017).

Parenting behaviour/style, parent-child relationship quality, maternal characteristics, attachment, impulsivity, experiential avoidance, disturbances in self-representation, dissociation, comorbid oppositional defiant disorder, comorbid conduct disorder, somatisation, general psychosocial functioning, and social and physical aggression in childhood were examined only in BPD studies. Attachment, impulsivity, experiential avoidance, disturbances in self representation, dissociation, comorbid oppositional defiant disorder, somatisation, general psychosocial functioning, social and physical aggression in childhood consistently predicted later BPD symptoms. Interestingly again, none of the BD at-risk reviews mentioned impulsivity although it is commonly found both in BD and BPD patients (di Giacomo et al., 2017; Pauselli, Verdolini, Santucci, Moretti, & Quartesan, 2015; Reich, Zanarini, & Fitzmaurice, 2012).

Previous studies comparing BD and BPD patients showed that BPD patients had significantly more difficulties in interpersonal relationships, endorsed negative and distressing beliefs about themselves and their relationships, and had dysfunctional maternal relationships as compared to BD patients (Bayes et al., 2015; Fletcher, Parker, Bayes, Paterson, & McClure, 2014; Nilsson et al., 2010). Our findings also indicate that relational difficulties with the self and others, such as disturbances in self representation, negative experiences in current relationships and insecure attachment, are evident in people with BPD features. Conflictive interpersonal relationships could distinguish BPD from BD (Masso Rodriguez et al., 2021). However, to be able to support this, these factors should also be studied in BD at-risk populations.

Relatively less evidence has accumulated about precursors related to the BPD development. The reason might be ascribed to the fact that the BPD phenotype is less clearly identified compared to the BD prodromal phase, although its underlying dimensions are evident in the reviews included in this study. This might be attributable to the short follow-up periods and

not integrating contemporary methods for defining biological, psychological, and social precursor signs for the development of BPD (Chanen & Kaess, 2011). Staging models, like in BD or psychosis, could be utilised to help predict the course of prognosis with external validation through biomarkers (Hutsebaut & Aleva, 2021; Videler, Hutsebaut, Schulkens, Sobczak, & van Alphen, 2019). However, early stages of most of these symptoms are non-specific and overlap with other disorders (Berk et al., 2017).

Most of the precursors and vulnerability factors evident in the reviews were shared in both disorders, but some factors were either more evident in BD at-risk or BPD at-risk or they differed in phenomenological aspects. For example, BD at-risk patients had decreased need for sleep, hypersomnia, low social rhythm regularity and high energy whereas BPD patients had chronic nightmares and it was mediated by emotional and behavioural problems. BD at-risk patients showed "bipolar depression" rather than unipolar depression, but in emerging BPD the course was unipolar depression. In BPD at-risk, there was risk of self-harm, but it was not stable after post-hospitalisation. As DSM criteria state that BPD traits are chronic and pervasive (American Psychiatric Association, 2013), the nature of BPD as a personality disorder thereby is doubtful. Further, previous research has observed similar frequency in self-harm in BD patients (Joyce, Light, Rowe, Cloninger, & Kennedy, 2010). Therefore, although self-harm is evident only in BPD studies, it does not distinguish these disorders diagnostically. Importantly, subjects at-risk for attempting suicide usually approach it through searching information and news regarding self-harm and suicidal behaviours on the Internet (Solano et al., 2016). Better insight and understanding of suicide and suicidal risk in these at-risk populations may ultimately help clinicians to adequately detect and prevent suicidal acts.

Whilst AI is transdiagnostic (Marwaha et al., 2016), it is also regarded as a shared feature in BD and BPD diagnosis. AI was evident in BD onset coexistent with baseline MDD, and it was defined as "having ups and downs" whereas in BPD onset, it was part of negative affectivity, aggression, and impulsivity. Difficulties in relationships are a core BPD feature, manifested by idealisation and devaluation as well as by rejection sensitivity (Bayes et al., 2015; Gunderson, 2007). Considering the findings, they are in line with the previous cross-diagnostic studies. Saunders, Goodwin, and Rogers (2015) reported that patients with BPD had higher negative affect, impulsivity, aggression and reduced cooperative relationships. Likewise, Henry et al. (2001) suggested that BPD is not simply an attenuated subgroup of affective disorders and that it could be distinguished from BD on the basis of temperament and character. Additionally, the valence, frequency and nature of mood / affect regulation or mood swings is key to both BD and BPD, and likely especially as the conditions are developing (Marwaha et al., 2014). It was therefore surprising that this aspect of psychopathology has not been comprehensively assessed in people with at-risk conditions. Indeed, this is one way that the conditions could be distinguished. Advancing this field will require future comparative studies of affect / mood regulation in young people with emerging BD vs BPD. The time scale of the mood fluctuations can be a useful marker in clinical practice to differentiate BD and BPD in at-risk asymptomatic periods.

Childhood adversity was evident in both disorders (e.g., Palmier-Claus, Berry, Bucci, Mansell, & Varese, 2016; Ratheesh et al., 2017; Skabeikyte & Barkauskiene, 2021; Stepp et al., 2016; Winsper et al., 2016b). However, the evidence was much scarcer and sparser in BD studies. For example, apart from childhood sexual, physical, and verbal abuse and neglect, peer victimisation and abuse in romantic relationships were also evident in BPD. These findings are

consistent with the previous literature stating that there is a higher likelihood of experiencing childhood adversity in BPD patients compared to BD (Afifi et al., 2011; Cotter, Kaess, & Yung, 2014). These adverse experiences might be the reason why BPD patients tend to show higher aggressiveness and anger in mood shifts compared to BD patients.

In line with the recent research on the circadian rest-activity patterns in BD and BPD patients (McGowan, Goodwin, Bilderbeck, & Saunders, 2019), sleep disturbances and difficulty falling asleep were common to both disorders. In BPD studies, chronic nightmares were significantly predictive of the onset whereas in BD, participants had decreased need of sleep and it was part of hypomanic symptoms. Vöhringer et al. (2016) too indicated that decreased need for sleep was part of manic symptoms and were specific to BD and not to BPD patients.

Comorbid SUD, anxiety disorders, psychotic symptoms, ADHD were common to both disorder onsets. In BD studies comorbid generalised anxiety disorder and social phobia and ADHD with and without baseline comorbid conduct disorder predicted BD onset whereas in BPD, ADHD and OCD predicted BPD. Further, psychotic symptoms in BD at-risk studies were most often linked to affective states which is in line with previous research (Bassett, 2012). However, the nature of the psychotic symptoms in BPD at-risk studies were not evident. Temperamental dimensions were also evident in both. Higher levels of activity and poor psychosocial functioning were common to both, but in BD onset daydreaming, cyclothymia, and temperamental instability during MDD episodes were predictors of transition. Additionally, sensitivity, hyper alertness, excessive talk or talking too loudly, somatic complaints, and impaired role in school predicted conversion to BD. In BPD studies, on the contrary, higher levels of emotionality, low levels of sociability and shyness predicted BPD symptoms. These

traits again might be attributable to the fact that BPD patients having more conflictive interpersonal relationships (MacKinnon & Pies, 2006).

Depression was also predictive of BD onset and later BPD symptoms although most of the studies pertained to BD at-risk reviews. In BD at-risk studies, depressive episodes or MDD, chronicity, severity, age at onset, psychomotor retardation and frequency of depression predicted BD transition. In emerging BPD studies, only early onset of depression was related to later BPD symptoms. In BD at-risk studies, there is also coexistence of atypical depressive symptoms that are considered to be "bipolar depression" and distinct in phenomenology from unipolar depression such as pathological guilt, cyclothymia, mood lability, psychotic symptoms, and subthreshold hypomania (Berk et al., 2007; Berk et al., 2010). Detailed studies about depressive states in emerging BPD populations are urgently needed to be able to understand whether they can be distinguished based on the depressive symptomatology.

Family history of BD, although the results were inconsistent, was the prominent predictor of BD conversion compared to family history of depression or any affective disorders. For BPD, apart from maternal BPD symptoms (Winsper et al., 2016a), paternal SUD, family history of psychiatric hospitalisation, and maternal psychopathology were significantly associated with BPD. Consistent with the previous research the family history of BD might be a prominent distinguishing feature when comparing BD and BPD (Galione & Zimmerman, 2010; Mitchell, Goodwin, Johnson, & Hirschfield, 2008). However, there is paucity of research pertaining to BPD. Further, despite existing family history of BD data might support the conclusion that BD is highly heritable and unrelated to BPD, no studies have examined the familial relationship of BPD traits and conversion to BD or vice versa.

Our review has strengths. We utilised systematic search procedures to reduce risk of bias and ensure comprehensive coverage of the current literature. Inter-rater reliability was consistent with no requirement for arbitration regarding inclusion of SRs and MAs. However, several limitations of the current findings here should be considered when interpreting the results. First, we only included relevant prospective studies from the systematic reviews and excluded primary studies with any other designs. This inhibited synthesising the articles as a whole and reporting the pooled results from eligible MA's. Second, the evidence was limited by the data that included SRs and MAs provided and some relevant prospective studies were inevitably missed. Third, there were many non-systematic literature reviews including prospective studies that the reviews we included missed out. For example, Hartmann, Nelson, Ratheesh, Treen, and McGorry's (2018) scoping review, they provided additional evidence for family history of BD, subthreshold depression and hypomania, sleep disturbance, mood lability and later BD conversion. They also provided data for impulsivity and fun-seeking which was not investigated by the reviews included here. Fourth, we were not able to conduct an MA due to the substantial methodological and clinical heterogeneity with respect to cohort characteristics such as study design and sample size among primary studies included in the reviews. Further, not being able to pool the data precluded definitively clarifying the timing and duration of the precursors, notwithstanding the heterogeneity in at-risk populations (Radua et al., 2018). Fifth, because of the short follow-up periods and small number of follow-up assessments in most of the included prospective studies, the validity and utility of these factors for predicting an early prodrome of BD and BPD remains unknown. If we do not know the actual starting point of the onset of the disorder, these and any other identified factors may indicate relapse or maintenance of the disorder (Stepp & Lazarus, 2017). Sixth, none of the reviews discussed the sensitivity,

specificity, and predictive value of reported precursors, important aspects that may enable better assessment of clinical utility. Therefore, again a cautious interpretation of the findings as to their generalisability is necessary. Seventh, none of the studies mentioned sub-score analyses for the examined antecedents making it challenging to compare how the two disorders presented different patterns of the shared features. Eight, the majority of the BD at-risk reviews examined youth at genetic high risk. However, most genetically high-risk individuals do not develop BD. A combination of genetic and clinical risk factors is required to optimally predict conversion to BD (Keramatian et al., 2021). Nineth, despite our comprehensive search, we identified relatively very few studies pertaining to the BPD onset.

In conclusion, although the findings of this review may lead to support the view of BD and BPD as two distinct disorders, there is scant evidence from existing studies to either indicate that BD and BPD are separate nosological entities or that BPD should be considered as an extension of BD disorders. In clinical practice, these differences can be subtle, especially between BPD and BD-II (Masso Rodriguez et al., 2021).

Whilst the comparative literature is in its infancy there are several implications from this meta-review. On an etio-pathological level, our findings corroborate the notion that there is a prodromal stage in BD and BPD. There are overlapping risk factors in the young people with at-risk BD and BPD, these being family history of psychopathology, affective instability, attention deficit hyperactivity disorder, anxiety disorders, depression, sleep disturbances, substance abuse, psychotic symptoms, suicidality, childhood adversity and temperament. However, there are risk factors specific to the at-risk BD and BPD states. Gender, differences in the white matter, changes in the amygdala, neural reward circuit dysfunctions, DBD, subsyndromal hypomania, cyclothymia or bipolar NOS, frequency and loading of affective symptoms, and antidepressant

use were evident only in people with at-risk BD. Parenting behaviour/style, parent-child relationship quality, maternal characteristics, attachment, impulsivity, experiential avoidance, disturbances in self representation, dissociation, comorbid oppositional defiant disorder, comorbid conduct disorder, somatisation, general psychosocial functioning, and social and physical aggression in childhood were evident only in at-risk BPD. These factors could form the basis of initial prediction modelling approaches which could improve clinical staging and clinical interventions. Clinicians should be aware of the high degree of comorbid psychopathology in young people developing BD and BPD and should consider both conditions in young people presenting with one. From a transdiagnostic perspective, the current review may provide a benchmark for comparing the magnitude of association of these factors with other mental health disorders. The results can also substantially advance our ability to prognosticate the onset of BD and BPD in populations at-risk, who ultimately may benefit from preventative interventions.

To be able to reliably identify target populations with greater specificity, future research is required to increase our understanding of the development of BD and BPD onset and their complex interplay by conducting prospective studies which concurrently examine multiple measures including biological, environmental, psychosocial, and clinical factors in BD and BPD at-risk populations. Systematic longitudinal studies investigating genetically and clinically high-risk youths in a structured multifactorial approach can help us understand whether both these disorders belong to the affective spectrum or not as well as their development over time (e.g., Brietzke et al., 2012). Greater predictive validity could be provided by future research identifying potential BD and BPD biomarkers whilst charting these along the illness trajectory. It is also important that future research studies use consistent recruitment criteria to ensure that

findings are comparable and generalisable to other studies as far as is practicable (Malhi et al., 2017).

Large, multilevel data sets will enable deep phenotyping and distinguish pathophysiological pathways (Phillips & Kendler, 2021). For example, remote monitoring can complement symptom monitoring and capture signals more representative of the underlying pathophysiology of BD and BPD (Gillett & Saunders, 2019; Gillett et al., 2021). One of the ways to conduct remote monitoring is Experience Sampling Methodology (ESM). The temporal pattern in mood may be captured by ESM (Larson & Csikszentmihalyi, 2014). Researchers have widely used ESM to assess the temporal patterns of regulations of mood / affect in individuals with mood disorders as the method is more suited to capturing momentary temporal fluctuations in affect (e.g., Dubad, Elahi, & Marwaha, 2021; Merikangas et al., 2019; Schwartz, Schultz, Reider, & Saunders, 2016; Tsanas et al., 2016). Further, some types of ESM are not subject to recall biases as the studies do not rely on retrospective memory recall of events between assessments (Myin-Germeys et al., 2009). The data gained through ESM could also identify new behavioural biomarkers which may lead to the identification of novel phenotypes in these disorders (Gillett & Saunders, 2019). Additionally, identifying common criteria such as AI is easy but focusing on differential symptoms is a complex task (Masso Rodriguez et al., 2021). ESM could also be useful to be able to achieve this. These prospective studies may also help identifying a validated BPD prodrome criteria, despite previous resistance to the diagnosis of BPD in adolescents due to the fears of stigmatisation (Chanen, 2015; Laurenssen, Hutsebaut, Feenstra, Van Busschbach, & Luyten, 2013; Stepp & Lazarus, 2017).

Making an accurate diagnosis of BD and BPD is further complicated by comorbidity with various other conditions such as attention deficit hyperactivity disorder (ADHD) and unipolar

depression (Asherson et al., 2014; Mneimne, Fleeson, Arnold, & Furr, 2018). ADHD has been reported to coexist in around 20% of adult patients with BPD or BD (Asherson et al., 2014; Philipsen et al., 2009; Skirrow, Hosang, Farmer, & Asherson, 2012), while rates of co-occurrence between BPD and current major depressive disorder (MDD) or BD range from as low as 4% to as high as 48% (Mneimne et al., 2018). Since deficits in affect regulation such as AI are also strongly linked to the hyperactive/impulsivity symptoms of ADHD (Skirrow & Asherson, 2013) and unipolar depression (Balbuena, Bowen, Baetz, & Marwaha, 2016), it is imperative to include these groups too for comparison to better understand the symptom profiles between at-risk BD and BPD.

Table 2. Similarities and differences in shared factors in emerging Bipolar Disorder and Borderline Personality Disorder

Factor	Bipolar Disorder Onset	Borderline Personality Disorder Onset	Bipolar Disorder and Borderline Personality Disorder Onset
Childhood Adversity	Higher rates of childhood adversity than participants who do not develop BD	Type of trauma is not limited to family caused trauma but also peer and romantic relationship related trauma in BPD onset	A shared factor, more marked in BPD onset
Sleep Disturbances	Decreased need for sleep, middle insomnia, frequent night time awakenings, high energy in offspring of BD or as part of hypomanic symptoms Low social rhythm regularity, daytime dysfunction, hypersomnia and anergia, decreased REM sleep in cohorts reporting first onset of BD Time to fall asleep	Chronic nightmares (mediated by emotional and behavioural problems)	Both show difficulty falling asleep and waking earlier than desired
Depression	Bipolar depression rather than unipolar depression; presence of psychotic symptoms, feelings of guilt, hypomanic symptoms "Hypersomnic retarded depression" Psychomotor retardation	The course of depression is unipolar	Early onset of depression predicted both disorders but differentiating features are evident

	Chronic and frequent Higher recurrence rates Major depressive episodes		
Suicidality	Specific plan for committing a suicide Recurrent thoughts of death	Risk of self-harm	A shared factor but suicidal ideation was not stable after post-hospitalisation in BPD
Family Psychopathology	A loaded family pedigree or family history of affective disorders spanning three generations	Paternal substance use disorder Maternal psychopathology (e.g., internalising and externalising disorders, BPD symptoms) Family history of psychiatric hospitalisation	Family history of mental illnesses is associated with later symptomatology in both disorders
Substance Use Disorders	Baseline cannabis use significantly predicted hypo/sub-threshold mania	BPD traits and SUD are correlates rather than causal antecedents of each other The role of behavioural disinhibition	SUDs are common to both disorders
Affective Instability	Coexistent with baseline MDD Having 'ups and downs'	Negative affectivity as affective instability, emotionality, aggressiveness/tantrums	AI is common to both disorders
Anxiety	Comorbid GAD Comorbid SP	Comorbid OCD	Comorbid anxiety disorders are common to both disorders
Temperament	Temperamental instability during MDD episodes Daydreaming Cyclothymic disorder	Higher levels of emotionality and low levels of sociability and shyness in middle childhood	High activity levels and poor psychosocial functioning are evident in both disorders

	Hyperthymic temperament Sensitivity, hyper alertness, excessive talk, talking too loudly, easily excited, poor attention, impaired role in school, somatic complaints		
Psychotic Symptoms	Psychosis NOS, schizotypal features and schizophrenia nuclear symptoms predicted conversion Comorbidity with MDD	Children in the extreme borderline group exhibited more psychotic symptoms	Symptoms common to both disorders but marked and detailed more in BD
ADHD	Switches were predicted by presence of parental mood disorder, school behaviour problems, and baseline comorbid conduct disorder	ADHD was predictive of both changes in BPD symptoms and onset	Shared feature; greater risk of BD and BPD occurrence in ADHD patients

Note. ADHD = Attention deficit hyperactivity disorder; BD = Bipolar Disorder; BPD = Borderline Personality Disorder; GAD = Generalised Anxiety Disorder; MDD = Major Depressive Disorder; NOS = Not Otherwise Specified; OCD = Obsessive Compulsive Disorder; SP = Social Phobia; SUD = Substance Use Disorder

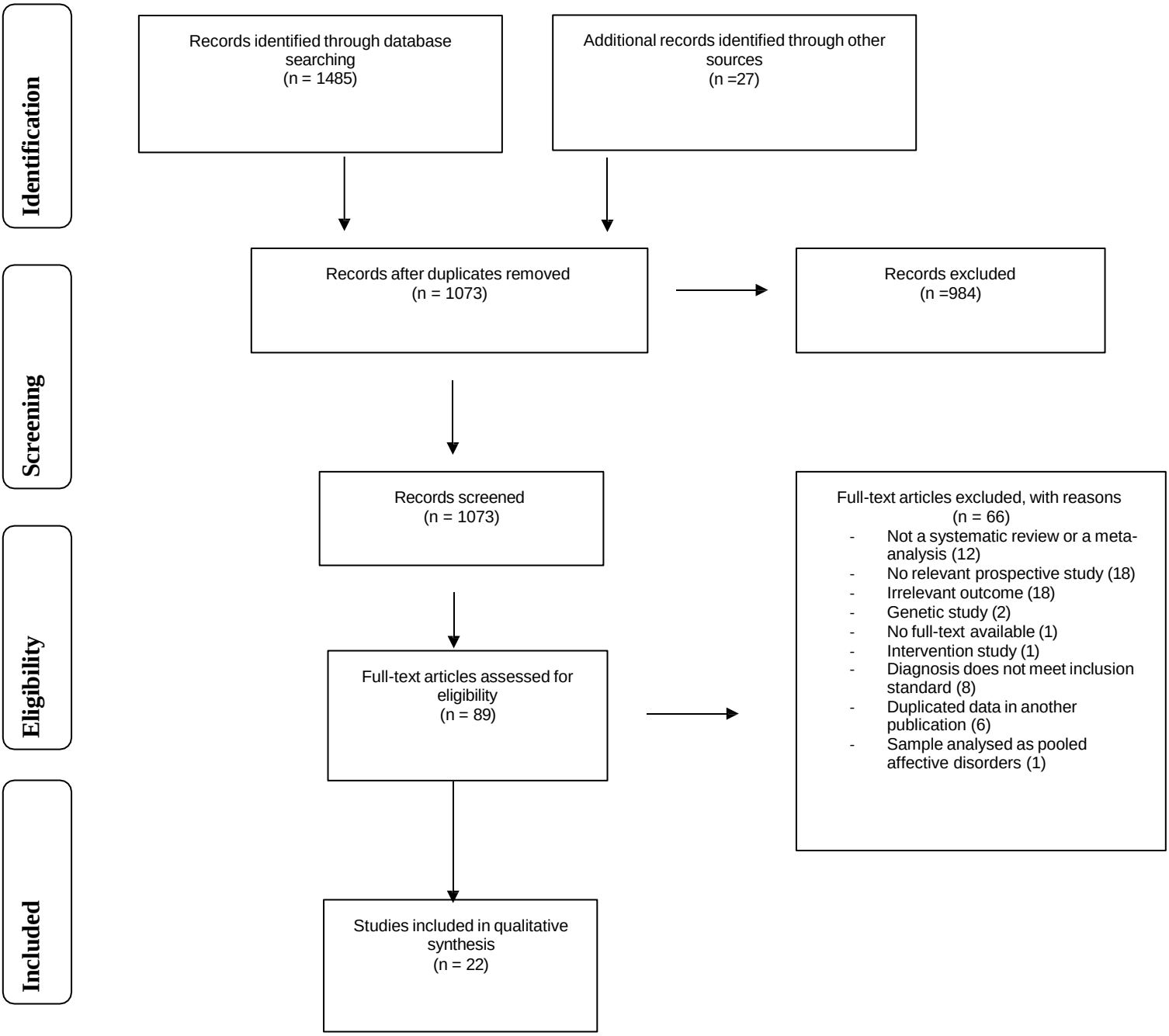


Figure 1. Flowchart of main search strategy and article selection for systematic review of review

Chapter 3

Justifying the Use of ALSPAC Cohort

used in Chapter 4 and 5

Chapter Overview

This chapter describes a broad overview of the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, in terms of sample characteristics and cohort design, and the methods used to address the aims of this thesis in Chapters 4 and 5. The outcome variable is described fully, and a brief overview of the independent variables and analytic methods used are presented; however, these will be described in more detail in Chapter 4 and 5.

3.1. Avon Longitudinal Study of Parents and Children (ALSPAC)

3.1.1. Baseline Sample:

Sample recruitment and procedures

The Avon Longitudinal Study of Parents and Children (ALSPAC; http://www.bris.ac.uk/alspac/) is an ongoing large longitudinal, population-based, birth cohort that recruited pregnant women resident in Avon, UK with expected delivery dates between 1st April 1991 and 31st December 1992 (Boyd et al., 2013; Fraser et al., 2013). The cohort was established to understand multiple genetic, epigenetic, biological, psychological, social and other environmental exposures in relation to a similarly diverse range of health, social and developmental outcomes (Boyd et al., 2013; Fraser et al., 2013).

Pregnant women resident in Avon, UK with expected dates of delivery between 1st April 1991 and 31st December 1992 were invited to take part in the study. 20,248 pregnancies have been identified as being eligible and the initial number of pregnancies enrolled was 14,541. Of the initial pregnancies, 13,988 children who were alive at 1 year of age (Boyd et al., 2013; Fraser et al., 2013).

When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally (Boyd et al., 2013;

Fraser et al., 2013). The number of new pregnancies not in the initial sample that are currently represented in the released data and reflecting enrolment status at the age of 24 is 906, resulting in an additional 913 children being enrolled (Boyd et al., 2013; Fraser et al., 2013). Therefore, the total sample size for analyses using any data collected after the age of seven is 14,901 children who were alive at 1 year of age (Boyd et al., 2013; Fraser et al., 2013).

Of the original 14,541 initial pregnancies, 338 were from women who had already enrolled with a previous pregnancy, meaning 14,203 unique mothers were initially enrolled in the study (Boyd et al., 2013; Fraser et al., 2013). As a result of the additional phases of recruitment, a further 630 women who did not enrol originally have provided data since their child was 7 years of age. This provides a total of 14,833 unique women (i.e., G0 mothers) enrolled in ALSPAC as of September 2021 (Boyd et al., 2013; Fraser et al., 2013).

The children from these pregnancies have been followed up at multiple time points since recruitment using a range of questionnaires including physiological and psychological assessments (Fraser et al., 2013). Between birth and age 18 years there have been 68 data collection time-points, with 59 questionnaires and 9 clinic assessment visits completed (Boyd et al., 2013). Additional follow-up of the 'eligible sample' has also been made through school-administered questionnaires and assessments completed by the child's teacher (Boyd et al., 2013).

Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. The study website contains details of all the data,

searchable through the data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

3.1.2. Justifying ALSPAC's Use

There are several reasons why ALSPAC has been selected to be utilised in this PhD thesis. ALSPAC has a scale and richness in data that is unprecedented in epidemiological studies and is comprised of a large sample unselected by disease status (Fraser et al., 2013). A defining feature of the ALSPAC data set is the breadth of repeat measures taken at frequent intervals across the life course since pregnancy until currently 30 years old. This is currently a unique resource in the UK and is one of the most phenotypically rich studies in the world (Kordas & Park, 2015). ALSPAC has also deliberately involved cohort participants in research design and governance (Kordas & Park, 2015). Further, the prospective design developmental trajectories have been assessed over a wide variety of physical, behavioural, and mental health aspects (Boyd et al., 2013). For example, the cohort design and the availability of repeated measures allows researchers to utilise group-based model trajectory and growth mixture modelling techniques, such as Latent Class Growth Analyses (LCGA), which was used in the following chapters. Additionally, there is a wide variety of informants utilised (e.g., parent reported, teacher reported, self-reported and clinician rated) and the frequent contact with mothers and their partners, and child's teacher is maintained by sending postal questionnaires at regular intervals (see Table 3). Lastly, ALSPAC included well-validated measures and interviews to assess the main variables of interest in this thesis, which is rare in large cohort studies where mental health assessments are often reduced to a limited number of items.

3.1.3 Target Sample:

The sample used for the purpose of this thesis included those who completed The Hypomania Checklist-32 (HCL-32) at 21-23 years of age. HCL-32, a self-administered questionnaire that

was designed to screen for the presence of lifetime hypomania symptoms in patients with depression (Angst et al., 2005), was assessed via postal and online questionnaires. In total, 9,359 participants were invited to complete the HCL-32, however, only 3,448 (36.8%) returned the questionnaire (see Figure 2), which is the sample size included for Chapters 4 and 5. This attrition rate is typical in ALSPAC (e.g., Morales-Muñoz et al., 2024; Weavers et al., 2021) as the attrition rate increases over time. Further, compared to other UK based cohorts like Millenium Cohort Study (MCS), ALSPAC missing data is more common in ALSPAC than in MCS (Armitage et al., 2023). Nevertheless, research shows that the validity of regression models is only marginally affected despite range restrictions after selective drop-out in ALSPAC (Wolke et al., 2009).

3.2 Measures

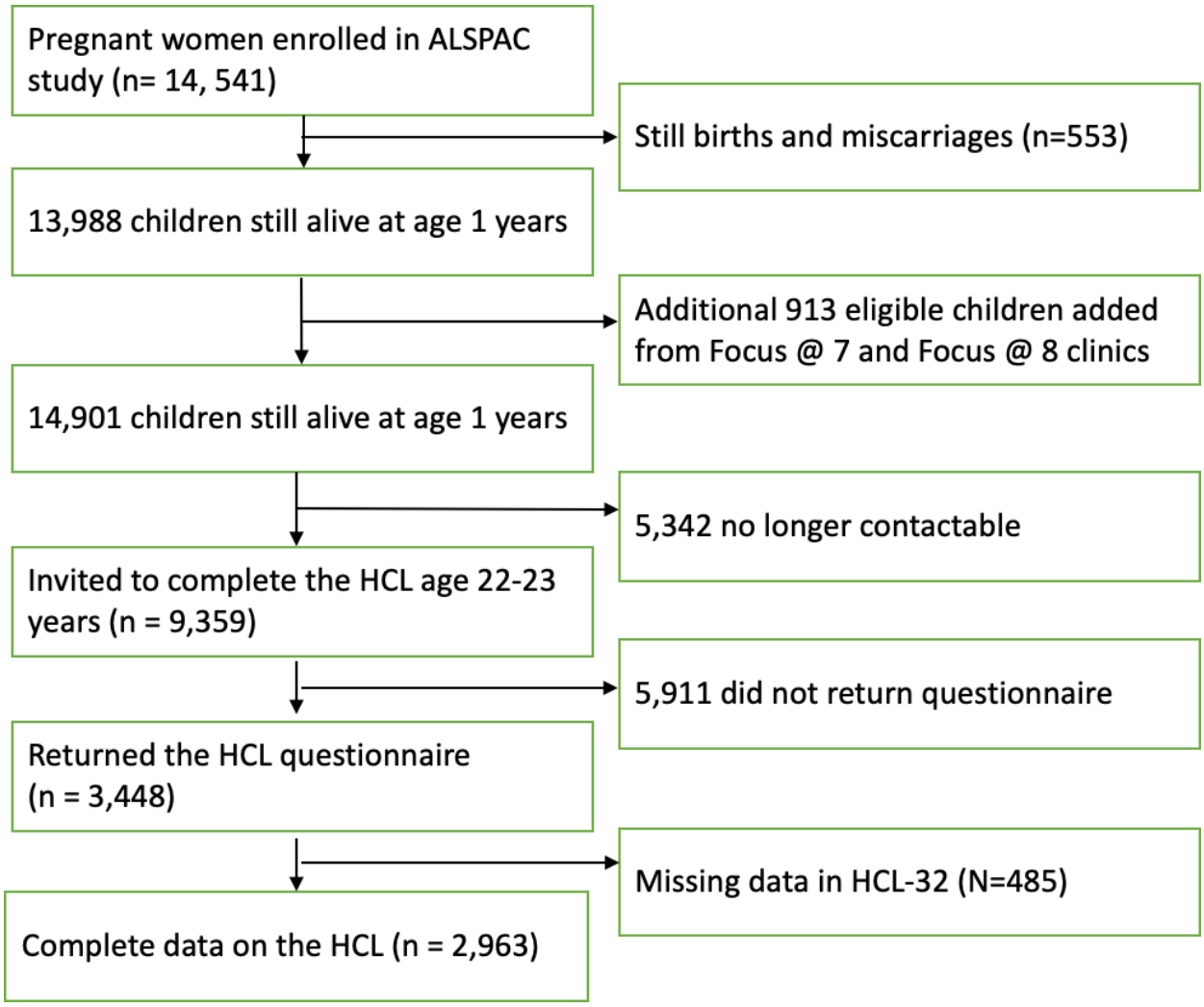
As mentioned above, the ALSPAC study collected multiple questionnaires related to physical, behavioural and psychological aspects, at multiple time points from the first trimester of pregnancy onwards. Only the measures relevant to this thesis are described here.

3.2.1 Main outcome: The Hypomania Checklist-32 (HCL-32)

Building on accumulated knowledge about early BD symptoms, researchers have tried to design reliable screening tests that could help to predict conversion to BD (Vieta et al., 2018). The use of self-report screening instruments for BD that are both time- and cost-effective may aid in the timely and accurate diagnosis of this illness (Carvalho et al., 2015). These screening tools can also raise the possibility of suspected sub-threshold bipolarity and suggest the need for clinical verification, including input from significant others (Carta & Angst, 2016). To date, the predictive value of a few clinical scales has been tested in longitudinal studies such as the mood disorders questionnaire (MDQ; Hirschfeld et al., 2000), the bipolar spectrum diagnostic scale (BSDS; Ghaemi et al., 2005), the mood swings questionnaire/survey (MSQ/MSS; Parker et al., 2006, 2008) and the Hypomania

Symptom Checklist (HCL-32; Angst et al., 2005), which is the one included in ALSPAC and the one used for Chapters 4 and 5.

Figure 2. Attrition of participants from the ALSPAC cohort



The BSDS, HCL-32 and MDQ have been the most extensively investigated screening tools for bipolar spectrum disorders in accuracy studies and epidemiological surveys (Carvalho et al., 2015). A systematic review evaluated and compared the diagnostic accuracy of these three screening tools in different clinical settings and found that the sensitivity of the MDQ is lower in primary care and general population settings than in mental health centre settings and that the HCL-32 is more accurate for the detection of type II BD than the MDQ (Carvalho et al., 2015). Another study tested whether the HCL-32 can be used for screening in the community settings and found, despite the low base rate of BD in the sample, the screening properties of the HCL-32 remained almost as good (Meyer et al., 2017). Another recent meta-analysis concluded that the HCL-32 and the MDQ have similar and acceptable psychometric properties to identify BD, although the MDQ (i.e., 70%) evidenced higher specificity than the HCL-32 (i.e., 57%; Wang et al., 2019).

Although subsyndromal hypomanic symptoms may be especially predictive of later BD (Bechdolf et al., 2014; Goodday et al., 2017; Mesman et al., 2017), hypomanic symptoms are commonly reported as part of the normative adolescent experience (Faedda et al., 2019). It is also suggested that although the hypomanic symptoms are relatively sensitive, they are not necessarily specific in predicting BD (Faedda et al., 2019). The predictive specificity for BD would be increased if symptoms are deemed to be clinically significant, representing a change from normal function and of concern to others that know the person well (Goodday et al. 2017). That is why, to enhance the psychometric properties of the HCL-32 and to meet clinically significant hypomanic symptoms criteria, those with a symptom score of 14 or more (out of 32) were classed as having hypomania if they also reported a) at least one incident of "negative consequences" or of "negative plus positive consequences," as a result of hypomanic symptoms;

and b) that mood changes caused a reaction in close others; and c) that symptoms lasted for a duration of 4 or more. This produced a binary measure of clinically significant hypomanic symptoms, in which, 1.8% (N=25) individuals were classified as having clinically significant hypomanic symptoms. This prevalence is consistent with findings from Moreira et al. (2017), which estimated a 1.02% prevalence rate for bipolar spectrum disorders in adults globally.

3.2.2. Brief Description of Predictor Variables

Independent and confounding variables were chosen according to existing evidence, discussed in chapters one and two. A brief outline of predictors and confounders used in chapter 4 and 5 are presented in Table 3. A full description of variables, including details of construction, will be presented in the following chapters.

3.2.3. Statistical Methods

Logistic Regression

Although there are a variety of approaches for modelling binary response variables, logistic regression is often used by researchers as it is flexible in assumptions are made in order to fit the model to the data (Boateng & Abaye, 2019; Uanhoro et al., 2021). Thus, logistic regression was used to measure the association between the exposure and the binary outcome. Odds Ratios (ORs) with 95% confidence intervals (CI) were provided to interpret the relationship.

Latent Class Growth Analyses

To identify ADHD and depression trajectories in Chapter 4 and 5 LCGAs were used. LCGA is a common explanatory modelling technique in which participant-level trajectories of an outcome can be classified into groupings (Mori et al., 2020).

Mediation Analysis

To disentangle the different pathways that could explain the effect of an exposure on an outcome (Steen et al., 2017) (Little et al., 2024), mediation analyses were applied in Chapter 5.

3.2.4. Approach to missing data

Due to the high attrition rates in the ALSPAC cohort, two approaches were used to deal with missing data: inverse probability weighting (IPW) and full information maximum likelihood (FIML). IPW method, which weights complete units by the inverse of an estimate of the probability of response (Little et al., 2024), was used in logistic regression analyses. This is because data is not missing at random in ALSPAC and IPW has been recommended over alternative methods for dealing with missing data (e.g., multiple imputation) in situations where blocks of data are missing (Weavers et al., 2021). In line with previous publications based on this cohort (Armitage et al., 2023; Morales-Muñoz et al., 2024), I used data from early time points in the ALSPAC dataset on birthweight, maternal age, child's sex, child's ethnicity, family adversity score, preterm delivery and maternal socioeconomic status to predict missingness in the analysis sample (those who did not complete HCL-32 measurement at 21-23 years, n = 6396). The regression coefficients from this model were used to determine probability weights for the covariates in the primary and secondary logistic regression analyses. According to the results, characteristics associated with attrition at 21–23 years old were being a male, having a younger mother who had lower socioeconomic levels and having higher scores on family adversity index.

FIML method, which can be used to obtain consistent parameter estimates when data are missing completely at random or missing at random, is the default for incomplete data in MPlus (Lee & Shi, 2021; Zhang & Savalei, 2022). FIML was only used in LCGA and path analyses in MPlus and not in logistic regression analyses. The details of these approaches are discussed in detail in the following relevant chapters.

3.2.5. Correlation between ADHD, Depression and Hypomanic symptoms

Correlations between ADHD, depression and hypomanic symptom were examined using

Pearson’s correlation (see Table 4, Table 5, and Table 6).

Table 3. Summary of Independent and Control Variables Used in Subsequent Studies

Independent Variables	**Variable**	**Time-points**	**Respondent details**
Chapter 4: ADHD symptoms	Development and Well-Being Assessment (DAWBA)	At 8, 10, and 13 years	Parent-rated and teacher-rated
Chapter 5: Depression Symptoms	The Short Moods and Feelings Questionnaire (SMFQ)	At 10.5, 12.5, 13.5, and 16.5 years	Child reported
Psychotic Experiences	The Psychosis-Like Symptom Interview (PLIKS)	At 17.5 years	Child reported during focus 17.5 assessment clinic
Atypical Depression Symptoms	The Clinical Interview Schedule-Revised (CIS-R)	At 17.5 years	Child reported during focus 17.5 assessment clinic
Confounding Variables			
Childhood adverse experiences	Family Adversity Index[a]	During pregnancy, at 2 years and 4 years	Mother postal questionnaire
Childhood psychopathology	DAWBA diagnosis[b]	Approximately 8 years	Mother and teacher report and then clinician rated
Adolescence psychopathology	The UK Childhood Interview for DSM-IV Borderline Personality Disorder (UK-CI-BPD)[c]	11 years	Child reported during focus 11+ assessment clinic
Variables used in Inverse Probability Weighting[d]			
	Birthweight	At Birth	Mother reported

	Maternal Age at Birth	During pregnancy	Mother reported
	Family Adversity Index	During pregnancy, at 2 years and 4 years	Mother reported
	Maternal Socioeconomic Status	During pregnancy	Mother reported
	Preterm Delivery Status	At Birth	Mother reported
	Child's Sex	At Birth	Mother reported
	Child's Ethnicity	At Birth	Mother reported

[a] **Chapter 4 & 5**
[b] **Chapter 5**
[c] **Chapter 4 & 5**
[d] **Chapter 4 & 5**

Table 4. Correlation between DAWBA ADHD and SMFQ Depression Scores

	SMFQ at 10.5 years	SMFQ at 12.5 years	SMFQ at 13.5 years	SMFQ at 16.5 years
DAWBA ADHD at 8 years	0.07 (0.05-0.01)*	0.04 (0.02-0.07)**	0.05 (0.02-0.08)**	0.01 (-0.02-0.04)
DAWBA ADHD at 10 years	0.08 (0.06-0.11)*	0.03 (0.01-0.06)	0.05 (0.02-0.08)*	-0.00 (-0.03-0.03)
DAWBA ADHD at 13 years	0.11 (0.08-0.13)*	0.05 (0.02-0.07)*	0.04 (0.01-0.07)**	-0.00 (-0.03-0.03)

* p <.001
** p <.05

Table 5. Correlation between DAWBA ADHD Scores and HCL-32 total and reduced item scores

	HCL-32 Full Scale	HCL 4 removed items for sensitivity analysis
DAWBA ADHD at 8 years	0.02 (-0.02-0.06)	
DAWBA ADHD at 10 years	0.02 (-0.02-0.06)	
DAWBA ADHD at 13 years	0.03 (-0.01-0.07)	

* p <.001

** p <.05

[a] To investigate whether removal of hypomania items from HCL-32 that are similar to ADHD items would affect the results, we removed the following 4 items from HCL-32;

- I am more easily distracted
- I talk more
- I feel more energetic and more active
- I am physically more active (sport etc.)

Table 6. Correlation between SMFQ Depression Scores and HCL-32 total scores

	HCL-32 Full Scale
SMFQ at 10.5 years	0.06 (0.02-0.10)**
SMFQ at 12.5 years	0.09 (0.05-0.13)*
SMFQ at 13.5 years	0.10 (0.06-0.14)*
SMFQ at 16.5 years	0.13 (0.09-0.17)*

* p <.001
** p <.05

Chapter 4

ADHD symptom trajectories across childhood and early adolescence and risk for hypomanic symptoms in young adulthood

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Abstract

Background: There is increasing evidence that childhood Attention-Deficit Hyperactivity Disorder (ADHD) elevates the risk of later Bipolar Spectrum Disorder (BD). However, it remains unclear whether different trajectories of ADHD symptoms confer differential risk for BD.

Methods: Data from the Avon Longitudinal Study of Parents and Children were available from 7811 children at age 8 years, 7435 at 10, 6798 at 13, and 1217 at 21–23 years. ADHD symptoms were assessed at 8, 10, and 13 years with the Development and Well-Being Assessment. Clinically significant hypomanic symptoms (CSHS) at 21–23 years were assessed using the Hypomania Symptom Checklist (HCL-32). Group trajectories of ADHD and its subtypes were estimated using latent class growth analysis. The prospective associations between different ADHD trajectories and CSHS were tested using logistic regression analysis.

Results: Persistently high, increasing, remitting, and persistently low ADHD symptom trajectories were identified for the three ADHD-related categories. Individuals with persistently high and increasing levels of ADHD symptoms had increased odds of CSHS compared to persistently low class. Sensitivity analyses validated these results. In separate analyses, persistently high levels of hyperactivity and inattentive, and increasing levels of inattentive symptoms were also independently associated with CSHS.

Conclusions: Young people with a longitudinal pattern of high and increasing ADHD symptoms are at higher risk for developing CSHS in young adulthood compared to individuals with low symptom patterns. These two trajectories in childhood and adolescence may represent distinct phenotypic risk profiles for subsequently developing BD and be clinically significant targets for prevention and treatment of BD.

Keywords: ADHD; hypomania; LCGA; trajectories; ALSPAC

4.1. Introduction

There is growing evidence suggesting that bipolar disorder (BD) is preceded by childhood ADHD (Hosang et al., 2019; Meier et al., 2018). Mania shares many overlapping symptoms with ADHD, such as irritability, increased activity, aggression, problems in social situations, disinhibition, and/or distractibility. It is estimated that up to 1 in 13 patients with ADHD have comorbid BD, up to 1 in 6 patients with BD have comorbid ADHD in adult populations (Schiweck et al., 2021) and that about 10% of children and adolescents with ADHD will develop BD (Brancati et al., 2021). Further, young people with comorbid ADHD and hypomania, or BD, have an increased risk of suicide (Moran et al., 2019), more psychiatric hospitalizations, less treatment adherence, higher rates of additional psychopathology (Brancati et al., 2021; Serrano et al., 2013) and an earlier age of onset (Schiweck et al., 2021) than individuals without such comorbidity. A recent study also found that most offspring of BD parents did not develop BD, but those with preschool ADHD were at particularly high risk for developing BD (Birmaher et al., 2021).

Most studies investigating the association between ADHD and BD development have been limited by measuring ADHD either at one time point or by simply reporting the diagnostic proportions for the sample at various follow-up times. This method does not capture intraindividual variability in ADHD symptoms or their longitudinal course and could mask a potentially complex association or mechanism. The presence of subgroups may also explain apparent divergent results within the literature (Arnold et al., 2020; Brancati et al., 2021; Tillman & Geller, 2006). This is also important as ADHD is a neurodevelopmental disorder starting early in life and developing with a highly variable trajectory (Breda et al., 2021; Brinksma et al., 2023; Franke et al., 2018; Murray et al., 2019, 2022). It remains unclear whether different trajectories of ADHD symptoms confer differential risk for development of BD. Further, although modest

correlations between adolescent hypomanic and hyperactivity symptoms have been reported, recent research has detected higher estimates for genetic risk factors between hypomania and symptoms of hyperactivity (10%-25%) than with inattention (6%-16%; (Hosang et al., 2019). Another study found that BD was associated with inattentive and combined but not with hyperactive ADHD presentations (Friedrichs et al., 2012). Thus, since the ADHD symptom domains of hyperactivity and inattention may be differentially associated with BD and there are incongruent findings in the literature, ideally these domains need to be further investigated separately.

Understanding unique trajectories of ADHD symptoms and how these subgroups influence the development of BD could help identify at-risk groups and could guide specific interventions. One way to identify the earliest clinical manifestations of BD is to study hypomanic symptoms, a common feature of BD in youth which often heralds a subsequent manic episode (Grande et al., 2016). Recent research has found that traits of ADHD across childhood and adolescence were associated with adolescent hypomania (Hosang et al., 2019). Significant, modest correlations between adolescent hypomanic and hyperactivity symptoms have also been reported (Holtmann et al., 2009; Hosang et al., 2017).

Given the existing knowledge gaps we sought to characterize ADHD symptom trajectories across childhood and early adolescence from age 8 to 13, and to describe their prospective associated risk for subsequent hypomanic symptoms assessed between 21-23 years old. We also sought to distinguish inattention from hyperactivity to further examine the origins of the ADHD-BD overlap and investigate the prospective relationship between subtypes of ADHD (hyperactivity and inattentive symptoms) and hypomanic symptoms.

4.2. Materials and Methods

4.2.1. Participants

The current study used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), an ongoing longitudinal UK birth cohort study designed to investigate the factors associated with the development, health, and disease during childhood and beyond (Boyd et al., 2013; Fraser et al., 2013; Northstone et al., 2023). All women resident in Avon, UK, with expected dates of delivery between 1 April 1991 and 31 December 1992 were contacted and eligible for participation.(Golding et al., 2001). The study cohort consisted of 14,541 pregnancies and 13,988 children still alive at 1 year of age (see Supplement, for further details). Ethical approval was obtained from the ALSPAC Law and Ethics committee and the local research ethics committees. Informed consent was obtained from the parents of the children.

4.2.2. Measures

ADHD across childhood and adolescence

ADHD at the age of 8, 10, and 13 was assessed using parental reports of the Development and Wellbeing Assessment (DAWBA). DAWBA is a validated instrument including both structured and semi-structured questions related to the International Classification of Diseases-10 (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) diagnostic criteria.(Goodman et al., 2000). See Supplement for additional details on all measures. Items used for calculating the total scores for ADHD, and the total scores for its subtypes (inattention and hyperactivity) to obtain the trajectories can be found in Supplementary-Table 1. ADHD items prevalence in the cohort can be found in Supplementary-Table 2.

Clinically Significant Hypomanic symptoms in young people

Study participants completed the Hypomania Checklist Questionnaire (HCL-32), a self-report measure of lifetime experience of manic symptoms (Angst & Cassano, 2005) comprising 32 items when they were 21-23 years old. Consistent with previous work (Marwaha et al., 2018), we constructed a dichotomous clinically significant hypomanic symptoms variable; a) those with a symptom score of 14 or more (out of 32) were classed as having hypomania if they also reported b) at least one incident of "negative consequences" or of "negative plus positive consequences," as a result of hypomanic symptoms, c) that mood changes caused a reaction in people close to the participant and d) that symptoms lasted for "4 days" or more. HCL-32 item prevalence in the cohort can be found in Supplementary-Table 3.

4.2.3 Confounders

Child's sex, and ethnicity were reported by the mother. Multiple adverse childhood experiences including but not limited to family psychopathology, socioeconomic status and childhood abuse were assessed using the Family Adversity Index (FAI) during pregnancy and at 2 and 4 years (see Methods-Supplementary).

Borderline features were assessed using a face-to-face semi – structured interview, which was the Childhood Interview for DSM-IV Borderline Personality Disorder: UK Version (CI-BPD-UK), based on the borderline module of the Diagnostic Interview for DSM-IV Personality Disorders (Zanarini, 2003) at 11 years old (see further details in Methods-Supplement). We controlled for BPD traits as its highly associated with both ADHD and BD.(Baryshnikov et al., 2015; Mistry et al., 2017).

4.2.4 Statistical Analysis

A multi-staged analysis plan was developed. In the first stage, we described the normative patterns of ADHD, subtypes of ADHD (hyperactivity only and inattention only), hypomanic symptoms and covariates across childhood, adolescence, and young adulthood using descriptive analysis implemented in SPSS, v29.

In the second stage as a primary analysis, we conducted latent class growth analyses (LCGA) using Mplus, v8 to potentially identify differing levels of ADHD symptoms across childhood and adolescence. We also conducted separate LCGAs for the subgroups of ADHD as a secondary analysis. The variables that were included in the LCGA analysis were DAWBA scores of ADHD at ages 8, 10, and 13 years. Several models were fitted by increasing the number of classes (Jung & Wickrama, 2008) from 2 to 6 classes. The best-fitting classification model was chosen using the following parameters: lower sample size–adjusted Bayesian information criteria, significant Vuong-Lo-Mendell-Rubin and Lo, Mendell, and Rubin likelihood ratio tests, higher entropy value, and the proportion of individuals in each class (Jung & Wickrama, 2008). Missing values due to attrition were handled by the full information maximum likelihood estimation method (Wardenaar, 2022).

In the third stage, we conducted logistic regression analyses to explore the associations between ADHD trajectories and hypomania. Among 15645 participants in the original sample of ALSPAC, 13951participants were lost to follow-up at age 21-23 years. Therefore, to deal with missingness which was unlikely to be missing at random, we conducted weighted analysis using inverse probability to account for those lost to follow-up (See Supplementary-Methods). Characteristics associated with attrition at 21-23 years old were being a male, having a younger mother who had lower socioeconomic levels, and had higher scores on FAI (see Supplementary-

Table 4). Using the variables associated with selective dropout as the factors to predict missingness in our analysis sample, we fitted a logistic regression model (nonresponse vs response outcome) to determine weights for each individual using the inverse probability of response. The regression coefficients from this model were used to determine probability weights for the covariates in the primary and secondary analyses. Subsequently, unadjusted, and adjusted associations between ADHD (primary analyses) and subgroups of ADHD (secondary analyses) trajectories, and hypomanic symptoms in young adulthood were assessed using separate logistic regression analysis (i.e., three separate analyses). Additionally, we conducted sensitivity analyses to investigate whether reducing four HCL-32 items that are similar to ADHD items (i.e., talking fast, easily distracted, more energetic, and physically more active) would affect the results.

4.3. Results

Table 4 shows the frequencies and descriptive values of the variables of interest in this study.

4.3.1 Primary Analyses

Latent Classes of ADHD

Table 5 shows the values of log-likelihood VLMR, ABIC, and number of other parameters for all models assessed. Overall, a 4-class model offered the best model fit and theoretical explanation (see Supplementary).

Figure 3 shows the four trajectory classes: persistently low (66.1%, N=6294), with ADHD symptoms that remained low at all time points; adolescence-increasing (10.3%, N=981), with symptoms that began to increase later in adolescence; persistently high (9.1%, N=865), with childhood onset ADHD symptoms that persisted into adolescence, with a very high probability

of clinically significant ADHD symptoms at age 13; and remitting (14.5%, N=1381), with clinically significant ADHD symptoms that began in childhood and remitted by adolescence.

ADHD Classes and risk for clinically significant hypomanic symptoms

The weighted adjusted logistic regression model (with persistent low ADHD symptom levels as the reference) showed that persistently high levels of ADHD symptoms (OR=2.36; CI 95%=1.12-4.99; p=0.024) and increasing levels of ADHD symptoms (OR=3.60; CI 95%=1.92-6.74; p<0.001) were significantly associated with clinically significant hypomanic symptoms at the age of 21-23 compared to persistently low class (Table 6).

Sensitivity Analyses

Removal of hypomania items that were similar to ADHD items (four HCL-32 items; being more easily distracted, talking more, feeling more energetic and more active, and being physically more active) did not affect the results (Supplementary-Table 5).

4.3.2 Secondary analyses

Latent Classes of Inattentive Symptoms and risk for clinically significant hypomanic symptoms

Overall, a 4-class model offered the best fit and theoretical explanation (see Table 5, Supplementary, Table S6 and Table S7). Figure S1 shows the four trajectory classes: persistently low (63.8%, N=6099); increasing (15.5%, N=1486), persistently high (10.1%, N=963), and remitting (6.5%, N=1014).

The weighted adjusted logistic regression model (with persistent low levels as the reference) showed that persistently high levels class (OR=2.47; CI 95%=1.07-5.70; p=0.034) and increasing levels class (OR=3.25; CI 95%=1.32-8.04; p=0.011) were significantly associated

with clinically significant hypomanic symptoms at age 21-23, compared to persistently low class (see Table 6).

Latent Classes of Hyperactivity Symptoms and risk clinically significant for hypomanic symptoms

Overall, a 4-class model offered the best fit and theoretical explanation. We selected the 4-class model as this provided the best fit to the data and theoretical interpretation for hyperactivity (see Table 2 and Supplementary). Figure S2 shows the four trajectory classes: persistently low (74.3%, N=7129); increasing (7.7%, N=735), persistently high (7.5%, N=722), and remitting (10.5%, N=1011).

The weighted adjusted logistic regression model (with persistent low levels as the reference) showed that only persistently high levels class was significantly associated with clinically significant hypomanic symptoms at age 21-23 (OR=3.47, CI 95%=1.69-7.12, $p<0.001$; Table 6) compared to persistently low class.

4.4. Discussion

To our knowledge, this is the first study to examine the extent to which, and how ADHD trajectories across childhood and adolescence, including ADHD subtypes, are associated with later clinically significant hypomanic symptoms. First, we identified a group of individuals characterized by persistently high, increasing, remitting and persistently low levels of ADHD, inattentive and hyperactivity symptoms across childhood and adolescence. Second, we found that persistently high levels and increasing levels of ADHD were independently associated with clinically significant hypomanic symptoms at the age of 21-23. Third, persistently high levels of hyperactivity and inattentive symptoms and increasing inattentive symptoms were also independently associated with subsequent clinically significant hypomanic symptoms.

Our results suggest that tracking ADHD symptoms over time in childhood and adolescence may help identify individuals at risk for clinically significant hypomanic symptoms. More specifically, our findings indicate that children and adolescents with persistently high ADHD symptoms (including hyperactivity and inattentive domains) and a greater cumulative burden of ADHD symptoms (including inattention domain only) are at higher risk of developing clinically significant hypomanic symptoms in young adulthood. The chronic levels of ADHD symptom trajectories may be reflecting children with ADHD with possibly developing BD, since young people with ADHD plus BD compared to those with ADHD alone have greater number of ADHD symptoms (Wilens et al., 2003). What we add to these findings is that even sub-threshold ADHD symptoms in childhood increasing in time could be a risk factor for developing clinically significant hypomanic symptoms later in life. Based on our results, chronicity and increasing levels could be critical to identify at-risk populations for BD and the dose response signal adds validity to these findings.

When looked at the ADHD sub-domain classes, persistently high inattention and persistently high hyperactivity were significantly associated with clinically significant hypomanic symptoms. Interestingly, increasing inattentive levels were also significantly associated with clinically significant hypomanic symptoms but increasing hyperactivity levels were not. This is partly in line with previous research in which they found persistently high hyperactivity and inattention levels classes had the worst manic symptom severity scores (Arnold et al., 2014). Further, although they did not find a remitting class for inattentive levels, they did find for hyperactivity symptom trajectories suggesting that hyperactivity symptoms wane more over time. They added that the remitting trajectory was associated with the highest rate of ADHD and lowest rate of bipolar diagnoses. Building on these previous findings, our study adds that

both ADHD sub-domains with the most favorable (persistently low) and remitting trajectory classes had the lowest risk for subsequent clinically significant hypomanic symptoms and both ADHD sub-domains wane over time. A pattern of inattention symptoms that are both chronically high and increasing over time appears to be particularly impactful in developing hypomanic symptoms.

There are many potential mechanisms by which ADHD symptoms may either lead to hypomanic symptoms or reflect comorbidity. Whilst there are some common symptomatic features in both conditions, diagnostic criterion overlap may not entirely explain the comorbidity of both (Schiweck et al., 2021). It has also been found that some shared clinical features are due to shared genetic factors (Faraone & Larsson, 2019). For example, a twin study found that more than a quarter of the variance for hypomania was associated with shared genetic risk factors for ADHD traits and environmental influences appeared to have a negligible role in the associations between the two disorders (Hosang et al., 2019). Another large cohort study found that BD polygenic risk scores were strongly associated with childhood ADHD (Mistry et al., 2019). Additionally, a cross-disorder meta-analysis of the existing genome-wide association studies (GWAS; van Hulzen et al., 2017) provided evidence for genetic overlap between ADHD and BD such as G protein-coupled signaling already known for their role in hyperactivity and emotional behaviors. Further, another recent GWAS study (O'Connell et al., 2021) provided five novel risk loci showing concordant directions of effect for ADHD and BD. Future research is needed to clarify whether mechanisms driving associations between ADHD symptoms and hypomanic symptoms may differ depending on the pattern of ADHD symptoms that young people experience over time, including its subtypes. In line with previous research (Hosang et al., 2019)

our findings are unlikely to be explainable by symptom overlap given that exclusion of ADHD-like symptoms from the HCL variable did not modify our results.

There are several implications arising from the current findings. First, the present findings suggest that childhood and adolescent ADHD symptom trajectories, including its subtypes may confer risk for clinically significant hypomanic symptoms in young adulthood. Practitioners and patients would be best served in completing multiple assessments of ADHD symptoms over time to identify individuals who are most at risk of future BD. Formally classifying child trajectories to target the reduction in high-risk trajectories and encourage preventative treatments is a critical next step (Shore et al., 2018). This is crucial also because treatment earlier in the illness course is more effective (Berk et al., 2017; Nierenberg et al., 2023). If replicated in individuals entering health service systems, the results can substantially help refine clinical staging models (Shah et al., 2022). Future longitudinal research is needed to demonstrate the complex patterns of emergence of psychopathology in youth at-risk for BD, along with their homotypic and heterotypic continuity, within a developmental framework utilising multidisciplinary approaches (Manchia et al., 2020). Additionally, given the multidimensional nature of most mental disorders (Piazza et al., 2024; Stefan Leucht et al., 2024), transdiagnosticity of these associations should also be examined (Arribas et al., 2024; Destrée et al., 2024; Scott et al., 2024; Shah et al., 2020). This way, robust specific risk trajectories might also be identified. In the same vein, future research should also investigate the potential underlying mechanisms of the observed associations. Previous research has suggested that a history or current diagnosis of ADHD should be taken into account as a possible predictor of mixed or bipolar depression in patients with a major depressive episode (MDE; Purper-Ouakil et al., 2017). For example, a study looking at the prevalence of ADHD in adult patients with BD observed a higher frequency of atypical depression (i.e., hypersomnia, hyperphagia,

and increased appetite and weight gain) and a lower frequency of melancholic depression in the patients of the BD + ADHD group (Torres et al., 2015). Another study found that mixed features during current MDE, earlier onset of depression before the age of 20, higher number of previous depressive and mood episodes, shorter duration of current MDE, and psychotic symptoms were more common in patients with comorbid major depression and ADHD comparing to the remaining sample (Vannucchi et al., 2019). Thus, one of the potential mechanisms future studies could investigate may be clinical characteristics suggestive of a bipolar depression diathesis (e.g., atypical depression features, psychotic symptoms, abrupt onset and offset, non-response to antidepressants, or antidepressant emergent elation, and family history of BD).

Our study has several limitations. First, despite our methods and results meeting several of the Bradford Hill criteria (Hill, 1965), we have not demonstrated causation. Second, our cohort consisted of prepubertal children who tend to exhibit non-clinical symptomatology and derive from genetically heterogenous families. Therefore, our results may differ from young people who are seen in clinical settings. Third, ALSPAC has only one assessment timepoint of hypomanic symptoms. That is why, a baseline measure against which to compare stability symptoms over time was not available. Further, the HCL-32 was used as a measure of lifetime clinically significant hypomanic symptoms, but this will not always equate with a clinical diagnosis of hypomania and hypomanic symptoms were not clinically verified in the cohort (Marwaha et al., 2018b). The HCL-32 was self-reported, and this may have diminished the accuracy of the data due to recall biases. There is also a lack of chronology of hypomanic symptoms. Although we used a well-recognized cut-off score for lifetime hypomanic symptoms to improve the capacity of the HCL to identify clinical levels, amplified by measures of duration and impact on functioning, the combination of self-reports, parent reports and clinical structured interviews would be the ideal approach to increase the predictive value of our findings than the

use of a single scale (Vieta et al., 2018). That is why, replicating these findings in help-seeking clinical populations utilising both screening tools and clinical structured interviews is warranted. Fourth, only parent-reported data was available for all the ADHD assessments; however, symptoms may differ across settings and in interaction with different informants such as teachers and peers (Murray et al., 2020). Fifth, we were only able to look at ADHD symptoms from age 8 to 13. However, the trajectory classes we have observed are in line with the highly dynamic changes in ADHD presentation from childhood to adulthood evident in the previous literature (Franke et al., 2018; Murray et al., 2022; Rice et al., 2019). Sixth, the ALSPAC cohort was recruited in one region in Southwest England comprising mainly White participants, and therefore our findings may not generalize to other settings or birth cohorts. Additionally, although inverse probability weighting partially addressed cohort-specific patterns of non-response by adjusting samples to better represent the initial population, we cannot dismiss the biases that might stem from unmeasured factors that may influence missingness (Armitage et al., 2023). Seventh, although we focused on the associations with clinically significant hypomanic symptoms, given the multidimensional nature of most mental disorders (Arribas et al., 2024; McGorry et al., 2018; Scott et al., 2024; Shah et al., 2022), the same risk trajectories observed here may be associated with multiple types of disorders. Eight, there is the risk of residual confounding, as it is the case with all observational analyses. For example, childhood ADHD may increase the risk of developing substance-related disorders (Groenman et al., 2017; Ottosen et al., 2016; Skoglund et al., 2015) and there is a higher risk of developing BD in children and adolescents with ADHD with comorbid substance use disorders (SUDs; Lalli et al., 2021; Salvi et al., 2021). Past or current substance misuse may also confound the reliability of bipolar self-assessment screening (Goldberg et al., 2012) as SUDs can mimic affective episodes (Carvalho et al., 2020). Cannabis use, particularly, may compound dopaminergic signaling in adolescence and lead to an increased propensity to experience hypomanic symptomatology (Marwaha et al., 2018). Additionally, the

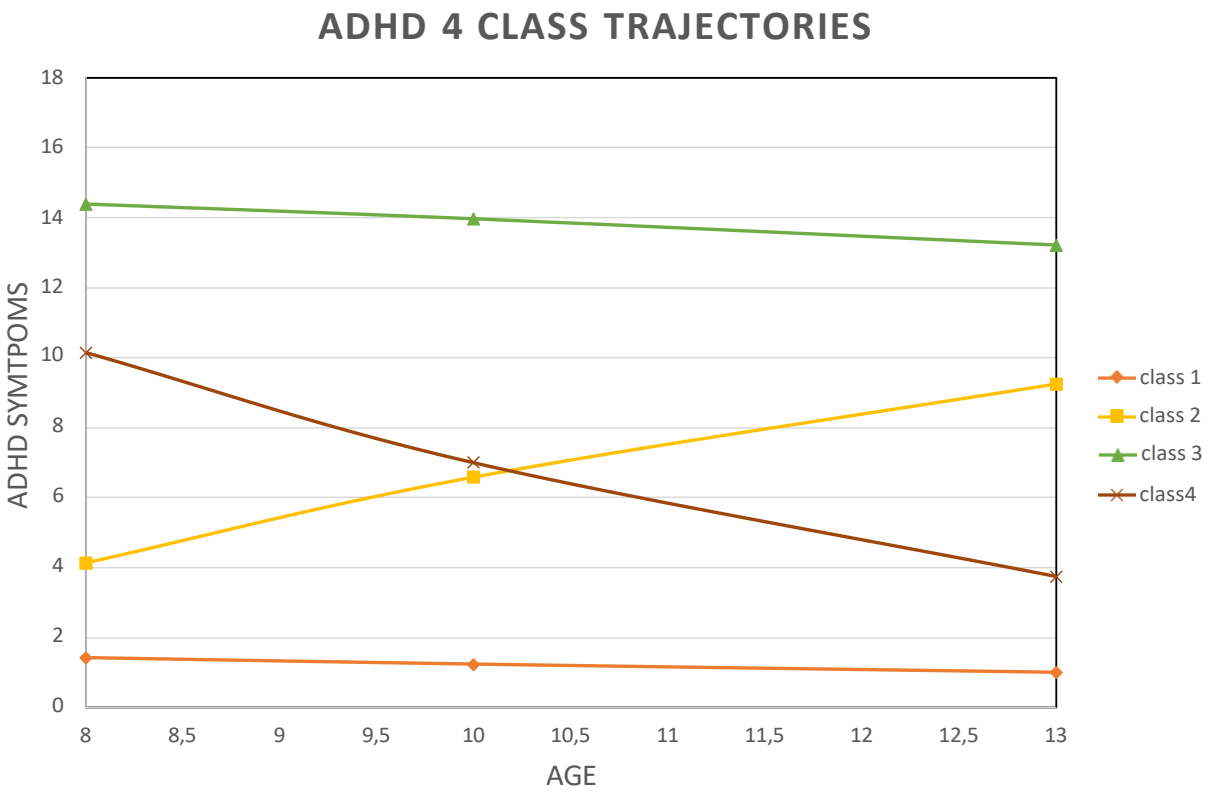
psychostimulant methylphenidate, one of the most widely used medications for ADHD, may increase the risk of treatment-emergent mania in patients suffering from BD when it is used without a concomitant mood-stabilizing treatment (Viktorin et al., 2017). However, it must also be noted that the available evidence with regards to manic switch risk with commonly used ADHD medications is limited and somewhat inconsistent (Miskowiak et al., 2024). For example, one study found that children with ADHD who were prescribed long-term methylphenidate (i.e., more than 365 days) had a lower risk of being diagnosed with BD (Wang et al., 2016). Additionally, given the similar cognitive impairments in BD and ADHD (Miskowiak et al., 2024), if the observed associations between persistent and increasing inattention trajectories and clinically significant hypomanic symptoms are replicated in high-risk samples, identifying effective pro-cognitive treatments alongside mood stabilisers might be a helpful early intervention strategy for cognitive impairments. Lastly, although we were not able to control for ADHD medication use, evidence coming from other UK cohort studies highlight that the proportion of children with ADHD using medication remains lower than in North America, East Asia, France and Central Europe (Raman et al., 2018; Russell et al., 2019) possibly due to stigma and lack of recognition of the condition (Young et al., 2021) and resource limitations (Asherson et al., 2022). Further, most of those who stop ADHD medication in adolescence do not have their prescriptions resumed in early adulthood (Newlove-Delgado, Ford, et al., 2019; Newlove-Delgado, Hamilton, et al., 2019). That is why, ADHD medication use might have had a negligible role in the associations we observed.

4.5. Conclusions

We identified a pattern of chronically high ADHD and increasing ADHD symptoms across childhood and early adolescence as independent risk factors for clinically significant hypomanic symptoms in young adulthood compared to persistently low and decreasing levels. We have also

found that a pattern of chronically high hyperactivity and inattention and increasing inattention levels were also independent risk factor for clinically significant hypomanic symptoms. These ADHD symptom profiles and trajectories represent a new and critical way of identifying at risk populations for BD. Further validation in help seeking clinical populations is warranted.

Figure 3. Four Class Model ADHD Symptoms - Developmental course of Development and Wellbeing Assessment (DAWBA) ADHD from 8 to 13 years old.



The latent class growth analyses detected a best model fit for 4 classes. Class 1 (orange line on the bottom) represents individuals with persistent low levels of ADHD across time points. Class 2 (yellow line) represents individuals with increasing levels of ADHD. Class 3 (green line on the top) represents individuals with persistent high levels of ADHD. Class 4 (brown line) represents individuals with decreasing levels of inattentiveness.

Table 4. Descriptive values of sociodemographic variables, ADHD symptom trajectories, and clinically significant hypomanic symptoms in ALSPAC Cohort[a]

Variable	Mean (SD)	No. (%)
Child's Sex		
Female	-	7348 (48.9)
Male	-	7691 (51.1)
Ethnicity		
White	-	12062 (97.4)
Bangladeshi	-	7 (0.1)
Black African	-	11 (0.1)
Black Caribbean	-	76 (0.6)
Black Other	-	44 (0.4)
Chinese	-	30 (0.2)
Indian	-	54 (0.4)
Pakistani	-	22 (0.2)
Other	-	82 (0.7)
FAI, total scores[b]	4.38 (4.31)	-
BPD symptoms at 11 years, total score	0.35 (0.86)	-
DAWBA ADHD symptoms at 8 years total score (n=7811), mean (SD)	4.21 (5.07)	-
DAWBA ADHD symptoms at 10 years total score (n=7435), mean (SD)	3.87 (4.91)	-

DAWBA ADHD symptoms at 13 years total score (n=6798), mean (SD)	3.42 (4.59)	-
Hypomanic symptoms total score at 21-23 years[c]	15.14 (16.00)	-
Clinically significant hypomanic symptoms at 21-23 years		
Yes	-	25 (1.8)
No	-	1348 (98.2)

Note: ADHD = Attention Deficit/hyperactivity disorder; BPD = Borderline Personality Disorder; DAWBA = Development and Well-Being Assessment; SD, Standard Deviation.

[a] Unweighted descriptive values for the total sample.

[b]The total Family Adversity Index scores for 3 time-points (i.e., during pregnancy, age 2 years, and age 4 years) were summed.

[c] Participants were asked to consider a time when they were in a "high or hyper" state and endorse a number of statements about their emotions, thoughts, and behaviours at that time.

Table 5. BIC, VLMR Likelihood Test p Values, and Entropy for Classes 2–6 of the DAWBA Scores of ADHD, Inattentive Only, and Hyperactivity Only

Composite Score of ADHD	AIC	BIC	ABIC	VLMR P-Value	LMRALT P-Value	Entropy
2 classes	121631.994	121689.284	121663.861	0.0000	0.0000	0.898
3 classes	118935.147	119013.921	118978.964	0.0000	0.0000	0.865
4 classes	117185.608	117285.865	117285.865	0.0000	0.0000	0.848
5 classes	116292.692	116414.433	116360.410	0.0549	0.0593	0.834
Hyperactivity Only						
2 classes	92437.058	92494.411	92468.988	0.0000	0.0000	0.927
3 classes	89626.816	89705.678	89670.721	0.0000	0.0000	0.893
4 classes	87450.031	87550.400	87505.910	0.0038	0.0045	0.875
5 classes	85894.420	86016.296	85962.273	0.1924	0.1997	0.859
Inattentive Only						
2 classes	100774.221	100831.546	100806.123	0.0000	0.0000	0.898
3 classes	98851.228	98930.049	98895.093	0.0000	0.0000	0.833
4 classes	95529.744	95630.062	95585.572	0.0000	0.0000	0.853
5 classes	94702.548	94824.362	94770.339	0.0061	0.0071	0.833

Abbreviations: ABIC, Sample-size Adjusted Bayesian Information Criterion; AIC, Akaike Information Criterion; ADHD; Attention deficit/hyperactivity disorder; BIC, Bayesian information criterion; DAWBA, Development and Well-Being Assessment; VLMR, Vuong-Lo-Mendell-Rubin; LMRALT, Lo-Mendell-Rubin Adjusted LRT Test P-Value.

Table 6. Associations of Latent Classes of ADHD, Hyperactivity Only, and Inattention Only and Risk of Clinically Significant Hypomanic Symptoms at 21-23 Years[a]

	Unadjusted Model			Adjusted Model		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
ADHD composite score						
Persistently low class (Ref)	-	-	<0.001			<0.001
Remitting class	0.00	0.00	0.992	0.00	0.00	0.990
Increasing class	3.88	2.12-7.08	<0.001	3.60	1.92-6.74	<0.001
Persistently high class	3.26	1.65-6.45	<0.001	2.36	1.12-4.99	0.024
Child's sex	-	-	-	1.18	0.68-2.04	0.560
Child's ethnicity	-	-	-	0.00	0.00	0.996
Family Adversity Index	-	-	-	1.19	1.13-1.25	<0.001
BPD traits at 11 years	-	-	-	1.26	1.07-1.49	0.007
Hyperactivity Only						
Persistently low levels (Ref)	-	-	<0.001	-	-	0.005
Remitting class	0.00	0.00	0.992	0.00	0.00	0.991
Increasing class	2.03	0.91-4.53	0.084	0.92	0.35-2.43	0.868
Persistently high class	4.77	2.44-9.29	<0.001	3.47	1.69-7.12	<0.001
Child's sex	-	-	-	0.97	0.55-1.71	0.911
Child's ethnicity	-	-	-	0.00	0.00	0.996
Family Adversity Index	-	-	-	1.14	1.09-1.20	<0.001
BPD traits at 11 years	-	-	-	1.20	1.00-1.44	0.048
Inattentive Only						
Persistently low levels (Ref)	-	-	0.011	-	-	0.039
Remitting class	0.00	0.00	0.995	0.00	0.00	0.995
Increasing class	3.58	1.47-8.70	0.005	3.25	1.32-8.04	0.011
Persistently high class	2.75	1.26-6.00	0.011	2.47	1.07-5.70	0.034
Child's sex	-	-	-	0.51	0.24-1.09	0.082
Child's ethnicity	-	-	-	0.00	0.00	0.997
Family Adversity Index	-	-	-	0.93	0.84-1.04	0.211
BPD traits at 11 years	-	-	-	1.37	1.10-1.70	0.004

Note: ADHD = Attention Deficit/hyperactivity disorder; BPD = Borderline Personality Disorder; DAWBA = Development and Well-Being Assessment; OR = Odds Ratio.

[a] All analyses were weighted for sex, ethnicity, maternal age, maternal socioeconomic status, preterm delivery, birthweight and family adversity; Adjusted Model: associations adjusted for child's sex, child's ethnicity, family adversity scores during pregnancy, at 2 years of age and 4 years of age, and BPD traits at 11 years.

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Chapter 5

Depression symptom trajectories across adolescence and risk of hypomanic symptoms in young adulthood: A UK Birth Cohort Study

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Abstract

Background: Depression is usually the index presentation of bipolar disorder (BD). However, it remains unclear whether and which trajectories of depression symptoms confer differential risk for developing BD. Further, potential underlying markers of risk of transition, such as psychotic symptoms and atypical depression features, to BD remain unknown.

Aims: To investigate the association between trajectories of depression symptoms in adolescence and risk of clinically significant hypomanic symptoms in young adulthood.

Methods: This cohort study used data from the Avon Longitudinal Study of Parents and Children. Self-reported depression symptoms were assessed at 10.5, 12.5, 13.5, and 16.5 years with the Short Moods and Feelings Questionnaire. Clinically significant hypomanic symptoms were assessed at 21-23 years using the Hypomania Symptom Checklist-32. Latent class growth analyses (LCGAs) were applied to detect trajectories of depression symptoms across adolescence, and logistic regressions were applied for the longitudinal associations between trajectories of depression symptoms and hypomania at 21-23 years. Path analyses were applied to test psychotic symptoms and atypical depression features at 18 years as potential mediators.

Results: The LCGA identified three depression symptom trajectories: increasing, decreasing, and persistently low levels. Adolescents with increasing levels of depression symptoms over 6 years were more likely to develop clinically significant hypomanic symptoms, compared to those with persistently low levels. Both atypical depression features and psychotic symptoms partially mediated the association of increasing depression levels with hypomanic symptoms.

Discussion: Adolescents with increasing depression symptoms in childhood are at higher risk for subsequent clinically significant hypomanic symptoms. Atypical depression and psychotic

symptoms partially mediate this. Consistently tracking young people's depression symptoms with a clinical focus on atypical and psychotic symptoms may more accurately inform the risk for developing BD. Our findings highlight the need for adopting a longitudinal approach integrating course trajectories and awareness of 'bipolar signature' features which can help to distinguish and appropriately treat young people who might be at-risk for developing BD.

Keywords: Depression, trajectories, hypomania, ALSPAC

5.1. Introduction

Early and accurate diagnosis of bipolar disorder (BD) is complicated because retrospective studies show most people with BD have depression as their index presentation, with hypomania and mania often presenting later (McIntyre et al., 2020) and with that the ability to confirm BD diagnosis. A meta-analysis showed that 22.5% of adults and adolescents with MDD followed up for longer than 12 years developed BD, with the greatest risk in the first 5 years of follow-up (Ratheesh et al., 2017). Therefore, depression is a precursor stage of BD. Detecting the signature phenotype could help earlier identification of young people who will go on to develop BD, offer them specialist treatment and avoid potentially harmful interventions (Ratheesh et al., 2017). However, the phenomenology and course of depression prior to BD onset is highly heterogenous, with evidence supporting different temporal associations between depression symptoms and BD onset (Bauer et al., 2018). Systematic reviews looking at predictors of conversion from unipolar to BD did not find consistent predictors related to the course of depression such as severity, recurrent MDD, chronicity, higher number of episodes (Kessing et al., 2017; Ratheesh et al., 2017). For example, some studies found that chronic depression increased the probability of conversion, others found it to be protective (Kessing et al., 2017; Ratheesh et al., 2017).

Most prospective studies investigating the association between depression symptoms and BD development have been limited by simply reporting depression symptom levels' mean or diagnostic proportions for the sample at various follow-up times. Characterizing heterogeneity in depression symptom course and phenomenology is important because this approach can capture intraindividual variability in symptoms which may also help explain apparent contradictory and inconsistent findings within the literature on the course of depression and its link to transition to

BD (Kessing et al., 2017; Ratheesh et al., 2017). Identifying which symptom trajectories are associated with the development of BD have the potential to clarify how we understand the relationship between depression and subsequent BD and/or hypomania, particularly during times of major neurobiological and socio-developmental transition such as adolescence to young adulthood (Shah et al., 2022). This could aid early prevention and intervention efforts, which is a critical missing gap in the care provision of this group. Further, this would help us better understand potential underlying mechanisms of BD. Since BD is commonly misdiagnosed as unipolar depression, special vigilance for symptoms that probabilistically suggest bipolar versus unipolar depression is also called for (McIntyre & Calabrese, 2019), even in at-risk stages (Frankland et al., 2018). This is necessary to avoid potential iatrogenic harms caused by antidepressants.

Mitchell and colleagues described a "bipolar signature", highlighting clinical features that might be associated with a greater probability of a depressive episode being associated with a bipolar diathesis (Mitchell et al., 2008). They highlighted atypical depressive features like hypersomnia, hyperphagia, and leaden paralysis, and psychotic features as the elements of this signature. When investigating the factors that might predict conversion from MDD to BD in at-risk populations, some studies found that atypical depression and psychotic symptoms occur significantly more frequently in depressed youth at-risk of early transition to BD (Diler et al., 2017; Duffy et al., 2019; James et al., 2015; Scott et al., 2017). Altogether, these studies underscore that atypical depression and psychotic symptoms might be potential indicators in the transition period from MDD and BD. However, their role needs to be examined longitudinally because the existing findings are inconsistent (Kessing et al., 2017; Ratheesh et al., 2017).

Our first aim was to examine the associations between trajectories of depression symptoms across adolescence and subsequent hypomanic symptoms in young adulthood. The second aim was to evaluate the potential mediating role of atypical depression features and psychotic symptoms on these prospective associations.

5.2. Methods

5.2.1. Participants

This study used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), an ongoing longitudinal UK birth cohort study designed to investigate the factors associated with the development, health, and disease during childhood and beyond (Boyd et al., 2013a; Fraser et al., 2013). All women resident in Avon, UK, with expected dates of delivery between 1 April 1991 and 31 December 1992 were contacted and eligible for participation (Golding et al., 2001) The study cohort consisted of 14,541 pregnancies and 13,988 children still alive at 1 year of age. Ethical approval was obtained from the ALSPAC Law and Ethics committee and the local research ethics committees (see Supplementary-Methods).

5.2.2. Measures

Depression symptoms across adolescence

The Short Mood and Feelings Questionnaire (SMFQ; Angold et al., 1995) was used to measure self-reported depression symptoms at 10.5, 12.5, 13.5, and 16.5 years old. SMFQ is a well-validated 13-item questionnaire enquiring about the occurrence of depression symptoms over the past 2 weeks (Eyre et al., 2021). While the items in the SMFQ do not completely reflect diagnostic criteria, the SMFQ shows good reliability and validity (Thabrew et al., 2018). We used the SMFQ total score, with higher scores indicating greater depression symptoms.

Clinically Significant Hypomanic symptoms at age 21-23

Study participants completed the Hypomania Checklist Questionnaire (HCL-32; Angst et al., 2005) a self-report measure of lifetime experience of manic symptoms comprising 32 items when they were 21-23 years old (see Supplementary-Methods). Consistent with previous work (Marwaha et al., 2018), we constructed a dichotomous clinically significant hypomanic symptoms variable; a) those with a symptom score ≥ 14 (out of 32) were classed as having hypomania if they also reported b) at least one incident of "negative consequences" or "negative plus positive consequences," as a result of hypomanic symptoms, c) that mood changes caused a reaction in people close to the participant and d) that symptoms lasted for "4 days" or more (Ratheesh et al., 2023). These approximate relatively closely to diagnostic criteria set out in the DSM-5 and ICD-11, though a clinical interview was not conducted in the ALSPAC cohort.

5.2.3. Mediators

Psychotic Experiences (PEs) at 17.5 years

PEs at 17.5 years were assessed by the Psychosis-Like Symptom Interview (PLIKS; Zammit et al., 2013). Interviewers rated PEs as not present, suspected, or definitely psychotic (see Supplementary-Methods; Zammit et al., 2013). We included definite PEs as a mediator in the analyses.

Atypical depression symptoms at 17.5 years

Atypical depression symptoms at 17.5 years were assessed by the Revised Clinical Interview Schedule (Lewis et al., 1992; CIS-R; see Supplementary-Methods). In line with previous research using ALSPAC (Donnelly et al., 2022). we derived an atypical depression symptoms score composed of the sum of participants scores on 4 items from the CIS-R: increased appetite, increased weight, hypersomnia and low energy. We have also looked at these features separately.

5.2.4. Confounders

Child's sex, and ethnicity were parent-reported. Multiple adverse childhood experiences were parent-reported using the Family Adversity Index (FAI) during pregnancy and at 2 and 4 years (see Supplementary Methods; Hines et al., 2023).

Any diagnosis of childhood psychopathology at 8 years were assessed using the parent version of the Development and Well-Being Assessment (Goodman et al., 2011; DAWBA; see Supplementary-Methods). The presence of any of any psychiatric disorder was coded as 1 and those without any diagnosis as 0, to account for possible comorbidities (Fahrendorff et al., 2023). Borderline personality disorder (BPD) traits were assessed using a face-to-face semi – structured interview, which was the Childhood Interview for DSM-IV Borderline Personality Disorder: UK Version (CI-BPD-UK), based on the borderline module of the Diagnostic Interview for DSM-IV Personality Disorders at 11 years old (see Supplementary-Methods; Zanarini, 2003). We controlled for BPD traits as these are highly associated with both depression and BD (Saunders et al., 2021; Zimmerman et al., 2021).

5.2.5. Statistical Analysis

Descriptive analyses were conducted in SPSS, v29. Latent class growth analyses (LCGA) were conducted using Mplus, v8 to potentially identify differing levels of depression symptoms across adolescence. The indicator variables were SMFQ scores at ages 10.5, 12.5, 13.5, and 16.5 years. Several models were fitted by increasing the number of classes (Jung & Wickrama, 2008) from 2 to 6 classes. The best-fitting classification model was chosen using lower sample size–adjusted Bayesian information criteria, significant Vuong-Lo-Mendell-Rubin and Lo, Mendell, and Rubin likelihood ratio tests, higher entropy value (Jung & Wickrama, 2008) and the proportion of individuals and interpretability of each class (Weavers et al., 2021) Missing values due to

attrition were handled by full information maximum likelihood estimation (FIML; Wardenaar, 2022).

We next explored the prospective associations between the depression symptoms trajectories identified by LCGA, and clinically significant hypomanic symptoms at 21-23 years. We conducted logistic regression analyses using SPSS, v29. The trajectories were the predictors (with the class with larger sample as reference), and clinically significant hypomanic symptoms at 21-23 years the outcome. We tested unadjusted associations, as well as adjusted associations. To deal with missingness, we conducted logistic regressions to identify significant factors associated with attrition (see Supplementary-Methods, Table S1). Using the variables associated with selective dropout as the factors to predict missingness, we fitted a logistic regression model (nonresponse vs response outcome) to determine weights for each individual using the inverse probability of response. We used this weighting variable in the logistic regression analyses.

Finally, we conducted path analyses using Mplus,v8. We examined the potential mediating role of psychotic symptoms and atypical depression symptoms at 17.5 years in the association between depression symptom trajectories and clinically significant hypomanic symptoms. We conducted separate mediation analyses for each atypical feature. The independent variable was dichotomized (1=LCGA class that was significantly associated with clinically significant hypomanic symptoms in the logistic regression analyses; 0=persistently low class). We controlled for sex, FAI, any childhood psychopathology at 8 years, and BPD symptoms at 11 years. Consistent with previous work (Winsper et al., 2013), the weighted least square mean and variance adjusted estimator were used for their robustness when analysing continuous and categorical outcomes (Flora & Curran, 2004). Missing data were dealt with using the FIML method.

5.3. Results

Data were available on 2,962 participants who reported on hypomania symptoms at 21 to 23 years. Table 7 gives the frequencies and descriptive values of sociodemographic and clinical variables for the entire cohort.

Latent Classes of depression symptoms

Table S2 shows the values of log-likelihood VLMR, ABIC, and other parameters for all models assessed. Evaluating fit, theory, and existing evidence, the 3-class model offered the best model fit and theoretical explanation (see Supplementary-Methods, Table S2 and 3, Figure S1).

Figure 4 shows the three trajectory classes: increasing levels (N=905, 10.3%), decreasing levels (N=579, 6.6%) and persistently low levels (N=7308, 83.1%).

Prospective associations between LCGA classes and clinically significant hypomanic symptoms

The adjusted logistic regression model (with persistent low depression symptom levels as the reference) showed that the increasing levels class was significantly associated with subsequent clinically hypomanic symptoms at 21-23 years (OR=3.30; 95% CI=1.78-6.12; p<0.001); while decreasing class was not (see Table 8).

Mediating associations of psychotic symptoms

When examining whether psychotic symptoms at 17.5 years mediated the prospective associations, path analysis model fit indexes yielded good model fit (Root Mean Square Error of Approximation [RMSEA]=0.05; Comparative Fit Index [CIF]=0.95). Psychotic symptoms at 17.5 partially mediated the association between exposure and outcome (β=0.05; SE=0.02; p=0.016), mediating 0.08% of the proportion. Direct associations appear in Figure 5.

Mediating associations of atypical depression features

Similar results were obtained for atypical depression features at 17.5 years as the mediating factor with a good model fit (RMSEA=0.04; CIF=0.98) and partially mediating the association between exposure and outcome (β=0.04; SE=0.02; p=0.014), mediating 0.20% of the proportion. Direct associations appear in Figure 6.

When looking at the atypical depression symptoms in separate models as an additional analysis, only low energy levels (RMSEA=0.04; CIF=0.96) mediated the association between exposure and outcome (β=0.03; SE=0.02; p=0.038), mediating 0.17% of the proportion (see Figure 7 for direct associations). Increased appetite and weight gain yielded a good model fit (RMSEA=0.04; CIF=0.98) but did not mediate the association between exposure and outcome (β=0.01; SE=0.00; P=0.170). Similar results were obtained for hypersomnia as the mediating factor with a good model fit (RMSEA=0.04; CIF=0.97) but not mediating the association between exposure and outcome (β=0.01; SE=0.02; P=0.592) although it was associated directly with hypomanic symptoms.

5.4. Discussion

To our knowledge, this is the first study to examine the extent to which depression symptom trajectories across adolescence are associated with later clinically significant hypomanic symptoms in young adulthood. We identified three groups of individuals with distinct trajectories: increasing, decreasing and persistently low levels of depression across adolescence. We found that an increasing trajectory of depression symptoms was associated with hypomanic symptoms at 21-23 years, and these associations were partially mediated by psychotic and atypical depression symptoms.

Emerging psychopathology in youth is highly dynamic and can vary substantially over time (Nelson et al., 2017). Our findings indicate that adolescents showing increasing levels of

depression symptoms might be at higher risk of developing clinically significant hypomanic symptoms in young adulthood. Previous prospective studies have also shown an association between greater number of depressive episodes and the later onset of BD (Duffy et al., 2019; Frankland et al., 2018; Tijssen et al., 2010). However, these studies have assessed depression at specific time points retrospectively. Further, most of these studies followed up the offspring of patients with BD, which are a minority of people with BD, and this may impact generalisability of those findings. Although there is significant heterogeneity in the emergent course of BD (Duffy et al., 2017), based on our results, increasing depression levels could be critical to identify at-risk populations for BD.

We additionally tested for the potential mediating role of atypical depression and psychotic symptoms, with both factors partially mediating these associations. This may suggest that atypical and psychotic symptoms could be early markers of the processes by which emergent hypomania is unmasked. Several prospective studies have looked at clinical features that might be useful to discriminate bipolar and unipolar depression in at-risk samples finding that at-risk populations tend to have more atypical depression features and psychotic symptoms (Diler et al., 2017; Durdurak et al., 2022; Frankland et al., 2018; Ratheesh et al., 2017b; Scott et al., 2017). Our findings arising from a population-based cohort suggest that these features may be particularly important for developing clinically significant hypomanic symptoms, if depression symptoms follow an increasing pattern over time. These features can be incorporated into screening tools (e.g., Bipolar at-risk criteria; Scott et al., 2017) that can be applied in a range of settings and clinical staging models (Corponi et al., 2020). Lastly, these data support the validity of Mitchell's 'bipolar signature' model (Frankland et al., 2018; Mitchell et al., 2008).

Further, when we looked at the atypical depression features in separate models, only low energy was significant. The reason might be the fact that there might be other relevant co-mediating factors we have not looked at. Recent evidence shows that the presence of immunometabolic dysregulations (e.g., increased inflammation and disrupted energy-regulating neuroendocrine signalling) in depressed patients map more consistently to atypical symptoms reflecting altered energy intake/expenditure balance (Lamers et al., 2018; Milaneschi et al., 2020). Immunometabolic dysregulations are also linked to mitochondrial dysfunction, and has been linked to BD (Morris & Berk, 2015). Thus, further research is needed to delineate specific immunometabolic dysregulation signatures and their relationship with atypical depression in youth presenting depressive trajectory who might transition to BD, along with adjusting for putative confounders such as current BMI and chronic diseases. This is imperative because if each of these atypical features' potential discriminative validity in the differential diagnosis between unipolar and bipolar depression is proven, at-risk youth could benefit from an integrated approach aimed at reducing the impact of these modifiable risk factors through the improvement of dietary habits, physical activity, sleep hygiene, lifestyle behaviours, along with tolerable pharmacological treatments, which can in return improve the illness course and outcome (Murru et al., 2019).

Implications

Our findings highlight the need for a more nuanced understanding of developmental trajectories accompanied by building mental health state service infrastructures for early intervention in BD. Given the complexity of diagnosing BD (Berk et al., 2017), rather than using one-off sampling cross-sectional data, monitoring early depression symptom trajectories to detect higher-risk trajectories and encouraging preventative treatments is critical. This is crucial also because

treatment earlier in the illness course is more effective (Berk et al., 2017; Nierenberg et al., 2023) and time to diagnosis is longer in patients with depressive onset polarity (Dagani et al., 2017). Further, since BD is commonly misdiagnosed as unipolar depression, practitioners should still remain vigilant for the risk of later BD in youth who initially seek help only for depression and screen negative for previous manic/hypomanic episodes, because they might later present clinically significant hypomanic symptoms, particularly if the symptoms are increasing over time with co-occurring factors that might suggest a bipolar diathesis like psychotic symptoms and atypical depression features. This has substantial clinical implications, not least awareness of risk of switch and cycling induced by antidepressants, and hence identifying this pattern might indicate to clinicians to avoid antidepressants in favour of alternative treatments. Because of the potentially progressive nature of the disorder (Kloiber et al., 2020; Yatham et al., 2024), early introduction of mood stabilisers and use of therapies with transdiagnostic utility such as psychotherapy and lifestyle interventions may prevent an adverse course of illness, aided by identification of this at-risk phenotype. Future longitudinal cohort studies with large samples are necessary to incorporate multidisciplinary approaches to better characterise the course and outcome of the disease (Kessing et al., 2021; Manchia et al., 2020; Vieta & Angst, 2021).

Strengths and limitations

Strengths of our study include the large population-based sample size, and a developmental approach integrating longitudinal dimensional methodology. However, there are also several limitations. First, despite our methods and results meeting several of the Bradford Hill criteria (Hill, 1965), we have not demonstrated causation. Second, since ALSPAC is a population-based cohort, our results may not be generalisable to actual help-seeking populations. Thus, replication in help-seeking clinical populations is warranted. Third**,** ALSPAC has only one assessment

timepoint of hypomanic symptoms which is the self-reported HCL-32, but this will not always equate with a clinical diagnosis of hypomania and retrospective insight in self-ratings of mania may not equate to clinical diagnoses. We also lack chronological data on hypomanic symptoms. However, we used a well-recognized cut-off score for hypomanic symptoms to improve the capacity of the HCL to identify clinical levels, amplified by dimensional measures of duration, observations by close ones and impact on functioning. Additionally, HCL-32 measures lifetime hypomanic symptoms reducing the recall bias, and it has demonstrated sufficient specificity and sensitivity.(Wang et al., 2019). Fourth, the ALSPAC cohort was recruited in one region comprising mainly White participants, reducing the generalisability of our findings. Additionally, although inverse probability weighting partially addressed cohort-specific patterns of non-response, biases from unmeasured factors influence missingness cannot be dismissed (Armitage et al., 2023). Fifth, due to the assessment time points of mediators and HCL-32, we were only able to look at SMFQ time points from 10.5-16.5. However, previous research using ALSPAC and looking at SMFQ symptom trajectories from 10.5 to 25.5 years consistently found the trajectories we observed, with additional persistently high and adolescent-limited classes (Kwong et al., 2019; Weavers et al., 2021). Sixth, atypical depression features assessed in the study do not completely overlap with DSM classification of atypical depression, limiting the comparability of the present findings with those from studies using clinical diagnostic criteria for subtype classification. Seventh, other potential underlying factors suggestive of a bipolar diathesis, such as episodic course of depression, abrupt onset and offset, prior cyclothymic features, non-response to antidepressants, or antidepressant emergent elation, family history of BD, lability of mood as well as mixed features (Faedda et al., 2019) or yet-to-be-defined and/or

evaluated factors such as biomarkers (Abi-Dargham et al., 2023) replicating sensitivity and specificity (Berk, 2023; Salagre et al., 2018; Yatham, 2023) could partially explain our results.

5.5 Conclusions

Our findings suggest that increasing levels of depression symptoms across adolescence may constitute a risk marker for developing clinically significant hypomanic symptoms in young adulthood. Further, "bipolar signature" elements, in particular atypical depression and psychotic symptoms partially mediated these prospective associations. If replicated in help-seeking clinical populations, the findings may aid future targeted early interventions and help clinicians with diagnostic challenges in differentiating early depressive illness that may later meet criteria for BD. Individualised interventions need to focus on modelling change over several points in time to truly characterise variation in the emerging BD rather than utilising only baseline predictions.

Author Contributions:

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Drafting of the manuscript: Durdurak.

Critical revision of the manuscript for important intellectual content: Berk, Morales-Munoz, Marwaha, Ratheesh.

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Table 7. Descriptive values of sociodemographic variables, depression symptom trajectories, atypical depression symptoms, psychotic experiences, and clinically significant hypomanic symptoms in ALSPAC Cohort[a]

Variable	Mean (SD)	No. (%)
Child's Sex		
Female	-	7348 (48.9)
Male	-	7691 (51.1)
Ethnicity		
White	-	12062 (97.4)
Bangladeshi	-	7 (0.1)
Black African	-	11 (0.1)
Black Caribbean	-	76 (0.6)
Black Other	-	44 (0.4)
Chinese	-	30 (0.2)
Indian	-	54 (0.4)
Pakistani	-	22 (0.2)
Other	-	82 (0.7)
FAI, total scores[b]	4.38 (4.31)	-
Any childhood psychopathology at 8 years		
Yes	-	555 (6.8)
No	-	7644 (93.2)
BPD symptoms at 11 years, total score	0.35 (0.86)	-
SMFQ depression symptoms at 10.5 years total score	4.04 (3.00)	-
SMFQ depression symptoms at 12.5 years total score	3.97 (3.00)	-
SMFQ depression symptoms at 13.5 years total score	4.92 (4.00)	-
SMFQ depression symptoms at 16.5 years total score	5.91 (4.00)	-
Psychotic experiences at 17.5 years	0.13 (0.55)	-
Atypical depressive symptoms at 17.5 years	0.41 (0.57)	-
Hypomanic symptoms total score at 21-23 years[c]	15.14 (16.00)	-
Clinically significant hypomanic symptoms at 21-23 years		
Yes	-	25 (1.8)
No	-	1348 (98.2)

Abbreviations: BPD, Borderline Personality Disorder; FAI, Family Adversity Index; SD, Standard Deviation; SMFQ, Short Moods and Feelings Questionnaire.

[a] Unweighted descriptive values for the total sample.
[b] The total Family Adversity Index scores for 3 time-points (i.e., during pregnancy, age 2 years, and age 4 years) were summed.
[c] Participants were asked to consider a time when they were in a "high or hyper" state and endorse a number of statements about their emotions, thoughts, and behaviours at that time.

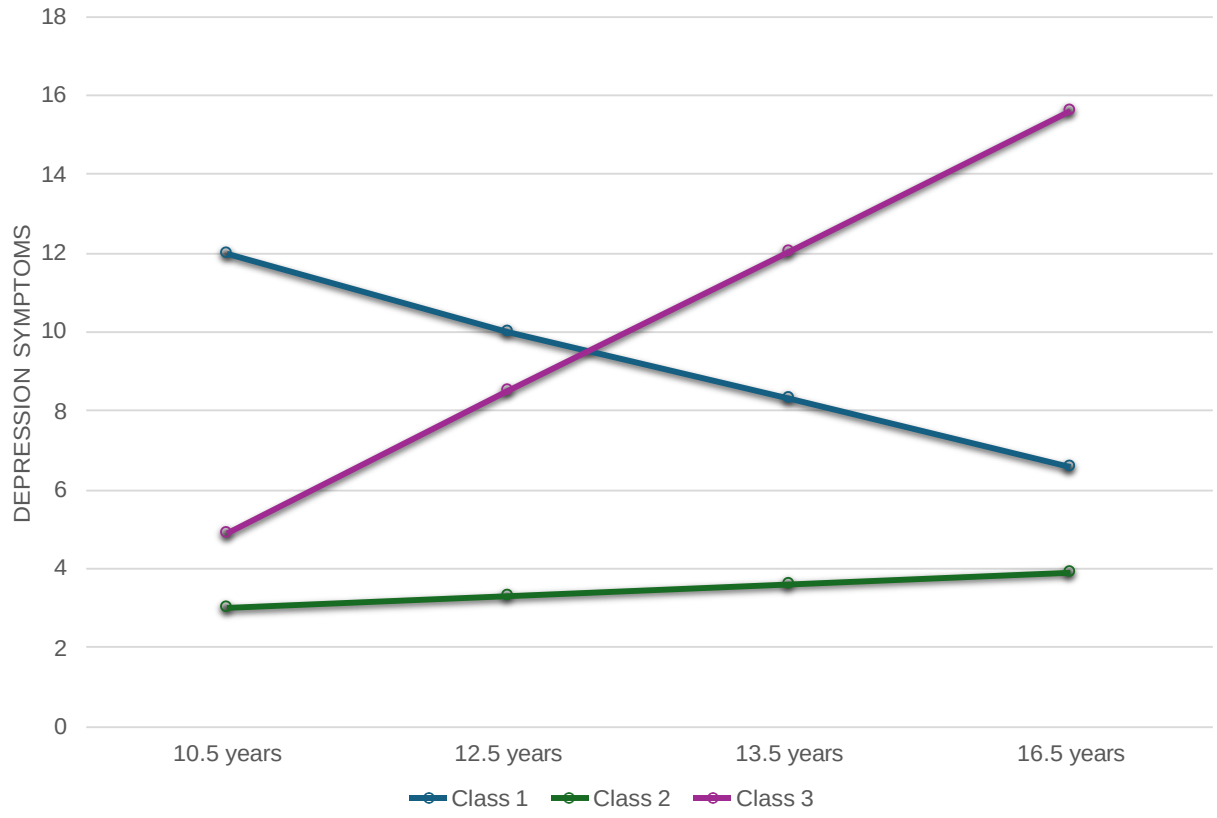
Table 8. Associations of Latent Classes of SMFQ and Risk of Clinically Significant Hypomanic Symptoms at 21-23 Years[a]

	Unadjusted Model			Adjusted Model		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Hypomanic symptoms at 21-23 Years						
SMFQ persistent low levels class (Reference)	-	-	<0.001	-	-	<0.001
SMFQ increasing class	4.48	2.64-7.58	<0.001	3.30	1.78-6.12	<0.001
SMFQ decreasing levels class	0.00	0.00	0.993	0.00	0.00	0.993
Child's sex	-	-	-	0.89	0.50-1.58	0.679
Child's ethnicity	-	-	-	0.00	0.00	0.996
Family Adversity Index	-	-	-	1.19	1.13-1.25	<0.001
Any Childhood psychopathology at 8 years	-	-	-	4.03	2.00-8.08	<0.001
BPD symptoms at 11 years	-	-	-	1.27	1.08-1.51	0.005

Abbreviations: BPD, Borderline Personality Disorder; OR, Odds Ratio; SMFQ, Short Moods and Feelings Questionnaire.

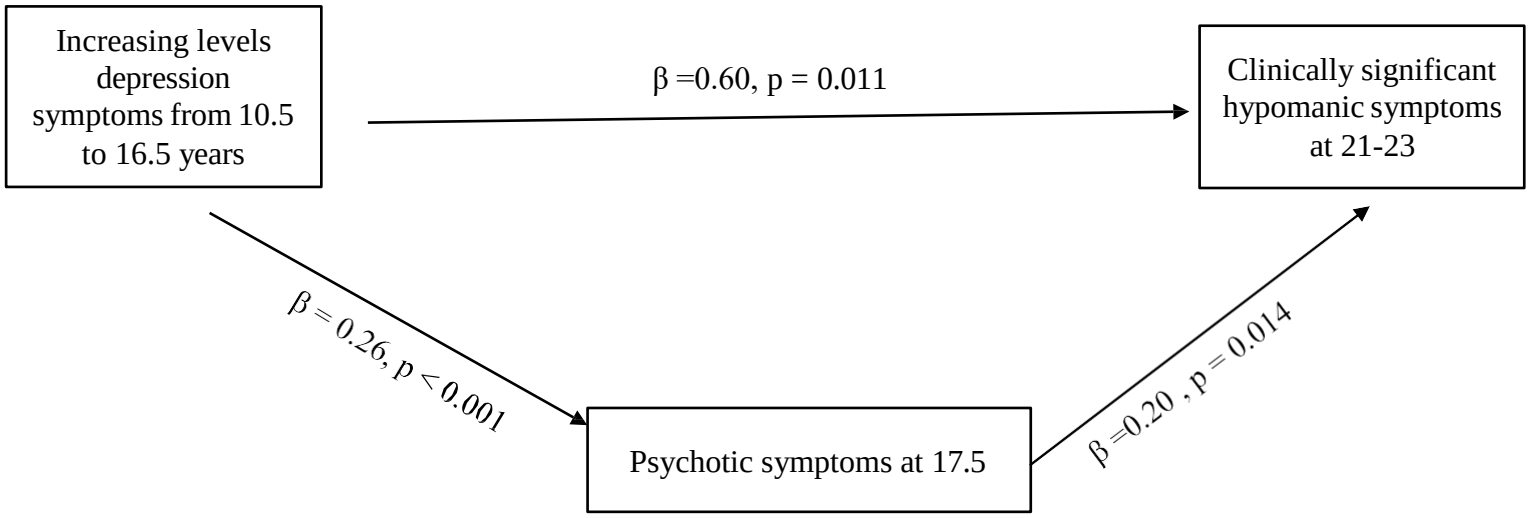
[a] All analyses were weighted for sex, ethnicity, family adversity, age of mother at pregnancy, child's birthweight, preterm delivery, and mother's socioeconomic status; Unadjusted Model : unadjusted associations; Adjusted Model: associations adjusted for child's sex, child's ethnicity, family adversity, any clinician diagnosis of childhood psychopathology (i.e., oppositional defiant disorder, conduct disorder, attention deficit hyperactivity disorder including inattentive only and hyperactivity only type, disruptive behaviour disorder not otherwise specified, pervasive development disorder, separation anxiety disorder, specific phobia, social phobia, obsessive compulsive disorder, generalised anxiety disorder, anxiety disorder not otherwise specified and posttraumatic stress disorder) at 8 years, and BPD symptoms at 11 years.

Figure 4. Three Class Model SMFQ Symptoms – Short Moods and Feelings Questionnaire (SMFQ) from 10.5 to 16.5 years old.



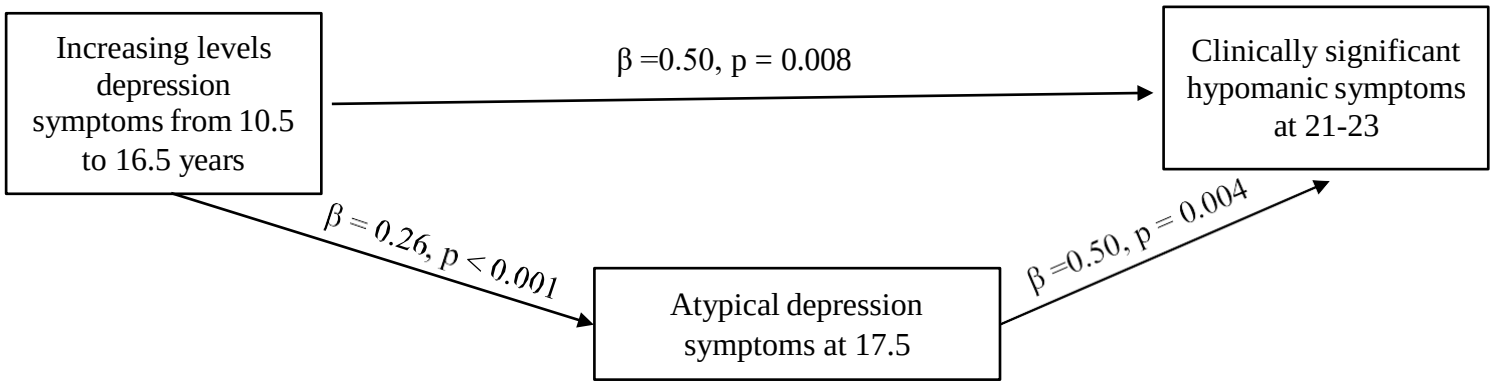
The latent class growth analyses detected a best model fit for 3 classes. Class 1 (blue line, 579 participants [6.6%]) represents individuals with decreasing levels of depression symptoms across time points. Class 2 (green line, 7308 participants [83.1%]) represents individuals with persistent low levels of depression symptoms. Class 3 (purple line, 905 participants [10.3%]) represents individuals with increasing levels of depression symptoms.

Figure 5. Direct Path Between Increasing levels of depression symptoms, psychotic symptoms at 17.5 years and clinically significant hypomanic symptoms at 21-23 years



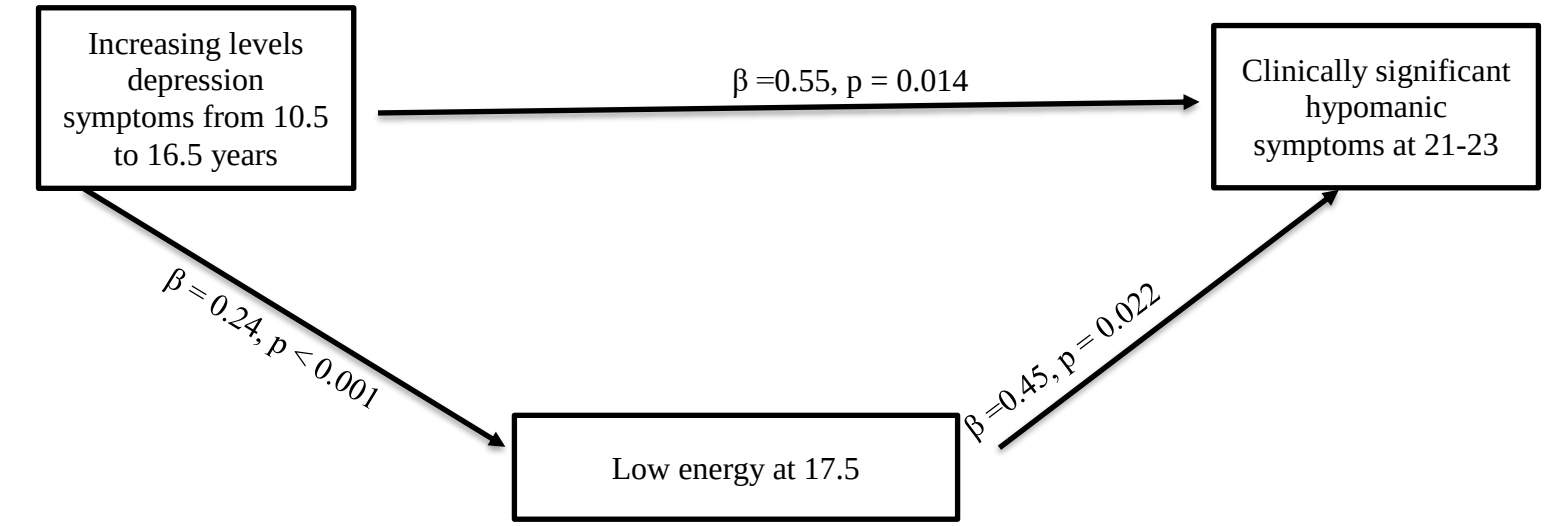
This figure shows the direct significant associations of the independent, mediating, and dependent variable. Increasing depression symptom levels from 10.5 to 16.5 years of age represent independent variable; psychotic symptoms at 17.5 represent the mediator, and clinically hypomanic symptoms at 21-23 years represent the dependent variable (outcome). The covariates also included in this path analyses were child's sex, childhood adverse experiences, any childhood psychopathology diagnosis at 8 years, and BPD traits at 11 years. Significant pathways are signified by solid arrows.

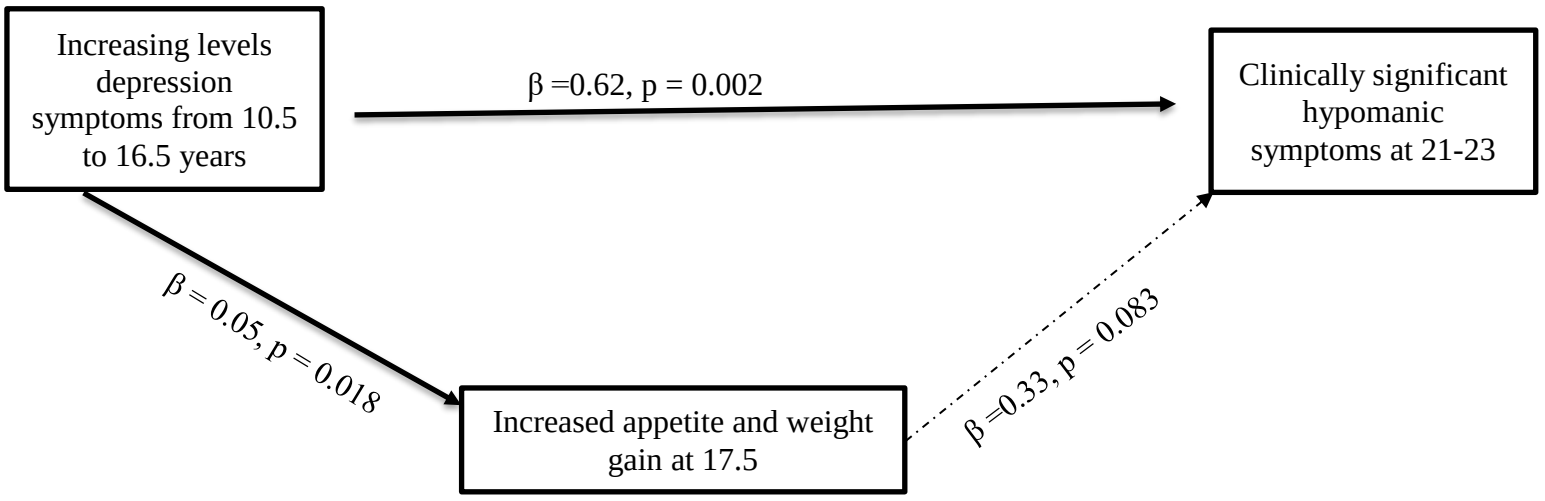
Figure 6. Direct Path Between Increasing levels of depression symptoms, atypical depression symptoms at 17.5 years, and clinically significant hypomanic symptoms at 21-23 years

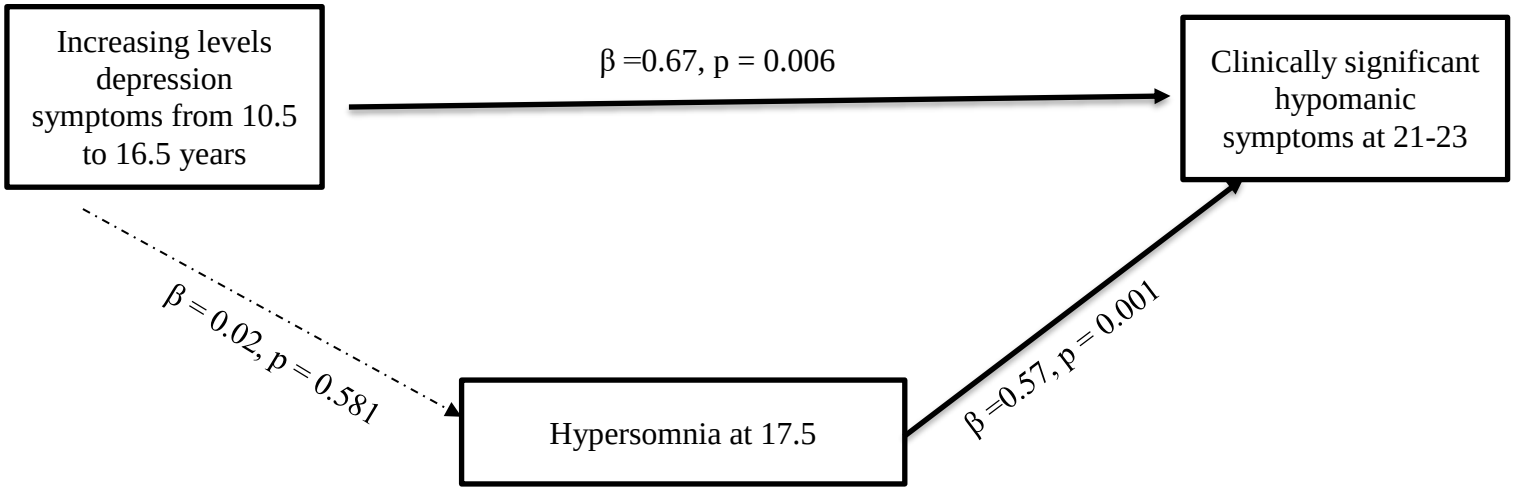


This figure shows the direct significant associations of the independent, mediating, and dependent variable. Increasing depression symptom levels from 10.5 to 16.5 years of age represent independent variable; atypical depression symptoms at 17.5 years represent the mediator, and clinically hypomanic symptoms at 21-23 years represent the dependent variable (outcome). The covariates also included in this path analyses were child's sex, childhood adverse experiences, any childhood psychopathology diagnosis at 8 years, and BPD traits at 11 years. Significant pathways are signified by solid arrows.

Figure 7. Direct Path Between Increasing levels of depression symptoms, psychotic and clinically significant hypomanic symptoms at 21-23 years







This figure shows the direct significant associations of the independent, mediating, and dependent variable. Increasing depression symptom levels from 10.5 to 16.5 years of age represent independent variable; low energy, increased appetite and weight gain, and hypersomnia represent the mediators, and clinically hypomanic symptoms at 21-23 years represent the dependent variable (outcome). The covariates also included in this path analyses were child's sex, childhood adverse experiences, any childhood psychopathology diagnosis at 8 years, and BPD traits at 11 years. Significant pathways are signified by solid arrows and nonsignificant pathways by dashed arrows.

Chapter 6

General Discussion

6.1. Summary of findings

The overall aim of the work presented in this thesis was to understand the developmental pathways to BD. Three work packages were used to achieve this aim. This involved firstly, synthesising the available evidence for risk factors for BD and BPD onset in at-risk populations (Chapter 2); secondly, investigating whether, different trajectories of ADHD symptoms in childhood and early adolescence (Chapter 4) are associated with risk of clinically significant hypomanic symptoms in young adulthood, in a longitudinal population sample; and finally, investigating whether in the same longitudinal population sample, different trajectories of depressive symptoms in adolescence (Chapter 5) are associated with risk of clinically significant hypomanic symptoms in young adulthood, and whether these associations are mediated by bipolar signature elements such as atypical depression and psychotic symptoms.

The findings from the meta-review of reviews in Chapter 2 have contributed to knowledge by synthesising prognostic risk factors for transition to BD and BPD in at-risk populations. The results suggest that BD and BPD share several common risk factors even in the at-risk stages such as family history of psychopathology, affective instability, ADHD, anxiety disorders, depression, sleep disturbances, substance abuse, psychotic symptoms, suicidality, childhood adversity and temperament. These identified risk factors could potentially be used as predictors in future prognostic models, including transdiagnostic staging models.

This synthesised knowledge was also groundwork for the subsequent Chapter 4 and Chapter 5 as the findings demonstrated further that ADHD and depression are potential risk factors for the

risk of developing of BD. However, there is still a need for prospective studies, particularly in population-based cohorts, with different methodological approaches to better reflect developmental course of symptoms and potentially uncover risk phenotypes. That is why, in chapter 4 and 5, LCGA methodology was used to identify homogeneous groups of sub-populations that would have been masked if only a single regression line was estimated and map the developmental course of ADHD and depression symptoms, in a population-based cohort. In Chapter 4, it was observed that, a trajectory of high and increasing ADHD symptoms in childhood and early adolescence was associated with clinically significant hypomanic symptoms at 21-23 years. Further to this, when looked at the ADHD sub-domains (i.e., hyperactivity type only and inattentive type only), persistent hyperactivity and inattentive and increasing inattentive symptoms were significantly associated with clinically significant hypomanic symptoms. These findings appear to contrast with those reported by Friedreichs et al. (2012) which used data from a population-representative Swedish Twin Registry. They found that ADHD hyperactivity-impulsivity subtype (based on DSM-IV criteria; APA, 2000) had a lower risk of having comorbid BD than other subtypes (i.e., combined and inattentive only). One potential explanation for these discrepant findings lies in differences in study design and methodology. The study assessed ADHD symptoms at a single time point in adulthood, whereas the study in Chapter 4 utilised a longitudinal developmental approach that captured ADHD symptom trajectories from childhood through adolescence. These limitations may have led to underestimation of hyperactive-impulsive symptoms in individuals with early-onset ADHD and, consequently, an attenuated association with BD. This also highlights the importance of considering symptom progression over time rather than relying on static, cross-sectional assessments.

In Chapter 5, the same methodology was implemented to examine whether and which

trajectories of depressive symptoms in adolescence confer differential risk for clinically significant hypomanic symptoms at 21-23 years. The results showed that a trajectory of increasing depressive symptoms was associated with clinically significant hypomanic symptoms at 21-23 years. In addition to these, when looked at the potential mediating roles of atypical depression and psychotic symptoms between the increasing levels of depression symptoms and clinically significant hypomanic symptoms, both of these "bipolar signature elements" partially mediated the association between increasing levels of depression symptoms and clinically significant hypomanic symptoms. However, when looked at the each atypical depression symptoms in three separate models as additional analyses, only low energy levels partially mediated this

association. All these associations remained present after taking into account all covariates, including BPD symptoms at 11 years.

Overall, the results from Chapters 4 and 5 suggest that persistent ADHD symptoms (including its subtypes), increasing ADHD (including inattentive only type) and increasing depression symptoms across childhood and adolescence may be important risk factors for the increased risk of developing clinically significant hypomanic symptoms in young adulthood. Further, and in relation to increasing depression symptoms over time as a potential risk factor, atypical and psychotic symptoms may be particularly important for developing clinically significant hypomanic symptoms, if depression symptoms follow an increasing pattern over time in adolescence. If our findings are replicated, particularly in help seeking clinical high risk and/or offspring of parents with BD samples, they have the potential to be incorporated into screening tools and clinical staging models and used potentially as robust factors associated with transition risk in at-risk BD individuals. The findings of this thesis also lead to further questions and suggestions for future research which will be discussed at the end of this chapter.

6.2. Implications of findings

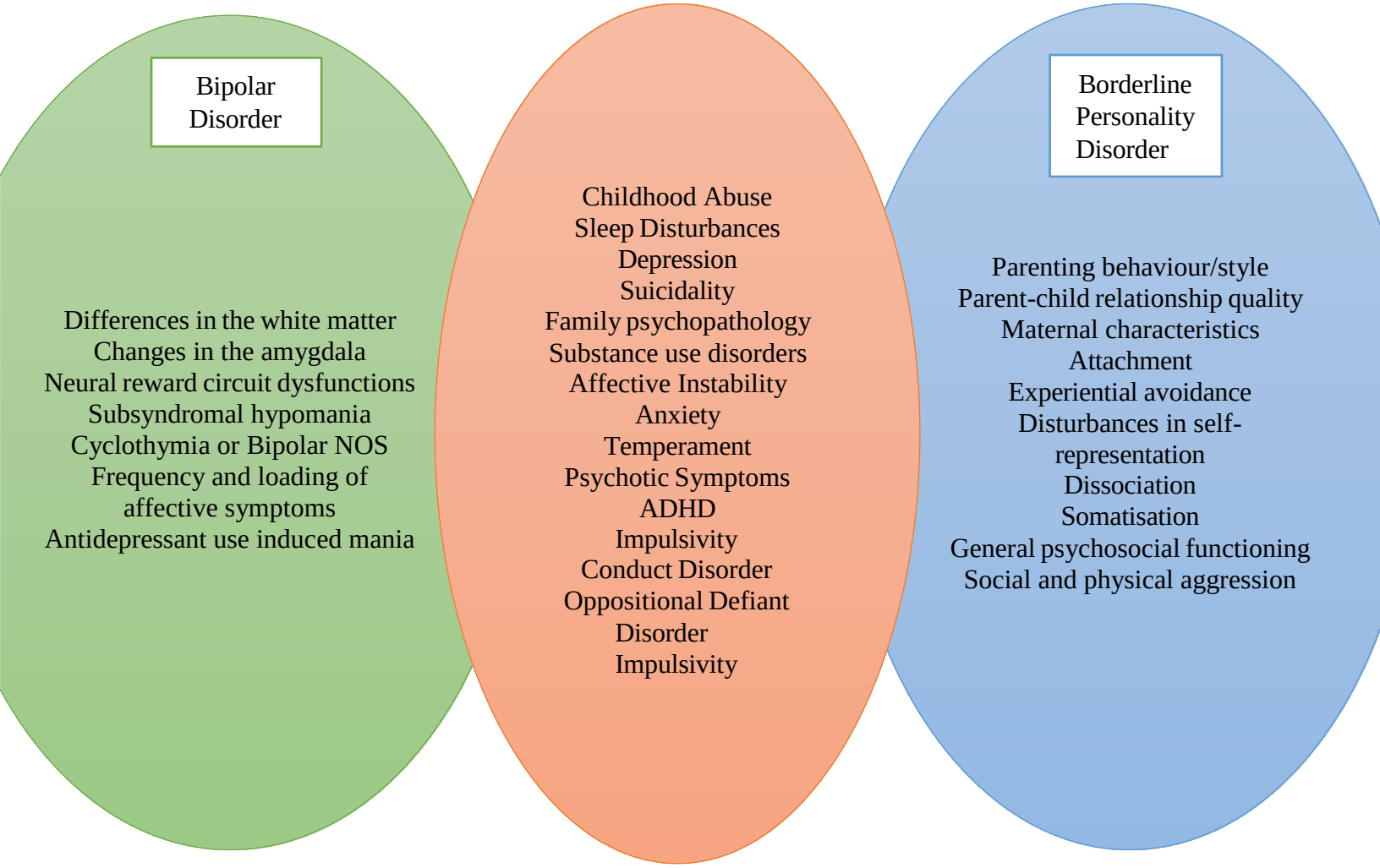
6.2.1 Bipolar Disorder and Borderline Personality Disorder

The observation that BD and BPD share common risk trajectories even in at-risk stages have important potential implications (Chapter 2). As has been discussed in Chapter 1, distinguishing BPD from BD is challenging and difficult due to the phenomenological overlap of symptoms (Zimmerman et al., 2021). In addition to the overlap of symptoms, according to a GWAS study, they share genetic overlap as well (Witt et al., 2017). The two disorders also often co-occur together (Palmer et al., 2021; Zimmerman et al., 2021) and when BD and BPD co-occur, the prognosis of the disease is worse than for either condition alone (Zimmerman et al., 2021). Research has also showed that sub-threshold BPD features were common in both BD I and BD II, and even the presence of a single BPD feature was significantly associated with earlier age at onset and higher prevalence of lifetime alcohol misuse in both BD groups (Saunders et al., 2021). However, most of these phenomenological studies trying to distinguish BD and BD have been undertaken in adults, when the disorders are "formed" and have mostly "run their course" (Chanen et al., 2016).

Like BD, BPD usually has its onset in the period between puberty and emerging adulthood (Chanen et al., 2017). BPD is associated with long term adverse outcomes underscoring the public health priority to minimise or avoid such outcomes through early diagnosis and treatment (Chanen et al., 2017; Chanen et al., 2020). Therefore, the concept of clinical staging and the "at risk mental state", which has been applied to psychosis and BD, has been applied to BPD too (Chanen et al., 2017; Hutsebaut et al., 2019). Evidence indicated that many of the risk factors associated with BPD are also risk factors for a later diagnosis of BD such as ADHD, disruptive behaviour disorders, unipolar depression, anxiety disorders, childhood abuse, substance abuse

(Bohus et al., 2021; Leichsenring et al., 2023). In fact, Chanen and colleagues (2016) proposed a potential clinical-staging model for BD and BPD highlighting that BPD and mood disorders frequently co-occur, can reinforce one another, and can be difficult to differentiate clinically (Chanen et al., 2016). Synthesising the available evidence now regarding the risk trajectories associated with BD and BPD onset was the first attempt to understand borderline-BD related psychopathology and potentially improve the prediction of the onset of these disorders. Through this, I was able to highlight that a) BD and BPD share many common risk factors such as family history of psychopathology, affective instability, attention deficit hyperactivity disorder, anxiety disorders, depression, sleep disturbances, substance abuse, psychotic symptoms, suicidality, childhood adversity and temperament; b) there are factors that are studied either only in BD at-risk studies or in BPD at-risk studies meaning their distinctive nature is questionable until they are studied both in BD at-risk and BPD at-risk populations; c) there is a lack of research into robust prognostic factors lacking specificity and sensitivity in both populations although the research into BPD is much scarce; d) research on the early signs and symptoms of mental disorders tends to be confined to discrete "silos" and thus there is an urgent need for prospective at-risk studies including both populations looking at their developmental and phenomenological change and evolution (see Figure 7).

Figure 7. Developmental risk factors for the development of BD and BPD



Note. Overview of findings arising from Chapter 2.
BD and BPD share many common risk factors as indicated in the middle. There are also risk factors associated with only BD at-risk and BPD at-risk. However, since these "distinct" risk factors are not studied in both populations, their distinctive nature (i.e., specificity) cannot be ascertained until future studies examine them concurrently.

6.2.2 Bipolar Disorder and ADHD

As discussed, like with BPD and BD, differential diagnosis between ADHD and BD remains a challenge, due to overlapping symptoms and high rates of comorbidity (Schiweck et al., 2021). Further, there is shared underlying genetic risk for ADHD and BD (O'Connell et al., 2021). The two disorders also show similar cognitive impairments across several domains such as working memory or abnormal dopamine signalling (i.e., dysfunction of the dopamine transporter; Miskowiak et al., 2017; Torres et al., 2017). There is also substantial evidence that childhood ADHD precede BD (Brancati et al., 2021; Khoury et al., 2023; Martini et al., 2024)but the results are inconsistent and the majority of the previous studies either looked at the association between ADHD and BD cross-sectionally, or prospectively but only reporting symptom means or diagnostic percentages. Thus, the work presented in Chapter 4 addressed a clear limitation in our ability to understand the association between childhood and early adolescence ADHD trajectories and their association with clinically significant hypomanic symptom in young adulthood by using dimensional measures for ADHD and for hypomania and utilising group-based trajectory modelling such as LCGA to examine developmental psychopathology, instead of classifying individuals into discrete diagnostic categories (Nagin et al., 2024). This is important also because ADHD-related difficulties may behave as continuous traits and many individuals who do not meet diagnostic criteria may still experience adverse outcomes (Thapar et al., 2017). Moreover, I have advanced knowledge by demonstrating that these associations are unlikely to be explainable by symptom overlap given that exclusion of ADHD-like symptoms from the hypomania measure did not modify the results. Future replicating work is needed in clinical at-risk samples to clarify whether these ADHD trajectories associated with clinically significant hypomanic symptoms may represent distinct early-onset subtypes for the onset of BD. If replicated, identifying these patterns in childhood and adolescence might foster research

regarding the most appropriate pharmacological management to avoid triggering mania/hypomania as there might be a risk of treatment emergent mania with methylphenidate monotherapy (Miskowiak et al., 2017; Viktorin et al., 2017). However, it must be noted that the available evidence with regards to manic switch risk with commonly used ADHD medications is limited (Miskowiak et al., 2024) and inconsistent. For example, one study found that children with ADHD who were prescribed long-term methylphenidate (i.e., more than 365 days) had a lower risk of being diagnosed with BD (Wang et al., 2016). Additionally, given the similar cognitive impairments in BD and ADHD (Miskowiak et al., 2024), if the observed associations between persistent and increasing inattention trajectories and clinically significant hypomanic symptoms are replicated in high-risk samples, identifying effective pro-cognitive treatments alongside mood stabilisers might be a helpful early intervention strategy for cognitive impairments.

6.2.3 Bipolar Disorder and Depression

To date, while numerous prospective studies have looked at the transition from depression to BD, they have been restricted by mainly reporting transition percentages or symptom means. Further, like BD, depression is highly heterogenous in its course, particularly in young people (Weavers et al., 2021). The work presented in Chapter 5 provides a novel contribution by characterizing heterogeneity in depression symptom course and phenomenology and exploring which trajectories may confer risk for developing BD. Although replication is warranted in help seeking high-risk samples, the results observed underscore the further need to better characterise the clinical course of depressive symptoms to optimise the design and implementation of early detection and intervention programs and refine existing staging models. In addition, the observed partial mediation for common characteristics related to bipolar depression (i.e., atypical depression and psychotic symptoms) in Chapter 5 advanced knowledge by demonstrating that

there might be clinically meaningful differences in the depression symptom profiles experienced by those who might be at-risk of developing BD compared to those who are not. The results indicate careful monitoring of these bipolar depression risk phenotypes because the presence of these clinical characteristics might be a gateway for developing BD in youth with an increasing depression symptom course. There are currently no accepted diagnostic criteria for bipolar depression for either research or clinical purposes. If replicated, these risk phenotypes may form the basis of risk prediction models (e.g., Bechdolf et al., 2014; Birmaher et al., 2018; Fusar-Poli et al., 2018; Hafeman et al., 2017; Leopold et al., 2012), increasing their utility. Additionally, there may be a long delay between an index depressive episode and a first (hypo)manic episode (Kupka et al., 2021). Thus, these results also encourage caution in initiating treatment with an antidepressant in youth with an increasing depressive symptomatology in the presence of bipolar depression elements, to prevent the risk of iatrogenic switch to mania.

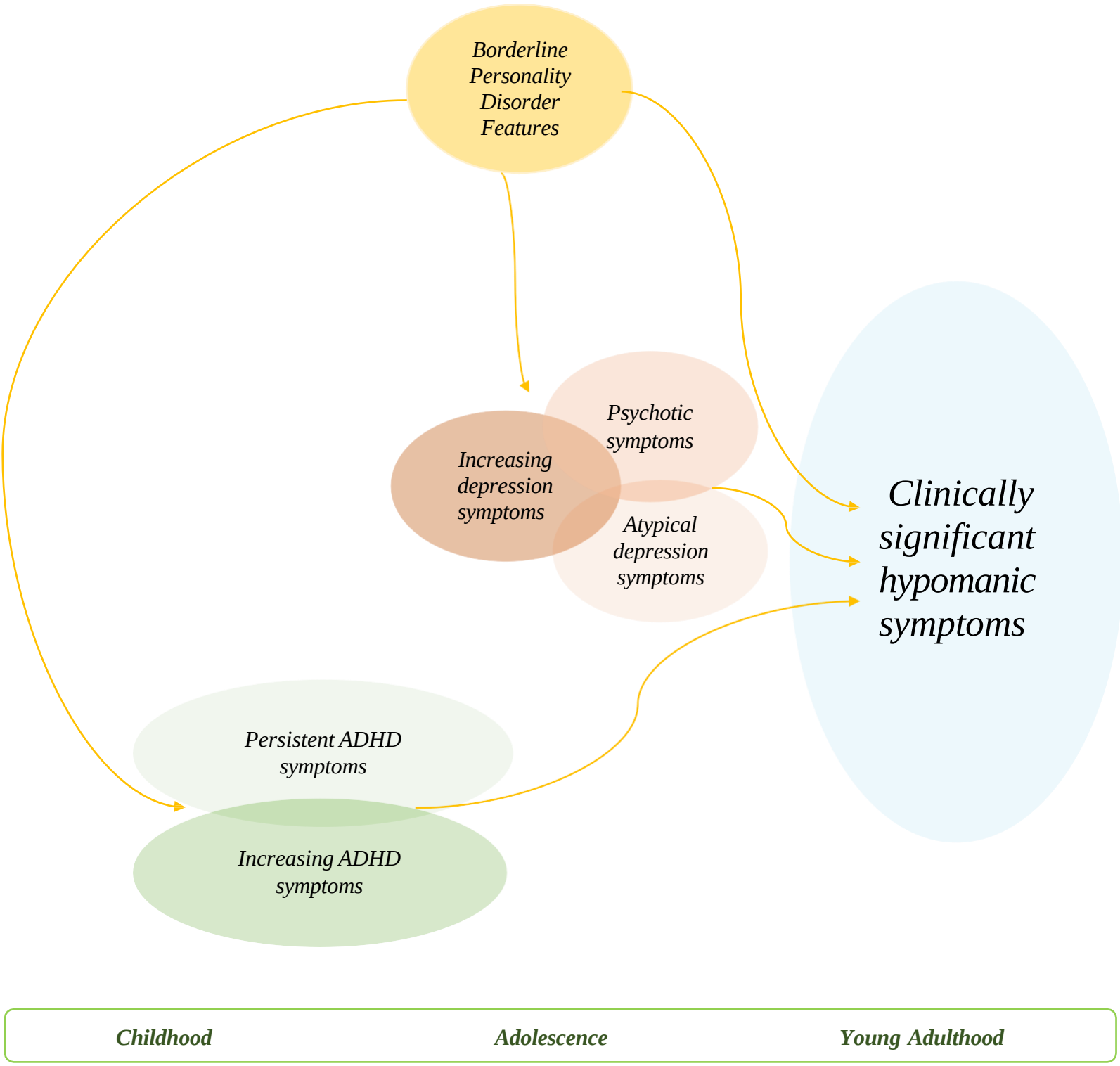
6.2.4 *The Importance of long-term monitoring in understanding aetiological pathways*

The work presented in Chapter 4 and 5 have demonstrably underscored the importance of repeated assessments by identifying potential distinct phenotypic risk profiles for developing BD (see Figure 8). As stated previously, BD is a heterogeneous disorder marked by complex aetiology and highly variable clinical presentation, longitudinal course, and response to treatment (Mignogna & Goes, 2024). Emerging psychopathology, in general, is highly dynamic; symptoms can vary substantially over time and defy diagnostic boundaries (Nelson et al., 2017). However, progress in conceptualizing mental disorders has been delayed by the field's limiting focus on cross-sectional information assuming that a single baseline assessment of clinical variables may index level of risk for the emergence of diagnosable mental disorder (Caspi et al., 2020; Nelson et al., 2017). Researchers and clinicians in mental health fields typically assess a patient at one

point in the patient's life, and, accordingly, tend to study or treat the disorders that can be diagnosed at that time (Caspi et al., 2020), possibly partly due to high costs and low funding (McGorry et al., 2024).

Epidemiologic research focusing on a particular snapshot of clinical state in time may therefore ignore aetiologic heterogeneity due to the composition of differing symptom course in the study population (Paksarian et al., 2016). After rigorous replication in other community and high-risk cohorts, the findings of this thesis can help future research and clinical practice steer away from relying solely on single baseline assessment of clinical variables. In addition, individuals who follow different trajectories will likely have different treatment needs (Paksarian et al., 2016). As such, the selection of optimum treatments for the management of BD is often undermined by the heterogeneity of clinical presentations (M'Bailara et al., 2013). The potential distinct risk phenotypes identified in Chapter 4 and 5 may be clinically significant targets for primary prevention and if replicated in high-risk offspring populations, early intervention efforts for BD.

Figure 8. Overview of Chapter 4 and 5 findings



Note. The figure represents an overview of the study findings arising from Chapter 4 and 5. Persistent and increasing ADHD symptoms in childhood and early adolescence and increasing depression symptoms in adolescence - partially mediated by atypical depression and psychotic symptoms - were associated with clinically significant hypomanic symptoms in young adulthood. In all these associations, BPD symptoms at 11 years were a significant covariate.

6.3. Strengths and limitations

6.3.1. Strengths

6.3.1.1. The Meta-Review of Reviews

Several previous systematic reviews to date had already examined the prospective risk factors associated with developing BD and BPD, presumably due to the severe societal burden that is associated with these disorders and thus the urgent need to understand their developmental pathways. However, none of these reviews compared and contrasted the risk of developing BD and BPD. Lastly, since there were many systematic reviews and meta-analyses on the same subject area, separately for BD and BPD, there was a need to synthesise all the available evidence. This PhD therefore identified and addressed the need for a meta-review of reviews examining prospective risk factors associated both with BD and BPD.

According to the included studies in the review, the mean or median length of follow-up varied from 8 months to 31 years for BD whereas the duration of the follow-ups ranged from 1 to 28 years for BPD studies. The review highlighted factors that are common to both which subsequently helped identify the aims and methodology of the subsequent chapters of this PhD. For example, since ADHD and depression were common risk factors to both, BPD traits at 11 years were controlled in all analyses which potentially increased the robustness of the observed associations.

6.3.1.2 ALSPAC cohort

A data source of the magnitude of the ALSPAC cohort provides several advantages when considering the developmental risk factors for clinically hypomanic symptoms. Previous prospective research mainly recruited familial or clinical at-risk populations. As such, by utilising a large longitudinal population-based cohort to address the research aims, the under-representativeness, greater level of comorbidity and sampling bias inherent in at-risk sampling studies was likely reduced. Additionally, the data source in ALSPAC is prospective allowing to examine the risk factors as they occur along the developmental trajectory. The rich source of data

in ALSPAC also allows for the control of various highly relevant potential confounders such as childhood abuse, family history of psychopathology, and childhood psychopathology. Further,

the assessments, both self-report questionnaires and clinic interviews, were available from a variety of sources (i.e., child's parents, child's teachers and the study child) and these were all well-validated measures, aiding interpretation of results.

6.3.1.3. Statistical analyses

A number of state-of-the-art statistical techniques were carefully chosen to fully utilise the available prospective data in ALSPAC. Most longitudinal studies in BD at-risk studies took a variable-cantered approach, which allows only for the estimation of conditional effects or marginal effects for an entire population based on a set of observed variables and does not uncover meaningful patterns of change that vary across individuals (Hetherington et al., 2020). By utilising LCGA technique, it was possible to identify homogeneous groups of sub-populations that would have been masked if only a single regression line was estimated (Mori et al., 2020). In addition to identifying hidden clinical phenotypes, group-based trajectory models like LCGA can also be used to map the developmental course of symptoms (Nagin & Odgers, 2010). Further, by utilising longitudinal mediation analyses, it was possible to improve statistical inference and allow the examination of intraindividual variation while taking into account the temporal ordering of assessments (Selig & Preacher, 2009).

6.3.2 Limitations

6.3.2.1 The Systematic Review of Reviews' Limitations

Due to the heterogeneity within the data available in the included meta-analyses, it was not possible to conduct an umbrella review. Umbrella reviews can assess the level of evidence provided by systematic reviews and meta-analyses for each risk or protective factor, controlling at the same time several biases (e.g., Kim et al., 2020; Kim et al., 2019; Radua et al., 2018; Tortella-Feliu et al., 2019). This method can potentially overcome the conflicting results arising by the published meta-analyses and refine the risk prediction in BD and BPD at-risk populations

and inform early intervention efforts (Fusar-Poli & Radua, 2018). Additionally, due to the inclusion criteria, there were inevitably many primary articles not included in the reviews missed. Further, the review focused solely on BD and BPD as outcomes. However, many of the evident clinical risk factors are also risk factors for other mental illnesses (i.e., pluripotentiality of at-risk mental states; Hartmann et al., 2019, 2021; McGorry et al., 2018), as widespread heterotypic continuity has been shown even when controlling for homotypic continuities (Shevlin et al., 2017). For example, the recent findings arising from a prospective study aimed to identify help seeking young people at transdiagnostic risk and validate the CHARMS criteria found that a high proportion (61 %) of individuals who transitioned to a Stage 2 disorder (i.e., any of first episode psychosis, first episode mania, severe MDD, or BPD) met criteria for multiple at-risk groups at baseline (i.e., at-risk for either BD, BPD, psychosis or depression; Destrée et al., 2024). Additionally, heterotypic continuity can be also observed not just in at-risk populations but also in a "full-blown established" disorder (Caspi et al., 2020; Plana-Ripoll et al., 2019). Thus, the structure of mental disorders may be better described by underlying latent factors as certain mental disorders share risk architectures (e.g., common gene variants; De Jonge et al., 2018; Kotov et al., 2018).

6.3.2.2 ALSPAC Cohort Sample Size and Attrition

Despite the utility of the ALSPAC cohort resource for the study of developmental psychopathology, there are several limitations to highlight. Firstly, the cohort had a high rate of children lost to follow-up. Although the initial study sample used for analyses was considerably large (i.e., >14,000 pregnant women), a significant proportion of the sample (78.3%) had missing data on the outcome of clinically significant hypomanic symptoms. Attrition in ALSPAC is not completely at random, whereby individuals with higher levels of psychopathology and coming from disadvantaged families are more likely to dropped out in the study (Martin et al., 2016;

Taylor et al., 2018; Wolke et al., 2009). This ultimately has the potential to bias results such as underestimated associations. Further, the attrition rate might have affected the ability to detect other trajectory classes (Riglin et al., 2019), such as a limited number of individuals in the high-symptom groups which in return can reduce power to detect smaller effect size associations. To mitigate the effects of missingness, several statistical approaches were carried out such as inverse probability weighting and full information maximum likelihood (FIML). However, biases that might arise from unmeasured factors that can systematically influence missingness cannot be ruled out.

6.3.2.3. ALSPAC Cohort Measurement Issues

Measurement of BPD features:

BPD symptoms were assessed at one time point only at 11 years. Thus, it was not possible to apply LCGA methods and examine whether different trajectories of BPD features confer differential risk for clinically significant hypomanic symptoms. It was also not possible to look at BPD features as a potential mediator between ADHD symptom trajectories, depression symptom trajectories and the risk of clinically significant hypomanic symptoms. Finally, it was also not possible to look at hypomania and BPD risk together as an outcome. That is why, BPD features could only be utilised as a potential confounder in Chapter 4 and 5.

Measurement of ADHD symptoms:

ADHD symptoms were parent-reported, which may not generalise to diagnoses and subject to parents' biases, although the DAWBA is a well-validated measure which can be used to derive DSM-IV diagnoses (Goodman et al., 2000). Further, using the same measure and informant can be considered a strength for assessing developmental trajectories because change in symptoms and/or trajectories might then be explained by measurement differences.

Measurement of Depression and Atypical Depression symptoms:

Self-reported depression symptoms were assessed via the Short Mood and Feelings Questionnaire (SMFQ). Although SMFQ has been extensively validated in population-based samples of children and adolescents aged 6 to 17 years (Turner et al., 2014), the self-reported SMFQ items are not fully reflective of diagnostic criteria and subject to biases (Schlechter et al., 2023).

Atypical depression symptoms at 17.5 years were assessed by a self-administered computerized version of the Revised Clinical Interview Schedule. Like SMFQ, the CIS-R is not designed to assess atypical features, although CIS-R has been extensively used in community samples (Duffy et al., 2023; Khandaker et al., 2018). The items used do also not strictly reflect the DSM criteria for the atypical specifier. The DSM-5 (American Psychiatric Association, 2013) defines atypical depression as follows: a) mood reactivity; b) plus two or more of the following symptoms: weight gain or increased appetite, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity; c) plus criteria not meeting for melancholic features or catatonia. This may have inherently limited the comparability of the present findings with those from studies using clinical diagnostic criteria for subtype classification. However, the definition of atypical depression has been debated as some studies do not find that mood reactivity is correlated to the other atypical symptoms (Angst et al., 2002; Antonijevic, 2006; Parker et al., 2002). Additionally, the criterion of interpersonal rejection sensitivity has been criticised for being a personality trait rather than a symptom (Lamers et al., 2018). Thus, in epidemiological research, the definition of atypical depression is generally simplified to having increased appetite/weight, hypersomnia and leaden paralysis (Angst et al., 2006; Lamers et al., 2010), which is the definition used in this PhD thesis.

Measurement of clinically significant hypomanic symptoms:

Hypomanic symptoms were assessed at one time point only at 21-23 years via HCL-32. That is why, a baseline measure against which to compare stability symptoms over time was not available. Secondly, HCL was self-reported, which may have diminished the accuracy of the data due to recall biases. Thirdly, hypomanic symptoms were not clinically verified in the cohort. Fourthly, there have not yet been sensitivity and specificity tests of the HCL-32 as a categorical measure which includes duration, impact on functioning and observation by friends and parents.

Reliability and Stability of Hypomanic Symptoms as a Dependent Measure:

The absence of a baseline measure and a lack of clinician-rating also prevented an evaluation of symptom stability over time, making it difficult to determine whether hypomanic symptoms reflect "normal" or a clinically elated and irritable mood indicative of BD onset. A longitudinal assessment of hypomanic symptoms would have allowed for a more nuanced understanding of symptom trajectories and their predictive validity.

As mentioned before, one of the significant challenges in the diagnosis and assessment of BD is the lack of standardized and routine evaluation of hypomanic symptoms, particularly in clinical settings (Phillips & Kupfer, 2013). Extensive research has examined the correlation between self-reported and clinician-rated measures of depression, with studies consistently finding moderate-to-strong associations (e.g., Schneibel et al., 2012; Uher et al., 2012). However, in contrast to depression, the development of self-report tools for (hypo)mania emerged later, largely due to concerns regarding the reliability of patient-reported symptoms, given potential insight deficits and issues with symptom underreporting or exaggeration (Meyer et al., 2020). Some individuals experiencing hypomania may also deny or fail to report symptoms, either due to a lack of insight or because they enjoy the increased energy and positive mood associated with hypomanic states (Regeer et al., 2015). This has led to an ongoing debate about whether self-reported or clinician-rated assessments are more valid, reliable, and objective in BD

diagnosis (Meyer et al., 2020).

The implications of these challenges are particularly relevant for this thesis' limitations. In exploring the developmental trajectories of BD, it is important to consider that hypomanic symptom measurement may be subject to greater variability compared to depressive symptoms. Given these methodological challenges, a multi-method assessment approach, incorporating both self-reports and clinician-rated measures, would have offered a more comprehensive evaluation of BD symptomatology.

6.3.3. Analyses

Latent Class Growth Analyses

Although LCGA has a number of advantages, there are also a number of limitations associated with data-driven approaches to trajectory modelling. Trajectory modelling inherently simplifies the variability of individual trajectories within each class (Allswede et al., 2020). Some individuals may exhibit greater change compared with others within their group, and conclusions about individual outcomes should be approached with caution (Allswede et al., 2020; Nagin & Odgers, 2010). In other words, although grouping based on latent class facilitates data presentation and interpretation, participants do not actually belong to a single group (Mori et al., 2020). Some participants have similar probabilities of belonging to multiple groups, but the group membership is assigned based on the highest probability (Mori et al., 2020). Given the importance of selecting the number of classes and shape of the trajectories, more information about class enumeration performance is crucial to assess the potential utility of these methods as there is a risk providing conflicting conclusions and irreproducible results (Hetherington et al., 2020). Lastly, as the level of missingness increases, or if data are not missing at random, smaller latent groups may become undetectable, and parameter estimates may become highly biased (Bauer, 2007). Since there is a high level of attrition and the data are not missing at random in

ALSPAC, this might have resulted in introducing bias in the observed and non-observed trajectories.

Observed Associations and Causality

A risk factor, while can be associated with developing BD, does not necessarily imply inevitability of illness, or illness causality (Kupka et al., 2021). However, given the prospective nature of staging models, defining a prodrome for mania in the context of staging BD is not possible (Kupka et al., 2021). Thus, prospective studies are still very much needed to identify robust risk factors or at-risk phenotypes which can lead to the development of new models with revised information or updating the existing models. Another limitation would be the risk of residual confounding, as it is the case with all observational analyses. For example, data on confirmed family history of BD was not available. Therefore, it was not possible to ascertain whether familial BD history had any impact on the observed associations. Likewise, since atypical depression features are highly associated with increased proinflammatory response and dysregulation of homeostatic hormones responsible for energy metabolism, putative covariate such as lifestyle characteristics (e.g., being a current smoker, alcohol consumption, physical activity), current Body Mass Index, and chronic diseases (e.g., cardiovascular disorders, diabetes, lung disease, arthritis, cancer, ulcer, intestinal problem, liver disease, epilepsy, and thyroid gland disease) could have an impact on the observed associations (Milaneschi, Lamers, Bot, et al., 2017; Milaneschi, Lamers, Peyrot, et al., 2017).

Lastly, this PhD thesis focused only on the associations with clinically significant hypomanic symptoms. However as stated previously, given the multidimensional nature of most mental disorders (Piazza et al., 2024; Leucht et al., 2024), transdiagnosticity of these associations should also be examined (Arribas et al., 2024; Destrée et al., 2024; Scott et al., 2024; Shah et al., 2020).

This way, robust specific risk trajectories might also be identified. In the same vein, for the LCGA analyses, one outcome of interest was used for trajectory modelling in each chapter (i.e., ADHD and depression). However, modelling change in multiple outcomes (i.e., ADHD and depression symptoms) in the same analysis can provide more information in epidemiological research, particularly in mental health research given the complexity of developing psychopathology. By modelling change in multiple outcomes in the same analysis, one can identify patterns of co-development (i.e., parallel process growth mixture modelling) and/or co-occurrence of patterns (i.e., multi-trajectory or joint trajectory modelling). How these methods could be implemented in BD at-risk studies will be discussed further in the Future Directions at the end of this Chapter.

Unexplored potential underlying mechanisms

Although mediators studied were hypothesis-driven, finite number of mediators were investigated in Chapter 5 due to the availability and the assessment time points of the data in ALSPAC. A number of other potential mediators could have explained the results such as other factors suggestive of a bipolar diathesis (e.g., mixed features, abrupt early-onset, family history of BD).

6.4. Future Research

Understanding the BD at-risk and BPD at-risk from a heuristic framework

As per the findings arising from the meta-review of reviews in Chapter 2, there were no prospective studies looking at BD and BPD at-risk concurrently. Currently, to my knowledge, there is only the Clinical High At-Risk Mental State (CHARMS) criteria which strives to identify young people at transdiagnostic risk for Stage 2 psychosis, BD, MDD, and BPD (Hartmann et al., 2019; Hartmann et al., 2021). A recent prospective study using these criteria found that the

CHARMS+ group showed a significantly higher transition rate and more severe symptomatology at follow-up compared to the CHARMS- group (Destree et al., 2024). Similarly, another study explored the interrelationships between mood, psychotic, and anxiety symptom stages and their shared risk factors to develop data-informed transdiagnostic stages using ALSPAC (Ratheesh et al., 2023a). This study employed similar CHARMS criteria to operationalize these stages; however, a BPD-specific group was not included due to BPD being assessed only at age 11 in ALSPAC. Their findings indicated that comorbidity was relatively low, with only 19–20% of individuals classified as having a Stage 1b disorder (young adults experiencing significant depressive, anxiety, or attenuated psychotic symptoms) meeting the criteria for a second disorder. Additionally, while anxiety and depression exhibited moderate to high overlap, neither consistently co-occurred with psychosis or hypomania. Notably, hypomania appeared largely isolated, with 95% of individuals classified as Stage 1b hypomania meeting criteria for this disorder alone.

While examining clinical characteristics cross-diagnostically is crucial, investigating affect fluctuations in BD and BPD at- risk populations can be more informative of their evolving developmental course, due to highly shared emotion dynamics between the two disorders (Mneimne et al., 2018). The temporal pattern in affect variability could be captured by experience sampling methodology (ESM).

Further, sleep disturbances are associated with symptomatic relapse in both BD and BPD (Bradley et al., 2017) and variability in sleep may contribute to mood symptoms in BD and BPD (Carr et al., 2018). That is why, monitoring of rest-activity circadian rhythmicity and sleep macrostructure, using technologies such as wrist-worn actigraphy in BD and BPD at-risk populations can also inform us better about differences in the sleep and circadian rhythm disruption patterns and to what degree these disturbances are related to symptom severity in BD

and BPD at-risk populations.

In light of the results from the review (Chapter 2), there is a current need for collecting fine-grained data. Future prospective studies could examine the clinical characteristics, sleep-wake patterns and mood variability in young people at-risk of developing BD and BPD by utilising actigraphy and ESM. More specifically, future research could seek to examine a) certain clinical characteristics such as sleep disturbances, childhood trauma, substance abuse, self-harm, psychotic symptoms, depressive symptoms, anxiety disorders, impulsivity, affective liability, self-rated mania, and ADHD traits in BD at-risk, BPD at-risk , unipolar depression (DD) and healthy control groups (HC) ; b) the differences among these four groups with respect to these clinical characteristics; c) whether mood variability and actigraphy-based sleep and activity patterns discriminate BD at-risk and BPD at-risk groups from unipolar depression and HC and

more critically from each other, via utilising ESM. Secondarily, this prospective study could examine longitudinally a) the variability in mood characteristics of BD at-risk, BPD at-risk, DD and HC participants and see if mood fluctuations are associated significantly with the clinical characteristics; and b) the circadian profile of the activity-rest cycles of BD at-risk, BPD at-risk, DD and HC participants and see if disruptions in the circadian rhythms are associated significantly with the clinical characteristics. If conducted, the results could potentially advance our limited understanding of the BD and BPD related psychopathology.

Potential underlying mechanisms between early ADHD symptom trajectories and risk of BD

Evidence of a link between childhood persistent and increasing ADHD symptoms and clinically significant hypomanic symptom in young adulthood is clinically important, with implications discussed earlier in this chapter. However, in addition to replicating these findings in help-seeking clinical populations, another critical next step would be investigating the potential underlying mechanisms of the observed associations. Research have suggested that a history or current diagnosis of ADHD should be taken into account as a possible predictor of mixed or bipolar depression in patients with a major depressive episode (MDE; Purper-Ouakil et al., 2017). Thus, one of the potential mechanisms could be clinical characteristics suggestive of a bipolar depression diathesis, such as the ones observed in Chapter 5, atypical depression and psychotic symptoms in a depressive state. A study looking at the prevalence of ADHD in adult patients with BD observed a higher frequency of atypical depression (i.e., hypersomnia, hyperphagia, and increased appetite and weight gain) and a lower frequency of melancholic depression in the patients of the BD + ADHD group (Torres et al., 2015). Another study found that mixed features during current MDE, earlier onset of depression before the age of 20, higher number of previous depressive and mood episodes, shorter duration of current MDE, and

psychotic symptoms were more common in patients with comorbid MDD and ADHD comparing to the remaining sample (Vannucchi et al., 2019). Emotion dysregulation and BPD related psychopathology could also be potential mediating factors.

In addition to childhood ADHD, although results are not consistent across studies, offspring of parents with BD may also show higher rates of disruptive behaviour disorders (i.e., Oppositional Defiant Disorder and Conduct Disorder), and anxiety compared to offspring of the control parents (Birmaher et al., 2021; Hafeman et al., 2023; Takami Lageborn et al., 2024; Weintraub et al., 2020). A recent study also suggested that genetic risk for BD may manifest as disruptive behaviours like oppositional defiant and conduct difficulties in childhood in the general population (Askeland et al., 2023). Assessing all these risk factors longitudinally, preferably starting as early as preschool years, by modelling change in multiple risk trajectories (e.g., ADHD, depression, anxiety, ODD and CD symptom trajectories), can identify co-development of these risk trajectories and whether belonging in one trajectory (e.g., persistent depression symptoms) predicts belonging in another trajectory (e.g., persistent ADHD symptoms) and their association with the risk of developing BD. This way, more nuanced developmental pathways can be identified for developing BD. However, group level results may fail to detect nuances related to an individual patient, and significant results may not represent a real benefit for individuals (Passos et al., 2019). To mitigate this, machine learning techniques can be utilised, where one can use symptom data to predict transition to BD in populations at high-risk (Jauhar et al., 2018). As opposed to group-based models, this technique can examine model accuracy to classify at an individual level, rather than at group level (Jauhar et al., 2018)and can help develop empirically driven childhood predictors of future onset of BD (Uchida et al., 2022).

The role of depression symptom profile, its biological underpinnings and the risk of developing BD

Depression is the most frequently diagnosed syndrome in clinical practice and is not a homogenous entity (Maj et al., 2020). There are different depression subtypes (e.g., melancholic, atypical, psychotic, mixed and anxious subtypes), but this is often ignored by clinicians in practice (Maj et al., 2020). However, there may be different symptom profiles or clinical subtypes associated with the response to different treatments (Boschloo et al., 2019; Chekroud et al., 2017). For example, the evidence on the treatment validity of melancholic subtyping of depression is not consistent (e.g., Brown, 2007; Cuijpers et al., 2017). Thus, there is a current need for more systematic effort to personalise the management of depression (Maj et al., 2020). This is even more crucial for bipolar depression as the treatment of bipolar depression is far less well investigated than MDD, and the efficacy of available pharmacological treatments (e.g., antidepressants, antipsychotics, lithium, anticonvulsants) for bipolar depression remain low and risk adverse metabolic or neurological effects (Baldessarini et al., 2020). Further, as indicated previously, there are also no features of depression in the DSM-5-TR or ICD-11 that distinguish and/or are pathognomonic of BD (McIntyre et al., 2022). That is why, identifying objective markers of BD that might help improve accuracy in differentiating between BD and unipolar depression is crucial. Through my work in Chapter 5, I have demonstrated that increasing depression symptom levels with co-occurring psychotic and atypical depression symptoms might be indicative of developing BD. However, there is still a pressing need for identifying biomarkers that reflect underlying pathophysiologic mechanisms to guide treatment choice in addition to identifying differences in clinical characteristics (Benedetti et al., 2020). Recently, there has been ongoing efforts to identify robust biomarkers to identify differential biomarkers

for bipolar depression. For example, a study using machine learning found that the most relevant predictor variables to differentiate patients with bipolar depression from unipolar depression were the cytokines (i.e., interleukin-10 and interleukin-4) and levels of lipid peroxidation (Wollenhaupt-Aguiar et al., 2020). Additionally, a meta-analysis looking at existing evidence of inflammatory markers, neurotrophins and oxidative stress markers in BD focusing on the mood phase of illness found that both high sensitivity CRP and interleukin-6 discriminated bipolar depression, their levels being no different from controls (Rowland et al., 2018). Further, a study examining the differential connectivity between anterior insula and functional networks in patients with unipolar versus bipolar depression found impaired functional connectivity between the anterior insula and the inferior parietal lobule of the executive control network in patients with bipolar depression compared to those with unipolar depression and healthy control subjects, meaning bipolar depression patients had greater impairments in the behavioural dimensions of perceived emotion control and reward sensitivity (Ellard et al., 2018). Future studies should incorporate multidisciplinary approaches where they look at not only the longitudinal course of depression subtypes, but also combine neuroimaging, genetics, and peripheral blood biomarker data with other biological data (i.e., fusion data approach) to develop more accurate signatures, particularly in at-risk populations. As stated previously, appropriate diagnosis not only can shorten the time to provide effective treatment but also can prevent the risk of iatrogenic switch to mania from antidepressants and reduce duration of untreated illness.

The Need to Improve Phenotyping: International BD at-risk Data Network

The prodrome of BD is the early warning signs or symptoms that had occurred prior to the first episode of (hypo)manic episode. However, prodromal symptoms can only be examined retrospectively, after the person has experiences the index (hypo)manic episode (Faedda et al.,

2019). Given the prospective nature of clinical staging models in psychiatry, defining a prodrome in the context of staging models is not possible (Kupka et al., 2021). That is why, longitudinal cohort studies are warranted to advance our knowledge of the evolving nature of BD and its long-term prognosis. However, despite the need for large cohort studies, obtaining funding has been a hurdle (Vieta & Angst, 2021). Many cohort studies (e.g., Iowa 500, STEP-BD, EMBLEM, WAVE-BD, the Stanley Foundation Network, FACE-BD, CIBERSAM) were limited in time due to short-term funding, missing the opportunity of following the participants over a long time (Vieta & Angst, 2021).

The creation of an international early BD data network could coordinate international big data approaches and integrate with real-world clinical interventions (Manchia et al., 2020). As discussed earlier in Chapter 1, there is a lack of reliable disease biomarkers in BD (Berk, 2023; Carvalho et al., 2016). This is also partly due to the cross-sectional nature of the biomarker studies (Manchia et al., 2020), although there are some ongoing longitudinal studies (e.g., the BIO cohort; Kessing et al., 2017). The approach would be multidisciplinary including, genotyping, biomarkers, brain imaging, and deep phenotyping (Manchia et al., 2020; Passos et al., 2019). The big data sets generated by a large-scale cohort could be mined by machine learning techniques (Vieta & Angst, 2021).

Recognising this need for coordinated action, building a worldwide international learning health care system for early BD could be the solution. The ultimate aim of this initiative would be that the network will become a unique research database that will be available to collaborators to support research and improve early identification, clinical assessment, intervention effectiveness, and recovery outcomes among individuals experiencing their first symptoms of BD and will provide a framework for streamlining the translation of research into real-world practice.

6.5. Conclusions

Overall, in this thesis, the findings suggest that a) BD and BPD share many common nonspecific developmental trajectories; b) different ADHD and depression symptom trajectories in childhood and adolescence might be distinct risk phenotypes for developing BD; c) there is a need to consider integrating BPD related psychopathology when examining developmental pathways to BD. If replicated in BD at-risk samples, the results can refine clinical staging models and increase their utility. This would then lead consequently to achieve better clinical outcomes and increase the quality of the lives of many young people at risk for BD. Together, the work presented here has advanced our understanding of the development of BD and opened new avenues of research enquiry.

References

Studies included in the meta-review are denoted with an asterisk.

Aas, M., Bellivier, F., Bettella, F., Henry, C., Gard, S., Kahn, J. P., Lagerberg, T. V., Aminoff, S. R., Melle, I., Leboyer, M., Jamain, S., Andreassen, O. A., & Etain, B. (2020). Childhood maltreatment and polygenic risk in bipolar disorders. Bipolar Disorders, 22(2), 174–181. https://doi.org/10.1111/bdi.12851

Aas, M., Henry, C., Andreassen, O. A., Bellivier, F., Melle, I., & Etain, B. (2016). The role of childhood trauma in bipolar disorders. International Journal of Bipolar Disorders, 4(1), 1–10. https://doi.org/10.1186/s40345-015-0042-0

Abi-Dargham, A., Moeller, S. J., Ali, F., DeLorenzo, C., Domschke, K., Horga, G., Jutla, A., Kotov, R., Paulus, M. P., Rubio, J. M., Sanacora, G., Veenstra-VanderWeele, J., & Krystal, J. H. (2023). Candidate biomarkers in psychiatric disorders: state of the field. World Psychiatry, 22(2), 236–262. https://doi.org/10.1002/wps.21078

Afifi, T. O., Mather, A., Boman, J., Fleisher, W., Enns, M. W., MacMillan, H., … Sareen, J. (2011). Childhood adversity and personality disorders: Results from a nationally representative population-based study. *Journal of Psychiatric Research*, *45*(6), 814–822. https://doi.org/10.1016/j.jpsychires.2010.11.008

Agnew-Blais, J., & Danese, A. (2016). Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: A systematic review and meta-analysis. The Lancet Psychiatry, 3(4), 342–349. https://doi.org/10.1016/S2215-0366(15)00544-1

Akiskal, H. S. (2004). Demystifying borderline personality: Critique of the concept and unorthodox reflections on its natural kinship with the bipolar spectrum. *Acta Psychiatrica Scandinavica*, *110*(6), 401–407. https://doi.org/10.1111/j.1600-0447.2004.00461.x

Allswede, D. M., Addington, J., Bearden, C. E., Cadenhead, K. S., Cornblatt, B. A., Mathalon, D. H., McGlashan, T., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., & Cannon, T. D. (2020). Characterizing Covariant Trajectories of Individuals at Clinical High Risk for Psychosis across Symptomatic and Functional Domains. American Journal of Psychiatry, 177(2), 164–171. https://doi.org/10.1176/APPI.AJP.2019.18111290

Altamura, A. C., Dell'Osso, B., Berlin, H. A., Buoli, M., Bassetti, R., & Mundo, E. (2010). Duration of untreated illness and suicide in bipolar disorder: A naturalistic study. European Archives of Psychiatry and Clinical Neuroscience, 260(5), 385–391. https://doi.org/10.1007/s00406-009-0085-2

American Psychiatric Association (2000). Diagnostic and statistical manual of mental disorders, *DSM-IV-TR* (4th ed., text rev.). Washington, DC: Author.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders. https://doi.org/10.1176/appi.books.9780890425596

Angold, A., Costello, E. J., Messer, S. C., & Pickles, A. (1995). Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents: Factor composition and structure across development. International Journal of Methods in Psychiatric Research, 5(4), 251–262. http://ezp-prod1.hul.harvard.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=1996-02633-003&site=ehost-live&scope=site

Angst, J., & Cassano, G. (2005). The mood spectrum: Improving the diagnosis of bipolar disoder. Bipolar Disorders, Supplement, 7(4), 4–12. https://doi.org/10.1111/j.1399-5618.2005.00210.x

Angst, J., & Marneros, A. (2001). Bipolarity from ancient to modern times: Conception, birth and rebirth. Journal of Affective Disorders, 67(1–3), 3–19. https://doi.org/10.1016/S0165-0327(01)00429-3

Angst, J., & Sellaro, R. (2000). Historical perspectives and natural history of bipolar disorder. Biological Psychiatry, 48(6), 445–457. https://doi.org/10.4324/9781315054308-7

Angst, J., Adolfsson, R., Benazzi, F., Gamma, A., Hantouche, E., Meyer, T. D., Skeppar, P., Vieta, E., & Scott, J. (2005). The HCL-32: Towards a self-assessment tool for hypomanic symptoms in outpatients. Journal of Affective Disorders, 88(2), 217–233. https://doi.org/10.1016/j.jad.2005.05.011

Angst, J., Gamma, A., Benazzi, F., Silverstein, B., Dominique, V. A., & Wulf, E. (2006). Atypical depressive syndromes in varying definitions. 44–54. https://doi.org/10.1007/s00406-005-0600-z

Angst, J., Gamma, A., Sellaro, R., Zhang, H., & Merikangas, K. (2002). T oward validation of atypical depression in the community : results of the Zurich cohort study. 72, 125–138.

Antonijevic, I. A. (2006). Depressive disorders — is it time to endorse different pathophysiologies ? 1–15. https://doi.org/10.1016/j.psyneuen.2005.04.004

Armitage, J. M., Kwong, A. S. F., Tseliou, F., Sellers, R., Blakey, R., Anthony, R., Rice, F., Thapar, A., & Collishaw, S. (2023). Cross-cohort change in parent-reported emotional problem trajectories across childhood and adolescence in the UK. The Lancet Psychiatry, 10(7), 509–517. https://doi.org/10.1016/S2215-0366(23)00175-X

Arnold, L. E., Ganocy, S. J., Mount, K., Youngstrom, E. A., Frazier, T., Fristad, M., Horwitz, S. M., Birmaher, B., Findling, R., Kowatch, R. A., Demeter, C., Axelson, D., Gill, M. K., & Marsh, L. (2014). Three-year latent class trajectories of attention-deficit/hyperactivity disorder (ADHD) symptoms in a clinical sample not selected for ADHD. Journal of the American Academy of Child and Adolescent Psychiatry, 53(7), 745–760. https://doi.org/10.1016/j.jaac.2014.03.007

Arnold, L. E., Van Meter, A. R., Fristad, M. A., Youngstrom, E. A., Birmaher, B. B., Findling, R. L., Horwitz, S., & Black, S. R. (2020). Development of bipolar disorder and other comorbidity among youth with attention-deficit/hyperactivity disorder. Journal of Child Psychology and Psychiatry and Allied Disciplines, 61(2), 175-181file:///Users/busedurdurak/Downloads/contro. https://doi.org/10.1111/jcpp.13122

Arnone, D., Cavanagh, J., Gerber, D., Lawrie, S. M., Ebmeier, K. P., & McIntosh, A. M. (2009). Magnetic resonance imaging studies in bipolar disorder and schizophrenia: Meta-analysis. British Journal of Psychiatry, 195(3), 194–201. https://doi.org/10.1192/bjp.bp.108.059717

Arribas, M., Oliver, D., Patel, R., Kornblum, D., Shetty, H., Damiani, S., Krakowski, K., Provenzani, U., Stahl, D., Koutsouleris, N., McGuire, P., & Fusar-Poli, P. (2024). A transdiagnostic prodrome for severe mental disorders: an electronic health record study. Molecular Psychiatry, September 2023. https://doi.org/10.1038/s41380-024-02533-5

Asherson, P., Young, A. H., Eich-Höchli, D., Moran, P., Porsdal, V., & Deberdt, W. (2014). Differential diagnosis, comorbidity, and treatment of attention-deficit/hyperactivity disorder in relation to bipolar disorder or borderline personality disorder in adults. *Current Medical Research and Opinion*, *30*(8), 1657-1672.

Asherson, P., Buitelaar, J., Faraone, S. V., & Rohde, L. A. (2016). Adult attention-deficit hyperactivity disorder: key conceptual issues. The Lancet Psychiatry, 3(6), 568-578.

Asherson, P., Leaver, L., Adamou, M., Arif, M., Askey, G., Butler, M., Cubbin, S., Newlove-Delgado, T., Kustow, J., Lanham-Cook, J., Findlay, J., Maxwell, J., Mason, P., Read, H., van Rensburg, K., Müller-Sedgwick, U., Sedgwick-Müller, J., & Skirrow, C. (2022). Mainstreaming adult ADHD into primary care in the UK: guidance, practice, and best practice recommendations. BMC Psychiatry, 22(1), 1–20. https://doi.org/10.1186/s12888-022-04290-7

Askeland, R. B., Hannigan, L. J., O'Connell, K. S., Corfield, E. C., Frei, O., Thapar, A., & ... & Havdahl, A. (2023). Developmental manifestations of polygenic risk for bipolar disorder from infancy to middle childhood. Translational Psychiatry, 13(1), 222. https://doi.org/10.1038/s41398-023-02522-2

Badner, J. A., Koller, D., Foroud, T., Edenberg, H., Nurnberger, J. I., Zandi, P. P., Willour, V. L., McMahon, F. J., Potash, J. B., Hamshere, M., Grozeva, D., Green, E., Kirov, G., Jones, I., Jones, L., Craddock, N., Morris, D., Segurado, R., Gill, M., … Byerley, W. (2012). Genome-wide linkage analysis of 972 bipolar pedigrees using single-nucleotide polymorphisms. Molecular Psychiatry, 17(8), 818–826. https://doi.org/10.1038/mp.2011.89

Balbuena, L., Bowen, R., Baetz, M., & Marwaha, S. (2016). Mood instability and irritability as core symptoms of major depression: An exploration using Rasch analysis. *Frontiers in psychiatry*, *7*, 174.

* Bart, C. P., Titone, M. K., Ng, T. H., Nusslock, R., & Alloy, L. B. (2021). Neural reward circuit dysfunction as a risk factor for bipolar spectrum disorders and substance use disorders: A review and Integration. *Clinical Psychology Review*, *87*, 102035.

https://doi.org/10.1016/j.cpr.2021.102035

Bartoli, F., Callovini, T., Cavaleri, D., Cioni, R. M., Bachi, B., Calabrese, A., Moretti, F., Canestro, A., Morreale, M., Nasti, C., Palpella, D., Piacenti, S., Nacinovich, R., Riboldi, I., Crocamo, C., & Carrà, G. (2023). Clinical correlates of comorbid attention deficit hyperactivity disorder in adults suffering from bipolar disorder: A meta-analysis. Australian and New Zealand Journal of Psychiatry, 57(1), 34–48. https://doi.org/10.1177/00048674221106669

Baryshnikov, I., Aaltonen, K., Koivisto, M., Näätänen, P., Karpov, B., Melartin, T., … Isometsä, E. (2015). Differences and overlap in self-reported symptoms of bipolar disorder and borderline personality disorder. *European Psychiatry*, *30*(8), 914–919. https://doi.org/10.1016/j.eurpsy.2015.08.002

Bassett, D. (2012). Borderline personality disorder and bipolar affective disorder. spectra or Spectre? A Review. *Australian & New Zealand Journal of Psychiatry*, *46*(4), 327–339. https://doi.org/10.1177/0004867411435289

Bassett, D., Mulder, R., Outhred, T., Hamilton, A., Morris, G., Das, P., … Malhi, G. S. (2017). Defining disorders with permeable borders: You say bipolar, I say borderline! *Bipolar Disorders*, *19*(5), 320–323. https://doi.org/10.1111/bdi.12528

Bauer, D. J. (2007). Observations on the Use of Growth Mixture Models in Psychological Research. Multivariate Behavioral Research, 42(4), 757–786. https://doi.org/10.1080/00273170701710338

Bauer, M., Andreassen, O. A., Geddes, J. R., Vedel Kessing, L., Lewitzka, U., Schulze, T. G., & Vieta, E. (2018). Areas of uncertainties and unmet needs in bipolar disorders: clinical and research perspectives. The Lancet Psychiatry, 5(11), 930–939. https://doi.org/10.1016/S2215-0366(18)30253-0

Bayes, A. J., & Parker, G. B. (2020). Differentiating borderline personality disorder (BPD) from bipolar disorder: diagnostic efficiency of DSM BPD criteria. Acta Psychiatrica Scandinavica, 141(2), 142–148. https://doi.org/10.1111/acps.13133

Bayes, A. J., McClure, G., Fletcher, K., Román Ruiz del Moral, Y. E., Hadzi-Pavlovic, D., Stevenson, J. L., … Parker, G. B. (2015). Differentiating the bipolar disorders from borderline personality disorder. *Acta Psychiatrica Scandinavica*, *133*(3), 187–195. https://doi.org/10.1111/acps.12509

Bechdolf, A., Ratheesh, A., Cotton, S. M., Nelson, B., Chanen, A. M., Betts, J., Bingmann, T., Yung, A. R., Berk, M., & Mcgorry, P. D. (2014). The predictive validity of bipolar at-risk (prodromal) criteria in help-seeking adolescents and young adults: A prospective study. Bipolar Disorders, 16(5), 493–504. https://doi.org/10.1111/bdi.12205

Benazzi, F. (2006). Borderline personality–bipolar spectrum relationship. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *30*(1), 68–74. https://doi.org/10.1016/j.pnpbp.2005.06.010

Benedetti, F., Aggio, V., Pratesi, M. L., Greco, G., & Furlan, R. (2020). Neuroinflammation in Bipolar Depression. Frontiers in Psychiatry, 11(February), 1–12. https://doi.org/10.3389/fpsyt.2020.00071

Berk, M. (2023). Biomarkers in psychiatric disorders: status quo, impediments and facilitators. World Psychiatry, 22(2), 174–176. https://doi.org/10.1002/wps.21071

Berk, M., Conus, P., Lucas, N., Hallam, K., Malhi, G. S., Dodd, S., Yatham, L. N., Yung, A., & McGorry, P. (2007). Setting the stage: From prodrome to treatment resistance in bipolar disorder. Bipolar Disorders, 9(7), 671–678. https://doi.org/10.1111/j.1399-5618.2007.00484.x

Berk, M., Hallam, K., Malhi, G. S., Henry, L., Hasty, M., Macneil, C., … McGorry, P. D. (2010). Evidence and implications for early intervention in bipolar disorder. *Journal of Mental Health, 19*(2), 113–126. https://doi.org/10.3109/09638230903469111

Berk, M., Post, R., Ratheesh, A., Gliddon, E., Singh, A., Vieta, E., Carvalho, A. F., Ashton, M. M., Berk, L., Cotton, S. M., McGorry, P. D., Fernandes, B. S., Yatham, L. N., & Dodd, S. (2017). Staging in bipolar disorder: from theoretical framework to clinical utility. World Psychiatry, 16(3), 236–244. https://doi.org/10.1002/wps.20441

Birmaher, B., Merranko, J. A., Goldstein, T. R., Gill, M. K., Goldstein, B. I., Hower, H., Yen, S., Hafeman, D., Strober, M., Diler, R. S., Axelson, D., Ryan, N. D., & Keller, M. B. (2018). A Risk Calculator to Predict the Individual Risk of. Journal of the American Academy of Child & Adolescent Psychiatry, 57(10), 755-763.e4. https://doi.org/10.1016/j.jaac.2018.05.023

Birmaher, B., Merranko, J., Hafeman, D., Goldstein, B. I., Diler, R., Levenson, J. C., Monk, K., Iyengar, S., Hickey, M. B., Sakolsky, D., Axelson, D., & Goldstein, T. (2021). A Longitudinal Study of Psychiatric Disorders in Offspring of Parents With Bipolar Disorder From Preschool to Adolescence. Journal of the American Academy of Child and Adolescent Psychiatry, 60(11), 1419–1429. https://doi.org/10.1016/j.jaac.2021.02.023

Boateng, E. Y., & Abaye, D. A. (2019). A Review of the Logistic Regression Model with Emphasis on Medical Research. Journal of Data Analysis and Information Processing, 07(04), 190–207. https://doi.org/10.4236/jdaip.2019.74012

Bohus, M., Stoffers-Winterling, J., Sharp, C., Krause-Utz, A., Schmahl, C., & Lieb, K. (2021). Borderline personality disorder. The Lancet, 398(10310), 1528–1540. https://doi.org/10.1016/S0140-6736(21)00476-1

Bonsall, M. B., Wallace-Hadrill, S. M., Geddes, J. R., Goodwin, G. M., & Holmes, E. A. (2012). Nonlinear time-series approaches in characterizing mood stability and mood instability in bipolar disorder. *Proceedings of the Royal Society B: Biological Sciences*, *279*(1742), 3632–3632. https://doi.org/10.1098/rspb.2012.1390

Boschloo, L., Bekhuis, E., Erica, S., Reijnders, M., Derubeis, R. J., Dimidjian, S., Dunner, D. L., Dunlop, B. W., Hegerl, U., Hollon, S. D., Robin, B., Kennedy, S. H., Miranda, J., Mohr, D. C., Schoevers, A., & Cuijpers, P. (2019). The symptom-specific efficacy of antidepressant medication vs . cognitive behavioral therapy in the treatment of depression : results from an individual patient data meta-analysis. June, 183–191. https://doi.org/10.1002/wps.20630

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., Molloy, L., Ness, A., Ring, S., & Smith, G. D. (2013). Cohort profile: The 'Children of the 90s'-The index offspring of the avon longitudinal study of parents and children. International Journal of Epidemiology, 42(1), 111–127. https://doi.org/10.1093/ije/dys064

Bradley, A. J., Hazu, A., Slater, N., Middleton, B., & Gallagher, P. (2017). Sleep and circadian rhythm disturbance in bipolar disorder. 1678–1689. https://doi.org/10.1017/S0033291717000186

* Brancati, G. E., Perugi, G., Milone, A., Masi, G., & Sesso, G. (2021). Development of bipolar disorder in patients with attention-deficit/hyperactivity disorder: A systematic review and meta-analysis of prospective studies. *Journal of Affective Disorders*, *293*, 186–196. https://doi.org/10.1016/j.jad.2021.06.033

Breda, V., Rohde, L. A., Menezes, A. M. B., Anselmi, L., Caye, A., Rovaris, D. L., Vitola, E. S., Bau, C. H. D., & Grevet, E. H. (2021). The neurodevelopmental nature of attention-deficit

hyperactivity disorder in adults. British Journal of Psychiatry, 218(1), 43–50. https://doi.org/10.1192/bjp.2020.200

Brietzke, E., Mansur, R. B., Soczynska, J. K., Kapczinski, F., Bressan, R. A., & McIntyre, R. S. (2012). Towards a multifactorial approach for prediction of bipolar disorder in at risk populations. *Journal of Affective Disorders*, *140*(1), 82-91.

Brinksma, D. M., Hoekstra, P. J., de Bildt, A., Buitelaar, J. K., van den Hoofdakker, B. J., Hartman, C. A., & Dietrich, A. (2023). Parental rejection in early adolescence predicts a persistent ADHD symptom trajectory across adolescence. European Child and Adolescent Psychiatry, 32(1), 139–153. https://doi.org/10.1007/s00787-021-01844-0

Brown, W. A. (2007). Treatment response in melancholia. Acta Psychiatrica Scandinavica, 115(SUPPL. 433), 125–129. https://doi.org/10.1111/j.1600-0447.2007.00970.x

Buoli, M., Serati, M., Caldiroli, A., Cremaschi, L., & Altamura, A. C. (2017). Neurodevelopmental versus neurodegenerative model of schizophrenia and bipolar disorder: Comparison with physiological brain development and aging. Psychiatria Danubina, 29(1), 24–27. https://doi.org/10.24869/psyd.2017.24

* Cahn, A. J., Keramatian, K., Frysch, C., Yatham, L. N., & Chakrabarty, T. (2021). Longitudinal Grey matter changes following first episode mania in bipolar I disorder: A systematic review. *Journal of Affective Disorders*, *291*, 198–208. https://doi.org/10.1016/j.jad.2021.04.051

* Cardoso, T. de, Mondin, T. C., Azevedo, L. B., Toralles, L. M., & de Mattos Souza, L. D. (2018). Is suicide risk a predictor of diagnosis conversion to bipolar disorder? *Psychiatry Research*, *268*, 473–477. https://doi.org/10.1016/j.psychres.2018.08.026

Carr, O., Saunders, K. E. A., Tsanas, A., Bilderbeck, A. C., Palmius, N., Geddes, J. R., Foster, R., Goodwin, G. M., & De Vos, M. (2018). Variability in phase and amplitude of diurnal rhythms is related to variation of mood in bipolar and borderline personality disorder. Scientific Reports, 8(1), 1–11. https://doi.org/10.1038/s41598-018-19888-9

Carta, M. G., & Angst, J. (2016). Screening for bipolar disorders: A public health issue. Journal of Affective Disorders, 205, 139–143. https://doi.org/10.1016/j.jad.2016.03.072

Carvalho, A. F., Firth, J., & Vieta, E. (2020). Bipolar Disorder Bipolar Disorder 2016. New England Journal of Medicine, 383(1), 58–66. https://doi.org/10.1056/NEJMra1906193

Carvalho, A. F., Köhler, C. A., Fernandes, B. S., Quevedo, J., Miskowiak, K. W., Brunoni, A. R., Machado-Vieira, R., Maes, M., Vieta, E., & Berk, M. (2016). Bias in emerging biomarkers for bipolar disorder. Psychological Medicine, 46(11), 2287–2297. https://doi.org/10.1017/S0033291716000957

Carvalho, A. F., Takwoingi, Y., Sales, P. M. G., Soczynska, J. K., Köhler, C. A., Freitas, T. H., Quevedo, J., Hyphantis, T. N., McIntyre, R. S., & Vieta, E. (2015). Screening for bipolar spectrum disorders: A comprehensive meta-analysis of accuracy studies. Journal of Affective Disorders, 172, 337–346. https://doi.org/10.1016/j.jad.2014.10.024

Caspi, A., Houts, R. M., Ambler, A., Danese, A., Elliott, M. L., Hariri, A., Harrington, H. L., Hogan, S., Poulton, R., Ramrakha, S., Rasmussen, L. J. H., Reuben, A., Richmond-Rakerd, L., Sugden, K., Wertz, J., Williams, B. S., & Moffitt, T. E. (2020). Longitudinal Assessment of Mental Health Disorders and Comorbidities Across 4 Decades Among Participants in the Dunedin Birth Cohort Study. JAMA Network Open, 3(4), e203221. https://doi.org/10.1001/jamanetworkopen.2020.3221

Cattarinussi, G., Di Giorgio, A., Wolf, R. C., Balestrieri, M., & Sambataro, F. (2019). Neural signatures of the risk for bipolar disorder: A meta-analysis of structural and functional neuroimaging studies. Bipolar Disorders, 21(3), 215–227. https://doi.org/10.1111/bdi.12720

Chanen, A. M. (2015). Borderline personality disorder in young people: are we there yet? *Journal of Clinical Psychology*, *71*(8), 778-791.

Chanen, A. M., & Kaess, M. (2011). Developmental pathways to borderline personality disorder. *Current Psychiatry Reports*, *14*(1), 45–53. https://doi.org/10.1007/s11920-011-0242-y

Chanen, A. M., Berk, M., & Thompson, K. (2016). Integrating early intervention for borderline personality disorder and mood disorders. Harvard Review of Psychiatry, 24(5), 330–341. https://doi.org/10.1097/HRP.0000000000000105

Chanen, A., Sharp, C., & Hoffman, P. (2017). Prevention and early intervention for borderline personality disorder: a novel public health priority. World Psychiatry, 16(2), 215–216. https://doi.org/10.1002/wps.20429

Chekroud, A. M., Lane, C. E., & Ross, D. A. (2017). Computational psychiatry: embracing uncertainty and focusing on individuals, not averages. Biological Psychiatry, 82(6), e45–e47. https://doi.org/10.1177/0022146515594631.Marriage

Chen, C. H., Suckling, J., Lennox, B. R., Ooi, C., & Bullmore, E. T. (2011). A quantitative meta-analysis of fMRI studies in bipolar disorder. Bipolar Disorders, 13(1), 1–15. https://doi.org/10.1111/j.1399-5618.2011.00893.x

Coello, K., Kjærstad, H. L., Stanislaus, S., Melbye, S., Faurholt-Jepsen, M., Miskowiak, K. W., McIntyre, R. S., Vinberg, M., Kessing, L. V., & Munkholm, K. (2019). Thirty-year cardiovascular risk score in patients with newly diagnosed bipolar disorder and their

unaffected first-degree relatives. Australian and New Zealand Journal of Psychiatry, 53(7), 651–662. https://doi.org/10.1177/0004867418815987

Comparelli, A., Polidori, L., Sarli, G., Pistollato, A., & Pompili, M. (2022). Differentiation and comorbidity of bipolar disorder and attention deficit and hyperactivity disorder in children, adolescents, and adults: A clinical and nosological perspective. Frontiers in Psychiatry, 13(5). https://doi.org/10.3389/fpsyt.2022.949375

Corponi, F., Anmella, G., Verdolini, N., Pacchiarotti, I., Samalin, L., Popovic, D., Azorin, J. M., Angst, J., Bowden, C. L., Mosolov, S., Young, A. H., Perugi, G., Vieta, E., & Murru, A. (2020). Symptom networks in acute depression across bipolar and major depressive disorders: A network analysis on a large, international, observational study. European Neuropsychopharmacology, 35(March), 49–60. https://doi.org/10.1016/j.euroneuro.2020.03.017

Cotter, J., Kaess, M., & Yung, A. R. (2014). Childhood trauma and functional disability in psychosis, bipolar disorder and borderline personality disorder: A review of the literature. *Irish Journal of Psychological Medicine*, *32*(1), 21–30. https://doi.org/10.1017/ipm.2014.74

Craddock, N., & Sklar, P. (2013). Bipolar Disorder 1 - Genetics of bipolar disorder. The Lancet, 381(9878), 1654–1662. https://doi.org/10.1016/S0140-6736(13)60855-7

Cuijpers, P., Weitz, E., Lamers, F., Penninx, B. W., Twisk, J., DeRubeis, R. J., Dimidjian, S., Dunlop, B. W., Jarrett, R. B., Segal, Z. V., & Hollon, S. D. (2017). Melancholic and atypical depression as predictor and moderator of outcome in cognitive behavior therapy and pharmacotherapy for adult depression. Depression and Anxiety, 34(3), 246–256. https://doi.org/10.1002/da.22580

Dagani, J., Signorini, G., Nielssen, O., Bani, M., Pastore, A., Girolamo, G. De, & Large, M. (2017). Meta-analysis of the Interval between the Onset and Management of Bipolar Disorder. Canadian Journal of Psychiatry, 62(4), 247–258. https://doi.org/10.1177/0706743716656607

Daveney, J., Panagioti, M., Waheed, W., & Esmail, A. (2019). Unrecognized bipolar disorder in patients with depression managed in primary care: A systematic review and meta-analysis. General Hospital Psychiatry, 58(March), 71–76. https://doi.org/10.1016/j.genhosppsych.2019.03.006

De Jonge, P., Wardenaar, K. J., Lim, C. C. W., Aguilar-Gaxiola, S., Alonso, J., Andrade, L. H., Bunting, B., Chatterji, S., Ciutan, M., Gureje, O., Karam, E. G., Lee, S., Medina-Mora, M. E., Moskalewicz, J., Navarro-Mateu, F., Pennell, B. E., Piazza, M., Posada-Villa, J., Torres, Y., … Scott, K. (2018). The cross-national structure of mental disorders: Results from the World Mental Health Surveys. Psychological Medicine, 48(12), 2073–2084. https://doi.org/10.1017/S0033291717003610

DelBello, M. P., & Geller, B. (2001). Review of studies of child and adolescent offspring of bipolar parents. *Bipolar Disorders*, *3*(6), 325–334. https://doi.org/10.1034/j.1399-5618.2001.30607.x

Deltito, J., Martin, L., Riefkohl, J., Austria, B., Kissilenko, A., & Corless C. Morse, P. (2001). Do patients with borderline personality disorder belong to the bipolar spectrum? *Journal of Affective Disorders*, *67*(1-3), 221–228. https://doi.org/10.1016/s0165-0327(01)00436-0

Destrée, L., McGorry, P., Chanen, A., Ratheesh, A., Davey, C., Polari, A., Amminger, P., Yuen, H. P., Hartmann, J., Dwyer, D., Spooner, R., & Nelson, B. (2024). Transdiagnostic risk identification: A validation study of the Clinical High At Risk Mental State (CHARMS)

criteria. Psychiatry Research, 333(September 2023). https://doi.org/10.1016/j.psychres.2024.115745

di Giacomo, E., Aspesi, F., Fotiadou, M., Arntz, A., Aguglia, E., Barone, L., … Zaccheroni, D. (2017). Unblending borderline personality and bipolar disorders. *Journal of Psychiatric Research*, *91*, 90–97. https://doi.org/10.1016/j.jpsychires.2017.03.006

Di Nicola, M., Tedeschi, D., Mazza, M., Martinotti, G., Harnic, D., Catalano, V., Bruschi, A., Pozzi, G., Bria, P., & Janiri, L. (2010). Behavioural addictions in bipolar disorder patients: Role of impulsivity and personality dimensions. Journal of Affective Disorders, 125(1–3), 82–88. https://doi.org/10.1016/j.jad.2009.12.016

Dickinson, T., Becerra, R., & Coombes, J. (2017). Executive functioning deficits among adults with Bipolar Disorder (types I and II): A systematic review and meta-analysis. Journal of Affective Disorders, 218(April), 407–427. https://doi.org/10.1016/j.jad.2017.04.010

Diler, R. S., Goldstein, T. R., Hafeman, D., Merranko, J., Liao, F., Goldstein, B. I., Hower, H., Gill, M. K., Hunt, J., Yen, S., Keller, M. B., Axelson, D., Strober, M., Iyengar, S., Ryan, N. D., & Birmaher, B. (2017). Distinguishing Bipolar Depression from Unipolar Depression in Youth: Preliminary Findings. Journal of Child and Adolescent Psychopharmacology, 27(4), 310–319. https://doi.org/10.1089/cap.2016.0154

Dong, M., Lu, L., Zhang, L., Zhang, Q., Ungvari, G. S., Ng, C. H., Yuan, Z., Xiang, Y., Wang, G., & Xiang, Y. (2019). Prevalence of suicide attempts in bipolar disorder : a systematic review and meta-analysis of observational studies.

Donnelly, N. A., Perry, B. I., Jones, H. J., & Khandaker, G. M. (2022). Childhood immuno-metabolic markers and risk of depression and psychosis in adulthood: A prospective birth

cohort study. Psychoneuroendocrinology, 139(October 2021), 105707. https://doi.org/10.1016/j.psyneuen.2022.105707

Dubad, M., Elahi, F. & Marwaha, S., 2021. The clinical impacts of mobile mood-monitoring in young people with mental health problems: The MeMO Study. *Frontiers in Psychiatry*, *12*.

Duffy, A., Alda, M., Hajek, T., Sherry, S. B., & Grof, P. (2010). Early stages in the development of bipolar disorder. Journal of Affective Disorders, 121(1–2), 127–135. https://doi.org/10.1016/j.jad.2009.05.022

Duffy, A., Carlson, G., Dubicka, B., & Hillegers, M. H. (2020). Pre-pubertal bipolar disorder: Origins and current status of the controversy. *International Journal of Bipolar Disorders*, *8*(1). https://doi.org/10.1186/s40345-020-00185-2

Duffy, A., Doucette, S., Lewitzka, U., Alda, M., Hajek, T., & Grof, P. (2011). Findings from bipolar offspring studies: Methodology matters. *Early Intervention in Psychiatry*, *5*(3), 181–191. https://doi.org/10.1111/j.1751-7893.2011.00276.x

Duffy, A., Goodday, S., Keown-Stoneman, C., & Grof, P. (2019). The emergent course of bipolar disorder: Observations over two decades from the Canadian high-risk offspring cohort. American Journal of Psychiatry, 176(9), 720–729. https://doi.org/10.1176/appi.ajp.2018.18040461

Duffy, A., Vandeleur, C., Heffer, N., & Preisig, M. (2017). The clinical trajectory of emerging bipolar disorder among the high-risk offspring of bipolar parents: current understanding and future considerations. International Journal of Bipolar Disorders, 5(1). https://doi.org/10.1186/s40345-017-0106-4

Duffy, L., Marston, L., Lewis, G., & Lewis, G. (2023). Reliability of the retrospective Clinical Interview Schedule Revised (rCIS-R) to assess relapse in depression in primary care patients. PLoS ONE, 18(3 March), 1–12. https://doi.org/10.1371/journal.pone.0280997

Durdurak, B. B., Altaweel, N., Upthegrove, R., & Marwaha, S. (2022). Understanding the development of bipolar disorder and borderline personality disorder in young people: a meta-review of systematic reviews. Psychological Medicine, 52(16), 3769–3782. https://doi.org/10.1017/S0033291722003002

Eich, D., Gamma, A., Malti, T., Vogt Wehrli, M., Liebrenz, M., Seifritz, E., & Modestin, J. (2014). Temperamental differences between bipolar disorder, borderline personality disorder, and attention deficit/hyperactivity disorder: Some implications for their diagnostic validity. *Journal of Affective Disorders*, *169*, 101–104. https://doi.org/10.1016/j.jad.2014.05.028

Ellard, K. K., Zimmerman, J. P., Kaur, N., Van Dijk, K. R. A., Roffman, J. L., Nierenberg, A. A., Dougherty, D. D., Deckersbach, T., & Camprodon, J. A. (2018). Functional Connectivity Between Anterior Insula and Key Nodes of Frontoparietal Executive Control and Salience Networks Distinguish Bipolar Depression From Unipolar Depression and Healthy Control Subjects. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 3(5), 473–484. https://doi.org/10.1016/j.bpsc.2018.01.013

Etain, B., Lajnef, M., Loftus, J., Henry, C., Raust, A., Gard, S., Kahn, J. P., Leboyer, M., Scott, J., & Bellivier, F. (2017). Association between childhood dimensions of attention deficit hyperactivity disorder and adulthood clinical severity of bipolar disorders. Australian and New Zealand Journal of Psychiatry, 51(4), 382–392. https://doi.org/10.1177/0004867416642021

Eyre, O., Bevan Jones, R., Agha, S. S., Wootton, R. E., Thapar, A. K., Stergiakouli, E., Langley, K., Collishaw, S., Thapar, A., & Riglin, L. (2021). Validation of the short Mood and Feelings Questionnaire in young adulthood. Journal of Affective Disorders, 294(July), 883–888. https://doi.org/10.1016/j.jad.2021.07.090

Faedda, G. L., Baldessarini, R. J., Marangoni, C., Bechdolf, A., Berk, M., Birmaher, B., Conus, P., DelBello, M. P., Duffy, A. C., Hillegers, M. H. J., Pfennig, A., Post, R. M., Preisig, M., Ratheesh, A., Salvatore, P., Tohen, M., Vázquez, G. H., Vieta, E., Yatham, L. N., … Correll, C. U. (2019). An International Society of Bipolar Disorders task force report: Precursors and prodromes of bipolar disorder. Bipolar Disorders, 21(8), 720–740. https://doi.org/10.1111/bdi.12831

* Faedda, G. L., Marangoni, C., Serra, G., Salvatore, P., Sani, G., Vázquez, G. H., … Koukopoulos†, A. (2015). Precursors of bipolar disorders. *The Journal of Clinical Psychiatry*, *76*(05), 614–624. https://doi.org/10.4088/jcp.13r08900

Fahrendorff, A. M., Pagsberg, A. K., Kessing, L. V., & Maigaard, K. (2023). Psychiatric comorbidity in patients with pediatric bipolar disorder – A systematic review. Acta Psychiatrica Scandinavica, 148(2), 110–132. https://doi.org/10.1111/acps.13548

Faraone, S. V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological Medicine*, *36*(2), 159-165.

Faraone, S. V. (2015). Attention deficit hyperactivity disorder and premature death. *The Lancet*, *385*(9983), 2132-2133.

Faraone, S. V., & Larsson, H. (2019). Genetics of attention deficit hyperactivity disorder. Molecular Psychiatry, 24(4), 562–575. https://doi.org/10.1038/s41380-018-0070-0

Faraone, S. V., Banaschewski, T., Coghill, D., Zheng, Y., Biederman, J., Bellgrove, M. A., ... & Wang, Y. (2021). The world federation of ADHD international consensus statement: 208 evidence-based conclusions about the disorder. Neuroscience & biobehavioral reviews, 128, 789-818.

Fletcher, K., Parker, G., Bayes, A., Paterson, A., & McClure, G. (2014). Emotion Regulation Strategies in Bipolar II Disorder and Borderline Personality Disorder: Differences and relationships with perceived parental style. *Journal of Affective Disorders, 157*, 52–59. https://doi.org/10.1016/j.jad.2014.01.001

Flora, D. B., & Curran, P. J. (2004). An empirical evaluation of alternative methods of estimation for confirmatory factor analysis with ordinal data. Psychological Methods, 9(4), 466–491. https://doi.org/10.1037/1082-989X.9.4.466

Fornaro, M., Daray, F. M., Hunter, F., Anastasia, A., Stubbs, B., De Berardis, D., Shin, J. Il, Husain, M. I., Dragioti, E., Fusar-Poli, P., Solmi, M., Berk, M., Vieta, E., & Carvalho, A. F. (2021). The prevalence, odds and predictors of lifespan comorbid eating disorder among people with a primary diagnosis of bipolar disorders, and vice-versa: Systematic review and meta-analysis. Journal of Affective Disorders, 280(June 2020), 409–431. https://doi.org/10.1016/j.jad.2020.11.015

Fornaro, M., Orsolini, L., Marini, S., De Berardis, D., Perna, G., Valchera, A., … Stubbs, B. (2016). The prevalence and predictors of bipolar and borderline personality disorders comorbidity: Systematic Review and meta-analysis. *Journal of Affective Disorders*, *195*, 105–118. https://doi.org/10.1016/j.jad.2016.01.040

Franke, B., Michelini, G., Asherson, P., Banaschewski, T., Bilbow, A., Buitelaar, J. K., Cormand, B., Faraone, S. V., Ginsberg, Y., Haavik, J., Kuntsi, J., Larsson, H., Lesch, K. P., Ramos-Quiroga, J. A., Réthelyi, J. M., Ribases, M., & Reif, A. (2018). Live fast, die young? A review on the developmental trajectories of ADHD across the lifespan. European Neuropsychopharmacology, 28(10), 1059–1088. https://doi.org/10.1016/j.euroneuro.2018.08.001

Frankland, A., Roberts, G., Holmes-Preston, E., Perich, T., Levy, F., Lenroot, R., Hadzi-Pavlovic, D., Breakspear, M., & Mitchell, P. B. (2018). Clinical predictors of conversion to bipolar disorder in a prospective longitudinal familial high-risk sample: Focus on depressive

features. Psychological Medicine, 48(10), 1713–1721. https://doi.org/10.1017/S0033291717003233

Fraser, A., Macdonald-wallis, C., Tilling, K., Boyd, A., Golding, J., Davey smith, G., Henderson, J., Macleod, J., Molloy, L., Ness, A., Ring, S., Nelson, S. M., & Lawlor, D. A. (2013). Cohort profile: The avon longitudinal study of parents and children: ALSPAC mothers cohort. International Journal of Epidemiology, 42(1), 97–110. https://doi.org/10.1093/ije/dys066

Frías, Á., Baltasar, I., & Birmaher, B. (2016). Comorbidity between bipolar disorder and borderline personality disorder: Prevalence, explanatory theories, and clinical impact. https://doi.org/10.1016/j.jad.2016.05.048

Friedrichs, B., Igl, W., Larsson, H., & Larsson, J. O. (2012). Coexisting psychiatric problems and stressful life events in adults with symptoms of ADHD-A large swedish population-based study of twins. Journal of Attention Disorders, 16(1), 13–22. https://doi.org/10.1177/1087054710376909

Fusar-Poli, P., & Radua, J. (2018b). Ten simple rules for conducting umbrella reviews. Evidence-Based Mental Health, 21(3), 95–100. https://doi.org/10.1136/ebmental-2018-300014

Fusar-Poli, P., De Micheli, A., Rocchetti, M., Cappucciati, M., Ramella-Cravaro, V., Rutigliano, G., Bonoldi, I., McGuire, P., & Falkenberg, I. (2018a). Semistructured Interview for Bipolar At Risk States (SIBARS). Psychiatry Research, 264(April), 302–309. https://doi.org/10.1016/j.psychres.2018.03.074

Galione, J., & Zimmerman, M. (2010). A comparison of depressed patients with and without borderline personality disorder: Implications for interpreting studies of the validity of the bipolar spectrum. *Journal of Personality Disorders*, *24*(6), 763–772. https://doi.org/10.1521/pedi.2010.24.6.763

Gardner, H. H., Kleinman, N. L., Brook, R. A., Rajagopalan, K., Brizee, T. J., & Smeeding, J. E. (2006). The economic impact of bipolar disorder in an employed population from an employer perspective. Journal of Clinical Psychiatry, 67(8), 1209–1218. https://doi.org/10.4088/JCP.v67n0806

Geoffroy, P. A., & Scott, J. (2017). Prodrome or risk syndrome: what's in a name? International Journal of Bipolar Disorders, 5(1). https://doi.org/10.1186/s40345-017-0077-5

Ghaemi, S. N., Miller, C. J., Berv, D. A., Klugman, J., Rosenquist, K. J., & Pies, R. W. (2005). Sensitivity and specificity of a new bipolar spectrum diagnostic scale. Journal of Affective Disorders, 84(2–3), 273–277. https://doi.org/10.1016/S0165-0327(03)00196-4

* Gibbs, M., Winsper, C., Marwaha, S., Gilbert, E., Broome, M., & Singh, S. P. (2015). Cannabis use and mania symptoms: A systematic review and meta-analysis. *Journal of Affective Disorders*, *171*, 39–47. https://doi.org/10.1016/j.jad.2014.09.016

Gillett, G., & Saunders, K. E. (2019). Remote monitoring for understanding mechanisms and prediction in psychiatry. *Current Behavioral Neuroscience Reports*, *6*(2), 51–56. https://doi.org/10.1007/s40473-019-00176-3

Gillett, G., McGowan, N. M., Palmius, N., Bilderbeck, A. C., Goodwin, G. M., & Saunders, K. E. (2021). Digital communication biomarkers of mood and diagnosis in borderline personality disorder, bipolar disorder, and healthy control populations. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/fpsyt.2021.610457

Godman, B., Grobler, C., Van-De-Lisle, M., Wale, J., Barbosa, W. B., Massele, A., Opondo, P., Petrova, G., Tachkov, K., Sefah, I., Abdulsalim, S., Alrasheedy, A. A., Unnikrishnan, M. K.,

Garuoliene, K., Bamitale, K., Kibuule, D., Kalemeera, F., Fadare, J., Khan, T. A., … Barbui, C. (2019). Pharmacotherapeutic interventions for bipolar disorder type II: addressing multiple symptoms and approaches with a particular emphasis on strategies in lower and middle-income countries. Expert Opinion on Pharmacotherapy, 20(18), 2237–2255. https://doi.org/10.1080/14656566.2019.1684473

Gold, A. K., Otto, M. W., Deckersbach, T., Sylvia, L. G., Nierenberg, A. A., & Kinrys, G. (2018). Substance use comorbidity in bipolar disorder: A qualitative review of treatment strategies and outcomes. American Journal on Addictions, 27(3), 188–201. https://doi.org/10.1111/ajad.12713

Goldberg, J. F., Garakani, A., & Ackerman, S. H. (2012). Clinician-rated versus self-rated screening for bipolar disorder among inpatients with mood symptoms and substance misuse. Journal of Clinical Psychiatry, 73(12), 1525–1530. https://doi.org/10.4088/JCP.12m07926

Golding, G., Pembrey, P., & Jones, J. (2001). ALSPAC - The Avon Longitudinal Study of Parents and Children I. Study methodology. Paediatric and Perinatal Epidemiology, 15(1), 74–87. https://doi.org/10.1046/j.1365-3016.2001.00325.x

Goodday, S. M., Preisig, M., Gholamrezaee, M., Grof, P., Angst, J., & Duffy, A. (2017). The association between self-reported and clinically determined hypomanic symptoms and the onset of major mood disorders. BJPsych Open, 3(2), 71–77. https://doi.org/10.1192/bjpo.bp.116.004234

Goodman, A., Heiervang, E., Collishaw, S., & Goodman, R. (2011). The “DAWBA bands” as an ordered-categorical measure of child mental health: Description and validation in British and Norwegian samples. Social Psychiatry and Psychiatric Epidemiology, 46(6), 521–532. https://doi.org/10.1007/s00127-010-0219-x

Goodman, R., Ford, T., Richards, H., Gatward, R., & Meltzer, H. (2000). The Development and

Well-Being Assessment: Description and initial validation of an integrated assessement of

child and adolescent psychopathology. Journal of Child Psychology and Psychiatry and Allied Disciplines, 41(5), 645–655. https://doi.org/10.1017/S0021963099005909

Gordovez, F. J. A., & McMahon, F. J. (2020). The genetics of bipolar disorder. Molecular Psychiatry, 25(3), 544–559. https://doi.org/10.1038/s41380-019-0634-7

Grande, I., Berk, M., Birmaher, B., & Vieta, E. (2016). Bipolar disorder. The Lancet, 387(10027), 1561–1572. https://doi.org/10.1016/S0140-6736(15)00241-X

Greenwood, T. A. (2020). Creativity and Bipolar Disorder: A Shared Genetic Vulnerability. Annual Review of Clinical Psychology, 16, 239–264. https://doi.org/10.1146/annurev-clinpsy-050718-095449

Groenman, A. P., Janssen, T. W. P., & Oosterlaan, J. (2017). Childhood Psychiatric Disorders as Risk Factor for Subsequent Substance Abuse: A Meta-Analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*(7), 556–569. https://doi.org/10.1016/j.jaac.2017.05.004

Gunderson, J. G. (2007). Disturbed relationships as a phenotype for borderline personality disorder. *American Journal of Psychiatry*, *164*(11), 1637-1640.

Gunderson, J. G., Herpertz, S. C., Skodol, A. E., Torgersen, S., & Zanarini, M. C. (2018). Borderline personality disorder. *Nature Reviews Disease Primers*, *4*(1), 1-20.

Hafeman, D. M., Merranko, J., Goldstein, T. R., Axelson, D., Goldstein, B. I., Monk, K., Hickey, M. B., Sakolsky, D., Diler, R., Iyengar, S., Brent, D. A., Kupfer, D. J., Kattan, M. W., & Birmaher, B. (2017). Assessment of a person-level risk calculator to predict new-onset bipolar spectrum disorder in youth at familial risk. JAMA Psychiatry, 74(8), 841–847. https://doi.org/10.1001/jamapsychiatry.2017.1763

Hafeman, D. M., Merranko, J., Joseph, H. M., Goldstein, T. R., Goldstein, B. I., Levenson, J.,

Axelson, D., Monk, K., Sakolsky, D., Iyengar, S., & Birmaher, B. (2023). Early indicators of bipolar risk in preschool offspring of parents with bipolar disorder. Journal of Child Psychology and Psychiatry and Allied Disciplines, 64(10), 1492–1500. https://doi.org/10.1111/jcpp.13739

Harrison, P. J., Colbourne, L., & Harrison, C. H. (2020). The neuropathology of bipolar disorder: systematic review and meta-analysis. Molecular Psychiatry, 25(8), 1787–1808. https://doi.org/10.1038/s41380-018-0213-3

Hartmann, J. A., Mcgorry, P. D., Destree, L., Amminger, G. P., Chanen, A. M., Davey, C. G., Ghieh, R., Polari, A., Ratheesh, A., Yuen, H. P., & Nelson, B. (2021). Pluripotential Risk and Clinical Staging : Theoretical Considerations and Preliminary Data From a Transdiagnostic Risk Identification Approach. 11(January), 1–11. https://doi.org/10.3389/fpsyt.2020.553578

Hartmann, J. A., Nelson, B., Ratheesh, A., Treen, D., & McGorry, P. D. (2018). At-risk studies and clinical antecedents of psychosis, bipolar disorder and depression: A scoping review in the context of clinical staging. *Psychological Medicine*, *49*(2), 177–189. https://doi.org/10.1017/s0033291718001435

Hartmann, J. A., Nelson, B., Spooner, R., Paul Amminger, G., Chanen, A., Davey, C. G., McHugh, M., Ratheesh, A., Treen, D., Yuen, H. P., & McGorry, P. D. (2019). Broad clinical high-risk mental state (CHARMS): Methodology of a cohort study validating criteria for pluripotent risk. Early Intervention in Psychiatry, 13(3), 379–386. https://doi.org/10.1111/eip.12483

Henry, C., Mitropoulou, V., New, A. S., Koenigsberg, H. W., Silverman, J., & Siever, L. J. (2001). Affective instability and impulsivity in borderline personality and bipolar II disorders: Similarities and differences. *Journal of Psychiatric Research*, *35*(6), 307–312. https://doi.org/10.1016/s0022-3956(01)00038-3

Hetherington, E., Plamondon, A., & Williamson, T. (2020). Trajectory Modeling with Latent Groups: Potentials and Pitfalls. Current Epidemiology Reports, 7(4), 171–178. https://doi.org/10.1007/s40471-020-00242-5

Hibar, D. P., Westlye, L. T., Doan, N. T., Jahanshad, N., Cheung, J. W., Ching, C. R. K., Versace, A., Bilderbeck, A. C., & Uhlmann, A. (2018). Cortical abnormalities in bipolar disorder : an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. 932–942. https://doi.org/10.1038/mp.2017.73

Hibar, D. P., Westlye, L. T., Erp, T. G. M. Van, Rasmussen, J., Leonardo, C. D., Faskowitz, J., Haukvik, U. K., Hartberg, C. B., Doan, N. T., & Agartz, I. (2016). Subcortical volumetric abnormalities in bipolar disorder. Nature Publishing Group, February, 1710–1716. https://doi.org/10.1038/mp.2015.227

Hill, A. B. (1965). The Environment and Disease: Association or causation? Proc R Soc Med, 58, 295–300.

Hines, L. A., Jones, H. J., Hickman, M., Lynskey, M., Howe, L. D., Zammit, S., & Heron, J. (2023). Adverse childhood experiences and adolescent cannabis use trajectories: findings from a longitudinal UK birth cohort. The Lancet Public Health, 8(6), e442–e452. https://doi.org/10.1016/S2468-2667(23)00095-6

Hirschfeld, R. M. A., Williams, J. B. W., Spitzer, R. L., Calabrese, J. R., Flynn, L., Keck, J., Lewis, L., McElroy, S. L., Post, R. M., Rapport, D. J., Russell, J. M., Sachs, G. S., & Zajecka, J. (2000). Development and validation of a screening instrument for bipolar spectrum disorder: The mood disorder questionnaire. American Journal of Psychiatry, 157(11), 1873–1875. https://doi.org/10.1176/appi.ajp.157.11.1873

Holtmann, M., Pörtner, F., Duketis, E., Flechtner, H. H., Angst, J., & Lehmkuhl, G. (2009). Validation of the Hypomania Checklist (HCL-32) in a nonclinical sample of German adolescents. Journal of Adolescence, 32(5), 1075–1088. https://doi.org/10.1016/j.adolescence.2009.03.004

Hosang, G. M., Cardno, A. G., Freeman, D., & Ronald, A. (2017). Characterization and structure of hypomania in a British nonclinical adolescent sample. Journal of Affective Disorders, 207(October 2016), 228–235. https://doi.org/10.1016/j.jad.2016.08.033

Hosang, G. M., Fisher, H. L., Hodgson, K., Maughan, B., & Farmer, A. E. (2018). Childhood maltreatment and adult medical morbidity in mood disorders: Comparison of unipolar depression with bipolar disorder. British Journal of Psychiatry, 213(5), 645–653. https://doi.org/10.1192/bjp.2018.178

Hosang, G. M., Lichtenstein, P., Ronald, A., Lundström, S., & Taylor, M. J. (2019). Association of Genetic and Environmental Risks for Attention-Deficit/Hyperactivity Disorder with Hypomanic Symptoms in Youths. JAMA Psychiatry, 76(11), 1150–1158. https://doi.org/10.1001/jamapsychiatry.2019.1949

Hosang, G. M., Martin, J., Karlsson, R., Lundström, S., Larsson, H., Ronald, A., Lichtenstein, P., & Taylor, M. J. (2022). Association of Etiological Factors for Hypomanic Symptoms, Bipolar Disorder, and Other Severe Mental Illnesses. 79(2), 143–150. https://doi.org/10.1001/jamapsychiatry.2021.3654

* Hu, R., Stavish, C., Leibenluft, E., & Linke, J. O. (2020). White matter microstructure in individuals with and at risk for bipolar disorder: Evidence for an endophenotype from a voxel-based meta-analysis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *5*(12), 1104–1113. https://doi.org/10.1016/j.bpsc.2020.06.007

Huang, J., Perlis, R. H., Lee, P. H., Ph, D., Rush, A. J., Fava, M., Sachs, G. S., Lieberman, J., Hamilton, S. P., Ph, D., Sullivan, P., Sklar, P., Ph, D., Purcell, S., Ph, D., Smoller, J. W., & Sc, D. (2010). Cross-disorder genomewide analysis of schizophrenia, bipolar disorder, and depression. American Journal of Psychiatry, 167(10), 1254–1263.

Hutsebaut, J., & Aleva, A. (2021). The identification of a risk profile for young people with borderline personality pathology: A review of recent literature. *Current Opinion in Psychology*, *37*, 13–20. https://doi.org/10.1016/j.copsyc.2020.06.004

Hutsebaut, J., Videler, A. C., Verheul, R., & Van Alphen, S. P. J. (2019). Managing borderline personality disorder from a life course perspective: Clinical staging and health management. Personality Disorders: Theory, Research, and Treatment, 10(4), 309–316. https://doi.org/10.1037/per0000341

James, A., Wotton, C. J., Duffy, A., Hoang, U., & Goldacre, M. (2015). Conversion from depression to bipolar disorder in a cohort of young people in England, 1999-2011: A national record linkage study. Journal of Affective Disorders, 185, 123–128. https://doi.org/10.1016/j.jad.2015.06.018

Janiri, D., Sani, G., De Rossi, P., Piras, F., Banaj, N., Ciullo, V., Simonetti, A., Arciniegas, D. B., & Spalletta, G. (2019). Hippocampal subfield volumes and childhood trauma in bipolar disorders. Journal of Affective Disorders, 253(September 2018), 35–43. https://doi.org/10.1016/j.jad.2019.04.071

Jauhar, S., Krishnadas, R., Nour, M. M., Cunningham-Owens, D., Johnstone, E. C., & Lawrie, S. M. (2018). Is there a symptomatic distinction between the affective psychoses and

schizophrenia? A machine learning approach. Schizophrenia Research, 202, 241–247. https://doi.org/10.1016/j.schres.2018.06.070

John, H., & Sharma, V. (2009). Misdiagnosis of bipolar disorder as borderline personality disorder: Clinical and economic consequences. *The World Journal of Biological Psychiatry*, *10*(4-2), 612–615. https://doi.org/10.1080/15622970701816522

Joyce, P. R., Light, K. J., Rowe, S. L., Cloninger, C. R., & Kennedy, M. A. (2010). Self-mutilation and suicide attempts: Relationships to bipolar disorder, borderline personality disorder, temperament and character. *Australian & New Zealand Journal of Psychiatry*, *44*(3), 250–257. https://doi.org/10.3109/00048670903487159

Jung, T., & Wickrama, K. A. S. (2008). An Introduction to Latent Class Growth Analysis and Growth Mixture Modeling. Social and Personality Psychology Compass, 2(1), 302–317. https://doi.org/10.1111/j.1751-9004.2007.00054.x

Kaess, M., Brunner, R., & Chanen, A. (2014). Borderline personality disorder in adolescence. *Pediatrics*, *134*(4), 782-793.

Kempton, M. J., Haldane, M., Jogia, J., Grasby, P. M., Collier, D., & Frangou, S. (2009). Dissociable brain structural changes associated with predisposition, resilience, and disease expression in bipolar disorder. Journal of Neuroscience, 29(35), 10863–10868. https://doi.org/10.1523/JNEUROSCI.2204-09.2009

Kent, L., & Craddock, N. (2003). Is there a relationship between attention deficit hyperactivity disorder and bipolar disorder? Journal of Affective Disorders, 73(3), 211–221. https://doi.org/10.1016/S0165-0327(02)00092-7

* Keramatian, K., Chakrabarty, T., Saraf, G., & Yatham, L. N. (2021). Transitioning to bipolar disorder: A systematic review of prospective high-risk studies. *Current Opinion in Psychiatry*, *35*(1), 10–21. https://doi.org/10.1097/yco.0000000000000762

Kessing, L. V., González-Pinto, A., Fagiolini, A., Bechdolf, A., Reif, A., Yildiz, A., Etain, B., Henry, C., Severus, E., Reininghaus, E. Z., Morken, G., Goodwin, G. M., Scott, J., Geddes, J. R., Rietschel, M., Landén, M., Manchia, M., Bauer, M., Martinez-Cengotitabengoa, M., … Vieta, E. (2021). DSM-5 and ICD-11 criteria for bipolar disorder: Implications for the prevalence of bipolar disorder and validity of the diagnosis – A narrative review from the ECNP bipolar disorders network. European Neuropsychopharmacology, 47, 54–61. https://doi.org/10.1016/j.euroneuro.2021.01.097

Kessing, L. V., Munkholm, K., Faurholt-Jepsen, M., Miskowiak, K. W., Nielsen, L. B., Frikke-Schmidt, R., Ekstrøm, C., Winther, O., Pedersen, B. K., Poulsen, H. E., McIntyre, R. S., Kapczinski, F., Gattaz, W. F., Bardram, J., Frost, M., Mayora, O., Knudsen, G. M., Phillips, M., & Vinberg, M. (2017). The Bipolar Illness Onset study: Research protocol for the BIO cohort study. BMJ Open, 7(6), 1–12. https://doi.org/10.1136/bmjopen-2016-015462

Kessing, L. V., Vradi, E., & Andersen, P. K. (2015a). Life expectancy in bipolar disorder. Bipolar Disorders, 17(5), 543–548. https://doi.org/10.1111/bdi.12296

Kessing, L. V., Vradi, E., McIntyre, R. S., & Andersen, P. K. (2015b). Causes of decreased life expectancy over the life span in bipolar disorder. Journal of Affective Disorders, 180, 142–147. https://doi.org/10.1016/j.jad.2015.03.027

Kessing, L. V., Willer, I., Andersen, P. K., & Bukh, J. D. (2017). Rate and predictors of conversion from unipolar to bipolar disorder: A systematic review and meta-analysis. Bipolar Disorders, 19(5), 324–335. https://doi.org/10.1111/bdi.12513

Khandaker, G. M., Zammit, S., Burgess, S., Lewis, G., & Jones, P. B. (2018). Association between a functional interleukin 6 receptor genetic variant and risk of depression and psychosis in a population-based birth cohort. Brain, Behavior, and Immunity, 69, 264–272. https://doi.org/10.1016/j.bbi.2017.11.020

Khoury, E., Acquaviva, E., Purper-Ouakil, D., Delorme, R., & Ellul, P. (2023). Meta-analysis of personal and familial co-occurrence of Attention Deficit/Hyperactivity Disorder and Bipolar Disorder. Neuroscience and Biobehavioral Reviews, 146(October 2022), 105050. https://doi.org/10.1016/j.neubiorev.2023.105050

Kim, J. H., Kim, J. Y., Lee, J., Jeong, G. H., Lee, E., Lee, S., Lee, K. H., Kronbichler, A., Stubbs, B., Solmi, M., Koyanagi, A., Hong, S. H., Dragioti, E., Jacob, L., Brunoni, A. R., Carvalho, A. F., Radua, J., Thompson, T., Smith, L., … Fusar-Poli, P. (2020). Environmental risk factors, protective factors, and peripheral biomarkers for ADHD: an umbrella review. The Lancet Psychiatry, 7(11), 955–970. https://doi.org/10.1016/S2215-0366(20)30312-6

Kim, J. Y., Son, M. J., Son, C. Y., Radua, J., Eisenhut, M., Gressier, F., Koyanagi, A., Carvalho, A. F., Stubbs, B., Solmi, M., Rais, T. B., Lee, K. H., Kronbichler, A., Dragioti, E., Shin, J. Il, & Fusar-Poli, P. (2019). Environmental risk factors and biomarkers for autism spectrum disorder: an umbrella review of the evidence. The Lancet Psychiatry, 6(7), 590–600. https://doi.org/10.1016/S2215-0366(19)30181-6

Kirsch, A. C., Huebner, A. R. S., Mehta, S. Q., Howie, F. R., Weaver, A. L., Myers, S. M., Voigt, R. G., & Katusic, S. K. (2020). Association of Comorbid Mood and Anxiety Disorders With Autism Spectrum Disorder. 55905(1), 63–70. https://doi.org/10.1001/jamapediatrics.2019.4368

Kloiber, S., Rosenblat, J. D., Husain, M. I., Ortiz, A., Berk, M., Quevedo, J., Vieta, E., Maes, M., Birmaher, B., Soares, J. C., & Carvalho, A. F. (2020). Neurodevelopmental pathways in bipolar disorder. Neuroscience and Biobehavioral Reviews, 112(January), 213–226. https://doi.org/10.1016/j.neubiorev.2020.02.005

Kordas, K., & Park, A. (2015). European birth cohorts offer insights on environmental factors affecting human development and health. International Journal of Epidemiology, 44(3), 731–734. https://doi.org/10.1093/ije/dyv132

Kotov, R., Krueger, R. F., & Watson, D. (2018). A paradigm shift in psychiatric classification: the Hierarchical Taxonomy Of Psychopathology (HiTOP). World Psychiatry, 17(1), 24–25. https://doi.org/10.1002/wps.20478

Kupka, R., Duffy, A., Scott, J., Almeida, J., Balanzá-Martínez, V., Birmaher, B., Bond, D. J., Brietzke, E., Chendo, I., Frey, B. N., Grande, I., Hafeman, D., Hajek, T., Hillegers, M., Kauer-Sant'Anna, M., Mansur, R. B., van der Markt, A., Post, R., Tohen, M., … Kapczinski, F. (2021). Consensus on nomenclature for clinical staging models in bipolar disorder: A narrative review from the International Society for Bipolar Disorders (ISBD) Staging Task Force. Bipolar Disorders, 23(7), 659–678. https://doi.org/10.1111/bdi.13105

Kwong, A. S. F., López-López, J. A., Hammerton, G., Manley, D., Timpson, N. J., Leckie, G., & Pearson, R. M. (2019). Genetic and Environmental Risk Factors Associated with Trajectories of Depression Symptoms from Adolescence to Young Adulthood. JAMA Network Open, 2(6), 1–14. https://doi.org/10.1001/jamanetworkopen.2019.6587

Kyaga, S., Lichtenstein, P., Boman, M., & Landén, M. (2015). Bipolar disorder and leadership - a total population study. Acta Psychiatrica Scandinavica, 131(2), 111–119. https://doi.org/10.1111/acps.12304

Lalli, M., Brouillette, K., Kapczinski, F., & de Azevedo Cardoso, T. (2021). Substance use as a risk factor for bipolar disorder: A systematic review. Journal of Psychiatric Research, 144(July), 285–295. https://doi.org/10.1016/j.jpsychires.2021.10.012

Lamers, F., De Jonge, P., Nolen, W. A., Smit, J. H., Zitman, F. G., Beekman, A. T. F., & Penninx, B. W. J. H. (2010). Identifying depressive subtypes in a large cohort study: Results from the Netherlands Study of Depression and Anxiety (NESDA). Journal of Clinical Psychiatry, 71(12), 1582–1589. https://doi.org/10.4088/JCP.09m05398blu

Lamers, F., Milaneschi, Y., & Penninx, B. W. J. H. (2018). Depression subtypes and inflammation: Atypical rather than melancholic depression is linked with immunometabolic dysregulations. In Inflammation and Immunity in Depression: Basic Science and Clinical Applications. Elsevier Inc. https://doi.org/10.1016/B978-0-12-811073-7.00026-X

Larson, R., & Csikszentmihalyi, M. (2014). *The experience sampling method. In Flow and the foundations of positive psychology*. Dordrecht: Springer.

Lau, P., Hawes, D. J., Hunt, C., Frankland, A., Roberts, G., & Mitchell, P. B. (2017). Prevalence of psychopathology in bipolar high-risk offspring and siblings: A meta-analysis. *European Child & Adolescent Psychiatry*, *27*(7), 823–837. https://doi.org/10.1007/s00787-017-1050-7

* Lau, P., Hawes, D. J., Hunt, C., Frankland, A., Roberts, G., & Mitchell, P. B. (2018). Prevalence of psychopathology in bipolar high-risk offspring and siblings: a meta-analysis. European Child and Adolescent Psychiatry, 27(7), 823–837. https://doi.org/10.1007/s00787-017-1050-7

Laurenssen, E. M. P., Hutsebaut, J., Feenstra, D. J., Van Busschbach, J. J., & Luyten, P. (2013). Diagnosis of personality disorders in adolescents: A study among psychologists. *Child and Adolescent Psychiatry and Mental Health, 7*(1), 1-4.

Laursen, T. M., Wahlbeck, K., Hä Llgren, J., Westman, J., Sby, U. O. ¨, Alinaghizadeh, H., Gissler, M., & Nordentoft, M. (2013). Life Expectancy and Death by Diseases of the Circulatory System in Patients with Bipolar Disorder or Schizophrenia in the Nordic Countries. https://doi.org/10.1371/journal.pone.0067133

Lee, T., & Shi, D. (2021). Supplemental Material for A Comparison of Full Information Maximum Likelihood and Multiple Imputation in Structural Equation Modeling With Missing Data. Psychological Methods, 26(4), 466–485. https://doi.org/10.1037/met0000381.supp

Leichsenring, F., Heim, N., Leweke, F., Spitzer, C., Steinert, C., & Kernberg, O. F. (2023). Borderline Personality Disorder: A Review. Jama, 329(8), 670–679. https://doi.org/10.1001/jama.2023.0589

Leopold, K., Ritter, P., Correll, C. U., Marx, C., Özgürdal, S., Juckel, G., Bauer, M., & Pfennig, A. (2012). Risk constellations prior to the development of bipolar disorders: Rationale of a new risk assessment tool. Journal of Affective Disorders, 136(3), 1000–1010. https://doi.org/10.1016/j.jad.2011.06.043

Leucht, S. M., Jim van Os, M., Markus Jäger, M., & John M. Davis, M. (2024). Prioritization of Psychopathological Symptoms and Clinical Characterization in Psychiatric Diagnoses A Narrative Review. 1–10. https://doi.org/10.1001/jamapsychiatry.2024.2652

Lewis, G., Pelosi, A. J., Araya, R., & Dunn, G. (1992). Measuring psychiatric disorder in the community: A standardized assessment for use by lay interviewers. Psychological Medicine, 22(2), 465–486. https://doi.org/10.1017/S0033291700030415

Little, R. J., Carpenter, J. R., & Lee, K. J. (2024). A Comparison of Three Popular Methods for Handling Missing Data: Complete-Case Analysis, Inverse Probability Weighting, and Multiple Imputation. Sociological Methods and Research, 53(3), 1105–1135. https://doi.org/10.1177/00491241221113873

Loftus, J., Scott, J., Vorspan, F., Icick, R., Henry, C., Gard, S., Kahn, J. P., Leboyer, M., Bellivier, F., & Etain, B. (2020). Psychiatric comorbidities in bipolar disorders: An examination of the prevalence and chronology of onset according to sex and bipolar subtype. Journal of Affective Disorders, 267(December 2019), 258–263. https://doi.org/10.1016/j.jad.2020.02.035

López-Muñoz, F., Shen, W. W., D'ocon, P., Romero, A., & Álamo, C. (2018). A history of the pharmacological treatment of bipolar disorder. International Journal of Molecular Sciences, 19(7), 1–38. https://doi.org/10.3390/ijms19072143

M'Bailara, K., Cosnefroy, O., Vieta, E., Scott, J., & Henry, C. (2013). Group-based trajectory modeling: A novel approach to examining symptom trajectories in acute bipolar episodes. Journal of Affective Disorders, 145(1), 36–41. https://doi.org/10.1016/j.jad.2012.07.007

MacKinnon, D. F., & Pies, R. (2006). Affective instability as rapid cycling: Theoretical and clinical implications for borderline personality and Bipolar Spectrum Disorders. *Bipolar Disorders*, *8*(1), 1–14. https://doi.org/10.1111/j.1399-5618.2006.00283.x

Macneil, C. A., Hasty, M. K., Berk, M., Henry, L., Evans, M., Redlich, C., Daglas, R., Mcgorry, P. D., & Conus, P. (2011). Psychological needs of adolescents in the early phase of bipolar disorder: Implications for early intervention. Early Intervention in Psychiatry, 5(2), 100–107. https://doi.org/10.1111/j.1751-7893.2011.00273.x

Maj, M., Stein, D. J., Parker, G., Zimmerman, M., Fava, G. A., De Hert, M., Demyttenaere, K., McIntyre, R. S., Widiger, T., & Wittchen, H. U. (2020). The clinical characterization of the adult patient with depression aimed at personalization of management. World Psychiatry, 19(3), 269–293. https://doi.org/10.1002/wps.20771

Malhi, G. S., Moore, J., & McGuffin, P. (2000). The genetics of major depressive disorder. *Current Psychiatry Reports*, *2*(2), 165–169. https://doi.org/10.1007/s11920-000-0062-y

Malhi, G. S., Morris, G., Hamilton, A., Outhred, T., & Mannie, Z. (2017). Is "Early intervention" in bipolar disorder what it claims to be? *Bipolar Disorders*, *19*(8), 627–636. https://doi.org/10.1111/bdi.12576

Manchia, M., Vieta, E., Smeland, O. B., Altimus, C., Bechdolf, A., Bellivier, F., Bergink, V., Fagiolini, A., Geddes, J. R., Hajek, T., Henry, C., Kupka, R., Lagerberg, T. V., Licht, R. W., Martinez-Cengotitabengoa, M., Morken, G., Nielsen, R. E., Pinto, A. G., Reif, A., … Andreassen, O. A. (2020). Translating big data to better treatment in bipolar disorder - a manifesto for coordinated action. European Neuropsychopharmacology, 36, 121–136. https://doi.org/10.1016/j.euroneuro.2020.05.006

Marangoni, C., De Chiara, L., & Faedda, G. L. (2015). Bipolar Disorder and ADHD: Comorbidity and Diagnostic Distinctions. Current Psychiatry Reports, 17(8). https://doi.org/10.1007/s11920-015-0604-y

Marangoni, C., Faedda, G. L., & Baldessarini, R. J. (2018). Clinical and environmental risk factors for bipolar disorder: Review of prospective studies. Harvard Review of Psychiatry, 26(1), 1–7. https://doi.org/10.1097/HRP.0000000000000161

Marneros, A. (2001). Expanding the group of bipolar disorders. Journal of Affective Disorders, 62(1–2), 39–44. https://doi.org/10.1016/S0165-0327(00)00349-9

Martin, J., Tilling, K., Hubbard, L., Stergiakouli, E., Thapar, A., Davey Smith, G., O'Donovan, M. C., & Zammit, S. (2016). Association of genetic risk for schizophrenia with nonparticipation over time in a population-based cohort study. American Journal of Epidemiology, 183(12), 1149–1158. https://doi.org/10.1093/aje/kww009

Martini, J., Bröckel, K. L., Leopold, K., Berndt, C., Sauer, C., Maicher, B., Juckel, G., Krüger-Özgürdal, S., Fallgatter, A. J., Lambert, M., Bechdolf, A., Reif, A., Matura, S., Biere, S., Kittel-Schneider, S., Stamm, T., Bermpohl, F., Kircher, T., Falkenberg, I., … Pfennig, A. (2024). Young people at risk for developing bipolar disorder: Two-year findings from the multicenter prospective, naturalistic Early-BipoLife study. European Neuropsychopharmacology, 78(September 2023), 43–53. https://doi.org/10.1016/j.euroneuro.2023.10.001

Martins, D. S., Hasse-Sousa, M., Petry-Perin, C., Arrial-Cordeiro, R. T., Rabelo-da-Ponte, F. D., Lima, F. M., Rosa, A. R., Bücker, J., Gama, C. S., & Czepielewski, L. S. (2019). Perceived childhood adversities: Impact of childhood trauma to estimated intellectual functioning of individuals with bipolar disorder. Psychiatry Research, 274(February), 345–351. https://doi.org/10.1016/j.psychres.2019.02.046

Marwaha, S., Briley, P. M., Perry, A., Rankin, P., Diflorio, A., Craddock, N., Jones, I., Broome, M., Gordon-smith, K., & Jones, L. (2020). Explaining why childhood abuse is a risk factor for poorer clinical course in bipolar disorder : a path analysis of 923 people with bipolar I disorder.

Marwaha, S., Gordon-Smith, K., Broome, M., Briley, P. M., Perry, A., Forty, L., Craddock, N., Jones, I., & Jones, L. (2016). Affective instability, childhood trauma and major affective disorders. Journal of Affective Disorders, 190(0), 764–771. https://doi.org/10.1016/j.jad.2015.11.024

Marwaha, S., He, Z., Broome, M., Singh, S. P., Scott, J., Eyden, J., & Wolke, D. (2014). How is affective instability defined and measured? A systematic review. *Psychological Medicine, 44*(9), 1793-1808.

Marwaha, S., Winsper, C., Bebbington, P., & Smith, D. (2018). Cannabis use and hypomania in young people: A prospective analysis. Schizophrenia Bulletin, 44(6), 1267–1274. https://doi.org/10.1093/schbul/sbx158

Mason, B. L., Sherwood Brown, E., & Croarkin, P. E. (2016). Historical underpinnings of bipolar disorder diagnostic criteria. Behavioral Sciences, 6(3). https://doi.org/10.3390/bs6030014

Massó Rodriguez, A., Hogg, B., Gardoki-Souto, I., Valiente-Gómez, A., Trabsa, A., Mosquera, D., … Amann, B. L. (2021). Clinical features, neuropsychology and neuroimaging in bipolar and borderline personality disorder: A systematic review of cross-diagnostic studies. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/fpsyt.2021.681876

McDonald, C., Marshall, N., Sham, P. C., Bullmore, E. T., Schulze, K., Chapple, B., Bramon, E., Filbey, F., Quraishi, S., Walshe, M., & Murray, R. M. (2006). Regional brain morphometry in patients with schizophrenia or bipolar disorder and their unaffected relatives. American Journal of Psychiatry, 163(3), 478–487. https://doi.org/10.1176/appi.ajp.163.3.478

McGlashan, T. H. (1983). The borderline syndrome. *Archives of General Psychiatry*, *40*(12), 1319. https://doi.org/10.1001/archpsyc.1983.01790110061011

McGorry, P. D., & Mei, C. (2021). Clinical Staging for Youth Mental Disorders: Progress in Reforming Diagnosis and Clinical Care. Annual Review of Developmental Psychology, 3(1), 15–39. https://doi.org/10.1146/annurev-devpsych-050620-030405

McGorry, P. D., Hartmann, J. A., Spooner, R., & Nelson, B. (2018). Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry. World Psychiatry, 17(2), 133–142. https://doi.org/10.1002/wps.20514

McGorry, P. D., Hickie, I. B., Yung, A. R., Pantelis, C., & Jackson, H. J. (2006). Clinical staging of psychiatric disorders: A heuristic framework for choosing earlier, safer and more effective interventions. Australian and New Zealand Journal of Psychiatry, 40(8), 616–622. https://doi.org/10.1111/j.1440-1614.2006.01860.x

McGorry, P. D., Mei, C., Dalal, N., Alvarez-Jimenez, M., Blakemore, S. J., Browne, V., Dooley, B., Hickie, I. B., Jones, P. B., McDaid, D., Mihalopoulos, C., Wood, S. J., El Azzouzi, F. A., Fazio, J., Gow, E., Hanjabam, S., Hayes, A., Morris, A., Pang, E., … Killackey, E. (2024). The Lancet Psychiatry Commission on youth mental health. The Lancet Psychiatry, 11(9), 731–774. https://doi.org/10.1016/S2215-0366(24)00163-9

McGowan, N. M., Goodwin, G. M., Bilderbeck, A. C., & Saunders, K. E. (2019). Circadian rest-activity patterns in bipolar disorder and borderline personality disorder. *Translational Psychiatry*, *9*(1). https://doi.org/10.1038/s41398-019-0526-2

McGrath, J. J., Al-Hamzawi, A., Alonso, J., Altwaijri, Y., Andrade, L. H., Bromet, E. J., Bruffaerts, R., de Almeida, J. M. C., Chardoul, S., Chiu, W. T., Degenhardt, L., Demler, O. V., Ferry, F.,

Gureje, O., Haro, J. M., Karam, E. G., Karam, G., Khaled, S. M., Kovess-Masfety, V., … Zaslavsky, A. M. (2023). Age of onset and cumulative risk of mental disorders: a cross-national analysis of population surveys from 29 countries. The Lancet Psychiatry, 10(9), 668–681. https://doi.org/10.1016/S2215-0366(23)00193-1

McGuffin, P., Rijsdijk, F., Andrew, M., Sham, P., Katz, R., & Cardno, A. (2003). The heritability of bipolar affective disorder and the genetic relationship to Unipolar Depression. *Archives of General Psychiatry*, *60*(5), 497. https://doi.org/10.1001/archpsyc.60.5.497

McIntyre, R. S., & Calabrese, J. R. (2019). Bipolar depression: the clinical characteristics and unmet needs of a complex disorder. Current Medical Research and Opinion, 35(11), 1993–2005. https://doi.org/10.1080/03007995.2019.1636017

Mcintyre, R. S., & Correll, C. (2014). Predicting and preventing bipolar disorder: The need to fundamentally advance the strategic approach. Bipolar Disorders, 16(5), 451–454. https://doi.org/10.1111/bdi.12216

McIntyre, R. S., Alda, M., Baldessarini, R. J., Bauer, M., Berk, M., Correll, C. U., Fagiolini, A., Fountoulakis, K., Frye, M. A., Grunze, H., Kessing, L. V., Miklowitz, D. J., Parker, G., Post, R. M., Swann, A. C., Suppes, T., Vieta, E., Young, A., & Maj, M. (2022). The clinical characterization of the adult patient with bipolar disorder aimed at personalization of management. World Psychiatry, 21(3), 364–387. https://doi.org/10.1002/wps.20997

McIntyre, R. S., Berk, M., Brietzke, E., Goldstein, B. I., López-Jaramillo, C., Kessing, L. V., Malhi, G. S., Nierenberg, A. A., Rosenblat, J. D., Majeed, A., Vieta, E., Vinberg, M., Young, A. H., & Mansur, R. B. (2020). Bipolar disorders. The Lancet, 396(10265), 1841–1856. https://doi.org/10.1016/S0140-6736(20)31544-0

McIntyre, R. S., Konarski, J. Z., & Yatham, L. N. (2004). Comorbidity in bipolar disorder : a framework for rational treatment selection. April, 369–386.

McIntyre, R. S., Zimmerman, M., Goldberg, J. F., & First, M. B. (2019). Differential diagnosis of major depressive disorder versus bipolar disorder: current status and best clinical practices. The Journal of Clinical Psychiatry, 80(3), 20884. https://doi.org/10.4088/jcp.ot18043ah2

Meier, S. M., Pavlova, B., Dalsgaard, S., Nordentoft, M., Mors, O., Mortensen, P. B., & Uher, R. (2018). Attention-deficit hyperactivity disorder and anxiety disorders as precursors of bipolar disorder onset in adulthood. British Journal of Psychiatry, 213(3), 555–560. https://doi.org/10.1192/bjp.2018.111

Merikangas, K. R., Akiskal, H. S., Angst, J., Greenberg, P. E., Hirschfeld, R. M. A., Petukhova, M., & Kessler, R. C. (2007). Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. Archives of General Psychiatry, 64(5), 543–552. https://doi.org/10.1001/archpsyc.64.5.543

Merikangas, K. R., Cui, L., Heaton, L., Nakamura, E., Roca, C., Ding, J., Qin, H., Guo, W., Zarate, C., & Angst, J. (2014). Independence of familial transmission of mania and depression : results of the NIMH family study of affective spectrum disorders. April 2013, 214–219. https://doi.org/10.1038/mp.2013.116

Merikangas, K. R., Jin, R., He, J. P., Kessler, R. C., Lee, S., Sampson, N. A., Viana, M. C., Andrade, L. H., Hu, C., Karam, E. G., Ladea, M., Medina-Mora, M. E., Ono, Y., Posada-Villa, J., Sagar, R., Wells, J. E., & Zarkov, Z. (2011). Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. Archives of General Psychiatry, 68(3), 241–251. https://doi.org/10.1001/archgenpsychiatry.2011.12

Merikangas, K. R., Swendsen, J., Hickie, I. B., Cui, L., Shou, H., Merikangas, A. K., ... Zipunnikov, V. (2019). Real-time mobile monitoring of the dynamic associations among motor activity, energy, mood, and sleep in adults with bipolar disorder. *JAMA Psychiatry*, *76*(2), 190-198.

Merikangas, K., & Yu, K. (2002). Genetic epidemiology of bipolar disorder. Clinical Neuroscience Research, 2(3–4), 127–141. https://doi.org/10.1016/S1566-2772(02)00038-5

Mesman, E., Wa, N., Keijsers, L., & Baseline, H. M. H. J. (2017). Baseline dimensional psychopathology and future mood disorder onset : findings from the Dutch Bipolar Offspring Study. 201–209. https://doi.org/10.1111/acps.12739

Messer, T., Lammers, G., Müller-Siecheneder, F., Schmidt, R. F., & Latifi, S. (2017). Substance abuse in patients with bipolar disorder: A systematic review and meta-analysis. Psychiatry Research, 253(February), 338–350. https://doi.org/10.1016/j.psychres.2017.02.067

Meyer, T. D., Castelao, E., Gholamrezaee, M., Angst, J., & Preisig, M. (2017). Hypomania Checklist-32 – cross-validation of shorter versions screening for bipolar disorders in an epidemiological study. Acta Psychiatrica Scandinavica, 135(6), 539–547. https://doi.org/10.1111/acps.12715

Meyer, T. D., Crist, N., La Rosa, N., Ye, B., Soares, J. C., & Bauer, I. E. (2020). Are existing self-ratings of acute manic symptoms in adults reliable and valid?—A systematic review. *Bipolar Disorders*, *22*(6), 558-568.

Middeldorp, C. M., De Moor, M. H. M., McGrath, L. M., Gordon, S. D., Blackwood, D. H., Costa, P. T., Terracciano, A., Krueger, R. F., De Geus, E. J. C., Nyholt, D. R., Tanaka, T., Esko, T., Madden, P. A. F., Derringer, J., Amin, N., Willemsen, G., Hottenga, J. J., Distel, M. A., Uda, M., … Boomsma, D. I. (2011). The genetic association between personality and major depressi0on or bipolar disorder. A polygenic score analysis using genome-wide association data. Translational Psychiatry, 1(August), 1–8. https://doi.org/10.1038/tp.2011.45

Mignogna, K. M., & Goes, F. S. (2024). Characterizing the longitudinal course of symptoms and functioning in bipolar disorder. Psychological Medicine, 54(1), 79–89. https://doi.org/10.1017/S0033291722001489

Milaneschi, Y., Lamers, F., Berk, M., & Penninx, B. W. J. H. (2020). Depression Heterogeneity and Its Biological Underpinnings: Toward Immunometabolic Depression. Biological Psychiatry, 88(5), 369–380. https://doi.org/10.1016/j.biopsych.2020.01.014

Milaneschi, Y., Lamers, F., Bot, M., Drent, M. L., & Penninx, B. W. J. H. (2017). Leptin Dysregulation Is Specifically Associated With Major Depression With Atypical Features: Evidence for a Mechanism Connecting Obesity and Depression. Biological Psychiatry, 81(9), 807–814. https://doi.org/10.1016/j.biopsych.2015.10.023

Milaneschi, Y., Lamers, F., Peyrot, W. J., Baune, B. T., Breen, G., Dehghan, A., Forstner, A. J., Grabe, H. J., Homuth, G., Kan, C., Lewis, C., Mullins, N., Nauck, M., Pistis, G., Preisig, M., Rivera, M., Rietschel, M., Streit, F., Strohmaier, J., … Sullivan, P. F. (2017). Genetic association of major depression with a typical features and obesity-related immunometabolic dysregulations. JAMA Psychiatry, 74(12), 1214–1225. https://doi.org/10.1001/jamapsychiatry.2017.3016

Miskowiak, K. W., Kjærstad, H. L., Meluken, I., Petersen, J. Z., Maciel, B. R., Köhler, C. A., Vinberg, M., Kessing, L. V., & Carvalho, A. F. (2017). The search for neuroimaging and cognitive endophenotypes: A critical systematic review of studies involving unaffected first-degree relatives of individuals with bipolar disorder. Neuroscience and Biobehavioral Reviews, 73, 1–22. https://doi.org/10.1016/j.neubiorev.2016.12.011

Mistry, S., Escott-Price, V., Florio, A. D., Smith, D. J., & Zammit, S. (2019). Genetic risk for bipolar disorder and psychopathology from childhood to early adulthood. Journal of Affective Disorders, 246(September 2018), 633–639. https://doi.org/10.1016/j.jad.2018.12.091

Mistry, S., Zammit, S., Price, V. E., Jones, H. J., & Smith, D. J. (2017). Borderline personality and attention-deficit hyperactivity traits in childhood are associated with hypomanic features in early adulthood. Journal of Affective Disorders, 221(May), 246–253. https://doi.org/10.1016/j.jad.2017.06.039

Mitchell, P. B., Goodwin, G. M., Johnson, G. F., & Hirschfeld, R. M. A. (2008). Diagnostic guidelines for bipolar depression: A probabilistic approach. *Bipolar Disorders*, *10*(1p2), 144–152. https://doi.org/10.1111/j.1399-5618.2007.00559.x

Mneimne, M., Fleeson, W., Arnold, E. M., & Furr, R. M. (2018). Differentiating the everyday emotion dynamics of borderline personality disorder from major depressive disorder and bipolar disorder. Personality Disorders: Theory, Research, and Treatment, 9(2), 192–196. https://doi.org/10.1037/per0000255

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., … Stewart, L. A. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*, *4*(1), 1-9. https://doi.org/10.1186/2046-4053-4-1

Morales-Muñoz, I., Mallikarjun, P. K., Chandan, J. S., Thayakaran, R., Upthegrove, R., & Marwaha, S. (2023). Impact of anxiety and depression across childhood and adolescence on adverse outcomes in young adulthood: a UK birth cohort study. The British Journal of Psychiatry, 222(5), 212-220.

Moran, L. V., Guvenek-Cokol, P. E., & Perlis., R. H. (2019). Attention-Deficit/Hyperactivity Disorder, Hypomania, and Bipolar Disorder in Youth. JAMA Psychiatry, 76(11), 1119–1121. https://doi.org/10.2307/3088897

Moreira, A. L. R., Van Meter, A., Genzlinger, J., & Youngstrom, E. A. (2017). Review and meta-analysis of epidemiologic studies of adult bipolar disorder. The Journal of clinical psychiatry, 78(9), 11720.

Mori, M., Krumholz, H. M., & Allore, H. G. (2020). Using latent class analysis to identify hidden clinical phenotypes. JAMA Psychiatry, 324(7), 700–701. https://doi.org/10.4159/9780674041318

Morris, G., & Berk, M. (2015). The many roads to mitochondrial dysfunction in neuroimmune and neuropsychiatric disorders. BMC Medicine, 13(1), 1–24. https://doi.org/10.1186/s12916-015-0310-y

Mullins, N., Forstner, A. J., O'Connell, K. S., Coombes, B., Coleman, J. R. I., Qiao, Z., Als, T. D., Bigdeli, T. B., Børte, S., Bryois, J., Charney, A. W., Drange, O. K., Gandal, M. J., Hagenaars, S. P., Ikeda, M., Kamitaki, N., Kim, M., Krebs, K., Panagiotaropoulou, G., … Andreassen, O. A. (2021). Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nature Genetics, 53(6), 817–829. https://doi.org/10.1038/s41588-021-00857-4

Murray, A. L., Booth, T., Auyeung, B., Eisner, M., Ribeaud, D., & Obsuth, I. (2020). Outcomes of ADHD Symptoms in Late Adolescence: Are Developmental Subtypes Important? Journal of Attention Disorders, 24(1), 113–125. https://doi.org/10.1177/1087054718790588

Murray, A. L., Booth, T., Eisner, M., Auyeung, B., Murray, G., & Ribeaud, D. (2019). Sex differences in ADHD trajectories across childhood and adolescence. Developmental Science, 22(1), 1–11. https://doi.org/10.1111/desc.12721

Murray, A. L., Hall, H. A., Speyer, L. G., Carter, L., Mirman, D., Caye, A., & Rohde, L. (2022a). Developmental trajectories of ADHD symptoms in a large population-representative

longitudinal study. Psychological Medicine, 52(15), 3590–3596. https://doi.org/10.1017/S0033291721000349

Murray, A. L., Hall, H. A., Speyer, L. G., Carter, L., Mirman, D., Caye, A., & Rohde, L. (2022b). Developmental trajectories of ADHD symptoms in a large population-representative longitudinal study. In Psychological Medicine (Vol. 52, Issue 15). https://doi.org/10.1017/S0033291721000349

Murru, A., Guiso, G., Barbuti, M., Anmella, G., Verdolini, N., Samalin, L., Azorin, J. M., Angst, J. J., Bowden, C. L., Mosolov, S., Young, A. H., Popovic, D., Valdes, M., Perugi, G., Vieta, E., & Pacchiarotti, I. (2019). The implications of hypersomnia in the context of major depression: Results from a large, international, observational study. European Neuropsychopharmacology, 29(4), 471–481. https://doi.org/10.1016/j.euroneuro.2019.02.011

Myin-Germeys, I., Oorschot, M., Collip, D., Lataster, J., Delespaul, P., & Van Os, J. (2009). Experience sampling research in psychopathology: Opening the black box of daily life. *Psychological Medicine*, *39*(9), 1533-1547.

Nagin, D. S., & Odgers, C. L. (2010). Group-based trajectory modeling in clinical research. Annual Review of Clinical Psychology, 6, 109–138. https://doi.org/10.1146/annurev.clinpsy.121208.131413

Nagin, D. S., Jones, B. L., & Elmer, J. (2024). Recent Advances in Group-Based Trajectory Modeling for Clinical Research. Annual Review of Clinical Psychology, 20(1), 285–305. https://doi.org/10.1146/annurev-clinpsy-081122-012416

* Narayan, A. J., Allen, T. A., Cullen, K. R., & Klimes-Dougan, B. (2013). Disturbances in reality testing as markers of risk in offspring of parents with bipolar disorder: A systematic review

from a developmental Psychopathology Perspective. *Bipolar Disorders*, *15*(7), 723–740. https://doi.org/10.1111/bdi.12115

Nelson, B., McGorry, P. D., Wichers, M., Wigman, J. T. W., & Hartmann, J. A. (2017). Moving from static to dynamic models of the onset of mental disorder a review. JAMA Psychiatry, 74(5), 528–534. https://doi.org/10.1001/jamapsychiatry.2017.0001

Newlove-Delgado, T., Ford, T. J., Hamilton, W., Janssens, A., Stein, K., & Ukoumunne, O. C. (2019). Resumption of attention-deficit hyperactivity disorder medication in early adulthood: findings from a UK primary care prescribing study. European Child and Adolescent Psychiatry, 28(12), 1589–1596. https://doi.org/10.1007/s00787-019-01325-5

Newlove-Delgado, T., Hamilton, W., Ford, T. J., Stein, K., & Ukoumunne, O. C. (2019). Prescribing for young people with attention deficit hyperactivity disorder in UK primary care: analysis of data from the Clinical Practice Research Datalink. ADHD Attention Deficit and Hyperactivity Disorders, 11(3), 255–262. https://doi.org/10.1007/s12402-019-00288-6

Nierenberg, A. A., Agustini, B., Köhler-Forsberg, O., Cusin, C., Katz, D., Sylvia, L. G., Peters, A., & Berk, M. (2023). Diagnosis and Treatment of Bipolar Disorder: A Review. Jama, 330(14), 1370–1380. https://doi.org/10.1001/jama.2023.18588

Nilsson, A. K., Jørgensen, C. R., Straarup, K. N., & Licht, R. W. (2010). Severity of affective temperament and maladaptive self-schemas differentiate borderline patients, bipolar patients, and controls. *Comprehensive Psychiatry*, *51*(5), 486–491. https://doi.org/10.1016/j.comppsych.2010.02.006

Northstone, K., Ben Shlomo, Y., Teyhan, A., Hill, A., Groom, A., Mumme, M., Timpson, N., & Golding, J. (2023). The Avon Longitudinal Study of Parents and children ALSPAC G0 Partners: A cohort profile. Wellcome Open Research, 8, 37.

https://doi.org/10.12688/wellcomeopenres.18782.2

O'Connell, K. S., & Coombes, B. J. (2021). Genetic contributions to bipolar disorder: Current status and future directions. Psychological Medicine, 51(13), 2156–2167. https://doi.org/10.1017/S0033291721001252

O'Connell, K. S., Shadrin, A., Bahrami, S., Smeland, O. B., Bettella, F., Frei, O., Krull, F., Askeland, R. B., Walters, G. B., Davíðsdóttir, K., Haraldsdóttir, G. S., Guðmundsson, Ó., Stefánsson, H., Fan, C. C., Steen, N. E., Reichborn-Kjennerud, T., Dale, A. M., Stefánsson,

K., Djurovic, S., & Andreassen, O. A. (2021). Identification of genetic overlap and novel risk loci for attention-deficit/hyperactivity disorder and bipolar disorder. Molecular Psychiatry, 26(8), 4055–4065. https://doi.org/10.1038/s41380-019-0613-z

Oldis, M., Murray, G., Macneil, C. A., Hasty, M. K., Daglas, R., Berk, M., Conus, P., & Cotton, S. M. (2016). Trajectory and predictors of quality of life in first episode psychotic mania. Journal of Affective Disorders, 195, 148–155. https://doi.org/10.1016/j.jad.2016.02.018

Ottosen, C., Petersen, L., Larsen, J. T., & Dalsgaard, S. (2016). Gender Differences in Associations between Attention-Deficit/Hyperactivity Disorder and Substance Use Disorder. Journal of the American Academy of Child and Adolescent Psychiatry, 55(3), 227-234.e4. https://doi.org/10.1016/j.jaac.2015.12.010

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., … Moher, D. (2021). The Prisma 2020 statement: An updated guideline for reporting systematic reviews. *International Journal of Surgery*, *88*, 105906. https://doi.org/10.1016/j.ijsu.2021.105906

Paksarian, D., Cui, L., Angst, J., Ajdacic-Gross, V., Rössler, W., & Merikangas, K. R. (2016). Latent trajectories of common mental health disorder risk across 3 decades of adulthood in a population-based cohort. JAMA Psychiatry, 73(10), 1023–1031. https://doi.org/10.1001/jamapsychiatry.2016.1921

Palmer, B. A., Pahwa, M., Geske, J. R., Kung, S., Nassan, M., Schak, K. M., Alarcon, R. D., Frye, M. A., & Singh, B. (2021). Self-report screening instruments differentiate bipolar disorder and borderline personality disorder. Brain and Behavior, 11(7), 1–8. https://doi.org/10.1002/brb3.2201

* Palmier-Claus, J. E., Berry, K., Bucci, S., Mansell, W., & Varese, F. (2016). Relationship between

childhood adversity and bipolar affective disorder: Systematic review and meta-analysis. *British Journal of Psychiatry, 209*(6), 454–459. https://doi.org/10.1192/bjp.bp.115.179655

Palmier-Claus, J., Golby, R., Stokes, L. J., Saville, C. W. N., Velemis, K., Varese, F., Marwaha, S., Tyler, E., & Taylor, P. (2024). The relationship between childhood adversity and affective instability across psychiatric disorders: A meta-analysis. Acta Psychiatrica Scandinavica, July. https://doi.org/10.1111/acps.13745

* Pancheri, C., Verdolini, N., Pacchiarotti, I., Samalin, L., Delle Chiaie, R., Biondi, M., … Murru, A. (2019). A systematic review on sleep alterations anticipating the onset of bipolar disorder. *European Psychiatry*, *58*, 45–53. https://doi.org/10.1016/j.eurpsy.2019.02.003

Paris, J. (2004). Borderline or bipolar? distinguishing borderline personality disorder from Bipolar Spectrum Disorders. *Harvard Review of Psychiatry*, *12*(3), 140–145. https://doi.org/10.1080/10673220490472373

Paris, J., & Black, D. W. (2015). Borderline personality disorder and bipolar disorder. *Journal of Nervous & Mental Disease*, *203*(1), 3–7. https://doi.org/10.1097/nmd.0000000000000225

Parker, G., Fletcher, K., Barrett, M., Synnott, H., Breakspear, M., Hyett, M., & Hadzi-pavlovic, D. (2008). Screening for bipolar disorder : The utility and comparative properties of the MSS and MDQ measures. 109, 83–89. https://doi.org/10.1016/j.jad.2007.11.003

Parker, G., Hadzi-pavlovic, D., & Tully, L. (2006). Distinguishing bipolar and unipolar disorders : An isomer model. 96, 67–73. https://doi.org/10.1016/j.jad.2006.05.014

Parker, G., Roy, K., Mitchell, P., Wilhelm, K., Malhi, G., & Hadzi-Pavlovic, D. (2002). Atypical depression: A reappraisal. American Journal of Psychiatry, 159(9), 1470–1479. https://doi.org/10.1176/appi.ajp.159.9.1470

Passos, I. C., Ballester, P. L., Barros, R. C., Librenza-Garcia, D., Mwangi, B., Birmaher, B., Brietzke, E., Hajek, T., Lopez Jaramillo, C., Mansur, R. B., Alda, M., Haarman, B. C. M., Isometsa, E., Lam, R. W., McIntyre, R. S., Minuzzi, L., Kessing, L. V., Yatham, L. N., Duffy, A., & Kapczinski, F. (2019). Machine learning and big data analytics in bipolar disorder: A position paper from the International Society for Bipolar Disorders Big Data Task Force. Bipolar Disorders, 21(7), 582–594. https://doi.org/10.1111/bdi.12828

Pauselli, L., Verdolini, N., Santucci, A., Moretti, P., & Quartesan, R. (2015). Bipolar and borderline personality disorders: a descriptive comparison of psychopathological aspects in patients discharged from an Italian Inpatient Unit using PANSS and BPRS. *Psychiatria Danubina*, *27*, 170-176.

Perez-Rodriguez, M. M., Bulbena-Cabré, A., Bassir Nia, A., Zipursky, G., Goodman, M., & New, A. S. (2018). The neurobiology of borderline personality disorder. *Psychiatric Clinics of North America*, *41*(4), 633–650. https://doi.org/10.1016/j.psc.2018.07.012

Perugi, G., Angst, J., Azorin, J. M., Bowden, C. L., Caciagli, A., Mosolov, S., Vieta, E., & Young, A. H. (2016). Relationships between mixed features and borderline personality disorder in 2811 patients with major depressive episode. Acta Psychiatrica Scandinavica, 133(2), 133–143. https://doi.org/10.1111/acps.12457

Pezzoli, S., Emsell, L., Yip, S. W., Dima, D., Giannakopoulos, P., Zarei, M., Tognin, S., Arnone, D., James, A., Haller, S., Frangou, S., Goodwin, G. M., McDonald, C., & Kempton, M. J. (2018). Meta-analysis of regional white matter volume in bipolar disorder with replication in an independent sample using coordinates, T-maps, and individual MRI data. Neuroscience

and Biobehavioral Reviews, 84(October 2017), 162–170. https://doi.org/10.1016/j.neubiorev.2017.11.005

Philipsen, A., Feige, B., Hesslinger, B., Scheel, C., Ebert, D., Matthies, S., ... Lieb, K. (2009). Borderline typical symptoms in adult patients with attention deficit/hyperactivity disorder. *ADHD Attention Deficit and Hyperactivity Disorders*, *1*(1), 11-18.

Phillips, M. L., & Kupfer, D. J. (2013). Bipolar disorder diagnosis: challenges and future directions. The Lancet, 381(9878), 1663-1671.

Phillips, M. L., & Kendler, K. S. (2021). Three important considerations for studies examining pathophysiological pathways in psychiatric illness. *JAMA Psychiatry*, *78*(7), 697. https://doi.org/10.1001/jamapsychiatry.2021.0022

Piazza, G. G., Allegrini, A. G., Eley, T. C., Epskamp, S., Fried, E., Isvoranu, A. M., Roiser, J. P., & Pingault, J. B. (2024). Polygenic Scores and Networks of Psychopathology Symptoms. JAMA Psychiatry, 81(9), 902–910. https://doi.org/10.1001/jamapsychiatry.2024.1403

Pieper, D., Antoine, S.-L., Mathes, T., Neugebauer, E. A. M., & Eikermann, M. (2014). Systematic review finds overlapping reviews were not mentioned in every other overview. *Journal of Clinical Epidemiology*, *67*(4), 368–375. https://doi.org/10.1016/j.jclinepi.2013.11.007

Plana-Ripoll, O., Pedersen, C. B., Holtz, Y., Benros, M. E., Dalsgaard, S., De Jonge, P., Fan, C. C., Degenhardt, L., Ganna, A., Greve, A. N., Gunn, J., Iburg, K. M., Kessing, L. V., Lee, B. K., Lim, C. C. W., Mors, O., Nordentoft, M., Prior, A., Roest, A. M., … McGrath, J. J. (2019). Exploring Comorbidity Within Mental Disorders among a Danish National Population. JAMA Psychiatry, 76(3), 259–270. https://doi.org/10.1001/jamapsychiatry.2018.3658

Plans, L., Barrot, C., Nieto, E., Rios, J., Schulze, T. G., Papiol, S., Mitjans, M., Vieta, E., &

Benabarre, A. (2019). Association between completed suicide and bipolar disorder: A

systematic review of the literature. Journal of Affective Disorders, 242(July 2018), 111–122. https://doi.org/10.1016/j.jad.2018.08.054

Pompili, M., Girardi, P., Ruberto, A., & Tatarelli, R. (2005). Suicide in borderline personality disorder: a meta-analysis. *Nordic Journal of Psychiatry*, *59*(5), 319-324.

Pompili, M., Gonda, X., Serafini, G., Innamorati, M., Sher, L., Amore, M., ... Girardi, P. (2013). Epidemiology of suicide in bipolar disorders: A systematic review of the literature. *Bipolar Disorders*, *15*(5), 457-490.

Prathikanti, S., & McMahon, F. J. (2001). Genome scans for susceptibility genes in bipolar affective disorder. Annals of Medicine, 33(4), 257–262. https://doi.org/10.3109/07853890108998754

Prousali, E., Haidich, A. B., Fontalis, A., Ziakas, N., Brazitikos, P., & Mataftsi, A. (2019). Efficacy and safety of interventions to control myopia progression in children: An overview of systematic reviews and meta-analyses. *BMC Ophthalmology*, *19*(1). https://doi.org/10.1186/s12886-019-1112-3

Purper-Ouakil, D., Porfirio, M. C., Le Strat, Y., Falissard, B., Gorwood, P., & Masi, G. (2017). What do childhood attention deficit/hyperactivity symptoms in depressed adults tell us about the bipolar spectrum? Psychiatry Research, 249(December 2016), 244–251. https://doi.org/10.1016/j.psychres.2016.12.055

Radua, J., Ramella-Cravaro, V., Ioannidis, J. P. A., Reichenberg, A., Phiphopthatsanee, N., Amir, T., Yenn Thoo, H., Oliver, D., Davies, C., Morgan, C., McGuire, P., Murray, R. M., & Fusar-Poli, P. (2018). What causes psychosis? An umbrella review of risk and protective factors. World Psychiatry, 17(1), 49–66. https://doi.org/10.1002/wps.20490

* Rasic, D., Hajek, T., Alda, M., & Uher, R. (2013). Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: A meta-analysis of family high-risk studies. *Schizophrenia Bulletin*, *40*(1), 28–38. https://doi.org/10.1093/schbul/sbt114

Raman, S. R., Man, K. K. C., Bahmanyar, S., Berard, A., Bilder, S., Boukhris, T., Bushnell, G., Crystal, S., Furu, K., KaoYang, Y. H., Karlstad, Ø., Kieler, H., Kubota, K., Lai, E. C. C., Martikainen, J. E., Maura, G., Moore, N., Montero, D., Nakamura, H., … Wong, I. C. K. (2018). Trends in attention-deficit hyperactivity disorder medication use: a retrospective observational study using population-based databases. The Lancet Psychiatry, 5(10), 824–835. https://doi.org/10.1016/S2215-0366(18)30293-1

* Ratheesh, A., Davey, C., Hetrick, S., Alvarez-Jimenez, M., Voutier, C., Bechdolf, A., … Cotton, S. M. (2017). A systematic review and meta-analysis of prospective transition from major depression to bipolar disorder. *Acta Psychiatrica Scandinavica*, *135*(4), 273–284. https://doi.org/10.1111/acps.12686

Ratheesh, A., Hammond, D., Gao, C., Marwaha, S., Thompson, A., Hartmann, J., Davey, C., Zammit, S., Berk, M., McGorry, P., & Nelson, B. (2023a). Empirically driven transdiagnostic stages in the development of mood, anxiety and psychotic symptoms in a cohort of youth followed from birth. Translational Psychiatry, 13(1), 1–10. https://doi.org/10.1038/s41398-023-02396-4

Ratheesh, A., Hammond, D., Watson, M., Betts, J., Siegel, E., McGorry, P., Berk, M., Cotton, S., Chanen, A., Nelson, B., & Bechdolf, A. (2023b). Bipolar At-Risk Criteria and Risk of Bipolar Disorder over 10 or More Years. JAMA Network Open, 6(9), E2334078. https://doi.org/10.1001/jamanetworkopen.2023.34078

Regeer, E. J., Kupka, R. W., Have, M. T., Vollebergh, W., & Nolen, W. A. (2015). Low self-

recognition and awareness of past hypomanic and manic episodes in the general population. *International Journal of Bipolar Disorders, 3*, 1-7.

Reich, D. B., Zanarini, M. C., & Fitzmaurice, G. (2012). Affective lability in bipolar disorder and borderline personality disorder. *Comprehensive Psychiatry*, *53*(3), 230–237. https://doi.org/10.1016/j.comppsych.2011.04.003

Renaud, S., Corbalan, F., & Beaulieu, S. (2012). Differential diagnosis of bipolar affective disorder type II and borderline personality disorder: Analysis of the affective dimension. *Comprehensive Psychiatry*, *53*(7), 952–961. https://doi.org/10.1016/j.comppsych.2012.03.004

Rice, F., Riglin, L., Thapar, A. K., Heron, J., Anney, R., O'Donovan, M. C., & Thapar, A. (2019). Characterizing Developmental Trajectories and the Role of Neuropsychiatric Genetic Risk Variants in Early-Onset Depression. JAMA Psychiatry, 76(3), 306–313. https://doi.org/10.1001/jamapsychiatry.2018.3338

Riglin, L., Eyre, O., Thapar, A. K., Stringaris, A., Leibenluft, E., Pine, D. S., Tilling, K., Smith, G. D., O'Donovan, M. C., & Thapar, A. (2019). Identifying novel types of irritability using a developmental genetic approach. American Journal of Psychiatry, 176(8), 635–642. https://doi.org/10.1176/appi.ajp.2019.18101134

* Ritter, P. S., Marx, C., Bauer, M., Lepold, K., & Pfennig, A. (2011). The role of disturbed sleep in the early recognition of bipolar disorder: A systematic review. *Bipolar Disorders*, *13*(3), 227–237. https://doi.org/10.1111/j.1399-5618.2011.00917.x

Rodriguez, A. M., Hogg, B. M., Amann, B. L., Gardoki, I., Moreno-alcázar, A., Rodriguez, A. M., Hogg, B. M., Amann, B. L., Gardoki, I., & Moreno-, A. (2018). International prospective register of systematic reviews Systematic review of the similarities and differences between patients with bipolar disorder and borderline personality disorder in terms of clinical features , neuropsychology and neuroimaging Cita. 1–5.

Rodriguez, V., Alameda, L., Trotta, G., Spinazzola, E., Marino, P., Matheson, S. L., Laurens, K. R., Murray, R. M., & Vassos, E. (2021). Environmental Risk Factors in Bipolar Disorder and

Psychotic Depression: A Systematic Review and Meta-Analysis of Prospective Studies. Schizophrenia Bulletin, 47(4), 959–974. https://doi.org/10.1093/schbul/sbaa197

Rowland, T. A., & Marwaha, S. (2018a). Epidemiology and risk factors for bipolar disorder. Therapeutic Advances in Psychopharmacology, 8(9), 251–269. https://doi.org/10.1177/2045125318769235

Rowland, T., Perry, B. I., Upthegrove, R., Barnes, N., Chatterjee, J., Gallacher, D., & Marwaha, S. (2018b). Neurotrophins, cytokines, oxidative stress mediators and mood state in bipolar disorder: Systematic review and meta-analyses. British Journal of Psychiatry, 213(3), 514–525. https://doi.org/10.1192/bjp.2018.144

Rubia, K. (2018). Cognitive neuroscience of attention deficit hyperactivity disorder (ADHD) and its clinical translation. Frontiers in Human Neuroscience, 12(March), 1–23. https://doi.org/10.3389/fnhum.2018.00100

Ruggero, C. J., Zimmerman, M., Chelminski, I., & Young, D. (2010). Borderline personality disorder and the misdiagnosis of bipolar disorder. *Journal of Psychiatric Research*, *44*(6), 405–408. https://doi.org/10.1016/j.jpsychires.2009.09.011

Russell, A. E., Ford, T., & Russell, G. (2019). Barriers and predictors of medication use for childhood ADHD: findings from a UK population-representative cohort. *Social Psychiatry and Psychiatric Epidemiology*, *54*(12), 1555–1564. https://doi.org/10.1007/s00127-019-01720-y

Salagre, E., Dodd, S., Aedo, A., Rosa, A., Amoretti, S., Pinzon, J., Reinares, M., Berk, M., Kapczinski, F. P., Vieta, E., & Grande, I. (2018). Toward Precision Psychiatry in Bipolar Disorder: Staging 2.0. Frontiers in Psychiatry, 9(November). https://doi.org/10.3389/fpsyt.2018.00641

Salvi, V., Ribuoli, E., Servasi, M., Orsolini, L., & Volpe, U. (2021). Adhd and bipolar disorder in adulthood: Clinical and treatment implications. Medicina (Lithuania), 57(5), 1–11. https://doi.org/10.3390/medicina57050466

Sanches, M. (2019). The limits between bipolar disorder and borderline personality disorder: A review of the evidence. *Diseases*, *7*(3), 49. https://doi.org/10.3390/diseases7030049

Sandstrom, A., Perroud, N., Alda, M., Uher, R., & Pavlova, B. (2021). Prevalence of attention-deficit/hyperactivity disorder in people with mood disorders: A systematic review and meta-analysis. Acta Psychiatrica Scandinavica, 143(5), 380–391. https://doi.org/10.1111/acps.13283

Saraf, G., Moazen-Zadeh, E., Pinto, J. V., Ziafat, K., Torres, I. J., Kesavan, M., & Yatham, L. N. (2021). Early intervention for people at high risk of developing bipolar disorder: a systematic review of clinical trials. The Lancet Psychiatry, 8(1), 64–75. https://doi.org/10.1016/S2215-0366(20)30188-7

Saunders, K. E. A., Jones, T., Perry, A., Di Florio, A., Craddock, N., Jones, I., Gordon-Smith, K., & Jones, L. (2021). The influence of borderline personality traits on clinical outcomes in bipolar disorder. Bipolar Disorders, 23(4), 368–375. https://doi.org/10.1111/bdi.12978

Saunders, K. E., Goodwin, G. M., & Rogers, R. D. (2015). Borderline personality disorder, but not EUTHYMIC bipolar disorder, is associated with a failure to sustain reciprocal cooperative behaviour: Implications for spectrum models of mood disorders. *Psychological Medicine*, *45*(8), 1591–1600. https://doi.org/10.1017/s0033291714002475

SayuriYamagata, A., Brietzke, E., Rosenblat, J. D., Kakar, R., & McIntyre, R. S. (2017). Medical comorbidity in bipolar disorder: The link with metabolic-inflammatory systems. Journal of Affective Disorders, 211(January), 99–106. https://doi.org/10.1016/j.jad.2016.12.059

Schiweck, C., Arteaga-Henriquez, G., Aichholzer, M., Edwin Thanarajah, S., Vargas-Cáceres, S., Matura, S., Grimm, O., Haavik, J., Kittel-Schneider, S., Ramos-Quiroga, J. A., Faraone, S. V., & Reif, A. (2021). Comorbidity of ADHD and adult bipolar disorder: A systematic

review and meta-analysis. Neuroscience and Biobehavioral Reviews, 124(September 2020), 100–123. https://doi.org/10.1016/j.neubiorev.2021.01.017

Schlechter, P., Wilkinson, P. O., Ford, T. J., & Neufeld, S. A. S. (2023). The Short Mood and Feelings Questionnaire From Adolescence to Emerging Adulthood: Measurement Invariance Across Time and Sex. Psychological Assessment, 35(5), 405–418. https://doi.org/10.1037/pas0001222

Schneibel, R., Brakemeier, E. L., Wilbertz, G., Dykierek, P., Zobel, I., & Schramm, E. (2012). Sensitivity to detect change and the correlation of clinical factors with the Hamilton Depression Rating Scale and the Beck Depression Inventory in depressed inpatients. *Psychiatry Research*, *198*(1), 62-67.

Schwartz, S., Schultz, S., Reider, A., & Saunders, E. F. (2016). Daily mood monitoring of symptoms using smartphones in bipolar disorder: a pilot study assessing the feasibility of ecological momentary assessment. *Journal of Affective Disorders*, *191*, 88-93.

Scott, J., Graham, A., Yung, A., Morgan, C., Bellivier, F., & Etain, B. (2022a). A systematic review and meta-analysis of delayed help-seeking, delayed diagnosis and duration of untreated illness in bipolar disorders. Acta Psychiatrica Scandinavica, 146(5), 389–405. https://doi.org/10.1111/acps.13490

* Scott, J., Etain, B., Miklowitz, D., Crouse, J. J., Carpenter, J., Marwaha, S., … Hickie, I. (2022b). A systematic review and meta-analysis of sleep and circadian rhythms disturbances in individuals at high-risk of developing or with early onset of bipolar disorders. *Neuroscience & Biobehavioral Reviews*, *135*, 104585. https://doi.org/10.1016/j.neubiorev.2022.104585

Scott, J., Iorfino, F., Capon, W., Crouse, J., Nelson, B., Chanen, A. M., Dwyer, D., Conus, P.,

Bechdolf, A., Ratheesh, A., Raballo, A., Yung, A., Berk, M., McKenna, S., Hockey, S., Hutcheon, A., Scott, E., McGorry, P., Shah, J., & Hickie, I. B. (2024). Staging 2.0: refining transdiagnostic clinical staging frameworks to enhance reliability and utility for youth mental

health. The Lancet Psychiatry, 11(6), 461–471. https://doi.org/10.1016/S2215-0366(24)00060-9

* Scott, J., Kallestad, H., Vedaa, O., Sivertsen, B., & Etain, B. (2021). Sleep disturbances and first onset of major mental disorders in adolescence and early adulthood: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *57*, 101429. https://doi.org/10.1016/j.smrv.2021.101429

Scott, J., Marwaha, S., Ratheesh, A., Macmillan, I., Yung, A. R., Morriss, R., Hickie, I. B., & Bechdolf, A. (2017). Bipolar At-Risk Criteria: An Examination of Which Clinical Features Have Optimal Utility for Identifying Youth at Risk of Early Transition from Depression to Bipolar Disorders. Schizophrenia Bulletin, 43(4), 737–744. https://doi.org/10.1093/schbul/sbw154

Selig, J. P., & Preacher, K. J. (2009). Mediation Models for Longitudinal Data in Developmental Research. Research in Human Development, 6(2–3), 144–164. https://doi.org/10.1080/15427600902911247

Serafini, G., Pompili, M., Borgwardt, S., Houenou, J., Geoffroy, P. A., Jardri, R., ... Amore, M. (2014). Brain changes in early-onset bipolar and unipolar depressive disorders: a systematic review in children and adolescents. *European Child & Adolescent Psychiatry*, *23*(11), 1023-1041.

Serrano, E., Ezpeleta, L., & Castro-Fornieles, J. (2013). Comorbidity and Phenomenology of Bipolar Disorder in Children With ADHD. Journal of Attention Disorders, 17(4), 330–338. https://doi.org/10.1177/1087054711427553

Shah, J. L., Jones, N., van Os, J., McGorry, P. D., & Gülöksüz, S. (2022). Early intervention service systems for youth mental health: integrating pluripotentiality, clinical staging, and transdiagnostic lessons from early psychosis. The Lancet Psychiatry, 9(5), 413–422. https://doi.org/10.1016/S2215-0366(21)00467-3

Shah, J. L., Scott, J., McGorry, P. D., Cross, S. P. M., Keshavan, M. S., Nelson, B., Wood, S. J., Marwaha, S., Yung, A. R., Scott, E. M., Öngür, D., Conus, P., Henry, C., & Hickie, I. B. (2020). Transdiagnostic clinical staging in youth mental health: a first international consensus statement. World Psychiatry, 19(2), 233–242. https://doi.org/10.1002/wps.20745

Shea, B. J., Grimshaw, J. M., Wells, G. A., Boers, M., Andersson, N., Hamel, C., … Bouter, L. M. (2007). Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology*, *7*(1). https://doi.org/10.1186/1471-2288-7-10

Shevlin, M., McElroy, E., & Murphy, J. (2017). Homotypic and heterotypic psychopathological continuity: a child cohort study. Social Psychiatry and Psychiatric Epidemiology, 52(9), 1135–1145. https://doi.org/10.1007/s00127-017-1396-7

Shintani, A. O., Rabelo-da-Ponte, F. D., Marchionatti, L. E., Watts, D., Ferreira de Souza, F., Machado, C. dos S., Pulice, R. F., Signori, G. M., Luzini, R. R., Kauer-Sant'Anna, M., & Passos, I. C. (2023). Prenatal and perinatal risk factors for bipolar disorder: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews, 144(November 2022). https://doi.org/10.1016/j.neubiorev.2022.104960

Shore, L., Toumbourou, J. W., Lewis, A. J., & Kremer, P. (2018). Review: Longitudinal trajectories of child and adolescent depressive symptoms and their predictors – a systematic review and

meta-analysis. Child and Adolescent Mental Health, 23(2), 107–120. https://doi.org/10.1111/camh.12220

Simon, J., Pari, A. A. A., Wolstenholme, J., Berger, M., Goodwin, G. M., & Geddes, J. R. (2021). The costs of bipolar disorder in the United Kingdom. Brain and Behavior, 11(10), 1–14. https://doi.org/10.1002/brb3.2351

* Skabeikyte, G., & Barkauskiene, R. (2021). A systematic review of the factors associated with the course of borderline personality disorder symptoms in adolescence. *Borderline Personality Disorder and Emotion Dysregulation, 8*(1). https://doi.org/10.1186/s40479-021-00151-z

Skirrow, C., Hosang, G. M., Farmer, A. E., & Asherson, P. (2012). An update on the debated association between ADHD and bipolar disorder across the lifespan. *Journal of Affective Disorders*, *141*(2-3), 143-159.

Skjelstad, D. V., Malt, U. F., & Holte, A. (2010). Symptoms and signs of the initial PRODROME OF BIPOLAR DISORDERA systematic review. *Journal of Affective Disorders*, *126*(1-2), 1–13. https://doi.org/10.1016/j.jad.2009.10.003

Skoglund, C., Chen, Q., Franck, J., Lichtenstein, P., & Larsson, H. (2015). Attention-Deficit/Hyperactivity Disorder and Risk for Substance Use Disorders in Relatives. *Biological Psychiatry*, *77*(10), 880–886. https://doi.org/10.1016/j.biopsych.2014.10.006

Smith, D. J., Muir, W. J., & Blackwood, D. H. (2004). Is borderline personality disorder part of the bipolar spectrum? *Harvard Review of Psychiatry*, *12*(3), 133–139. https://doi.org/10.1080/10673220490472346

Smoller, J. W., & Finn, C. T. (2003). Family, Twin, and Adoption Studies of Bipolar Disorder. American Journal of Medical Genetics - Seminars in Medical Genetics, 123 C(1), 48–58.

https://doi.org/10.1002/ajmg.c.20013

Soares, J. C. & Young, A. H. (2016). *Bipolar Disorder: Basic Mechanisms and Therapeutic Implications*. (3rd Edition). Cambridge University Press.

Socada, J. L., Söderholm, J. J., Rosenström, T., Ekelund, J., & Isometsä, E. (2021). Presence and overlap of bipolar symptoms and borderline features during major depressive episodes. *Journal of Affective Disorders, 280,* 467–477. https://doi.org/10.1016/j.jad.2020.11.043

Solano, P., Ustulin, M., Pizzorno, E., Vichi, M., Pompili, M., Serafini, G., & Amore, M. (2016). A Google-based approach for monitoring suicide risk. *Psychiatry Research, 246,* 581-586.

Souza-Queiroz, J., Boisgontier, J., Etain, B., Poupon, C., Duclap, D., D'Albis, M. A., Daban, C., Hamdani, N., Le Corvoisier, P., Delavest, M., Bellivier, F., Guevara, P., Leboyer, M., Henry, C., & Houenou, J. (2016). Childhood trauma and the limbic network: A multimodal MRI study in patients with bipolar disorder and controls. Journal of Affective Disorders, 200, 159–164. https://doi.org/10.1016/j.jad.2016.04.038

Stahl, E. A., Breen, G., Forstner, A. J., McQuillin, A., Ripke, S., Trubetskoy, V., Mattheisen, M., Wang, Y., Coleman, J. R. I., Gaspar, H. A., de Leeuw, C. A., Steinberg, S., Pavlides, J. M. W., Trzaskowski, M., Byrne, E. M., Pers, T. H., Holmans, P. A., Richards, A. L., Abbott, L., … Sklar, P. (2019). Genome-wide association study identifies 30 loci associated with bipolar disorder. Nature Genetics, 51(5), 793–803. https://doi.org/10.1038/s41588-019-0397-8

Steel, Z., Marnane, C., Iranpour, C., Chey, T., Jackson, J. W., Patel, V., & Silove, D. (2014). The global prevalence of common mental disorders: A systematic review and meta-analysis 1980-2013. International Journal of Epidemiology, 43(2), 476–493. https://doi.org/10.1093/ije/dyu038

Stepp, S. D., & Lazarus, S. A. (2017). Identifying a borderline personality disorder prodrome: Implications for community screening. *Personality and Mental Health, 11*(3), 195–205. https://doi.org/10.1002/pmh.1389

* Stepp, S. D., Lazarus, S. A., & Byrd, A. L. (2016). A systematic review of risk factors prospectively associated with borderline personality disorder: Taking stock and moving forward. *Personality Disorders: Theory, Research, and Treatment*, *7*(4), 316–323. https://doi.org/10.1037/per0000186

Stevelink, R., Abramovic, L., Verkooijen, S., Begemann, M. J. H., Sommer, I. E. C., Boks, M. P., Mandl, R. C. W., van Haren, N. E. M., & Vinkers, C. H. (2018). Childhood abuse and white matter integrity in bipolar disorder patients and healthy controls. European Neuropsychopharmacology, 28(7), 807–817. https://doi.org/10.1016/j.euroneuro.2018.05.003

Stone, M. H. (2006). Relationship of borderline personality disorder and bipolar disorder. *American Journal of Psychiatry*, *163*(7), 1126–1128. https://doi.org/10.1176/ajp.2006.163.7.1126

Strakowski, S. M., Adler, C. M., Almeida, J., Altshuler, L. L., Blumberg, H. P., Chang, K. D., Delbello, M. P., Frangou, S., McIntosh, A., Phillips, M. L., Sussman, J. E., & Townsend, J. D. (2012). The functional neuroanatomy of bipolar disorder: A consensus model. Bipolar Disorders, 14(4), 313–325. https://doi.org/10.1111/j.1399-5618.2012.01022.x

Strakowski, S. M., DelBello, M. P., & Adler, C. M. (2005). The functional neuroanatomy of bipolar disorder: A review of neuroimaging findings. Molecular Psychiatry, 10(1), 105–116. https://doi.org/10.1038/sj.mp.4001585

Swann, A. C., Pazzaglia, P., Nicholls, A., Dougherty, D. M., & Moeller, F. G. (2003). Impulsivity and phase of illness in bipolar disorder. *Journal of Affective Disorders, 73*(1-2), 105–111. https://doi.org/10.1016/s0165-0327(02)00328-2

Sylvia, L. G., Shelton, R. C., Kemp, D. E., Bernstein, E. E., Friedman, E. S., Brody, B. D., Mcelroy, S. L., Singh, V., Tohen, M., Bowden, C. L., Ketter, T. A., Deckersbach, T., Thase, M. E., Reilly-Harrington, N. A., Nierenberg, A. A., Rabideau, D. J., Kinrys, G., Kocsis, J. H., Bobo, W. V., … Calabrese, J. R. (2015). Medical burden in bipolar disorder: Findings from the Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder study (Bipolar CHOICE). Bipolar Disorders, 17(2), 212–223. https://doi.org/10.1111/bdi.12243

Takami Lageborn, C., Zhou, M., Boman, M., Sjölander, A., Larsson, H., D'Onofrio, B. M., Pettersson, E., Lichtenstein, P., & Landén, M. (2024). Childhood and adolescence outcomes in offspring to parents with bipolar disorder: the impact of lifetime parental comorbidity, parental sex, and bipolar subtype. Journal of Child Psychology and Psychiatry and Allied Disciplines, 10, 1355–1368. https://doi.org/10.1111/jcpp.13982

Taylor, A. E., Jones, H. J., Sallis, H., Euesden, J., Stergiakouli, E., Davies, N. M., Zammit, S., Lawlor, D. A., Munafò, M. R., Smith, G. D., & Tilling, K. (2018). Exploring the association of genetic factors with participation in the Avon Longitudinal Study of Parents and Children. International Journal of Epidemiology, 47(4), 1207–1216. https://doi.org/10.1093/ije/dyy060

Thabrew, H., Stasiak, K., Bavin, L. M., Frampton, C., & Merry, S. (2018). Validation of the Mood and Feelings Questionnaire (MFQ) and Short Mood and Feelings Questionnaire (SMFQ) in New Zealand help-seeking adolescents. International Journal of Methods in Psychiatric Research, 27(3), 1–9. https://doi.org/10.1002/mpr.1610

Thapar, A., Cooper, M., & Rutter, M. (2017). Neurodevelopmental disorders. The Lancet Psychiatry, 4(4), 339–346. https://doi.org/10.1016/S2215-0366(16)30376-5

Tijssen, M. J. A., Van Os, J., Wittchen, H. U., Lieb, R., Beesdo, K., Mengelers, R., & Wichers, M. (2010). Prediction of transition from common adolescent bipolar experiences to bipolar disorder: 10-year study. British Journal of Psychiatry, 196(2), 102–108. https://doi.org/10.1192/bjp.bp.109.065763

Tillman, R., & Geller, B. (2006). Controlled study of switching from attention-deficit/hyperactivity disorder to a prepubertal and early adolescent bipolar I disorder phenotype during 6-year prospective follow-up: Rate, risk, and predictors. Development and Psychopathology, 18(4), 1037–1053. https://doi.org/10.1017/S0954579406060512

Torres, I., Gómez, N., Colom, F., Jiménez, E., Bosch, R., Bonnín, C. M., Martínez-Aran, A., Casas, M., Vieta, E., Ramos-Quiroga, J. A., & Goikolea, J. M. (2015). Bipolar disorder with comorbid attention-deficit and hyperactivity disorder. Main clinical features and clues for an accurate diagnosis. Acta Psychiatrica Scandinavica, 132(5), 389–399. https://doi.org/10.1111/acps.12426

Torres, I., Sole, B., Corrales, M., Jiménez, E., Rotger, S., Serra-Pla, J. F., Forcada, I., Richarte, V., Mora, E., Jacas, C., Gómez, N., Mur, M., Colom, F., Vieta, E., Casas, M., Martinez-Aran, A., Goikolea, J. M., & Ramos-Quiroga, J. A. (2017). Are patients with bipolar disorder and comorbid attention-deficit hyperactivity disorder more neurocognitively impaired? Bipolar Disorders, 19(8), 637–650. https://doi.org/10.1111/bdi.12540

Tortella-Feliu, M., Fullana, M. A., Pérez-Vigil, A., Torres, X., Chamorro, J., Littarelli, S. A., Solanes, A., Ramella-Cravaro, V., Vilar, A., González-Parra, J. A., Andero, R., Reichenberg, A., Mataix-Cols, D., Vieta, E., Fusar-Poli, P., Ioannidis, J. P. A., Stein, M. B., Radua, J., &

Fernández de la Cruz, L. (2019). Risk factors for posttraumatic stress disorder: An umbrella review of systematic reviews and meta-analyses. Neuroscience and Biobehavioral Reviews, 107(July), 154–165. https://doi.org/10.1016/j.neubiorev.2019.09.013

Tsanas, A., Saunders, K. E. A., Bilderbeck, A. C., Palmius, N., Osipov, M., Clifford, G. D., ... De Vos, M. (2016). Daily longitudinal self-monitoring of mood variability in bipolar disorder and borderline personality disorder. *Journal of Affective Disorders*, *205*, 225-233.

Turner, N., Joinson, C., Peters, T. J., Wiles, N., & Lewis, G. (2014). Validity of the Short Mood and feelings questionnaire in late adolescence. Psychological Assessment, 26(3), 752–762. https://doi.org/10.1037/a0036572

Uanhoro, J. O., Wang, Y., & O'Connell, A. A. (2021). Problems with Using Odds Ratios as Effect Sizes in Binary Logistic Regression and Alternative Approaches. Journal of Experimental Education, 89(4), 670–689. https://doi.org/10.1080/00220973.2019.1693328

Uchida, M., Bukhari, Q., DiSalvo, M., Green, A., Serra, G., Hutt Vater, C., Ghosh, S. S., Faraone, S. V., Gabrieli, J. D. E., & Biederman, J. (2022). Can machine learning identify childhood characteristics that predict future development of bipolar disorder a decade later? Journal of Psychiatric Research, 156, 261–267. https://doi.org/10.1016/j.jpsychires.2022.09.051

Uher, R., Perlis, R. H., Placentino, A., Dernovšek, M. Z., Henigsberg, N., Mors, O., ... & Farmer, A. (2012). Self-report and clinician-rated measures of depression severity: can one replace the other?. *Depression and Anxiety*, *29*(12), 1043-1049.

van Hulzen, K. J. E., Scholz, C. J., Franke, B., Ripke, S., Klein, M., McQuillin, A., Sonuga-Barke, E. J. S., Kelsoe, J. R., Landén, M., Andreassen, O. A., Lesch, K. P., Weber, H., Faraone, S. V., Arias-Vasquez, A., Reif, A., Anney, R. J. L., Vasquez, A. A., Arranz, M. J., Asherson, P., … Zöllner, S. (2017). Genetic Overlap Between Attention-Deficit/Hyperactivity Disorder

and Bipolar Disorder: Evidence From Genome-wide Association Study Meta-analysis. Biological Psychiatry, 82(9), 634–641. https://doi.org/10.1016/j.biopsych.2016.08.040

Van Meter, A. R., Hafeman, D. M., Merranko, J., Youngstrom, E. A., Birmaher, B. B., Fristad, M. A., Horwitz, S. M., Arnold, L. E., & Findling, R. L. (2021b). Generalizing the Prediction of Bipolar Disorder Onset Across High-Risk Populations. Journal of the American Academy of Child and Adolescent Psychiatry, 60(8), 1010-1019.e2. https://doi.org/10.1016/j.jaac.2020.09.017

Van Meter, A., Correll, C. U., Ahmad, W., Dulin, M., & Saito, E. (2021a). Symptoms and Characteristics of Youth Hospitalized for Depression: Subthreshold Manic Symptoms Can Help Differentiate Bipolar from Unipolar Depression. Journal of Child and Adolescent Psychopharmacology, 31(8), 545–552. https://doi.org/10.1089/cap.2021.0057

Vandeleur, C. L., Merikangas, K. R., Strippoli, M.-P. F., Castelao, E., & Preisig, M. (2013). Specificity of psychosis, mania and major depression in a contemporary family study. *Molecular Psychiatry*, *19*(2), 209–213. https://doi.org/10.1038/mp.2013.132

Vannucchi, G., Medda, P., Pallucchini, A., Bertelli, M., Angst, J., Azorin, J. M., Bowden, C., Vieta, E., Young, A. H., Mosolov, S., & Perugi, G. (2019). The relationship between attention deficit hyperactivity disorder, bipolarity and mixed features in major depressive patients: Evidence from the BRIDGE-II-Mix Study. Journal of Affective Disorders, 246(September 2018), 346–354. https://doi.org/10.1016/j.jad.2018.12.089

Varcin, K. J., Herniman, S. E., Lin, A., Chen, Y., Perry, Y., Pugh, C., Chisholm, K., Whitehouse, A. J. O., & Wood, S. J. (2022). Occurrence of psychosis and bipolar disorder in adults with autism: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews, 134(April 2021), 104543. https://doi.org/10.1016/j.neubiorev.2022.104543

Videler, A. C., Hutsebaut, J., Schulkens, J. E., Sobczak, S., & van Alphen, S. P. (2019). A life span perspective on borderline personality disorder. *Current Psychiatry Reports*, *21*(7). https://doi.org/10.1007/s11920-019-1040-1

Vieta, E., & Angst, J. (2021). Bipolar disorder cohort studies: Crucial, but underfunded. European Neuropsychopharmacology, 47, 31–33. https://doi.org/10.1016/j.euroneuro.2021.03.008

Vieta, E., Reinares, M., & Rosa, A. R. (2011). Staging bipolar disorder. Neurotoxicity Research, 19(2), 279–285. https://doi.org/10.1007/s12640-010-9197-8

Vieta, E., Salagre, E., Grande, I., Carvalho, A. F., Fernandes, B. S., Berk, M., Birmaher, B., Tohen, M., & Suppes, T. (2018). Early intervention in Bipolar disorder. American Journal of Psychiatry, 175(5), 411–426. https://doi.org/10.1176/appi.ajp.2017.17090972

Vigo, D., Thornicroft, G., & Atun, R. (2016). Estimating the true global burden of mental illness. The Lancet Psychiatry, 3(2), 171–178. https://doi.org/10.1016/S2215-0366(15)00505-2

Viktorin, A., Rydén, E., Thase, M. E., Chang, Z., Lundholm, C., D'Onofrio, B. M., Almqvist, C., Magnusson, P. K. E., Lichtenstein, P., Larsson, H., & Landén, M. (2017). The risk of treatment-emergent mania with methylphenidate in bipolar disorder. American Journal of Psychiatry, 174(4), 341–348. https://doi.org/10.1176/appi.ajp.2016.16040467

Vöhringer, P. A., Barroilhet, S. A., Alvear, K., Medina, S., Espinosa, C., Alexandrovich, K., … Ghaemi, S. N. (2016). The International Mood Network (IMN) Nosology Project: Differentiating borderline personality from bipolar illness. *Acta Psychiatrica Scandinavica*, *134*(6), 504–510. https://doi.org/10.1111/acps.12643

Wang, L. J., Shyu, Y. C., Yuan, S. S., Yang, C. J., Yang, K. C., Lee, T. L., & Lee, S. Y. (2016). Attention-deficit hyperactivity disorder, its pharmacotherapy, and the risk of developing

bipolar disorder: A nationwide population-based study in Taiwan. Journal of Psychiatric Research, 72, 6–14. https://doi.org/10.1016/j.jpsychires.2015.10.014

Wang, Y. Y., Xu, D. D., Liu, R., Yang, Y., Grover, S., Ungvari, G. S., Hall, B. J., Wang, G., & Xiang, Y. T. (2019). Comparison of the screening ability between the 32-item Hypomania Checklist (HCL-32) and the Mood Disorder Questionnaire (MDQ) for bipolar disorder: A meta-analysis and systematic review. Psychiatry Research, 273(January), 461–466. https://doi.org/10.1016/j.psychres.2019.01.061

Wardenaar, K. J. (2022). Latent class growth analysis and growth mixture modeling using R: A tutorial for two R-packages and a comparison with Mplus. PsyArXiv, December, 1–23.

Weavers, B., Heron, J., Thapar, A. K., Stephens, A., Lennon, J., Bevan Jones, R., Eyre, O., Anney, R. J., Collishaw, S., Thapar, A., & Rice, F. (2021). The antecedents and outcomes of persistent and remitting adolescent depressive symptom trajectories: a longitudinal, population-based English study. The Lancet Psychiatry, 8(12), 1053–1061. https://doi.org/10.1016/S2215-0366(21)00281-9

Weber, H., Kittel-Schneider, S., Gessner, A., Domschke, K., Neuner, M., Jacob, C. P., Buttenschon, H. N., Boreatti-Hümmer, A., Volkert, J., Herterich, S., Baune, B. T., Gross-Lesch, S., Kopf, J., Kreiker, S., Nguyen, T. T., Weissflog, L., Arolt, V., Mors, O., Deckert, J., … Reif, A. (2011). Cross-disorder analysis of bipolar risk genes: Further evidence of dGKH as a risk gene for bipolar disorder, but also unipolar depression and adult ADHD. Neuropsychopharmacology, 36(10), 2076–2085. https://doi.org/10.1038/npp.2011.98

Weintraub, M. J., Schneck, C. D., Axelson, D. A., Birmaher, B., Kowatch, R. A., & Miklowitz, D. J. (2020). Classifying Mood Symptom Trajectories in Adolescents With Bipolar Disorder.

Journal of the American Academy of Child and Adolescent Psychiatry, 59(3), 381–390. https://doi.org/10.1016/j.jaac.2019.04.028

Wilens, T. E., Biederman, J., Wozniak, J., Gunawardene, S., Wong, J., & Monuteaux, M. (2003). Can adults with attention-deficit/hyperactivity disorder be distinguished from those with comorbid bipolar disorder? Findings from a sample of clinically referred adults. Biological Psychiatry, 54(1), 1–8. https://doi.org/10.1016/S0006-3223(02)01666-9

Wilson, S. T., & Stanley, B. (2007). Comparing impulsiveness, hostility, and depression in borderline personality disorder and bipolar II disorder. *The Journal of Clinical Psychiatry*, *68*(10), 1533–1539. https://doi.org/10.4088/jcp.v68n1010

* Winsper, C., Lereya, S. T., Marwaha, S., Thompson, A., Eyden, J., & Singh, S. P. (2016a). The aetiological and psychopathological validity of borderline personality disorder in youth: A systematic review and meta-analysis. *Clinical Psychology Review*, *44*, 13–24. https://doi.org/10.1016/j.cpr.2015.12.001

* Winsper, C., Marwaha, S., Lereya, S. T., Thompson, A., Eyden, J., & Singh, S. P. (2016b). A systematic review of the neurobiological underpinnings of borderline personality disorder (BPD) in childhood and adolescence. *Reviews in the Neurosciences*, *27*(8), 827–847. https://doi.org/10.1515/revneuro-2016-0026

Winsper, C., Singh, S. P., Marwaha, S., Amos, T., Lester, H., Everard, L., Jones, P., Fowler, D., Marshall, M., Lewis, S., Sharma, V., Freemantle, N., & Birchwood, M. (2013). Pathways to violent behavior during first-episode psychosis: A report from the UK national EDEN study. JAMA Psychiatry, 70(12), 1287–1293. https://doi.org/10.1001/jamapsychiatry.2013.2445

* Winsper, C., Tang, N. K. Y., Marwaha, S., Lereya, S. T., Gibbs, M., Thompson, A., & Singh, S. P. (2017). The sleep phenotype of borderline personality disorder: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews, 73*, 48–67. https://doi.org/10.1016/j.neubiorev.2016.12.008

Winsper, C., Wolke, D., Scott, J., Sharp, C., Thompson, A., & Marwaha, S. (2020). Psychopathological outcomes of adolescent borderline personality disorder symptoms. Australian and New Zealand Journal of Psychiatry, 54(3), 308–317. https://doi.org/10.1177/0004867419882494

Wise, T., Radua, J., Via, E., Cardoner, N., Abe, O., Adams, T. M., Amico, F., Cheng, Y., Cole, J. H., Périco, C. de A. M., Dickstein, D. P., Farrow, T. F. D., Frodl, T., Wagner, G., Gotlib, I. H., Gruber, O., Ham, B. J., Job, D. E., Kempton, M. J., … Arnone, D. (2017). Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: Evidence from voxel-based meta-analysis. Molecular Psychiatry, 22(10), 1455–1463. https://doi.org/10.1038/mp.2016.72

Witt, S. H., Streit, F., Jungkunz, M., Frank, J., Awasthi, S., Reinbold, C. S., Treutlein, J., Degenhardt, F., Forstner, A. J., Heilmann-Heimbach, S., Dietl, L., Schwarze, C. E., Schendel, D., Strohmaier, J., Abdellaoui, A., Adolfsson, R., Air, T. M., Akil, H., Alda, M., … Rietschel, M. (2017). Genome-wide association study of borderline personality disorder reveals genetic overlap with bipolar disorder, major depression and schizophrenia. Translational Psychiatry, 7(6), e1155. https://doi.org/10.1038/tp.2017.115

Wolke, D., Waylen, A., Samara, M., Steer, C., Goodman, R., Ford, T., & Lamberts, K. (2009). Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. British Journal of Psychiatry, 195(3), 249–256. https://doi.org/10.1192/bjp.bp.108.053751

Wollenhaupt-Aguiar, B., Librenza-Garcia, D., Bristot, G., Przybylski, L., Stertz, L., Kubiachi Burque, R., Ceresér, K. M., Spanemberg, L., Caldieraro, M. A., Frey, B. N., Fleck, M. P., Kauer-Sant'Anna, M., Cavalcante Passos, I., & Kapczinski, F. (2020). Differential biomarker signatures in unipolar and bipolar depression: A machine learning approach. Australian and New Zealand Journal of Psychiatry, 54(4), 393–401. https://doi.org/10.1177/0004867419888027

World Health Organization. (2015). International statistical classification of diseases and related health problems, 10th revision, Fifth edition, 2016. World Health Organization.

Yapici Eser, H., Kacar, A. S., Kilciksiz, C. M., Yalçinay-Inan, M., & Ongur, D. (2018). Prevalence and Associated Features of Anxiety Disorder Comorbidity in Bipolar Disorder: A Meta-Analysis and Meta-Regression Study. Frontiers in Psychiatry, 9(June), 1–15. https://doi.org/10.3389/fpsyt.2018.00229

Yatham, L. N. (2023). Biomarkers for clinical use in psychiatry: where are we and will we ever get there? World Psychiatry, 22(2), 263–264. https://doi.org/10.1002/wps.21079

Yatham, L. N., Schaffer, A., Kessing, L. V., Miskowiak, K., Kapczinski, F., Vieta, E., Post, R. M., & Berk, M. (2024). Early intervention, relapse prevention, and neuroprogression in bipolar disorder: The evidence matters. Bipolar Disorders, 26(4), 313–316. https://doi.org/10.1111/bdi.13435

Young, A.H., Juruena, M.F. (2020). The Neurobiology of Bipolar Disorder. In: Young, A.H., Juruena, M.F. (eds) Bipolar Disorder: From Neuroscience to Treatment. Current Topics in Behavioral Neurosciences, vol 48. Springer, Cham. https://doi.org/10.1007/7854_2020_179

Young, S., Asherson, P., Lloyd, T., Absoud, M., Arif, M., Colley, W. A., Cortese, S., Cubbin, S., Doyle, N., Morua, S. D., Ferreira-Lay, P., Gudjonsson, G., Ivens, V., Jarvis, C., Lewis, A., Mason, P., Newlove-Delgado, T., Pitts, M., Read, H., … Skirrow, C. (2021). Failure of Healthcare Provision for Attention-Deficit/Hyperactivity Disorder in the United Kingdom: A Consensus Statement. *Frontiers in Psychiatry*, *12*(March), 1–16. https://doi.org/10.3389/fpsyt.2021.649399

Zammit, S., Kounali, D., Cannon, M., David, A. S., Gunnell, D., Heron, J., Jones, P. B., Lewis, S., Sullivan, S., Wolke, D., & Lewis, G. (2013). Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. American Journal of Psychiatry, 170(7), 742–750. https://doi.org/10.1176/appi.ajp.2013.12060768

Zanarini, M. C. (2003). Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): A continuous measure of DSM-IV borderline psychopathology. Journal of Personality Disorders, 17(3), 233–242. https://doi.org/10.1521/pedi.17.3.233.22147

Zanarini, M. C., Frankenburg, F. R., Hennen, J., Reich, D. B., & Silk, K. R. (2005). The McLean Study of Adult Development (MSAD): Overview and implications of the first six years of prospective follow-up. *Journal of Personality Disorders*, *19*(5), 505–523. https://doi.org/10.1521/pedi.2005.19.5.505

Zarp Petersen, J., Varo, C., Skovsen, C. F., Ott, C. V., Kjærstad, H. L., Vieta, E., Harmer, C. J., Knudsen, G. M., Kessing, L. V., Macoveanu, J., & Miskowiak, K. W. (2022). Neuronal underpinnings of cognitive impairment in bipolar disorder: A large data-driven functional magnetic resonance imaging study. Bipolar Disorders, 24(1), 69–81. https://doi.org/10.1111/bdi.13100

Zhang, L., Cao, X. L., Wang, S. Bin, Zheng, W., Ungvari, G. S., Ng, C. H., Zhong, B. L., Wang, G., & Xiang, Y. T. (2017). The prevalence of bipolar disorder in China: A meta-analysis. Journal of Affective Disorders, 207(October 2016), 413–421. https://doi.org/10.1016/j.jad.2016.08.062

Zhang, X., & Savalei, V. (2022). New Computations for RMSEA and CFI Following FIML and TS Estimation With Missing Data. Psychological Methods, 28(2), 263–283. https://doi.org/10.1037/met0000445

Zhao, Y., Liang, X., Zhu, F., Wen, Y., Xu, J., Yang, J., Ding, M., Cheng, B., Ma, M., Zhang, L., Cheng, S., Wu, C., Wang, S., Wang, X., Ning, Y., Guo, X., & Zhang, F. (2018). A large-scale integrative analysis of GWAS and common meQTLs across whole life course identifies genes, pathways and tissue/cell types for three major psychiatric disorders. Neuroscience and Biobehavioral Reviews, 95(July), 347–352. https://doi.org/10.1016/j.neubiorev.2018.10.005

Zimmerman, M., & Morgan, T. A. (2013a). Problematic boundaries in the diagnosis of bipolar disorder: The interface with borderline personality disorder. *Current Psychiatry Reports*, *15*(12). https://doi.org/10.1007/s11920-013-0422-z

Zimmerman, M., & Morgan, T. A. (2013b). The relationship between borderline personality disorder and bipolar disorder. *Dialogues in Clinical Neuroscience*, *15*(2), 155–169. https://doi.org/10.31887/dcns.2013.15.2/mzimmerman

Zimmerman, M., Balling, C., Chelminski, I., & Dalrymple, K. (2021). Patients with borderline personality disorder and bipolar disorder: A descriptive and comparative study. Psychological Medicine, 51(9), 1479–1490. https://doi.org/10.1017/S0033291720000215

Zimmerman, M., Martinez, J., Young, D., Chelminski, I., Morgan, T. A., & Dalrymple, K. (2014). Comorbid bipolar disorder and borderline personality disorder and history of suicide attempts. *Journal of Personality Disorders*, *28*(3), 358.

Zimmerman, M., Ruggero, C. J., Chelminski, I., & Young, D. (2008). Is bipolar disorder overdiagnosed? *The Journal of Clinical Psychiatry*, *69*(6), 935–940. https://doi.org/10.4088/jcp.v69n0608

Zimmerman, M., Ruggero, C. J., Chelminski, I., & Young, D. (2009). Psychiatric diagnoses in patients previously overdiagnozed with bipolar disorder. *The Journal of Clinical Psychiatry*, *71*(01), 26–31. https://doi.org/10.4088/jcp.08m04633

Zuk, O., Hechter, E., Sunyaev, S. R., & Lander, E. S. (2012). The mystery of missing heritability: Genetic interactions create phantom heritability. Proceedings of the National Academy of Sciences of the United States of America, 109(4), 1193–1198. https://doi.org/10.1073/pnas.1119675109

Appendix A. Chapter 2 Supplement

Understanding the development of Bipolar Disorder and Borderline Personality Disorder in young people: A meta-review of systematic reviews

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Supplementary Methods and Results

Supplementary 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Checklist

Supplementary 2. Search Strategy

Supplementary 3. Included primary studies contained within systematic reviews and meta-analyses.

Supplementary 4. Vulnerability Factors

Table S1. Characteristics of systematic reviews and meta-analyses examining the developmental pathways and onset of Bipolar Disorder

Table S2. Characteristics of systematic reviews and meta-analyses examining the developmental pathways and onset of Borderline Personality Disorder

Table S3 Evidence across systematic reviews and meta-analyses of factors for Bipolar Disorder

outcome

Table S4 Evidence across systematic reviews and meta-analyses of factors for Borderline

Personality outcome

Table S5. Excluded studies after full-text review with reasons

Table S6. Methodological quality of included systematic reviews and meta-analyses based on AMSTAR tool for Bipolar Disorder

Table S7. Methodological quality of included systematic reviews and meta-analyses based on AMSTAR tool for Borderline Personality Disorder

Table S8. Citation matrix for Bipolar Disorder

Table S9. Citation matrix for Borderline Personality Disorder

Figure S1. Pairwise CCA for reviews on BD

Figure S2. Pairwise CCA for reviews on BPD

Supplementary 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	-
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5 & Supplement
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	-
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary	-

Section and Topic	Item #	Checklist item	Location where item is reported
		statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5 & Supplement
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5-6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	6
Study characteristics	17	Cite each included study and present its characteristics.	6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	-
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	6
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9-12
	23b	Discuss any limitations of the evidence included in the review.	12

Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	12
	23d	Discuss implications of the results for practice, policy, and future research.	12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	13
Competing interests	26	Declare any competing interests of review authors.	13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplement

Supplementary 3. Included primary studies contained within systematic reviews and meta-analyses.

Acuff, H. E., Versace, A., Bertocci, M. A., Ladouceur, C. D., Hanford, L. C., Manelis, A., ... Phillips, M. L. (2019). Baseline and follow-up activity and functional connectivity in reward neural circuitries in offspring at risk for bipolar disorder. *Neuropsychopharmacology*, *44*(9), 1570-1578.

Akiskal, H. S., Djenderedjian, A. H., Rosenthal, R. H., & Khani, M. K. (1977). Cyclothymic disorder: Validating criteria for inclusion in the bipolar affective group. *The American Journal of Psychiatry*.

Akiskal, H. S., Bitar, A. H., Puzantian, V. R., Rosenthal, T. L., & Walker, P. W. (1978). The nosological status of neurotic depression: a prospective three-to four-year follow-up examination in light of the primary-secondary and unipolar-bipolar dichotomies. *Archives of General Psychiatry*, *35*(6), 756-766.

Akiskal, H. S., Walker, P., Puzantian, V. R., King, D., Rosenthal, T. L., & Dranon, M. (1983). Bipolar outcome in the course of depressive illness: phenomenologic, familial, and pharmacologic predictors. *Journal of affective disorders*, *5*(2), 115-128.

Akiskal, H. S., Downs, J., Jordan, P., Watson, S., Daugherty, D., & Pruitt, D. B. (1985). Affective disorders in referred children and younger siblings of manic-depressives: mode of onset and prospective course. *Archives of General Psychiatry*, *42*(10), 996-1003.

Akiskal, H. S., Maser, J. D., Zeller, P. J., Endicott, J., Coryell, W., Keller, M., ... Goodwin, F. (1995). Switching from'unipolar'to bipolar II: an 11-year prospective study of clinical and temperamental predictors in 559 patients. *Archives of General Psychiatry*, *52*(2), 114-123.

Alloy, L. B., Urošević, S., Abramson, L. Y., Jager-Hyman, S., Nusslock, R., Whitehouse, W. G., & Hogan, M. (2012). Progression along the bipolar spectrum: a longitudinal study of predictors of conversion from bipolar spectrum conditions to bipolar I and II disorders. *Journal of Abnormal Psychology*, *121*(1), 16.

Alloy, L. B., Boland, E. M., Ng, T. H., Whitehouse, W. G., & Abramson, L. Y. (2015). Low social rhythm regularity predicts first onset of bipolar spectrum disorders among at-risk individuals with reward hypersensitivity. *Journal of Abnormal Psychology*, *124*(4), 944.

Anderson, C. A., & Hammen, C. L. (1993). Psychosocial outcomes of children of unipolar depressed, bipolar, medically ill, and normal women: a longitudinal study. *Journal of Consulting and Clinical Psychology*, *61*(3), 448.

Angst, J., Gamma, A., & Endrass, J. (2003). Risk factors for the bipolar and depression spectra. *Acta Psychiatrica Scandinavica*, *108*, 15-19.

Angst, J., Sellaro, R., Stassen, H. H., & Gamma, A. (2005). Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. *Journal of Affective Disorders*, *84*(2-3), 149-157.

Arnold, L. E., Van Meter, A. R., Fristad, M. A., Youngstrom, E. A., Birmaher, B. B., Findling, R. L., ... Black, S. R. (2020). Development of bipolar disorder and other comorbidity among youth with attention-deficit/hyperactivity disorder. *Journal of Child Psychology and Psychiatry*, *61*(2), 175-181.

Axelson, D. A., Birmaher, B., Strober, M. A., Goldstein, B. I., Ha, W., Gill, M. K., ... Keller, M. B. (2011). Course of subthreshold bipolar disorder in youth: diagnostic progression from bipolar disorder not otherwise specified. *Journal of the American Academy of Child & Adolescent Psychiatry*, *50*(10), 1001-1016.

Axelson, D., Goldstein, B., Goldstein, T., Monk, K., Yu, H., Hickey, M. B., ... Birmaher, B. (2015). Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: a longitudinal study. *American Journal of Psychiatry*, *172*(7), 638-646.

Bauwens, F., Pardoen, D., Staner, L., Dramaix, M., & Mendlewicz, J. (1998). Social adjustment and the course of affective illness: A one-year controlled longitudinal study involving bipolar and unipolar outpatients. *Depression and Anxiety*, *8*(2), 50-57.

Barnow, S., Aldinger, M., Arens, E. A., Ulrich, I., Spitzer, C., Grabe, H. J., & Stopsack, M. (2013). Maternal transmission of borderline personality disorder symptoms in the community-based Greifswald Family Study. *Journal of Personality Disorders*, *27*(6), 806-819.

Bechdolf, A., Ratheesh, A., Cotton, S. M., Nelson, B., Chanen, A. M., Betts, J., ... McGorry, P. D. (2014). The predictive validity of bipolar at-risk (prodromal) criteria in help-seeking adolescents and young adults: a prospective study. *Bipolar Disorders*, *16*(5), 493-504.

Beesdo, K., Höfler, M., Leibenluft, E., Lieb, R., Bauer, M., & Pfennig, A. (2009). Mood episodes and mood disorders: patterns of incidence and conversion in the first three decades of life. *Bipolar Disorders*, *11*(6), 637-649.

Belsky, D. W., Caspi, A., Arseneault, L., Bleidorn, W., Fonagy, P., Goodman, M., ... Moffitt, T. E. (2012). Etiological features of borderline personality related characteristics in a birth cohort of 12-year-old children. *Development and Psychopathology*, *24*(1), 251-265.

Benvenuti, A., Rucci, P., Miniati, M., Papasogli, A., Fagiolini, A., Cassano, G. B., ... Frank, E. (2008). Treatment-emergent mania/hypomania in unipolar patients. *Bipolar Disorders*, *10*(6), 726-732.

Bertocci, M. A., Hanford, L., Manelis, A., Iyengar, S., Youngstrom, E. A., Gill, M. K., ... Phillips, M. L. (2019). Clinical, cortical thickness and neural activity predictors of future affective lability in youth at risk for bipolar disorder: initial discovery and independent sample replication. *Molecular Psychiatry*, *24*(12), 1856-1867.

Bezirganian, S., Cohen, P., & Brook, J. S. (1993). The impact of mother-child interaction on the development of borderline personality disorder. *The American Journal of Psychiatry*.

Biederman, J., Faraone, S., Milberger, S., Guite, J., Mick, E., Chen, L., ... Perrin, J. (1996). A prospective 4-year follow-up study of attention-deficit hyperactivity and related disorders. *Archives of General Psychiatry, 53*(5), 437-446.

Biederman, J., Petty, C. R., Dolan, C., Hughes, S., Mick, E., Monuteaux, M. C., & Faraone, S. V. (2008). The long-term longitudinal course of oppositional defiant disorder and conduct disorder in ADHD boys: findings from a controlled 10-year prospective longitudinal follow-up study. *Psychological Medicine, 38*(7), 1027-1036.

Biederman, J., Petty, C. R., Byrne, D., Wong, P., Wozniak, J., & Faraone, S. V. (2009). Risk for switch from unipolar to bipolar disorder in youth with ADHD: a long term prospective controlled study. *Journal of Affective Disorders, 119*(1-3), 16-21.

Biederman, J., Wozniak, J., Tarko, L., Serra, G., Hernandez, M., McDermott, K., ... Faraone, S. V. (2014). Re-examining the risk for switch from unipolar to bipolar major depressive disorder in youth with ADHD: a long term prospective longitudinal controlled study. *Journal of Affective Disorders, 152,* 347-351.

Birmaher, B., Merranko, J., Hafeman, D., Goldstein, B. I., Diler, R., Levenson, J. C., ... Goldstein, T. (2021). A longitudinal study of psychiatric disorders in offspring of parents with bipolar disorder from preschool to adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry, 60*(11), 1419-1429.

Birmaher, B., Merranko, J. A., Goldstein, T. R., Gill, M. K., Goldstein, B. I., Hower, H., ... Keller, M. B. (2018). A risk calculator to predict the individual risk of conversion from subthreshold bipolar symptoms to bipolar disorder I or II in youth. *Journal of the American Academy of Child & Adolescent Psychiatry*, *57*(10), 755-763.

Bitter, S. M., Mills, N. P., Adler, C. M., Strakowski, S. M., & DelBello, M. P. (2011). Progression of amygdala volumetric abnormalities in adolescents after their first manic episode. *Journal of the American Academy of Child & Adolescent Psychiatry*, *50*(10), 1017-1026.

Boschloo, L., Spijker, A. T., Hoencamp, E., Kupka, R., Nolen, W. A., Schoevers, R. A., & Penninx, B. W. (2014). Predictors of the onset of manic symptoms and a (hypo) manic episode in patients with major depressive disorder. *PLoS One*, *9*(9), e106871.

Bornovalova, M. A., Hicks, B. M., Iacono, W. G., & McGue, M. (2009). Stability, change, and heritability of borderline personality disorder traits from adolescence to adulthood: A longitudinal twin study. *Development and Psychopathology*, *21*(4), 1335-1353.

Bornovalova, M. A., Hicks, B. M., Iacono, W. G., & McGue, M. (2013). Longitudinal twin study of borderline personality disorder traits and substance use in adolescence: developmental change, reciprocal effects, and genetic and environmental influences. *Personality Disorders: Theory, Research, and Treatment*, *4*(1), 23.

Bornovalova, M. A., Huibregtse, B. M., Hicks, B. M., Keyes, M., McGue, M., & Iacono, W. (2013). Tests of a direct effect of childhood abuse on adult borderline personality disorder traits: a longitudinal discordant twin design. *Journal of Abnormal Psychology, 122*(1), 180.

Bornovalova, M. A., Verhulst, B., Webber, T., McGue, M., Iacono, W. G., & Hicks, B. M. (2018). Genetic and environmental influences on the codevelopment among borderline personality disorder traits, major depression symptoms, and substance use disorder symptoms from adolescence to young adulthood. *Development and Psychopathology, 30*(1), 49-65.

Bromet, E. J., Kotov, R., Fochtmann, L. J., Carlson, G. A., Tanenberg-Karant, M., Ruggero, C., & Chang, S. W. (2011). Diagnostic shifts during the decade following first admission for psychosis. *American Journal of Psychiatry*, *168*(11), 1186-1194.

Bukh, J. D., Andersen, P. K., & Kessing, L. V. (2016). Personality and the long-term outcome of first-episode depression: a prospective 5-year follow-up study. *The Journal of Clinical Psychiatry, 77*(6), 14149.

Bukh, J. D., Andersen, P. K., & Kessing, L. V. (2016). Rates and predictors of remission, recurrence and conversion to bipolar disorder after the first lifetime episode of depression–a prospective 5-year follow-up study. *Psychological Medicine, 46*(6), 1151-1161.

Burke, J. D., & Stepp, S. D. (2012). Adolescent disruptive behavior and borderline personality disorder symptoms in young adult men. *Journal of Abnormal Child Psychology, 40*(1), 35-44.

Carlson, E. A., Egeland, B., & Sroufe, L. A. (2009). A prospective investigation of the development of borderline personality symptoms. *Development and Psychopathology, 21*(4), 1311-1334.

Cassano, P., Lattanzi, L., Soldani, F., Navari, S., Battistini, G., Gemignani, A., & Cassano, G. B. (2004). Pramipexole in treatment-resistant depression: An extended follow-up. *Depression and Anxiety, 20*(3), 131-138.

Castro-Fornieles, J., Baeza, I., de la Serna, E., Gonzalez-Pinto, A., Parellada, M., Graell, M., ... Arango, C. (2011). Two-year diagnostic stability in early-onset first-episode psychosis. *Journal of Child Psychology and Psychiatry, 52*(10), 1089-1098.

Chung, K. H., Li, C. Y., Kuo, S. Y., Sithole, T., Liu, W. W., & Chung, M. H. (2015). Risk of psychiatric disorders in patients with chronic insomnia and sedative-hypnotic prescription: a nationwide population-based follow-up study. *Journal of Clinical Sleep Medicine, 11*(5), 543-551.

Cohen, P., Chen, H., Gordon, K., Johnson, J., Brook, J., & Kasen, S. (2008). Socioeconomic background and the developmental course of schizotypal and borderline personality disorder symptoms. *Development and Psychopathology, 20*(2), 633-650.

Conway, C. C., Hammen, C., & Brennan, P. A. (2015). Adolescent Precursors of Adult Borderline Personality Pathology in a High Risk Community Sample. *Journal of Personality Disorders, 29*(3), 316.

Coryell, W., Andreasen, N. C., Endicott, J., & Keller, M. (1987). The significance of past mania or hypomania in the course and outcome of major depression. *The American Journal of Psychiatry*.

Coryell, W., Endicott, J., Maser, J. D., Keller, M. B., Leon, A. C., & Akiskal, H. S. (1995). Long-term stability of polarity distinctions in the affective disorders. *The American Journal of Psychiatry*.

Curry, J., Silva, S., Rohde, P., Ginsburg, G., Kratochvil, C., Simons, A., ... March, J. (2011). Recovery and recurrence following treatment for adolescent major depression. *Archives of General Psychiatry*, *68*(3), 263-269.

Crawford, T. N., Cohen, P. R., Chen, H., Anglin, D. M., & Ehrensaft, M. (2009). Early maternal separation and the trajectory of borderline personality disorder symptoms. *Development and Psychopathology*, *21*(3), 1013-1030.

Crick, N. R., Murray-Close, D., & Woods, K. (2005). Borderline personality features in childhood: A short-term longitudinal study. *Development and Psychopathology*, *17*(4), 1051-1070.

DelBello, M. P., Carlson, G. A., Tohen, M., Bromet, E. J., Schwiers, M., & Strakowski, S. M. (2003). Rates and predictors of developing a manic or hypomanic episode 1 to 2 years following a first hospitalization for major depression with psychotic features. *Journal of Child and Adolescent Psychopharmacology*, *13*(2), 173-185.

DeGeorge, D. P., Walsh, M. A., Barrantes-Vidal, N., & Kwapil, T. R. (2014). A three-year longitudinal study of affective temperaments and risk for psychopathology. *Journal of Affective Disorders, 164*, 94-100.

Dixon-Gordon, K. L., Whalen, D. J., Scott, L. N., Cummins, N. D., & Stepp, S. D. (2016). The main and interactive effects of maternal interpersonal emotion regulation and negative affect on adolescent girls' borderline personality disorder symptoms. *Cognitive Therapy and Research, 40*(3), 381-393.

Doucette, S., Horrocks, J., Grof, P., Keown-Stoneman, C., & Duffy, A. (2013). Attachment and temperament profiles among the offspring of a parent with bipolar disorder. *Journal of Affective Disorders*, *150*(2), 522-526.

Duffy, A., Alda, M., Crawford, L., Milin, R., & Grof, P. (2007). The early manifestations of bipolar disorder: a longitudinal prospective study of the offspring of bipolar parents. *Bipolar Disorders*, *9*(8), 828-838.

Duffy, A., Alda, M., Hajek, T., & Grof, P. (2009). Early course of bipolar disorder in high-risk offspring: prospective study. *The British Journal of Psychiatry*, *195*(5), 457-458.

Duffy, A., Alda, M., Hajek, T., Sherry, S. B., & Grof, P. (2010). Early stages in the development of bipolar disorder. *Journal of Affective Disorders*, *121*(1-2), 127-135.

Duffy, A., Horrocks, J., Milin, R., Doucette, S., Persson, G., & Grof, P. (2012). Adolescent substance use disorder during the early stages of bipolar disorder: a prospective high-risk study. *Journal of Affective Disorders*, *142*(1-3), 57-64.

Duffy, A., Horrocks, J., Doucette, S., Keown-Stoneman, C., McCloskey, S., & Grof, P. (2014). The developmental trajectory of bipolar disorder. *The British Journal of Psychiatry*, *204*(2), 122-128.

Duffy, A., Goodday, S., Keown-Stoneman, C., & Grof, P. (2019). The emergent course of bipolar disorder: observations over two decades from the Canadian high-risk offspring cohort. *American Journal of Psychiatry*, *176*(9), 720-729.

Dunn, V., & Goodyer, I. M. (2006). Longitudinal investigation into childhood-and adolescence-onset depression: psychiatric outcome in early adulthood. *The British Journal of Psychiatry*, *188*(3), 216-222.

Egeland, J. A., Shaw, J. A., Endicott, J., Pauls, D. L., Allen, C. R., Hostetter, A. M., & Sussex, J. N. (2003). Prospective study of prodromal features for bipolarity in well Amish children. *Journal of the American Academy of Child & Adolescent Psychiatry*, *42*(7), 786-796.

Egeland, J. A., Endicott, J., Hostetter, A. M., Allen, C. R., Pauls, D. L., & Shaw, J. A. (2012). A 16-year prospective study of prodromal features prior to BPI onset in well Amish children. *Journal of Affective Disorders*, *142*(1-3), 186-192.

Ehrenreich, S. E., Beron, K. J., & Underwood, M. K. (2016). Social and physical aggression trajectories from childhood through late adolescence: Predictors of psychosocial maladjustment at age 18. *Developmental Psychology, 52*(3), 457.

Fiedorowicz, J. G., Endicott, J., Leon, A. C., Solomon, D. A., Keller, M. B., & Coryell, W. H. (2011). Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. *American Journal of Psychiatry, 168*(1), 40-48.

Fiedorowicz, J. G., Endicott, J., Solomon, D. A., Keller, M. B., & Coryell, W. H. (2012). Course of illness following prospectively observed mania or hypomania in individuals presenting with unipolar depression. *Bipolar Disorders, 14*(6), 664-671.

Findling, R. L., Jo, B., Frazier, T. W., Youngstrom, E. A., Demeter, C. A., Fristad, M. A., ... Horwitz, S. M. (2013). The 24-month course of manic symptoms in children. *Bipolar Disorders, 15*(6), 669-679.

Frankland, A., Roberts, G., Holmes-Preston, E., Perich, T., Levy, F., Lenroot, R., ... Mitchell, P. B. (2018). Clinical predictors of conversion to bipolar disorder in a prospective longitudinal familial high-risk sample: focus on depressive features. *Psychological Medicine, 48*(10), 1713-1721.

Fusar-Poli, P., De Micheli, A., Rocchetti, M., Cappucciati, M., Ramella-Cravaro, V., Rutigliano, G., ... Falkenberg, I. (2018). Semistructured interview for bipolar at risk states (SIBARS). *Psychiatry Research, 264*, 302-309.

Furukawa, T. A., Konno, W., Morinobu, S., Harai, H., Kitamura, T., & Takahashi, K. (2000). Course and outcome of depressive episodes: comparison between bipolar, unipolar and subthreshold depression. *Psychiatry Research*, *96*(3), 211-220.

Gan, Z., Diao, F., Wei, Q., Wu, X., Cheng, M., Guan, N., ... & Zhang, J. (2011). A predictive model for diagnosing bipolar disorder based on the clinical characteristics of major depressive episodes in Chinese population. *Journal of Affective Disorders*, *134*(1-3), 119-125.

Ganzola, R., Nickson, T., Bastin, M. E., Giles, S., Macdonald, A., Sussmann, J., ... Duchesne, S. (2017). Longitudinal differences in white matter integrity in youth at high familial risk for bipolar disorder. *Bipolar Disorders*, *19*(3), 158-167.

Garber, J., Kriss, M. R., Koch, M., & Lindholm, L. (1988). Recurrent depression in adolescents: A follow-up study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *27*(1), 49-54.

Geller, B., Fox, L. W., & Clark, K. A. (1994). Rate and predictors of prepubertal bipolarity during follow-up of 6-to 12-year-old depressed children. *Journal of the American Academy of Child & Adolescent Psychiatry*, *33*(4), 461-468.

Geller, B., Zimerman, B., Williams, M., Bolhofner, K., & Craney, J. L. (2001). Bipolar disorder at prospective follow-up of adults who had prepubertal major depressive disorder. *American Journal of Psychiatry, 158*(1), 125-127.

Gilman, S. E., Ni, M. Y., Dunn, E. C., Breslau, J., McLaughlin, K. A., Smoller, J. W., & Perlis, R. H. (2015). Contributions of the social environment to first-onset and recurrent mania. *Molecular Psychiatry, 20*(3), 329-336.

Gilman, S. E., Dupuy, J. M., & Perlis, R. H. (2012). Risks for the transition from major depressive disorder to bipolar disorder in the National Epidemiologic Survey on Alcohol and Related Conditions. *The Journal of Clinical Psychiatry, 73*(6), 18480.

Gogtay, N., Ordonez, A., Herman, D. H., Hayashi, K. M., Greenstein, D., Vaituzis, C., ... Rapoport, J. L. (2007). Dynamic mapping of cortical development before and after the onset of pediatric bipolar illness. *Journal of Child Psychology and Psychiatry, 48*(9), 852-862.

Goldberg, J. F., Harrow, M., & Grossman, L. S. (1995). Recurrent affective syndromes in bipolar and unipolar mood disorders at follow-up. *The British Journal of Psychiatry, 166*(3), 382-385.

Goldberg, J. F., Harrow, M., & Whiteside, J. E. (2001). Risk for bipolar illness in patients initially hospitalized for unipolar depression. *American Journal of Psychiatry, 158*(8), 1265-1270.

Greenfield, B., Henry, M., Lis, E., Slatkoff, J., Guilé, J. M., Dougherty, G., ... de Castro, F. (2015). Correlates, stability and predictors of borderline personality disorder among previously suicidal youth. *European Child & Adolescent Psychiatry*, *24*(4), 397-406.

Hallquist, M. N., Hipwell, A. E., & Stepp, S. D. (2015). Poor self-control and harsh punishment in childhood prospectively predict borderline personality symptoms in adolescent girls. *Journal of Abnormal Psychology*, *124*(3), 549.

Halperin, J. M., Rucklidge, J. J., Powers, R. L., Miller, C. J., & Newcorn, J. H. (2011). Childhood CBCL bipolar profile and adolescent/young adult personality disorders: A 9-year follow-up. *Journal of Affective Disorders*, *130*(1-2), 155-161.

Haltigan, J. D., & Vaillancourt, T. (2016). Identifying trajectories of borderline personality features in adolescence: antecedent and interactive risk factors. *The Canadian Journal of Psychiatry*, *61*(3), 166-175.

Hafeman, D. M., Merranko, J., Axelson, D., Goldstein, B. I., Goldstein, T., Monk, K., ... & Birmaher, B. (2016). Toward the definition of a bipolar prodrome: dimensional predictors of bipolar spectrum disorders in at-risk youths. *American Journal of Psychiatry*, *173*(7), 695-704.

Hafeman, D. M., Merranko, J., Goldstein, T. R., Axelson, D., Goldstein, B. I., Monk, K., ... & Birmaher, B. (2017). Assessment of a person-level risk calculator to predict new-onset bipolar spectrum disorder in youth at familial risk. *JAMA Psychiatry*, *74*(8), 841-847.

Hammen, C., Burge, D., Burney, E., & Adrian, C. (1990). Longitudinal study of diagnoses in children of women with unipolar and bipolar affective disorder. *Archives of General Psychiatry*, *47*(12), 1112-1117.

Hammen, C., Bower, J. E., & Cole, S. W. (2015). Oxytocin receptor gene variation and differential susceptibility to family environment in predicting youth borderline symptoms. *Journal of Personality Disorders*, *29*(2), 177-192.

Henquet, C., Krabbendam, L., de Graaf, R., ten Have, M., & van Os, J. (2006). Cannabis use and expression of mania in the general population. *Journal of Affective Disorders*, *95*(1-3), 103-110.

Hillegers, M. H., Reichart, C. G., Wals, M., Verhulst, F. C., Ormel, J., & Nolen, W. A. (2005). Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. *Bipolar Disorders*, *7*(4), 344-350.

Holma, K. M., Melartin, T. K., Holma, I. A., & Isometsä, E. T. (2008). Predictors for switch from unipolar major depressive disorder to bipolar disorder type I or II: a 5-year prospective study. *The Journal of Clinical Psychiatry*, *69*(8), 15174.

Homish, G. G., Marshall, D., Dubovsky, S. L., & Leonard, K. (2013). Predictors of later bipolar disorder in patients with subthreshold symptoms. *Journal of Affective Disorders*, *144*(1-2), 129-133.

Iorfino, F., Scott, E. M., Carpenter, J. S., Cross, S. P., Hermens, D. F., Killedar, M., ... Hickie, I. B. (2019). Clinical stage transitions in persons aged 12 to 25 years presenting to early intervention mental health services with anxiety, mood, and psychotic disorders. *JAMA Psychiatry*, *76*(11), 1167-1175.

Johnson, J., Horwath, E., & Weissman, M. M. (1991). The validity of major depression with psychotic features based on a community study. *Archives of General Psychiatry*, *48*(12), 1075-1081.

Johnson, J. G., Cohen, P., Brown, J., Smailes, E. M., & Bernstein, D. P. (1999). Childhood maltreatment increases risk for personality disorders during early adulthood. *Archives of General Psychiatry*, *56*(7), 600-606.

Johnson, J. G., Cohen, P., Chen, H., Kasen, S., & Brook, J. S. (2006). Parenting behaviors associated with risk for offspring personality disorder during adulthood. *Archives of General Psychiatry*, *63*(5), 579-587.

Johnson, J. G., Smailes, E. M., Cohen, P., Brown, J., & Bernstein, D. P. (2000). Associations between four types of childhood neglect and personality disorder symptoms during adolescence and early adulthood: Findings of a community-based longitudinal study. *Journal of Personality Disorders*, *14*(2), 171.

Jonsson, U., Bohman, H., von Knorring, L., Olsson, G., Paaren, A., & Von Knorring, A. L. (2011). Mental health outcome of long-term and episodic adolescent depression: 15-year follow-up of a community sample. *Journal of Affective Disorders*, *130*(3), 395-404.

Jovev, M., McKenzie, T., Whittle, S., Simmons, J. G., Allen, N. B., & Chanen, A. M. (2013). Temperament and maltreatment in the emergence of borderline and antisocial personality pathology during early adolescence. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, *22*(3), 220.

Judd, L. L., Schettler, P. J., Coryell, W., Akiskal, H. S., & Fiedorowicz, J. G. (2013). Overt irritability/anger in unipolar major depressive episodes: past and current characteristics and implications for long-term course. *JAMA Psychiatry*, *70*(11), 1171-1180.

Kane, J. M., Quitkin, F. M., Rifkin, A., Ramos-Lorenzi, J. R., Nayak, D. D., & Howard, A. (1982). Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness: a prospective, placebo-controlled comparison. *Archives of General Psychiatry*, *39*(9), 1065-1069.

Kaymaz, N., van Os, J., de Graaf, R., Ten Have, M., Nolen, W., & Krabbendam, L. (2007). The impact of subclinical psychosis on the transition from subclinicial mania to bipolar disorder. *Journal of Affective Disorders*, *98*(1-2), 55-64.

Klein, R. G., Mannuzza, S., Olazagasti, M. A. R., Roizen, E., Hutchison, J. A., Lashua, E. C., & Castellanos, F. X. (2012). Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. *Archives of General Psychiatry*, *69*(12), 1295-1303.

Klimes-Dougan, B., Long, J. D., Lee, C. Y. S., Ronsaville, D. S., Gold, P. W., & Martinez, P. E. (2010). Continuity and cascade in offspring of bipolar parents: a longitudinal study of externalizing, internalizing, and thought problems. *Development and Psychopathology*, *22*(4), 849-866.

Klimes-Dougan, B., Desjardins, C. D., James, M. G., Narayan, A. J., Long, J. D., Cullen, K. R., ... Martinez, P. E. (2013). The development of thought problems: a longitudinal family risk study of offspring of bipolar, unipolar, and well parents. *Development and Psychopathology*, *25*(4pt1), 1079-1091.

Kochman, F. J., Hantouche, E. G., Ferrari, P., Lancrenon, S., Bayart, D., & Akiskal, H. S. (2005). Cyclothymic temperament as a prospective predictor of bipolarity and suicidality in children and adolescents with major depressive disorder. *Journal of Affective Disorders*, *85*(1-2), 181-189.

Kovacs, M., Akiskal, H. S., Gatsonis, C., & Parrone, P. L. (1994). Childhood-onset dysthymic disorder: Clinical features and prospective naturalistic outcome. *Archives of General Psychiatry*, *51*(5), 365-374.

Kuehner, C., & Huffziger, S. (2012). Response styles to depressed mood affect the long-term course of psychosocial functioning in depressed patients. *Journal of Affective Disorders*, *136*(3), 627-633.

Krabbendam, A. A., Colins, O. F., Doreleijers, T. A., van der Molen, E., Beekman, A. T., & Vermeiren, R. R. (2015). Personality disorders in previously detained adolescent females: A prospective study. *American Journal of Orthopsychiatry*, *85*(1), 63.

Kwapil, T. R., Miller, M. B., Zinser, M. C., Chapman, L. J., Chapman, J., & Eckblad, M. (2000). A longitudinal study of high scorers on the hypomanic personality scale. *Journal of Abnormal Psychology*, *109*(2), 222.

LaRoche, C., Sheiner, R., Lester, E., Benierakis, C., Marrache, M., Engelsmann, F., & Cheifetz, P. (1987). Children of parents with manic-depressive illness: a follow-up study. *The Canadian Journal of Psychiatry*, *32*(7), 563-569.

Lazarus, S. A., Choukas-Bradley, S., Beeney, J. E., Byrd, A. L., Vine, V., & Stepp, S. D. (2019). Too much too soon?: borderline personality disorder symptoms and romantic relationships in adolescent girls. *Journal of Abnormal Child Psychology*, *47*(12), 1995-2005.

Levenson, J. C., Axelson, D. A., Merranko, J., Angulo, M., Goldstein, T. R., Mullin, B. C., ... Birmaher, B. (2015). Differences in sleep disturbances among offspring of parents with and without bipolar disorder: association with conversion to bipolar disorder. *Bipolar Disorders*, *17*(8), 836-848.

Lenzenweger, M. F., & Castro, D. D. (2005). Predicting change in borderline personality: Using neurobehavioral systems indicators within an individual growth curve framework. *Development and Psychopathology, 17*(4), 1207-1237.

Lereya, S. T., Winsper, C., Tang, N. K., & Wolke, D. (2017). Sleep problems in childhood and borderline personality disorder symptoms in early adolescence. *Journal of Abnormal Child Psychology*, *45*(1), 193-206.

Levenson, J. C., Soehner, A., Rooks, B., Goldstein, T. R., Diler, R., Merranko, J., ... Birmaher, B. (2017). Longitudinal sleep phenotypes among offspring of bipolar parents and community controls. *Journal of Affective Disorders*, *215*, 30-36.

Lyons-Ruth, K., Bureau, J. F., Holmes, B., Easterbrooks, A., & Brooks, N. H. (2013). Borderline symptoms and suicidality/self-injury in late adolescence: Prospectively observed relationship correlates in infancy and childhood. *Psychiatry Research*, *206*(2-3), 273-281.

Li, Z., Zhang, C., Fan, J., Yuan, C., Huang, J., Chen, J., ... Fang, Y. (2014). Brain-derived neurotrophic factor levels and bipolar disorder in patients in their first depressive episode: 3-year prospective longitudinal study. *The British Journal of Psychiatry*, *205*(1), 29-35.

Maj, M., Pirozzi, R., Magliano, L., Fiorillo, A., & Bartoli, L. (2007). Phenomenology and prognostic significance of delusions in major depressive disorder: a 10-year prospective follow-up study. *Journal of Clinical Psychiatry*, *68*(9), 1411-1417.

McCAULEY, E., Myers, K., Mitchell, J., Calderon, R., Schloredt, K., & Treder, R. (1993). Depression in young people: initial presentation and clinical course. *Journal of the American Academy of Child & Adolescent Psychiatry*, *32*(4), 714-722.

Melvin, G. A., Dudley, A. L., Gordon, M. S., Ford, S., Taffe, J., & Tonge, B. J. (2013). What happens to depressed adolescents? A follow-up study into early adulthood. *Journal of Affective Disorders*, *151*(1), 298-305.

Meijer, M., Goedhart, A. W., & Treffers, P. D. (1998). The persistence of borderline personality disorder in adolescence. *Journal of Personality Disorders*, *12*(1), 13.

Mesman, E., Nolen, W. A., Reichart, C. G., Wals, M., & Hillegers, M. H. (2013). The Dutch bipolar offspring study: 12-year follow-up. *American Journal of Psychiatry*, *170*(5), 542-549.

Mesman, E., Nolen, W. A., Keijsers, L., & Hillegers, M. H. J. (2017). Baseline dimensional psychopathology and future mood disorder onset: findings from the Dutch Bipolar Offspring Study. *Acta Psychiatrica Scandinavica*, *136*(2), 201-209.

Miller, C. J., Flory, J. D., Miller, S. R., Harty, S. C., Newcorn, J. H., & Halperin, J. M. (2008). Childhood attention-deficit/hyperactivity disorder and the emergence of personality disorders in adolescence: a prospective follow-up study. *Journal of Clinical Psychiatry*, *69*(9), 1477.

Musliner, K. L., & Østergaard, S. D. (2018). Patterns and predictors of conversion to bipolar disorder in 91 587 individuals diagnosed with unipolar depression. *Acta Psychiatrica Scandinavica*, *137*(5), 422-432.

Nadkarni, R. B., & Fristad, M. A. (2010). Clinical course of children with a depressive spectrum disorder and transient manic symptoms. *Bipolar Disorders*, *12*(5), 494-503.

Nery, F. G., Wilson, A. R., Schneider, M. R., Strawn, J. R., Patino, L. R., McNamara, R. K., ... DelBello, M. P. (2020). Medication exposure and predictors of first mood episode in offspring of parents with bipolar disorder: a prospective study. *Brazilian Journal of Psychiatry*, *42*, 481-488.

Nurnberger, J. I., McInnis, M., Reich, W., Kastelic, E., Wilcox, H. C., Glowinski, A., ... Monahan, P. O. (2011). A high-risk study of bipolar disorder: childhood clinical phenotypes as precursors of major mood disorders. *Archives of General Psychiatry*, *68*(10), 1012-1020.

Opjordsmoen, S. (1989). Long-term course and outcome in unipolar affective and schizoaffective psychoses. *Acta Psychiatrica Scandinavica*, *79*(4), 317-326.

Papachristou, E., Ormel, J., Oldehinkel, A. J., Kyriakopoulos, M., Reinares, M., Reichenberg, A., & Frangou, S. (2013). Child Behavior Checklist—Mania Scale (CBCL-MS): Development and evaluation of a population-based screening scale for bipolar disorder. *PloS One*, *8*(8), e69459.

Papachristou, E., Oldehinkel, A. J., Ormel, J., Raven, D., Hartman, C. A., Frangou, S., & Reichenberg, A. (2017). The predictive value of childhood subthreshold manic symptoms for adolescent and adult psychiatric outcomes. *Journal of Affective Disorders*, *212*, 86-92.

Päären, A., Bohman, H., von Knorring, L., Olsson, G., von Knorring, A. L., & Jonsson, U. (2014). Early risk factors for adult bipolar disorder in adolescents with mood disorders: a 15-year follow-up of a community sample. *BMC psychiatry*, *14*(1), 1-13.

Perich, T., Lau, P., Hadzi-Pavlovic, D., Roberts, G., Frankland, A., Wright, A., ... Mitchell, P. B. (2015). What clinical features precede the onset of bipolar disorder? *Journal of Psychiatric Research*, *62*, 71-77.

Pfennig, A., Ritter, P. S., Höfler, M., Lieb, R., Bauer, M., Wittchen, H. U., & Beesdo-Baum, K. (2016). Symptom characteristics of depressive episodes prior to the onset of mania or hypomania. *Acta Psychiatrica Scandinavica*, *133*(3), 196-204.

Preisig, M., Strippoli, M. P. F., Castelao, E., Merikangas, K. R., Gholam-Rezaee, M., Marquet, P., ... Vandeleur, C. L. (2016). The specificity of the familial aggregation of early-onset bipolar disorder: a controlled 10-year follow-up study of offspring of parents with mood disorders. *Journal of Affective Disorders*, *190*, 26-33.

Prien, R. F., Kupfer, D. J., Mansky, P. A., Small, J. G., Tuason, V. B., Voss, C. B., & Johnson, W. E. (1984). Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders: report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. *Archives of General psychiatry*, *41*(11), 1096-1104.

Radke-Yarrow, M., Nottelmann, E., Martinez, P., Fox, M. B., & Belmont, B. (1992). Young children of affectively ill parents: A longitudinal study of psychosocial development. *Journal of the American Academy of Child & Adolescent Psychiatry*, *31*(1), 68-77.

Ramklint, M., von Knorring, A-L., von Knorring, L., & Ekselius, L. (2003). Child and adolescent psychiatric disorders predicting adult personality disorder: a follow-up study. *Nordic Journal of Psychiatry, 57*(1), 23-28.

Rao, U. M. A., Ryan, N. D., Birmaher, B., Dahl, R. E., Williamson, D. E., Kaufman, J., ... Nelson, B. (1995). Unipolar depression in adolescents: clinical outcome in adulthood. *Journal of the American Academy of Child & Adolescent Psychiatry*, *34*(5), 566-578.

Rao, U., Dahl, R. E., Ryan, N. D., Birmaher, B., Williamson, D. E., Rao, R., & Kaufman, J. (2002). Heterogeneity in EEG sleep findings in adolescent depression: unipolar versus bipolar clinical course. *Journal of Affective Disorders*, *70*(3), 273-280.

Ratheesh, A., Cotton, S. M., Betts, J. K., Chanen, A., Nelson, B., Davey, C. G., ... Bechdolf, A. (2015). Prospective progression from high-prevalence disorders to bipolar disorder: exploring characteristics of pre-illness stages. *Journal of Affective Disorders*, *183*, 45-48.

Regeer, E. J., Krabbendam, L., De Graaf, R., Ten Have, M., Nolen, W. A., & Van Os, J. (2006). A prospective study of the transition rates of subthreshold (hypo) mania and depression in the general population. *Psychological Medicine*, *36*(5), 619-627.

Reichart, C. G., van der Ende, J., Wals, M., Hillegers, M. H., Nolen, W. A., Ormel, J., & Verhulst, F. C. (2005). The use of the GBI as predictor of bipolar disorder in a population of adolescent offspring of parents with a bipolar disorder. *Journal of Affective Disorders*, *89*(1-3), 147-155.

Reinelt, E., Stopsack, M., Aldinger, M., Ulrich, I., Grabe, H. J., & Barnow, S. (2014). Longitudinal transmission pathways of borderline personality disorder symptoms: from mother to child? *Psychopathology*, *47*(1), 10-16.

Rey, J. M., Morris-Yates, A., Singh, M., Andrews, G., & Stewart, G. W. (1995). Continuities between psychiatric disorders in adolescents and personality disorders in young adults. *American Journal of Psychiatry*, *152*(6), 895-900.

Riihimäki, K. A., Vuorilehto, M. S., Melartin, T. K., & Isometsä, E. T. (2014). Five-year outcome of major depressive disorder in primary health care. *Psychological Medicine*, *44*(7), 1369-1379.

Ritter, P. S., Höfler, M., Wittchen, H. U., Lieb, R., Bauer, M., Pfennig, A., & Beesdo-Baum, K. (2015). Disturbed sleep as risk factor for the subsequent onset of bipolar disorder–data from a 10-year prospective-longitudinal study among adolescents and young adults. *Journal of Psychiatric Research*, *68*, 76-82.

Rössler, W., Hengartner, M. P., Ajdacic-Gross, V., Haker, H., Gamma, A., & Angst, J. (2011). Sub-clinical psychosis symptoms in young adults are risk factors for subsequent common mental disorders. *Schizophrenia Research*, *131*(1-3), 18-23.

Rudaz, D., Vandeleur, C. L., Gholam, M., Castelao, E., Strippoli, M. P. F., Marquet, P., ... Preisig, M. (2021). Psychopathological precursors of the onset of mood disorders in offspring of parents with and without mood disorders: results of a 13-year prospective cohort high-risk study. *Journal of Child Psychology and Psychiatry*, *62*(4), 404-413.

Ruggero, C. J., Kotov, R., Carlson, G. A., Tanenberg-Karant, M., González, D. A., & Bromet, E. J. (2011). Diagnostic consistency of major depression with psychosis across 10 years. *The Journal of Clinical Psychiatry*, *72*(9), 4445.

Salvatore, P., Baldessarini, R. J., Tohen, M., Khalsa, H. M. K., Sanchez-Toledo, J. P., Zarate Jr, C. A., ... Maggini, C. (2009). McLean-Harvard International First-Episode Project: two-year stability of DSM-IV diagnoses in 500 first-episode psychotic disorder patients. *Journal of Clinical Psychiatry*, *70*(4), 458.

Salvatore, P., Baldessarini, R. J., Khalsa, H. M. K., Amore, M., Di Vittorio, C., Ferraro, G., ... Tohen, M. (2013). Predicting diagnostic change among patients diagnosed with first-episode DSM-IV-TR major depressive disorder with psychotic features. *The Journal of Clinical Psychiatry*, *74*(7), 14983.

Scott, J., Marwaha, S., Ratheesh, A., Macmillan, I., Yung, A. R., Morriss, R., ... Bechdolf, A. (2017). Bipolar at-risk criteria: an examination of which clinical features have optimal utility for identifying youth at risk of early transition from depression to bipolar disorders. *Schizophrenia Bulletin*, *43*(4), 737-744.

Scott, J., Byrne, E., Medland, S., & Hickie, I. (2020). Self-reported sleep-wake disturbances preceding onset of full-threshold mood and/or psychotic syndromes in community residing adolescents and young adults. *Journal of Affective Disorders*, *277*, 592-595.

Scott, J., Byrne, E., Medland, S., & Hickie, I. (2020). Self-reported sleep-wake disturbances preceding onset of full-threshold mood and/or psychotic syndromes in community residing adolescents and young adults. *Journal of Affective Disorders*, *277*, 592-595.

Selby, E. A. (2013). Chronic sleep disturbances and borderline personality disorder symptoms. *Journal of Consulting and Clinical Psychology*, *81*(5), 941.

Selby, E. A., & Yen, S. (2014). Six-month trajectory of suicidal ideation in adolescents with borderline personality disorder. *Suicide and Life-Threatening Behavior*, *44*(1), 89-100.

Sharp, C., Vanwoerden, S., Jouriles, E. N., Godfrey, D. A., Babcock, J., McLaren, V., ... Temple, J. R. (2020). Exposure to interparental intimate partner violence and the development of borderline features in adolescents. *Child Abuse & Neglect*, *103*, 104448.

Sharp, C., Kalpakci, A., Mellick, W., Venta, A., & Temple, J. R. (2015). First evidence of a prospective relation between avoidance of internal states and borderline personality disorder features in adolescents. *European Child & Adolescent psychiatry*, *24*(3), 283-290.

Shaw, J. A., Egeland, J. A., Endicott, J., Allen, C. R., & Hostetter, A. M. (2005). A 10-year prospective study of prodromal patterns for bipolar disorder among Amish youth. *Journal of the American Academy of Child & Adolescent Psychiatry*, *44*(11), 1104-1111.

Schwartz, J. E., Fennig, S., Tanenberg-Karant, M., Carlson, G., Craig, T., Galambos, N., ... Bromet, E. J. (2000). Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis. *Archives of General Psychiatry*, *57*(6), 593-600.

Sharma, V., Xie, B., Campbell, M. K., Penava, D., Hampson, E., Mazmanian, D., & Pope, C. J. (2014). A prospective study of diagnostic conversion of major depressive disorder to bipolar disorder in pregnancy and postpartum. *Bipolar Disorders*, *16*(1), 16-21.

Sharp, C., Kalpakci, A., Mellick, W., Venta, A., & Temple, J. R. (2015). First evidence of a prospective relation between avoidance of internal states and borderline personality disorder features in adolescents. *European Child & Adolescent Psychiatry*, *24*(3), 283-290.

Shen, G. H., Sylvia, L. G., Alloy, L. B., Barrett, F., Kohner, M., Iacoviello, B., & Mills, A. (2008). Lifestyle regularity and cyclothymic symptomatology. *Journal of Clinical Psychology*, *64*(4), 482-500.

Shur-Fen Gau, S., Lin, Y. J., Tai-Ann Cheng, A., Chiu, Y. N., Tsai, W. C., & Soong, W. T. (2010). Psychopathology and symptom remission at adolescence among children with attention-deficit–hyperactivity disorder. *Australian & New Zealand Journal of Psychiatry*, *44*(4), 323-332.

Solomon, D. A., Keller, M. B., Leon, A. C., Mueller, T. I., Shea, M. T., Warshaw, M., ... Endicott, J. (1997). Recovery from major depression: a 10-year prospective follow-up across multiple episodes. *Archives of General Psychiatry*, *54*(11), 1001-1006.

Stepp, S. D., Burke, J. D., Hipwell, A. E., & Loeber, R. (2012). Trajectories of attention deficit hyperactivity disorder and oppositional defiant disorder symptoms as precursors of borderline personality disorder symptoms in adolescent girls. *Journal of Abnormal Child Psychology*, *40*(1), 7-20.

Stepp, S. D., Olino, T. M., Klein, D. N., Seeley, J. R., & Lewinsohn, P. M. (2013). Unique influences of adolescent antecedents on adult borderline personality disorder features. *Personality Disorders: Theory, Research, and Treatment*, *4*(3), 223.

Stepp, S. D., Keenan, K., Hipwell, A. E., & Krueger, R. F. (2014). The impact of childhood temperament on the development of borderline personality disorder symptoms over the course of adolescence. *Borderline Personality Disorder and Emotion Dysregulation*, *1*(1), 1-10.

Stepp, S. D., Whalen, D. J., Scott, L. N., Zalewski, M., Loeber, R., & Hipwell, A. E. (2014). Reciprocal effects of parenting and borderline personality disorder symptoms in adolescent girls. *Development and Psychopathology*, *26*(2), 361-378.

Stepp, S. D., Scott, L. N., Jones, N. P., Whalen, D. J., & Hipwell, A. E. (2016). Negative emotional reactivity as a marker of vulnerability in the development of borderline personality disorder symptoms. *Development and Psychopathology*, *28*(1), 213-224.

Stepp, S. D., & Lazarus, S. A. (2017). Identifying a borderline personality disorder prodrome: implications for community screening. *Personality and Mental Health*, *11*(3), 195-205.

Strandholm, T., Kiviruusu, O., Karlsson, L., Pankakoski, M., Pelkonen, M., & Marttunen, M. (2017). Stability and change in personality disorder symptoms in 1-year follow-up of depressed adolescent outpatients. *The Journal of Nervous and Mental Disease*, *205*(1), 15-22.

Stoléru, S., Nottelmann, E. D., Belmont, B., & Ronsaville, D. (1997). Sleep problems in children of affectively ill mothers. *Journal of Child Psychology and Psychiatry*, *38*(7), 831-841.

Strober, M., & Carlson, G. (1982). Bipolar illness in adolescents with major depression: clinical, genetic, and psychopharmacologic predictors in a three-to four-year prospective follow-up investigation. *Archives of General Psychiatry*, *39*(5), 549-555.

Strober, M., Lampert, C., Schmidt, S., & Morrell, W. (1993). The course of major depressive disorder in adolescents: I. Recovery and risk of manic switching in a follow-up of psychotic and nonpsychotic subtypes. *Journal of the American Academy of Child & Adolescent Psychiatry*, *32*(1), 34-42.

Thatcher, D. L., Cornelius, J. R., & Clark, D. B. (2005). Adolescent alcohol use disorders predict adult borderline personality. *Addictive Behaviors*, *30*(9), 1709-1724.

Thomsen, P. H., & Mikkelsen, H. U. (1993). Development of personality disorders in children and adolescents with obsessive-compulsive disorder A 6-to 22-year follow-up study. *Acta Psychiatrica Scandinavica*, *87*(6), 456-462.

Tillman, R., & Geller, B. (2006). Controlled study of switching from attention-deficit/hyperactivity disorder to a prepubertal and early adolescent bipolar I disorder phenotype during 6-year prospective follow-up: rate, risk, and predictors. *Development and Psychopathology*, *18*(4), 1037-1053.

Tijssen, M. J., van Os, J., Wittchen, H. U., Lieb, R., Beesdo, K., Mengelers, R., & Wichers, M. (2010). Prediction of transition from common adolescent bipolar experiences to bipolar disorder: 10-year study. *The British Journal of Psychiatry*, *196*(2), 102-108.

Tijssen, M. J., Van Os, J., Wittchen, H. U., Lieb, R., Beesdo, K., & Wichers, M. (2010). Risk factors predicting onset and persistence of subthreshold expression of bipolar psychopathology among youth from the community. *Acta Psychiatrica Scandinavica*, *122*(3), 255-266.

Tohen, M., Khalsa, H. M. K., Salvatore, P., Vieta, E., Ravichandran, C., & Baldessarini, R. J. (2012). Two-year outcomes in first-episode psychotic depression: The McLean–Harvard first-episode project. *Journal of Affective Disorders*, *136*(1-2), 1-8.

Tondo, L., Visioli, C., Preti, A., & Baldessarini, R. J. (2014). Bipolar disorders following initial depression: modeling predictive clinical factors. *Journal of Affective Disorders*, *167*, 44-49.

Tragesser, S. L., Solhan, M., Brown, W. C., Tomko, R. L., Bagge, C., & Trull, T. J. (2010). Longitudinal associations in borderline personality disorder features: Diagnostic Interview for Borderlines—Revised (DIB-R) scores over time. *Journal of Personality Disorders*, *24*(3), 377.

Tragesser, S. L., Solhan, M., Schwartz-Mette, R., & Trull, T. J. (2007). The role of affective instability and impulsivity in predicting future BPD features. *Journal of Personality Disorders*, *21*(6), 603-614.

Vanwoerden, S., Leavitt, J., Gallagher, M. W., Temple, J. R., & Sharp, C. (2019). Dating violence victimization and borderline personality pathology: Temporal associations from late adolescence to early adulthood. *Personality Disorders: Theory, Research, and Treatment*, *10*(2), 132.

Van Meter, A. R., Hafeman, D. M., Merranko, J., Youngstrom, E. A., Birmaher, B. B., Fristad, M. A., ... Findling, R. L. (2021). Generalizing the prediction of bipolar disorder onset across high-risk populations. *Journal of the American Academy of Child & Adolescent Psychiatry*, *60*(8), 1010-1019.

Vaillancourt, T., Brittain, H. L., McDougall, P., Krygsman, A., Boylan, K., Duku, E., & Hymel, S. (2014). Predicting borderline personality disorder symptoms in adolescents from childhood physical and relational aggression, depression, and attention-deficit/hyperactivity disorder. *Development and Psychopathology*, *26*(3), 817-830.

Weintraub, S. (1987). Risk factors in schizophrenia: The Stony Brook high-risk project. *Schizophrenia Bulletin*, *13*(3), 439-450.

Weissman, M. M., Wolk, S., Wickramaratne, P., Goldstein, R. B., Adams, P., Greenwald, S., ... Steinberg, D. (1999). Children with prepubertal-onset major depressive disorder and anxiety grown up. *Archives of General Psychiatry*, *56*(9), 794-801.

Weissman, M. M., Wolk, S., Goldstein, R. B., Moreau, D., Adams, P., Greenwald, S., ... Wickramaratne, P. (1999). Depressed adolescents grown up. *JAMA Psychiatry*, *281*(18), 1707-1713.

Widom, C., Czaja, S. J., & Paris, J. (2009). A prospective investigation of borderline personality disorder in abused and neglected children followed up into adulthood. *Journal of Personality Disorders*, *23*(5), 433.

Winokur, G., & Morrison, J. (1973). The Iowa 500: follow-up of 225 depressives. *The British Journal of Psychiatry*, *123*(576), 543-548.

Winokur, G., & Wesner, R. (1987). From unipolar depression to bipolar illness: 29 who changed. *Acta Psychiatrica Scandinavica*, *76*(1), 59-63.

Winsper, C., Wolke, D., & Lereya, T. (2015). Prospective associations between prenatal adversities and borderline personality disorder at 11–12 years. *Psychological Medicine*, *45*(5), 1025-1037.

Winsper, C., Zanarini, M., & Wolke, D. (2012). Prospective study of family adversity and maladaptive parenting in childhood and borderline personality disorder symptoms in a non-clinical population at 11 years. *Psychological Medicine*, *42*(11), 2405-2420.

Wolke, D., Waylen, A., Samara, M., Steer, C., Goodman, R., Ford, T., & Lamberts, K. (2009). Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *The British Journal of Psychiatry*, *195*(3), 249-256.

Wolke, D., Schreier, A., Zanarini, M. C., & Winsper, C. (2012). Bullied by peers in childhood and borderline personality symptoms at 11 years of age: a prospective study. *Journal of Child Psychology and Psychiatry*, *53*(8), 846-855.

Zahn-Waxler, C., Mayfield, A., Radke-Yarrow, M., McKnew, D. H., Cytryn, L., & Davenport, Y. B. (1988). A follow-up investigation of offspring of parents with bipolar disorder. *The American Journal of Psychiatry, 145*(4), 506–509. https://doi.org/10.1176/ajp.145.4.506

Zimmermann, P., Brückl, T., Nocon, A., Pfister, H., Lieb, R., Wittchen, H. U., ... Angst, J. (2009). Heterogeneity of DSM-IV major depressive disorder as a consequence of subthreshold bipolarity. *Archives of General Psychiatry, 66*(12), 1341-1352.

Supplementary 2. Search Strategy

PUBMED

#1 ("bipolar disorder"[All Fields] OR bipolar [All Fields] OR "hypomania"[All Fields] OR "cyclothymic"[All Fields] OR "bipolar disorder"[MeSH Terms] OR "hypomani*"[All Fields] OR manic*[All Fields] OR mania*[All Fields] OR "cyclothym*"[All Fields] OR BD-I[All Fields] OR BD-II[All Fields] OR "bipolar*"[All Fields] OR borderline personality disorder[MeSH Terms] OR "borderline personalit*"[All Fields] OR "BPD"[All Fields] OR "borderline personality disorder"[All Fields] OR "borderline personality"[All Fields] OR “emotionally unstable personality disorder”[All Fields] OR “borderline” [All Fields] OR “pediatric bipolar” [All Fields]) Filters: Meta-Analysis, Systematic Review, Child: birth-18 years, Newborn: birth-1 month, Infant: birth-23 months, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years, Young Adult: 19-24 years

#2 "precursor*"[All Fields] OR "anteceden*"[All Fields] OR "predict*"[All Fields] OR "prodrom*"[All Fields] OR genomic*, OR biologic* OR "polygenic risk score*" OR "genetic*" OR inciden* OR onset* OR biomarker* OR etiolog* OR aetiolog* OR "life-course trajector*" OR at-risk* OR high-risk* OR risk* OR "clinical characteristic*" OR "clinical feature*" OR "clinical manifestation*" OR "predisposing factor*" OR neurobiologic* OR genotype* OR phenotype* OR "temperamental" OR "causal pathway*" OR environmental OR socioeconomic* OR risk* OR predict* or diagnos* or develop* or risk factor[MeSH Terms] Filters: Meta-Analysis, Systematic Review, Child: birth-18 years, Newborn: birth-1 month, Infant: birth-23 months, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years, Young Adult: 19-24 years

#3 ("longitudinal study"[All Fields] OR "longitudinal"[All Fields] OR "prospective study"[All Fields] OR "prospect*"[All Fields] OR "follow up"[All Fields] OR "birth cohort" OR "population cohort" OR “prospective study”[MeSH Terms] OR “follow up study”[MeSH Terms]

OR “longitudinal study”[MeSH Terms]) Filters: Meta-Analysis, Systematic Review, Child: birth-18 years, Newborn: birth-1 month, Infant: birth-23 months, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years, Young Adult: 19-24 years

#4 #1 AND #2 AND #3 Filters: Meta-Analysis, Systematic Review, Child: birth-18 years, Newborn: birth-1 month, Infant: birth-23 months, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years, Young Adult: 19-24 years

EMBASE

#1 exp bipolar disorder/ or exp bipolar i disorder/ or exp bipolar ii disorder/ or exp cyclothymic disorder/ or exp mania/ or exp bipolar mania/ or exp cyclothymia/ or exp "mixed mania and depression"/ or exp rapid cycling bipolar disorder/ or 'manic depress*'.mp. or 'bipolar disorder*'.mp. or cyclothymi*.mp. or manic.mp. or mania.mp. or exp borderline personality disorder/ or 'borderline personality'.mp. or 'emotionally unstable personality disorder'.mp. or borderline.mp. or 'pediatric bipolar'.mp. or 'bipolar feature*'.mp. or bipolar.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

#2 (longitudinal or prospect* or follow-up* or 'follow up*').mp. or exp Longitudinal Studies/ or 'birth cohort'.mp. or 'population cohort'.mp. or exp prospective study/ or exp follow up/ [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

#3 exp risk factors/ or precursor*.mp. or antecedent*.mp. or prodrom*.mp. or biologic*.mp. or genomic*.mp. or genetic*.mp. or inciden*.mp. or onset*.mp. or biomarker*.mp. or "polygenic risk score*".mp. or etiolog*.mp. or aetiolog*.mp. or "life-course trajector*".mp. or at-risk*.mp. or high-risk*.mp. or "clinical characteristic*".mp. or "clinical feature*".mp. or "clinical manifestation*".mp. or "predisposing factor*".mp. or neurobiologic*.mp. or genotype*.mp. or phenotype*.mp. or "temperamental".mp. or environmental.mp. or socioeconomic*.mp. or "causal pathway*".mp. or exp risk/ or exp diagnosis/ or exp development/ or risk*.mp. or develop*.mp. or diagno*.mp. or predict*.mp. or exp biological marker/ or exp genotype/ or exp phenotype/ or exp etiology/ or exp precursor/ or exp clinical feature/ or exp socioeconomics/ or exp environmental factor/ or exp incidence/

#4 ('meta analysis' or meta-analysis or 'meta review' or 'systematic review').mp. or exp meta analysis/ or exp "systematic review"/ [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

#5 (child* or "young adult" or "young people" or adolescen* or infant* or boy* or girl* or newborn* or youth* or teen* or student* or baby or young*).mp. or exp child/ or exp adolescent/ or exp young adult/ or exp infant/ or exp boy/ or exp girl/ or exp baby/ or exp newborn/

[mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

#6 1 and 2 and 3 and 4 and 5

MEDLINE

#1 exp bipolar disorder/ or exp bipolar i disorder/ or exp bipolar ii disorder/ or exp cyclothymic disorder/ or exp mania/ or exp bipolar mania/ or exp cyclothymia/ or exp "mixed mania and depression"/ or exp rapid cycling bipolar disorder/ or 'manic depress*'.mp. or 'bipolar disorder*'.mp. or cyclothymi*.mp. or manic.mp. or mania.mp. or exp borderline personality disorder/ or 'borderline personality'.mp. or 'emotionally unstable personality disorder'.mp. or borderline.mp. or 'pediatric bipolar'.mp. or 'bipolar feature*'.mp. or bipolar.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

#2 (longitudinal or prospect* or follow-up* or 'follow up*').mp. or exp Longitudinal Studies/ or 'birth cohort'.mp. or 'population cohort'.mp. or exp prospective study/ or exp follow up/ [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

#3 ('meta analysis' or meta-analysis or 'meta review' or 'systematic review').mp. or exp meta analysis/ or exp "systematic review"/ [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

#4 (child* or "young adult" or "young people" or adolescen* or infant* or boy* or girl* or newborn* or youth* or teen* or student* or baby or young*).mp. or exp child/ or exp adolescent/ or exp young adult/ or exp infant/ or exp boy/ or exp girl/ or exp baby/ or exp newborn/ [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

#5 exp risk factors/ or precursor*.mp. or antecedent*.mp. or prodrom*.mp. or biologic*.mp. or genomic*.mp. or genetic*.mp. or inciden*.mp. or onset*.mp. or biomarker*.mp. or "polygenic risk score*".mp. or etiolog*.mp. or aetiolog*.mp. or "life-course trajector*".mp. or at-risk*.mp. or high-risk*.mp. or "clinical characteristic*".mp. or "clinical feature*".mp. or "clinical manifestation*".mp. or "predisposing factor*".mp. or neurobiologic*.mp. or genotype*.mp. or phenotype*.mp. or "temperamental".mp. or environmental.mp. or socioeconomic*.mp. or "causal pathway*".mp. or exp risk/ or exp diagnosis/ or exp development/ or risk*.mp. or develop*.mp. or diagno*.mp. or predict*.mp. or exp biological marker/ or exp genotype/ or exp

phenotype/ or exp etiology/ or exp precursor/ or exp clinical feature/ or exp socioeconomics/ or exp environmental factor/ or exp incidence/ or exp diagnosis/

#6 1 and 2 and 3 and 4 and 5.

APA PsychINFO

#1 exp bipolar disorder/ or exp bipolar i disorder/ or exp bipolar ii disorder/ or exp cyclothymic disorder/ or exp mania/ or exp bipolar mania/ or exp cyclothymia/ or exp "mixed mania and depression"/ or exp rapid cycling bipolar disorder/ or 'manic depress*'.mp. or 'bipolar disorder*'.mp. or cyclothymi*.mp. or manic.mp. or mania.mp. or exp borderline personality disorder/ or 'borderline personality'.mp. or 'emotionally unstable personality disorder'.mp. or borderline.mp. or 'pediatric bipolar'.mp. or 'bipolar feature*'.mp. or bipolar.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

#2 (longitudinal or prospect* or follow-up* or 'follow up*').mp. or exp Longitudinal Studies/ or 'birth cohort'.mp. or 'population cohort'.mp. or exp prospective study/ or exp follow up/ [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

#3 ('meta analysis' or meta-analysis or 'meta review' or 'systematic review').mp. or exp meta analysis/ or exp "systematic review"/ [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

#4 (child* or "young adult" or "young people" or adolescen* or infant* or boy* or girl* or newborn* or youth* or teen* or student* or baby or young*).mp. or exp child/ or exp adolescent/ or exp young adult/ or exp infant/ or exp boy/ or exp girl/ or exp baby/ or exp newborn/ [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh]

#5 exp risk factors/ or precursor*.mp. or antecedent*.mp. or prodrom*.mp. or biologic*.mp. or genomic*.mp. or genetic*.mp. or inciden*.mp. or onset*.mp. or biomarker*.mp. or "polygenic risk score*".mp. or etiolog*.mp. or aetiolog*.mp. or "life-course trajector*".mp. or at-risk*.mp. or high-risk*.mp. or "clinical characteristic*".mp. or "clinical feature*".mp. or "clinical manifestation*".mp. or "predisposing factor*".mp. or neurobiologic*.mp. or genotype*.mp. or phenotype*.mp. or "temperamental".mp. or environmental.mp. or socioeconomic*.mp. or "causal pathway*".mp. or exp risk/ or exp diagnosis/ or exp development/ or risk*.mp. or develop*.mp. or diagno*.mp. or predict*.mp. or exp biological marker/ or exp genotype/ or exp phenotype/ or exp etiology/ or exp precursor/ or exp clinical feature/ or exp socioeconomics/ or exp environmental factor/ or exp incidence/ or exp diagnosis/

#6 1 and 2 and 3 and 4 and 5

Web of Science

ALL=('borderline personality' OR 'borderline trait*' OR 'borderline feature*' OR “emotiona lly unstable personality disorder” OR borderline OR 'bipolar disorder' OR manic OR man ia OR cychlothymi* OR BD-
* OR hypomani* or "bipolar symptomotology" or "pediatric bipolar" or "bipolar feature*" OR “manic depress*” OR bipolar) AND ALL=(longitudinal OR follow-
up* OR prospect* OR "population cohort*" OR "birth cohort" OR "follow up*") AND ALL=(precursor* OR antecedent* OR prodrom* OR biologic* or genomic* or genetic* o r inciden* or onset* or biomarker* or "polygenic risk score*" or etiolog* or aetiolog* or "life-course trajectories" or at-risk* or high-
risk* or "clinical characteristic*" or "clinical feature*" or "clinical manifestation*" or neur obiologic* or genotype* or phenotype* or "temperamental" or environmental or socioecon omic* OR diagno* OR predict* OR risk* OR develop*) AND ALL=('meta analysis' or meta-
analysis or 'meta review' or 'systematic review') AND ALL=(child* or adolescen* or infa nt* or boy* or girl* or newborn* or youth* or teen* or student* or young*)

CINAHL
TX ('Bipolar Disorder' OR hypomani* OR manic OR mania OR cyclothymi* OR 'borderline personality' OR 'borderline personality disorder' OR "emotionally unstable personality disorder*" OR borderline OR “pediatric bipolar” OR bipolar) AND TX (prospect* OR longitudinal OR follow-up* OR "birth cohort" OR "population cohort" or “follow up”) AND TX (antecedent* OR precursor* OR prodrom* OR inciden* OR biomarker* OR genetic* OR genomic* OR ‘polygenic risk score*’ OR onset* OR biologic* OR etiolog* or aetiolog* or "life-course trajector*" or at-risk* or high-risk* or "clinical characteristic*" or "clinical feature*" or "clinical manifestation*" or "predisposing factor*" or neurobiologic* or genotype* or phenotype* or "temperamental" or environmental or socioeconomic* or 'causal pathways' or risk* or develop* or diagno* or predict*) AND TX (child* OR adolescen* OR ‘young adult*’ OR ‘young people’ OR infant* OR newborn* OR boy* OR girl* OR teen* OR student* OR youth* OR young*) AND TX ('meta analysis' or meta-analysis or 'meta review' or 'systematic review')

COCHRANE
#1 'Bipolar Disorder' OR hypomani* OR manic OR mania OR cyclothymi* OR 'borderline personality' OR 'borderline personality disorder' OR "emotionally unstable personality disorder*" OR borderline OR bipolar OR "manic depress*" OR BD* OR BPD

#2 MeSH descriptor: [Borderline Personality Disorder] explode all trees
#3 MeSH descriptor: [Bipolar Disorder] explode all trees
#4 #1 OR #2 OR #3
#5 MeSH descriptor: [Longitudinal Studies] explode all trees
#6 MeSH descriptor: [Prospective Studies] explode all trees
#7 MeSH descriptor: [Follow-Up Studies] explode all trees
#8 prospect* OR longitudinal OR follow-up* OR "birth cohort" OR "population cohort"
#9 #5 OR #6 OR #7 OR #8
#10 MeSH descriptor: [Risk Factors] explode all trees

#11 antecedent* OR precursor* OR prodrom* OR inciden* OR biomarker* OR genetic* OR genomic* OR ‘polygenic risk score*’ OR onset* OR biologic* OR etiolog* or aetiolog* or "life-course trajector*" or at-risk* or high-risk* or "clinical characteristic*" or "clinical feature*" or "clinical manifestation*" or "predisposing factor*" or "onset pattern*" or neurobiologic* or genotype* or phenotype* or "temperamental" or environmental or socioeconomic* or 'causal pathways' or develop* or predict* or diagno* or risk*
#12 MeSH descriptor: [Risk] explode all trees
#13 MeSH descriptor: [Diagnosis] explode all trees
#14 MeSH descriptor: [Biomarkers] explode all trees
#15 MeSH descriptor: [Phenotype] explode all trees
#16 MeSH descriptor: [Genotype] explode all trees
#17 MeSH descriptor: [Socioeconomic Factors] explode all trees
#18 MeSH descriptor: [Sociological Factors] explode all trees
#19 #11 or #10 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 MeSH descriptor: [Child] explode all trees
#21 MeSH descriptor: [Adolescent] explode all trees
#22 MeSH descriptor: [Infant, Newborn] explode all trees
#23 child* or adolescen* or infant* or boy* or girl* or newborn* or youth* or teen* or student* or young*
#24 #20 or #21 #22 #23
#26 #24 AND #4 AND #9 AND #19.

Supplementary 4. Vulnerability Factors

Environmental Factors

Gender

In the SR/MA by Ratheesh et al. (2011), gender was not a significant predictor of transition to BD. No comparable reviews were available for BPD.

Family History of Psychopathology

Five reviews examined the effects of family history of psychopathology and onset of BD (Keramatian, Chakrabarty, Saraf, & Yatham, 2021; Lau et al., 2017; Narayan, Allen, Cullen, & Klimnes-Dougan, 2013; Rasic, Hajek, Alda, & Uher, 2014; Ratheesh et al. 2017). Most of the primary studies they included demonstrated that offspring of parents with BD, MDD, or psychosis had at least one mental illness diagnosis including BD. Family history of depression, on the other hand, did not predict transition to BD (Ratheesh et al., 2017).

For BPD, data were provided by three reviews (Skabeikyte & Barkauskiene, 2021; Stepp, Lazarus, & Byrd, 2016; Winsper et al., 2016a). Results indicated a moderate to high level of heritability of trait BPD in child and adolescent populations (Winsper et al., 2016a) and maternal psychopathology in general had significant associations with later BPD symptoms (Skabeikyte & Barkauskiene, 2021; Stepp, Lazarus, & Byrd, 2016). However, parental depression did not predict changes in BPD symptoms in the offspring (Skabeikyte & Barkauskiene, 2021).

Psychosocial Factors

Childhood Adversity

Data regarding the effect of childhood adversity on risk for BD was provided by two reviews (Palmier-Claus, Berry, Bucci, Mansell, & Varese, 2016; Ratheesh et al., 2017). Findings indicated that severity of childhood abuse, neglect, physical abuse, verbal abuse, and sexual abuse were significantly associated with higher risks of both first onset and recurrent mania.

A greater quantity of primary studies was synthesised by three reviews for BPD than BD regarding the effects of childhood adversity (Skabeikyte & Barkauskiene, 2021; Stepp et al., 2016; Winsper et al., 2016b). Results demonstrated significant associations with relational aggression in the context of friendship, physical and verbal aggression in romantic relationships, physical abuse, parental hostility/ verbal abuse, emotional abuse, childhood neglect and later BPD symptoms. Additionally, peer victimisation was predictive of higher levels of BPD symptoms in adolescents (Stepp et al., 2016).

Family Relations and Adversity

Three reviews studied the effects of family relations on the risk for later BPD symptoms (Skabeikyte & Barkauskiene, 2021; Stepp et al., 2016; Winsper et al., 2016b). Results demonstrated a significant association between parental conflict and higher BPD symptoms (Winsper et al., 2016b). However, results were inconsistent for parent-child relationship quality, family adversity, and later BPD symptoms (Stepp et al., 2016). There were no significant associations between family relations, social support from family or friends and subsequent BPD symptoms (Skabeikyte & Barkauskiene, 2021). The relationship quality with the father, on the other hand, predicted declines in BPD features in adolescence. No comparable evidence was available for BD.

Parenting Style

Two reviews found evidence concerning the association between parenting style and later BPD symptoms (Skabeikyte & Barkauskiene, 2021; Stepp et al., 2016). Inconsistent results were found for low warmth, rejection, low maternal satisfaction with the child, hostility, inconsistent parenting, and harsh punishment/discipline predicting later BPD symptoms (Stepp et al., 2016). Results for intimate partner violence, maternal communication, maternal over-involvement, and maternal expressed negative emotion and later BPD symptoms were consistent (Skabeikyte & Barkauskiene, 2021; Stepp et al., 2016).

Non-significant associations were found for low warmth, parental harsh punishment and maternal support/validation and later BPD (Skabeikyte & Barkauskiene, 2021). No comparable data were available for BD.

General Psychosocial Functioning

One BPD review reported that lower levels of a child's general psychosocial functioning predicted BPD onset at follow-up (Skabeikyte and Barkauskiene 2021). One BD indicated that poor general psychosocial functioning predicted new onset of BD (Keramatian, 2021).

Table S1

Characteristics of systematic reviews and meta-analyses examining the developmental pathways and onset of Bipolar Disorder

Study (Type)	Sample Size and Characteristics	Factors examined	N/n	Databases searched (last assessed)	Types of studies included (publication date range)	AMSTAR index
Bart et al. 2021 (SR)	5495 in total, 392 offspring of BD parents or first-degree relative "At-risk" individuals based on having a first-degree relative either with BD or SUD, but no current diagnosis themselves and euthymic/remitted samples compared to healthy controls or to in-episode individuals	Neural reward circuit dysfunction	34/2	PsychINFO, and PubMed (Up to February 14, 2021)	Prospective and Cross-sectional (2008 – 2020)	3
Brancati et al. 2021 (SR/MA)	2823 in total Only children and adolescents aged ≤ 18 years at first	Development of BD in patients with ADHD	10/10	Medline, Embase, and Web of Science (NR)	Prospective (2003-2009)	6

	clinical assessment for ADHD diagnosis based on DSM-III-R or subsequent criteria and BD assessment was performed at follow-up					
Cardoso et al. 2018 (SR)	3374 participants in total Individuals who experienced at least one depressive episode with no history of hypomanic or manic episode	Suicidality	3/ 3	PubMed, Bireme, Scopus, and PsychINFO (Up to December 2017)	Prospective (2015-2016)	4
Cahn et al. 2021 (SR)	752 participants in total A BD-I cohort with a current or recent first episode mania, with diagnosis established using standardized assessment criteria	Longitudinal grey matter changes	15/1	Medline, Embase, and Web of Science (Up to September 17, 2020)	Prospective (2003-2019)	6

Faedda et al. 2013 (SR)	22,048 participants in total Individuals who are diagnosed with MDE, MDD, dysthymia, cyclothymia, or bipolar NOS as well as subjects with subsyndromal affective disorders or symptoms at intake and bipolar I or bipolar II during follow-up	Precursors of BD	26/ 26	PubMed, CINAHL, PsychINFO, EMBASE, SCOPUS, and ISI Web of Science (Up to May 31)	Prospective (1977-2013)	3
Gibbs et al. 2015 (SR/MA)	14918 participants diagnosed with BD I or II or described as experiences mania during the follow-up	Cannabis Use	6/ 3	PsychINFO, Cochrane, SCOPUS, EMBASE, and Medline (Up to June 2014)	Prospective (2000-2012)	9
Hu et al. 2020 (MA)	6605 participants in total Individuals diagnosed with BD or at-risk for BD	Aberrancies in White Matter	57/ 1	PubMed, EMBASE, and Web of Science (Up to April 23)	Cross-sectional and prospective (2008-2020)	7
Keramatian et al., (2022)	7969 participants in total Individuals who are at genetic	Predictors of transitioning to BD	23/23	Ovid Medline (Up to July 16 2021)	Prospective (1985 – 2021)	4

	and/or clinical high risk for BD					
Lau et al. 2018 (MA)	3454 participants in total BD high-risk offspring and siblings	Family history of BD	17/ 7	PsychINFO, EMBASE, Medline, and Scopus (Up to July 2015)	Cross-sectional and prospective (1988-2015)	8
Narayan et al. 2013 (SR)	2417 participants in total BD high-risk offspring	Family history of BD	13/ 4	PubMed, PsychINFO, and Medline	Cross-sectional and prospective (1975-2012)	2
Palmier-Claus et al. 2016 (SR/MA)	2102377 participants in total Individuals with a formal diagnosis of BD (including prospective studies reporting first-onset mania as an outcome)	Childhood Adversity	11/ 1	Medline, EMBASE, PsychINFO, and Web of Science (NR)	Case-control, cross-sectional and prospective (1980-2014)	9
Pancheri et al. 2019 (SR)	34459 participants in total Prospective Studies: BD high-risk individuals who are later diagnosed with BD and individuals with sleep	Sleep Alterations	17/ 6	Medline, PubMed, Index Medicus, and Cochrane Library (Up to January 1st)	Prospective and retrospective (2000-2017)	6

	alterations and develop full-blown BD at follow up Retrospective studies: Individuals with a diagnosis of BD					
Rasic et al. 2014 (MA)	3863 participants in total Offspring of parents with severe mental illness (SMI; schizophrenia, BD, MDD)	Family history of BD	33/ 3	Medline, PubMed, EMBASE, PsychINFO (Up to December 31, 2012)	Cross-sectional and prospective (1989-2012)	6
Ratheesh et al. 2011 (SR/MA)	17688 participants in total Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up	Any factor that is related to the transition from MDD to BD	56/ 56	Medline, PsychINFO, and EMBASE (Up to September 2016)	Prospective (1973 – 2016)	9
Ritter at al. 2011 (SR/MA)	85957 participants in total Prospective Studies: Offspring of parents with BD, individuals with a diagnosis of	Disturbed Sleep	21/ 6	ISI- Web of Science including, amongst others: Science Citation Index Expanded, Social Sciences Citation Index, Arts and	Prospective and retrospective (1989-2008)	2

	insomnia or disturbed sleep Retrospective studies: Patients with a diagnosis of BD			Humanities Citation Index, Con- ference Proceedings Citation Index–Science, Con-ference Proceedings Citation Index–Social Science and Humanities, and Medline (NR)		
Scott et al. 2021 (SR/MA)	58496 participants in total Participants had a mean age ≤30 at the time of assessment of any sleep disturbances or the mean age at onset of the sleep disturbances was <30 and had first onset mental disorders which are BD, depressive disorders, and psychotic disorders at follow-up	Sleep Disturbances	41/11	PubMed, PsychINFO, Embase, and Web of Science	Prospective (1996-2020)	11

Scott et al. 2022 (SR/MA)	25830 in total Offspring of BD, subthreshold manifestations of BD assessed using BAR, full-threshold diagnostic criteria for BD-I or BD-II with first onset by about 25 years	Sleep and circadian rhythm disturbances	76/20	PubMed, PsychInfo, CINAHL, Embase, Web of Science	Case-control, cross-sectional, prospective	10

Note. ADHD = Attention Deficit Hyperactivity Disorder, BAR = youth with bipolar at-risk states; BD = Bipolar Disorder; MA = meta-analysis; MDE = Major Depressive Episodes; MDD = Major Depressive Disorder; N = Number of included studies; n = number of relevant prospective studies; NOS = Not Otherwise Specified; NR = Not reported; SMI = Severe Mental Illness; SR = Systematic Review, SUD = Substance Use Disorders.

Table S2

Characteristics of systematic reviews and meta-analyses examining the developmental pathways and onset of Borderline Personality Disorder

Study (Type)	Sample Size and Characteristics	Factors examined	N/n	Databases searched (last assessed)	Types of studies included (publication date range)	AMSTAR index

Skabeikyte & Barkauskiene 2021 (SR)	16157 adolescents aged ten to eighteen years old who showed BPD features or symptoms or had diagnosis at the follow-up period	Any predictor (i.e., putative risk factor) associated with BPD features, symptoms, or diagnosis	14/14	Medline, PubMed, PsychINFO, PsychARTICLES, SocINDEX, Proquest and Scopus (NR)	Prospective (2013-2020	9
Stepp et al. 2016 (SR)	43681 high-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment	Any predictor (i.e., putative risk factor) associated with BPD features, symptoms, or diagnosis	39/39	PubMed, CINAHL, PsychINFO, ISI Web of Science (Up to September 15)	Prospective (1993-2015)	5
Winsper et al. 2016a (SR)	6313 participants nineteen years of age or younger who were diagnosed with BPD or showed BPD symptoms as an outcome	Neurobiological correlates (i.e., genetic, neurophysiological , structural brain characteristics, neuropsychological) of BPD	34/2	Medline, EMBASE, PsychINFO, and PubMed (Up to 28th January 2014)	Cross-sectional and prospective (1999-2016)	8
Winsper et al. 2016b (SR/MA)	29395 participants nineteen years of age or under and have a diagnosis of BPD or have BPD features	Psychopathological (i.e., psychiatric disorders and suicidality) and etiological (i.e., adverse life events) factors	61/9	Medline, EMBASE, PsychINFO, PubMed	Cross-sectional, retrospective and prospective (1985-2015)	10

Winsper et al. 2017 (SR/MA)	29860 participants with BPD or have BPD symptoms	Sleep profile (i.e., continuity, architecture, and nightmares)	32/2	EMBASE, PsychINFO, and PubMed (Up to December 2015)	Cross-sectional and prospective (1983-2016)	10

Note. MA = meta-analysis; N = Number of included studies; n = number of relevant prospective studies; NR = Not reported; SR = Systematic Review

Table S3

Evidence across systematic reviews and meta-analyses of factors for Bipolar Disorder outcome

Study (Sample)	Factor Examined	k	Main Findings
Vulnerability Factors			
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Gender	10	Out of ten studies only one study found a significant association between male gender and transition to BD
Lau et al. 2018 (BD high-risk offspring and siblings)	Family history of BD	7	All seven studies reported at least one mental illness diagnosis in high-risk offspring including anxiety disorders, problems in psychosocial functioning, internalising and externalising behaviours, MDD, sleep, SUD, schizoaffective disorder. Only two of them found life-time prevalence of BD in the high-risk offspring
Keramatian et al. 2022 (Individuals who are at clinical or genetic risk of developing BD)	Family History of BD	5	The first study found that most offspring of BD parents did not develop BD, but they were at specific high risk for developing BD, particularly those with preschool ADHD and

			early-onset parental BD. The second study also found that earlier parental age at onset individually and collectively predicted new onset BD. Third study also found that offspring of parents with early onset BD entailed a higher risk of BD and substance use disorders than those with later onset and controls. Forth study found that more than half of the Dutch BD offspring cohort had developed a mood disorder including 13% with bipolar spectrum disorders (3% with bipolar I disorder; 8% with bipolar II disorder; 1% with schizoaffective disorder, bipolar type; and 1% with cyclothymia) and 41% with a unipolar depressive disorder (major depressive disorder; dysthymia; depressive disorder not otherwise specified; or adjustment disorder, mood). Fifth study found that familial hypomania/mani predicted conversion.
Narayan et al. 2013 (BD high-risk offspring)	Family History of BD	7	Six studies reported at least one mental illness diagnosis including schizoaffective disorder, thought problems and psychosis-NOS. Two studies did not find significant group differences between offspring risk groups for cluster A personality disorders
Pancheri et al. 2019 (BD Offspring)	Family history of BD and sleep disorders	4	First study found that 50% of children later diagnosed with BD presented decreased sleep as an antecedent. Second study also found that high-risk offspring has a higher risk of sleep disorders and the sleep difficulties started about 6 years before the onset of the first major mood episode. Third study found that bipolar offspring youth

			with poor sleep were 4 times more likely to develop BD and sleep symptoms presented about 3 years before BD onset, but the results were not significant. The fourth study found that in the BD offspring group who converted to BD with a hypomanic onset, decreased need of sleep and middle insomnia were significantly associated with BD conversion.
Rasic et al. 2014 (Offspring of individuals with SMI)	Family history of BD	3	First study found that offspring of BD developed major mood episodes in adolescence and not before and concluding that adolescence marks the beginning of the high-risk period for major mood episodes related to BD onset. Second study also found that the lifetime prevalence of mood disorders in general and BD in particular increased from 3 to 10% at follow-up among children of BD parents. The third study found that 24% of the offspring of BD parents received a positive diagnosis clustered in the affective illness spectrum.
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Family history of BD	8	Five study out of eight identified a positive association between family history of BD and later BD in the offspring
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Family history of Affective Disorder	4	Out of 4 studies only one study identified a significant association between family history of AD and later BD
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and	Family History of depression	3	Only one study found significant associations between having first degree relatives with MDD and later BD

later converted to BD I or II at follow-up)			
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Other familial history predictors	2	Two studies found significant associations between risk of developing BD and either family history of AD spanning three generations or multiple affected family members
Ritter et al. 2013 (BD Offspring)	Family history of BD and sleep disturbances in the offspring	6	Two studies following the same cohort of high-risk offspring found that antecedent conditions to BD included sleep and anxiety disorders. Two other studies again investigating early symptoms in the same high-risk cohort first found that 14% of high-risk children had either hypersomnia or unspecified sleep problems but results were not significant. Later in the updated publication of the cohort, decreased sleep problems reached statistical significance among at-risk adolescents. Last two studies following the same cohort, sleep disturbances were not found to be a significant predictor although the measure were not reported in the article itself (the author of this review got in contact with the authors)
Keramatian et al. 2022 (Individuals who are at clinical or genetic risk of developing BD)	Psychosocial functioning	1	The study found that poor general psychosocial functioning predicted new onset of BD
Palmier-Claus et al. 2016 (Individuals with a formal diagnosis of BD (including prospective studies reporting first-onset mania as an outcome)	Childhood Adversity	1	The study found that childhood physical, verbal, sexual abuse and neglect were significantly associated with higher risks of both first-onset and recurrent mania

Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Childhood Adversity	2	One study found child abuse and the other study found severity of childhood trauma were associated with later BD
Biomarkers			
Bart et al. 2021 (Individuals at familial risk for BD)	Neural reward circuit dysfunction	2	One study found that; BD offspring had lower connectivity between the ventral striatum (VS) and left central anterior cingulate cortex during loss trials compared to not BD (nBD) offspring and control offspring, they had greater connectivity between the pars orbitalis and orbitofrontal cortex (OFC) during reward trials compared to not nBD offspring, nBD offspring had lower connectivity between pars orbitalis and right OFC during reward trials compared to control offspring, BD offspring had greater connectivity between the pars triangularis and right OFC during loss trials compared to control offspring. The other study found that lower bilateral parietal cortical thickness, greater left ventrolateral prefrontal cortex thickness, lower right transverse temporal cortex thickness, greater self-reported depression, mania severity, and age at scan predicted greater future mixed/mania factor score and lower bilateral parietal cortical thickness, greater right entorhinal cortical thickness, greater right fusiform gyral activity during emotional face processing, diagnosis of major depressive disorder, and greater self-reported depression

			severity predicted greater irritability factor score.
Cahn et al. 2021 (Individuals with first episode mania)	Longitudinal grey matter changes	1	The study found that adolescents with mania failed to exhibit normal increases in amygdala volume that occur during healthy adolescent neurodevelopment
Hu et al. 2020 (Individuals at familial risk for BD)	Aberrancies in White Matter	1	The study found that fractional anisotropy reduction did not differ significantly between high familial risk individuals for BD and controls
Clinical Factors/Features			
Cardoso et al. 2018 (Individuals who experienced at least one depressive episode with no history of hypomanic or manic episode)	Suicidality	3	Out of three studies, one found suicide risk (i.e., recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt or a specific plan for committing suicide) as a predictor of diagnosis conversion to BD One study found significant results for alcohol use or SUD at baseline, family history of mood disorders and failure to respond to antidepressant treatments were associated with development of BD Third study also found that alcohol use disorder and family history of SUD were predictors of BD conversion
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Suicide ideation or attempts	4	Three out of four studies found significant associations between suicidality and later BD

Faedda et al. 2015 (Participants who are diagnosed with MDE, MDD, dysthymia, cyclothymia, or bipolar NOS as well as subjects with subsyndromal affective disorders or symptoms at intake and bipolar I or bipolar II during follow-up)	Affective Instability	3	One study found affective instability predicted BD II but not BD I. They also found that BP II converters were distinguished from those who remained unipolar on the basis of energy activity, temperamental instability and daydreaming. BD II switchers also had a more tempestuous course with shorter intervals. Another study also found that it predicted BD II and BD spectrum disorders (MDD and subsyndromal hypomania) and having 'ups and downs' was an indicator of disturbed mood regulation Another study, on the contrary, found past or current affective instability at baseline predicted conversion to BD I and Bipolar NOS in adults hospitalised for MDD with psychotic features
Faedda et al. 2015 (Participants who are diagnosed with MDE, MDD, dysthymia, cyclothymia, or bipolar NOS as well as subjects with subsyndromal affective disorders or symptoms at intake and bipolar I or bipolar II during follow-up)	Subsyndromal Depression	3	Higher rates of later conversion to BD, especially BD II in two studies, were reported in all three studies
Keramatian et al. 2022 (Individuals who are at clinical or genetic risk of developing BD)	Major Depressive Episodes	1	The study found that major depressive episodes were indicators for close monitoring of emergent BD in high-risk offspring.
Keramatian et al. 2022 (Individuals who are at	Depression in offspring of BD	2	One study found that a unipolar depression in bipolar offspring is associated with the development of BD. The other study found that

clinical or genetic risk of developing BD)			elevated scores on the Depression scale in General Behavior Inventory (GBI) predicted a switch from unipolar to BD. The other study found that major depressive episodes were predicted the onset of (hypo)manic episodes.
Faedda et al. 2015 (Participants who are diagnosed with MDE, MDD, dysthymia, cyclothymia, or bipolar NOS as well as subjects with subsyndromal affective disorders or symptoms at intake and bipolar I or bipolar II during follow-up)	Subsyndromal hypomanic symptoms	5	First study found higher scores on Hypomanic Personality Scale significantly predicted conversion to BD, especially BD II. Second study found the same results for BD I and Bipolar NOS. Third study found the combination of subclinical mania with subclinical psychosis at intake predicted onset of BD three times more. Fourth study found symptoms of elation or irritability, especially their combination predicted later hypomania or mania. Fifth study found number and persistence of hypomania or mania symptoms increased monotonically at follow-up before full-blown BD criteria were met
Keramatian et al. 2022 (Individuals who are at clinical or genetic risk of developing BD)	Subthreshold manic symptoms	5	Three studies found that subthreshold manic symptoms or hypomanic episodes are predictive of BD. Fourth study found that "high mania" predicted BD conversion. Fifth study found that subthreshold manic subgroup of Bipolar-At-Risk (BAR) criteria predicted conversion to BD
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Subthreshold (hypo)manic features		Three studies identified a significant association between subthreshold hypomanic symptoms and BD transition. Two of those studies also found a dose-response relationship between the number of manic symptoms and later BD. Two studies found an association between antidepressant associated subthreshold hypomanic episodes and transition to BD.

Faedda et al. 2015 (Participants who are diagnosed with MDE, MDD, dysthymia, cyclothymia, or bipolar NOS as well as subjects with subsyndromal affective disorders or symptoms at intake and bipolar I or bipolar II during follow-up)	Subsyndromal hypomanic symptoms in major depression	5	One study reported that hyperenergetic involvement in activities predicted conversion to BD presenting more hypomanic than manic episodes. However, one-third of those individuals with BD II later developed mania meaning that mood elevation intensifies progressively Another study found that hypomanic symptoms, specifically decreased need for sleep, unusually high energy, increased and goal directed activity, significantly predicted both hypomania and mania. Grandiosity, on the other hand, predicted only mania Another study also found that subsyndromal hypomania with MDD significantly increased the likelihood of conversion to BD. One study reported that subsyndromal hypomanic symptoms significantly predicted conversion to BD I and Bipolar NOS in adults with psychotic MDD. Lastly, conversion rates to BD for children with MDD and/or dysthymia presenting transient manic symptoms were significantly higher compared to the children with only MDD and/or dysthymia
Faedda et al. 2015 (Participants who are diagnosed with MDE, MDD, dysthymia, cyclothymia, or bipolar NOS as well as subjects with subsyndromal affective disorders or symptoms at intake and	Cyclothymic disorder and Bipolar NOS	5	First study found that outpatients diagnosed with cyclothymic disorder later developed BD Second study found that children and adolescents hospitalised with MDD and have high scores on the Cyclothymic-Hypersensitive Temperament Rating Scale significantly predicted conversion to BD. Third study found 16.5% of the youths with hypomania but without a MDD converted to BD II. Fourth study found higher conversion

bipolar I or bipolar II during follow-up)			rates from bipolar NOS to BD I and II. Similarly, fifth study found that individuals with bipolar NOS or cyclothymic disorder, more than half of them developed BD, particularly BD II
Keramatian et al. 2022 (Individuals who are at clinical or genetic risk of developing BD)	Cyclothymic/irritable and hyperthymic temperament	1	The study found that cyclothymic/irritable and hyperthymic temperaments predicted both total cases and new cases of bipolar spectrum disorders at the follow-up.
Keramatian et al. 2022 (Individuals who are at clinical or genetic risk of developing BD)	Bipolar NOS	1	Earlier onset Bipolar NOS predicted conversion to BD.
Faedda et al. 2015 (Participants who are diagnosed with MDE, MDD, dysthymia, cyclothymia, or bipolar NOS as well as subjects with subsyndromal affective disorders or symptoms at intake and bipolar I or bipolar II during follow-up)	Psychotic Symptoms in Major Depression	7	All seven studies identified significant relationships between MDD with psychotic features and later BD both in adolescents and adults
Faedda et al. 2015 (Participants who are diagnosed with MDE, MDD, dysthymia, cyclothymia, or bipolar NOS as well as subjects with subsyndromal affective disorders or symptoms at intake and	Psychotic Disorders	3	Two studies reported that psychosis NOS predicted later BD. Third study found that schizotypal features and schizophrenia nuclear symptoms predicted conversion to BD but lacked specificity

bipolar I or bipolar II during follow-up)			
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Presence of psychotic symptoms	5	Four studies identified a significant association between psychotic symptoms and transition to BD
Faedda et al. 2015 (Participants who are diagnosed with MDE, MDD, dysthymia, cyclothymia, or bipolar NOS as well as subjects with subsyndromal affective disorders or symptoms at intake and bipolar I or bipolar II during follow-up)	Age at onset of Major Depression	4	All four studies reported early onset of depression predicted conversion to BD
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Age of onset of depression	9	Seven studies out of nine found a significant association between lower age of onset of depression and higher rates of transition to BD Another finding was that age at onset of MDD in individuals who did develop BD was 4.8 years earlier than age at onset of MDD in those who did not develop BD
Keramatian et al. 2022 (Individuals who are at clinical or genetic risk of developing BD)	Psychomotor retardation and Mood Disorder Episodes	1	The study found that psychomotor retardation and mood disorder episodes predicted conversion to BD in those at high familial risk.
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and	Severity of depression with baseline MDD	2	Both studies found significant association with severity of depression and onset of BD. One of them also found significant associations for psychomotor retardation and mood congruent

later converted to BD I or II at follow-up)			psychotic features. The other study found that switch from MDD to BD was also predicted by cluster B personality disorder symptoms and OCD
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Guilt with baseline MDD	3	Three studies found guilt coexistent with MDD was associated with transition to BD. One of them also found that converters to BD from MDD were significantly characterised also by diurnal variation and complete loss of pleasure. They did not find differences for hyperphagia, psychomotor alterations and hypersomnia
Keramatian et al. 2022 (Individuals who are at clinical or genetic risk of developing BD)	Mood lability	2	Both studies found that mood lability predicted BD conversion.
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Affective instability with baseline MDD	2	Affective instability with baseline MDD was associated with BD onset in both studies
Faedda et al. 2015 (Participants who are diagnosed with MDE, MDD, dysthymia, cyclothymia, or bipolar NOS as well as subjects with subsyndromal affective disorders or symptoms at intake and bipolar I or bipolar II during follow-up)	Frequency and loading of affective symptoms	2	First study found that the risk of conversion to BD increased with the number of lifetime depressive episodes and with the number of hypomanic symptoms Second study found that longer episodes of depression, greater loading of depressive symptoms, and higher recurrence rates predicted later BD

Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Recurrent MDD	6	Four study found a significant association between MDD and later BD while the other two studies did not
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Chronicity of depression	2	One study found chronicity of depression episode predicted shifts from nonbipolar to bipolar II whereas the other study did not find a significant association
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	'Hypersomnic-retarded' depression	6	Only one study of six studies identified an association between 'hypersomnic-retarded' depression and transition to BD
Keramatian et al. 2022 (Individuals who are at clinical or genetic risk of developing BD)	Sleep difficulties	3	One study found that those in the poor sleep group had almost twice the odds of developing BD as those in the good and variable sleep group. The other study found that frequent waking during the night, insufficient sleep, and time to fall asleep significantly predicted the development of BD. Third study found that childhood sleep disorders significantly predicted 1.6 fold and 1.8 fold increases in risk of mood disorders in offspring of BD.
Pancheri et al. 2019 (Patients with sleep disorder/symptoms who later develop BD)	Sleep disorders	2	First study found that patients with insomnia treated with hypnotic drugs had a higher risk of developing BD compared to those without insomnia and with insomnia not on hypnotics. Second study reported that disturbed sleep at baseline (trouble falling asleep and early morning awakening) significantly increased the risk for the development of BD, even when they adjusted

			age, gender, parental mood disorder and lifetime cannabis or alcohol use
Scott et al. 2021 (Individuals with sleep disturbances who later develop BD, depressive disorders or psychotic disorders)	Sleep Disturbances	11	All eleven studies found that, individuals with a history of any type of sleep disturbance (e.g., decreased need for sleep, insomnia, hypersomnia with fatigue, inadequate sleep, frequent night time awakening, circadian disturbance) had an increased odds of BD
Scott et al. 2022 (Offspring of BD)	Sleep and circadian rhythm disturbances	11	All eleven studies reported that sleep problems were significantly more frequent in offspring of BD compared to controls. Characteristics of the sleep problems were decreased need for sleep, middle insomnia, frequent night-time awakenings, inadequate sleep, and high energy One study found that decreased need for sleep' was associated with transition to BD as did middle insomnia. However, neither hypersomnia nor daytime fatigue showed any association with onset of any mood disorder. Another study found that parental rating of chronotype was predictive of BD onset, but OSBD self-rating of chronotype was not. Another study indicated that high-risk group showed a shift from more internalizing symptoms (including anxiety/worry & somatic complaints) in childhood to more 'manic-like behaviours' (including high energy, reduced need for sleep), excessive and loudness and concentration difficulties in adolescence. During school years (but not in pre-school), periodic symptoms that mainly differentiated offspring of BD-I from controls were: mood (sad), fearfulness, changes in energy levels and sleep and circadian rhythm

			disturbances (either decreased, difficulty falling asleep or early waking: ~23% v. 8%).
Scott et al. 2022 (Stage 2, full-threshold diagnostic criteria for BD-I or BD-II with first onset by about 25 years)	Sleep and circadian rhythm disturbances	9	All studies found that sleep and circadian rhythm disturbances were significantly higher in cohorts with first onset of BD. The predictors were trouble sleeping, low social rhythm regularity, insomnia, daytime dysfunction, hypersomnia, anergia, circadian disturbance, decreased REM sleep, hypersomnia with fatigue, and low regularity.
Keramatian et al. 2022 (Individuals who are at clinical or genetic risk of developing BD)	Antidepressant Use	1	The study found that exposure to antidepressants during follow-up was associated with increased risk of conversion
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Antidepressant Use	4	None of the studies found a significant association between antidepressant use and later BD
Keramatian et al. 2022 (Individuals who are at clinical or genetic risk of developing BD)	Disruptive Behaviour Disorders	1	The study found that disruptive behaviour disorders were associated with subsequent manic, mixed, or hypomanic episodes.

Keramatian et al. 2022 (Individuals who are at clinical or genetic risk of developing BD)	Baseline anxiety disorders and subsyndromal mood disorders	4	The study found that baseline anxiety disorders and depressive disorders NOS were associated with increased risk of conversion during follow-up. ADHD and disruptive disorders were not associated with conversion. Second study also found that anxiety and depression predicted BD. Third study found that childhood anxiety disorders significantly predicted conversion to BD. Fourth study found that anxiety predicted conversion to BD in youth with bipolar NOS.
Keramatian et al. 2022 (Individuals who are at clinical or genetic risk of developing BD)	Temperament	1	The study found that key symptoms to identify children with BD from well children in cohort samples were sensitivity, crying, hyper alertness, anxiety/worry, somatic complaints, bold/intrusive, excessive talk, talk too loudly, easily excited, poor attention, decreased sleep, and impaired role in school.
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Comorbid anxiety disorder as a group	2	One study found comorbid anxiety disorder predicted the onset of manic symptoms whereas the other study did not find significant relationships with comorbid anxiety disorder and later BD
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Comorbid GAD	2	One study found significant associations between GAD and later BD while the other one did not find
Gibbs et al. 2015 (Participants described as experiences mania during the follow-up)	Cannabis Use	3	All three studies found that baseline cannabis use significantly predicted hypo/sub-threshold mania symptoms at follow-up
Keramatian et al. 2022 (Individuals who are at	Drug Use Disorder	1	The study found that drug use disorders predicted (hypo)manic episodes.

clinical or genetic risk of developing BD)			
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Comorbid SUD	4	Two studies found significant associations between substance use disorders and later BD while the other 2 did not find a significant association
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Comorbid SP	2	Both studies found an association between SP and later BD
Brancati et al. 2021 (Individuals with ADHD who later developed BD)	Comorbid ADHD	10	All ten studies showed a significantly greater risk of BD occurrence in ADHD patients versus healthy controls
Ratheesh et al. 2017 (Individuals diagnosed with MDD at intake and later converted to BD I or II at follow-up)	Comorbid ADHD	1	The study found that ADHD was significantly associated with a higher risk for conversion from unipolar to BD. The switches were predicted by presence of parental mood disorder, school behaviour problems, and baseline comorbid conduct disorder

Note. ADHD = Attention Deficit Hyperactivity Disorder; BD = Bipolar Disorder; GAD = Generalised Anxiety Disorder; k = number of prospective studies for each factor; OCD = Obsessive Compulsive Disorder; MDD = Major Depressive Disorder; NOS = Not Otherwise Specified; NR = Not Reported; SMI = Severe Mental Illness; SP = Social Phobia; SUD = Substance Use Disorder

Table S4

Evidence across systematic reviews and meta-analyses of factors for Borderline Personality Disorder outcome

Study (Sample)	Factor Examined	k	Main Findings
Environmental Factors			
Winsper et al. 2016a (Participants nineteen years of age or younger who were diagnosed with BPD or showed BPD symptoms as an outcome)	Heritability of BPD	2	First study found that monozygotic (MZ) correlations were higher than dizygotic (DZ) correlations and heritability co-efficient BPD symptoms ranged from 0.3 to 0.5. The results of the study also indicated that BPD traits decline as individuals mature from adolescence to adulthood and trait BPD is highly influenced by genetic factors and modestly by non-shared environmental factors. Second study also identified that there was a higher correlation of BPD symptoms between MZ than DZ twins and genetic factors accounted for 66% of the variance in BPD symptoms and BPD symptoms measured at twelve years were highly heritable and were preceded by behavioural and affective dysregulation and poor cognitive function
Psychosocial Factors			

Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Low SES	4	All four studies found a prospective association with later BPD symptoms.
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Stressful life events	3	Two studies identified that stressful life events (i.e., various psychosocial stressors) predicted BPD symptoms in adults. Chronic and school stressors in adolescence were also associated with BPD symptoms in adulthood. Only one study did not find a link between stressful life events and a BPD diagnosis at the age of fifteen. However, Stepp et al. (2016) notes this might be due to differences in sampling strategies
Skabeikyte & Barkauskiene 2021 (Adolescents aged ten to eighteen years old who showed BPD features or symptoms or had diagnosis at the follow-up period)	Stressful Life Events	2	One study looking at stressful life events (e.g., suspension from school, death of a parent, changes in peer acceptance) at ages twelve to seventeen did not find significant associations. The other study looking at the link between academic functioning at age eight and later BPD features did not find significant predictive associations
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Family Adversity	4	Two studies found that family adversity during pregnancy and across childhood and adolescence predicted BPD symptoms. Two other studies looking at family disruption and marital conflict did not find significant associations with later BPD outcomes
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical	Maternal Psychopathology	6	All six studies identified a significant association with maternal psychopathology (i.e., internalising and externalising disorders) and offspring BPD

samples who had BPD symptoms, features or diagnosis at follow-up assessment)			
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Maternal BPD symptoms	1	The study reported an indirect effect of maternal BPD symptoms on offspring BPD symptoms via maladaptive parenting (especially an overprotective and rejecting parenting style and high discrepancies in internalising problems) behaviours. The results were consistent for various offspring symptoms which were associated with BPD such as impulsivity and dissociation
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Paternal Substance Abuse	1	The study found that paternal substance use predicted later BPD symptoms in the offspring
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Parenting behaviour/style	12	Seven studies identified significant associations with affective parenting dimensions (i.e., low warmth, rejection, low maternal satisfaction with the child, hostility, harsh punishment/discipline) and higher BPD symptoms. Additionally, one study found reciprocal association between harsh punishment, low warmth and BPD symptoms across adolescence, meaning that low warmth and harsh punishment predicted higher BPD symptoms and in turn BPD symptoms predicted increased parental harsh punishment and low warmth. Only two studies did not find predictive associations with harsh discipline and low affection. One study found that disrupted maternal communication at eighteen months predicted BPD symptoms at age eighteen. Similarly, another study reported predictive

			association with maternal hostility at 42 months and BPD symptoms at age twenty-eight. One other study identified that maternal expressed negative emotion in middle childhood significantly predicted BPD features at age 12. Two other studies looked at the influence of behavioural control dimensions of parenting and only one identified higher levels of maternal inconsistency and over-involvement predicted BPD diagnosis at age 16. The other study did not find significant associations between inconsistent parenting and later BPD symptoms. Lastly, one study found significant associations between poor parenting (i.e., behavioural and affective dimensions) and BPD symptoms in adolescence and adulthood
Skabeikyte & Barkauskiene 2021 (Adolescents aged ten to eighteen years old who showed BPD features or symptoms or had diagnosis at the follow-up period)	Parenting Style	4	First study found that parental low warmth and changes in parental harsh punishment were not predictive of changes in BPD features. Second study also found the non-significant results for parental harsh punishment. Third study looking at maternal support/validation also did not find predictive associations with changes in BPD features. Fourth study found that exposure to intimate partner violence among parents was predictive of slower declines in BPD symptoms throughout adolescence
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Parent-child relationship quality	5	Only two studies identified significant prospective associations between parent-child relationship and later BPD. One study reported that mother-child discord in adolescence predicted BPD symptoms at age thirty. The other study found that family relationship quality predicted BPD symptoms for those with the oxytocin receptor gene variation risk genotype
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical	Family History of Psychiatric Hospitalisation	1	The study identified that history of psychiatric hospitalisation interacted with maltreatment and

samples who had BPD symptoms, features or diagnosis at follow-up assessment)			maternal negative emotion predicted later BPD symptoms
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Maternal Characteristics	3	Three studies looking at maternal ego integration, impulsivity, interpersonal difficulties, and history of serious medical problems were not associated with later BPD
Skabeikyte & Barkauskiene 2021 (Adolescents aged ten to eighteen years old who showed BPD features or symptoms or had diagnosis at the follow-up period)	Maternal Characteristics	2	Both studies found that maternal BPD symptoms and maternal depression were predictive of higher mean BPD levels in the offspring
Skabeikyte & Barkauskiene 2021 (Adolescents aged ten to eighteen years old who showed BPD features or symptoms or had diagnosis at the follow-up period)	Parental Depression Severity	2	Both studies did not find significant association between parental depression severity and changes in BPD symptoms
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or	Childhood Abuse	8	Four studies found significant associations with physical abuse, one study found with verbal abuse, one another study found with emotional abuse and four studies found with sexual abuse and later BPD symptoms. Three studies looked at maltreatment as a composite of types of abuse and neglect and all three of them found

diagnosis at follow-up assessment)			significant associations with BPD outcomes. Two studies did not find a significant association between physical and sexual abuse and BPD outcomes. Additionally, three other studies examining combined indices of maltreatment and other trauma did not report significant findings. One study, on the other hand, found a significant association between cumulative trauma (e.g., family suicide, death of a parent, parent arrest or imprisonment) and later BPD symptoms
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Childhood Neglect	3	All three studies reported significant links between BPD and childhood neglect including neglect in general, early maternal separation, inadequate supervision and poor parental care
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Peer Victimisation	1	The study reported that chronicity and severity of bullying in late childhood was significantly associated with BPD symptoms at age twelve
Skabeikyte & Barkauskiene 2021 (Adolescents aged ten to eighteen years old who showed BPD features or symptoms or had diagnosis at the follow-up period)	Relational Aggression	1	The study found that relational aggression in the context of friendship predicted higher levels of BPD symptoms

Skabeikyte & Barkauskiene 2021 (Adolescents aged ten to eighteen years old who showed BPD features or symptoms or had diagnosis at the follow-up period)	Psychological and Sexual Violence	2	First study found that psychological and sexual violence predicted increases in the average levels of later BPD features. Second study found the same findings for perceived support and antagonism in romantic relationships
Skabeikyte & Barkauskiene 2021 (Adolescents aged ten to eighteen years old who showed BPD features or symptoms or had diagnosis at the follow-up period)	Physical and Verbal Aggression	1	The study found that physical and verbal aggression experienced in romantic relationships did not predict later BPD features
Skabeikyte & Barkauskiene 2021 (Adolescents aged ten to eighteen years old who showed BPD features or symptoms or had diagnosis at the follow-up period)	Relationship quality with the father	1	The study found that relationship quality with the father predicted slower declines in BPD features during adolescence
Skabeikyte & Barkauskiene 2021 (Adolescents aged ten to eighteen years old who showed BPD features or symptoms or had diagnosis at the follow-up period)	Family relations and social support	2	Two studies failed to find significant associations between family relations, social support from friends and family and changes in BPD symptoms

Winsper et al. 2016b (Participants nineteen years of age or under and have a diagnosis of BPD or have BPD features)	Physical Abuse	1	The study found significant associations between physical abuse and later BPD symptoms
Winsper et al. 2016b (Participants nineteen years of age or under and have a diagnosis of BPD or have BPD features)	Parental hostility/ verbal abuse	3	All three studies found that maternal hostility or verbal abuse increased the risk of developing BPD
Winsper et al. 2016b (Participants nineteen years of age or under and have a diagnosis of BPD or have BPD features)	Parental conflict	1	The study found that parental conflict was significantly associated with increased odds of BPD symptoms
Clinical Factors			
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Cognitive Function	4	All four studies identified significant associations with low IQ and BPD symptoms
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Attachment	3	First study found that disorganised/controlling behaviour at age eight predicted BPD symptoms at age nineteen but not attachment disorganisation and security. Second study found the same non-significant results for attachment disorganisation and security in infancy and toddlerhood and later BPD symptoms in adulthood. Third study reported that insecure

			attachment in peer relationships at age sixteen predicted BPD symptoms across adolescence and adulthood
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Negative Affectivity and Impulsivity	11	All eleven studies found significant association between negative affectivity (e.g., affective instability, emotionality, aggressiveness/tantrums), impulsivity (e.g., low self-control, effortful control, low constraint) and BPD symptoms in adolescence
Skabeikyte & Barkauskiene 2021 (Adolescents aged ten to eighteen years old who showed BPD features or symptoms or had diagnosis at the follow-up period)	Temperament Dimensions	1	The study reported that high levels of emotionality, activity and low levels of sociability and shyness in middle childhood were predictive of higher and increases in average levels of BPD features through adolescence
Skabeikyte & Barkauskiene 2021 (Adolescents aged ten to eighteen years old who showed BPD features or symptoms or had diagnosis at the follow-up period)	Negative Affectivity	3	Two study examining the same cohort identified that negative affectivity in early and middle adolescence predicted only higher mean levels of BPD features but change in these features over time. Third study also looking at the same cohort found that the association between higher mean levels of BPD features from middle adolescence and negative affectivity in early adolescence was mediated by decreases in self-control skills
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or	Poor self-control	1	The study found that poor self-control predicted later BPD symptoms via reciprocal effects between poor self-control and parental harsh discipline

diagnosis at follow-up assessment)			
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Experiential Avoidance	1	The study reported that a higher level of experiential avoidance increased BPD features after a year
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Disturbances in self representation	1	The study found predictive association between disturbances in self representation and BPD symptoms at age twenty-eight
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Internalising psychopathology	10	Nine studies out of ten found significant prospective relationships between internalising psychopathology (i.e., suicidality, dissociation, anxiety, depression, psychosis symptoms) and later BPD symptoms
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Externalising psychopathology	14	Twelve studies found significant predictive associations with externalising psychopathology (i.e., substance abuse, ADHD, oppositional defiant disorder, conduct disorder) and later BPD outcomes. Two study did not find prospective associations with externalising disorders and BPD

Skabeikyte & Barkauskiene 2021 (Adolescents aged ten to eighteen years old who showed BPD features or symptoms or had diagnosis at the follow-up period)	Childhood and Adolescence Psychopathology	8	One study found that childhood inattention, oppositional behaviour, depression severity, hyperactivity/impulsivity predicted the new onset of BPD. Another study also found that impulsivity/hyperactivity predicted higher levels of BPD symptoms throughout adolescence. SUD, MDD, anxiety symptoms, ADHD and somatisation were predictive of changes in BPD features during adolescence. Another study reported that individual social and physical aggression in childhood did not predict BPD symptoms change from fourteen to eighteen years of age. Another study found that comorbidity and decreases in depression severity were significantly related to faster declines in mean levels of later BPD symptoms. Last study reported that lower levels of a child's general psychosocial functioning was significantly predictive of BPD diagnosis at follow-up
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Comorbid OCD	1	The study did not detect a significant relationship between OCD and BPD diagnosis
Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Comorbid DSM-IV Axis 1 disorders	2	First study did not find a significant association between DSM-IV Axis I disorders at eight years and later BPD symptoms at age twelve. Second study using the same community sample identified significant associations between any childhood disorder and later BPD symptoms

Stepp, Lazarus, & Byrd 2016 (High-risk, community or clinical samples who had BPD symptoms, features or diagnosis at follow-up assessment)	Infant Characteristics	1	The study found that infant anomalies at birth and overall non-optimal functioning were not significantly associated with BPD symptoms in adulthood
Winsper et al. 2016b (Participants nineteen years of age or under and have a diagnosis of BPD or have BPD features)	Comorbid Depression	6	All six studies found significant associations between comorbid depression and BPD symptoms
Winsper et al. 2016b (Participants nineteen years of age or under and have a diagnosis of BPD or have BPD features)	Comorbid Substance Abuse	1	The study found that BPD traits and substance abuse are correlates rather than causal antecedents of each other and their association might rather be related to behavioural disinhibition
Winsper et al. 2016b (Participants nineteen years of age or under and have a diagnosis of BPD or have BPD features)	Suicidality	2	One study found that suicidal ideation in adolescents who were later diagnosed with BPD was not stable after posthospitalisation whereas the other study identified increased risk of self-harm in participants with borderline personality characteristics
Winsper et al. 2017 (Participants with BPD or have BPD symptoms)	Sleep Disturbances	2	First study reported that chronic nightmare significantly predicted BPD. They also found that the association was significantly mediated by emotional and behavioural problems at 9.5 years of age. Persistent sleep-onset and maintenance problems were not significantly associated with later BPD symptoms. Second study found that chronic sleep disturbances (difficulty initiating sleep, difficulty maintaining sleep, and waking earlier than desired) were significantly associated with later BPD symptoms

Note. ADHD = Attention deficit hyperactivity disorder; BPD = Borderline Personality Disorder; k = number of prospective studies for each factor; MDD = Major Depressive Disorder; OCD = Obsessive compulsive Disorder; SES = Socioeconomic status; SUD = Substance Use Disorder

Table S5. Excluded studies after full-text review with reasons.

Study Name	***Include***	***Exclude***	***Excluding Reason***
Akingbuwa WA, Hammerschlag AR, Jami ES, Allegrini AG, Karhunen V, Sallis H, Ask H, Askeland RB, Baselmans B, Diemer E, Hagenbeek FA. Genetic associations between childhood psychopathology and adult depression and associated traits in 42 998 individuals: a meta-analysis. JAMA psychiatry. 2020 Jul 1;77(7):715-28.		Exclude	Genetic study

Almeida J, Wegbreit E, Cushman G, Weissman A, Kim K, Laird A, Dickstein D. Fronto-Amygdalar Alterations During Emotional Face Processing May Differentiate Children with Bipolar Disorder from those with Major Depressive Disorder: A Functional Neuroimaging Meta-Analysis. In NEUROPSYCHOPHARMACOLOGY 2014 Dec 1 (Vol. 39, pp. S219-S219). MACMILLAN BUILDING, 4 CRINAN ST, LONDON N1 9XW, ENGLAND: NATURE PUBLISHING GROUP.	Exclude	Abstract for a conference poster and was never published in full text form.
Álvarez-Tomás I, Ruiz J, Guilera G, Bados A. Long-term clinical and functional course of borderline personality disorder: A meta-analysis of prospective studies. European Psychiatry. 2019 Feb;56(1):75-83.	Exclude	Intervention Study + clinical populations (full course of disorder)

Benarous X, Consoli A, Milhiet V, Cohen D. Early interventions for youths at high risk for bipolar disorder: a developmental approach. European Child & Adolescent Psychiatry. 2016 Mar;25(3):217-33.	Exclude	Literature Review
Carvalho AF, McIntyre RS, Dimelis D, Gonda X, Berk M, Nunes-Neto PR, Cha DS, Hyphantis TN, Angst J, Fountoulakis KN. Predominant polarity as a course specifier for bipolar disorder: a systematic review. Journal of affective disorders. 2014 Jul 1;163:56-64.	Exclude	Patients are already diagnosed with BD - Diagnosis does not meet inclusion standards

Cerimele JM, Katon WJ. Associations between health risk behaviors and symptoms of schizophrenia and bipolar disorder: a systematic review. General hospital psychiatry. 2013 Jan 1;35(1):16-22.	EXCLUDE	association studies - irrelevant outcome
Coleman JR, Gaspar HA, Bryois J, Byrne EM, Forstner AJ, Holmans PA, de Leeuw CA, Mattheisen M, McQuillin A, Pavlides JM, Pers TH. The genetics of the mood disorder spectrum: genome-wide association analyses of more than 185,000 cases and 439,000 controls. Biological psychiatry. 2020 Jul 15;88(2):169-84.	Exclude	GWAS study + not a systematic review

Craney JL, Geller B. A prepubertal and early adolescent bipolar disorder-I phenotype: review of phenomenology and longitudinal course. Bipolar disorders. 2003 Aug;5(4):243-56.	Exclude	Not a systematic review- a literature review
Daglas R, Yücel M, Cotton S, Allott K, Hetrick S, Berk M. Cognitive impairment in first-episode mania: a systematic review of the evidence in the acute and remission phases of the illness. International journal of bipolar disorders. 2015 Dec;3(1):1-8.	Exclude	No longitudinal studies

Duarte D, Belzeaux R, Etain B, Greenway KT, Rancourt E, Correa H, Turecki G, Richard-Devantoy S. Childhood-maltreatment subtypes in bipolar patients with suicidal behavior: systematic review and meta-analysis. Brazilian Journal of Psychiatry. 2020 Jun 8;42:558-67.	Exclude	Irrelevant study design (not longitudinal) + patients have already been diagnosed
Duffy A. The nature of the association between childhood ADHD and the development of bipolar disorder: a review of prospective high-risk studies. American Journal of Psychiatry. 2012 Dec;169(12):1247-55.	Exclude	Not an SR

Duffy A, Vandeleur C, Heffer N, Preisig M. The clinical trajectory of emerging bipolar disorder among the high-risk offspring of bipolar parents: current understanding and future considerations. International journal of bipolar disorders. 2017 Dec;5(1):1-1.	Exclude	Not an SR
Duko B, Ayano G, Pereira G, Betts K, Alati R. Prenatal tobacco use and the risk of mood disorders in offspring: a systematic review and meta-analysis. Social Psychiatry and Psychiatric Epidemiology. 2020 Dec;55(12):1549-62.	Exclude	Irrelevant outcome - only risk factors, not related to the onset

Elias LR, Miskowiak KW, Vale AM, Köhler CA, Kjærstad HL, Stubbs B, Kessing LV, Vieta E, Maes M, Goldstein BI, Carvalho AF. Cognitive impairment in euthymic pediatric bipolar disorder: a systematic review and meta-analysis. Journal of the American Academy of Child & Adolescent Psychiatry. 2017 Apr 1;56(4):286-96.	Exclude	Patients are already diagnosed, treated with medications
Estrada-Prat X, Van Meter AR, Camprodon-Rosanas E, Batlle-Vila S, Goldstein BI, Birmaher B. Childhood factors associated with increased risk for mood episode recurrences in bipolar disorder—A systematic review. Bipolar disorders. 2019 Sep;21(6):483-502.	Exclude	Patients are already diagnosed - full blown bipolar and mood recurrences - irrelevant outcome

de Aquino Ferreira LF, Pereira FH, Benevides AM, Melo MC. Borderline personality disorder and sexual abuse: a systematic review. Psychiatry research. 2018 Apr 1;262:70-7.	Exclude	Irrelevant outcome - only risk factors, not related to the onset
Fornaro M, Daray FM, Hunter F, Anastasia A, Stubbs B, De Berardis D, Shin JI, Husain MI, Dragioti E, Fusar-Poli P, Solmi M. The prevalence, odds and predictors of lifespan comorbid eating disorder among people with a primary diagnosis of bipolar disorders, and vice-versa: systematic review and meta-analysis. Journal of affective disorders. 2021 Feb 1;280:409-31.	Exclude	No precursors/factors or signs mentioned

Foxhall M, Hamilton-Giachritsis C, Button K. The link between rejection sensitivity and borderline personality disorder: A systematic review and meta-analysis. British Journal of Clinical Psychology. 2019 Sep;58(3):289-326.	Exclude	Not a longitudinal design -Cross-sectional or case-control design
Fraguas D, Díaz-Caneja CM, Pina-Camacho L, Janssen J, Arango C. Progressive brain changes in children and adolescents with early-onset psychosis: A meta-analysis of longitudinal MRI studies. Schizophrenia research. 2016 Jun 1;173(3):132-9.	Exclude	only one relevant study Arango but Patients are already diagnosed - full blown bipolar

Frías Á, Palma C, Farriols N. Comorbidity in pediatric bipolar disorder: prevalence, clinical impact, etiology and treatment. Journal of affective disorders. 2015 Mar 15;174:378-89.	Exclude	Not a systematic review
Frías Á, Palma C, Farriols N. Neurocognitive impairments among youth with pediatric bipolar disorder: a systematic review of neuropsychological research. Journal of affective disorders. 2014 Sep 1;166:297-306.	Exclude	One longitudinal study (pavuluri) but patients are on medication and have full-blown BD
Frías Á, Palma C, Farriols N, González L. Sexuality-related issues in borderline personality disorder: A comprehensive review. Personality and mental health. 2016 Aug;10(3):216-31.	Exclude	No longitudinal design -Cross-sectional or case-control design + patients are already diagnosed with BPD

Friborg O, Martinsen EW, Martinussen M, Kaiser S, Øvergård KT, Rosenvinge JH. Comorbidity of personality disorders in mood disorders: a meta-analytic review of 122 studies from 1988 to 2010. Journal of affective disorders. 2014 Jan 1;152:1-1.	Exclude	Prevalance study
Geller B, Luby J. Child and adolescent bipolar disorder: a review of the past 10 years. Journal of the American Academy of Child & Adolescent Psychiatry. 1997 Sep 1;36(9):1168-76.	Exclude	Not a systematic review- a literature review and no missed studies

Hartmann JA, Nelson B, Ratheesh A, Treen D, McGorry PD. At-risk studies and clinical antecedents of psychosis, bipolar disorder and depression: a scoping review in the context of clinical staging. Psychological medicine. 2019 Jan;49(2):177-89.	Exclude	Not an SR
Ibrahim J, Cosgrave N, Woolgar M. Childhood maltreatment and its link to borderline personality disorder features in children: A systematic review approach. Clinical child psychology and psychiatry. 2018 Jan;23(1):57-76.	Exclude	Duplicated data in another study

Laurens KR, Luo L, Matheson SL, Carr VJ, Raudino A, Harris F, Green MJ. Common or distinct pathways to psychosis? A systematic review of evidence from prospective studies for developmental risk factors and antecedents of the schizophrenia spectrum disorders and affective psychoses. BMC psychiatry. 2015 Dec;15(1):1-20.	Exclude	Sample analysed as pooled affective disorders
Marangoni C, Hernandez M, Faedda GL. The role of environmental exposures as risk factors for bipolar disorder: a systematic review of longitudinal studies. Journal of affective disorders. 2016 Mar 15;193:165-74.	Exclude	Irrelevant outcome - only risk factors, not related to the onset

McKay MT, Cannon M, Chambers D, Conroy RM, Coughlan H, Dodd P, Healy C, O'Donnell L, Clarke MC. Childhood trauma and adult mental disorder: A systematic review and meta-analysis of longitudinal cohort studies. Acta Psychiatrica Scandinavica. 2021 Mar;143(3):189-205.	Exclude	No longitudinal studies with BD outcome
Parellada M, Gomez-Vallejo S, Burdeus M, Arango C. Developmental differences between schizophrenia and bipolar disorder. Schizophrenia Bulletin. 2017 Oct 21;43(6):1176-89.	Exclude	Not an SR
Pompili M, Girardi P, Ruberto A, Tatarelli R. Suicide in borderline personality disorder: a meta-analysis. Nordic journal of psychiatry. 2005 Jan 1;59(5):319-24.	Exclude	Different outcome + prevalence study

Porter C, Palmier-Claus J, Branitsky A, Mansell W, Warwick H, Varese F. Childhood adversity and borderline personality disorder: a meta-analysis. Acta Psychiatrica Scandinavica. 2020 Jan;141(1):6-20.	Exclude	Patients are already diagnosed with BPD
Rodriguez V, Alameda L, Trotta G, Spinazzola E, Marino P, Matheson SL, Laurens KR, Murray RM, Vassos E. Environmental risk factors in bipolar disorder and psychotic depression: a systematic review and meta-analysis of prospective studies. Schizophrenia bulletin. 2021 Jul;47(4):959-74.	Exclude	Irrelevant outcome - only risk factors, not related to the onset
Salagre E, Vizuete AF, Leite M, Brownstein DJ, McGuinness A, Jacka F, Dodd S, Stubbs B, Köhler CA, Vieta E, Carvalho AF. Homocysteine as a peripheral biomarker in bipolar disorder: a meta-analysis. European Psychiatry. 2017 Jun;43:81-91.	Exclude	Medications + doesnt say anything about the designs of the study, already diagnosed

Scott J, Murray G, Henry C, Morken G, Scott E, Angst J, Merikangas KR, Hickie IB. Activation in bipolar disorders: a systematic review. JAMA psychiatry. 2017 Feb 1;74(2):189-96.	Exclude	No longitudinal studies with emerging BD symptoms
Serafini G, Pompili M, Borgwardt S, Houenou J, Geoffroy PA, Jardri R, Girardi P, Amore M. Brain changes in early-onset bipolar and unipolar depressive disorders: a systematic review in children and adolescents. European child & adolescent psychiatry. 2014 Nov;23(11):1023-41.	Exclude	No longitudinal studies
Steele KR, Townsend ML, Grenyer BF. Parenting and personality disorder: An overview and meta-synthesis of systematic reviews. PloS one. 2019 Oct 1;14(10):e0223038.	Exclude	Not an SR- A review of reviews

Van Meter AR, Burke C, Kowatch RA, Findling RL, Youngstrom EA. Ten-year updated meta-analysis of the clinical characteristics of pediatric mania and hypomania. Bipolar disorders. 2016 Feb;18(1):19-32.	Exclude	No precursors/factors or signs mentioned
Van Meter AR, Burke C, Youngstrom EA, Faedda GL, Correll CU. The bipolar prodrome: meta-analysis of symptom prevalence prior to initial or recurrent mood episodes. Journal of the American Academy of Child & Adolescent Psychiatry. 2016 Jul 1;55(7):543-55.	Exclude	Pancheri has egeland 2012 so no need to analyse this paper
Wegbreit E, Cushman GK, Puzia ME, Weissman AB, Kim KL, Laird AR, Dickstein DP. Developmental meta-analyses of the functional neural correlates of bipolar disorder. JAMA psychiatry. 2014 Aug 1;71(8):926-35.	Exclude	no longitudinal studies

Winsper C, Marwaha S, Lereya ST, Thompson A, Eyden J, Singh SP. Clinical and psychosocial outcomes of borderline personality disorder in childhood and adolescence: a systematic review. Psychological medicine. 2015 Aug;45(11):2237-51.	Exclude	Irrelevant outcome - outcomes after receiving a diagnosis like changing schools, partner conflict etc or like early adolescent bor- derline symptoms predicted lower life satisfaction across two decades
Yapıcı Eser H, Taşkıran AS, Ertınmaz B, Mutluer T, Kılıç Ö, Özcan Morey A, Necef I, Yalçınay İnan M, Öngür D. Anxiety disorders comorbidity in pediatric bipolar disorder: a meta-analysis and meta-regression study. Acta Psychiatrica Scandinavica. 2020 Apr;141(4):327-39.	Exclude	Prevalence study

HAND SEARCHED STUDIES

Boucher MÈ, Pugliese J, Allard-Chapais C, Lecours S, Ahoundova L, Chouinard R, Gaham S. Parent–child relationship associated with the development of borderline personality disorder: a systematic review. Personality and mental health. 2017 Nov;11(4):229-55.	Exclude	Duplicated data in another publication -One relevant longitudinal study but Stepp already has that one
Keinänen MT, Johnson JG, Richards ES, Courtney EA. A systematic review of the evidence-based psychosocial risk factors for understanding of borderline personality disorder. Psychoanalytic Psychotherapy. 2012 Mar 1;26(1):65-91.	Exclude	Irrelevant outcome - only risk factors, not related to the onset
Kessing LV, Willer I, Andersen PK, Bukh JD. Rate and predictors of conversion from unipolar to bipolar disorder: A systematic review and meta-analysis. Bipolar Disorders. 2017 Aug;19(5):324-35.	Exclude	Duplicated data
Stead VE, Boylan K, Schmidt LA. Longitudinal associations between non-suicidal self-injury and borderline personality disorder in adolescents: a literature review. Borderline personality disorder and emotion dysregulation. 2019 Dec;6(1):1-2.	Exclude	Not an SR - literature review

Fusar-Poli P, Howes O, Bechdolf A, Borgwardt S. Mapping vulnerability to bipolar disorder: a systematic review and meta-analysis of neuroimaging studies. Journal of Psychiatry and Neuroscience. 2012 May 1;37(3):170-84.	Exclude	No longitudinal studies
Wu MK, Wang HY, Chen YW, Lin PY, Wu CK, Tseng PT. Significantly higher prevalence rate of asthma and bipolar disorder co-morbidity: a meta-analysis and review under PRISMA guidelines. Medicine. 2016 Mar;95(13).	Exclude	Prevalence rates
Scott J, McNeill Y, Cavanagh J, Cannon M, Murray R. Exposure to obstetric complications and subsequent development of bipolar disorder: systematic review. The British Journal of Psychiatry. 2006 Jul;189(1):3-11.	Exclude	Irrelevant outcome - only risk factors, not related to the onset
Tsuchiya KJ, Byrne M, Mortensen PB. Risk factors in relation to an emergence of bipolar disorder: a systematic review. Bipolar disorders. 2003 Aug;5(4):231-42.	Exclude	Irrelevant outcome - only risk factors, not related to the onset

Amad A, Ramoz N, Thomas P, Jardri R, Gorwood P. Genetics of borderline personality disorder: systematic review and proposal of an integrative model. Neuroscience & Biobehavioral Reviews. 2014 Mar 1;40:6-19.	Exclude	no longitudinal studies
Menculini G, Balducci PM, Attademo L, Bernardini F, Moretti P, Tortorella A. Environmental Risk Factors for Bipolar Disorders and High-Risk States in Adolescence: A Systematic Review. Medicina. 2020 Dec;56(12):689.	Exclude	Irrelevant outcome - only risk factors, not related to the onset
Skjelstad DV, Malt UF, Holte A. Symptoms and signs of the initial prodrome of bipolar disorder: a systematic review. Journal of affective disorders. 2010 Oct 1;126(1-2):1-3.	Exclude because van meter has already have egeland	Duplicated data
Yu H, Meng YJ, Li XJ, Zhang C, Liang S, Li ML, Li Z, Guo W, Wang Q, Deng W, Ma X. Common and distinct patterns of grey matter alterations in borderline personality disorder and bipolar disorder: voxel-based meta-analysis. The British Journal of Psychiatry. 2019 Jul;215(1):395-403.	Exclude	No longitudinal studies

Misiak B, Stramecki F, Gawęda Ł, Prochwicz K, Sąsiadek MM, Moustafa AA, Frydecka D. Interactions between variation in candidate genes and environmental factors in the etiology of schizophrenia and bipolar disorder: a systematic review. Molecular neurobiology. 2018 Jun;55(6):5075-100.	Exclude	No longitudinal studies
Dezhina Z, Ranlund S, Kyriakopoulos M, Williams SC, Dima D. A systematic review of associations between functional MRI activity and polygenic risk for schizophrenia and bipolar disorder. Brain imaging and behavior. 2019 Jun;13(3):862-77.	Exclude	No longitudinal studies
Bora E, Özerdem A. A meta-analysis of neurocognition in youth with familial high risk for bipolar disorder. European Psychiatry. 2017 Jul;44:17-23.	Exclude	No longitudinal studies
Mitchell AE, Dickens GL, Picchioni MM. Facial emotion processing in borderline personality disorder: a systematic review and meta-analysis. Neuropsychology review. 2014 Jun;24(2):166-84.	Exclude	No longitudinal studies

Howes OD, Lim S, Theologos G, Yung AR, Goodwin GM, McGuire P. A comprehensive review and model of putative prodromal features of bipolar affective disorder. Psychological medicine. 2011 Aug;41(8):1567-77.	Exclude	Not an SR
Luby JL, Navsaria N. Pediatric bipolar disorder: evidence for prodromal states and early markers. Journal of Child Psychology and Psychiatry. 2010 Apr;51(4):459-71.	Exclude	Not an SR
Szmulewicz A, Valerio MP, Martino DJ. Longitudinal analysis of cognitive performances in recent-onset and late-life Bipolar Disorder: A systematic review and meta-analysis. Bipolar disorders. 2020 Feb;22(1):28-37.	Exclude	No predictors - Stability of cognitive performances

Hanford LC, Nazarov A, Hall GB, Sassi RB. Cortical thickness in bipolar disorder: a systematic review. Bipolar disorders. 2016 Feb;18(1):4-18.	Exclude	Participants receive medication and Janssen: participants with bipolar disorder with psychotic symptoms - early onset of psychosis not early onset of bipolar
Díaz-Caneja CM, Pina-Camacho L, Rodríguez-Quiroga A, Fraguas D, Parellada M, Arango C. Predictors of outcome in early-onset psychosis: a systematic review. npj Schizophrenia. 2015 Mar 4;1(1):1-0.	Exclude	Irrelevant outcome
Trotta A, Murray RM, MacCabe JH. Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? A systematic review and meta-analysis. Psychological medicine. 2015 Jan;45(2):381-94.	Exclude	Parelleda has included all the prospective studies Trotta included

Wilde A, Chan HN, Rahman B, Meiser B, Mitchell PB, Schofield PR, Green MJ. A meta-analysis of the risk of major affective disorder in relatives of individuals affected by major depressive disorder or bipolar disorder. Journal of affective disorders. 2014 Apr 1;158:37-47.	Exclude	No relevant longitudinal study- Lau has Hammen and birmaher is not longitudinal and pilowsky is only about MDD
Rodriguez V, Alameda L, Trotta G, Spinazzola E, Marino P, Matheson SL, Laurens KR, Murray RM, Vassos E. Environmental risk factors in bipolar disorder and psychotic depression: a systematic review and meta-analysis of prospective studies. Schizophrenia bulletin. 2021 Jul;47(4):959-74.	Exclude	Irrelevant outcome - only risk factors, not related to the onset

Table S6. Methodological quality of included systematic reviews and meta-analyses based on AMSTAR tool for Bipolar Disorder

Reference	AMSTAR question											TOTAL
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Bart et al. (2021)	0	0	1	0	0	1	0	0	0	0	1	**3**
Brancati et al. (2021)	1	1	1	0	0	1	0	0	1	0	1	**6**
Cardoso et al. (2018)	0	1	1	1	0	1	0	0	0	0	0	**4**
Cahn et al. (2021)	1	1	1	0	0	1	1	0	0	0	1	**6**
Faedda et al. (2013)	0	0	1	1	0	1	0	0	0	0	0	**3**
Gibbs et al. (2015)	0	1	1	1	0	1	1	1	1	1	1	**9**
Hu et al. (2020)	0	1	1	0	0	1	1	0	1	1	1	**7**
Keramatian et al. (2022)	0	1	0	1	0	1	0	0	0	0	1	**4**
Lau et al. (2018)	0	1	1	1	0	1	1	1	1	0	1	**8**
Narayan et al. (2013)	0	0	1	0	0	1	0	0	0	0	0	**2**
Palmier-Claus et al. (2016)	1	1	1	1	0	1	1	1	0	1	1	**9**
Pancheri et al. (2019)	0	1	1	1	0	1	1	1	0	0	0	**6**
Rasic et al. (2014)	0	1	1	0	0	1	0	0	1	1	1	**6**
Ratheesh et al. (2011)	0	1	1	1	0	1	1	1	1	1	1	**9**
Ritter et al. (2011)	0	0	1	0	0	1	0	0	0	0	0	**2**

Scott et al. (2021)	1	1	1	1	1	1	1	1	1	1	1	**11**
Scott et al. (2022)	1	1	1	1	1	1	1	1	1	0	1	**10**

Table S7. Methodological quality of included systematic reviews and meta-analyses based on AMSTAR tool for Borderline Personality Disorder

Reference	**AMSTAR question**											**TOTAL**
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Skabeikyte & Barkauskiene (2021)	1	1	1	1	0	1	1	1	0	0	1	**9**
Stepp et al. (2016)	1	1	1	1	0	1	0	0	0	0	0	**5**
Winsper et al. (2016a)	1	1	1	1	0	1	1	1	1	1	1	**10**
Winsper et al. (2016b)	1	1	1	1	0	1	1	1	0	0	1	**8**
Winsper et al. (2017)	1	1	1	1	0	1	1	1	1	1	1	**10**

Table S8. Citation Matrix for Systematic Reviews and Meta-Analyses on Bipolar Disorder onset. Systematic reviews are represented in columns and primary studies in rows. (+) indicates longitudinal primary studies contained in a systematic review and (-) studies not included in a systematic review.

			Systematic Reviews															**Total number of reviews (/11)**
Primary Study	Bart et al. (2021)	Brancati et al. (2021)	Cahn et al. (2021)	Cardoso et al. (2018)	Faedda et al. (2013)	Gibbs et al. (2015)	Hu et al. (2020)	Keramatian et al. (2022)	Lau et al. (2018)	Narayan et al. (2013)	Palmier-Claus et al. (2016)	Pancheri et al. (2019)	Rasic et al. (2014)	Rathesh et al. (2007)	Ritter et al. (2011)	Scott et al. (2021)	Scott et al. (2022)	
Acuff et al. (2019)	+																	1
Alloy et al. (2012)					+													1

Alloy et al. (2015)																+	1
Akiskal et al. (1977)					+												1
Akiskal et al. (1978)					+												1
Akiskal et al. (1983)					+								+				2
Akiskal et al. (1985)								+									1
Akiskal et al. (1995)					+								+				2
Anderson & Ham									+								1

men (1993)																	
Angst et al. (2003)					+												1
Angst et al. (2005)													+				1
Arnold et al. 2020		+															1
Axelson et al. (2011)					+												1
Axelson et al. (2015)		+						+									2
Bauwens et al. (1998)													+				1

Bechdolf et al. (2014)								+										1
Beesdo et al. (2009)					+									+				2
Benvenuti et al. (2008)														+				1
Bertocci et al. (2019)	+																	1
Biederman et al. (1996)		+																1
Biedermann et al. (2008)		+																1

Biederman et al. (2009)														+				1
Biederman et al. (2014)														+				1
Birmaher et al. (2018)								+										1
Birmaher et al. (2021)								+										1
Bitter et al. (2011)			+															
Boschloo et al. (2014)														+				1
Bukh et al.				+														1

(2016a)																	
Bukh et al. (2016b)													+				1
Bromet et al. (2011)					+												1
Cassano et al. (2004)													+				1
Castro-Fornieles et al. (2011)					+												1
Chung et al. (2015)												+					1
Coryell et al. (1987)													+				1

Coryell et al. (1995)														+				1
Curry et al. (2011)														+				1
DeGeorge et al. (2014)								+										1
DelBello et al. (2003)					+									+				2
Doucette et al. (2013)																	+	1
Duffy et al. (2007)		+								+					+			3
Duffy et al.													+					1

(2009)																	
Duffy et al. (2010)														+			1
Duffy et al. (2012)						+											1
Duffy et al. (2014)									+			+				+	3
Duffy et al. (2019)								+							+	+	3
Dunn et al. (2006)													+				1
Egeland et al. (2003)														+		+	2
Egeland et								+				+			+	+	4

al. (2012)																	
Fiedorowicz et al. (2011)					+									+				2
Fiedorowicz et al. (2012)														+		+		2
Findling et al. (2013)								+										1
Frankland et al. (2018)								+										1
Furukawa et al. (2000)														+				1
Furukawa et al.														+				1

(2009)																	
Fusar Poli et al. (2018)								+									1
Ganzola et al. (2017)							+										1
Gan et al. (2011)														+			1
Garber et al. (1988)														+			1
Geller et al. (1994)														+			1
Geller et al. (2001)														+			1
Gilman et														+			1

al. (2012)																	
Gilman et al. (2014)											+						1
Gogtay et al. (2007)					+												1
Goldberg et al. (1995)													+				1
Goldberg et al. (2001)													+				1
Hafeman et al. (2016)																+	1
Hafeman et al. (2017)								+									1

Hammen et al. (1990)									+									1
Halperin et al. 2011		+																1
Henquet et al. (2006)						+												1
Hillegers et al. (2005)								+					+		+			3
Holma et al. (2008)														+				1
Homish et al. (2013)					+													1
Iorfino et al																+	+	2

(2019)																	
Johnson et al. (1991)													+				1
Johnson et al. (2011)													+				1
Judd et al. (2013)													+				1
Kane et al. (1982)													+				1
Kaymaz et al. (2007)					+												1
Klein et al. (2021)		+															1
Klimnes-Dougan et										+							1

al. (2010)																		
Klimnes-Dougan (2013)										+								1
Kovacs et al. (1994)														+				1
Kochman et al. (2005)					+													1
Kuehner et al. (2012)														+				1
Kwapil et al. (2000)					+													1
Laroche et al.													+					1

(1987)																	
Levenson (2015)								+								+	+	3
Levenson et al. (2017)								+				+					+	3
Li et al. (2014)														+				1
Maj et al. (2007)														+				1
McCauley et al. (1993)														+				1
Melvin et al. (2013)														+				1
Mesman et al.								+										1

(2013)																	
Mesman et al. (2017)												+				+	+	3
Nadkarni et al. (2010)					+													1
Nery et al. (2020)								+										1
Nurnberger et al. (2011)									+									1
Opjordsmoen et al. (1989)														+				1
Papachristou et al.																	+	1

(2012)																	
Papachristou et al. (2017)								+									1
Paaren et al. (2014)														+			1
Pfenning et al. (2016)				+										+		+	4
Perich et al. (2015)									+								1
Prien et al. (1984)														+			1
Preisig et al. (2016)								+									1

Radke-Yarrow et al. (1992)									+									1
Ratheesh et al. (2015)				+				+										2
Rao et al. (1995)														+				1
Rao (2002)																+	+	2
Reichart et al. (2005)								+							+			2
Regeer et al. (2006)					+													1
Riihimaki et al.														+				1

(2011)																	
Ritter et al. (2015)												+				+	+	3
Rössler et al. (2011)					+													1
Rudaz et al. (2020)		+																1
Rudaz et al. (2021)								+										1
Ruggero et al. (2011)														+				1
Salvatore et al. (2009)					+													1
Salvatore					+									+				2

et al. (2013)																	
Scott et al. (2017)															+	+	2
Scott et al. (2020)															+	+	2
Schwartz et al. (2000)														+			1
Sharma et al. (2014)														+			1
Shaw et al. 2005															+		+	2
Shen et al. (2008)																+	1
Solomon et al. (1997)														+			1

Shur-Fen Gau et al. (2010)		+															1
Stoleru et al. (1997)																+	1
Strober et al. (1982)														+			1
Strober et al. (1993)					+									+			2
Tillman & Geller 2006		+															1
Tjissen et al. (2010a)					+												1
Tijssen et						+											1

al. (2010b)																	
Tohen et al. (2012)					+									+			2
Tondo et al. (2014)														+			1
Van Meter et al. (2021)								+									1
Weintraub (1987)										+							1
Weismann et al. (1999a)														+			1
Weismann et al. (1999b)														+			1

Winokur et al. (1973)													+				1
Winokur et al. (1987)													+				1
Zahn-Waxler et al. (1988)									+								1
Zimmerman et al. (2009)					+												1

Table S9.
Citation Matrix for Systematic Reviews and Meta-Analyses on Borderline Personality Disorder onset. Systematic reviews are represented in columns and primary studies in rows. (+) indicates longitudinal primary studies contained in a systematic review and (-) studies not included in a systematic review.

	Systematic Reviews	

Primary Study	Boucher et al. (2007)	Skabeikyte & Barkauskiene (2021)	Stepp et al. (2016)	Winsper et al. (2016a)	Winsper et al. (2016b)	Winsper et al. (2017)	**Total number of reviews (/6)**
Arens, Grabe, Spitzer, & Barnow (2011)	+						1
Barnow et al. (2013)		+	+				2
Belsky et al. (2012)			+	+	+		3
Bezirganian et al. (1993)	+		+				2
Bornolova (2009)				+			1
Bornolova et al. (2013)a			+		+		2
Bornolova et al. (2013b)			+				1
Bornolova et al. (2018)		+					1
Burke & Stepp (2012)			+				1
Carlson, Egeland, & Sroufe (2009)			+				1
Cohen et al. (2008)			+				1
Conway, Hammen, & Brennan (2015)			+				1
Crawford et al. (2009)			+				1

Crick et al. (2005)					+		1
Dixon-Gordon et al. (2016)		+					1
Ehrenreich, Beron, & Underwood (2016)		+					1
Greenfield et al. (2015)		+	+		+		3
Hallquist, Hipwell, & Stepp (2015)		+	+				2
Haltigan & Vaillancourt (2016)		+					1
Hammen, Bower, & Cole (2015)			+				1
Johnson et al. (2006)			+				1
Johnson et al. (1999)			+				1
Johnson et al. (2000)			+				1
Jovey et al. (2013)			+				1
Krabbendam et al. (2015)			+				1
Lazarus et al. (2019)		+					1

Lenzenweger & Desantis Castro (2005)			+				1
Lereya et al. (2016)						+	1
Lyons-Ruth et al. (2013)			+				1
Miller et al. (2008)			+				1
Meijer et al. (1988)					+		1
Ramklint et al. (2003)			+				1
Reinelt et al. (2014)			+				1
Rey et al. (1995)			+				1
Selby et al. (2013)						+	1
Selby & Yen/Yen et al. (2014)					+		1
Sharp et al. (2014)					+		1
Sharp et al. (2015)			+				1
Sharp et al. (2020)		+					1
Stepp, Burke, Hipwell, & Loeber (2012)			+				1
Stepp et al. (2013)			+				1

Stepp, Keenan, Hipwell, & Krueger (2014a)		+	+				2
Stepp et al. (2014b)		+	+				2
Stepp et al. (2015)			+				1
Stepp & Lazarus (2017)		+					1
Strandholm et al. (2017)		+					1
Thatcher, Cornelius, & Clark (2005)			+				1
Thomsen & Mikkelsen (1993)			+				1
Tragesser et al. (2010)			+				1
Tragesser, Solhan, Schwartz-Mette, Trull (2007)			+				1
Vaillancourt et al. (2014)					+		1
Vanwoerden, Leavitt, Gallagher & Temple (2019)		+					1
Widom, Czaja, & Paris (2009)			+				1

Winsper et al. (2012)			+		+		2
Winsper, Wolke, & Lereya (2015)			+				1
Wolke, Schreier, Zanarini & Winsper (2012)			+				1

	Faedda et al. (2013)	
Rathees h et al. (2007)	~ 0.11%	Ratheesh et al. (2007)

Ritter et al. (2011)	0%	0%	Ritter et al. (2011)		
Rasic et al. (2014)	0%	0%	0.13 %	Rasic et al. (2014)	
Narayan et al. (2013)	0%	0%	0.11 %	0%	Narayan et al. (2013)

Pancheri et al. (2019)	0%	0%	0%	0%	0%	Pancheri et al. (2019)		
Lau et al. (2018)	0%	0%	0%	0%	0%	0.08 %	Lau et al. (2018)	
Faedda et al. (2013)	0%	~0.11%	0%	0%	0%	0%	0%	Faedda et al. (2013)

Palmier-Claus et al. (2016)	0%	0%	0%	0%	0%	0%	0%	0%	Palmier-Claus et al. (2016)								
Gibbs et al. (2015)	0%	0%	0%	0%	0%	0%	0%	0%	0%	Gibbs et al. (2015)							
Hu et al. (2020)	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	Hu et al. (2020)						

Cardoso et al. (2018)	0%	~0.02%	0%	0%	0%	0%	0%	0%	0%	0%	0%	Cardoso et al. (2018)					
Cahn et al. (2021)	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	Cahn et al. (2012)				
Brancati et al. (2021)	0%	0%	0.07%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	Brancati et al. (2021)			
Scott et al. (2021)	0%	~0.03%	0%	0%	0.2%	~0.21%	0%	0%	0%	0%	0%	0%	0%	0%	Scott et al. (2021)		

Scott et al. (2022)	0%	~0.03%	~0.08%	0%	0%	~0.24%	~0.04%	0%	0%	0%	0%	0%	0%	0%	~0.48%	Scott et al. (2022)		
Keramatian et al. (2022)	0%	0%	~0.04%	~0.04%	0%	~0.04%	0%	0%	0%	0%	0%	0.04%	0%	0.3%	~0.10%	0.10%	Keramatian et al. (2022	
Bart et al. (2022)	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	Bart et al. (2022)

Fig 1. Pairwise CCA for reviwes on Bipolar Disorder onset/symtpoms/prodrome. Colors indicate degree of overlap, as calculated with CCA. White = ≤5%, green 5.1–9.9% , yellow 10–14.9%

	Skabeikyte & Barkauskiene (2021)

Stepp et al. (2016)	0.10%	Stepp et al. (2016)				
Winsper et al. (2016a)	0%	0.02%	Winsper et al. (2016a)			
Winsper et al. (2016b)	0.04%	~%0.09	0.09%	Winsper et al. (2016b)		
Skabeikyte & Barkauskiene (2021)	0%	0.10%	0%	0.04%	Skabeikyte & Barkauskiene (2021)	
Winsper et al. (2017)	0%	0%	0%	0%	0%	Winsper et al. (2017)

Fig 1. Pairwise CCA for reviwes on Borderline Personality Disorder onset/symtpoms/prodrome. Colors indicate degree of overlap, as calculated with CCA. White = ≤5%, green 5.1–9.9% , yellow 10–14.9%

Appendix B. Chapter 4 Supplement

ADHD symptom trajectories across childhood and early adolescence and risk for hypomanic symptoms in young adulthood

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Supplementary Online Content

Methods. Additional Information on Study Population, Measures, and Analyses

Table 1. The DAWBA ADHD Items

Table 2. DAWBA ADHD item prevalence in the cohort

Table 3. HCL-32 item prevalence in the cohort

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Table 5. Associations of Latent Classes of ADHD and Risk of Hypomanic Symptoms with Reduced Items

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Figure 1. Attrition of participants from the ALSPAC cohort

Figure 2. Four Class Model Inattentiveness

Figure 3. Four Class Model Hyperactivity Model

References

Supplementary

Methods. Additional information on study population, measures, and analyses

Study Population

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a UK birth cohort study examining the determinants of development, health, and disease during childhood and beyond. ALSPAC recruited pregnant mothers in Avon whose anticipated delivery dates fell between April 1, 1991, and December 31, 1992. Initially, 14,541 pregnant women were enrolled in the study, and by July 19, 1999, they had either completed at least one questionnaire or attended a 'Children in Focus' clinic. Of these initial 14,541 pregnancies, there was a total of 14,676 foetuses. Among these, 14,477 were singletons, 195 were twins, 3 were triplets, and 1 was a quadruplet. There were 14,062 live births, and at the age of 1 year, 13,988 children were still alive. When the oldest children reached around 7 years old, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. Consequently, for variables collected from the age of 7 onwards, data is available for 14,701 children, representing an additional 713 children. Starting from the initial trimester of pregnancy, parents filled out postal questionnaires regarding the health and development of the study child. Additionally, the child participated in yearly assessment clinics, involving in-person interviews as well as psychological and physical evaluations. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Bristol (Harris et al., 2009a) REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. Data sources include self-report questionnaires, biological samples, clinical assessments and birth, medical, and educational records. The study website contains details of all the data available in a fully searchable format (http://www.bris.ac.uk/alspac/researchers /data-access/data-dictionary/).

Measures

Further details of the DAWBA:
The DAWBA is a package of interviews, questionnaires and rating techniques designed to generate ICD-10 and DSM-IV or DSM-5 psychiatric diagnoses on 2-17 years old. A briefer questionnaire is administered to teacher. The interviews and questionnaires involve a mixture of closed questions such as "Does he ever worry?" and open-ended questions such as "Please describe in your own words what it is that he worries about?" and can either be administered by trained lay interviewers or else self-completed online. With the computer-administered interviews, the respondent types the open-ended answers into the text boxes. With the interviewer-administered interviews, it is the interviewer who transcribes the answers. The full DAWBA package covers the following diagnoses: Separation anxiety, Specific phobia, Social phobia, Panic disorder/agoraphobia, Post-traumatic stress disorder, Obsessive compulsive disorder, Generalized anxiety disorder, Body dysmorphic disorder, Disruptive mood dysregulation disorder, Major depression, ADHD/hyperkinesis, Oppositional defiant disorder,

Conduct disorder, Eating disorders, including anorexia, bulimia and binge eating, Autism spectrum disorders, Tic disorders, including Tourette syndrome, and Bipolar Disorders. For each of these disorders, the interview asks about all the symptoms, and other criteria needed for an operationalized diagnosis according to both DSM-IV(American Psychiatric Association (APA), 1994) and the research diagnostic version of ICD-10 (World Health Organization., 1993a) The time frame of the interview is both the present and the recent past. Information from different informants is drawn together by a computer algorithm that predicts the likely diagnosis or diagnoses from responses to the closed questions, and generates six probability bands; < 0.1%, ~ 0.5%, ~ 3%, ~ 15%, ~ 50%, and > 70%. Each section contains around 20-25 questions, with skip-rules. For many disorders, the ICD-10 and DSM-IV diagnostic criteria stipulate that the symptoms need to have persisted for a specified period of time. That is why, the relevant section of the DAWBA interview focuses on the child's symptoms over these stipulated periods as well. The DAWBA has considerable potential as an epidemiological measure and may prove to be of clinical value too (R. Goodman et al., 2000a)

ADHD symptoms were measured using the "Attention and Activity" section of the DAWBA. Following previous work (Powell et al., 2020) symptoms were classed as present if mothers reported them occurring in their child "a little" or "a lot" more than in other children to create a count ranging from 0 to 18. First 9 hyperactivity items were used to calculate the total scores for hyperactivity only symptoms and the other 9 items were used to calculate the total scores for inattentive only subtype. To calculate the total scores for ADHD, all 18 items were used. See Table S1 for items used for calculating the total scores for ADHD and its subtypes.

Hypomania Symptom Checklist (HCL-32):

The HCL-32 is a self-reported questionnaire that assesses lifetime history of manic symptoms. It includes detailed assessments of bipolar mood, energy, and activity levels (in total 32 items). The instrument has been used extensively and validated in several studies (Angst et al., 2011a; Forty et al., 2009a; Meyer et al., 2007a, 2014a) In clinical settings, it is considered to be a clinically useful screening instrument for hypomania and bipolar disorder type II.(Smith et al., 2015a) In ALSPAC, when the cohort were 21-22 years of age, postal and online questionnaires for assessing lifetime history of hypomanic symptoms, using HCL-32 were sent. The HCL-32 has been used as both a continuous and categorical measure of hypomanic symptoms (Carvalho et al., 2015b; Court et al., 2014a) Respondents were asked to consider a time when they were in a "high or hyper" condition and endorse statements about their emotions, thoughts, and behaviour during this time. Although initially the HCL-32 was developed as a screening instrument for people with BD type II in people with recurrent depressive disorders, it is also a valid and sensitive tool for young, nonclinical populations (Meyer et al., 2014b). In our study, we used a categorical measure. Hypomanic symptoms were not clinically verified in the cohort.

Confounders

***Adverse Childhood Experiences using Family Adversity Index*:**

Family Adversity Index (FAI) total score was obtained using FAI index during pregnancy, and at 2 and 4 years, which includes items on (a)death or illness in family, (b) child's experience of

violent victimization(e.g., physical or sexual abuse), (c) inter-parental conflict, (d) family disruption (e.g., mother got divorced or separated), (e) parental employment difficulties, (f) parental legal difficulties, (g) parental psychopathology (e.g., mother or father reported high levels of depression or anxiety symptomatology), (h) parental substance use(e.g., mother or father reported heavy alcohol consumption or illegal drug use), (i) financial hardship, and (j) housing inadequacies or instability.

Borderline Personality Disorder Symptoms:

Borderline Personality Disorder (BPD) was evaluated through a face-to-face semi-structured interview: the UK Childhood Interview for DSM-IV Borderline Personality Disorder (UK-CI-BPD; (Zanarini, 2003a). This assessment tool is derived from the borderline module of the Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV; (Zanarini, 2003a), a widely utilized semi-structured interview designed for assessing all DSM-IV Axis II disorders. The inter-rater and test–retest reliability of the DSM-III, DSM-III-R and DSM-IV versions of this measure have all proven to be good to excellent (Zanarini & Frankenburg, 2001). It is the is first semi-structured interview assessing DSM-IV BPD in children and adolescents (Winsper, Hall, et al., 2017; Winsper, Tang, et al., 2017). The interview covers nine sections: intense inappropriate anger, affective instability, emptiness, identity disturbance, paranoid ideation/dissociation, frantic efforts to avoid abandonment, suicidal or self-mutilating behaviours, general impulsivity, and intense unstable relationships (Wolke et al., 2012). If the symptom occurred daily or approximately 25% of the time, the symptom was classed as definitely present; and probable if it had occurred repeatedly but did not meet criterion for definitely present.

Analyses

Determining the Optimal Number of Classes

Model fit was assessed using the following parameters sample size–adjusted Bayesian information criterion, Lo-Mendell- Rubin likelihood ratio test, Vuong-Lo-Mendell-Rubin test, entropy value and proportion of individuals in each class. In line with previous studies utilising LCGA methodology, ABIC was given priority instead of Bayesian Information Criteria (BIC) because of previous studies indicating that it outperforms other information criteria indices such as Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC; (Jones et al., 2018a; Morgan, 2015; Paksarian et al., 2016b; Tofighi & Enders, 2008), especially when small classes are present. Lower BIC values suggest better model fit. A significant VLMR value suggests that a k-class model fits the data better than a K − 1 class model. Entropy, a measure of the quality of classification, was additionally used to select the best model fit; an entropy value close to 1 is ideal. Finally, to decide the optimal class solution, an emphasis was also placed on proportion of individuals in each class, distinctiveness, and clinical relevance of the classes.

Determining ADHD Classes

We selected the 4-class model as this provided the best fit to the data and theoretical interpretation. It had the second lowest Sample-size Adjusted Bayesian Information Criteria (ABIC) value, and the Vuong-Lo-Mendell-Rubin test (VLMR) and Lo-Mendell-Rubin Adjusted LRT Test (LMRALT) P values suggested that it represented a significantly better fit than the 5-class model. While the 5-class model had a lower ABIC value, the entropy value was also lower compared to the 4-class model, suggesting a lower quality of classification. For these reasons, we selected the four-class solution over the five-class solution.

Determining Inattentiveness Classes

We also selected the 4-class model as this provided the best fit to the data and theoretical interpretation for inattentiveness. Although 5-class model had a lower ABIC value and VLMR and LMRALT tests were significant, the entropy value was lower compared to the 4-class model, suggesting a lower quality of classification. Additionally, although the smallest class in the five-class solution was not below the recommended 5%, 5-class model produced two very similar classes in terms of intercept and slope (which could be subsumed under the increasing levels of class). The difference between the four and five-class models was that the five-class solution added another increasing level class with a higher starting point as opposed to the other increasing levels class. The classification posterior probabilities for the five-class solution suggested it was difficult to distinguish those in higher levels increasing class to other classes, especially to those in the persistent high levels class. Classification posterior probabilities for the four and five class model can be seen in Table S9 and Table S10. For these reasons, we selected the four-class solution over the five-class solution.

Determining Hyperactivity Classes

We selected the 4-class model as this provided the best fit to the data and theoretical interpretation for hyperactivity. Very similar to the ADHD Classes output, 4-class model had the second lowest ABIC value, and the VLMR and LMRALT P values suggested that it represented a significantly better fit than the 5-class model. While the 5-class model had a lower ABIC value, the entropy value was higher compared to the 4-class model, suggesting a lower quality of classification. For these reasons, we selected the four-class solution over the five-class solution.

Inverse Probability Weighting

It is possible that selection may have induced bias due to non- random missingness of data in ALSPAC (Weavers et al., 2021b) To be able to assess the possibility of biased associations due to non-random missingness of the data, we used inverse probability weighting (IPW). This method has been recommended in epidemiological research over multiple imputation in situations where blocks of data are missing which is often the reason for attrition in ALSPAC where a variable is often missing due to non-participation in a clinic assessment visit (Weavers et al., 2021b) In IPW complete cases are weighted by the inverse of their probability of being a complete case and involves conducting an response/non-response model in order to account for any bias in patterns of association due to missingness (Seaman & White, 2013).

Selective dropout was determined by comparing those participants who completed the HCL-32 questionnaire to those who dropped out, using logistic regression analyses. In line with previous publications based on this cohort (Marwaha et al., 2018a; Morales-Muñoz et al., 2022, 2023) we used data from early time points in the ALSPAC dataset on child's sex and ethnicity, mother's socioeconomic status, maternal age, birthweight, preterm delivery and family adversity, to predict missingness in our analysis sample. The individuals associated with attrition at 21-23 years were more often males, and their mothers had higher scores on Family Adversity Index, they had lower socioeconomic status, had younger mother at birth (see Table S4).

Subsequently, we conducted IPW to account for those lost to follow-up. In accordance with previous research,(Morales-Muñoz et al., 2020, 2024) we used the variables associated with selective drop-out as the independent variables and fitted a logistic regression model (response vs. nonresponse as outcome) to determine weights for each individual using the inverse probability of response. Associations were not similar for the unweighted and weighted data, and thus we used the weighted data in all subsequent analysis.

Sensitivity Analyses

To investigate whether removal of hypomania items from HCL-32 that are similar to ADHD items would affect the results, we removed the following 4 items from HCL-32;

- I am more easily distracted
- I talk more
- I feel more energetic and more active
- I am physically more active (sport etc.)

Data Sources

ALSPAC data used within this study are accessible on request via an online proposal form. Please see http://www.bristol.ac.uk/alspac/researchers/access/ for further details. Please note that the ALSPAC website contains details of all data that are available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/).

Table S1. The DAWBA ADHD Items

Hyperactivity Items	
	1. Degree to which child often fidgeted in past 6 months relative to peers
	2. Degree to which child found it hard to sit down for long in past 6 months relative to peers
	3. Degree to which child ran or climbed about illicitly in past 6 months relative to peers
	4. Degree to which child found it hard to play quietly in past 6 months relative to peers
	5. Degree to which child found it hard to calm down in past 6 months relative to peers
	6. Degree to which child often blurted out answers in past 6 months relative to peers
	7. Degree to which child found it hard to wait own turn in past 6 months relative to peers
	8. Degree to which child often butted into conversations/games in past 6 months relative to peers
	9. Degree to which child often went on talking when asked to stop in past 6 months relative to peers
Inattentiveness Items	
	1. Degree to which child often made careless mistakes in past 6 months relative to peers
	2. Degree to which child often lost interest in activities in past 6 months relative to peers
	3. Degree to which child often didn't listen when addressed in past 6 months relative to peers
	4. Degree to which child often didn't finish a job properly in past 6 months relative to peers
	5. Degree to which child often found it hard to get organised in past 6 months relative to peers
	6. Degree to which child often tried to get out of activities involving thought in past 6 months relative to peers

	7. Degree to which child often lost things needed for school in past 6 months relative to peers
	8. Degree to which child was easily distracted in past 6 months relative to peers
	9. Degree to which child was often forgetful in past 6 months relative to peers

Table S2. DAWBA ADHD item prevalence in the cohort

	8 (n=7811) (%)	**10 (n=7435) (%)**	**13 (n=6798) (%)**
Hyperactivity Items			
Fidgeting	2142 (13.7)	1838 (11.7)	1322 (8.4)
Hard to sit down	1855 (11.9)	1418 (9.1)	910 (5.8)
Ran or climbed about illicitly	1597 (10.2)	776 (5.0)	382 (2.4)
Find it hard to play quietly	1353 (8.6)	881 (5.6)	615 (3.9)
Found it hard to calm down	1630 (10.4)	992 (6.3)	657 (4.2)
Blurted our answers	1479 (9.5)	1316 (8.4)	972 (6.2)
Hard to wait own turn	1685 (10.8)	1172 (7.5)	786 (5.0)
Butted into conversations/games	2520 (16.1)	1911 (12.2)	1365 (8.7)
Went on talking when asked to stop	2754 (17.6)	1980 (12.7)	1548 (9.9)
Inattentiveness Items			
Made careless mistakes	2264 (14.5)	2317 (14.8)	1796 (11.5)
Lost interest in activities	1507 (9.6)	1428 (9.1)	1155 (7.4)
Didn't listen when addressed	2396 (15.3)	2100 (13.4)	1820 (11.6)
Didn't finish a job properly	1888 (12.1)	1963 (12.5)	1790 (11.4)
Found it hard to get organised	1820 (11.6)	2058 (13.2)	1893 (12.1)
Tried to get out of activities involving thought	2020 (12.9)	2365 (15.1)	1971 (12.6)
Lost things needed for school	1265 (8.1)	1540 (9.8)	1545 (9.9)
Easily distracted	2420 (15.5)	2262 (14.5)	1951 (12.5)
Forgetful	1717 (11.0)	1887 (12.1)	1719 (11.0)

Table S3. HCL-32 item prevalence in the cohort

	(n=1694) (%)
Needs less sleep	1163 (7.4)
Feels more energetic and more active	2810 (18.0)
More self-confident	2694 (17.2)
Enjoys work more	2616 (16.7)
More sociable	2680 (17.1)
Wants to travel and/or do travel more	2344 (15.0)
Drive faster or take more risks while driving	491 (3.1)
Spends more/too much money	1397 (8.9)
Takes more risks in daily life	893 (5.7)
Physically more active	2090 (13.4)
Plans more activities or projects	2230 (14.3)
Has more ideas, is more creative	2236 (14.3)
Less shy or inhibited	2315 (14.8)
Wears more colourful and more extravagant clothes/make-up	824 (5.3)
Wants to meet or actually do meet more people	2005 (12.8)
More interested in sex and/or have increased sexual desire	1826 (11.7)
More flirtatious and/or more sexually active	1862 (11.9)
Talks more	2704 (17.3)
Thinks faster	1985 (12.7)
Makes more jokes or puns while talking	2224 (14.2)
More easily distracted	1155 (7.4)
Engages in lots of new things	1527 (9.8)
Thoughts jump from topic to topic	1284 (8.2)
Does things more quickly and more easily	2033 (13.0)
More impatient and/or get irritable more easily	559 (3.6)
Can be exhausting or irritating for others	629 (4.0)
Gets into more quarrels	226 (1.4)
Mood is higher, more optimistic	2654 (17.0)
Drinks more coffee	331 (2.1)
Smokes more cigarettes	241 (1.5)
Drinks more alcohol	571 (3.6)

Takes more drugs (both prescribed medications and recreational drugs)	132 (0.8)

Table S4. Differences in socio-demographic variables between non-participating and participating subjects in the study for clinically hypomanic symptoms at age 21-23 years

	Non-participating group in the study		**Participating group in the study**		**Non-participating versus participating**	
	Mean	*SD*	*Mean*	*SD*	*OR (95% CI)*	*p*
Family Adversity Score	4.54	4.39	3.46	3.67	0.96 (0.94-0.98)	<.001
Mother's Socioeconomic Status	52.22	13.53	56.45	13.45	1.01 (1.00-1.01)	0.014
Birthweight	3.38	58.59	3.42	5.39	1.00 (1.00)	0.418
Maternal Age	28.15	4.86	29.69	4.35	1.04 (1.02-1.06)	<.001
	Non-participating group in the study		**Participating group in the study**			
	N	*%*	*N*	*%*		
Sex					2.10 (1.79-2.46)	<.001
Male/Female	7082 / 6255	53.1 / 46.9	602 / 1091	35.6 / 64.6		
Ethnicity					0.95 (0.62-1.46)	0.815
White/Other	10011 / 554	94.8 / 5.2	1506 / 58	96.3 / 3.7		
Preterm Delivery					0.76 (0.52-1.11)	0.158
Yes/No	793 / 6663	10.6 / 89.4	946 / 63	93.8 / 6.2		

Table S5. Associations of Latent Classes of ADHD and Risk of Hypomanic Symptoms with Reduced Items[a]

	Unadjusted Model			Adjusted Model		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Hypomanic Symptoms at 21-23 Years (with reduced items)						
ADHD composite score						
ADHD persistently low levels class (Reference)	-	-	<0.001	-	-	<0.001
ADHD remitting class	0.00	0.00	0.993	0.00	0.00	0.993
ADHD increasing high class	5.71	2.11-15.43	0.001	5.08	1.86-13.83	0.001
ADHD persistently high class	15.02	6.78-33.31	<0.001	14.92	6.54-34.02	<0.001
Child's sex	-	-	-	1.52	0.74-3.11	0.252
Child's ethnicity	-	-	-	0.00	0.00	0.996
Family Adversity Index	-	-	-	1.10	1.03-1.18	0.006
BPD traits at 11 years	-	-	-	1.18	0.99-1.41	0.072
Hyperactivity Only						
Persistently low levels (Ref)	-	-	<0.001	-	-	<0.001
Remitting class	0.00	0.00	0.992	0.00	0.00	0.992
Increasing class	4.52	1.89-10.91	<0.001	3.37	1.28-8.88	0.014
Persistently high class	10.63	5.03-22.47	<0.001	8.10	4.02-20.12	<0.001
Child's sex	-	-	-	1.22	0.60-2.51	0.584
Child's ethnicity	-	-	-	0.00	0.00	0.996
Family Adversity Index	-	-	-	1.07	1.01-1.14	0.034
BPD traits at 11 years	-	-	-	1.21	0.99-1.47	0.058
Inattentive Only						
Persistently low levels (Ref)	-	-	<0.001	-	-	<0.001
Remitting class	0.00	0.00	0.993	0.00	0.00	0.993
Increasing class	5.71	2.11-15.43	<0.001	5.08	1.86-13.83	0.001
Persistently high class	15.02	6.78-33.31	<0.001	14.92	6.54-34.02	<0.001
Child's sex	-	-	-	1.52	0.74-3.11	0.252
Child's ethnicity	-	-	-	0.00	0.00	0.996
Family Adversity Index	-	-	-	1.10	1.03-1.18	0.006
BPD traits at 11 years	-	-	-	1.18	0.99-1.41	0.072
	Unadjusted Model			Adjusted Model		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Hypomanic Symptoms at 21-23 Years (with reduced items)						
ADHD composite score						
ADHD persistently low levels class (Reference)	-	-	<0.001	-	-	<0.001

ADHD remitting class	0.00	0.00	0.993	0.00	0.00	0.993
ADHD increasing high class	5.71	2.11-15.43	0.001	5.08	1.86-13.83	0.001
ADHD persistently high class	15.02	6.78-33.31	<0.001	14.92	6.54-34.02	<0.001
Child's sex	-	-	-	1.52	0.74-3.11	0.252
Child's ethnicity	-	-	-	0.00	0.00	0.996
Family Adversity Index	-	-	-	1.10	1.03-1.18	0.006
BPD traits at 11 years	-	-	-	1.18	0.99-1.41	0.072
Hyperactivity Only						
Persistently low levels (Ref)	-	-	<0.001	-	-	<0.001
Remitting class	0.00	0.00	0.992	0.00	0.00	0.992
Increasing class	4.52	1.89-10.91	<0.001	3.37	1.28-8.88	0.014
Persistently high class	10.63	5.03-22.47	<0.001	8.10	4.02-20.12	<0.001
Child's sex	-	-	-	1.22	0.60-2.51	0.584
Child's ethnicity	-	-	-	0.00	0.00	0.996
Family Adversity Index	-	-	-	1.07	1.01-1.14	0.034
BPD traits at 11 years	-	-	-	1.21	0.99-1.47	0.058
Inattentive Only						
Persistently low levels (Ref)	-	-	<0.001	-	-	<0.001
Remitting class	0.00	0.00	0.993	0.00	0.00	0.993
Increasing class	5.71	2.11-15.43	<0.001	5.08	1.86-13.83	0.001
Persistently high class	15.02	6.78-33.31	<0.001	14.92	6.54-34.02	<0.001
Child's sex	-	-	-	1.52	0.74-3.11	0.252
Child's ethnicity	-	-	-	0.00	0.00	0.996
Family Adversity Index	-	-	-	1.10	1.03-1.18	0.006
BPD traits at 11 years	-	-	-	1.18	0.99-1.41	0.072

Note: ADHD = Attention Deficit/hyperactivity disorder; BPD, Borderline Personality Disorder; DAWBA, Development and Well-Being Assessment; OR, Odds Ratio.

[a]All analyses were weighted for sex, ethnicity, maternal age, maternal socioeconomic status, preterm delivery, birthweight and family adversity; Adjusted Model: associations adjusted for BPD at 11 years, child's sex, child's ethnicity, and family adversity scores during pregnancy, at 2 years of age and 4 years of age.

Table S6. Classification Posterior Probabilities for 4-class ADHD model

	Increasing Levels Class	Decreasing Levels Class	Persistent Low Levels Class	Persistent High Levels Class
Increasing Levels Class	0.747	0.042	0.164	0.047
Decreasing Levels Class	0.033	0.791	0.122	0.054
Persistent Low Levels Class	0.011	0.009	0.980	0.000
Persistent High Levels Class	0.029	0.048	0.001	0.922

Table S7. Classification Posterior Probabilities for 5-class model

	Moderate Levels Increasing Class	Persistent High Levels Class	Decreasing Levels Class	Persistent Low Levels Class	High Levels Increasing Class
Moderate Levels Increasing Class	0.663	0.011	0.035	0.241	0.051
Persistent High Levels Class	0.004	0.925	0.048	0.001	0.023
Decreasing Levels Class	0.029	0.050	0.816	0.094	0.010
Persistent Low Levels Class	0.012	0.000	0.010	0.977	0.001
High Levels Increasing Class	0.061	0.122	0.059	0.103	0.655

Figure S1. Attrition of participants from the ALSPAC cohort

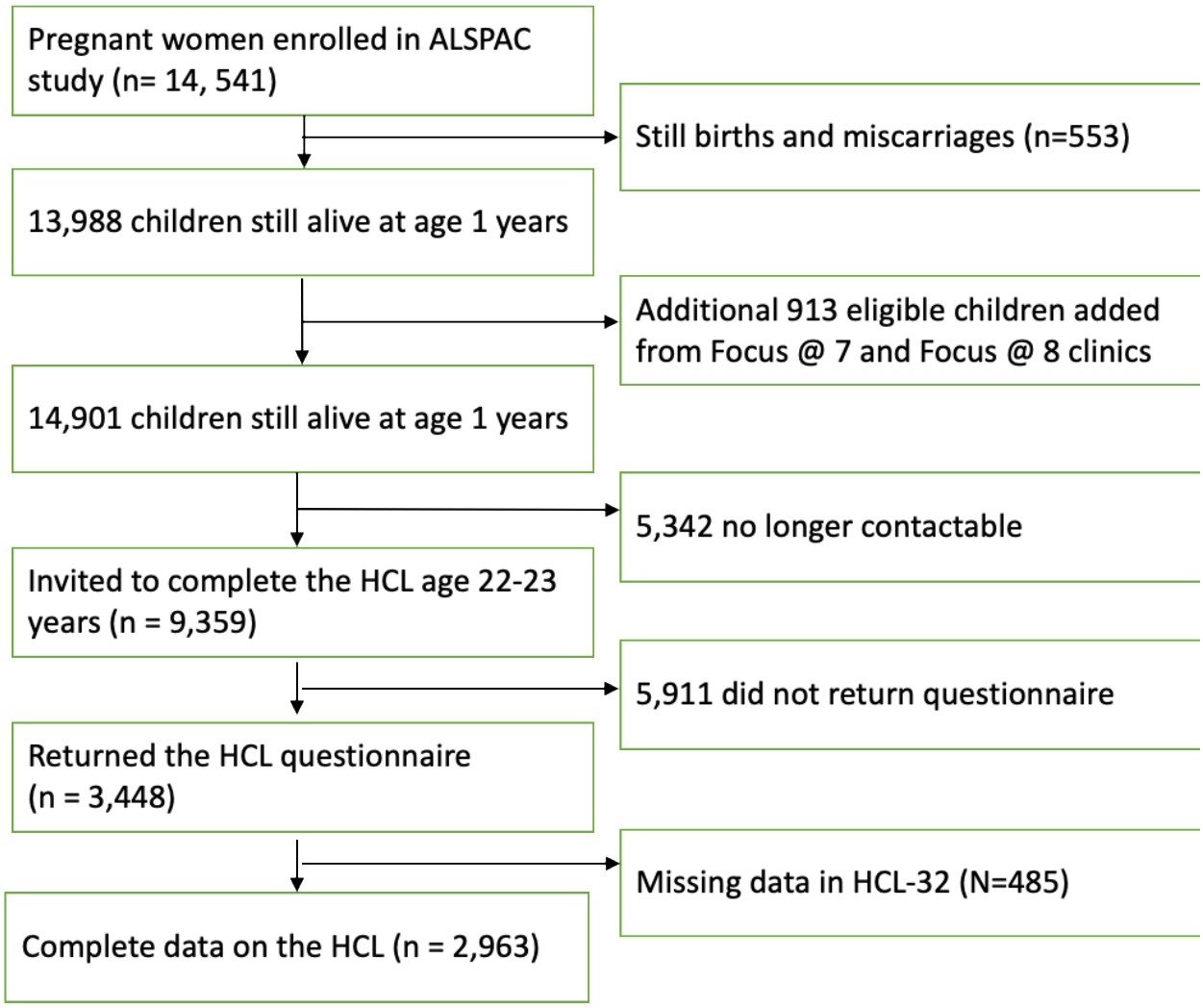


Figure S2. Four Class Model Inattentive Symptoms
Developmental course of Development and Wellbeing Assessment (DAWBA) inattentiveness subgroup from 8 to 13 years old. The latent class growth analyses detected a best model fit for 4 classes. Class 1 (orange line in the middle) represents individuals with increasing levels of inattentiveness across time points. Class 2 (yellow line) represents individuals with decreasing levels of inattentiveness. Class 3 (green line on the bottom) represents individuals with persistent low levels of inattentiveness. Class 4 (brown line) represents individuals with persistent high levels of inattentiveness.

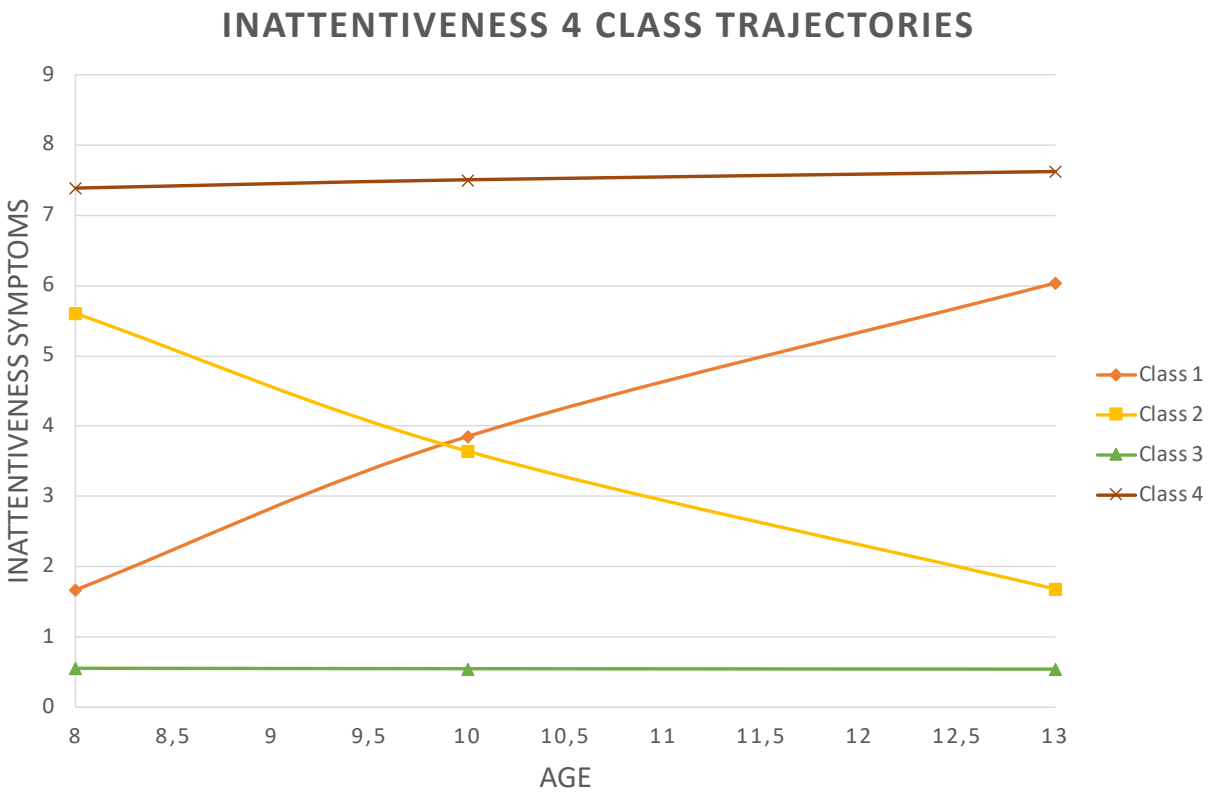
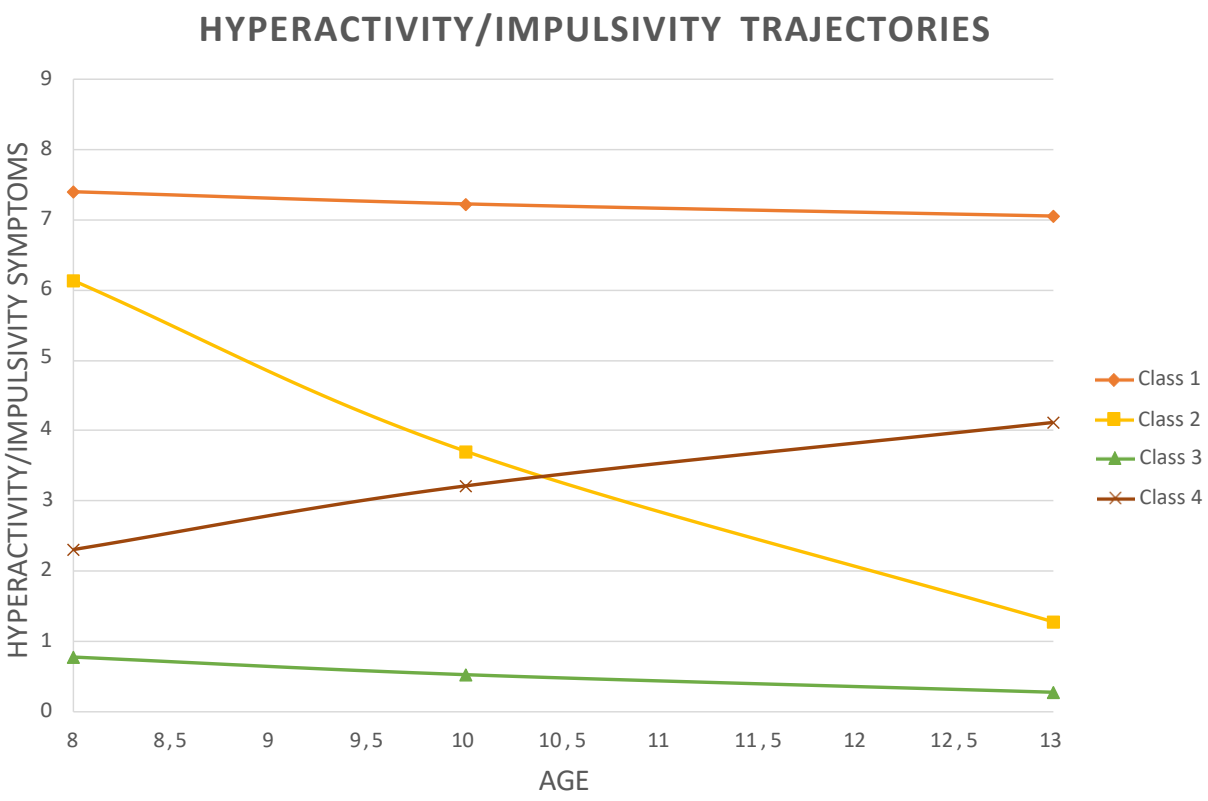


Figure S3. Four Class Model Hyperactivity Symptoms
Developmental course of Development and Wellbeing Assessment (DAWBA) hyperactivity subgroup from 8 to 13 years old. The latent class growth analyses detected a best model fit for 4 classes. Class 1 (orange line on the top) represents individuals with persistent high levels of hyperactivity across time points. Class 2 (yellow line) represents individuals with decreasing levels of hyperactivity. Class 3 (green line on the bottom) represents individuals with persistent low levels of hyperactivity. Class 4 (brown line) represents individuals with increasing levels of hyperactivity.



References

American Psychiatric Association (APA). (1994). Diagnostic and statistical manual of mental disorders. In Australasian Psychiatry (Vol. 29, Issue 3). https://doi.org/10.3109/00048679509064964

Angst, J., Azorin, J. M., Bowden, C. L., Perugi, G., Vieta, E., Gamma, A., & Young, A. H. (2011). Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: The BRIDGE study. Archives of General Psychiatry, 68(8), 791–799. https://doi.org/10.1001/archgenpsychiatry.2011.87

Carvalho, A. F., Takwoingi, Y., Sales, P. M. G., Soczynska, J. K., Köhler, C. A., Freitas, T. H., Quevedo, J., Hyphantis, T. N., McIntyre, R. S., & Vieta, E. (2015). Screening for bipolar spectrum disorders: A comprehensive meta-analysis of accuracy studies. Journal of Affective Disorders, 172, 337–346. https://doi.org/10.1016/j.jad.2014.10.024

Court, H., Forty, L., Jones, L., Gordon-Smith, K., Jones, I., Craddock, N., & Smith, D. J. (2014). Improving the psychometric utility of the hypomania checklist (HCL-32): A Rasch analysis approach. Journal of Affective Disorders, 152–154(1), 448–453. https://doi.org/10.1016/j.jad.2013.10.014

Forty, L., Smith, D., Jones, L., Jones, I., Caesar, S., Fraser, C., Gordon-Smith, K., & Craddock, N. (2009). Identifying hypomanic features in major depressive disorder using the hypomania checklist (HCL-32). Journal of Affective Disorders, 114(1–3), 68–73. https://doi.org/10.1016/j.jad.2008.07.017

Goodman, R., Ford, T., Richards, H., Gatward, R., & Meltzer, H. (2000). The Development and Well-Being Assessment: Description and initial validation of an integrated assessement of child and adolescent psychopathology. Journal of Child Psychology and Psychiatry and Allied Disciplines, 41(5), 645–655. https://doi.org/10.1017/S0021963099005909

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics, 42(2), 377–381. https://doi.org/10.1016/j.jbi.2008.08.010

Hosang, G. M., Lichtenstein, P., Ronald, A., Lundström, S., & Taylor, M. J. (2019). Association of Genetic and Environmental Risks for Attention-Deficit/Hyperactivity Disorder with Hypomanic Symptoms in Youths. JAMA Psychiatry, 76(11), 1150–1158. https://doi.org/10.1001/jamapsychiatry.2019.1949

Jones, H. J., Gage, S. H., Heron, J., Hickman, M., Lewis, G., Munafò, M. R., & Zammit, S. (2018). Association of combined patterns of tobacco and cannabis use in adolescence with psychotic experiences. JAMA Psychiatry, 75(3), 240–246. https://doi.org/10.1001/jamapsychiatry.2017.4271

Marwaha, S., Winsper, C., Bebbington, P., & Smith, D. (2018). Cannabis use and hypomania in young people: A prospective analysis. Schizophrenia Bulletin, 44(6), 1267–1274. https://doi.org/10.1093/schbul/sbx158

Meyer, T. D., Hammelstein, P., Nilsson, L. G., Skeppar, P., Adolfsson, R., & Angst, J. (2007). The Hypomania Checklist (HCL-32): its factorial structure and association to indices of impairment in German and Swedish nonclinical samples. Comprehensive Psychiatry, 48(1), 79–87. https://doi.org/10.1016/j.comppsych.2006.07.001

Meyer, T. D., Schrader, J., Ridley, M., & Lex, C. (2014a). The Hypomania Checklist (HCL) - Systematic review of its properties to screen for bipolar disorders. Comprehensive Psychiatry, 55(5), 1310–1321. https://doi.org/10.1016/j.comppsych.2014.03.002

Meyer, T. D., Schrader, J., Ridley, M., & Lex, C. (2014b). The Hypomania Checklist (HCL) - Systematic review of its properties to screen for bipolar disorders. Comprehensive Psychiatry, 55(5), 1310–1321. https://doi.org/10.1016/j.comppsych.2014.03.002

Morales-Muñoz, I., Broome, M. R., & Marwaha, S. (2020). Association of Parent-Reported Sleep Problems in Early Childhood with Psychotic and Borderline Personality Disorder Symptoms in Adolescence. JAMA Psychiatry, 77(12), 1256–1265. https://doi.org/10.1001/jamapsychiatry.2020.1875

Morales-Muñoz, I., Mallikarjun, P. K., Chandan, J. S., Thayakaran, R., Upthegrove, R., & Marwaha, S. (2023). Impact of anxiety and depression across childhood and adolescence on adverse outcomes in young adulthood: a UK birth cohort study. British Journal of Psychiatry, 45(4), 212–220. https://doi.org/10.1192/bjp.2023.23

Morales-Muñoz, I., Marwaha, S., Upthegrove, R., & Cropley, V. (2024). Role of Inflammation in Short Sleep Duration Across Childhood and Psychosis in Young Adulthood. JAMA Psychiatry, 1–9. https://doi.org/10.1001/jamapsychiatry.2024.0796

Morales-Muñoz, I., Palmer, E. R., Marwaha, S., Mallikarjun, P. K., & Upthegrove, R. (2022). Persistent Childhood and Adolescent Anxiety and Risk for Psychosis: A Longitudinal Birth Cohort Study. Biological Psychiatry, 92(4), 275–282. https://doi.org/10.1016/j.biopsych.2021.12.003

Morgan, G. B. (2015). Mixed Mode Latent Class Analysis: An Examination of Fit Index Performance for Classification. Structural Equation Modeling, 22(1), 76–86. https://doi.org/10.1080/10705511.2014.935751

Paksarian, D., Cui, L., Angst, J., Ajdacic-Gross, V., Rössler, W., & Merikangas, K. R. (2016). Latent trajectories of common mental health disorder risk across 3 decades of adulthood in a population-based cohort. JAMA Psychiatry, 73(10), 1023–1031. https://doi.org/10.1001/jamapsychiatry.2016.1921

Powell, V., Riglin, L., Hammerton, G., Eyre, O., Martin, J., Anney, R., Thapar, A., & Rice, F. (2020). What explains the link between childhood ADHD and adolescent depression? Investigating the role of peer relationships and academic attainment. European Child and Adolescent Psychiatry, 29(11), 1581–1591. https://doi.org/10.1007/s00787-019-01463-w

Seaman, S. R., & White, I. R. (2013). Review of inverse probability weighting for dealing with missing data. Statistical Methods in Medical Research, 22(3), 278–295. https://doi.org/10.1177/0962280210395740

Smith, D. J., Anderson, J., Zammit, S., Meyer, T. D., Pell, J. P., & Mackay, D. (2015). Childhood IQ and risk of bipolar disorder in adulthood: prospective birth cohort study. BJPsych Open, 1(1), 74–80. https://doi.org/10.1192/bjpo.bp.115.000455

Tofighi, D., & Enders, C. K. (2008). Identifying the correct number of classes in growth mixture models. Advances in Latent Variable Mixture Models, 317–341.

Weavers, B., Heron, J., Thapar, A. K., Stephens, A., Lennon, J., Bevan Jones, R., Eyre, O., Anney, R. J., Collishaw, S., Thapar, A., & Rice, F. (2021). The antecedents and outcomes of persistent and remitting adolescent depressive symptom trajectories: a longitudinal, population-

based English study. The Lancet Psychiatry, 8(12), 1053–1061. https://doi.org/10.1016/S2215-0366(21)00281-9

Winsper, C., Hall, J., Strauss, V. Y., & Wolke, D. (2017). Aetiological pathways to Borderline Personality Disorder symptoms in early adolescence: Childhood dysregulated behaviour, maladaptive parenting and bully victimisation. Borderline Personality Disorder and Emotion Dysregulation, 4(1), 1–10. https://doi.org/10.1186/s40479-017-0060-x

Winsper, C., Tang, N. K. Y., Marwaha, S., Lereya, S. T., Gibbs, M., Thompson, A., & Singh, S. P. (2017). The sleep phenotype of Borderline Personality Disorder: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews, 73, 48–67. https://doi.org/10.1016/j.neubiorev.2016.12.008

Wolke, D., Schreier, A., Zanarini, M. C., & Winsper, C. (2012). Bullied by peers in childhood and borderline personality symptoms at 11 years of age: A prospective study. Journal of Child Psychology and Psychiatry and Allied Disciplines, 53(8), 846–855. https://doi.org/10.1111/j.1469-7610.2012.02542.x

World Health Organization. (1993). The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. World Health Organization, 2. https://doi.org/10.1007/978-3-319-24612-3_301942

Zanarini, M. C. (2003). Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): A continuous measure of DSM-IV borderline psychopathology. Journal of Personality Disorders, 17(3), 233–242. https://doi.org/10.1521/pedi.17.3.233.22147

Zanarini, M. C., & Frankenburg, F. R. (2001). Attainment and maintenance of reliability of axis I and II disorders over the course of a longitudinal study. Comprehensive Psychiatry, 42(5), 369–374. https://doi.org/10.1053/comp.2001.24556

Appendix C. Chapter 5 Supplement

Depression symptom trajectories across adolescence and risk of hypomanic symptoms in young adulthood: A UK Birth Cohort Study

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References

Supplement

Methods. Additional Information on Study Population, Measures and Analyses

Study Population

Pregnant women resident in Avon, UK with expected dates of delivery between 1st April 1991 and 31st December 1992 were invited to take part in the study. 20,248 pregnancies have been identified as being eligible and the initial number of pregnancies enrolled was 14,541. Of the initial pregnancies, there was a total of 14,676 foetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. The total sample size for analyses using any data collected after the age of seven is therefore 15,447 pregnancies, resulting in 15,658 foetuses. Of these 14,901 children were alive at 1 year of age. Of the original 14,541 initial pregnancies, 338 were from a woman who had already enrolled with a previous pregnancy, meaning 14,203 unique mothers were initially enrolled in the study. As a result of the additional phases of recruitment, a further 630 women who did not enrol originally have provided data since their child was 7 years of age. This provides a total of 14,833 unique women (G0 mothers) enrolled in ALSPAC as of September 2021.

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Bristol.(Harris et al., 2009). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. Study participants have the right to withdraw their consent for specific elements of the study, or from the study as a whole, at any time.

Hypomania Symptom Checklist (HCL-32):

The HCL-32 is a self-reported questionnaire that assesses lifetime history of manic symptoms. It includes detailed assessments of bipolar mood, energy, and activity levels (in total 32 items). The instrument has been used extensively and validated in several studies (Angst et al., 2011; Forty et al., 2009; Meyer et al., 2007, 2014). In clinical settings, it is considered to be a clinically useful screening instrument for hypomania and bipolar disorder type II (Smith et al., 2015). In ALSPAC, when the cohort were 21-22 years of age, postal and online questionnaires for assessing lifetime history of hypomanic symptoms, using HCL-32 were sent. The HCL-32 has been used as both a continuous and categorical measure of hypomanic symptoms (Carvalho et al., 2015; Court et al., 2014). Respondents were asked to consider a time when they were in a “high or hyper” condition and endorse statements about their emotions, thoughts, and behaviour during this time. Although initially the HCL-32 was developed as a screening instrument for people with BD type II in people with recurrent depressive disorders, it is also a valid and sensitive tool for young, nonclinical populations (Meyer et al., 2014). In our study, we used a categorical measure. Hypomanic symptoms were not clinically verified in the cohort.

The Clinical Interview Schedule-Revised (CIS-R):

The CIS-R is designed for, and has been widely used within, community samples (Davies et al., 2016). Participants completed a self-administered computerized version of the CIS-R at a research clinic attended at age 18 years. The CIS-R uses criteria from the International Statistical Classification of Diseases, 10th Revision (ICD-10) and measures affective and anxiety disorders in the past week, enabling diagnoses for common mental disorders to be derived. The CIS-R includes 14 sections covering different symptom clusters: somatic symptoms, fatigue, concentration, sleep, irritability, worries over physical health, depression, depressive ideas, worry, anxiety, phobias, panic, compulsions, and obsessions. The sub-scale scores for symptom clusters range from 0 to 4, with the exception of the depressive ideas cluster sub-scale, which has a maximum score of 5. Within each cluster, symptoms are deemed 'clinically significant' if respondents score 2 or more on the corresponding sub-scale (Das-Munshi et al., 2008). The overall psychological morbidity score for the CIS–R is generated by summing the scores from all 14 sub-scales.

The Psychosis-Like Symptom Interview (PLIKS):

The PLIKS evaluates key psychotic experiences including hallucinations (visual and auditory); delusions (delusions of being spied on, persecution, thoughts being read, reference, control, grandiose ability and other unspecified delusions); and bizarre symptoms (thought broadcasting, insertion and withdrawal (Zammit et al., 2008). Participants were asked a series of semi-structured questions to gather information on these experiences (Zammit et al., 2008). Those who responded with "yes" or "maybe" were further questioned to assess the potential psychotic nature of their experiences in the past 6 months (Jones et al., 2018; Zammit et al., 2008). Interviewers, who were psychology graduates trained for this purpose and blinded to previous assessments, categorized experiences as not present, suspected, or definitely psychotic (English et al., 2018; Zammit et al., 2008). The classification of experiences as definitely psychotic required a clear example, with unclear responses being downgraded. To ensure consistency, a psychiatrist reviewed samples of recorded interviews to validate the accuracy of ratings.(Zammit et al., 2009). The inter-rater reliability of the PLIKS in the ALSPAC study at the age of 18 was high (κ=0.83; Zammit et al., 2013). Furthermore, test-retest reliability was assessed with 162 individuals reassessed after 47 days, resulting in a κ value of 0.76, and for the 46 individuals assessed by the same interviewer, a κ value of 0.86 was observed (Zammit et al., 2013).

Adverse Childhood Experiences using Family Adversity Index:

Family Adversity Index (FAI) total score was obtained using FAI index during pregnancy, and at 2 and 4 years, which includes items on death or illness in family, child's experience of violent victimization (e.g., physical or sexual abuse), inter-parental conflict, family disruption (e.g., mother got divorced or separated), parental employment difficulties, parental legal difficulties, parental psychopathology (e.g., mother or father reported high levels of depression or anxiety symptomatology), parental substance use (e.g., mother or father reported heavy alcohol consumption or illegal drug use), parental criminal offense, financial hardship, mother's and father's low educational attainment, age of mother at pregnancy and housing inadequacies or instability (Hines et al., 2023).

Further details of the DAWBA:

The DAWBA is a package of interviews, questionnaires and rating techniques designed to generate ICD-10 and DSM-IV or DSM-5 psychiatric diagnoses on 2-17 years old. A briefer questionnaire is administered to teacher. The interviews and questionnaires involve a mixture of closed questions such as "Does he ever worry?" and open-ended questions such as "Please describe in your own words what it is that he worries about?" and can either be administered by trained lay interviewers or else self-completed online. With the computer-administered interviews, the respondent types the open-ended answers into the text boxes. With the interviewer-administered interviews, it is the interviewer who transcribes the answers. The full DAWBA package covers the following diagnoses: Separation anxiety, Specific phobia, Social phobia, Panic disorder/agoraphobia, Post-traumatic stress disorder, Obsessive compulsive disorder, Generalized anxiety disorder, Body dysmorphic disorder, Disruptive mood dysregulation disorder, Major depression, ADHD/hyperkinesis, Oppositional defiant disorder, Conduct disorder, Eating disorders, including anorexia, bulimia and binge eating, Autism spectrum disorders, Tic disorders, including Tourette syndrome, and Bipolar Disorders. For each of these disorders, the interview asks about all the symptoms, and other criteria needed for an operationalized diagnosis according to both DSM-IV (American Psychiatric Association, 1994) and the research diagnostic version of ICD-10 (World Health Organization., 1993). The time frame of the interview is both the present and the recent past. Information from different informants is drawn together by a computer algorithm that predicts the likely diagnosis or diagnoses from responses to the closed questions, and generates six probability bands; < 0.1%, ~ 0.5%, ~ 3%, ~ 15%, ~ 50%, and > 70%. Each section contains around 20-25 questions, with skip-rules. For many disorders, the ICD-10 and DSM-IV diagnostic criteria stipulate that the symptoms need to have persisted for a specified period of time. That is why, the relevant section of the DAWBA interview focuses on the child's symptoms over these stipulated periods as well. The DAWBA has considerable potential as an epidemiological measure and may prove to be of clinical value too (Goodman et al., 2000).

DAWBA diagnosis of childhood psychopathology at 8 years in ALSPAC:

A postal questionnaire containing the parent-version of the DAWBA was sent to mothers when the study child was on average about 8 years old. The parent-completed DAWBA-questionnaire was the primary source of information for the diagnosis of psychiatric disorders. However, additional sources of information on a child's emotional and behavioural characteristics were also consulted such as the teacher version of the DAWBA for hyperactivity and conduct disorder, the teacher version of the Strengths and Difficulties Questionnaire (SDQ) at 8 years, parent completed SDQ at 7 years, basic reading and spelling competency of the child at age 7 years; and IQ at age 8 years using the Wechsler Intelligence Scale for Children (WISC III, 3rd UK edition Siebald et al., 2016). Child psychiatrists then reviewed the data for each participant, to determine a final definitive DSM_IV diagnosis (Tobarra-Sanchez et al., 2022). Therefore, psychiatric diagnoses were based on comprehensive developmental data from multiple sources. The presence of any of the following DSM-IV psychiatric diagnoses at 8 years were used in the analyses and coded as 1; any type of attention deficit hyperactivity disorder (i.e., combined ADHD, inattentive type only, hyperactive-impulsive type only), oppositional defiant disorder, conduct disorder, disruptive behaviour disorder not otherwise specified, pervasive developmental disorder, any anxiety disorder (i.e., separation anxiety disorder, specific phobia, social phobia, obsessive compulsive disorder, generalised anxiety disorder, anxiety disorder not otherwise specified), and post-traumatic stress disorder.

Borderline Personality Disorder Symptoms:

Borderline Personality Disorder (BPD) was evaluated through a face-to-face semi-structured interview: the UK Childhood Interview for DSM-IV Borderline Personality Disorder (UK-CI-BPD; Zanarini, 2003). This assessment tool is derived from the borderline module of the Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV; Zanarini, 2003), a widely utilized semi-structured interview designed for assessing all DSM-IV Axis II disorders. The inter-rater and test–retest reliability of the DSM-III, DSM-III-R and DSM-IV versions of this measure have all proven to be good to excellent (Zanarini & Frankenburg, 2001). It is the is first semi-structured interview assessing DSM-IV BPD in children and adolescents (Winsper et al., 2017a; Winsper et al., 2017b). The interview covers nine sections: intense inappropriate anger, affective instability, emptiness, identity disturbance, paranoid ideation/dissociation, frantic efforts to avoid abandonment, suicidal or self-mutilating behaviours, general impulsivity, and intense unstable relationships (Wolke et al., 2012). If the symptom occurred daily or approximately 25% of the time, the symptom was classed as definitely present; and probable if it had occurred repeatedly but did not meet criterion for definitely present.

Analyses

Inverse Probability Weighting:

In epidemiological research, inverse probability weighting (IPW) has been favoured over multiple imputation when dealing with missing data in blocks, which frequently occurs due to attrition in studies like ALSPAC, where variables are often missing because participants did not take part in clinic assessment visits (Weavers et al., 2021). In IPW complete cases are weighted by the inverse of their probability of being a complete case and involves conducting a response/non-response model in order to account for any bias in patterns of association due to missingness.

Attrition was determined by comparing those participants who completed the HCL-32 questionnaire to those who dropped out, using logistic regression analyses. Response rates significantly differed according to sex, socioeconomic status of the mother, and family adversity (see Table S1). The individuals associated with attrition at 21-23 years were more often males, and their mothers had lower scores on Family Adversity Index, and they had higher socioeconomic status. Subsequently, we conducted IPW to account for those lost to follow-up. In accordance with previous research,(Morales-Muñoz et al., 2024) we used the variables associated with selective drop-out as the independent variables and fitted a logistic regression model (response vs. nonresponse as outcome) to determine weights for each individual using the inverse probability of response. Weights ranged from 3·65 to 34.39.

Determining the SMFQ Classes

We selected the 3-class model as this provided the best fit to the data and theoretical interpretation. It had the second lowest ABIC value, and the VLMR and LMRALT p values suggested that it represented a significantly better fit than the 4-class models. While the 5-class model had significant VLMR AND LMRALT values, the entropy value was highest for the 3-class model, suggesting a higher quality of classification compared to the 5-class model. The difference between the three and five-class models was that the five-class solution added another increasing level class (N= 216, 2.5%) with a higher starting point as opposed to the other increasing levels class and persistently high-slightly decreasing class (N=168, 1.9%). The classification posterior probabilities for the five-class solution suggested it was difficult to distinguish those in higher levels increasing class to those in the increasing levels class with lower baseline scores and to distinguish those in persistently high class to those in the decreasing levels class. Classification posterior probabilities for the three and five class model can be seen in Table S2 and Table S3, respectively. Further, all classes from the 3-class model included sufficient sample sizes and were clinically relevant whereas the classes from the 5-class model were less than recommended (Weavers et al., 2021). For these reasons, we selected the three-class solution over the five-class solution.

Data Sources

ALSPAC data used within this study are accessible on request via an online proposal form. Please see http://www.bristol.ac.uk/alspac/researchers/access/ for further details. Please note that the ALSPAC website contains details of all data that are available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/).

Table S1. Differences in socio-demographic variables between non-participating and participating subjects in the study

	Non-participating group in the study		**Participating group in the study**		**Non-participating versus participating**	
	Mean	*SD*	*Mean*	*SD*	*OR (95% CI)*	*p*
Family Adversity Score	4.54	4.39	3.46	3.67	0.96 (0.94-0.98)	<.001
Mother's Socioeconomic Status	52.22	13.53	56.45	13.45	1.01 (1.00-1.01)	0.014
Birthweight	3.38	58.59	3.42	5.39	1.00 (1.00)	0.418
Maternal Age	28.15	4.86	29.69	4.35	1.04 (1.02-1.06)	<.001
	Non-participating group in the study		**Participating group in the study**			
	N	*%*	*N*	*%*		
Sex					2.10 (1.79-2.46)	<.001
Male/Female	7082 / 6255	53.1 / 46.9	602 / 1091	35.6 / 64.6		
Ethnicity					0.95 (0.62-1.46)	0.815
White/Other	10011 / 554	94.8 / 5.2	1506 / 58	96.3 / 3.7		
Preterm Delivery					0.76 (0.52-1.11)	0.158
Yes/No	793 / 6663	10.6 / 89.4	946 / 63	93.8 / 6.2		

Table S2. BIC, VLMR Likelihood Test p Values, and Entropy for Classes 2–6 of the SMFQ Scores

Depression symptoms trajectories	AIC	BIC	ABIC	VLMR P-Value	LMRALT P-Value	Entropy
2 classes	139124.665	139188.400	139159.799	0.0000	0.0000	0.822
3 classes	138101.417	138186.396	138148.262	0.0000	0.0000	0.827
4 classes	137304.941	137411.165	137363.498	0.0749	0.0800	0.804
5 classes	136950.692	137078.161	137020.960	0.0001	0.0001	0.799
6 classes	136956.692	137105.406	137038.671	0.5246	0.5246	0.580

Abbreviations: ABIC, Sample-size Adjusted Bayesian Information Criterion; AIC; Akaike information criterion; BIC, Bayesian information criterion; VLMR, Vuong-Lo-Mendell-Rubin; LMRALT, Lo-Mendell-Rubin Adjusted LRT Test P-Value.

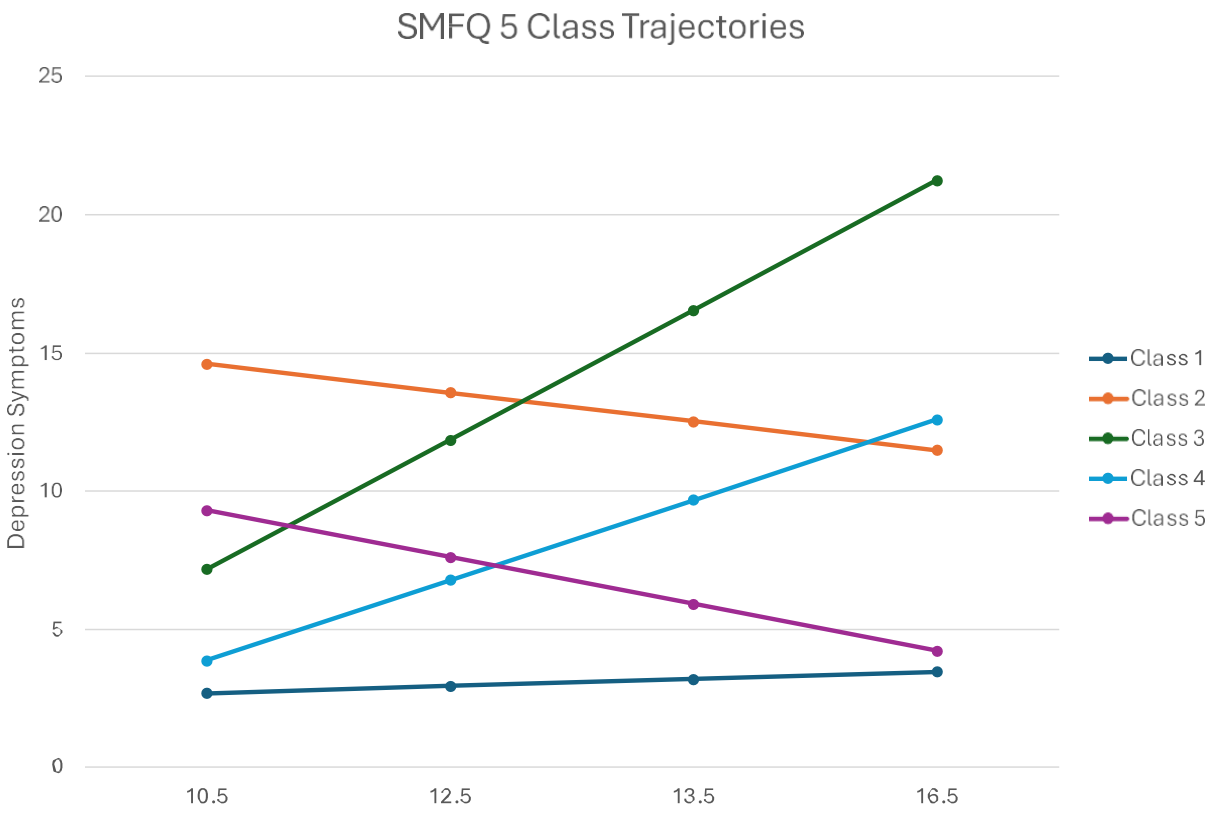
Table S3. Classification Posterior Probabilities for 3-class model

	Decreasing Levels Class	Persistent Low Levels Class	Increasing Levels Class
Decreasing Levels Class	0.722	0.204	0.073
Persistently Low Levels Class	0.006	0.982	0.012
Increasing Levels Class	0.044	0.236	0.720

Table S4. Classification Posterior Probabilities for 5-class model

	Persistently Low Levels Class	Persistently High Levels Class	Increasing levels class with higher baseline scores	Increasing levels class with lower baseline scores	Decreasing Levels Class
Persistently Low Levels Class	0.967	0.000	0.000	0.020	0.013
Persistently High Levels Class	0.028	0.735	0.044	0.076	0.117
Increasing levels class with higher baseline scores	0.050	0.044	0.690	0.142	0.074
Increasing Levels Class with lower baseline scores	0.280	0.002	0.020	0.658	0.040
Decreasing Levels Class	0.252	0.017	0.005	0.064	0.662

Figure S1. Five Class Model SMFQ Symptoms – Short Moods and Feelings Questionnaire (SMFQ) from 10.5 to 16.5 years old.



References

American Psychiatric Association (APA). (1994). Diagnostic and statistical manual of mental disorders. In Australasian Psychiatry (Vol. 29, Issue 3). https://doi.org/10.3109/00048679509064964

Angst, J., Azorin, J. M., Bowden, C. L., Perugi, G., Vieta, E., Gamma, A., & Young, A. H. (2011). Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: The BRIDGE study. Archives of General Psychiatry, 68(8), 791–799. https://doi.org/10.1001/archgenpsychiatry.2011.87

Carvalho, A. F., Takwoingi, Y., Sales, P. M. G., Soczynska, J. K., Köhler, C. A., Freitas, T. H., Quevedo, J., Hyphantis, T. N., McIntyre, R. S., & Vieta, E. (2015). Screening for bipolar spectrum disorders: A comprehensive meta-analysis of accuracy studies. Journal of Affective Disorders, 172, 337–346. https://doi.org/10.1016/j.jad.2014.10.024

Court, H., Forty, L., Jones, L., Gordon-Smith, K., Jones, I., Craddock, N., & Smith, D. J. (2014). Improving the psychometric utility of the hypomania checklist (HCL-32): A Rasch analysis approach. Journal of Affective Disorders, 152–154(1), 448–453. https://doi.org/10.1016/j.jad.2013.10.014

Das-Munshi, J., Goldberg, D., Bebbington, P. E., Bhugra, D. K., Brugha, T. S., Dewey, M. E., Jenkins, R., Stewart, R., & Prince, M. (2008). Public health significance of mixed anxiety and depression: Beyond current classification. British Journal of Psychiatry, 192(3), 171–177. https://doi.org/10.1192/bjp.bp.107.036707

Davies, S. J. C., Pearson, R. M., Stapinski, L., Bould, H., Christmas, D. M., Button, K. S., Skapinakis, P., Lewis, G., & Evans, J. (2016). Symptoms of generalized anxiety disorder but not panic disorder at age 15 years increase the risk of depression at 18 years in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort study. Psychological Medicine, 46(1), 73–85. https://doi.org/10.1017/S003329171500149X

English, J. A., Lopez, L. M., O'Gorman, A., Föcking, M., Hryniewiecka, M., Scaife, C., Sabherwal, S., Wynne, K., Dicker, P., Rutten, B. P. F., Lewis, G., Zammit, S., Cannon, M., Cagney, G., & Cotter, D. R. (2018). Blood-Based Protein Changes in Childhood Are Associated With Increased Risk for Later Psychotic Disorder: Evidence From a Nested Case-Control Study of the ALSPAC Longitudinal Birth Cohort. Schizophrenia Bulletin, 44(2), 297–306. https://doi.org/10.1093/schbul/sbx075

Forty, L., Smith, D., Jones, L., Jones, I., Caesar, S., Fraser, C., Gordon-Smith, K., & Craddock, N. (2009). Identifying hypomanic features in major depressive disorder using the hypomania checklist (HCL-32). Journal of Affective Disorders, 114(1–3), 68–73. https://doi.org/10.1016/j.jad.2008.07.017

Goodman, R., Ford, T., Richards, H., Gatward, R., & Meltzer, H. (2000). The Development and Well-Being Assessment: Description and initial validation of an integrated assessement of child and adolescent psychopathology. Journal of Child Psychology and Psychiatry and Allied Disciplines, 41(5), 645–655. https://doi.org/10.1017/S0021963099005909

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics, 42(2), 377–381. https://doi.org/10.1016/j.jbi.2008.08.010

Hines, L. A., Jones, H. J., Hickman, M., Lynskey, M., Howe, L. D., Zammit, S., & Heron, J. (2023). Adverse childhood experiences and adolescent cannabis use trajectories: findings from a longitudinal UK birth cohort. The Lancet Public Health, 8(6), e442–e452. https://doi.org/10.1016/S2468-2667(23)00095-6
Jones, H. J., Gage, S. H., Heron, J., Hickman, M., Lewis, G., Munafò, M. R., & Zammit, S. (2018). Association of combined patterns of tobacco and cannabis use in adolescence with psychotic experiences. JAMA Psychiatry, 75(3), 240–246. https://doi.org/10.1001/jamapsychiatry.2017.4271
Meyer, T. D., Hammelstein, P., Nilsson, L. G., Skeppar, P., Adolfsson, R., & Angst, J. (2007). The Hypomania Checklist (HCL-32): its factorial structure and association to indices of impairment in German and Swedish nonclinical samples. Comprehensive Psychiatry, 48(1), 79–87. https://doi.org/10.1016/j.comppsych.2006.07.001
Meyer, T. D., Schrader, J., Ridley, M., & Lex, C. (2014). The Hypomania Checklist (HCL) - Systematic review of its properties to screen for bipolar disorders. Comprehensive Psychiatry, 55(5), 1310–1321. https://doi.org/10.1016/j.comppsych.2014.03.002
Morales-Muñoz, I., Marwaha, S., Upthegrove, R., & Cropley, V. (2024). Role of Inflammation in Short Sleep Duration Across Childhood and Psychosis in Young Adulthood. JAMA Psychiatry, 1–9. https://doi.org/10.1001/jamapsychiatry.2024.0796
Siebald, C., Khandaker, G. M., Zammit, S., Lewis, G., & Jones, P. B. (2016). Association between childhood psychiatric disorders and psychotic experiences in adolescence: A population-based longitudinal study. Comprehensive Psychiatry, 69, 45–52. https://doi.org/10.1016/j.comppsych.2016.05.004
Smith, D. J., Anderson, J., Zammit, S., Meyer, T. D., Pell, J. P., & Mackay, D. (2015). Childhood IQ and risk of bipolar disorder in adulthood: prospective birth cohort study. BJPsych Open, 1(1), 74–80. https://doi.org/10.1192/bjpo.bp.115.000455
Tobarra-Sanchez, E., Riglin, L., Agha, S. S., Stergiakouli, E., Thapar, A., & Langley, K. (2022). Preschool development, temperament and genetic liability as early markers of childhood ADHD: A cohort study. JCPP Advances, 2(3). https://doi.org/10.1002/jcv2.12099
Weavers, B., Heron, J., Thapar, A. K., Stephens, A., Lennon, J., Bevan Jones, R., Eyre, O., Anney, R. J., Collishaw, S., Thapar, A., & Rice, F. (2021). The antecedents and outcomes of persistent and remitting adolescent depressive symptom trajectories: a longitudinal, population-based English study. The Lancet Psychiatry, 8(12), 1053–1061. https://doi.org/10.1016/S2215-0366(21)00281-9
Winsper, C., Hall, J., Strauss, V. Y., & Wolke, D. (2017). Aetiological pathways to Borderline Personality Disorder symptoms in early adolescence: Childhood dysregulated behaviour, maladaptive parenting and bully victimisation. Borderline Personality Disorder and Emotion Dysregulation, 4(1), 1–10. https://doi.org/10.1186/s40479-017-0060-x
Winsper, C., Tang, N. K. Y., Marwaha, S., Lereya, S. T., Gibbs, M., Thompson, A., & Singh, S. P. (2017). The sleep phenotype of Borderline Personality Disorder: A systematic review and meta-analysis. Neuroscience and Biobehavioral Reviews, 73, 48–67. https://doi.org/10.1016/j.neubiorev.2016.12.008
Wolke, D., Schreier, A., Zanarini, M. C., & Winsper, C. (2012). Bullied by peers in childhood and borderline personality symptoms at 11 years of age: A prospective study. Journal of Child Psychology and Psychiatry and Allied Disciplines, 53(8), 846–855. https://doi.org/10.1111/j.1469-7610.2012.02542.x

World Health Organization. (1993). The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. World Health Organization, 2. https://doi.org/10.1007/978-3-319-24612-3_301942
Zammit, S., Horwood, J., Thompson, A., Thomas, K., Menezes, P., Gunnell, D., Hollis, C., Wolke, D., Lewis, G., & Harrison, G. (2008). Investigating if psychosis-like symptoms (PLIKS) are associated with family history of schizophrenia or paternal age in the ALSPAC birth cohort. Schizophrenia Research, 104(1–3), 279–286. https://doi.org/10.1016/j.schres.2008.04.036
Zammit, S., Kounali, D., Cannon, M., David, A. S., Gunnell, D., Heron, J., Jones, P. B., Lewis, S., Sullivan, S., Wolke, D., & Lewis, G. (2013). Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. American Journal of Psychiatry, 170(7), 742–750. https://doi.org/10.1176/appi.ajp.2013.12060768
Zammit, S., Thomas, K., Thompson, A., Horwood, J., Menezes, P., Gunnell, D., Hollis, C., Wolke, D., Lewis, G., & Harrison, G. (2009). Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring. British Journal of Psychiatry, 195(4), 294–300. https://doi.org/10.1192/bjp.bp.108.062471
Zanarini, M. C. (2003). Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): A continuous measure of DSM-IV borderline psychopathology. Journal of Personality Disorders, 17(3), 233–242. https://doi.org/10.1521/pedi.17.3.233.22147
Zanarini, M. C., & Frankenburg, F. R. (2001). Attainment and maintenance of reliability of axis I and II disorders over the course of a longitudinal study. Comprehensive Psychiatry, 42(5), 369–374. https://doi.org/10.1053/comp.2001.24556