Psychopathology and cognition as markers of risk for bipolar disorder

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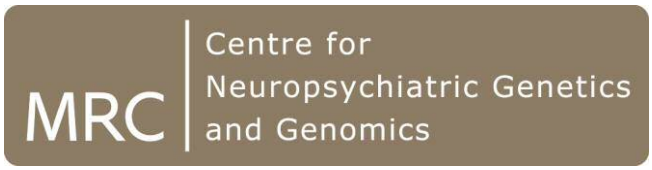

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Thesis Summary

Bipolar disorder (BD) is a fairly common, highly heritable psychiatric disorder which can be highly disabling to those who suffer from it. There is a limited understanding of early precursors to BD that might be helpful to inform prediction models and knowledge of aetiology. Few population-based longitudinal studies have examined associations between measures of childhood psychopathology/cognitive functioning and BD, or phenotypic manifestations of increased genetic risk for BD in childhood.

I investigated whether childhood psychopathology and cognitive domains examined from ages 8-11 years were associated with hypomania examined at ages 22-23 years. I then conducted a systematic review to identify phenotypes associated with genetic risk for BD, measured using a polygenic risk score (PRS) approach. Finally, I investigated whether increased genetic risk for BD, using a BD-PRS, was associated with various psychopathology and cognitive domains in childhood and hypomania in young adulthood.

Findings from Chapter 4 suggest that borderline personality disorder (BPD) traits in childhood are strongly associated with hypomania, particularly the 'risk-taking/irritable' factor. Better performance in the domains of working memory, problem solving ability, verbal learning and emotion recognition are also associated with hypomania, with stronger association with the 'active/elated' factor (Chapter 5). Findings from Chapter 6 highlight a limited literature on phenotypic manifestations of increased genetic risk for BD in childhood/adolescence. Individuals with increased genetic risk for BD are more likely to have ADHD, and have poorer executive functioning, processing speed and performance IQ in childhood (Chapters 7 and 8).

This thesis adds to a limited literature examining associations between measures of childhood psychopathology/cognition and hypomania in the general population, and about how increased genetic risk for BD is manifest in childhood/adolescence. Further work to examine the robustness of these

findings in other populations at various stages of development are required, and to elucidate the mechanisms that underlie the associations observed.

Publications resulting from work in this thesis

Mistry, S., Zammit, S., Escott-Price, V., Jones, H., Smith, D.J. (2017). Borderline Personality and Attention-Deficit Hyperactivity traits in childhood are associated with hypomanic feature in early adulthood. *Journal of Affective Disorders*, **221**, 246-253 https://doi.org/10.1016/j.jad.2017.06.039

Mistry, S., Harrison, J.R., Smith, D.J., Escott-Price, V., Zammit, S. (2017). The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: Systematic review. *Schizophrenia Research*, **197**, 2-8 https://doi.org/10.1016/j.schres.2017.10.037

Mistry, S., Harrison, J.R., Smith, D.J., Escott-Price, V., Zammit, S. (2018). The use of polygenic risk scores to identify phenotypes associated with genetic risk of bipolar disorder and depression: A systematic Review. *Journal of Affective Disorders*, **234**, 148-155 https://doi.org/10.1016/j.jad.2018.02.005

Mistry, S., Escott-Price, V., Florio, A.D., Smith, D.J., and Zammit, S. (2019). Genetic risk for bipolar disorder and psychopathology from childhood to early adulthood. *Journal of Affective Disorders*, **246**, 633-639

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Additional, related publications to which I have contributed

Richards, A., Horwood, J. O'Donnovan, M., Boden,J., Sellers, R., Riglin, L., **Mistry, S.,** Kennedy, M., Harold, G. (2019). Associations between schizophrenia genetic risk, anxiety disorders and manic/hypomanic episode in a longitudinal adult population cohort. *British Journal of Psychiatry* **214**, 96-102

Harrison, J.R., **Mistry, S.,** Muskett, N., Escott-Price, V. (2020). From polygenic scores to precision medicine in Alzheimer's Disease: A systematic review. *Journal of Alzheimer's Disease* (Article in press)

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Chapter 1: General Introduction

This thesis aims to inform understanding of the aetiology of bipolar disorder (BD) and the manifestations of BD genetic risk during childhood/early adulthood. This will be done using the population-based birth cohort the Avon Longitudinal Study of Parents and Children (ALSPAC). This first chapter will introduce the history of BD, its current nosology, known risk factors and the evolution of genetic studies of BD.

1.1 A short history of BD

The origins of BD can often be linked back to Hippocrates who is credited as the first person to systematically describe mania and melancholia, though it was Aretaeus of Cappadocia who began meticulously detailing symptoms in the medical field, particularly emphasizing the biological origin of melancholia. Up to the 19th century, mania and melancholia were considered as two separate disorders that encompassed a variety of syndromes. It was not until the 1850s when both Jean-Pierre Falret and Jules Baillarger described states of mania and melancholia as "*la foile circulaire*" meaning the circular insanity and "*folie à double forme"* (double insanity) respectively, in which the two mood states were linked. However, it is Emil Kraepelin, often labelled as the "father of modern psychiatry", who detailed the differences between *manic-depressive insanity* and *dementia praecox* (now termed schizophrenia (SZ)). He made a clear distinction between the features of manic-depressive insanity and *dementia praecox*, namely that *manic-depressive insanity* had an episodic nature, more benign prognosis and often presented in individuals with a history of manic-depressive illness. *Dementia praecox* on the other hand was characterized by disordered intellectual functioning, constant deterioration and poor prognosis (Angst and Marneros 2001; Angst 2002).

The term BD was first used by Karl Leonhard in 1957. He proposed a system which extended beyond a clinical description. As an example, he observed that within manic-depressive illness, some individuals had a history of both depression and mania, whilst others had a history of depression only. He also

reported that those with a history of mania had a higher incidence of mania in their families compared to those with recurrent depression only. He classified phasic psychoses into pure and polymorphous forms. The pure forms included: pure melancholia, pure mania, pure depressions and pure euphorias whilst polymorphous forms included: manic-depressive psychosis and the cycloid psychoses: anxiety-happiness psychosis, excited-inhibited confusion psychosis and hyperkinetic-akinetic mobility psychosis (Teichmann 1990).

1.2 Classification of BD

BD is a neuropsychiatric disorder characterised by recurrent changes in mood (mania, hypomania, depression or mixed episodes), energy and activity levels. The clinical presentation of BD is heterogeneous and differs from person to person, though there are nevertheless 4 main types of BD in the Diagnostic and Statistical Manual 5 (DSM 5): i) BD type I (BD-I) is characterised by experiencing a single episode of mania (lasting at least 1 week, or any duration if hospitalisation is required), ii) BD type II (BD-II) is characterised by experiencing at least one episode of hypomania (lasting at least 4 consecutive days, and present most of the day, nearly every day) and at least one episode of depression, iii) cyclothymia which is characterised by symptoms of hypomania and depression occurring for at least 2 years but these symptoms do not meet diagnostic criteria for a full episode of hypomania and/or depression, and iv) BD not otherwise specified (American Psychiatric Association 2013). It is therefore likely that there is a continuum of experiences ranging from normal mood to elevated mood but not meeting criteria for hypomania, hypomania and then mania being the most extreme experience. A number of studies have examined the underlying factor structure of hypomania, with suggestions of a dual structure (Hantouche et al. 2003; Angst et al. 2005a; Hantouche and Akiskal 2006; Brand et al. 2011). On the one hand, there are those who predominantly experience increased euphoria and energy-related symptoms (termed as “sunny-side” hypomania), and on the other hand those who predominantly experience more risk-taking and irritablity symptoms (termed as “dark-side” hypomania) (Hantouche et al. 2003; Brand et al. 2011). In this thesis, one of my main outcomes is hypomania which will be examined dimensionally (in line with Research Domain Criteria (RDoC) guidelines (see

section 1.2.2), and categorically (conforming more to the International Classification of Diseases-10 (ICD-10) criteria for bipolar affective disorder, current episode hypomanic (World-Health-Organisation 1993).

1.2.1 Issues with the current classification systems

The Kraepelin view of a clear distinction between SZ (*dementia praecox*) and BD (*manic-depressive insanity*) is still present in the modern classification systems (DSM-5 and ICD-10), despite some obvious overlap in symptom profile (e.g. presence of psychotic symptoms) between both disorders. A major criticism of current classification systems for diagnosing BD is that they rely exclusively on behavioural observations of the pattern and type of symptoms (i.e. they are a subjective and not objective way of defining someone as experiencing BD). This means there are often patients who do not "fit" into the clearly defined categories of BD or SZ, and often end up either classified under the "not-otherwise specified" category, or within other diagnostic groups e.g. schizoaffective disorder (Vieta and Phillips 2007; Phillips and Kupfer 2013). Using a categorical clinical diagnosis approach has its merits to inform communication between clinicians and appropriate treatment, however, their use in research, aimed at understanding the biological basis of psychiatric disorders and informing classification is more limited. Therefore, an alternative approach is to focus on dimensional measures of psychopathology, in which clinical diagnoses would be the extreme end of a distribution of traits in the general population (Craddock and Owen 2010). By adopting a dimensional approach, the sharp boundaries between meeting criteria for the disorder or not are removed, under the assumption that the dimensional approach also captures severity of impairment and chronicity. This may lead to addressing a common weakness of categorical clinical diagnosis and could help with the under-recognition, and therefore under-diagnosis, of bipolar disorders more generally (Angst et al. 2010; Angst et al. 2011).

1.2.2 The Research Domain Criteria (RDoC)

In an attempt to further progress in research on pathophysiology in the areas of Genomics and Neuroscience, the National Institute for Mental Health proposed

a framework, the RDoC (Insel et al. 2010). In a commentary piece clarifying the goal of the RDoC, the author wrote: “RDoC’s ultimate goal is precision medicine for psychiatry – a diagnostic system based on a deeper understanding of the biological and psychosocial basis of a group of disorders that is unambiguously among the most disabling disorders in medicine” (Insel 2014).

The RDoC framework has three assumptions: i) mental illnesses are brain disorders, which unlike neurological disorders, can be identified as disorders of brain circuitry, ii) abnormal neural circuitry can be identified using various clinical neuroscience methodology e.g. functional neuroimaging, and iii) data produced from research using the RDoC will identify “biosignatures” (Insel et al. 2010). At the most basic level, the RDoC is a 2-dimensional matrix, in which, each row represents a given behavioural/neurobiological domain (negative (e.g. response to adverse fear such as anxiety), positive (e.g. response to positive scenarios such as reward-seeking behaviour), cognitive (e.g. all cognitive processes), social processing (e.g. how you relate to other people including perception and interpretation) and arousal/regulatory system (e.g. regulation of systems for energy balance and sleep)), and each column the unit or measurement used to assess that domain (genes, molecules, cells, circuits, physiology, behaviour, self-report measure and paradigms). A completed version of this is shown in Table 1, with generic examples of units of analysis provided for each of the RDoC constructs (Morris and Cuthbert 2012). For a full list of potential units of analysis which can be used to investigate each of the constructs, the reader is directed to: https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/rdoc-constructs-with-units-of-analysis.shtml

Table 1 Research Domain Criteria Matrix

	Unit of analysis							
Domain/construct	**Genes[a]**	**Molecules**	**Cells**	**Circuits**	**Physiology**	**Behaviour**	**Self-report**	**Paradigms**
Negative		BDNF	GABAergic cells	Autonomic nervous system	Context startle	Avoidance	Fear survey schedule	Fear conditioning
Positive		Dopamine	Dopaminergic neurons	Amygdala	Cortical slow waves	Reward-related speeding	Affective forecasting	Drifting Double Bandit
Cognitive		Acetylcholine	Pyramidal cells	Posterior parietal cortex	Pupillometry	Impulsive behaviour	Conner's impulsivity scale	Antisaccade
Social processing		FMRP	Mirror neurons	Amygdala-brainstem	Local cerebral blood flow	Implicit mimicry	Face dimensional ratings scales	Penn emotion recognition
Arousal/regulatory systems		Serotonin	SCN "clock" cells	SCN core/shell	Neural activity	Sleep-related and waking behaviours	Sleep diary	Longitudinal actigraphy

[a] Research Domain Criteria guidelines as of May 2017 have guarded against referencing to specific genes within the RDoC matrix, hence this column being left blank; Examples provided in the respective columns are generic and taken from the RDoC website https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/rdoc-constructs-with-units-of-analysis.shtml; BDNF: Brain Derived Neurotrophic Factor; GABA: Gamma aminobutyric acid; FMRP: Fragile X Mental Retardation Protein; SCN: Suprachiasmatic Nucleus

Naturally, as with any tool, there are also criticisms with using the RDoC which are broken down into 4 key points: i) The RDoC places an overemphasis on biological units and measures, ii) there appears to be a neglect of consideration of measurement error, iii) the limitations of biological and psychometric endophenotypes, and iv) the distinction between biological predisposition to psychopathology and the behavioural manifestations of that psychopathology (Lilienfeld 2014). The ideal scenario is one in which categorical diagnoses incorporate information from dimensional measures of psychopathology. One such model has been proposed by Owen and colleagues, in which the clinical syndromes of mental retardation, Autism Spectrum Disorder (ASD), SZ, schizoaffective disorder and BD exist on a continuum. These clinical syndromes also lie on the neurodevelopmental impairment gradient, depending on the relative contributions of genetic and environmental risk (Owen 2014).

1.2.3 Impact of BD and pharmacological treatment

BD has a substantial impact on both the individual and society, with evidence from several studies reporting that unemployment, impaired friendships/social withdrawal and impaired functional recovery were common in those with BD up to 15 years after initial onset of symptoms (MacQueen et al. 2001; Dean et al. 2004; Conus et al. 2006). More broadly, these impairments also affect overall quality of life. Two systematic reviews on health related quality of life have reported those with BD (including during euthymia), when compared to the general population, have lower quality of life (Dean et al. 2004; Pascual-Sanchez et al. 2019).

A study in 2010 used data from the World Health Organisation's 2004 Global Burden of Disease study and reported that BD was the 4th highest leading cause of disability adjusted life years (DALYs), accounting for 3.8% of the total DALYs globally in the 10-24 years age group. This study also reported that neuropsychiatric disorders more generally accounted for 45% of years lost to premature mortality in the 10-24 years age group (Gore et al. 2011). In 2013, using data from the Global Burden of Diseases, Injuries, and Risk Factors Study, BD accounted for 7% of DALYs for all mental and substance use disorders, and was greatest between the age ranges 25 to 29 years of age

(Whiteford et al. 2013). A study using a further 3 years of data reported that amongst all mental and substance use disorders, BD was the 5th leading cause of DALYS, and accounted for 5.7% of the burden due to a mental or substance use disorder (Ferrari et al. 2016).

Current pharmacological treatment options tend to involve a combination of mood stabilisers, antipsychotics and antidepressants (Lopez-Munoz et al. 2018). When treating acute mania, antipsychotics are particularly effective, with evidence from meta-analysis suggesting haloperidol, risperidone and olanzapine being the most effective (Cipriani et al. 2011). When considering the most effective long term pharmacological treatment, evidence suggests the use of lithium carbonate, or lithium carbonate in combination with valproate (Goodwin et al. 2016). Unfortunately, even with treatment, up to one third of patients relapse into depression or mania within a year, with that figure rising to as high as 60% within 2 years (Gitlin et al. 1995). Effective treatments for the depressive phases of BD illness are under-researched, in spite of depression occurring more frequently than episodes of (hypo)mania (Solomon et al. 2010). Antidepressant monotherapy has the potential to cause a reverse in mood i.e. switch from depressed mood to (hypo)manic mood. However, as highlighted by the International Society for BD, this risk of mood switching appears to be higher in those with BD-I than with BD-II (Pacchiarotti et al. 2013). There is some evidence to suggest treatment using fluoxetine in combination with olanzapine being an efficacious option (Tohen et al. 2003; Taylor et al. 2014), though the Food and Drug Administration also suggest that Quetiapine or Lurasidone (monotherapy or in combination with lithium or valproate) may be used to treat bipolar depression (Shen 2018). Nevertheless, there are concerns over the limited efficacy of antidepressant use in the treatment of bipolar depression, with evidence from meta-analysis indicating its efficacy is no different from placebo (Sidor and MacQueen 2012; McGirr et al. 2016).

The episodic nature of BD can make its treatment difficult, especially in its early phases. It is clear that even though approved pharmacological treatments have efficacy, a substantial proportion of individuals will experience relapse in mood even with drug adherence.

1.3 Epidemiology of BD

A large-scale study of 61,392 community adults from 11 countries reported lifetime risk estimates for BD-I (0-1.0%), BD-II (0-1.1%), sub-threshold BD (0.1-2.4%) and bipolar spectrum (0.1-4.4%). The highest lifetime risk estimates irrespective of which BD type are in the United States, with lowest estimates in India (Merikangas et al. 2011). It is possible that international variations in lifetime risk might be attributed to differences in diagnostic criteria, cultural factors, ethnicity and study methodology (Rowland and Marwaha 2018).

A review (Diflorio and Jones 2010) reported little evidence of differences in 12-month prevalence of BD-I between males and females in 9 studies using data from Canada (Bland et al. 1988a; Bland et al. 1988b), the USA (Weissman et al. 1988; Weissman et al. 1996; Grant et al. 2005), Taiwan (Hwu et al. 1989), Korea (Lee et al. 1990), Australia (Mitchell et al. 2004), and New Zealand (Wells et al. 2006), but that 3 studies found higher 12 month prevalence of BD-II in women (Cassano et al. 1992; Baldassano et al. 2005; Schneck et al. 2008). A systematic review reported inconsistent evidence of differences in prevalence of BD based on ethnicity, which the authors proposed might be attributed to different levels of misdiagnosis as having SZ among different ethnicities, or that variations relate to different levels of migration across ethnic groups (Tsuchiya et al. 2003).

There is substantial clinical heterogeneity in those with BD, and one method to reduce this heterogeneity is to study individuals who share specific characteristics. One characteristic that has received substantial attention is age at onset of BD symptoms. Determining an accurate age of onset of first symptoms of BD can be difficult, particularly as patients are more likely to seek help when experiencing symptoms of depression than symptoms of (hypo)mania (Angst et al. 2005b; Fritz et al. 2017). This means an accurate diagnosis can be delayed by as much as 10 years after first presentation of symptoms of BD (Ghaemi et al. 2002; Baethge et al. 2003). Studies reporting data on age of onset of BD often base this on the age at which the BD patient accessed appropriate clinical services e.g. age when they were admitted to hospital, age at when they received a diagnosis, or age when they first received

treatment for BD, rather than the age the individual was when they first experienced BD symptoms (see Table 2).

A number of studies have examined age at onset of BD, with some studies reporting a two-peak, and others a three-peak distribution for age at onset. In those reporting a bimodal distribution, findings from large population-based cohorts report the peak age of onset ranges are: early (between ages 15-24 years) and late (between 35-54 years) (Schurhoff et al. 2000; Carter et al. 2003; Kroon et al. 2013; Manchia et al. 2017). For studies that have used admixture analysis, 3 peaks for age at onset for BD-I have been reported: early (mean age of ~17 years), intermediate (mean age of ~26 years) and late (mean age of ~ 35-46 years) (Bellivier et al. 2001; Bellivier et al. 2003; Lin et al. 2006; Manchia et al. 2008; Hamshere et al. 2009; Tozzi et al. 2011). It is yet to be determined as to whether a bimodal or trimodal distribution best fits data on age at onset of BD symptoms, and which threshold(s) are optimal for investigating clinical and genetic differences between subgroups based on age at onset. As shown in Table 2, sample sizes have been relatively small, and therefore potential differences between age at onset estimates may be due to chance attributed to low statistical power as opposed to true effects (Depp and Jeste 2004; Chu et al. 2010). Nevertheless, there is some evidence, albeit inconsistent, that compared to late-onset BD patients, early-onset BD patients have: i) more psychotic features (hallucinations and/or delusions), ii) higher familial loading for BD, iii) a longer time to accurate diagnosis, iv) more hospital admissions, v) a greater number of suicide attempts, and vi) a greater comorbidity with substance abuse and panic disorder (Schurhoff et al. 2000; Leboyer et al. 2005; Azorin et al. 2013).

Table 2 Summary of studies examining age at onset of BD

Study	Diagnosis	Country	Sample size	How age at onset was defined	Age at onset (years)
Schurhoff et al. 2000	DSM-IV BD-I and BD-II, and RDC BD	France	211	Age at diagnosis, age at treatment and age at first hospitalisation	Early (15.5); Late (48.5)
Bellivier et al. 2001	DSM-IV BD-I	France	211	Age at diagnosis	Early (16.9); Mid (26.9); Late (46.2)
Bellivier et al. 2003	DSM-IV BD-I	France, Switzerland, Germany and Ireland	368	Age at diagnosis	Early (17.6); Mid (24.6); Late (38.2)
Carter et al. 2003	DSM-IV BD-I and BD-II	Canada	319	Age at diagnosis	Early (14.6); Late (26.1)
Perlis et al. 2004	DSM-IV BD-I, BD-II and BDNOS	USA	983	Age at diagnosis	Early (<12); Mid (13-18); Late (>18)
Lin et al. 2006	DSM-III-R BD-I, SZA and RDC BD-II	USA	211	Self-report of onset of first symptoms	Early (16.6); Mid (26.0); Late (34.7)
Kessing et al. 2006	ICD BAD	Denmark	1,719	Age at contact with clinical services	Early (<50); Late (>50)

Table 2 continued

Study	Diagnosis	Country	Sample size	How age at onset was defined	Reported mean age of onset/age at first episode (years)
Subramaniam et al. 2007	ICD 10 BAD	UK	50	Age at diagnosis	Early (31.0); Late (72.0)
Manchia et al. 2008	RDC BD-I	Sardinia	181	Age at diagnosis	Early (18.1); Mid (24.3); Late (41.0)
Hamshere et al. 2009	DSM-IV BD-I	UK	1,369	Age of first impairment due to mood episode	Early (18.7); Mid (28.3); Late (43.4)
Tozzi et al. 2011	DSM-IV BD-I and BD-II or ICD-10 BD	Canada and the UK	964	Self-report of onset of first symptoms	Early (16.1); Mid (25.4); Late (32.2)
Kroon et al. 2013	DSM-IV BD-I or BD-II	The Netherlands	649	GP records	Early (15-24); Late (45-54)
Manchia et al. 2017	DSM-IV-TR BD I, BD-II or BDNOS	Italy	515	Age at diagnosis	Early (21.9); Late (37.6)

DSM-IV: Diagnostic and Statistical Manual-IV; DSM-III-R: Diagnostic and Statistical Manual-III-Revised; BD-I: Bipolar Disorder type I; BD-II: Bipolar Disorder type II; SZA: Schizoaffective Disorder; BDNOS: Bipolar Disorder Not Otherwise Specified; BAD: Bipolar Affective Disorder RDC: Research Diagnostic Criteria; ICD: International Classification of Diseases

1.4 Aetiology of BD

BD is a complex multifactorial disease whereby neither genetic nor environmental risk alone determine whether someone develops BD or not. In the next few sections, I will be describing evidence pertaining to the role of genetics, environment (pre, peri and post-natal), psychopathology and cognition.

1.4.1 Genetic studies of BD

Family, twin and adoption studies are different approaches used to estimate the effect of environment and genetic influences on a particular disorder/trait in individuals who differ in their degree of biological relatedness.

1.4.1.1 Family studies

Family studies aim to answer a simple question: Does the prevalence of the disorder among first degree relatives (FDRs) of affected probands differ from the prevalence in the general population or amongst relatives of unaffected probands? If this is true, the question arises as to whether this is due to genetic or environmental factors, or both.

Family studies prior to 1960 did not distinguish unipolar from BD, instead following the Kraepelinian definition of manic-depressive illness. Nevertheless, these studies were consistently reporting an excess risk (4.8-15.8%) of manic-depressive disorder in the FDRs of manic-depressive probands (Tsuang and Farone 1990). Post 1960, with collaborations between centres, a series of standardised instruments for assessing affective disorders was developed (Feighner et al. 1972; Spitzer et al. 1978). Following this refinement, numerous family studies were consistently reporting excess risk of BD among FDRs of affected BD probands compared to either FDRs of controls or the population baseline risk of 1% (Tsuang et al. 1980; Weissman et al. 1984; Maier et al. 1993; Craddock and Jones 1999). The lifetime risk of BD in FDRs of BD probands has been reported to be between 7-10, which is 7-10 times that of the general population of 1-2% (Barnett and Smoller 2009). There is also some evidence to suggest both the BD-I and BD-II subtypes might be partly, but not entirely genetically distinct. Several studies have reported the risk of BD-II is higher in the FDRs of BD-II probands than FDRs of BD-I probands, and risk of BD-I is higher in FDRs of BD-I probands than FDRs of BD-II probands (Gershon et al. 1982; Andreasen et al. 1987; Heun and Maier 1993; Song et al. 2018). Several of these studies also suggest that FDRs of BD probands are also at increased risk of depression when compared to FDRs of controls (Gershon et al. 1982; Heun and Maier 1993).

Whilst initial family studies used clinically-ascertained samples, these often had relatively small sample sizes. A shift towards using national registers and linking with hospital records provided larger sample sizes and validated earlier findings.

A study using data from two Swedish national registers from 1947 reported the relative risk (RR) for BD when the proband had BD or SZ for a number of different possible relationships. Increased risk of BD to FDRs was strongest for parent-offspring (RR = 6.4) and full sibling relationships (RR = 7.9), a result which is similar for SZ if the proband has SZ (RR = 9.9 for parent-offspring and RR = 9.0 full sibling relationships) (Lichtenstein et al. 2009). Later studies also using the same Swedish data as that from Lichtenstein and colleagues but longer follow-up have also reported excess risk of BD among FDRs for BD (Song et al. 2015; Chen et al. 2019), Attention Deficit Hyperactivity Disorder (ADHD) (Larsson et al. 2013) and ASD (Sullivan et al. 2012).

Other studies have examined risk for other psychiatric disorders in FDRs of BD probands and reported increased RR and/or odds of disease for SZ, MDD, ASD, ADHD, personality disorders and drug abuse (Song et al. 2015; Song et al. 2018; Chen et al. 2019), as well as the possibility of a dose-dependent relationship between risk for psychiatric illness and number of BD probands in FDRs. In brief, the greater the number of probands with a BD diagnosis a FDR has, the greater the increase in risk of psychiatric illness in the FDR (Gottesman et al. 2010; Chen et al. 2019).

1.4.1.2 Twin studies

Though family studies are consistent with a genetic component to BD, it is not possible to distinguish this from environmental contributions to BD. To try estimate this, classical twin research comparing concordance rates between monozygotic (MZ) and dizygotic twins (DZ) is used. MZ twins are assumed to share 100% of their genome, whilst DZ twins share on average 50%. It would be expected that there is a greater concordance rate for the genetic component in MZ twins compared to DZ twins. However, this is based on the equal environment assumption. The assumption is that shared environmental influences on MZ twins are not different from the shared environmental

influences on DZ twins i.e. MZ twins are not treated more similar than DZ twins throughout the life course (Fosse et al. 2015).

In a similar fashion to early family studies, early twin studies (pre-1960) also had a number of methodological shortcomings including lack of blinded study design, small sample sizes, non-specific structured assessments in diagnostic procedures and not distinguishing between unipolar disorder and BD (Tsuang and Farone 1990). Nevertheless, there was consistent evidence of higher concordance rates in MZ twins compared to DZ twins.

Much like with family studies, there was a shift towards using large population-based registers from the 1970s onwards (Allen et al. 1974; Bertelsen et al. 1977; Torgersen 1986; Kendler et al. 1995; Cardno et al. 1999; McGuffin et al. 2003; Kieseppa et al. 2004). There was also a shift towards using operational diagnostic criteria as opposed to the narrow Kraepelinian definition of manic-depressive illness. Concordance rates for studies published post 1970 range from 20-75% for MZ twins and 0-20% for DZ twins. From the available evidence, it is clear that genetics plays a substantial role in determining whether someone goes on to develop BD. Heritability estimates based on a recent twin study using data from the Swedish Twin Registry suggest heritability to be between 50-70% (Johansson et al. 2019).

1.4.1.3 Adoption studies

Adoption studies seek to estimate the extent to which variation in a given trait is due to environmental and genetic influences. Unlike the situation for SZ (Ingraham and Kety 2000), adoption studies for BD are few and with small sample sizes (Smoller and Finn 2003). One method that has been used is the adoptees' relative method which compares rates of BD between biological and adoptive relatives of adoptees with BD (probands). Rates of affective illness (BD, unipolar, schizoaffective disorder and cyclothymic disorder) in the biological parents of probands was higher (31.6%) than rates in the adopted parents (12.2%) (Mendlewicz and Rainer 1977). Similar findings were reported in another study examining rates of affective disorders (unipolar and BD) in which biological parents had higher rates (5.2%) than adopted parents (2.8%)

(Wender et al. 1986). More recently, two studies have used the adoptee's method, as opposed to earlier studies using the adoptee's relative method described above. In the adoptee's method, the proband is the parent who has BD as opposed to adoptee having BD. Using data from Swedish national registries, the RR in adopted away offspring of BD probands was higher (RR = 4.3) than for adoptees whose adoptive parent had BD (RR = 1.3) (Lichtenstein et al. 2009). Similarly, another study using the same registry but with a longer follow-up reported that RR in adopted away offspring of a BD parent was higher (RR = 5.0) than for adoptees whose adoptive parent had BD (RR = 3.1) (Song et al. 2015).

1.4.2 Molecular genetic studies of BD

Given that concordance rates for BD in MZ twins are not 100%, one can conclude that genetic risk factors alone cannot be sufficient causes of BD, though they are likely necessary (Barnett and Smoller 2009). A complete understanding of the genetic aetiology of BD still eludes researchers to this day, but it is likely there are multiple genetic and environmental influences, which can be different in different people, and which could help account for a heterogeneous phenotype. Similar to other complex psychiatric and non-psychiatric disorders, relatives of patients with BD likely carry an excess of risk alleles for BD which can be passed on to the offspring. To progress the understanding of the aetiology of BD, the search for chromosomal loci and specific genes conferring risk for BD has been aided by several technological changes. These have allowed the transition from linkage studies to association methods and from candidate gene studies to more genome-wide approaches.

1.4.2.1 Linkage studies

The purpose of linkage studies is to examine several hundred to thousand markers which are spread across the genome in an attempt to identify chromosomal regions where susceptibility genes may be found. By examining these markers, it is possible to determine which loci found near to one another appear to be co-inherited together more often than by chance.

Though individual studies themselves may provide suggestive evidence of potential chromosomal regions implicated in BD at both genome-wide and suggestive significance, meta-analyses pool this data together allowing greater statistical power using larger samples. Evidence from a number of meta-analyses highlight the following chromosomal regions as potentially implicated in BD: 13q, and 22q (Badner and Gershon 2002), 9p21.1-p22.3, 10q11.2-q22.1, 14q24.1-q32.12 and 18p11-q22.1 (Segurado et al. 2003), 6q, 8q, 9p and 20p (McQueen et al. 2005).

Though linkage studies for single gene Mendelian disorders such as Huntington's disease have been successful, the success for BD and other psychiatric disorders more generally has not mirrored this (Sklar 2002). As is evident from the numerous meta-analyses, there appears to be a lack of consistency in determining which chromosomal regions are implicated in the aetiology of BD.

1.4.2.2 Candidate gene association studies

Unlike linkage studies, the candidate gene study approach tests genetic markers with a presumed functional relevance to a particular disorder using either a case-control (unrelated cases vs population-based controls) or family study (using the trio design with the affected child having the disease and the unaffected parents acting as controls) design. Whilst linkage is a property of genes or loci within families, association is a property of alleles which can be studied across a population.

There are a number of promising candidate genes, most of which are neurotransmitter genes, particularly serotonin, dopamine and noradrenaline given their apparent pharmacological role in regulating mood (particularly depression). A recent meta-analysis of 487 candidate gene association studies of BD found the most widely studied gene was the *SL6A4* gene which is a serotonin transporter gene (n = 41). The second most studied gene was the serotonin receptor 2A (*HTR2A*) examined in 21 studies. The authors ran a random effects meta-analysis on 18 genes and reported significant associations for single polymorphisms in four different genes: Brain-derived neurotrophic

factor (*BDNF*) (p = 0.05), dopamine receptor 4 (*DRD4*) (p = 0.037), d-amino acid oxidase activator (*DAOA*) (p = 0.05) and tryptophan hydroxylase 1 (*TPH1*) (p = 0.001). However, these associations did not survive correction for multiple testing (Seifuddin et al. 2012). Despite a large number of potential candidate genes being reported as associated with BD, there are substantial limitations to the candidate gene approach (and a lack of replication across studies), including: i) selecting genes *a priori* depends on an accurate understanding about the aetiology of BD, which is not well understood, ii) individual studies using a candidate gene approach had sample sizes which would likely be underpowered to detect a small effect size, and iii) poorly matched cases and controls (including population stratification) can lead to spurious findings, likely overestimates of the true effect (Hirschhorn et al. 2002; Sullivan 2007; Button et al. 2013).

1.4.2.3 Genome-Wide Association Study (GWAS) findings for BD

GWAS offer a more powerful atheoretical alternative to both linkage and candidate gene studies. Linkage studies do not have the sample sizes to be sufficiently powerful enough to detect small to moderate effect sizes (OR = 1.1-1.5) for common diseases (Spencer et al. 2009), whilst candidate gene studies have a very low *a priori* likelihood of identifying any novel single nucleotide polymorphisms (SNPs). Using GWAS, variants across the whole genome can be examined in a hypothesis-free manner. Current GWAS chips are able to genotype between 500,000-1,000,000 SNPs simultaneously.

1.4.2.3.1 Methodological considerations

As with any method of analysis, there are also a number of considerations which must be adhered to when interpreting findings. Firstly, many genotype markers are often highly correlated and are inherited together more often than by chance. This occurrence is known as linkage disequilibrium (LD) and refers to the non-random occurrence of alleles at multiple loci in the genome. To account for this, SNPs can be clumped whereby the most significant p-value is retained per LD block. Another consideration is that testing so many SNPs simultaneously for association with a particular phenotype may lead to false

positive results i.e. increased type 1 error. There are several methods researchers can use to correct for multiple testing such as the Bonferroni correction, false discovery rate, positive false discovery rate and permutations. At the time of writing this thesis, a SNP is considered genome-wide significant if its p-value is equal to or lower than 5×10^{-8} which equates to (0.05/1,000,000 tests). Adjusting the threshold required to be considered as a significant finding reduces the type I error.

1.4.2.3.2 Early GWAS findings (before large-scale Psychiatric Genomics Consortium (PGC) work)

Several studies have used individual or pooled genotyped data to conduct GWAS to identify loci associated with BD. The first GWAS of BD was conducted by the Wellcome Trust Case-Control Consortium (WTCCC) and contained individual genotype data on 2000 BD cases and 3000 controls from the 1958 British Birth Cohort. Only one SNP (rs420259) on chromosome 16p12, in the Partner and Localiser of *BRCA2* (*PALB2*) gene (heterozygous OR = 2.08; homozygous OR = 2.07, both $p = 6.29 \times 10^{-8}$) was reported as genome-wide significant (Wellcome Trust Case Consortium et al. 2007).

Subsequent studies prior to the first PGC BD GWAS publication often used overlapping samples for meta or mega analysis but were not always able to replicate the most strongly associated SNP(s) (Baum et al. 2008a; Baum et al. 2008b; Ferreira et al. 2008; Sklar et al. 2008; Hattori et al. 2009; Schulze et al. 2009; Scott et al. 2009; Smith et al. 2009; Djurovic et al. 2010; Cichon et al. 2011; Jiang and Zhang 2011; Lee et al. 2011; Smith et al. 2011; Yosifova et al. 2011) (see Table 3 for order in which these GWAS were conducted). It is possible that inconsistencies and lack of replication were due to relatively small sample sizes, thus leading to underpowered analyses.

1.4.2.3.3 The PGC GWAS findings for BD

The PGC group was set up in 2007 with the aim of uniting researchers from around the world. This was to combine primary genotype data from studies with overlapping samples, for both meta and mega analysis, both within and across various psychiatric disorders.

To date, results from the PGC schizophrenia group have highlighted the necessity of larger sample sizes to detect loci of small effect size that reach genome-wide significance. Evidence supporting this comes from examining the updated PGC-2 schizophrenia sample (Ripke et al. 2014), which identified 108 loci at genome-wide significance, in stark contrast to using the original PGC-1 schizophrenia sample which identified around 7 loci, five of which were novel (Purcell et al. 2009).

The first paper published by the PGC BD group was in 2011 and had 7481 unique cases and 9,250 unique controls of European ancestry from 11 case-control GWASs of BD. Cases had the following diagnoses: BD-I, n = 6,289 (84%); BD-II, n = 824 (11%); schizoaffective disorder, n = 263 (4%) and bipolar disorder not otherwise specified, n = 104 (1%). The authors reported 38 SNPs reached genome-wide suggestive ($p<5x10^{-5}$) evidence, though only 4 regions contained SNPs which had a raw p-value at genome-wide significance; SNP rs1099437 located in the *ANK3* gene on chromosome 10q21 ($p = 5.5x10^{-10}$; OR = 1.15), SNP rs9371601 located in synaptic nuclear envelope protein 1 (*SYNE1*) on chromosome 6q25 ($p = 4.3x10^{-9}$; OR = 1.15), the intergenic SNP rs7296288 found in a region of linkage disequilibrium (LD) of ~100 kb on chromosome 12q13 containing 7 genes ($p = 9.4x10^{-9}$; OR = 1.15) and a novel SNP, SNP rs12576775 in the first intron of *ODZ4* on chromosome 11q14 ($p = 2.7x10^{-7}$; OR = 1.18). *ODZ4* is the human homolog of the Drosophila pair-rule gene ten-m (*odz*). However, only 2 SNPs, SNP rs1099437 (*ANK3*) and SNP rs9371601 (*SYNE1*) had a genomic control p-value at genome-wide significance ($p = 7.1x10^{-9}$ and $p = 4.3x10^{-8}$) respectively (Sklar et al. 2011).

In a replication analysis using an independent data set containing a further 4,493 BD cases and 42,542 controls, a fixed effects meta-analysis found 2 SNPs at genome-wide significance after correction for multiple testing: SNP rs4765913 on chromosome 12p13.33 in the *CACNA1C* gene encoding the α subunit of the L-type voltage-gated calcium channel (OR = 1.14; $p=1.82x10^{-9}$) and SNP rs12576775 in *ODZ4* (OR = 0.89; $p = 2.77x10^{-8}$) (Sklar et al. 2011).

Subsequent meta-analyses published which included PGC-1-BD data (but have not included the recent PGC-2BD GWAS) have identified 7 novel SNPs:

rs9834970, rs2271893 and rs4650608 located near the genes *TRANK1* (*LBA1*), *LMAN2L* and *PTGFR* respectively (Chen et al. 2013), rs17826816 in the gene Adenylate cyclase 2 (*ADCY2*) and rs12202969 found in a region between microRNA 2113 (*MIR2113*) and POU class 3 homeobox 2 (*POU3F2*) (Muhleisen et al. 2014), and finally rs174576 in the Fatty Acid Desaturase 2 gene (*FADS2*) and rs4926298 near Nuclear Family I/X (*NFIX*) (Ikeda et al. 2018).

At present, using the second PGC BD GWAS containing 20,352 BD cases (n = 14,879 BD-I; n = 3,421 BD-II, n = 977 schizoaffective disorder and n = 1,075 with BD unspecified) and 31,358 controls of European ancestry from 32 cohorts, 30 genome-wide significant loci have been identified, 20 of which were novel (Stahl et al. 2019).

Table 3 Comparison of findings between studies conducting GWAS of BD

Author and year	Population i.e. ancestry	Diagnoses	Genotyping platform(s) used	N	Top SNP(s)	Nearest gene	P value reported
WTCCC 2007	European	BD-I, BD-II, SZA and manic disorder	Affymetrix 500K	1,838 cases and 2,938 controls	rs420259	*PALB2*	$6.3x10^{-8}$
Baum et al. 2008a	European (NIMH waves 1-4)	BD-I	Illumina 550	1,233 cases and 1,439 controls	rs1012053	*DGKH*	$1.5x10^{-8}$
Sklar et al. 2008	European	BD-I	Affymetrix 500K or 5.0	1,461 cases and 2,008 controls	rs4939921	*MYO5B, TSPAN8* and *EGFR*	$1.7x10^{-7}$, $6.1x10^{-7}$ and $8.4x10^{-8}$
Ferreira et al. 2008a	European	BD-I and BD-II	Affymetrix 5.0 or 6.0	1,098 cases and 1,267 controls	rs7221510	*SKAP1*	$1.4x10^{-6}$
Baum et al. 2008b	Meta-analysis combining data from WTCCC sample and Baum et al. 2008a			3,101 cases and 4,377 controls	rs10791345 and rs4806874	*JAM3* and *SLC39A3*	$1x10^{-6}$ and $5x10^{-6}$
Ferreira et al. 2008b	Meta-analysis combining data from WTCCC sample, Sklar et al. 2008 and Ferreira et al. 2008a samples			4,387 cases and 6,209 controls	rs10994336 and rs1006737	*ANK3 and CACNA1C*	$9.1x10^{-9}$ and $7.0x10^{-8}$
Hattori et al. 2009	East Asian (Japanese)	BD-I, SZA and SAD	Affymetrix 100K and Illumina	107 cases and 107 controls	rs10994336	*ANK3*	$3x10^{-6}$

Table 3 continued

Author and year	Population (ancestry)	Diagnoses	Genotyping platform(s) used	N	Top SNP	Nearest gene	P value reported
Scott et al. 2009	European (meta-analysis containing samples from WTCCC sample, Baum et al. 2008a and Ferreira et al 2008b			3,683 cases and 14,507 controls	rs17418283; rs1042779; rs472913	*Intron of MCTP1; NEK4; NF1A*	1.3x10-7; $1.8x10^{-7}$; $2.0x10^{-7}$
Smith et al. 2009	European and African (contains overlapping samples with Baum et al. 2008a, Sklar et al. 2008 and Scott et al. 2009)	BD-I or SZA	Affymetrix 6.0	European (1,001 cases and 1,033 controls); African (345 cases and 670 controls)	European: rs5907577; African: rs2111504	European: Intergenic region at Xq27.1*;* African: *DPY19L3*	European: $1.6x10^{-6}$; African: $1.5x10^{-6}$
Djurovic et al. 2010	European (Norway and Iceland)	BD	Affymetrix 6.0 and HumanHap300	194 cases and 336 controls	rs4377455	*RBMS3* RNA binding motif	$5.39x10^{-7}$
Cichon et al. 2011	European (WTCCC sample), USA (Smith et al. 2009 sample) and Australia	BD-I, BD-II, SZA, BDNOS or MD	HumanHap550 (Illumina)	8,441 cases and 35,362 controls	rs1064395	*NCAN*	Meta-analysis P value: $2.14x10^{-9}$
Lee et al. 2011	East Asia (Taiwan)	BD-I	Illumina HapMap 550	1000 cases and 1000 controls	rs2709736	*SP8*	$4.87x10^{-7}$

Table 3 continued

Author and year	Population (ancestry)	Diagnoses	Genotyping platform(s) used	N	Top SNP	Nearest gene	P value reported
Yosifova et al. 2011	European (Bulgarian)	BD	Illumina Hap550v3	188 cases and 376 controls	rs8099939; rs6122972; rs2289700	*GRIK5, PARD6B* and *CTSH*	$9.86x10^{-8}$, $3.11x10^{-6}$ and $9.14x10^{-6}$
PGC-1-BD	European (received primary genotypes from 11 previously reported samples of European ancestry)			7,481 cases and 9,250 controls	rs10994397; rs9371601; rs7296288; rs12576775	*ANK3; SYNE1; Intergenic (many); ODZ4*	$7.1X10^{-9}$; $4.3X10^{-8}$; $8.4X10^{-8}$; $2.1X10^{-7}$
Chen et al. 2013	Meta-analysis of European (PGC-1-BD) and East Asian (Lee et al. 2011) samples			6,658 cases and 7,155 controls	rs9834970; rs2271893; rs4650608	*TRANK; LMAN2L; PTGFR*	$2.4x10^{-11}$; 1.1x10-[8]; $1.2x10^{-7}$
Muhleisen et al. 2014	Meta-analysis combining PGC-1-BD and data from MooDS (European, Australian and Canadian)			9,747 cases and 14,278 controls	rs17826816; rs12202969	*ADCY2; between MIR2113 and POU3F2*	$9.9x10^{-9}$; $1.1x10^{-8}$
Ikeda et al. 2018	Meta-analysis combining European (PGC-1-BD) and East Asian (Japanese) sample		Illumina Human Omni Express Exome	10,445 cases and 71,137 controls	rs174576; rs4926298	*FADS2;* NFIX	$1.3x10^{-10}$; $5.8x10^{-10}$

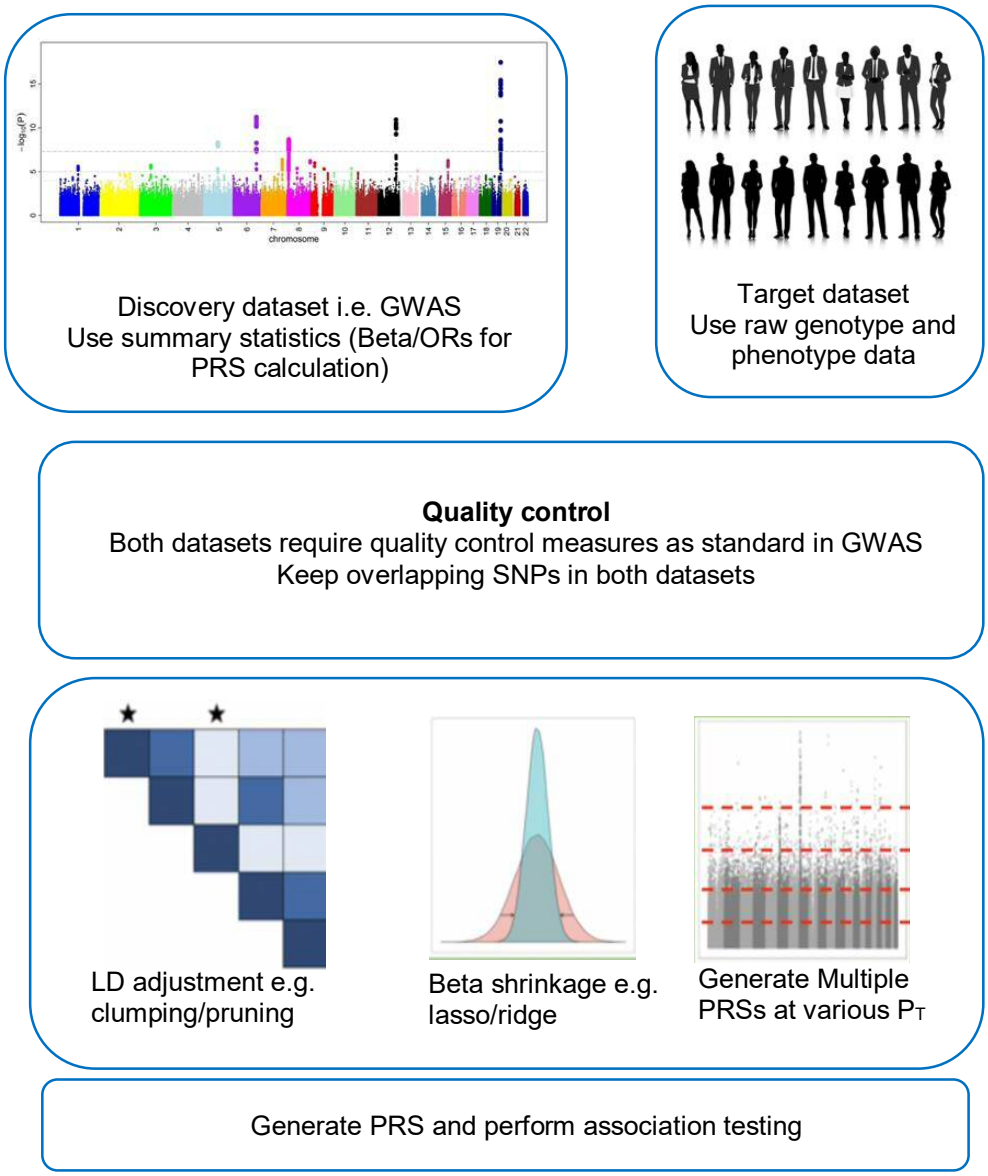
GWAS: Genome Wide Association Study; BD: Bipolar Disorder; WTCCC: Wellcome Trust Case Control Consortium; BD-I: Bipolar Disorder type I; BD-II: Bipolar Disorder type II; SZA: Schizoaffective Disorder; BDNOS: Bipolar Disorder Not Otherwise Specified; MD: Manic Disorder SNP: Single Nucleotide Polymorphism; ANK3: Ankyrin 3; CACNA1C: Calcium Voltage-Gated Channel Subunit Alpha1 C; JAM3: Junctional Adhesion Molecule 3; SLC39A3: Solute Carrier Family 39 Member 3; SKAP1: Src Kinase Associated Phosphoprotein 1; EGFR: Epidermal Growth Factor Receptor; TSPAN8: Tetraspanin 8; MYO5B: Myosin 5B; DGKH: Diacylglycerol Kinase eta; PALB2: Partner and Localiser of BRCA2; MooDS: Systematic Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia; GRIK5: Glutamate Ionotropic Receptor Kainate type subunit 4; PARD6B: Par-6 Family Cell Polarity Regulator Beta; CTSH: Cathepsin H; ANK3: Ankyrin 3; SYNE1: Spectrin Repeat Containing Nuclear Envelope Protein 1; TRANK4: Tetratricopeptide Repeat and Ankyrin repeat containing 4; LMAN2L: Lectin

Mannose binding 2 Like; PTGFR: Prostaglandin F receptor; ADCY2: Adenylate Cyclase 2; MIR2113: MicroRNA 2113; RNA: Ribonucleic Acid; POU3F2: POU class 3 homeobox; FADS2: Fatty Acid Desaturase 2; NFIX: Nuclear Family I/X; MCTP1: Multiple C2 and Transmembrane Domain Containing 1; NEK4: Never in mitosis gene A Kinase 4; NF1A: Nuclear Factor 1A; DPY19L3: DPY-19 Like C-Mannosyltransferase 3; RBMS3: RNA Binding Motif Single Stranded Interacting Protein 3; RNA: Ribonucleic Acid; NCAN: Neurocan; SP8: SP8 Transcription factor

1.4.2.4 Polygenic Risk Score (PRS)

It is clear that through GWAS, a number of SNPs occurring more frequently in BD cases compared to controls have been identified (Sklar et al. 2011; Ruderfer et al. 2018; Stahl et al. 2019), though the effect each of these SNPs has individually on disease risk is small and limits predictive power (Dudbridge 2013). A newer statistical technique, the PRS, combines trait-associated SNPs into a single score, with the aim of explaining a greater proportion of the variation in the trait of interest. The basic principles of PRS analyses involve using two datasets. The first is the discovery (or training) dataset which is selected as the largest available GWAS for the trait being investigated. For PRS analyses, summary statistics of the genotype-phenotype associations are used, and for the major psychiatric disorders, are freely available online from the PGC downloads page (https://www.med.unc.edu/pgc/results-and-downloads/). The second is the target dataset, in which, raw genotype and phenotype data are available for each individual within the dataset. The PRS is calculated as the sum of risk-associated alleles weighted by the effect size (usually an OR) from the largest and most powerful GWAS (Wray et al. 2014). A summary diagram of the basic stages involved in generating a PRS is shown in Figure 1. A more detailed overview of the steps involved in generating the PRS, including quality control measures can be found in Chapter 3, section 3.5.

Figure 1 Summary diagram for performing PRS analyses



Adapted from Choi et al. (2018); GWAS: Genome Wide Association Study; OR: Odds Ratio; PRS: Polygenic Risk Score; SNPs: Single Nucleotide Polymorphisms; LD: Linkage Disequilibrium; P_T: P-value threshold cut off score

The first study to use the PRS approach to investigate associations with any phenotype was that by the International Schizophrenia Consortium (ISC). The authors of the study investigated the extent to which common genetic variants i.e. SNPs occurring more frequently in SZ cases compared to controls contribute to risk of both SZ and BD. The authors found consistent evidence of association between the SZ-PRS and SZ, as well as evidence of association with BD. Their findings also highlighted that the inclusion of SNPs below

genome-wide significance in the derivation of the PRS increased the proportion of variance explained in both disorders (Purcell et al. 2009).
Some years later, using the same principles as the ISC, the PGC group collated information from 11 sites globally and conducted a GWAS to identify SNPs occurring more frequently in BD cases compared to controls. When performing PRS analyses, the authors tested multiple p-value threshold cut off scores (P_T's) and determined the threshold which explained the greatest proportion of variance in BD was a $P_T \leq 0.5$ (R^2 = ~3% on the observed scale and ~1% on the liability scale) (Sklar et al. 2011). More recently, using data from the 2nd PGC BD GWAS, the threshold which is now considered optimal to maximally capture variance in BD is a $P_T \leq 0.01$ (R^2 = ~8% on the observed scale and ~4% on the liability scale) (Stahl et al. 2019).

Originally, PRS analyses were used to examine the proportion of variance in disorder explained by common genetic variants. However, as shown by the ISC (Purcell et al. 2009), the PRS approach can also be used to investigate associations with non-discovery sample phenotypes. Therefore, using the PRS approach, it is possible to examine potential phenotypic manifestations of increased genetic risk in various populations across the lifespan. Chapter 6 of this thesis will examine the current known phenotypic manifestations of increased genetic risk for BD, though the published article contains information on phenotypic manifestations of genetic risk for depression as well as BD (Mistry et al. 2018a).

1.4.3 Environmental risk factors

As highlighted in the previous section, genetics plays an important role in determining whether an individual goes on to develop BD. However, it is likely that other non-genetic factors also play a role given concordance rates for BD in MZ twins is not 100%. Environmental risk factors can occur pre, peri and postnatally, and can be categorised into neurodevelopmental, substance abuse related and physical/psychological stress (Marangoni et al. 2016).

Data on studies investigating various environmental risk factors is limited. There has been inconsistent evidence for an association between: i) smoking during

pregnancy and risk of BD in the offspring (Talati et al. 2013; Chudal et al. 2015; Marangoni et al. 2016; Quinn et al. 2017), ii) birth complications and risk of BD (Bain et al. 2000; Chudal et al. 2014; O'Neill et al. 2016), iii) lower gestational age and risk of BD (Ogendahl et al. 2006; Nosarti et al. 2012) and iv) being exposed to infectious agents during pregnancy and BD in the offspring (Barichello et al. 2016). In contrast, there are some consistent findings across studies such as: i) little evidence of association between low birth weight (<2,500g) and BD (Ogendahl et al. 2006; Nosarti et al. 2012), ii) increased frequency of experiencing some form of childhood maltreatment, particularly emotional abuse (Palmier-Claus et al. 2016) and iii) increased risk of BD due to substance abuse (Marangoni et al. 2016).

Overall, data regarding perinatal and prenatal risk factors and associations with future risk of BD is weak and inconsistent. This is in contrast to much more consistent and stronger evidence of associations between perinatal and prenatal risk factors and risk of developing SZ (Davies et al. 2020). Postnatal risk factors for BD tend to be rather non-specific i.e. are also risk factors associated with increased risk of other psychiatric conditions, and in some instances is difficult to establish the temporal relationship.

1.4.4 Psychopathology and BD

As mentioned in section 1.3, the time taken for a patient to receive an accurate diagnosis of BD can be up to 10 years (Ghaemi et al. 2002; Baethge et al. 2003). This delay is associated with substantial impairment to the individual, increased number of hospitalisations, medical comorbidity and increased frequency of suicide attempts (Goldberg and Ernst 2002; Altamura et al. 2010; Forty et al. 2014). Given the negative consequences associated with BD, studying its aetiology may help to better characterise the early presentation of the disorder and minimise negative impacts for the patient.

1.4.4.1 Comorbidity in BD

When investigating possible aetiological mechanisms underlying BD, one possible way of examining this might be to examine those who already have the

disorder. There are high levels of comorbidity in those with BD, with a suggestion that “comorbidity is the rule rather than an exception” (Sartorious 2013). Comorbidities could develop after onset or be present prior to onset. Establishing an accurate temporal relationship between comorbidities and BD might aid earlier recognition and appropriate intervention, particularly because comorbidities are associated with poorer prognosis and can lead to reduced efficacy of treatment.

1.4.4.1.1 Psychiatric comorbidity with Axis I disorders

Evidence from international surveys have highlighted that 57-76% of individuals with BD have at least one other lifetime DSM-IV Axis I disorder, and that 16-44% have three or more lifetime DSM-IV Axis I disorders (McElroy et al. 2001; Grant et al. 2005; Merikangas et al. 2011). The most common comorbid Axis I disorders from meta analyses are reported to be: anxiety disorders, with panic disorder being the most common (20-64%), substance abuse disorders, most notably alcohol abuse (22-48%), eating disorders, particularly bulimia nervosa (3-33%), and behavioural disorders such as oppositional defiant disorder (25-29%) and intermittent explosive disorder (34%) (Merikangas et al. 2011; Hunt et al. 2016; Eser et al. 2018; Thiebaut et al. 2019).

1.4.4.1.2 Psychiatric comorbidity with Axis II disorders

In addition to a number of Axis I disorders, there is also evidence to suggest that comorbidity with Axis II personality disorders is common. Evidence from meta-analyses and systematic reviews suggest that 23-31% have a ‘Cluster B’ personality disorder (antisocial, borderline, histrionic, narcissistic), 15-26% have a ‘Cluster C’ personality disorder (avoidant, dependent, obsessive compulsive), and 7-13% have a ‘Cluster A’ personality disorder (paranoid, schizoid, schizotypal). The most frequent personality disorders are borderline personality disorder (BPD) and obsessive compulsive disorder (OCD) (Friborg et al. 2014; Bezerra et al. 2015), although these findings were based on data from three studies of European populations and cannot be generalised to other populations such as those from Asia, Africa and America.

1.4.4.1.3 Summary and limitations of work on psychiatric comorbidities

Findings from studies examining both Axis I and Axis II comorbidities with BD suggest that comorbidities are common in individuals with BD. When pooling data together to increase sample size, a more accurate account of the true lifetime risk for comorbid conditions is possible from meta-analysis. Nevertheless, the studies included in these meta-analyses are cross-sectional, and are based on recollection of symptoms being present. This can lead to recall bias, particularly when in a mood episode (depressed, (hypo)manic or mixed). Although these studies are useful in informing current clinical practice with regards to appropriate treatment options, they say nothing about the temporal relationship between the comorbidity and BD: it is not possible to determine whether there may be causal effects (i.e. the comorbidity causes BD), whether comorbidities may arise secondary to the effects of medication used to treat BD, or whether the presence of BD symptoms causes comorbidity (reverse causality). They also do not answer the question “what is the initial symptom presentation of BD in childhood/adolescence?” To answer this question, studies of psychopathology in the premorbid phase of BD are necessary.

1.4.4.1.4 Premorbid psychopathology

To better understand the manifestations of BD in childhood/adolescence, one approach is to follow high-risk offspring of BD parents longitudinally. It should then be possible to observe any potential psychopathology present at higher rates in offspring of BD parents compared to the offspring of control parents. Findings from prospective studies of high-risk offspring of BD parents suggest that prior to the first (hypo)manic episode, most patients with BD have one or more depressive episodes occurring in adolescence (Henin et al. 2005; Duffy et al. 2007; Mesman et al. 2016), and that presence of other psychopathologies such as childhood anxiety disorder and behavioural disorders such as ADHD may be present prior to puberty (Egeland et al. 2012; Duffy et al. 2013,2014).

Evidence from two meta-analyses of high-risk offspring of BD parents highlight a number of Axis I disorders being more common compared to controls. Anxiety

disorder are the most prevalent psychopathology reported (lifetime risk 7-32%). Lifetime risk of other non-bipolar diagnoses include depression (14-24%), ADHD (14-16%), at least one substance use disorder (12-15%), SZ (4%) and any behavioural disorder (12-14%) (Rasic et al. 2014; Lau et al. 2018).

From the findings of high-risk offspring studies, one group have proposed a model of clinical trajectory for emerging BD based on evidence spanning over 20 years. The model itself has 4 stages: 0 (well but at high familial risk); 1 (non-mood disorders e.g. sleep disorders or ADHD); 3 (minor mood disorders e.g. depression not otherwise specified or cyclothymia) and 4 (BD). This is summarised in Figure 2 (Duffy et al. 2019).

Figure 2 Clinical staging model for emerging bipolar disorder

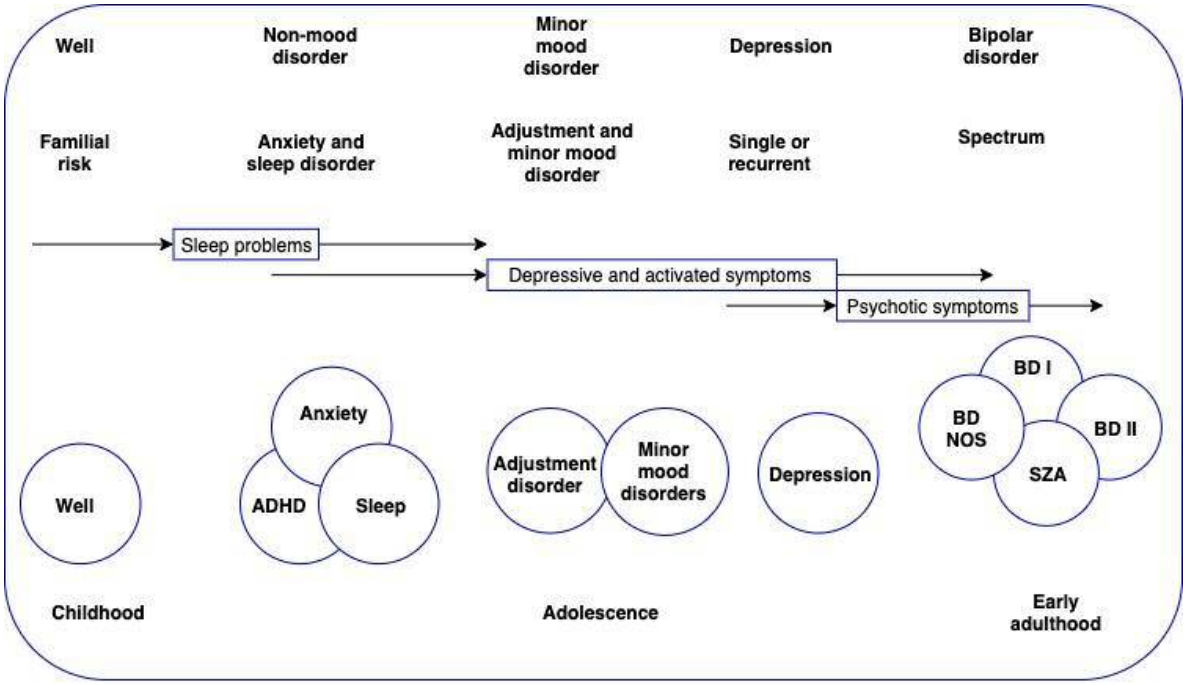


Figure adapted from Duffy et al. (2019)

BD: Bipolar Disorder; ADHD: Attention Deficit Hyperactivity Disorder; NOS: Not Otherwise Specified; SZA: Schizoaffective Disorder

To date, and to the best of my knowledge, there are no studies that have used birth cohort data to examine associations between measures of childhood/adolescent psychopathology and subsequent BD in the general population. This is in contrast to a large literature reporting associations

between a number of different psychopathology measures and schizophrenia (Welham et al. 2009).

1.4.5 Cognition and BD

Approximately 40-60% of people with BD have cognitive impairment in at least one cognitive domain, and this is present independent of mood state (Arts et al. 2008; Bora et al. 2009). Findings from several meta-analyses (Robinson et al. 2006; Arts et al. 2008; Bora et al. 2009) have suggested premorbid deficits in processing speed, executive functioning, verbal learning, visual learning and attention (reported Cohen's d effect sizes ranged from 0.28 to 1.09). Overall, there is consistency in reporting the most (executive functioning and verbal learning) and least (forward digit span test and sustained attention) affected cognitive domains across these studies (Robinson et al. 2006; Arts et al. 2008; Bora et al. 2009). The notable exception is the findings of one meta-analysis that reported large effect size for deficits in sustained and/or selective attention using the Continuous Performance Task (Torres et al. 2007). This finding should be interpreted with caution as the task itself often suffers from the "ceiling effect", which can lead to low false positive scores (Kahn et al. 2012).

1.4.5.1 Cognition in BD subtypes

When considering associations between cognition and BD, most studies have focused on those with a BD-I diagnosis. However, there are now a number of studies that have examined associations in those with BD-II and these might help to identify differences in the severity or type of the deficits between BD subtypes. Two meta-analyses examining cognitive performance in BD subtypes (BD-I vs BD-II) have reported consistent findings, that BD-I compared to BD-II cases have poorer global cognition, verbal memory, processing speed, executive functioning speed, and executive functioning accuracy (reported Cohen's d range from 0.16 to 0.26, in which the greatest deficits are for verbal memory), but no differences in social cognition or working memory (Bora et al. 2011; Bora 2018).

A recent meta-analysis investigated differences in cognitive functioning between psychotic BD cases vs non-psychotic BD cases. Psychotic BD cases had

poorer: global cognition, verbal memory, processing speed, executive functioning speed, executive functioning accuracy, working memory, and social cognition (reported Cohen's d range from 0.12 to 0.28, with more pronounced deficits in verbal memory), but no difference was observed in visual memory or attention cognitive domains (Bora 2018).

1.4.5.2 Cognition in youth at familial high risk for BD

It is well documented that there are neuropsychological impairments in youth who are at high genetic risk for schizophrenia (Hameed and Lewis 2016), and findings from one meta-analysis suggests this may also be the case for those at high genetic risk for BD. The authors included 18 studies, in which the offspring were aged 10-25. Overall, there was evidence of deficits in multiple domains: general cognition, visual memory, verbal memory, sustained attention, processing speed and social cognition (Cohen's d range from 0.21 to 0.36), though there was little evidence to support differences in cognitive domains of planning and working memory (Bora and Ozerdem 2017a). A major limitation of studies of high-risk offspring is that it is not possible to know whether cognitive deficits present in high-risk offspring are due to genetics or family environment given they likely have more risk genes since they have parent(s) with BD and are brought up in an environment in which the parent(s) BD might affect their cognitive abilities. The authors of the systematic review highlighted a lack of sufficient information available on factors such as potential comorbid conditions, or whether the youths had misused substances which would likely affect performance on completing the cognitive tasks assessed.

1.4.5.3 Cognition in the premorbid phase

A number of studies have examined associations between premorbid cognitive functioning and subsequent development of BD/(hypo)mania using a cohort study design and report inconsistent findings. Using data from the Swedish and Danish National registries, two studies found no difference in premorbid IQ (ages 16-25 years) between those who did and those who did not go on to be hospitalised with BD (Zammit et al. 2004; Mortensen et al. 2005). Others using Swedish (Gale et al. 2010) and Dutch data (Vreeker et al. 2016) have reported that lower premorbid IQ (ages 16-25 years) is associated with increased risk of

hospitalisation with BD and that lower premorbid IQ was reported in those who had a BD-I diagnosis respectively. The findings of the latter study are unusual as these individuals (with lower premorbid IQ) also had higher educational attainment compared to controls (Vreeker et al. 2016). Evidence from three studies, one using data from Dunedin in New Zealand (Koenen et al. 2009), another using data from Bristol in the UK (Smith et al. 2015), and a final study using data from Sweden (MacCabe et al. 2013) all reported that higher childhood IQ is associated with increased risk of adult mania, higher scores on the Hypomania Checklist-32 and increased risk of BD respectively. Finally, two studies have reported associations between both better and poorer premorbid IQ (ages 16-25 years) and risk of hospitalisation with BD using Swedish national registry data (MacCabe et al. 2010; Gale et al. 2013). It is therefore possible that the relationship between premorbid IQ and BD is non-linear, in which those with better and those with poorer IQ compared to average IQ are at increased risk of BD.

1.4.5.4 Summary of cognitive studies

Studies examining associations between cognitive performance (specifically IQ) in the premorbid phase and subsequent BD suggest that those with both lower and those with higher than average IQ may be at increased risk of developing BD. Evidence from studies examining clinical subtypes of BD suggest global impairments across multiple domains, with severity being greater in those with a BD-I (compared to BD-II) diagnosis and those with a psychotic BD (compared to non-psychotic BD) diagnosis. In youth at high genetic risk of BD because their parent(s) have BD, there are cognitive deficits similar to those observed in adults with BD who are in a euthymic state. It is therefore possible that certain cognitive deficits represent non-specific endophenotypes for BD (Kim et al. 2015).

1.5 Summary

The aetiology of BD is complex, with both genetic and environmental factors playing a role in determining whether someone develops the disorder. Whilst categorical diagnoses are necessary for guiding appropriate treatment, dimensional approaches such as the RDoC may be more useful for progressing

understanding of the aetiology BD. The use of GWAS has revolutionised the way we now interpret the genetic architecture of BD, and using polygenic risk scores it is now possible to investigate phenotypic manifestations of increased genetic risk for BD in different populations. Furthermore, whilst comorbid psychopathology and cognitive deficits are frequently described in people with BD, it is unclear whether these are present prior to illness onset, or are a consequence of having the illness itself. One way of studying this is to use general population samples of healthy children and follow them longitudinally over an extended period. The most consistently reported measures of psychopathology/cognition associated with hypomania have not yet been investigated, and even for studies examining this in BD, there is uncertainty as to the most reliable measures (Faedda et al. 2014; Faedda et al. 2015). Furthermore, most studies examining cognition in BD, particularly using general population samples, focus on IQ despite evidence from studies of adults with BD and youth at high familial risk of BD suggesting presence of deficits in multiple cognitive domains. Another limitation of a number of studies examining IQ and BD is not testing for the presence of non-linear effects of cognitive performance on risk. Therefore, it will be important to investigate the possibility of non-linear relationships between cognitive functioning and subsequent hypomania. Understanding the early (childhood) manifestations of BD genetic risk, and the childhood psychopathological and cognitive precursors of hypomania can help facilitate earlier identification of persons most at risk of developing BD, and perhaps provide suitable support mechanisms for these individuals and their families. The next chapter, Chapter 2 will outline the specific aims and objectives of this thesis.

Chapter 2: Aims and Objectives of this Thesis

This chapter outlines the aims and specific objectives of this thesis.

2.1 Aim 1

The first aim of this thesis is to identify childhood psychopathology and cognitive domains associated with hypomania in young adulthood.

2.1.1 Psychopathology in childhood

Behavioural/emotional difficulties and presence of psychopathology in childhood are reported in up to 60% of adults with bipolar disorder (BD). Most studies that have examined childhood precursors/risk factors for BD have used small samples of high-risk offspring of parents with BD and compared these to controls. There have been few population-based studies that have examined childhood psychopathology as a precursor/risk factor for BD/hypomania, or examined whether associations exist across the continuum or only at clinical levels of BD psychopathology, or with specific aspects of hypomania. Therefore, the first set of objectives within this aim of the thesis are:

1. To investigate whether childhood psychopathology (borderline personality disorder (BPD) traits, attention deficit hyperactivity disorder (ADHD), emotional/behavioural problems and depressive symptoms) in childhood are associated with a dimensional measure of hypomania assessed in early adulthood.

2. To investigate whether childhood psychopathology is associated more specifically with “sunny-side” or “dark-side” features of hypomania, or with clinically-defined hypomania in young adulthood.

3. To investigate whether any associations are likely to be due to confounding or selection bias.

Results for objectives 1-3 can be found in Chapter 4 of the thesis.

2.1.2 Cognition in childhood

Between 40-60% of adults with BD have cognitive deficits (Sole et al. 2017). However, the relationship between premorbid cognitive functioning in childhood and subsequent development of BD is unclear. As noted in Chapter 1, studies using large longitudinal national registry data, particularly from Scandinavian countries, have reported both better and worse childhood cognitive functioning (namely IQ) in the premorbid phase in those who eventually go on to develop BD. There are few studies examining the relationship between premorbid cognitive functioning and dimensional measures of hypomania in young adulthood. Furthermore, there are few studies examining whether associations with cognitive deficits exist across the continuum or only at clinical levels of psychopathology, or with specific aspects of hypomania. Therefore, the second set of objectives within this aim of the thesis are:

4. To investigate whether cognitive functioning (specifically the cognitive domains of processing speed, working memory, problem solving, executive functioning, attention, verbal learning and social cognition (emotion recognition)) in childhood is associated with a dimensional measure of hypomania in early adulthood.

5. To investigate whether a non-linear relationship exists, whereby both better and worse cognitive functioning in childhood is associated with higher scores on a dimensional measure of hypomania in young adulthood.

6. To investigate whether cognitive functioning is associated with “sunny-side” or “dark-side” features of hypomania, or clinically-defined hypomania in young adulthood.

7. To investigate whether any associations are likely to be due to confounding or selection bias.

Results for objectives 4-7 can be found in Chapter 5 of the thesis.

2.2 Aim 2

The second part of this thesis aims to understand how genetic risk for BD is manifest by reviewing the literature of studies that have used a polygenic risk score (PRS) approach to examine this.

In the last 10 years, there have been an increasing number of studies which have used a PRS approach to determine possible phenotypes associated with increased genetic risk for BD. Most notably, large genome-wide association studies (GWAS) of BD cases and controls show the ability of the PRS to distinguish BD cases from controls at the group level (Sklar et al. 2011; Ruderfer et al. 2018; Stahl et al. 2019). At the start of my PhD there were no systematic reviews or meta-analyses collating information on what the non-BD manifestations of genetic risk for BD, using a PRS approach are, though such studies could help inform understanding of the aetiology of BD. Therefore, the next objective of this thesis is:

8. To systematically review the literature to identify and describe studies that have examined the phenotypic (non-BD) manifestations of genetic risk for BD.

Results for objective 8 can be found in Chapter 6 of the thesis.

2.3 Aim 3

The final aim of this thesis aims to assess experimentally whether genetic risk for BD manifests during childhood as the psychopathology and cognitive phenotypes investigated in Aim 1 described above.

2.3.1 Genetic risk for BD and psychopathology from childhood into early adulthood

At the start of my PhD, there were few studies investigating associations between genetic risk for BD, using the PRS approach, and childhood

psychopathology or hypomania in young adulthood. Therefore, my next set of objectives are:

9. To investigate whether increased genetic risk for BD is associated with a dimensional measure of hypomania in young adulthood.

10. To investigate whether increased genetic risk for BD is associated more specifically with “sunny-side” or “dark-side” features of hypomania, or with clinically-defined hypomania in young adulthood.

11. To examine whether genetic risk for BD is associated with childhood psychopathology (as examined in Aim 1).

12. To investigate the possibility of associations being due to selection bias.

Results for objectives 9-12 can be found in Chapter 7 of the thesis.

2.3.2 Genetic risk for BD and cognition in childhood

When I started my PhD, there were no studies that had used a BD-PRS to investigate associations with childhood cognitive functioning, although there were a few studies examining cognitive functioning in adults. None of these studies had attempted to tease out to what extent any associations were driven by single nucleotide polymorphisms (SNPs) shared between BD and SZ and those which are independent. The final set of objectives of this thesis therefore, are:

13. To examine whether genetic risk for BD is associated with cognitive domains of general intelligence indexed by intelligence quotient (IQ) (performance, verbal and total), processing speed, working memory, problem solving ability, executive functioning, attention, verbal learning and social cognition (emotion recognition) in childhood.

14. To determine whether any associations between genetic risk for BD and cognitive functioning are non-linear.

15. To examine whether the relationship between genetic risk for BD and cognitive functioning is explained by risk alleles which are also shared with schizophrenia risk.

16. To investigate the possibility of associations being due to selection bias.

Results for objectives 13-16 can be found in Chapter 8 of the thesis.

Chapter 9 will conclude this thesis with an overall discussion of what I have found, the implications of these findings, which methodological considerations should be highlighted, the strengths and limitations of the work presented and suggestions for future research.

The next chapter, Chapter 3, will provide details of the ALSPAC sample used to address Aims 1 and 3. It gives a detailed description of the methods used in Chapters 4, 5, 7 and 8. The methodology used for Aim 2 (the systematic review) will be presented in Chapter 6.

Chapter 3: Methods

This chapter introduces causal inference, describes the Avon Longitudinal Study of Parents and Children (ALSPAC) sample used in this thesis, and provides an overview of all outcome and exposure measures, with some background information on the psychometric properties of these. In addition, the statistical analyses used in Chapters 4, 5, 7 and 8 are also described.

3.1 Epidemiology and Causal Inference

Epidemiology is concerned with describing and understanding the aetiology and outcomes of disease(s) in different populations.

Different study designs may be used to examine potential aetiological relationships between an exposure and outcome, including observational studies (such as longitudinal, case-control, or cross-sectional designs) and interventional studies (such as randomised-controlled trials (RCTs)). Where associations are identified, a number of explanations need to be ruled out before causality can be inferred. Explanations for any association include:

i) Chance: The finding is spurious due to random variation
ii) Confounding: The observed association between an exposure and outcome is explained by another variable, which is associated with both the exposure and outcome, but is not on the causal pathway between them
iii) Bias: An incorrect estimate of the association between an exposure and outcome occurs as a consequence of an error or flaw in the study, and can be due to the characteristics of the sample (selection bias), or of the measures (information bias)
iv) Reverse causation: Presence of the exposure occurs as a consequence of the outcome

v) Causation: The outcome occurs as a consequence of the exposure

The extent to which any of the explanations ii-iv above can be excluded as alternatives to a causal relationship depends in part on the study design. Whilst the strongest design for establishing causality is an RCT, most studies that aim to increase understanding of the aetiology of disease are observational rather than interventional. Of the observational designs, longitudinal studies are usually considered the strongest design as they are able to determine a temporal relationship between a given exposure and outcome, and as they are less likely to be affected by selection bias than case-control designs.

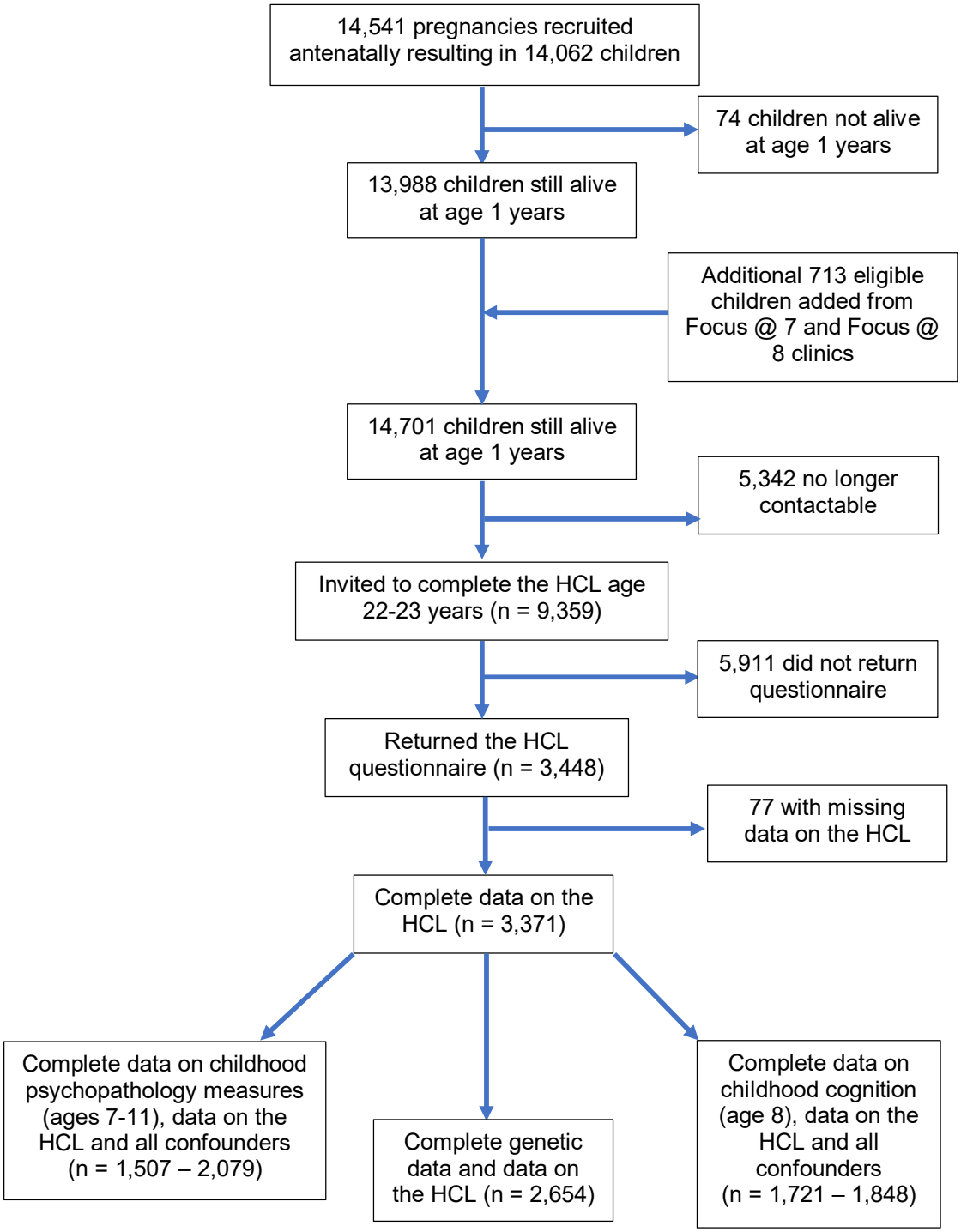
In this thesis, I will be using the ALSPAC birth cohort which has a longitudinal or cohort study design.

3.2 The ALSPAC cohort

3.2.1 Recruitment of participants

The ALSPAC cohort (http://www.bris.ac.uk/alspac/) is a large population-based longitudinal dataset set up in April 1991, recruiting pregnant women whose delivery date was between April 1st 1991 and December 31st 1992 (Boyd et al. 2013). These women were from the Avon area (Southmead, Bristol and Weston and Frenchay District Health Areas) and at the start of the study, 14,541 pregnant women were enrolled. Figure 1 shows a flow diagram of sample recruitment including final sample sizes for analyses in this thesis.

Figure 3 Flow diagram showing sample recruitment for the ALSPAC cohort



ALSPAC: Avon Longitudinal Study of Parents and Children; HCL: Hypomania Checklist

The study contains extensive baseline information from the first trimester of pregnancy onwards. From birth, a series of assessments and questionnaires regarding family circumstances and the child's health were sent to the parents. After the age of 7, the children were able to attend face-to-face interviews, from which a number of assessments assessing a variety of measures were conducted. In total, between birth and age 18 years, 68 data collection time points have occurred including 9 "Focus" clinical assessments, 34 child-completed questionnaires and 25 questionnaires about the child completed by the mother or other main caregiver (Boyd et al. 2013). 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/). The analyses presented in this thesis were approved by the ALSPAC Executive Committee (http://www.bristol.ac.uk/alspac/researchers/research-ethics/) (project reference B1340).

3.2.2 Sample representativeness

3.2.2.1 The Cohort

The ALSPAC research team investigated comparisons of socio-demographic characteristics and standard school assessments (at age 16 years) between a nationally representative sample and the enrolled ALSPAC sample. When compared to participants from the national sample, the enrolled ALSPAC participants: i) had higher educational attainment, ii) are more likely to be white, iii) less likely to be on free school meals and iv) more likely to be female (Boyd et al. 2013).

3.2.2.2 The Mothers

The ALSPAC research team also investigated differences in characteristics between mothers recruited to the study and the whole of the UK. When compared to mothers from the whole of Great

Britain, mothers of children living in the Avon area were: i) more likely to live in their own accommodation; ii) less likely to have >1 person per room in the household; iii) more likely to have a car available for the household and iv) less likely to be non-white. For the mothers enrolled in the study, when compared to either mothers in the whole of Great Britain and to mothers in the Avon area, the ALSPAC mothers were more likely to: i) own their own home, ii) have a car available to the household, iii) have more than 1 person per room in the household, iv) be married and more likely to be White (See Table 4) (Fraser et al. 2013).

Table 4 Differences in socio-economic characteristics between mothers in the whole of Great Britain, mothers of infants born in the Avon area (but not enrolled in the ALSPAC sample) and mothers who participated in the ALSPAC study

Characteristic	Mothers in the whole of Great Britain[1]	Mothers in the Avon area[1]	Enrolled mothers[2]
Owner occupied accommodation	63.4%	68.7%	79.1%
> 1 person per room in the household	30.8%	26.0%	33.5%
Has a car available to the household	75.6%	83.7%	90.8%
Married couple	71.8%	71.7%	79.4%
Non-white mother	7.6%	4.1%	2.2%

[1]Mothers with infants <1 year of age; [2] Assessed by questionnaire administered at approximately 8 months postnatally; ALSPAC: Avon Longitudinal Study of Parents and Children

3.3 Measures

For the continuous measures generated in the subsequent sections (exposure and outcome measures), Z score standardization was used so that the rescaled variables had a mean of 0 and SD of 1 to aid comparison of results within this study and across other studies.

3.3.1 Hypomania

The Hypomania Checklist-32 (HCL-32) is a self-administered questionnaire that was designed to screen for the presence of lifetime hypomania symptoms in patients with depression. It has been validated as a screening tool for bipolar II disorder in both clinical (Angst et al. 2005a; Carta et al. 2006; Forty et al. 2009; Rybakowski et al. 2010; Mosolov et al. 2014) and non-clinical (Meyer et al. 2007; Holtmann et al. 2009; Lee et al. 2016) settings. In general population samples, first onset of hypo(manic) episodes is rarely diagnosed before age 25 years (Leboyer et al. 2005). Sub-threshold hypo(manic) symptoms may be present in childhood/adolescence, and the detection of these symptoms may be useful for identifying individuals who are more likely to go on to develop BD (Fiedorowicz et al. 2011), or convert from unipolar depression to BD (Tijssen et al. 2010). The full questionnaire in its entirety can be found in Appendix 1. The 32 questions ask about a period when an individual was "in a 'high' state" and are summed to generate a total score.

Previous factor analyses of the HCL-32 suggests there are latent underlying constructs, the most consistently reported being a 2-factor model describing 'active/elated' and 'risk-taking/irritable' factors (Angst et al. 2005a; Meyer et al. 2007; Holtmann et al. 2009; Fornaro et al. 2015). Others have additionally suggested a 'disinhibited/stimulation-seeking' factor and a 'positive social interaction' factor (Haghighi et al. 2011).

3.3.1.1 Psychometric properties of the HCL-32

In a systematic review on the properties of the HCL-32, Meyer and colleagues reported that in 21 studies, using data from 22 independent samples, 15 studies reported the optimal threshold to be classed as having clinically-defined hypomania was a score of ≥14/32. The alternative optimum threshold score ranged between ≥7/32 to ≥21/32 in the remaining 6 studies. In the 15 studies

reporting an optimal threshold of ≥14/32, sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were estimated. Sensitivity in this instance indicates the probability of the HCL-32 correctly identifying BD cases i.e. a true positive, whilst specificity indicates the probability of the HCL-32 correctly identifying those without BD i.e. a true negative. In the 10 samples consisting of people with BD (24%) and people with depressive disorder (76%), the pooled values were: sensitivity (80%), specificity (65%), PPV (47%) and NPV (50%), suggesting the HCL-32 performs well at identifying true BD cases in individuals with a mood disorder diagnosis. In the same review, the authors identified a single study that used an alcohol and opiate dependent sample as the comparison group and reported that at a threshold score of ≥14/32, sensitivity was high (90%), though specificity was poor (39%) (Meyer et al. 2014). Since that review, a single study has examined sensitivity and specificity using a general population sample (in which there were BD cases and non-clinical controls), and reported poor specificity (36%), but higher sensitivity (82%) (Lee et al. 2016). This indicates that the HCL-32 over-estimates the proportion of people who have BD, and particularly in general population samples compared to clinical samples of people with mood disorders.

To enhance the psychometric properties of the HCL-32, a Rasch analysis for unidimensionality of the HCL-32 was conducted within a sample of 389 individuals with DSM-IV BD from the Bipolar Disorder Research Network (BDRN) (Court et al. 2014). Four questions were identified as redundant and could be excluded. These questions were questions 14 ‘I wear more extravagant clothes/more make-up’, 29 ‘I drink more coffee’, 30 ‘I smoke more’ and 32 ‘I take more drugs’. Thus, analyses in this thesis are based on the remaining 28 items, which were used to generate a HCL score, a binary measure of clinically-defined hypomania, and latent factors of the HCL.

3.3.1.2 Measure of hypomania in ALSPAC

Hypomania features were assessed via postal and online questionnaires using the HCL-32 when the ALSPAC cohort were aged 22-23 years. In total, 9,359 participants were invited to complete the HCL-32, though only 3,448 (36.8%) returned the questionnaire. The analyses used in this thesis are based on the 3,371 individuals with no missing data on the HCL.
To generate the HCL score, responses (0 = no and 1 = yes) on the 28 questions were summed (scores ranged from 0-28) and standardised to produce a continuous measure of hypomania. The 28 questions used to generate the HCL score are shown in Table 5.

Table 5 The 28-item HCL

Item
Need less sleep
More physically active
Want to travel
Enjoy work more
Make more jokes
Want to meet/do meet more people
Have more ideas/more creative
Think faster
Engage in lots of new things
Do things more quickly/easily
Less shy/inhibited
Plan more activities
More sociable
Feel more energetic
Talk more
More self-confident
Mood is higher/ more optimistic
More interested in sex
More flirtatious
More impatient/get irritable more easily
Get into more quarrels
Drink more alcohol
Tend to drive faster/take more risks when driving
Spend more/too much money
Can be exhausting/irritating to others
More easily distracted
Thoughts jump from topic to topic
Take more risks in daily life

HCL: Hypomania Checklist

Whilst the most often reported threshold cut-off score to define hypomania using the full 32-item checklist is ≥14/32 (see Meyer et al. (2014), there are no studies that have determined the optimal threshold cut off score when using only the 28 items as I am using in this thesis. Therefore, in line with the full 32-item HCL, I have used a cut-off score of ≥14/28 on the HCL. Additionally, to meet criteria for

clinically-defined hypomania, participants were required to have had symptoms that lasted 2-3 days or more (as this conforms to the ICD-10 criteria of hypomania having lasted “at least several days on end” (World-Health-Organisation 1993), and to endorse a ‘negative’, or ‘negative/positive’ response to questions about the impact of their ‘high’ on their family, social, leisure, or work life (see Appendix 1, Questions 4, 5 and 6). This produced a binary measure of clinically-defined hypomania, in which, 239 individuals (7.1%) were classified as having clinically-defined hypomania.

HCL factors were derived by Dr Hannah Jones at the University of Bristol using a confirmatory factor analysis (CFA) of the HCL-28. By running a CFA, it was possible to assign each of the 28 questions from the HCL to their corresponding factors (as previously identified through exploratory factor analysis) (Angst et al. 2005a; Vieta and Phillips 2007; Fornaro et al. 2015) using the mean and variance adjusted weighted least squares (WLSMV) method in Mplus. The WLSMV method incorporates diagonal elements of the full weight matrix allowing for factor loadings to be positive or negative. WLSMV estimates thresholds and polychoric correlations obtained using maximum likelihood methods. Parameter estimates can then be obtained from estimates of the asymptomatic variances of the threshold and polychoric correlations obtained from the diagonal weight matrix. This was because this method makes no assumptions regarding the underlying distribution of variables in the model, and has also been shown to produce less biased and more accurate factor loadings compared to the maximum likelihood methods. Additionally, this method is specifically designed to deal with data which are categorical (binary or ordinal) in which the normality assumption or continuity property of the variables is plausible (Li 2016). The two factors were derived based on 19 items representing an ‘active/elated’ factor and 9 items representing a ‘risk-taking/irritable’ factor (see Table 6 for factor loadings) and were continuous measures.

Table 6 Standardised factor loadings for the HCL factors

Item	'Active/elated' factor loading	'Risk-taking/irritable' factor loading
Need less sleep	**0.303**	0.091
More energetic and more active	**0.662**	-0.219
More self-confident	**0.680**	-0.184
Enjoy work more	**0.615**	-0.184
More sociable	**0.623**	-0.074
Want to travel and/or do travel more	**0.417**	0.114
Drive faster or take more risks when driving	0.039	**0.342**
Spend more/too much money	0.061	**0.401**
Take more risks in daily life	0.243	**0.351**
More physically active (sport)	**0.492**	-0.042
Plan more activities or projects	**0.599**	-0.025
Have more ideas, am more creative	**0.531**	0.061
Less shy or inhibited	**0.570**	0.018
Want to meet or actually do meet more people	**0.473**	0.174
More interested in sex	**0.416**	0.247
More flirtatious	**0.457**	0.251
Take more	**0.539**	0.057
Think faster	**0.474**	0.148
Make more jokes or puns	-0.079	**0.251**
More easily distracted	**0.471**	0.168
Engage in lots of new things	**0.471**	0.148
Thoughts jump from topic to topic	0.037	**0.533**
Do things more quickly and/or more easily	**0.491**	0.161
More impatient	-0.228	**0.571**
Can be exhausting or irritating for others	-0.054	**0.494**
Get into more quarrels	-0.213	**0.502**
Mood is higher, more optimistic	**0.672**	-0.120
Drink more alcohol	0.064	**0.304**

HCL: Hypomania Checklist; Factor loadings in bold indicate an item was loaded onto that factor

3.3.2 Childhood psychopathology

The following section refers to measures of psychopathology examined during childhood/adolescence. These measures were selected to be at the youngest age available from the data available to me, to minimize the likelihood of reverse causality.

3.3.2.1 Borderline personality disorder (BPD) traits

At age 11 years, the cohort was invited to face-to-face interviews to assess their experience of BPD traits over the preceding two years. In total, data was available on 6,413 children.

To assess for BPD traits, an interview was conducted by a trained psychologist using the Childhood Interview for DSM-IV Borderline Personality Disorder (CI-BPD). This is a semi-structured interview designed to assess BPD traits in children (ages 6-12 years) (Zanarini et al. 2004). Though originally developed by Mary Zanarini, the CI-BPD was adapted by Jeremy Horwood and Dieter Wolke to be used at the Focus 11+ clinic. The CI-BPD is based on the borderline module of the Diagnostic Interview for DSM-IV Personality Disorders (Zanarini et al. 1996). The convergent validity of the CI-BPD has been shown to be significantly associated with clinician diagnosis and other measures of BPD reported by patients and parents (Sharp et al. 2012a). Importantly, the purpose of the CI-BPD is not to diagnose a child as having BPD, rather it is to identify prevalence of the individual BPD traits in children and adolescence.

A total of nine BPD traits (anger symptoms, affective instability, emptiness, identity disturbance, paranoid ideation, fear of abandonment, suicidal behaviour, impulsivity and intense interpersonal relationships) were assessed. Judgements were made by a trained assessor in the ALSPAC research team and rated as absent, probably present or definitely present (coded as 0, 1 and 2 respectively). To meet criteria for being definitely present, the trait

had to be present at least 25% of the time (or daily). A ‘probably’ rating required the trait to be present regularly but not as often as definitely present.

Using the scores from the 9 individual BPD traits generated by ALSPAC researchers, I derived a BPD traits score, which is the sum of the 9 BPD traits (range 0-18), and I then standardised this continuous measure. I also used a ‘high-risk’ for BPD binary variable ALSPAC researchers had derived, with individuals classified as ‘high-risk’ if they met criteria for ‘probably present’ or ‘definitely present’ on 5 or more traits. There were 370 individuals (5.8%) who were defined as ‘high-risk’ for BPD.

3.3.2.2 Attention Deficit Hyperactivity Disorder (ADHD)

The presence of ADHD was assessed using the parent-rated and teacher-rated Development and Well-Being Assessment (DAWBA), when the cohort were age 7.6 years (n = 8,219).

The DAWBA is a semi-structured package of interviews, questionnaires and rating techniques used to generate either DSM-IV or ICD-10 diagnoses or symptom scores of childhood psychopathology. This covers common emotional, behavioural and hyperactivity disorders. The validity of the DAWBA has been shown in both clinical and community based samples (Goodman et al. 2000).

In the ALSPAC cohort, a diagnosis of ADHD was available based on the DSM-IV diagnostic criteria for ADHD, and was only given where data were available from both teacher and parent reports. There were 175 children (2.2%) who were classified as having any ADHD.

3.3.2.3 The Strengths and Difficulties Questionnaire (SDQ)

The SDQ is part of the DAWBA set of mental health measures and is a brief behavioural questionnaire designed to assess general

childhood psychopathology, particularly well adapted for use in general population studies. The SDQ has a five-factor structure where items load onto the measures of: hyperactivity-inattention, prosocial behaviour, emotional difficulties, conduct problems and peer relationship difficulties (Goodman 2001).

When the children were aged 115 months (9 years), the parents of the children completed the SDQ which asked about these behaviours during the previous 6 months. Data were available on 8,074 individuals (Goodman 1997).

Each SDQ subscale score was generated by ALSPAC researchers as the weighted sum of the score from the 5 questions within the questionnaire which corresponded to the psychopathology measure being assessed (range of subscale scores 0-10). The individual questions each parent was asked about their child related to the previous 6 months. I generated a total difficulties score which was the sum total of the hyperactivity, emotional difficulties, conduct problems and peer relationship difficulties scores to give a total difficulties score (range 0-40) (the prosocial behaviour subscale score does not contribute to the total difficulties score) (Goodman 1997). All scores were then standardized.

3.3.2.4 The Moods and Feelings Questionnaire (MFQ)

The MFQ is designed to detect the presence of a broad range of depressive symptoms in children and adolescents (Costello and Angold 1988). It is possible for both children (age 6–17 years) and the parents to complete the questionnaire which comprises of 32 questions in total. A review of its psychometric properties suggest that the MFQ is both a reliable and valid measure of assessing for presence of depression in childhood and adolescence (Wood et al. 1995; Daviss et al. 2006).

At age 9 years, the parents completed the short version of the MFQ (n = 8,066) which asked about how their child felt or acted in the previous 2 weeks (Angold et al. 1995).

The MFQ score was generated by the ALSPAC research team as the weighted sum of the score from each of the 13 questions (range 0-24), which I standardised.

3.3.3 Cognitive measures

An often used tool for assessing cognitive functioning in patients with schizophrenia (SZ) is the Measurement and Treatment Research in Cognition in Schizophrenia (MATRICS) consensus cognitive battery (MCCB) (Green and Nuechterlein 2004; Marder and Fenton 2004). It has been recommended by the Food and Drug Administration (FDA) in the USA to assess cognitive impairment in registry trials of SZ (Nuechterlein et al. 2008), and assesses the following 7 cognitive domains: i) Processing Speed, ii) Working Memory, iii) Attention/Vigilance, iv) Visual Learning i.e. immediate visual memory, v) Verbal Learning i.e. immediate verbal memory, vi) Problem Solving and Reasoning ability, and vii) Social Cognition (Nuechterlein et al. 2008).

However, for BD, the most appropriate tool for assessing cognitive functioning is not clear. In 2010, the International Society for Bipolar Disorder convened and suggested that based on the clinical and cognitive overlap between SZ and BD, the MCCB might be deemed an appropriate tool to examine cognitive functioning in BD patients (Yatham et al. 2010). Furthermore, this battery has been used more recently when assessing cognitive functioning in BD patients (Sperry et al. 2015; Bo et al. 2017).

In ALSPAC, cognitive functioning was assessed at age 8 years and measured the domains of: general intelligence as indexed by intelligence quotient (IQ) (performance, verbal and total), processing

speed, working memory, problem solving ability, executive functioning, attention, verbal learning and social cognition. These cognitive domains are loosely based on the domains identified in the MCCB, though there was no comparable measure of visual learning in the ALSPAC cohort, and therefore this cognitive domain was not assessed.

The cognitive domains in ALSPAC were assessed using a number of tools: i) the Wechsler's Intelligence Scale for Children – IIII (WISC-III) assessed cognitive domains of: general intelligence (IQ), processing speed, working memory and problem-solving ability (Wechsler et al. 1992), ii) the Test of Everyday Attention for Children (TEACh) assessed domains of: executive functioning and attention (Robertson et al. 1996), iii) the Children's Test of Non-Word Repetition (CTNWR) assessed verbal learning (Gathercole and Adams 1994), and iv) the Diagnostic Analysis of Non-Verbal Accuracy (DANVA) assessed social cognition (emotion recognition) (Nowicki and Duke 1994).

All cognitive domain scores, irrespective of which tool was used to assess them, were standardised to produce continuous measures. Any cognitive domain scores that were >3 SD from the mean were removed from the analysis, as these scores can have strong effects on estimates (either underestimating or overestimating effect sizes).

3.3.3.1 WISC-III

The children were administered the short form of the WISC-III at age 8 (n = 7,405). Alternate items were used for all subtests, except the coding subtest which was administered in its full form. In addition to the 10 subtests (information, similarities, arithmetic, vocabulary, comprehension, picture completion, coding, picture arrangement, object assembly and block design), the children were also assessed on the forwards and backwards digit span task. Each subtest was administered by a trained psychologist in the ALSPAC team.

IQ: A measure of performance IQ (PIQ) was derived from the spatial, sequencing and problem-solving abilities sub-tests (n= 7,371). Verbal IQ (VIQ) was derived from the general knowledge, language, reasoning and memory skills sub-tests (n = 7,379). Total IQ (TIQ) (n = 7,384) was derived from the summed total of both PIQ and VIQ using the WISC-III.

Processing speed: One of the subtests within the WISC-III, the coding subtest, was used to assess processing speed in 7,403 children. The children were shown a code in which numbers were assigned a symbol. The sheet contained various numbers (1-5) and required the children to correctly draw the symbol that corresponded to each number in the box as quickly as possible within a specified time limit.

Working memory: Working memory was assessed using the Freedom From Distractibility Index, originally derived by Wechsler in 7,174 children. This index score is the combination of the arithmetic and digit span (forwards and backwards) tasks. The arithmetic subtest was split into 3 parts: i) Questions 1-5 required the children to respond to questions asked by the assessor, related to pictures in a stimulus book, ii) Questions 6-18 required the children to solve problems read aloud by the assessor, and iii) Questions 19-24 required the children to read problems aloud that were printed in a stimulus book and then solve those problems.

The forward digit span task required the children to listen to an assessor who read aloud digits of increasing length and were required to repeat them back. Initially, the assessor started with one digit, and the number of digits within a sequence increased in length until the child could not correctly state the digits in the order they were spoken.

The backward digit span immediately followed the exact forward digit span sequence the child was unable to correctly state in the order it

was spoken. Again, the initial sequence was one digit long and increased in length. The children were required to repeat the sequence in reverse order.

Problem solving: Problem solving ability was assessed using the block design subtest in 7,362 children. The children were given two trials where they observed the assessor and constructed the same design as the assessor using blocks. The cubes had two sides that were coloured red, two sides that were coloured white, and two sides that were coloured both red and white. Following the demonstrations, the children were then shown pictures in a stimulus book and required to assemble the blocks to match the picture shown.

3.3.3.2 The TEACh

The TEACh was originally designed as a comprehensive assessment of attention performance in persons with specific attentional deficits (Robertson et al. 1996). Attention itself can be split into distinct systems: selective, divided and maintenance. Unlike other tests of attention, the focus of these assessments is on everyday life tasks as opposed to a forced laboratory setting (Posner and Petersen 1990).

Executive functioning: The cohort were invited to complete the opposite worlds task (n = 7,202). ALSPAC researchers administered the opposite worlds task where 24 numbers were shown to the children. The task is akin to a basic kind of Stroop task where the child was required to verbalise a response that contradicted the visual information seen as quickly as possible. If the child saw either a number 1 or 2, they would say number 2 or 1 respectively.
There were two trials for the opposite worlds task. To generate an executive functioning score, I standardised the mean time taken to complete the opposite worlds task.

Attention: The sky search task was used to measure attention in 7,184 children. This task required the children to identify identical (20

in total) from non-identical spaceships and draw a circle around all identical pairs they could see. This task was also repeated but the child only had the 20 identical spaceships and was required to circle all spaceships. The latter task was completed to identify the speed with which the child was able to draw the circles.

The score I used was the sky search task adjusted for motor speed, calculated by the ALSPAC research team. This was calculated as the time taken in the initial task of identifying identical from non-identical spaceships minus the time taken to complete the motor task for each child.

The initial coding by ALSPAC researchers was such that higher scores reflected poorer performance for executive functioning and attention cognitive domains. I therefore recoded these variables so that higher scores always reflect better performance on the task.

3.3.3.3 The CTNWR

The CTNWR is designed to assess the adequacy of temporary phonological representations of perceived speech in short-term memory. Poor scores on this task are closely linked to deficits in vocabulary, reading and comprehensive skills in early childhood compared to normally developing children of the same and younger age (Gathercole and Adams 1994).

Verbal learning: The children (n = 7,361) were required to listen to and repeat 12 nonsense words back to the assessor. Each word was played through an audio cassette, and after each word, the child repeated the word back to the assessor. Four of these words were 3 syllables long, four were 4 syllables long and four were 5 syllables long.

3.3.3.4 The DANVA

The DANVA is a research instrument designed to detect differences in a child's ability to accurately send and receive emotional information non-verbally by 4 means: facial expressions, gestures, tone of voice and posture. Differences in non-verbal processing ability might be attributed to various indicators of personal and social adjustment. Children with lower scores on the DANVA may have some form of dyssemia and should therefore be observed to determine the source of their non-verbal difficulties (Nowicki and Duke 1994).

Social cognition: In ALSPAC, 6,815 children completed the DANVA facial expressions task. Children were presented with 24 faces representing emotions of happiness, sadness, fearfulness or anger. The task required the children to make judgements and verbalise their interpretation of the emotion being shown on the screen. The emotion intensity was either low or high (making the task more difficult or easier respectively). Each image was shown on the screen for 2s.

Each emotion score (happy, sad, fearful and angry) was scored on a scale of 0 to 6 and I derived a total emotion errors score which was the sum total of the emotion face scores and standardised this. These were recoded so that higher scores always reflect better performance.

3.4 Confounding

In Chapters 4 and 5, I adjusted for a number of potential confounders, determined *a priori* based on evidence from the literature. They are known to be associated with both the exposure and outcome but not on the causal pathway. The following confounders were adjusted for in my analyses:

Gender was a binary variable coded as 0 = female and 1 = male (Rowland and Marwaha 2018).

Maternal age at birth was assessed by the ALSPAC research team in response to the mother providing her date of birth. A continuous variable was created by the research team, with ages ranging from 14-45 years (Menezes et al. 2010; Chang et al. 2014; Mikkelsen et al. 2017).

Maternal social class was assessed from returned reports at 32 weeks' gestation. The ALSPAC research team categorised responses into 6 levels (I-V, with I being the highest social class) and is in line with the 1991 Office of Population Censuses and Surveys classifications (Cohen et al. 2008; Russell et al. 2014; Arroyo-Borrell et al. 2017; Rowland and Marwaha 2018).

Maternal highest education level was created by the ALSPAC research team. Levels were based on the UK education system and in line with previous work (Smith et al. 2015) I categorised this into a dichotomous variable (0 = less than degree and 1 = degree or above). Mothers who were categorised in the less than degree group had completed either O' levels, secondary education, A levels or vocational training (Sagiv et al. 2013; Etherington et al. 2016; Lin et al. 2017).

History of maternal depression was assessed by the ALSPAC research team at 12 weeks of gestation. The ALSPAC research team generated a dichotomous variable, which I recoded so that 0 = no history of depression and 1 = positive history of depression) (Lieb et al. 2002; Cullen et al. 2014; Wolford et al. 2017; D'Souza et al. 2019).

Ethnicity was derived by the ALSPAC research team from responses received from self-reports at 32 weeks of gestation. This was a dichotomous variable which I recoded so that 0 = non-white and 1 =

white (Zilanawala et al. 2015; Coker et al. 2016; Akinhanmi et al. 2018).

Being a victim of bullying at school at age 8 assessed using the modified version of the Bullying and Friendships Interview Schedule (Wolke et al. 2001). If the child scored a response of “yes” on any of the 5 questions asked about the type of bullying they received, they were classified as a victim of being bullied and produced a dichotomous variable coded 0 = not bullied and 1 = bullied (Holmberg and Hjern 2008; Undheim and Sund 2010; Wolke et al. 2012; Palmier-Claus et al. 2016).

Being emotionally and/or physically abused by either parent since the child was 6 was assessed via questionnaire. The research team generated a categorical variable, in which several options for yes were included (“yes since 6th birthday”, “yes since the child’s 8th birthday” and “yes both since the child’s 6th birthday and from 8+”) and “no did not happen in the last 3 years”. However, in line with others who have examined childhood emotional and/or physical abuse (Lereya et al. 2015), I collapsed this into a dichotomous variable coded 0 = not abused and 1 = abused) (Dvir et al. 2014; Newnham and Janca 2014; Palmier-Claus et al. 2016; D'Souza et al. 2019).

Assessments of handedness were conducted by a trained Psychologist when the children were age 10 years. Though the purpose of the computer task was primarily to examined executive cognitive function, working memory and inhibition, a determination of the child’s dominant hand was recorded. This produced a dichotomous variable, which I coded as 0 = right-handed and 1 = left-handed.

In Chapters 4 and 5, a number of these confounders were adjusted for, with comparisons being made between unadjusted and adjusted models using multivariable regression. Where adjustment for

confounders made a substantial impact on effect size and/or strength of evidence of association, both unadjusted and adjusted results are reported in the main text. For the individual confounders adjusted for in each analysis, please see Chapters 4 and 5.

3.4.1 Addressing potential sources of confounding in genetic analyses

In polygenic risk score (PRS) analyses, the biggest source of confounding after performing quality control is population stratification. Population stratification is where differences in allele frequency between cases and controls are likely a result of ancestry as opposed to association of genes with the disease of interest. It is most commonly due to non-random mating between groups of individuals, often based on physical geographical distance, followed by genetic drift of allele frequencies in each of the groups. Not adjusting for population stratification in ethnically diverse populations can lead to detecting spurious loci which have nothing to do with the disease of interest (Liu et al. 2013; Choi et al. 2018). In my analyses (Chapters 7 and 8), I did not adjust for population stratification as the ALSPAC sample has been shown to be homogenous, and genome-wide analyses of phenotypes indicate low lambda, producing a genomic inflation factor ($\lambda \approx 1$) (Zammit et al. 2014; Martin et al. 2015). The other potential source of confounding in PRS analyses is linkage disequilibrium (LD) between SNPs i.e. the non-random occurrence of alleles at different loci. To account for LD between SNPs, clumping can be performed to retain SNPs that are largely independent of each other, and their effects summed. Therefore, as is common practice in PRS analyses, I clumped SNPs to preferentially retain SNPs most strongly associated with BD. Through clumping, it is also possible to retain multiple independent effects in the same genomic region and not simply the most strongly associated SNP in that region (Choi et al. 2018).

3.5 Genetic Data

In this thesis, I will be deriving PRSs using primary genotype data from the ALSPAC sample and summary statistics from the Psychiatric Genomics Consortium (PGC) samples. I will first describe, in detail, the quality control measures used by the research teams (ALSPAC and the PGC) before describing how I derived the PRS.

3.5.1 ALSPAC quality control measures

The quality control measures described in this section were conducted by the ALSPAC research team.

In the ALSPAC cohort, a total of 9,912 ALSPAC children were genotyped using the Illumina HumanHap550 quad genome wide single-nucleotide polymorphism (SNP) by 23andMe subcontracting the Wellcome Trust Sanger Institute, Cambridge, UK and the Laboratory Corporation of America, Burlington, NC, USA. Individuals were excluded from analyses if: i) their gender assignment was incorrect, ii) they had minimal or excessive herterozygosity (<0.320 and >0.345 for the Sanger Data and <0.210 and >0.330 for the LabCorp data), iii) there were disproportionate levels of missingness (>3%), iv) they were not of European-ancestry and v) showed evidence of cryptic relatedness (>10% identity by descent). Further, any SNPs with a minor allele frequency (MAF) <1%, a SNP call rate <95% or imputation quality (INFO score) <0.8 were excluded from the analyses. Finally, only SNPs which passed the exact test for Hardy-Weinberg Equilibrium ($p>5x10^{-7}$) were considered for further use. After the ALSPAC research team conducted quality control, imputation, and restriction to 1 young person per family, genetic data was available on 8,230 individuals. The two sites where genotyping was conducted had differing heterozygosity filters applied, though this is unlikely to confound results as genotyping site would also

need to be associated with the outcome of interest (as well as the exposure) for confounding to occur.

3.5.2 Psychiatric Genetics Consortium (PGC) quality control measures

All quality control measures described in this section were conducted by the PGC research team.

To genotype individuals in the second PGC GWAS for: BD (n = 20,352 cases and 31,358 controls) (Stahl et al. 2019), SZ (n = 36,989 SZ cases 113,075 controls) (Ripke et al. 2014) and SZvsBD (n = 33,426 SZ cases and 20,129 BD "controls") (Ruderfer et al. 2018), four genotyping platforms were used: Affymetrix 500K, 5.0, 6.0 and Illumina HumanHap500. SNPs were retained if their missing genotype rate per SNP was <0.02, Hardy-Weinberg in controls was $p>1x10^{-6}$ and the frequency difference to Hapmap-reference was <0.15.

3.5.3 Further quality control measures prior to constructing the PRS

In addition to the quality control measures run by the PGC and ALSPAC research teams, using R statistical software, I further removed SNPs in the PGC dataset if their INFO score was <0.8, if the SNPs had a MAF of <0.01. In addition, in line with recent guidelines on generating PRS (Choi et al. 2018), when discovery and target datasets have been genotyped on different chips, and the chromosome strand (positive or negative) is unknown, SNPs cannot be matched e.g. if A/T or C/G across datasets as it is not possible to determine whether the discovery or target datasets are referring to the same allele or not.

3.5.4 Constructing the PRS

To generate the PRS, I followed the methods first described by the International Schizophrenia Consortium (Purcell et al. 2009).

Having removed any further SNPs from either discovery or target datasets which did not meet criteria for inclusion in the PRS, using R, I generated the log odds ratio (OR) for the corresponding effect sizes from the PGC GWAS for BD, SZ and SZvsBD. I then merged the PGC summary statistics GWAS and ALSPAC datasets (PGC 2 BD GWAS with ALSPAC; PGC 2 SZ GWAS with ALSPAC, and PGC 2 SZvsBD GWAS with ALSPAC) which contained information on the SNP ID, risk allele (A1), non-risk allele (A2), log ORs and p-values. From this, a file that contained information on the SNP ID, allele A1 and corresponding log OR was generated, and a separate file, which contained a list of SNP IDs only were then used to construct the PRS in PLINK v1.9. Duplicate SNPs were identified and removed prior to clumping firstly by generating a file which contained duplicate SNPs in them and then using the grep command to remove duplicate SNPs from the merged file.

Using PLINK v1.9, SNPs were linkage disequilibrium (LD) clumped, with r^2 <0.2 within 1MB windows, as this is the typical size of an LD block using the –clump command. I flipped any alleles where there was mismatch between the target and discovery dataset i.e. A/C in one dataset and G/T in the other using the --flip-scan command and the clumped SNPs were then extracted using the –extract command.

Using R statistical software, I then generated training scores which contained SNPs with a p-value threshold (P_T) cut-off of ≤0.01 (Stahl et al. 2019) and ≤0.5 (Sklar et al. 2011) for BD, P_T≤0.05 for SZ (Ripke et al. 2014) and P_T≤0.5 for SZvsBD (Ruderfer et al. 2018). These P_T's were selected as they have been reported to maximally capture liability for the disorders in their respective GWAS. For the SZvsBD training score, a P_T≤0.5 was chosen as this is the P_T that

maximally captures variance for most other phenotypes (Ware et al. 2017). The training scores contained the SNP ID, allele A1 and corresponding effect size. The P_T approach performs no shrinkage of effect size estimates of the included SNPs, but does effectively shrink effect sizes of non-included SNPs to zero. I then used the training scores produced from R to generate profile scores (i.e. PRSs) for each individual in ALSPAC using the –score command in PLINK. Each PRS is the sum total of the number of risk alleles for each SNP (0, 1, 2) weighted by the log of its OR. Each PRS file contained information on the family ID (FID), individual ID (IID), phenotype (PHENO), number of non-missing SNPs used for scoring (CNT), number of named alleles (CNT2) and the PRS itself. The PRS files (BD-PRS at $P_T \leq 0.01$ and 0.05; SZ-PRS at $P_T \leq 0.05$ and SZvsBD-PRS at $P_T \leq 0.5$) were then merged with the ALSPAC dataset by FID to create a master dataset which contained the PRSs and all phenotypic data.

3.6 Statistics

3.6.1 Measures of association

Measures of association between an exposure and outcome can be relative (e.g. ratio measures) or absolute (e.g. difference measures).

3.6.1.1 Absolute measures

Absolute measures such as difference measures are used to examine the absolute change in risk of the disease according to different levels of exposure. One method of examining the differences in absolute risk of the disease when using continuous outcomes is linear regression.

3.6.1.1.1 Linear regression

Linear regression analyses rely on a number of assumptions: i) the relationship between exposure and outcome is linear, ii) there is no or little multicollinearity i.e. the exposure measures are not highly correlated with each other, iii) the residuals are normally distributed, iv) there is no heteroscedacity i.e. the errors should not vary systematically across values of the exposure, and v) the residuals are uncorrelated. If these assumptions are violated, the regression coefficient may be biased, or the variance of the estimate may be increased. Linear regression is reasonably robust in the presence of mild deviation from these assumptions, particularly those of linearity and normality of residuals. However, in instances where there is large deviation from these assumptions, non-parametric methods e.g. the Kruskal-Wallis test may provide a more valid and less biased measure of the association between exposure and outcome.

To determine whether linear regression was an appropriate statistical method to use in analyses using continuous outcomes, I tested the assumptions of linear regression described above. To examine the possibility of a non-linear relationship, I generated quadratic terms of the exposure measures, and where applicable, if a non-linear relationship was detected, both linear and quadratic term results are reported. Kernel density plots of continuous outcomes were used to determine whether the residuals were normally distributed, and tests for heteroscedacity were conducted post-analysis.

I report effect sizes (beta coefficients) and 95% confidence intervals (CI) to aid interpretation of the strength of evidence of association. These results reflect the standard deviation (SD) change in outcome per SD increase in exposure (if the exposure is continuous) or the SD change in outcome if the exposure is present compared to absent (if binary).

3.6.1.1.2 Aiding interpretation of non-linear relationships

Whilst the addition of a quadratic term provides information on whether a non-linear relationship is present, to facilitate the interpretation of this, I derived tertiles of the exposure and compared the outcome when being in the lowest or highest tertiles compared to the middle exposure tertile. Though deriving tertiles to help facilitate interpretation of a non-linear effect is useful, this method of investigating these relationships is not without flaw. The limitations of deriving the tertiles are i) the increase in parameters estimated increases the problems of multiple testing, ii) it requires an unrealistic step-function of risk that assumes homogeneity of risk within groups, leading to both a loss of power and inaccuracy in the estimation of effect, and iii) it leads to difficulty comparing results across studies due to the data-driven cut points used to define categories (Bennette and Vickers 2012).

3.6.1.2 Relative measures

Relative measures are used when examining associations with binary or categorical outcomes. Relative risk is a generic term which includes measures such as rate ratios and risk ratios which can only be derived from cohort studies. Though rate ratios and risk ratios can be used when using longitudinal data, in this thesis, I will be using odds ratios (ORs) since it provides a reasonable approximation of the relative risk when the outcome of interest is uncommon (<10%).

3.6.1.2.1 Odds Ratio (OR)

An OR can be derived to describe the change in odds of an outcome across increasing levels of an exposure. ORs can be used in a variety of study designs including case-control, cross-sectional and cohort studies.

It is possible to calculate the odds of disease which is the probability of a subject developing a disease divided by the probability that the subject does not develop the disease, and is calculated as follows:

From this equation, it is then possible (for a binary exposure) to calculate separate odds of outcome in those who are exposed compared to those who are not exposed:

Logistic regression, unlike linear regression has fewer assumptions that are required to determine its suitability in statistical analysis: i) the outcome variable is binary, ii) observations should be independent of each other i.e. not come from matched data or repeated measures (unless specific methods are used to deal with this e.g. conditional logistic regression for matched data), iii) there should be no/little multicollinearity as this can lead to imprecise estimates, iv) the association between the independent variables and the log odds of the outcome is linear, and v) the sample size should have a minimum of 10 cases with the least frequent outcome for each independent variable.

I investigated these assumptions and having done so, found that logistic regression was an appropriate statistical method to use for binary outcomes. Therefore, in this thesis, I provide ORs and 95% confidence intervals that represent the change in odds of the outcome per SD increase in exposure (if continuous and standardised) or presence compared to absence of the exposure (if binary).

3.6.1.3 Correlations between measures

When investigating the extent of co-linearity between 2 continuous variables that are normally distributed, I used a Pearson correlation test, or when not normally distributed I used Spearman's rho. If variables were ordinal, I used polychoric correlation. Where applicable, a Point-Biserial test was used to examine the correlation between a continuous and binary variable, and for two binary variables, tetrachoric correlation was used.

3.6.1.4 Multiple imputation

To address the potential for selection bias due to missing data in my analyses, I used multiple imputation. There are three ways that data can be missing: i) data are missing completely at random (MCAR), ii) data are missing at random (MAR), and iii) data are missing not at random (MNAR). The pattern of missingness will likely guide the approach to deal with the missingness.

If data are MCAR, this means that there is no relationship between the missingness of that data and any value, whether observed or missing i.e. the causes of missing data are unrelated to the data. Therefore, analyses on data that are MCAR are likely unbiased. However, in practice, this is rarely the case. If data are MAR, this means that there are systematic differences between missing and observed values, but these differences can be accounted for i.e. are conditional on variables in which complete information is available. Finally, if data are MNAR, this means the values of the missing data are related to the reason it is missing e.g. if data are missing on IQ and only those who have low IQ have missing data (Pedersen et al. 2017).

In the ALSPAC cohort, there is a large degree of attrition, where almost half the cohort have dropped out by age 7 years (Boyd et al.

2013). One method of dealing with missing data is to impute values for missing data using values from other variables in the dataset.

Using a single imputation often leads to over-precision of estimates as standard errors are too small, and does not account for the lack of uncertainty about the missing values. I therefore used the multiple imputation by chained equation model approach using the “ice” command in Stata 14. This works by firstly creating multiple copies of the dataset, and then replacing missing values with imputed values based on values from variables with complete data. Stage two of the process then uses statistical methods to fit whichever model is of interest to each of the imputed datasets. The estimates are then averaged across all the imputed datasets using Rubin’s rules, which will account for the uncertainty in results between imputed datasets. Although using 5 imputations has been reported to be sufficient on theoretical grounds, to reduce sampling variability as a consequence of the imputation process, a minimum of 20 imputations may help deal with the sampling variability (Sterne et al. 2009).

To make the assumption of data being missing at random more plausible, I ran 100 imputations and imputed all outcome, exposure and potential confounders, as well as adding auxiliary variables. These auxiliary variables were selected based on them being associated with either exposure/confounder measures and missingness.

3.6.2 A note on interpreting statistical output

In the scientific community, it has been common practice to determine whether findings are meaningful (rather than due to chance) based upon a significance threshold for the p value. The arbitrary threshold commonly used is $p \leq 0.05$; thus, anything less than this value would be deemed as significant and perhaps meaningful, and anything greater than this as not meaningful.

For reasons that are widely accepted in Epidemiology however, and in line with ALSPAC guidelines, in this thesis I take care not to rely on any arbitrarily-defined threshold to determine whether something is meaningful or not. A p-value is defined as the probability of finding an effect, at least as extreme as the observed, if the null hypothesis is true. Thus, all p-values provide some evidence against the null hypothesis, and it is more useful to therefore refer to the strength of evidence (for example extremely weak evidence, extremely strong evidence, or somewhere in between) based on the p-value and study characteristics such as the number of tests performed than to refer to a specific but arbitrary threshold (see (Amrhein et al. 2019), (Sterne and Smith 2001) and a statement along with the accompanying publications from the American Statistical Association (Wasserstein and Lazar 2016)).

Even where effect sizes are small and confidence intervals include the null, it may still be appropriate to interpret findings as weak evidence of association at best. Stronger confidence in support of a meaningful association can be seen when confidence intervals are highly asymmetric around the null, rather than when the intervals are symmetric around the null, in which case it is equally possible the effect is protective as well as associated with risk. Therefore, confidence intervals can convey useful information without ever relying on whether they include the null or not and can provide information on the strength of evidence of association.

The next chapter is the beginning of the results chapters, which firstly begins with the assessment of childhood psychopathology associated with subsequent hypomania.

Chapter 4: Childhood psychopathology and hypomania

The work presented in this chapter has been published and can be found online at:
http://www.sciencedirect.com/science/article/pii/S0165032716323874?via%3Dihub

Mistry, S., Zammit, S., Escott-Price, V., Jones, H., 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**, 246-253
https://doi.org/10.1016/j.jad.2017.06.039

The published article has been adapted for use in this chapter to include additional results (available as supplementary materials online).

4.1 Chapter summary

Patients with bipolar disorder (BD) often have delayed diagnosis by up to as long as 10 years. However, most report experiencing symptoms of psychopathology earlier on from childhood/adolescence.

In this chapter I investigated objectives 1-3 of this thesis as outlined in Chapter 2. Using a longitudinal birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC), I assessed whether a broad range of childhood psychopathology was associated with hypomania outcomes assessed in young adulthood.

I found strong evidence of association between measures of borderline personality disorder (BPD) traits and hypomania, as well as depressive symptoms with hypomania. For the former, associations were stronger for the 'active/elated' factor, whilst for the latter were stronger with the 'risk-taking/irritable' factor of hypomania. Associations between BPD traits and hypomania were not explained by confounding or selection bias. I also found evidence of association between attention deficit hyperactivity disorder (ADHD) and Strengths and Difficulties Questionnaire (SDQ) scores with the 'risk-taking/irritable' factor, but much less consistent evidence of association with the 'active/elated' factor. Confounding and selection bias appear, at least in part, to be possible explanations for associations between ADHD, SDQ and depression score with measures with hypomania.

These findings suggest that specific trait related psychopathology measures may represent early markers of risk or be potential risk factors for hypomania. Further studies are required to understand the mechanisms underlying these associations, and to inform earlier detection of BD.

4.2 Introduction

The lifetime risk of BD is estimated to be between 1-2% (Merikangas et al. 2007; Merikangas et al. 2011). Whilst a diagnosis of BD depends on a history of (hypo)mania (Anderson et al. 2013), the accurate detection of a history of (hypo)mania can be difficult because individuals are more likely to present for help with depression, and often have poor recollection of (hypo)manic symptoms (Ghaemi et al. 1995; Regeer et al. 2015). This can often lead to an under-diagnosis of BD in depressed patients (Angst et al. 2005a; Gamma et al. 2013).

There are a number of commonly used semi-structured interviews to assess for presence of BD. However, the time required to complete these interviews can be lengthy and therefore, a more time-efficient way of detecting presence of symptoms of (hypo)mania may be the use of self-report measures (Miller et al. 2009). One of the most studied self-report screening instruments to detect signs of (hypo)mania is the Hypomania Checklist-32 (HCL-32). Originally designed to detect less severe forms of bipolar disorders (specifically bipolar II disorder) in depressed patients (Angst et al. 2005a), it has since been used in community general population samples (Holtmann et al. 2009; Lee et al. 2016).

Several studies have used exploratory factor analysis to determine the underlying factor structure of the HCL in both clinical (Angst et al. 2005a; Wu et al. 2008) and general population samples (Holtmann et al. 2009; Brand et al. 2011). Irrespective of how many items are used in the questionnaire (e.g. the 32-item HCL or the 16-item HCL), at least two factors are consistently reported, in which items load onto an ‘active-elated’ or ‘risk-taking/irritable’ factor (Angst et al. 2005a; Forty et al. 2010; Hosang et al. 2017; Glaus et al. 2018). These two factors reflect the underlying factor structure of hypomania previously described as “sunny-side” and “dark-side” features respectively (Hantouche et al. 2003).

Typical age of onset (likely age at which the individual accessed clinical services) for BD ranges between 18-22 years (Merikangas et al. 2011), though a substantial proportion of those with BD (up to 60%) report the presence of

psychopathology during childhood/adolescence (Perlis et al. 2009). Therefore, the identification of early psychopathology preceding onset of BD may help with improving prediction and earlier diagnosis, though at present, there is uncertainty about the extent to which features of childhood psychopathology might be considered as reliable predictors for the later development of BD (Faedda et al. 2014; Faedda et al. 2015).

The objectives of this study were: i) to investigate whether childhood psychopathology (borderline personality disorder (BPD) traits, attention deficit hyperactivity disorder (ADHD), emotional/behavioural problems and depression score) in childhood are associated with a dimensional measure of hypomania, with latent traits underlying hypomania, or with clinically-defined hypomania in early adulthood, and ii) to examine whether any associations are likely to be due to confounding or selection bias (Objectives 1-3 in Chapter 2).

4.3 Method

4.3.1 Study participants

This study used data from individuals between ages 7 to 23 years. Recruitment procedures and inclusion criteria for the study can be found in Chapter 3 under section 3.2. Final sample numbers for outcome and exposure measures are shown in Figure 3 in Chapter 3.

4.3.2 Main outcome: Hypomania

The HCL-32 is a self-rating questionnaire designed to assess for a lifetime history of (hypo)manic symptoms (Angst et al. 2005a). A detailed overview of the HCL-32, its psychometric properties and how all hypomania outcomes (HCL score, clinically-defined hypomania and HCL factors) were derived can be found in Chapter 3 under section 3.3.1. The cohort completed the HCL-32 questionnaire when they were age 22-23 years and from the 32-item checklist, the 28-items used in this thesis are shown in Chapter 3, Table 5.

4.3.3 Childhood predictors: BPD traits, ADHD status, SDQ sub-scales and MFQ score

4.3.3.1 Assessment of BPD traits

At age 11 years, the cohort were interviewed to assess their experience of BPD traits over the preceding two years. Detailed information on the Childhood Interview for DSM-IV Borderline Personality Disorder (CI-BPD) can be found in Chapter 3 under section 3.3.2.1.

In the present study, children were classified as being high-risk for BPD if they were rated ‘probably’ or ‘definitely’ on five or more of the nine traits, as used previously (Wolke et al. 2012). Further details on the criteria required to receive a rating of definitely present or probably present can be found in a study by Zanarini and colleagues (Zanarini et al. 2004), and further details on how I generated the BPD traits score are found in Chapter 3, under section 3.3.2.1.

4.3.3.2 Assessment of childhood ADHD status

The presence of ADHD at age 7.6 years was assessed using the Development and Wellbeing Assessment (DAWBA) (Goodman et al. 2000). Details of the DAWBA package can be found in Chapter 3 under section 3.3.2.2.

4.3.3.3 SDQ subscales

At age 9 years, the cohort were invited to complete the SDQ. In total, there are five SDQ subscales (hyperactivity problems, prosocial behaviour, emotional difficulties, conduct problems and peer relationship difficulties), though prosocial behaviour does not contribute towards the total difficulties score (Goodman 1997,2001). More detailed information on recruitment, factor structure of the SDQ and how I generated the SDQ subscale scores can be found in Chapter 3 in section 3.3.2.3.

4.3.3.4 Moods and Feelings Questionnaire (MFQ)

At age 9 years, the cohort were invited to complete the short version of the MFQ (Angold et al. 1995). Further details on the MFQ can be found in Chapter 3 in section 3.3.2.4.

4.3.4 Statistical analyses

All analyses conducted in this chapter were performed using Stata statistical software (version 14.1 SE. College Station, TX: Statacorp LP). To determine whether there were differences in sociodemographic characteristics between the study sample (those with data on the HCL) and those without data on the HCL, I used a chi squared test for trend for maternal social class, and a t-test to examine differences between the study sample and those with no data on the HCL for all other sociodemographic characteristics. Further details including how these were coded can be found in Chapter 3, section 3.4.

I used linear regression to compare associations between exposures (BPD traits, high-risk for BPD, ADHD, SDQ sub-scale scores and depression score) and continuous hypomania outcomes (HCL score and HCL factors). Results from these analyses are presented as the standard deviation (SD) change in hypomania outcome per 1 unit increase in exposure. A Kernel density plot of the residuals showed they were normally distributed and tests for heteroskedasticity showed homogeneity within the sample.

For analyses examining associations between exposure measures and the binary clinically-defined hypomania outcome, I used logistic regression. Results from these analyses are presented as the change in odds of clinically-defined hypomania per 1 unit increase in exposure.

4.3.5 HCL-28 Confirmatory Factor Analysis (CFA)

Previous studies have used exploratory factor analysis to determine the underlying structure of the HCL in both general population (Holtmann et al. 2009; Brand et al. 2011) and clinical samples (Angst et al. 2005; Wu et al. 2008). The 28-items were loaded onto their corresponding factors, the

'active/elated' and 'risk-taking/irritable' HCL factors by Dr Hannah using the mean and variance adjusted weighted least squares method in Mplus (see Chapter 3, section 3.3.1.2 for further details and Table 6 for factor loadings).

4.3.6 Confounding

I investigated the possibility of relationships between exposures and outcomes being explained by confounding. To do this, I adjusted my main analyses (as described above) for a number of sociodemographic characteristics and markers of adversity: gender, ethnicity, maternal age at birth, maternal social class, highest maternal education level, confirmed history of maternal depression, being bullied at school and being emotionally and/or physically abused (see Chapter 3, section 3.4 for further details). Genetic risk for BD was initially adjusted for, however, this made little difference to the associations between exposure(s) and outcome measures. Therefore, to maximise sample size, results are presented without adjusting for genetic risk for BD.

4.3.7 Multiple imputation

To address the possibility of estimates being affected by selection bias, I used multiple imputation. I imputed all exposure and confounder measures, and included auxiliary variables which were predetermined on the basis of them being associated with either exposure/confounder measures and missingness. Further details on the multiple imputation approach can be found in Chapter 3, under section 3.6.1.4.

4.4 Results

4.4.1 Sample demographics

Table 7 shows the differences between the study sample (those with data on the HCL; n = 3,371) compared to those with no data on the HCL (n = 12,073). When compared to those with no data on the HCL, the study sample had a higher proportion of mothers who had a degree (21.5% vs 10.0%; p <0.001), a

smaller proportion of males (35.3% vs 56.2%; p <0.001), greater maternal age at birth (29.7 years vs 27.9 years; p <0.001), higher maternal social class (p <0.001) and a smaller proportion of mothers who had depression (18.4% vs 20.7%; p = 0.006). There was little evidence that ethnicity differed between the study sample and those with no data on the HCL.

Table 7 Characteristics of the ALSPAC cohort who completed the HCL and those who did not

Characteristic	Rest of ALSPAC cohort (N = 12,073)[a] n (%)	Completed HCL (N = 3,371) n (%)	P
Gender			
Male	6,449 (56.15%)	1,189 (35.26%)	<0.001
Maternal social class			
I	354 (3.76%)	243 (7.71%)	
II	2,168 (23.01%)	1,017 (32.28%)	
III (non-manual)	3,178 (33.72%)	1,150 (36.50%)	<0.001[b]
III (manual)	632 (79.90%)	159 (20.10%)	
IV	821 (9.71%)	176 (5.59%)	
V	191 (2.03%)	31 (0.98%)	
Ethnicity			
White	9,018 (97.26%)	3,060 (98.16%)	0.183
Maternal education			
Degree or above	934 (9.99)	676 (21.5%)	<0.001
Maternal Depression			
Yes	1,955 (20.65%)	577 (18.38%)	0.006
	Mean (SD)	**Mean (SD)**	
Maternal age at birth	27.9 (4.87)	29.7 (4.43)	<0.001

[a] Missing data for some variables means sample sizes vary. [b] P value tested by chi-squared test for trend; ALSPAC: Avon Longitudinal Study of Parents and Children; HCL: Hypomania Checklist; SD: Standard Deviation

4.4.2 BPD traits and hypomania in young adulthood

Results from the regression analyses are presented in Table 8. I found strong evidence of an association between the BPD traits score (β = 0.10, 95%CI 0.06, 0.14; p <0.001) and higher HCL score, which was unchanged after adjusting for potential confounders. There was very weak evidence to suggest an association between being in the high-risk for BPD group compared to non-high-risk group and HCL score (β = 0.21, 95%CI -0.04, 0.46; p = 0.095), which weakened further (reduction in effect size of 14%) after adjusting for potential confounders.

Associations with clinically-defined hypomania at a threshold score of ≥14/28 on the HCL were also strong for both the BPD traits score (OR = 1.39, 95%CI 1.16, 1.66; p <0.001) and high-risk for BPD (OR = 2.84, 95%CI 1.43, 5.64; p = 0.003). These associations were partly attenuated (reduction in effect size of 13% and 38% respectively) when adjusting for confounding (Table 8).

When examining the 2 factors that best summarised the 28-items of the HCL, I found that associations between the BPD traits score and HCL factors were stronger with the 'risk-taking/irritable' factor than with the 'active/elated' factor, though there was little evidence of association with either factor in those who were high-risk for BPD compared to those who were not high-risk (Table 8).

Table 8 Association between the BPD traits score/high-risk for BPD and hypomania

Exposure	Outcome	N	β unadjusted	95%CI	P value	β adjusted[a]	95%CI	Adjusted p value
BPD traits score	HCL score	1,319	0.12	0.06, 0.18	<0.001	0.12	0.05, 0.18	<0.001
High-risk for BPD			0.21	-0.04, 0.46	0.095	0.18	-0.07, 0.43	0.162
BPD traits score	Active-elated factor	1,297	0.08	0.03, 0.14	0.004	0.09	0.03, 0.15	0.002
	Risk-taking/irritable factor		0.11	0.06, 0.16	<0.001	0.08	0.03, 0.14	0.003
High-risk for BPD	Active-elated factor		0.15	-0.09, 0.39	0.224	0.16	-0.09, 0.40	0.214
	Risk-taking/irritable factor		0.14	-0.08, 0.38	0.206	0.07	-0.17, 0.30	0.581
Exposure	**Outcome**	**N**	**OR unadjusted**	**95%CI**	**P value**	**OR adjusted[a]**	**95%CI**	**P value**
BPD traits score	Clinically-defined hypomania	1,319	1.39	1.16, 1.66	<0.001	1.33	1.09, 1.64	0.006
High-risk for BPD			2.84	1.43, 5.64	0.003	2.51	1.21, 5.21	0.013

BPD: Borderline Personality Disorder; HCL: Hypomania Checklist; CI: Confidence Intervals; OR: Odds Ratio

[a] adjusted for: history of maternal depression, maternal age at birth, maternal education level, maternal social class, being a victim of bullying in school at age 8 years, gender, ethnicity, total difficulties score at ages 9 and 11, diagnosis of ADHD and experience of physical and emotional abuse when the child was 6 or 7 years old

I next investigated whether findings of association between the BPD traits score and clinically-defined hypomania were robust across different cut-off thresholds on the HCL. I conducted sensitivity analyses using increasing threshold symptom number count being required to be classified as having clinically-defined hypomania. The results at higher symptom threshold counts were, on the whole, consistent with those reported at a threshold of ≥14/28 (see Appendix 2).

I then wanted to determine whether the association between the BPD traits score and hypomania was driven by any particular BPD trait(s). The 9 BPD traits were correlated, with correlations ranging from 0.33 to 0.67. Most BPD traits were strongly associated with the HCL score, with the exception of fear of abandonment. Results were generally consistent when examining associations with clinically-defined hypomania, though there was much weaker evidence of association with BPD traits of anger ($p = 0.178$) and impulsivity ($p = 0.160$), and stronger evidence of association with fear of abandonment ($p = 0.003$) (Appendix 3).

As anger symptoms contribute to the derivation of both the BPD traits score and the HCL score, I conducted a sensitivity analysis where I removed the question which asked about “getting into more quarrels” from the HCL score to address the possibility that the association between BPD traits and hypomania is simply a persistence of anger traits into adulthood. Having done so, there was no change in effect size or the strength of evidence of association between the BPD traits score or high-risk for BPD and the HCL score.

When examining the relationship between the individual BPD traits and HCL factors, most traits showed stronger evidence of association with the ‘risk-taking/irritable’ factor than with the ‘active/elated’ factor, though fear of abandonment was the only trait not associated with either factor.

4.4.3 ADHD in childhood and hypomania in young adulthood

The association between a diagnosis of any ADHD disorder and hypomania outcomes are shown in Table 9. There was strong evidence of association

between childhood ADHD and the ‘risk-taking/irritable’ factor (β = 0.84, 95%CI 0.41, 1.27; p<0.001), but not with the other hypomania outcomes examined. Adjusting for potential confounders generally led to some attenuation of associations both in terms of effect size and strength of evidence of association, though the association with the ‘risk-taking/irritable’ factor remained strong despite a 7% reduction in effect size.

When examining ADHD subtypes, associations were observed between inattentive (p<0.001) and combined (p = 0.020) subtypes and the ‘risk-taking/irritable’ factor, but not with the hyperactive-impulsive subtype (p = 0.897). There was little evidence of association between ADHD subtypes and HCL score (all p>0.424), ‘active/elated’ factor (all p>0.181) or clinically-defined hypomania (all p>0.238).

Table 9 Association between a diagnosis of any ADHD and hypomania outcomes

Exposure	Outcome	N	β unadjusted	95%CI	P value	β adjusted[a]	95%CI	P value
Any ADHD diagnosis	HCL score	2,079	0.12	-0.33, 0.56	0.612	0.06	-0.39, 0.50	0.796
	Active/elated factor	1,839	-0.21	-0.67, 0.25	0.368	-0.28	-0.73, 0.18	0.238
	Risk-taking/irritability factor	1,839	0.84	0.41, 1.27	<0.001	0.78	0.35, 1.21	<0.001
Exposure	**Outcome**	**N**	**OR unadjusted**	**95%CI**	**P value**	**OR adjusted[a]**	**95%CI**	**P value**
Any ADHD diagnosis	Clinically-defined hypomania	2,079	2.53	0.73, 8.79	0.143	2.06	0.57, 7.49	0.273

[a] adjusted for: history of maternal depression, maternal age at birth, maternal education level, being a victim of bullying in school at age 8 years, gender and ethnicity

ADHD: Attention Deficit Hyperactivity Disorder; HCL: Hypomania Checklist; CI: Confidence Interval; OR: Odds Ratio

To address the problem of potentially overlapping questions in the HCL and the DAWBA that was used to generate a DSM-IV diagnosis of ADHD, I removed the following questions from the HCL: “feel more energetic”, “am more easily distracted”, “thoughts jump from topic to topic”, “am more impatient” and “can be exhausting to others”. There was little evidence of association between the diagnosis of any ADHD and the HCL factors re-derived after excluding the items listed above.

4.4.4 SDQ in childhood and hypomania in young adulthood

I found little evidence of association between the total difficulties score and both the HCL score ($p = 0.786$) and the ‘active/elated’ factor ($p = 0.436$). However, there was stronger evidence of association with both the ‘risk-taking/irritable’ factor ($\beta = 0.08$, 95%CI 0.03, 0.13; $p = 0.001$) and with clinically-defined hypomania (OR = 1.37, 95%CI 1.14, 1.64; $p = 0.001$), though in both instances, adjustment for confounders reduced effect sizes by 25% and 40% respectively, as well as the strength of evidence of association (see Table 10).

Table 10 Association between the total difficulties score and hypomania

Exposure	Outcome	N	β unadjusted	95%CI	P value	β adjusted[a]	95%CI	P value
Total difficulties score	HCL score	2,010	0.00^	-0.05, 0.06	0.886	0.00^	-0.05, 0.06	0.786
	Active/elated factor	1,779	-0.04	-0.09, 0.02	0.181	-0.02	-0.07, 0.03	0.436
	Risk-taking/irritability factor	1,779	0.08	0.03, 0.13	0.001	0.06	0.01, 0.11	0.020
Exposure	**Outcome**	**N**	**OR unadjusted**	**95%CI**	**P value**	**OR adjusted[a]**	**95%CI**	**P value**
Total difficulties score	Clinically-defined hypomania	2,010	1.37	1.14, 1.64	0.001	1.21	1.00, 1.47	0.048

[a] adjusted for: history of maternal depression, maternal age at birth, maternal education level, being a victim of bullying in school at age 8 years, gender and ethnicity; ^rounded to 2 decimal places; HCL: Hypomania Checklist; CI: Confidence Intervals; OR: Odds Ratio

I then investigated the association between the subscales within the SDQ to determine whether specific emotional or behavioural difficulties might be associated with hypomania. The individual SDQ subscale scores were correlated, with correlations ranging from -0.36 to 0.47. Negative correlations were observed between the prosocial subscale and other SDQ subscales, whereas the other SDQ subscale scores were all positively correlated with each other. Associations between individual SDQ subscale scores and hypomania are presented in Appendix 4. There was generally little or inconsistent evidence of association between the SDQ subscales and either the HCL score or clinically-defined hypomania. However, there was strong evidence of association between all subscales (except emotional difficulties) and the 'risk-taking/irritable' factor, whereas only greater prosocial behaviour and hyperactivity problems were associated with the 'active/elated' factor.

As some of the questions asked in the hyperactivity subscale of the SDQ are similar to those asked in the HCL, I re-ran the analysis excluding from the HCL score the ADHD-related questions as described above. Having excluded these questions, I found weak evidence of association between higher hyperactivity problems and a reduction in the 'active/elated' factor, but not with the 'risk-taking/irritable' factor.

4.4.5 Depression score (MFQ) and hypomania

I found weak evidence of association between the depression score and HCL score (β = 0.05, 95%CI 0.00, 0.11; p = 0.049), which weakened further after adjusting for potential confounders (p = 0.095), though no reduction in effect size was observed. Associations between the depression score and both the 'risk-taking/irritable' factor (β = 0.08, 95%CI 0.03, 0.13; p = 0.003) and clinically-defined hypomania (OR = 1.33, 95%CI 1.11, 1.58; p = 0.001) were stronger, though in both instances, adjusting for confounders reduced effect sizes by 13% and 22% respectively and a decrease in the strength of evidence of association was observed (see Table 11).

Table 11 Association between the MFQ and hypomania outcomes

Exposure	Outcome	N	β unadjusted	95%CI	P value	β adjusted[a]	95%CI	P value
MFQ	HCL score	1,824	0.05	0.00^, 0.11	0.049	0.05	-0.01, 0.10	0.095
	Active/elated factor	1,614	0.02	-0.03, 0.08	0.373	0.02	-0.03, 0.08	0.427
	Risk-taking/irritable factor	1,547	0.08	0.03, 0.13	0.003	0.07	0.01, 0.11	0.015
Exposure	**Outcome**	**N**	**OR unadjusted**	**95%CI**	**P value**	**OR adjusted[a]**	**95%CI**	**P value**
MFQ	Clinically-defined hypomania	1,824	1.33	1.11, 1.58	0.001	1.25	1.05, 1.50	0.012

[a] adjusted for: history of maternal depression, maternal age at birth, maternal education level, being a victim of bullying in school at age 8 years, gender and ethnicity; ^rounded to 2 decimal places; MFQ: Moods and Feelings Questionnaire; HCL: Hypomania Checklist; CI: Confidence Intervals; OR: Odds Ratio

4.4.6 Associations between childhood psychopathology and hypomania using imputed data

Associations between childhood psychopathology measures and hypomania outcomes after multiple imputation are shown in Table 12. When compared to associations with non-imputed data, effect sizes and strength of evidence of association between the BPD traits score and hypomania outcomes were very similar, whereas those for a diagnosis of any ADHD were weaker. For the total difficulties score, effect size differences between non-imputed and imputed data were more variable depending on which hypomania outcome was being examined. The effect size was larger and evidence of association stronger for associations with the 'risk-taking/irritable factor in the imputed data, whereas the effect size was smaller and evidence of association weaker for clinically-defined hypomania. Nevertheless, these differences did not alter the conclusions of the study. For the depression score, effect sizes were similar when comparing complete case data with imputed data for both the HCL score and HCL factors, though the strength of evidence for these association was in the most part stronger in the imputed data. For associations between the depression score and clinically-defined hypomania, there was a 22% reduction in effect size in the imputed data, though again this made no alteration to the conclusions of this study.

Table 12 Associations between childhood psychopathology and hypomania outcomes comparing imputed with non-imputed data

Exposure	Outcome	N	β non-imputed	95%CI	P value	N	β imputed	95%CI	P value
BPD traits score	HCL score	1,702	0.09[a]	0.04, 0.14	0.001	3,124	0.09[a]	0.05, 0.14	<0.001
Any ADHD diagnosis		2,079	0.06[b]	-0.39, 0.50	0.796		0.04[b]	-0.30, 0.39	0.802
Total difficulties score		2,010	0.00^[b]	-0.05, 0.06	0.786		0.01[b]	-0.04, 0.05	0.775
Depression score		2,091	0.06[b]	0.01, 0.11	0.018		0.06[b]	0.02, 0.10	0.004
BPD traits score	'Active/elated' factor'	1,507	0.07[a]	0.02, 0.12	0.007	2,770	0.07[a]	0.03, 0.12	0.002
Any ADHD diagnosis		1,839	-0.28[b]	-0.73, 0.18	0.238		-0.13[b]	-0.47, 0.21	0.450
Total difficulties score		1,779	-0.02[b]	-0.07, 0.03	0.436		-0.02[b]	-0.06, 0.02	0.359
Depression score		1,852	0.03[b]	-0.02, 0.08	0.243		0.03[b]	-0.00^, 0.08	0.065

HCL: Hypomania Checklist; ADHD: Attention Deficit Hyperactivity Disorder; BPD: Borderline Personality Disorder; CI: Confidence Intervals

NB: imputed sample sizes for HCL factors differ from the HCL score as the HCL score contains data on individuals with information on any of the 28 items, whereas the HCL factors contain data on individuals with information for all 28 items

[a] adjusted for: history of maternal depression, maternal age at birth, maternal education level, being a victim of bullying in school at age 8 years, gender, ethnicity, total difficulties score at ages 9 and 11, diagnosis of ADHD and experience of physical and emotional abuse when the child was 6 or 7 years old

[b] adjusted for: history of maternal depression, maternal age at birth, maternal education level, being a victim of bullying in school at age 8 years, gender, ethnicity, and experience of physical and emotional abuse when the child was 6 or 7 years old

Table 12 continued

Exposure	Outcome	N	β non-imputed	95%CI	P value	N	β imputed	95%CI	P value
BPD traits score	Risk-taking/irritability factor	1,507	0.07[a]	0.02, 0.12	0.004	2,770	0.08[a]	0.04, 0.12	<0.001
Any ADHD diagnosis		1,839	0.78[b]	0.35, 1.21	<0.001		0.53[b]	0.14, 0.91	0.007
Total difficulties score		1,779	0.06[b]	0.01, 0.11	0.020		0.08[b]	0.04, 0.12	<0.001
Depression Score		1,852	0.08[b]	0.04, 0.13	0.001		0.07[b]	0.03, 0.11	<0.001
Exposure	**Outcome**	**N**	**OR non-imputed**	**95%CI**	**P value**	**N**	**OR imputed**	**95%CI**	**P value**
BPD traits score	clinically-defined hypomania	1,702	1.22[a]	1.02, 1.46	0.032	3,124	1.22[a]	1.06, 1.41	0.006
Any ADHD diagnosis		2,079	2.06[b]	0.57, 7.49	0.273		1.22[b]	0.38, 4.01	0.732
Total difficulties score		2,010	1.21[b]	1.00, 1.47	0.048		1.13[b]	0.96, 1.33	0.129
Depression Score		2,091	1.26[b]	1.07, 1.49	0.007		1.18[b]	1.02, 1.37	0.023

HCL: Hypomania Checklist; ADHD: Attention Deficit Hyperactivity Disorder; BPD: Borderline Personality Disorder; CI: Confidence Intervals; OR: Odds Ratio

NB: imputed sample sizes for HCL factors differ from the HCL score as the HCL score contains data on individuals with information on any of the 28 items, whereas the HCL factors contain data on individuals with information for all 28 items

[a] adjusted for: history of maternal depression, maternal age at birth, maternal education level, being a victim of bullying in school at age 8 years, gender, ethnicity, total difficulties score at ages 9 and 11, diagnosis of ADHD and experience of physical and emotional abuse when the child was 6 or 7 years old

[b] adjusted for: history of maternal depression, maternal age at birth, maternal education level, being a victim of bullying in school at age 8 years, gender, ethnicity, and experience of physical and emotional abuse when the child was 6 or 7 years old

4.5 Discussion

4.5.1 Summary of findings

The first objective of this study was to assess whether a BPD traits score, being at high-risk for BPD, having a diagnosis of ADHD, scoring highly on subscales of the SDQ (including hyperactivity, prosocial behaviour, emotionality, conduct problems and peer relationship difficulties) and scoring highly on the MFQ assessed during childhood might be early markers of risk for hypomania in young adulthood.

I found that a higher BPD traits score and being high-risk for BPD at age 11 years was associated with hypomania outcomes. When I further investigated whether the relationship between the BPD traits score and hypomania was driven by any individual BPD traits, I found features of anger, affective instability, identity disturbance, paranoid ideation and intense interpersonal relationships were most strongly associated with the HCL score, but there was little evidence of association for fear of abandonment. On the whole, associations were similar for clinically-defined hypomania though, most notably, fear of abandonment was strongly associated with this 'clinical' outcome. There was little evidence to suggest confounding or selection bias was affecting the association between the BPD traits score and hypomania outcomes.

I found that emotional and behavioural problems (SDQ total difficulties) and depression (MFQ score) were associated with the 'risk-taking/irritable' factor and with clinically-defined hypomania, and a diagnosis of ADHD was also associated with the 'risk-taking/irritable' factor. All SDQ subscales (with the exception of emotional difficulties) were associated with the 'risk-taking/irritable' factor, whilst hyperactivity and prosocial behaviour were also associated with the 'active/elated' factor.

4.5.2 Findings in the context of previous work

4.5.2.1 Borderline personality traits and hypomania

My findings from this study suggest that associations between BPD traits and hypomania are more strongly related to “sunny-side” symptoms of hypomania as evidenced with stronger associations with the ‘active-elated factor (see Table 8 adjusted analyses).

There are several possible explanations which may explain why I found associations between BPD and hypomania outcomes. Firstly, BPD traits such as affective instability assessed in the CI-BPD may be capturing early manifestations of BD. For example, mood lability which may occur as a precursor to hypomania (Faedda et al. 2015) or may index mixed state depression (Sani et al. 2014). To address this, I removed questions from the HCL that overlapped closely with the anger trait captured by the CI-BPD. Associations between the BPD traits score and this revised measure of hypomania were almost identical to those when using the full HCL score. This suggests it is unlikely that the association observed between BPD traits score and HCL score is simply a persistence of anger into adulthood.

Secondly, it is possible that BPD and BD share common aetiological mechanisms e.g. childhood trauma (McDermid et al. 2015) or pleiotropic genetic effects (Witt et al. 2014; Song et al. 2015) which could lead to a non-causal explanation for an association between them. When I adjusted for a number of potential confounders, these had little impact on both effect size and strength of evidence of association between the BPD traits score and HCL score. Nevertheless, it is still possible there is residual confounding as a result of not adjusting for other important confounders, or if there is substantial measurement error in the measures of the confounders I did adjust for.

Thirdly, there may be causal effects of BPD on BD, for example secondary to substance use (Hidalgo-Mazzei et al. 2015) that may occur due to greater levels of impulsivity (Faedda et al. 2014) or as a means of coping with distressing emotional states (Van den Bosch et al. 2003) that are both characteristic

features of BPD. The minimal impact of adjusting for potential confounders would be consistent with a potential causal effect. Furthermore, when I examined associations between the BPD traits score and HCL score using imputed data, effect size and strength of evidence were identical to those using non-imputed data. This suggests that the associations observed are unlikely due to selection bias, consistent with either a causal explanation or BPD traits indexing early manifestation of BD onset.

4.5.2.2 ADHD and hypomania

To the best of my knowledge, this is the first study to investigate associations between childhood ADHD and hypomania as an outcome in early adulthood. My findings of little evidence of association between ADHD (irrespective of subtype) and clinically-defined hypomania are generally consistent with findings from a previous review on the association between childhood ADHD and BD in prospective high-risk studies, which reported that a diagnosis of ADHD was not a reliable predictor of future BD (Duffy 2012). In the ALSPAC cohort, there are no data on whether individuals have a BD diagnosis, and using the criteria for defining clinically-defined hypomania was as similar as I could get to the BD outcomes studied in high-risk populations.

Associations between a diagnosis of ADHD, and in particular, the inattentive and combined subtypes were stronger with the 'risk-taking/irritable' factor. It has been proposed that the core symptoms of ADHD, particularly those around inattention may occur as a precursor to hypomania (Youngstrom et al. 2010; Duffy 2012). It is possible there is a causal relationship between childhood ADHD and the 'risk-taking/irritable' aspect of hypomania, which might occur secondary to the psychotogenic effects of substance abuse in adolescents with ADHD (Erskine et al. 2016), which in itself is associated with earlier onset of BD symptoms (Strakowski and DelBello 2000).

However, after removing potentially overlapping questions, there was little evidence of association between ADHD and hypomania, suggesting the association with the 'risk-taking/irritable' factor might just be a persistence of ADHD traits into adulthood.

I also found substantial attenuation in effect size and/or the strength of evidence of association between ADHD and hypomania outcomes when adjusting for confounding, and when comparing imputed data to complete-case data. Other research investigating associations between ADHD and BD have shown confounding can reduce effect sizes by as much as 50% (Youngstrom et al. 2010). Polygenic risk score analyses show that common variants associated with risk of BD are able to predict childhood ADHD (Hamshere et al. 2013), and that to some extent there are common variants that are implicated in the aetiology of both disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013; O'Connell et al. 2019). It seems more plausible that confounding and selection bias more likely explain my findings for ADHD in this study.

4.5.2.3 SDQ and hypomania

Associations between the total difficulties score and hypomania were strongest with the 'risk-taking/irritable' factor, whilst all SDQ subscales with the exception of emotional difficulties were also associated with the 'risk-taking/irritable' factor. On an individual SDQ subscale level, findings between studies examining this relationship are inconsistent in terms of which subscales are associated with the 'risk-taking/irritable' HCL factor (Holtmann et al. 2009; Hosang et al. 2017). It is possible that the inconsistencies might be attributed to the person completing the SDQ. In the current study, the SDQ was completed by the parents of the children whereas those from other studies were completed by adolescents. Adolescents may have better recognition of the types of behaviours they exhibit, and may be more likely report minor disturbances which the parents of the children in the current study may not detect (Arman et al. 2013; Liu et al. 2017).

I found inconsistent evidence of associations between the total difficulties score and hypomania when adjusting for potential confounders, and when comparing imputed to non-imputed data estimates. Whilst adjusting for confounding led to some attenuation of association, suggesting estimates may have been over-estimated, results from imputed data suggest that selection bias might have led to underestimating causal effects in the observed (non-imputed) data.

Therefore, it is unclear to what extent my findings might be over-estimates (due to residual confounding) or under-estimates (due to uncorrected selection bias) of a causal effect of childhood emotional and behavioural problems on adult hypomania.

Epidemiological evidence suggests that having depression is strongly associated with increased risk of developing BD (Weissman et al. 1996). However, when I examined the association between emotional difficulties assessed using the SDQ and hypomania outcomes, (irrespective of how they were defined), I found little evidence of association. The most likely explanation for this is that emotionality assessed using the SDQ is not an adequate measure of depression. Closer examination of the individual questions that are asked in the SDQ emotional difficulties subscale highlights that these questions are more closely aligned with anxiety symptoms than with depressive symptoms.

4.5.2.4 MFQ and hypomania

To the best of my knowledge, at the time of the original publication (Mistry et al. 2017), I was not aware of any studies that have examined associations between measures of childhood depression and either BD or hypomania using a general population sample. Since that time, one study reported strong evidence of a correlation between those who scored highly on the MFQ at age 17 years and the HCL-16. When examining associations with the HCL factors, stronger evidence of correlation between the MFQ and the 'risk-taking/irritable' factor was found (Hosang et al. 2017), a finding which is consistent with the findings in the current study. Findings from high-risk offspring of BD parents suggest that compared to non-high-risk offspring, high-risk offspring often have presence of minor mood disorders including depression prior to developing BD (Duffy et al. 2017b; Duffy et al. 2019).

One possible explanation for finding evidence of association between the MFQ and both the 'risk-taking/irritable' factor and clinically-defined hypomania is overlap in common variants implicated in both depression and BD (Cross-

Disorder Group of the Psychiatric Genomics Consortium 2013; Amare et al. 2019).

Alternatively, the association between childhood depression symptoms and hypomania could be a result of childhood neglect/abuse which in itself increases risk of experiencing symptoms of both depression (Nanni et al. 2012) and BD (Aas et al. 2016). One meta-analysis reported that adults with BD were 2.63 times more likely than controls to have experienced any kind of childhood maltreatment, and if broken down into subtypes of abuse, fourfold more likely (OR = 4.04) to have experienced emotional abuse (Palmier-Claus et al. 2016). It is therefore possible that traumatic experience in childhood is a non-specific risk factor which leads to increased levels of psychopathology which may further increase the risk of developing BD amongst other psychiatric conditions (van Nierop et al. 2015).

4.5.3 Strengths and Limitations

There are a number of strengths and limitations of this study. Firstly, at the beginning of the study, ALSPAC was considered representative of the UK general population in terms of socio-demographic characteristics, and this cohort has extensive information from the first trimester of pregnancy onwards (Boyd et al. 2013; Fraser et al. 2013). However, I found a number of differences in socio-demographic and background characteristics between the study sample (those with data on the HCL), and the rest of the cohort (those with no data on the HCL). This could introduce selection bias due to missing data. To examine whether this was the case, I used multiple imputation to impute values for exposures and confounders. Whilst I used a range of auxiliary variables in the imputation models to make the missing at random assumption more plausible, it is nevertheless possible that some selection bias remains, even in the imputed analyses. However, a previous study using simulation of missing data in the ALSPAC cohort reported that missingness has little impact on the association between early life exposures and psychopathology measures (including disruptive disorders such as ADHD) (Wolke et al. 2009).

To the best of my knowledge, this is also the largest study to date that has investigated associations between childhood psychopathology and hypomania as an outcome, though others have investigated associations with BD (Henin et al. 2007; Rubino et al. 2009).

Thirdly, the assessments of BPD, ADHD, emotional/behavioural difficulties and depression were conducted well before the assessment of hypomanic features. The associations I observe are therefore not due to bias in the recall of presence of childhood psychopathology by adult hypomania severity level.

It also seems unlikely that the association between these childhood psychopathology measures and hypomania are due to reverse causation, whereby child psychopathology arises due to the presence of hypomanic symptoms in childhood, although as there wasn't a screen for hypomania symptoms in childhood, I cannot rule this out definitively.

I have used valid and reliable measures wherever possible. DAWBA-generated DSM-IV diagnoses of psychiatric disorders have been shown to reliably discriminate those with psychiatric disorders from those who do not in both clinical and community samples (Goodman et al. 2000). Similarly, the CI-BPD has been validated in an adolescent inpatient psychiatric sample reliably discriminating those with a BPD diagnosis compared to those without a BPD diagnosis (Sharp et al. 2012b), and the SDQ is a widely used screening tool for assessing presence of emotional/behavioural difficulties in children (Mieloo et al. 2012). The shortened version of MFQ has been validated in both child and adolescent samples and reliably discriminates those with a depression diagnosis defined by ICD/DSM criteria from those who do not have depression (Thapar and McGuffin 1998; Thabrew et al. 2018). However, both ADHD diagnoses and the SDQ were based on parent and/or teacher reports which might increase measurement error when compared to the CI-BPD.

Though there are several strengths, there are also a number of limitations important to acknowledge. Firstly, the hypomania outcomes I examined (HCL score and HCL factors) are not the same as a DSM-IV or ICD-10 diagnosis of BD. However, the clinically-defined hypomania outcome I derived was based

loosely on ICD-10 criteria for a hypomanic episode and took into consideration both a symptom number count required as well as the impact on function. My findings cannot be interpreted as association with BD per se, but rather a propensity to BD. Data were not available on the number of participants who have gone on to receive a diagnosis of BD, which means it is unclear as to how valid the HCL is as a proxy measure for BD. Nevertheless, previous studies have used the HCL to distinguish those with BD from controls drawn from the general population (Holtmann et al. 2009; Lee et al. 2016). In one such study, Lee and colleagues recruited super healthy controls as a comparison group to those with BD, and reported in a sample of 220 BD patients and 313 controls, that the HCL-32 had the following values: sensitivity (0.36), specificity (0.82), positive predictive value (58%) and negative predictive value (65%) indicating that the HCL-32 does not adequately distinguish BD cases from these super healthy controls (Lee et al. 2016). Unlike categorical diagnoses of BD, adopting a dimensional approach can be particularly useful, as a first episode of clinical-level (hypo)mania is unlikely to have been diagnosed by a clinician at the time (hypo)mania symptoms were assessed at age 22-23 years in the ALSPAC sample (Leboyer et al. 2005). In addition, when investigating the aetiology of psychiatric disorders more generally, as exemplified using the Research Domain Criteria, dimensional approaches allow the characterisation of psychopathology as a distribution of departure from the norm, which allows for the heterogeneous presentation of complex psychiatric phenotypes (Cuthbert and Insel 2013; Cuthbert 2015).

The HCL questionnaire is a self-report measure and therefore reporting bias, often termed “social desirability bias” may be introduced. This is particularly evident when asking questions about sexual activity, risk-taking and alcohol use, in which participants are more likely to deliberately report the more favourable option (Latkin et al. 2017). This could lead to non-differential misclassification bias (i.e. irrespective of childhood psychopathology status, the response would bias the hypomania measure in the same way). This would likely lead to an underestimate of the effect size and true strength of evidence of association reported. Alternatively, there may be differential misclassification bias if social desirability bias is affected by childhood psychopathology, and this could lead to either under-estimates or over-estimates.

Another potential limitation is the use of the binary exposure high-risk for BPD at age 11 years. At this age, a diagnosis of any personality disorder is not possible, and the symptom presentation may transition to one of several disorders (e.g. depression disorders, anxiety disorders, substance abuse disorders and eating disorders) or none as the child develops. However, it is important to recognise that in the current study high-risk for BPD does not mean the child has a clinical DSM-IV or ICD-10 diagnosis of BPD. Rather, it is indexing the child having any 5 or more BPD traits occurring at least 25% of the time and daily. Although the assessment of a child being classified as high-risk for BPD has been assessed using a reliable measure, and the criteria required to be classified as high-risk are comparable to criteria required for an adult diagnosis of BPD, there are no data available in the ALSPAC cohort to determine the proportion of children who have subsequently gone on to meet criteria for BPD in adulthood. However, presence of BPD traits in adolescence has been shown to be associated with later adult BPD diagnosis (Winograd et al. 2008), and therefore suggests this may be an accurate reflection of the BPD phenotype.

Finally, I examined many exposure-outcome relationships which could lead to stronger evidence for some associations simply as a result of chance (random error). To minimise the impact of this, exposure and outcome measures were determined *a priori*, and results are discussed based on the strength of evidence from statistical testing (rather than based on an arbitrary cut-off) within the context of this (and other) study limitations.

4.5.4 Conclusions

In this study, I found BPD trait measures were consistently associated with hypomania outcomes, irrespective of how these were defined, and do not appear to be explained by a range of confounders or selection bias. Associations between other psychopathology measures and the risk-taking factor of hypomania were also observed, but were less consistent and more likely to be explained by confounding and selection bias.

Further studies are needed to determine what explains the associations I observed between psychopathology measures and hypomania. For example, whether there may be causal effects of psychopathology on hypomania, whether these psychopathology measures are early expressions of BD/hypomania, or early expressions of genetic risk for BD. I will examine the latter in Chapter 7 by using a polygenic risk score (PRS) approach to investigate whether higher genetic risk for BD is associated with the childhood psychopathology and hypomania outcome measures assessed in this chapter.

The next chapter, Chapter 5 will explore the associations between cognitive functioning in childhood and hypomania outcomes (HCL score, latent HCL factors and clinically-defined hypomania) in early adulthood.

Chapter 5: Cognitive functioning in childhood and hypomania

5.1 Summary

The relationship between cognitive functioning in childhood and subsequent development of mania or hypomania in adulthood is unclear. Studies of adults with BD have found mixed results on premorbid cognitive function.

In this chapter, I investigated objectives 4-7 of this thesis as outlined in Chapter 2. I examined whether cognitive functioning in childhood was associated with hypomania outcomes in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort.

Overall, there was little evidence of association between cognitive functioning in childhood and clinically-defined hypomania in adulthood, but better functioning in the domains of working memory, problem solving, verbal learning and emotion recognition was associated with Hypomania Checklist (HCL) score and the 'active-elated' factor in adulthood, and for some domains this relationship was non-linear.

Tentatively, my findings suggest that better performance on specific cognitive domains in childhood may represent early markers of risk for hypomanic symptoms. These findings may aid earlier detection of BD and could guide clinical treatment.

5.2 Introduction

The relationship between enhanced intelligence, creativity and sociability with bipolar disorder (BD) has been of interest for centuries (Murray and Johnson 2010; Johnson et al. 2012). A substantial body of research now exists examining the relationship between cognitive functioning and BD across all phases of the illness (premorbid, acute or euthymic).

Cognitive deficits are present in approximately 40-60% of those with BD (Sole et al. 2017), and evidence from meta-analyses suggests these deficits persist independent of mood state (Torres et al. 2007; Arts et al. 2008; Bora et al. 2009). A number of cognitive domains have been identified as impaired in adults with BD: i) general intelligence as indexed by intelligence quotient (IQ), ii) processing speed, iii) working memory, iv) problem solving, v) verbal learning, vi) visual learning, vii) executive functioning, and viii) social cognition (Bora et al. 2009; Hidiroglu et al. 2015; Bora et al. 2016; Bora and Ozerdem 2017b; Bora 2018). However, assessing cognitive functioning after someone has developed BD does not allow one to examine the temporal relationship between early cognitive functioning and BD as an outcome, i.e. to establish whether cognitive deficits are present in the premorbid phase, or only present after illness onset.

To study cognitive functioning in the premorbid phase, a longitudinal/cohort study design can be employed, and one of two groups of individuals can be studied. Offspring of BD parents (sometimes termed high-risk offspring) and offspring of control parents (non-high-risk offspring) can be followed up over time and cognitive ability during development compared between those who develop BD and those who do not. Alternatively, general population samples can be used, and cognitive functioning at baseline can be related to incidence of BD during follow up.

There have been a number of studies investigating premorbid cognitive functioning using birth cohorts and military conscription data, with these studies reporting: i) no differences in premorbid IQ (Reichenberg et al. 2002; Zammit et al. 2004; Mortensen et al. 2005) or scholastic achievement (Kendler et al. 2016b), ii) higher IQ (Koenen et al. 2009; MacCabe et al. 2010; Gale et al. 2013; Smith et al. 2015), better arithmetic ability (Tiihonen et al. 2005) and social functioning (Reichenberg et al. 2002), and higher levels of academic achievement in those who develop BD (Vreeker et al. 2016), and iii) poorer IQ (Gale et al. 2010; MacCabe et al. 2010; Gale et al. 2013; Hiyoshi et al. 2017) and visuospatial reasoning (Tiihonen et al. 2005) in those subsequently hospitalised with BD. On face value, these studies appear contradictory in their findings. One possible explanation for this is that the relationship between cognitive functioning in childhood and BD is non-linear, whereby those with

lower and those with higher than average cognitive ability are at increased risk of developing BD (Parellada et al. 2017). A recent review on cognitive functioning across all phases of BD illness reported that overall, findings are generally inconsistent, and based on much fewer studies than those examining premorbid IQ and schizophrenia (SZ). Furthermore, studies do not necessarily separate psychotic from non-psychotic BD individuals, which may be important given that those with psychotic BD often show cognitive impairments which are quantitatively more similar to those with SZ than those with non-psychotic BD (Van Rheenen et al. 2019).

The high-risk offspring study design provides researchers with a distinct population of participants deemed at high genetic risk whose clinical trajectory can be meticulously detailed (some will develop psychopathology whereas others will remain well). Evidence from one recent meta-analysis of high-risk offspring of BD parents compared to controls suggests strong evidence of impairments in the domains of global cognition (lower IQ) and visual memory, with weaker evidence of impairments in domains of verbal memory, processing speed, sustained attention, executive functioning, and social cognition, and little evidence of impairments in working memory (Bora and Ozerdem 2017a). Therefore, presence of deficits is detectable irrespective of clinical disease state. Importantly, the findings of this meta-analysis are reporting studies using genetic risk for BD as the exposure and cognition as the outcome, as opposed to cognition as the exposure and association with BD as the outcome.

Whilst the high-risk-offspring design has clear advantages of a distinct population of individuals who are at much higher than average risk of developing the disorder, an often-reported limitation of such studies is small sample size, and therefore limited power to detect small-medium effects. The other limitation of such a study design is that it is not possible to distinguish whether associations are due to familial risk or family environment since high-risk offspring will likely have both. Studies using general population samples tend to be better powered, but just as with the high-risk study design, can be subject to attrition which may introduce selection bias.

In contrast to consistent evidence reporting premorbid deficits in domains of general intelligence (IQ) from population-based studies (Khandaker et al. 2011), or evidence from youth at high-risk for developing schizophrenia in which deficits are reported in domains of general intelligence (IQ), visual memory, executive functioning, sustained attention, fluency, visual and verbal learning (Bora et al. 2014), it is unclear whether premorbid cognitive deficits are present in those who eventually go on to develop BD. Most longitudinal study designs using general population samples have typically focussed on examining IQ only, and it is possible that deficits may be present in some domains but not others. Furthermore, whilst a large body of research exists examining associations between cognitive functioning and a diagnosis of BD, there are few studies examining associations with dimensional measures of hypomanic symptoms. Using a dimensional approach (with hypomania as a continuous measure) has the potential advantage of being statistically more powerful if the effect of cognition operates across the whole hypomania dimension rather than relying on a somewhat arbitrary threshold for classifying clinically-relevant hypomania.

The objectives of this study were to: i) determine whether childhood cognitive functioning (processing speed, working memory, problem solving ability, executive functioning, attention, verbal learning and emotion recognition) is associated with dimensional measures of hypomania (including “sunny-side” and “dark-side” hypomania) and clinically-defined hypomania, ii) determine whether both higher and lower cognitive functioning is associated with hypomania (i.e. whether associations are non-linear), and iii) examine whether any associations are due to confounding or selection bias (Objectives 4-7).

5.3 Methods

5.3.1 Participants

This study used data from individuals between ages 8 to 23 years from the ALSPAC cohort. Full details of recruitment procedures and inclusion criteria for the study can be found in Chapter 3 under section 3.2.

5.3.2 Outcome measures: Hypomania features

The Hypomania Checklist 32 (HCL-32) is a self-report questionnaire designed to assess lifetime hypomanic symptoms (Angst et al. 2005a). Further detailed information on the HCL-32, including how all hypomania outcomes (HCL score, HCL factors and clinically-defined hypomania) were derived, can be found in Chapter 3 under section 3.3.1. The 28 items used to derive the HCL score can be found in Chapter 3, Table 5.

5.3.3 Exposure measures: Cognitive domains

At age 8 years, the children were invited to complete a series of tasks assessing cognitive functioning. The cognitive domains available in ALSPAC are loosely based on the domains assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Battery (MCCB), which the International Society for Bipolar Disorder deemed appropriate to use for assessing cognitive functioning in BD (Yatham et al. 2010): processing speed, working memory, problem solving, executive functioning, attention, verbal learning and social cognition. I standardised all cognitive domains examined in this chapter.

Detailed information on how cognitive domains assessed using the Wechsler Intelligence Scale – III (WISC-III) (Wechsler et al. 1992) were derived by ALSPAC researchers can be found in Chapter 3, in section 3.3.3.1. I used the following tasks to investigate domains of:

Processing Speed: I used the coding subtest where the children were required to correctly place a symbol above each number as quickly as possible.

Working Memory: I used the previously derived Freedom From Distractibility index score which was a combination of the arithmetic and digit span tasks.

Problem Solving: I used the block design task where the children needed to copy specific patterns of blocks on a picture and replicate using real blocks.

Details of how ALSPAC researchers calculated scores for cognitive domains assessed using the TEACh (Robertson et al. 1996) can be found in Chapter 3, section 3.3.3.2. I assessed the following cognitive domains:

Executive Functioning: I used the opposite world's task where the child saw a number 1 or 2 and was required to verbalise an answer which contradicted what they saw.

Attention: I used the sky search task adjusted for motor speed. Here, the child had to distinguish identical from non-identical spaceships and circle all pairs as quickly as possible.

Other cognitive domains investigated included:

Verbal Learning: I used the nonword repetition task taken from the Children's Test of Nonword Repetition (CTNWR) (Gathercole and Adams 1994). The child listened to 12 nonsense words and repeated each word back to the assessor (see Chapter 3, section 3.3.3.3 for further details).

Social cognition: I used the emotion recognition task assessed using the Diagnostic Analysis of Nonverbal Accuracy (DANVA) (Nowicki and Carton 1993) to assess social cognition. The child saw a facial expression and was required to identify whether the image they saw was that of a happy, sad, fearful or angry face. My primary outcome of interest was an emotion errors score which was the sum total of each of the individual face scores. Further details can be found in Chapter 3, in section 3.3.3.4.

5.3.4 Confounding variables

I adjusted my analyses for a number of potential confounders. These were determined *a priori* based on evidence from the literature and included gender, maternal education level, maternal age at birth, maternal social class, childhood emotional abuse, childhood physical abuse, childhood victimization, and being left-handed (Rich et al. 2008; MacCabe et al. 2010; Higier et al. 2014; Smith et al. 2015; Vierck et al. 2015; Dunn et al. 2018).

5.3.5 Multiple imputation

As with Chapter 4, I investigated the possibility of estimates being affected by selection bias by using multiple imputation. All exposure and confounder measures were imputed, along with a number of auxiliary variables predetermined on the basis of being associated with either the exposure/confounder and missingness. Details on the multiple imputation approach can be found in Chapter 3, section 3.6.1.4.

5.3.6 Statistical analyses

All analyses in this chapter were performed using Stata statistical software (version 14.1 SE. College Station, TX: Statacorp LP).

I used a Pearson correlation test to determine the extent of co-linearity between the cognitive domains, with these results presented in Table 13. Cognitive domains assessed using the same tool i.e. WISC-III and TEACh were most strongly correlated with each other.

Table 13 Correlations between cognitive domains

	PS	WM	PrS	EF	ATT	VL	ER
PS	1.00						
WM	0.31	1.00					
PrS	0.25	0.36	1.00				
EF	0.33	0.24	0.19	1.00			
ATT	0.34	0.16	0.21	0.25	1.00		
VL	0.12	0.41	0.21	0.13	0.08	1.00	
ER	0.14	0.14	0.10	0.14	0.11	0.17	1.00

PS: Processing Speed; WM: Working Memory; PrS: Problem Solving; EF: Executive Functioning; ATT: Attention; VL: Verbal Learning; ER: Emotion Recognition

Where necessary, cognitive domain scores were recoded so that higher scores on all cognitive tasks always reflect better performance (see Chapter 3, section 3.3.3). Furthermore, any cognitive domain scores >3 SD from the mean were removed from the analysis because they can have strong effects on estimates.

I used linear regression to examine associations between cognitive domain scores and dimensional hypomania (HCL score/HCL factors), with results presented as the standard deviation (SD) change in HCL score per SD increase in cognitive domain score.

To examine for a non-linear relationship between cognitive functioning and hypomania, I included a quadratic term in the regression model. P values reported are from likelihood ratio tests comparing models with linear and quadratic terms with models with the linear term only. To further clarify this relationship, any domains for which a non-linear relationship was found, I derived tertiles of cognitive domain scores and compared associations with hypomania outcomes in the lowest and the highest tertiles with the middle cognitive tertile.

Logistic regression analyses were used to examine associations between cognitive domain scores and clinically-defined hypomania. These results are presented as the change in odds of clinically-defined hypomania per SD increase in cognitive domain score.

5.4 Results

Both unadjusted and adjusted results for analyses comparing associations between cognitive domain scores and the HCL score are found in Table 14.

5.4.1 Associations with the HCL score

Adjusting for confounding when examining the associations between cognitive domains and HCL score made little difference. Therefore, adjusted results are presented in the main text and the reader is directed to Table 14 for full results. For domains of working memory (adjusted ß = 0.09, 95%CI 0.04, 0.14; p

<0.001), problem solving (adjusted ß = 0.10, 95%CI 0.05, 0.14; p <0.001), verbal learning (adjusted ß = 0.08, 95%CI 0.03, 0.13; p = 0.001) and emotion recognition (adjusted ß = 0.07, 95%CI 0.02, 0.12; p = 0.005), I found strong evidence that better cognitive performance was associated with higher HCL scores. There was weaker evidence of association between better performance in domains of processing speed (adjusted ß = 0.04, 95%CI -0.00, 0.09; p = 0.078) and executive functioning (adjusted ß = 0.06, 95%CI 0.01, 0.10; p = 0.026) and higher HCL score, but little evidence of association with attention (adjusted ß = 0.02, 95%CI -0.04, 0.08; p = 0.480).

Table 14 Association between cognitive domains in childhood and HCL score in early adulthood

Exposure	N	ß unadjusted	95%CI	P	ß adjusted*	95%CI	P
Processing speed	1,848	0.03	-0.01, 0.08	0.178	0.04	-0.00^, 0.09	0.078
Working memory	1,802	0.11	0.06, 0.15	<0.001	0.09	0.04, 0.14	<0.001
Problem Solving	1,836	0.12	0.07, 0.17	<0.001	0.10	0.05, 0.14	<0.001
Executive functioning	1,796	0.05	0.00^, 0.10	0.031	0.06	0.01, 0.10	0.021
Attention	1,782	0.01	-0.04, 0.06	0.777	0.02	-0.04, 0.08	0.480
Verbal learning	1,845	0.10	0.05, 0.14	<0.001	0.08	0.03, 0.13	0.001
Emotion recognition	1,721	0.06	0.01, 0.11	0.014	0.07	0.02, 0.12	0.005

^rounded to 2 decimal places; HCL: Hypomania Checklist; CI: Confidence Intervals
*Adjusted for: gender, maternal education level, maternal age at birth, maternal social class, child being emotionally abused, child being physically abused, child being a victim of bullying and being left-handed

5.4.2 Test for quadratic effects of cognitive functioning and HCL score

I next investigated whether the association between cognitive functioning and the HCL score is non-linear and consistent with hypomania being more common both in those with higher than average cognition, and in those with lower than average cognitive function. Full results are presented in Table 15.

I found strong evidence of a quadratic effect for processing speed (p quadratic = 0.001), weaker evidence for working memory (p quadratic = 0.01), for verbal learning (p quadratic = 0.03) and for attention (p quadratic = 0.063), and little evidence to suggest quadratic effects of the other cognitive domains (all p>0.487).

Table 15 Association between linear and quadratic terms for cognitive domains and HCL score

Exposure	N		β unadjusted	95%CI	P	β adjusted*	95%CI	P
Processing speed	1,967	Linear	0.05	0.00^, 0.10	0.048	0.06	0.01, 0.11	0.016
		Quadratic	-0.06	-0.09, -0.02	0.002	-0.06	-0.09, -0.02	0.001
Working memory	1,917	Linear	0.13	0.08, 0.17	<0.001	0.11	0.06, 0.16	<0.001
		Quadratic	-0.04	-0.07, -0.00^	0.079	-0.05	-0.08, -0.01	0.010
Problem solving	1,954	Linear	0.14	-0.06, 0.35	0.177	0.17	-0.04, 0.37	0.112
		Quadratic	-0.00^	-0.00^, 0.00^	0.839	-0.00^	-0.00^, 0.00^	0.487
Executive functioning	1,915	Linear	0.06	-0.01, 0.13	0.118	0.05	-0.02, 0.13	0.136
		Quadratic	0.00^	-0.00^, 0.00^	0.877	-0.00^	-0.00^, 0.00^	0.943
Attention	1,903	Linear	-0.03	-0.10, 0.04	0.349	-0.02	-0.09, 0.05	0.583
		Quadratic	-0.02	-0.05, -0.00^	0.048	-0.02	-0.05, 0.00^	0.063
Verbal learning	1,965	Linear	0.09	0.05, 0.14	<0.001	0.08	0.03, 0.12	0.002
		Quadratic	-0.04	-0.08, -0.00^	0.028	-0.04	-0.08, -0.00^	0.030
Emotion recognition	2,357	Linear	0.06	0.00^, 0.11	0.047	0.06	0.01, 0.12	0.023
		Quadratic	-0.01	-0.04, 0.02	0.677	-0.01	-0.04, 0.02	0.638

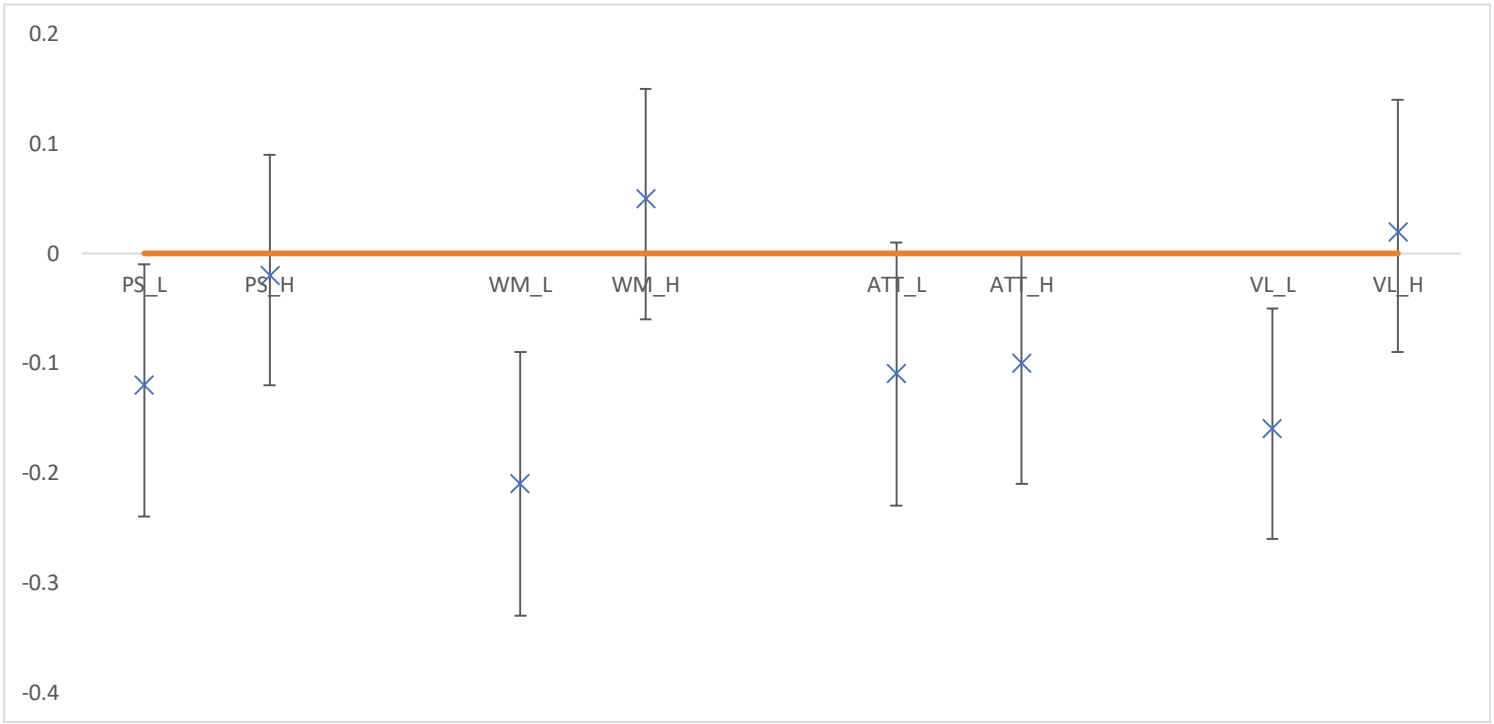
^rounded to 2 decimal places; HCL: Hypomania Checklist; CI: Confidence Intervals

*Adjusted for: gender, maternal education level, maternal age at birth, maternal social class, child being emotionally abused, child being physically abused, child being a victim of bullying and being left-handed

As shown in Table 15, positive linear and negative quadratic terms were present for domains of processing speed, working memory and verbal learning. This suggests that the biggest difference in HCL score appears to be at the lower end of the cognitive distribution. However, for attention, there was some very weak evidence of a quadratic effect, in which both linear and quadratic terms were negative. This suggests that the largest differences in HCL score is in those at both the lower and higher end of the cognitive distribution i.e. an inverted U-shape.

To further clarify the patterns of non-linearity, I derived tertiles of cognitive functioning for domains of processing speed, working memory, verbal learning and attention. For domains of processing speed, working memory and verbal learning, the relationship suggested that those in the lowest compared to middle cognitive tertile had the lowest HCL scores, with little difference in HCL score in those in the highest tertile compared to those in the middle tertile. For attention, there was very weak evidence to suggest that those in both the lowest and highest compared to middle cognitive tertile had lower HCL scores (Figure 4 and Appendix 5).

Figure 4 Association between low and high cognitive performance and HCL score after adjusting for potential confounders



Horizontal line is β = 0; PS: Processing Speed; WM: Working Memory; ATT: Attention; VL: Verbal Learning; Error bars represent 95% confidence intervals; _L: Lowest tertile; _H: Highest tertile; Adjusted for: gender, maternal education level, maternal age at birth, maternal social class, child being emotionally abused, child being physically abused, child being a victim of bullying and being left-handed

5.4.3 Associations with HCL factors

Having investigated associations with the HCL score, I also investigated whether cognitive functioning might be associated with the different aspects of hypomania. Overall, the same cognitive domains associated with the HCL score as described above were associated with the 'active-elated' but not with 'risk-taking/irritable' factor (Appendix 6). Similarly, the same cognitive domains for which a non-linear effect was detected in section 5.4.2, were also present with the 'active-elated' but not 'risk-taking/irritable' factor.

5.4.4 Associations with clinically-defined hypomania

Associations between cognitive functioning and odds of being classified as having clinically-defined hypomania are shown in Table 16. On the whole, there was little evidence to suggest an association between most cognitive measures and clinically-defined hypomania, though there was some weak evidence of association between better processing speed and reduced odds of hypomania (adjusted OR = 0.83, 95%CI 0.70, 1.03; p = 0.089).

Table 16 Association between cognitive functioning and clinically-defined hypomania

Exposure	N	OR unadjusted	95%CI	P	OR adjusted*	95%CI	P
Processing speed	1,848	0.81	0.68, 0.98	0.028	0.83	0.70, 1.03	0.089
Working memory	1,802	0.85	0.71, 1.02	0.089	0.89	0.74, 1.08	0.236
Problem solving	1,836	0.92	0.76, 1.11	0.373	0.94	0.77, 1.14	0.532
Executive functioning	1,796	0.96	0.83, 1.12	0.633	0.98	0.84, 1.15	0.827
Attention	1,782	0.91	0.75, 1.12	0.389	0.92	0.74, 1.13	0.405
Verbal learning	1,845	0.90	0.75, 1.09	0.290	0.91	0.75, 1.09	0.305
Emotion recognition	1,721	1.04	0.85, 1.28	0.678	1.08	0.88, 1.33	0.459

CI: Confidence Interval; OR: Odds Ratio

*Adjusted for: gender, maternal education level, maternal age at birth, maternal social class, child being emotionally abused, child being physically abused, child being a victim of bullying and being left-handed

With the possible exception of attention (p quadratic = 0.063) and the emotion errors score (p quadratic = 0.035), there was little evidence of non-linear relationships between most cognitive domains and clinically-defined hypomania (all p>0.376) (Appendix 7).

5.4.5 Associations using imputed data

I investigated whether selection bias might be affecting my results by using multiple imputation. Overall, there was little evidence to suggest selection bias had an impact on associations between most cognitive domains with hypomania outcomes. However, for the domains of processing speed and executive functioning, a reduction in effect size of 50-60% and 30-50% respectively was observed in the imputed data (see Appendices 8, 9 and 10 for full results). Despite the reductions in effect size and strength of evidence of association in the imputed data, this does not alter the conclusions of this study.

5.5 Discussion

5.5.1 Summary of findings

5.5.1.1 Associations with hypomania

The first objective of this study was to determine whether cognitive functioning in childhood was associated with hypomania. When examining associations between cognitive domains and dimensional hypomania (HCL score and HCL factors), the strongest associations were with working memory, problem solving ability, verbal learning, and emotion recognition. The association was such that better performance on these measures was associated with an increase in HCL score, and from the analyses with the HCL factors, these associations were primarily with the ‘active-elated’ rather than ‘risk-taking/irritable’ factor. There was little evidence to support associations between cognitive domains and clinically-defined hypomania.

5.5.1.2 Testing for non-linear effects

The second objective of this study was to examine whether there was a non-linear relationship between cognitive functioning and hypomania. For the

domains of processing speed, working memory, verbal learning and attention, a non-linear effect was detected. I found that for the former three domains, poorer compared to average performance on these cognitive measures was associated with lower HCL score, with little difference in HCL score in those with high compared to average cognitive performance in these domains. This can be seen more clearly when looking at the results using the tertiles of cognitive performance. For problem solving ability and emotion recognition, a linear pattern was detected i.e. increasing HCL score across the whole range of cognitive performance, and for attention, both higher and lower compared to average attention performance was associated with a reduction in HCL score.

5.5.1.3 Examining the impact of confounding and selection bias

The third objective of this study was to determine the extent to which any associations observed are likely due to confounding or selection bias. For most cognitive domains, there was little evidence to suggest that either confounding or selection bias were impacting the associations observed, irrespective of how hypomania was defined. Nevertheless, there will likely be some residual confounding which could not be accounted for which may bias my findings.

One reason why average, and better than average cognition might be associated with reporting more hypomania symptoms is that increased energy/activity levels in childhood, if not at an extreme, might allow children to maintain their concentration for longer periods of time, enabling them to perform better on cognitive tasks. If these energy/activity levels persist, they may also lead to higher scores on hypomania assessments in adulthood. Similarly, other precursors of hypomania, if present in childhood and affecting cognitive ability, could confound the association between cognition and hypomania/BD.

However, I found that for processing speed and executive functioning, the adjusted results suggest that confounding (and perhaps residual confounding) might lead to an underestimate in the effect size in the unadjusted model, and therefore the likely impact of residual confounding on the association between cognition and hypomania is unclear.

When examining the impact of selection bias on my findings, a 33% and 50% reduction in effect size was observed in the imputed data for associations between executive functioning and processing speed with dimensional hypomania respectively, suggesting that selection bias in the complete-case analysis was over-estimating the true association for these domains. The main findings however, of associations between working memory, problem solving ability, verbal learning, and emotion recognition and hypomania were unchanged.

5.5.2 Findings in the context of previous work

Placing these findings in the context of previous work is difficult for a number of reasons: i) longitudinal general population studies examine associations between cognitive functioning and BD as an outcome rather than hypomania as an outcome, ii) in these studies examining cognition and BD, the focus is typically on examining associations with general intelligence (IQ) and not with specific cognitive domains, and iii) the time-point at which cognition has been assessed is often in late adolescence/early adulthood, rather than childhood as I examine here.

To the best of my knowledge, this is the first and largest study of its kind examining associations between a broad range of tests of cognitive function in childhood and hypomania as an outcome in early adulthood within the general population. One study, using the ALSPAC sample, examined associations between IQ categories and the HCL. The authors reported that children who scored in the superior and very superior IQ category reported higher lifetime hypomania features compared to the mid-IQ group, but that those who scored in the borderline or extremely low category did not report higher lifetime hypomania features (Smith et al. 2015). Higher, but not lower childhood IQ has also been reported in those who eventually go on to develop BD in the Dunedin (Koenen et al. 2009) and Swedish (Gale et al. 2013) cohorts. In the Swedish general population, both poorer, and particularly better compared to average scholastic achievement assessed at age 16 years was associated with increased risk of BD (MacCabe et al. 2010). Whilst one possible explanation for inconsistencies in the literature on premorbid IQ and BD might be a result of

both better and poorer IQ being associated with increased risk of BD, the findings from the current study do not support this explanation for the specific cognitive domains investigated. Whilst a larger body of literature seems to show that BD/hypomania is more common in those with the highest cognitive ability than in those with the lowest, it is less clear as to whether this pattern is linear or not. Further, if this pattern is non-linear, it remains to be determined whether the biggest difference in BD/hypomania risk is between those with the lowest compared to average cognitive ability, or between those with the highest compared to average cognitive ability.

Evidence from several meta-analyses examining cognitive functioning in adults with BD report deficits in multiple domains across all phases of the illness, with severity of deficits typically greater in those with BD type I compared to BD type II, and in those with psychotic compared to non-psychotic BD (Arts et al. 2008; Bora et al. 2009; Bora et al. 2011; Bo et al. 2017; Bora 2018). My findings of associations between better cognition and higher HCL score do not appear consistent with the findings from these meta-analyses. However, the studies examined in these meta-analyses have examined cognition after the individual has developed BD, rather than before, or at an older age than was assessed in my study. It is therefore possible that cognition in childhood is relatively preserved, and that deficits in those who develop BD occur as a consequence of the disorder or treatment. Some studies have suggested that deficits are related to increasing number of mood episodes (Latalova et al. 2011), or only become evident once mood symptoms reach syndromal levels (Duffy et al. 2017a). To determine the extent to which any of these situations may occur, cohort studies with repeat measures of cognition from childhood through to adulthood would be needed.

5.5.3 Strengths and limitations

This study has a number of strengths and limitations. Firstly, at the time of enrolment, ALSPAC was considered as representative of the UK general population in terms of maternal social class, ethnicity and educational level attained. It is also one of the most detailed birth cohort studies worldwide, with extensive data on both environmental and genetic factors that can affect a

person's health and development (Boyd et al. 2013). This meant that it was possible to adjust my analyses for a number of potential confounders which might affect the association between cognitive performance and hypomania, though there may still be residual confounding present. However, over time attrition has occurred which might introduce selection bias due to missing data. As mentioned in Chapter 4 section 4.5.2, by imputing values for exposures, confounders and auxiliary variables, it was possible to build an imputation model to make the missing at random assumption of the multiple imputation approach more plausible. Though every effort was made to minimise selection bias, it is still possible that some bias remains, even in the imputed analyses.

Whilst a broad range of cognitive domains in childhood and their associations with hypomania as an outcome were examined, based on the cognitive domains identified as impaired in those with BD using the MCCB (Yatham et al. 2010), I was unable to examine visual learning as no comparable measure was available in the ALSPAC cohort. Nevertheless, most studies examining premorbid cognitive functioning using a longitudinal study design in individuals from the general population and subsequent development of BD typically focus on examining one or two domains (Zammit et al. 2004; Smith et al. 2015; Koike et al. 2018), whereas the current study was able to examine 6 cognitive domains.

The assessment of cognitive domains at age 8 years, approximately 14 years before the assessment of hypomania features means that the observed effects are more likely to represent change in risk of hypomania in relation to cognitive performance as opposed to reverse causation by the presence of hypomanic symptoms. However, with no assessment of hypomanic symptoms in childhood to confirm this, it is not possible to rule this out definitively.

Although I used well validated measures for assessing cognitive functioning in childhood (Wechsler et al. 1992; Nowicki and Carton 1993; Gathercole and Adams 1994; Robertson et al. 1996), the measures used may less than perfectly capture the domains I examined which could introduce measurement error and bias the results. This is further complicated by the knowledge that

neuropsychological tests rarely examine a single cognitive domain in isolation (Howieson 2019).

When examining associations with hypomania, I have done so dimensionally (HCL score and HCL factors) and categorically (clinically-defined hypomania). To avoid repetition, the reader is directed to Chapter 4, section 4.5.2 for a discussion surrounding the HCL and the relative advantages of using the dimensional approach when investigating the aetiology of psychiatric disorders as exemplified using the RDoC (Cuthbert and Insel 2013; Cuthbert 2015). However, it is unclear as to the extent to which my findings using the HCL directly translate onto (hypo)mania/BD in clinical samples.

Finally, as mentioned in Chapter 4, I have examined many exposure-outcome relationships which could lead to stronger evidence for some associations due to chance (random error). To minimise the impact of this, exposure and outcome measures were determined *a priori*, and results are discussed based on the strength of evidence from statistical testing (rather than based on an arbitrary cut-off) within the context of this (and other) study limitations.

5.5.4 Conclusions

Within this prospective study, I found better performance on specific cognitive domains was associated with a dimensional measure of hypomanic symptoms, although for some domains this was non-linear. Associations were primarily with the 'active-elated' rather than 'risk-taking/irritable' factor of hypomania, with little to no evidence of association between cognitive domains and clinically-defined hypomania.

Further work in large population samples is required to determine the replicability of these findings in other general population samples at a similar age. Further work could also investigate whether associations with these cognitive measures changes with age, and to determine whether genetic risk for BD is associated with these cognitive domains. In Chapter 8 I will examine the latter by using a polygenic risk score approach (PRS) to determine whether

increased genetic risk for BD is associated with the cognitive domains examined in this chapter.

The next chapter, Chapter 6 will systematically review the literature investigating associations between a BD-PRS and non-BD phenotypes.

Chapter 6: Systematic review

The work presented in this chapter has been published and can be found online at https://www.sciencedirect.com/science/article/pii/S016503271732373X?via%3Dihub

Mistry, S., Harrison, J.R., Smith, D.J., Escott-Price, V., Zammit, S. (2018). The use of polygenic risk scores to identify phenotypes associated with genetic risk of bipolar disorder and depression: A systematic Review. *Journal of Affective Disorders*, **234**, 148-155 https://doi.org/10.1016/j.jad.2018.02.005

The published article has been adapted for use in this chapter to include additional results (that were available as supplementary materials in the published article). The focus of this Chapter will be reporting the results of phenotypes associated with genetic risk for bipolar disorder only.

6.1 Chapter summary

One way to enhance understanding of the aetiology of bipolar disorder (BD) is to identify the phenotypic manifestations of increased genetic liability for BD. One method to investigate increased genetic liability for BD is the polygenic risk score (PRS) approach. This approach allows the exploration of how genetic risk is manifest in different populations.

In this chapter, I investigated objective 8 of this thesis as outlined in Chapter 2. To do this, I conducted a systematic review of the literature to identify studies examining associations between a BD-PRS and a broad range of phenotypic outcomes. I followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and searched three databases: Medline, EMBASE and PsycINFO (from 6th August 2009 – 14th March 2016) in addition to the references of included studies.

For the purpose of this Chapter, 18 studies were included. Overall, the BD-PRS was more strongly associated with other (non-discovery sample phenotypes i.e. not BD) psychiatric disorders such as depression and schizophrenia, and with greater symptom severity of depression, although it explained only a small proportion of the variance in most phenotypes (<2%). I also developed and published a reporting framework for future studies to use, that can help interpret findings across studies and allow meta-analyses to be conducted.

By using larger discovery and adequately powered target samples to determine which phenotypes are associated with increased genetic for BD, the PRS approach could be used in the future to develop stratified medicine approaches.

6.2 Introduction

Evidence from twin, family and adoption studies suggest mood disorders such as depression and BD are common, highly heritable psychiatric conditions (Sullivan et al. 2000; Oswald et al. 2003; Shih et al. 2004; Bienvenu et al. 2011). Given the negative impact on the lives of those with BD, the early identification of individuals who are at high genetic risk of BD, may help to inform risk prediction. One method to examine phenotypes associated with genetic risk is to prospectively follow high-risk offspring of BD parents. Recent reviews on the clinical trajectory of BD (Duffy et al. 2017b; Pfennig et al. 2017; Duffy et al. 2019), using offspring of BD parents compared to offspring of parents without BD, have highlighted several phenotypes being present at higher rates in high-risk offspring compared to non-high-risk offspring and include: i) having anxiety and sleep disorders in childhood (Duffy et al. 2010; Nurnberger et al. 2011; Ritter et al. 2012; Duffy et al. 2014), ii) increased risk of any psychopathology, but particularly substance use disorders if having a parent with diagnosed BD prior to birth and being exposed to the parent showing BD symptoms from birth to ≤10 years (no comparison group was reported) (Goodday et al. 2018) iii) exposure to early life events (family disruption, parental somatic illness, parental psychopathology, parental labour market exclusion, parental criminality, placement in out-of-home care, parental natural death and parental unnatural death) compared to exposure to no life events (Bergink et al. 2016), v) increased maternal but not paternal perceived neglect (Doucette et al. 2016), vi) presence of ADHD and other behavioural disorders (Nurnberger et al. 2011; Duffy 2012; Egeland et al. 2012; Axelson et al. 2015) and vii) having a parent who was diagnosed with BD before age 22 years (Preisig et al. 2016).

From the available evidence using prospective longitudinal studies of offspring of BD parents, the manifestations of being at increased genetic risk for BD in childhood/adolescence varies, extending beyond increased risk of having the same disorder as the parent (i.e. a BD diagnosis) (Rasic et al. 2014). These high-risk studies can at times report conflicting results, particularly when comparing results to population-based registries. These discrepant findings may

be attributed to i) small sample sizes when assessing rates of psychopathology in the offspring, which may lead to lack of statistical power to detect small effect sizes (Cohen's d ≤0.2), and ii) methodological differences between studies, particularly in the validity of diagnostic instruments used.

Newer molecular genetic approaches such as genome-wide association studies (GWAS), alongside collaborative consortia, mean that is it now possible to overcome the limitations of using the high-risk offspring of BD parents study design. GWAS are able to examine many genetic variants in the genome simultaneously, without an *a priori* hypothesis.

Since the first GWAS of BD using the Wellcome Trust Case Control Consortium (Wellcome Trust Case Consortium et al. 2007), a number of GWAS have been conducted and have reported, albeit inconsistently, a number of risk variants occurring more frequently in BD cases compared to controls (Baum et al. 2008a; Ferreira et al. 2008; Sklar et al. 2008; Cichon et al. 2009; Schulze et al. 2009; Scott et al. 2009; Smith et al. 2009; Djurovic et al. 2010; Sklar et al. 2011). Though the number of risk variants is lower than for schizophrenia (Purcell et al. 2009; Ripke et al. 2014), this is most likely attributed to the smaller sample numbers used in the GWAS for BD.

On an individual level, single nucleotide polymorphisms (SNPs) have very small effect on disease risk, but summing the weighted allelic dosage across all SNPs and collapsing into a single polygenic risk score (PRS), allows the exploration of how genetic risk is manifest in individuals from different populations (Wray et al. 2014).

Initially, the first paper to use a PRS approach found that a schizophrenia PRS (SZ-PRS), derived from summary statistics of a GWAS of schizophrenia, was associated with schizophrenia case status compared to controls, and to a lesser extent BD case status compared to controls (Purcell et al. 2009). Since that time, there have been many studies published examining associations between other psychiatric and non-psychiatric polygenic risk scores and a range of phenotypic outcomes.

The PRS was initially used to predict case status and determine the extent to which common genetic variants can explain variation in a particular disorder. However, the investigation of associations between a PRS and other phenotypes, (different from those in the GWAS used to derive the PRS), may help understanding of the aetiology of the disorder, as well as its manifestations which may be useful markers of risk. I previously conducted a systematic review and identified a number of non-schizophrenia diagnosis phenotypes associated with increased genetic risk for schizophrenia using a PRS approach. The strongest associations were with other psychiatric disorders, particularly depression and BD, though explained little of the variance in these phenotypes (<2%) (Mistry et al. 2018b).

Over the last 10 years, there has been an accumulation of studies that have used a PRS approach to determine possible non-BD diagnosis phenotypes associated with increased genetic risk for BD. Identifying these phenotypic manifestations may help understand the aetiology of BD, the PRS's usefulness in risk prediction, and potentially facilitate earlier intervention prior to the onset of clinically relevant symptoms. Therefore, the purpose of this study was to explore the phenotypic (non-BD diagnosis) manifestations of increased genetic liability for BD by conducting a systematic review of the literature (Objective 8).

6.3 Methods

I followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting systematic reviews and meta-analyses (Moher et al. 2009). A completed version of the table recommended for use by Moher and colleagues can be found in the original publication (Mistry et al. 2018a).

Initially, I had planned to conduct a single systematic review examining phenotypes associated with increased genetic risk for schizophrenia, BD and depression. However, upon conducting the search, a collective decision was made between my supervisors and I to split the findings into two separate systematic reviews; one examining literature of phenotypes associated with a

SZ-PRS (Mistry et al. 2018b), and the other examining associations with either a BD-PRS or a depression PRS (Mistry et al. 2018a).

6.3.1 Search strategy

6.3.1.1 Data sources

I searched three databases (EMBASE, Medline via Ovid and PsychINFO) from 06/08/2009 to 14/03/2016. In addition, I hand searched the references of articles included in this chapter. The start date was chosen as this was the first paper to use the PRS approach, and the end date was selected based on when I began the original search.

6.3.1.2 Search terms and delimiters

I searched for articles using the terms “bipolar (or variations of)” AND “polygenic (or variations of)”. Full search strategy terms from the original systematic review are listed in Appendix 11.

6.3.1.3 Inclusion/Exclusion criteria

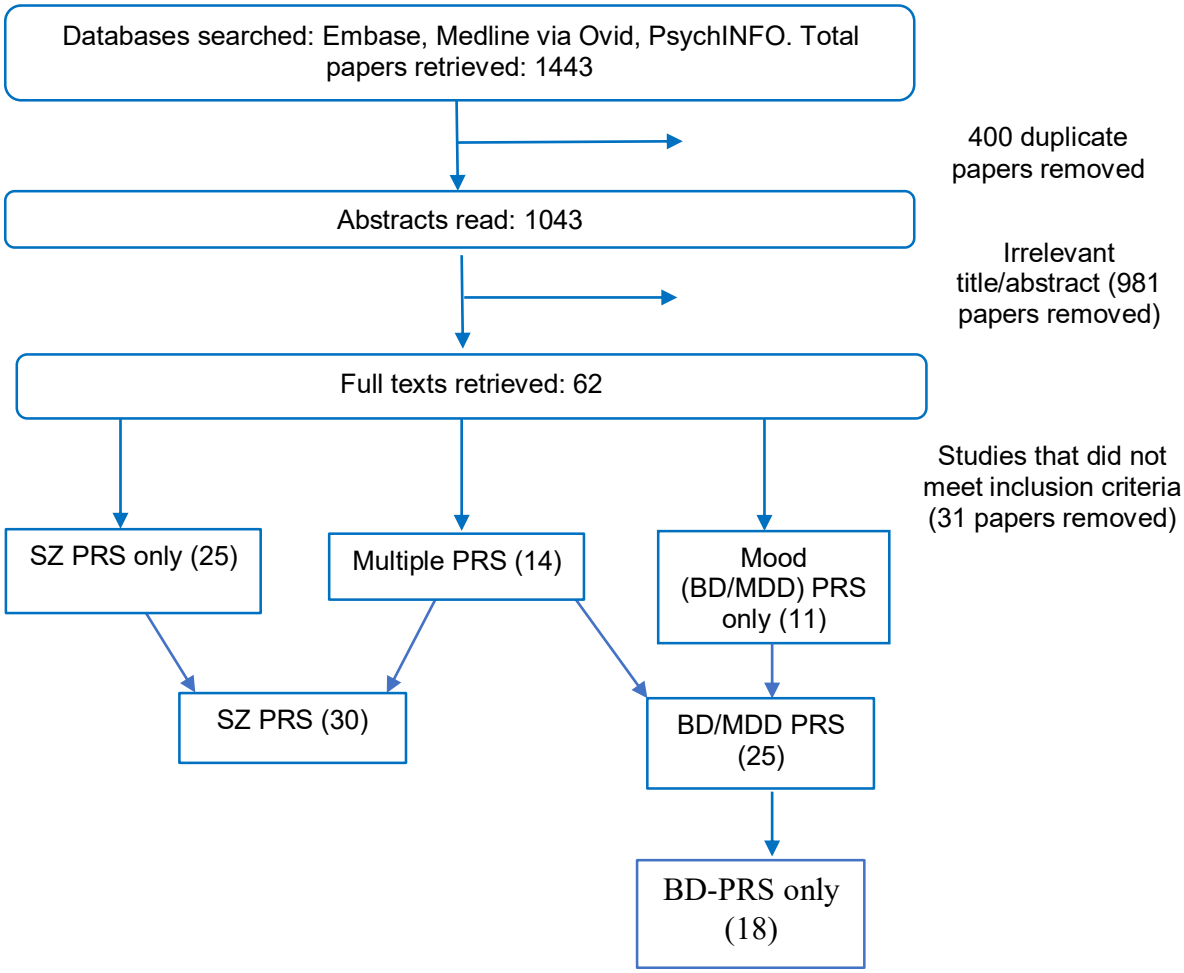
I included articles that examined associations between a BD-PRS (derived from a GWAS of participants with a diagnosis of BD and a measurable phenotype but excluding neuro-imaging outcomes). Neuroimaging outcomes were not included because this represents a more specialised area of work beyond the focus of this review. As the purpose of this study was to identify non-BD diagnosis phenotypes, articles reporting associations only between the BD-PRS and a diagnosis of BD were not included. Articles were required to be in peer reviewed journals and published in English (see Appendix 12 for inclusion/exclusion criteria specific to this chapter).

6.3.2 Data collection and analysis

6.3.2.1 Selection of studies

Once I had identified all potential studies, after de-duplication, I screened the title and abstract of each study (see Figure 5 for flow diagram). If it was unclear whether the paper contained relevant data, or the abstract was not available, I retrieved the full-text article. Full-text articles were reviewed and checked against inclusion/exclusion criteria by Dr Judith Harrison and I independently. Any disagreements were resolved by a third author (Professor Stanley Zammit). I extracted relevant data using a data extraction form see (Mistry et al. 2018a) for a blank version of this. From this, I summarised the results using a narrative approach as most studies did not report standardised effect sizes, (or provide data that would allow me to calculate this) as is required to conduct a meta-analysis.

Figure 5 Study selection flow diagram



SZ; Schizophrenia, PRS; Polygenic Risk Score, BD; Bipolar Disorder, MDD; Major Depressive Disorder

6.4 Results

In total, 18 studies assessed associations between the BD-PRS and a measurable phenotype. The majority of these studies used the first GWAS from the Psychiatric Genomics Consortium (PGC) (Sklar et al. 2011) as a discovery set from which the derive the PRS, with individual studies using different p-value threshold cut-off scores (P_Ts) to assess the relationship between genetic risk for BD and phenotype(s) (Tables 18-22). Most studies were of White/Caucasian adults of European ancestry. Table 17 provides a summary of these 18 studies.

Table 17 Summary of studies examining associations between genetic risk of BD and phenotypes

Phenotype group	Number of studies examined	Number of studies with evidence of association at p<0.05
BD related phenotypes	10	6
MDD related phenotypes	17	13
SZ related phenotypes	18	8
Other psychiatric phenotypes	9	5
Other phenotypes	8	4

BD; Bipolar Disorder, MDD; Major Depressive Disorder, SZ; Schizophrenia

[a] A 'study' is defined as an examination between the BD-PRS and a phenotype. As many publications examine multiple phenotypes, the number of studies in this table exceeds the number of publications included in this chapter

6.4.1 Associations with adult psychiatric disorders

The data extracted from studies examining associations between the BD-PRS and adult psychiatric disorders can be found in Table 16.

Using data from the PGC, the BD-PRS was strongly associated with SZ (strongest P_T<0.3, p = $1x10^{-50}$) and Major Depressive Disorder (MDD) (strongest P_T<0.5, p = $1x10^{-16}$ (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013).

Support of these findings of associations between the BD-PRS and both depression and SZ came from a study that used the GAIN-MDD and GAIN-SZ samples. The authors reported the BD-PRS was higher in SZ cases compared to controls (no P_T reported, p = $2.9x10^{-9}$; AUC = 0.56) and depression cases compared to controls (no P_T reported, p = $7.32x10^{-7}$; AUC = 0.55) (Schulze et al. 2014).

There was strong evidence of associations between the BD-PRS and Seasonal Affective Disorder (SAD) (strongest $P_T<0.1$, $p = 0.004$) using data from the Australian Twin Registry (ATR) and Midwest Alcohol Research Centre (Byrne et al. 2015), and weaker evidence of association with post-traumatic stress disorder (PTSD) (strongest $P_T<0.3$, $p = 0.028$) in the Marine Resilience Studies (Nievergelt et al. 2015).

Associations between the BD-PRS and post-partum depression (PPD) varied according to which dataset(s) the authors used. When data were combined from the Netherlands Study of Depression and Anxiety (NESDA)/Netherlands Twin Registry (NTR) samples, the Queensland Institute of Medical Research (QIMR) sample, the ALSPAC sample and the Swedish Twin Registry (STR) sample, there was strong evidence of association with PPD (strongest $P_T<0.1$, $p = 0.005$), and similarly when examining data from the QIMR study alone (strongest $P_T<0.1$, $p = 3.04x10^{-5}$) and NESDA/NTR samples (strongest $P_T<0.001$, $p = 0.001$) alone. There was no evidence to support association between the BD-PRS and PPD in either the ALSPAC or STR samples (Byrne et al. 2014).

Table 18 Associations between the BD-PRS and adult psychiatric disorders

Author and Year	Discovery sample	Target sample	Outcome (measure used)	N	P_T	ß/OR/correlation	95%CI	P	R^2 (%)
Cross Disorders 2013	PGC-1-BD	PGC 1 SZ	SZ (Clinical interview - DSM-IV or ICD-10)	9397 cases and 7736 controls	0.3	Not reported	Not reported	$1x10^{-50}$	2.2
		PGC MDD	MDD (Clinical interview - DSM-IV or ICD-10)	9227 cases and 7383 controls	0.5			$1x10^{-12}$	0.48
Schulze et al., 2014	WTCCC BD	GAIN SZ	SZ (Clinical interview – RDC or DSM-IV)	1343 SZ cases and 1378 controls	Not reported	Not reported	Not reported	$2.9x10^{-9}$	Not reported
		GAIN MDD						$7.32x10^{-7}$	
Byrne et al., 2015	PGC-1-BD	ATR and the Midwest Alcohol Research Centre study	Global seasonality score (SPAQ)	4156 general population adults	0.01	Not reported	Not reported	0.250	0
					0.1	Not reported	Not reported	0.004	0.4

BD: Bipolar Disorder; PRS: Polygenic Risk Score; P_T: P-value threshold; OR: Odds Ratio; CI: Confidence Interval; PGC: Psychiatric Genomicsso Consortium; SZ: Schizophrenia; MDD: Major Depressive Disorder; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-IV; ICD-10: International Classification of Diseases-10; MRS: Marine Resilience Studies: PTSD: Post-Traumatic Stress Disorder; CAPS: Clinician Administered PTSD Scale; ATR: Australian Twin Registry; SPAQ: Seasonal Pattern Assessment Questionnaire; NEDSA: Netherlands Study of Depression and Anxiety; QIMR: Queensland Institute of Medical Research; NTR: Netherlands Twin Registry; STR: Swedish Twin Registry; ALSPAC: Avon Longitudinal Study of Parents and Children; PPD: Post-Partum Depression; EPDS: Edinburgh Postnatal Depression Scale; GAIN: Genetic Association Information Network; RDC: Research Domain Criteria; P_T reported is either the only one examined or one with strongest evidence if more than one P_T was examined

Table 18 continued

Author and Year	Discovery sample	Target sample	Outcome (measure used)	N	P_T	ß/OR/correlation	95%CI	P	R^2 (%)
Bryne et al., 2014	PGC-1-BD	QIMR + NESDA/NTR + STR + ALSPAC	PPD (EPDS)	1420 cases of and 9473 controls	0.1	Not reported	Not reported	0.005	0.13
		NESDA/NTR		208 cases and 761 controls	0.01			0.001	0.17
		STR		100 cases and 1209 controls	1			0.270	0.22
		ALSPAC		616 cases and 6311 controls	1			0.420	0.02
		QIMR		484 cases and 1024 controls	0.1			$3.04x10^{-5}$	1.64
Nievergelt et al., 2015	PGC-1-BD	MRS	PTSD (Clinical interview - CAPS)	940 cases and 2554 controls	0.3	Not reported	Not reported	0.028	0.025

BD: Bipolar Disorder; PRS: Polygenic Risk Score; P_T: P-value threshold; OR: Odds Ratio; CI: Confidence Interval; PGC: Psychiatric Genomicsso Consortium; SZ: Schizophrenia; MDD: Major Depressive Disorder; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-IV; ICD-10: International Classification of Diseases-10; MRS: Marine Resilience Studies: PTSD: Post-Traumatic Stress Disorder; CAPS: Clinician Administered PTSD Scale; ATR: Australian Twin Registry; SPAQ: Seasonal Pattern Assessment Questionnaire; NEDSA: Netherlands Study of Depression and Anxiety; QIMR: Queensland Institute of Medical Research; NTR: Netherlands Twin Registry; STR: Swedish Twin Registry; ALSPAC: Avon Longitudinal Study of Parents and Children; PPD: Post-Partum Depression; EPDS: Edinburgh Postnatal Depression Scale; GAIN: Genetic Association Information Network; RDC: Research Domain Criteria; P_T reported is either the only one examined or one with strongest evidence if more than one P_T was examined

6.4.2 Associations with childhood psychiatric disorders

There were two studies that reported associations between the BD-PRS and childhood psychiatric disorders (Table 19). The first reported weak evidence of association between the BD-PRS and both ADHD and autism spectrum disorder (ASD) (strongest $P_T<0.4$, $p<0.05$; strongest $P_T<0.001$, $p<0.05$ respectively) (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013).

A second study also found weak evidence of a higher BD-PRS in ADHD cases compared to controls (strongest $P_T<0.5$; $p = 0.052$) using combined data from UK community child psychiatry and paediatric clinics from Dublin, Ireland. (Hamshere et al. 2013).

Table 19 Associations between the BD-PRS and childhood psychiatric disorders

Author and Year	Discovery sample	Target sample	Outcome (measure used)	N	P_T	ß/OR/correlation	95%CI	P	R^2 (%)
Cross Disorder Group 2013	PGC-1-BD	PGC ADHD	ADHD (Clinical interview - DSM-IV or ICD-10)	840 cases and 688 controls	0.0001	Not reported	Not reported	<0.05	0.18
		PGC ASD	ASD (Clinical interview - DSM-IV or ICD-10)	161 cases and 526 controls	0.4			<0.05	0.078
Hamshere et al., 2013	PGC-1-BD	UK/Irish ADHD GWAS	ADHD (DSM-III-R or DSM-IV or ICD-10)	727 cases with ADHD and 2067 controls without any psychiatric or neurological disorders	0.5	Not reported	Not reported	0.052	0.11

BD: Bipolar Disorder; PRS: Polygenic Risk Score; P_T: P-value threshold; OR: Odds Ratio; CI: Confidence Interval; PGC: Psychiatric Genomics Consortium; ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; P_T reported is either the only one examined or one with strongest evidence if more than one P_T was examined

6.4.3 Association with psychotic disorders and symptoms

There were 5 studies in total that examined associations between a BD-PRS and psychotic disorders and symptoms (see Table 20).

In individuals with SZ drawn from the first PGC GWAS of SZ, the BD-PRS was associated with a manic symptom factor (strongest $P_T<0.3$, p = 0.003), but not with positive, negative or depressive symptom factors across any P_T (no statistics reported) (Ruderfer et al. 2014).

There was weak evidence that the BD-PRS was associated with a positive history of psychosis in individuals with BD (strongest $P_T<0.05$, p = 0.079) in the Thematically Organised Psychosis (TOP) sample (Aminoff et al. 2015).

A study using data from the first PGC SZ sample reported strong evidence of association between the BD-PRS and SZ, either when comparing those with SZ and a negative family history of psychotic illness to controls (strongest at $P_T<1$, 1-sided $p<1x10^{-300}$), or when comparing those with SZ and a positive family history of psychotic illness to controls (strongest at $P_T<1$, 1-sided $p = 7.11x10^{-149}$). Evidence of association between the BD-PRS and SZ cases with a positive family history of psychotic illness compared to SZ cases with a negative family history of psychotic illness was substantially weaker (strongest $P_T <0.4$, one-sided p = 0.012) (Bigdeli et al. 2016).

Using data from a Norwegian sample, the BD-PRS was not associated with a lifetime history of psychosis in BD-spectrum cases compared to BD-spectrum cases with no lifetime history of psychosis (no P_T or p value reported), or when SZ spectrum cases were compared to BD spectrum cases (strongest $P_T<0.05$; p = 0.13). However, the BD-PRS was higher in SZ-spectrum cases compared to controls without SZ, BD or MDD (strongest $P_T<0.05$; p = 0.01) (Tesli et al. 2014).

One study found weak evidence of association between the BD-PRS and both decreased paranoia (strongest $P_T<0.5$, one-sided p = 0.064) and decreased anhedonia (one-sided p = 0.048), but not with parent-rated negative symptoms,

grandiosity, cognitive/disorganization symptoms and hallucinations in adolescents from the population-based Longitudinal Experiences and Perceptions (LEAP) study at $P_T<0.5$ (Sieradzka et al. 2014).

Table 20 Associations between the BD-PRS and psychotic disorders and symptoms

Author and Year	Discovery sample	Target sample	Outcome (measure used)	N	P_T	ß/OR/correlation	95%CI	P	R^2 (%)
Tesli et al., 2014	PGC-1-BD	Norwegian sample	SZA (Clinical interview - DSM-IV)	64 with SZA and 415 controls with no history of psychiatric disorder	Not reported	Not reported	Not reported	Not reported	Not reported
			PNOS (Clinical interview - DSM-IV)	96 with PNOS and 415 controls with no history of psychiatric disorder					
			BDNOS (Clinical interview - DSM-IV)	47 with BDNOS and 415 controls with no history of psychiatric disorder					
			SZ spectrum (Clinical interview - DSM-IV)	268 with SZ spectrum disorder and 415 controls with no history of psychiatric disorder		Mean difference = 0.2	0.04, 0.35	0.01	
			Lifetime psychosis (Clinical interview - DSM-IV)	465 with lifetime psychosis and 415 controls with no history of psychiatric disorder		Not reported	Not reported	0.012	

Table 20 continued

Author and Year	Discovery sample	Target sample	Outcome (measure used)	N	P_T	ß/OR/correlation	95%CI	P	R^2 (%)
Sieradzka et al. 2014	PGC -1-BD	TEDS	Cognitive/disorganised symptoms (SPEQ)	2157 general population adolescents	0.5	β = -1256	β = -5243, 2731	0.269	0
			Grandiosity symptoms (SPEQ)	2160 general population adolescents		β = -243	β = -712, 226	0.156	0
			Parent-rated negative symptoms (SPEQ)	2162 general population adolescents		β = -204	β = -720, 311	0.219	0
			Paranoia symptoms (SPEQ)	2157 general population adolescents		β = -440	β = -1008, 127	0.064	0.001
			Anhedonia symptoms (SPEQ)	2158 general population adolescents		β = -243	β = -19999, 1610	0.048	0.062
			Hallucinations (SPEQ)	2138 general population adolescents		β = -204	β = -878, 331	0.188	0
Ruderfer et al. 2014	PGC-1-BD	PGC-2-SZ	Manic symptom factor (EFA)	9369 with SZ and 8723 controls with no history of neurological or psychiatric disorder	0.3	Not reported	Not reported	0.003	2
			Depressive symptom factor (EFA)		0.001			0.160	0.5
			Positive symptom factor (EFA)		0.01			0.470	0.01
			Negative symptom factor (EFA)		0.001			0.550	0

NB: Beta values for the Sieradzka et al. 2014 study are unstandardised

Table 20 continued

Author and Year	Discovery sample	Target sample	Outcome (measure used)	N	P_T	ß/OR/correlation	95%CI	P	R^2 (%)
Aminoff et al. 2015	PGC-1-BD	TOP	Positive history of psychosis in BD (having one or more lifetime psychotic episodes)	148 with history of psychosis and 107 without	0.05	Not reported	Not reported	0.079	Not reported
			BD I vs BD II (Clinical interview - SCID-I)	181 with BD I and 74 with BD II		Mean for BD I = 0.16; Mean for BD II = 0.15	BD I (-0.83, 1.15) BD II (-0.90, 1.20)	0.913	
			Presenting polarity (Clinical interview – SCID-I)	152 with depressive polarity and 91 with elated polarity		Mean for depressive = 0.14 Mean for elated = 0.20	Depressive (-0.85, 1.13) Elated (-0.85, 1.25)	0.568	
			Age at onset (Clinical interview – SCID-I)	150 early onset, 71 mid onset and 32 late onset		Mean for early = 0.10 Mean for mid = 0.27 Mean for late = 0.17	Early (-0.92, 1.12) Mid (-0.73, 1.27) Late (-0.78, 1.12)	0.628	

Table 20 continued

Author and Year	Discovery sample	Target sample	Outcome (measure used)	N	P_T	ß/OR/ correlation	95%CI	P	R^2 (%)
Bigdeli et al., 2016	PGC-1-BD	PGC-1-SZ	SZ (OPCRIT) – (DSM-IV)	978 cases with SZ and a family history of psychotic illness and 8285 controls	1	β = 0.175	Not reported	$7.11x10^{-149}$	16.9
				4503 cases of SZ with no family history of psychotic illness and 8285 controls	1	β = 0.160		$<10x10^{-300}$	22.3
				978 cases with SZ and a family history of psychotic illness and 4503 cases of SZ with no family history of psychotic illness	0.3	β = 0.016		0.012	0.14

BD: Bipolar Disorder; PRS: Polygenic Risk Score; P_T: P-value threshold; OR: Odds Ratio; CI: Confidence Interval; PGC: Psychiatric Genomics Consortium, SZ: Schizophrenia; OPCRIT: Operational Criteria; DSM-IV: Diagnostic and Statistical Manual for Mental Disorders-IV; SZA: Schizoaffective Disorder; PNOS: Psychosis Not Otherwise Specified; BDNOS: Bipolar Disorder Not Otherwise Specified; TEDS: Twins Early Development Study; SPEQ: Specific Psychotic Experiences Questionnaire; TOP: Thematically Organised Psychosis; SCID-I: Structured Clinical Interview for DSM-IV Axis I Disorders; EFA: Exploratory Factor Analysis; P_T reported is either the only one examined or one with strongest evidence if more than one P_T was examined

6.4.4 Association with depression related symptoms/severity

Table 21 shows the data extracted from the five studies examined associations between a BD-PRS and depression related symptoms/severity.

A study used combined data from the NESDA and NTR samples and reported the BD-PRS was associated with MDD (strongest P_T<0.5, p = 0.001) and both severe typical (strongest P_T<0.5; p = 0.018) and severe atypical MDD (strongest P_T<0.1, p = 0.032) (Milaneschi et al. 2016).

Another study investigated the relationship between the BD-PRS and episode count of MDD in individuals with MDD. The authors reported some evidence of associations with greater episode count of MDD (strongest P_T<0.2, p = 0.015) and stronger evidence in MDD cases and a positive family history of MDD (strongest P_T<0.2, p = 0.004) using data from the RADIANT sample (Ferentinos et al. 2014).

There was inconsistent evidence of associations between the BD-PRS and characteristics of depression (including severity, age of onset, history of suicide attempt, recurrence, and atypicality) within a multivariate framework, or with subclinical mania, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), Mannheim and NESDA samples (Wiste et al. 2014).

The BD-PRS was not associated with antidepressant response in individuals with MDD treated with Noradrenaline Reuptake Inhibitors (NRIs) monotherapy, Selective Serotonin Reuptake Inhibitors (SSRIs) monotherapy, or either antidepressant in the New Medications in Depression and Schizophrenia (NEWMEDS) sample. This pattern was similar when examining associations with response to citalopram in the STAR*D sample (Tansey et al. 2014).

Finally, in a combined analysis using data from three different samples (RADIANT, GSK-Munich and the Bipolar Association Case Control Study (BACCS)), the BD-PRS was not associated with a greater number of suicide attempts (strongest P_T<0.1; no p-value reported) (Mullins et al. 2014).

Table 21 Associations between the BD-PRS and depression related symptoms/severity

Author and Year	Discovery sample	Target sample	Outcome (measure used)	N	P_T	ß/OR/correlation	95%CI	P	R^2 (%)
Ferentinos et al., 2014	PGC-1-BD	RADIANT	Episode count of depression (SCAN)	1966 cases of MDD	0.2	Not reported	Not reported	0.015	0.3
			Episode count of depression with a positive family history of depression (SCAN)	1364 cases of MDD with a family history of MDD				0.004	1.8
Mullins et al., 2014	PGC-1-BD	RADIANT, GSK-Munich and BACCs combined	Suicide attempt number (SCAN)	3270 cases of depression	0.1	Not reported	Not reported	Not reported	0.001
Tansey et al., 2014	PGC-1-BD	NEWMEDS	Antidepressant response using either SSRIs or NRIs (HRSD/MADRS/BDI/clinician rated QIDS)	1790 with MDD and treated with an antidepressant	0.3	Not reported	Not reported	0.623	0.0001
			Antidepressant response using SSRIs (HRSD/MADRS/BDI/clinician rated QIDS)	1222 with MDD and treated with an antidepressant	0.05			0.613	0.0002
			Antidepressant response using NRIs (HRSD/MADRS/BDI/clinician rated QIDS)	568 with MDD and treated with an antidepressant	0.1			0.168	0.0034
		STAR*D	Antidepressant response using citalopram (HRSD/MADRS/BDI/clinician rated QIDS)	1107 with MDD and treated with an antidepressant	0.3			0.826	0.0001

Table 21 continued

Author and Year	Discovery sample	Target sample	Outcome (measure used)	N	P_T	ß/OR/correlation	95%CI	P	R^2 (%)
Wiste et al. 2014	PGC-1-BD	STAR*D	Multi-level model of MDD (Clinical interview - HRSD, SCID, PDSQ/MDQ + OPCRIT/IDS)	1274 with MDD	0.1	Not reported	Not reported	0.03	Not reported
		NESDA		992 with MDD	0.01			0.02	
		Mannheim		583 with MDD	0.05			0.300	
		STAR*D	Severity of MDD (HRSD score)	1274 with MDD	Not reported	OR = 0.98	Not reported	0.800	Not reported
			Early onset of MDD (Clinical interview - SCID)			OR = 1.21		0.002	0.02
			Recurrent MDD (Clinical interview - SCID)			OR = 1.14		0.04	0.05
			History of suicide attempt (medical records)			OR = 1.26		0.006	0.01
			Manic symptom (PDSQ)			OR = 1.18		0.04	0.05
			Psychotic symptom (PDSQ)			OR = 1.05		0.500	Not reported
			Atypical depression (SCID)			OR = 0.96		0.600	Not reported
		NESDA	History of suicide attempt (medical records)	992 with MDD		OR = 0.69		0.002	0.023
			Subclinical mania (PDSQ)		0.05	OR = 1.3		0.048	Not reported
		STAR*D		1274 with MDD	0.01	OR = 1.18		0.006	
		Mannheim		583 with MDD	0.2	OR = 1.21		0.300	

Table 21 continued

Author and Year	Discovery sample	Target sample	Outcome (measure used)	N	P_T	ß/OR/correlation	95%CI	P	R^2 (%)
Milaneschi et al., 2016	PGC-1-BD	NESDA and NTR	MDD (CIDI)	1530 with MDD and 1700 controls with no history of a psychiatric disorder	0.5	OR = 1.13	1.05, 1.21	0.001	0.3
			MDD (CIDI)	228 with severe typical MDD and 1700 controls with no history of a psychiatric disorder	0.5	OR = 1.19	1.03, 1.37	0.018	0.3
			MDD (CIDI)	251 with severe atypical MDD and 1700 controls with no history of a psychiatric disorder	0.1	OR = 1.16	1.01, 1.33	0.032	0.3

BD: Bipolar Disorder; PRS: Polygenic Risk Score; P_T: P-value threshold; OR: Odds Ratio; CI: Confidence Interval; PGC: Psychiatric Genomics Consortium; SCAN: Schedules for Clinical Assessment in Neuropsychiatry; MDD: Major Depressive Disorder; OPCRIT: Operational Criteria; DSM-IV: Diagnostic and Statistical Manual for Mental Disorders-IV; SCID: Structured Clinical Interview for DSM-IV; STAR*D: Sequenced Treatment Alternatives to Relieve*Depression; NEDSA: Netherlands Study of Depression and Anxiety; HRSD: Hamilton Rating Scale for Depression; PDSQ: Psychiatric Diagnostic Screening Questionnaire; MDS: Mood Disorders Questionnaire; IDS: Inventory of Depressive Symptomology; NEWMEDS: Novel Methods leading to New Medications in Depression and Schizophrenia; SSRIs:

Selective Serotonin Reuptake Inhibitors; NRIs: Noradrenaline Reuptake Inhibitors; MADRS: Montgomery-Asberg Depression Rating Scale; BDI: Beck Depression Inventory; QIDS: Quick Inventory for Depression Symptomology; CIDI: Composite International Diagnostic Interview; NTR: Netherlands Twin Registry; P_T reported is either the only one examined or one with strongest evidence if more than one P_T was examined

6.4.5 Other phenotypes

The BD-PRS was also associated with other phenotypes which do not link with the subsections of the results section in this chapter (see Table 22).

One study used data from the National Institute of Neurological Disorders and stroke (NINDS) sample and reported no evidence of association between the BD-PRS and Parkinson's disease (no P_T or p-value reported; AUC = 0.5) (Schulze et al. 2014).

The BD-PRS was not associated with measures of latent inhibition (Auditory Steady State Response (ASSR), P3 latency or P50 ratio), but there was strong evidence of an association between the BD-PRS and P3 amplitude (strongest $P_T<1x10^{-5}$; p = 0.005) in a sample of individuals with psychotic illness and controls (Hall et al. 2015).

Lastly, in an Icelandic general population study, the BD-PRS was associated with greater scholastic achievement defined as greater number of years in school ($p = 4.8x10^{-9}$) and having a university degree ($p = 5.2x10^{-7}$), and with creativity (strongest at $P_T<0.2$; $p = 5.2x10^{-6}$), defined as belonging to a creative profession (actors, dancers, musicians, visual artists and writers) (Power et al. 2015).

Table 22 Associations between the BD-PRS and other phenotypes

Author and Year	Discovery sample	Target sample	Outcome (measure used)	N	P_T	ß/OR/correlation	95%CI	P	R^2 (%)
Power et al. 2015	PGC-1-BD	Icelandic general population	Creativity (CAQ)	1024 general population adults	0.2	OR = 1.17	Not reported	$3.8x10^{-6}$	0.26
			Number of years in school (national register)			ß = 0.15		$4.8x10^{-9}$	Not reported
			Having a university degree (national register)			OR = 1.09		$5.2x10^{-7}$	0.13
Schulze et al., 2014	PGC-1-BD	NINDS PD	PD (Clinical diagnosis)	984 PD cases and 908 controls	Not reported	Not reported	Not reported	Not reported	Not reported

Table 22 continued

Author and Year	Discovery sample	Target sample	Outcome (measure used)	N	P_T	ß/OR/correlation	95%CI	P	R^2 (%)
Hall et al., 2015	PGC-1-BD	Not reported	P3 amplitude (AOB)	127 cases of BD and 148 controls	$1x10^{-4}$	Not reported	Not reported	0.005	3
			P3 latency (AOB)		$1x10^{-5}$			Not reported	0.7
			ASSR (Gamma oscillation (auditory steady state 40-Hz click stimulation paradigm)		$1x10^{-3}$				1
			P50 ratio (EEG)		$1x10^{-4}$				0.3

BD: Bipolar Disorder; PRS: Polygenic Risk Score; P_T: P-value threshold; OR: Odds Ratio; CI: Confidence Interval; PGC: Psychiatric Genomics Consortium; CAQ: Creative Achievement Questionnaire; NINDS: National Institute of Neurological Disorders and Stroke; PD: Parkinson's Disease; AOB: Auditory Odd Ball; ASSR: Auditory Steady State Response; EEG: Electroencephalogram; P_T reported is either the only one examined or one with strongest evidence if more than one P_T was examined

6.5 Discussion

This study investigated objective 8 of this thesis which was to determine what the phenotypic (non-BD) manifestations of increased genetic risk for BD might be. To do this, I conducted a systematic review of the literature. This work is the first systematic review collating information from studies investigating non discovery sample phenotypes for BD.

Overall, I found a higher BD-PRS was associated with increased risk of different psychopathologies and that, on the whole, R^2 values for other psychiatric disorders (0.5-2%) was greater than for other phenotypes examined (most <1%). A possible anomaly is the study by Bigdeli and colleagues that reported the BD-PRS explained either 17% or 22% of the variance for SZ (based on presence or absence of family history of psychotic illness respectively). These values seem likely to be over-estimates given that in their study, Bigdeli and colleagues reported the SZ-PRS explained 12%-13% of the variance for SZ (Bigdeli et al. 2016). I contacted the authors of this study to see if they could provide a potential explanation of this finding, or for them to check this finding, though they did not respond.

6.5.1 Associations with psychiatric disorders

Associations between genetic risk for BD and psychiatric disorders was stronger for disorders typically presenting in adulthood rather than in childhood, most notably SZ and MDD. The variance explained in SZ by the BD-PRS was larger (R^2 = 2.2%) than that for MDD (R^2 = 0.48%), ADHD (R^2 = 0.18%) and ASD (R^2 = 0.08%), in line with higher genetic correlation between BD/SZ (r = 0.68) compared to between BD/MDD (r = 0.47), BD/ADHD (r = 0.05) and BD/ASD (r = 0.04) (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013). These findings may have been attributed to the limited sample sizes and therefore lack of power in childhood onset psychiatric disorders used by the Cross-Disorder Group. More recently, the Cross Disorders Group conducted LD score regression analyses for the 8 psychiatric disorders (the 5 main psychiatric disorders described above in addition to

Tourette's Syndrome (TS), Obsessive Compulsive Disorder (OCD) and Anorexia Nervosa (AN)). Findings were consistent with the 2013 study, with the strongest correlations being between BD/SZ (r = 0.70) and BD/MDD (r = 0.36), whilst increased genetic correlation compared to the 2013 study was found for BD/ADHD (r = 0.14) and BD/ASD (r = 0.14). It is therefore more likely that evidence of pleiotropy between the main psychiatric disorders found in the 2013 study are true effects. However, further investigation is needed to determine the precise genetic structure underlying these conditions.

Findings for associations between the BD-PRS and MDD are consistent with a systematic review that reported a 2.5 fold increase in odds of MDD in a first degree relative (FDR) with at least one proband who has a BD diagnosis compared to a FDR of a healthy control proband (Wilde et al. 2014). They are also consistent with a recent study reporting an increased risk of MDD in those at high genetic risk for BD in the Danish population (Musliner et al. 2019).

Findings of association between increased genetic liability to BD and SZ are supported by evidence of increased recurrence risk (RR) of having offspring (RR = 2.4), or a sibling (RR = 3.9) with SZ when the proband has BD. This highlights a substantial genetic overlap between these two disorders (Lichtenstein et al. 2009).

Molecular genetic research into BD and adult psychiatric disorders including SZ and MDD supports evidence of pleiotropy across these disorders, rather than them being considered as aetiologically independent (Gale et al. 2016). Furthermore, through GWAS, a number of shared common risk loci have been identified between SZ and BD (Andreassen et al. 2013; Forstner et al. 2015; Ruderfer et al. 2018), between MDD and SZ (Wray et al. 2018; Amare et al. 2019), and more recently between BD and MDD (Amare et al. 2019).

6.5.2 Association with psychotic disorders and symptoms

The strength of evidence for associations between the BD-PRS and psychotic disorders and symptoms were, on the whole, weaker than most other phenotypes assessed (with the possible exception of one study) (Bigdeli et al.

2016). More recently, similar to the findings of studies reported in this review, others have also reported little evidence of association with depressive, negative, anhedonia, cognitive/disorganised and parent-rated negative symptom dimensions of schizophrenia (Jones et al. 2018; Pain et al. 2018; Ruderfer et al. 2018). Similarly, recent studies have also reported findings consistent with those in the current chapter including: i) with a manic symptom factor and psychotic disorder (Ruderfer et al. 2018), ii) broadly defined psychosis (Calafato et al. 2018) and iii) paranoia (Pain et al. 2018).

These genetic findings of associations with psychosis more generally support the hypothesis of shared genetic architecture across BD/schizophrenia/psychosis, and provide evidence of these psychotic disorders existing on a psychosis continuum (DeRosse and Karlsgodt 2015). They also fit with evidence suggesting a substantial proportion of those experiencing psychotic symptoms have a current diagnosis of a mood disorder (Hanssen et al. 2003).

6.5.2 Association with depression symptoms/severity

The BD-PRS was associated with greater episode count of MDD, particularly in those who also had a family history of MDD and earlier age of onset of MDD (Ferentinos et al. 2014; Wiste et al. 2014; Milaneschi et al. 2016). More recent studies published after the review end date find consistent evidence of association with earlier age at onset of depression (Power et al. 2017; Verduijn et al. 2017), but inconsistent evidence with higher BD-PRS in those with a positive family history of depression (Verduijn et al. 2017).

In line with earlier age of onset of MDD being a risk factor for developing BD, these genetic findings suggest that age of onset may be a useful way of indexing individuals who may be more likely to have an underlying BD than unipolar depression. Using information on age of onset could reduce the likelihood of someone transitioning to a (hypo)manic episode as a result of antidepressant monotherapy, particularly if their age of onset is earlier than mid-twenties (Benazzi and Akiskal 2008; Woo et al. 2015).

Irrespective of which antidepressant class was investigated, genetic risk for BD was not associated with antidepressant response. However, this does not rule out the possibility that associations may be observed with response to other antidepressant classes, such as tricyclics or monoamine oxidases which have not been investigated. I am not aware of any further studies that have investigated the relationship between the BD-PRS and antidepressant response, though two recent studies have investigated whether a depression PRS is associated with antidepressant response. These studies also reported little evidence of such association when using the same antidepressant classes used by Tansey and colleagues (Garcia-Gonzalez et al. 2017; Ward et al. 2018).

This suggests that neither genetic risk for BD nor MDD is currently helpful in determining whether an individual will respond better to a particular class of antidepressant. However, preliminary findings examining associations between increased genetic risk for schizophrenia and lithium response in BD patients, suggest lower polygenic load for psychiatric disorders is associated with better response to lithium, and lower genetic loading for MDD is also associated with better response to lithium in BD patients (Amare et al. 2018). These findings highlight that using a PRS approach may be useful in predicting response to other classes of drugs, though at present, this is not the case for antidepressants.

6.5.3 Associations with other phenotypes

Increased genetic risk for BD was associated with creativity and greater educational attainment (Power et al. 2015). These genetic findings are consistent with epidemiological studies suggesting that those with BD, as well as their family members are overrepresented in artistic professions (Kyaga et al. 2011; Kyaga et al. 2013; MacCabe et al. 2018). One possible explanation for these findings is that individuals with BD have increased openness to experience, impulsivity and extraversion (Murray and Johnson 2010). This may lead those with BD to choose a creative occupation which better suits an unconventional lifestyle, given the difficulties of maintaining stable employment as a result of having BD (Marwaha et al. 2013; Tse et al. 2014).

The BD-PRS was strongly associated with reduced P3 amplitude, which was strongest at the most stringent P_T, indicating that this reduction in amplitude is likely limited to a small subset of SNPs, which might be more causally related to BD than SNPs at higher P_T's (Hall et al. 2015). These genetic findings are consistent with epidemiological evidence from meta analyses reporting reduced P3 amplitude in BD patients, particularly those with the bipolar I disorder subtype (Johannesen et al. 2013; Morsel et al. 2018).

6.5.4 Quality of the studies included in this chapter

There were a number of limitations with some of the studies included in this systematic review. Firstly, a large number of studies examined in this review (see Tables 18-22) did not report confidence intervals or standardised effect sizes which would help interpret the strength of evidence of associations observed (or not). In isolation, a p-value alone does not provide sufficient information to allow someone to understand the range of values within which the true population value lies, nor does it allow one to examine the magnitude of the effect being reported. It is possible, for example, to have a highly significant result (i.e. very small p-value) and yet have a very small effect size with wide confidence intervals that limits the clinical relevance of the findings, with the 'highly significant result' largely being attributable to a very large sample size (Ranstam 2012; Sullivan and Feinn 2012).

A second limitation is that some studies included in this chapter failed to give a clear description of sample ascertainment, and at times provided insufficient information to determine which comparison groups had a high PRS. This is problematic as it does not allow you to determine whether genetic risk is associated with an increased or decreased risk of the outcome, and it is therefore difficult to interpret these findings in relation to other studies which asses similar phenotypes using the same study design. Following on from this, if it is not clear which target sample(s) are used, it is not possible to determine whether both discovery and target datasets are independent of each other. If there is any overlap, this will likely inflate risk estimates (Choi et al. 2018).

It is also necessary to have adequately powered discovery and target sample sizes to optimise association testing and risk prediction (Dudbridge 2013). The majority of the studies included in this chapter were adequately powered to detect small-to-moderate effect sizes (OR = 1.2 - 1.5 per standard deviation increase in PRS), based on the assumption of no measurement error in the PRS. The power to detect these effect sizes will likely increase as newer and larger GWAS of BD cases and controls becomes available.

The use of a one-sided p-value as reported in one study (Bigdeli et al. 2016) is inappropriate as, whilst the literature may consistently report an effect in one direction only, the possibility of an effect going in the opposite direction is automatically ruled out when using a one-sided test, which may restrict the ability to make informed inferences about the underlying biology (Kim and Bang 2016).

As a means of trying to address some of the limitations of the studies included in this chapter, alongside my co-authors, I developed a reporting framework which future studies could use to improve interpretation and comparison between studies. The guidelines suggested can be used in a tick box like fashion to ensure robust reporting of PRS analyses (see Table 23).

Table 23 Framework for future studies checklist

PRS criteria	Yes/No
Discovery sample(s) and n number if phenotype is binary	
Discovery sample(s) and mean (SD) if phenotype is continuous	
Target sample(s) used and n number if phenotype is binary	
Target sample(s) used and mean (SD) if phenotype is continuous	
Phenotype(s) of interest and how this is defined	
Pre-QC SNP number	
Post-QC SNP number	
Which genotyping platform(s) have been used	
Has the MAF been reported?	
Has the H-W equilibrium been reported for each sample?	
Have the authors a priori identified a primary p-value threshold to test for association along with a justification for using this threshold?	
Has population stratification been adjusted for?	
Has the PRS been standardized to allow comparison across studies?	
Has an estimate of association been reported (e.g. OR/ß) and units of exposure and outcome provided to allow interpretation of effect size?	
Have the confidence intervals been reported?	
Have the authors used a 2-tailed test for association, or if 1-tailed, has this been adequately justified?	
Do the results in the abstract accurately reflect the findings in the results?	

SD: Standard Deviation; QC: Quality Control; SNP: Single Nucleotide Polymorphism; MAF: Minor Allele Frequency used to determine which SNPs can potentially contribute to PRS; H-W: Hardy Weinberg; PRS: Polygenic Risk Score; OR: Odds Ratio

6.5.5 Strengths and limitations

By investigating a broad range of phenotypic outcomes, I was able to provide a comprehensive and thorough overview of the phenotypic manifestations of increased genetic liability for BD. Another strength is that I used a comprehensive search strategy, and in doing so, have reduced the likelihood of omitting eligible studies. As I used a systematic search strategy, I will likely have omitted potential reviewer selection bias which would result in inaccurately representing information on the phenotypic manifestations of increased genetic risk for BD. In addition, by supplementing the results from my systematic review with studies published since the end date of my search strategy, I have been able to examine whether the findings from the systematic review are supported.

One of the limitations in the methodology used in this chapter is that I have omitted any articles not in the English language. This means there may be articles which may have provided additional information on further phenotypes associated with increased genetic liability for BD.

A second limitation is that I excluded neuroimaging phenotypes as this was beyond the focus of the systematic review, and beyond the expertise of any of the authors. However, a recent systematic review investigated associations between a BD-PRS and functional magnetic resonance imaging studies and suggested the effects of the BD-PRS on brain functioning are not limited to specific neuronal pathways. However, much like the current chapter, the authors reported inconsistent findings in the literature, which appear to be in part due to small sample sizes and differences in methodology (Dezhina et al. 2018).

A third limitation of the current chapter is that I was unable to perform a meta-analysis of the studies included. This was not possible as there were insufficient studies reporting standardised effect sizes or confidence intervals to allow comparisons across studies. Further, as I was not able to conduct a meta-analysis, I was also unable to assess for the presence of publication bias, or to explore whether any heterogeneity was present, and if so, what possible reasons there may be for this. It is possible that publication and citation bias have occurred, and this would mean information on phenotypes not associated with increased genetic risk for BD will not have been captured.

6.5.6 Conclusions

In the current chapter, I investigated objective 8 of this thesis. I found the BD-PRS was associated with a broad range of phenotypic outcomes, and the strongest associations were with other psychiatric disorders, typically explaining up to 2% of the variance.

In addition to using adequately powered target samples, larger discovery BD GWAS datasets, and well-validated phenotypic measures, it would be useful for future studies to follow a framework for reporting results from PRS analyses,

such as the one I developed with my supervisors (see Table 23), to help make meta-analysis possible and aid comparison between studies.

In my systematic review, with the exception of the Cross-Disorders Group study and the study by Hamshere and colleagues, there were no peer reviewed published studies that investigated associations between a BD-PRS and childhood/adolescent phenotypes. Chapters 7 and 8 will build on the findings from Chapters 4 and 5 respectively, to address a largely unexplored area of scientific investigation – how genetic risk for BD is manifest in childhood in relation to both psychopathology and cognition.

Chapter 7: Genetic risk for bipolar disorder and psychopathology

The work presented in this chapter has been published and can be found online at https://www.sciencedirect.com/science/article/pii/S0165032718321177?via%3Dihub

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

The published article has been adapted for use in this chapter to include additional results (available as supplementary materials online).

7.1 Chapter summary

Studying the phenotypic manifestations of increased genetic liability for Bipolar Disorder (BD) can increase understanding of its aetiology and potentially help earlier identification.

In this chapter, I investigated objectives 9-12 of this thesis as outlined in Chapter 2. I used the 2nd Psychiatric Genomics Consortium (PGC) BD genome wide association study (GWAS) as a discovery dataset, and the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort as a target dataset to derive a BD polygenic risk score (BD-PRS). I investigated whether increased genetic risk for BD was associated with a broad range of psychopathology measures, assessed in Chapter 4, from childhood to early adulthood.

Increased genetic risk for BD was very weakly associated with clinically-defined hypomania, though evidence strengthened as the hypomania symptom count required to be classified as having hypomania increased. I found strong evidence of association between the BD-PRS and a diagnosis of attention deficit hyperactivity disorder (ADHD), particularly inattentive ADHD, but there was little evidence to suggest associations between the BD-PRS and other childhood psychopathology or hypomania measures.

The findings from this chapter suggest that, with the possible exception of ADHD, and to a lesser extent clinically-defined hypomania, genetic risk for BD does not appear to manifest in childhood to the same extent as schizophrenia genetic risk has been reported to do.

7.2 Introduction

Given the long delay in first diagnosis of BD, as described in Chapter 1, section 1.3, identifying potential clinical markers of risk for BD in childhood/adolescence may help to predict future onset of BD. Evidence from cohort studies following up high-risk offspring of BD parents suggests that up to 60% of those who develop BD report presence of psychopathology in childhood/adolescence (Raouna et al. 2018; Duffy et al. 2019). These psychopathologies extend beyond depressive symptoms (Duffy et al. 2010; Topor et al. 2013), and include ADHD, conduct problems and hyperactivity in childhood (Henin et al. 2007; Donfrancesco et al. 2011; Singh et al. 2014). Borderline personality disorder (BPD) is also a frequently observed comorbidity in adults with BD (Friborg et al. 2014; Bezerra et al. 2015; Fornaro et al. 2016; Parker et al. 2016), though onset of potential traits can be traced back to childhood/adolescence (Biskin 2015; Bozzatello et al. 2019).

One possible explanation for the phenomenological overlap and high rates of comorbidity between the measures of psychopathology described above and BD is that this may be attributed to shared genetic heritability (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013; Witt et al. 2017). As is evident from my findings in Chapter 6 of this thesis, the phenotypic manifestations of increased genetic risk for BD during childhood, adolescence, and early adulthood in the general population have not yet been thoroughly investigated. By understanding and identifying the most robustly associated phenotypic manifestations of genetic risk for BD, it may be possible to minimise misdiagnosis and incorrect treatment such as antidepressant monotherapy (Ghaemi et al. 1995; Hirschfeld and Vornik 2004; Keck et al. 2008).

Narrow sense heritability estimates from twin, adoption and molecular genetic studies of BD suggest BD has a heritability of approximately 60-85% (Craddock and Sklar 2013). GWAS have identified a number of single nucleotide polymorphism (SNP) risk alleles occurring more frequently in BD cases relative to controls (Sklar et al. 2011; Cross-Disorder Group of the Psychiatric Genomics Consortium 2013; Ruderfer et al. 2018; Stahl et al. 2019). As these

SNP risk alleles have small effect on disease risk, one method, the PRS approach, combines these alleles into a single genetic score, previously shown to provide biologically valid indicators of disease risk for research (Purcell et al. 2009; Cross-Disorder Group of the Psychiatric Genomics Consortium 2013). Taken together, alleles on current GWAS platforms explain approximately 4% of the genetic variation for BD on the liability scale (Ikeda et al. 2018; Ruderfer et al. 2018; Stahl et al. 2019).

The purpose of the work in this chapter was to address objectives 9-12 as outlined in Chapter 2. These objectives were to: i) examine whether a BD-PRS is associated with dimensional, categorical and factor structures of hypomania, ii) examine whether a BD-PRS is associated with measures of childhood psychopathology as assessed in Chapter 4 (BPD (traits score and 'high-risk' categorisation), ADHD (any ADHD diagnosis, inattentive ADHD, hyperactive-impulsive ADHD and combined ADHD), emotional and behavioural difficulties (hyperactivity problems, prosocial behaviour, emotional difficulties, conduct problems and peer relationship difficulties) and a depression score, and iii) to investigate the possibility that associations between genetic risk for BD and psychopathology were due to selection bias.

7.3 Methods

7.3.1 Participants

The current study used data on individuals aged 7-23 years from the ALSPAC cohort. Recruitment procedures and inclusion criteria are described in Chapter 3, section 3.2.1. Final sample numbers for all outcome measures are shown in Table 24.

Table 24 Table showing number of individuals with outcome measures

Outcome Measure	Instrument	Age (years)	Measure type	N (%)
HCL score	HCL-28	22-23	Standardised score	2,654
Clinically-defined hypomania*			Binary outcome	2,654 (7%)
Active/elated factor			Standardised score	2,654
Risk-taking/irritable factor				
Total difficulties score	SDQ	9	Standardised score	6,111
ADHD	DAWBA	7.6	Binary outcome	6,105 (2%)
Borderline personality disorder traits score	CI-BPD	11	Standardised score	5,246
'High-risk' categorisation			Binary outcome	6,412 (6%)
Depression score	MFQ	9	Standardised score	8,066

*Threshold score used to define clinically-defined hypomania was a score of ≥14/28; HCL: Hypomania Checklist; SDQ: Strengths and Difficulties Questionnaire; ADHD: Attention Deficit Hyperactivity Disorder; DAWBA: Development and Wellbeing Assessment; CI-BPD: Childhood Interview for DSM-IV Borderline Personality Disorder; MFQ: Moods and Feelings Questionnaire

7.3.2 Hypomania

Hypomania outcomes in ALSPAC were assessed using the Hypomania Checklist-32 (HCL-32). Detailed information providing an overview of the psychometric properties and how hypomania outcomes were derived can be found in Chapter 3 under section 3.3.1. For the 28 items used to generate the HCL score, please see Table 5 found in Chapter 3.

7.3.3 Assessment of BPD traits

When the children were 11 years old, they were interviewed to assess their experience of BPD traits over the preceding two years. Further information on

the procedures and how outcomes were derived can be found in Chapter 3 under section 3.3.2.1.

7.3.4 Assessment of childhood ADHD

At age 7.6 years, using the Development and Wellbeing Assessment (DAWBA), the presence of ADHD was assessed. Further information on the DAWBA package can be found in Chapter 3 under section 3.3.2.2.

7.3.5 Emotional and behavioural difficulties

When the children were age 9 years, emotional and behavioural difficulties were assessed using the Strengths and Difficulties Questionnaire (SDQ), which was completed by the parents. Further information on the SDQ subscales and how these were derived can be found in Chapter 3 under section 3.3.2.3.

7.3.6 Depression score

When the children were 9 years old, they were invited to complete the short version of the Moods and Feelings Questionnaire (MFQ) which measures aspects of depression. Further details can be found in Chapter 3 in section 3.3.2.4.

7.3.7 Genetic data

7.3.7.1 Genetic data in ALSPAC

Of the 9,912 participants with genetic data, 8,230 were left with data after quality control, restriction to one young person per family and imputation. Detailed information on the genotyping platforms and the quality control measures ALSPAC researchers conducted can be found in Chapter 3 under section 3.5.1.

7.3.7.2 Genetic data in the PGC

For the PGC 2 BD GWAS, a total of 4 genotyping platforms were used on 20,385 BD cases and 31,358 controls. The details of quality control measures performed by the PGC team can be found in Chapter 3 under section 3.5.2.

7.3.7.3 Further quality control measures prior to constructing the BD-PRS

In addition to the quality control measures conducted by the ALSPAC research team and the PGC as described in Chapter 3, section 3.5.1 and 3.5.2 respectively, I performed additional quality control measures (see Chapter 3, section 3.5.3 for further details). After doing so, I generated a file using R statistical software that contained information on the SNP ID, risk allele (A1) and corresponding log odds ratio.

7.3.7.4 Constructing the BD-PRS

To construct the BD-PRS, I used the file containing information on SNP ID, risk allele (A1) and log odds ratio, generated by merging the ALSPAC dataset with summary statistics from the PGC 2 BD GWAS to linkage disequilibrium clump SNPs using PLINK v 1.9. From this, I retained SNPs with a $P_T \leq 0.01$ (Stahl et al. 2019) and $P_T \leq 0.5$ (Sklar et al. 2011) as these have been reported to maximally capture BD liability in their respective GWASs. I then generated a training score file in R, which was used to derive a PRS for each individual in ALSPAC. Further information on clumping parameters and what each of the different files generated contained can be found in Chapter 3 under section 3.5.4.

7.3.8 Multiple imputation

To address the possibility of selection bias due to missing data affecting the results, I used multiple imputation. Details on the multiple imputation approach can be found in Chapter 3, section 3.6.1.4. All exposure/confounder measures along with auxiliary variables were predetermined on the basis of being associated with either the exposure/confounder and missingness.

7.3.9 Statistics

All association analyses in this chapter were performed using Stata statistical software (version 14.1 SE. College Station, TX: StataCorp LP). To examine associations between the BD-PRS and binary outcomes (clinically-defined hypomania, ADHD subtypes and 'high-risk' for BPD), I used logistic regression. Results from these analyses are reported as change in odds of outcome per standard deviation (SD) increase in PRS. For analyses assessing associations between the BD-PRS and continuous outcomes (HCL score, HCL factors, BPD traits score, SDQ scores and depression score), I used linear regression. For these results, findings are presented as the SD change in outcome per SD increase in PRS. As a measure of reporting variance in outcome explained by the BD-PRS, I used R^2 values (and Naglekerke r^2 for logistic).

Previous studies have shown that the ALSPAC sample has no significant population stratification, and genome-wide analyses of phenotypes indicate a low genomic inflation factor ($\lambda \approx 1$) (Zammit et al. 2014; Martin et al. 2015). Therefore, I did not adjust for population stratification using principle components analysis. Genotyping site was not included as a covariate in the analysis, though it seems unlikely that this would confound the relationship between genetic risk and psychopathology. Whilst it seems plausible that genotyping site may lead to higher PRS from one site over another, it seems to be less likely that genotyping site would be related to psychopathology outcomes. Further details on sources of confounding in genetic analyses can be found in Chapter 3, section 3.4.1.

In the published article of this work (Mistry et al. 2019), I examined associations between genetic risk for BD and psychopathology using a PRS derived at a $P_T \leq 0.5$, as this was the previously reported threshold which maximally captures BD liability (Sklar et al. 2011). However, for the purposes of this Chapter, I now use a $P_T \leq 0.01$ for my primary analyses as this is the most recent threshold reported to maximally capture BD liability (Stahl et al. 2019).

7.4 Results

7.4.1 BD-PRS and hypomania

The proportion of individuals who were deemed to meet criteria for clinically-defined hypomania was 7%, a finding similar to that in another birth cohort study based in New Zealand (Richards et al. 2019), and within the 5-10% range reported by other longitudinal general population studies based in Germany and Sweden (Meyer et al. 2007; Holtmann et al. 2009). There was little evidence to suggest increased genetic risk for BD was associated with the HCL score (p = 0.998), HCL factors (both p >0.546), or clinically-defined hypomania (p = 0.382). These results are presented in Table 25.

Table 25 Associations between the BD-PRS and hypomania outcomes at $P_T \leq 0.01$

Exposure	Outcome	N	β	95%CI	P	R^2 (%)
BD-PRS at $P_T \leq 0.01$	HCL score	2654	0.00^	-0.04, 0.04	0.998	0
	Active/elated factor	2363	0.01	-0.03, 0.05	0.546	0.02
	Risk-taking/irritable factor		-0.01	-0.04, 0.03	0.747	0
	Outcome	**N (%)**	**OR**	**95%CI**	**P**	**R^2 (%)**
BD-PRS at $P_T \leq 0.01$	Clinically-defined hypomania*	239 (7.1)	1.07	0.92, 1.24	0.382	0.06

*Threshold score used to defined clinically-defined hypomania was a score of ≥14/28 on the HCL; ^rounded to 2 decimal places; BD-PRS: Bipolar Disorder-Polygenic Risk Score; HCL: Hypomania Checklist; CI: Confidence intervals; P_T: P-value threshold

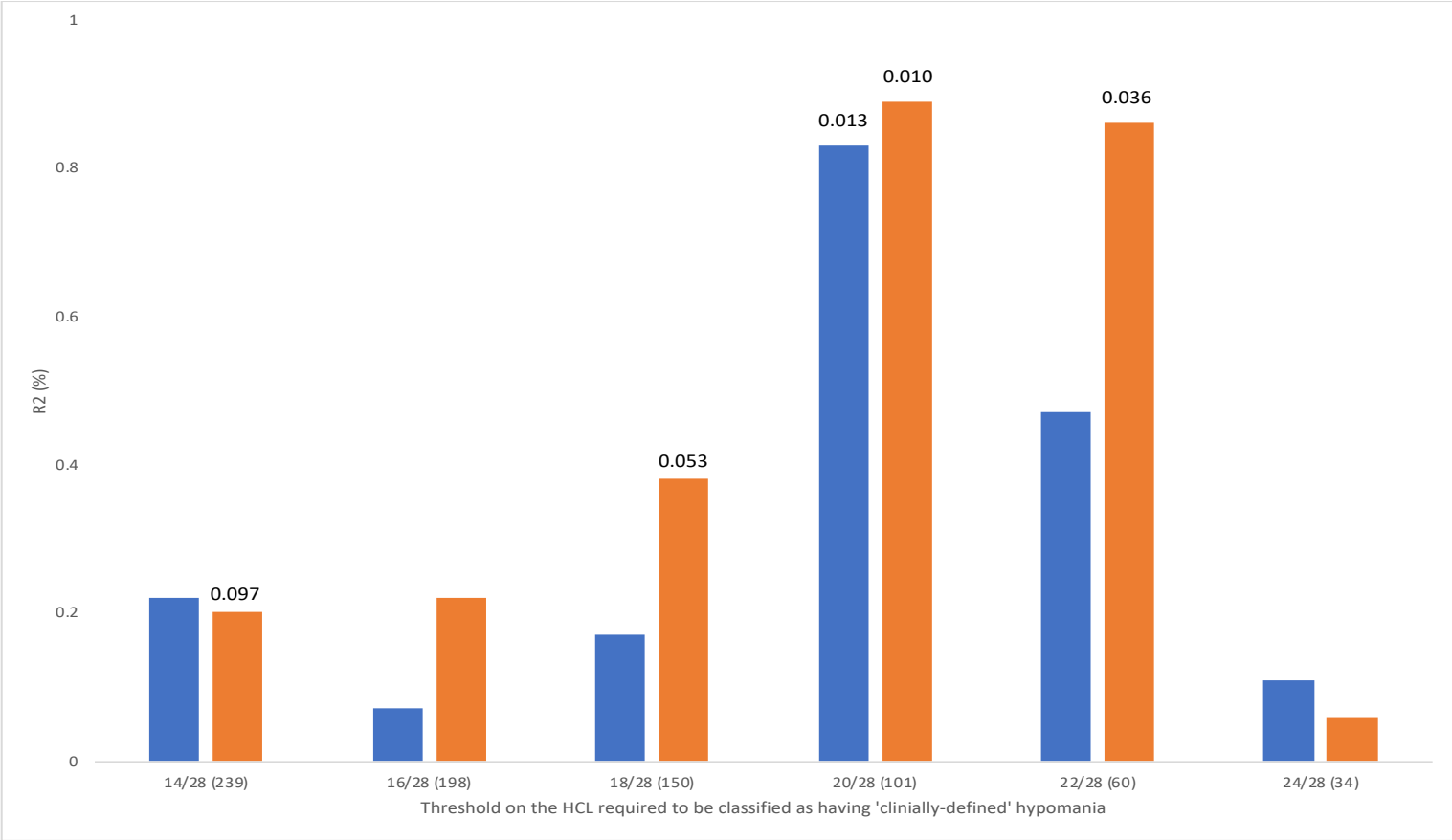
At my secondary P_T of ≤0.5, I also found little evidence to suggest the BD-PRS was associated with the HCL score (p = 0.336) or HCL factors (both p >0.292). However, I did find very weak evidence that the BD-PRS was associated with increased odds of being classified as having hypomania at the threshold cut off score of ≥14/28 (OR = 1.13, 95%CI 0.98, 1.32; p = 0.097) (see Appendix 13).

7.4.1.1 Sensitivity analysis

As a sensitivity analysis, I examined clinically-defined hypomania outcomes that required increasing symptom number counts to be classified as having hypomania (the same thresholds examined in Chapter 4). No corrections for multiple testing were made as the purpose of the sensitivity analysis was exploratory and to determine whether associations were consistent across the thresholds used to define hypomania.

Associations between genetic risk for BD and clinically-defined hypomania at my primary P_T showed little evidence of association, with the exception of a HCL score of ≥20/28 (OR = 1.32, 95%CI 1.06, 1.64; p = 0.013) (Appendix 14). Associations between the BD-PRS and clinically-defined hypomania at my secondary P_T were stronger than those at my primary P_T, and the strongest evidence of association was also when the threshold to be classified as having clinically-defined hypomania was also at a score of ≥20/28 (OR = 1.33, 95%CI 1.07, 1.65; p = 0.01) (Appendix 14). As a visual representation, Figure 6 shows the proportion of variance explained in clinically-defined hypomania by the BD-PRS at both P_T's.

Figure 6 Results of sensitivity analyses when examining associations between the BD-PRS and clinically-defined hypomania



Values in brackets on the x axis represent the number of individuals classified as having clinically-defined hypomania; HCL: Hypomania Checklist; P_T: P-value threshold; BD-PRS: Bipolar Disorder Polygenic Risk Score; Blue bars represent values at my primary $P_T \leq 0.01$ and red bars represent values at my secondary $P_T \leq 0.5$

7.4.2 BD-PRS and BPD outcomes

When examining associations between increased genetic risk for BD and the BPD outcomes, I found little evidence of association with the BPD traits score at either P_T (both p >0.183), and similarly little evidence of an association with being classified as 'high-risk' for BPD (both p >0.107) (see Table 26).

Table 26 Association between the BD-PRS and BPD outcomes

Exposure	Outcome	N	β	95%CI	P	R^2
BD-PRS at $P_T \leq 0.01$	BPD traits score	5,246	-0.02	-0.05, 0.01	0.183	0.03
BD-PRS at $P_T \leq 0.5$		5,246	0.00^	-0.03, 0.03	0.898	0.00
	Outcome	**N (% with outcome)**	**OR**	**95%CI**	**P**	**r^2 (%)**
BD-PRS at $P_T \leq 0.01$	'High risk' for BPD	5,247 (5.8%)	0.91	0.81, 1.02	0.107	0.11
BD-PRS at $P_T \leq 0.5$			1.01	0.90, 1.13	0.860	0.00

^rounded to 2 decimal places; BD-PRS: Bipolar Disorder-Polygenic Risk Score; P_T: P-value threshold; BPD: Borderline Personality Disorder; CI: Confidence Intervals; OR: Odds Ratio

7.4.3 BD-PRS and ADHD

When I examined associations between the BD-PRS and ADHD subtypes, there was little evidence of association at my primary P_T of ≤0.01 (all p >0.265), but at the less stringent P_T of ≤0.5, I found strong evidence of association between the BD-PRS and increased odds of being diagnosed with any ADHD disorder (OR = 1.31, 95%CI 1.10, 1.57; p = 0.003). There was also stronger evidence of association for inattentive ADHD (OR = 1.37, 95%CI 1.06, 1.79; p = 0.018) than hyperactive-impulsive or combined ADHD (both p >0.119); however, confidence intervals for all subtypes overlapped substantially at both P_T's (see Table 27).

Table 27 Associations between the BD-PRS and diagnosis of ADHD subtypes

Exposure	Outcome	N (% with outcome)	OR	95%CI	P	r^2 (%)
BD-PRS at $P_T \leq 0.01$	ADHD	6,105 (7.00)	1.11	0.93, 1.32	0.265	0.11
	Inattentive ADHD	6,102 (0.85)	1.12	0.86, 1.46	0.407	0.11
	Hyperactive-impulsive ADHD	6,102 (0.30)	1.12	0.70, 1.77	0.644	0.09
	Combined ADHD	6,102 (0.97)	1.09	0.82, 1.44	0.556	0.06
Exposure	**Outcome**	**N (% with outcome)**	**OR**	**95%CI**	**P**	**r^2 (%)**
BD-PRS at $P_T \leq 0.5$	ADHD	6,105 (7.00)	1.31	1.10, 1.57	0.003	0.73
	Inattentive ADHD	6,102 (0.85)	1.37	1.06, 1.79	0.018	0.88
	Hyperactive-impulsive ADHD	6,102 (0.30)	1.44	0.91, 2.30	0.119	0.99
	Combined ADHD	6,102 (0.97)	1.19	0.90, 1.57	0.230	0.25

BD-PRS: Bipolar Disorder-Polygenic Risk Score; ADHD: Attention Deficit Hyperactivity Disorder; P_T: P-value threshold; CI: Confidence Interval; OR: Odds Ratio

7.4.4 BD-PRS and the SDQ

When investigating associations between the BD-PRS and the SDQ, there was little evidence of association with the total difficulties score, nor any of the SDQ subscales at both primary (all p >0.319) and secondary (all p >0.131) P_T's (Table 28).

Table 28 Association between the BD-PRS and SDQ

Exposure	Outcome	N	β	95%CI	P	R^2 (%)
BD-PRS at P_T<0.01	Hyperactivity	6,134	0.00^	-0.02, 0.03	0.736	0.00
	Prosocial	6,138	-0.00^	-0.03, 0.02	0.800	0.00
	Emotional	6,117	0.01	-0.01, 0.03	0.435	0.01
	Conduct	6,133	0.01	-0.01, 0.04	0.319	0.02
	Peer relationship	6,128	0.01	-0.02, 0.03	0.509	0.01
	Total difficulties	6,111	0.01	-0.01, 0.04	0.357	0.01
Exposure	**Outcome**	**N**	**β**	**95%CI**	**P**	**R^2**
BD-PRS at $P_T \leq 0.5$	Hyperactivity	6,134	-0.00^	-0.03, 0.02	0.760	0.00
	Prosocial	6,138	-0.001	-0.03, 0.02	0.951	0.00
	Emotional	6,117	0.02	-0.01, 0.04	0.175	0.03
	Conduct	6,133	0.02	-0.01, 0.04	0.131	0.04
	Peer relationship	6,128	0.02	-0.01, 0.04	0.231	0.02
	Total difficulties	6,111	0.01	-0.01, 0.04	0.302	0.00

^ Rounded to 2 decimal places; BD-PRS: Bipolar Disorder-Polygenic Risk Score; P_T: P-value threshold; CI: Confidence Intervals; SDQ: Strengths and Difficulties Questionnaire

7.4.5 BD-PRS and the MFQ

I found little evidence of association between increased genetic risk for BD and depression score at either P_T (both p >0.405) (see Table 29).

Table 29 Association between the BD-PRS and MFQ

Exposure	Outcome	N	β	95%CI	P	R^2 (%)
BD-PRS at $P_T \leq 0.01$	Depression score	6,128	0.00^	-0.02, 0.02	0.985	0.00
BD-PRS at $P_T \leq 0.5$			0.01	-0.01, 0.03	0.405	0.01

^ Rounded to 2 decimal places; BD-PRS: Bipolar Disorder Polygenic Risk Score; MFQ: Moods and Feelings Questionnaire; CI: Confidence Intervals; P_T: P value threshold cut off score

7.4.6 Associations between the BD-PRS and psychopathology measures using imputed data

In an attempt to address the possibility of my results being affected by selection bias due to attrition, I compared the results from my complete-case analyses to those using imputed data. When examining associations with measures of hypomania as the outcome, the effect sizes and strength of evidence were similar for the HCL score, whereas those with clinically-defined hypomania were slightly weaker, though they did not alter the conclusions of this study (see Table 30).

Table 30 Associations between the BD-PRS and hypomania outcomes comparing imputed with non-imputed data

Exposure	Outcome	N	β non-imputed	95%CI	P value	N	β imputed	95%CI	P value
BD-PRS at $P_T \leq 0.01$	HCL score	2,654	0.00^	-0.04, 0.04	0.998	3,371	-0.00^	-0.04, 0.04	0.944
Exposure	**Outcome**	**N**	**OR non-imputed**	**95%CI**	**P value**	**N**	**OR imputed**	**95%CI**	**P value**
BD-PRS at $P_T \leq 0.01$	Clinically-defined hypomania at threshold ≥14/28	2,654	1.07	0.92, 1.24	0.382	3,371	1.06	0.92, 1.23	0.405
	Clinically-defined hypomania at threshold ≥20/28		1.32	1.06, 1.64	0.013		1.29	1.03, 1.60	0.023
Exposure	**Outcome**	**N**	**β non-imputed**	**95%CI**	**P value**	**N**	**β imputed**	**95%CI**	**P value**
BD-PRS at $P_T \leq 0.5$	HCL score	2,654	0.02	-0.02, 0.06	0.336	3,371	0.02	-0.03, 0.06	0.448
Exposure	**Outcome**	**N**	**OR non-imputed**	**95%CI**	**P value**	**N**	**OR imputed**	**95%CI**	**P value**
BD-PRS at $P_T \leq 0.5$	Clinically-defined hypomania at threshold ≥14/28	2,654	1.13	0.98, 1.32	0.097	3,371	1.12	0.96, 1.35	0.144
	Clinically-defined hypomania at threshold ≥20/28		1.33	1.07, 1.65	0.010		1.29	1.03, 1.61	0.025

^ Rounded to 2 decimal places; BD-PRS: Bipolar Disorder Polygenic Risk Score; CI: Confidence Intervals; P_T: P value threshold cut off score; HCL: Hypomania Checklist; OR: Odds Ratio

When examining associations between genetic risk for BD and measures of childhood psychopathology, effect sizes and strength of evidence of association in the imputed and complete-case data were similar for most outcomes, regardless of which P_T was being used to derive the BD-PRS. However, there was much stronger evidence of association and a substantial increase in effect size for inattentive ADHD at my primary P_T in the imputed data (see Table 31).

Table 31 Associations between the BD-PRS and measures of childhood psychopathology comparing imputed and non-imputed data

Exposure	Outcome	N	β non-imputed	95%CI	P value	N	β imputed	95%CI	P value
BD-PRS at $P_T \leq 0.01$	BPD traits score	5,246	-0.02	-0.05, 0.01	0.183	6,411	-0.02	-0.04, 0.01	0.228
BD-PRS at $P_T \leq 0.5$			0.00^	-0.03, 0.03	0.898		0.00^	-0.02, 0.03	0.971
BD-PRS at $P_T \leq 0.01$	Total difficulties score	6,108	0.01	-0.01, 0.04	0.357	8,034	0.01	-0.01, 0.04	0.383
BD-PRS at $P_T \leq 0.5$			0.01	-0.01, 0.04	0.305		0.01	-0.01, 0.04	0.314
BD-PRS at $P_T \leq 0.01$	Depression score	5,246	-0.02	-0.05, 0.01	0.183	6,411	-0.02	-0.04, 0.01	0.228
BD-PRS at $P_T \leq 0.5$			0.00^	-0.03, 0.03	0.898		0.00^	-0.02, 0.03	0.971
Exposure	**Outcome**	**N**	**OR non-imputed**	**95%CI**	**P value**	**N**	**OR imputed**	**95%CI**	**P value**
BD-PRS at $P_T \leq 0.01$	Inattentive ADHD	6,102	1.12	0.86, 1.46	0.407	8,216	1.29	1.03, 1.60	0.023
BD-PRS at $P_T \leq 0.5$			1.37	1.06, 1.79	0.018		1.34	1.03, 1.74	0.030

^ Rounded to 2 decimal places; BD-PRS: Bipolar Disorder Polygenic Risk Score; P_T: P value threshold cut off; CI: Confidence Intervals; BPD: Borderline Personality Disorder; MFQ: Moods and Feelings Questionnaire; OR: Odds Ratio; ADHD: Attention Deficit Hyperactivity Disorder

7.5 Discussion

7.5.1 Summary of findings

7.5.1.1 Associations with hypomania

The first objective of this study was to determine whether increased genetic risk for BD was associated with hypomania outcomes (HCL score, HCL factors and clinically-defined hypomania) in young adulthood.

I found that associations between the BD-PRS and hypomania were strongest for clinically-defined hypomania, particularly when a greater symptom number count was required to be classified as having clinically-defined hypomania. However, I found little evidence of association between the BD-PRS and dimensional measures of hypomania (HCL score/HCL factors). There was little to suggest that selection bias was affecting associations between genetic risk for BD and hypomania outcomes as evidenced by similar effect sizes/strength of evidence of association in the complete-case and imputed data.

7.5.1.2 Associations with childhood psychopathology

The second objective of this study was to assess whether the BD-PRS was associated with a broad range of childhood psychopathology measures as examined in Chapter 4 of this thesis. Overall, there was little evidence to suggest an association between the BD-PRS and most psychopathology measures, with the possible exception of inattentive ADHD. Furthermore, there was little evidence to suggest selection bias was affecting the association between the BD-PRS and these measures. However, for inattentive ADHD, the results following multiple imputation suggests that selection bias led to an underestimate in the effect size and strength of evidence of association at my primary P_T in the complete-case analysis.

7.5.2 Interpretation of findings in the context of previous work

7.5.2.1 BD-PRS and hypomania

The findings from the current study suggest that genetic risk for BD is weakly associated with clinically-defined hypomania (the association was stronger for hypomania defined using a higher threshold of symptoms). To the best of my knowledge there are no studies examining associations between a BD-PRS and hypomania as an outcome per se, although two studies have examined whether the BD-PRS can discriminate BD subtypes (BD-I vs BD-II), reporting inconsistent results (Aminoff et al. 2015; Charney et al. 2017). My findings of association with clinically-defined hypomania are weaker than those from a number of studies have examined associations with BD case status in clinical samples (Schulze et al. 2014; Tesli et al. 2014; Power et al. 2015; Charney et al. 2017).

Given the potential for greater statistical power using dimensional (rather than symptom threshold) measures of hypomania, it was perhaps surprising to find little evidence of associations between the BD-PRS and either the total HCL score or HCL factors.

Researchers investigating psychosis have described an extended phenotype whereby psychotic experiences and psychotic disorders are at different ends of a distribution (van Os and Reininghaus 2016), with genetic risk for schizophrenia showing stronger associations with phenotypes at the more severe end of this spectrum (Mistry et al. 2018b). It is possible that hypomanic experiences and BD also exist as an extended phenotype, and that BD genetic risk is more strongly associated with more severe than less severe phenotypes. Other (non-genetic) factors might influence the presence of HCL items to a greater extent than they do the presence of BD, and hence the association between the BD-PRS and HCL score would be diluted; this might explain why I observe an association with clinically-defined hypomania, but not with the HCL score or HCL factors.

Alternatively, the lack of evidence of association with the HCL score might be related to the ability of the HCL to reliably distinguish those with BD from those without. As is evident from a recent systematic review and meta-analysis, the HCL has high sensitivity (82%), but low specificity (57%) indicating that its ability to determine true negatives i.e. people who do not have BD is poor (Wang et al. 2019). There are few studies that have examined sensitivity and specificity in general population samples, though one study in a Chinese population found high sensitivity but even poorer specificity (32%) (Lee et al. 2016). Therefore, if the HCL does not accurately capture hypomania in general population samples, this could explain the weak evidence of association between the BD-PRS and HCL-related outcomes in my study.

It is also possible that my finding of a lack of evidence of association between the BD-PRS and trait measures of hypomania is due to selection bias in the BD discovery sample GWAS. If individuals with BD were more likely to be part of the GWAS because they spent more time in clinical services, for example due to more severe symptoms/behavioural issues or psychotic experiences, then it is possible that the BD-PRS indexes these characteristics rather than genetic risk for BD per se. Selection bias in the GWAS from which the BD-PRS was derived could partly explain why there is little evidence of association with hypomania traits in a general population sample such as ALSPAC.

Despite the evidence of association with hypomania in my study being weaker than that published for BD case status, they are nevertheless consistent with a causal relationship between genes conferring risk for BD and developing clinically-defined hypomania. The minimal difference observed when comparing effect size and strength of evidence of association in imputed vs non-imputed data suggests selection bias is an unlikely explanation for this, though nevertheless cannot be entirely ruled out.

On the whole though, the findings in this study suggest that genetic risk for BD does not strongly influence hypomania, as captured by the HCL, in the young adult general population.

7.5.2.2 BD-PRS and BD-PRS and measures of childhood psychopathology

I found little evidence of association between the BD-PRS and most measures of childhood psychopathology, with the possible exception of ADHD, and in particular the inattentive subtype.

Data on possible childhood phenotypic manifestations of increased genetic risk for BD is limited (Mistry et al. 2018a), however, the BD-PRS (derived using the smaller PGC-1-BD GWAS) has previously been reported as associated with ADHD (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013; Hamshere et al. 2013), but not with either externalising or internalising scales on the Child Behavioural Checklist (Jansen et al. 2018), a measure assessing similar constructs to the SDQ used in the current study. Therefore, the findings of the current study are consistent with these previous studies, though my findings of association with ADHD are stronger than previously reported. Stronger evidence of association with ADHD could be attributed to using a more accurate and precise PRS (derived from the larger and more recent PGC-2-BD GWAS) (Dudbridge 2013,2016).

For most childhood psychopathology measures, selection bias had little impact on the associations with genetic risk, with the exception of inattentive ADHD where stronger evidence of association (and an increase in effect size) was found at my primary P_T in the imputed data. Post hoc analyses showed that children with ADHD were more likely to have missing data on the HCL compared to either the MFQ or being 'high-risk' for BPD which means that associations in the complete-case data are more likely to have been underestimated for ADHD.

As is evident from several GWAS, genetic overlap exists between BD and: i) ADHD (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013; van Hulzen et al. 2017; Demontis et al. 2019), ii) depression (Power et al. 2017; Wray et al. 2018; Howard et al. 2019) and BPD (Witt et al. 2014; Witt et al. 2017). Findings from high-risk offspring of BD parents suggest that compared to non-high-risk offspring, high-risk offspring are more likely to have experienced ADHD and behavioural problems in childhood/adolescence (Raouna et al.

2018; Duffy et al. 2019). However my findings suggest that in contrast to evidence of association between genetic risk for schizophrenia and childhood psychopathology (Nivard et al. 2017), genetic risk for BD might not be manifest to the same extent, or might manifest later in development. However, with so few studies examining associations between increased genetic risk for BD (using a PRS) and childhood/adolescent phenotypes, it is difficult to know the extent to which this statement is true or not. A recent study also using the ALSPAC cohort examined associations between a BD-PRS (derived using the smaller PGC-1-BD GWAS) and depression examined using the MFQ at age 16 years and also reported little evidence of association (Jones et al. 2018).

Therefore, evidence from family studies reporting presence of these psychopathologies in high-risk offspring suggests the environment in which the child is brought up may have greater importance in the expression of these psychopathologies than the child's own genetic risk (Duffy et al. 2019).

Alternatively, given the low number of individuals with an ADHD diagnosis in the current study, it is possible that sparse data bias is present and estimates are being biased away from the null (Greenland et al. 2016).

Nevertheless, the BD-PRS is still likely to be underpowered and therefore lack of association between the BD-PRS and psychopathology measures might be a result of lack of power.

7.5.3 Strengths and limitations

This study has a number of strengths and limitations. This is the first study that has investigated associations between a BD-PRS (derived using summary statistics from the PGC-2-BD GWAS) and psychopathology from childhood into early adulthood. I have therefore used the largest and most recent Bipolar Disorder GWAS from the PGC as the discovery dataset (PGC-2-BD) (Stahl et al. 2019) from which to derive the PRS, thus minimising measurement error and maximising power. Nevertheless, the variance explained in BD by the PRS is still only 4% and it is therefore likely that there is still substantial measurement error. Second, ALSPAC is one of the most phenotypically rich birth cohort

studies of its kind, and using this rich phenotypic data allowed me to examine a broad range of potential manifestations of increased genetic risk for BD in childhood.

Third, with the exception of the hypomania outcomes, all phenotypes were assessed in childhood, and irrespective of which phenotype was examined, all measures are well validated which reduces information bias. Nevertheless, it is unlikely they perfectly capture psychopathological domains without error, which could bias my results. Given the number of phenotypes investigated, multiple testing could have led to some false positive results. I specified primary measures of exposure (p-thresholds) and outcomes *a priori* to reduce this, and conducted sensitivity analyses where possible (for example using different cut-off thresholds to define clinically-defined hypomania) to determine whether associations were consistent across the thresholds used. I have avoided relying on p-value thresholds to determine 'significance' of results, but tried to interpret the strength of evidence in support of associations in the context of the number of associations examined and the study design limitations, as recommended for epidemiological studies (Sterne and Smith 2001).

I also investigated the possibility that selection bias might be affecting the interpretation of associations between the BD-PRS and psychopathology measures. By including a number of auxiliary variables that are associated with the measures I examined and with missingness in my imputation model, I have made the missing at random assumption more plausible. However, it is possible that the imputation model I used might not adequately deal with the missing at random assumption, in which case the results in the imputed data would still be biased.

Importantly, my results are only applicable to effects of common variants, which means that they do not reflect the possible effects of rare copy number variants (CNVs) on risk of BD. These CNVs are usually larger (>100kb) and rarer in the population, though findings are inconsistent as to which CNVs are present in BD cases (McQuillin et al. 2011; Olsen et al. 2011; Ono et al. 2015). On the whole, these inconsistent findings suggest CNVs may not play as important a role in susceptibility to BD as compared to schizophrenia (Lowther et al. 2017;

Zhuo et al. 2017), though recent evidence has suggested CNVs may play a greater role in schizoaffective disorder (Charney et al. 2019).

7.5.4 Conclusions

Overall, I found little evidence that genetic risk for BD (as captured by the BD-PRS) manifests as psychopathology in childhood, or dimensional measures of hypomania in young adulthood. However, there was some evidence genetic risk for BD manifests as inattentive ADHD/clinical hypomania, though it is unclear as to the robustness of these findings given they are based on small numbers for the former, and inconsistent with other HCL measures for the latter. Therefore, further work using large, general population-based longitudinal study designs is required to determine the replicability of the findings in this study, and to explore whether phenotypic manifestation of increased genetic risk for BD changes with age. By studying and understanding the phenotypic manifestations of increased genetic risk for BD in childhood/adolescence, it may be possible to inform early recognition in those who are at greatest risk of developing the BD.

The next chapter, Chapter 8 will explore associations between increased genetic risk for BD and cognitive functioning in childhood.

Chapter 8: Genetic risk for bipolar disorder and cognitive functioning in childhood

The work presented in this chapter has been published and can be found online at

https://www.sciencedirect.com/science/article/pii/S0165032719301296?via%3Dihub

Mistry, S., Escott-Price, V., D. Florio, A., Smith, D.J., Zammit, S. (2019). Investigating associations between genetic risk for bipolar disorder and cognitive functioning in childhood. *Journal of Affective Disorders*, **259**, 112-120 https://doi.org/10.1016/j.jad.2019.08.040

The published article has been adapted for use in this chapter to include additional results (available as supplementary materials online).

8.1 Chapter summary

Identifying the phenotypic manifestations of genetic risk for bipolar disorder (BD) in childhood could increase understanding of aetiological mechanisms underlying the disorder.

In this chapter, I investigated objectives 13-16 as outlined in Chapter 2. To derive a BD polygenic risk score (BD-PRS), I used the 2nd Psychiatric Genomics Consortium (PGC) BD genome wide association study (GWAS), and the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort as a target dataset. I also derived a schizophrenia PRS (SZ-PRS) and a SZvsBD PRS using summary statistics from the second PGC-SZ GWAS and second SZvsBD GWAS respectively. I investigated whether increased genetic risk for BD was associated with childhood cognitive functioning. I also examined whether associations were due to single nucleotide polymorphism (SNP) risk alleles that have shared risk effects on schizophrenia.

At my primary P_T, $P_T \leq 0.01$, I found the BD-PRS was associated with poorer executive functioning and, more weakly with poorer processing speed. At my secondary P_T, $P_T \leq 0.5$, associations were still with poorer executive functioning, and were stronger for poorer processing speed and performance IQ. In the current study, associations with performance IQ and processing speed were primarily driven by genetic effects that are shared with schizophrenia risk, whereas those for executive functioning were more specific to BD risk.

The findings from this chapter suggest that genetic risk for BD manifests as impaired cognition in childhood, and this is driven by risk SNP risk alleles that are also shared with SZ genetic risk (for performance IQ and processing speed) and potentially more specific to BD (for executive functioning). Further elucidation of which cognitive domains are most affected by genetic risk for BD could help understanding of aetiology and improve prediction of BD.

8.2 Introduction

From the initial works of Kraepelin who first distinguished *dementia praecox* (now schizophrenia) from *manic-depressive insanity* (now termed bipolar disorder (BD), cognitive deficits have long been recognised as being a core part of the schizophrenia phenotype. For BD, this was initially viewed as a mood disorder with a remitting course, not typically associated with cognitive deterioration (Angst 2002). However, a substantial proportion (approximately 40-60%) of adults with BD exhibit cognitive deficits even when they are euthymic (Arts et al. 2008; Bora et al. 2009). Several meta-analyses in adults with BD have found impairments in the domains of general intelligence, as indexed by intelligence quotient (IQ), processing speed, working memory, problem solving, verbal learning, visual learning, executive functioning, and social cognition (Bora et al. 2009; Bortolato et al. 2015; Bora and Ozerdem 2017b).

Findings from both familial high-risk and cohort study designs have suggested cognitive deficits in childhood being a potential precursor to BD (Bora and Ozerdem 2017a,b). When compared to studies examining cognitive deficits in the premorbid phase in those who eventually develop schizophrenia (Khandaker et al. 2011), it is unclear whether differences in premorbid cognitive ability in those who eventually go on to develop BD are present (Bortolato et al. 2015; Martino et al. 2015). As highlighted in a recent review on the trajectory of cognitive functioning and BD (Van Rheenen et al. 2019), whilst some studies suggest normal (Zammit et al. 2004; Kendler et al. 2016a) or higher cognitive abilities and scholastic achievement in those who develop BD compared to controls (MacCabe et al. 2010; Gale et al. 2013), others report deficits (Meyer et al. 2004; Sharma et al. 2017).

As described in previous chapters (Chapters 3 and 7), BD is a highly heritable disorder (Barnett and Smoller 2009), and through genome wide association studies (GWAS), a number of single nucleotide polymorphism (SNP) risk alleles (henceforth referred to as SNPs) occurring more frequently in BD cases relative to controls have been identified (Sklar et al. 2011; Ruderfer et al. 2018; Stahl et

al. 2019). When trait-associated alleles across many genetic loci are summed into a single polygenic risk score (PRS), it is possible to examine the effect of multiple disease-associated risk SNPs on phenotypes in other samples (Purcell et al. 2009; Cross-Disorder Group of the Psychiatric Genomics Consortium 2013).

As identified in a recent systematic review (see Chapter 6 of this thesis), there is a limited understanding of how genetic risk for BD is manifest during childhood/adolescence in the general population (Mistry et al. 2018a). Most studies have relied on studying relatively small numbers of offspring of adults with BD to characterize genetically high-risk individuals (Nurnberger et al. 2011; de la Serna et al. 2017). To the best of my knowledge, only one study has assessed the associations between a BD-PRS and cognitive measures in childhood in the general population. The authors found no association between a BD-PRS and a measure of social cognition (emotion recognition) using the smaller PGC-1-BD GWAS to derive the PRS (Coleman et al. 2017).

The objectives of the current study were: i) to examine whether genetic risk for BD is associated with a broad range of cognitive domains (general intelligence as indexed by IQ, processing speed, working memory, problem solving ability, executive functioning, attention, verbal learning and social cognition (emotion recognition)), ii) to examine whether the relationship between the BD-PRS and cognitive functioning is non-linear i.e. do those at high and low compared to average genetic risk for BD have different cognition, iii) to examine the extent to which any associations between the BD-PRS and cognitive domains are due to risk alleles shared with schizophrenia risk given the high genetic correlation between these two disorders (Bulik-Sullivan et al. 2015) and iv) to investigate the extent to which my findings might be due to selection bias (objectives 13-16).

8.3 Methods

8.3.1 Participants

In the current study, I used data on individuals from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. A detailed description of recruitment procedures and the inclusion criteria can be found in Chapter 3, section 3.2.1. Descriptive statistics for all outcome measures in the entire ALSPAC sample are shown in Table 32.

Table 32 Descriptive statistics for cognitive measures used in the entire ALSPAC sample

Test	N	Mean	SD	Minimum	Maximum
WISC-III					
PIQ	7,371	99.46	17.12	46	151
VIQ	7,379	106.96	16.80	46	155
TIQ	7,348	103.97	16.54	45	151
PS	7,405	10.50	3.05	1	19
WM	7,174	20.81	6.01	2	38
PrS	7,362	10.54	3.81	1	19
TEACh					
EF	7,204	17.47	5.65	8.5	300
ATT	7,184	5.21	1.92	0.60	46.58
CTNWR					
VL	7,361	7.23	2.51	0	12
DANVA					
ER	6,815	4.60	2.79	0	22

ALSPAC: Avon Longitudinal Study of Parents and Children; WISC-III: Wechsler Intelligence Scale-III; TIQ: Total Intelligence Quotient; VIQ: Verbal Intelligence Quotient; PIQ: Performance Intelligence Quotient; PS: Processing Speed; WM: Working Memory; PrS: Problem Solving; EF: Executive Functioning; ATT: Attention; VL: Verbal Learning; ER: Emotion Recognition; TEACh: Test of Everyday Attention for Children; CTNWR: Children's Test of Nonword Repetition; DANVA: Diagnostic Analysis of Nonverbal Accuracy

8.3.2 Cognitive assessments

When the children were aged 8 years, their cognitive functioning was assessed. The cognitive domains I examined in this study (general intelligence (IQ), processing speed, working memory, problem solving, attention, executive function, verbal learning, and social cognition) were selected *a priori* based on the literature of cognitive deficits in adults with BD. As highlighted in Chapter 3, section 3.3.3, the cognitive tasks I used cover most of the domains described in the Measurement and Treatment Research in Cognition in Schizophrenia Research Consensus Battery (MCCB), but do not map precisely onto them. Where required, cognitive domain scores were re-coded so that higher scores always reflect better cognitive performance.

Chapter 3, section 3.3.3.1 details how ALSPAC researchers derived the cognitive domain scores examined by the Wechsler Intelligence Scale - III (WISC-III) (Wechsler et al. 1992). From the WISC-III, the following domains were investigated:

General intelligence: I used scores for Verbal IQ (VIQ), Performance IQ (PIQ) and Total IQ (TIQ) (VIQ and PIQ combined). Details on the subtests which make up these measures can be found in Chapter 3, section 3.3.3.1.

Processing speed: The coding subtest was used which required the children to place the correct symbol above each number as quickly as possible within a set time period.

Working memory: This was assessed using the Freedom From Distractibility index score that combined scores from both the arithmetic subtest and the digit span task.

Problem solving: The block design subtest was used and required the children to copy specific patterns of blocks seen on a picture and replicate these patterns using real blocks.

From the Test of Everyday Attention in Children (TEACh), domains of executive functioning and attention were examined. Chapter 3, section 3.3.3.2 details how ALSPAC researchers derived these scores:

Executive function: The opposite world's task required the children to verbalise a number (either 1 or 2) that contradicted what they saw on a screen as quickly as possible.

Attention: The sky search task adjusted for motor speed was used and required the children to distinguish identical from non-identical spaceships and draw a circle around only identical spaceships.

From the Children's Test of Nonword Repetition, the nonword reptition task was used. Details on how ALSPAC researchers derived this variable can be found in Chapter 3, section 3.3.3.3. The task required the child to listen to 12 nonsense words and repeat each word back.

From the Diagnostic Analysis of Nonverbal Accuracy (DANVA), I derived a total emotion errors score which was the sum total of the scores for each emotion (happy, sad, fearful and angry). Further details can be found in Chapter 3, section 3.3.3.4.

8.3.3 Genetic data in ALSPAC

In ALSPAC, 9,912 participants provided genetic data, though after quality control, imputation, and restriction to 1 young person per family, genetic data were available on 8,230 individuals. Genotyping platforms and quality control measures ALSPAC researchers performed can be found in section 3.5.1. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004).

8.3.4 Construction of the Polygenic Risk Scores (PRS)

I used summary statistics from the second PGC-BD GWAS (20,352 BD cases and 31,358 controls) (Stahl et al. 2019), second PGC SZ GWAS (n = 36,989

cases and 113,075 controls) (Ripke et al. 2014), and the second SZvsBD GWAS (33,426 SZ cases and 20,129 BD cases) (Ruderfer et al. 2018) to create PRSs for each individual in ALSPAC.

To avoid repetition, the reader is guided to Chapter 7, section 7.3.7.4 for clumping parameters used, and Chapter 3, section 3.5.4 for a justification of the P_T's used. For the BD-PRS, I retained SNPs with a $P_T \leq 0.01$ for my primary analyses, and for secondary analyses at a $P_T \leq 0.5$.

For the SZ PRS, I retained SNPs with a $P_T \leq 0.05$, as this is the threshold which maximally captures SZ liability (Ripke et al. 2014), and for the SZvsBD PRS, I used SNPs with a $P_T \leq 0.5$ (Ruderfer et al. 2018) as this is the threshold that maximally captures variance for most other phenotypes (Ware et al. 2017).

To generate a PRS for each individual in ALSPAC, I used the --score command in PLINK. This PRS is the sum of the total number of risk alleles present for each SNP (0, 1, 2) weighted by the log of its odds ratio (OR) for BD/SZ/SZvsBD from the repspective GWASs.

8.3.5 Multiple imputation

I used multiple imputation to address the possibility of my results being affected by attrition bias. Chapter 3, section 3.6.1.4 provides details on the multiple imputation approach.

8.3.6 Statistical analysis

For all association analyses examined in this chapter, I used STATA statistical software (version 14.1 SE. College Station, TX: StataCorp LP). Data for all cognitive tasks were standardized, and any individuals with scores >3 standard deviations from the mean were omitted. I used linear regression to determine associations between the BD-PRS and continuous outcomes, with results presented as beta coefficients per standard deviation (SD) increase in PRS. The residuals for all cognitive tasks were normally distributed. Further details on linear regression can be found in Chapter 3 section 3.6.1.1.1.

To examine whether there was a non-linear relationship between the BD-PRS and cognitive functioning, I included quadratic terms in the models, with p-values derived from likelihood ratio tests comparing models with linear and quadratic terms to models with linear terms only. To more explicitly test whether both higher and lower genetic risk for BD is associated with cognitive performance, I also derived tertiles of the BD-PRS, and compared cognitive performance in those with higher/lower genetic risk tertile compared to the middle (reference category) tertile (see Chapter 3, section 3.6.1.1.2 for further details).

To examine the extent to which the strongest association(s) between genetic risk for BD and cognitive performance was due to risk alleles for BD that are also risk alleles for SZ, I used three approaches:

1. I used a multivariable model to adjust for the SZ-PRS to determine the extent to which the effect of the BD-PRS is due to shared effects with SZ.
2. I conducted a principal components analysis (PCA) to obtain 2 orthogonal factors that described: i) shared variance (i.e. what is similar genetically) between the BD-PRS and SZ-PRS, and ii) non-shared variance (what is genetically different) between the two risk scores. From herein, the former will be referred to as the shared component and the latter as the difference component.
3. My final approach was to use summary statistics from the second PGC GWAS of SZ cases vs BD cases to generate a PRS to determine whether common genetic variants associated with increased risk of being a SZ case relative to a BD case were associated with cognition. From herein, this PRS will be referred to as the SZvsBD PRS.

As mentioned in Chapter 3, section 3.4.1, genetic variation is often associated with geographical and historical populations. However, the ALSPAC sample has been shown to be homogeneous with no significant population stratification, and genome-wide analyses of phenotypes indicate a low genomic inflation factor ($\lambda \approx 1$) (Zammit et al. 2014; Martin et al. 2015). Therefore, in my analyses, I have not adjusted for population stratification using PCA.

8.4 Results

8.4.1 Sample characteristics

From the 8,230 ALSAPC individuals whose genetic data passed quality control checks (51.2% male), between 6,555 to 7,405 participated in cognitive assessments at age 8 years. When I investigated the extent of correlation between cognitive tests, those assessed using the WISC-III were the most strongly correlated measures (correlations ranged between 0.25 and 0.89), with other cognitive domain measures showing weaker correlations (correlations ranged from 0.08 to 0.38) (see Table 33).

Table 33 Pearson correlations between cognitive tasks

	PIQ	VIQ	TIQ	PS	WM	PrS	EF	ATT	VL	ER
PIQ	1.00									
VIQ	0.50	1.00								
TIQ	0.84	0.89	1.00							
PS	0.44	0.28	0.44	1.00						
WM	0.41	0.70	0.65	0.31	1.00					
PrS	0.71	0.41	0.63	0.25	0.36	1.00				
EF	0.26	0.20	0.27	0.33	0.24	0.19	1.00			
ATT	0.27	0.15	0.24	0.34	0.16	0.21	0.25	1.00		
VL	0.23	0.38	0.36	0.12	0.41	0.21	0.13	0.08	1.00	
ER	0.19	0.17	0.21	0.14	0.14	0.10	0.14	0.11	0.17	1.00

TIQ: Total Intelligence Quotient; VIQ: Verbal Intelligence Quotient; PIQ: Performance Intelligence Quotient; PS: Processing Speed; WM: Working Memory; PrS: Problem Solving; EF: Executive Functioning; ATT: Attention; VL: Verbal Learning; ER: Emotion Recognition

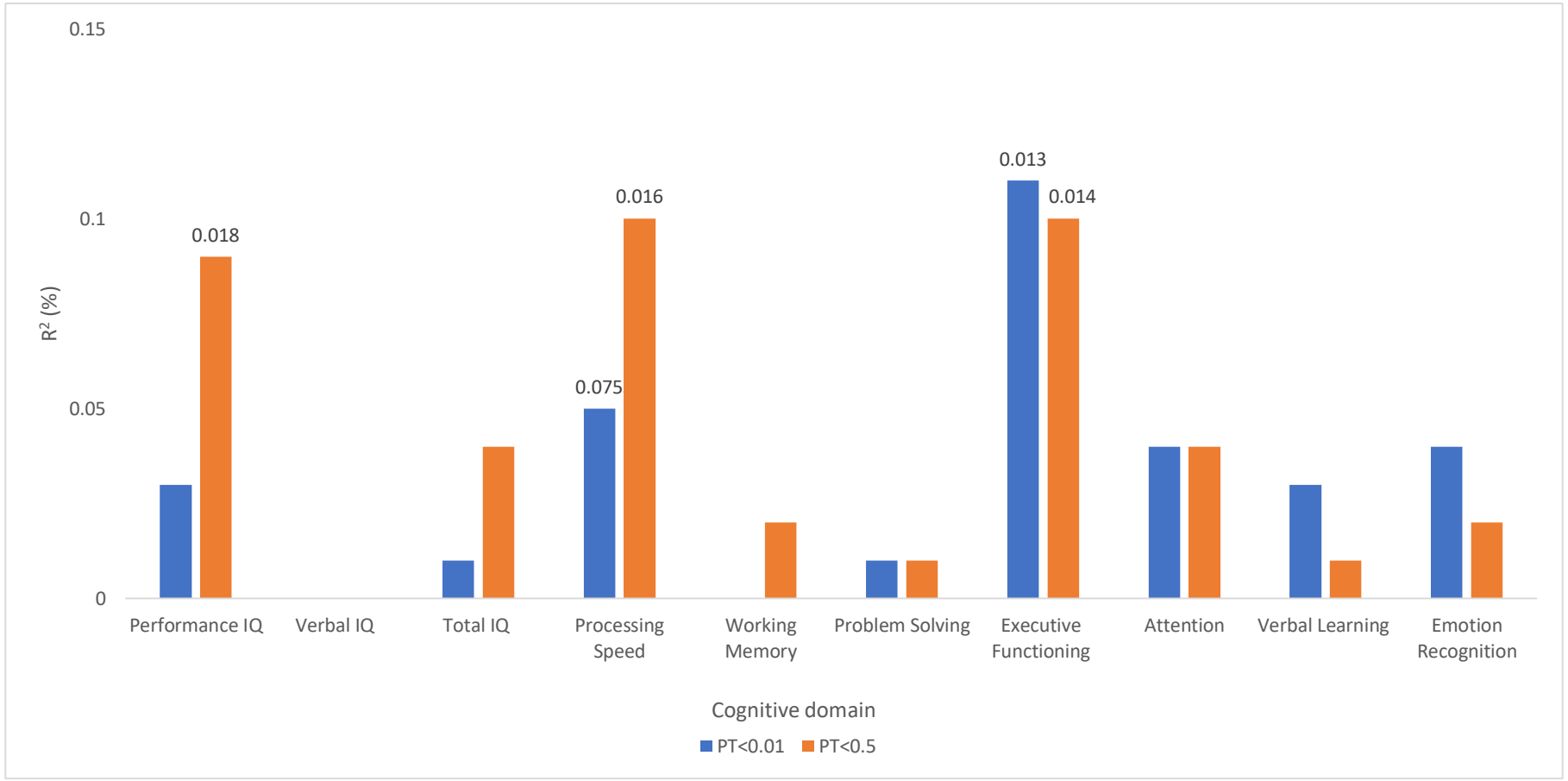
8.4.2 BD-PRS and cognitive functioning

Figure 7 shows the proportion of variance explained in cognition by the BD-PRS at both P_T's, though full results including individual effect sizes, confidence intervals and p-values can be found in Appendices 15 and 16, for $P_T \leq 0.01$ and $P_T \leq 0.5$ respectively.

At my primary P_T, there was evidence to suggest an association between the BD-PRS and poorer executive functioning (β = -0.03, 95%CI -0.06, -0.01; p = 0.013), and more weakly with poorer processing speed (ß = -0.02, 95%CI -0.05, 0.02; p = 0.075). There was little evidence to suggest association with other cognitive domains (all p >0.115).

Using my secondary P_T, I found evidence of association between increased genetic risk for BD and poorer executive functioning (β = -0.03, 95%CI -0.06, -0.01; p = 0.014), poorer Performance IQ (β = -0.03, 95%CI -0.06, -0.01; p = 0.018), and poorer processing speed (ß = -0.03, 95%CI -0.04, -0.01; p = 0.016), but little evidence of association to suggest the BD-PRS was associated with other cognitive domains examined (all p >0.115).

Figure 7 R^2 values for associations between the BD-PRS and cognitive domains



BD-PRS: Bipolar Disorder Polygenic Risk Score; P_T: P value threshold; IQ: Intelligence Quotient

8.4.3 Investigating possible non-linear relationships

I next investigated whether there was a non-linear relationship between genetic risk and cognitive domains, in which those at low and those at high compared to average genetic risk might have different cognitive functioning. Full results can be found in Appendix 17 for $P_T \leq 0.01$, and Appendix 18 for $P_T \leq 0.5$.

At both primary and secondary P_T's, I found weak evidence to support non-linear effects of genetic risk for domains of: Performance IQ (both p quadratic <0.065), Total IQ (both p quadratic <0.075) and executive functioning (both p quadratic <0.089), but not other cognitive domains examined (all p quadratic >0.229).

8.4.3.1 Tertiles of genetic risk and associations with cognitive outcomes

To further clarify the non-linear patterns of association identified, I derived tertiles of genetic risk for both primary (Appendix 19) and secondary (Appendix 20) P_T's. The pattern of association was such that those in the highest genetic risk tertile had the poorest cognition, whereas those in the lowest genetic risk tertile had cognitive scores similar to those in the middle genetic risk tertile.

8.4.4 Shared and non-shared effects of BD-PRS and SZ-PRS on cognition

To examine the extent to which associations between the BD-PRS and cognition are due to risk alleles shared (or independent) of those with schizophrenia risk, I used three approaches. These results are presented in Table 34 (approaches 1 and 3) and 35 (approach 2).

The first approach was to examine the association between the BD-PRS and cognition whilst adjusting for the SZ-PRS, and vice versa. In the unadjusted (univariable) models, associations between genetic risk for SZ and cognitive domains of performance IQ and processing speed were stronger than for the BD-PRS, whereas associations for executive function were stronger for the BD-PRS. After adjusting the BD-PRS for the SZ-PRS in the multivariable model, effect sizes for the association between the BD-PRS and performance IQ and

processing speed weakened substantially, though the association with executive function remained relatively unchanged.

Following the PCA of both risk scores (BD-PRS and SZ-PRS), I found strong evidence of association between the shared component and performance IQ (ß = -0.03, 95%CI -0.06, -0.01; p = 0.004) and processing speed (ß = -0.04, 95%CI -0.06, -0.01; p = 0.001). There was weaker evidence of association between the shared component and executive function (ß = -0.03, 95%CI -0.04, 0.00; p = 0.027), and little evidence of association between the difference component and these measures.

Finally, when I investigated associations using a risk score derived from SNPs that were more frequent in people with schizophrenia relative to those with BD, I found strong evidence of association between the SZvsBD PRS and performance IQ (ß= -0.03, 95%CI -0.06, -0.01; p=0.009), but little evidence of association with either processing speed or executive function (both p >0.499).

Table 34 Associations between genetic risk and cognitive measures when i) adjusting for the other (SZ-PRS or BD-PRS) risk score, and ii) using the SZvsBD PRS

Exposure	Outcome	N	ß unadjusted	95%CI	P	R^2	ß adjusted	95%CI	P	R^2
BD-PRS	PIQ	5,911	-0.03	-0.06, -0.01	0.018	0.09	-0.02[a]	-0.05, 0.01	0.146	0.22
SZ-PRS	PIQ	5,911	-0.04	-0.07, -0.02	0.001	0.19	-0.04[b]	-0.06, -0.01	0.006	0.22
BD-PRS	PS	5,935	-0.03	-0.06 -0.01	0.016	0.10	-0.02[a]	-0.05, 0.01	0.127	0.22
SZ-PRS	PS	5,936	-0.04	-0.07, -0.02	0.001	0.18	-0.04[b]	-0.06, -0.01	0.007	0.22
BD-PRS	EF	5,788	-0.03	-0.06, -0.01	0.013	0.11	-0.03[a]	-0.06, -0.00^	0.022	0.11
SZ-PRS	EF	5,788	-0.01	-0.04, 0.01	0.297	0.02	-0.01[b]	-0.03, 0.02	0.695	0.11
SZvsBD PRS	PIQ	5,911	-0.03	-0.06, -0.01	0.009	0.12				
SZvsBD PRS	PS	5,936	-0.01	-0.02, 0.12	0.499	0.01				
SZvsBD PRS	EF	5,788	-0.00[*]	-0.03, 0.03	0.919	0				

^rounded to 2 decimal places; Associations between genetic risk for BD and cognitive domains of PIQ and PS are reported at $P_T \leq 0.5$ and associations with EF are reported at $P_T \leq 0.01$; [a] adjusted for the SZ-PRS; [b] adjusted for the BD-PRS; BD-PRS: Bipolar Disorder-Polygenic Risk Score; SZ-PRS: Schizophrenia -Polygenic Risk Score; P_T: P-value threshold; IQ: Intelligence Quotient; CI: Confidence Intervals; P_T: P-value threshold; PIQ: Performance Intelligence Quotient; PS: Processing Speed; SZvsBD PRS: Schizophrenia vs Bipolar Disorder Polygenic Risk Score

Table 35 Association between the shared and difference principal components and cognitive measures

Exposure	Outcome	N	ß unadjusted	95%CI	P	R^2
Shared component	PIQ	5,911	-0.04	-0.06, -0.02	<0.001	0.21
Difference component			0.01	-0.02, 0.04	0.407	0.01
Shared component	PS	5,935	-0.04	-0.06, -0.02	<0.001	0.19
Difference component			0.01	-0.02, 0.04	0.456	0.01
Shared component	EF	5,788	-0.03	-0.05, -0.00[b]	0.027	0.08
Difference component			-0.02	0.05, 0.01	0.241	0.02

CI: Confidence Intervals; IQ: Intelligence Quotient; PIQ: Performance IQ; PS: Processing Speed; EF: Executive Functioning

8.4.5 Associations when using imputed data

For domains which showed the strongest evidence of association, I also examined the extent to which associations might be due to selection bias. There was little evidence to suggest selection bias was affecting the association between genetic risk and cognitive domains as effect sizes in the imputed data were identical to those observed in the complete data (see Appendix 21).

8.5 Discussion

8.5.1 Summary of findings

8.5.1.1 Associations between the BD-PRS and cognition

The first objective of this study was to examine associations between genetic risk for BD and cognitive functioning in healthy children from the general population.

I found consistent evidence that increased genetic risk for BD was associated with poorer executive functioning (for both primary and secondary P_T's). I found less consistent evidence of association between the BD-PRS and poorer Performance IQ and poorer processing speed, and little to no evidence to suggest associations between the BD-PRS and other cognitive measures at either P_T.

8.5.1.2 Modelling non-linear effects of genetic risk

The second objective of this study was to examine whether the relationship between genetic risk for BD and cognition is non-linear. I found that for domains of performance IQ, total IQ and executive functioning a non-linear effect was present. The pattern was such that the association between genetic risk and poorer performance in these domains is driven primarily by those at the higher end of the genetic risk spectrum. For all other cognitive domains, poorer performance was observed across the entire spectrum of genetic risk.

8.5.1.3 Shared and non-shared effects of BD-PRS and SZ-PRS on cognition

For the strongest associations, I examined the extent to which associations between genetic risk for BD and cognition were due to those alleles also shared with schizophrenia genetic risk. Associations between the BD-PRS and both performance IQ and processing speed seem to be driven primarily by the genetic component shared with schizophrenia risk, whereas those with executive functioning were primarily due to risk alleles that are BD specific.

8.5.2 Interpreting findings in the context of previous work

Epidemiological studies examining associations between cognition and BD suggest that cognitive deficits occur in a substantial proportion (40-60%) of adults with BD (Szmulewicz et al. 2015; Bora 2018). When comparing cognitive deficits in adults with BD to adults with SZ, they are qualitatively similar, i.e. cognitive domains affected are the same, but the severity is typically less in BD (Bortolato et al. 2015).

I found the BD-PRS was more strongly associated with impaired executive function than the SZ-PRS was, which remained even after adjusting for the SZ-PRS. The term executive functioning is often used as a general umbrella term that captures 3 core domains: response inhibition, interference control, and cognitive flexibility (Diamond 2013). Evidence from meta-analyses and systematic reviews show medium to large effect size deficits in executive functioning in both BD (Torres et al. 2007) and schizophrenia (Fioravanti et al. 2012) cases, as well as their first-degree relatives (Bortolato et al. 2015). The findings from the review describing executive functioning deficits in people with schizophrenia suggest deficits are mainly seen within the domain of cognitive flexibility, whereas the review of executive functioning deficits in those with BD described deficits across all 3 core domains. This may be of relevance as the opposite world's task that I used to assess executive functioning primarily assesses response inhibition, which might explain why I found stronger evidence of association with the BD-PRS than the SZ-PRS. Nevertheless, deficits in response inhibition have been described in people with schizophrenia (Ettinger et al. 2018).

My findings for IQ implicate effects of genetic risk for BD on fluid (performance IQ) but not crystalised intelligence (verbal IQ), a finding similar to that in healthy children from the general population at high genetic risk for SZ (Hubbard et al. 2016). Furthermore, my findings suggest genetic effects of BD on fluid intelligence are driven by risk SNPs shared between both the BD-PRS and SZ-PRS, i.e. the effects are by and large a result of risk SNPs shared with those of schizophrenia risk, with SNPs that are specific to schizophrenia also having an effect on this domain. This is consistent with the observation that adults with schizophrenia typically have greater IQ deficits compared to adults with BD (Bora and Ozerdem 2017b). There are however, instances where severity of IQ deficits in adults with BD are quantitatively more similar to adults with schizophrenia, and this is often linked to the presence of psychotic symptoms (Tsitsipa and Fountoulakis 2015; McCarthy et al. 2016). One study examined individuals with BD who had manic psychosis and reported that when compared to adults with BD and no history of psychosis, those with manic psychosis had higher SZ-PRS (Markota et al. 2018). My findings, alongside these studies suggest that both cognitive deficits and presence of psychotic phenomena in people with BD are illness severity indicators that are primarily driven by risk SNPs that are shared across BD and schizophrenia.

Interestingly, a previous study using the ALSPAC cohort reported that superior IQ was associated with reporting more hypomania symptoms assessed using the Hypomania Checklist-32 (HCL-32) (Smith et al. 2015). However, this finding does not appear to be consistent with the findings for BD genetic risk in this study in that I found that increased genetic risk is associated with poorer and not better IQ. In Chapter 5, my findings from modelling linear effects of cognitive performance on hypomania suggested that better performance was associated with higher HCL scores for domains of verbal learning, problem solving, working memory and more weakly with executive functioning. However, for some domains, a non-linear effect was detected and suggested that those with the poorest cognitive performance had the lowest HCL scores, whilst those with the highest cognitive scores had similar HCL scores to those with average cognitive ability. One possibility for these inconsistencies is that hypomanic features, as captured by measures such as the HCL-32 in community samples, do not

accurately index individuals with high propensity to develop full-blown or clinically severe BD.

I also found some weak evidence of association between the BD-PRS and poorer processing speed, which was stronger at my secondary P_T. However, when examining associations whilst adjusting for the SZ-PRS, these associations attenuated substantially. When examining the most affected cognitive domains in BD, processing speed is often reported as one of the most impaired domains, evidenced by large effect size from meta-analyses in adults with BD (Bora et al. 2009; Bora 2018), and similarly in young people at high familial risk of BD (Bora and Ozerdem 2017a). In the current study, I used data from children within the general population who are at high genetic risk for BD, and my findings suggest that such children do not appear to be as impaired in processing speed as they are in executive functioning.

To the best of my knowledge there has only been one other study which has investigated associations between a BD-PRS and social cognition in childhood. This study also used the ALSPAC sample but used the smaller PGC-1-BD GWAS to derive the PRS, and also found no evidence of association between the BD-PRS and emotion recognition (Coleman et al. 2017). Even though I used a larger and more powerful GWAS to derive the BD-PRS, I also found little evidence for such a relationship between genetic risk for BD and social cognition. Social cognition deficits are reported in the literature in adults with BD, however, these tend to be for Theory of Mind (Mitchell and Young 2016), whereas the measure of social cognition I used in the current study is emotion recognition.

It is possible that weaker evidence of deficits in processing speed, or indeed lack of deficits in some domains more generally might be due to developmental changes in cognitive processes (Kail 1991; Luna et al. 2004; Chronaki et al. 2015). Maturation of the brain can often be linked to the first phase of synaptic pruning, in which the brain removes additional weaker synapses, axons and dendrites (Chechik et al. 1998). This is a gradual process which begins at posterior (visual) regions of the brain and will work towards frontal areas over time. More complex functions such as response inhibition (executive

functioning), working memory, processing speed and attention would therefore be last to mature (in the late teens/early twenties) (Anderson et al. 2001; Luna et al. 2004).

8.5.3 Strengths and limitations

When interpreting the findings of this study, it is important to acknowledge the strengths as well as the weaknesses of the measures used, and the analyses conducted. Firstly, this is the first and largest study of its kind to examine how genetic risk for BD is manifest across a broad range of cognitive domains in healthy children in the general population, and to examine the extent to which these associations are due to shared or non-shared genetic effects with schizophrenia. Although I was able to examine multiple domains as identified as impaired in adults with BD in the MCCB, I was not able to examine visual learning given there was no comparable measure in the ALSPAC cohort. Nevertheless, these tests of neurocognitive ability are well validated which reduces information bias.

Second, by using the largest and most up-to-date GWAS for BD (Stahl et al. 2019), SZ (Ripke et al. 2014) and BDvsSZ (Ruderfer et al. 2018), I have maximized power and minimized measurement error in the PRS. Nevertheless, even though I used the largest BD GWAS to date to derive the BD-PRS, the PRS still only explains a small proportion of variance in BD, and lack of evidence of association reported for some cognitive measures might result from my analyses being under-powered to detect smaller effect sizes. By using PRS in my analyses means my findings only reflect common variant influences on childhood neurocognitive outcomes rather than the effects of all genetic risk. A recent study has provided some evidence that the role of Copy Number Variants (CNVs) may be limited to the schizoaffective bipolar type, rather than treating BD as a single diagnostic entity (Charney et al. 2019).

Third, by using a well characterized general population-based sample for analyzing neurocognitive phenotypes at an early age, well before onset of BD, this means I can be confident the associations are not biased by presence of

cognitive deficits arising as a result of BD (reverse causation) or treatment effects.

Fourth, ALSPAC has a large degree of attrition which might have led to selection bias. Previous studies using the ALSPAC sample have shown that increased genetic risk for schizophrenia is associated with non-participation by both mothers and children in the ALSPAC sample (Martin et al. 2016), and that lower cognitive ability is also associated with higher levels of attrition (Boyd et al. 2013). However, the findings in this chapter suggest that for my most strongly associated measures, selection bias made no difference to the effect sizes observed in the imputed data. Though imputation was performed, there is still the possibility that selection bias could still be present.

Fifth, in total, there were a number of cognitive domain outcomes examined which could lead to an increase in type I error. The cognitive domains examined were selected *a priori* based on prior literature, however the strength of evidence of the associations reported should be interpreted in the context of the study limitations, including the testing of multiple cognitive outcomes. Therefore, a replication of these findings in other large population-based samples is required.

Sixth, there is no data on whether parents of the children had BD, however, given the low lifetime risk of bipolar disorder (1-2%) (Merikangas et al. 2011), it seems unlikely that this would have had any significant impact on my results.

As with previous my previous chapters, testing multiple exposure-outcome relationships may increase the possibility of findings being due to chance. Therefore, exposure and outcome measures were determined *a priori* in accordance with the literature to minimize this. Results are thus discussed based on the strength of evidence from statistical testing (rather than based on an arbitrary cut-off) within the context of this (and other) study limitations.

8.5.4 Implications

As highlighted in section 8.5.2, the severity of deficits for performance IQ and processing speed are similar to those observed in healthy children from the general population at high genetic risk for schizophrenia (Hubbard et al. 2016). The evidence reported in this chapter of cognitive deficits in genetically higher risk for BD children from the general population supports other evidence suggesting that BD, like schizophrenia, should also be considered as being on the neurodevelopmental spectrum (Fioravanti et al. 2012). This is predominantly for more severe forms of BD characterized by psychotic symptoms in childhood (Arango et al. 2014).

Overall, my findings are more consistent with epidemiological studies that suggest an increased risk of BD in those with lower cognitive ability in childhood (Meyer et al. 2004; Sharma et al. 2017) than studies reporting increased BD risk in those with higher cognitive ability (MacCabe et al. 2010; Gale et al. 2013). A recent study examined risk alleles for BD, schizophrenia and intelligence with the findings suggesting that for BD, most risk alleles (9 of 12) were associated with better cognition, though 4 of the 12 risk alleles were associated with poorer cognition. This was in comparison to 61 of 75 SZ risk alleles being associated with poorer cognition (Smeland et al. 2019). This might lead to low levels of genetic correlation between BD and cognition and hence less consistent evidence of association between BD genetic risk and cognition compared to schizophrenia genetic risk, as well as less consistent evidence of association between childhood cognition and BD compared to that for schizophrenia.

8.5.5 Conclusions

Within this study of healthy children from the ALSPAC prospective population-based birth cohort, I found associations between the BD-PRS and poorer executive functioning, performance IQ and processing speed, but less consistent evidence of association with other cognitive domains. My results for performance IQ and processing speed suggest that these associations appear to be driven primarily by the genetic component shared between BD and schizophrenia, whereas those for executive functioning appear to be more

strongly driven by BD specific alleles. As executive functioning deficits are common in individuals with SZ this finding might be a consequence of the executive functioning domain (response inhibition) examined in this study.

Further work using both population-based longitudinal studies and clinical samples are required to determine the cognitive profiles of those at high genetic risk of BD, to inform studies of prediction, improve detection, and facilitate early intervention where appropriate.

The next and final chapter, Chapter 9 will be the general discussion chapter.

Chapter 9: General Discussion

This chapter will bring together the findings of this thesis and discuss their implications, the strengths and limitations of the measures, study sample and analytical methods used, and will conclude with possible directions for future research in this area.

9.1 Overview

Bipolar Disorder (BD) is a lifelong mood disorder affecting both the individual and impacting on society. Its aetiology is complex and not well understood, though a combination of genetic and environmental factors ultimately determines whether an individual will go on to develop the disorder.

Studying high-risk individuals, for example offspring of BD parents or those with higher polygenic risk, longitudinally, allows you to determine the temporal relationship between psychopathology and disorder. However, there is limited research investigating associations between measures of psychopathology/cognitive functioning and hypomania in general population samples.

This thesis set out to investigate which measures of psychopathology and cognitive functioning are associated with hypomania, defined both categorically and dimensionally in children from the general population. It also sought to determine whether children at increased genetic risk for BD had greater levels of psychopathology and/or altered cognitive functioning compared to those with lower genetic risk for BD.

To address these aims, I used the longitudinal birth cohort study the Avon Longitudinal Study of Parent And Children (ALSPAC).

In Chapter 4 I examined whether measures of attention deficit hyperactivity disorder (ADHD), borderline personality disorder (BPD) traits, depression score and emotional/behavioural difficulties were associated with measures of

hypomania assessed using the Hypomania Checklist (HCL). The results from these analyses highlighted that irrespective of how hypomania was defined, a BPD traits score was consistently associated, and that these associations were not explained by confounding or selection bias.

In Chapter 5 I examined whether cognitive functioning in childhood was associated with hypomania, and whether there was a non-linear relationship. Better performance on cognitive domains of working memory, problem solving ability, verbal learning, executive functioning and emotion recognition was associated with a higher HCL score. There was also evidence of non-linear effects of cognitive functioning on the HCL score for processing speed and working memory, and weaker evidence for attention and verbal learning. The evidence suggested that those with the poorest compared to average cognitive functioning on these domains had lower HCL scores.

Chapter 6 investigated the current understanding around the phenotypic manifestations of increased genetic risk for BD when using the polygenic risk score (PRS) approach. Overall, the results highlighted that genetic risk for BD is associated with a broad range of phenotypes, though the greatest proportion of the variance explained by the BD-PRS was for psychiatric disorders such as schizophrenia and depression. Nevertheless, with the possible exception of one study that reported the variance explained in schizophrenia by the BD-PRS to be 23% and was a clear outlier, variance explained for other phenotypes was typically less than 2%. I also found that there was a sparse literature on studies using the PRS approach to investigate associations with childhood phenotypes in any population.

Chapter 7 built on the findings of Chapters 4 and 6. I investigated whether higher genetic risk for BD was associated with a broad range of psychopathology measures from childhood into early adulthood. My findings suggest that the BD-PRS was strongly associated with ADHD, and more specifically the inattentive rather than hyperactive-impulsive or combined subtypes. Furthermore, whilst there was little evidence of association between the BD-PRS and HCL score/HCL factors, there was some evidence that it was associated with clinically-defined hypomania.

Finally, Chapter 8 investigated whether increased genetic risk for BD was associated with cognitive functioning in childhood, with cognitive domains being those examined in Chapter 5. The results suggested that the BD-PRS was associated with impaired executive functioning, and less so with poorer performance IQ and processing speed. When examining the extent to which these associations were due to risk SNPs shared or distinct from those with schizophrenia, I found that associations with performance IQ and processing speed were largely due to genetic effects shared with that for schizophrenia risk, but those for executive functioning appear to be due to bipolar specific genetic effects i.e. SNPs not shared with schizophrenia genetic risk.

9.2 Bringing findings together

Rather than detail the interpretations of each of the findings, which are already discussed in previous chapters, this next section will focus on bringing together the findings across chapters and briefly outline what this might mean. I found the strongest associations between measures of psychopathology and hypomania were for BPD traits. Given evidence from studies examining Axis II comorbidities with BD (Friborg et al. 2014; Bezerra et al. 2015), it is possible that presence of BPD traits in childhood might reflect an early manifestation of eventual BD. However, when examining associations between the BD-PRS and BPD traits, there was little evidence of an association. This suggests that presence of BPD traits in childhood is not a consequence of high genetic risk for BD, and that the association between the BPD traits score and hypomania in Chapter 4 is also unlikely confounded by shared genetic effects. It is more likely that the presence of other risk factors, and most likely childhood trauma (McDermid et al. 2015) such as emotional/physical abuse (Porter et al. 2020) has a greater role than genetic risk for BD in determining the expression of these BPD traits in childhood. As the association between BPD traits and hypomania were hardly attenuated when I adjusted for confounders, including bullying in childhood, the most likely explanation for my findings is that childhood trauma (or other risk factors) lead to BPD traits which then lead to an increased risk of developing BD. It is possible that presence of BPD traits might lead someone to misuse substances to deal with how they are feeling (Trull et

al. 2018) which in turn might lead to further increasing risk of developing BD earlier (Leite et al. 2015).

Most psychopathology measures examined were associated with the 'risk-taking/irritable' but not 'active-elated' factor. This suggests that at a young age, prior to onset of clinically relevant symptoms, presence of psychopathology is more closely related to "dark-side" than "sunny-side" features (Hantouche et al. 2003) i.e. presence of psychopathology is more closely aligned to the negative aspects of hypomania rather than the positive aspects.

However, when examining associations between cognitive domains and the factor structure of hypomania, associations were with the 'active-elated' factor but not the 'risk-taking/irritable' factor. This suggests that whilst psychopathology may reflect the negative aspects of hypomania, cognitive functioning appears to be more closely aligned to the positive aspects of hypomania. Taken together, this suggests that the aetiology of both positive and negative aspects of hypomania may be driven by different mechanisms; better cognition and psychopathology respectively.

Associations between cognitive functioning and hypomania indicated that those who had better cognitive functioning had higher HCL scores. However, where evidence of a non-linear effect was detected, this appeared that this was driven primarily by those with the poorest cognitive ability having the lowest HCL scores i.e. that those with average and above average cognitive function had similar (higher) HCL scores than those with poorer cognitive function. When examining associations between genetic risk for BD and cognitive functioning, associations were with poorer cognitive functioning, driven by those who have the highest genetic risk compared to average genetic risk. Therefore, there seems to be some inconsistency in my findings i.e. poorer cognitive ability was associated with lower HCL scores, but higher genetic risk for BD was associated with poorer cognition and more weakly with clinically-defined hypomania which is difficult to explain. One possibility for this inconsistency is that hypomania captured using the HCL in general population samples does not accurately index individuals with a high propensity to develop BD.

When examining the manifestations of genetic risk for BD I found that the strongest evidence was for childhood cognitive ability, and not for hypomania as I would have expected. One reason why genetic risk for BD might be more weakly associated with clinically-defined hypomania than with a diagnosis of BD, as discussed in Chapter 7, is that hypomania might exist as an extended phenotype in the population, and although those with higher genetic risk for BD may report more HCL symptoms, other non-genetic factors might have a greater influence on these symptoms which "dampens down" this association. This suggests that hypomania as assessed using the HCL might be less heritable than both BD and cognitive functioning hence the BD-PRS explaining less of the variance in hypomania than for BD or cognitive functioning.

Associations were also strong between genetic risk for BD and ADHD, but not other measures of psychopathology. This is somewhat surprising given there was little evidence of association between ADHD and the HCL with the possible exception of the 'risk-taking/irritable' factor. However, there is uncertainty as to whether ADHD is a reliable future predictor of BD in cohort studies of high-risk offspring of BD parents (Duffy 2012).

Evidence of impairments in domains of performance IQ and processing speed appeared to be driven by risk SNPs shared between the BD-PRS and SZ-PRS. This might reflect a subgroup of individuals whose developmental trajectory is more similar to that seen in schizophrenia than pure BD; for example they may be more likely to experience psychotic symptoms or go on to develop a schizoaffective (bipolar subtype) disorder (Arango et al. 2014).

Overall therefore, my findings suggest that there is little evidence that genetic risk for BD is manifest in childhood, with the possible exception for poorer cognitive ability and possibly inattentive ADHD. However, there is strong evidence that a range of childhood psychopathology measures, particularly BPD traits is associated with future risk of hypomania.

9.3 Strengths and Limitations

The work presented in this thesis has a number of strengths and limitations which have been discussed at length in Chapters 4-8. For the strengths and limitations of individual measures, please see the respective chapters. This next section will summarise the strengths and limitations of the study sample, measures used and the analyses.

9.3.1 Study sample

The ALSPAC sample is one of the most comprehensive prospective birth cohort studies of its kind. The long duration of follow-up and availability of genotype data and extensive amounts of phenotypic data collected both prior to birth and currently ongoing represent strengths of this sample (Boyd et al. 2013; Fraser et al. 2013). One limitation of the ALSPAC sample is that the majority of participants recruited are of White ethnicity and it is therefore not clear if my findings will extend to other ethnic groups (Martin et al. 2017; Kim et al. 2018). Conversely, this homogeneity is also an advantage as it means that population stratification is unlikely to be biasing my genetic results. The main limitation however, as with most longitudinal studies, is that attrition has occurred which might introduce selection bias. When compared to the rest of the ALSPAC sample (those with no data on the HCL), the study sample had higher maternal social class, older mothers, a smaller proportion of mothers with depression and a higher proportion of mothers who were educated to degree level or above (see Table 5, Chapter 4). To address the issue of selection bias due to missing data, I used multiple imputation by chained approach as outlined in Chapter 3, section 3.6.1.4. Having investigated the impact of selection bias, my findings suggest that with the possible exception for ADHD, selection bias had little impact on the associations observed in the imputed data and did not drastically alter the interpretation of the findings.

9.3.2 Measures used

Measures of psychopathology and cognitive functioning were all examined using well validated measures which means I can be confident that the measures these tests report to assess are being assessed. Nevertheless, it is

unlikely these measures perfectly capture psychopathological or cognitive domains without error, which could bias my findings.

Assessments of psychopathology and cognitive functioning were conducted between ages 7-11, long before the likely development of hypomania. This therefore reduces the likelihood of associations between measures of psychopathology/cognitive functioning and hypomania being a result of reverse causality i.e. presence of hypomania causing psychopathology/changes in cognitive functioning.

The cognitive domains I examined were selected *a priori* based on their resemblance to the domains examined using the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Battery (MCCB). However, the domains examined by the MCCB reflect those most affected in individuals with schizophrenia. It is possible therefore that I am underestimating the association between genetic risk for BD and some cognitive sub-domains as a result of the tasks I used not adequately capturing the domains most affected in BD. I was also not able to examine the cognitive domain of visual learning as there was no comparable measure in the ALSPAC sample. A previous systematic review of studies using the MCCB reported deficits in visual learning of large effect size in those with BD compared to controls (Bo et al. 2017).

For my genetic analyses (Chapters 7 and 8), I used the largest and most up-to-date GWASs for BD (Stahl et al. 2019), schizophrenia (Ripke et al. 2014) and SZvsBD (Ruderfer et al. 2018) which provides the greatest statistical power and predictive accuracy for the phenotypes of interest. As has been shown through simulations, increasing the sample size of the discovery/target dataset does produce greater predictive accuracy (Dudbridge 2013,2016). Therefore, further increases in sample size may help to support or provide evidence against the associations reported in this thesis.

9.3.3 Analyses

Throughout this thesis, I have tried to adopt a thorough analytical strategy. I have investigated the assumptions of the statistical methods I used, and in

doing so can be more confident that my findings are accurate. I also investigated the possibility of non-linear effects of cognitive functioning on hypomania, and also non-linear effects of genetic risk on cognitive functioning to make sure that it was possible to determine whether associations between cognitive functioning and hypomania or genetic risk for BD and cognitive functioning was present across the entire spectrum of cognitive functions/genetic risk or confined to those with values in the extremities.

For analyses in Chapters 4 and 5, I adjusted my analyses for a range of sociodemographic and environmental confounders to reduce the likelihood of my findings being a result of confounding, and therefore strengthen inferences of causality. Though I adjusted for a range of potential confounders, there may well be some residual confounding which was not accounted for.

In Chapters 4, 5, 7 and 8, I tested associations between multiple independent phenotypes and various outcome measures. I did not correct for multiple testing in my analyses as the measures were determined *a priori* based on the literature. Furthermore, adjustment for multiple testing is built upon the foundation that a p-value threshold of 0.05 has a clear interpretation. Therefore, throughout my analyses, I have provided effect sizes and confidence intervals and not just p-values, and taken care to word my findings in terms of the strength of evidence of association rather than relating them to arbitrary thresholds for ‘significance’, so that the reader can interpret my findings appropriately (Sterne and Smith 2001; Wasserstein and Lazar 2016). However, as discussed in previous chapters, where weaker evidence of association is reported, this may well be due to chance, particularly in the context of testing multiple outcomes. Independent replication of these associations is therefore needed.

For my systematic review in Chapter 6, I followed PRISMA guidelines for reporting the findings in systematic reviews. In doing so, I was able to provide a comprehensive view of what the phenotypic manifestations of increased genetic risk for BD might be in different populations. However meta-analysis was not possible which meant I could not test for presence of publication bias. Presence

of publication bias might mean information on phenotypes not associated with increased genetic risk for BD will not have been captured.

9.4 Implications of my findings

The findings in this thesis may have some implications for research and perhaps also clinically too, as highlighted in this next section.

From my analyses in Chapter 4, there was consistent evidence that BPD traits were strongly associated with hypomania irrespective of how this was defined, and most measures of psychopathology were associated with the 'risk-taking/irritable' factor. One possible research implication is that studying factor structure of hypomania in different populations might be more useful for understanding aetiological mechanisms underlying BD than examining hypomania as a single construct, particularly as associations with most psychopathology measures were often observed with the 'risk-taking/irritable' factor but not with the total HCL score.

One potential clinical implication of these findings is that whilst a number of individual BPD traits were strongly associated with the HCL score, fear of abandonment was not. Therefore, the presence or absence of this trait might turn out to be a useful discriminator for clinicians to use when they are unsure as to whether someone has BPD or BD, or where children/adolescents show signs of BPD traits but have a family history of BD. A second potential clinical implication of the findings is that if clinicians are aware of a positive family history of BD, children presenting with presence of psychopathology such as BPD traits, ADHD and a range of behavioural difficulties are likely at higher risk of developing BD compared to those children presenting with no family history of BD.

In Chapter 5, I found that better cognitive performance on specific domains rather than globally was associated with higher HCL score, and that some relationships were non-linear. Whilst a larger body of research exists examining associations between IQ and subsequent BD (Zammit et al. 2004; Mortensen et al. 2005; MacCabe et al. 2010; Gale et al. 2013), the findings in this thesis

highlight that studying specific cognitive domains that extend beyond simply IQ might be important to further increase understanding of the aetiology and prediction of BD.

From Chapter 6, it is clear that researchers have not generally reported results from genetic-phenotypic association studies in a way that would allow a meta-analysis to be conducted or results across studies to be compared. From a research perspective, use of the framework I suggested (Mistry et al. 2018b) and Table 23 might improve reporting and perhaps stronger evidence of associations may arise from this. It was also clear that there are few studies which have investigated associations between the BD-PRS and childhood/adolescent phenotypes and therefore this might stimulate/encourage other research groups to investigate these associations.

My findings from Chapter 7 suggest that overall there is little evidence that genetic risk for BD is manifest in childhood and therefore an implication for research might be to examine manifestations of increased genetic risk for BD at a later time point. It might also suggest that genetic risk for BD doesn't manifest until onset of (or very close to onset of) clinical symptoms.

A further research implication is that the weak evidence of association between the BD-PRS and hypomania outcomes calls into question the usefulness of the HCL in identifying individuals from the general population who have hypomania or are at higher risk of developing BD (see Chapter 7 section 7.5.2.1) (Lee et al. 2016). Therefore, more studies, particularly using general population samples are required to determine this, particularly as there are few studies that have used the HCL in a general population sample.

My findings in Chapter 7 are inconsistent with studies of high-risk offspring of BD parents and suggest that the presence of psychopathology in high-risk offspring might be more likely to be due to the family environment arising from parental psychopathology rather than the child's own genetic risk per se. Therefore, a potential clinical implication might be to offer more support to parents with BD, particularly as evidence from high-risk offspring studies have

shown that longer duration of exposure to parental BD illness is associated with increased risk of psychopathology in the offspring (Goodday et al. 2018).

In Chapter 8, my findings were that increased genetic risk for BD was associated, in a non-linear pattern, with poorer cognitive functioning in specific domains. Therefore, one research implication of these findings is that it might be important to determine whether the effect of genetic risk on phenotypes exists across the entire spectrum of genetic risk, or is confined to those at the extremities. Another potential research implication is that it might be possible to identify specific phenotypes that result from increased genetic risk for BD independent of (i.e. not due to shared effects with) schizophrenia genetic risk, which could help with prediction. The findings from this chapter also highlight that where cognitive difficulties are detected during childhood, it might be important to closely monitor children if they have a parent with BD to improve early detection and provide further support mechanisms if required.

Although I have provided some potential clinical implications of my findings, there are a number of disadvantages to screening and monitoring which are: i) it can lead to worrying parents/children unnecessarily and ii) there can be substantial cost and difficulties in the practicality of using these tools. Thus, for screening to be justified, the following would be required: i) there should be robust evidence that it can usefully predict something in the future e.g. disorder, ii) there should be something that can then be done about it i.e. there might be little point in telling someone they are at high risk for something if there is not something that can be offered to them to reduce the risk, and iii) it should be cost-efficient and practically feasible for it to happen.

9.5 Future research

The work in this PhD highlights the need for future studies to further investigate whether measures of psychopathology/cognition during childhood in general population samples have causal effects on BD, how any such effects are mediated, and whether these measures could help predict who is most likely to develop this disorder.

Ideally, well-characterised general population cohort studies are required to further understanding of these questions which should account for known confounders in the relationship between exposure and outcome. This should then increase the likelihood of being able to draw causal inferences between given exposure and outcome measures. However, as BD is an uncommon outcome this will undoubtedly prove difficult given the costs and time required to recruit large enough samples to be followed up for adequate periods of time. Whilst using self-report measures such as the HCL may help to capture the entire spectrum of (hypo)manic experiences and is likely more common in the general population than BD, it is not yet clear as to how valid a measure the HCL is in general population samples at measuring BD pathology. Therefore, future studies may wish to investigate the ability of the HCL to distinguish true BD cases from controls drawn from the general population, given that community rates may be as high as 5-10% (Mistry et al. 2019; Richards et al. 2019). As a screening tool, it has been well validated in clinical samples internationally. However, there are few studies which have examined its use in general population samples, and the one study where they did showed good sensitivity (0.82) but poor specificity (0.36) (Lee et al. 2016). Therefore, more studies are required to determine whether its use in general population samples can be justified, as its psychometric properties are not nearly as good when compared to use in clinical samples (see Meyer et al. (2014)) for a review on its psychometric properties.

Further studies are also needed to increase our understanding of how genetic risk for BD is manifest during childhood/adolescence. In fact, since the end date of the search of the systematic review described in Chapter 6, which has now been published (Mistry et al. 2018a), there have been a number of additional studies that have investigated associations between a BD-PRS and a variety phenotypes. These studies have reported associations between a BD-PRS and i) substance use/addiction (Reginsson et al. 2017; Polimanti et al. 2018a), ii) exposure to increased number of hours of daylight (Polimanti et al. 2018b), iii) higher scores of self-reported tiredness (Deary et al. 2017), iv) fewer days in a relationship (Hjorthoj et al. 2019), v) reduced odds of gambling, and more weakly with disordered gambling (Piasecki et al. 2019) and vi) a lower BD-PRS

was associated with reporting more severe childhood maltreatment (Aas et al. 2020).

Other studies have reported little or inconsistent evidence of association between the BD-PRS and i) telomere length (Palmos et al. 2018), ii) loneliness (Abdellaoui et al. 2018), iii) theory of mind in adolescence (Warrier and Baron-Cohen 2018), iv) childhood internalising and externalising symptoms (Jansen et al. 2018), v) emotion recognition (Coleman et al. 2017), vi) cognitive executive functioning (Benca et al. 2017), vii) sleep preference (being a night owl vs being an early bird) (Melroy-Greif et al. 2017), viii) frequency of mood episodes (Smedler et al. 2019), ix) female reproductive health during adulthood (Ni et al. 2019), x) age of onset of BD (either when treated as a continuous or binary (<18 years vs >18 years) outcome) (Kalman et al. 2019), xi) a range of cardiometabolic traits (So et al. 2019), xii) lower scores on the Mood Disorder Questionnaire (either self-rated or parent-rated) assessed at age 18 years (Taylor et al. 2019) and xiii) a range of potential cognitive endophenotypes (Ranlund et al. 2018). At present however, it is not known which of these findings are robust.

As highlighted in Chapter 1 of this thesis, there are also a range of environmental risk factors for BD, though investigations into these effects pale in comparison to a much larger literature for schizophrenia (see Marangoni et al. (2018) for a review of these). Associations between childhood abuse/maltreatment have gained more interest in recent years. However, as highlighted in a systematic review and meta-analysis, 19 studies examining the associations between childhood abuse and BD were retrospective in design. Nevertheless, those with BD are fourfold more likely than those with no psychiatric illness to have experienced emotional abuse. Therefore, clinicians when faced with new patients exhibiting symptoms of BD may wish to consider enquiring about past abusive experiences and documenting the types of abuse e.g. physical, emotional etc. It will be difficult to establish causal links between abuse and BD, particularly as childhood abuse is also more frequently reported in those with depression and SZ compared to those with no history of psychiatric illness (Palmier-Claus et al. 2016). However, given that different

types of abuse may confer differences in BD risk, it will be important to investigate this further.

As mentioned throughout this thesis, chip type is being increasingly used as a covariate in analyses concerning PRS and future research should aim to include this in the analysis where possible (Choi et al. 2018). Studies may also begin to tease apart disorder specific effects of genetic risk on phenotype by using methods such as those described and conducted in Chapter 8 of this thesis. An often heard term in psychiatric research is to identify endophenotypes, and running these types of analyses may help to satisfy some of the proposed criteria as outlined by Gottesman and Gould (Gottesman and Gould 2003). Alternatively, as conducted by Hamshere and colleagues, for the SZ-PRS, they derived refined SZ-PRSs based on whether the direction of effect of risk alleles was the same or different between the BD and SZ GWAS (Hamshere et al. 2013).

Overall, it is evident that there are still relatively few studies which are taking advantage of the PRS approach and investigating possible phenotypic manifestations of increased genetic risk for BD in childhood/adolescence. Furthermore, of the more recent studies mentioned in this section (section 9.5), few have used the 2nd PGC BD GWAS to derive the PRS.. Even in those that have done so, the proportion of variance explained in these phenotypes by the BD-PRS is small (<3%). This could indicate one of two possibilities: i) either discovery and/or target sample sizes need to increase substantially to increase the proportion of variance explained in these phenotypes, or ii) the PRS approach may not be useful in identifying early phenotypic signs of BD pathology in individuals who are at higher genetic risk of developing BD.

9.6 Concluding remarks

BD is a complex multifactorial disease and a clear understanding of its aetiology remains lacking. Within this thesis, I examined whether a broad range of psychopathologies and cognitive domains were associated with dimensional and categorical measures of hypomania in the general population. I also sought to summarise the published literature describing the phenotypic manifestations

of increased genetic liability for BD, and examined the extent to which increased genetic risk for BD was associated with psychopathology and cognitive measures in childhood.

Overall my results suggest that different aspects of hypomania may be expressed as specific cognitive domains and psychopathology examined in childhood/adolescence. My results also suggest that there is little evidence that genetic risk for BD is manifest in childhood/adolescence, with the possible exception of poorer cognitive functioning, particularly executive functioning, and possibly inattentive ADHD.

Appendices

Appendix 1 Structure of the full Hypomania Checklist-32 (HCL-32) questionnaire

At different times in their life everyone experiences changes or swings in energy, activity and mood ("highs and lows" or "ups and down"). The aim of this questionnaire is to assess the characteristics of the "high" periods.

1. First of all, how are you feeling today compared to your usual state:

Much worse than usual	Worse than usual	A little worse than usual	Neither better nor worse than usual	A little better than usual	Better than usual	Much better than usual

2. How are you usually compared to other people?

Independently of how you feel today, please tell us how you are normally compared to other people, by marking which of the following statements describes you best?

Compared to other people my level of activity, energy and mood…

Is always rather stable and even	Is generally higher	Is generally lower	Repeatedly shows periods of ups and downs

Appendix 1 continued

3. Please try to remember a period when you were in a "high" state. In such a state:

Question	Yes	No
Please try to remember a period of time when you were in a "high" state. In such a state:		
1. I need less sleep		
2. I feel more energetic and more active		
3. I am more self-confident		
4. I enjoy my work more		
5. I am more sociable (make more phone calls, go out more		
6. I want to travel and/or do travel more		
7. I tend to drive faster or take more risks when driving		
8. I spend more money/too much money		
9. I take more risks in my daily life (in my work and/or other activities)		
10. I am physically more active (sports etc)		
11. I plan more activities or projects		
12. I have more ideas, I am more creative		
13. I am less shy or inhibited		
14. I wear more colourful and more extravagant clothes/make up		
15. I want to meet or do actually meet more people		
16. I am more interested in sex		
17. I am more flirtatious and/or am more sexually active		
18. I talk more		
19. I think faster		
20. I make more jokes or puns when I am talking		
21. I am more easily distracted		
22. I engage in lots of new things		
23. My thoughts jump from topic to topic		
24. I do things more quickly and/or more easily		
25. I am more impatient and/or irritable more easily		
26. I can be exhausting or irritating for others		
27. I get into more quarrels		
28. My mood is higher, more optimistic		
29. I drink more coffee		
30. I smoke more cigarettes		
31. I drink more alcohol		
32. I take more drugs (sedatives, anxiolytics, stimulants)		

If you have never experienced a "high" please stop here

4. Impact of your "highs" on various aspects of your life:

	Positive and negative	Positive	Negative	No impact
Family life				
Social life				
Work				
Leisure				

Appendix 1 continued

5. How did people close to you react to or comment on your “highs?”

Positively (encouraging or supportive	Neutral	Negatively concerned, annoyed, irritated, critical	Positively and negatively	No reactions

6. Lengths of your “highs” as a rule (on average)

1 day	
2-3 days	
4-7 days	
Longer than 1 week	
Longer than 1 month	
I can’t judge/don’t know	

7. Have you experienced such “highs” in the past twelve months?

Yes	No

8. If yes, please estimate how many days you spend in “highs” during the last twelve months:

Taken all together: about _____ days

Appendix 2 Association between BPD exposures and clinically-defined hypomania at varying threshold cut off scores on the HCL

Exposure	Outcome	N	OR	95% CI	P
High-risk for BPD	HCL score ≥16/28	2,543	3.72	2.25, 6.16	<0.001
BPD traits score			1.36	1.19, 1.55	<0.001
High-risk for BPD	HCL score ≥18/28		3.40	1.91, 6.05	<0.001
BPD traits score			1.32	1.13, 1.54	<0.001
High-risk for BPD	HCL score ≥20/28		4.54	2.42, 8.50	<0.001
BPD traits score			1.41	1.19, 1.67	<0.001
High-risk for BPD	HCL score ≥20/28		5.00	2.36, 10.58	<0.001
BPD traits score			1.50	1.23, 1.84	<0.001
High-risk for BPD	HCL score ≥20/28		3.39	1.16, 9.91	0.026
BPD traits score			1.43	1.10, 1.87	0.008

BPD: Borderline Personality Disorder; HCL: Hypomania Checklist; OR: Odds Ratio; CI: Confidence Intervals

Appendix 3 Association between individual BPD traits and a) the HCL score and b) clinically-defined hypomania

Exposure	N (%[a])	β	95%CI	P value
Anger	2,542 (22.5%)	0.13	0.06, 0.19	<0.001
Affective instability	2,540 (19.8%)	0.15	0.08, 0.23	<0.001
Emptiness	2,539 (7.72%)	0.13	0.02, 0.24	0.020
Identity disturbance	2,538 (8.07%)	0.23	0.12, 0.34	<0.001
Paranoid ideation	2,534 (11.9%)	0.17	0.07, 0.26	<0.001
Fear of abandonment	2,534 (7.1%)	0.02	-0.10, 0.15	0.737
Suicidal behaviour	2,529 (3.8%)	0.13	-0.01, 0.27	0.064
Impulsivity	2,530 (18.2%)	0.07	0.01, 0.13	0.016
Intense interpersonal relationships	2,530 (12.9%)	0.16	0.07, 0.25	0.001
Exposure	**N (%[a])**	**OR**	**95%CI**	**P value**
Anger	2,542 (22.5%)	1.19	0.92, 1.53	0.178
Affective instability	2,540 (19.8%)	1.45	1.14, 1.86	0.003
Emptiness	2,539 (7.72%)	2.00	1.48, 2.69	<0.001
Identity disturbance	2,538 (8.07%)	1.71	1.24, 2.38	0.001
Paranoid ideation	2,534 (11.9%)	1.41	1.03, 1.93	0.030
Fear of abandonment	2,534 (7.1%)	1.76	1.22, 2.55	0.003
Suicidal behaviour	2,529 (3.8%)	1.84	1.26, 2.69	0.002
Impulsivity	2,530 (18.2%)	1.16	0.94, 1.43	0.160
Intense interpersonal relationships	2,530 (12.9%)	1.57	1.17, 2.10	0.003

[a] (% of individuals with a rating of probably present or definitely present); BPD: Borderline Personality Disorder; HCL: Hypomania Checklist

Appendix 4 Association between SDQ subscales and hypomania

Exposure	Outcome	N	β	95% CI	P value
Hyperactivity Problems	HCL score	2,914	-0.00^	-0.04, 0.38	0.950
Prosocial behaviour		2,917	-0.07	-0.10, -0.03	<0.001
Emotional difficulties		2,913	0.03	-0.01, 0.06	0.176
Conduct problems		2,918	0.00^	-0.03, 0.05	0.522
Peer relationship difficulties		2,913	0.02	-0.01, 0.06	0.205
Exposure	**Outcome**	**N**	**OR**	**95% CI**	**P value**
Hyperactivity Problems	Clinically-defined hypomania	2,914	1.04	0.89, 1.22	0.601
Prosocial behaviour		2,917	1.08	0.93, 1.25	0.317
Emotional difficulties		2,913	1.04	0.90, 1.20	0.595
Conduct problems		2,918	1.38	1.21, 1.58	<0.001
Peer relationship difficulties		2,913	1.11	0.96, 1.28	0.146

^ rounded to 2 decimal places; SDQ: Strengths and Difficulties Questionnaire; HCL: Hypomania Checklist; CI: Confidence Intervals; OR: Odds Ratio

Appendix 4 continued

Exposure	Outcome	N	β	95% CI	P value
Hyperactivity problems	Active/elated	2591	-0.05	-0.09, -0.01	0.013
	Risk-taking/irritable		0.11	0.08, 0.15	<0.001
Prosocial behavior	Active/elated	2594	0.06	0.02, 0.10	0.002
	Risk-taking/irritable		0.06	0.03, 0.10	<0.001
Emotional difficulties	Active/elated	2591	0.02	-0.02, 0.06	0.254
	Risk-taking/irritable		0.03	-0.01, 0.06	0.122
Conduct problems	Active/elated	2595	-0.02	-0.06, 0.02	0.285
	Risk-taking/irritable		0.08	0.04, 0.12	<0.001
Peer relationship difficulties	Active/elated	2592	0.02	-0.02, 0.06	0.309
	Risk-taking/irritable		0.04	0.01, 0.08	0.017

^ rounded to 2 decimal places; SDQ: Strengths and Difficulties Questionnaire; HCL: Hypomania Checklist; CI: Confidence Intervals

Appendix 5 Association between low and high cognitive performance and total HCL score

Outcome	N	Exposure	β unadjusted	95%CI	P	β adjusted*	95%CI	P
Processing speed	5,936	Lowest	-0.11	-0.23, 0.00^	0.060	-0.12	-0.24, -0.01	0.039
		Highest	-0.02	-0.12, 0.08	0.691	-0.02	-0.12, 0.09	0.735
Working memory	2,644	Lowest	-0.21	-0.33, -0.00^	0.001	-0.21	-0.33, -0.09	0.001
		Highest	0.08	-0.03, 0.19	0.136	0.05	-0.06, 0.15	0.379
Attention	5,773	Lowest	-0.08	-0.20, 0.04	0.174	-0.11	-0.23, 0.01	0.068
		Highest	-0.09	-0.20, 0.02	0.099	-0.10	-0.21, 0.00^	0.058
Verbal learning	5,925	Lowest	-0.19	-0.29, -0.09	<0.001	-0.16	-0.26, -0.05	0.003
		Highest	0.03	-0.09, 0.14	0.659	0.02	-0.09, 0.14	0.718

^rounded to 2 decimal places; HCL: Hypomania Checklist; CI: Confidence Intervals;

*Adjusted for: gender, maternal education level, maternal age at birth, maternal social class, child being emotionally abused, child being physically abused, child being a victim of bullying and being left-handed

Appendix 6 Association between cognitive functioning and HCL factors

Exposure	HCL factor	N	ß unadjusted	95%CI	P	ß adjusted*	95%CI	P
Processing speed	Active/elated	1,642	0.05	0.00^, 0.10	0.037	0.05	0.00^, 0.10	0.039
	Risk-taking/irritable		-0.01	-0.05, 0.03	0.667	0.00^	-0.04, 0.05	0.892
Working memory	Active/elated	1,598	0.14	0.09, 0.18	<0.001	0.11	0.07, 0.16	<0.001
	Risk-taking/irritable		-0.04	-0.08, 0.00^	0.070	-0.03	-0.07, 0.01	0.179
Problem Solving	Active/elated	1,631	0.14	0.10, 0.17	<0.001	0.11	0.07, 0.16	<0.001
	Risk-taking/irritable		0.00^	-0.04, 0.05	0.870	0.00^	-0.04, 0.05	0.721
Executive functioning	Active/elated	1,591	0.10	0.03, 0.17	0.003	0.10	0.03, 0.17	0.006
	Risk-taking/irritable		-0.05	-0.11, 0.01	0.120	-0.04	-0.11, 0.03	0.232
Attention	Active/elated	1,577	0.03	-0.01, 0.09	0.230	0.02	-0.04, 0.08	0.480
	Risk-taking/irritable		-0.01	-0.06, 0.04	0.724	0.04	-0.02, 0.09	0.154
Verbal learning	Active/elated	1,637	0.13	0.08, 0.17	<0.001	0.10	0.05, 0.15	<0.001
	Risk-taking/irritable		-0.03	-0.07, 0.02	0.207	-0.02	-0.06, 0.03	0.448
Emotion recognition	Active/elated	1,530	0.08	0.03, 0.13	0.003	0.08	0.03, 0.13	0.001
	Risk-taking/irritable		0.03	-0.02, 0.07	0.298	0.03	-0.01, 0.08	0.175

^rounded to 2 decimal places; HCL: Hypomania Checklist; CI: Confidence Intervals

*Adjusted for: gender, maternal education level, maternal age at birth, maternal social class, child being emotionally abused, child being physically abused, child being a victim of bullying and being left-handed

Appendix 7 Association between linear and quadratic terms for cognitive domains and clinically-defined hypomania

Exposure	N		OR unadjusted	95%CI	P	OR adjusted*	95%CI	P
Processing speed	1,848	Linear	0.81	0.67, 0.98	0.029	0.85	0.70, 1.03	0.091
		Quadratic	0.99	0.86, 1.14	0.891	0.99	0.86, 1.15	0.927
Working memory	1,802	Linear	0.84	0.70, 1.01	0.061	0.88	0.73, 1.07	0.199
		Quadratic	1.05	0.92, 1.20	0.457	1.04	0.90, 1.19	0.610
Problem solving	1,836	Linear	0.92	0.76, 1.11	0.388	0.94	0.77, 1.15	0.546
		Quadratic	1.00	0.87, 1.14	0.957	0.99	0.77, 1.14	0.942
Executive functioning	1,796	Linear	0.85	0.62, 1.16	0.302	0.87	0.63, 1.20	0.400
		Quadratic	0.97	0.81, 1.15	0.708	0.96	0.82, 1.13	0.638
Attention	1,782	Linear	0.82	0.62, 1.09	0.175	0.82	0.61, 1.09	0.583
		Quadratic	0.94	0.83, 1.06	0.326	0.94	0.82, 1.06	0.063
Verbal learning	1,845	Linear	0.89	0.74, 1.09	0.259	0.93	0.76, 1.14	0.501
		Quadratic	0.93	0.79, 1.10	0.406	0.93	0.78, 1.10	0.376
Emotion recognition	1,721	Linear	0.94	0.73, 1.20	0.623	0.97	0.75, 1.24	0.783
		Quadratic	0.80	0.64, 1.00	0.046	0.79	0.63, 0.98	0.035

^rounded to 2 decimal places; HCL: Hypomania Checklist; CI: Confidence Intervals; OR: Odds Ratio

*Adjusted for: gender, maternal education level, maternal age at birth, maternal social class, child being emotionally abused, child being physically abused, child being a victim of bullying and being left-handed

Appendix 8 Associations between childhood cognitive functioning and HCL score comparing adjusted non-imputed with adjusted imputed

Exposure	Outcome	N	β non-imputed	95%CI	P value	N	β imputed*	95%CI	P value
Processing speed	HCL score	1,848	0.04	-0.00^, 0.09	0.078	2,631	0.02	-0.02, 0.06	0.117
Working memory		1,802	0.09	0.04, 0.14	<0.001		0.08	0.04, 0.12	<0.001
Problem Solving		1,836	0.10	0.05, 0.14	<0.001		0.10	0.06, 0.14	<0.001
Executive functioning		1,796	0.06	0.01, 0.10	0.021		0.04	-0.00^, 0.09	0.056
Attention		1,782	0.02	-0.04, 0.08	0.480		0.02	-0.03, 0.06	0.443
Verbal learning		1,845	0.08	0.03, 0.13	0.001		0.07	0.03, 0.11	<0.001
Emotion recognition		1,721	0.07	0.02, 0.12	0.005		0.06	0.02, 0.10	0.005

^rounded to 2 decimal places; HCL: Hypomania Checklist; CI: Confidence Intervals

*Adjusted for: gender, maternal education level, maternal age at birth, maternal social class, child being emotionally abused, child being physically abused, child being a victim of bullying and being left-handed

Appendix 9 Associations between childhood cognitive functioning and HCL factors comparing adjusted non-imputed with adjusted imputed

Exposure	HCL factor	N	ß non-imputed	95%CI	P	N	ß imputed*	95%CI	P
Processing speed	Active/elated	1,642	0.05	0.00^, 0.10	0.037	2,331	0.05	0.00^, 0.10	0.039
	Risk-taking		0.00^	-0.04, 0.05	0.892		-0.01	-0.05, 0.02	0.479
Working memory	Active/elated	1,598	0.14	0.09, 0.18	<0.001		0.11	0.07, 0.16	<0.001
	Risk-taking		-0.04	-0.08, 0.00^	0.070		-0.03	-0.07, 0.01	0.179
Problem Solving	Active/elated	1,631	0.14	0.10, 0.17	<0.001		0.11	0.07, 0.16	<0.001
	Risk-taking		0.00^	-0.04, 0.05	0.870		0.00^	-0.04, 0.05	0.721
Executive functioning	Active/elated	1,591	0.10	0.03, 0.17	0.003		0.10	0.03, 0.17	0.006
	Risk-taking		-0.05	-0.11, 0.01	0.120		-0.04	-0.11, 0.03	0.232
Attention	Active/elated	1,577	0.04	-0.02, 0.09	0.154		0.03	-0.02, 0.07	0.236
	Risk-taking		0.00^	-0.05, 0.05	0.979		0.00^	-0.04, 0.04	0.974
Verbal Learning	Active/elated	1,637	0.10	0.05, 0.15	<0.001		0.08	0.04, 0.13	<0.001
	Risk-taking		-0.02	-0.06, 0.03	0.448		-0.02	-0.06, 0.02	0.351
Emotion recognition	Active/elated	1,530	0.08	0.03, 0.13	0.001		0.07	0.02, 0.11	0.003
	Risk-taking		0.03	-0.01, 0.08	0.175		0.02	-0.02, 0.06	0.434

^rounded to 2 decimal places; HCL: Hypomania Checklist; CI: Confidence Intervals

*Adjusted for: gender, maternal education level, maternal age at birth, maternal social class, child being emotionally abused, child being physically abused, child being a victim of bullying and being left-handed

Appendix 10 Associations between cognitive functioning and clinically-defined hypomania comparing adjusted non-imputed with adjusted imputed

Exposure	Outcome	N	OR non-imputed	95%CI	P value	N	OR imputed*	95%CI	P value
Processing speed	Clinically-defined hypomania	1,848	0.83	0.70, 1.03	0.089	2,631	0.87	0.74, 1.03	0.113
Working memory		1,802	0.89	0.74, 1.08	0.236		0.91	0.77, 1.09	0.310
Problem Solving		1,836	0.94	0.77, 1.14	0.532		0.96	0.81, 1.13	0.594
Executive functioning		1,796	0.98	0.84, 1.15	0.827		0.99	0.85, 1.15	0.891
Attention		1,782	0.92	0.74, 1.13	0.405		0.99	0.82, 1.19	0.934
Verbal learning		1,845	0.91	0.75, 1.09	0.305		1.01	0.85, 1.19	0.912
Emotion recognition		1,721	1.08	0.88, 1.33	0.459		1.05	0.89, 1.24	0.587

^rounded to 2 decimal places; HCL: Hypomania Checklist; CI: Confidence Intervals; OR: Odds Ratio

*Adjusted for: gender, maternal education level, maternal age at birth, maternal social class, child being emotionally abused, child being physically abused, child being a victim of bullying and being left-handed

Appendix 11 Search strategy terms and delimiters used for searching Embase, Medline via Ovid and PsychINFO

Key word
1. Explode Psychotic disorders
2. Explode bipolar disorder
3. mania.mp
4. manic.mp
5. Explode schizophrenia
6. Psychosis.mp
7. hypoman*.mp
8. Explode schizophren*.mp
9. depress*.mp
10. 10 or/ 1-9
11. polygenic risk score.mp
12. risk profile score.mp
13. polygenic variation.mp
14. GWAS.mp
15. gene score.mp
16. genetic score.mp
17. allele score.mp
18. SNP[b] score.mp
19. explode single nucleotide polymorphism
20. polygenic.mp
21. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 10 and 21
23. limit 22 as follows: - years= '2009- 16th March 2016' - English language - Peer reviewed journal articles

GWAS: Genome-Wide Association Study

Appendix 12 Inclusion/exclusion criteria

Factors	**Assessment**
Type of study	
1. Has the study been peer reviewed and is it already published? NB: Both must apply.	Yes Unclear No ↓ ↓ ↓ **Exclude**
2. Does the study present data on an association between a risk score (derived from GWAS data of participants with a diagnosis of bipolar (either I or II) and a measurable phenotype?	Yes Unclear No ↓ ↓ ↓ **Exclude**
3. Does the study report a risk score and the same phenotype in both the discovery and target sample?	Yes Unclear No ↓ ↓ ↓ **Exclude**
4. Does the study present an association between a risk score and imaging modalities?	Yes Unclear No ↓ ↓ ↓ **Exclude**
5. Is the paper in English?	Yes Unclear No ↓ ↓ ↓ **Exclude**

GWAS; Genome Wide Association Studies, SNP; Single Nucleotide Polymorphism

Appendix 13 Associations between the BD-PRS and hypomania outcomes at $P_T \leq 0.5$

Exposure	Outcome	N	β	95%CI	P	R^2 (%)
BD-PRS at $P_T \leq 0.5$	HCL score	2654	0.02	-0.02, 0.06	0.336	0.03
	Active/elated factor	2363	0.02	-0.02, 0.06	0.292	0.05
	Risk-taking/irritable factor		0.01	-0.03, 0.05	0.572	0.01
	Outcome	**N with outcome (%)**	**OR**	**95%CI**	**P**	**r^2 (%)**
BD-PRS at $P_T \leq 0.5$	Clinically-defined hypomania	239 (7.1)	1.13	0.98, 1.32	0.097	0.20

*Threshold score used to defined clinically-defined hypomania was a score of ≥14/28 on the HCL; BD-PRS: Bipolar Disorder-Polygenic Risk Score; HCL: Hypomania Checklist; OR: Odds Ratio; P_T: P-value threshold

Appendix 14 Results of sensitivity analyses using different threshold cut-off scores on the HCL

Exposure	Outcome	N with outcome if binary (%)	OR	95%CI	P	R^2 (%)
BD-PRS at $P_T \leq 0.01$	Threshold ≥14/28	239 (7.1)	1.07	0.92, 1.24	0.382	0.22
	Threshold ≥16/28	198 (5.9)	1.08	0.92, 1.27	0.348	0.07
	Threshold ≥18/28	150 (4.4)	1.13	0.94, 1.36	0.193	0.17
	Threshold ≥20/28	101 (3.0)	1.32	1.06, 1.64	0.013	0.83
	Threshold ≥22/28	60 (1.8)	1.24	0.94, 1.64	0.120	0.47
	Threshold ≥24/28	34 (1.0)	1.12	0.78, 1.61	0.541	0.11
BD-PRS at $P_T \leq 0.5$	Threshold ≥14/28	239 (7.1)	1.13	0.98, 1.32	0.097	0.20
	Threshold ≥16/28	198 (5.9)	1.14	0.97, 1.34	0.105	0.22
	Threshold ≥18/28	150 (4.4)	1.20	1.00, 1.44	0.053	0.38
	Threshold ≥20/28	101 (3.0)	1.33	1.07, 1.65	0.01	0.89
	Threshold ≥22/28	60 (1.8)	1.34	1.02, 1.76	0.036	0.86
	Threshold ≥24/28	34 (1.0)	1.09	0.76, 1.56	0.645	0.06

HCL: Hypomania Checklist; BD-PRS: Bipolar Disorder-Polygenic Risk Score; P_T: P-value threshold; CI: Confidence Interval; OR: Odds Ratio

Appendix 15 Association between the BD-PRS and cognitive measures at $P_T \leq 0.01$

Outcome	N	ß	95%CI	P	R^2
Total IQ	5,895	-0.01	-0.03, 0.02	0.485	0.01
Verbal IQ	5,921	0.00^	-0.02, 0.03	0.922	0.00
Performance IQ	5,911	-0.02	-0.04, 0.01	0.204	0.03
Processing speed	5,936	-0.02	-0.05, 0.00^	0.075	0.05
Working memory	5,763	-0.00^	-0.03, 0.03	0.959	0.00
Problem solving	5,905	0.01	-0.02, 0.03	0.514	0.01
Executive functioning	5,788	-0.03	-0.06, -0.01	0.013	0.11
Attention	5,767	-0.02	-0.04, 0.01	0.146	0.04
Verbal learning	5,925	0.02	-0.01, 0.04	0.173	0.03
Emotion recognition	5,457	-0.02	-0.05, 0.01	0.134	0.04

^rounded to 2 decimal places; BD-PRS: Bipolar Disorder-Polygenic Risk Score; IQ: Intelligence Quotient; CI: Confidence Intervals; P_T: P-value threshold

Appendix 16 Association between the BD-PRS and cognitive measures at $P_T \leq 0.5$

Outcome	N	ß	95%CI	P	R^2
Total IQ	5,895	-0.02	-0.04, 0.01	0.147	0.04
Verbal IQ	5,921	-0.00^	-0.03, 0.02	0.858	0.00
Performance IQ	5,911	-0.03	-0.06, -0.01	0.018	0.09
Processing speed	5,936	-0.03	-0.06 -0.01	0.016	0.10
Working memory	5,763	-0.01	-0.04, 0.01	0.329	0.02
Problem solving	5,905	-0.01	-0.03, 0.02	0.570	0.01
Executive functioning	5,788	-0.03	-0.06, -0.01	0.014	0.10
Attention	5,767	-0.02	-0.05, 0.01	0.115	0.04
Verbal learning	5,925	0.01	-0.02, 0.03	0.505	0.01
Emotion recognition	5,457	-0.02	-0.04, 0.01	0.250	0.02

^rounded to 2 decimal places; BD-PRS: Bipolar Disorder-Polygenic Risk Score; IQ: Intelligence Quotient; CI: Confidence Intervals; P_T: P-value threshold

Appendix 17 Examining quadratic effects of the BD-PRS on cognitive domains at $P_T \leq 0.01$

Exposure	N	Exposure	ß	95%CI	P	R^2
Performance IQ	5,911	Linear	-0.02	-0.04, 0.01	0.204	0.08
		Quadratic	-0.02	-0.04, 0.00^	0.066	
Verbal IQ	5,921	Linear	0.00^	-0.02, 0.03	0.922	0.02
		Quadratic	0.00^	-0.03, 0.01	0.229	
Total IQ	5,895	Linear	-0.01	-0.03, 0.02	0.485	0.06
		Quadratic	-0.02	-0.03, 0.00^	0.077	
Processing speed	5,936	Linear	-0.02	-0.05, 0.02	0.075	0.05
		Quadratic	-0.01	-0.00^, 0.02	0.961	
Working memory	5,763	Linear	-0.00^	-0.03, 0.03	0.959	0.00
		Quadratic	-0.00^	-0.02, 0.01	0.638	
Problem solving	5,905	Linear	0.01	-0.02, 0.03	0.514	0.03
		Quadratic	-0.01	-0.03, 0.01	0.289	
Executive functioning	5,788	Linear	-0.03	-0.06, -0.01	0.013	0.16
		Quadratic	-0.02	-0.04, 0.00^	0.089	
Attention	5,773	Linear	-0.02	-0.04, 0.01	0.149	0.04
		Quadratic	0.01	-0.01, 0.02	0.473	
Verbal learning	5,925	Linear	0.02	-0.01, 0.04	0.173	0.05
		Quadratic	0.01	-0.01, 0.03	0.292	
Emotion recognition	5,963	Linear	-0.02	-0.05, 0.01	0.134	0.04
		Quadratic	-0.01	-0.02, 0.01	0.773	

^rounded to 2 decimal places; P-value reported for the linear model includes only the BD-PRS; P-value for the quadratic term is from likelihood ratio tests comparing models with linear and quadratic terms to models with linear terms only; BD-PRS: Bipolar Disorder-Polygenic Risk Score; IQ: Intelligence Quotient; CI: Confidence Intervals; P_T: P-value threshold

Appendix 18 Examining the non-linear effects of the BD-PRS on cognitive domains at $P_T \leq 0.5$

Exposure	N	Exposure	ß	95%CI	P	R^2
Performance IQ	5,911	Linear	-0.03	-0.06, -0.01	0.018	0.15
		Quadratic	-0.02	-0.04, 0.00^	0.063	
Verbal IQ	5,921	Linear	-0.00^	-0.03, 0.02	0.857	0.02
		Quadratic	-0.01	-0.03, 0.01	0.229	
Total IQ	5,895	Linear	-0.02	-0.04, 0.01	0.147	0.09
		Quadratic	-0.02	-0.03, 0.00^	0.075	
Processing speed	5,936	Linear	-0.03	-0.06, -0.01	0.016	0.10
		Quadratic	-0.00^	-0.02, 0.02	0.943	
Working memory	5,763	Linear	-0.01	-0.04, 0.01	0.330	0.02
		Quadratic	-0.00^	-0.02, 0.01	0.638	
Problem solving	5,905	Linear	-0.01	-0.03, 0.02	0.570	0.02
		Quadratic	-0.01	-0.03, 0.01	0.293	
Executive functioning	5,788	Linear	-0.03	-0.06, -0.01	0.014	0.16
		Quadratic	-0.02	-0.04, 0.00*	0.083	
Attention	5,773	Linear	-0.02	-0.05, 0.15	0.123	0.05
		Quadratic	0.01	-0.01, 0.01	0.466	
Verbal learning	5,925	Linear	0.01	-0.02, 0.03	0.508	0.03
		Quadratic	0.01	-0.01, 0.03	0.284	
Emotion recognition	5,963	Linear	-0.02	-0.04, 0.01	0.250	0.03
		Quadratic	-0.00^	-0.02, 0.02	0.758	

^rounded to 2 decimal places; P-value reported for the linear term includes only the BD-PRS; P-value for the quadratic term is from likelihood ratio tests comparing models with linear and quadratic terms to models with linear terms only; BD-PRS: Bipolar Disorder-Polygenic Risk Score; IQ: Intelligence Quotient; CI: Confidence Intervals; P_T: P-value threshold

Appendix 19 Association between tertiles of the BD-PRS at $P_T \leq 0.01$ and cognitive domains

Exposure	N	Exposure	ß	95%CI	P	R^2
Performance IQ	5,911	Lowest GR	0.00^	-0.06, 0.06	0.923	0.08
		Highest GR	-0.06	-0.12, 0.00	0.064	
Verbal IQ	5,921	Lowest GR	0.01	-0.05, 0.07	0.790	0.01
		Highest GR	-0.02	-0.08, 0.04	0.524	
Total IQ	5,895	Lowest GR	0.01	-0.06, 0.07	0.844	0.06
		Highest GR	-0.05	-0.11, 0.02	0.138	
Processing speed	5,936	Lowest GR	0.04	-0.02, 0.10	0.228	0.07
		Highest GR	-0.03	-0.09, 0.04	0.415	
Working memory	5,763	Lowest GR	-0.00^	-0.07, 0.06	0.920	0.04
		Highest GR	-0.04	-0.10, 0.02	0.210	
Problem solving	5,905	Lowest GR	0.01	-0.05, 0.08	0.659	0.01
		Highest GR	-0.01	-0.07, 0.05	0.785	
Executive functioning	5,788	Lowest GR	0.01	-0.06, 0.07	0.852	0.06
		Highest GR	-0.05	-0.12, 0.01	0.120	
Attention	5,773	Lowest GR	0.02	-0.04, 0.08	0.209	0.03
		Highest GR	-0.02	-0.08, 0.04	0.527	
Verbal learning	5,925	Lowest GR	-0.02	-0.08, 0.04	0.518	0.02
		Highest GR	0.01	-0.05, 0.07	0.736	
Emotion recognition	5,963	Lowest GR	0.04	-0.02, 0.11	0.185	0.08
		Highest GR	-0.02	-0.09, 0.04	0.459	

^rounded to two decimal places BD-PRS: Bipolar Disorder-Polygenic Risk Score; IQ: Intelligence Quotient; CI: Confidence Intervals; P_T: P-value threshold; GR: Genetic Risk

Appendix 20 Association between tertiles of the BD-PRS at $P_T \leq 0.5$ and cognitive domains

Exposure	N	Exposure	β	95%CI	P	R^2
Performance IQ	5,911	Lowest GR	-0.01	-0.07, 0.05	0.725	0.18
		Highest GR	-0.10	-0.16, -0.03	0.003	
Verbal IQ	5,921	Lowest GR	0.02	-0.04, 0.08	0.509	0.02
		Highest GR	-0.01	-0.07, 0.05	0.763	
Total IQ	5,895	Lowest GR	0.01	-0.05, 0.07	0.695	0.09
		Highest GR	-0.06	-0.12, 0.01	0.073	
Processing speed	5,936	Lowest GR	0.06	-0.00^, 0.12	0.055	0.14
		Highest GR	-0.03	-0.09, 0.03	0.360	
Working memory	5,763	Lowest GR	0.03	-0.03, 0.09	0.358	0.02
		Highest GR	-0.00^	-0.07, 0.06	0.964	
Problem solving	5,905	Lowest GR	0.01	-0.05, 0.07	0.719	0.04
		Highest GR	-0.03	-0.10, 0.03	0.270	
Executive functioning	5,788	Lowest GR	0.00^	-0.06, 0.07	0.883	0.07
		Highest GR	-0.06	-0.12, 0.01	0.084	
Attention	5,773	Lowest GR	0.04	-0.02, 0.10	0.209	0.06
		Highest GR	-0.02	-0.08, 0.05	0.608	
Verbal learning	5,925	Lowest GR	0.02	-0.04, 0.08	0.564	0.06
		Highest GR	0.06	-0.00^, 0.12	0.061	
Emotion recognition	5,963	Lowest GR	-0.07	-0.13, -0.00^	0.046	0.14
		Highest GR	-0.09	-0.15, -0.02	0.007	

^rounded to two decimal places BD-PRS: Bipolar Disorder-Polygenic Risk Score; IQ: Intelligence Quotient; CI: Confidence Intervals; P_T: P-value threshold; GR: Genetic Risk

Appendix 21 Associations between genetic risk and cognitive domains comparing non-imputed with imputed data

Exposure	Outcome	N	ß non-imputed	95%CI	P	N	ß imputed	95%CI	P
BD-PRS	PIQ	5,911	-0.02[a]	-0.05, 0.01	0.146	7,370	-0.02[a]	-0.05, 0.01	0.176
SZ-PRS	PIQ	5,911	-0.04[b]	-0.06, -0.01	0.006		-0.04[b]	-0.06, -0.01	0.006
BD-PRS	PS	5,935	-0.02[a]	-0.05, 0.01	0.127	7,403	-0.02[a]	-0.05, 0.01	0.208
SZ-PRS	PS	5,936	-0.04[b]	-0.06, -0.01	0.007		-0.04[b]	-0.06, -0.01	0.009
BD-PRS	EF	5,788	-0.03[a]	-0.06, -0.00^	0.022	7,202	-0.03[a]	-0.05, -0.00^	0.027
SZ-PRS	EF	5,788	-0.01[b]	-0.03, 0.02	0.695		-0.01[b]	-0.03, 0.02	0.661
SZvsBD PRS	PIQ	5,911	-0.03	-0.06, -0.01	0.009	7,370	-0.03	-0.06, -0.01	0.009
SZvsBD PRS	PS	5,936	-0.01	-0.03, 0.02	0.499	7,403	-0.01	-0.04, 0.02	0.400
SZvsBD PRS	EF	5,788	-0.00^	-0.03, 0.03	0.919	7,202	-0.00^	-0.03, 0.02	0.845

^rounded to 2 decimal places; Associations between genetic risk for BD and cognitive domains of PIQ and PS are reported at $P_T \leq 0.5$ and associations with EF are reported at $P_T \leq 0.01$; [a] adjusted for the SZ-PRS; [b] adjusted for the BD-PRS; BD-PRS: Bipolar Disorder-Polygenic Risk Score; SZ-PRS: Schizophrenia -Polygenic Risk Score; P_T: P-value threshold; IQ: Intelligence Quotient; CI: Confidence Intervals; PIQ: Performance Intelligence Quotient; PS: Processing Speed; SZvsBD PRS: Schizophrenia vs Bipolar Disorder Polygenic Risk Score

References

Aas, M. et al. 2020. Childhood maltreatment and polygenic risk in bipolar disorders. *Bipolar Disorders* 22(2), pp. 174-181. doi: 10.1111/bdi.12851

Aas, M. et al. 2016. The role of childhood trauma in bipolar disorders. *International Journal of Bipolar Disorders* 4, doi: 10.1186/s40345-015-0042-0

Abdellaoui, A. et al. 2018. Predicting loneliness with polygenic scores of social, psychological and psychiatric traits. *Genes Brain and Behavior* 17(6), doi: 10.1111/gbb.12472

Akinhanmi, M. O. et al. 2018. Racial disparities in bipolar disorder treatment and research: A call to action. *Bipolar Disorders* 20(6), pp. 506-514. doi: 10.1111/bdi.12638

Allen, M. G. et al. 1974. Affective illness in veteran twins: A diagnostic review. *American Journal of Psychiatry* 131, pp. 1234-1239.

Altamura, A. C. et al. 2010. Duration of untreated illness and suicide in bipolar disorder: A naturalistic study. *European Archives of Psychiatry and Clinical Neuroscience* 260(5), pp. 385-391. doi: 10.1007/s00406-009-0085-2

Amare, A. T. et al. 2018. Polygenic scores for major depressive disorder and depressive symptoms predict response to lithium in patients with bipolar disorder. *BioRxiv*, doi: 10.1101/449363

Amare, A. T. et al. 2019. Bivariate genome-wide association analyses of the broad depression phenotype combined with major depressive disorder, bipolar disorder or schizophrenia reveal eight novel genetic loci for depression. *Mol Psychiatry*, pp. 1420-1429. doi: 10.1038/s41380-018-0336-6

American Psychiatric Association. 2013. *The Diagnostic and Statistical Manual of Mental Disorders-5*. 5th Edition ed. Washington, DC.

Aminoff, S. R. et al. 2015. Polygenic risk scores in bipolar disorder subgroups. *Journal of Affective Disorders* 183, pp. 310-314. doi: 10.1016/j.jad.2015.05.021

Amrhein, V. et al. 2019. Retire statistical significance. *Nature* 567(7748), pp. 305-307. doi: 10.1038/d41586-019-00857-9

Anderson, I. M. et al. 2013. Bipolar disorder. *BMJ (Online)* 346(7889), doi: 10.1136/bmj.e8508

Anderson, V. A. et al. 2001. Development of executive functions through late childhood and adolescence in an Australian sample. *Developmental Neuropsychology* 20(1), pp. 385-406. doi: 10.1207/s15326942dn2001_5

Andreasen, N. C. et al. 1987. Familial rates of affective disorder: A report from the National Institute of Mental Health collaborative study. *Archives of General Psychiatry* 44(5), pp. 461-469.

Andreassen, O. A. et al. 2013. Improved detection of common variants associated with schizophrenia and bipolar disorder using pleiotropy-informed conditional false discovery rate. *Plos Genetics* 9(4), doi: 10.1371/journal.pgen.1003455

Angold, A. et al. 1995. Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research* 5(4), pp. 237-249.

Angst, J. 2002. Historical aspects of the dichotomy between manic-depressive disorders and schizophrenia. *Schizophrenia Research* 57(1), pp. 5-13. doi: 10.1016/s0920-9964(02)00328-6

Angst, J. et al. 2005a. The HCL-32: Towards a self-assessment tool for hypomanic symptoms in outpatients. *Journal of Affective Disorders* 88(2), pp. 217-233. doi: 10.1016/j.jad.2005.05.011

Angst, J. et al. 2011. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: The BRIDGE study. *Archives of General Psychiatry* 68(8), pp. 791-799. doi: 10.1001/archgenpsychiatry.2011.87

Angst, J. et al. 2010. Major depressive disorder with subthreshold bipolarity in the National Comorbidity Survey replication. *American Journal of Psychiatry* 167(10), pp. 1194-1201. doi: 10.1176/appi.ajp.2010.09071011

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

Angst, J. et al. 2005b. Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. *Journal of Affective Disorders* 84(2-3), pp. 149-157. doi: 10.1016/s0165-0327(03)00195-2

Arango, C. et al. 2014. Differential neurodevelopmental trajectories in patients with early-onset bipolar and schizophrenia disorders. *Schizophrenia Bulletin* 40, pp. S138-S146. doi: 10.1093/schbul/sbt198

Arman, S. et al. 2013. Comparison of parent adolescent scores on Strengths and Difficulties Questionnaire. *Journal of Research in Medical Sciences* 18(6), pp. 501-505.

Arroyo-Borrell, E. et al. 2017. Influence maternal background has on children's mental health. *International Journal for Equity in Health* 16(1), doi: 10.1186/s12939-017-0559-1

Arts, B. et al. 2008. Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychological Medicine* 38(6), pp. 771-785. doi: 10.1017/s0033291707001675

Axelson, D. et al. 2015. Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: A longitudinal study. *American Journal of Psychiatry* 172(7), pp. 638-646. doi: 10.1176/appi.apj.2014.14010035

Azorin, J. M. et al. 2013. Characteristics and profiles of bipolar I patients according to age-at-onset: Findings from an admixture analysis. *Journal of Affective Disorders* 150(3), pp. 993-1000. doi: 10.1016/j.jad.2013.05.026

Badner, J. A. and Gershon, E. S. 2002. Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. *Molecular Psychiatry* 7(4), pp. 405-411. doi: 10.1038/sj/mp/4001012

Baethge, C. et al. 2003. Prophylaxis latency and outcome in bipolar disorders. *Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie* 48(7), pp. 449-457. doi: 10.1177/070674370304800704

Bain, M. et al. 2000. Obstetric complications and affective psychoses - Two case-control studies based on structured obstetric records. *British Journal of Psychiatry* 176, pp. 523-526. doi: 10.1192/bjp.176.6.523

Baldassano, C. F. et al. 2005. Gender differences in bipolar disorder: Retrospective data from the first 500 STEP-BD participants. *Bipolar Disorders* 7(5), pp. 465-470. doi: 10.1111/j.1399-5618.2005.00237.x

Barichello, T. et al. 2016. Exposure to perinatal infections and bipolar disorder: A systematic review. *Current Molecular Medicine* 16(2), pp. 106-118. doi: 10.2174/1566524016666160126143741

Barnett, J. H. and Smoller, J. W. 2009. The genetics of bipolar disorder. *Neuroscience* 164(1), pp. 331-343. doi: 10.1016/j.neuroscience.2009.03.080

Baum, A. E. et al. 2008a. A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. *Molecular Psychiatry* 13(2), pp. 197-207. doi: 10.1038/sj.mp.4002012

Baum, A. E. et al. 2008b. Meta-analysis of two genome-wide association studies of bipolar disorder reveals important points of agreement. *Molecular Psychiatry* 13(5), pp. 466-467. doi: 10.1038/mp.2008.16

Bellivier, F. et al. 2001. Admixture analysis of age at onset in bipolar I affective disorder. *Archives of General Psychiatry* 58(5), pp. 510-512. doi: 10.1001/archpsyc.58.5.510

Bellivier, F. et al. 2003. Age at onset in bipolar I affective disorder: Further evidence for three subgroups. *American Journal of Psychiatry* 160(5), pp. 999-1001. doi: 10.1176/appi.ajp.160.5.999

Benazzi, F. and Akiskal, H. S. 2008. How best to identify a bipolar-related subtype among major depressive patients without spontaneous hypomania: Superiority of age at onset criterion over recurrence and polarity? *Journal of Affective Disorders* 107(1-3), pp. 77-88. doi: 10.1016/j.jad.2007.07.032

Benca, C. E. et al. 2017. Predicting cognitive executive functioning with polygenic risk scores for psychiatric disorders. *Behavior Genetics* 47(1), pp. 11-24. doi: 10.1007/s10519-016-9814-2

Bennette, C. and Vickers, A. 2012. Against quantiles: Categorization of continuous variables in epidemiologic research, and its discontents. *Bmc Medical Research Methodology* 12, doi: 10.1186/1471-2288-12-21

Bergink, V. et al. 2016. Childhood adverse life events and parental psychopathology as risk factors for bipolar disorder. *Translational Psychiatry* 6, doi: 10.1038/tp.2016.201

Bertelsen, A. et al. 1977. Danish twin study of manic-depressive disorders. *British Journal of Psychiatry* 130, pp. 330-351. doi: 10.1192/bjp.130.4.330

Bezerra, S. et al. 2015. Personality disorders in euthymic bipolar patients: A systematic review. *Revista Brasileira De Psiquiatria* 37(2), pp. 162-167. doi: 10.1590/1516-4446-2014-1459

Bienvenu, O. J. et al. 2011. Psychiatric 'diseases' versus behavioral disorders and degree of genetic influence. *Psychological Medicine* 41(1), pp. 33-40. doi: 10.1017/s003329171000084x

Bigdeli, T. B. et al. 2016. Genome-wide association study reveals greater polygenic loading for schizophrenia in cases with a family history of illness. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics* 171(2), pp. 276-289. doi: 10.1002/ajmg.b.32402

Biskin, R. S. 2015. The lifetime course of borderline personality disorder. *Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie* 60(7), pp. 303-308. doi: 10.1177/070674371506000702

Bland, R. C. et al. 1988a. Period prevalence of psychiatric disorders in Edmonton. *Acta Psychiatrica Scandinavica* 77, pp. 33-42. doi: 10.1111/j.1600-0447.1988.tb08545.x

Bland, R. C. et al. 1988b. Lifetime prevalence of psychiatric disorders in Edmonton. *Acta Psychiatrica Scandinavica* 77, pp. 24-32. doi: 10.1111/j.1600-0447.1988.tb08544.x

Bo, Q. J. et al. 2017. Use of the MATRICS consensus cognitive battery (MCCB) to evaluate cognitive deficits in bipolar disorder: A systematic review and meta-analysis. *Plos One* 12(4), doi: 10.1371/journal.pone.0176212

Bora, E. 2018. Neurocognitive features in clinical subgroups of bipolar disorder: A meta-analysis. *Journal of Affective Disorders* 229, pp. 125-134. doi: 10.1016/j.jad.2017.12.057

Bora, E. et al. 2016. Meta-analysis of theory of mind (ToM) impairment in bipolar disorder. *Psychological Medicine* 46(2), pp. 253-264. doi: 10.1017/s0033291715001993

Bora, E. et al. 2014. Cognitive deficits in youth with familial and clinical high risk to psychosis: A systematic review and meta-analysis. *Acta Psychiatrica Scandinavica* 130(1), pp. 1-15. doi: 10.1111/acps.12261

Bora, E. and Ozerdem, A. 2017a. A meta-analysis of neurocognition in youth with familial high risk for bipolar disorder. *European Psychiatry* 44, pp. 17-23. doi: 10.1016/j.eurpsy.2017.02.483

Bora, E. and Ozerdem, A. 2017b. Meta-analysis of longitudinal studies of cognition in bipolar disorder: Comparison with healthy controls and schizophrenia. *Psychological Medicine* 47(16), pp. 2753-2766. doi: 10.1017/S0033291717001490

Bora, E. et al. 2009. Cognitive endophenotypes of bipolar disorder: A meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *Journal of Affective Disorders* 113(1–2), pp. 1-20. doi: 10.1016/j.jad.2008.06.009

Bora, E. et al. 2011. Meta-analytic review of neurocognition in bipolar II disorder. *Acta Psychiatrica Scandinavica* 123(3), pp. 165-174. doi: 10.111.j.1600-0447.2010.01638

Bortolato, B. et al. 2015. Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses. *Neuropsychiatric Disease and Treatment* 11, pp. 3111-3125. doi: 10.2147/ndt.s76700

Boyd, A. et al. 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), pp. 111-127. doi: 10.1093/ije/dys064

Bozzatello, P. et al. 2019. Early detection and outcome in borderline personality disorder. *Frontiers in Psychiatry* 10, doi: 10.3389/fpsyt.2019.00710

Brand, S. et al. 2011. 'Bright side' and 'dark side' hypomania are associated with differences in psychological functioning, sleep and physical activity in a non-clinical sample of young adults. *Journal of Affective Disorders* 131(1-3), pp. 68-78. doi: 10.1016/j.jad.2010.12.007

Bulik-Sullivan, B. et al. 2015. An atlas of genetic correlations across human diseases and traits. *Nature Genetics* 47(11), pp. 1236-1241.

Button, K. S. et al. 2013. Power failure: Why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience* 14(5), pp. 365-376. doi: 10.1038/nrn3475

Byrne, E. M. et al. 2014. Applying polygenic risk scores to postpartum depression. *Archives of Womens Mental Health* 17(6), pp. 519-528. doi: 10.1007/s00737-014-0428-5

Byrne, E. M. et al. 2015. Seasonality shows evidence for polygenic architecture and genetic correlation with schizophrenia and bipolar disorder. *Journal of Clinical Psychiatry* 76(2), pp. 128-134.

Calafato, M. S. et al. 2018. Use of schizophrenia and bipolar disorder polygenic risk scores to identify psychotic disorders. *British Journal of Psychiatry* 213(3), pp. 535-541. doi: 10.1192/bjp.2018.89

Cardno, A. G. et al. 1999. Heritability estimates for psychotic disorders - The Maudsley Twin psychosis series. *Archives of General Psychiatry* 56(2), pp. 162-168. doi: 10.1001/archpsyc.56.2.162

Carta, M. G. et al. 2006. The accuracy of the Italian version of the Hypomania Checklist (HCL-32) for the screening of bipolar disorders and comparison with the Mood Disorder Questionnaire (MDQ) in a clinical sample. *Clinical practice and epidemiology in mental health : CP & EMH* 2, pp. 2-20. doi: 10.1186/1745-0179-2-2

Carter, T. D. C. et al. 2003. Early age at onset as a risk factor for poor outcome of bipolar disorder. *Journal of Psychiatric Research* 37(4), pp. 297-303. doi: 10.1016/s0022-3956(03)00052-9

Cassano, G. B. et al. 1992. Proposed subtypes of bipolar II and related disorders: with hypomanic episodes (or cyclothymia) and with hyperthymic temperament. *Journal of Affective Disorders* 26(2), pp. 127-140.

Chang, Z. et al. 2014. Maternal age at childbirth and risk for ADHD in offspring: A population-based cohort study. *International Journal of Epidemiology* 43(6), pp. 1815-1824. doi: 10.1093/ije/dyu204

Charney, A. W. et al. 2017. Evidence for genetic heterogeneity between clinical subtypes of bipolar disorder. *Translational Psychiatry* 7, doi: 10.1038/tp.2016.242

Charney, A. W. et al. 2019. Contribution of rare copy number variants to bipolar disorder risk is limited to schizoaffective cases. *Biological Psychiatry* 86(2), pp. 110-119. doi: 10.1016/j.biopsych.2018.12.009

Chechik, G. et al. 1998. Neuronal regulation: A mechanism for efficient synaptic pruning during brain maturation. *Neuroscience Letters* 11(8), pp. 2061-2068.

Chen, D. T. et al. 2013. Genome-wide association study meta-analysis of European and Asian-ancestry samples identifies three novel loci associated with bipolar disorder. *Molecular Psychiatry* 18(2), pp. 195-205.

Chen, M. H. et al. 2019. Coaggregation of Major Psychiatric Disorders in First-Degree Relatives of Individuals With Attention-Deficit/Hyperactivity Disorder: A Nationwide Population-Based Study. *Journal of Clinical Psychiatry* 80(3), doi: 10.4088/JCP.18m12371

Choi, S. W. S. et al. 2018. A guide to performing polygenic risk score analyses. *bioRxiv*, doi: 10.1101/416545

Chronaki, G. et al. 2015. The development of emotion recognition from facial expressions and non-linguistic vocalizations during childhood. *British Journal of Developmental Psychology* 33(2), pp. 218-236. doi: 10.1111/bjdp.12075

Chu, D. et al. 2010. Does age at onset have clinical significance in older adults with bipolar disorder? *International Journal of Geriatric Psychiatry* 25(12), pp. 1266-1271. doi: 10.1002/gps.2466

Chudal, R. et al. 2015. Is maternal smoking during pregnancy associated with bipolar disorder in offspring? *Journal of Affective Disorders* 171, pp. 132-136. doi: 10.1016/j.jad.2014.09.030

Chudal, R. et al. 2014. Perinatal factors and the risk of bipolar disorder in Finland. *Journal of Affective Disorders* 155, pp. 75-80. doi: 10.1016/j.jad.2013.10.026

Cichon, S. et al. 2009. Genomewide association studies: History, rationale and prospects for psychiatric disorders. *American Journal of Psychiatry* 166(5), pp. 540-556. doi: 10.1176/appi.ajp.2008.08091354

Cichon, S. et al. 2011. Genome-wide association study identifies genetic variation in Neurocan as a susceptibility factor for bipolar disorder. *American Journal of Human Genetics* 88(3), pp. 372-381. doi: 10.1016/j.ajhg.2011.01.017

Cipriani, A. et al. 2011. Comparative efficacy and acceptability of antimanic drugs in acute mania: A multiple-treatments meta-analysis. *Lancet* 378(9799), pp. 1306-1315. doi: 10.1016/s0140-6736(11)60873-8

Cohen, P. et al. 2008. Socioeconomic background and the developmental course of schizotypal and borderline personality disorder symptoms. *Development and Psychopathology* 20(2), pp. 633-650. doi: 10.1017/s095457940800031x

Coker, T. R. et al. 2016. Racial and ethnic disparities in ADHD diagnosis and treatment. *Pediatrics* 138(3), doi: 10.1542/peds.2016-0407

Coleman, J. R. et al. 2017. Genome-wide association study of facial emotion recognition in children and association with polygenic risk for mental health disorders. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics.* 174(7), pp. 701-711.

Conus, P. et al. 2006. Symptomatic and functional outcome 12 months after a first episode of psychotic mania: Barriers to recovery in a catchment area sample. *Bipolar Disorders* 8(3), pp. 221-231. doi: 10.1111/j.1399-5618.2006.00315.x

Costello, E. J. and Angold, A. 1988. Scales to assess child and adolescent depression - Checklists, screens, and nets. *Journal of the American Academy of Child and Adolescent Psychiatry* 27(6), pp. 726-737. doi: 10.1097/00004583-198811000-00011

Court, H. et al. 2014. Improving the psychometric utility of the hypomania checklist (HCL-32): A Rasch analysis approach. *Journal of Affective Disorders* 152, pp. 448-453. doi: 10.1016/j.jad.2013.10.014

Craddock, N. and Jones, I. 1999. Genetics of bipolar disorder. *Journal of Medical Genetics* 36(8), pp. 585-594.

Craddock, N. and Owen, M. J. 2010. The Kraepelinian dichotomy - going, going ... but still not gone. *British Journal of Psychiatry* 196(2), pp. 92-95. doi: 10.1192/bjp.bp.109.073429

Craddock, N. and Sklar, P. 2013. Genetics of bipolar disorder. *The Lancet* 381(9878), pp. 1654-1662.

Cross-Disorder Group of the Psychiatric Genomics Consortium. 2013. Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. *Lancet* 381(9875), pp. 1371-1379. doi: 10.1016/S0140-6736(12)62129-1

Cullen, K. R. et al. 2014. Personality disorders in offspring of mothers with mood disorders: Results from a longitudinal family study. *Psychiatry Research* 218(3), pp. 303-310. doi: 10.1016/j.psychres.2014.04.044

Cuthbert, B. N. 2015. Research Domain Criteria: Toward future psychiatric nosologies. *Dialogues in Clinical Neuroscience* 17(1), pp. 89-97.

Cuthbert, B. N. and Insel, T. R. 2013. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *Bmc Medicine* 11, doi: 10.1186/1741-7015-11-126

D'Souza, S. et al. 2019. Determinants of persistence and change in early childhood behavioural problems: The roles of parenting and maternal mental health. *Journal of Child and Family Studies* 28(7), pp. 1826-1842. doi: 10.1007/s10826-019-01404-w

Davies, C. et al. 2020. Prenatal and perinatal risk and protective factors for psychosis: A systematic review and meta-analysis. *Lancet Psychiatry* 7(5), pp. 399-410. doi: 10.1016/s2215-0366(20)30057-2

Daviss, W. B. et al. 2006. Criterion validity of the Mood and Feelings Questionnaire for depressive episodes in clinic and non-clinic subjects. *Journal of Child Psychology and Psychiatry* 47(9), pp. 927-934. doi: 10.1111/j.1469-7610.2006.01646.x

de la Serna, E. et al. 2017. Neuropsychological characteristics of child and adolescent offspring of patients with schizophrenia or bipolar disorder. *Schizophrenia Research* 183, pp. 110-115. doi: 10.1016/j.schres.2016.11.007

Dean, B. B. et al. 2004. A systematic review evaluating health-related quality of life, work impairment, and healthcare costs and utilization in bipolar disorder. *Current Medical Research and Opinion* 20(2), pp. 139-154. doi: 10.1185/030079903125002801

Deary, V. et al. 2017. Genetic contributions to self-reported tiredness. *Molecular Psychiatry.* 14, pp. 609-620.

Demontis, D. et al. 2019. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nature Genetics* 51(1), pp. 63-75. doi: 10.1038/s41588-018-0269-7

Depp, C. A. and Jeste, D. V. 2004. Bipolar disorder in older adults: A critical review. *Bipolar Disorders* 6(5), pp. 343-367. doi: 10.1111/j.1399-5618.2004.00139.x

DeRosse, P. and Karlsgodt, K. H. 2015. Examining the psychosis continuum. *Current Behavioural Neuroscience Reports* 2(1), pp. 80-89.

Dezhina, Z. et al. 2018. A systematic review of associations between functional MRI activity and polygenic risk for schizophrenia and bipolar disorder. *Brain Imaging and Behaviour*, doi: 10.1007/s11682-018-9879-z

Diamond, A. 2013. Executive Functions. *Annual Review of Psychology* 64, pp. 135-168. doi: 10.1146/annurev-psych-113011-143750

Diflorio, A. and Jones, I. 2010. Is sex important? Gender differences in bipolar disorder. *International Review of Psychiatry* 22(5), pp. 437-452. doi: 10.3109/09540261.2010.514601

Djurovic, S. et al. 2010. A genome-wide association study of bipolar disorder in Norwegian individuals, followed by replication in Icelandic sample. *Journal of Affective Disorders* 126(1-2), pp. 312-316.

Donfrancesco, R. et al. 2011. Bipolar disorder co-morbidity in children with attention deficit hyperactivity disorder. *Psychiatry Research* 186(2-3), pp. 333-337. doi: 10.1016/j.psychres.2010.07.008

Doucette, S. et al. 2016. Early parent-child relationships and risk of mood disorder in a Canadian sample of offspring of a parent with bipolar disorder: findings from a 16-year prospective cohort study. *Early Intervention in Psychiatry* 10(5), pp. 381-389. doi: 10.1111/eip.12195

Dudbridge, F. 2013. Power and predictive accuracy of polygenic risk scores. *PLoS Genetics* 9(3), doi: 10.1371/journal.pgen.1003348

Dudbridge, F. 2016. Polygenic Epidemiology. *Genetic Epidemiology* 40(4), pp. 268-272. doi: 10.1002/gepi.21966

Duffy, A. 2012. 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* 169(12), pp. 1247-1255. doi: 10.1176/appi.ajp.2012.11111725

Duffy, A. et al. 2007. The early manifestations of bipolar disorder: A longitudinal prospective study of the offspring of bipolar parents. *Bipolar Disorders* 9(8), pp. 828-838. doi: 10.1111/j.1399-5618.2007.00421.x

Duffy, A. et al. 2010. Early stages in the development of bipolar disorder. *Journal of Affective Disorders* 121(1-2), pp. 127-135. doi: 10.1016/j.jad.2009.05.022

Duffy, A. et al. 2019. The emergent course of bipolar disorder: Observations over two decades from the Canadian high-risk offspring cohort. *American Journal of Psychiatry* 176(9), pp. 720-729. doi: 10.1176/appi.ajp.2018.18040461

Duffy, A. et al. 2013. Childhood anxiety: An early predictor of mood disorders in offspring of bipolar parents. *Journal of Affective Disorders* 150(2), pp. 363-369. doi: 10.1016/j.jad.2013.04.021

Duffy, A. et al. 2014. The developmental trajectory of bipolar disorder. *British Journal of Psychiatry* 204(2), pp. 122-128. doi: 10.1192/bjp.bp.113.126706

Duffy, A. et al. 2017a. Do the trajectories of bipolar disorder and schizophrenia follow a universal staging model? *Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie* 62(2), pp. 115-122. doi: 10.1177/0706743716649189

Duffy, A. et al. 2017b. 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, pp. 1-11. doi: 10.1186/s40345-017-0106-4

Dunn, E. C. et al. 2018. Exposure to childhood adversity and deficits in emotion recognition: Results from a large, population-based sample. *Journal of Child Psychology and Psychiatry* 59(8), pp. 845-854. doi: 10.1111/jcpp.12881

Dvir, Y. et al. 2014. Childhood maltreatment, emotional dysregulation, and psychiatric comorbidities. *Harvard Review of Psychiatry* 22(3), pp. 149-161. doi: 10.1097/hrp.0000000000000014

Egeland, J. A. et al. 2012. A 16-year prospective study of prodromal features prior to BPI onset in well Amish children. *Journal of Affective Disorders* 142(1-3), pp. 186-192. doi: 10.1016/j.jad.2012.04.023

Erskine, H. E. et al. 2016. Long-term outcomes of attention-deficit/hyperactivity disorder and conduct disorder: A systematic review and meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry* 55(10), pp. 841-850. doi: 10.1016/j.jaac.2016.06.016

Eser, H. Y. et al. 2018. Prevalence and associated features of anxiety disorder comorbidity in bipolar disorder: A meta-analysis and meta-regression study. *Frontiers in Psychiatry* 9, doi: 10.3389/fpsyt.2018.00229

Etherington, N. et al. 2016. Maternal factors and the emotional and behavioural functioning of adolescents with chronic health conditions. *Disability and Rehabilitation* 38(14), pp. 1359-1369. doi: 10.3109/09638288.2015.1099055

Ettinger, U. et al. 2018. Response inhibition and interference control: Effects of schizophrenia, genetic risk, and schizotypy. *Journal of Neuropsychology* 12(3), pp. 484-510. doi: 10.1111/jnp.12126

Faedda, G. L. et al. 2015. Precursors of bipolar disorders: A systematic literature review of prospective studies. *Journal of Clinical Psychiatry* 76(5), pp. 614-624. doi: 10.4088/JCP.13r08900

Faedda, G. L. et al. 2014. Clinical risk factors for bipolar disorders: A systematic review of prospective studies. *Journal of Affective Disorders* 168, pp. 314-321. doi: 10.1016/j.jad.2014.07.013

Feighner, J. P. et al. 1972. Diagnostic criteria for use in psychiatric research. *Archives of General Psychiatry* 26(1), pp. 57-63.

Ferentinos, P. et al. 2014. Investigating the genetic variation underlying episodicity in major depressive disorder: Suggestive evidence for a bipolar contribution. *Journal of Affective Disorders* 155, pp. 81-89. doi: 10.1016/j.jad.2013.10.027

Ferrari, A. J. et al. 2016. The prevalence and burden of bipolar disorder: Findings from the Global Burden of Disease Study 2013. *Bipolar Disorders* 18(5), pp. 440-450. doi: 10.1111/bdi.12423

Ferreira, M. A. R. et al. 2008. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. *Nature Genetics* 40(9), pp. 1056-1058. doi: 10.1038/ng.209

Fiedorowicz, J. G. et al. 2011. Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. *American Journal of Psychiatry* 168(1), pp. 40-48. doi: 10.1176/appi.ajp.2010.10030328

Fioravanti, M. et al. 2012. Cognitive deficits in schizophrenia: an updated metanalysis of the scientific evidence. *Bmc Psychiatry* 12, doi: 10.1186/1471-244x-12-64

Fornaro, M. et al. 2015. Factor structure and reliability of the Italian adaptation of the Hypomania Check List-32, second revision (HCL-32-R2). *Journal of Affective Disorders* 178, pp. 112-120. doi: 10.1016/j.jad.2015.03.001

Fornaro, M. et al. 2016. The prevalence and predictors of bipolar and borderline personality disorders comorbidity: Systematic review and meta-analysis. *Journal of Affective Disorders* 195, pp. 105-118. doi: 10.1016/j.jad.2016.01.040

Forstner, A. J. et al. 2015. Identification of shared risk loci and pathways between bipolar disorder and schizophrenia. *Medizinische Genetik* 27 (1), pp. 103-104.

Forty, L. et al. 2010. Reducing the Hypomania Checklist (HCL-32) to a 16-item version. *Journal of Affective Disorders* 124(3), pp. 351-356. doi: 10.1016/j.jad.2010.01.004

Forty, L. et al. 2009. Identifying hypomanic features in major depressive disorder using the Hypomania Checklist (HCL-32). *Journal of Affective Disorders* 114(1-3), pp. 68-73. doi: 10.1016/j.jad.2008.07.017

Forty, L. et al. 2014. Comorbid medical illness in bipolar disorder. *British Journal of Psychiatry* 205(6), pp. 465-472. doi: 10.1192/bjp.bp.114.152249

Fosse, R. et al. 2015. A critical assessment of the equal-environment assumption of the twin method for schizophrenia. *Frontiers in Psychiatry* 6, p. 10. doi: 10.3389/fpsyt.2015.00062

Fraser, A. et al. 2013. Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *International Journal of Epidemiology* 42(1), pp. 97-110. doi: 10.1093/ije/dys066

Friborg, O. et al. 2014. Comorbidity of personality disorders in mood disorders: A meta-analytic review of 122 studies from 1988 to 2010. *Journal of Affective Disorders* 152, pp. 1-11. doi: 10.1016/j.jad.2013.08.023

Fritz, K. et al. 2017. Is a delay in the diagnosis of bipolar disorder inevitable? *Bipolar Disorders* 19(5), pp. 396-400. doi: 10.1111/bdi.12499

Gale, C. R. et al. 2013. Is bipolar disorder more common in highly intelligent people? A cohort study of a million men. *Molecular Psychiatry* 18(2), pp. 190-194. doi: 10.1038/mp.2012.26

Gale, C. R. et al. 2010. Intelligence in early adulthood and subsequent hospitalization for mental disorders. *Epidemiology* 21(1), pp. 70-77. doi: 10.1097/EDE.0b013e3181c17da8

Gale, C. R. et al. 2016. Pleiotropy between neuroticism and physical and mental health: Findings from 108038 men and women in UK Biobank. *Translational Psychiatry* 6(4), doi: 10.1038/tp.2016.56

Gamma, A. et al. 2013. Transcultural validity of the Hypomania Checklist-32 (HCL-32) in patients with major depressive episodes. *Bipolar Disorders* 15(6), pp. 701-712. doi: 10.1111/bdi.12101

Garcia-Gonzalez, J. et al. 2017. Pharmacogenetics of antidepressant response: A polygenic approach. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 75, pp. 128-134.

Gathercole, S. E. and Adams, A. M. 1994. Children's phonological working memory: Contribution of long term knowledge rehearsal. *Journal of Memory and Language* 33(5), pp. 672-688. doi: 10.1006/jmla.1994.1032

Gershon, E. S. et al. 1982. A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal probands. *Archives of General Psychiatry* 39(10), pp. 1157-1167.

Ghaemi, S. N. et al. 2002. "Cade's disease" and beyond: Misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. *Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie* 47(2), pp. 125-134. doi: 10.1177/070674370204700202

Ghaemi, S. N. et al. 1995. Lack of insight in bipolar disorder - The acute manic episode. *Journal of Nervous and Mental Disease* 183(7), pp. 464-467. doi: 10.1097/00005053-199507000-00007

Gitlin, M. J. et al. 1995. Relapse and impairment in bipolar disorder. *American Journal of Psychiatry* 152(11), pp. 1635-1640.

Glaus, J. et al. 2018. Factorial structure and familial aggregation of the Hypomania Checklist-32 (HCL-32): Results of the NIMH family study of affective spectrum disorders. *Comprehensive Psychiatry* 84, pp. 7-14. doi: 10.1016/j.comppsych.2018.03.010

Goldberg, J. F. and Ernst, C. L. 2002. Features associated with the delayed initiation of mood stabilizers at illness onset in bipolar disorder. *Journal of Clinical Psychiatry* 63(11), pp. 985-991. doi: 10.4088/JCP.v63n1105

Goodday, S. et al. 2018. Early exposure to parental bipolar disorder and risk of mood disorder: The Flourish Canadian prospective offspring cohort study. *Early Intervention in Psychiatry* 12(2), pp. 160-168. doi: 10.1111/eip.12291

Goodman, R. 1997. The strengths and difficulties questionnaire: A research note. *Journal of Child Psychology and Psychiatry and Allied Disciplines* 38(5), pp. 581-586. doi: 10.1111/j.1469-7610.1997.tb01545.x

Goodman, R. 2001. Psychometric properties of the Strengths and Difficulties Questionnaire. *Journal of the American Academy of Child and Adolescent Psychiatry* 40(11), pp. 1337-1345. doi: 10.1097/00004583-200111000-00015

Goodman, R. et al. 2000. The Development and Well-Being Assessment: Description and initial validation of an integrated assessment of child and adolescent psychopathology. *Journal of Child Psychology and Psychiatry and Allied Disciplines* 41(5), pp. 645-655. doi: 10.1111/j.1469-7610.2000.tb02345.x

Goodwin, G. M. et al. 2016. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology* 30(6), pp. 495-553.

Gore, F. M. et al. 2011. Global burden of disease in young people aged 10-24 years: A systematic analysis. *Lancet* 377(9783), pp. 2093-2102. doi: 10.1016/s0140-6736(11)60512-6

Gottesman, I. I. and Gould, T. D. 2003. The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry* 160(4), pp. 636-645. doi: 10.1176/appi.ajp.160.4.636

Gottesman, I. I. et al. 2010. Severe mental disorders in offspring with 2 psychiatrically ill parents. *Archives of General Psychiatry* 67(3), pp. 252-257. doi: 10.1001/archgenpsychiatry.2010.1

Grant, B. F. et al. 2005. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry* 66(10), pp. 1205-1215. doi: 10.4088/JCP.v66n1001

Green, M. F. and Nuechterlein, K. H. 2004. The MATRICS initiative: Developing a consensus cognitive battery for clinical trials. *Schizophrenia Research* 72(1), pp. 1-3. doi: 10.1016/j.schres.2004.09.006

Greenland, S. et al. 2016. Sparse data bias: A problem hiding in plain sight. *Bmj-British Medical Journal* 353, doi: 10.1136/bmj.i1981

Haghighi, M. et al. 2011. The Farsi version of the Hypomania Check-List 32 (HCL-32): Applicability and indication of a four-factorial solution. *Bmc Psychiatry* 11, doi: 10.1186/1471-244x-11-14

Hall, M.-H. et al. 2015. Genomewide association analyses of electrophysiological endophenotypes for schizophrenia and psychotic bipolar disorders: A preliminary report. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 168(3), pp. 151-161.

Hameed, M. A. and Lewis, A. J. 2016. Offspring of parents with schizophrenia: A systematic review of developmental features across childhood. *Harvard Review of Psychiatry* 24(2), pp. 104-117. doi: 10.1097/hrp.0000000000000076

Hamshere, M. L. et al. 2009. Age-at-onset in bipolar-I disorder: Mixture analysis of 1369 cases identifies three distinct clinical sub-groups. *Journal of Affective Disorders* 116(1-2), pp. 23-29. doi: 10.1016/j.jad.2008.10.021

Hamshere, M. L. et al. 2013. Shared polygenic contribution between childhood attention-deficit hyperactivity disorder and adult schizophrenia. *British Journal of Psychiatry* 203(2), pp. 107-111.

Hanssen, M. et al. 2003. How psychotic are individuals with non-psychotic disorders? *Social Psychiatry and Psychiatric Epidemiology* 38(3), pp. 149-154. doi: 10.1007/s00127-003-0622-7

Hantouche, E. G. and Akiskal, H. S. 2006. Toward a definition of a cyclothymic behavioral endophenotype: which traits tap the familial diathesis for bipolar II disorder? *Journal of Affective Disorders* 96(3), pp. 233-237. doi: 10.1016/j.jad.2004.08.013

Hantouche, E. G. et al. 2003. Factor structure of hypomania: Interrelationships with cyclothymia and the soft bipolar spectrum. *Journal of Affective Disorders* 73(1-2), pp. 39-47. doi: 10.1016/s0165-0327(02)00319-1

Hattori, E. et al. 2009. Preliminary genome-wide association study of bipolar disorder in the Japanese population. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics* 150(8), pp. 1110-1117.

Henin, A. et al. 2007. Childhood antecedent disorders to bipolar disorder in adults: A controlled study. *Journal of Affective Disorders* 99(1-3), pp. 51-57. doi: 10.1016/j.jad.2006.09.001

Henin, A. et al. 2005. Psychopathology in the offspring of parents with bipolar disorder: A controlled study. *Biological Psychiatry* 58(7), pp. 554-561. doi: 10.1016/j.biopsych.2005.06.010

Heun, R. and Maier, W. 1993. The distinction of bipolar II disorder from bipolar I and recurrent unipolar depression: Results of a controlled family study. *Acta Psychiatrica Scandinavica* 87(4), pp. 279-284. doi: 10.1111/j.1600-0447.1993.tb03372.x

Hidalgo-Mazzei, D. et al. 2015. Comorbid bipolar disorder and borderline personality disorder and substance use disorder. *Journal of Nervous and Mental Disease* 203(1), pp. 54-57. doi: 10.1097/nmd.0000000000000235

Hidiroglu, C. et al. 2015. Response inhibition and interference control in patients with bipolar I disorder and first-degree relatives. *Bipolar Disorders* 17(7), pp. 781-794. doi: 10.1111/bdi.12335

Higier, R. G. et al. 2014. Enhanced neurocognitive functioning and positive temperament in twins discordant for bipolar disorder. *American Journal of Psychiatry* 171(11), pp. 1191-1198. doi: 10.1176/appi.ajp.2014.13121683

Hirschfeld, R. M. A. and Vornik, L. A. 2004. Recognition and diagnosis of bipolar disorder. *Journal of Clinical Psychiatry* 65, pp. 5-9.

Hirschhorn, J. N. et al. 2002. A comprehensive review of genetic association studies. *Genetics in Medicine* 4(2), pp. 45-61. doi: 10.1097/00125817-200203000-00002

Hiyoshi, A. et al. 2017. Precursors in adolescence of adult-onset bipolar disorder. *Journal of Affective Disorders* 218, pp. 353-358. doi: 10.1016/j.jad.2017.04.071

Hjorthoj, C. et al. 2019. Polygenic risk for psychiatric disorder and singleness in patients with severe mental illness and controls. *Journal of Psychiatric Research* 119, pp. 60-66. doi: 10.1016/j.jpsychires.2019.09.013

Holmberg, K. and Hjern, A. 2008. Bullying and attention-deficit-hyperactivity disorder in 10-year-olds in a Swedish community. *Developmental Medicine and Child Neurology* 50(2), pp. 134-138. doi: 10.1111/j.1469-8749.2007.02019.x

Holtmann, M. et al. 2009. Validation of the Hypomania Checklist (HCL-32) in a nonclinical sample of German adolescents. *Journal of Adolescence* 32(5), pp. 1075-1088. doi: 10.1016/j.adolescence.2009.03.004

Hosang, G. M. et al. 2017. Characterization and structure of hypomania in a British nonclinical adolescent sample. *Journal of Affective Disorders* 207, pp. 228-235. doi: 10.1016/j.jad.2016.08.033

Howard, D. M. et al. 2019. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience* 22(3), pp. 343-352. doi: 10.1038/s41593-018-0326-7

Howieson, D. 2019. Current limitations of neuropsychological tests and assessment procedures. *Clinical Neuropsychologist* 33(2), pp. 200-208. doi: 10.1080/13854046.2018.1552762

Hubbard, L. et al. 2016. Evidence of Common Genetic Overlap Between Schizophrenia and Cognition. *Schizophrenia Bulletin* 42(3), pp. 832-842. doi: 10.1093/schbul/sbv168

Hunt, G. E. et al. 2016. Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990-2015: Systematic review and meta-analysis. *Journal of Affective Disorders* 206, pp. 331-349. doi: 10.1016/j.jad.2016.07.011

Hwu, H. G. et al. 1989. Prevalence of psychiatric disorders in Taiwan defined by the Chinese diagnostic interview schedule. *Acta Psychiatrica Scandinavica* 79(2), pp. 136-147. doi: 10.1111/j.1600-0447.1989.tb08581.x

Ikeda, M. et al. 2018. A genome-wide association study identifies two novel susceptibility loci and trans population polygenicity associated with bipolar disorder. *Molecular Psychiatry* 23(3), pp. 639-647. doi: 10.1038/mp.2016.259

Ingraham, L. J. and Kety, S. S. 2000. Adoption studies of schizophrenia. *American Journal of Medical Genetics* 97(1), pp. 18-22. doi: 10.1002/(sici)1096-8628(200021)97:1<18::aid-ajmg4>3.0.co;2-l

Insel, T. et al. 2010. Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. *American Journal of Psychiatry* 167(7), pp. 748-751. doi: 10.1176/appi.ajp.2010.09091379

Insel, T. R. 2014. The NIMH Research Domain Criteria (RDoC) project: Precision medicine for psychiatry. *American Journal of Psychiatry* 171(4), pp. 395-397. doi: 10.1176/appi.ajp.2014.14020138

Jansen, P. R. et al. 2018. Polygenic scores for schizophrenia and educational attainment are associated with behavioural problems in early childhood in the general population. *Journal of Child Psychology and Psychiatry* 59(1), pp. 39-47. doi: 10.1111/jcpp.12759

Jiang, Y. A. and Zhang, H. P. 2011. Propensity score-based nonparametric test revealing genetic variants underlying bipolar disorder. *Genetic Epidemiology* 35(2), pp. 125-132. doi: 10.1002/gepi.20558

Johannesen, J. K. et al. 2013. Diagnostic specificity of neurophysiological endophenotypes in schizophrenia and bipolar disorder. *Schizophrenia Bulletin* 39(6), pp. 1219-1229. doi: 10.1093/schbul/sbs093

Johansson, V. et al. 2019. A population-based heritability estimate of bipolar disorder - In a Swedish twin sample. *Psychiatry Research* 278, pp. 180-187. doi: 10.1016/j.psychres.2019.06.010

Johnson, S. L. et al. 2012. Creativity and bipolar disorder: Touched by fire or burning with questions? *Clinical Psychology Review* 32(1), pp. 1-12. doi: 10.1016/j.cpr.2011.10.001

Jones, H. J. et al. 2018. Investigating the genetic architecture of general and specific psychopathology in adolescence. *Translational Psychiatry* 8, doi: 10.1038/s41398-018-0204-9

Kahn, P. V. et al. 2012. Standardizing the use of the Continuous Performance Test in schizophrenia research: A validation study. *Schizophrenia Research* 142(1-3), pp. 153-158. doi: 10.1016/j.schres.2012.09.009

Kail, R. 1991. Development of processing speed in childhood and adolescence. *Advances in Child Development and Behavior* 23, pp. 151-185. doi: 10.1016/s0065-2407(08)60025-7

Kalman, J. L. et al. 2019. Investigating polygenic burden in age at disease onset in bipolar disorder: Findings from an international multicentric study. *Bipolar Disorders* 21(1), pp. 68-75. doi: 10.1111/bdi.12659

Keck, P. E. et al. 2008. Clinical and economic effects of unrecognized or inadequately treated bipolar disorder. *Journal of Psychiatric Practice* 14, pp. 31-38. doi: 10.1097/01.pra.0000320124.91799.2a

Kendler, K. S. et al. 2016a. Observed cognitive performance and deviation from familial cognitive aptitude at age 16 years and ages 18 to 20 Years and risk for schizophrenia and bipolar illness in a Swedish national sample. *Jama Psychiatry* 73(5), pp. 465-471. doi: 10.1001/jamapsychiatry.2016.0053

Kendler, K. S. et al. 2016b. A Swedish national prospective and co-relative study of school achievement at age 16, and risk for schizophrenia, other nonaffective psychosis, and bipolar illness. *Schizophrenia Bulletin* 42(1), pp. 77-86. doi: 10.1093/schbul/sbv103

Kendler, K. S. et al. 1995. A pilot Swedish twin study of affective illness including hospital ascertained and population ascertained subsamples: Results of model fitting. *Behavior Genetics* 25(3), pp. 217-232. doi: 10.1007/bf02197180

Khandaker, G. M. et al. 2011. A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophrenia Research* 132(2-3), pp. 220-227. doi: 10.1016/j.schres.2011.06.017

Kieseppa, T. et al. 2004. High concordance of bipolar I disorder in a nationwide sample of twins. *American Journal of Psychiatry* 161(10), pp. 1814-1821. doi: 10.1176/appi.ajp.161.10.1814

Kim, D. et al. 2015. Shared and distinct neurocognitive endophenotypes of schizophrenia and psychotic bipolar disorder. *Clinical Psychopharmacology and Neuroscience* 13(1), pp. 94-102. doi: 10.9758/cpn.2015.13.1.94

Kim, J. and Bang, H. 2016. Three common misuses of P values. *Dental Hypotheses* 7(3), pp. 73-80.

Kim, M. S. et al. 2018. Genetic disease risks can be misestimated across global populations. *Genome Biology* 19, doi: 10.1186/s13059-018-1561-7

Koenen, K. C. et al. 2009. Childhood IQ and Adult Mental Disorders: A Test of the Cognitive Reserve Hypothesis. *American Journal of Psychiatry* 166(1), pp. 50-57. doi: 10.1176/appi.ajp.2008.08030343

Koike, S. et al. 2018. Cognitive profiles in childhood and adolescence differ between adult psychotic and affective symptoms: A prospective birth cohort study. *Psychological Medicine* 48(1), pp. 11-22. doi: 10.1017/s0033291717000393

Kroon, J. S. et al. 2013. Incidence rates and risk factors of bipolar disorder in the general population: A population-based cohort study. *Bipolar Disorders* 15(3), pp. 306-313. doi: 10.1111/bdi.12058

Kyaga, S. et al. 2013. Mental illness, suicide and creativity: 40-Year prospective total population study. *Journal of Psychiatric Research* 47(1), pp. 83-90. doi: 10.1016/j.jpsychires.2012.09.010

Kyaga, S. et al. 2011. Creativity and mental disorder: Family study of 300 000 people with severe mental disorder. *British Journal of Psychiatry* 199(5), pp. 373-379. doi: 10.1192/bjp.bp.110.085316

Larsson, H. et al. 2013. Risk of bipolar disorder and schizophrenia in relatives of people with attention-deficit hyperactivity disorder. *British Journal of Psychiatry* 203(2), pp. 103-106. doi: 10.1192/bjp.bp.112.120808

Latalova, K. et al. 2011. Cognitive impairment in bipolar disorder. *Biomedical Papers-Olomouc* 155(1), pp. 19-26. doi: 10.5507/bp.155.2011.003

Latkin, C. A. et al. 2017. The relationship between social desirability bias and self-reports of health, substance use, and social network factors among urban substance users in Baltimore, Maryland. *Addictive Behaviors* 73, pp. 133-136. doi: 10.1016/j.addbeh.2017.05.005

Lau, P. et al. 2018. Prevalence of psychopathology in bipolar high-risk offspring and siblings: A meta-analysis. *European Child & Adolescent Psychiatry* 27(7), pp. 823-837. doi: 10.1007/s00787-017-1050-7

Leboyer, M. et al. 2005. Age at onset in bipolar affective disorders: A review. *Bipolar Disorders* 7(2), pp. 111-118. doi: 10.1111/j.1399-5618.2005.00181.x

Lee, C. K. et al. 1990. Psychiatric epidemiology in Korea. Part 1: Gender and age differences in Seol. *Journal of Nervous and Mental Disease* 178(4), pp. 242-246.

Lee, K. et al. 2016. Investigation of the clinical utility of the Hypomania Checklist 32 (HCL-32) for the screening of bipolar disorders in the non-clinical adult population. *Bmc Psychiatry* 16, doi: 10.1186/s12888-016-0831-8

Lee, M. T. M. et al. 2011. Genome-wide association study of bipolar I disorder in the Han Chinese population. *Molecular Psychiatry* 16(5), pp. 548-556. doi: 10.1038/mp.2010.43

Leite, R. T. P. et al. 2015. The use of cannabis as a predictor of early onset of bipolar disorder and suicide attempts. *Neural Plasticity*, doi: 10.1155/2015/434127

Lereya, S. T. et al. 2015. Adult mental health consequences of peer bullying and maltreatment in childhood: Two cohorts in two countries. *Lancet Psychiatry* 2(6), pp. 524-531. doi: 10.1016/s2215-0366(15)00165-0

Li, C. H. 2016. Confirmatory factor analysis with ordinal data: Comparing robust maximum likelihood and diagonally weighted least squares. *Behavior Research Methods* 48(3), pp. 936-949. doi: 10.3758/s13428-015-0619-7

Lichtenstein, P. et al. 2009. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: A population-based study. *Lancet* 373(9659), pp. 234-239. doi: 10.1016/s0140-6736(09)60072-6

Lieb, R. et al. 2002. Parental major depression and the risk of depression and other mental disorders in offspring - A prospective-longitudinal community study. *Archives of General Psychiatry* 59(4), pp. 365-374. doi: 10.1001/archpsyc.59.4.365

Lilienfeld, S. O. 2014. The Research Domain Criteria (RDoC): An analysis of methodological and conceptual challenges. *Behaviour Research and Therapy* 62, pp. 129-139. doi: 10.1016/j.brat.2014.07.019

Lin, A. et al. 2017. Academic performance in children of mothers with schizophrenia and other severe mental illness, and risk for subsequent development of psychosis: A population-based study. *Schizophrenia Bulletin* 43(1), pp. 205-213. doi: 10.1093/schbul/sbw042

Lin, P. I. et al. 2006. Clinical correlates and familial aggregation of age at onset in bipolar disorder. *American Journal of Psychiatry* 163(2), pp. 240-246. doi: 10.1176/appi.ajp.163.2.240

Liu, B. J. et al. 2017. Child self-report and parent ratings for the Strengths and Difficulties Questionnaire: Norms and agreement in a Swedish random population sample. *Scandinavian Journal of Child and Adolescent Psychiatry and Psychology* 5(1), pp. 13-27. doi: 10.21307/sjcapp-2017-002

Liu, J. H. et al. 2013. Confounding and heterogeneity in genetic association studies with admixed populations. *American Journal of Epidemiology* 177(4), pp. 351-360. doi: 10.1093/aje/kws234

Lopez-Munoz, F. et al. 2018. A history of the pharmacological treatment of bipolar disorder. *International Journal of Molecular Sciences* 19(7), doi: 10.3390/ijms19072143

Lowther, C. et al. 2017. Genomic disorders in psychiatry - What does the clinician need to know? *Current Psychiatry Reports* 19(11), doi: 10.1007/s11920-017-0831-5

Luna, B. et al. 2004. Maturation of cognitive processes from late childhood to adulthood. *Child Development* 75(5), pp. 1357-1372. doi: 10.1111/j.1467-8624.2004.00745.x

MacCabe, J. H. et al. 2010. Excellent school performance at age 16 and risk of adult bipolar disorder: National cohort study. *British Journal of Psychiatry* 196(2), pp. 109-115. doi: 10.1192/bjp.bp.108.060368

MacCabe, J. H. et al. 2018. Artistic creativity and risk for schizophrenia, bipolar disorder and unipolar depression: A Swedish population-based case-control study and sib-pair analysis. *British Journal of Psychiatry* 212(6), pp. 370-376. doi: 10.1192/bjp.2018.23

MacCabe, J. H. et al. 2013. Decline in cognitive performance between ages 13 and 18 years and the risk for psychosis in adulthood: A Swedish longitudinal cohort study in males. *Jama Psychiatry* 70(3), pp. 261-270. doi: 10.1001/2013.jamapsychiatry.43

MacQueen, G. M. et al. 2001. A review of psychosocial outcome in patients with bipolar disorder. *Acta Psychiatrica Scandinavica* 103(3), pp. 163-170. doi: 10.1034/j.1600-0447.2001.00059.x

Maier, W. et al. 1993. Continuity and discontinuity of affective disorders and schizophrenia: Results of a controlled family study. *Archives of General Psychiatry* 50(11), pp. 871-883.

Manchia, M. et al. 2008. Age at onset in Sardinian bipolar I patients: Evidence for three subgroups. *Bipolar Disorders* 10(3), pp. 443-446. doi: 10.1111/j.1399-5618.2007.00572.x

Manchia, M. et al. 2017. Clinical correlates of age at onset distribution in bipolar disorder: A comparison between diagnostic subgroups. *International Journal of Bipolar Disorders* 5, pp. 1-9. doi: 10.1186/s40345-017-0097-1

Marangoni, C. et al. 2016. The role of environmental exposures as risk factors for bipolar disorder: A systematic review of longitudinal studies. *Journal of Affective Disorders* 193, pp. 165-174. doi: 10.1016/j.jad.2015.12.055

Marder, S. R. and Fenton, W. 2004. Measurement and Treatment Research to Improve Cognition in Schizophrenia: NIMH MATRICS initiative to support the development of agents for improving cognition in schizophrenia. *Schizophrenia Research* 72(1), pp. 5-9. doi: 10.1016/j.schres.2004.09.010

Markota, M. et al. 2018. Association of schizophrenia polygenic risk score with manic and depressive psychosis in bipolar disorder. *Translational Psychiatry* 8, doi: 10.1038/s41398-018-0242-3

Martin, A. R. et al. 2017. Human demographic history impacts genetic risk prediction across diverse populations. *American Journal of Human Genetics* 100(4), pp. 635-649. doi: 10.1016/j.ajhg.2017.03.004

Martin, J. et al. 2015. Neurocognitive abilities in the general population and composite genetic risk scores for attention-deficit hyperactivity disorder. *Journal of Child Psychology and Psychiatry* 56(6), pp. 648-656. doi: 10.1111/jcpp.12336

Martin, J. et al. 2016. Association of genetic risk for schizophrenia with nonparticipation over time in a population-based cohort study. *American Journal of Epidemiology* 183(12), pp. 1149-1158.

Martino, D. J. et al. 2015. Neurocognitive functioning in the premorbid stage and in the first episode of bipolar disorder: A systematic review. *Psychiatry Research* 226(1), pp. 23-30. doi: 10.1016/j.psychres.2014.12.044

Marwaha, S. et al. 2013. Employment outcomes in people with bipolar disorder: a systematic review. *Acta Psychiatrica Scandinavica* 128(3), pp. 179-193. doi: 10.1111/acps.12087

McCarthy, J. B. et al. 2016. Impact of psychotic symptoms on cognitive functioning in child and adolescent psychiatric inpatients with severe mood disorders. *Psychiatry Research* 244, pp. 223-228. doi: 10.1016/j.psychres.2016.07.049

McDermid, J. et al. 2015. Co-morbidity of bipolar disorder and borderline personality disorder: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *Comprehensive Psychiatry* 58, pp. 18-28. doi: 10.1016/j.comppsych.2015.01.004

McElroy, S. L. et al. 2001. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *American Journal of Psychiatry* 158(3), pp. 420-426. doi: 10.1176/appi.ajp.158.3.420

McGirr, A. et al. 2016. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: A systematic review and meta-analysis of randomised placebo-controlled trials. *Lancet Psychiatry* 3(12), pp. 1138-1146. doi: 10.1016/s2215-0366(16)30264-4

McGuffin, P. et al. 2003. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Archives of General Psychiatry* 60(5), pp. 497-502. doi: 10.1001/archpsyc.60.5.497

McQueen, M. B. et al. 2005. Combined analysis from eleven linkage studies of bipolar disorder provides strong evidence of susceptibility loci on chromosomes 6q and 8q. *American Journal of Human Genetics* 77(4), pp. 582-595. doi: 10.1086/491603

McQuillin, A. et al. 2011. Analysis of genetic deletions and duplications in the University College London bipolar disorder case control sample. *European Journal of Human Genetics* 19(5), pp. 588-592. doi: 10.1038/ejhg.2010.221

Melroy-Greif, W. E. et al. 2017. Genetic influences on evening preference overlap with those for bipolar disorder in a sample of Mexican Americans and American Indians. *Twin Research and Human Genetics* 20(6), pp. 499-510. doi: 10.1017/thg.2017.62

Mendlewicz, J. and Rainer, J. 1977. Adoption study supporting genetic transmission in manic-depressive illness. *Nature* 268(5618), pp. 327-329. doi: 10.1038/268327a0

Menezes, P. R. et al. 2010. Paternal and maternal ages at conception and risk of bipolar affective disorder in their offspring. *Psychological Medicine* 40(3), pp. 477-485. doi: 10.1017/s003329170999064x

Merikangas, K. R. et al. 2007. Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. *Archives of General Psychiatry* 64(5), pp. 543-552. doi: 10.1001/archpsyc.64.5.543

Merikangas, K. R. et al. 2011. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Archives of General Psychiatry* 68(3), pp. 241-251.

Mesman, E. et al. 2016. Categorical and dimensional psychopathology in Dutch and US offspring of parents with bipolar disorder: A preliminary cross-national comparison. *Journal of Affective Disorders* 205, pp. 95-102. doi: 10.1016/j.jad.2016.06.011

Meyer, S. E. et al. 2004. A prospective study of the association among impaired executive functioning, childhood attentional problems, and the development of bipolar disorder. *Development and Psychopathology* 16(2), pp. 461-476. doi: 10.1017/s095457940404461x

Meyer, T. D. et al. 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), pp. 79-87. doi: 10.1016/j.comppsych.2006.07.001

Meyer, T. D. et al. 2014. The Hypomania Checklist (HCL) - Systematic review of its properties to screen for bipolar disorders. *Comprehensive Psychiatry* 55(5), pp. 1310-1321. doi: 10.1016/j.comppsych.2014.03.002

Mieloo, C. et al. 2012. Validity and reliability of the Strengths and Difficulties Questionnaire in 5-6 year olds: Differences by gender or by parental education? *Plos One* 7(5), doi: 10.1371/journal.pone.0036805

Mikkelsen, S. H. et al. 2017. Parental age and attention-deficit/hyperactivity disorder (ADHD). *International Journal of Epidemiology* 46(2), pp. 409-420. doi: 10.1093/ije/dyw073

Milaneschi, Y. et al. 2016. Polygenic dissection of major depression clinical heterogeneity. *Molecular Psychiatry* 21(4), pp. 516-522.

Miller, C. J. et al. 2009. Assessment tools for adult bipolar disorder. *Clinical Psychology-Science and Practice* 16(2), pp. 188-201. doi: 10.1111/j.1468-2850.2009.01158.x

Mistry, S. et al. 2019. Genetic risk for bipolar disorder and psychopathology from childhood to early adulthood. *Journal of Affective Disorders* 246, pp. 633-639. doi: 10.1016/j.jad.2018.12.091

Mistry, S. et al. 2018a. The use of polygenic risk scores to identify phenotypes associated with genetic risk of bipolar disorder and depression: A systematic review. *Journal of Affective Disorders* 234, pp. 148-155. doi: 10.1016/j.jad.2018.02.005

Mistry, S. et al. 2018b. The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: Systematic review. *Schizophrenia Research* 197, pp. 2-8. doi: 10.1016/j.schres.2017.10.037

Mistry, S. et al. 2017. Borderline personality and attention-deficit hyperactivity traits in childhood are associated with hypomanic features in early adulthood. *Journal of Affective Disorders* 221, pp. 246-253. doi: 10.1016/j.jad.2017.06.039

Mitchell, P. B. et al. 2004. Twelve-month prevalence and disability of DSM-IV bipolar disorder in an Australian general population survey. *Psychological Medicine* 34(5), pp. 777-785.

Mitchell, R. L. C. and Young, A. H. 2016. Theory of mind in bipolar disorder, with comparison to the impairments observed in schizophrenia. *Frontiers in Psychiatry* 6, p. 21. doi: 10.3389/fpsyt.2015.00188

Moher, D. et al. 2009. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Plos Medicine* 6(7), p. 6. doi: 10.1371/journal.pmed.1000097

Morris, S. E. and Cuthbert, B. N. 2012. Research Domain Criteria: Cognitive systems, neural circuits, and dimensions of behaviour. *Dialogues in Clinical Neuroscience* 14(1), pp. 29-37.

Morsel, A. M. et al. 2018. Systematic review of cognitive event related potentials in euthymic bipolar disorder. *Clinical Neurophysiology* 129(9), pp. 1854-1865. doi: 10.1016/j.clinph.2018.05.025

Mortensen, E. L. et al. 2005. IQ and mental disorder in young men. *British Journal of Psychiatry* 187, pp. 407-415. doi: 10.1192/bjp.187.5.407

Mosolov, S. N. et al. 2014. Validation of the Russian version of the Hypomania Checklist (HCL-32) for the detection of bipolar II disorder in patients with a current diagnosis of recurrent depression. *Journal of Affective Disorders* 155, pp. 90-95.

Muhleisen, T. W. et al. 2014. Genome-wide association study reveals two new risk loci for bipolar disorder. *Nature Communications* 5(3339), doi: 10.1038/ncomms4339

Mullins, N. et al. 2014. Genetic relationships between suicide attempts, suicidal ideation and major psychiatric disorders: A genome-wide association and polygenic scoring study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 165(5), pp. 428-437.

Murray, G. and Johnson, S. L. 2010. The clinical significance of creativity in bipolar disorder. *Clinical Psychology Review* 30(6), pp. 721-732. doi: 10.1016/j.cpr.2010.05.006

Musliner, K. L. et al. 2019. Association of polygenic liabilities for major depression, bipolar disorder, and schizophrenia with risk for depression in the Danish population. *JAMA Psychiatry* 76(5), pp. 516-525. doi: 10.1001/jamapsychiatry.2018.4166

Nanni, V. et al. 2012. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. *American Journal of Psychiatry* 169(2), pp. 141-151. doi: 10.1176/appi.ajp.2011.11020335

Newnham, E. A. and Janca, A. 2014. Childhood adversity and borderline personality disorder: a focus on adolescence. *Current Opinion in Psychiatry* 27(1), pp. 68-72. doi: 10.1097/yco.0000000000000028

Ni, G. Y. et al. 2019. The genetic relationship between female reproductive traits and six psychiatric disorders. *Scientific Reports* 9, doi: 10.1038/s41598-019-48403-x

Nievergelt, C. M. et al. 2015. Genomic predictors of combat stress vulnerability and resilience in U.S. Marines: A genome-wide association study across multiple ancestries implicates PRTFDC1 as a potential PTSD gene. *Psychoneuroendocrinology* 51, pp. 459-471.

Nivard, M. G. et al. 2017. Genetic overlap between schizophrenia and developmental psychopathology: Longitudinal and multivariate polygenic risk prediction of common psychiatric traits during development. *Schizophrenia Bulletin* 43(6), pp. 1197-1207. doi: 10.1093/schbul/sbx03

Nosarti, C. et al. 2012. Preterm birth and psychiatric disorders in young adult life. *Archives of General Psychiatry* 69(6), pp. 610-617.

Nowicki, S. and Carton, J. 1993. The measurement of emotional intensity from facial expressions. *Journal of Social Psychology* 133(5), pp. 749-750.

Nowicki, S. and Duke, M. P. 1994. Individual difference in the non-verbal communication of affect: The Diagnostic Analysis of NonVerbal Accuracy scale. *Journal of Nonverbal Behavior* 18(1), pp. 9-35. doi: 10.1007/bf02169077

Nuechterlein, K. H. et al. 2008. The MATRICS consensus cognitive battery, part 1: Test selection, reliability, and validity. *American Journal of Psychiatry* 165(2), pp. 203-213. doi: 10.1176/appi.ajp.2007.07010042

Nurnberger, J. I. et al. 2011. A high-risk study of bipolar disorder childhood clinical phenotypes as precursors of major mood disorders. *Archives of General Psychiatry* 68(10), pp. 1012-1020. doi: 10.1001/archgenpsychiatry.2011.126

O'Connell, K. S. et al. 2019. Identification of genetic overlap and novel risk loci for attention-deficit/hyperactivity disorder and bipolar disorder. *Molecular Psychiatry* doi: 10.1038/s41380-019-0613-z

O'Neill, S. M. et al. 2016. Birth by caesarean section and the risk of adult psychosis: A population-based cohort study. *Schizophrenia Bulletin* 42(3), pp. 633-641. doi: 10.1093/schbul/sbv152

Ogendahl, B. K. et al. 2006. Indicators of fetal growth and bipolar disorder: A Danish national register-based study. *Psychological Medicine* 36(9), pp. 1219-1224. doi: 10.1017/s0033291706008269

Olsen, L. et al. 2011. Copy number variations in affective disorders and meta-analysis. *Psychiatric Genetics* 21(6), pp. 319-322. doi: 10.1097/YPG.0b013e3283463deb

Ono, S. et al. 2015. Genomic structural variation in affective, anxiety, and stress-related disorders. *Journal of Neural Transmission* 122(1), pp. 69-78. doi: 10.1007/s00702-014-1309-9

Oswald, P. et al. 2003. Molecular genetics of affective disorders. *Current Opinion in Psychiatry* 16, pp. S63-S70. doi: 10.1097/00001504-200304002-00010

Owen, M. J. 2014. New approaches to psychiatric diagnostic classification. *Neuron* 84(3), pp. 564-571. doi: 10.1016/j.neuron.2014.10.028

Pacchiarotti, I. et al. 2013. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *American Journal of Psychiatry* 170(11), pp. 1249-1262. doi: 10.1176/appi.ajp.2013.13020185

Pain, O. et al. 2018. Genome-wide analysis of adolescent psychotic-like experiences shows genetic overlap with psychiatric disorders. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics* 177(4), pp. 416-425. doi: 10.1002/ajmg.b.32630

Palmier-Claus, J. E. et al. 2016. Relationship between childhood adversity and bipolar affective disorder: Systematic review and meta-analysis. *British Journal of Psychiatry* 209(6), pp. 454-459. doi: 10.1192/bjp.bp.115.179655

Palmos, A. B. et al. 2018. Genetic risk for psychiatric disorders and telomere length. *Frontiers in Genetics* 9, doi: 10.3389/fgene.2018.00468

Parellada, M. et al. 2017. Developmental differences between schizophrenia and bipolar disorder. *Schizophrenia Bulletin* 43(6), pp. 1176-1189. doi: 10.1093/schbul/sbx126

Parker, G. et al. 2016. Clinical status of comorbid bipolar disorder and borderline personality disorder. (209), pp. 209–215. doi: 10.1192/bjp.bp.115.177998

Pascual-Sanchez, A. et al. 2019. Quality of life in euthymic bipolar patients: A systematic review and meta-analysis. *Journal of Affective Disorders* 255, pp. 105-115. doi: 10.1016/j.jad.2019.05.032

Pedersen, A. B. et al. 2017. Missing data and multiple imputation in clinical epidemiological research. *Clinical Epidemiology* 9, pp. 157-165. doi: 10.2147/clep.s129785

Perlis, R. H. et al. 2009. Retrospective age at onset of bipolar disorder and outcome during two-year follow-up: Results from the STEP-BD study. *Bipolar Disorders* 11(4), pp. 391-400. doi: 10.1111/j.1399-5618.2009.00686.x

Pfennig, A. et al. 2017. Longitudinal changes in the antecedent and early manifest course of bipolar disorder: A narrative review of prospective studies. *Australian and New Zealand Journal of Psychiatry* 51(5), pp. 509-523. doi: 10.1177/0004867417700730

Phillips, M. L. and Kupfer, D. J. 2013. Bipolar disorder diagnosis: Challenges and future directions. *Lancet* 381(9878), pp. 1663-1671. doi: 10.1016/s0140-6736(13)60989-7

Piasecki, T. M. et al. 2019. Polygenic risk scores for psychiatric disorders reveal novel clues about the genetics of disordered gambling. *Twin Research and Human Genetics* 22(5), pp. 283-289. doi: 10.1017/thg.2019.90

Polimanti, R. et al. 2018a. Trauma exposure interacts with the genetic risk of bipolar disorder in alcohol misuse of US soldiers. *Acta Psychiatrica Scandinavica* 137(2), pp. 148-156. doi: 10.1111/acps.12843

Polimanti, R. et al. 2018b. Local adaptation in European populations affected the genetics of psychiatric disorders and behavioral traits. *Genome Medicine* 10, doi: 10.1186/s13073-018-0532-7

Porter, C. et al. 2020. Childhood adversity and borderline personality disorder: A meta-analysis. *Acta Psychiatrica Scandinavica* 141(1), pp. 6-20. doi: 10.1111/acps.13118

Posner, M. I. and Petersen, S. E. 1990. The attention system of the human brain. *Annual Review of Neuroscience* 13, pp. 25-42. doi: 10.1146/annurev.neuro.13.1.25

Power, R. A. et al. 2015. Polygenic risk scores for schizophrenia and bipolar disorder predict creativity. *Nature Neuroscience* 18(7), pp. 953-955. doi: 10.1038/nn.4040

Power, R. A. et al. 2017. Genome-wide association for major depression through age at onset stratification: Major Depressive Disorder working group of the Psychiatric Genomics Consortium. *Biological Psychiatry* 81(4), pp. 325-335. doi: 10.1016/j.biopsych.2016.05.010

Preisig, M. et al. 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, pp. 26-33. doi: 10.1016/j.jad.2015.10.005

Purcell, S. M. et al. 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 460(7256), pp. 748-752. doi: 10.1038/nature08185

Quinn, P. D. et al. 2017. Association between maternal smoking during pregnancy and severe mental illness in offspring. *Jama Psychiatry* 74(6), pp. 589-596. doi: 10.1001/jamapsychiatry.2017.0456

Ranlund, S. et al. 2018. A polygenic risk score analysis of psychosis endophenotypes across brain functional, structural, and cognitive domains. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics* 177(1), pp. 21-34. doi: 10.1002/ajmg.b.32581

Ranstam, J. 2012. Why the P-value culture is bad and confidence intervals a better alternative. *Osteoarthritis and Cartilage* 20(8), pp. 805-808. doi: 10.1016/j.joca.2012.04.001

Raouna, A. et al. 2018. Clinical staging model in offspring of parents with bipolar disorder: A systematic review. *Bipolar Disorders* 20(4), pp. 313-333. doi: 10.1111/bdi.12604

Rasic, D. et al. 2014. 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), pp. 28-38. doi: 10.1093/schbul/sbt114

Regeer, E. J. et al. 2015. Low self-recognition and awareness of past hypomanic and manic episodes in the general population. *International Journal of Bipolar Disorders* 3(1), doi: 10.1186/s40345-015-0039-8

Reginsson, G. W. et al. 2017. Polygenic risk scores for schizophrenia and bipolar disorder associate with addiction. *Addiction Biology* 23(1), pp. 485-492. doi: 10.1111/adb.12496

Reichenberg, A. et al. 2002. A population-based cohort study of premorbid intellectual, language, and behavioral functioning in patients with schizophrenia, schizoaffective disorder, and nonpsychotic bipolar disorder. *American Journal of Psychiatry* 159(12), pp. 2027-2035. doi: 10.1176/appi.ajp.159.12.2027

Rich, B. A. et al. 2008. Face emotion labeling deficits in children with bipolar disorder and severe mood dysregulation. *Development and Psychopathology* 20(2), pp. 529-546. doi: 10.1017/s0954579408000266

Richards, A. et al. 2019. Associations between schizophrenia genetic risk, anxiety disorders and manic/hypomanic episode in a longitudinal population cohort study. *British Journal of Psychiatry* 214(2), pp. 96-102. doi: 10.1192/bjp.2018.227

Ripke, S. et al. 2014. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511(7510), pp. 421-427.

Ritter, P. S. et al. 2012. The characteristics of sleep in patients with manifest bipolar disorder, subjects at high risk of developing the disease and healthy controls. *Journal of Neural Transmission* 119(10), pp. 1173-1184. doi: 10.1007/s00702-012-0883-y

Robertson, I. H. et al. 1996. The structure of normal human attention: The test of everyday attention. *Journal of the International Neuropsychological Society* 2(6), pp. 525-534.

Robinson, L. J. et al. 2006. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *Journal of Affective Disorders* 93(1-3), pp. 105-115. doi: 10.1016/j.jad.2006.02.016

Rowland, T. A. and Marwaha, S. 2018. Epidemiology and risk factors for bipolar disorder. *Therapeutic Advances in Psychopharmacology* 8(9), pp. 251-269. doi: 10.1177/2045125318769235

Rubino, I. A. et al. 2009. A comparative study of axis I antecedents before age 18 of unipolar depression, bipolar disorder and schizophrenia. *Psychopathology* 42(5), pp. 325-332. doi: 10.1159/000232975

Ruderfer, D. M. et al. 2014. Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia. *Molecular Psychiatry* 19(9), pp. 1017-1024.

Ruderfer, D. M. et al. 2018. Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. *Cell* 173(7), pp. 1705-1715. doi: 10.1016/j.cell.2018.05.046

Russell, G. et al. 2014. The association of attention deficit hyperactivity disorder with socioeconomic disadvantage: Alternative explanations and evidence. *Journal of Child Psychology and Psychiatry* 55(5), pp. 436-445. doi: 10.1111/jcpp.12170

Rybakowski, J. et al. 2010. Polish version of the Hypomania Checklist (HCL-32) scale: The results in treatment-resistant depression. *European Archives of Psychiatry and Clinical Neuroscience* 260(2), pp. 139-144. doi: 10.1007/s00406-009-0030-4

Sagiv, S. K. et al. 2013. Pre - and postnatal risk factors for ADHD in a nonclinical pediatric population. *Journal of Attention Disorders* 17(1), pp. 47-57. doi: 10.1177/1087054711427563

Sani, G. et al. 2014. Mixed depression: Clinical features and predictors of its onset associated with antidepressant use. *Psychotherapy and Psychosomatics* 83(4), pp. 213-221. doi: 10.1159/000358808

Sartorious, N. 2013. Comorbidity of mental and physical diseases: A main challenge for medicine of the 21st century. *Shanghai Jingshen Yixue* 25(2), pp. 68-69.

Schneck, C. D. et al. 2008. The prospective course of rapid-cycling bipolar disorder: Findings from the STEP-BD. *American Journal of Psychiatry* 165(3), pp. 370-377. doi: 10.1176/appi.ajp.2007.05081484

Schulze, T. et al. 2009. Two variants in Ankyrin 3 (ANK3) are independent genetic risk factors for bipolar disorder. *Molecular Psychiatry* 14(5), pp. 487-491.

Schulze, T. G. et al. 2014. Molecular genetic overlap in bipolar disorder, schizophrenia, and major depressive disorder. *World Journal of Biological Psychiatry* 15(3), pp. 200-208.

Schurhoff, F. et al. 2000. Early and late onset bipolar disorders: Two different forms of manic-depressive illness? *Journal of Affective Disorders* 58(3), pp. 215-221. doi: 10.1016/s0165-0327(99)00111-1

Scott, L. J. et al. 2009. Genome-wide association and meta-analysis of bipolar disorder in individuals of European ancestry. *Proceedings of the National Academy of Sciences of the United States of America* 106(18), pp. 7501-7506. doi: 10.1073/pnas.0813386106

Segurado, R. et al. 2003. Genome scan meta-analysis of schizophrenia and bipolar disorder, part III: Bipolar disorder. *American Journal of Human Genetics* 73(1), pp. 49-62. doi: 10.1086/376547

Seifuddin, F. et al. 2012. Meta-analysis of genetic association studies on bipolar disorder. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics* 159B(5), pp. 508-518. doi: 10.1002/ajmg.b.32057

Sharma, A. et al. 2017. Neuropsychological study of IQ scores in offspring of parents with bipolar I disorder. *Cognitive Neuropsychiatry* 22(1), pp. 17-27. doi: 10.1080/13546805.2016.1259103

Sharp, C. et al. 2012a. The incremental validity of borderline personality disorder relative to major depressive disorder for suicidal ideation and deliberate self-harm in adolescents. *Journal of Personality Disorders* 26(6), pp. 927-938.

Sharp, C. et al. 2012b. Borderline personality disorder in adolescents: Evidence in support of the Childhood Interview for DSM-IV Borderline Personality Disorder in a sample of adolescent inpatients. *Comprehensive Psychiatry* 53(6), pp. 765-774. doi: 10.1016/j.comppsych.2011.12.003

Shen, Y. C. 2018. Treatment of acute bipolar depression. *Tzu Chi Medical Journal* 30(3), pp. 141-147. doi: 10.4103/tcmj.tcmj_71_18

Shih, R. A. et al. 2004. A review of the evidence from family, twin and adoption studies for a genetic contribution to adult psychiatric disorders. *International Review of Psychiatry* 16(4), pp. 260-283. doi: 10.1080/09540260400014401

Sidor, M. M. and MacQueen, G. M. 2012. An update on antidepressant use in bipolar depression. *Current Psychiatry Reports* 14(6), pp. 696-704. doi: 10.1007/s11920-012-0323-6

Sieradzka, D. et al. 2014. Are genetic risk factors for psychosis also associated with dimension-specific psychotic experiences in adolescence? *PLoS ONE* 9(4), p. e94398. doi: 10.1371/journal.pone.0094398

Singh, M. K. et al. 2014. Distinguishing bipolar disorder from other psychiatric disorders in children. *Current Psychiatry Reports* 16(12), doi: 10.1007/s11920-014-0516-2

Sklar, P. 2002. Linkage analysis in psychiatric disorders: The emerging picture. *Annual Review of Genomics and Human Genetics* 3, pp. 371-413. doi: 10.1146/annurev.genom.3.022502.103141

Sklar, P. et al. 2011. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nature Genetics* 43(10), pp. 977-985.

Sklar, P. et al. 2008. Whole-genome association study of bipolar disorder. *Molecular Psychiatry* 13(6), pp. 558-569. doi: 10.1038/sj.mp.4002151

Smedler, E. et al. 2019. Genes, biomarkers, and clinical features associated with the course of bipolar disorder. *European Neuropsychopharmacology* 29(10), pp. 1152-1160. doi: 10.1016/j.euroneuro.2019.07.132

Smeland, O. B. et al. 2019. Genome-wide analysis reveals extensive genetic overlap between schizophrenia, bipolar disorder, and intelligence. *Molecular Psychiatry* 25, pp. 844-853. doi: 10.1038/s41380-018-0332-x

Smith, D. J. et al. 2015. Childhood IQ and risk of bipolar disorder in adulthood: Prospective birth cohort study. *British Journal of Psychiatry Open* 1(1), pp. 74-80.

Smith, E. N. et al. 2009. Genome-wide association study of bipolar disorder in European American and African American individuals. *Molecular Psychiatry* 14(8), pp. 755-763. doi: 10.1038/mp.2009.43

Smith, E. N. et al. 2011. Genome-wide association of bipolar disorder suggests an enrichment of replicable associations in regions near genes. *PLoS Genetics* 7(6), p. e1002134.

Smoller, J. W. and Finn, C. T. 2003. Family, twin, and adoption studies of bipolar disorder. *American Journal of Medical Genetics Part C-Seminars in Medical Genetics* 123C(1), pp. 48-58. doi: 10.1002/ajmg.c.20013

So, H. C. et al. 2019. Exploring shared genetic bases and causal relationships of schizophrenia and bipolar disorder with 28 cardiovascular and metabolic traits. *Psychological Medicine* 49(8), pp. 1286-1298. doi: 10.1017/s0033291718001812

Sole, B. et al. 2017. Cognitive impairment in bipolar disorder: Treatment and prevention strategies. *International Journal of Neuropsychopharmacology* 20(8), pp. 670-680. doi: 10.1093/ijnp/pyx032

Solomon, D. A. et al. 2010. Longitudinal course of bipolar I disorder duration of mood episodes. *Archives of General Psychiatry* 67(4), pp. 339-347. doi: 10.1001/archgenpsychiatry.2010.15

Song, J. et al. 2015. Bipolar disorder and its relation to major psychiatric disorders: A family-based study in the Swedish population. *Bipolar Disorders* 17(2), pp. 184-193. doi: 10.1111/bdi.12242

Song, J. et al. 2018. Specificity in etiology of subtypes of bipolar disorder: Evidence from a Swedish population-based family study. *Biological Psychiatry* 84(11), pp. 810-816. doi: 10.1016/j.biopsych.2017.11.014

Spencer, C. C. A. et al. 2009. Designing genome-wide association studies: Sample size, power, imputation, and the choice of genotyping chip. *Plos Genetics* 5(5), doi: 10.1371/journal.pgen.1000477

Sperry, S. H. et al. 2015. Measuring cognition in bipolar disorder with psychosis using the MATRICS consensus cognitive battery. *Journal of the International Neuropsychological Society* 21(6), pp. 468-472. doi: 10.1017/s1355617715000442

Spitzer, R. L. et al. 1978. Research Diagnostic Criteria - Rationale and reliability. *Archives of General Psychiatry* 35(6), pp. 773-782.

Stahl, E. et al. 2019. Genomewide association study identifies 30 loci associated with bipolar disorder *Nature Genetics* 51(5), pp. 793-803. doi: 10.1101/173062

Sterne, J. A. C. and Smith, G. D. 2001. Sifting the evidence - What's wrong with significance tests? *British Medical Journal* 322(7280), pp. 226-231. doi: 10.1136/bmj.322.7280.226

Sterne, J. A. C. et al. 2009. Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. *Bmj-British Medical Journal* 339, doi: 10.1136/bmj.b2393

Strakowski, S. M. and DelBello, M. P. 2000. The co-occurrence of bipolar and substance use disorders. *Clinical Psychology Review* 20(2), pp. 191-206. doi: 10.1016/s0272-7358(99)00025-2

Sullivan, G. M. and Feinn, R. 2012. Using effect size - or why the P value is not enough. *Journal of graduate medical education* 4(3), pp. 279-282. doi: 10.4300/JGME-D-12-00156.1

Sullivan, P. F. 2007. Spurious genetic associations. *Biological Psychiatry* 61(10), pp. 1121-1126. doi: 10.1016/j.biopsych.2006.11.010

Sullivan, P. F. et al. 2012. Family history of schizophrenia and bipolar disorder as risk factors for Autism. *Archives of General Psychiatry* 69(11), pp. 1099-1103. doi: 10.1001/archgenpsychiatry.2012.730

Sullivan, P. F. et al. 2000. Genetic epidemiology of major depression: Review and meta-analysis. *American Journal of Psychiatry* 157(10), pp. 1552-1562. doi: 10.1176/appi.ajp.157.10.1552

Szmulewicz, A. G. et al. 2015. An updated review on the neuropsychological profile of subjects with bipolar disorder. *Archives of Clinical Psychiatry* 42(5), pp. 139-146. doi: 10.1590/0101-60830000000064

Talati, A. et al. 2013. Maternal smoking during pregnancy and bipolar disorder in offspring. *American Journal of Psychiatry* 170(10), pp. 1178-1185. doi: 10.1176/appi.ajp.2013.12121500

Tansey, K. E. et al. 2014. Genetic susceptibility for bipolar disorder and response to antidepressants in major depressive disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 165(1), pp. 77-83.

Taylor, D. M. et al. 2014. Comparative efficacy and acceptability of drug treatments for bipolar depression: A multiple-treatments meta-analysis. *Acta Psychiatrica Scandinavica* 130(6), pp. 452-469. doi: 10.1111/acps.12343

Taylor, M. J. et al. 2019. Association of genetic risk factors for psychiatric disorders and traits of these disorders in a Swedish population twin sample. *Jama Psychiatry* 76(3), pp. 280-289. doi: 10.1001/jamapsychiatry.2018.3652

Teichmann, G. 1990. The influence of Karl Kleist on the nosology of Karl Leonhard. *Psychopathology* 23(4-6), pp. 267-276. doi: 10.1159/000284671

Tesli, M. et al. 2014. Polygenic risk score and the psychosis continuum model. *Acta Psychiatrica Scandinavica* 130(4), pp. 311-317.

Thabrew, H. et al. 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), doi: 10.1002/mpr.1610

Thapar, A. and McGuffin, P. 1998. Validity of the shortened Mood and Feelings Questionnaire in a community sample of children and adolescents: A preliminary research note. *Psychiatry Research* 81(2), pp. 259-268. doi: 10.1016/s0165-1781(98)00073-0

Thiebaut, S. et al. 2019. Crossed prevalence results between subtypes of eating disorder and bipolar disorder: A systematic review of the literature. *Encephale-Revue De Psychiatrie Clinique Biologique Et Therapeutique* 45(1), pp. 60-73. doi: 10.1016/j.encep.2018.06.001

Tiihonen, J. et al. 2005. Premorbid intellectual functioning in bipolar disorder and schizophrenia: Results from a cohort study of male conscripts. *American Journal of Psychiatry* 162(10), pp. 1904-1910. doi: 10.1176/appi.ajp.162.10.1904

Tijssen, M. J. A. et al. 2010. Prediction of transition from common adolescent bipolar experiences to bipolar disorder: 10-year study. *British Journal of Psychiatry* 196(2), pp. 102-108. doi: 10.1192/bjp.bp.109.065763

Tohen, M. et al. 2003. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Archives of General Psychiatry* 60(11), pp. 1079-1088. doi: 10.1001/archpsyc.60.11.1079

Topor, D. R. et al. 2013. Manic symptoms in youth with bipolar disorder: Factor analysis by age of symptom onset and current age. *Journal of Affective Disorders* 145(3), pp. 409-412. doi: 10.1016/j.jad.2012.06.024

Torgersen, S. 1986. Genetic factors in moderately severe and mild affective disorders. *Archives of General Psychiatry* 43(3), pp. 222-226.

Torres, I. J. et al. 2007. Neuropsychological functioning in euthymic bipolar disorder: A meta-analysis. *Acta Psychiatrica Scandinavica* 116, pp. 17-26. doi: 10.1111/j.1600-0447.2007.01055.x

Tozzi, F. et al. 2011. Admixture analysis of age at onset in bipolar disorder. *Psychiatry Research* 185(1-2), pp. 27-32. doi: 10.1016/j.psychres.2009.11.025

Trull, T. J. et al. 2018. Borderline personality disorder and substance use disorders: An updated review. *Borderline Personality Disorder and Emotion Dysregulation* 5, doi: 10.1186/s40479-018-0093-9

Tse, S. et al. 2014. Meta-analysis of predictors of favorable employment outcomes among individuals with bipolar disorder. *Bipolar Disorders* 16(3), pp. 217-229. doi: 10.1111/bdi.12148

Tsitsipa, E. and Fountoulakis, K. N. 2015. The neurocognitive functioning in bipolar disorder: A systematic review of data. *Annals of General Psychiatry* 14, p. 29. doi: 10.1186/s12991-015-0081-z

Tsuang, M. T. and Farone, S. V. 1990. *The Genetics of Mood Disorders*. Baltimore: The John Hopkins University Press.

Tsuang, M. T. et al. 1980. Morbidity risks of schizophrenia and affective disorders among 1st degree relatives of patients with schizophrenia, mania, depression and surgical conditions. *British Journal of Psychiatry* 137(DEC), pp. 497-504. doi: 10.1192/bjp.137.6.497

Tsuchiya, K. J. et al. 2003. Risk factors in relation to an emergence of bipolar disorder: A systematic review. *Bipolar Disorders* 5(4), pp. 231-242. doi: 10.1034/j.1399-5618.2003.00038.x

Undheim, A. M. and Sund, A. M. 2010. Prevalence of bullying and aggressive behavior and their relationship to mental health problems among 12-to 15-year-old Norwegian adolescents. *European Child & Adolescent Psychiatry* 19(11), pp. 803-811. doi: 10.1007/s00787-010-0131-7

Van den Bosch, L. M. C. et al. 2003. Trauma, dissociation, and posttraumatic stress disorder in female borderline patients with and without substance abuse problems. *Australian and New Zealand Journal of Psychiatry* 37(5), pp. 549-555. doi: 10.1046/j.1440-1614.2003.01199.x

van Hulzen, K. J. E. et al. 2017. Genetic overlap between attention-deficit/hyperactivity disorder and bipolar disorder: Evidence from genome-wide association study meta-analysis. *Biological Psychiatry* 82(9), pp. 634-641. doi: 10.1016/j.biopsych.2016.08.040

van Nierop, M. et al. 2015. Childhood trauma is associated with a specific admixture of affective, anxiety, and psychosis symptoms cutting across traditional diagnostic boundaries. *Psychological Medicine* 45(6), pp. 1277-1288. doi: 10.1017/s0033291714002372

van Os, J. and Reininghaus, U. 2016. Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry* 15(2), pp. 118-124. doi: 10.1002/wps.20310

Van Rheenen, T. E. et al. 2019. Current understandings of the trajectory and emerging correlates of cognitive impairment in bipolar disorder: An overview of evidence. *Bipolar Disorders*, pp. 1-15. doi: 10.1111/bdi.12821

Verduijn, J. et al. 2017. Using clinical characteristics to identify which patients with major depressive disorder have a higher genetic load for three psychiatric disorders. *Biological Psychiatry* 81(4), pp. 316-324. doi: 10.1016/j.biopsych.2016.05.024

Vierck, E. et al. 2015. Facial recognition deficits as a potential endophenotype in bipolar disorder. *Psychiatry Research* 230(1), pp. 102-107. doi: 10.1016/j.psychres.2015.08.033

Vieta, E. and Phillips, M. L. 2007. Deconstructing bipolar disorder: A critical review of its diagnostic validity and a proposal for DSM-V and ICD-11. *Schizophrenia Bulletin* 33(4), pp. 886-892. doi: 10.1093/schbul/sbm057

Vreeker, A. et al. 2016. High educational performance is a distinctive feature of bipolar disorder: a study on cognition in bipolar disorder, schizophrenia patients, relatives and controls. *Psychological Medicine* 46(4), pp. 807-818. doi: 10.1017/s0033291715002299

Wang, Y. Y. et al. 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, pp. 461-466. doi: 10.1016/j.psychres.2019.01.061

Ward, J. et al. 2018. Polygenic risk scores for major depressive disorder and neuroticism as predictors of antidepressant response: Meta-analysis of three treatment cohorts. *Plos One* 13(9), doi: 10.1371/journal.pone.0203896

Ware, E. B. et al. 2017. Heterogeneity in polygenic scores for common human traits. *BioRxiv*, doi: 10.1101/106062

Warrier, V. and Baron-Cohen, S. 2018. Genetic contribution to 'theory of mind' in adolescence. *Scientific Reports* 8, doi: 10.1038/s41598-018-21737-8

Wasserstein, R. L. and Lazar, N. A. 2016. The ASA's statement on p-values: Context, process, and purpose. *American Statistician* 70(2), pp. 129-131. doi: 10.1080/00031305.2016.1154108

Wechsler, D. et al. 1992. *WISC-III UK: Wechsler Intelligence Scale for Children*. 3rd ed. Sidcup, UK: The Psychological Corporation.

Weissman, M. M. et al. 1996. Cross-national epidemiology of major depression and bipolar disorder. *Jama-Journal of the American Medical Association* 276(4), pp. 293-299. doi: 10.1001/jama.276.4.293

Weissman, M. M. et al. 1984. Psychiatric disorders in the relatives of probands with affective disorders. *Archives of General Psychiatry* 41(1), pp. 13-21.

Weissman, M. M. et al. 1988. Affective disorders in five United States communities. *Psychological Medicine* 18(1), pp. 141-153.

Welham, J. et al. 2009. The antecedents of schizophrenia: A review of birth cohort studies. *Schizophrenia Bulletin* 35(3), pp. 603-623. doi: 10.1093/schbul/sbn084

Wellcome Trust Case Consortium et al. 2007. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 447(7145), pp. 661-678. doi: 10.1038/nature05911

Wells, J. E. et al. 2006. Prevalence, interference with life and severity of 12 month DSM-IV disorders in Te Rau Hinengaro: The New Zealand Mental Health Survey. *Australian and New Zealand Journal of Psychiatry* 40(10), pp. 845-854. doi: 10.1080/j.1440-1614.2006.01903.x

Wender, P. H. et al. 1986. Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. *Archives of General Psychiatry* 43(10), pp. 923-929.

Whiteford, H. A. et al. 2013. Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *Lancet* 382(9904), pp. 1575-1586. doi: 10.1016/s0140-6736(13)61611-6

Wilde, A. et al. 2014. 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* 158, pp. 37-47. doi: 10.1016/j.jad.2014.01.014

Winograd, G. et al. 2008. Adolescent borderline symptoms in the community: Prognosis for functioning over 20 years. *Journal of Child Psychology and Psychiatry* 49(9), pp. 933-941. doi: 10.1111/j.1469-7610.2008.01930.x

Wiste, A. et al. 2014. Bipolar polygenic loading and bipolar spectrum features in major depressive disorder. *Bipolar Disorders* 16(6), pp. 608-616.

Witt, S. H. et al. 2014. Analysis of genome-wide significant bipolar disorder genes in borderline personality disorder. *Psychiatric Genetics* 24(6), pp. 262-265. doi: 10.1097/ypg.0000000000000060

Witt, S. H. et al. 2017. Genome-wide association study of borderline personality disorder reveals genetic overlap with bipolar disorder, major depression and schizophrenia. *Translational Psychiatry* 7, p. 9. doi: 10.1038/tp.2017.115

Wolford, E. et al. 2017. Maternal depressive symptoms during and after pregnancy are associated with attentiondeficit/hyperactivity disorder symptoms in their 3- to 6-year-old children. *PLoS One* 12(12), pp. 1-13. doi: 10.1371/journal.pone.0190248

Wolke, D. et al. 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), pp. 846-855. doi: 10.1111/j.1469-7610.2012.02542.x

Wolke, D. et al. 2009. Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *British Journal of Psychiatry* 195(3), pp. 249-256. doi: 10.1192/bjp.bp.108.053751

Wolke, D. et al. 2001. Bullying and victimization of primary school children in England and Germany: Prevalence and school factors. *British Journal of Psychology* 92, pp. 673-696. doi: 10.1348/000712601162419

Woo, Y. S. et al. 2015. A diagnosis of bipolar spectrum disorder predicts diagnostic conversion from unipolar depression to bipolar disorder: A 5-year retrospective study. *Journal of Affective Disorders* 174, pp. 83-88. doi: 10.1016/j.jad.2014.11.034

Wood, A. et al. 1995. Properties of the Mood and Feelings Questionnaire in adolescent psychiatric outpatients - A research note. *Journal of Child Psychology and Psychiatry and Allied Disciplines* 36(2), pp. 327-334. doi: 10.1111/j.1469-7610.1995.tb01828.x

World-Health-Organisation. 1993. *The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research*. Geneva : World Health Organization.

Wray, N. R. et al. 2014. Research review: Polygenic methods and their application to psychiatric traits. *Journal of Child Psychology and Psychiatry* 55(10), pp. 1068-1087.

Wray, N. R. et al. 2018. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics* 50(5), pp. 668-681. doi: 10.1038/s41588-018-0090-3

Wu, Y. S. et al. 2008. Validation of the Chinese version of the Hypomania Checklist (HCL-32) as an instrument for detecting hypo(mania) in patients with mood disorders. *Journal of Affective Disorders* 106(1-2), pp. 133-143. doi: 10.1016/j.jad.2007.06.004

Yatham, L. N. et al. 2010. The International Society for Bipolar Disorders-Battery for Assessment of Neurocognition (ISBD-BANC). *Bipolar Disorders* 12(4), pp. 351-363. doi: 10.1111/j.1399-5618.2010.00830.x

Yosifova, A. et al. 2011. Genome-wide association study on bipolar disorder in the Bulgarian population. *Genes, Brain and Behavior* 10(7), pp. 789-797.

Youngstrom, E. A. et al. 2010. Bipolar and ADHD comorbidity: Both artifact and outgrowth of shared mechanisms. *Clinical Psychology-Science and Practice* 17(4), pp. 350-359. doi: 10.1111/j.1468-2850.2010.01226.x

Zammit, S. et al. 2004. A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Archives of General Psychiatry* 61(4), pp. 354-360. doi: 10.1001/archpsyc.61.4.354

Zammit, S. et al. 2014. A population-based study of genetic variation and psychotic experiences in adolescents. *Schizophrenia Bulletin* 40(6), pp. 1254-1262. doi: 10.1093/schbul/sbt146

Zanarini, M. et al. 1996. *The Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV)*. Belmont, MA: McLean Hospital.

Zanarini, M. C. et al. 2004. The UK Version of the Childhood Interview for DSM-IV Borderline Personality Disorder (UK-CI-BPD). University of Bristol.

Zhuo, C. J. et al. 2017. Potential value of genomic copy number variations in schizophrenia. *Frontiers in Molecular Neuroscience* 10, doi: 10.3389/fnmol.2017.00204

Zilanawala, A. et al. 2015. Ethnic differences in children's socioemotional difficulties: Findings from the Millennium Cohort Study. *Social Science & Medicine* 134, pp. 95-106. doi: 10.1016/j.socscimed.2015.04.012