Phenotypic and genotypic associations across the psychosis spectrum

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Summary

Current diagnostic categories for psychosis and affective disorders are at odds with the continuous nature of clinical phenotypes and the shared genetic architecture of these disorders. Phenotypic analyses within and across diagnoses are required to dissect the relationship between genetic risk and phenotypic features of psychosis-spectrum disorders.

To examine the relationship between schizoaffective disorder depressive-type (SA-D) and schizophrenia, I investigated phenotypic and polygenic differences between individuals with these diagnoses. SA-D was associated with greater severity of depression and risk factors for depression, including elevated polygenic risk score (PRS) for depression, but not for schizophrenia or bipolar disorder. These findings are consistent with SA-D being a hybrid of schizophrenia and depression.

Next, I used factor analysis to derive symptom dimensions in individuals with schizophrenia, schizoaffective disorder, and bipolar disorder and used latent class analysis to cluster individuals into phenotypically-homogenous groups. Symptom domains were able to capture an additional degree of polygenic risk that was not explained by diagnosis. I identified three clusters, characterised by relatively lower functioning, intermediate functioning, and higher functioning. The classes were also able to capture an additional level of polygenic risk not explained by diagnosis. These findings suggest that dimensional or alternative categorical approaches to conceptualising psychosis-spectrum disorders may reflect underlying genetic liability to a greater extent than current systems.

Lastly, I examined physical activity as a dimensional phenotype of relevance across disorders. Levels of physical activity differed substantially between individuals with and without psychiatric disorders but were modestly associated with PRS in the general population, indicating that reduced activity in psychiatric disorders may be a consequence of the disorder, rather than due to genetic liability.

This thesis identifies novel associations between dimensional phenotypes and PRS for psychiatric disorders and contributes evidence towards refining diagnostic systems in order to improve the validity of psychosis-spectrum disorders.

Contributions

The work undertaken in this thesis was made possible by the National Institute for Mental Health, in the form of a grant awarded to the Psychiatric Genomics Consortium on which I was employed as a research assistant for the duration of my PhD. Funding from the Medical Research Council also supported the development of my research.

The ideas for this PhD arose from my research interests and were developed through discussions between myself and my supervisors, James Walters, Michael O'Donovan, Sophie Legge, and Leon Hubbard. I performed all statistical analyses described in the thesis, with guidance from the Bioinformatics and Biostatistics Unit and Cardiff University. Contributions by other individuals are described below:

Chapter 1: Sections from this chapter discussing the genetic aetiology of schizophrenia and shared genetic architecture of schizophrenia and bipolar disorder were included in a review paper I wrote, with editing and revisions by Prof James Walters, Dr Sophie Legge, and Dr Antonio Pardiñas (see section 'Publications based on this thesis').

Chapter 2: Data collection and clinical ratings for the three samples included in this chapter were undertaken by various teams between 1994 and 2017, supervised by Prof James Walters, Prof Michael Owen, Prof Stanley Zammit, and Dr Alastair Cardno. I was responsible for phenotypic ratings for a portion of individuals in the CardiffCOGS sample. Genotyping, quality control, and calculation of the polygenic risk scores included in this chapter was completed by Dr Sophie Legge and Dr Leon Hubbard. I conducted all analyses in this sample, with guidance from my supervisors and broader members of the psychosis team. I wrote the paper that arose from this work, with editing and revisions supported by my co-authors (see section 'Publications based on this thesis').

Chapter 3: Data collection and clinical ratings are as described above, with the addition of the Bipolar Disorder Research Network (BDRN) sample, which was collected by field

teams under the supervision of Prof Nicholas Craddock and Prof Lisa Jones. Dr Sophie Legge completed the initial cleaning and merging of the Cardiff F-series and Cardiff Affected-sibs samples, which I then amalgamated with the CardiffCOGS and BDRN samples. Genotyping of the samples included in this chapter was conducted by the MRC Centre for Neuropsychiatric Genetics and Genomics and the Wellcome Trust Case Control Consortium. Imputation and initial quality control of the genotype data was conducted by Dr Leon Hubbard. I was responsible for amalgamating the different genotype samples together and conducted further quality control checks on the combined samples. I calculated the polygenic risk scores and conducted all analyses included in this chapter.

Chapter 4: The data used in this chapter was provided by UK Biobank, with collection and processing of the accelerometer data undertaken by the accelerometer working group, supervised by Dr Aiden Doherty. Extraction of the data used to define diagnosis was conducted by Dr Matthew Bracher-Smith. Genotype data processing and quality control was conducted by Prof Valentina Escott-Price and Dr Georgina Menzies; Dr Sophie Legge calculated the polygenic risk scores. I conducted all analyses in this chapter with guidance from the Bioinformatics and Biostatistics Unit and the MRC Centre for Neuropsychiatric Genetics and Genomics. I wrote the paper that arose from this work with editing and revisions supported by my co-authors (see section 'Publications based on this thesis').

Publications based on this thesis

Chapter 1

Dennison, C.A., Legge, S.E., Pardiñas, A.F. and Walters, J.T., 2020. Genome-wide association studies in schizophrenia: Recent advances, challenges, and future perspective. Schizophrenia research, 217, pp.4-12.

Chapter 2

Dennison, C.A., Legge, S.E., Hubbard, L., Lynham, A.J., Zammit, S., Holmans, P., Cardno, A.G., Owen, M.J., O'Donovan, M.C. and Walters, J.T., 2021. Risk factors, clinical features, and polygenic risk scores in schizophrenia and schizoaffective disorder depressive-type. Schizophrenia Bulletin.

Chapter 4

Dennison, C.A., Legge, S.E., Bracher-Smith, M., Menzies, G., Escott-Price, V., Smith, D.J., Doherty, A.R., Owen, M.J., O'Donovan, M.C. and Walters, J.T., 2021. Association of genetic liability for psychiatric disorders with accelerometer-assessed physical activity in the UK Biobank. Plos one, 16(3), p.e0249189.

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Chapter 1

Background Literature

1.1 Introduction

The validity of categorical approaches to psychiatric nosology is under debate. Particular attention has been paid to whether dimensional models would be a more valid and reliable approach to diagnosing psychotic and affective disorders, following evidence that the genetic architecture of these disorders is substantially shared and argues against independent categories (Craddock and Owen, 2005; Lee *et al.*, 2019). The aim of this thesis is to examine associations between categorical diagnoses and dimensional phenotypes and polygenic risk, in psychosis-spectrum disorders. Specifically, I aim to i) examine phenotypic and polygenic differences between schizophrenia and schizoaffective disorder depressive-type (SA-D), ii) investigate polygenic associations with symptom dimensions and phenotypic clusters in schizophrenia, schizoaffective disorder, and bipolar disorder, and iii) examine the relationship between psychiatric diagnosis, polygenic risk, and levels of physical activity. This introduction will provide an overview of schizophrenia, bipolar disorder, and schizoaffective disorder, covering the conception, clinical features, and aetiology of these disorders. Then, I will discuss the validity of these diagnoses including criticisms and alternative approaches to nosology, focussing on literature examining dimensional approaches and subtyping within and across the psychosis-affective spectrum

1.2 Schizophrenia

Schizophrenia is a severe psychiatric disorder characterised by positive, negative, and disorganised symptoms, as well as associated features such as cognitive impairments (Tandon, Keshavan and Nasrallah, 2008). Although there is significant heterogeneity in clinical presentation, individuals with schizophrenia typically experience a chronic course of illness with substantially reduced functioning and are at increased risk of

several physical health problems and premature death (Tandon, Keshavan and Nasrallah, 2008).

1.2.1 Conception and criteria

In 1899, Emil Kraepelin used the term 'dementia praecox' to describe a progressive, deteriorating disorder (dementia), marked by a considerably earlier onset (praecox) than other dementias. Kraepelin believed the signs and symptoms of 'dementia praecox' to be distinguishable from psychosis in the presence of affective symptoms, which he termed 'manic-depressive illness' (a disorder we now term bipolar disorder). Kraepelin described nine different subtypes of 'dementia praecox' based on longitudinal observation of his patients, including hebephrenic, paranoid, and catatonic (Carpenter and Stephens, 1979), which were used in both the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of mental disorders (DSM), until the most recent versions (ICD-11 and DSM-5). Whilst the specific features varied between subtypes, they were linked together by the presence of cognitive impairments (Jablensky, 2010). The term schizophrenia was first used by Bleuler, who believed that schizophrenia was not one single disorder but a group of disorders. Bleuler distinguished between signs that he deemed fundamental to a diagnosis of schizophrenia, such as disorganised speech, ambivalence, and incongruent affect, and symptoms that were associated but not essential features to make a diagnosis, such as hallucinations and delusions (Jablensky, 2010). Schneider developed this concept further and defined eight symptoms that could be considered unique to schizophrenia that he termed 'first rank' symptoms. These included many symptoms which are still specified in current diagnostic criteria, including third person auditory hallucinations, running commentary, thought interference, and delusions of passivity (Jablensky, 2010). Despite the inclusion of these symptoms in the ICD definition of schizophrenia, they have been criticised as lacking specificity and frequency in schizophrenia (Nordgaard *et al.*, 2008) and have since been removed from ICD-11. Other prominent psychiatrists during the 20th century developed their own criteria for diagnosing schizophrenia, and defined subtypes based on the signs and symptoms they observed. Leonhard developed a system for classifying psychosis, based on course of illness, outcomes, and family history (Jablensky, 2010). Under Leonhard's system,

psychotic disorders were split into categories termed systematic, unsystematic, and cycloid, with several further subtypes under each of these categories (Fish, 1964). The clinical utility and validity of dividing schizophrenia into many subcategories has been criticised, and Leonhard's system was not widely adopted (Carpenter and Stephens, 1979). Others have attempted to categorise schizophrenia in simpler ways, including separating positive and negative schizophrenia, also known as type one and type two schizophrenia. The positive/negative distinction was proposed by Crow and was based on whether positive or negative symptoms were prominent in the clinical picture (Jablensky, 2010). Carpenter and colleagues (1988) proposed a similar concept they termed deficit schizophrenia, thought to be a distinct disorder on the psychosis spectrum characterised by persistent negative symptoms and poorer prognosis. Unlike in negative schizophrenia, positive symptoms could still be prevalent in deficit schizophrenia and were observed to the same extent as in non-deficit schizophrenia (Carpenter, Heinrichs and Wagman, 1988). It has since been suggested that deficit may be more informative as a continuous dimension, rather than a binary trait, to quantify the degree of deficit (Tandon, Nasrallah and Keshavan, 2009). More recent attempts to subdivide schizophrenia using data-driven techniques are described in section 1.7.2 of this chapter.

The first edition of the DSM (American Psychiatric Association, 1952) described schizophrenia as a disorder defined by delusions, withdrawal from reality, and disturbances to thought processes (Thomas, 2001). Specific criteria for diagnosing schizophrenia were not introduced until DSM-III in 1980 and required at least one of Schneider's first rank symptoms for a period of 6 months or more alongside impairment in multiple areas of everyday functioning (Thomas, 2001). Schneider's first-rank symptoms were also incorporated into ICD-9 and listed subtypes of schizophrenia including paranoid, hebephrenic, catatonic, latent, residual, and simple(World Health Organisation, 1975). ICD-10 kept Schneider's symptoms as prominent indicators of schizophrenia (World Health Organisation., no date), whilst DSM-IV departed from this and instead required any two of hallucinations, delusions, negative symptoms, disorganisation, or catatonia (American Psychiatric Association, 1994). Both diagnostic systems retained the traditional subtypes of schizophrenia,

although these were dropped for DSM-5 (American Psychiatric Association., 2013) and ICD-11. Although published in 2019, ICD-11 is not due to be adopted into clinical practice until 2022, thus I refer to ICD-10 throughout this thesis as it is currently the most applicable criteria. Table 1.1 details the diagnostic criteria for schizophrenia in ICD-10 and DSM-5.

ICD-10 and DSM-5 criteria for schizophrenia		
	ICD-10	**DSM-5**
Symptoms	*One of:* • Thought echo, insertion, withdrawal, or broadcasting • Delusions of control, influence, or passivity, or delusional perception • 3rd person auditory hallucinations or running commentary • Culturally inappropriate or completely impossible delusions *Or two of:* • Persistent hallucinations every day for >1month with non-affective delusions • Incoherent or irrelevant speech • Catatonic behaviour • Negative symptoms	*Two or more of the following, including at least one of the first three:* • Delusions • Hallucinations • Disorganised speech • Grossly disorganised or catatonic behaviour • Negative symptoms *And* • Level of functioning in one or more major areas is markedly below the level achieved prior to onset
Duration	Symptoms present for most of the time during an episode lasting at least 1 month.	Continuous signs present for at least 6 months, including at least 1 month of symptoms - or less if successfully treated.
Exclusions	Also meets criteria for manic or depressive episode before onset of psychosis. Disorder attributable to organic brain disease or alcohol or drug-related intoxication.	Schizoaffective disorder and depression or bipolar disorder with psychosis have been ruled out. Disturbance not attributable to the effects of substance or another medical condition.

Table 1.1. Diagnostic criteria for schizophrenia in the International Classification of Diseases (ICD-10)(World Health Organisation., no date) and Diagnostic and Statistical Manual of Mental Disorders (DSM-5)(American Psychiatric Association., 2013).

1.2.2 Symptoms

Schizophrenia is now considered to be a multi-domain disorder, though the primary symptoms of have remained consistent since Kraepelin's early descriptions. Individuals with schizophrenia are likely to experience a combination of positive, negative, and disorganised symptoms to varying degrees, in addition to possible cognitive deficits (Tandon, Nasrallah and Keshavan, 2009).

1.2.2.1 Positive symptoms

Positive symptoms of schizophrenia include hallucinations and delusions and are termed positive as their presence is gained rather than lost (Fletcher and Frith, 2008). Hallucinations are perceptions that are not the result of external stimuli. Whilst auditory hallucinations are the most common, and certain types of auditory hallucinations are included in Schneider's first-rank symptoms, hallucinations can be in any sensory modality, including visual, olfactory, gustatory, and tactile (Tandon, Nasrallah and Keshavan, 2009).

Delusions are false beliefs, inconsistent with the person's cultural background, that are firmly held even in the presence of contradictory evidence (Fletcher and Frith, 2008). Delusions can take many different forms, but typically will be persecutory, grandiose, jealous, religious, or somatic in content. Bizarre delusions are delusions that are physically impossible, and have been previously considered a hallmark of schizophrenia, as have delusions regarding thought interference, although neither are necessary for a diagnosis (Tandon, Nasrallah and Keshavan, 2009). Thought insertion, withdrawal, or broadcasting refer to the individual believing that an external source is placing or removing thoughts from their head, or that their thoughts are being transmitted in a way that makes them audible to others. These types of delusions were considered first-rank and are still included as cardinal symptoms of schizophrenia in ICD-10.

1.2.2.2 Negative symptoms

Negative symptoms, so called as they represent the loss of a function or ability, include blunted affect, alogia, anhedonia, asociality, and avolition (Marder and Galderisi, 2017). Blunted affect refers to the dampening of the observed expression of emotion and can be seen in reduced facial expressivity and gestures (Marder and Galderisi, 2017). Alogia concerns impoverished speech, including slowed thought processes that can be marked by brief, vague responses, and limited spontaneous elaboration. In factor analytical studies of negative symptoms, blunted affect and alogia tend to group together into one factor, representing reduced expressivity, whilst anhedonia, asociality, and avolition form a second factor characterised by reduced motivation and pleasure (Strauss *et al.*, 2018). Anhedonia in schizophrenia is marked by lack of interest and ability to anticipate feelings of pleasure, indicated by withdrawal from activities and premorbid interests. Asociality refers to a reduced motivation for social contact, which may be observed through few or no social or intimate relationships due to a lack of interest in forming those relationships, rather than an inability to form or maintain them. Avolition refers to a lack of motivation and goal-directed activity and includes signs such as poor grooming and hygiene habits, poor social and occupational functioning, and excessive sedentary behaviour (Marder and Galderisi, 2017). Negative symptoms can occur as primary or secondary phenomena (Sarkar, Hillner and Velligan, 2015). Primary negative symptoms are persistent and enduring symptoms resulting from the pathophysiology of schizophrenia. Secondary negative symptoms arise as consequences of another factor, such as medication side effects or symptoms of depression, and are typically less persistent than primary negative symptoms (Sarkar, Hillner and Velligan, 2015). Whether primary or secondary, negative symptoms are difficult to treat and represent one of the largest barriers to recovery in schizophrenia (Remington *et al.*, 2016).

1.2.2.3 Disorganised symptoms

Disorganisation primarily involves positive formal thought disorder, but also includes bizarre, agitated, or repetitive behaviour and inappropriate affect. Positive formal thought disorder is characterised by disordered thought and language processes that

make speech difficult to understand and follow. Individuals with disorganised speech may show derailment, where ideas fall off track, tangentiality, where the person replies in an irrelevant and idiosyncratic manner, or they may draw illogical conclusions as they speak, making it difficult to follow (Tandon, Nasrallah and Keshavan, 2009). Inappropriate affect refers to emotional expression that is incongruent with the circumstance, and commonly groups with other disorganised symptoms in factor analytical studies (Cardno *et al.*, 1996). Disorganised symptoms are the hallmark of the hebephrenia subtype of schizophrenia, which has been associated with poorer prognosis and greater genetic transmission (McGlashan and Fenton, 1991).

1.2.2.4 Cognitive impairments

Despite cognitive impairments being recognised as a feature of schizophrenia since Kraepelin, they have not been included in diagnostic criteria of schizophrenia due to lack of specificity. Almost all individuals with schizophrenia show some degree of cognitive impairment (Keefe, Eesley and Poe, 2005), with performance on average falling between 1.5 and 2.5 standard deviations lower than the population mean on composite measures of cognition (Hill *et al.*, 2013; Lynham *et al.*, 2018). Impairments have been observed across all domains of cognition, indicating a global impairment, with specific greater deficits observed in processing speed and episodic memory(Schaefer *et al.*, 2013). People with schizophrenia also show a greater degree of cognitive impairment compared to individuals with schizoaffective disorder and bipolar disorder, indicating a spectrum effect with increasing liability to schizophrenia (Hill *et al.*, 2013). Cognitive decline during adolescence is associated with increased risk of schizophrenia in adulthood (MacCabe *et al.*, 2013), and cognitive impairments are observed in antipsychotic-naïve individuals (Fatouros-Bergman *et al.*, 2014) and in relatives of people with schizophrenia (Sitskoorn *et al.*, 2004). Thus, these studies indicate that cognition in schizophrenia may have a genetic component and secondary effects of the disorder itself are not entirely responsible for these impairments. Some degree of cognitive decline post-onset may occur in schizophrenia, although there is a lack of methodologically rigorous studies in this area (Hedman *et al.*, 2013). Poorer

functional outcomes are associated with impairments in cognition, including independent living, social functioning, and occupational functioning (Fett *et al.*, 2011), yet antipsychotic treatment does not improve cognitive performance once practice effects are taken into consideration (Goldberg *et al.*, 2010).

1.2.3 Epidemiology

Schizophrenia has an incidence of 15.2 per 100,000 people per year (McGrath *et al.*, 2004) and a lifetime prevalence of 4 per 1000 people (Saha *et al.*, 2005). Incidence is consistent across all areas of the globe and does not vary by economic status of the country, although is higher amongst males than females, in migrants than in native people, and in urban areas than in rural areas (McGrath *et al.*, 2004). Conversely, estimates of prevalence are consistent amongst males and females, and between urban and rural environments (Saha *et al.*, 2005). However, prevalence estimates for less developed economies are lower than for emerging and developed economies (Saha *et al.*, 2005). Prevalence was also significantly higher in migrants compared to natives, providing further evidence for migration as a risk factor for schizophrenia (Saha *et al.*, 2005).

In 2016, schizophrenia was responsible for 1.7% of total years lived with disability, equivalent to 13.4 million years lived with disability (Charlson *et al.*, 2018), and is responsible for 4.1% of years lost to disability in individuals aged 10-24 years (Gore *et al.*, 2011). Disease burden peaks at age 30-40 years and is comparable in males and females, although the number of years lived with disability is higher in upper-middle and lower-middle income countries (Charlson *et al.*, 2018). A systematic review of studies estimating the economic burden of schizophrenia across the globe found estimates ranged from US$94 million to US$102 billion, dependent on the country and the methodology used to ascertain costs (Chong *et al.*, 2016). These findings indicate a substantial burden of costs associated with schizophrenia, primarily resulting from indirect costs, i.e., costs resulting from loss of productivity, such as unemployment, early retirement, and sick leave for the person and their caregivers, rather than direct medical costs (Chong *et al.*, 2016).

The life expectancy of people with schizophrenia is around 65 years (Hjorthøj *et al.*, 2017), compared to a life expectancy of 79.4 years for males and 83.1 years for

females in the UK (ONS, 2020). A systematic review and meta-analysis of studies examining mortality in schizophrenia found that people with schizophrenia had a standardised mortality ratio (SMR) of 2.58 for all-cause mortality compared to the general population, indicating that in a given time period, people with schizophrenia are two and a half times more likely to die than people without schizophrenia (Saha, Chant and McGrath, 2007). SMR for males for all causes was higher than for females, 3.02 compared to 2.37, respectively, although this difference was not statistically significant (Saha, Chant and McGrath, 2007). People with schizophrenia were more likely to die from all specific causes of death, apart from cerebrovascular diseases (Saha, Chant and McGrath, 2007), although it is possible this could reflect survivor bias. There was insufficient evidence to evaluate the impact of urbanicity, migration, and geographical location on SMR in schizophrenia. The epidemiological studies described above systematically reviewed the literature and conducted meta-analyses on all available and appropriate studies, thus presenting the most reliable estimates of incidence, prevalence, and mortality. However, the findings of Saha and colleagues (2007) demonstrate an increase in SMRs over time and suggest that they may continue to do so once the long-term effects of atypical antipsychotics can be evaluated. Thus, more recent data are needed to assess whether SMRs have continued to increase in schizophrenia.

1.2.4 Illness course and treatment

Symptoms of schizophrenia typically emerge in late adolescence or early adulthood with the distribution of age at onset peaking at 15-25 years for men and 20-29 years for women, with an additional, smaller peak observed in women around the time of menopause (Häfner *et al.*, 1993). The onset of schizophrenia is often preceded by a prodromal period whereby an individual may experience changes in their behaviour, mood, thoughts, and functioning prior to the development of psychotic symptoms (Yung and McGorry, 1996). The length of the initial prodromal period can vary substantially and is often present for several years prior to the onset of psychosis. One study reported an average length of five and a half years from the onset of the prodrome to the transition to schizophrenia, although for some individuals the prodrome lasted less than a year, whilst in others it was longer than six years

(Schultze-Lutter *et al.*, 2007). Other premorbid markers of schizophrenia have also been observed, including deterioration in academic and social functioning from childhood to adolescence (Allen *et al.*, 2005) and lower IQ (Agnew-Blais *et al.*, 2015). The identification of premorbid markers has led to a substantial body of literature aiming to identify high-risk individuals and predict whether they will develop psychosis. A meta-analysis of such studies reported a mean transition rate of 29.2% over an average of 31 months follow-up in individuals at high-risk of psychosis (Fusar-Poli *et al.*, 2012). Whilst these findings demonstrate a potential window for early intervention in psychosis, the premorbid markers of schizophrenia lack specificity and are not deterministic. Furthermore, studies examining transition to psychosis in high-risk individuals report highly variable transition rates dependent on how high-risk is defined, suggesting that ascertainment bias and other methodological issues may be driving some of these findings. Therefore, identifying individuals for early intervention whilst minimising the risk of unnecessary treatment remains a challenge (Larsen *et al.*, 2001).

The illness course of schizophrenia is typically chronic, with some remission between episodes. Recovery rates from schizophrenia are generally poor, a systematic review and meta-analysis of studies reporting recovery rates in individuals with broadly defined schizophrenia found that a median of 13.5% of individuals showed both clinical remission and recovery of social functioning for at least two years (Jääskeläinen *et al.*, 2013). Recovery rates were higher in low and low-middle income countries, a median of 36.4% compared to 13% in high income countries, but did not significantly differ by sex. The study also reported an annual recovery rate of 1.4%, indicating that only one or two people per 100 with schizophrenia would be expected to recover each year (Jääskeläinen *et al.*, 2013). These estimates are similar to those found by Harrow and colleagues (2005), who conducted a 15-year longitudinal study measuring recovery in a sample of individuals with psychotic and mood disorders who were hospitalised due to psychiatric illness. At best, 22% of people with schizophrenia were deemed in recovery at any given follow-up point. Only 41% of people with schizophrenia experienced at least one period of recovery during the study, demonstrating that most people with schizophrenia did not experience a remission in

symptoms alongside reasonable psychosocial functioning for at least a year during 15 years of their illness. However, of those deemed to be in remission at 15 years, 40% were not taking any medication, suggesting that recovery is possible. In a longitudinal study examining predictors of remission, having a spouse, being in paid employment, and having social contacts at initial assessment were associated with greater likelihood of remission, as was female sex (Haro *et al.*, 2008). Studies examining remission and recovery vary considerably in their definition of these terms, thus findings vary across studies. Moreover, many studies consider a statistically significant improvement to indicate recovery, which may not relate to a meaningful improvement in symptoms or functioning. A particular strength of the study by Jääskeläinen and colleagues (2013) was that they defined recovery *a priori* as both symptomatic remission and recovery of social functioning, with at least one of these persisting for a period of at least two years.

National Institute for Health and Care Excellence (NICE) guidelines recommend antipsychotic treatment alongside cognitive behavioural therapy (CBT) and family intervention in the first episode of psychosis (National Institute for Health and Care Excellence, 2014b). Antipsychotics have been shown through randomised control trials (RCTs) to be twice as likely as placebo to improve symptoms in people with schizophrenia (Leucht *et al.*, 2017). However, the number of people showing a good response to treatment, as opposed to any response, is much smaller and has led to criticisms of antipsychotics (Leucht *et al.*, 2017). The limited improvement in cognitive and negative symptoms following antipsychotic treatment has also been criticised, and currently no pharmaceutical treatment has proven beneficial in reducing these symptoms (Murphy *et al.*, 2006). Antipsychotics are associated with various adverse effects, including extrapyramidal side effects, weight gain, and type 2 diabetes, that contribute to the discontinuation of these treatments (Leucht et al., 2013; Bak et al., 2014) Furthermore, approximately 30% of individuals do not respond to antipsychotics, and for these individuals, the antipsychotic clozapine is the only licensed pharmaceutical treatment (Meltzer, 2008). Almost half of people treated with clozapine have been shown to discontinue treatment within two years, largely due to adverse drug reactions, including neutropenia (Legge *et al.*, 2016). Individuals with

schizophrenia may also be offered electroconvulsive therapy (ECT). The advantages of ECT are mostly limited to short-term improvements, and any improvements are less than those observed in individuals taking antipsychotic medication (Tharyan and Adams, 2009). However, some evidence suggests a combination of antipsychotic medication with ECT may be more effective than either treatment alone (Tharyan and Adams, 2009).

Psychological interventions have been shown to improve outcomes in people with schizophrenia when combined with pharmaceutical treatment. A large meta-analysis found that family intervention was associated with higher medication compliance and significantly lower rates of relapse and number of hospital admissions in the two years after treatment, compared to treatment as usual (Pilling *et al.*, 2002). Cognitive behavioural therapy (CBT) is also recommended by NICE for treatment of individuals with schizophrenia, although research has found no clear evidence that CBT is able to prevent relapse or alleviate hallucinations and negative symptoms (Pilling *et al.*, 2002; Birchwood *et al.*, 2014; Jauhar, Laws and McKenna, 2019). However, CBT has been shown to be effective in improving mental state in the 18 months following treatment, suggesting that its benefits may be limited to particular areas of illness (Pilling *et al.*, 2002).

1.2.5 Environmental aetiology

A number of key environmental risk factors for schizophrenia have been identified, including season of birth, obstetric complications, paternal age, migration, cannabis use, and urbanicity.

Historical incidents of famine, such as the Dutch winter famine of 1944-45 and the Chinese famine of 1959-61, led to ecological studies identifying approximately a two-fold increased risk of schizophrenia amongst individuals who were *in utero* during a famine (Susser and Lin, 1992; St Clair *et al.*, 2005). This led to the suggestion that early life insults could be a risk factor for schizophrenia through their impact on the developing brain (McGrath and Murray, 2011). Season of birth has also been implicated as a risk factor for schizophrenia, with an excess of births in spring amongst

individuals with schizophrenia, suggesting that higher viral exposures *in utero* and/or seasonal vitamin deficiencies could be increasing risk of schizophrenia (McGrath and Murray, 2011). Studies have examined rates of schizophrenia among individuals who were foetuses during periods of high influenza rates, finding that individuals with schizophrenia were more likely to have been in their second trimester during influenza outbreaks, compared to control participants (Mednick *et al.*, 1988; Barr, Mednick and Munk Jorgensen, 1990). However, these studies did not compare known exposure to influenza to schizophrenia status, but rather compared the number of reported influenza cases during gestation. Brown and colleagues (2004) compared maternal serum for influenza antibodies in individuals with and without schizophrenia and found a seven-times greater risk of schizophrenia in individuals exposed to influenza in the first trimester, although their sample size was considerably smaller than that of Mednick *et al.*(1988) and Barr *et al.*(1990). Nevertheless, evidence suggests that exposure to influenza during foetal development is associated with later risk of schizophrenia.

Obstetric complications have consistently been associated with elevated risk of schizophrenia, although to a fairly modest extent (McGrath and Murray, 2011). Individuals with schizophrenia are more likely than both controls and individuals with other psychiatric disorders to have a history of obstetric complications (Lewis and Murray, 1987), including differences in complications related to pregnancy, abnormal development, and complications during delivery (Cannon, Jones and Murray, 2002). Researchers have suggested that the common feature underlying obstetric complications associated with schizophrenia is hypoxia or anoxia, which will have a neurotoxic effect leading to the development of schizophrenia later in life (Cannon, Jones and Murray, 2002). A study found that the risk of schizophrenia increased with the number of hypoxia-related obstetric complications, but not with the number of non-hypoxic complications (Cannon *et al.*, 2000). It has also been suggested that foetuses at high genetic risk for schizophrenia may be more likely to experience obstetric complications. There is some evidence in support of this hypothesis (Ursini *et al.*, 2018), although others have been unable to replicate these findings (Vassos *et al.*, 2021). Methodological differences in the ascertainment of obstetric complications may

explain differences between studies, but further research is needed in this area to establish possible gene-environment interactions and the mechanisms by which they may increase susceptibility to schizophrenia.

Older paternal age has also been implicated as a risk factor for schizophrenia. Malaspina and colleagues (2001) used the Israeli birth cohort containing over 87,000 individuals with linked psychiatric registry records and found that older paternal age was associated with increased risk of schizophrenia, with a three-fold increased risk in children of fathers over 50 years of age, compared to fathers under 25 years. Maternal age was not associated with schizophrenia risk, and paternal age was not associated with any other psychiatric disorders (Malaspina *et al.*, 2001). The association between paternal age and schizophrenia may be due to the increasing rate of de novo mutations in paternal sperm with age, which in turn may increase susceptibility to schizophrenia (McGrath and Murray, 2011).

Adverse childhood experiences (ACEs) have often been reported in people with schizophrenia at a greater rate than in controls. A meta-analysis of case-control studies published between 1980 and 2011 examining childhood adversity and psychosis found that individuals with psychosis were almost three times as likely to have experienced childhood adversity than unaffected controls (Varese *et al.*, 2012). Rosenberg and colleagues (2007) found that 86% of participants with schizophrenia in their study reported at least one ACE, with most people reporting more than one and 46% reporting three or more ACEs. The number of ACEs was associated with poorer functional outcomes, including earlier age at first hospitalisation, five or more lifetime psychiatric hospitalisations, homelessness within the past six months, and substance abuse (Rosenberg *et al.*, 2007). ACEs have been associated with increased risk of several psychiatric disorders, particularly depression(Chapman *et al.*, 2004). Thus, the mechanisms underlying the association between ACEs and schizophrenia may not be specific to schizophrenia.

A seminal study by Andréasson and colleagues (1987) in over 50,000 men conscripted for the Swedish military found that individuals who had used cannabis on more than

50 occasions were at a six-fold increased risk of developing schizophrenia over a 15-year follow up period than non-users. Individuals reporting having used cannabis at least once were at a two-fold increased risk compared to non-users (Andréasson *et al.*, 1987), suggesting that cannabis use increases the risk of developing schizophrenia. However, cannabis use is also associated with elevated schizophrenia polygenic risk score (PRS), indicating that the causal relationship between cannabis use and schizophrenia is complex. Cannabis use is genetically correlated with schizophrenia (r_g=0.25) (Pasman *et al.*, 2018) and Mendelian Randomisation (MR) analyses support a bi-directional relationship between the two, although stronger associations have been reported for schizophrenia risk predicting cannabis use (Gage *et al.*, 2017). However, studies examining genetic relationships between cannabis use and schizophrenia frequently define cannabis use as a binary trait (ever/never used), which may miss important associations relating to frequency and timing of use in the context of illness onset and course.

Higher rates of schizophrenia have been observed amongst migrants compared to natives, an effect that is not explained by genetic pre-disposition as the prevalence of schizophrenia is consistent worldwide and effects of migration are not population-specific. A meta-analysis of 18 studies found a mean relative risk of 2.7 for developing schizophrenia in first-generation migrants compared to native-born people. Second-generation migrants were also at a 4.5-times increased risk of schizophrenia, suggesting that the mechanisms increasing susceptibility to schizophrenia through migration are present and affect children of migrants as well. Such mechanisms may include deprivation, socioeconomic disadvantage, and discrimination (Robinson and Bergen, 2021).

Individuals living in an urban environment have more than a two-fold increased risk of schizophrenia compared to individuals living in a rural area (Vassos *et al.*, 2012). In a study using Danish registry data, higher schizophrenia PRS was associated with living in the capital city, compared to rural areas, at age 15, but was not associated with residence at birth (Paksarian *et al.*, 2018), suggesting that genetic risk for schizophrenia may be associated with the tendency to move to urban areas, rather

than the association between urbanicity and schizophrenia being entirely driven by the effects of the urban environment itself.

1.2.6 Genetic aetiology

It has been well established through twin and family studies that schizophrenia has a strong genetic component, with heritability estimates of around 80-85% (Cardno and Gottesman, 2000). Prior to genome-wide association studies (GWAS), research relied on the use of candidate gene and linkage approaches to identify variants associated with the disorder. These methods proved largely unsuccessful for schizophrenia gene discovery, with prime targets such as *DISC1* lacking replication within candidate studies and failing to gain support from subsequent GWAS (Mathieson, Munafò and Flint, 2012; Sullivan, 2013). Advances in genotyping technology allowed the field to move away from such methods, enabling genome-wide hypothesis free approaches and the potential of identifying common variants of individually small effect that cumulatively increase predisposition to the disorder. Currently, over 300 independent single nucleotide polymorphisms (SNPs) and 12 copy number variants (CNVs) have been associated with schizophrenia, that, alongside evidence from exome sequencing studies, implicate synaptic and neuronal functioning as key mechanisms of disease (Schizophrenia Working Group of the Psychiatric Genomics Consortium. *et al.*, 2020).

1.2.6.1 GWAS in schizophrenia

Schizophrenia is polygenic in nature, with many associated common variants from across the genome conferring relative risks lower than 1.5 (Sullivan, Daly and O'Donovan, 2012). Early schizophrenia GWAS failed to identify markers reaching genome-wide significance due to their lack of power, and when samples were combined, and thus increased, the first genome-wide significant alleles were identified (O'Donovan *et al.*, 2008; Sullivan *et al.*, 2008; Shi *et al.*, 2009; Stefansson *et al.*, 2009). The last fifteen years have seen large-scale international collaboration enabling the field to move from the first studies that identified one genome-wide significant locus for psychosis (*ZNF804A*) in just over 7,000 cases (O'Donovan *et al.*, 2008), to the amalgamation of datasets containing almost 70,000 cases identifying 270 significant

loci (Schizophrenia Working Group of the Psychiatric Genomics Consortium. *et al.*, 2020). Early partnerships between the International Schizophrenia Consortium (ISC), Molecular Genetics of Schizophrenia (MGS), and SGENE groups unearthed the first major findings of common variants in the major histocompatibility complex (MHC), as well as markers in *TCF4* and *NRGN*, implicating dysfunctional brain development and cognitive functioning as key pathophysiological processes of potential relevance in schizophrenia (Stefansson *et al.*, 2009). The first wave of Psychiatric Genetics Consortium schizophrenia data (PGC1) identified single nucleotide polymorphisms (SNPs) across seven loci in a total combined sample of 17,836 cases and 33,859 controls (The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011). The data from this study was combined with additional samples, mainly from a large Swedish case control cohort, in a meta-analysis with total sample size 21,246 cases and 38,072 controls, and identified 22 loci, 13 of which were novel associations (Ripke *et al.*, 2013). In these initial schizophrenia GWAS consortia studies one of the most consistent findings was strong support for association for the Major Histocompatibility Complex (MHC) region on chromosome 6, although identifying specific causal variants at this locus has been challenging due to the size, complexity, and high linkage disequilibrium (LD) of the region (Irish Schizophrenia Consortium and Wellcome Trust Case Control Consortium 2, 2012; Lehner, 2012).

The second wave of research from the schizophrenia working group of the PGC (PGC2), identified 128 genome-wide significant SNPs across 108 independent loci, in a sample of 34,241 cases and 45,604 controls, analysed together with 1,235 parent-offspring samples and a replication sample of 1,513 cases and 66,236 controls (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The PGC2 study identified multiple novel candidate genes and pathways of potential therapeutic relevance, including the first identification of a polymorphism implicating the *DRD2* gene. *DRD2* encodes the Dopamine D2 receptor, which is the therapeutic target of all currently licensed antipsychotic medications, thus providing a further validation of the GWAS approach in schizophrenia. Moreover, the group reported 82 novel associations, including SNPs implicating genes enriched for glutamatergic neurotransmission and synaptic plasticity. Building on this work with the addition of new schizophrenia samples in the CLOZUK cohort, Pardiñas and colleagues (2018) extended the PGC2

findings using up-to-date gene set analyses to demonstrate an enrichment of variants in genes that are intolerant to rare loss-of-function mutations, as well as in gene sets involved in synaptic and neuronal functioning and also highlighted the strong enrichment of SNPs in regions under strong background selection. Most recently, the third wave of the PGC (PGC3) has analysed a total sample of 69,369 people with schizophrenia and 236,642 controls, leading to the identification of 329 genome-wide significant SNPs spanning 270 independent loci that are associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium. *et al.*, 2020). SNP associations were highly enriched for expression in the brain, especially in cortical inhibitory interneurons and excitatory neurons, confirming previous findings of the importance of neuronal functioning in schizophrenia. Despite schizophrenia being more prevalent in males than females, no sex-specific effects were observed, and separate GWAS of males and females had a genetic correlation not significantly different from one, suggesting that polygenic liability to schizophrenia is equivalent in males and females (Schizophrenia Working Group of the Psychiatric Genomics Consortium. *et al.*, 2020).

The majority of GWAS in schizophrenia have been conducted in European populations, and their findings have been shown to have limited predictive power in non-European populations (Bigdeli *et al.*, 2020). Studies of diverse ancestries will be necessary to prevent future health inequalities and to fully capture the variation in liability to schizophrenia in all populations. Sampling different ancestries can provide insights into SNPs with minor allele frequencies (MAF) that are too rare to be studied in any single population. In a sample of Han Chinese ancestry, Yu *et al.* (2017) identified a significant SNP within the *GABBR1* gene with a MAF of 0.13 in an Asian sample, compared to 0.01 a European sample. Dysfunction in the GABA system has been implicated in schizophrenia (Wassef, Baker and Kochan, 2003), suggesting that variation within this gene could play a role in both European and Asian populations. In work by the PGC, 21 variants spanning 19 loci were found to be significant in an East Asian sample (Lam *et al.*, 2018). Of these, 15 loci had a higher MAF in the Asian sample compared to European samples. The locus containing *CACNA2D2* was significant in the Asian sample only, likely owing to vastly different MAF in the index SNP; 45% in Asian and 0.07% in

European samples. The association with this variant suggests that whilst different patterns of LD and MAF may implicate different causal SNPs and/or haplotypes, the underlying genes and pathways implicated are shared across populations. A recent GWAS of individuals of African-American and Latino ancestry, meta-analysed with PGC2 summary statistics, identified 20 novel associations with schizophrenia and found highly consistent directions of effect for alleles in all ancestries (Bigdeli *et al.*, 2020), indicating that the genetic architecture of schizophrenia is largely consistent across these two populations (Lam *et al.*, 2018).

1.2.6.2 Fine-mapping and functional annotation

Functional annotation of significant variants allows for analysis across pathways and gene sets, marking an important next step toward understanding the biological role of these variants. Additionally, grouping SNPs by function may better identify SNPs and genes to create an easier target for therapy development in the near future (O'Donovan and Owen, 2016). Pardiñas *et al.*(2018) assessed central nervous system-related gene sets and found six associated with schizophrenia, including targets of Fragile X mental retardation protein (FMRP), voltage-gated calcium ion channel complexes, and abnormal long-term potentiation. Voltage-gated calcium ion channels have been robustly implicated in schizophrenia, with GWAS and gene set analysis reporting associations in European and Asian populations (Green *et al.*, 2010; Ripke *et al.*, 2013; Jiang *et al.*, 2015; Li *et al.*, 2017). Furthermore, variants in this gene set have been consistently implicated in other psychiatric disorders, notably bipolar disorder, suggesting a mechanism through which phenotypic and genotypic overlap may occur (Ferreira *et al.*, 2008; Psychiatric GWAS Consortium Bipolar Disorder Working Group., 2011). In PGC3, genes prioritised through fine-mapping were enriched for loss-of-function intolerance and expression in the brain, compared to other genes in the same locus. Of note, fine-mapping identified associations with *CACNA1I* and *ATP2A2*, both of which play a role in calcium channels. Across multiple strategies, prioritised genes were associated with genes encoding neurotransmitter receptors, ion channels, and other proteins involved in synapse organisation and differentiation, and in trans-synaptic signalling. Consistent evidence was found implicating post-synaptic biology

across the brain, suggesting that disrupted neuronal functioning in numerous areas of the brain may be a key source of psychopathology in schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium. *et al.*, 2020). Including samples of diverse ancestries improves fine-mapping resolution, including reducing the number of credible SNPs and reducing the length of the corresponding genomic interval. Bigdeli and colleagues (2020) identified improved resolution in several regions, including two regions that were each reduced to a single credible SNP, when analysing PGC2 summary statistics in combination with samples of African-American and Latino ancestry.

1.2.6.3 Application of GWAS results

PRS have rapidly emerged as a powerful application of GWAS results with research utility and potentially clinically useful application, although currently clinical use is not recommended for schizophrenia (Wray *et al.*, 2021). SNPs identified through GWAS as being significant at a given threshold are weighted by the odds ratios for a particular allele and summed for each individual to create a risk score in an independent dataset, with higher scores indicating greater genetic liability to the disorder. The ISC(2009) were the first to use this method to predict schizophrenia case-control status, finding that schizophrenia PRS was a highly significant predictor of the disorder in European samples. Moreover, schizophrenia PRS significantly predicted bipolar disorder case status, adding further weight to evidence from GWAS that the two disorders share a common genetic architecture, which was later further quantified through genetic correlation (r_g=0.70) (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Lee et al., 2019). Such powerful genetic prediction has the potential to be clinically useful, although the situations in which such information may be clinically employed require careful consideration including the limitations in the application of PRS across populations (Martin et al., 2019). Hence, there is an ongoing debate about whether PRS can safely and effectively be implemented in medical genetic settings (Torkamani, Wineinger and Topol, 2018). At the moment, PRS is only able to explain a small amount of the variance in schizophrenia status, with an area under the curve (AUC) of 0.71 (Schizophrenia Working Group of the Psychiatric Genomics Consortium.

et al., 2020). Consequently, current scores are not sufficient for diagnostic purposes. Increasing sample sizes and diversity may improve PRS-based prediction, with Li *et al.* (2017) reporting up to 8% of variance in schizophrenia status within their sample explained by PRS derived from the PGC2 plus the Chinese ancestry data, an improvement of 5% from PGC2 alone. Although these improvements are relatively small, they indicate that missing heritability may in part be explained by the under-representation of non-European populations within GWAS cohorts. Further sampling of individuals from multiple ancestries will improve schizophrenia prediction across worldwide populations.

Given the explanatory power of PRS for susceptibility to schizophrenia, studies have investigated whether these scores can be informative regarding clinical heterogeneity within the disorder. Chronicity of illness, indexed by number and length of hospital admissions, has been associated with schizophrenia PRS (Meier *et al.*, 2016), yet treatment-resistance to medication does not appear to be predicted by PRS (Wimberley *et al.*, 2017; Legge, Dennison, *et al.*, 2019). These findings suggest a complex relationship between polygenic risk scores and outcomes which may in part depend on the constitution of the schizophrenia training dataset used for the polygenic risk score derivation (i.e., the mixture of poor and good outcome cases). Attempts to predict cognitive ability have also provided inconsistent results, with schizophrenia PRS significantly predicting cognition in healthy adults and children but not in schizophrenia cases (Germine et al., 2016; Shafee et al., 2018). Variation in symptoms of schizophrenia has been associated with different patterns of polygenic risk for psychiatric disorders, in particular elevated schizophrenia PRS is associated with separate domains of disorganised and negative symptoms, but not with positive symptoms (Legge, Cardno, *et al.*, 2021). Consistent with this are findings that schizophrenia PRS does not predict psychotic experiences in adolescence but in contrast does predict negative symptoms at age 16 (Jones *et al.*, 2016). These associations suggest that genetic liability for schizophrenia may manifest as disorganised and negative symptoms (Mistry *et al.*, 2018b), and that further exploration of positive symptoms is required in order to understand the aetiology of this phenotype.

1.2.6.4 Rare variation

CNVs are large changes in the sequence of the DNA resulting from deletions, duplications, insertions, or translocation of sections 1kb or larger (Feuk, Carson and Scherer, 2006). CNVs can be inherited from a parent or arise *de novo*. Research has identified an increased prevalence of schizophrenia in individuals with 22q11.2 deletion syndrome (30% compared to <1% in the general population) (Murphy, Jones and Owen, 1999) as well as in individuals with neurodevelopmental disorders such as autism spectrum disorders (ASD) (Zheng, Zheng and Zou, 2018) and intellectual disability (Morgan *et al.*, 2008). Together with technological and methodological developments, this led to the identification of several CNVs associated with schizophrenia through parent-proband trio designs, as well as through case-control studies. Twelve CNVs have been robustly associated with increased risk of schizophrenia, occurring in around 2.5% of individuals with the disorder (Rees *et al.*, 2014). Greater burden of CNVs is associated with increased risk of schizophrenia across several metrics, including the size of CNVs, number of affected genes, and number of individual CNVs (Marshall *et al.*, 2017). CNVs associated with schizophrenia were enriched for genes involving the synapse, other neuronal components, and the nervous system, but not for genes involving organs and systems unrelated to the brain (Marshall *et al.*, 2017). Whilst certain CNVs are associated with a substantially increased risk of schizophrenia, they are not deterministic and are often transmitted from an unaffected parent. Moreover, phenotypic expression of CNVs is highly heterogeneous, and all CNVs associated with schizophrenia are also implicated in other neurodevelopmental disorders, indicating shared genetic architecture of these disorders (Owen *et al.*, 2011).

Rare variation involving single nucleotides, known as single nucleotide variants (SNVs), have not been significantly associated with schizophrenia, as studies to date have not been sufficiently powered to detect significant associations given the rarity of individual SNVs (minor allele frequency <0.01) (Legge, Santoro, *et al.*, 2021). However, overall burden of SNVs has been compared between cases and controls, finding that

individuals with schizophrenia carry more disrupting and damaging ultra-rare variants than controls (Legge, Santoro, *et al.*, 2021). Ten genes, including *SETD1A* and *TRIO*, which are also associated with severe neurodevelopmental disorders, have been found to contain a significant excess of these variants, and are involved in various processes related to synaptic and neuronal function (Singh, Neale and Daly, 2020). Loss of function (LoF) *de novo* variants (DNVs), i.e., variants that disrupt the function of a gene and arise from a new mutation rather than being inherited from a parent, have been observed in excess amongst individuals with schizophrenia in genes that are intolerant to LoF mutations (Rees *et al.*, 2020). In particular, LoF DNVs are enriched in genes known to confer risk for neurodevelopmental disorders (Rees *et al.*, 2020). These findings suggest that *de novo* mutations are one mechanism by which genetic risk for schizophrenia is maintained in the population, as well as evidencing a shared genetic architecture between schizophrenia and neurodevelopmental disorders.

Gene sets implicated by common variant studies overlap with those discovered through CNV and rare variant analyses. *De novo* mutations have been shown to be enriched in genes involved in calcium ion channels, synaptic plasticity, and FMRP targets (Fromer *et al.*, 2014; Purcell *et al.*, 2014). Genes identified as containing damaging ultra-rare mutations in the most recent and largest study of exome-wide sequencing in schizophrenia (SCHEMA) were also enriched for common variant associations in PGC3, as were rare variants associated with ASD and developmental disorder (Schizophrenia Working Group of the Psychiatric Genomics Consortium. *et al.*, 2020). Two genes prioritised through fine-mapping in PGC3 were included in ten exome-wide significant genes in SCHEMA - *GRIN2A* and *SP4*. *GRIN2A* encodes glutamatergic NMDA receptor subunit 2A and *SP4* is a transcription factor expressed in the brain and regulated by NMDA transmission, further implicating synaptic biology in schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium. *et al.*, 2020). Several studies report an enrichment of rare mutations in ARC and NMDAR gene sets (Kirov *et al.*, 2012; Fromer *et al.*, 2014; Purcell *et al.*, 2014; Pocklington *et al.*, 2015), which has not been reported robustly in common variant analysis. It remains possible that increasing power of GWAS and sampling of non-

European populations may reveal common variants in these pathways that have thus far been too rare to detect.

1.3 Bipolar disorder

1.3.1 Conception and criteria

Bipolar disorder is characterised by fluctuations between extremes of mood, mania on one end, and depression on the other. Symptoms of mania include elation and/or irritability, alongside restlessness, grandiosity, and recklessness, whilst depression is characterised by dysphoria, loss of interest, poor concentration, and changes in appetite and sleep. Individuals with bipolar disorder typically experience cycling between the two mood states, which may lead directly into one another or be separated by a period of euthymia.

The constructs of mania and depression have been known for millennia, with Hippocrates describing two extremes of mood that he thought resulted from imbalances in the humours (Mason, Brown and Croarkin, 2016). Aristotle further described extremes of mood which he deemed to be due to heating and cooling of what Hippocrates termed 'black bile' - or melancholia. It was thought that when black bile became too hot, it led to excessive cheerfulness, talkativeness, and madness. Conversely, when black bile became too cold, it led to despair and sluggishness (Pies, 2007). Whilst these descriptions are remarkably similar to what we now know as mania and depression, bipolar disorder wasn't recognised as a psychiatric disorder encompassing both mania and depression until 1851, when Jean-Pierre Falret described 'folie circulaire' as a continuous cycling between depression, mania, and euthymic mood (Mason, Brown and Croarkin, 2016). This description was built upon by Kraepelin, who defined manic-depressive insanity as a disorder of extreme mood, be that through episodes of mania, depression, or a mixture of both (Mason, Brown and Croarkin, 2016). In the 8th edition of Kraepelin's text on psychiatric disorders, *Lehrbuch*, he detailed numerous types of manic-depressive illness, believing that all mood states were manifestations of the same disease process (Mondimore, 2005). Kraepelin's subtypes were grouped under manic, depressive, or mixed states, with the

subtypes representing different combinations of symptoms that would now be recognised broadly as either mania, depression, or a mixed episode, without any further distinction. Whilst Kraepelin's work was highly influential and arguably formed the basis of current diagnostic systems for affective disorders, his consideration of all mood disorders as one illness was later criticised as overly simplistic (Mondimore, 2005). Nevertheless, the first edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1952 listed manic-depression as one disorder with three subtypes - manic, depressed, and other (American Psychiatric Association, 1952; Mason, Brown and Croarkin, 2016). The 'other' subtype was analogous to current definitions of bipolar disorder, defined by cycling between episodes of mania and depression, whilst the other two subtypes represented unipolar mood states of mania and depression, respectively. This definition did not substantially change for the second edition of the DSM, except that it was now considered an affective disorder rather than a psychotic one. The eighth edition of the International Classification of Diseases (ICD-8), published by the World Health Organisation (WHO) in 1965, also used the term manic-depressive psychosis, which encapsulated unipolar manic and depressive episodes, as well as cycling between the two (World Health Organisation, 1965). These terms persisted into the ninth edition of the ICD in 1979 (World Health Organisation, 1975).

DSM-III (American Psychiatric Association, 1980), published in 1980, was the first to formally use the term 'bipolar disorder' and introduced operationalised criteria to make a diagnosis. Unipolar depression was also separated from bipolar disorder and hypomania was introduced as a less severe form of mania, although was not in itself a diagnosis until DSM-IV (American Psychiatric Association, 1994). Hypomania was defined by the same symptoms as a manic episode with the exception of psychosis, which could not be present, and required a minimum of 4 days duration, compared to one week for a manic episode. Individuals experiencing only hypomanic episodes are given a diagnosis of bipolar disorder type II, compared to bipolar disorder type I where a full manic episode is present, to distinguish the milder level of impairment in a hypomanic episode. The symptom criteria for mania have remained largely the same since DSM-III, with the only substantial change for DSM-5 being the requirement for an increase in goal-directed activity alongside the mood disturbance (American

Psychiatric Association., 2013). Prior to DSM-5, increased activity was listed as a symptom of mania, but was not necessary for a diagnosis. ICD-10 criteria for bipolar disorder are very similar to DSM-IV and DSM-5, but do not distinguish between type I and type II bipolar disorder (World Health Organisation., no date). Instead, an individual is given the diagnosis 'bipolar affective disorder' followed by a specifier to indicate their current episode, be that mania with or without psychosis, hypomania, or depression either with or without psychosis. Tables 1.2-1.4 display the criteria for both ICD-10 and DSM-5 for mania, depression, and bipolar disorder. DSM-5 distinguishes between bipolar disorder type I and type II dependent on the presence or absence of a history of mania, respectively. However, ICD-10 uses one diagnosis, bipolar affective disorder, to categorise individuals with mania or hypomania, but uses specifiers to indicate the current episode. For instance, an individual who had previously experienced an episode of depression and was currently experiencing mania could be diagnosed with bipolar affective disorder, current episode manic under ICD-10, and as having bipolar disorder type I under DSM-5.

ICD-11 reorganises bipolar disorder to bring the diagnosis in line with DSM-5 classification. Bipolar disorder is divided into types I and II, reflecting the presence of mania or hypomania, respectively, and mania is no longer a coded diagnosis but is instead provided as a description to guide the diagnosis of bipolar disorder type I (Angst, Ajdacic-Gross and Rössler, 2020).

ICD-10 and DSM-5 criteria for a manic episode		
	ICD-10	**DSM-5**
Symptoms	Predominantly elevated, expansive, or irritable mood, and definitely abnormal for the individual concerned. *At least three of the following, or four if the mood is irritable:* 1. Increased activity or physical restlessness 2. Increased talkativeness - pressure of speech 3. Flight of ideas or thoughts racing 4. Loss of normal social inhibitions resulting in inappropriate behaviour 5. Decreased need for sleep 6. Inflated self-esteem or grandiosity 7. Distractibility 8. Foolhardy or reckless behaviour, individual does not recognise these risks 9. Marked sexual energy or sexual indiscretions Can be with or without psychotic symptoms.	Abnormally and persistently elevated, expansive, or irritable mood, *and* persistently increased goal-directed activity or energy. *During the mood disturbance, three of more of the following, or four if mood is irritable:* 1. Inflated self-esteem or grandiosity 2. Decreased need for sleep 3. More talkative or pressure to keep talking 4. Flight of ideas or thoughts racing 5. Distractibility 6. Increase in goal-directed activity or psychomotor agitation. 7. Excessive involvement in activities with a high potential for painful consequences *Mood disturbance sufficiently severe to:* • Cause marked impairment in social or occupational functioning • Necessitate hospitalisation • Or there are psychotic features
Duration	Mood change prominent and sustained for at least one week, unless severe enough to warrant hospitalisation.	Mood disturbance for at least one week.
Exclusions	Episode not attributable to psychoactive substance use or to any organic mental disorder.	Episode not attributable to physiological effects of a substance or another medical condition.

Table 1.2. Diagnostic criteria for a manic episode in the International Classification of Diseases (ICD-10)(World Health Organisation., no date) and Diagnostic and Statistical Manual of Mental Disorders (DSM-5)(American Psychiatric Association., 2013).

ICD-10 and DSM-5 criteria for a depressive episode		
	ICD-10	**DSM-5**
Symptoms	*At least two of the following:* • Depressed mood for most of the day almost every day • Loss of interest or pleasure in activities • Decreased energy or fatiguability *Any of the following to give a combined total of 4 (mild), 6 (moderate), or 8 (severe, including all three of the above):* 1. Loss of confidence or self-esteem 2. Unreasonable feelings of self-reproach or guilt 3. Recurrent thoughts of death or suicide, or any suicidal behaviour 4. Diminished ability to think or concentrate 5. Change in psychomotor activity 6. Sleep disturbance of any type 7. Change in appetite with corresponding weight change	*Five or more of the following, at least one is either depressed mood or loss of interest:* 1. Depressed mood most of the day, nearly every day 2. Diminished interest or pleasure in all or most activities 3. Significant weight loss or gain, or decrease or increase in appetite 4. Insomnia or hypersomnia 5. Psychomotor agitation or retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness or excessive/inappropriate guilt 8. Diminished ability to think or concentrate 9. Recurrent thoughts of death, suicidal ideation with or without a plan, or a suicide attempt. Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Duration	Episode should last at least two weeks.	Symptoms persist for at least two weeks.
Exclusions	Episode not attributable to psychoactive substance use or to organic mental disorder If psychotic symptoms are present, cannot be those listed as typically schizophrenic in criterion. Does not meet criteria for schizophrenia or schizoaffective disorder	Episode not attributable to the physiological effects of a substance or another medical condition.

Table 1.3 Diagnostic criteria for a depressive episode in the International Classification of Diseases (ICD-10)(World Health Organisation., no date) and Diagnostic and Statistical Manual of Mental Disorders (DSM-5)(American Psychiatric Association., 2013).

Criteria for bipolar disorder	
ICD-10 Bipolar affective disorder	*Current episode meets criteria for either:* - Hypomania - Mania (with/without psychotic symptoms) There has been at least one hypomanic, manic, depressive, or mixed affective episode in the past. *Or* *Current episode meets criteria for depressive episode of either*: - Mild or moderate severity - Severe with/without psychotic symptoms There has been at least one hypomanic, manic, or mixed affective episode in the past. *Or* *Current episode mixed:* - Characterised by either mixture or rapid alternation of (hypo)manic and depressive symptoms - Both manic and depressive symptoms prominent most of the time during a period of 2 weeks There has been at least one manic, hypomanic, depressive, or mixed episode in the past
DSM-5 Bipolar disorder type I	Criteria have been met for at least one manic episode Occurrence of mania and depressive episodes are not better explained by schizoaffective disorder, schizophrenia, or other schizophrenia spectrum disorder. Depressive episode is not required for bipolar disorder type I diagnosis in DSM-5, but may be present.
DSM-5 Bipolar disorder type II	Criteria have been met for at least hypomanic episode and at least one major depressive episode. There has never been a manic episode Occurrence of hypomanic episode and major depressive episode not better explained by schizoaffective disorder or other schizophrenia-spectrum disorders

Table 1.4. Criteria for bipolar disorder in the International Classification of Diseases (ICD-10)(World Health Organisation., no date) and Diagnostic and Statistical Manual of Mental Disorders (DSM-5)(American Psychiatric Association., 2013).

1.3.2 Symptoms of bipolar disorder

Bipolar disorder is primarily characterised by manic and depressive episodes, but individuals may also experience psychosis within mood episodes and cognitive impairments in active and residual phases of the disorder (Martínez-Arán *et al.*, 2004).

1.3.2.1 Mania

Mania is the hallmark of bipolar disorder and distinguishes it from unipolar depression. In diagnostic manuals, a distinction is made between mania and hypomania, the latter being a milder episode of shorter duration, with less impairment in social and occupational functioning (Müller-Oerlinghausen, Berghöfer and Bauer, 2002). Symptoms of (hypo)mania include elated or irritable mood, alongside a reduced need for sleep, increased activity, reckless behaviour, and pressure of speech (described further in Table 1.2). Individuals with mania may also experience psychotic symptoms, discussed below. Elevated or irritable mood, excessive activity, racing thoughts, and reduced need for sleep are the most common symptoms, occurring in over 90% of individuals with mania (Morgan, Mitchell and Jablensky, 2005).

1.3.2.2 Depression

Although mania is considered the defining feature of bipolar disorder, depressive episodes form much of the illness and account for around two-thirds of time spent symptomatic (Judd *et al.*, 2002). The criteria for a depressive episode in bipolar disorder is identical to that of unipolar depression, and is defined by a combination of low mood, loss of interest or pleasure, poor concentration, loss of energy, feelings of worthlessness, and sleep and appetite disturbances (American Psychiatric Association., 2013).

1.3.2.3 Psychosis

Psychosis is common in bipolar disorder, affecting around two thirds of individuals with a bipolar disorder type I diagnosis (Keck *et al.*, 2003). Psychotic symptoms can occur in either manic or depressive episodes, but do not occur in hypomania as by

definition the presence of psychosis and hypomanic symptoms qualifies as a manic episode diagnosis (American Psychiatric Association., 2013). Individuals typically experience mood-congruent symptoms, for example grandiose delusions in a manic episode, although mood-incongruent symptoms also occur (Keck *et al.*, 2003). Demographic differences between people with bipolar disorder with and without psychosis have not been observed, but individuals with psychosis may be more likely to have a younger age at onset, lower educational attainment, and poorer cognition (Bora, Yücel and Pantelis, 2010).

1.3.2.4 Cognition

Cognitive impairments have been observed in bipolar disorder across manic, depressive, and euthymic mood states, compared to controls. Impairments are observed across multiple domains, including executive function, attention, and verbal and non-verbal memory, although are less severe than the deficits seen in schizophrenia (Lynham *et al.*, 2018). Cognitive impairments are associated with poorer psychosocial functioning, more chronic illness, and a higher number of hospitalisations, indicating a direct relationship between cognition and functioning that occurs independent of mood (Martínez-Arán *et al.*, 2004). In contrast to schizophrenia, premorbid cognitive impairments are not seen in bipolar disorder when assessed prospectively (Trotta, Murray and MacCabe, 2015), and adolescents who later developed bipolar disorder were shown to perform better than the population average on standardised cognitive tests (MacCabe *et al.*, 2013).

1.3.3 Epidemiology

The Global Burden of Disease Study 2013, which reported prevalence data from 26 countries, found a lifetime prevalence rate of 0.7% for all bipolar spectrum disorders. A large multi-site study of the prevalence of bipolar disorder found that in most of the countries surveyed, the prevalence did not vary between males and females, except in a few countries where men had marginally higher rates (Weissman, 1996). However, other studies, including the Global Burden of Disease Study, have indicated that the prevalence of bipolar disorder is slightly higher amongst females than males (Kennedy

et al., 2005; Pini *et al.*, 2005; Ferrari *et al.*, 2016). Bipolar disorder as a broad category has an incidence rate of approximately 7 per 100,000 people per year, whilst bipolar disorder type I has an incidence of 4.3 per 100,000 people per year and type II has an incidence of 1.9 per 100,000 people per year (Kroon *et al.*, 2013).

Disability adjusted life years (DALYs) is a metric used to quantify the number of healthy years lost to a particular disease, one DALY is equivalent to one year. Bipolar disorder accounted for 9.9 million DALYs in 2013, representing 0.4% of total DALYs and 1.3% of all years lived with a disability (Ferrari *et al.*, 2016). This placed bipolar disorder as the 16th leading cause of years lost to disability worldwide, and the fifth leading cause amongst mental and substance use disorders. These rates have remained consistent since the first measurement in 1990, although the actual number of individuals living with bipolar disorder has increased due to population growth(Ferrari *et al.*, 2016). The economic burden of bipolar disorder was estimated in a systematic review of studies published between 2000 and 2012 (Kleine-Budde *et al.*, 2014). Costs were standardised using the purchasing power parities metric, to account for variation in costs between countries. Direct healthcare costs were estimated to be between $1,012 and $13,791 per person, per year, whilst indirect costs were estimated to be between $2,224 - $4,094 per person, per year. Overall healthcare costs for people with bipolar disorder ranged from 3.17 to 12.6 times higher than overall costs for controls (Kleine-Budde *et al.*, 2014).

1.3.4 Illness course and treatment

The median age at onset for mania is 28 years, and is older in women (31 years), compared to men (26 years) (Kennedy *et al.*, 2005). Onset of mania occurs by age 25 years in 48% of men, compared to one third of women, whilst 80% of men can expect onset by age 35, compared to 64% of women. In individuals identified as having their first episode of hypomania, 94% had previously had a depressive episode, whilst in individuals experiencing their first episode of mania, 63% had previously had a depressive episode (Kroon *et al.*, 2013), indicating that depression typically begins prior to onset of mania. There is evidence to suggest that most individuals with bipolar disorder experience an initial prodrome. Skjelstad and colleagues (2010) conducted a systematic review and found eight studies reporting signs and symptoms in the initial

prodrome. Subclinical features of bipolar disorder were commonly reported, including irritability, aggressiveness, sleep disturbance, hyperactivity, depressed mood, and mood swings. Research into the prodrome depends heavily on the definition of onset, which varies between studies. Some define onset as first meeting criteria for a manic episode and others as time until a diagnosis, these differences can make comparisons difficult, particularly when drawing conclusions on the length of the prodrome.

The course of bipolar disorder is typically chronic, but with relative recovery between episodes. A study of individuals with bipolar disorder type I gathered data on symptoms over a period in which 90% of participants were followed up for five years, and 56% for at least 20 years (Solomon *et al.*, 2010). The median number of mood episodes per person was four, with an annual mean of 0.4. On average, 31% of the follow up time was spent ill with a depressive, manic, or mixed episode, and 67% of individuals experienced three or more episodes over the course of the study (Solomon *et al.*, 2010). Recovery rates from mood episodes varied substantially dependent on the nature of the episode. For mania, 75% of individuals recovered within 15 weeks, whereas for mixed cycling episodes, defined as transition from mania to depression (or vice versa) with no more than 8 weeks of euthymic mood in between, 25% of episodes lasted longer than two years. When the cycling included a mixed episode, 25% of episodes lasted longer than 7 years, indicating that mixed episodes in particular may be associated with lower rates of remission and more chronic course (Solomon *et al.*, 2010). A study following participants for at least two years found that 85% achieved symptomatic recovery from their first manic or mixed episode within six months. However, only 40% of people showed functional recovery by six months and only 43% were functionally recovered at two years, with 13% having gained and subsequently lost functional recovery. Thus, even when symptoms are in remission, regaining previous occupational and residential status is more difficult to achieve, a conclusion that has been supported by other studies (MacQueen, Young and Joffe, 2001). Good levels of premorbid functioning are associated with better psychosocial recovery (MacQueen, Young and Joffe, 2001), as are older age at onset of mania, white ethnicity, and being married (Tohen *et al.*, 2003).

NICE guidelines for the treatment of bipolar disorder recommend treating acute mania and hypomania with an antipsychotic, such as olanzapine, and if this is not effective at the maximum dose, then consider adding lithium treatment (National Institute for Health and Care Excellence, 2014a). Lithium is recommended for long-term management of bipolar disorder, or alternatively valproate if lithium is poorly tolerated. A psychological intervention should also be offered to individuals with bipolar disorder experiencing a depressive episode, for instance CBT or an intervention specifically designed for bipolar disorder (National Institute for Health and Care Excellence, 2014a). Traditionally, lithium has been the first-line treatment for mania as RCTs have proven it to be effective in preventing relapse in bipolar disorder, although it is more effective at preventing manic than depressive episodes (Geddes *et al.*, 2004). However, in a longitudinal study of prescription patterns for people with bipolar disorder in Denmark, lithium went from being the most prescribed treatment in 2000 to the least prescribed in 2011, whilst the opposite effect occurred for antipsychotics (Kessing, Vradi and Andersen, 2016). A similar study in the UK found an increase in the use of antipsychotics to treat bipolar disorder, although lithium use remained fairly consistent between 1995 and 2009 (Hayes *et al.*, 2011), suggesting that changes in prescription rates of lithium may be country-specific. In a systematic review and meta-analysis of randomised control trials comparing atypical antipsychotics and mood stabilisers, combined treatment with an antipsychotic and a mood stabiliser was associated with significantly better improvements in manic symptoms than a mood stabiliser alone (Scherk, Pajonk and Leucht, 2007).

Psychological interventions are recommended by NICE to treat depressive episodes in bipolar disorder, but no specific recommendations are made regarding psychological treatment for mania (National Institute for Health and Care Excellence, 2014a). However, a review of the evidence measuring the effect of CBT compared to treatment as usual concluded that CBT provided only a small benefit in reducing symptoms, which was not maintained at follow up, and no benefit in preventing relapse (Jauhar, McKenna and Laws, 2016). Psychoeducation, delivered online or in a group format, was not effective in reducing symptoms compared to treatment as usual, although some benefit was seen for family psychoeducation. Furthermore,

individual psychoeducation did not reduce relapse rates compared to usual treatment, but a lower relapse rate was observed following carer psychoeducation (Jauhar, McKenna and Laws, 2016). Thus, evidence supporting the use of psychological interventions is limited, despite NICE recommending their use in both short-term and long-term treatment of bipolar disorder (Jauhar, McKenna and Laws, 2016).

1.3.5 Environmental aetiology

Three main categories of environmental risk factors for bipolar disorder have been identified: perinatal risk, trauma and stress, and substance abuse. There is some overlap between environmental risk factors for bipolar disorder and schizophrenia, although typically evidence for bipolar disorder risk is weaker and more inconsistent than evidence for schizophrenia (Robinson and Bergen, 2021).

A study of the Northern California Birth Cohort found a 4-fold increased risk of bipolar disorder in individuals exposed to influenza during pregnancy, increasing to a 6-fold risk when exposure occurred during the third trimester (Parboosing *et al.*, 2013). The study by Parboosing and colleagues (2013) used maternal medical records to identify influenza exposure, which may have selected for more severe cases of influenza. Another study in the same cohort utilised a more definitive method of ascertaining exposure, an assay of maternal serum, and found a significantly increased risk of bipolar disorder with psychotic symptoms following exposure to influenza, but not for bipolar disorder overall (Canetta *et al.*, 2014). A study of individuals born during or shortly after the Finnish Influenza epidemic did not identify increased risk of bipolar disorder (Machón, Mednick and Huttunen, 1997). However, in this study bipolar disorder diagnosis rates were compared between individuals born during and prior to the epidemic, and therefore could not categorically confirm the presence or absence of influenza exposure. Such methodological differences have led to inconsistent evidence and research has so far been unable to draw any definitive conclusions about viral infection *in utero* and risk for bipolar disorder (Barichello *et al.*, 2016).

Nine studies have examined season of birth and risk of bipolar disorder, with six finding a significant association between winter/spring birth and increased risk of bipolar disorder (Robinson and Bergen, 2021). However, a study of 2.1 million people

was amongst the three studies that did not find an association with season of birth, limiting the ability to draw definitive conclusions about risk of bipolar disorder. Preterm birth is another perinatal factor that has received inconsistent evidence for its association with bipolar disorder. In one study, babies born preterm were at an almost 3-fold increased risk of hospitalisation for bipolar disorder, with babies born before 32 weeks at a 7-fold increased risk (Nosarti *et al.*, 2012). However, in a separate study no significant associations were observed between bipolar disorder and preterm birth (Øgendahl *et al.*, 2006). Both studies derived their data from nationwide registries, allowing for reliable, systematic ascertainment of obstetric data. However, Nosarti and colleagues (2012) defined bipolar disorder using hospital discharge records in a sample of individuals under the age of 30 years, which may have biased the sampling towards early onset, severe cases. Øgendahl and colleagues (2006) considered both in-patient and out-patient diagnoses, but in a sample of individuals aged 26 years and under, which will also have biased their study to early-onset cases, given the median age at onset in bipolar disorder is 28 years (Kennedy *et al.*, 2005). Maternal smoking during pregnancy has been associated with an increased risk of bipolar disorder after covarying for the effects of maternal ethnicity, alcohol use, psychiatric history, and offspring birth weight (Talati *et al.*, 2013). However, a similar study in a considerably larger sample (79 cases vs 724 cases) did not find a significant association between maternal smoking and bipolar disorder after accounting for the effects of maternal age, maternal education, and parental psychiatric history (Chudal *et al.*, 2015). It is difficult to control for all possible sources of confounding in studies of *in utero* environment and later outcomes. Therefore, it possible that uncontrolled factors could impact the findings of these studies, including gene-environment correlations as has been seen in research examining ADHD and maternal smoking (Thapar et al., 2009).

The reported prevalence of childhood adversity in bipolar disorder varies substantially across studies, ranging from 8% to 77% in studies included in a recent systematic review and meta-analysis (Palmier-Claus *et al.*, 2016), which found that individuals who experienced childhood adversity were 2.6-times more likely to have bipolar disorder than individuals without childhood adversity. In a comparison of subtypes of childhood adversity, the strongest effect observed was for emotional abuse, with

individuals experiencing emotional abuse at a 4-fold increased risk of bipolar disorder. All forms of adversity assessed were associated with increased risk of bipolar disorder, except parental loss (Palmier-Claus *et al.*, 2016). However, research using Danish registry data found the only environmental risk factor significantly associated with increased risk of bipolar disorder was parental loss (Mortensen *et al.*, 2003). Maternal loss prior to the age of five was associated with a 4-fold increased risk of bipolar disorder, maternal loss after the age of five and paternal loss prior to the age of five were also significantly associated with bipolar disorder, albeit to a lesser extent (Mortensen *et al.*, 2003). Thus, it is possible that the timing of adverse events may impact risk for bipolar disorder and may in part explain inconsistencies in findings. Evidence from retrospective studies suggests that stressful life events can precipitate the onset of bipolar disorder, as well as recurrent mood episodes (Alloy *et al.*, 2005). Studies using prospective methods provide limited evidence in support of this association, with some studies finding that relapse was not associated with life events, and others finding an association only for particular types of stress and mood episodes, although findings for types of life events across studies are inconsistent (Alloy *et al.*, 2005).

Bipolar disorder is associated with increased rates of substance misuse compared to the general population (Strakowski and Delbello, 2000), leading to the suggestion that substance misuse may cause bipolar disorder, or vice versa. In people with comorbid bipolar disorder and substance misuse, 60% experience substance misuse prior to the onset of bipolar disorder (Strakowski and Delbello, 2000). In a longitudinal study of over 34,000 people, prescription medication abuse – defined as use of medication without a prescription or in greater amounts, more often, for longer duration, or for a different reason than prescribed – was associated with 2.6-fold increased risk of developing bipolar disorders in individuals with no previous history of psychopathology (Schepis and Hakes, 2011). This suggests that substance misuse may casually contribute to bipolar disorder. However, substance abuse may occur prior to affective symptoms for various reasons, including shared genetic and environmental risk factors. Others have suggested that substance misuse may be a manifestation of increased risk taking in bipolar disorder, or that substance misuse may be a form of

self-medication. There is evidence in support of each of these conclusions (Strakowski and Delbello, 2000), indicating that many factors contribute to the association between bipolar disorder and substance misuse and that establishing a causal relationship will not be a simple undertaking.

1.3.6 Genetic aetiology

Early family studies estimated the heritability of bipolar disorder to be between 44 and 90% following evidence of substantial genetic effects in bipolar disorder (O'Connell and Coombes, 2021). First-degree relatives of individuals with bipolar disorder are at almost an 8-fold increased risk of developing bipolar disorder (Song *et al.*, 2015) and monozygotic twins have shown a concordance rate of 50% (Craddock and Jones, 1999). As in schizophrenia, genetic research in bipolar disorder was initially based on the assumption that a handful of major genes determined the development of the disorder, which could be identified through linkage and candidate gene studies. Linkage studies in large pedigrees suggested the possibility of causal markers on chromosome 11 and the X chromosome, but these findings were later refuted both by the original authors of the studies and other researchers attempting to replicate the findings (Craddock and Jones, 1999). Furthermore, the pattern of inheritance shown in large pedigrees as well as concordance between monozygotic twins demonstrated that bipolar disorder is not a Mendelian disease. A polygenic architecture is now widely accepted as the best explanation of genetic susceptibility to bipolar disorder.

1.3.6.1 GWAS in bipolar disorder

The first GWAS of bipolar disorder was published by the Wellcome Trust Case-Control Consortium (WTCCC) in 2007 on 2000 cases and 3000 controls (Wellcome Trust Case Control Consortium *et al.*, 2007). No genome-wide significant SNPs were identified; one SNP reach a significance of $p<5x10^{-7}$ but failed to be replicated, indicating the need for greater sample sizes. The first GWAS conducted by the Bipolar Disorder Working Group of the PGC gathered 7,481 cases and 9,250 controls, with replication and meta-analysis in an additional 4,493 cases and 42,542 controls (Sklar *et al.*, 2011). They identified strong evidence for two genome-wide significant SNPs in the genes

CACNA1C and *ODZ4*. *CACNA1C* encodes a subunit of calcium volage-gated ion channels, and its association is consistent with evidence showing a therapeutic benefit in bipolar disorder of drugs that block calcium channels (Sklar *et al.*, 2011). Most recently, the third wave of the PGC bipolar disorder GWAS identified 64 genome-wide significant loci in a sample of 41,917 cases and 371,549 controls. Of these 64 loci, 33 had not previously been reported in any bipolar disorder GWAS, and 28 of the 30 loci identified in the wave two GWAS were replicated (Mullins *et al.*, 2014). Consistent with observations in schizophrenia, SNPs associated with bipolar disorder are enriched for gene sets related to synaptic signalling and are associated with expression in the brain. Fifteen genes were found to have causal effects on bipolar disorder via causal analyses based on gene expression in the brain and blood, including potential druggable targets. Genes encoding targets of existing medications were also associated with bipolar disorder, including calcium channel blockers and GABA receptor anaesthetics, indicating the potential for repurposing existing medications to treat bipolar disorder. Despite a substantial increase in hits compared to previous GWAS of bipolar disorder, the PGC wave 3 GWAS did not identify as many significant associations as comparably sized GWAS in schizophrenia, despite similar heritability (Cardno and Gottesman, 2000; O'Connell and Coombes, 2021). It is possible that this is due to heterogeneity within bipolar disorder, as analysis of the separate subtypes found a SNP-heritability of 20.9% for type I and 11.6% for type II, suggesting mania may be more heritable than hypomania (Mullins *et al.*, 2021). The two subtypes had a genetic correlation of 0.85, and bipolar disorder type I was more highly correlated with schizophrenia (r_g = 0.66) than was type II (r_g = 0.54), whilst type II was more highly correlated with depression (r_g = 0.66), than was type I (r_g = 0.34) (Mullins *et al.*, 2021). Thus, suggesting that mania may share more of its genetic architecture with schizophrenia, whilst hypomania may be more similar to depression.

Almost all GWAS of bipolar disorder have been conducted in samples of European ancestry (Ikeda *et al.*, 2018), and the few studies of non-European individuals are vastly underpowered compared to European-ancestry GWAS. Li and colleagues (2021) recently conducted a GWAS in 1,822 individuals with bipolar disorder and 4,650 controls, all of Han Chinese ancestry. They identified one novel locus associated with

bipolar disorder in Han Chinese participants, *TMEM108*, and two novel loci in a meta-analysis of their sample and the PGC2 Bipolar disorder GWAS – *VRK2* and *RHEBL1*. *TMEM108* is involved in dendritic spine development and was found to be widely expressed in the brain, particularly during prenatal development. *VRK2* has been shown to affect neuronal proliferation and migration and has been identified in GWAS of schizophrenia and depression. Although less is known about *RHEBL1*, it encodes a G-protein activator that is enriched in the brain and is thought to be involved in neurodevelopmental disorders.

Bigdeli and colleagues (2021) conducted a GWAS of bipolar disorder in United States veterans, including 1,037 cases and 4,669 controls of African-American ancestry and 3,080 case and 45,767 controls of European ancestry. Two genome-wide significant loci were identified – SORCS3 and variants downstream of PCDH11X. SORCS3 has been associated with various psychiatric disorders, including schizophrenia and depression, and is involved in long-term depression of neurons in the hippocampus. PCDH11X is associated with regulating dendritic branching and neuronal differentiation and proliferation. Together, the associations identified in non-European ancestry GWAS add further evidence to the role of neuronal developmental and function in bipolar disorder.

1.3.6.2 Rare genetic variation

Approximately 96% of loci identified from GWAS that are estimated to influence bipolar disorder are also estimated to influence schizophrenia, with 80% showing the same direction of effect for both disorders (Mullins *et al.*, 2021), suggesting that the vast majority of common variants are shared between both disorders. Differences in burden of rare variants have been proposed as one potential mechanism by which schizophrenia and bipolar disorder differ (Charney *et al.*, 2019). Rare genetic variation has been strongly implicated in schizophrenia, as discussed above, and is also robustly associated in neurodevelopmental disorders. However, there has been little evidence to date to suggest that rare variation is associated with bipolar disorder. Jia and colleagues (2021) did not find any significant differences in the burden of pathogenic or likely-pathogenic rare exonic variants between 3,987 cases with bipolar disorder

and 5,322 controls. Furthermore, no significant differences were found between cases and controls for burden of rare protein-altering variants, or in gene-level burden of pathogenic and likely-pathogen variants. Pathogenic and likely-pathogenic variants were more likely to fall within genes associated with bipolar disorder in GWAS (Jia *et al.*, 2021), suggesting that there may be an enrichment of rare variation but limitation of power and have prevented identification. However, this association was not replicated in a larger independent sample of 9,929 cases and 14,018 controls, suggesting that any SNVs associated with bipolar may be either too rare or of too small effect to be detected in current sample sizes (Jia *et al.*, 2021).

Only one CNV has been strongly associated with bipolar disorder – a duplication at 16p11.2 conferring a four-fold increased risk of having the disorder (Green *et al.*, 2015), and is also associated with autism, intellectual disability, and schizophrenia (O'Connell and Coombes, 2021). Charney and colleagues (2019) found no association between CNVs and bipolar disorder case-control status when measured by number of total CNVs, number of deletions and duplications separately, number of genes involved, total length of all CNVs, rare CNVs only, or large CNVs only (Charney *et al.*, 2019). However, individuals with SA-BP had an increased burden of CNVs compared to controls, as well as compared to individuals with bipolar disorder type I and type II, suggesting that CNVs may be a mechanism by which different psychotic disorders and subtypes arise (Charney *et al.*, 2019). It is possible that additional CNVs may increase risk for bipolar disorder, but thus far samples have been underpowered to detect an association due to smaller sample sizes and lower prevalence compared to CNVs in schizophrenia. The study by Green and colleagues (2015) examined 6,353 cases and 8,656 controls and identified one CNV associated with bipolar disorder and levels of statistical significance surviving correction for multiple testing. In comparison, the largest CNV study in schizophrenia identified eight disorder-associated CNVs in 21,094 cases and 20,227 controls (Marshall *et al.*, 2017). The one CNV associated with bipolar disorder, 16p11.2 duplication, was found in 0.13% of cases (Green *et al.*, 2015), whereas 22q11.2 deletion, the most robustly associated CNV with schizophrenia, is found in approximately 1% of people with schizophrenia (Bassett and Chow, 2008), and thus will be easier to detect.

1.3.6.3 Polygenic risk and genetic correlations

PRS for bipolar disorder, trained on the most recent GWAS (Mullins *et al.*, 2021), explain only 4.6% of the variance in bipolar disorder, corresponding to an AUC of 65%. This number is even lower for individuals of non-European ancestry, explaining only 2.3% of the variance in an East Asian sample and 1.2% in an African-American sample (Mullins *et al.*, 2021). Individuals of European ancestry with the top 10% bipolar disorder PRS were nine times more likely to have a bipolar disorder diagnosis than individuals of European ancestry in the bottom 10% of scores, suggesting that whilst bipolar disorder PRS does not currently possess useful predictive power, there may be a benefit to examining those with the highest risk for the disorder.

Bipolar disorder PRS has been associated with several traits, including greater creativity and higher educational attainment (Power *et al.*, 2015), as well as increased risk of schizophrenia, depression, and ADHD (Mistry *et al.*, 2018a). The strongest genetic correlation for bipolar disorder is with schizophrenia (rg=0.7)(Lee *et al.*, 2019), indicating that a substantial proportion of SNPs that increase or decrease risk for bipolar disorder share the same direction of effect in schizophrenia. Genetic correlations have also been observed between bipolar disorder and measures of smoking, alcohol use, and sleep quality (Mullins *et al.*, 2021). Of these traits, the strongest genetic correlation was found between bipolar disorder and problematic alcohol use (r_g = 0.35), suggesting that associations between bipolar disorder and substance use may result from a shared genetic architecture (Mullins *et al.*, 2021).

Other PRS have been shown to influence phenotypic heterogeneity within bipolar disorder. Most evidence suggests that the presence of psychosis in bipolar disorder is associated with increased PRS for schizophrenia, particularly for mood-incongruent psychotic symptoms (Allardyce *et al.*, 2018) and for psychosis in mania than in depression (Markota *et al.*, 2018). Higher schizophrenia PRS has also been associated with having bipolar disorder type I, compared to type II, and with SA-BP compared to bipolar disorder type I (Charney *et al.*, 2017). Bipolar disorder PRS was found to be higher in individuals with type I or SA-BP compared to type II, but not between type I and SA-BP (Charney *et al.*, 2017). Thus, variation in liability to schizophrenia and bipolar disorder is associated with phenotypic characteristics that define each subtype

of bipolar disorder. However, as discussed above, these studies are conducted in individuals of European ancestry, and thus any potential clinical applications of PRS in bipolar disorder would not be applicable or appropriate for individuals of non-European ancestry.

1.4 Schizoaffective disorder

Schizoaffective disorder is characterised by the co-occurrence of both psychotic and affective symptoms. Many consider schizoaffective disorder to be a controversial diagnosis, and it's nosological status has long been debated (Jäger *et al.*, 2011). There are arguments for and against schizoaffective disorder as its own distinct diagnosis, with alternative arguments believing it is a form of schizophrenia, a form of affective disorder, or a transitional state between the two (Maj, 1984a).

1.4.1 Conception and criteria

Concepts of schizoaffective disorder originated in Europe in the late 19th century, with French psychiatrist Magnan describing 'bouffée délirante' - an acute psychotic illness marked by rapidly changing symptoms, short episode duration, and recurrent course (Maj, 1984b). Similar descriptions were made by German psychiatrists during the early 20th century, termed 'degenrationspsychosen', which were recurrent psychotic episodes independent of schizophrenia and bipolar disorder. Kleist defined cycloid psychosis in 1928, which included several subtypes pertaining to symptoms of mania and depression, paranoia, and psychosis in epilepsy (Maj, 1984b). Kasanin, an American psychiatrist, was the first to formally describe schizoaffective disorder in 1933, following observation of nine individuals with a sudden onset psychosis characterised by a combination of psychotic and affective symptoms that were preceded by an environmental stressor (Maj, 1984a). All patients recovered within a few weeks or months and their outcomes were noted to be very different to those described by Kraepelin for individuals with schizophrenia (Kasanin, 1933). Other research around this time identified individuals who did not neatly fit a schizophrenia or bipolar disorder diagnosis, and found that these patients recovered much better than individuals with schizophrenia, yet worse than those with bipolar disorder (Hunt

and Appel, 1936). Individuals with a diagnosis of schizophrenia who had recovered from their illness were more likely to have better premorbid social adjustment, factors precipitating illness onset, acute onset, family history of bipolar disorder, and a clinical picture marked by mixed psychotic and affective symptoms, typically without affective flattening (Maj, 1984a). Whilst some argued that this evidence justified considering schizoaffective a separate diagnostic entity, others concluded that there was little justification in distinguishing schizophrenia and schizoaffective disorder, given that any person with schizophrenia who recovers would be diagnosed with schizoaffective disorder (Maj, 1984a). Others argued that the prominence of affective disorders in the family history, alongside some evidence of positive lithium response in schizoaffective disorder, justified classifying schizoaffective disorder as a variant of bipolar disorder (Maj, 1984a).

Nevertheless, others persisted in attempting to define specific criteria for schizoaffective disorder. In the 1970s, Perris developed Leonhard's concept of cycloid psychosis and proposed the following diagnostic criteria: i) affective symptoms alongside at least two of: confusion with agitation or retardation, paranoia or hallucinations, hypo/hyperkinesia, or episodes of ecstasy, ii) psychotic symptoms, and iii) complete remission between episodes (Maj, 1984b). Perris's research found that individuals diagnosed with schizoaffective disorder according to his criteria were more likely to be women, have an acute onset, and have a family history specifically for schizoaffective disorder and less so for schizophrenia or bipolar disorder. He noted that external factors precipitating illness onset were common but were often absent (Perris, 1974). Cutting and colleagues (1978) applied Perris's criteria to 2,500 individuals admitted to hospital, identifying 73 individuals fulfilling the criteria, and followed them up to assess long-term outcomes. Individuals diagnosed with Perris's schizoaffective disorder had better recovery rates than all individuals with any other psychotic disorder, but also had the highest number of readmissions and illness episodes (Cutting, Clare and Mann, 1978).

Whilst definitions have varied between individuals and cultures, research attempting to distinguish and define the concept of schizoaffective disorder consistently identified the most prominent features as acute onset, mixed affective and psychotic symptomatology, greater occurrence in women, good premorbid adjustment, and

recurrent episodes marked by recovery and remission. However, this definition does not greatly overlap with any DSM or ICD definition of schizoaffective disorder.

The first two editions of DSM, ICD-8, and ICD-9 defined schizoaffective disorder as a subtype of schizophrenia, noting that individuals with schizoaffective disorder typically transition to schizophrenia over time. By DSM-III, schizoaffective disorder was listed as a separate diagnosis, albeit without any criteria, and was categorised as psychotic disorder to be used when the clinician was unable to definitively diagnose schizophrenia or bipolar disorder. Schizoaffective disorder has remained under the broad category of psychotic disorders, rather than affective disorders, throughout all subsequent editions of the DSM and ICD. DSM-IV first operationalised criteria for a schizoaffective disorder diagnosis, listing two subtypes: depressive-type and bipolar-type (SA-D, and SA-BP, respectively). To meet DSM-IV criteria for schizoaffective disorder, an individual needed to experience an uninterrupted period of illness with the symptom criteria for schizophrenia (Table 1.1), alongside an episode of depression, for SA-D, or mania, for SA-BP (Tables 1.2 and 1.3). Psychosis needed to be present for at least two weeks without affective symptoms, and the mood episode needed to be present for a substantial portion of the total illness (American Psychiatric Association, 1994). In practice, this led to inconsistency in the diagnosis of schizoaffective disorder as 'substantial portion' was open to a wide degree of interpretation, creating a perception of schizoaffective disorder as an unreliable diagnosis (Maj *et al.*, 2000). Thus, for DSM-5, this criterion was updated as being present for 'the majority of the total duration' of the illness. ICD-10 differed slightly in that individuals do not have to meet the full symptom criteria for schizophrenia, but instead needed only one of a series of symptoms, based on Schneider's first-rank symptoms, for at least two weeks. A mood episode of at least moderate severity had to occur in the same episode as psychosis and both sets of symptoms needed to be prominent in the clinical picture. For ICD-11, which is due to be adopted into clinical practice in 2022, manic and depressive subtypes have been removed. Table 1.5 details criteria for DSM-5 and ICD-10 criteria for schizoaffective disorder. A further discussion of the controversies and criticisms of schizoaffective disorder is provided in section 1.6.

ICD-10 and DSM-5 criteria for schizoaffective disorder		
	ICD-10	**DSM-5**
Symptoms	*G1:* • Affective disorder of at least moderate or severe degree. • For manic type: manic disorder • For depressive type: depressive disorder *G2: Symptoms from at least one of the following groups:* 1. Thought echo, insertion, withdrawal, or broadcasting 2. Delusions of control, influence, or passivity 3. Hallucinatory voices giving running commentary or discussing the patient among themselves 4. Persistent delusions that are culturally inappropriate and completely impossible 5. Grossly irrelevant or incoherent speech 6. Catatonic behaviour G1 and G2 must be met within the same episode of the disorder, and concurrently for at least part of the episode. Both G1 and G2 must be prominent in the clinical picture.	*A:* - Major mood episode concurrent with criterion A for schizophrenia *B:* - Delusions or hallucinations for two or more weeks in the absence of a major mood episode during the lifetime duration of the illness. *Bipolar type*: manic episode is part of the presentation *Depressive type*: only major depressive episodes are part of the presentation
Duration	Symptoms from G2 must be clearly present for most of the time during a period of at least two weeks.	Symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the active and residual portions of the illness.
Exclusions	Not attributable to organic mental disorder or to psychoactive substance intoxication, dependence, or withdrawal.	Not attributable to the effects of a substance or another medical condition.

Table 1.5. Diagnostic criteria for schizoaffective disorder in the International Classification of Diseases (ICD-10)(World Health Organisation., no date) and Diagnostic and Statistical Manual of Mental Disorders (DSM-5)(American Psychiatric Association., 2013).

1.4.2 Epidemiology

Schizoaffective disorder is typically studied in conjunction with schizophrenia or bipolar disorder. Consequently, little research has sought to establish the prevalence and incidence specifically of schizoaffective disorder. A study of all individuals diagnosed with schizophrenia, schizoaffective disorder, and bipolar disorder in a small county in Ireland found a prevalence of 1.1 per 1000 individuals for schizoaffective disorder (Scully *et al.*, 2004). A nationally representative study of individuals in Finland reported a lifetime prevalence of 0.32% for schizoaffective disorder (Perälä *et al.*, 2007). Whilst these studies are population-specific and therefore may reflect cultural-specific risk, their estimates suggest that the prevalence of schizoaffective disorder falls between 0.11% and 0.32%. In contrast, the prevalence of schizophrenia and bipolar disorder is 0.4% and 0.7%, respectively, indicating that schizoaffective disorder may be less common than either of these disorders.

1.4.3 Illness course and treatment

Research specifically studying individuals with schizoaffective disorder has typically compared them to individuals with schizophrenia and/or bipolar disorder. Pagel and colleagues (2013) systematically reviewed such studies published prior to 2009, and found that for some characteristics, including marital status, ethnicity, and age at onset, schizoaffective disorder occupied an intermediate position between schizophrenia and bipolar disorder. Compared to individuals with schizophrenia, individuals with schizoaffective disorder were more likely to have ever been married, to be of white ethnicity, to have had a longer duration of illness, and to have scored higher on the Global Assessment Scale, indicating better functioning in the worst episode of illness (Pagel *et al.*, 2013). Compared to individuals with bipolar disorder, individuals with schizoaffective disorder were more likely to have a lower educational attainment, to not have been married, to have more psychotic symptoms, and have a higher IQ score. The pooled mean age at onset across studies for schizoaffective disorder was 23.3 years, compared to 21.9 years in schizophrenia and 26.1 years in bipolar disorder. Whilst these estimates are younger than those described previously

for schizophrenia and bipolar disorder, they are consistent in demonstrating schizoaffective disorder as an intermediary category. Pagel and colleagues (2013) also compared whether schizoaffective disorder was more frequently similar to schizophrenia or bipolar disorder, concluding that it was not any closer to one disorder over the other. This may indicate that schizoaffective disorder is a category formed of a mixture of individuals with schizophrenia and bipolar disorder. Alternatively, it could suggest that schizoaffective disorder is a diagnosis in its own right, falling in the middle of the psychosis-affective spectrum. The findings of Pagel and colleagues (2013) indicated a large degree of heterogeneity between studies, which may in part be due to differences in the way schizoaffective disorder is defined, i.e., using ICD or DSM criteria and the edition of each manual, but may also result from most studies not delineating between subtypes of schizoaffective disorder. Harrow and colleagues (2000) conducted a 10-year longitudinal study of individuals with schizophrenia, schizoaffective disorder, bipolar disorder with psychosis, and psychotic depression, which was not included in the review by Pagel and colleagues (2013). They found that individuals with schizoaffective disorder had better outcomes at each stage of follow-up compared to people with schizophrenia, but worse outcomes than individuals with a psychotic bipolar disorder or depression diagnosis. At each time point, between 28% and 37% of individuals with schizoaffective disorder showed poor functioning in all areas measured, and no more than 40% of individuals showed complete recovery at any point. The number of hospitalisations was lower amongst individuals with schizoaffective disorder than with schizophrenia at two years follow up, but did not significantly differ at later time points. At 10 years after their index hospitalisation, 50% of people with schizoaffective disorder were being treated with antipsychotics, 20% were prescribed a mood stabiliser, and 17% were taking an antidepressant (these categories were not mutually exclusive). The results of this study further suggest that outcomes in schizoaffective disorder are typically poor, although are somewhat better than in schizophrenia (Harrow *et al.*, 2000). However, as with the review by Pagel and colleagues (2013), subtypes of schizoaffective disorder were not considered. Consequently, variation in clinical characteristics and outcomes may be related to subtype, and such evidence would prove valuable in refining these diagnostic concepts. A comparison of SA-BP and SA-D found that both disorders had

poor psychosocial and premorbid functioning and younger age at onset than individuals with bipolar disorder or unipolar depression. However, SA-D had a more insidious mode of onset and greater levels of stress prior to onset, whilst SA-BP was associated with a greater amount of time spent in hospital, indicating some important clinical differences between the two diagnoses (van Eerdewegh *et al.*, 1987). Whilst this research offers valuable insights into differences between schizoaffective subtypes, individuals were diagnosed using Research Diagnostic Criteria (RDC). RDC is considered to have a broad definition of schizoaffective disorder, and thus is not entirely consistent with a diagnosis made on the basis of ICD and DSM. Research is needed that uses current clinical criteria in order to examine differences between subtypes and further efforts to refine the diagnostic criteria for schizoaffective disorder in order to improve its reliability.

1.4.4 Aetiology

Twin studies have shown a concordance rate of 39% for schizoaffective disorder, with slightly higher concordance for SA-D than for SA-BP (41.7% v 30.8%, respectively), and a heritability of around 80%, indicating a substantial genetic component (Cardno *et al.*, 2012). A study of Danish registry data examined relative risk of schizoaffective disorder in individuals with and without a family history of psychotic and affective disorders (Laursen *et al.*, 2005). History of schizophrenia, bipolar disorder, or schizoaffective disorder in a first-degree relative were all associated with substantially increased risk of developing schizoaffective disorder. Individuals with a parent with schizophrenia did not significantly differ in risk from individuals with a parent with bipolar disorder, suggesting that both disorders contribute a similar level of risk (Laursen *et al.*, 2005). Relatives of probands with schizoaffective disorder are at a greater risk of developing bipolar disorder compared to relatives of probands with schizophrenia, whereas no significant differences were observed in risk of schizophrenia, further suggesting that schizoaffective disorder may result from elevated liability to both schizophrenia and bipolar disorder (Kendler, Gruenberg and Tsuang, 1986). However, it is possible these studies were limited by not considering independent effects of SA-D and SA-BP. Cardno and colleagues examined SA-D and SA-BP separately, measuring co-occurrence of SA-D, SA-BP, schizophrenia, bipolar disorder, and psychotic depression in

monozygotic twins. They observed significant co-occurrence between SA-BP and all other disorders, whilst SA-D was associated only with schizophrenia, SA-D, and psychotic depression (Cardno *et al.*, 2012). Thus, SA-BP may result from elevated liability to bipolar disorder and schizophrenia, whilst SA-D may be marked by elevated liability to schizophrenia and depression (Cardno and Owen, 2014).

Molecular genetic studies of schizoaffective disorder have been limited, largely due to the inclusion of these disorders with either schizophrenia or bipolar disorder. One study, measuring candidate gene associations following evidence from GWAS in bipolar disorder, reported an association between various $GABA_A$ receptor genes and SA-BP, which was not found with bipolar disorder or schizophrenia (Craddock *et al.*, 2010). Although more recent GWAS of schizophrenia have reported associations with GABA receptors (Schizophrenia Working Group of the Psychiatric Genomics Consortium. *et al.*, 2020) and associations in bipolar disorder were enriched for targets of GABA-receptor medications (Mullins *et al.*, 2021), suggesting that limitations of power may have affected the earlier findings (Cardno and Owen, 2014). Studies using PRS have found that individuals with SA-BP have higher schizophrenia PRS than individuals with bipolar disorder (Hamshere *et al.*, 2011; Allardyce *et al.*, 2018), supporting evidence from twin studies of elevated schizophrenia liability in schizoaffective disorder. Consistent with this observation is evidence of elevated CNV burden in individuals with SA-BP, but not bipolar disorder (Charney *et al.*, 2019). Genetic studies of SA-D have only been conducted using a family design rather than at a molecular level, although individuals with SA-D are commonly included in schizophrenia research.

1.5 Cross-disorder genetic liability

A substantial amount of evidence has demonstrated considerable overlap in the genetic aetiology of schizophrenia, schizoaffective disorder, and bipolar disorder. A GWAS jointly analysing schizophrenia and bipolar disorder compared to controls identified 32 loci associated with case status and eight significant pathways, of which seven are involved in synaptic and neuronal functioning (Ruderfer *et al.*, 2018). These findings suggest that disrupted neuronal signalling plays a key role across both

disorders and is consistent with previous findings within each disorder (Nurnberger *et al.*, 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The

of the PGC has looked across eight psychiatric disorders, including schizophrenia and bipolar disorder, to identify pleiotropic loci and their role in shared aetiology. Eleven loci were shown to have opposite effects on risk between disorders, including two with opposite effects on schizophrenia and ASD. Notably, no loci had opposite effects on schizophrenia and bipolar disorder (Lee *et al.*, 2019). They found 136 loci reaching genome-wide significance, including 23 associated with at least four disorders. SNPs showing pleiotropic effects were more likely to be involved in neurodevelopmental processes, for example neurogenesis, than disorder-specific SNPs, suggesting that alterations to neurodevelopment may be a common factor underlying psychiatric disorders (Lee *et al.*, 2019). One SNP, located in the gene *DCC*, was associated with all eight disorders, and is involved in axonal growth during prenatal development. Gene set analysis implicated neurogenesis and neuron differentiation, as well as synaptic signalling sets, including voltage gated calcium channels. However, these findings may be influenced by the differences in the proportion of individuals with each disorder included in analyses. Over 33,000 people with schizophrenia were included, compared to disorders such as anorexia nervosa and obsessive-compulsive disorder that were represented by less than 3,500 participants each. Thus, associations may be biased towards schizophrenia, as well as bipolar disorder and depression as these three disorders comprised 79% of the cases included.

Research by the Brainstorm Consortium measured genetic correlations between 25 neurological and psychiatric disorders, as well as several behavioural and cognitive phenotypes. Several significant genetic correlations were observed between psychiatric disorders were strongly genetically correlated, indicating that that a significant proportion of the SNPs conferring risk for these disorders have pleiotropic effects on multiple disorders. Schizophrenia and bipolar disorder were significantly genetically correlated with each other and with ADHD, depression, and obsessive-compulsive disorder; schizophrenia was also correlated with anorexia nervosa (The Brainstorm Consortium, 2018). In comparison, few significant correlations were

observed between neurological disorders, suggesting that these diagnoses represent genetically-discrete entities. The authors suggest this may reflect a general psychopathology factor on which other genetic and environmental factors influence illness presentation, as previously proposed (Caspi *et al.*, 2014). Alternatively, it may also be due to endophenotypes or symptom dimensions that traverse disorders. Both these explanations may be true, and identification of additional risk loci for different disorders may further elucidate the mechanisms underlying these associations. Overall, the findings of the Cross-disorder group of the PGC and the Brainstorm Consortium illustrate the complexity of cross disorder relationships and the heterogeneity of schizophrenia and bipolar disorder, but also highlight the fact that cross disorder analytic approaches may offer insights into aetiology and classification of schizophrenia and related disorders.

1.6 Validity of diagnostic categories

The validity of existing diagnostic categories for psychotic and mood disorders has often been questioned (Allardyce *et al.*, 2007), particularly given the evidence of a spectrum of illness and the existence of intermediary categories that fit neatly on neither side of the dichotomy, such as schizoaffective disorder. Even Kraepelin increasingly recognised the issues of dichotomising schizophrenia and bipolar disorder given the presence of cases that did not fit this dichotomy, and later in his career he advocated for a more dimensional approach to the conceptualisation of these disorders (Jablensky, 2010).

The diagnosis of psychiatric disorders relies primarily on observing signs and symptoms that differentiate different syndromes, as opposed to measuring disease-specific biomarkers (Kendell and Jablensky, 2003). Consequently, psychiatry is reliant on defining disorders by differences in symptoms rather than differences in aetiology, and thus the validity of existing diagnostic categories is often called into question (Kendell and Jablensky, 2003). The validity of schizoaffective disorder as a psychiatric diagnosis has been debated by experts in the field, with some calling for its omission from the ICD and DSM, whilst others argue that a lack of research into schizoaffective disorder means we cannot definitively conclude whether it should remain a diagnosis or not

(Jäger *et al.*, 2011). Arguments against schizoaffective disorder question the validity of the diagnosis, which stems largely from a lack of unique psychopathology and poorly defined criteria that make diagnosis inconsistent and unreliable (Jäger *et al.*, 2011). Inter-rater reliability is moderate for schizoaffective disorder (Cohen's kappa =0.57), whilst schizophrenia and bipolar disorder typically show high reliability (Cohen's kappa scores >0.8) (Santelmann *et al.*, 2016). This may be due to heterogeneity across diagnostic systems in defining schizoaffective disorder, as well as ambiguity within systems. Maj and colleagues (2000) found that each criterion for schizoaffective disorder in DSM-IV was open to interpretation and led to disagreement amongst psychiatrists. DSM-IV provides no detail as to whether psychotic symptoms can be affective in content or secondary to mood disturbance, such as disorganised speech and behaviour in mania. Criterion B states that prominent mood symptoms must be absent for two weeks, yet 'prominent' was interpreted to mean clinically significant by some, and meeting criteria for a mood episode by others. Lastly, there is a large degree of ambiguity in criterion C, stating that mood symptoms must be present for a 'substantial portion' of the illness without a definition of 'substantial' (Maj *et al.*, 2000). This last issue has been addressed for DSM-5, which now states that mood symptoms must be present for the majority of the total duration of the illness (Malaspina *et al.*, 2013). Studies have frequently demonstrated poor stability of schizoaffective disorder over time, with one study finding only 36% of individuals initially diagnosed with schizoaffective disorder receiving the same diagnosis two years later, compared to 92% of people with schizophrenia and 83% for people with bipolar disorder (Schwartz *et al.*, 2000). Poor reliability presents a significant challenge to schizoaffective disorder as a diagnosis, yet lack of reliability should not be considered synonymous with lack of validity or utility.

A diagnosis may be considered to have validity and clinical utility if the defining features of the disorder are able to provide further information to the clinician and the patient (Kendell and Jablensky, 2003). Evidence that individuals with schizoaffective disorder show a different course of illness (Harrow *et al.*, 2000), treatment response (Cheniaux *et al.*, 2008), and pattern of cognitive impairments (Hill *et al.*, 2013) than individuals with schizophrenia and bipolar disorder would argue towards schizoaffective disorder as a valid construct. Moreover, whilst there is limited evidence

for unique genetic markers of schizoaffective disorder, evidence from family studies indicates co-occurrence of elevated liability to psychotic and affective disorders, suggesting a specific pattern of genetic risk.

Furthermore, it is necessary to consider how modern definitions of schizoaffective disorder have contributed to its negative reputation. There is no agreed upon definition of schizoaffective disorder, and diagnostic manuals vary greatly in the degree of specificity for its diagnosis. Research Diagnostic Criteria (RDC) and ICD-10 have been considered broad definitions, as they do not require an individual to meet the criteria for schizophrenia, as is the case with DSM. Pagel and colleagues (2014) found a number of differences in findings between studies using broad vs narrow criteria for schizoaffective disorder, including fewer hospital admissions, greater number of females, and lower likelihood of being married in broad compared to narrowly defined schizoaffective disorder. Findings from broadly defined studies also showed a greater degree of heterogeneity in their results than did narrowly defined studies, indicating that variability in definitions of schizoaffective disorder may be hindering research progress. DSM-5 has sought to rectify this by refining the criteria to improve the reliability of schizoaffective disorder and allow for further research that will advance future conceptualisations. Such advancements may also critically depend on ICD definitions of schizoaffective disorder, which for ICD-11 has been updated to require symptom criteria of schizophrenia be met, as was not the case in ICD-10 (Gaebel, 2012).

The categorical distinctions imposed on what are increasingly considered continuous, dimensional phenotypes has led to criticism of psychotic and affective disorders more broadly. A number of domains of psychopathology underlie psychotic and affective disorders, including positive, negative, and disorganised symptoms, mania, depression, and cognition. To define categorical diagnoses, distinctions need to be applied to these continuous traits that will ultimately be arbitrary in nature. For instance, the symptom criteria for schizophrenia and schizophreniform disorder are the same and differ only in the length of the disturbance - at six months a diagnosis of schizophrenia can be made. This has been criticised as an arbitrary distinction lacking in evidence, as in

practice few differences would be expected between someone experiencing five months and three weeks of illness, compared to six months (Wong, 2014).

1.7 Alternative approaches to nosology

It has been suggested that a dimensional approach to the classification of psychotic and affective disorders may better represent the underlying structures of psychopathology than a categorical approach. A dimensional model of classification would allow for greater statistical power in research, as categorical data minimises the level of detail available and can miss important aspects of heterogeneity within a category (Esterberg and Compton, 2009). Studies have found dimensional approaches to have better temporal stability (Esterberg and Compton, 2009), and thus may be particularly useful in the context of mixed psychotic and affective symptoms. However, a specific dimensional approach has not been agreed on. Keshavan and colleagues (2011) proposed the 'Schizo-bipolar scale', a 10-point scale rating non-affective psychosis, duration of mania, and predominant mood. They found that individuals with bipolar disorder diagnosis typically scored on the low end of the scale, individuals with schizophrenia fell on the high end, and schizoaffective disorder was distributed across the middle, demonstrating that variation in psychotic and affective symptoms can be captured in a dimensional approach. The neurodevelopmental model proposes that schizophrenia, and to a lesser extent bipolar disorder, should be positioned on a spectrum alongside disorders such as ASD, ADHD and intellectual disability, ordered by increasing level of neurodevelopmental impairment (Owen and O'Donovan, 2017). This follows evidence of a continuum of neurodevelopmental burden, indexed by cognitive impairments, age at onset, greater prevalence in males, and comorbidity between disorders (Owen *et al.*, 2011). Evidence from common and rare variant studies also indicates substantial overlap in the genetic architecture of these disorders, with a greater burden of rare variants of large effect as severity of cognitive impairments increases (Owen and O'Donovan, 2017). In the United Kingdom, implementing a neurodevelopmental model would need to overcome barriers including the separation of adult psychiatric services from child and adolescent

services, as well as the split between general psychiatric and intellectual disability services (Owen *et al.*, 2011).

1.7.1 Symptom dimensions

The approaches discussed above focus on encapsulating all signs and symptoms of psychosis and affective disorders into one dimension or model. Other research has focussed specifically on individual symptom dimensions to examine their utility within and across psychotic and affective disorders.

1.7.1.1 Symptom dimensions in schizophrenia

Research has frequently identified three primary symptom domains within schizophrenia: positive, negative, and disorganised (Cardno *et al.*, 1996; Derks, Allardyce, *et al.*, 2012; Shafer and Dazzi, 2019). These dimensions have been consistently identified across a range of symptom measurements, including Operational Criteria Checklist for Psychotic and Affective Illness (OPCRIT) (Cardno *et al.*, 1996), the Comprehensive Assessment of Symptoms and History (Derks, Allardyce, *et al.*, 2012), Positive And Negative Syndrome Scale (Shafer and Dazzi, 2019), and the Scale for Assessment of Positive/Negative Symptoms (Cardno, Jones, *et al.*, 1999; Legge, Cardno, *et al.*, 2021). Recently, others have suggested that additional domains may exist, including at least two subtypes of negative symptoms - diminished expressivity and diminished motivation and pleasure (Strauss *et al.*, 2013, 2018; Legge, Cardno, *et al.*, 2021). Identification of these domains may depend on the instrument used to measure negative symptom as well as the metric used to define model fit, as different factor solutions have been able to provide different degrees of fit dependent on the assessment method (Strauss *et al.*, 2018).

There is evidence that different symptom factors may differ in heritability and may be indexed by polygenic risk for different disorders. In a sample of individuals with schizophrenia and schizoaffective disorder, McGrath and colleagues (2009) identified nine phenotypic factors, five of which indexed symptoms, and found evidence that all factors were heritable. Vassos and colleagues (2008) also found that several symptom factors derived from the PANSS showed familial aggregation. However, Cardno and

colleagues (1999) did not find evidence of familial aggregation of positive symptoms in twins with schizophrenia or schizoaffective disorder, and only identified a correlation between twins for disorganised symptoms. In people with schizophrenia, genetic risk for schizophrenia as indexed by PRS has not been significantly associated with positive symptoms (Derks, Vorstman, *et al.*, 2012; Fanous *et al.*, 2012; Jonas *et al.*, 2019; Legge, Cardno, *et al.*, 2021), suggesting that variability in the severity of positive symptoms within individuals with schizophrenia is not being captured by schizophrenia PRS.

Several studies found disorganisation to be the symptom domain with the highest heritability and strongest familial aggregation in people with schizophrenia (Cardno, Jones, *et al.*, 1999; Cardno *et al.*, 2001; Vassos *et al.*, 2008; McGrath *et al.*, 2009). Disorganised symptoms were also more strongly associated with schizophrenia PRS than were positive symptoms in two large studies (Fanous *et al.*, 2012; Legge, Cardno, *et al.*, 2021), although not all studies have supported this finding. Derks and colleagues (2012) did not find association between schizophrenia PRS and disorganised symptoms in a within-case analysis, and Jonas and colleagues (2019) did not find an association between disorganisation assessed at first admission and schizophrenia PRS. In individuals experiencing their first episode of psychosis, disorganised symptoms were not associated with schizophrenia PRS, but positive and negative symptoms were significantly associated with higher schizophrenia PRS. However, it is possible that disorganised symptoms are less prevalent in first episode samples than in established schizophrenia and thus there may not be sufficient variation to detect a statistically significant association.

Some studies supported an association between schizophrenia PRS and negative symptoms, although evidence is inconclusive. In adolescents, schizophrenia PRS was associated with increased self-reported negative symptoms in one study (Jones *et al.*, 2016), but with reduced parent-reported negative symptoms in another (Sieradzka *et al.*, 2014). Schizophrenia PRS was more strongly associated with a domain comprising negative and disorganised symptoms combined, than with other symptom domains, although this was found to be driven by the disorganised symptoms rather than the negative symptoms (Fanous *et al.*, 2012). When negative symptoms were split into two

domains, diminished expressivity, but not reduced motivation/pleasure, was associated with increased schizophrenia PRS, however this association did not remain after co-varying for disorganised symptoms (Legge, Cardno, *et al.*, 2021). Thus, it is possible that schizophrenia PRS may be associated with negative symptoms, but the findings likely depend on the granularity of methodology used to measure the negative symptoms and whether the measurements used were able to distinguish between negative and disorganised symptoms.

Cognitive functioning in people with schizophrenia is not associated with schizophrenia PRS, but is associated with PRS for educational attainment and IQ (Richards *et al.*, 2020). Cognition was measured as a composite score (*g*), thus it is possible that schizophrenia PRS could influence specific domains of cognition not examined in this study. In contrast, schizophrenia PRS is associated with worse cognitive functioning in controls (Shafee et al., 2018), suggesting that schizophrenia PRS does affect cognition to a certain extent. Thus, schizophrenia PRS may predispose to poorer cognitive functioning, but the marked deficits seen in schizophrenia may results from other genetic and nongenetic influences. Overall, there is some evidence that clinical heterogeneity within schizophrenia may result from variation in genetic liability to schizophrenia, but further research is necessary to understand genetic and nongenetic influences on clinical presentation.

1.7.1.2 Symptom dimensions in bipolar disorder

Factor analysis research within bipolar disorder typically identifies three to five factors (Cassidy *et al.*, 1998; Dilsaver *et al.*, 1999; Serretti *et al.*, 1999; Kumar *et al.*, 2001; Rossi *et al.*, 2001; Faraone, Su and Tsuang, 2004; Picardi *et al.*, 2008; Hanwella and de Silva, 2011; Swann *et al.*, 2013), although one study reported seven factors (Sato *et al.*, 2002). Dimensions of elation, irritability, and psychosis are the most consistently identified, a sleep disturbance factor (Dilsaver *et al.*, 1999; Rossi *et al.*, 2001; Faraone, Su and Tsuang, 2004; Swann *et al.*, 2013) and a depression factor (Cassidy *et al.*, 1998; Rossi *et al.*, 2001; Sato *et al.*, 2002; Picardi *et al.*, 2008; Swann *et al.*, 2013) are also sometimes reported. Differences in the instrument used to measure symptoms may in part explain the variation in the number of factors observed, as some studies use

scales that do not include depressive items or use larger questionnaires and interviews that may increase the number of factors identified. Furthermore, definitions of bipolar disorder vary across studies, some include individuals with SA-BP and with mixed manic episodes, whilst others exclude individuals with these diagnoses (Cassidy *et al.*, 1998; Faraone, Su and Tsuang, 2004; Hanwella and de Silva, 2011).

Despite a large body of research establishing dimensions of bipolar disorder (irritability, elation, and psychosis) and evidence that bipolar disorder is highly heritable (estimated heritability between 44% and 90% (O'Connell and Coombes, 2021), little research has looked at the link between genetic liability for psychiatric disorders and dimensions of bipolar disorder. In one study measuring heritability in a sample of individuals with bipolar disorder types 1 and 2 and SA-BP, a factor indexing irritability vs elation was found to be heritable, as was a depression factor. However, factors for sleep disturbances, psychosis, and psychomotor acceleration were not found to be heritable (Faraone, Su and Tsuang, 2004). Guzman-Parra and colleagues (2021) did not observe significant differences in bipolar disorder PRS between individuals with bipolar disorder type I and type II, despite identifying phenotypic differences, suggesting that bipolar disorder PRS may not contribute substantially to clinical heterogeneity within bipolar disorder types I and II.

There is evidence that genetic risk for other traits and psychiatric disorders may impact phenotypic variation in bipolar disorder. Schizophrenia PRS has been associated with psychosis in bipolar disorder, in particular with increasing presence of mood-incongruent psychosis (Allardyce *et al.*, 2018), and with SA-BP compared to other bipolar disorders (Hamshere *et al.*, 2011). Whilst some studies have not observed a significant difference in schizophrenia PRS between individuals with bipolar disorder with and without a history of psychosis (Hamshere *et al.*, 2011; Ruderfer *et al.*, 2014), more recent studies in larger samples have observed higher schizophrenia PRS in bipolar disorder with psychosis (Markota *et al.*, 2018; Ruderfer *et al.*, 2018). Individuals with bipolar disorder who experienced psychosis during mania also showed higher schizophrenia PRS compared to individuals with psychosis only in depression (Markota

et al., 2018). Additionally, schizophrenia PRS has been associated with transition from affective to non-affective psychosis in a longitudinal study (Jonas *et al.*, 2019).

1.7.1.3 Cross-disorder symptom dimensions

Given the phenotypic overlap between schizophrenia and bipolar disorder, and that genetic liability for each disorder influences symptomatic variation in both disorders, there is interest in examining symptom dimension structure across the disorder samples. A five-factor symptom model, with factors indicating positive, negative, and disorganised symptoms, mania, and depression, has been identified in samples of individuals with schizophrenia and bipolar disorder (Serretti and Olgiati, 2004; Dikeos *et al.*, 2006; Reininghaus *et al.*, 2016, 2019), as well as in a first episode psychosis cohort (Quattrone *et al.*, 2019). Serretti and colleagues (2004) demonstrated that a five-factor model had better fit than a two-, three-, or four-factor solution. Some have also proposed a bifactor model with an overarching general psychopathology dimension, encompassing all items within the five specific factors (Reininghaus *et al.*, 2016, 2019). In one study, higher scores for the proposed general dimension were associated with later age at onset, gradual mode of onset, and poor premorbid functioning (Reininghaus *et al.*, 2016). Another study observed better model fit when considering two additional overarching dimensions, affective and non-affective, to explain further variation beyond that which was captured by the five primary symptom factors and the general factor (Reininghaus *et al.*, 2019). Higher scores for the non-affective and affective factors were associated with a schizoaffective diagnosis compared to psychotic bipolar disorder; higher nonaffective and lower affective scores were observed in individuals with schizophrenia compared to psychotic bipolar disorder (Reininghaus *et al.*, 2019). Van Os and colleagues (1999) compared categorical diagnosis to a dimensional model, containing scales for depression, mania, negative symptoms, and positive symptoms, in ability to predict clinical phenotypes that inform treatment plans. They found that the dimensional model explained a greater amount of variance than a categorical diagnosis for all clinical phenotypes they assessed, suggesting that dimensions of psychopathology may be more informative when deciding on treatment for psychosis (Van Os et al., 1999).

Thus far, diagnostic manuals have been reluctant to fully adopt a dimensional approach to the classification of psychotic and affective disorders but have taken steps to begin this process. DSM-5 uses the terms 'domains', 'gradients', and 'dimensions' to define psychopathology in schizophrenia-spectrum disorders, reflecting advances in our understanding of the structure of psychosis and providing a platform from which future editions may integrate dimensions into classification (Heckers *et al.*, 2013). ICD-11 has incorporated dimensional specifiers for schizophrenia, indicating symptom severity, but has maintained the categorical distinctions between schizophrenia, schizoaffective disorder, and bipolar disorder(Gaebel, 2012). This reluctance to embrace a fully dimensional approach may reflect a lack of research establishing the clinical utility of such an approach (Heckers *et al.*, 2013).

1.7.2 Subtyping and cluster approaches

Whilst dimensional approaches to symptoms may be a viable alternative to categorical diagnoses in research, it can also be argued that refining categories to specify more homogenous groups may improve validity and estimates of prognosis, and could be more useful in clinical settings than dimensional approaches.

1.7.2.1 Subtyping in schizophrenia

Schneider argued there was no single characteristic common to all individuals with schizophrenia (Thomas, 2001). This heterogeneity has led to extensive efforts to classify individuals with schizophrenia into subtypes based on the presence of characteristics including specific symptoms, premorbid characteristics, and outcomes. Classical subtypes of schizophrenia, which are used to varying degrees throughout editions of the DSM and ICD and have only recently been removed in for ICD-11 (World Health Organisation, 2018) and/or DSM-5 (American Psychiatric Association., 2013), include paranoid, hebephrenic, catatonic, undifferentiated, residual, latent, and simple schizophrenia. These subtypes, which are defined by the most prominent symptoms and clinical signs, have been used extensively in research aiming to gain insights into the aetiology and make more accurate predictions of treatment and prognosis (McGlashan and Fenton, 1991). The paranoid subtype has been associated with older

age at onset and at first admission, better social functioning, a more acute course of disorder, and a greater number of obstetric complications (McGlashan and Fenton, 1991). Conversely, the hebephrenic subtype has been associated with a more insidious onset, chronic course, a younger age at onset, and worse outcomes than the paranoid and undifferentiated subtypes (Fenton and McGlashan, 1991; McGlashan and Fenton, 1991). However, others have not observed differences in outcomes between individuals with hebephrenic and undifferentiated subtypes, suggesting that a distinction within non-paranoid subtypes may not be valid (Kendler, Gruenberg and Tsuang, 1984). Carpenter and colleagues (1976) compared symptom profiles across subtypes in a large international cohort and found a high degree of similarity between the classical subtypes, suggesting few differences in symptoms despite these being the main feature distinguishing subtypes. A cluster analysis of the symptoms found that 76% of individuals were classified into one subtype, termed 'typical schizophrenia', whilst the remaining participants were split over three clusters, two of which contained 5% or less of the sample (Carpenter *et al.*, 1976). The results of this study indicate that subdividing schizophrenia on the basis of symptoms does not explain much heterogeneity, as most people are assigned to the same cluster, thus questioning the validity of this approach. The classical subtypes have further been criticised for lacking stability over time. Parnas and colleagues (1988) found that a paranoid vs non-paranoid distinction between women with schizophrenia was stable over a six-year follow up period. However, Pfohl and Winokur (1983) found an increase in the undifferentiated subtype over time, suggesting that classification based on initial symptoms may not be useful or accurate in predicting long-term prognosis.

Attempts to empirically derive subtypes has found limited evidence to support categorising schizophrenia into paranoid, hebephrenic, and undifferentiated subtypes. Dollfus and colleagues (1996) instead suggested a positive/negative dichotomy may better characterise the heterogeneity within schizophrenia. They found four clusters characterised by mild symptomatology, high negative and low positive symptoms, low negative and high positive symptoms, and both high negative and high positive symptoms. Individuals experiencing high negative and low positive symptoms had poorer premorbid work adjustment, lower educational attainment, and poorer

outcomes than the other classes. Helmes and Landmark (2003) were unable to replicate these findings in a similar sized sample, instead reporting that no cluster solution fit their data well. The authors note that the symptom data in their study was rated on a lifetime basis, whilst others often use current symptoms, which may explain the discrepancy in findings. The classical subtypes have also been criticised for lacking specificity, as individuals frequently present with symptoms spanning multiple subtypes or that do not entirely fulfil the criteria for any one subtype (Carpenter and Stephens, 1979).

Nevertheless, some evidence has been found suggesting genetic transmission of subtypes. Kendler and Davis (1981) conducted a literature review of studies examining risk of schizophrenia in relatives of individuals with schizophrenia. They concluded that relatives of individuals with paranoid schizophrenia were at reduced risk compared to relatives of individuals with the non-paranoid subtypes, suggesting a higher genetic risk for non-paranoid schizophrenia. They also found a high subtype concordance in monozygotic twins, suggesting that paranoid and non-paranoid subtypes may have different genetic aetiologies, although the influence of shared environment could not be ruled out (Kendler and Davis, 1981). Fenton and McGlashan (1991) supported the finding of greater genetic transmission in non-paranoid schizophrenia, observing a greater amount of general psychopathology in families of individuals with the hebephrenic subtype than the paranoid subtype.

1.7.2.2 Subtyping in bipolar disorder

Kraepelin first separated hypomania from mania and proposed a spectrum of severity ranging from hypomania at the mildest end to delirious mania at the most severe end, with the middle defined as acute mania (Maldeniya and Vasudev, 2013). Others have suggested a division between elated and aggressive types of mania (Beigel and Murphy, 1971), a distinction that has received some support in the literature. Double (1991) identified four clusters of individuals, characterised by mild symptomatology, elation, psychosis, and irritability and/or aggression. Sato and colleagues (2002) found evidence to support these subtypes and found that subtypes significantly differed in terms of sex, global functioning, suicidality, and number of symptoms. Similar classes

were also observed by Swann and colleagues (2013), who identified four clusters that they termed depression, delusional, classic, and irritable mania. The depression cluster was associated with suicidal plans and rapid cycling, the classic cluster was associated with higher functioning than the other classes, and the irritable cluster was associated with high levels of hostility and low levels of hyperactivity. Two studies have found evidence of a group marked by both manic episodes and substance abuse, termed 'dual mania' (Haro *et al.*, 2006; Azorin *et al.*, 2008). In an international cohort of 3,500 individuals with bipolar disorder type I, Haro and colleagues (2006) found that dual mania was associated with male sex, poorer treatment compliance, and greater amount of time spent in inpatient settings. Azorin and colleagues (2008) supported these findings and further found that dual mania was associated with earlier age at onset and more severe manic symptoms.

Whilst most studies appear to distinguish between 'pure' mania, irritability, and psychosis, it is important to note that the majority of these recruited participants were hospitalised at the time of assessment and made ratings based on the current episode. Therefore, such studies will likely over-represent individuals experiencing a more severe illness, and do not typically account for lifetime course and the likelihood that picture in a given individual may shift over time. Thus, whilst clustering research within bipolar disorder has indicated the potential for distinct subtypes, beyond evidence that bipolar disorder type I and type II may be more genetically similar to schizophrenia and depression, respectively (Mullins *et al.*, 2021), there has not yet been evidence validating empirically-derived subtypes as even partially discrete biological entities.

1.7.2.3 Cross-disorder clustering

Given the substantial phenotypic and genetic overlap between schizophrenia and bipolar disorder, as well as controversy about the status of schizoaffective disorder, several studies have applied clustering methods to cross-disorder samples to identify groups of individuals that might have shared aetiology and pathophysiology regardless of primary diagnosis. The Roscommon family study recruited families with multiple members with a psychotic or affective diagnosis and identified six clusters, which they

termed schizophrenia, depression, schizophreniform, bipolar-schizomania, schizo-depression, and hebephrenia. The authors found an increased risk of schizophrenia in relatives of probands in all classes except the depression class, compared to relatives of controls. A lower risk was seen for relatives of people in the schizomania class, and a particularly high risk of schizophrenia was observed in relatives of individuals in the hebephrenia class, consistent with evidence of greater familial risk in individuals with diagnosed hebephrenic schizophrenia (Fenton and McGlashan, 1991). Derks and colleagues (2012) identified seven clusters in a sample of individuals with schizophrenia, schizoaffective disorder, bipolar disorder, and depression. The first class, termed 'Kraepelinian schizophrenia' by the authors, was associated with low IQ, early age at onset, and longer duration of untreated psychosis. 85% of people with schizophrenia or schizoaffective disorder were classified into the Kraepelinian cluster, suggesting that individuals with schizophrenia may represent a relatively homogenous group without needing to be subdivided. However, 41% of individuals with bipolar disorder were also assigned to the Kraepelinian schizophrenia class and only 10% of individuals with bipolar disorder were assigned to the class characterised by high mania and depression symptoms. Therefore, the Kraepelinian schizophrenia class may have represented a more severely affected group, rather than reflecting the traditional schizophrenia-bipolar dichotomy. Labbe and colleagues (2012) conducted separate latent class analyses on 10 symptoms rated in individuals with schizophrenia and bipolar disorder and found that, for most symptoms, individuals could be distinguished into two subtypes. These subtypes represented the presence or absence of the symptom and each subtype included people with schizophrenia and bipolar disorder, suggesting that these subtypes were not identifying a typical schizophrenia-bipolar disorder dichotomy. Whilst the studies described above indicate that schizophrenia and bipolar disorder might be subdivided into more phenotypically homogenous groups, specific subtypes have not been reliably replicated or validated in independent samples.

1.8 Limitations of existing literature

Schizoaffective disorder has been heavily criticised as a diagnosis, yet little research has sought to determine phenotypic and genotypic differences between individuals with schizoaffective disorder in comparison to schizophrenia or bipolar disorder. This dearth of research has limited progress in our understanding of schizoaffective disorder and our ability to implement evidence-based changes in diagnostic manuals (Malaspina *et al.*, 2013). Moreover, lack of consistent findings with modern definitions of schizoaffective disorder may also be due to the failure to delineate subtypes in research. Differences in the proportion of individuals with SA-D and SA-BP may in part explain contradictory findings such as a closer phenotypic resemblance to bipolar disorder in some studies but closer resemblance to schizophrenia in others (Pagel *et al.*, 2013). Research that examines subtypes of schizophrenia using modern diagnostic definitions is needed to evaluate the nature of schizoaffective disorder and the determine the best way of conceptualising and defining it as a diagnosis.

Both phenotypic and genomic studies indicate that schizophrenia, schizoaffective disorder, and bipolar disorder lie on a spectrum defined by dimensions of psychopathology and common and rare genetic variation. Despite compelling evidence, schizophrenia and bipolar disorder are typically studied in isolation, limiting the potential for stratification on the basis of common phenotypes or genetic liability. Cross-disorder examination of common phenotypes would allow for greater insights into the aetiology of these phenotypes and the utility of dimensional approaches to nosology.

Although many support a transition to a dimensional approach to classifying psychosis and affective disorders, research determining the clinical utility of dimensional models is limited, and a specific model is yet to be agreed upon and validated. A unidimensional approach, such as the Schizo-Bipolar scale, may miss heterogeneity in other important aspects of psychopathology and risk, such as cognitive impairment and neurodevelopmental burden. A multi-dimensional approach would require widespread agreement on the number of dimensions, the nature of such dimensions, and an appropriate method of measurement that captures both change in severity

over time as well as cultural influences on psychopathology (Dutta *et al.*, 2007). Whilst dimensional approaches may be useful in a research context, their clinical utility has yet to be determined. Categorical approaches are able to facilitate the decision-making process between clinicians and patients, for instance in deciding treatment, and they enable communication within and between clinicians, researchers, patients, and the general public that improves understanding and reduces the stigma surrounding psychosis (Esterberg and Compton, 2009). In order to be adopted into clinical practice, a dimensional model of classification would need to demonstrate a substantial benefit beyond categorical diagnosis in these areas, and in particular show evidence of improved ability for clinicians to communicate, and patients to understand, the causes, characteristics, prognosis, and treatment of psychotic and affective illness.
Genetic validation of dimensions would add considerable strength to these approaches, yet such research is limited and has yet to take full advantage of the opportunities afforded by large-scale GWAS of psychiatric disorders. By nature, a dimensional approach assumes sub-clinical presence of the phenotype in the general population. Little research has sought to determine influences on dimensions of psychopathology in the general population, with the exception of cognition, yet research in this area may provide greater insights into the aetiology of common cross-disorder phenotypes. Research that aims to replicate existing findings and determine the role of genetic liability in dimensional variation is needed to increase the clinical translation, improve reliability, and validate dimensional models of psychosis. Furthermore, dimensional phenotypes offer greater analytical power than categorical variables, and thus research examining continuous dimensions has the potential to provide much greater insights into the aetiology of these phenotypes.

1.9 Aims

The aim of this thesis is to examine the relationships between schizophrenia, schizoaffective disorder, and bipolar disorder and evaluate whether dimensional approaches to conceptualising these disorders provide an advantage over existing diagnoses in terms of explaining clinical heterogeneity and genetic variation. The main objectives are:

1. Investigate differences in demographics, clinical characteristics, and polygenic risk between individuals with SA-D and schizophrenia (Chapter 2). Research examining differences in aetiology, clinical course, and outcomes in schizoaffective disorder is needed to determine the validity of SA-D and refine the nosology of schizoaffective disorder. This study utilises genotypic and phenotypic data from the CardiffCOGS cohort, with replication and meta-analysis in two UK cohorts, to investigate whether SA-D is better considered a form of schizophrenia or a distinct diagnosis.
2. Examine the association between polygenic risk for psychiatric disorders and symptom dimensions across the psychosis-affective spectrum (Chapter 3). Across four UK cohorts of individuals with schizophrenia, schizoaffective disorder, and bipolar disorder, I applied confirmatory factor analysis to calculate factor scores for symptom domains in these disorders and examined polygenic associations with each domain.
3. Identify and examine clusters of individuals across the psychosis spectrum marked by relative phenotypic homogeneity (Chapter 3). I applied latent class analysis to identify clusters across the psychosis spectrum and used polygenic risk scores to test whether there are differences between clusters that are not simply explained by categorical diagnosis.
4. Examine the relationship between psychiatric diagnosis, polygenic risk, and levels of physical activity (Chapter 4). Examination of whether common cross-disorder phenotypic dimensions have a shared genetic liability in the general population may provide insights into the aetiology of these dimensions and their utility in clinical practice, for instance in dimensional models or as an endophenotype. Many psychiatric disorders are associated with changes in level of physical activity, including schizophrenia, bipolar disorder, depression, ASD, and ADHD. I utilised actigraphy data in the UK Biobank cohort to assess the relationship between polygenic risk for the aforementioned disorders and level of activity in the general population, as well as investigate the extent to which the genetic architecture of physical activity is shared with psychiatric disorders.

Chapter 2

Risk factors, clinical features, and polygenic risk scores in schizophrenia and schizoaffective disorder depressive-type.

2.1 Introduction

Since early conceptions of schizophrenia and bipolar disorder, there have been descriptions of individuals with mixed psychotic and affective symptoms who did not appear to fit neatly on either side of the traditional divide (Maj, 1984b). Kasanin first used the term schizoaffective disorder to describe this mixed clinical presentation, and research over the 20th century consistently identified a group of patients with an illness characterised by rapid onset of psychosis and mood symptoms and a remitting course with good recovery between episodes (Maj, 1984a). Individuals with schizoaffective disorder had better outcomes than was typical of individuals with schizophrenia, yet worse than was seen in bipolar disorder, and frequently had a family history of affective disorders (Maj, 1984b).

Diagnostic manuals categorised schizoaffective disorder as a psychotic disorder with two subtypes: depressive-type (SA-D) and bipolar-type (SA-BP). SA-D is characterised by the co-occurrence of depressive episodes with core features of schizophrenia (World Health Organisation., no date), whilst in SA-BP episodes of mania are also present. However, the validity of schizoaffective disorder, both depressive-type and bipolar-type, has long been debated (Malaspina *et al.*, 2013), particularly given evidence of limited inter-rater reliability and low stability over time (Maj *et al.*, 2000; Schwartz *et al.*, 2000). Issues with reliability and stability may in part be driven by a lack of consensus on the definition of SA-D, particularly in terms of the duration and overlap of psychosis and depression. ICD-10 requires two weeks or more of psychosis, with psychosis and depression concurrent for at least part of the episode. DSM-IV

requires psychosis for at least one month, including at least two weeks of hallucinations or delusions in the absence of any prominent symptoms of depression; depression must also occur for a substantial portion of the total illness. However, 'substantial portion' was not clearly defined and was a key contributor to poor inter-rater reliability (Maj *et al.*, 2000). Thus, the major change in DSM-5 was that depression was required to be present for the majority of the total duration of the lifespan of the illness (see Table 2.1 for full criteria). This criterion requires longitudinal observation and means that individuals can fluctuate between meeting and not meeting the diagnostic criteria, which may exaggerate the perception of schizoaffective disorder as an unstable diagnosis (Craddock, O'Donovan and Owen, 2009).

	ICD-10	DSM-IV	DSM-5
Psychosis criteria	Symptoms from at least one group: a) Thought echo, insertion, withdrawal, or broadcasting b) Delusions of control, influence, or passivity c) Running commentary, third person voices, or voices coming from part of the body d) Bizarre or impossible delusions e) Grossly irrelevant or incoherent speech, or frequent use of neologisms f) Intermittent but frequent catatonic behaviour	Two or more of the following: a) Delusions b) Hallucinations c) Disorganised speech d) Grossly disorganized or catatonic behaviour e) Negative symptoms - Only one symptom is required if delusions are bizarre or hallucinations consist of running commentary or two or more voices conversing with each other.	Two or more of the following, at least one must be a), b), or c): a) Delusions b) Hallucinations c) Disorganised speech d) Grossly disorganized or catatonic behaviour e) Negative symptoms
Depression criteria	A depressive episode of at least moderate severity.	A major depressive episode that must include depressed mood.	A major depressive episode that must include depressed mood.
Duration	- Psychosis criteria must be present for most of the time during a period of at least two weeks. - Psychosis and depression must be met within the same episode, and concurrently for at least part of the episode.	- Uninterrupted period during which depression is concurrent with psychosis. - Psychosis criteria must be present for a significant portion of time during a one-month period. - Delusions or hallucinations for two or more weeks in the absence of mood during the lifetime duration of the illness. - Depression symptoms are present for a substantial portion of the total duration of the active and residual portions of the illness.	- Uninterrupted period during which depression is concurrent with psychosis. - Psychosis criteria must be present for a significant portion of time during a one-month period. - Delusions or hallucinations for two or more weeks in the absence of mood during the lifetime duration of the illness. - Depression symptoms are present for the majority of the total duration of the active and residual portions of the illness.

Table 2.1. Criteria for schizoaffective disorder depressive-type in ICD-10 (World Health Organisation., no date), DSM-IV (American Psychiatric Association, 1994), and DSM-5 (American Psychiatric Association., 2013).

Research into schizoaffective disorder has often combined bipolar and depressive subtypes, yet evidence from twin studies has shown that SA-D and SA-BP are no more likely to co-occur with each other than with other psychotic disorders, suggesting they are separate disorders (Cardno *et al.*, 2012).

Studies combining subtypes have found that people with schizoaffective disorder are more likely than people with schizophrenia to have better cognitive functioning, better treatment response, and a higher rate of recovery, but have poorer functioning in these areas compared to people with bipolar disorder (Harrow *et al.*, 2000; Pagel *et al.*, 2013). Thus, it has been suggested that schizoaffective disorder may represent an intermediate category between schizophrenia and bipolar disorder on a spectrum of psychosis, or that it is a hybrid of both disorders (Maj, 1984a). Patterns of familial aggregation of psychotic and affective disorders have also been reported to differ between individuals with schizophrenia, schizoaffective disorder, and bipolar disorder. People with schizoaffective disorder have a higher family history of schizophrenia, schizoaffective disorder, and bipolar disorder than controls (Kendler, Gruenberg and Tsuang, 1986; Laursen *et al.*, 2005), suggesting that schizoaffective disorder may be marked by elevated liability to all of these disorders. In comparison, schizophrenia is strongly associated with family history of schizophrenia and weakly associated with family history of bipolar disorder, suggesting that genetic liability to bipolar disorder is higher in schizoaffective disorder than in schizophrenia. The opposite pattern of effect is observed in bipolar disorder, suggesting people with schizoaffective disorder have higher genetic risk for schizophrenia than people with bipolar disorder (Laursen *et al.*, 2005). However, as noted above, much of this research has combined (or not distinguished between) bipolar and depressive subtypes of schizoaffective disorder, and therefore it is unclear whether these findings are applicable to both or only one subtype of this disorder.

In the context of shared symptoms, SA-D might be better considered an intermediate between schizophrenia and major depressive disorder (Rink *et al.*, 2016) rather than between schizophrenia and bipolar disorder, as by definition people with SA-D experience depression and not mania. Consistent with this view, studies that have specifically investigated SA-D have found that people with SA-D typically have poorer

functioning than individuals with a diagnosis of psychotic depression, but better functioning than individuals with schizophrenia across a range of measures, including cognitive, premorbid, and overall functioning (Coryell and Zimmerman, 1986; Maj, 1986). However, other findings suggest that SA-D may be associated with elevated genetic liability to bipolar disorder. A twin study found that co-twins of individuals with SA-D were more likely to experience schizophrenia, SA-D, SA-BP, mania, and psychotic depression, than co-twins of unaffected controls (Cardno *et al.*, 2012). Therefore, SA-D may arise from elevated liability to schizophrenia and a range of affective disorders (Cardno and Owen, 2014). Family studies have supported this hypothesis, showing that relatives of individuals with SA-D are at higher risk of schizophrenia, depression, and bipolar disorder (Coryell and Zimmerman, 1988), compared to relatives of individuals without a psychiatric disorder. SA-D, like schizophrenia and bipolar disorder, is highly heritable (around 80%) (Cardno, Marshall, *et al.*, 1999), yet there has been very little genetic research into SA-D, as individuals with SA-D are generally treated as if they have a diagnosis of schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

2.2 Aims

Research is needed to improve our understanding of the aetiology of SA-D and to clarify the relationship between SA-D and other disorders, particularly schizophrenia and depression. Psychiatric nosology currently relies on the observation of signs and symptoms, rather than biomarkers, and thus evidence of substantial clinical differences between schizophrenia and SA-D would add validity to SA-D as a distinct disorder. Conversely, lack of such evidence may indicate that SA-D is a form of schizophrenia. Many existing psychiatric diagnoses have been validated by evidence of specific genomic variation increasing the risk of the disorder. SA-D has not been studied at a polygenic level, and thus establishing whether there are differences in the genetic liability between schizophrenia and SA-D would further clarify the relationship between these two disorders. Here, I aimed to establish whether individuals with SA-D differ from those with schizophrenia in terms of demographics, family history,

premorbid factors, lifetime clinical characteristics, and genetic liability to schizophrenia, depression, and bipolar disorder.

2.3. Method

2.3.1 Participants

Participants were drawn from CardiffCOGS(Lynham *et al.*, 2018), a cross-sectional study of individuals with a clinical diagnosis of schizophrenia or a related psychotic disorder, including schizophreniform, delusional disorder, and psychosis not otherwise specified. Two additional samples were used for replication: the Cardiff Affected-sibs and the Cardiff F-series samples. Cardiff Affected-sibs recruited families where at least two affected siblings had a diagnosis of schizophrenia or schizoaffective disorder. Affected sibling pairs where both individuals had a diagnosis of SA-BP were excluded. Unrelated individuals with a clinical diagnosis of schizophrenia or schizoaffective disorder were recruited to the F-series study (Norton *et al.*, 2005). For all samples, individuals were recruited from community and inpatient mental health services and voluntary services across the UK. All participants completed a research interview based on the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) and donated a blood sample for genetic analyses (Wing *et al.*, 1990). Replication was restricted to phenotypes that were available across all three datasets. All studies have relevant NHS ethical approvals and all participants provided written informed consent.

For all three samples, trained researchers reviewed information from and completed lifetime assessments of symptoms and clinical phenotypes using the Operational Checklist Criteria for Psychotic Illness and Affective Illness (OPCRIT) (McGuffin, Farmer and Harvey, 1991) and the Scale for Assessment of Positive Symptoms (SAPS) (Andreasen, 1984b) and Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1984a), and reached a consensus diagnosis using ICD-10 (World Health Organisation., no date) criteria. Individuals were included in the present study who had a lifetime research diagnosis of ICD-10 schizophrenia or SA-D (Table 2.2). Cohen's κ for inter-rater reliability for ICD-10 diagnoses within the Cardiff COGS sample was substantial (κ=0.76). Cardiff Affected-sibs have previously reported an average κ score

of 0.9 against consensus, indicating excellent inter-rater reliability for diagnosis (Williams *et al.*, 1999). Cardiff F-series previously reported a κ>0.8 between raters for diagnosis.

Study	Schizophrenia	SA-D	Total
CardiffCOGS	713	151	**864**
Affected-sibs	330	24	**354**
F-series	505	19	**524**
Total	**1548**	**194**	**1724**

Table 2.2 Number of participants included with an ICD-10 diagnosis of schizophrenia and SA-D.

2.3.2 Phenotype data

Full definitions of all phenotype data used are detailed in Table 2.3. Details of demographics, family history, and premorbid characteristics were taken from the research interview, clinical case notes, and OPCRIT items. For primary analysis in CardiffCOGS, information was obtained on the following demographics: sex, family history of psychiatric illness, marital status, number of children, maximum educational attainment, and urbanicity, as well as on the following premorbid factors: premorbid social functioning, obstetric complications, premorbid IQ (estimated from the National Adult Reading Test (Nelson, 1982)), and history of childhood physical or sexual abuse (Upthegrove *et al.*, 2015).

Lifetime clinical characteristics were also derived from interview, clinical case notes, and OPCRIT items, and included course of disorder, mode of onset, antipsychotic response, MATRICS (Nuechterlein *et al.*, 2008) composite cognition, alcohol dependence, cannabis dependence, and other substance dependence. The following were included with respect to psychosis: age at onset of impairment, number of admissions, ever detained under the UK Mental Health Act 1983 for psychotic symptoms, number of episodes, and Global Assessment Scale (GAS) score regarding lowest level of functioning in worst episode.

Measures of symptom severity were derived by adding the raw global scores from the lifetime most severe SAPS (ranging from 0-5) and SANS (ranging from 0-5) ratings (Legge, Cardno, *et al.*, 2021). A positive symptoms score was calculated by adding the global hallucinations and global delusions scores; a disorganised symptoms score was calculated by adding the global positive formal thought disorder and the inappropriate affect item; a diminished expressivity score was calculated by adding the global affective flattening and global alogia; a reduced motivation and pleasure score was calculated from the global scores for avolition/apathy and anhedonia/asociality. This symptom structure has been consistently found in factor analyses studies of schizophrenia (Legge, Cardno, *et al.*, 2021).

For individuals who had experienced at least one depressive episode based on ICD-10 criteria, I included the following characteristics related to depressive episode(s): age at first impairment, age at first admission, ever admitted to hospital for depression, longest episode duration, number of episodes, GAS score in worst episode, and whether depression onset occurred prior to psychosis onset.

Variable	Descriptions	CardiffCOGS N (864)
Demographics and family history		
Sex	Self-reported sex. 1 = male, 2 = female.	864 (100%)
Family history of schizophrenia	OPCRIT item 13 Family history of schizophrenia in a first or second degree relative.	739 (86%)
Family history of other psychiatric illness	OPCRIT item 14 First or second degree relative with psychiatric disorder severe enough to warrant psychiatric referral, excluding schizophrenia	735 (85%)
Marital history	Ever been married. 0 = no, 1= yes.	842 (97%)
Number of children	Number of children.	491 (57%)
Educational attainment	Highest educational attainment: 0 = none, 1 = 11+, 2 = CSE, 3 = O-Level or GCSE, 4 = A-level, 5 = Degree	840 (97%)
Urbanicity	Main place of upbringing. 0 = village or town, 1 = city	714 (83%)
Premorbid functioning		
Premorbid social functioning	OPCRIT item 10: Patient found difficulty entering or maintaining normal social relationships, showed persistent social isolation, withdrawal or maintained solitary interests prior to onset of psychotic symptoms.	821 (95%)
Obstetric complications	Complication with the participant's birth such as low birth weight, hypoxia or assisted delivery, and/or complication with their mother's pregnancy such as prematurity, pre-eclampsia or placental problems.	860 (99%)
Premorbid IQ	Premorbid IQ estimated from the National Adult Reading Test (NART). Predicted WAIS-R full scale IQ = 130.6-1.24*NART error score.	696 (82%)
Childhood physical or sexual abuse	Childhood physical or sexual abuse reported in the Childhood Life Events Questionnaire(Upthegrove *et al.*, 2015) (CLEQ) delivered at interview. Participants were not explicitly asked about abuse, but were asked "are there any other significant life events you experienced as a child that are not mentioned above".	795 (92%)
Lifetime clinical characteristics		
Course of disorder	OPCRIT item 90. 1 = single episode with good recovery, 2 = multiple episodes with good recovery between, 3 = multiple episodes with partial recovery between, 4 = continuous chronic illness, 5 = continuous chronic illness with deterioration	847 (98%)

Mode of onset	OPCRIT item 5. 1 = abrupt onset definable to within hours or up to three days, 2 = acute onset definable to within one week, 3 = moderately acute onset definable within one month, 4 = gradual onset over a period up to six months, 5 = Insidious onset over period greater than six months	686 (79%)
Antipsychotic response	OPCRIT item 89. 1 = Substantial improvement in psychotic symptoms either subjectively or according to medical records, or if relapse occurs when medication is stopped. Rated 0 if patient did not meet these criteria or was treated with Clozapine for treatment resistance.	809 (94%)
Cognition	Full scale composite cognition score as measured by the MATRICS Consensus Cognitive Battery, imputed and standardised into z-scores.	809 (94%)
Alcohol dependence	OPCRIT item 78. One of the following must have occurred persistently for at least one month: Continued use despite knowledge of having a persistent or recurrent social, occupational, psychological or physical problem that is caused or exacerbated by alcohol; or recurrent use in situations in which it is physically hazardous; or symptoms definitely indicative of dependence.	775 (90%)
Cannabis dependence	OPCRIT item 79. One of the following must have occurred persistently for at least one month: continued use despite knowledge of having a persistent or recurrent social, occupational, psychological or physical problem that is caused or exacerbated by cannabis; or recurrent use in situations in which it is physically hazardous; or symptoms definitely indicative of dependence.	790 (91%)
Other substance dependence	OPCRIT item 80. One of the following must have occurred persistently for at least one month: Continued use despite knowledge of having a persistent or recurrent social, occupational, psychological or physical problem that is caused or exacerbated by substance use; or recurrent use in situations in which it is physically hazardous; or symptoms definitely indicative of dependence.	811 (94%)
Psychosis		
Age of onset	OPCRIT item 4. The age at which treatment was first sought or if earlier when symptoms caused significant impairment.	829 (96%)

Number of admissions	Total number of psychiatric hospital admissions for psychosis, including inpatient, day hospital and intensive home treatment by the crisis team.	829 (96%)
Ever detained under the mental health act	Ever detained under section 2 or 3 of the Mental Health Act for psychosis.	744 (86%)
Number of episodes	Number of episodes of psychosis.	748 (87%)
Global assessment scale score in worst episode of psychosis	Lifetime worst Global Assessment Scale (GAS) score in a psychotic episode. Higher score indicates better functioning.	847 (88%)
Positive symptoms	Lifetime severity of positive symptoms, on a scale of 0 – 10. Derived from SAPS Global Hallucinations and SAPS Global Delusions	
Disorganised symptoms	Lifetime severity of disorganised symptoms, on a scale of 0 – 10. Derived from SAPS Global Positive Thought Disorder (0-5) and SANS Inappropriate Affect (0-5)	
Diminished expressivity	Lifetime severity of negative symptoms of diminished expressivity, on a scale of 0 - 10. Derived from SANS Global Affective Flattening (0-5) and SANS Global Alogia (0-5).	
Reduced motivation and pleasure	Lifetime severity of negative symptoms of motivation and pleasure, on a scale of 0 – 10. Derived from SANS Global Anhedonia and SANS Global Avolition/Apathy.	

Depression

NB: only participants with at least one episode of major depression are included in these categories (n=577). Percentage is of the 577.

Age at first impairment	Age at which depressive episode caused significant impairment, such as received treatment, disruption to work or school, police involvement, psychotic features, or family split up.	517 (90%)
Ever admitted to hospital	Ever admitted to psychiatric hospital for depression, including inpatient, day hospital and intensive home treatment by the crisis team.	577 (100%)
Longest episode duration	Duration of the longest episode of depression meeting ICD-10 diagnostic criteria for major depressive episode.	454 (79%)
Number of episodes	Number of episodes of depression that met ICD-10 diagnostic criteria for major depressive episode.	498 (86%)
Global assessment scale score in worst episode of depression	Lifetime worst GAS score in a depressive episode. Higher score indicates better functioning.	549 (95%)
Depression onset first	Onset of depression occurred prior to onset of psychosis.	332 (58%)

Table 2.3 Variable definitions.
Definition of each clinical characteristic and number included from CardiffCOGS sample.

2.3.3 Genetic data

Genotyping, quality control of genotype data, and calculation of PRS was conducted by researchers at the MRC Centre for Neuropsychiatric Genetics and Genomics. The CardiffCOGS sample was genotyped in two waves on the Illumina HumanOmniExpressExome-8 and on the Illumina HumanOmniExpress-12. SNPs were excluded if: minor allele frequency (MAF) <0.01, genotyping rate <0.95, or Hardy-Weinberg equilibrium (HWE) p-value $<1x10^{-6}$. Samples missing >5% of genotypes were also excluded. Genotypes were imputed using the Haplotype Reference Consortium (McCarthy *et al.*, 2016) v1.1 reference panel. Best estimate genotype data were filtered to exclude those with imputation quality score <0.8 and HWE p-value $<1x10^{-4}$. PLINK v2.0(Chang et al., 2015) was used to derive principal components for ancestry using SNPs with low levels of linkage disequilibrium, defined as $r^2<0.2$, within 500kb windows. Principal components were used to restrict genetic analyses to individuals of European ancestry. Pairs of individuals with a kinship score >0.15 were identified and one member of each related pair removed, preferentially retaining those with more complete phenotype data. Post genomic-QC, genetic data were available for 692 individuals. Ten individuals were excluded due to ancestry restrictions, and 12 due to relatedness leaving 670 individuals (561 with schizophrenia and 109 with SA-D). Genetic analyses within the Cardiff Affected-sibs and Cardiff F-series samples was not possible due to the small number of individuals with SA-D. Thus, I restricted polygenic analyses to the CardiffCOGS sample only.

2.3.4 Polygenic risk scores

Polygenic risk scores (PRS) were derived using PRSice (Euesden, Lewis and O'Reilly, 2015) based on SNPs with INFO >0.9, MAF >0.10, and in relative linkage equilibrium (r^2 <0.2 within 500kb windows), following criteria used by the Psychiatric Genomics Consortium (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The extended major histocompatilibty complex (MHC) was excluded (chromosome 6 25-35mb), due to its complex pattern of linkage disequilibrium. PRS were calculated using the largest available genome-wide association summary statistics (as of July 2020) for schizophrenia (Schizophrenia Working Group of the

Psychiatric Genomics Consortium. *et al.*, 2020), depression (Howard *et al.*, 2018), and bipolar disorder (Stahl *et al.*, 2019) at six p-value thresholds for SNP inclusion: $5x10^{-8}$, $1x10^{-4}$, 0.001, 0.05, 0.1, and 0.5. Schizophrenia summary statistics used to define the association thresholds excluded the samples included in this study and were derived for the purposes of this study by the Schizophrenia Working Group of the Psychiatric Genomics Consortium.

I standardised each PRS as Z-scores and chose a pre-specified primary threshold of $p<0.05$ for risk alleles for each disorder. There is no field standard for p-value threshold for SNP inclusion, therefore I chose a threshold of $p<0.05$ given evidence that it is the optimal threshold for capturing schizophrenia liability within schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and to maintain consistency and comparability across PRS. I also analysed the other thresholds to ensure the results were not highly sensitive to the primary test threshold.

2.4. Analysis

2.4.1 Primary univariable analysis - demographics and clinical characteristics

Primary analyses were conducted within the CardiffCOGS sample as it had the largest sample size. I standardised all continuous variables as Z-scores to allow for comparison across characteristics. Primary analyses involved testing for differences between schizophrenia and SA-D via logistic regression with respect to demographics and clinical characteristics. As I found a significant association between sex and diagnosis (OR=3.19 [2.23-4.59]), all other analyses were covaried for sex. Age at interview was also included as a covariate. Phenotypes related to depression were analysed only in those with at least one depressive episode (N=426 with schizophrenia, n=151 with SA-D).

2.4.2 Secondary analysis

I divided the CardiffCOGS sample into male-only and female-only subsets, in order to examine sex-specific effects. I repeated all primary univariable regressions in the male-only and female-only datasets, covarying for age at interview.

The use of ICD compared to DSM definitions of schizoaffective disorder has resulted in heterogeneity in research findings (Pagel, Franklin and Baethge, 2014). To examine whether findings were consistent across different definitions of SA-D, I repeated the primary univariable analysis using DSM-IV defined schizophrenia and SA-D (schizophrenia n=755, SA-D n=169).

A small number of individuals with SA-BP were recruited into the CardiffCOGS sample (n=104) with phenotype data. I used logistic regression to measure the association between each phenotype and SA-D vs SA-BP diagnosis, covarying for age at interview and sex. Genotype data were not available in the SA-BP samples.

2.4.3 Replication analysis

The demographic and clinical characteristics that were significantly associated in the primary univariable analysis at $p<0.05$ and that were available in both the Cardiff Affected-sibs and Cardiff F-series samples were tested for replication (Table 2.9 in section 2.5.6). Phenotypes in the replication samples were taken from the same source (e.g., OPCRIT, SCAN) and were defined in the same way as the phenotypes in CardiffCOGS (Table 2.3). I conducted a meta-analysis of the results from the Cardiff Affected-sibs and Cardiff F-series samples, using a fixed effect model weighted by standard error, conducted in the R package *meta* (Balduzzi, Rücker and Schwarzer, 2019).

2.4.4 Multivariable analysis

For variables that were associated with SA-D at $p<0.05$ in the primary univariable analyses, I performed multivariable analysis to clarify whether the associations were independent. Characteristics were grouped into four categories which were analysed separately: demographics and premorbid; psychosis; depression; and other clinical.

Each regression model contained sex and age at interview as covariates, with diagnosis as the outcome.

2.4.5 Polygenic risk scores

Polygenic risk scores (PRS) were analysed using logistic regressions, with principal components one to five and sex included as covariates.

2.5. Results

Table 2.4 displays the age and sex of individuals included in the study, split by diagnosis and dataset.

	CardiffCOGS			**Replication datasets**	
	Schizophrenia	**SA-D**	**SA-BP**	**Schizophrenia**	**SA-D**
Sample size	713	151	104	844	43
Age (years)	42.9	44.0	42.3	40.6	43.6
Female sex	213 (29.8%)	87 (57.6%)	53 (50.9%)	245 (29.0%)	21 (48.8%)

Table 2.4 Sample size, mean age at interview, and number and percentage of sample of female sex for CardiffCOGS and Replication datasets

2.5.1 Demographics, family history, and premorbid characteristics

All regressions were conducted with diagnosis as the outcomes, thus odds ratio indicates the odds of having SA-D with a one unit increase in the phenotype. Full results are displayed in Figure 2.1 and Table 2.5. In the univariable analyses, compared to schizophrenia, SA-D was associated with female sex (OR=3.19, 95% confidence intervals (CI)=2.23-4.59, $p=2.8x10^{-10}$), and was included as a covariate for all other characteristics assessed. SA-D was also associated with self-disclosed experience of childhood abuse (OR=2.07, CI=1.35-3.17, $p=7.9x10^{-4}$), obstetric complications (OR=1.62, CI=1.03-2.50, p=0.03), and family history of psychiatric disorder other than schizophrenia (OR=1.50, CI= 1.01-2.22, p=0.04). There was no evidence for association with family history of schizophrenia (OR=0.73 (0.45 – 1.15), p=0.18). Individuals with SA-D had more children (OR=1.34, CI=1.08-1.67, p=0.01), and higher premorbid IQ (OR=1.28, CI= 1.04-1.60, p=0.02) than individuals with schizophrenia.

2.5.2 Lifetime clinical characteristics

Full results for the association of each phenotypic variable with SA-D diagnosis are presented in Figure 2.1 and Table 2.5. Compared to schizophrenia, SA-D was associated with lifetime alcohol dependence (OR=2.12, CI=1.41 – 3.20, $p=3.2x10^{-4}$), positive antipsychotic response (OR=1.59, CI=1.08-2.35, p=0.02), better current cognitive functioning (OR=1.20, CI =1.04-1.40, p=0.01), and a less chronic course of disorder (OR=0.81, CI=0.67-0.97, p=0.02). SA-D was also associated with milder psychosis related phenotypes, namely better functioning GAS score in worst episode of psychosis (OR=1.44, CI=1.20-1.72, $p=5.8x10^{-5}$), older age at onset of psychosis (OR=1.26, CI=1.03-1.54, p=0.02), reduced severity of disorganised symptoms (OR=0.81, CI=0.72-0.91, $p=5.3x10^{-4}$), and a lower risk for being detained under the mental health act for psychosis (OR=0.40, CI=0.22-0.75, $p=3.2x10^{-3}$).

To investigate differences in depression symptoms and outcomes between those with SA-D and schizophrenia, I restricted the schizophrenia sample to those who had experienced at least one episode of ICD-10 defined depression. SA-D was strongly associated with the onset of depression occurring prior to psychosis onset (OR=2.88, CI=1.59-5.47, $p=7.1x10^{-4}$) and a greater likelihood of an inpatient hospital admission for depression (OR=2.24, CI=1.48-3.40, $p=1.4x10^{-4}$). SA-D was also associated with a longer duration of the longest episode of depression (OR=1.46, CI=1.19-1.84, $p=6.0x10^{-4}$), more episodes of depression (OR=1.43, CI=1.18-1.75, $p=3.7x10^{-4}$), and lower functioning GAS score in worst episode of depression (OR=0.47, CI=0.37-0.59, $p=2.0x10^{-10}$).

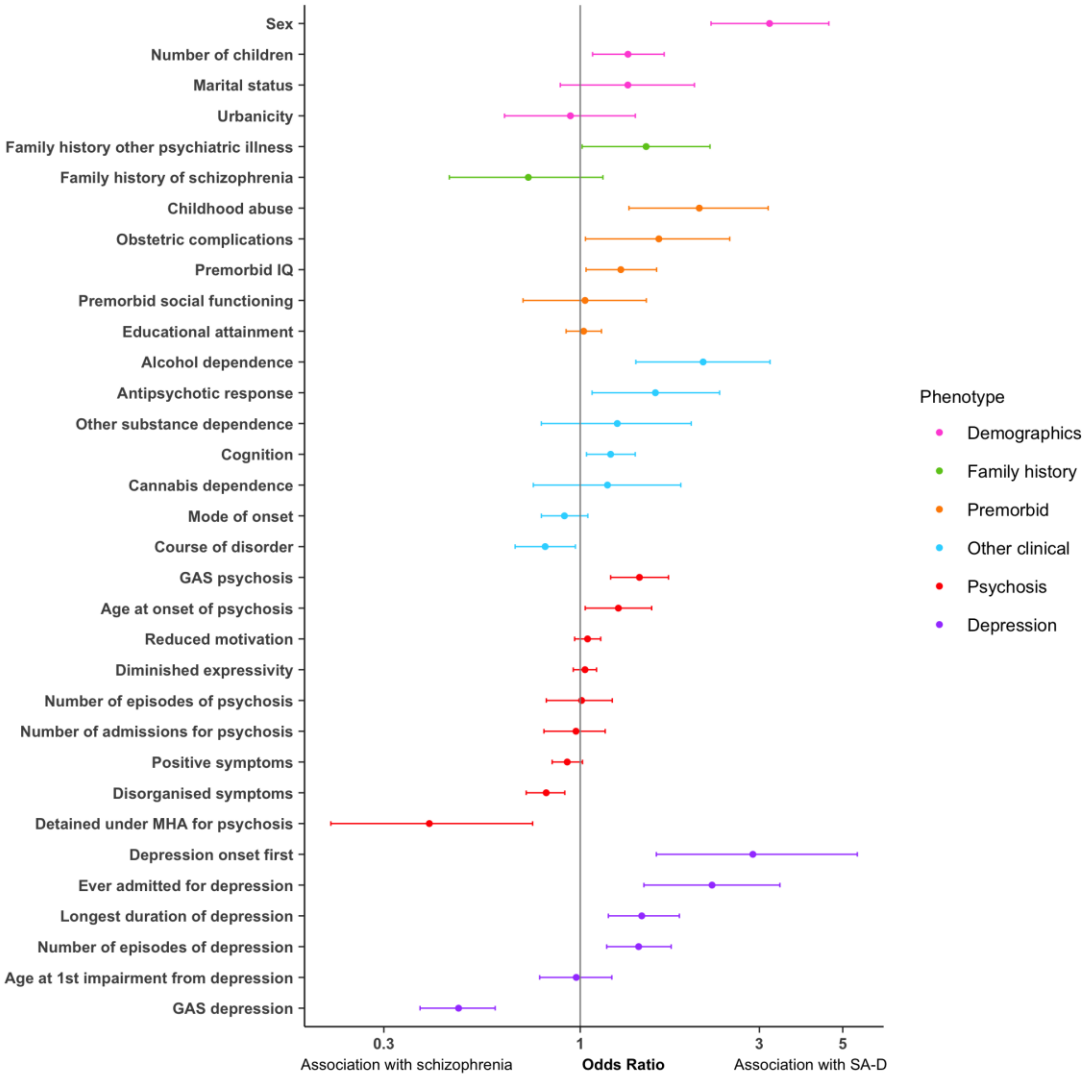

Figure 2.1. Odds ratios and confidence interval for each lifetime clinical characteristic in the CardiffCOGS sample.
Odds ratio >1 indicates association with SA-D; odds ratio <1 indicates association with schizophrenia. For course of disorder, odds ratio >1 indicates more chronic course in SA-D, whilst odds ratio <1 indicates a more chronic course in schizophrenia and thus a more episodic course in SA-D. Colour indicates category of the phenotype: pink is demographics, green is family history, orange is premorbid characteristics, blue is other clinical characteristics, red is characteristics of psychosis and purple is characteristics of depression. Clinical characteristics of depression are analysed only in participants with at least one episode of depression.

Phenotype	SCZ	SA-D	OR (95% CI)	P-value
	N (%) / Mean (SD)	N (%) / Mean (SD)		
Female sex	213 (29.87%)	87 (57.62%)	3.19 (2.23 – 4.59)	$2.8x10^{-10}$
Number of children	0.67 (1.26)	1.27 (1.47)	1.34 (1.08 – 1.67)	0.01
Marital history	185 (26.62%)	55 (37.41%)	1.34 (0.88 – 2.01)	0.16
Urbanicity	243 (41.68%)	51 (38.93%)	0.94 (0.63 – 1.40)	0.77
Family history of other psychiatric illness	224 (37.27%)	68 (50.75%)	1.50 (1.01 – 2.22)	0.04
Family history of schizophrenia	152 (25%)	28 (21.37%)	0.73 (0.45 – 1.15)	0.18
Childhood abuse	112 (17.02%)	46 (33.58%)	2.07 (1.35 – 3.17)	$7.9x10^{-4}$
Obstetric complications	118 (16.62%)	36 (24%)	1.62 (1.03 – 2.50)	0.03
Premorbid IQ	104.67 (10.32)	106.7 (9.29)	1.28 (1.04 – 1.60)	0.02
Premorbid social functioning	277 (40.92%)	63 (43.75%)	1.03 (0.70 – 1.50)	0.88
Educational attainment	2.59 (1.7)	2.62 (1.73)	1.02 (0.92 – 1.14)	0.70
Alcohol dependence	166 (25.98%)	51 (37.5%)	2.12 (1.41 – 3.20)	$3.2x10^{-4}$
Antipsychotic response	312 (46.15%)	78 (58.65%)	1.59 (1.08 – 2.35)	0.02
Other substance dependence	172 (25.83%)	35 (24.14%)	1.26 (0.79 – 1.97)	0.33
Cognition	-2.42 (1.35)	-2.14 (1.44)	1.20 (1.04 – 1.40)	0.01
Cannabis dependence	232 (35.75%)	42 (29.79%)	1.18 (0.75 – 1.85)	0.47
Mode of onset	3.68 (1.4)	3.48 (1.42)	0.91 (0.79 – 1.05)	0.18
Course of disorder	3.45 (0.94)	3.22 (0.96)	0.81 (0.67 – 0.97)	0.02
GAS psychosis	19.51 (6.78)	22.11 (7.68)	1.44 (1.20 – 1.72)	$5.8x10^{-5}$
Age at onset of psychosis	24.1 (8.61)	26.41 (9.54)	1.26 (1.03 – 1.54)	0.02
Reduced motivation/pleasure	4.55 (2.29)	4.8 (2.41)	1.05 (0.97 – 1.13)	0.42
Diminished expressivity	2.99 (2.63)	3.02 (2.51)	1.03 (0.96 – 1.10)	0.27
Number of episodes of psychosis	5.94 (7.54)	6.05 (7.72)	1.01 (0.81 – 1.22)	0.94
Number admissions for psychosis	4.66 (5.13)	4.68 (4.77)	0.97 (0.80 – 1.17)	0.78
Positive symptoms	6.29 (1.95)	6.06 (1.8)	0.92 (0.84 – 1.01)	0.09
Disorganised symptoms	1.56 (1.84)	0.98 (1.65)	0.81 (0.72 – 0.91)	$5.3x10^{-4}$
Detained under MHA for psychosis	570 (93.14%)	114 (86.36%)	0.40 (0.22 – 0.75)	$3.2x10^{-3}$
Depression onset first	267 (74.17%)	121 (88.32%)	2.88 (1.59 – 5.47)	$7.1x10^{-4}$
Ever admitted for depression	90 (21.13%)	59 (39.07%)	2.24 (1.48 – 3.40)	$1.4x10^{-4}$
Longest duration of depression	39.81 (69.99)	75.29 (118.12)	1.46 (1.19 – 1.84)	$6.0x10^{-4}$
Number of episodes of depression	139.31 (338.36)	142.73 (338.4)	1.43 (1.18 – 1.75)	$3.7x10^{-4}$
Age at first impairment from depression	22.88 (8.76)	22.62 (8.35)	0.98 (0.78 – 1.21)	0.83
GAS depression	32.64 (10.75)	25.17 (8.58)	0.47 (0.37 – 0.59)	$2.0x10^{-10}$

Table 2.5. Demographic and lifetime clinical characteristic results in CardiffCOGS.
N (%) indicates number and percentage of individuals within the diagnostic group that positively report the clinical characteristic for binary traits. For continuous traits, the means and standard deviations are reported. Odds ratio with 95% confidence intervals and p-value are reported for the association between each phenotype and SA-D in the primary univariate analysis.

2.5.3 Secondary analysis of sex-specific effects

As sex was the strongest predictor of diagnosis, I looked for sex-specific effects across all lifetime demographic and clinical characteristics by repeating the primary analyses in a female-only subset and a male-only subset of the CardiffCOGS sample. Some phenotypes were significant in only one sample, but no significant associations showed different directions of effect, indicating that the results were consistent between females and males (Table 2.6).

Phenotype	Female-only		Male-only	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Number of children	1.18 (0.84 - 1.68)	0.33	1.58 (1.20 - 2.06)	$8.4x10^{-4}$
Marital history	0.92 (0.52 - 1.59)	0.75	2.11 (1.16 - 3.80)	0.01
Urbanicity	1.05 (0.60 - 1.83)	0.86	0.86 (0.47 - 1.53)	0.61
Family history of other psychiatric illness	1.27 (0.75 - 2.16)	0.38	1.80 (1.01 - 3.21)	0.04
Family history of schizophrenia	0.61 (0.32 - 1.14)	0.13	0.91 (0.45 - 1.75)	0.79
Childhood abuse	1.46 (0.82 - 2.56)	0.19	3.14 (1.65 - 5.81)	$3.4x10^{-4}$
Obstetric complications	1.48 (0.79 - 2.72)	0.22	1.70 (0.88 - 3.13)	0.10
Premorbid IQ	1.19 (0.89 - 1.59)	0.25	1.35 (1.00 - 1.87)	0.06
Premorbid social functioning	0.93 (0.55 - 1.55)	0.77	1.13 (0.64 - 1.95)	0.67
Educational attainment	0.95 (0.82 - 1.59)	0.52	1.09 (0.93 - 1.29)	0.28
Alcohol dependence	1.95 (1.04 - 3.61)	0.04	2.24 (1.29 - 3.89)	$4.1x10^{-3}$
Antipsychotic response	1.58 (0.93 - 2.72)	0.09	1.63 (0.92 - 2.94)	0.10
Other substance dependence	1.20 (0.59 - 2.40)	0.60	1.34 (0.71 - 2.48)	0.35
Cognition	1.18 (0.97 - 1.45)	0.10	1.23 (0.99 - 1.54)	0.07
Cannabis dependence	1.06 (0.53 - 2.04)	0.86	1.45 (0.77 - 2.74)	0.25
Mode of onset	0.95 (0.77 - 1.17)	0.61	0.84 (0.69 - 1.03)	0.08
Course of disorder	0.85 (0.66 - 1.08)	0.18	0.75 (0.56 - 1.00)	0.04
GAS psychosis	1.28 (1.00 - 1.64)	0.05	1.65 (1.28 - 2.13)	$1.0x10^{-4}$
Age at onset of psychosis	1.15 (0.86 - 1.55)	0.34	1.36 (1.03 - 1.79)	0.03
Reduced motivation/pleasure	1.05 (0.94 - 1.18)	0.36	1.03 (0.91 - 1.16)	0.67
Diminished expressivity	1.08 (0.98 - 1.20)	0.12	0.97 (0.88 - 1.07)	0.59
Number of episodes of psychosis	1.07 (0.81 - 1.40)	0.62	0.97 (0.68 - 1.27)	0.83
Number admissions for psychosis	1.22 (0.94 - 1.56)	0.12	0.64 (0.41 - 0.91)	0.03
Positive symptoms	1.00 (0.87 - 1.14)	0.97	0.85 (0.74 - 0.96)	0.01
Disorganised symptoms	0.81 (0.68 - 0.94)	0.01	0.82 (0.68 - 0.97)	0.03
Detained under the MHA for psychosis	0.58 (0.21 - 1.65)	0.29	0.31 (0.15 - 0.69)	$2.6x10^{-3}$
Depression onset first	1.86 (0.82 - 4.44)	0.15	4.41 (1.84 - 12.36)	$1.9x10^{-3}$
Ever admitted for depression	2.47 (1.37 - 4.49)	$2.7x10^{-3}$	2.15 (1.17 - 3.88)	0.01
Longest duration of depression	1.15 (0.86 - 1.56)	0.33	1.85 (1.34 - 2.72)	$7.4x10^{-4}$
Number of episodes of depression	1.67 (1.23 - 2.33)	$1.6x10^{-3}$	1.27 (0.96 - 1.66)	0.08
Age at first impairment from depression	1.04 (0.76 - 1.40)	0.81	0.91 (0.66 - 1.22)	0.53
GAS depression	0.42 (0.29 - 0.58)	$8.1x10^{-7}$	0.52 (0.38 - 0.71)	$4.1x10^{-5}$

Table 2.6 Demographic, premorbid, and lifetime clinical characteristic results separated by sex.
Odds ratios, confidence intervals, and p-values for the association between each lifetime clinical characteristic analysed in female-only and male-only samples from the CardiffCOGS. Clinical characteristics of depression are analysed only in participants with at least one episode of major depression.

2.5.4 Secondary analysis of DSM-IV diagnosis

Univariable analyses were repeated using DSM-IV rather than ICD-10 definitions of schizophrenia and SA-D. Effect sizes were consistent between both diagnostic manual for all characteristics (Table 2.7), indicating that the use of ICD-10 rather than DSM-IV is not impacting the results of the study.

Phenotype	ICD-10		DSM-4	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Female sex	3.19 (2.23 – 4.59)	$2.8x10^{-10}$	3.21 (2.28 - 4.53)	$2.7x10^{-11}$
Number of children	1.34 (1.08 – 1.67)	0.01	1.23 (1.00 - 1.52)	0.04
Marital history	1.34 (0.88 – 2.01)	0.16	1.47 (1.00 - 2.17)	0.05
Urbanicity	0.94 (0.63 – 1.40)	0.77	0.84 (0.58 - 1.23)	0.38
Family history of other psychiatric illness	1.50 (1.01 – 2.22)	0.04	1.63 (1.12 - 2.37)	0.01
Family history of schizophrenia	0.73 (0.45 – 1.15)	0.18	0.64 (0.40 - 1.01)	0.06
Childhood abuse	2.07 (1.35 – 3.17)	$7.9x10^{-4}$	2.18 (1.45 - 3.25)	$1.5x10^{-4}$
Obstetric complications	1.62 (1.03 – 2.50)	0.03	1.52 (0.98 - 2.31)	0.05
Premorbid IQ	1.28 (1.04 – 1.60)	0.02	1.25 (1.02 - 1.53)	0.04
Premorbid social functioning	1.03 (0.70 – 1.50)	0.88	1.03 (0.71 - 1.47)	0.88
Educational attainment	1.02 (0.92 – 1.14)	0.70	1.02 (0.92 - 1.13)	0.70
Alcohol dependence	2.12 (1.41 – 3.20)	$3.2x10^{-4}$	1.82 (1.23 - 2.69)	$2.7x10^{-3}$
Antipsychotic response	1.59 (1.08 – 2.35)	0.02	1.68 (1.16 - 2.45)	0.01
Other substance dependence	1.26 (0.79 – 1.97)	0.33	1.14 (0.73 - 1.76)	0.57
Cognition	1.20 (1.04 – 1.40)	0.01	1.17 (1.02 - 1.35)	0.03
Cannabis dependence	1.18 (0.75 – 1.85)	0.47	1.15 (0.75 - 1.76)	0.51
Mode of onset	0.91 (0.79 – 1.05)	0.18	0.97 (0.85 - 1.12)	0.68
Course of disorder	0.81 (0.67 – 0.97)	0.02	0.78 (0.66 - 0.93)	0.01
GAS psychosis	1.44 (1.20 – 1.72)	$5.8x10^{-5}$	1.49 (1.26 - 1.76)	$3.8x10^{-6}$
Age at onset of psychosis	1.26 (1.03 – 1.54)	0.02	1.31 (1.08 - 1.59)	0.01
Reduced motivation/pleasure	1.05 (0.97 – 1.13)	0.42	1.04 (0.97 - 1.11)	0.25
Diminished expressivity	1.03 (0.96 – 1.10)	0.27	1.07 (0.99 - 1.16)	0.07
Number of episodes of psychosis	1.01 (0.81 – 1.22)	0.94	0.98 (0.79 - 1.18)	0.86
Number admissions for psychosis	0.97 (0.80 – 1.17)	0.78	0.94 (0.78 - 1.12)	0.52
Positive symptoms	0.92 (0.84 – 1.01)	0.09	0.91 (0.84 - 0.99)	0.04
Disorganised symptoms	0.81 (0.72 – 0.91)	$5.3x10^{-4}$	0.79 (0.70 - 0.89)	$9.3x10^{-5}$
Positive symptoms	0.92 (0.84 – 1.01)	0.09	0.91 (0.84 - 0.99)	0.04
Disorganised symptoms	0.81 (0.72 – 0.91)	$5.3x10^{-4}$	0.79 (0.70 - 0.89)	$9.3x10^{-5}$
Detained under the MHA for psychosis	0.40 (0.22 – 0.75)	$3.2x10^{-3}$	0.41 (0.23 - 0.73)	$1.8x10^{-3}$
Depression onset first	2.88 (1.59 – 5.47)	$7.1x10^{-4}$	2.70 (1.55 - 4.88)	$6.9x10^{-4}$
Ever admitted for depression	2.24 (1.48 – 3.40)	$1.4x10^{-4}$	2.20 (1.47 - 3.28)	$1.1x10^{-4}$
Longest duration of depression	1.46 (1.19 – 1.84)	$6.0x10^{-4}$	1.38 (1.14 - 1.69)	$1.4x10^{-3}$
Number of episodes of depression	1.43 (1.18 – 1.75)	$3.7x10^{-4}$	1.39 (1.16 - 1.68)	$5.2x10^{-4}$
Age at first impairment from depression	0.98 (0.78 – 1.21)	0.83	1.00 (0.80 - 1.23)	0.97
GAS depression	0.47 (0.37 – 0.59)	$2.0x10^{-10}$	0.49 (0.39 - 0.60)	$7.2x10^{-11}$

Table 2.7. Comparison of demographic, premorbid, and lifetime clinical characteristic results using ICD-10 and DSM-4 defined diagnosis.
Odds ratio with 95% confidence intervals and p-value are reported for the association between each phenotype and SA-D when diagnosis was defined according to either ICD-10 or DSM-IV criteria.

2.5.5 Secondary analysis of SA-D and SA-BP

Additionally, I tested for differences between individuals with SA-D and SA-BP. However, since the SA-BD sample is small (N=104 individuals with ICD-10 SA-BP), and replication samples were not available, the results are provisional (Table 2.8).
SA-D and SA-BP did not significantly differ in terms of demographics or family history of psychiatric disorders, although SA-D was associated with more children (OR=1.63, CI=1.14-2.43, p=0.01). SA-D was also associated with measures of poorer cognition, including lower educational attainment (OR=0.75, CI=0.63-0.88, $p=7.4x10^{-4}$), lower premorbid IQ (OR=0.71, CI=0.52-0.97, p=0.04), and lower cognition (OR=0.80, CI=0.64 - 0.99, p=0.04) than SA-BP. In terms of psychosis related phenotypes, SA-D was associated with higher GAS score in worst episode of psychosis (OR=1.59, CI=1.20-2.13, $p=1.6x10^{-3}$), lower lifetime severity of disorganised symptoms (OR=0.74, CI=0.64 - 0.85, $p=6.2x10^{-5}$), and greater lifetime severity of diminished expressivity symptoms (OR=1.15, CI=1.03-1.30, p=0.02) compared to SA-BP. Individuals with SA-D, compared to those with SA-BP, also had more severe depression phenotypes, including a longer duration of longest episode of depression (OR=1.86, CI=1.17-3.38, p=0.02), lower GAS score in worst episode of depression (OR=0.62, CI=0.45-0.83, $p=2.0x10^{-3}$), and depression onset was more likely to be prior to the onset of psychosis (OR=3.24, CI=1.50-7.18, $p=3.1x10^{-3}$).

A spectrum effect was observed for premorbid IQ and current cognitive functioning, indicating that individuals with schizophrenia were the most impaired for these phenotypes, SA-D were intermediate, and SA-BP were the least impaired. SA-D was associated with more severe depression phenotypes and milder psychosis phenotypes than both SA-BP and schizophrenia (Table 2.8).

Phenotype	SA-D vs SA-BP		SA-D vs SCZ	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Female sex	1.37 (0.82 - 2.28)	0.23	3.19 (2.23 – 4.59)	$2.8x10^{-10}$
Number of children	1.63 (1.14 - 2.43)	0.01	1.34 (1.08 – 1.67)	0.01
Marital history	0.93 (0.52 - 1.67)	0.82	1.34 (0.88 – 2.01)	0.16
Urbanicity	0.63 (0.35 - 1.11)	0.11	0.94 (0.63 – 1.40)	0.77
Family history of other psychiatric illness	0.78 (0.45 - 1.36)	0.39	1.50 (1.01 – 2.22)	0.04
Family history of schizophrenia	1.33 (0.66 - 2.79)	0.43	0.73 (0.45 – 1.15)	0.18
Childhood abuse	1.61 (0.87 - 3.06)	0.14	2.07 (1.35 – 3.17)	$7.9x10^{-4}$
Obstetric complications	1.12 (0.62 - 2.06)	0.72	1.62 (1.03 – 2.50)	0.03
Premorbid IQ	0.71 (0.52 - 0.97)	0.04	1.28 (1.04 – 1.60)	0.02
Premorbid social functioning	1.23 (0.71 - 2.14)	0.46	1.03 (0.70 – 1.50)	0.88
Educational attainment	0.75 (0.63 - 0.88)	$7.4x10^{-4}$	1.02 (0.92 – 1.14)	0.70
Alcohol dependence	1.04 (0.60 - 1.83)	0.89	2.12 (1.41 – 3.20)	$3.2x10^{-4}$
Antipsychotic response	1.16 (0.66 -2.04)	0.60	1.59 (1.08 – 2.35)	0.02
Other substance dependence	1.33 (0.70 - 2.59)	0.39	1.26 (0.79 – 1.97)	0.33
Cognition	0.80 (0.64 - 0.99)	0.04	1.20 (1.04 – 1.40)	0.01
Cannabis dependence	1.15 (0.62 - 2.16)	0.66	1.18 (0.75 – 1.85)	0.47
Mode of onset	1.08 (0.88 - 1.33)	0.48	0.91 (0.79 – 1.05)	0.18
Course of disorder	1.22 (0.93 - 1.62)	0.16	0.81 (0.67 – 0.97)	0.02
GAS psychosis	1.59 (1.20 - 2.13)	$1.6x10^{-3}$	1.44 (1.20 – 1.72)	$5.8x10^{-5}$
Age at onset of psychosis	1.31 (0.96 - 1.81)	0.10	1.26 (1.03 – 1.54)	0.02
Reduced motivation/pleasure	1.05 (0.94 - 1.18)	0.37	1.05 (0.97 – 1.13)	0.42
Diminished expressivity	1.15 (1.03 - 1.30)	0.02	1.03 (0.96 – 1.10)	0.27
Number of episodes of psychosis	0.81 (0.60 - 1.08)	0.16	1.01 (0.81 – 1.22)	0.94
Number admissions for psychosis	0.76 (0.52 - 1.02)	0.10	0.97 (0.80 – 1.17)	0.78
Positive symptoms	0.99 (0.70 - 1.14)	0.87	0.92 (0.84 – 1.01)	0.09
Disorganised symptoms	0.74 (0.64 - 0.85)	$6.2x10^{-5}$	0.81 (0.72 – 0.91)	$5.3x10^{-4}$
Detained under the MHA for psychosis	0.69 (0.28 - 1.60)	0.40	0.40 (0.22 – 0.75)	$3.2x10^{-3}$
Depression onset first	3.24 (1.50 - 7.18)	$3.1x10^{-3}$	2.88 (1.59 – 5.47)	$7.1x10^{-4}$
Ever admitted for depression	1.07 (0.60 - 1.93)	0.81	2.24 (1.48 – 3.40)	$1.4x10^{-4}$
Longest duration of depression	1.86 (1.17 - 3.38)	0.02	1.46 (1.19 – 1.84)	$6.0x10^{-4}$
Number of episodes of depression	1.18 (0.88 - 1.64)	0.28	1.43 (1.18 – 1.75)	$3.7x10^{-4}$
Age at first impairment from depression	1.27 (0.92 - 1.81)	0.16	0.98 (0.78 – 1.21)	0.83
GAS depression	0.62 (0.45 - 0.83)	$2.0x10^{-3}$	0.47 (0.37 – 0.59)	$2.0x10^{-10}$

Table 2.8 Comparison of demographic, premorbid, and lifetime clinical characteristic results between schizoaffective bipolar-type and depressive-type.
Odds ratios, 95% confidence intervals and p-values are presented comparing schizoaffective disorder bipolar-type (SA-BP) to SA-D. Primary results in schizophrenia compared to SA-D are presented for reference. Odds ratio >1 indicates association with SA-D.

2.5.6 Replication

Variables that were significant in the primary univariable analysis and available in both the Cardiff Affected-sibs and Cardiff F-series, displayed in Table 2.9, were meta-analysed in the two replication samples.

Variable	SCZ Total N	SA-D Total N
Sex	835	43
Family history of other psychiatric disorder	792	42
Course of disorder	679	32
Alcohol dependence	791	42
Age at onset of psychosis	811	40

Table 2.9. Characteristics included in the replication meta-analysis.
Variables and total number of individuals with data for each variable with a diagnosis of schizophrenia or SA-D in the Cardiff Affected-sibs and Cardiff F-series samples.

In the replication meta-analysis of Cardiff Affected-sibs and Cardiff F-series, SA-D was significantly associated with female sex (OR=2.32, CI=1.21-4.44, p=0.01), family history of psychiatric disorder other than schizophrenia (OR=2.83, CI=1.31-6.13, p=0.01), and older age at onset of psychosis (OR=1.73, CI= 1.26-2.37, $p=7.4x10^{-4}$) (Table 2.10). Although the association with course of disorder and alcohol dependence was not statistically significant in the replication meta-analysis, the direction of effect was consistent with the initial findings from CardiffCOGS. When all three samples were meta-analysed, SA-D was significantly associated with all five characteristics (Figure 2.2).

Phenotype	Univariable CardiffCOGS		Replication meta-analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Sex	3.19 (2.23 – 4.59)	$2.8x10^{-10}$	2.32 (1.21 – 4.44)	0.01
Family history of other psychiatric disorder	1.50 (1.01 – 2.22)	0.04	2.83 (1.31 – 6.13)	0.01
Course of disorder	0.81 (0.67 – 0.97)	0.02	0.75 (0.51 – 1.11)	0.16
Alcohol dependence	2.12 (1.41 – 3.20)	$3.2x10^{-4}$	1.76 (0.87 – 3.57)	0.12
Age at onset of psychosis	1.26 (1.03 – 1.55)	0.02	1.73 (1.26 – 2.37)	$7.4x10^{-4}$

Table 2.10. Odds ratios and 95% confidence intervals for each characteristic included in the replication.
Columns indicate the odds ratio (OR) and p-value of the univariable association in CardiffCOGS only, and the OR and p-value of the association in the replication meta-analysis of Cardiff Affected-sibs and Cardiff F-series. OR >1 indicates association with SA-D.

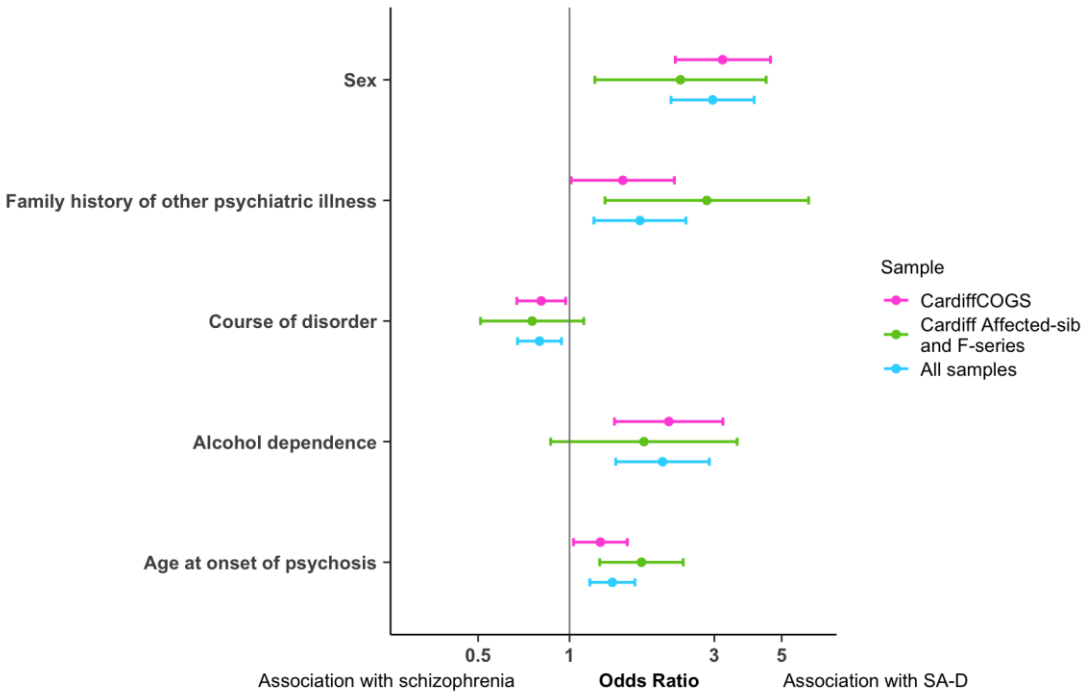

Figure 2.2. Results of the replication and meta-analysis phenotypes.
A comparison of the odds ratios and confidence intervals for the associations between the phenotype and diagnosis in the primary univariate analysis of CardiffCOGS (pink points), the replication meta-analysis of Cardiff Affected-sibs and Cardiff F-series (green points), and the meta-analysis of all samples with phenotypic data (blue points).

2.5.7 Multivariable models

Multivariable models were analysed including all significant predictors from the univariable analysis, grouped by category, to assess whether associations were independent. Multivariable models are presented in Table 2.11.

In the demographics and premorbid model, SA-D remained significantly associated with female sex (OR=2.22, CI=1.14-4.36, p=0.02), and experience of childhood abuse (OR=2.80, CI=1.36-5.71, $p=4.6x10^{-3}$), but not with family history of psychiatric illness, number of children, obstetric complications, premorbid IQ, or age at onset of psychosis. In the clinical characteristics model, greater alcohol dependence was significantly associated with SA-D (OR=2.08, CI=1.31-3.28, $p=1.8x10^{-3}$), but not with course of disorder, cognition, or antipsychotic response. In the psychosis model, SA-D was significantly associated with better functioning GAS score in worst episode of psychosis (OR=1.31, CI=1.07-1.61, p=0.01) and reduced lifetime severity of disorganised symptoms (OR=0.84, CI=0.74-0.96, p=0.01), but not with being detained under the mental health act for psychosis. In the depression model, SA-D was associated with a greater number of episodes of depression (OR=1.62, CI=1.14-2.32, p=0.01), and lower functioning GAS score in worst episode of depression (OR=0.49, CI=0.33-0.72, $p=4.8x10^{-4}$), but not with ever being admitted for depression, longest duration of depression, or having depression onset prior to psychosis onset.

Given the restricted sample size as a result of missing data in the multivariable analysis, I repeated the univariable analyses restricted to individuals who had complete data for the variables entered into the appropriate multivariable model, for more accurate comparison between the univariable and multivariable analyses. Effect sizes remained consistent between the restricted and full sample analyses and are presented in Table 2.11.

Phenotype		SCZ sample size	SA-D sample size	Restricted univariable analysis		Multivariable analysis	
				OR (95% CI)	P-value	OR (95% CI)	P-value
Demographics and premorbid characteristics	Female sex	219	54	2.97 (1.61 – 5.53)	$5.0x10^{-4}$	2.22 (1.14 – 4.36)	0.02
	Family history of other psychiatric illness			2.03 (1.08 – 3.84)	0.03	1.77 (0.91 – 3.44)	0.09
	Number of children			1.10 (0.81 – 1.49)	0.52	1.18 (0.85 – 1.62)	0.32
	Obstetric complications			1.88 (0.84 – 4.03)	0.11	1.96 (0.84 – 4.41)	0.11
	NART IQ			1.18 (0.86 – 1.65)	0.31	1.16 (0.83 – 1.63)	0.40
	Childhood abuse			2.67 (1.33 – 5.30)	0.01	2.80 (1.36 – 5.71)	$4.6x10^{-3}$
	Age at onset of psychosis			1.12 (0.80 – 1.55)	0.50	1.06 (0.75 – 1.49)	0.72
Clinical characteristics	Course of disorder	562	110	0.81 (0.65 – 1.00)	0.04	0.86 (0.68 – 1.10)	0.24
	Cognition			1.14 (0.97 – 1.35)	0.12	1.09 (0.91 – 1.30)	0.35
	Alcohol dependence			1.99 (1.26 – 3.13)	$2.8x10^{-3}$	2.08 (1.31 – 3.28)	$1.8x10^{-3}$
	Antipsychotic response			1.53 (1.00 – 2.34)	0.05	1.32 (0.81 – 2.14)	0.26
Psychosis	Detained under the mental health act for psychosis	584	127	0.38 (0.21 – 0.72)	$2.4x10^{-3}$	0.55 (0.29 – 1.09)	0.08
	GAS psychosis			1.42 (1.17 – 1.73)	$4.0x10^{-4}$	1.31 (1.07 – 1.61)	0.01
	Disorganised symptoms			0.82 (0.72 – 0.93)	$2.3x10^{-3}$	0.84 (0.74 – 0.96)	0.01
Depression	Ever admitted for depression	184	71	2.42 (1.31 – 4.46)	$4.6x10^{-3}$	1.65 (0.83 – 3.27)	0.15
	Longest duration of depression			1.31 (1.01 – 1.71)	0.04	1.30 (0.96 – 1.78)	0.10
	Number of episodes of depression			2.03 (1.48 – 2.80)	$1.3x10^{-5}$	1.62 (1.14 – 2.32)	0.01
	GAS depression			0.39 (0.27 – 0.55)	$6.7x10^{-7}$	0.49 (0.33 – 0.72)	$4.8x10^{-4}$
	Depression onset first			2.20 (1.14 – 4.47)	0.02	1.27 (0.60 – 2.76)	0.54

Table 2.11. Demographic and clinical characteristics in restricted sample univariate and multivariable models. Odds ratios (OR) with 95% confidence intervals (CI) and p-values for the association between each characteristic and SA-D in the CardiffCOGS sample restricted to only those with complete data for the multivariable model. OR with 95% CI and p-values for the association between each characteristic and SA-D when analysed as part of a multivariable model. Table shading indicates the characteristics included in each model.

2.5.8 Polygenic risk scores

At the primary p-value threshold of p<0.05, schizophrenia PRS was not significantly different between individuals with SA-D and with schizophrenia (OR=0.94, CI=0.77-1.17, p=0.60). Bipolar disorder PRS was also not significantly different between individuals with SA-D and with schizophrenia (OR=1.13, CI=0.91-1.42, p=0.27). However, depression PRS was significantly higher in individuals with SA-D compared to individuals with schizophrenia (OR=1.26, CI=1.02-1.56, p=0.03) (Figure 2.3). Secondary analyses showed these results were broadly consistent across p-value thresholds (Table 2.12).

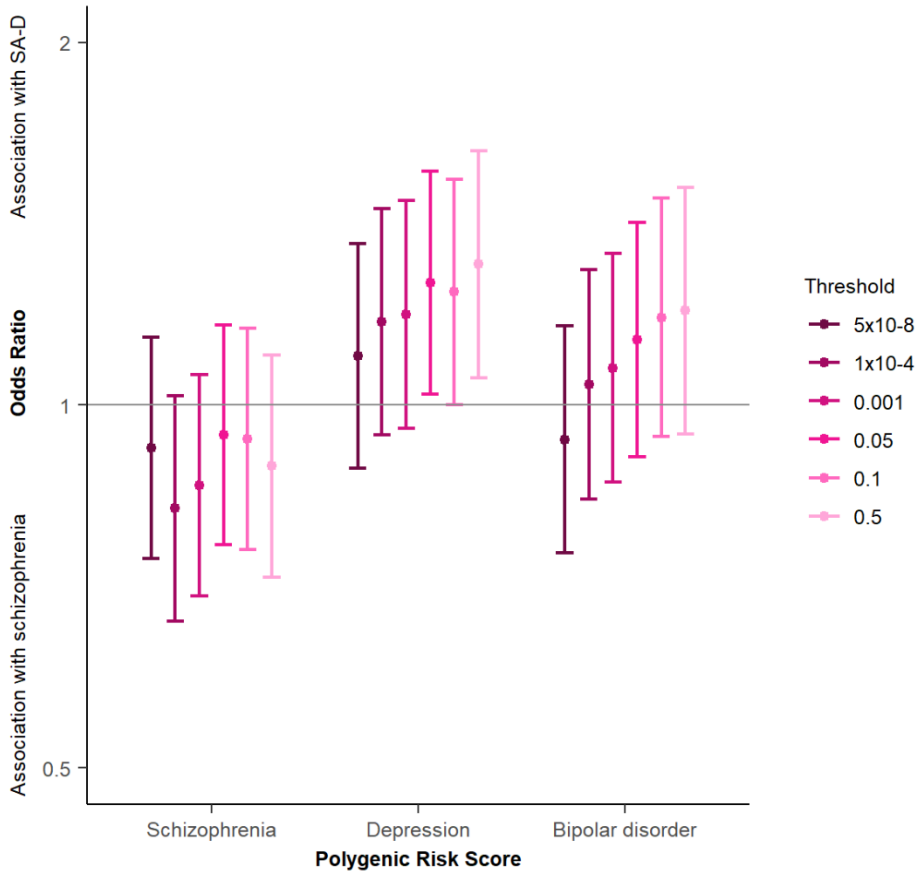

Figure 2.3. Polygenic risk score results.
Odds ratios and 95% confidence intervals for all thresholds tested for schizophrenia and depression polygenic risk scores in the Cardiff COGS sample. Odds ratio>1 indicated association with SA-D; odds ratio <1 indicates association with schizophrenia.

PRS	Threshold	OR (95% CI)	P-value
Schizophrenia	$5x10^{-8}$	0.92 (0.75 – 1.14)	0.45
	$1x10^{-4}$	0.82 (0.66 – 1.02)	0.07
	0.001	0.86 (0.69 – 1.06)	0.16
	0.05	0.94 (0.77 – 1.17)	0.60
	0.1	0.94 (0.76 – 1.16)	0.55
	0.5	0.89 (0.72 – 1.10)	0.28
Depression	$5x10^{-8}$	1.10 (0.89 – 1.36)	0.39
	$1x10^{-4}$	1.17 (0.94 – 1.45)	0.15
	0.001	1.19 (0.96 – 1.48)	0.12
	0.05	1.26 (1.02 – 1.56)	0.03
	0.1	1.24 (1.00 – 1.54)	0.05
	0.5	1.31 (1.05 – 1.63)	0.02
Bipolar disorder	$5x10^{-8}$	0.94 (0.75 - 1.16)	0.55
	$1x10^{-4}$	1.04 (0.83 - 1.30)	0.73
	0.001	1.07 (0.86 - 1.34)	0.52
	0.05	1.13 (0.91 - 1.42)	0.27
	0.1	1.18 (0.94 - 1.48)	0.15
	0.5	1.20 (0.95 - 1.52)	0.13

Table 2.12. Polygenic risk score results.
Results for all thresholds tested for schizophrenia, depression, and bipolar disorder polygenic risk scores. Columns represent threshold used to define SNPs for inclusion, odds ratio and 95% confidence intervals, and p-values for the association between each PRS and diagnosis of SA-D vs schizophrenia.

2.6. Discussion

I present novel evidence to show that SA-D differs from schizophrenia in terms of demographics, clinical course, outcomes, and genetic liability to depression, but both disorders are similar with respect to genetic liability to schizophrenia and bipolar disorder.

2.6.1 Greater environmental and genetic risk for depression in SA-D

Several risk factors for depression occurred more frequently in people with SA-D, compared with those with schizophrenia, including female sex, alcohol dependence, and experience of childhood physical and/or sexual abuse, which has also been implicated in schizophrenia (Nolen-Hoeksema, 1987; Grant and Harford, 1995; Chapman *et al.*, 2004). Previous twin research has suggested that individuals with SA-D have an elevated genetic liability to depression (Cardno *et al.*, 2012). My findings support this with novel evidence that PRS for depression is elevated in individuals with SA-D compared to those with schizophrenia, who themselves are known to have elevated genetic liability to depression compared with controls (Lee *et al.*, 2019). Family history of psychiatric disorders, other than schizophrenia, was also associated with SA-D in the univariable analysis and replicated in additional samples, suggesting that relative to those with schizophrenia, individuals with SA-D may have an elevated genetic liability to other disorders, although shared environment could also contribute to this finding. Individuals with schizophrenia and SA-D did not significantly differ in terms of genetic liability to schizophrenia or environmental exposures that are typically considered risk factors for schizophrenia, including urbanicity, poor premorbid social functioning, and cannabis dependence (van Os, Kenis and Rutten, 2010). Thus, SA-D may represent a subset of people with typical liability to schizophrenia but who have an additional burden of environmental and genetic risk factors for depression. These findings are consistent with the hybrid model of schizoaffective disorder, but does not eliminate the possibility that SA-D is a subtype of schizophrenia.

2.6.2 Greater severity of depression

Prominence of depressive episodes in the clinical picture is a criterion for SA-D, suggesting that individuals with SA-D should experience more severe depression than individuals with schizophrenia. The findings of the univariable analyses support this, and the multivariable analysis of depression characteristics found that the number of episodes of depression and the functioning in the worst episode of depression were the variables most strongly associated with SA-D. As the analysis of depression characteristics was restricted to individuals who had experienced at least one episode of depression, the associations with depression characteristics are not simply due to dilution of those characteristics by the inclusion of individuals with schizophrenia without comorbid depression.

2.6.3 Reduced burden of psychosis

Individuals with SA-D had milder psychosis related phenotypes, predominantly characterised in the multivariable analysis by better functioning in the worst episode of psychosis and reduced lifetime severity of disorganised symptoms. These findings are consistent with a number of studies showing reduced severity of psychotic symptoms in schizoaffective disorders compared to schizophrenia (Cheniaux *et al.*, 2008; Goghari and Harrow, 2016), although those studies did not stratify by subtype of schizoaffective disorder. Despite the clinical characteristics suggesting a less severe psychosis phenotype in those with SA-D, schizophrenia polygenic risk score did not significantly differentiate between SA-D and schizophrenia. Previous research has found that schizophrenia PRS is not significantly associated with psychosis related variables including positive symptom severity (Fanous *et al.*, 2012; Legge, Cardno, *et al.*, 2021) in people with schizophrenia. In this respect, schizophrenia PRS does not seem to relate to psychosis severity measures or outcomes within those with schizophrenia or SA-D.

2.6.4 Neurodevelopmental spectrum

It has been postulated that schizophrenia lies on a spectrum of neurodevelopmental disorders, with intellectual disability and autism spectrum disorders having a greater

neurodevelopmental component than schizophrenia, and affective disorders having less (Owen and O'Donovan, 2017). Indicators of greater neurodevelopmental burden include cognitive impairments, increased prevalence in males, developmental delay, chronic course of illness, and early age at onset (Owen and O'Donovan, 2017). Compared to schizophrenia, SA-D was associated with better current cognitive functioning, female sex, less chronic course of disorder, and older age at onset of psychosis, suggesting that SA-D may occupy a less severe position on this proposed spectrum than schizophrenia (Owen *et al.*, 2011). Whilst not all of these neurodevelopmental risk factors were associated in the multivariable models, the effect sizes of these variables are comparable to those found in the univariable model, indicating that the reduced statistical significance may be due to lower power in the multivariable models rather than a lack of independent effects.

Early conceptions of schizoaffective disorder characterised it not only by mixed psychotic and affective symptoms, but also as being more common in women, associated with family history of affective disorders, an episodic course, higher premorbid IQ, and a greater number of episodes of illness than in schizophrenia (Maj, 1984b, 1984a). The results of this study are consistent with these observations, although some findings from studies using early definitions of schizoaffective disorder were not identified, including fewer negative symptoms, acute onset, and better premorbid social functioning (Maj, 1984b, 1984a), which did not significantly differ between SA-D and schizophrenia in this study.

More recent research using DSM and ICD definitions of schizoaffective disorder have reported that individuals with schizoaffective disorder, not stratified by subtype, are more likely than people with schizophrenia to be women and have higher scores on the GAS (Pagel, Franklin and Baethge, 2014), findings which were also observed in this study. However, other findings, including more positive symptoms and fewer negative symptoms in schizoaffective disorder compared to schizophrenia, were not replicated in this study (Mancuso *et al.*, 2015). A higher number of disorganised symptoms were also associated with schizoaffective disorder in one study (Mancuso *et al.*, 2015), whereas I observed fewer disorganised symptom in SA-D than schizophrenia. Thus, it is

possible that previous findings may be specific to SA-BP, and that combining subtypes could be obscuring differences between schizophrenia, SA-D, and SA-BP.

2.6.5 Limitations

My study is limited by the relatively small number of individuals with SA-D, and although I have replicated some of the key findings, validation in other samples is necessary to examine whether the findings are fully robust to, for example, unknown biases in ascertainment. Whilst I did not detect any between group differences in schizophrenia or bipolar disorder PRS, given the relatively small target sample there could be differences between the group that the study was not powered to detect. The proportion of individuals with SA-D differed across the samples, with the Cardiff Affected-sibs and Cardiff F-series samples containing fewer individuals with SA-D compared to schizophrenia than was seen in the CardiffCOGS. This is likely to be because depression data for participants in the CardiffCOGS was derived from both clinical records and from direct questions about depressive symptoms and episodes as part of the SCAN interview, whereas for participants in Cardiff Affected-sibs and Cardiff F-series these data were drawn only from clinical notes.

2.6.6 Conclusions

Compared to schizophrenia, SA-D was associated with several risk factors for depression, including female sex and greater alcohol dependence. I observed more severe depression in individuals with SA-D, including number of depressive episodes and level of functioning during worst depressive episode. Individuals with SA-D, compared to individuals with schizophrenia, had higher PRS for depression but did not differ in PRSs for schizophrenia or bipolar disorder. The findings from this study are consistent with SA-D being a sub-type of schizophrenia which is modified by an elevated liability to depression. Replication in larger samples of SA-D is necessary to clarify whether the phenotypic differences observed between people with SA-D and schizophrenia are substantial enough to warrant SA-D being a distinct diagnosis.

Chapter 3

Polygenic associations with symptom dimensions and phenotypic clusters across the psychosis-affective spectrum.

3.1 Introduction

Schizophrenia, schizoaffective disorder, and bipolar disorder have substantial overlaps in their clinical presentations and treatments. As many as two thirds of individuals with bipolar disorder report experiencing psychosis during a mood episode (Keck *et al.*, 2003), whilst manic symptoms occur in up to 20% of people with schizophrenia (Morrissette and Stahl, 2011). Schizoaffective disorder is characterised as having the core symptoms of both schizophrenia and affective disorders. Antipsychotics, the only effective pharmacological treatment for schizophrenia, are also recommended in National Institute for Health and Care Excellence (NICE) guidelines for the treatment of an acute manic episode in bipolar disorder (National Institute for Health and Care Excellence, 2014a). Schizophrenia and bipolar disorder also have a substantially shared genetic component with recent estimates indicating a genetic correlation of 0.7 (Lee *et al.*, 2019), and large population-based family studies have demonstrated familial aggregation of schizophrenia, schizoaffective disorder, and bipolar disorder (Laursen *et al.*, 2005). Despite clear genetic and clinical overlaps, schizophrenia and bipolar disorder have typically been studied separately and considered clinically distinct.

3.1.1 Symptom dimensions

Many are increasingly calling for the categorical distinction between schizophrenia, schizoaffective disorder, and bipolar disorder to be replaced with a dimensional approach to classification (Esterberg and Compton, 2009). One suggestion has been to implement symptom dimensions to capture the heterogeneity within, and overlap

between, disorders (Van Os et al., 1999). Within schizophrenia, three symptom domains have consistently been identified: positive, negative, and disorganised, with some also suggesting that negative symptoms may be split into two domains relating to diminished expressivity and diminished motivation and pleasure (Strauss *et al.*, 2018; Legge, Cardno, *et al.*, 2021). In people with schizophrenia, genetic risk for schizophrenia, as indexed by polygenic risk scoring (PRS), is not associated with severity of positive symptoms (Fanous *et al.*, 2012; Ruderfer *et al.*, 2018; Legge, Cardno, *et al.*, 2021). Disorganised symptoms have been the most strongly associated with schizophrenia PRS (Fanous *et al.*, 2012; Legge, Cardno, *et al.*, 2021), consistent with evidence of familial aggregation of disorganised symptoms but not positive symptoms (Cardno, Jones, *et al.*, 1999). However, some studies have not identified a significant association between disorganised symptoms and schizophrenia PRS (Derks, Allardyce, *et al.*, 2012; Jonas *et al.*, 2019), potentially due to smaller sample sizes. There is weak evidence to support an association between schizophrenia PRS and negative symptoms. One study reported an association with schizophrenia PRS only when negative symptoms were combined with disorganised symptoms, which was found to be explained by the disorganised symptoms (Fanous et al., 2012). A more recent study reported a nominally significant association with diminished expressivity and schizophrenia PRS, which was not significant after covarying for disorganised symptoms (Legge, Cardno, *et al.*, 2021). Ruderfer and colleagues (2018) found negative symptoms to be significantly associated with schizophrenia PRS. However, they did not examine whether disorganised symptoms were confounding this association. Thus, further research is needed to evaluate the role of genetic liability in negative symptoms, which will rely on sufficiently detailed measurement of these symptoms and other highly correlated phenotypes.

Within bipolar disorder, factor analysis studies identify three main factors: elation, irritability, and psychosis (Cassidy *et al.*, 1998; Serretti *et al.*, 1999; Hanwella and de Silva, 2011), with some also reporting a sleep disturbance factor and a depression factor (Rossi *et al.*, 2001; Swann *et al.*, 2013). Polygenic associations with symptom dimensions in bipolar disorder have primarily focused on associations with psychosis. Higher schizophrenia PRS is associated with psychosis in bipolar disorder (Ruderfer *et*

al., 2018; Coombes *et al.*, 2020), and in particular with mood-incongruent psychosis (Allardyce *et al.*, 2018) and psychosis during mania (Markota *et al.*, 2018). Higher bipolar disorder PRS has been associated with psychosis in bipolar disorder (Ruderfer *et al.*, 2018), and one study also reported lower PRS for anhedonia and BMI in individuals with bipolar disorder with psychosis, compared to without psychosis (Coombes *et al.*, 2020).

Research jointly examining schizophrenia and bipolar disorder, as well as a first-episode psychosis sample, has identified five specific symptom factors (positive, negative, disorganised, mania, and depression) encompassed within an overarching dimension of psychopathology that encapsulates all symptom (Reininghaus *et al.*, 2016; Quattrone *et al.*, 2019). Scores for positive, negative, and disorganised domains were higher in individuals with schizophrenia and schizoaffective disorder than in bipolar disorder, whilst mania scores were highest in bipolar disorder and depression scores were highest in schizoaffective disorder. Poor premorbid adjustment was associated with higher scores on the positive, negative, and disorganised domains, and lower scores on the mania domain. These findings suggest that dimensional approaches to symptoms are able to discriminate between diagnoses and are associated with clinically-relevant phenotypes, and thus may be a valid alternative to categorical diagnosis (Reininghaus *et al.*, 2016). However, cross-disorder symptom dimensions have yet to be validated against genetic liability to psychiatric disorders and require replication in larger samples before they can be introduced into clinical practice.

3.1.2 Subtyping and cluster analysis

The vast heterogeneity in schizophrenia has led to extensive efforts to divide and classify schizophrenia into subtypes, a detailed overview of this research is provided in Chapter 1. Classical subtypes of schizophrenia, characterised by the most prominent symptoms and clinical signs, are used to varying degrees throughout editions of the DSM and ICD and have only recently been removed in ICD-11 (World Health Organisation, 2018) and DSM-5 (American Psychiatric Association., 2013). The classical

subtypes have been criticised for lacking specificity, temporal stability, and clinical utility. Individuals frequently present with symptoms spanning multiple subtypes or that do not entirely fulfil the criteria for any one subtype (Carpenter and Stephens, 1979). Longitudinal studies report an increase in the number of individuals diagnosed with the undifferentiated subtype, characterised by features of more than one subtype, over the course of follow-up (McGlashan and Fenton, 1991), suggesting that classical subtypes do not capture long-term course of illness. Despite symptoms being the predominant feature defining each subtype, symptom profiles across the classical subtypes were not found to differ in any substantial way (Carpenter *et al.*, 1976), questioning the validity of this approach. However, some evidence suggests that a distinction between paranoid and non-paranoid subtypes may be valid. The paranoid subtype is associated with better outcomes and reduced genetic transmission compared to the non-paranoid subtype (Fenton and McGlashan, 1991; McGlashan and Fenton, 1991), suggesting that subdividing schizophrenia may provide insights into aetiology and prognosis.

In the DSM and ICD, subtypes of bipolar disorder fall along a spectrum of severity, with cyclothymia as the mildest form and bipolar disorder type I as the most severe. Schizoaffective disorder bipolar-type (SA-BP) is classified as a psychotic disorder, rather than an affective disorder, in both ICD-10 and DSM-5. Research in genetics has found evidence to support the validity of subtypes of bipolar disorder. Bipolar disorder type I has a significantly higher SNP-based heritability than type II (0.35 compared to 0.25, respectively) (Charney *et al.*, 2017). Bipolar disorder types I and II have a genetic correlation of 0.78, indicating highly shared, but independent, genetic architectures. Consistent with this observation is evidence that bipolar disorder type I is more genetically correlated with schizophrenia than with major depressive disorder (MDD) (r_g=0.66 compared to r_g=0.34, respectively), whilst bipolar disorder type II is more genetically correlated with MDD than schizophrenia (r_g=0.66 compared to r_g=0.54, respectively) (Mullins *et al.*, 2021). Therefore, indicating that bipolar disorder type I is more closely related to schizophrenia, whilst bipolar disorder type II is more closely related to MDD. A spectrum of schizophrenia PRS has been observed in bipolar disorder, ordered from highest to lowest as follows: SA-BP, bipolar disorder type I with

psychotic features, bipolar disorder type I without psychosis, and bipolar disorder type II (Charney *et al.*, 2017; Allardyce *et al.*, 2018), suggesting that higher risk for schizophrenia is associated with a more severe bipolar disorder phenotype. Cluster analysis studies of mania in bipolar disorder, which aim to identify data-driven subtypes, have supported a distinction between classical, psychotic, irritable, and depressive/mixed mania (Double, 1991; Swann *et al.*, 2001; Sato *et al.*, 2002; Haro *et al.*, 2006; Azorin *et al.*, 2008). However, research has not compared the validity of these clusters in comparison to the existing clinical subtypes, and thus their clinical utility remains unknown.

The substantial phenotypic and genetic overlap between schizophrenia, schizoaffective disorder, and bipolar disorder has led to investigations in cross-disorder samples to identify clusters of individuals with common phenotypes marked by specific genetic risk. Most recently, Dwyer and colleagues (2020) examined individuals with a psychotic or affective diagnosis using a clustering method that condensed variables into factors and clustered on the basis of these factors. They identified five clusters, including a 'severe psychosis' cluster of individuals characterised by lower educational attainment, low verbal intelligence, and more severe psychotic symptoms (Dwyer *et al.*, 2020). The other four clusters were characterised by high functioning, high suicidal ideation, high depressive symptoms, and high environmental risk. Schizophrenia, bipolar disorder, and depression PRS did not significantly differ between the clusters but educational attainment PRS was significantly lower in the severe psychosis cluster. Pelin and colleagues (2021) implemented a form of Gaussian mixture modelling and also identified a cluster of individuals with high scores on dimensions of negative symptoms, depression, and childhood trauma, and was associated with lower educational attainment PRS and higher schizophrenia and depression PRS. The remaining four clusters identified by Pelin and colleagues (2021) were characterised by healthy controls, symptomatic controls, moderately symptomatic cases with depression, and individuals with high positive symptoms but low negative symptoms. The results of the studies discussed above indicate that severity of symptoms may be associated with a specific genetic aetiology, regardless of diagnosis, and highlight the

need for further research in cross-disorder samples to extend and replicate these findings.

Although Dwyer *et al.* and Pelin *et al.* both identify a cluster marked by lower educational attainment and greater symptom severity, the remaining subtypes they identify varied substantially between the two studies. Replication of specific subtypes is needed to advance research into the aetiology and prognosis of such subtypes, as well as examine their clinical utility. Thus far, cross-disorder studies have been limited in their power to examine polygenic differences between subtypes, and validation in this manner would strengthen arguments for their use in research and clinical practice. Furthermore, there is substantial variation in the phenotypic measures included across studies, impacting the ability to replicate findings. Many studies focus on specific questionnaires and items, and consequently identify highly specific subtypes that may not be clinically useful. A multifaceted approach encompassing demographics, premorbid risk, illness progression, and outcomes may be more useful in identifying subtypes with specific genetic aetiology and clinical relevance.

3.2 Aims

The overarching hypothesis underpinning the work in this chapter is that there are ways of grouping individuals with psychosis by clinically-informative phenotypes to identify subgroups that are relatively more homogeneous with respect to genetic liability, illness progression, and outcomes. In part A of this chapter, the specific aims are:

i) examine factors representing the range of symptoms seen in schizophrenia, schizoaffective disorder, and bipolar disorder.

ii) determine the relationship between genetic risk for psychiatric disorders and the above factors.

In part B, I aim to:

i) identify clusters of individuals across the psychosis spectrum marked by relative phenotypic homogeneity.

ii) determine whether the clusters define more homogenous groups than diagnosis using polygenic risk score analysis to test for differences that are not simply explained by categorical diagnoses.

3.3 Methods

3.3.1 Participants

Participants were ascertained from four datasets: CardiffCOGS, Cardiff Affected-sibs, Cardiff F-series, and Bipolar Disorder Research Network (BDRN). Individuals with a clinical diagnosis of schizophrenia or a schizophrenia-spectrum disorder were recruited to the CardiffCOGS (Lynham *et al.*, 2018) from 2009 - 2017 and Cardiff F-series (Norton *et al.*, 2005) from 1997 - 2001 via secondary psychiatric services. The Cardiff Affected-sibs study (Williams *et al.*, 1999) recruited families from 1994 - 1997 with at least two affected siblings, each with a diagnosis of schizophrenia, schizoaffective disorder depressive-type (SA-D), or SA-BP. Sibling pairs where both individuals had a clinical diagnosis of SA-BP were not recruited. CardiffCOGS, Cardiff Affected-sibs, and Cardiff F-series are described in further detail in Chapter 2.

BDRN is a cohort of individuals with bipolar disorder recruited from the UK via mental health services, lithium clinics, and advertisements through the BDRN website and patient support organisations (Gordon-Smith *et al.*, 2020). Inclusion criteria for the BDRN cohort included i) aged 18 years or older, ii) onset of mood symptoms prior to the age of 65, and iii) self-declared UK white ethnicity. Participants were excluded from BDRN if their symptoms resulted from alcohol or substance use, or were secondary to medical illness or medication.

Individuals with an ICD-10 research diagnosis of schizophrenia (n=1,557), SA-D (n=194), SA-BP (n=317), and bipolar disorder (n=2,975) were included in the present study. I excluded individuals with a diagnosis of bipolar disorder who did not have a lifetime history of mania, as the primary focus of the study is on the psychosis-spectrum. Psychosis is a common feature in bipolar disorder type I, and has a common genetic architecture with schizophrenia, whereas the overlap between bipolar disorder type II and schizophrenia is much less substantial (Mullins *et al.*, 2021). I also excluded individuals with other psychotic diagnoses, for example psychosis not-otherwise-

specified (NOS), due to a lack of understanding of the genetic basis of these disorders in relation to schizophrenia and bipolar disorder, and concerns about the validity of these diagnoses when made on a lifetime basis in a research context.

3.3.2 Phenotype data

Details of the phenotypic variables available across the datasets used in this chapter are shown in Table 3.1, excluding OPCRIT symptom items, which are detailed in the analysis section 3.4.1 in Table 3.3. Participants in all studies completed a comprehensive research interview which included the Schedules for Clinical Assessment in Neuropsychiatry (World Health Organisation, 1992) (SCAN). Trained researchers used information from the interview and, where available, secondary mental health clinical records, to produce lifetime OPCRIT (McGuffin, Farmer and Harvey, 1991) ratings and derive lifetime research diagnoses based on ICD-10 (World Health Organisation., no date) and DSM-IV (American Psychiatric Association, 2000) criteria. All studies showed good inter-rater reliability: CardiffCOGS report a Cohen's kappa of 0.76 for inter-rater reliability for ICD-10 diagnoses, Cardiff Affected-sibs have a kappa of 0.9 against consensus, Cardiff F-series have a kappa >0.8 between raters for diagnosis, BDRN a mean kappa of 0.85 for diagnosis, and 0.81 - 0.99 for other clinical phenotypes (Gordon-Smith *et al.*, 2020).

The protocol for CardiffCOGS was designed to mirror that for BDRN in order to facilitate cross disorder analyses. Individuals responsible for data collection in the Cardiff Affected-sibs and Cardiff F-series samples were involved in training researchers to administer the SCAN and complete OPCRIT ratings for both BDRN and CardiffCOGS. Thus, it was appropriate to merge matched phenotypes across the four samples due to the careful consideration and planning of the development of these studies, including dedicated researcher training and inter-rater reliability sessions.

Variable	Description	N (5043)
Age first contact	Age at which first contact was made with secondary psychiatric services.	3773 (75%)
Educational attainment	Highest educational attainment: 0 = none, 1 = 11+, 2 = CSE, 3 = O-Level or GCSE, 4 = A-level, 5 = Degree	4544 (90%)
Suicidal ideation	Rated most severe lifetime-ever. 0 = absent, 1 = tedium vitae, 2 = suicidal ideation, 3 = suicide attempt unlikely to result in death 4 = suicide attempt likely to result in death 5 = multiple suicide attempts likely to result in death	3851 (76%)
Lowest GAS	Lifetime worst GAS score in a psychotic, manic, or depressive episode. Higher score indicates better functioning.	3235 (64%)
Highest occupation	Lifetime highest occupation. 1 = Unemployed/unable to work, 2= manual/trade work, 3= professional. Groupings are based on ONS Standard Occupational Classification (Professional = classes 1-4, manual/trade = classes 5-10).	3099 (61%)
Current occupation	Occupation at interview. 1 = Unemployed/unable to work, 2= manual/trade work, 3= professional.	3043 (60%)
Sex	Self-reported sex. 1 = male, 2 = female.	5033 (99%)
Married	Ever been married. 0 = no, 1= yes.	4409 (97%)
Ever detained under the mental health act	Ever detained under section 2 or 3 of the Mental Health Act.	3850 (76%)
Alcohol abuse within year of onset	Alcohol abuse where quantity is excessive, where alcohol related complications occur, during the year prior to first psychiatric contact. OPCRIT item 12.	4279 (85%)
Unemployed at onset	Unemployed at onset of illness. Parent working full time in the home scored as employed. Students attending classes on full time course, scored as employed. OPCRIT item 7.	4138 (82%)
Poor premorbid work adjustment	Prior to illness onset, unable to keep any job for more than 6 months, had a history of frequent changes of job or was only able to sustain a job well below that expected by educational level or training. OPCRIT item 9.	4198 (83%)
Poor premorbid social adjustment	Difficulty entering or maintaining normal social relationships, showed persistent social isolation, withdrawal or maintained solitary interests prior to onset of illness. OPCRIT item 10	4056 (80%)
Psychosocial stressor prior to onset	A severely or moderately severely threatening event has occurred prior to onset of disorder that is unlikely to have resulted from the individual's own behaviour (i.e., the event can be seen as independent or uncontrollable). Stressor must have been experienced within 6 months prior to onset. 0=no, 1=yes. OPCRIT item 16.	3586 (71%)
Cannabis abuse	One of the following must have occurred persistently for at least one month: continued use despite knowledge of having a persistent or recurrent social, occupational, psychological or physical problem that is caused or exacerbated by cannabis; or recurrent use in situations	4128 (82%)

	in which it is physically hazardous; or symptoms definitely indicative of dependence. OPCRIT item 82.	
Substance abuse	One of the following must have occurred persistently for at least one month: Continued use despite knowledge of having a persistent or recurrent social, occupational, psychological or physical problem that is caused or exacerbated by substance use; or recurrent use in situations in which it is physically hazardous; or symptoms definitely indicative of dependence. OPCRIT item 83.	4180 (83%)
Deterioration from premorbid functioning	Individual does not regain their premorbid social, occupational, or emotional functioning after an acute episode of illness. OPCRIT item 88.	3983 (79%)
Treatment resistance	Evidence of resistance to either antipsychotic or lithium therapy. For antipsychotic resistance, 0= substantial improvement in psychotic symptoms either subjectively or according to medical records, or if relapse occurs when medication is stopped. Rated 1 if person did not meet these criteria or was treated with Clozapine for treatment resistance. OPCRIT item 89. Lithium resistance defined as no subjective or objective evidence of beneficial response to lithium treatment. 0 = responsive, 1 = resistant.	4114 (82%)
Alcohol abuse	One of the following must have occurred persistently for at least one month: Continued use despite knowledge of having a persistent or recurrent social, occupational, psychological or physical problem that is caused or exacerbated by alcohol; or recurrent use in situations in which it is physically hazardous; or symptoms definitely indicative of dependence. OPCRIT item 81.	3964 (79%)
Age at interview	Age at interview in years	4932 (98%)
Source of rating	1= Hospital case notes (charts). 2= Structured interview with subject [rated only no case-notes have been obtained] 3= Prepared abstract 4= Interview with informant 5= Combined sources including structured interview 6= Combined sources not including structured interview OPCRIT item 1.	4492 (89%)
Duration of illness	Duration of time since illness onset. Calculated as age at interview - age at first contact with secondary services.	3721 (73%)

Table 3.1. Definition of each item included in the latent class analysis. Columns indicate variable, description, and total number and percentage of individuals with data for the item.

3.3.3 Genotyping and quality control

Individuals from CardiffCOGS, Cardiff Affected-sibs, and Cardiff F-series were genotyped using the Illumina HumanOmniExpress 8/12 v1 chips. Individuals from BDRN were genotyped across three platforms: Illumina HumanOmniExpressExome-8, Affymetrix Genome-Wide Human SNP 6.0, Illumina PsychChip_v1.1 (Table 3.2). Control samples were ascertained from the 1958 Birth Cohort (n=4082), a cohort born in England, Scotland, and Wales during one week in 1958 (Power and Elliott, 2006; Wellcome Trust Case Control Consortium *et al.*, 2007). Control participants were not screened for psychiatric disorders, however it has previously been demonstrated that if even as many as 5% of the sample were to have or develop any of the disorders of interest, that this would constitute a loss of power comparable to reducing the sample size by around 10% (Wellcome Trust Case Control Consortium *et al.*, 2007). Given that schizophrenia and bipolar disorder type 1 each have a lifetime prevalence of <1% (Pini *et al.*, 2005; Saha *et al.*, 2005), for case-control analyses, greater power is achieved by using a large unscreened set of controls than using a typically much smaller set of screened controls. Controls were genotyped using the Affymetrix GeneChip 500K Mapping Array Set through the Wellcome Trust Case-Control Consortium (WTCCC) (Wellcome Trust Case Control Consortium *et al.*, 2007), and underwent processing and quality control by the central data management group of the MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University.

	Cardiff COGS	Affected-sibs	F-series	BDRN	Controls	Total
Affymetrix Genome-Wide Human SNP 6.0	0	0	0	706	4082	4788
Illumina HumanOmniExpress 8/12 v1	730	235	366	1727	0	2996
Illumina PsychChip_v1.1	0	0	0	564	0	564

Table 3.2. Number of genotyped participants. Number of people who met study inclusion criteria genotyped on each platform separated by study sample, prior to exclusions based on ancestry and relatedness.

In the first stage, samples underwent quality control (QC) checks prior to imputation. Genotype Harmoniser v1.42 was used to align SNPs against the Haplotype Reference Consortium (HRC) panel v1.1. SNPs with discordant information were updated to match the reference panel, in order to maximise the number of SNPs available for imputation. Sex checks were performed in PLINK; discordant results were manually checked to determine whether the sex was inaccurately recorded or whether sample contamination had occurred. Where this could not be determined, the sample was excluded from further analysis. Finally, the following exclusion filters were applied: SNP call rate <0.95, participant genotyping rate <0.95, SNPs with Hardy-Weinberg Equilibrium (HWE) p-value<$1x10^{-6}$, SNPs with minor allele frequency (MAF) <0.01. Samples genotyped on the same array were imputed together, regardless of original study. Imputation was conducted on the Michigan Imputation Server using the HRC v1.1 reference panel (McCarthy *et al.*, 2016). Following imputation, a second round of SNP QC filters were applied, SNPs were excluded if: genotype probability <0.9 per individual, MAF <0.01, genotyping rate <0.95, HWE p-value<$1x10^{-4}$, and INFO score <0.3.

Following initial quality control and imputation which was performed by the central data management group of the MRC Centre in Cardiff, I used PLINK v1.9 (Chang et al., 2015; Purcell and Chang, 2019) to merge all samples, including only SNPs that were available across all three genotyping arrays that had an INFO score >0.9 (n=3,398,557).

I performed a second round of quality control on the merged data, applying the following exclusions: genotyping rate <0.98, HWE p-value $<1x10^{-6}$, MAF <0.01, and sample missingness >0.05. Six individuals were excluded due to sample missingness. I selected relatively independent SNPs for principal component analysis and IBD. I pruned SNPs using the --indep-pairwise flag in PLINK v1.9 (Purcell, no date) to retain one SNP from each pair with an R^2 >0.2 in a 500kb window. I performed principal components analysis (PCA) using the --pca flag in PLINK v1.9 (Purcell, no date), in order to investigate effects due to the mixture of genotyping platforms and ascertain ancestry. I used the function 'covMCD' from the R package 'robustbase' (Conomos *et al.*, 2016) to identify individuals with European ancestry, using the first six principal components (PCs). This function models the PCs in a multi-dimensional space to create a cluster of points containing the majority of individuals and calculates the distance of each point from the central point. The centre of the cluster represents the predominant ancestry of the sample, which for the samples used in this study is European ancestry. Individuals of non-European ancestry fall furthest away from the central point, and thus distance from the centre can be used as a metric to define ancestry. For polygenic analyses, I retained individuals with a distance within the 95^{th} percentile of the centre point of the multi-dimensional space (281 cases excluded). Figure 3.1 summarises the results of the PCA, including PCs before and after selecting for ancestry. I did not identify effects related to the different genotyping platforms.
I conducted an Identity-By-Descent (IBD) analysis using the --genome flag in PLINK v1.9 (Purcell, no date) to identify related pairs with a kinship score greater than 0.15, meaning that first and second-degree relatives were identified for exclusion. One individual from each related pair was retained for analysis, prioritising cases over controls in a case-control pair, or by highest genotyping rate in case-case and control-control pairs. 79 individuals were excluded due to relatedness.

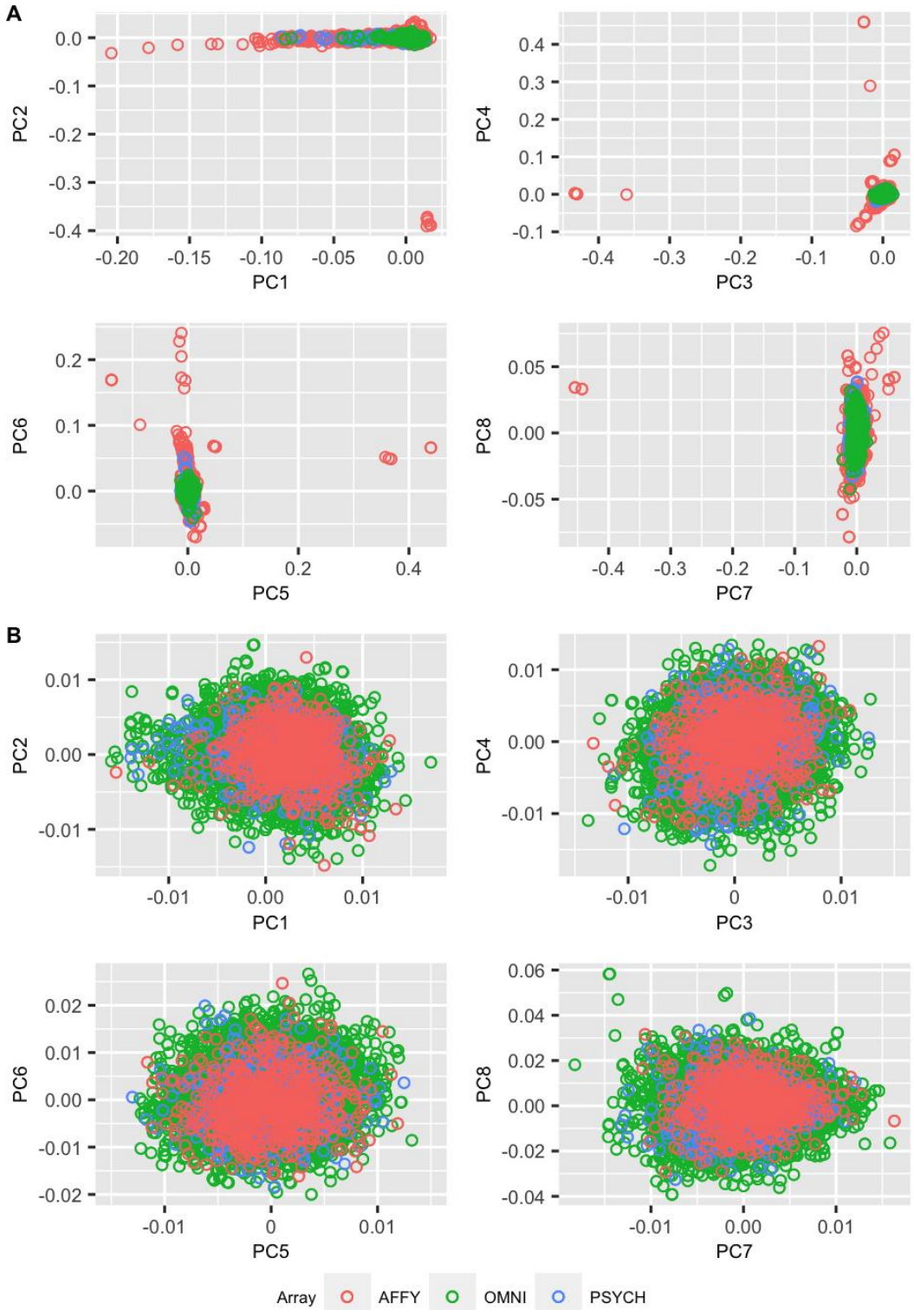

Figure 3.1. A) Principal components (PC) one to eight, colour indicates genotyping platform. B) Principal components (PC) one to eight after selecting for European ancestry, colour indicates genotyping platform.

3.3.4 Polygenic risk scores

I calculated polygenic risk scores (PRS) in PRSice version 2 (Euesden, Lewis and O'Reilly, 2015) using high quality SNPs (INFO >0.9) in relative linkage equilibrium (500kb window r^2 >0.1), and the first five principal components in an additive model. I used a SNP inclusion threshold of p<0.05 for calculating PRS, using the largest available GWAS for schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium. *et al.*, 2020), bipolar disorder (Stahl *et al.*, 2019), depression (Howard *et al.*, 2018), attention deficit hyperactivity disorder (ADHD) (Demontis *et al.*, 2019), autism spectrum disorders (ASD) (Grove *et al.*, 2019), and intelligence (Savage *et al.*, 2018). There is no field standard for p-value threshold for SNP inclusion, therefore I chose the p-value threshold for all PRS of 0.05 for due to it explaining the greatest amount of variance in schizophrenia case-control status (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and to maintain consistency across different PRS. I chose these phenotypes given evidence for shared genetic architecture with schizophrenia and/or bipolar disorder (Lee *et al.*, 2019) and the availability of well-powered GWAS for polygenic scoring.

Summary statistics for schizophrenia and bipolar disorder were derived specifically for this study after excluding the samples used in my analyses by the corresponding Working Group of the Psychiatric Genomics Consortium. I standardised all PRS as Z-scores, using the mean and standard deviation from the control sample to create scores that reflected the population distribution.

3.4 Analysis

3.4.1 Part A: Confirmatory factor analysis

I conducted confirmatory factor analysis (CFA) using OPCRIT data from all samples to create a five-factor model, with factors representing positive symptoms, negative symptoms, disorganised symptoms, mania, and depression. Table 3.3 details the OPCRIT items used in each model. I used confirmatory, as opposed to exploratory factor analysis, as several studies have previously applied factor analysis to symptom data in psychotic and affective disorders, and these factors are widely regarded to represent the spectrum of symptoms in schizophrenia and bipolar disorder (Fanous *et*

al., 2012; Reininghaus *et al.*, 2016; Quattrone *et al.*, 2019; Legge, Cardno, *et al.*, 2021). I assigned items to their specific factor based on previous literature and prior theoretical knowledge (Reininghaus *et al.*, 2016; Quattrone *et al.*, 2019).

CFA model selection was undertaken in two stages - model selection and fitting in R, and implementation of the final model in MPlus (Muthén and Muthen, 2017). First, I used the 'cfa' function in the R package 'lavaan' (Rosseel, 2012) to create a five-factor model. I set the parameters of the model such that factors were allowed to be correlated and were standardised to have a mean of zero and a variance of one (Legge, Cardno, *et al.*, 2021). All other parameters remained in the default setting for lavaan (Rosseel, 2012). OPCRIT items rated positively in over 5% of individuals and missing in less than 20% were included in the initial model (Table 3.3). For subsequent iterations of the model, items were removed on the basis of high loading onto multiple factors (indicating that an item is associated with more than one factor), or high correlation between two items, in which instance the item with the lowest missingness was retained (Table 3.3). This process was repeated until adjustments suggested by the modification indices did not substantially improve the model fit. Model fit was compared using several fit indices: i) Comparative Fit Index (CFI), ii) Tucker Lewis Index (TLI), iii) Root Mean Square Error of Approximation (RMSEA), and iv) Standardised Root Mean square Residual (SRMR). The CFI measures how well the model fits the data compared to a null model. The TLI is similar in that it compares to a baseline model but differs in that the TLI penalises an overly complex model. For both the CFI and TLI, higher values indicate better fit, with a value >0.9 considered good fit (Finch, 2020). RMSEA measures how closely the model fit compares to a perfect fitting model, by comparing the deviation of the chi-square statistic from the degrees of freedom. Lower RMSEA values indicate closer proximity to a perfect model, and values <0.05 indicate a good fit (Finch, 2020). SRMR is similar to RMSEA except that it is a standardised measure that does not consider the degrees of freedom when comparing the observed and expected covariance matrices. Lower SRMR values indicate better fit, with values <0.05 indicating good fit (Cangur and Ercan, 2015). The best fitting model, based on model fit indices, was retained for subsequent analysis.

Factor	OPCRIT item	N (%)	% Positive	Included in Model 1	Included in Model 2	Included in Model 3	Included in Model 4	Included in Model 5
Depression	50. Increased appetite	4323 (85.7%)	26.6	Yes	No	No	No	No
	23. Agitated activity	4248 (84.2%)	36.0	Yes	Yes	Yes	No	No
	37. Dysphoria	4834 (95.9%)	85.2	Yes	Yes	No	No	No
	46. Early wakening	4265 (84.6%)	36.5	Yes	No	No	No	No
	47. Excessive sleep	4256 (84.4%)	40.9	Yes	No	No	No	No
	44. Initial insomnia	4390 (87.1%)	51.1	Yes	No	No	No	No
	25. Loss of energy	4561 (90.4%)	73.6	Yes	Yes	Yes	Yes	Yes
	39. Loss of pleasure	4594 (91.1%)	75.7	Yes	Yes	Yes	Yes	Yes
	45. Middle insomnia	4274 (84.8%)	44.8	Yes	No	No	No	No
	48. Poor appetite	4486 (89.0%)	56.5	Yes	No	No	No	No
	41. Poor concentration	4496 (89.2%)	73.7	Yes	Yes	Yes	Yes	Yes
	42. Self-reproach	4494 (89.1%)	68.0	Yes	No	Yes	Yes	Yes
	24. Slowed activity	4187 (83.0%)	46.2	Yes	Yes	Yes	Yes	Yes
	43. Suicidal ideation	4716 (93.5%)	74.2	Yes	Yes	Yes	Yes	No
	51. Weight gain	4193 (83.1%)	22.8	Yes	No	No	No	No
	49. Weight loss	4249 (84.3%)	38.8	Yes	No	No	No	No
Disorganised	17. Bizarre behaviour	4407 (87.4%)	37.6	Yes	No	No	No	No
	28. Positive formal thought disorder	4695 (93.1%)	14.0	Yes	Yes	Yes	Yes	Yes
	34. Inappropriate affect	4816 (95.5%)	9.3	Yes	Yes	Yes	Yes	Yes
	26. Speech difficult to understand	4696 (93.1%)	25.0	Yes	Yes	Yes	No	No
Mania	21. Distractibility	4594 (91.1%)	59.1	Yes	Yes	Yes	Yes	Yes
	35. Elation	4842 (96.0%)	69.4	Yes	Yes	Yes	Yes	Yes

	19. Excess activity	4805 (95.3%)	66.7	Yes	Yes	Yes	Yes	Yes
	53. Increased sociability	4521 (89.6%)	55.4	Yes	Yes	Yes	Yes	Yes
	36. Irritable	4741 (94.0%)	58.8	Yes	Yes	Yes	Yes	Yes
	30. Pressured speech	4818 (95.5%)	67.6	Yes	Yes	Yes	Yes	Yes
	20. Reckless activity	4499 (89.2%)	55.1	Yes	Yes	Yes	Yes	Yes
	22. Reduced need for sleep	4790 (95.0%)	65.7	Yes	Yes	Yes	Yes	Yes
	56. Self-esteem	4626 (91.7%)	61.5	Yes	Yes	Yes	Yes	Yes
	31. Thoughts racing	4797 (95.1%)	68.0	Yes	Yes	Yes	Yes	Yes
Negative	29. Negative formal thought disorder	4812 (95.4%)	11.5	Yes	Yes	Yes	Yes	Yes
	32. Restricted affect	4811 (95.4%)	18.0	Yes	Yes	Yes	Yes	Yes
Positive	73. 3rd person auditory hallucinations	4542 (90.1%)	18.8	Yes	Yes	Yes	Yes	Yes
	59. Bizarre delusions	4787 (94.9%)	13.5	Yes	Yes	No	No	No
	58. Delusions of influence	4356 (86.4%)	62.2	Yes	Yes	No	No	No
	76. Nonaffective auditory hallucinations	4311 (85.5%)	32.1	Yes	No	No	No	No
	54.Persecutory delusions	4469 (88.6%)	47.8	Yes	Yes	Yes		Yes
	75. Persecutory voices	4528 (89.8%)	31.7	Yes	Yes	Yes	Yes	Yes
	74. Running commentary	4581 (90.8%)	8.1	Yes	No	No	No	No
	67. Thought withdrawal	4849 (96.2%)	5.2	Yes	Yes	No	No	No
	61. Passivity	4721 (93.6%)	8.9	Yes	Yes	Yes	Yes	Yes
	63. Primary delusions	4830 (95.8%)	11.1	Yes	No	No	No	No
	66. Thought insertion	4721 (93.6%)	10.8	Yes	Yes	Yes	Yes	Yes

Table 3.3. OPCRIT items included in each CFA model. Columns indicate OPCRIT item, corresponding factor, total number and percentage with data, percentage positively endorsing the item, and whether the item was included in each model.

Only individuals with complete data can be included in the lavaan model, meaning that factors scores were available for 2,163 individuals. Therefore, in the second stage, I implemented the best fitting model in MPlus using the maximum likelihood estimator and Montecarlo integration to obtain factor scores for the full sample. The first four models were not tested in MPlus as Montecarlo integration on five factors is computationally demanding. I correlated factor scores between the lavaan and MPlus methods to assess whether factor scores generated by MPlus were similar to those generated by lavaan.

I used linear regression to assess the association between scores for each factor and PRS for schizophrenia, bipolar disorder, depression, ADHD, ASD, and intelligence. I included the first five PCs as covariates, as well as any of the first 20 PCs that were significantly associated with the symptom dimension. Primary PRS analyses were corrected for multiple comparisons using false discovery rate (FDR) ($p<0.05$).

3.4.2 Part B: Latent class analysis

Latent class analysis (LCA) is a statistical technique that aims to identify hidden, or latent, clusters of individuals that are more similar to each other than to the rest of the group. LCA is related to factor analysis in that both attempt to identify relatively homogenous groups, but they differ in that factor analysis tries to combine variables with similar scores across individuals, whilst LCA combines individuals with similar scores across variables (Nylund-Gibson and Choi, 2018). The two techniques are complementary and frequently used together to identify phenotypically homogenous clusters. I used the R package 'depmixS4' (Visser and Speekenbrink, 2010) to conduct LCA, using the phenotypes in Table 3.1 as indicator variables. I chose this package for its ability to handle missing data and model both categorical and continuous data, whilst also allowing the inclusion of covariates. Whilst individuals with missing data can be included in the analysis using the 'depmixS4' package, it does require that individuals have complete data for any covariates included in the model. Other more commonly used packages for LCA, such as 'poLCA', are unable to handle mixed data types or to include covariates, and so were unsuitable. I chose LCA over other clustering techniques for these same reasons, as commonly used clustering methods,

such as k-means, typically require complete data of the same type (e.g., continuous variables) and are unable to integrate covariates.

I excluded the symptom factors from the LCA because they are the symptoms used to derive a diagnosis, making it likely that a model would simply separate on the basis of diagnosis rather than identifying whether other latent classes existed that were defined by demographic, premorbid, and other clinical phenotypes. For this reason, I also excluded total number of episodes of depression and mania, and family history of schizophrenia or other psychiatric illness as these are *a priori* diagnosis-linked variables. I tested four latent class models based on different covariates to explore their impact on class assignment and model fit: model A included all indicator variables in Table 3.1 with no covariates; model B included all indicator variables with age at interview as a covariate; model C included all indicator variables, with age at interview and source of rating as covariates; model D included all indicator variables, with age at interview, source of rating, and duration of illness as covariates. Definitions of all indicator variables and covariates are in Table 3.1. I tested a two-class and a three-class solution for each model; I also attempted to test a four-class solution but this could not be identified for any model, so I did not test a greater number of class solutions. I used the 'mix' function to define each model, and the 'multistart' function to fit the model (Visser and Speekenbrink, 2021), using 50 starts and a maximum of 100 iterations of the expectation-maximisation (EM) algorithm per start to minimise the risk of converging on a local, rather than global, solution (Nylund-Gibson and Choi, 2018). Regardless of which covariates were used, all models were tested only on participants with complete data for all three covariates to ensure tests of each model were based on the same number of individuals, and thus ensure that the Bayesian Information Criterion (BIC) values, which are sensitive to sample size, were comparable across models. Model fit was compared using the BIC, which has been shown to be the most reliable indicator of model fit, and on theoretical interpretability (Weller, Bowen and Faubert, 2020).

I used logistic regressions to analyse the relationship between class membership and PRS for schizophrenia, bipolar disorder, depression, ADHD, ASD, and intelligence. In order to assess whether associations between class membership and PRS could be explained by diagnosis, I repeated the PRS analyses including diagnosis as a covariate

in the regression models. I used logistic regression to measure the association of PRS with each class compared to controls. For all PRS analyses, I included the first five PCs as covariates, as well as any of the first 20 PCs that were significantly associated with the outcome ($p<0.05$). For class vs class comparisons, I additionally included genotyping array as a covariate.

Primary PRS analyses were corrected for multiple comparisons using false discovery rate (FDR) ($p<0.05$).

3.4.3 Sensitivity analyses

To ensure that PRS associations with symptom dimensions and latent classes were not due to batch effects resulting from the different genotyping arrays, I repeated the symptom factors and class v class PRS analyses using only individuals who had been genotyped using the Illumina Omni-Express (n=2,957), as most cases were genotyped on this array.

To investigate differences between individuals with the same diagnosis classified into different latent classes, I examined the distribution of phenotypic variables between classes and measured PRS associations with class membership in a subset of data restricted to individuals with schizophrenia, and separately in a dataset restricted to individuals with bipolar disorder.

3.5 Results

A total of 5,043 individuals were included in the study, characteristics of each sample are presented in Table 3.4 and the number of individuals with genotype data by study and diagnosis are presented in Table 3.5.

	CardiffCOGS (1001)	Affected-sib (381)	F-series (636)	BDRN (3025)	All studies (5043)
Male sex (%)	627 (63%)	254 (67%)	428 (67%)	1007 (33%)	2316 (46%)
Mean age	43.3	40.9	41.7	47.5	45.5
Diagnosis schizophrenia (%)	713 (71%)	330 (87%)	514 (81%)	0 (0%)	1557 (31%)
Diagnosis SA-D (%)	151 (15%)	24 (6%)	19 (3%)	0 (0%)	194 (4%)
Diagnosis SA-BP (%)	95 (9%)	23 (6%)	36 (6%)	163 (5%)	317 (6%)
Diagnosis bipolar disorder (%)	42 (4%)	4 (1%)	67 (11%)	2862 (95%)	2975 (59%)
Genotype data available	729 (73%)	235 (62%)	364 (57%)	2995 (99%)	4323 (86%)

Table 3.4. Phenotypic characteristics of each individual cohort, and the sample as a whole. Percentages refer to proportion within each sample.

	CardiffCOGS	Affected-sib	F-series	BDRN	All studies
Diagnosis schizophrenia	538	204	345	0	**1087**
Diagnosis SA-D	105	15	13	0	**133**
Diagnosis SA-BP	67	15	6	163	**251**
Diagnosis bipolar disorder	19	1	0	2832	**2852**
Total	**729 (73%)**	**235 (62%)**	**364 (57%)**	**2995 (99%)**	**4323**

Table 3.5. Numbers of individuals with genotype data available, broken down by diagnosis and study. Numbers provided are prior to exclusions for ancestry and relatedness.

A flowchart showing the number of participants included in each stage of analysis is displayed in Figure 3.2.

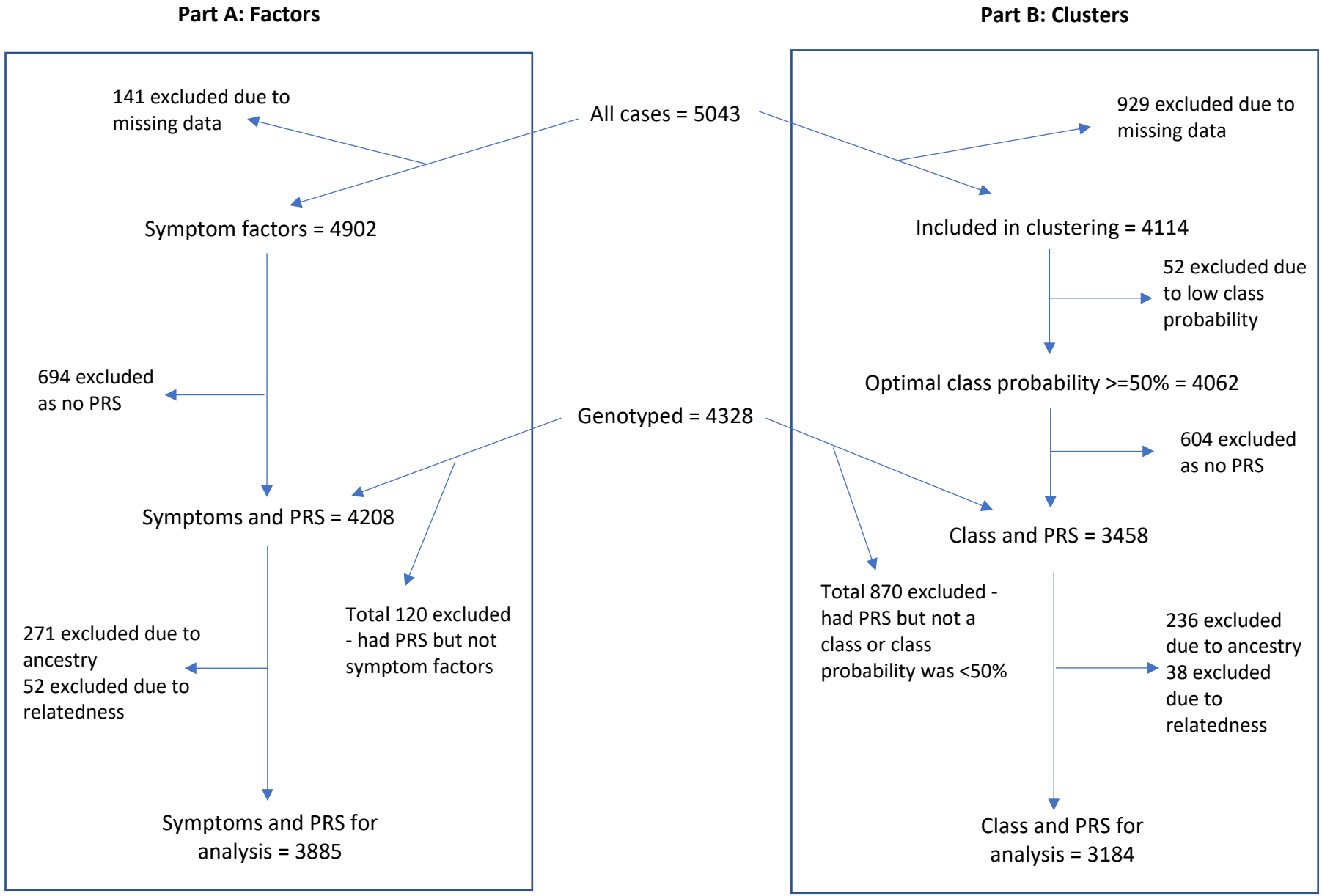

Figure 3.2. Flowchart indicating number of individuals included at each stage of the primary analysis, and reasons for exclusion.

3.5.1 Part A: Symptom factors

Table 3.6 displays the fit indices for each CFA model. I selected model five as the best fitting model as it consistently performed better across the fit indices, all of which indicated excellent fit, and made clinical and theoretical sense. Items included in each model are shown in Table 3.3.

Model	CFI	TLI	RMSEA (95% CI)	SRMR
One	0.996	0.996	0.77 (0.75 - 0.78)	0.113
Two	0.999	0.999	0.032 (0.03 - 0.04)	0.057
Three	1	1	0.024 (0.02 - 0.03)	0.044
Four	1	1	0.017 (0.01 - 0.02)	0.033
Five	1	1	0.015 (0.01 - 0.02)	0.032

Table 3.6. Fit indices for all CFA models tested using lavaan. Columns refer to Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA), Standardised Root Mean Square Residual (SRMR). For CFI and TLI, values closer to one indicate better fit, with a value >0.9 considered indicative of good fit. For RMSEA and SRMR, lower values indicate better fit, with values <0.05 considered a good fit.

Model five included 22 OPCRIT items (Table 3.3), each of which loaded strongly onto its specified factor when implemented in MPlus, shown in Figure 3.3.

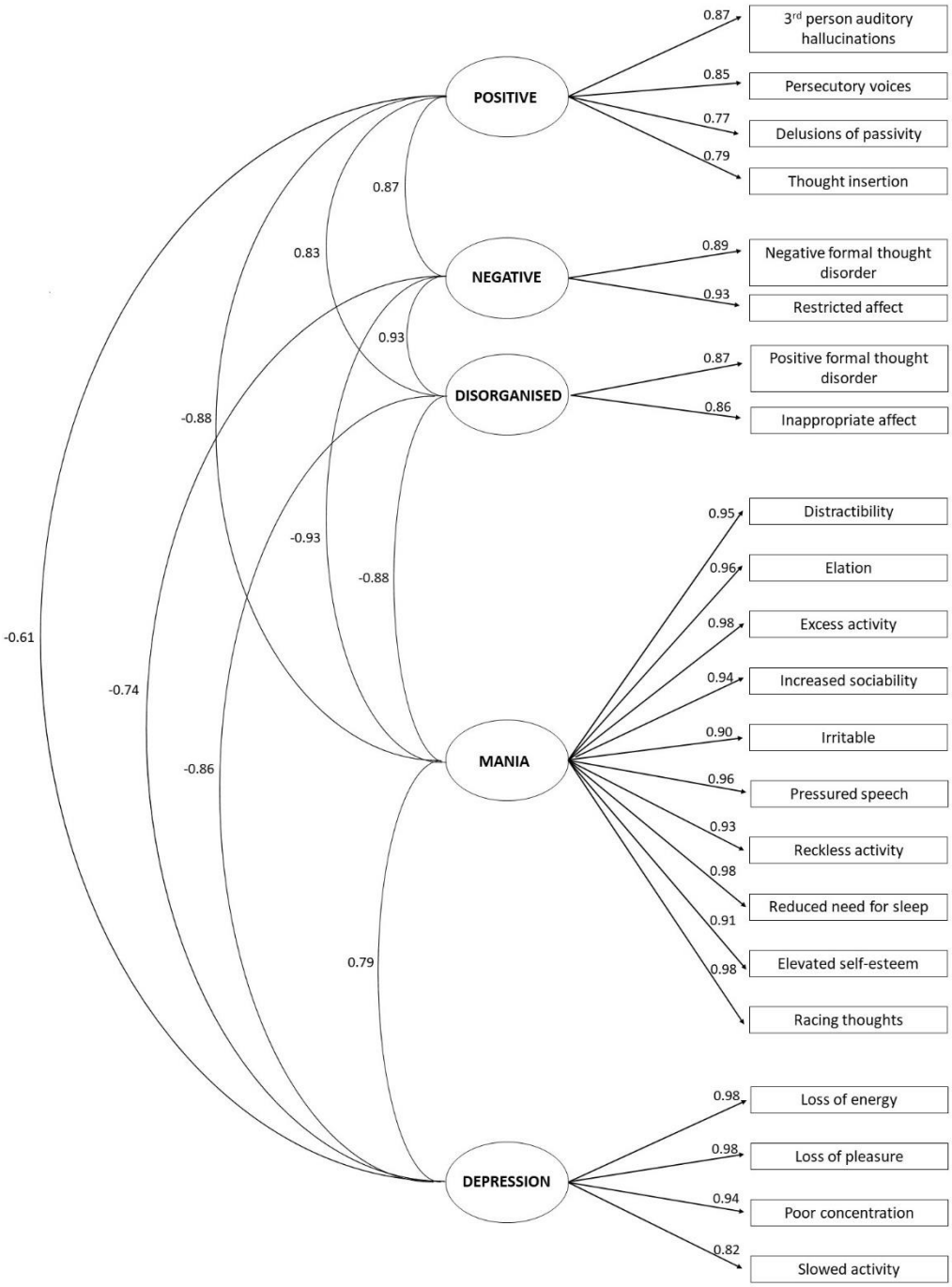

Figure 3.3. Structure of confirmatory factor analysis for model five, the best fitting model, in MPlus. Values indicate the loading of each item onto the corresponding factor and correlations between factors.

For individuals with complete data, I correlated factor scores between the lavaan model and the MPlus model. Each factor correlated strongly with its corresponding factor (Table 3.7), indicating that the MPlus model did not substantially deviate from the lavaan model.

Factor	R
Positive	0.97
Negative	0.97
Disorganised	0.98
Mania	0.99
Depression	0.99

Table 3.7. Correlation between corresponding factors generated using the lavaan model and the MPlus model.

3.5.2 PRS associations with symptom factors

The associations between the symptom factor scores and PRS are detailed in Table 3.8 and Figure 3.4.

Higher scores for the positive, negative, and disorganised factors were associated with increased schizophrenia PRS, lower bipolar disorder PRS, and lower intelligence PRS. The associations with positive symptom factor scores attenuated when covarying for diagnosis. Negative symptom factor scores remained significantly associated with lower intelligence PRS and was additionally nominally associated with lower ASD PRS ($p=0.04$). Disorganised symptom factor scores remained significantly associated with higher schizophrenia PRS and was also associated with lower depression PRS.

The mania and depression factor scores were both associated with higher bipolar disorder PRS and lower schizophrenia PRS as factor score increased. Higher factor scores for mania factor were also associated with higher intelligence PRS and higher factor scores for depression were associated with higher depression PRS. After covarying for diagnosis, schizophrenia PRS was not significantly associated with either mania or depression factor scores, and mania was not significantly associated with intelligence PRS. Higher mania scores remained significantly associated with higher bipolar disorder PRS. Higher depression PRS remained significantly associated with

higher depression factor scores and was newly associated with higher mania scores (Table 3.8 and Figure 3.4).

In order to assess the impact of different genotyping arrays, I repeated the primary PRS analysis in only those who were genotyped using the Illumina Omni-Express array. All effect sizes were consistent with the primary estimate, suggesting that the analysis was not confounded by type of array (Table 3.8). In most instances the effect sizes observed for the Omni-Express samples were larger than those observed across all chips, suggesting that array type may have biased the effect sizes downwards.

Symptom dimension	PRS	Primary analysis		Covary diagnosis		Omni-Express samples	
		Beta	FDR P-value	Beta	P-value	Beta	P-value
Positive	Schizophrenia	0.09 (0.06, 0.13)	$1.8x10^{-9}$	0.00 (-0.01, 0.02)	0.64	0.13 (0.09, 0.16)	$5.4x10^{-11}$
	Bipolar disorder	-0.07 (-0.10, -0.04)	$2.9x10^{-6}$	-0.02 (-0.03, 0.00)	0.05	-0.10 (-0.14, -0.06)	$1.2x10^{-7}$
	Depression	0.00 (-0.02, 0.03)	0.81	-0.01 (-0.02, 0.01)	0.29	0.01 (-0.03, 0.05)	0.65
	ADHD	0.03 (0.00, 0.06)	0.12	0.02 (0.00, 0.03)	0.05	0.04 (0.00, 0.08)	0.03
	ASD	-0.01 (-0.03, 0.04)	0.69	0.00 (-0.02, 0.02)	0.99	0.00 (-0.04, 0.04)	0.97
	Intelligence	-0.05 (-0.08, -0.02)	$1.3x10^{-3}$	-0.02 (-0.03, 0.00)	0.06	-0.06 (-0.10, -0.02)	$2.0x10^{-3}$
Negative	Schizophrenia	0.10 (0.07, 0.14)	$1.5x10^{-11}$	0.01 (0.00, 0.03)	0.11	0.14 (0.10, 0.17)	$2.7x10^{-13}$
	Bipolar disorder	-0.06 (-0.09, -0.03)	$2.2x10^{-5}$	-0.02 (-0.02, 0.01)	0.25	-0.09 (-0.12, -0.05)	$2.7x10^{-6}$
	Depression	0.00 (-0.03, 0.02)	0.81	-0.01 (-0.03, 0.00)	0.06	0.00 (-0.03, 0.04)	0.91
	ADHD	0.01 (-0.02, 0.05)	0.69	0.00 (-0.02, 0.01)	0.54	0.02 (-0.02, 0.05)	0.42
	ASD	-0.02 (-0.05, 0.02)	0.16	-0.02 (-0.03, 0.00)	0.04	-0.02 (-0.06, 0.01)	0.17
	Intelligence	-0.06 (-0.08, -0.03)	$1.1x10^{-4}$	-0.02 (-0.04, -0.01)	$3.4x10^{-3}$	-0.07 (-0.11, -0.03)	$1.6x10^{-4}$
Disorganised	Schizophrenia	0.11 (0.08, 0.15)	$1.1x10^{-13}$	0.03 (0.01, 0.04)	$2.7x10^{-3}$	0.15 (0.11, 0.18)	$1.6x10^{-15}$
	Bipolar disorder	-0.05 (-0.08, -0.02)	$5.2x10^{-4}$	0.00 (-0.02, 0.02)	0.92	-0.07 (-0.10, -0.03)	$1.8x10^{-4}$
	Depression	-0.02 (-0.05, 0.01)	0.24	-0.03 (-0.04, -0.01)	$4.7x10^{-4}$	-0.02 (-0.05, 0.02)	0.33
	ADHD	0.01 (-0.02, 0.05)	0.69	0.00 (-0.02, 0.01)	0.69	0.02 (-0.02, 0.06)	0.32
	ASD	-0.01 (-0.04, 0.02)	0.39	-0.01 (-0.02, 0.01)	0.36	-0.01 (-0.05, 0.02)	0.41
	Intelligence	-0.04 (-0.07, -0.02)	$2.9x10^{-3}$	-0.01 (-0.03, 0.01)	0.21	-0.06 (-0.10, -0.02)	$1.3x10^{-3}$
Mania	Schizophrenia	-0.09 (-0.12, -0.08)	$8.4x10^{-10}$	0.00 (-0.02, 0.01)	0.70	-0.13 (-0.17, -0.09)	$1.9x10^{-11}$
	Bipolar disorder	0.07 (0.05, 0.10)	$9.0x10^{-7}$	0.02 (0.00, 0.03)	0.02	0.10 (0.07, 0.14)	$3.3x10^{-8}$
	Depression	0.01 (-0.02, 0.03)	0.67	0.02 (0.00, 0.04)	0.01	0.00 (-0.04, 0.04)	0.94
	ADHD	-0.01 (-0.03, 0.01)	0.73	0.01 (-0.01, 0.02)	0.37	-0.01 (-0.05, 0.02)	0.49
	ASD	0.02 (-0.01, 0.03)	0.24	0.01 (0.00, 0.03)	0.11	0.02 (-0.02, 0.06)	0.29
	Intelligence	0.05 (0.02, 0.09)	$9.0x10^{-4}$	0.01 (0.00, 0.03)	0.06	0.06 (0.02, 0.10)	$1.2x10^{-3}$
Depression	Schizophrenia	-0.09 (-0.12, -0.07)	$4.8x10^{-8}$	-0.02 (-0.04, 0.01)	0.20	-0.12 (-0.15, -0.08)	$1.2x10^{-9}$
	Bipolar disorder	0.05 (0.02, 0.07)	$1.8x10^{-3}$	0.00 (-0.02, 0.03)	0.73	0.06 (0.03, 0.10)	$8.6x10^{-4}$
	Depression	0.04 (0.01, 0.06)	0.01	0.05 (0.02, 0.07)	$4.3x10^{-5}$	0.04 (0.00, 0.08)	0.03
	ADHD	0.01 (-0.02, 0.03)	0.69	0.02 (0.00, 0.04)	0.09	0.00 (-0.04, 0.04)	0.95
	ASD	0.01 (-0.02, 0.04)	0.69	0.00 (-0.02, 0.02)	0.81	0.01 (-0.03, 0.04)	0.67
	Intelligence	0.02 (-0.01, 0.06)	0.30	-0.01 (-0.03, 0.01)	0.30	0.04 (0.00, 0.08)	0.04

Table 3.8. Association between each PRS and symptom factor scores derived through CFA for the primary analysis, and for the analysis including diagnosis as a covariate, and when restricted to samples genotyped using the Omni-Express array.

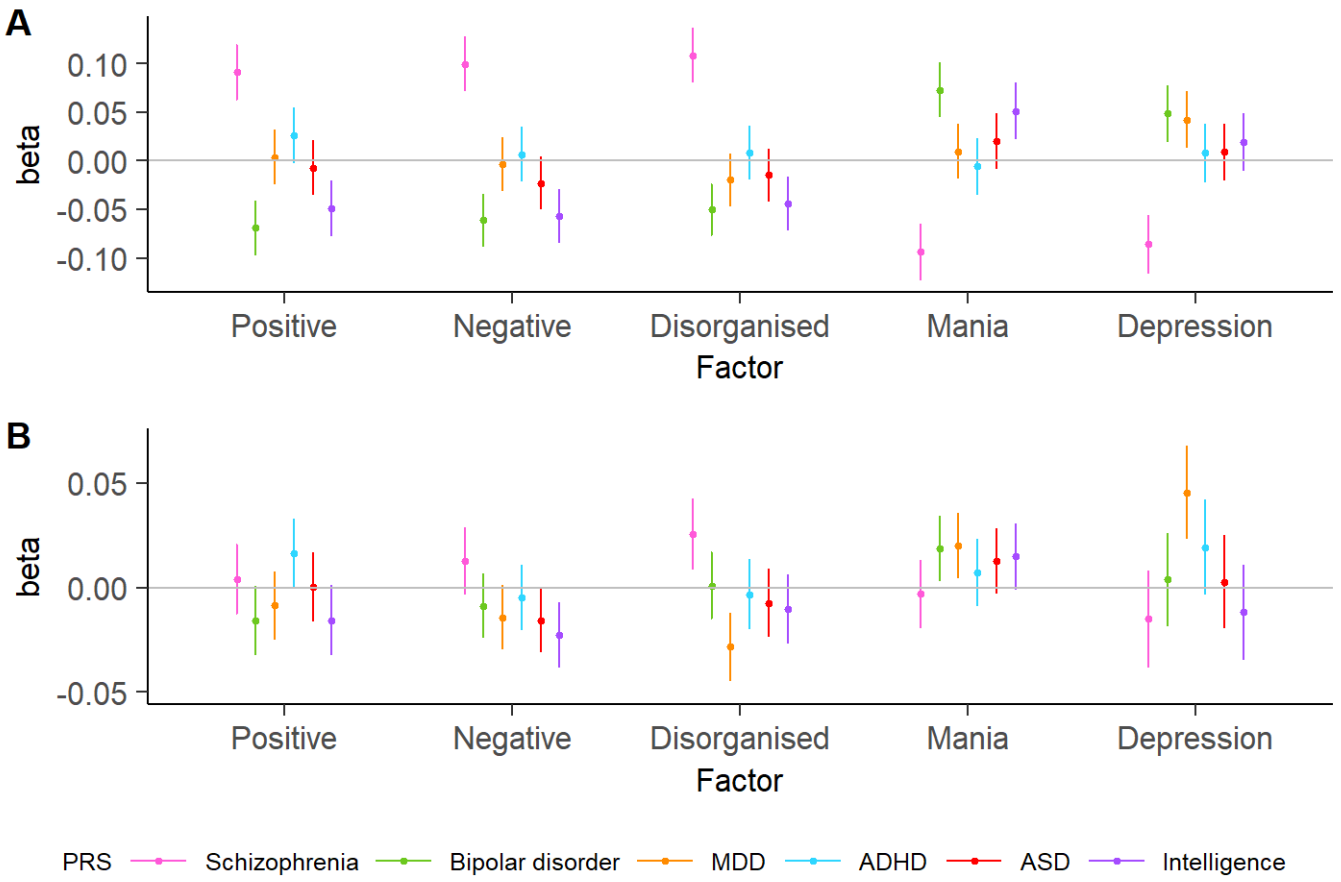

Figure 3.4. PRS associations with symptom factors in A) the primary analysis, and B) when covarying for diagnosis. Points indicate odds ratio, with error bars showing 95% confidence intervals. Colour indicates PRS with pink for schizophrenia, green for bipolar disorder, orange for depression, blue for ADHD, red for ASD, and purple for intelligence.

The results of the factor analysis in Part A suggest that schizophrenia and bipolar disorder PRS are more strongly associated with the symptom factors seen in psychotic and bipolar disorders than are PRS for other disorders. Intelligence PRS was also significantly associated with all symptom dimensions except depression, indicating an effect of intelligence on symptom variation. The heterogeneity explained by schizophrenia, bipolar disorder, and intelligence PRS is largely being captured by diagnosis. However, there were significant effects of PRS on symptoms, independent of diagnosis, that may have implications for our understanding of these phenotypes.

3.5.3 Part B: Latent Class Analysis

In part B, I aimed to use clinical and demographic information to identify clusters of individuals, and test whether these clusters represent genetically more homogenous groups than are obtained by diagnostic label.

Of the eight models tested, a three-class solution of model D gave the lowest BIC value, indicating the best fit. For all models, a three-class solution performed better than a two-class solution, and amongst the two-class solutions, model D performed best based on the BIC value (Table 3.9). Model D included age at interview, source of rating, and duration of illness as covariates.

Model	Number of classes	BIC
A	2	127820
	3	54146
B	2	127626
	3	53600
C	2	127530
	3	54145
D	2	127495
	3	53430

Table 3.9. Bayesian Information Criteria (BIC) values for each latent class analysis model tested. Model A includes no covariates, model B includes age at interview as a covariate, model C includes age at interview and source of rating as covariates, model D includes age at interview, source of rating, and duration of illness as covariates. Lower BIC indicates a better fitting model.

Individuals assessed under the model as having less than a 50% probability of being in their optimal class were excluded from further analysis (n=52).

The comparisons between phenotypes and classes are displayed in Figures 3.5 and 3.6. Consistent with previous literature (Kendler, Karkowski and Walsh, 1998), I characterised the classes descriptively rather than conducting formal statistical comparisons between classes. Class one (n=1,161) had the highest endorsements of items indexing poor premorbid functioning, including lower educational attainment and poor premorbid social functioning, compared to the other classes. Class one was further characterised by worse outcomes than the other two classes, with the lowest rates of current employment, highest rates of treatment resistance, and almost all individuals experiencing deterioration from their premorbid level of functioning. In terms of demographics, class one contained more males than the other two classes and had the lowest rates of marriage.

Class two (n=1,518) had high rates of involuntary hospitalisation, with everyone in this class scoring 20 on the GAS, which is the maximum score that can be given when an individual has been detained under the Mental Health Act. Compared to class one, class two had fewer individuals reporting poor premorbid functioning, but greater rates than class three on some items, including unemployment in the year prior to onset. In some aspects class two was similar to class three, with the groups not

substantially differing in age at onset, educational attainment, drug abuse, or treatment response. However, class two contained more males than class three, had a lower proportion experiencing a psychosocial stressor prior to onset, and had higher rates of deterioration from premorbid functioning.

Class three (n=1,383) was characterised by better premorbid functioning and better outcomes than the other two classes, but with a higher proportion of individuals reporting a psychosocial stressor in the six months prior to illness onset. Class three had the highest proportion of females, highest rates of marriage, and the lowest rates of unemployment and of deterioration from premorbid functioning.

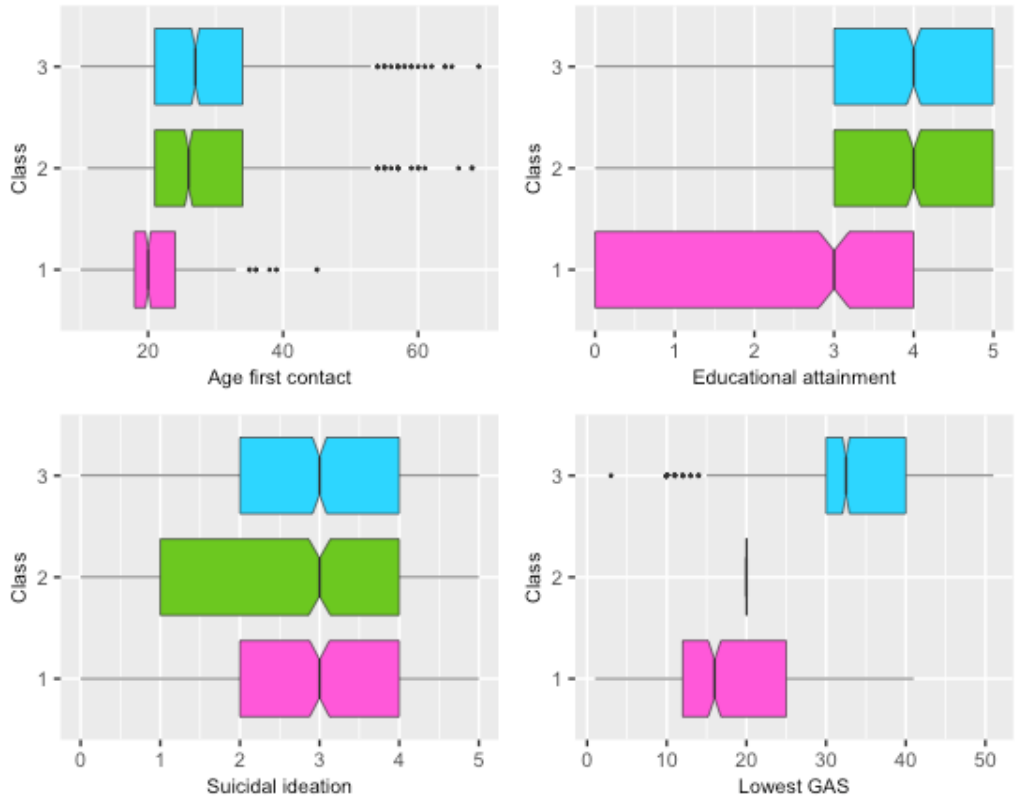

Figure 3.5. Boxplots indicating the median, interquartile range, minimum and maximum values, and outliers for continuous items included in the latent class analysis, separated by class. Box colour indicates the class; pink indicates class 1, green indicates class 2, and blue indicates class 3.

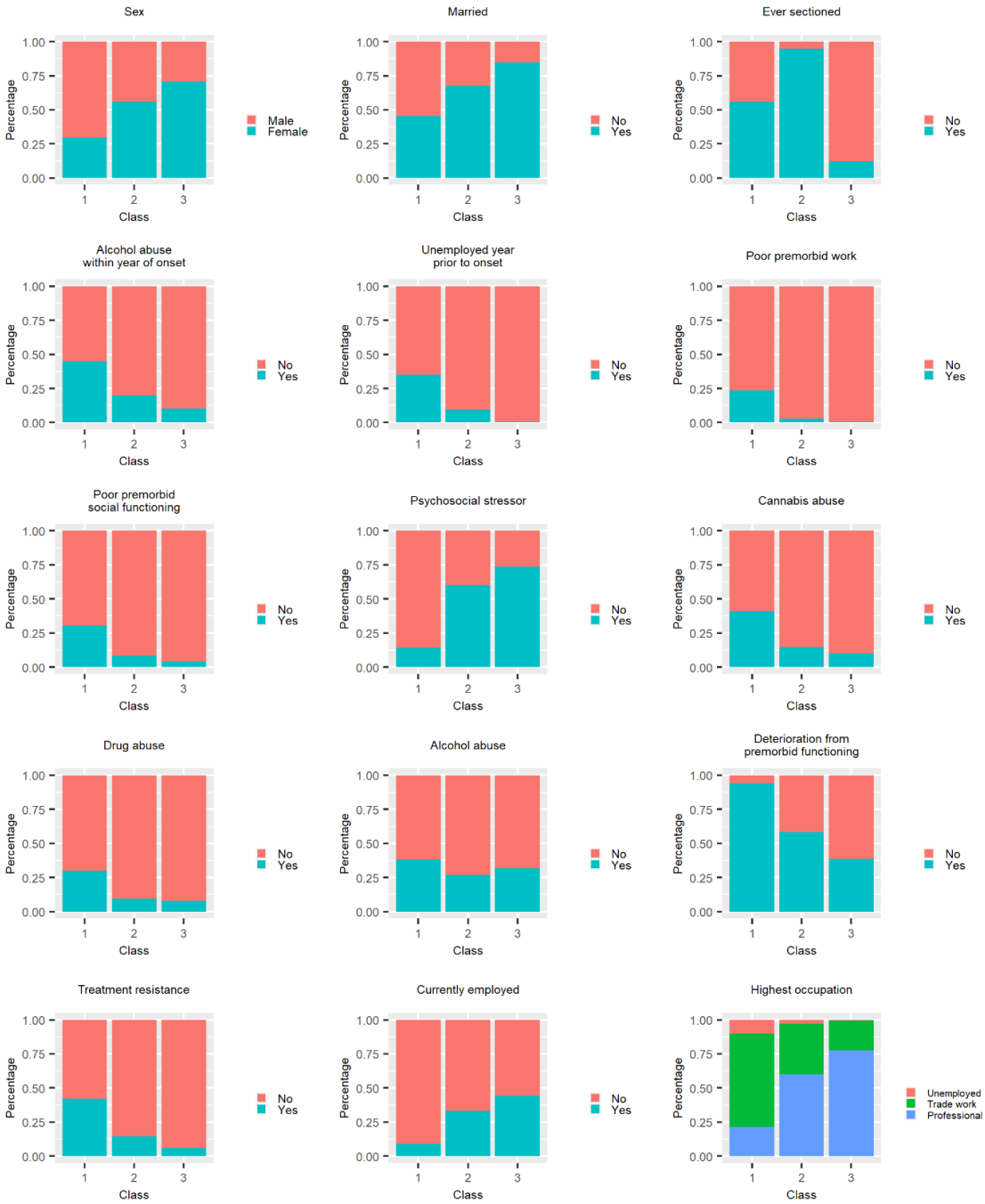

Figure 3.6. Distribution of responses by class for categorical items included in the latent class analysis.

I also examined the distribution of phenotypes not included in the model but that typically inform diagnosis, including the symptom dimensions defined in part A of this chapter (Figure 3.7). Class one had higher rates of positive, negative, and disorganised, symptoms, with lower rates of depression and mania. Conversely, class three had lower rates of positive, negative, and disorganised symptoms, with higher rates of depression and mania, whilst class two had intermediate levels of each symptom dimension. Class one had the highest rates of family history of schizophrenia, whilst class three had the highest rates of family history of other psychiatric disorders.

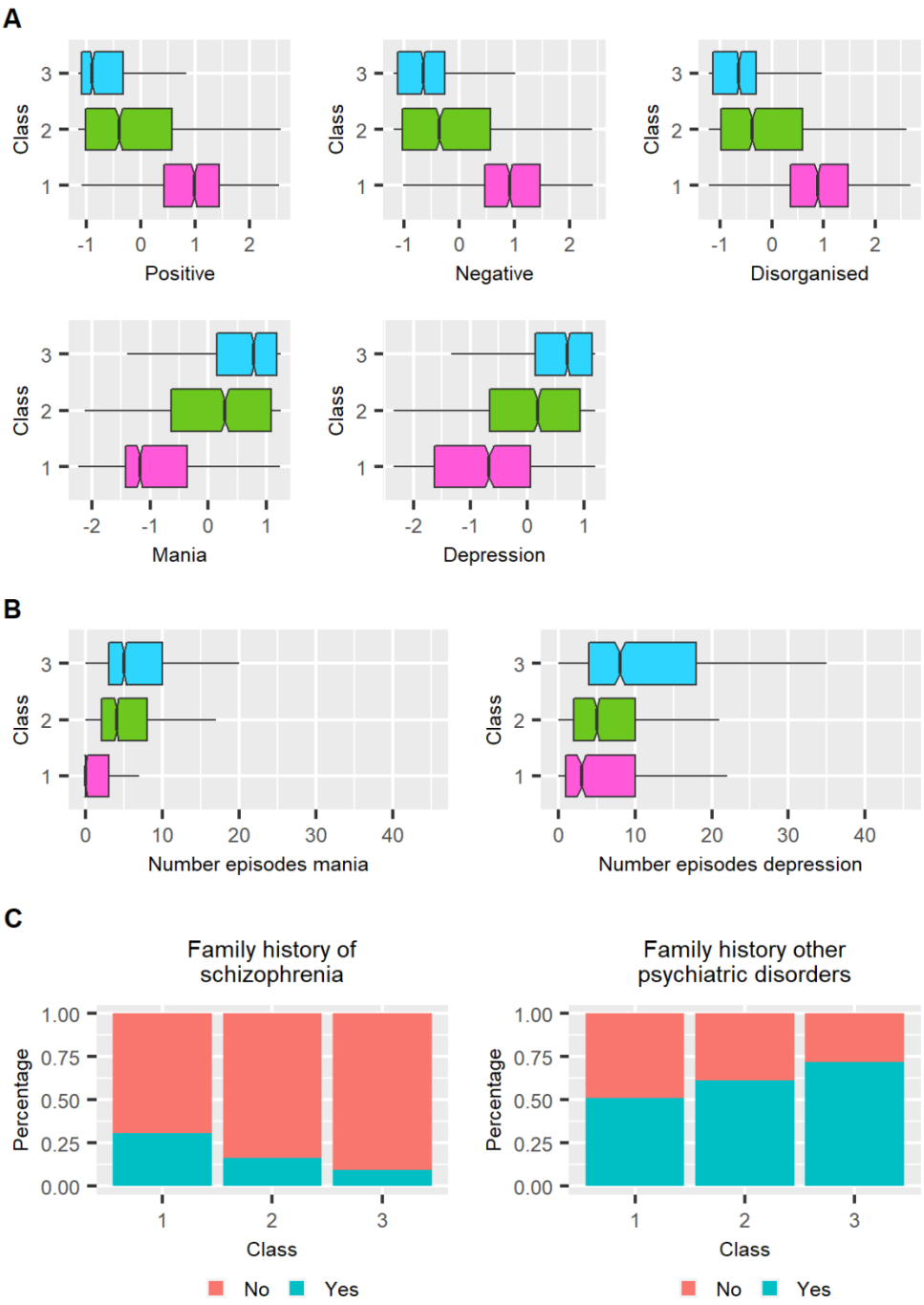

Figure 3.7. Boxplots indicating the median, interquartile range, minimum and maximum values, and outliers for A) symptom dimensions (Z-score) and B) number of episodes of mania and depression. C) Distribution of responses to family history of schizophrenia and of other psychiatric disorders.

Each class contained a mixture of individuals with all diagnoses, although the majority of individuals with schizophrenia (64%) and SA-D (56%) were in class one and just over half of people with bipolar disorder were in class three (Table 3.10). Individuals with SA-BP were relatively evenly split across the classes.

	Class one	**Class two**	**Class three**
Schizophrenia [1302] (%)	830 (64%)	389 (30%)	83 (6%)
SA-D [178] (%)	100 (56%)	60 (34%)	18 (10%)
SA-BP [257] (%)	92 (36%)	94 (37%)	71 (28%)
Bipolar disorder [2325] (%)	139 (6%)	975 (42%)	1211 (52%)

Table 3.10. Number of individuals with each diagnosis in each class. Percentage of the total number of individuals with that diagnosis in the class.

3.5.4 PRS associations with class membership

PRS associations with class membership are displayed in Table 3.11 and Figure 3.8. Compared to class two, class one was significantly associated with lower bipolar disorder PRS, and higher ADHD PRS. Compared to class three, class one was significantly associated with higher schizophrenia PRS and lower intelligence PRS. Compared to class three, class two was significantly associated with higher schizophrenia PRS and lower intelligence PRS.

After covarying for diagnosis, class one remained significantly associated with lower intelligence PRS compared to class three. Class two remained significantly associated with higher schizophrenia PRS and lower intelligence PRS than class three. Class two was also associated with higher bipolar disorder PRS, compared to class three (Table 3.11 and Figure 3.8).

I repeated the primary PRS analysis in only those who were genotyped using the Illumina Omni-Express array, to assess whether there were systematic differences resulting from the different genotyping platforms. All effect sizes were consistent with primary estimate, indicating that the analysis was not the result of array effects (Table 3.11). Table 3.12 shows the number of individuals in each class by genotyping array.

Class	PRS	Primary analysis		Covary diagnosis		Omni-Express samples	
		OR	FDR P-value	OR	P-value	OR	P-value
1 v 2	Schizophrenia	1.10 (1.00 - 1.22)	0.14	0.98 (0.87 - 1.10)	0.74	1.13 (1.02 - 1.25)	0.02
	Bipolar disorder	0.88 (0.80 - 0.97)	0.03	0.98 (0.87 - 1.09)	0.70	0.89 (0.80 - 0.98)	0.02
	Depression	1.03 (0.94 - 1.14)	0.60	0.99 (0.89 - 1.11)	0.90	1.04 (0.94 - 1.15)	0.44
	ADHD	1.14 (1.04 - 1.26)	0.03	1.10 (0.98 - 1.24)	0.10	1.15 (1.03 - 1.27)	0.01
	ASD	1.00 (0.91 - 1.10)	0.96	1.03 (0.92 - 1.15)	0.58	1.01 (0.91 - 1.12)	0.83
	Intelligence	0.94 (0.85 - 1.04)	0.42	0.99 (0.88 - 1.11)	0.84	0.93 (0.83 - 1.03)	0.15
1 v 3	Schizophrenia	1.36 (1.23 - 1.50)	$8.2x10^{-8}$	1.10 (0.95 - 1.28)	0.19	1.41 (1.27 - 1.57)	$2.5x10^{-10}$
	Bipolar disorder	0.89 (0.81 - 0.99)	0.07	0.99 (0.86 - 1.15)	0.90	0.90 (0.81 - 1.00)	0.05
	Depression	1.03 (0.94 - 1.14)	0.60	1.08 (0.93 - 1.24)	0.31	1.04 (0.94 - 1.15)	0.50
	ADHD	1.10 (0.99 - 1.21)	0.14	1.14 (0.99 - 1.32)	0.07	1.08 (0.97 - 1.20)	0.16
	ASD	0.95 (0.86 - 1.05)	0.44	0.93 (0.81 - 1.07)	0.31	0.98 (0.89 - 1.08)	0.70
	Intelligence	0.82 (0.74 - 0.90)	$4.6x10^{-4}$	0.84 (0.73 - 0.97)	0.02	0.81 (0.73 - 0.90)	$6.8x10^{-5}$
2 v 3	Schizophrenia	1.21 (1.11 - 1.31)	$7.5x10^{-5}$	1.16 (1.07 - 1.29)	$6.2x10^{-4}$	1.28 (1.16 - 1.41)	$5.1x10^{-7}$
	Bipolar disorder	1.05 (0.98 - 1.14)	0.33	1.10 (1.01 - 1.19)	0.02	1.04 (0.95 - 1.14)	0.38
	Depression	1.01 (0.93 - 1.09)	0.83	1.01 (0.93 - 1.09)	0.89	0.99 (0.90 - 1.08)	0.77
	ADHD	0.97 (0.89 - 1.05)	0.60	0.97 (0.90 - 1.06)	0.52	0.97 (0.88 - 1.06)	0.46
	ASD	0.98 (0.90 - 1.06)	0.63	0.99 (0.92 - 1.08)	0.87	1.00 (0.91 - 1.09)	0.92
	Intelligence	0.90 (0.83 - 0.98)	0.03	0.91 (0.84 - 0.99)	0.02	0.89 (0.81 - 0.98)	0.01

Table 3.11. Association of each PRS with class membership for class one compared to class two, class one compared to class three, and class two compared to class three, presented with and without covarying for diagnosis. Odds ratio refers to the first group listed in the 'class' column with the second group as the reference category (i.e., class 2 is the reference category in class 1v2).

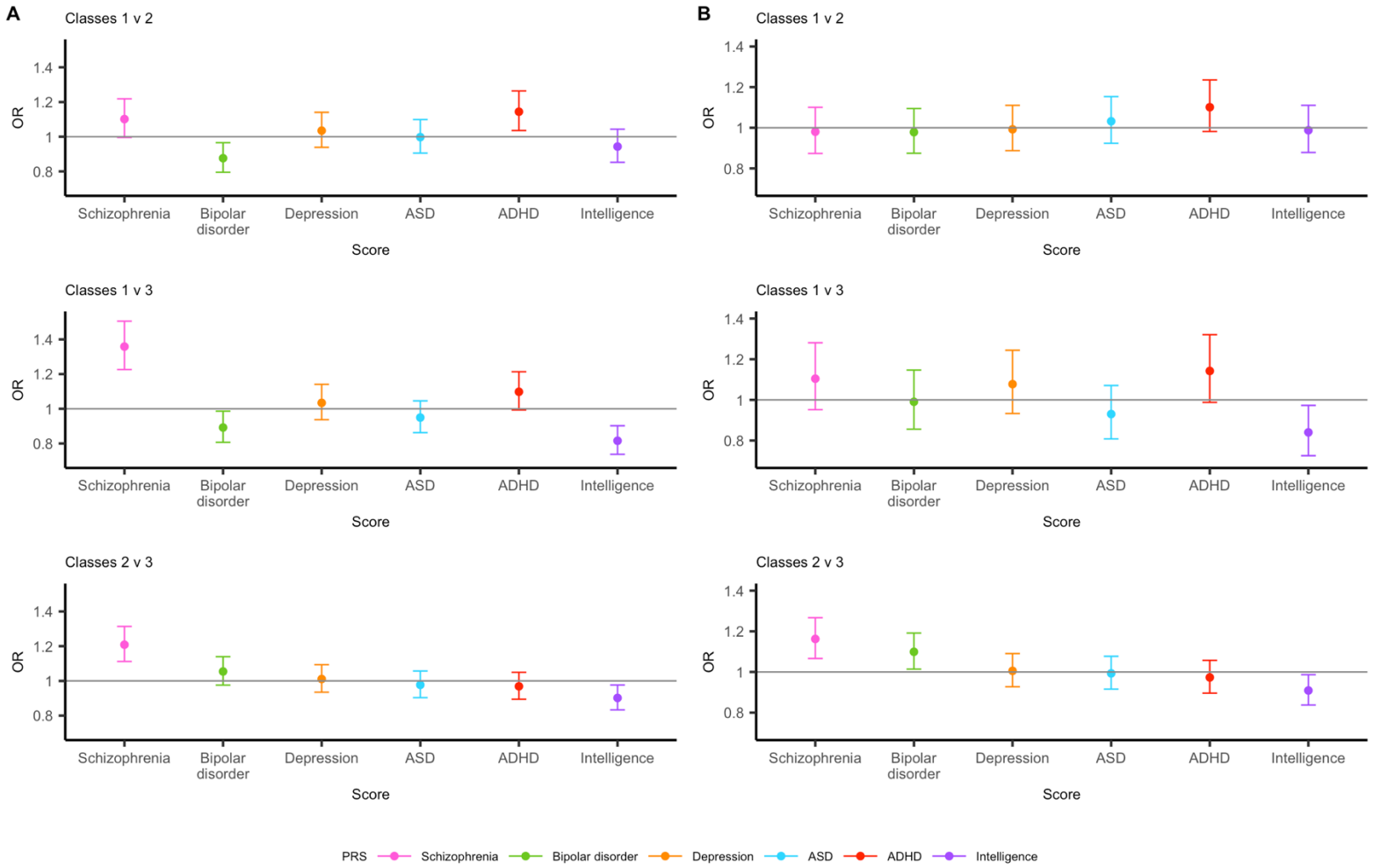

Figure 3.8. PRS associations with class membership for A) the primary analysis, and B) when covarying for diagnosis. Points indicate odds ratio, with bars showing 95% confidence intervals.

	Class one	Class two	Class three
Affymetrix Genome-Wide Human SNP 6.0	19	59	69
Illumina HumanOmniExpress 8/12 v1	682	886	967
Illumina PsychChip_v1.1	19	264	219

Table 3.12. Number of individuals in each class by genotyping array.

3.5.5 Within-schizophrenia class analysis

Comparing the classes across the full sample revealed several demographic, premorbid, and clinical differences between the groups, and demonstrated that diagnosis did not neatly separate with class membership. Therefore, to investigate how individuals with the same diagnosis varied according to class, I compared the distribution of phenotypes across the classes, restricting to only individuals with schizophrenia, and separately for bipolar disorder.

Figures 3.9 and 3.10 display the distribution of the phenotypes included in the LCA by class, when restricted to individuals with a schizophrenia diagnosis. In the full sample, class one was associated with higher levels of poor premorbid functioning and worse outcomes. In the schizophrenia-only sample, class one remained characterised by the highest levels of poor premorbid social and work functioning, unemployment in the year prior to onset, treatment resistance, and deterioration from premorbid functioning, consistent with the full sample results. In contrast to the full sample results, educational attainment did not differ between classes one and two, and suicidal ideation, which in the full sample did not differ between classes, was greater amongst people with schizophrenia in class one than in classes two and three. In the full sample, the most distinguishing feature of class two was a high rate of ever having been detained under the mental health act; this remained the most prominent feature of class two when the sample is restricted to those with schizophrenia. People with schizophrenia in class three had better premorbid functioning and improved outcomes than people with schizophrenia in classes one and two, although functioning was generally lower than was seen in the full sample. For instance, class three had the lowest levels of deterioration from premorbid functioning, however 67% of individuals

with schizophrenia in class three showed deterioration (Figure 3.10), compared to 39% of all individuals in class three (Figure 3.6).

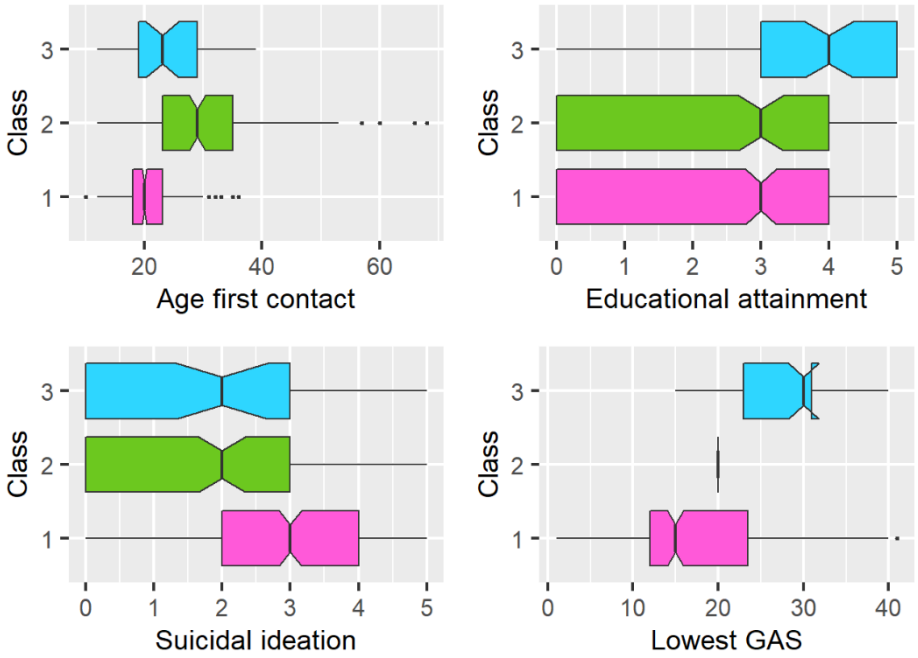

Figure 3.9. Boxplots indicating the median, interquartile range, minimum and maximum values, and outliers for continuous items included in the latent class analysis, separated by class for individuals with schizophrenia only.

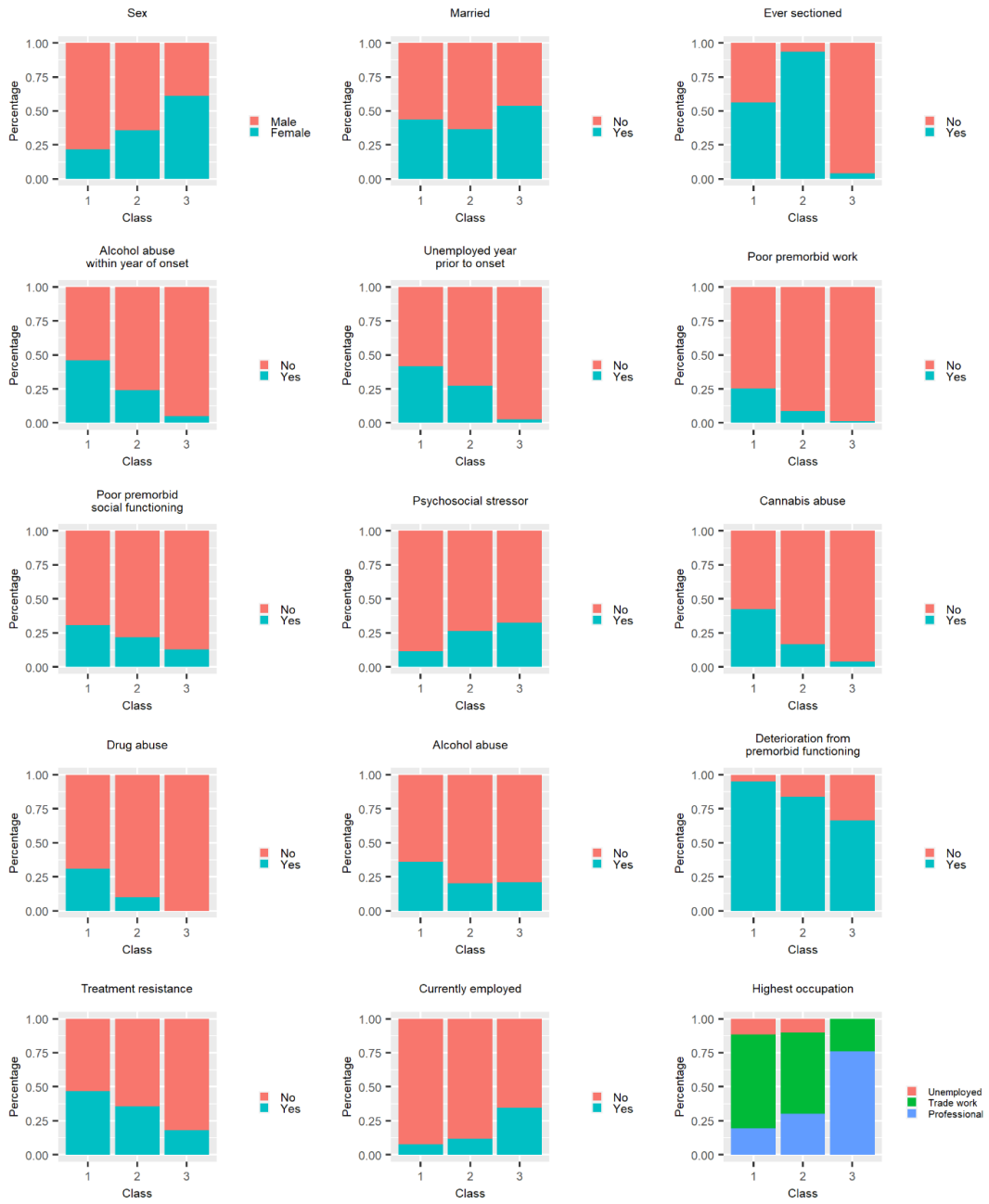

Figure 3.10. Distribution of responses by class for categorical items included in the latent class analysis, for individuals with schizophrenia only.

I analysed the association between PRS and class membership, restricted to only people with schizophrenia (Table 3.13 and Figure 3.11). Fewer significant associations were observed between classes in the schizophrenia-only sample than for the full sample. Schizophrenia PRS did not significantly differ between any of the classes. Individuals with schizophrenia in classes one and two did not significantly differ by any PRS, whereas in the full sample class one had lower bipolar disorder PRS and higher ADHD PRS than class two. In individuals with schizophrenia, class one was associated with significantly higher ADHD PRS and lower intelligence PRS than class three; the association with intelligence PRS was also seen in the full sample. Class two was significantly associated with higher ADHD PRS than class three, a finding that was not seen in the full sample.

Class	PRS	OR	Lower CI	Upper CI	P-value
1 v 2 (n=485 v n=225)	Schizophrenia	1.05	0.89	1.23	0.56
	Bipolar disorder	1.05	0.89	1.23	0.56
	Depression	0.98	0.83	1.14	0.75
	ADHD	1.11	0.94	1.31	0.21
	ASD	1.07	0.91	1.25	0.42
	Intelligence	1.00	0.85	1.18	0.98
1 v 3 (n=485 v n=55)	Schizophrenia	1.25	0.95	1.66	0.11
	Bipolar disorder	1.05	0.78	1.41	0.75
	Depression	1.26	0.96	1.66	0.10
	ADHD	1.59	1.19	2.14	$1.9x10^{-3}$
	ASD	0.90	0.68	1.19	0.45
	Intelligence	0.74	0.55	0.98	0.04
2 v 3 (n=225 v n=55)	Schizophrenia	1.21	0.88	1.66	0.24
	Bipolar disorder	0.98	0.73	1.31	0.90
	Depression	1.26	0.93	1.70	0.13
	ADHD	1.47	1.07	2.02	0.02
	ASD	0.82	0.61	1.10	0.19
	Intelligence	0.76	0.56	1.02	0.07

Table 3.13. Polygenic risk score associations with class membership in individuals with schizophrenia. Columns indicate classes being compared with number of individuals in each class, PRS, odds ratio with 95% confidence intervals, and p-value.

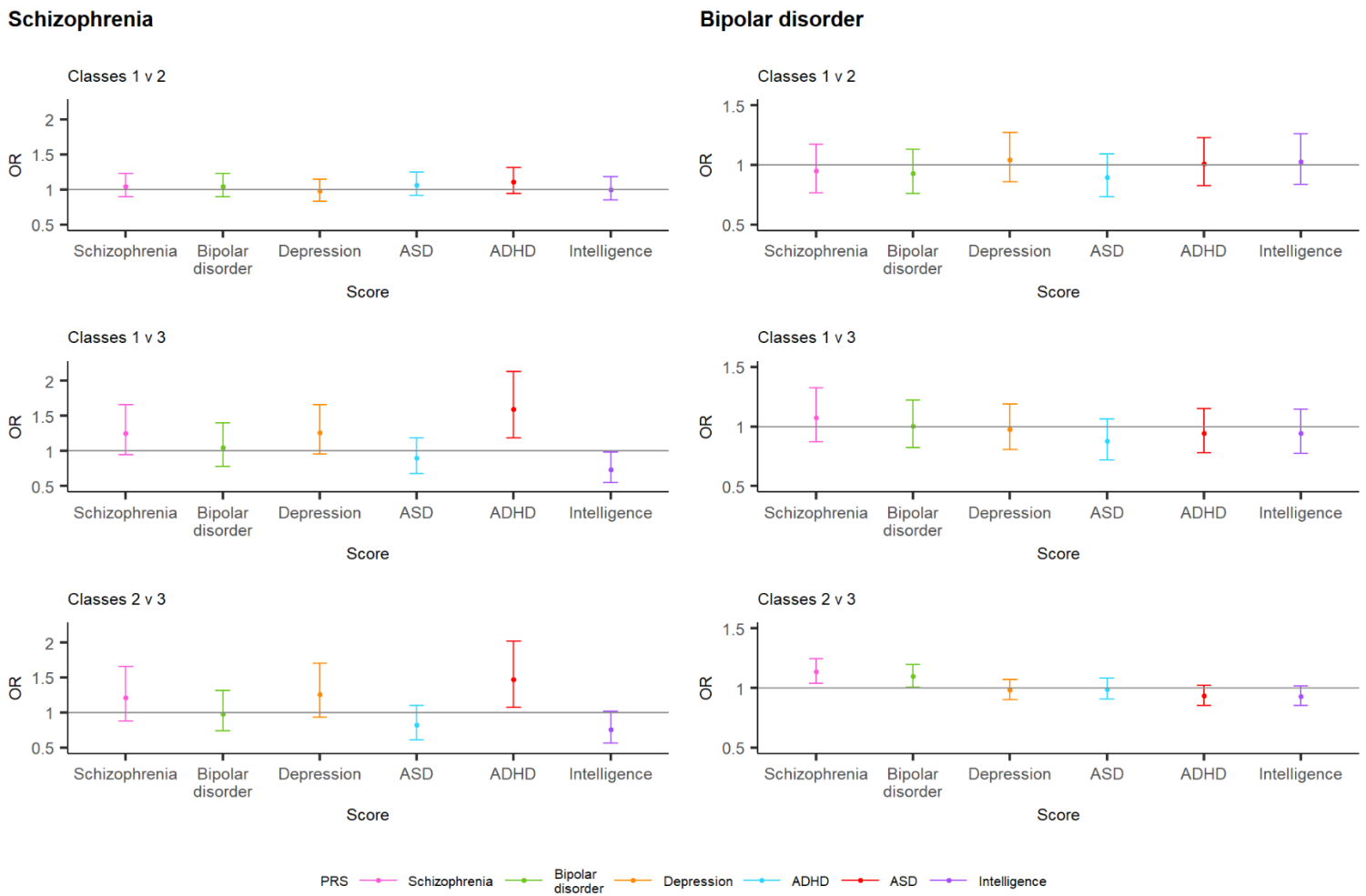

Figure 3.11. PRS associations with class membership, restricted to individuals with a diagnosis of schizophrenia (left), or bipolar disorder (right). Points indicate odds ratio, with error bars showing 95% confidence intervals.

3.5.6 Within-bipolar disorder class analysis

Figures 3.12 and 3.13 display the distribution of phenotypes included in the LCA by class, when restricted to individuals with a diagnosis of bipolar disorder (class one n= 139, class two n=975, class three n=1211). In the full sample, a pattern emerged whereby class one was characterised by the lowest levels of premorbid and current functioning, class three was characterised by the highest levels of premorbid and current functioning, and class two was characterised by intermediate levels of functioning but with high rates of involuntary hospitalisation (Figure 3.6). In the bipolar disorder-only sample, class one remained the lowest functioning sample, characterised by earlier age at onset, lower educational attainment, higher rates of unemployment prior to onset, higher rates of poor premorbid work and social adjustment, higher rates of treatment resistance, and lower rates of current employment. Whilst in the full sample, classes two and three differed in terms of several phenotypes including sex, marital status, unemployment prior to onset, treatment resistance, and deterioration from premorbid functioning, few differences were observed between classes two and three when restricted to only individuals with bipolar disorder. Classes two and three did differ in that class two had lower rates of suicidal ideation, poorer functioning in the worst episode, and the highest rates of involuntary hospitalisation - a key characteristic of class two in the full sample. In the full sample, class three was marked by the highest rates of a psychosocial stressor, however when restricted to only those with bipolar disorder, rates were similar between classes two and three (72% v 79%). Overall, the phenotypic differences between classes were smaller when comparing only individuals with bipolar disorder than in the whole sample, but a pattern of differences was still evident that was consistent with the findings in the full sample.

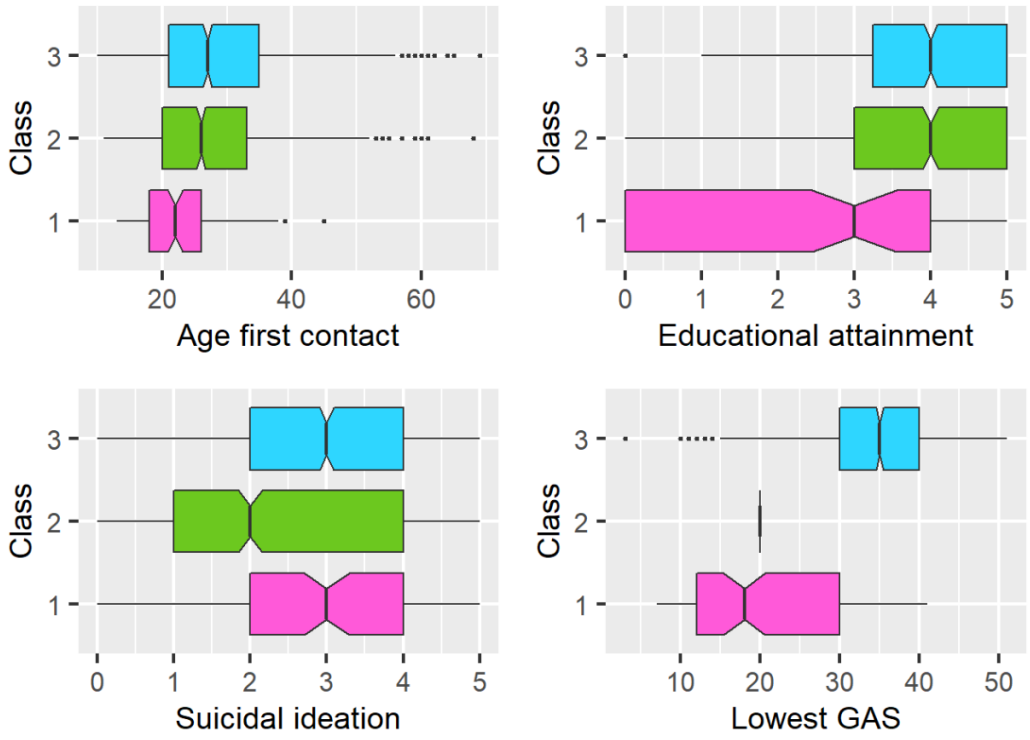

Figure 3.12. Boxplots indicating the median, interquartile range, minimum and maximum values, and outliers for continuous items included in the latent class analysis, separated by class for individuals with bipolar disorder only.

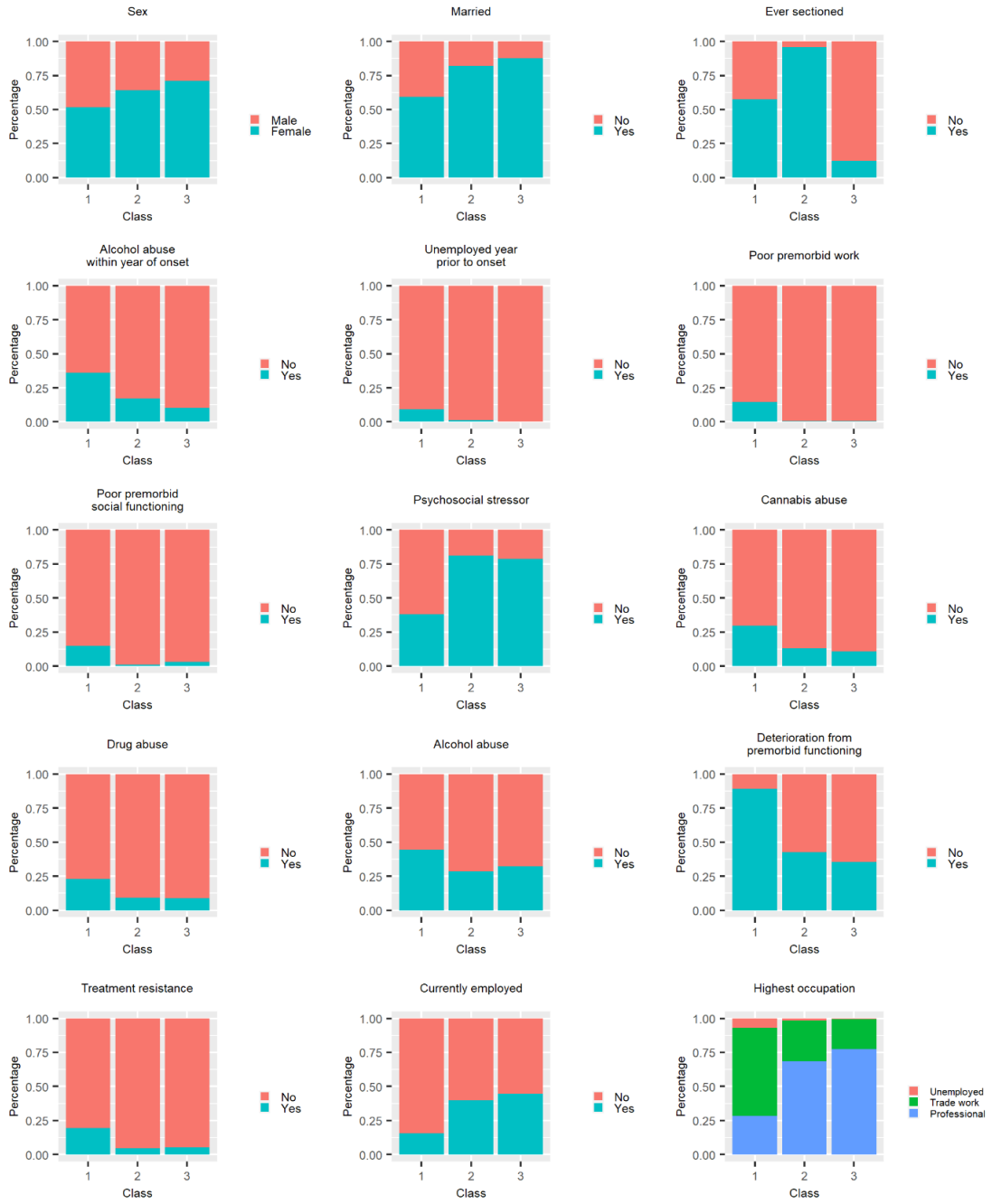

Figure 3.13. Distribution of responses by class for categorical items included in the latent class analysis, for individuals with bipolar disorder only.

I analysed the association between PRS and class membership, restricted to only individuals with bipolar disorder (Table 3.14 and Figure 3.11). Few significant differences were found between the classes in the bipolar sample, with no significant differences observed between classes one and two, or between classes one and three, which may reflect that only 112 people with bipolar disorder were included in class one. Class two had significantly higher schizophrenia and bipolar disorder PRS than class three, whereas in the full sample class two had higher schizophrenia and lower intelligence PRS than class three.

Class	PRS	OR	Lower CI	Upper CI	P-value
1 v 2 (n=112 v n=884)	Schizophrenia	0.95	0.77	1.17	0.62
	Bipolar disorder	0.93	0.76	1.13	0.45
	depression	1.04	0.86	1.27	0.67
	ADHD	1.01	0.83	1.23	0.93
	ASD	0.90	0.73	1.09	0.28
	Intelligence	1.03	0.84	1.26	0.79
1 v 3 (n=112 v n=1129)	Schizophrenia	1.07	0.87	1.32	0.50
	Bipolar disorder	1.00	0.82	1.22	0.99
	depression	0.98	0.80	1.19	0.81
	ADHD	0.95	0.78	1.15	0.57
	ASD	0.87	0.72	1.06	0.18
	Intelligence	0.94	0.77	1.14	0.54
2 v 3 (n=884 v n=1129)	Schizophrenia	1.14	1.04	1.25	0.01
	Bipolar disorder	1.10	1.01	1.20	0.04
	depression	0.98	0.90	1.07	0.71
	ADHD	0.93	0.85	1.02	0.14
	ASD	0.99	0.91	1.08	0.85
	Intelligence	0.93	0.85	1.01	0.10

Table 3.14. Polygenic risk score associations with class membership in individuals with bipolar disorder. Columns indicate classes being compared with number of individuals in each class, PRS, odds ratio with 95% confidence intervals, and p-value.

3. 6 Discussion

In a sample of individuals with schizophrenia, schizoaffective disorders, and bipolar disorder, I used factor analysis and latent class analysis to examine polygenic associations with symptoms of these disorders, identify phenotypically homogenous clusters across the psychosis spectrum, and measure the association between polygenic risk and cluster membership. I used CFA to derive factor scores for positive, negative, disorganised, depression, and mania symptoms, and identified several associations between factor scores and PRS. Notably, positive, negative, and disorganised symptoms were associated with higher schizophrenia PRS and lower bipolar disorder and intelligence PRS, whilst mania and depression factor scores were associated with lower schizophrenia PRS and higher bipolar disorder and intelligence PRS. After covarying for diagnosis, significant associations remained between symptoms and PRS. In particular, lower intelligence PRS was associated with higher negative symptoms, higher schizophrenia PRS was associated with higher disorganised symptoms, and higher depression PRS was associated with lower disorganised symptoms, higher mania symptoms, and higher depression symptoms. These findings suggest that although categorical diagnoses are capturing a large degree of variation in genetic liability to symptoms of schizophrenia, schizoaffective disorder, and bipolar disorder, dimensional approaches to symptoms are able to capture additional effects of genetic burden to different psychiatric disorders.

LCA identified three classes marked by distinct patterns of premorbid risk, clinical outcomes, and polygenic liability, which could be broadly described as lower, intermediate, and higher functioning groups. The lower functioning class was associated with lower bipolar disorder PRS and higher ADHD PRS, whilst the higher functioning class was associated with higher intelligence PRS and lower schizophrenia PRS than the other classes. Most associations between PRS and class membership were explained by diagnosis. However, some associations remained significant including higher intelligence PRS in the higher functioning class than in the other two classes and higher schizophrenia PRS in the intermediate functioning class compared to the higher functioning class. The findings of the LCA suggest that phenotypic clusters characterised by similar premorbid functioning and outcomes can be

identified across the psychosis-affective spectrum that are independent of diagnosis. Whilst diagnosis explains a large degree of the association between genetic liability and clusters, the clusters are able to capture phenotypic homogeneity across diagnoses that is associated with genetic liability not captured by current diagnostic systems.

Previous research on symptom dimensions and subtyping within and across schizophrenia and bipolar disorder has been conducted on considerably smaller samples than are included in my study and either have not examined polygenic associations or have been underpowered to do so in a cross-disorder cohort. Thus, my study provides a novel contribution to the field by demonstrating the role of polygenic risk in explaining variation in symptom dimensions and common phenotypes across the psychosis-affective spectrum. Additionally, I present novel evidence identifying phenotypically homogenous classes that are characterised by clear differences in demographics, premorbid functioning, clinical characteristics, and outcomes, which I was able to validate by demonstrating specific patterns of polygenic risk for each class.

3.6.1 Symptom factors

Using a CFA framework, I identified five symptom dimensions relating to positive, negative, disorganised, depressive, and manic symptoms. Schizophrenia and bipolar disorder PRS were significantly associated with all symptoms, and intelligence PRS was significantly associated with all domains with the exception of depression. Diagnosis explained most of the associations between PRS and factor scores, indicating that the majority of the variation in symptoms that is explained by polygenic risk score is being captured by the current diagnostic categories. Disorganised symptoms were significantly associated with schizophrenia PRS both before and after covarying for diagnosis, and was the strongest association observed between factor scores and PRS. Others have found that disorganised symptoms are more strongly associated with schizophrenia PRS than are positive or negative symptoms (Cardno *et al.*, 2001; McGrath *et al.*, 2009; Fanous *et al.*, 2012; Legge, Cardno, *et al.*, 2021), a finding that I was able to extend to a cross-disorder sample in this study. Evidence for association between negative symptoms and schizophrenia genetic liability has previously been

mixed (Fanous *et al.*, 2012; Legge, Cardno, *et al.*, 2021); here I found that negative symptoms were significantly associated with higher schizophrenia PRS and lower bipolar disorder and intelligence PRS, but after covarying for diagnosis, negative symptoms remained associated only with lower intelligence PRS. This suggests that whilst diagnosis is able to capture a large proportion of the polygenic effects on negative symptoms, i.e., schizophrenia PRS, variation in negative symptoms may additionally be influenced by PRS for intelligence.

Higher depression factor score was associated with depression PRS both before and after covarying for the effects of diagnosis, suggesting that depression in individuals with other psychiatric disorders may be influenced by additional genetic susceptibility to depression independent of what would be expected by diagnosis. This is important when understanding why depression is a common comorbidity amongst individuals with psychiatric disorders (Rush *et al.*, 2005), and suggests that depressive symptoms may share a common genetic aetiology independent of the primary diagnosis. Higher depression PRS was also associated with fewer disorganised symptoms and more manic symptoms, consistent with the view that risk alleles for depression (and other psychiatric disorders) have pleiotropic effects on psychopathology.

Studies of manic symptoms in individuals with bipolar disorder have suggested the possibility of separate symptom domains for elated mania and irritable mania (Cassidy *et al.*, 1998; Swann *et al.*, 2013). I found that all items in the mania dimension loaded strongly onto a single mania factor, and that no items were removed from the factor across the various CFA models, indicating that most symptoms of mania can be explained well by one underlying factor. However, it does not rule out the possibility of sub-domains within mania that I did not examine.

3.6.2 Latent Classes

3.6.2.1 Lower functioning class

I identified three latent classes, distinguished by relatively lower, intermediate, and higher functioning. The lower functioning class was characterised by phenotypes that typically indicate a higher neurodevelopmental burden, including a high proportion of males, higher rates of poor premorbid social functioning, earlier age at first contact

with psychiatric services, and lower educational attainment. The lower functioning class also had significantly higher ADHD PRS than the intermediate functioning class, suggesting that the class may represent a subset of individuals with relatively higher neurodevelopmental risk. The classic symptoms of schizophrenia: positive, negative, and disorganised symptoms, were all higher in the lower functioning class than the other classes, whilst depression and mania were lowest in this class. Previous studies in samples of people with psychotic and affective disorders have identified a subgroup of individuals characterised by more severe symptoms and lower educational attainment (Dwyer *et al.*, 2020; Pelin *et al.*, 2021). The subgroups identified by these studies appear conceptually similar to the lower functioning class I have identified, in that despite differences in the phenotypes and polygenic scores used to characterise and compare classes, these studies all identify a group with more severe symptoms and lower levels of functioning.

3.6.2.2 Intermediate-functioning class

The second class was characterised by intermediate levels of functioning in comparison to the other two classes. For instance, the intermediate functioning class had lower levels of unemployment prior to onset than the lower functioning class, but higher levels than the higher functioning class. This pattern was also observed for a range of phenotypes, including alcohol abuse prior to onset, premorbid social functioning, psychosocial stressor prior to onset, and deterioration from premorbid functioning. Thus, indicating that the intermediate class generally had better functioning than the lower functioning class, but worse functioning than the higher functioning class. The most prominent feature in the intermediate functioning class was high rates of having ever been detained under the mental health act, which occurred in almost every individual in this class. This could suggest that the class is associated with an acute illness requiring intensive medical attention that is more severe than is seen in the higher functioning class but does not progress into a chronic disorder with poor outcomes, as is seen in the lower functioning class.
The intermediate class had higher bipolar disorder PRS than the lower functioning class, but did not significantly differ for schizophrenia PRS. Conversely, the

intermediate functioning class had higher schizophrenia PRS than the higher functioning class, but did not significantly differ in terms of bipolar disorder PRS. Therefore, class two may be characterised as having high schizophrenia and bipolar disorder polygenic risk, but without the additional burden of ADHD PRS that was seen in the lower functioning class and without the protective effect of elevated intelligence PRS seen in the higher functioning class.

The intermediate functioning class had more psychotic symptoms than the higher functioning class and more affective symptoms than the lower functioning class, suggesting that it may be an intermediary category on the psychosis-affective spectrum. Schizoaffective disorder has been considered an intermediary diagnosis between schizophrenia and bipolar disorder in terms of symptoms experienced. However, only 34% of people with SA-D and 37% of people with SA-BP were assigned to the intermediate class, which also included 42% of people with bipolar disorder and 30% of people with schizophrenia, suggesting that the intermediate functioning class is not directly comparable to a schizoaffective disorder diagnosis. Instead, the intermediate functioning class may be conceptually similar to the psychosis subgroup identified in bipolar disorder research (Double, 1991; Sato *et al.*, 2002), which was associated with more severe phenotypes than the 'classic' mania subtype (Sato *et al.*, 2002), or to the paranoid subtype identified in schizophrenia research, which is associated with fewer negative and disorganised symptoms and better outcomes than other subtypes of schizophrenia (Kendler, Gruenberg and Tsuang, 1984; McGlashan and Fenton, 1991).

3.6.2.3 Higher functioning class

The third class identified was characterised by better premorbid functioning and outcomes, including lower rates of unemployment, high rates of treatment response, and the lowest rates of deterioration from premorbid functioning. The higher functioning class was predominantly formed of individuals with bipolar disorder, consistent with the observation that symptoms of mania and depression were highest in this class, whilst positive, negative, and disorganised symptoms were lowest in this class. Notably, the higher functioning class had the highest rates of a psychosocial

stressor in the six months prior to onset. The higher number of stressors could suggest that this group in particular may benefit from treatments that aim to reduce and manage psychosocial stressors, although this requires further investigation. In comparison to the previous literature, the higher functioning class is most consistent with observations of clusters termed 'classic mania' or 'pure mania', characterised by better functioning and outcomes than is typically seen in mania with psychosis (Sato *et al.*, 2002; Azorin *et al.*, 2008).

3.6.3 Within-disorder heterogeneity

Class comparisons restricted to only individuals with schizophrenia or only individuals with bipolar disorder revealed several associations important to understanding within-disorder heterogeneity. I did not compare only individuals with SA-D or with SA-BP as the small number of individuals with these diagnoses did not permit class comparisons or polygenic analyses. Within schizophrenia, ADHD PRS was significantly lower in the higher functioning class than the other two classes, whilst schizophrenia PRS did not significantly differ between classes, suggesting that neurodevelopmental risk may contribute to phenotypic differences within schizophrenia.

Within bipolar disorder, the intermediate class (containing 42% of people with bipolar disorder) was associated with significantly higher bipolar disorder PRS and schizophrenia PRS than the higher functioning class (containing 52% of people with bipolar disorder), suggesting that liability to these disorders may be explaining heterogeneity within bipolar disorder. Previous research has mostly shown that psychosis in bipolar disorder is associated with greater schizophrenia liability (Allardyce *et al.*, 2018; Ruderfer *et al.*, 2018), although not all studies have supported this conclusion (Hamshere *et al.*, 2011). My findings suggest that within bipolar disorder, a subgroup characterised by higher psychotic symptoms have higher schizophrenia PRS than a subgroup experiencing few psychotic symptoms. Whilst in the full sample, higher intelligence PRS was a marker of the higher functioning class, this observation was not significant in bipolar-only sample. However, it is important to consider the limitations of power in the within-disorder analyses, as the groups are considerably smaller and may be underpowered to detect some genetic effects.

3.6.4 Cross-disorder homogeneity

My findings suggest that common cross-disorder phenotypes may have a shared genetic aetiology, for instance depression symptom factor scores were associated with lower schizophrenia PRS, and higher bipolar disorder and depression PRS. Thus, variation in these symptoms, which are prevalent across schizophrenia, schizoaffective disorder, and bipolar disorder, may be affected by PRS in a manner that is shared across the disorders. Classes were defined by common phenotypes that are not used as criteria to define diagnosis, and each class contained a mixture of individuals with each diagnosis, suggesting that homogenous subgroups may exist independent of categorical diagnosis. PRS associations with class were also apparent even after covarying for diagnosis, including higher intelligence PRS in the higher functioning class than in the other classes. This suggests that phenotypes used to define classes, such as premorbid functioning and outcomes, may share a common genetic aetiology, regardless of categorical diagnosis.

3.6.5 Strengths and limitations

A strength of my study is the sample size and ability to examine polygenic associations. Previous research has typically been limited by small sample sizes that do not permit polygenic analysis, or was undertaken prior to the availability of GWAS and thus only familial aggregation or linkage analysis could be conducted.

Nonetheless, there are several limitations of my study to consider. Whilst I was able to include a large number of variables, some phenotypes were not available in all cohorts and thus could not be included without introducing systematic differences between the samples. For instance, cognition and premorbid IQ were not available in most of the sample. Given associations between diagnosis and cognition (Lynham *et al.*, 2018), research suggesting different trajectories of cognition in psychosis (Dickinson *et al.*, 2020), and the relationships in the present study with intelligence PRS, wide access to cognitive measures would have been valuable.

I was unable to replicate the associations from my study due to the lack of availability of comparable samples and thus the novel results reported here require replication.

Nevertheless, the classes I identified are consistent with the literature, and I took steps in the methodology to maximise the probability of a model fit that was widely applicable, rather than simply fitting my data. Additionally, indicators of a good model fit were present in my solution, for instance no class contained <5% of the sample, and the vast majority of participants had a >90% probability of being in their optimal class. I also examined the possibility of batch effects resulting from different genotyping arrays and did not identify any notable effects. Future research should aim to replicate the associations I have identified as well as expand my findings to include items such as cognition.

3.6.6 Future directions

The findings of this chapter raise several aims for future research. The results of the symptom dimensions analysis demonstrated that disorder-specific PRS can influence multiple types of symptoms. This raises the question of how different PRS act together to influence clinical presentation. Recent advances in statistical methods, such as genomic structural equation modelling, may be useful in addressing this and could provide insights into the effects of risk SNPs that are shared between disorders and the biological mechanisms through which they increase risk for psychiatric illness.

The results of the latent class analysis require replication in independent samples and examination of how other clinically relevant traits and behaviours are distributed across classes, particularly cognition. An aim of this research was to identify whether the classes represent more homogenous groups than diagnosis, as this may indicate greater utility of the classes. I have demonstrated that the classes are able to capture an additional degree of genetic homogeneity, but to determine whether the classes may be more useful in research or clinical settings requires further investigation. In particular, specific markers, whether biological or phenotypic, of each class would need to be identified to refine the classes and allow for more precise classification and prediction of prognosis. Refining the classes on the basis of biological homogeneity may also advance drug target identification, which in the long-term could lead to improved treatment options.

3.6.7 Conclusions

Overall, I found evidence to suggest there are subtypes of phenotypic presentation across the psychosis-spectrum that reflect differences in polygenic risk for several different psychiatric disorders and intelligence. My findings suggest that using data-driven subtypes may be able to explain additional phenotypic and genetic heterogeneity across psychotic and affective disorders, and could further aid prognostic predictions in schizophrenia, schizoaffective disorder, and bipolar disorder.

Chapter 4

Association of genetic liability for psychiatric disorders with accelerometer-assessed physical activity in the UK Biobank

4.1 Introduction

Dimensional models of psychosis and affective disorders aim to provide a better representation of the underlying structure of psychopathology across these disorders (Esterberg and Compton, 2009). In addition, dimensional approaches may better reflect evidence of a spectrum of neurodevelopmental risk and shared genetic architecture between many psychiatric disorders, including schizophrenia, bipolar disorder, depression, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) (Lee *et al.*, 2019). Examining the influence of genetic liability to psychiatric disorders on common cross-disorder phenotypes may elucidate the mechanisms underlying such dimensions and provide greater insights into the utility and feasibility of introducing dimensions of psychopathology into clinical practice. Physical activity can be a core indicator of mental illness; increased activity is a criterion in the diagnosis of ADHD and mania, and decreased activity is frequently seen in depression and as part of the negative symptoms of schizophrenia (Goodwin, 2003; Janney *et al.*, 2014; Stubbs *et al.*, 2016; Barker *et al.*, 2019). People with schizophrenia, bipolar disorder, and depression spend significantly more time sedentary and are less likely to meet recommended levels of physical activity than controls (Vancampfort *et al.*, 2017). Adolescents with psychiatric disorders are three times as likely to report low levels of activity than adolescents without psychiatric disorders, with the highest rates of inactivity reported amongst individuals with mood disorders and ASD (Mangerud *et al.*, 2014). Despite hyperactivity being a hallmark of ADHD, almost half of adolescents with ADHD reported low levels of activity, compared to a quarter of adolescents

without a psychiatric diagnosis (Mangerud *et al.*, 2014), indicating that physical activity can be affected in a multitude of ways across disorders.

Estimates suggest that physical inactivity causes 9% of premature mortality and 6-10% of the major non-communicable diseases worldwide (Lee *et al.*, 2012). Research consistently shows that individuals who engage in less physical activity report more stress (VanKim and Nelson, 2013), perform worse on cognitive tasks (Penedo and Dahn, 2005), and are at increased risk of cardiovascular disease, cancer, hypertension and diabetes (Warburton, Nicol and Bredin, 2006). Understanding the factors contributing to physical activity may assist in improving mental health in individuals with and without psychiatric disorders (Penedo and Dahn, 2005), as well as reducing risk of chronic physical health conditions, many of which are known to be increased in individuals with severe mental illness (Momen *et al.*, 2020).

Studies of physical activity have predominantly relied on self-report measures, but this may lead to unreliable estimates of activity especially for those with mental illness. A recent study reported marked differences when comparing accelerometer-measured activity between individuals with schizophrenia and controls, but not for self-reported activity (Firth *et al.*, 2018). This suggests that objective measures may better characterise physical activity in individuals with mental health disorders, and such approaches are being considered as part of clinical psychiatric care (Collier *et al.*, 2018). Exercise-based interventions have been trialled for several psychiatric disorders and some have shown positive results in alleviating psychiatric symptoms in schizophrenia and depression (Paluska and Schwenk, 2000; Firth *et al.*, 2015, 2016; Dauwan *et al.*, 2016). However, there is poor consistency in the methodology used between trials, with studies using lower quality methods reporting larger effect sizes than those of a higher quality (Rosenbaum *et al.*, 2014). Furthermore, many trials do not sufficiently detail the exercise protocol, preventing replication and limiting the interpretability of their findings (Rosenbaum *et al.*, 2014).

Physical activity has been hypothesised as a risk factor for developing psychiatric disorders, particularly depression (Choi *et al.*, 2019). In a meta-analysis of prospective studies measuring incidence of depression, individuals with high levels of physical

activity were at lower risk of developing depression, an effect that was observed across age groups and geographical locations, suggesting causality between physical activity and depression (Schuch *et al.*, 2018). However, it is possible that genetic liability to psychiatric disorders may predispose to altered levels of activity. Research using accelerometers in the UK Biobank has shown physical activity to be a polygenic trait, with a heritability of around 23% in women and 20% in men (Doherty *et al.*, 2018). A small number of studies have applied Mendelian Randomisation (MR) methodology (Smith and Hemani, 2014) to examine the hypothesis that physical activity is a causal risk factor for psychiatric illness, focussing on depression and schizophrenia (Choi *et al.*, 2019; Papiol *et al.*, 2020). Some have reported findings consistent with the hypothesis that low physical activity might be causally related to depression, although there is a lack of robust genetic instruments for MR analyses in this context.

Currently, the relationship between genetic liability to physical activity and psychiatric disorders is unclear. Physical activity in people with psychiatric disorders may be influenced by genetic liability to activity in the wider population, although it may primarily reflect disorder-specific factors. Conversely, it is possible that genetic liability for psychiatric disorders influences physical activity, rather than activity differences being a consequence of the illness. Other factors known to be associated with both psychiatric disorders and physical activity, such as smoking, obesity, and social deprivation (Fone and Dunstan, 2006; McNeill, Kreuter and Subramanian, 2006; Chwastiak, Rosenheck and Kazis, 2011) may also confound this relationship and thus require investigation. Examination of genetic relationships between physical activity and psychiatric disorders will aid in clarifying the extent to which the mechanisms underlying altered physical activity are shared across disorders, and whether alterations are the result of primary risk factors for psychiatric disorders (i.e., genetic liability) or are better explained as secondary to the illness.

4.1.1 Aims

I aimed to (i) assess the levels of objectively-measured physical activity in individuals with psychiatric disorders compared to controls, (ii) examine whether polygenic risk

for psychiatric disorders is associated with levels of physical activity in a population sample, and (iii) investigate the degree to which the genetic architecture of physical activity is shared with that of psychiatric disorders using genetic correlations.

4.2 Method

4.2.1 Participants

Study participants were from the population-based UK Biobank sample, a national cohort study of over 500,000 individuals aged 40-69 at the time of recruitment from 22 assessment centres across the UK from 2006 - 2010 (Sudlow *et al.*, 2015). Between 2013 and 2015, a subset of individuals was invited to participate in a study of device-measured physical activity (see Figure 4.1 for timeline of data collection). A random group of participants with a valid email address were invited, with the exception of those residing in the North-West region, who were excluded due to concerns over participant burden. Of the 236,519 individuals approached, 106,053 consented to participate (Doherty *et al.*, 2017).

This study was conducted as part of UK Biobank project number 13310. Ethical approval for UK Biobank was granted by the North-West Multi-Centre Ethics Committee and all participants provided written informed consent. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

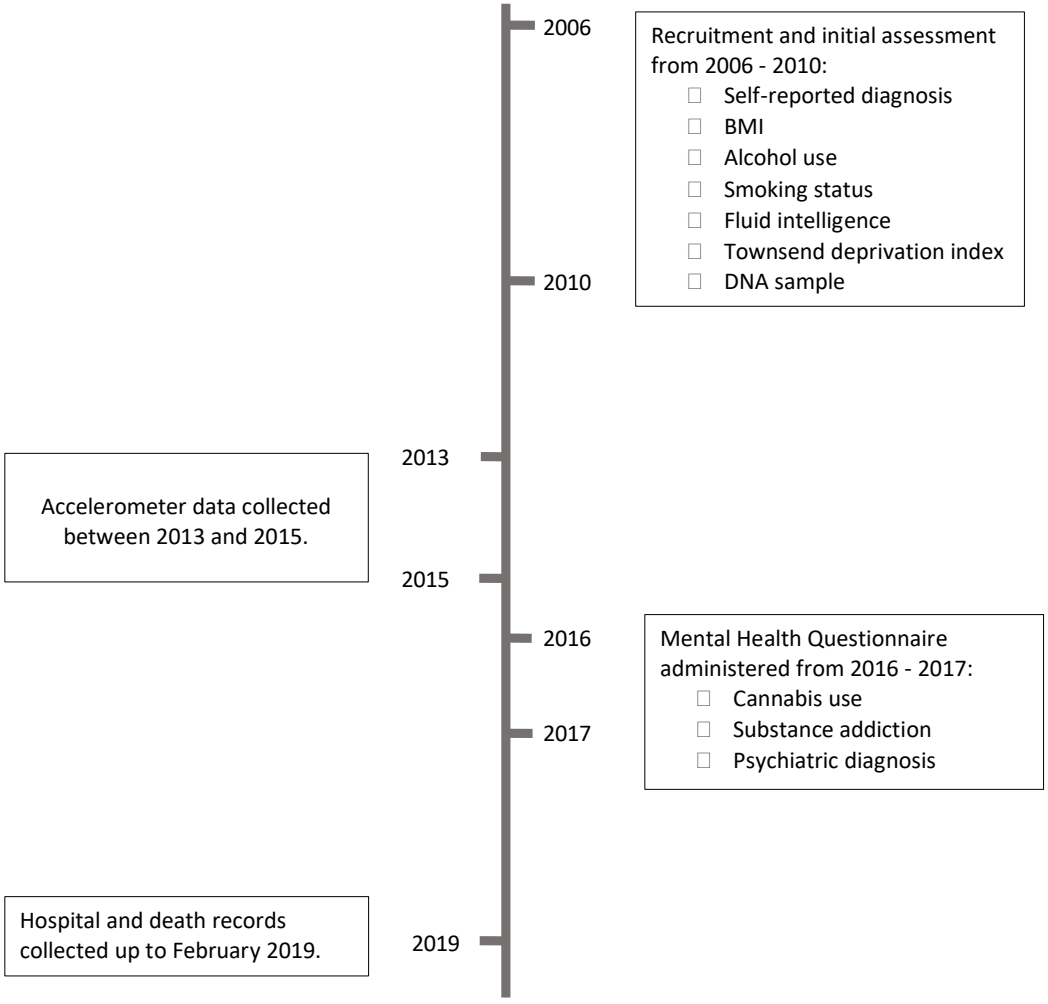

Figure 4.1 Timeline of data collection.

4.2.2 Psychiatric diagnosis

Researchers at the MRC Centre for Neuropsychiatric Genetics and Genomics gathered evidence of a psychiatric diagnosis from: (i) self-report at the initial assessment, (ii) the mental health questionnaire (Davis *et al.*, 2020), (iii) a diagnosis recorded on a hospital record, or (iv) a diagnosis recorded on a death record. For hospital and death records, participants were deemed to have a diagnosis when the following ICD-10 codes (plus child terms e.g., F20.1) were present: F20 for schizophrenia, F20-F29 for psychotic disorder, F30 or F31 for bipolar disorder, F32 or F33 for depression, F84 for ASD, and F90 for ADHD. I amalgamated this information to identify individuals with a diagnosis of schizophrenia, bipolar disorder, depression, ADHD, or ASD, including evidence from at least one category as indicative of a diagnosis. Where individuals reported multiple diagnoses, I included them in each appropriate diagnostic group. I selected these disorders as altered activity can be a prominent feature of the disorder and substantial genome-wide association studies (GWAS) existed to allow for the testing of genetic hypotheses.

4.2.3 Genetic data

Initial genotyping and quality control was undertaken by UK Biobank (Bycroft *et al.*, 2017).Participants were assayed at the Affymetrix Research Services laboratory using the UK Biobank Axiom or UK BiLEVE Axiom arrays, which were purpose built for the UK Biobank and designed to share 95% of markers. UK Biobank applied its own quality control pipeline to the genotype data, to accommodate the ethnic diversity in the sample (Bycroft *et al.*, 2017), which included marker-based and sample-based quality control. Both the Haplotype Reference Consortium (HRC) (McCarthy *et al.*, 2016) and the UK10K haplotype reference (Huang *et al.*, 2015) panels were used for imputation, preferentially using the HRC panel.

Additional quality control was undertaken by researchers at the MRC Centre for Neuropsychiatric Genetics and Genomics. Filters were applied to select high-quality SNPs, including: minor allele frequency > 0.01, imputation score > 0.8, missingness < 0.05, and Hardy-Weinberg equilibrium p-value > $1x10^{-6}$. SNPs imputed using the UK10K reference panel were removed, following advice from UK Biobank

(http://www.ukbiobank.ac.uk/2017/07/important-note-about-imputed-genetics-data/) (Legge, Jones, *et al.*, 2019). All genetic analyses were restricted to participants of European ancestry, firstly by filtering for self-reported European ancestry (UK Biobank Field ID: 21000), then confirmed through principal components (UK Biobank Field ID: 22009) using the *covMCD* function in the R package *robustbase* (Maechler *et al.*, 2018; Legge, Jones, *et al.*, 2019). Related individuals, defined as kinship coefficient greater than 0.15, were removed at random.

4.2.4 Polygenic risk scores

Polygenic risk score (PRS) calculation was undertaken by researchers at the MRC Centre for Neuropsychiatric Genetics and Genomics. PRSice(Euesden, Lewis and O'Reilly, 2015) was used to derive polygenic risk scores (PRS) for schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium. *et al.*, 2020), bipolar disorder (Stahl *et al.*, 2019), major depressive disorder (MDD) (Wray *et al.*, 2018), ADHD (Demontis *et al.*, 2019), and ASD (Grove *et al.*, 2019), following the methods used by the Psychiatric Genomics Consortium (PGC) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Legge, Jones, *et al.*, 2019). PRS were calculated at six thresholds: $p<5x10^{-8}$, $5x10^{-6}$, $5x10^{-4}$, 0.05, 0.1, 0.5.
I standardised PRS as Z-scores for each disorder, to allow for comparison between disorders. None of the GWAS discovery datasets included the UK Biobank as a sample, however I was unable to check for duplicate participants and therefore cannot exclude the possibility of this.

4.2.5 Accelerometer-measured physical activity

Participants wore an Axivity AX3 tri-axial accelerometer for one week on the wrist of their dominant hand. The accelerometer captures activity at 100Hz with a dynamic range of ±8*g* and is comparable to the GENEActiv devices worn in several other cohort studies (Doherty *et al.*, 2017). Data were processed by the accelerometer working group (Doherty *et al.*, 2017) in line with standard protocols, including calibration to local gravity and removal of one gravitational unit from the vector magnitude (da Silva *et al.*, 2014; Sabia *et al.*, 2014; van Hees *et al.*, 2014; Doherty *et al.*, 2017). A measure

of overall physical activity was computed by partitioning the data into five second epochs and calculating the mean vector magnitude of each epoch. Periods of non-wear were removed, defined as a period of 60 minutes or more where all axes of the device had a standard deviation less than 13m*g*, and the missing data imputed using data from a similar time of day, consistent with previous studies (da Silva *et al.*, 2014; Doherty *et al.*, 2017). The group then derived an overall mean acceleration from the average of all worn and imputed epochs (UK Biobank Field ID: 90012).

A recent study by Doherty and colleagues (2018) classified the accelerometer activity being undertaken into sedentary, walking, moderate, or sleeping. Participants in an independent sample wore wrist-worn accelerometers and a wearable camera for one week, in order to map the accelerometer readings to an observable activity. Machine learning methods were then used to create a model that was able to accurately classify accelerometer readings into a pre-defined type of activity (Doherty *et al.*, 2018). The researchers used these data to derive an overall probability of each participant in the wider sample engaging in each type of activity at any given time (Return UK Biobank Field ID: 1942).

I standardised overall level activity as a Z-score and I converted moderate, walking, sedentary, and sleep into minutes spent per day engaging in the activity type. Individuals with insufficient device wear time, poor device calibration, or an overall mean activity Z score greater than 3 were excluded from analysis.

Doherty and colleagues(2018) conducted a GWAS on each of the activity subtypes; I used the summary statistics from these GWAS for genetic correlation analyses, as described below. As the GWAS of physical activity was conducted in the UK Biobank sample, I was unable to derive polygenic risk scores for activity as an independent target sample was not available.

4.2.6 Genetic correlations

I measured genetic correlations to extend the PRS findings and examine the relationship between genetic risk for psychiatric disorders and five classes of activity: overall, moderate, walking, sedentary, and sleep duration. I used LD score regression (Bulik-Sullivan, Finucane, *et al.*, 2015; Bulik-Sullivan, Loh, *et al.*, 2015) to calculate genetic correlations between summary statistics for each activity class and

schizophrenia, bipolar disorder, MDD, ADHD, and ASD, using the same discovery sets as the PRS analyses. This method is robust to sample overlaps and hence complements the polygenic analysis.

4.2.7 Analysis

I conducted all analyses described in the Chapter and corrected all associations for multiple comparisons using a false discovery rate (FDR) of $p<0.05$.

I conducted linear regressions to measure the effect of diagnosis of schizophrenia, bipolar disorder, depression, ADHD, and ASD on all types of activity: overall, moderate, walking, sedentary, and sleep. I included age, sex, and BMI as covariates in all models.

I used linear regressions to measure the associations between each disorder PRS and each type of activity, with age, sex, BMI, principal components, and genotyping array included as covariates in all PRS models. PRS associations were conducted at the $p<.05$ threshold for SNP inclusion in the primary analyses; the remaining five thresholds were also tested for robustness. Individuals with a psychotic disorder, bipolar disorder, depression, ADHD, or ASD diagnosis were excluded from all PRS analyses in order to remove confounding effects of case status on PRS and activity levels, leaving a total of 76,409 participants.

In order to assess whether the relationship between PRS for psychiatric disorders and physical activity could be influenced by other confounders, I added alcohol use (Field ID: 20414), cannabis use (Field ID: 20453), substance or behavioural addiction (Field ID: 20401), smoking status (Field ID: 20116), fluid intelligence (Field ID: 20016), and Townsend deprivation index (Field ID: 189) as additional covariates in the overall levels of activity PRS models. These data were available on 15,285 participants who had also completed the mental health questionnaire.

4.3 Results

4.3.1 Sample characteristics

A total of 236,502 individuals were invited to participate in the accelerometer study. Participation in the accelerometer study was significantly, yet minimally, associated with age at recruitment (OR=1.002; 95% CI=1.001, 1.003; $p=2.7x10^{-6}$) and female sex

(OR=1.14; 95% CI= 1.13, 1.16; $p=4.7x10^{-59}$). Individuals with a psychiatric disorder diagnosis (schizophrenia, bipolar disorder, depression, ADHD, or ASD) were significantly less likely to participate than individuals without a psychiatric disorder (OR= 0.95; 95% CI= 0.92, 0.98; p=0.002).

A total of 95,744 participants were included in the study with high quality accelerometer data (56.4% female, mean age at recruitment [SD] 56.2 years [7.8], see Figure 4.2). 6,527 individuals were classified as having depression, 466 with bipolar disorder, 95 with schizophrenia, 87 with ASD, and 53 with ADHD. Figure 4.2 displays the number of participants included and excluded at each stage and reasons for exclusions.

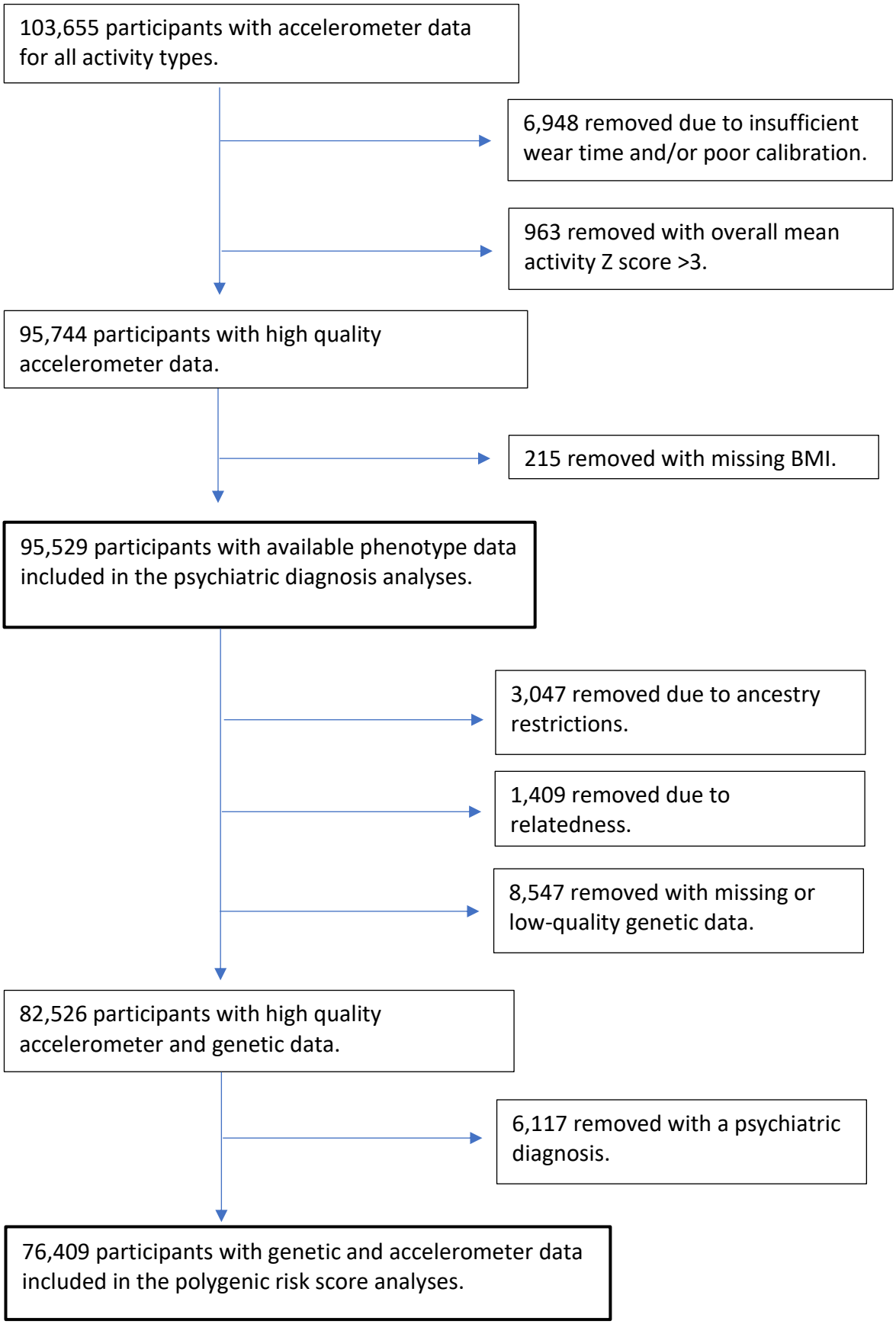

Figure 4.2. Flowchart indicating number of participants included and reasons for exclusion.

4.3.2 Activity levels in psychiatric disorders

Firstly, I assessed the differences in levels of activity between individuals with and without psychiatric disorders. Results are presented in Table 4.1 and Figures 4.3 and 4.4. After correcting for multiple comparisons, schizophrenia was associated with reduced levels of overall activity, reduced time spent in moderate activity and longer sleep duration. Bipolar disorder and depression were both associated with reduced levels of overall activity, reduced time spent in moderate activity and walking, and longer sleep duration. ASD was associated with reduced levels of overall activity, reduced time spent walking, and increased time spent in sedentary activity. ADHD was not significantly associated with changes in any type of activity.

4.3.3 Polygenic Risk Scores

To establish the extent to which genetic liability for psychiatric disorders influences levels of physical activity in the general population, I measured the association between PRS for each disorder and levels of overall activity, moderate activity, walking, sedentary activity, and sleep. Results are presented in Table 4.2, Figures 4.3 and 4.4. In individuals without a mental health disorder, after correcting for multiple comparisons, schizophrenia PRS was associated with reduced levels of overall activity, increased time spent in moderate activity, increased time spent walking, reduced time spent in sedentary activity, and longer sleep duration. Bipolar disorder PRS was associated with increased time spent in moderate activity, increased time spent walking, and reduced time spent in sedentary activity. MDD PRS was associated with reduced levels of overall activity, reduced time spent in moderate activity, reduced time spent walking, and longer sleep duration. ADHD PRS was associated with increased levels of overall activity, increased time spent in moderate activity, reduced time spent in sedentary activity, and longer sleep duration. ASD PRS was associated with reduced levels of overall activity, reduced time spent walking, increased time spent in sedentary activity, and shorter duration of sleep.

Disorder	Activity	Beta (95% CI)	P-value
Schizophrenia	Overall	-0.4 (-0.5, -0.2)	$9.3x10^{-5}$
	Moderate	-14.8 (-25.1, -4.4)	0.01
	Walking	-5.8 (-18.5, 7.0)	0.50
	Sedentary	-14.3 (-34.7, 6.1)	0.25
	Sleep	42.2 (27.1, 57.3)	$1.9x10^{-7}$
Bipolar disorder	Overall	-0.3 (-0.4, -0.2)	$2.5x10^{-12}$
	Moderate	-10.3 (-15.0, -5.7)	$4.3x10^{-5}$
	Walking	-9.5 (-15.2, -3.7)	$3.0x10^{-3}$
	Sedentary	-3.0 (-12.2, 6.3)	0.63
	Sleep	22.7 (15.8, 29.5)	$4.3x10^{-10}$
Depression	Overall	-0.2 (-0.2, -0.1)	$1.5x10^{-51}$
	Moderate	-1.7 (-3.0, -0.4)	0.02
	Walking	-11.8 (-13.4, -10.2)	$4.0x10^{-46}$
	Sedentary	2.6 (0.1, 5.2)	0.07
	Sleep	11.9 (10.0, 13.8)	$8.4x10^{-34}$
ADHD	Overall	0.01 (-0.2, 0.2)	0.97
	Moderate	5.2 (-8.7, 19.1)	0.58
	Walking	-4.8 (-21.8, 12.2)	0.66
	Sedentary	-3.0 (-30.3, 24.3)	0.87
	Sleep	-4.0 (-24.3, 16.2)	0.76
ASD	Overall	-0.4 (-0.6, -0.2)	$1.8x10^{-5}$
	Moderate	-8.1 (-18.9, 2.7)	0.22
	Walking	-23.1 (-36.4, -9.9)	$1.0x10^{-3}$
	Sedentary	48.4 (27.1, 69.7)	$2.7x10^{-5}$
	Sleep	-7.1 (-22.9, 8.7)	0.50

Table 4.1. Association between activity and diagnosis of a psychiatric disorder in the UK Biobank.
Columns represent the disorder, type of activity, effect size (beta), 95% confidence intervals, and FDR-corrected p-value of the association between diagnosis of the disorder and level of activity. Effect size for overall activity corresponds to standard deviation change in activity, effect sizes for all other types of activity correspond to minutes per day of activity.

Polygenic risk score	Activity	Beta (95% CI)	P-value
Schizophrenia	Overall	-0.01 (-0.01, -0.002)	0.01
	Moderate	0.4 (0.03, 0.8)	0.04
	Walking	1.0 (0.5, 1.5)	$9.6x10^{-5}$
	Sedentary	-1.2 (-2.0, -0.5)	$3.0x10^{-3}$
	Sleep	0.8 (0.3, 1.3)	0.01
Bipolar disorder	Overall	0.002 (-0.004, 0.01)	0.51
	Moderate	0.5 (0.1, 0.8)	0.02
	Walking	0.7 (0.2, 1.1)	0.01
	Sedentary	-0.8 (-1.5, -0.1)	0.04
	Sleep	-0.01 (-0.5, 0.5)	0.96
Depression	Overall	-0.02 (-0.02, -0.01)	$2.1x10^{-6}$
	Moderate	-0.6 (-0.9, -0.2)	0.01
	Walking	-0.8 (-1.2, -0.3)	$3.0x10^{-3}$
	Sedentary	0.1 (-0.6, 0.8)	0.83
	Sleep	1.0 (0.4, 1.5)	$1.8x10^{-3}$
ADHD	Overall	0.01 (0.003, 0.02)	0.01
	Moderate	0.6 (0.2, 0.9)	0.01
	Walking	-0.2 (-0.7, 0.2)	0.39
	Sedentary	-1.7 (-2.5, -1.0)	$1.4x10^{-5}$
	Sleep	0.9 (0.4, 1.4)	$3.0x10^{-3}$
ASD	Overall	-0.01 (-0.01, -0.002)	0.01
	Moderate	-0.1 (-0.5, 0.2)	0.54
	Walking	-0.6 (-1.0, -0.1)	0.02
	Sedentary	1.9 (1.2, 2.6)	$2.5x10^{-6}$
	Sleep	-0.8 (-1.4, -0.3)	0.01

Table 4.2. Association between activity and polygenic risk scores for psychiatric disorders in the UK Biobank.
Columns represent the polygenic risk score, type of activity, effect size (beta), 95% confidence intervals, and FDR-corrected p-value of the association between PRS and level of activity. Effect size for overall activity corresponds to standard deviation change in activity, effect sizes for all other types of activity correspond to minutes per day of activity. I excluded individuals with a psychiatric disorder for PRS analyses.

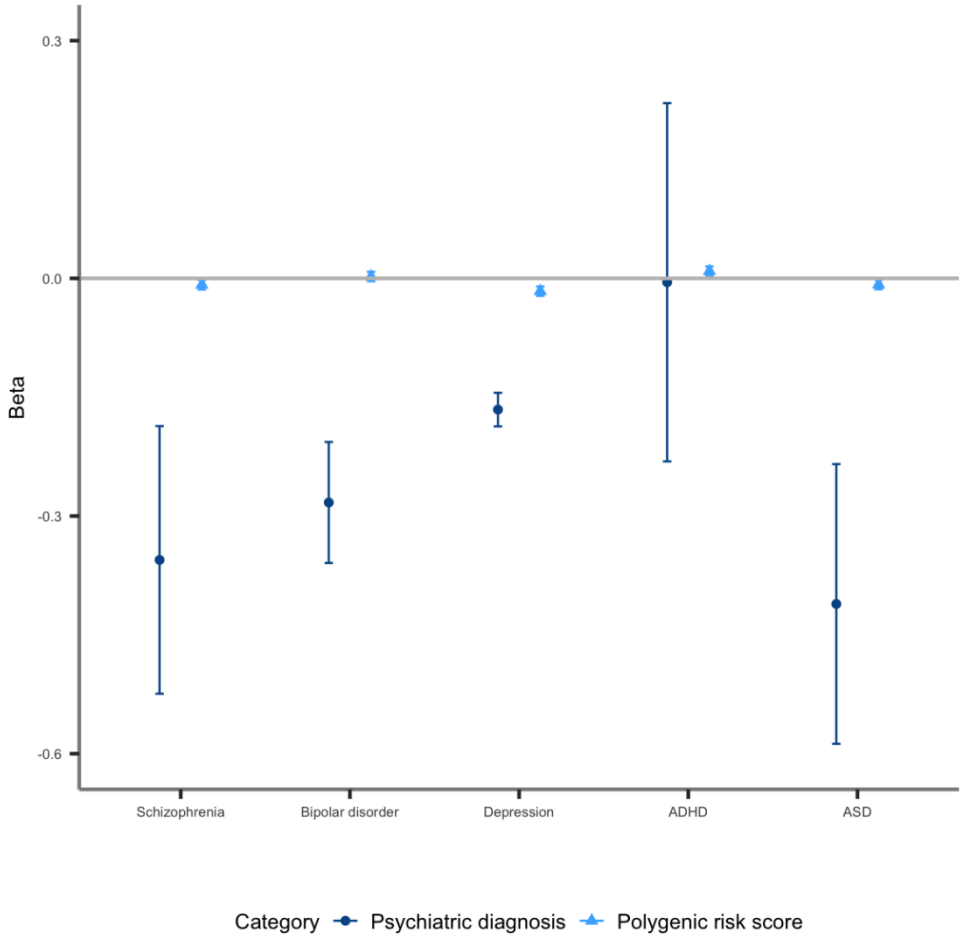

Figure 4.3. The effect size (beta) for associations between overall activity and diagnoses of, and PRS for, each psychiatric disorder.
Error bars indicate 95% confidence intervals. A beta of 1 is equivalent to a 1 standard deviation (SD) change in level of activity between individuals with and without a psychiatric disorder or per 1 SD increase in PRS. I excluded individuals with a psychiatric disorder for PRS analyses.

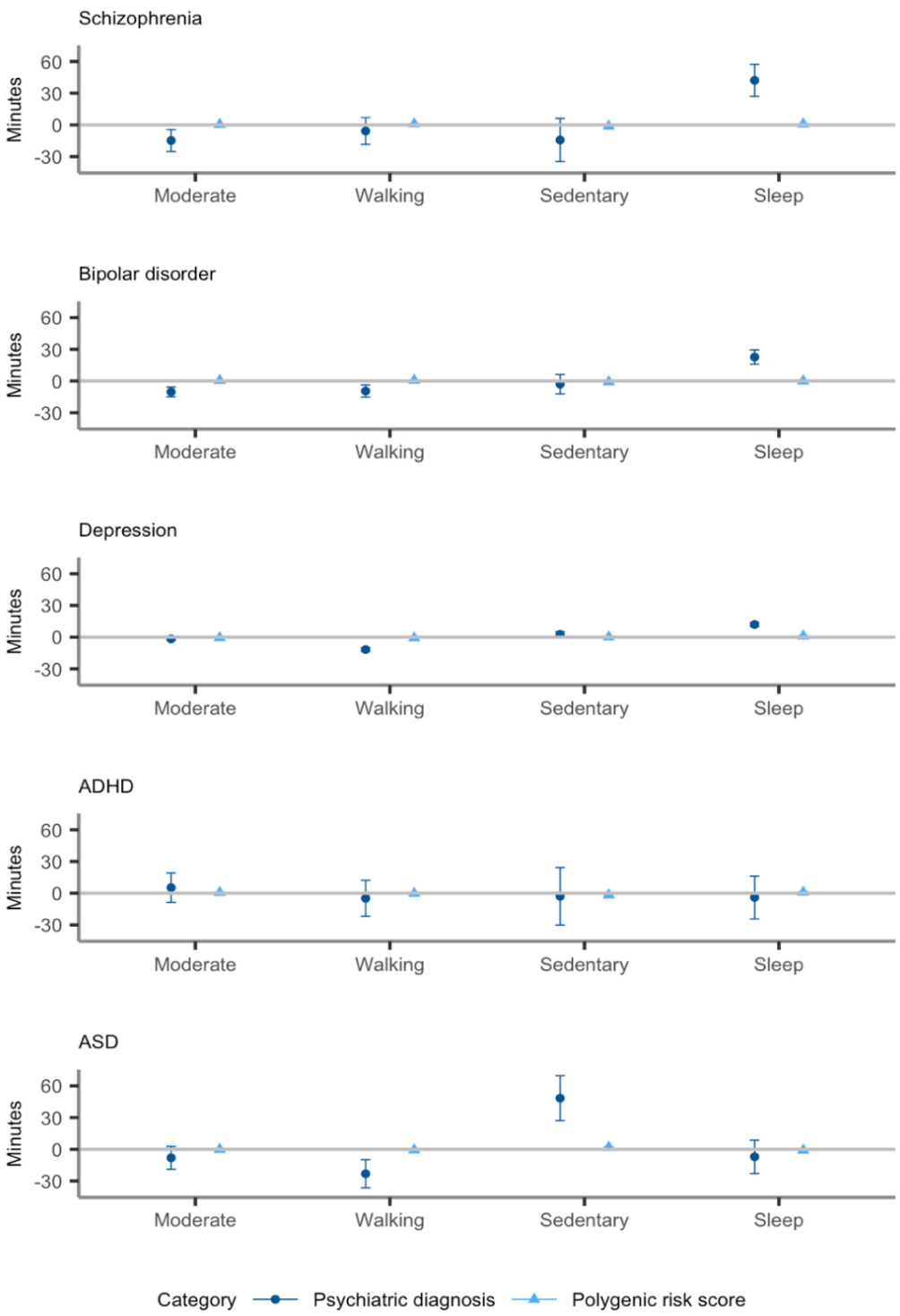

Figure 4.4. Associations between type of activity in minutes and diagnoses of, and PRS for, each psychiatric disorder.
Error bars indicate 95% confidence intervals. A beta of 1 is equivalent to a 1 standard deviation (SD) change in level of activity between individuals with and without a psychiatric disorder or per 1 SD increase in PRS. I excluded individuals with a psychiatric disorder for PRS analyses.

To assess whether the associations with PRS were highly sensitive to the primary SNP inclusion threshold ($p<0.05$), I measured the association between activity levels and five additional PRS thresholds. Results were consistent across the thresholds tested (Tables 4.3 - 4.7). The proportion of variance explained by PRS for each type of activity are shown in Tables 4.3- 4.7. The greatest amount of variance in overall activity level was explained by MDD PRS at a p-value threshold of $p<0.5$. However, this was a negligible amount of variance ($R^2=3.5x10^{-4}$) indicating that despite statistical significance, the actual level of activity influenced by PRS for psychiatric disorders is very small and is unlikely to correspond to a meaningful amount of activity.

Activity	Threshold	beta	Lower CI	Upper CI	P-value	R^2
Overall	$5x10^{-8}$	-0.01	-0.01	-0.002	0.01	$7.5x10^{-5}$
	$5x10^{-6}$	-0.01	-0.01	-0.003	$2.9x10^{-3}$	$8.9x10^{-5}$
	$5x10^{-4}$	-0.01	-0.01	-0.001	0.02	$4.7x10^{-5}$
	0.05	-0.01	-0.01	-0.002	0.01	$6.8x10^{-5}$
	0.1	-0.01	-0.01	-0.001	0.02	$4.5x10^{-5}$
	0.5	-0.005	-0.01	0.001	0.14	$1.4x10^{-5}$
Moderate	$5x10^{-8}$	0.25	-0.11	0.61	0.17	$1.1x10^{-5}$
	$5x10^{-6}$	0.28	-0.08	0.64	0.13	$1.6x10^{-5}$
	$5x10^{-4}$	0.38	0.02	0.74	0.04	$3.9x10^{-5}$
	0.05	0.39	0.03	0.76	0.04	$4.1x10^{-5}$
	0.1	0.31	-0.06	0.68	0.10	$2.1x10^{-5}$
	0.5	0.33	-0.03	0.70	0.08	$2.6x10^{-5}$
Walking	$5x10^{-8}$	0.28	-0.17	0.72	0.23	$5.9x10^{-6}$
	$5x10^{-6}$	0.46	0.01	0.91	0.04	$3.9x10^{-5}$
	$5x10^{-4}$	0.72	0.27	1.17	$1.6x10^{-3}$	$1.2x10^{-4}$
	0.05	1.00	0.55	1.46	$9.6x10^{-5}$	$2.3x10^{-4}$
	0.1	1.14	0.68	1.59	$1.0x10^{-6}$	$3.0x10^{-4}$
	0.5	1.25	0.79	1.71	$7.9x10^{-8}$	$3.6x10^{-4}$
Sedentary	$5x10^{-8}$	-0.76	-1.48	-0.05	0.04	$2.9x10^{-4}$
	$5x10^{-6}$	-0.66	-1.38	0.05	0.07	$2.8x10^{-4}$
	$5x10^{-4}$	-1.04	-1.76	-0.33	$4.2x10^{-3}$	$3.4x10^{-4}$
	0.05	-1.25	-1.97	-0.53	$3.0x10^{-3}$	$3.8x10^{-4}$
	0.1	-1.31	-2.03	-0.59	$3.9x10^{-4}$	$3.9x10^{-4}$
	0.5	-1.43	-2.15	-0.70	$1.2x10^{-4}$	$4.2x10^{-4}$
Sleep	$5x10^{-8}$	0.71	0.18	1.23	0.01	$7.8x10^{-5}$
	$5x10^{-6}$	0.63	0.10	1.15	0.02	$5.9x10^{-5}$
	$5x10^{-4}$	0.77	0.25	1.30	$3.9x10^{-3}$	$9.5x10^{-5}$
	0.05	0.79	0.26	1.33	0.01	$9.9x10^{-5}$
	0.1	0.71	0.18	1.24	0.01	$7.7x10^{-5}$
	0.5	0.66	0.12	1.19	0.02	$6.2x10^{-5}$

Table 4.3. Schizophrenia PRS results.

Results for all thresholds tested for association between schizophrenia PRS and level of activity. For overall activity, the beta refers to change in level of activity in standard deviations (SD) per 1SD increase in PRS. For all other types of activity, beta refers to change in minutes of activity.

Activity	Threshold	beta	Lower CI	Upper CI	P-value	R^2
Overall	$5x10^{-8}$	-0.01	-0.01	0.001	0.08	$2.3x10^{-5}$
	$5x10^{-6}$	0.002	-0.004	0.01	0.55	$-7.2x10^{-6}$
	$5x10^{-4}$	0.002	-0.004	0.01	0.59	$-7.9x10^{-6}$
	0.05	0.002	-0.004	0.01	0.51	$-4.7x10^{-6}$
	0.1	0.004	-0.002	0.01	0.19	$8.4x10^{-6}$
	0.5	0.004	-0.002	0.01	0.16	$1.1x10^{-5}$
Moderate	$5x10^{-8}$	-0.09	-0.45	0.27	0.64	$-9.3x10^{-6}$
	$5x10^{-6}$	0.52	0.16	0.88	$4.6x10^{-3}$	$8.4x10^{-5}$
	$5x10^{-4}$	0.44	0.08	0.80	0.02	$5.7x10^{-5}$
	0.05	0.46	0.10	0.83	0.02	$6.2x10^{-5}$
	0.1	0.54	0.18	0.91	$3.7x10^{-3}$	$8.9x10^{-5}$
	0.5	0.51	0.15	0.88	0.01	$7.8x10^{-5}$
Walking	$5x10^{-8}$	-0.25	-0.69	0.20	0.28	$1.9x10^{-6}$
	$5x10^{-6}$	0.12	-0.33	0.57	0.60	$-9.3x10^{-6}$
	$5x10^{-4}$	0.32	-0.13	0.77	0.16	$1.2x10^{-5}$
	0.05	0.66	0.21	1.11	0.01	$9.3x10^{-5}$
	0.1	0.79	0.33	1.24	$6.8x10^{-4}$	$1.4x10^{-4}$
	0.5	0.82	0.36	1.27	$4.1x10^{-4}$	$1.5x10^{-4}$
Sedentary	$5x10^{-8}$	0.15	-0.56	0.86	0.68	$2.4x10^{-4}$
	$5x10^{-6}$	-0.69	-1.41	0.02	0.06	$2.8x10^{-4}$
	$5x10^{-4}$	-0.58	-1.30	0.13	0.11	$2.7x10^{-4}$
	0.05	-0.77	-1.49	-0.05	0.04	$2.9x10^{-4}$
	0.1	-0.99	-1.71	-0.27	0.01	$3.3x10^{-4}$
	0.5	-1.14	-1.87	-0.42	$1.9x10^{-3}$	$3.6x10^{-4}$
Sleep	$5x10^{-8}$	0.23	-0.29	0.76	0.39	$-3.2x10^{-6}$
	$5x10^{-6}$	0.40	-0.12	0.93	0.13	$1.7x10^{-5}$
	$5x10^{-4}$	0.35	-0.17	0.88	0.19	$9.6x10^{-6}$
	0.05	-0.01	-0.54	0.52	0.96	$-1.3x10^{-5}$
	0.1	-0.06	-0.59	0.47	0.82	$-1.2x10^{-5}$
	0.5	0.07	-0.46	0.60	0.79	$-1.2x10^{-5}$

Table 4.4. Bipolar disorder PRS results.
Results for all thresholds tested for association between bipolar PRS and level of activity. For overall activity, the beta refers to change in level of activity in standard deviations per 1SD increase in PRS. For all other types of activity, beta refers to change in minutes of activity.

Activity	Threshold	beta	Lower CI	Upper CI	P-value	R^2
Overall	$5x10^{-8}$	-0.003	-0.01	0.002	0.25	$3.5x10^{-6}$
	$5x10^{-6}$	-0.01	-0.01	0.000	0.05	$3.3x10^{-5}$
	$5x10^{-4}$	-0.01	-0.02	-0.01	$1.2x10^{-4}$	$1.5x10^{-4}$
	0.05	-0.02	-0.02	-0.01	$2.1x10^{-6}$	$3.1x10^{-4}$
	0.1	-0.02	-0.02	-0.01	$3.2x10^{-8}$	$3.3x10^{-4}$
	0.5	-0.02	-0.02	-0.01	$1.4x10^{-8}$	$3.5x10^{-4}$
Moderate	$5x10^{-8}$	-0.02	-0.38	0.34	0.91	$-1.2x10^{-5}$
	$5x10^{-6}$	-0.19	-0.56	0.17	0.29	$1.4x10^{-6}$
	$5x10^{-4}$	-0.38	-0.74	-0.02	0.04	$4.0x10^{-5}$
	0.05	-0.56	-0.92	-0.19	0.01	$9.7x10^{-5}$
	0.1	-0.56	-0.92	-0.20	$2.3x10^{-3}$	$9.9x10^{-5}$
	0.5	-0.52	-0.88	-0.16	$4.8x10^{-3}$	$8.3x10^{-5}$
Walking	$5x10^{-8}$	-0.20	-0.65	0.25	0.38	$-2.8x10^{-6}$
	$5x10^{-6}$	-0.55	-1.00	-0.10	0.02	$6.2x10^{-5}$
	$5x10^{-4}$	-0.52	-0.97	-0.08	0.02	$5.5x10^{-5}$
	0.05	-0.75	-1.20	-0.31	$3.0x10^{-3}$	$1.3x10^{-4}$
	0.1	-0.72	-1.17	-0.27	$1.7x10^{-3}$	$1.1x10^{-4}$
	0.5	-0.72	-1.17	-0.28	$1.5x10^{-3}$	$1.2x10^{-4}$
Sedentary	$5x10^{-8}$	0.47	-0.24	1.19	0.19	$2.6x10^{-4}$
	$5x10^{-6}$	0.72	0.01	1.43	0.05	$2.9x10^{-4}$
	$5x10^{-4}$	-0.03	-0.74	0.69	0.94	$2.4x10^{-4}$
	0.05	0.09	-0.62	0.81	0.83	$2.4x10^{-4}$
	0.1	0.03	-0.68	0.75	0.93	$2.4x10^{-4}$
	0.5	0.08	-0.63	0.79	0.82	$2.4x10^{-4}$
Sleep	$5x10^{-8}$	0.15	-0.37	0.68	0.56	$-8.6x10^{-6}$
	$5x10^{-6}$	0.39	-0.14	0.91	0.15	$1.4x10^{-5}$
	$5x10^{-4}$	0.96	0.43	1.48	$3.4x10^{-4}$	$1.5x10^{-4}$
	0.05	0.95	0.43	1.48	$1.8x10^{-3}$	$1.5x10^{-4}$
	0.1	0.95	0.42	1.47	$3.9x10^{-4}$	$1.5x10^{-4}$
	0.5	0.89	0.37	1.41	$8.8x10^{-4}$	$1.3x10^{-4}$

Table 4.5. Depression PRS results.

Results for all thresholds tested for association between depression PRS and level of activity. For overall activity, the beta refers to change in level of activity in standard deviations per 1SD increase in PRS. For all other types of activity, beta refers to change in minutes of activity.

Activity	Threshold	beta	Lower CI	Upper CI	P-value	R^2
Overall	$5x10^{-8}$	0.01	-0.001	0.01	0.09	$2.2x10^{-5}$
	$5x10^{-6}$	0.01	0.005	0.02	$3.4x10^{-4}$	$1.3x10^{-4}$
	$5x10^{-4}$	0.01	-0.001	0.01	0.08	$2.3x10^{-5}$
	0.05	0.01	0.003	0.02	0.01	$9.1x10^{-5}$
	0.1	0.01	0.003	0.01	$3.8x10^{-3}$	$8.3x10^{-5}$
	0.5	0.01	0.002	0.01	0.01	$7.1x10^{-5}$
Moderate	$5x10^{-8}$	0.20	-0.16	0.56	0.27	$2.5x10^{-6}$
	$5x10^{-6}$	0.35	-0.01	0.71	0.06	$3.1x10^{-5}$
	$5x10^{-4}$	0.43	0.07	0.79	0.02	$5.3x10^{-5}$
	0.05	0.57	0.21	0.93	0.01	$1.0x10^{-4}$
	0.1	0.61	0.25	0.97	$1.0x10^{-3}$	$1.2x10^{-4}$
	0.5	0.76	0.40	1.12	$4.0x10^{-5}$	$1.9x10^{-4}$
Walking	$5x10^{-8}$	-0.28	-0.73	0.17	0.22	$6.6x10^{-6}$
	$5x10^{-6}$	-0.11	-0.55	0.34	0.64	$-1.0x10^{-5}$
	$5x10^{-4}$	-0.36	-0.81	0.09	0.11	$1.9x10^{-5}$
	0.05	-0.23	-0.67	0.22	0.39	$-4.2x10^{-7}$
	0.1	-0.32	-0.77	0.13	0.16	$1.3x10^{-5}$
	0.5	-0.39	-0.83	0.06	0.09	$2.4x10^{-5}$
Sedentary	$5x10^{-8}$	-0.46	-1.17	0.26	0.21	$2.6x10^{-4}$
	$5x10^{-6}$	-1.04	-1.75	-0.32	$4.4x10^{-3}$	$3.4x10^{-4}$
	$5x10^{-4}$	-0.94	-1.66	-0.23	0.01	$3.2x10^{-4}$
	0.05	-1.74	-2.46	-1.03	$1.4x10^{-5}$	$5.2x10^{-4}$
	0.1	-1.72	-2.44	-1.01	$2.3x10^{-6}$	$5.1x10^{-4}$
	0.5	-1.65	-2.36	-0.93	$6.3x10^{-6}$	$4.9x10^{-4}$
Sleep	$5x10^{-8}$	0.45	-0.07	0.98	0.09	$2.4x10^{-5}$
	$5x10^{-6}$	0.29	-0.23	0.81	0.28	$2.3x10^{-6}$
	$5x10^{-4}$	0.54	0.01	1.06	0.04	$4.0x10^{-5}$
	0.05	0.89	0.36	1.41	$3.0x10^{-3}$	$1.3x10^{-4}$
	0.1	0.90	0.38	1.43	$7.6x10^{-4}$	$1.3x10^{-4}$
	0.5	0.88	0.35	1.40	$1.0x10^{-3}$	$1.3x10^{-4}$

Table 4.6 ADHD PRS results.

Results for all thresholds tested for association between ADHD PRS and level of activity. For overall activity, the beta refers to change in level of activity in standard deviations per 1SD increase in PRS. For all other types of activity, beta refers to change in minutes of activity.

Activity	Threshold	beta	Lower CI	Upper CI	P-value	R^2
Overall	$5x10^{-8}$	-0.003	-0.01	0.003	0.40	$-3.2x10^{-6}$
	$5x10^{-6}$	0.002	-0.004	0.01	0.48	$-5.7x10^{-6}$
	$5x10^{-4}$	-0.003	-0.01	0.003	0.31	$1.8x10^{-7}$
	0.05	-0.01	-0.01	-0.002	0.01	$6.6x10^{-5}$
	0.1	-0.01	-0.01	-0.002	0.01	$6.6x10^{-5}$
	0.5	-0.01	-0.01	-0.002	0.01	$6.2x10^{-5}$
Moderate	$5x10^{-8}$	-0.25	-0.61	0.11	0.18	$9.7x10^{-6}$
	$5x10^{-6}$	-0.02	-0.38	0.34	0.91	$-1.2x10^{-5}$
	$5x10^{-4}$	-0.04	-0.40	0.32	0.82	$-1.1x10^{-5}$
	0.05	-0.12	-0.49	0.24	0.54	$-6.4x10^{-6}$
	0.1	0.00	-0.36	0.36	0.99	$-1.2x10^{-5}$
	0.5	0.03	-0.33	0.39	0.86	$-1.2x10^{-5}$
Walking	$5x10^{-8}$	-0.60	-1.05	-0.15	0.01	$7.6x10^{-5}$
	$5x10^{-6}$	-0.47	-0.92	-0.02	0.04	$4.2x10^{-5}$
	$5x10^{-4}$	-0.73	-1.18	-0.28	$1.4x10^{-3}$	$1.2x10^{-4}$
	0.05	-0.57	-1.01	-0.12	0.02	$6.6x10^{-5}$
	0.1	-0.67	-1.12	-0.22	$3.2x10^{-3}$	$9.9x10^{-5}$
	0.5	-0.72	-1.16	-0.27	$1.7x10^{-3}$	$1.1x10^{-4}$
Sedentary	$5x10^{-8}$	0.71	-0.01	1.42	0.05	$2.9x10^{-4}$
	$5x10^{-6}$	0.46	-0.25	1.17	0.20	$2.6x10^{-4}$
	$5x10^{-4}$	1.31	0.60	2.02	$3.1x10^{-4}$	$4.0x10^{-4}$
	0.05	1.89	1.18	2.60	$2.5x10^{-6}$	$5.7x10^{-4}$
	0.1	1.92	1.21	2.63	$1.3x10^{-7}$	$5.8x10^{-4}$
	0.5	1.85	1.14	2.56	$3.5x10^{-7}$	$5.5x10^{-4}$
Sleep	$5x10^{-8}$	0.05	-0.48	0.57	0.86	$-1.3x10^{-5}$
	$5x10^{-6}$	-0.35	-0.87	0.17	0.19	$9.3x10^{-6}$
	$5x10^{-4}$	-0.70	-1.22	-0.17	0.01	$7.5x10^{-5}$
	0.05	-0.83	-1.35	-0.30	0.01	$1.1x10^{-4}$
	0.1	-0.86	-1.39	-0.34	$1.3x10^{-3}$	$1.2x10^{-4}$
	0.5	-0.80	-1.33	-0.28	$2.6x10^{-3}$	$1.0x10^{-4}$

Table 4.7. ASD PRS results.

Results for all thresholds tested for association between ASD PRS and level of activity. For overall activity, the beta refers to change in level of activity in standard deviations per 1SD increase in PRS. For all other types of activity, beta refers to change in minutes of activity.

4.3.4 Adjusted model covarying for environmental effects on activity

Physical activity levels may be affected by various environmental factors that in many instances are also associated with increased risk of psychiatric disorders. To examine whether potential confounding environmental factors would impact my findings, I assessed the association between PRS for psychiatric disorders and overall level of activity after covarying for alcohol use, cannabis use, substance use or behavioural addiction, smoking status, fluid intelligence, and Townsend deprivation index. Table 4.8 details the results of the adjusted model. The effect sizes for schizophrenia, bipolar disorder, and ADHD PRS in association with overall levels of activity remained consistent after covarying for these risk factors. However, effect sizes were reduced for MDD and ASD PRS when these covariates were included (Table 4.8).

Polygenic risk score	Beta	Lower CI	Upper CI	P-value
Schizophrenia	-0.01	-0.03	-0.001	0.04
Bipolar disorder	0.01	-0.01	0.02	0.42
Depression	-0.01	-0.02	0.01	0.25
ADHD	0.01	-0.002	0.02	0.10
ASD	0.002	-0.01	0.01	0.80

Table 4.8. Adjusted model PRS results.
Results of the association between PRS and overall level of activity when co-varying for alcohol use, cannabis use, substance or behavioural addiction, smoking status, fluid intelligence, and Townsend deprivation index.

4.3.5 Genetic Correlations

To establish the extent to which the genetic architecture of psychiatric disorders is shared with that of physical activity, I measured genetic correlations between each disorder and each type of activity. Results of the genetic correlations are presented in Table 4.9 and Figure 4.5. There were significant genetic correlations between schizophrenia and more time spent walking (r_g=0.11, p=0.006), reduced time spent in sedentary activity (r_g=-0.09, p=0.019), and greater sleep duration (r_g=0.07 p=0.039). Bipolar disorder showed significant genetic correlations with greater moderate activity (r_g=0.22, p=0.004) and more time spent walking (r_g=0.11, p=0.048). MDD was significantly genetically correlated with reduced overall activity (r_g=-0.10, p=0.011) and reduced walking (r_g=-0.10, p=0.022). ASD showed significant genetic correlations with greater sedentary activity (r_g=0.25, p=0.003), and reduced sleep duration (r_g=-0.20, p=0.006). ADHD was not significantly genetically correlated with any type of activity.

Psychiatric disorder	Activity type	Genetic correlation	Standard error	P-value	Intercept
Schizophrenia	Overall	-0.04	0.03	0.24	0.005
	Moderate	0.07	0.05	0.19	-0.001
	Walking	0.11	0.03	0.01	0.000
	Sedentary	-0.09	0.03	0.02	-0.002
	Sleep	0.07	0.03	0.04	-0.006
Bipolar disorder	Overall	0.03	0.04	0.50	-0.001
	Moderate	0.22	0.06	$4x10^{-3}$	-0.012
	Walking	0.11	0.04	0.05	-0.004
	Sedentary	-0.07	0.04	0.15	0.002
	Sleep	<0.00	0.04	0.98	-0.005
Depression	Overall	-0.10	0.03	0.01	-0.005
	Moderate	-0.01	0.05	0.98	-0.007
	Walking	-0.10	0.04	0.02	-0.004
	Sedentary	0.03	0.04	0.50	-0.005
	Sleep	0.04	0.03	0.21	0.008
ADHD	Overall	0.08	0.05	0.15	0.003
	Moderate	0.14	0.07	0.08	0.003
	Walking	<0.00	0.05	0.99	-0.008
	Sedentary	-0.08	0.05	0.15	-0.006
	Sleep	0.01	0.05	0.98	0.009
ASD	Overall	-0.11	0.05	0.05	0.004
	Moderate	-0.16	0.09	0.15	0.012
	Walking	-0.12	0.07	0.15	0.007
	Sedentary	0.25	0.06	$3.0x10^{-3}$	-0.009
	Sleep	-0.20	0.06	0.01	0.011

Table 4.9. Genetic correlations between neuropsychiatric disorders and types of activity.
Columns indicate the disorder and type of activity being correlated, the regression coefficient of the correlation, the standard error, and the p-value of the correlation. P-values are corrected for false discovery rate (P<0.05).

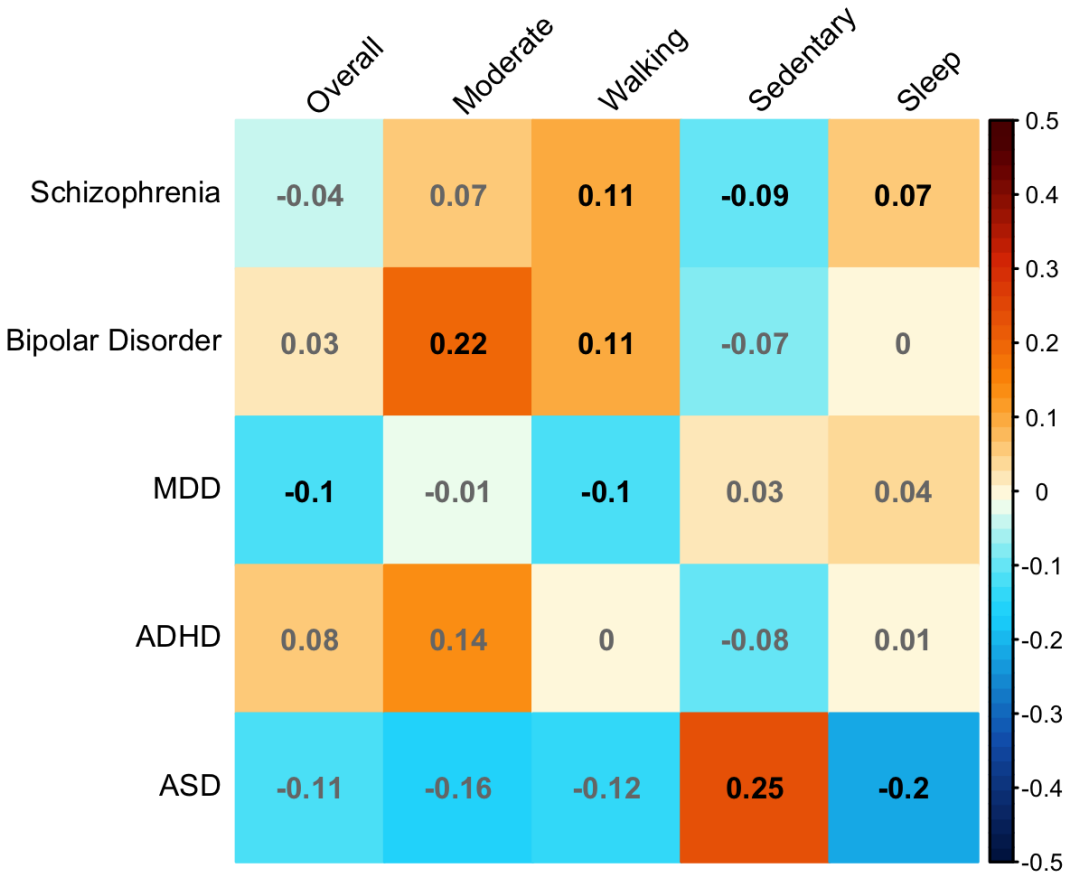

Figure 4.5. Genetic correlation matrix displaying the correlation coefficient (r_g). Square colour indicates direction of effect. Black text indicates correlation coefficients significant at FDR-corrected p<.05, grey text indicates non-significant correlations.

4.4 Discussion

In this study, I found levels of objectively-measured physical activity to be significantly affected in UK Biobank participants with a diagnosis of schizophrenia, bipolar disorder, depression, and ASD. Increased PRS for schizophrenia, bipolar disorder, MDD, ADHD, and ASD were associated with significant, yet modest, changes in levels of physical activity in individuals without mental health conditions. I observed several significant genetic correlations between psychiatric disorders and types of activity. These correlations mirrored the results observed between PRS and levels of activity, suggesting that the genetic architecture of physical activity is shared, to a small extent, with the genetic architecture of psychiatric disorders.

4.4.1 Activity levels in psychiatric disorders

I found that individuals with schizophrenia, bipolar disorder, depression, and ASD had reduced levels of overall physical activity in comparison to individuals without a psychiatric diagnosis, consistent with previous research demonstrating reduced levels of subjectively-measured activity in psychiatric disorders (Goodwin, 2003; Janney *et al.*, 2014; Stubbs *et al.*, 2016; Lyall *et al.*, 2018). My results expand upon existing findings by demonstrating these effects in a sample that is larger than has been reported previously, and by using objective methods to capture activity. Additionally, I present novel findings that individuals with psychiatric disorders show different patterns of activity, including reduced moderate activity and longer sleep duration in individuals with schizophrenia, bipolar disorder, and depression, and increased levels of sedentary activity in individuals with depression and ASD. Across the different disorders, individuals with schizophrenia and ASD showed the most substantial reduction in overall levels of activity. Individuals with schizophrenia also spent the least amount of time in moderate activity and the longest time asleep, whilst individuals with ASD spent the most time in a sedentary level of activity.

Previous research has suggested that disruption to circadian rhythm, measured by smaller differences between the most active and least active periods of the day, is associated with increased likelihood of depression and bipolar disorder (Lyall *et al.*, 2018). My results support and extend these findings by demonstrating a reduced

pattern of activity with longer sleep duration in individuals with these disorders. The disruption in physical activity observed in this study could arise either from disorder-related factors such as symptoms or medication side-effects, or from risk factors for the disorders. Together these findings suggest that disrupted activity may be an important aspect of psychiatric illness.

ADHD diagnosis, however, was not associated with altered levels of physical activity. Between 40 and 60% of children with ADHD continue to show symptoms in adulthood (Faraone, Biederman and Mick, 2006), thus it is possible that many participants with an ADHD diagnosis may be asymptomatic by the time of data collection. Alternatively, my result may reflect the fact that the UK Biobank is a cohort of individuals aged over 40, who may be less likely to have received a diagnosis of ADHD due to changes in the awareness of the disorder over time (Polanczyk *et al.*, 2014).

4.4.2 Genetic liability for psychiatric disorders

In individuals without a mental health disorder, genetic liability for schizophrenia, MDD, ADHD, and ASD was significantly associated with the overall level of physical activity. I also observed several associations between PRS and levels of subtypes of activity, including greater levels of moderate activity with increased PRS for schizophrenia, bipolar disorder, and ADHD. These findings are consistent with the hypothesis that physical activity is one of the behaviours that is influenced by genetic risk for psychiatric disorders in individuals without a psychiatric diagnosis. However, both the estimated effect sizes of PRS associations and the genetic correlations were small and correspond to a negligible amount of activity. Thus, differences observed in levels of activity in individuals with psychiatric disorders are more likely the result of manifesting the disorders *per se*, rather than reflections of genetic vulnerability to them. Such factors may be secondary, for example the use of psychotropic medication (Stubbs *et al.*, 2017) or could be symptoms of the disorder itself. The associations between overall levels of activity and MDD and ASD PRS were attenuated after controlling for alcohol use, cannabis use, substance addiction, smoking, cognition, and deprivation, further suggesting that non-genetic factors may have a stronger effect on levels of activity than PRS. This has important consequences for the physical health of

those with psychiatric disorders, particularly as these individuals are known to be at greater risk of numerous physical health conditions (Momen *et al.*, 2020) and early mortality (Chang *et al.*, 2011), which may in part be due to reduced levels of activity. Further research aiming to understand why physical activity is affected in psychiatric disorders is necessary to address and improve physical and mental health outcomes of individuals with these disorders.

4.4.3 Strengths and limitations

I was unable to exclude the possibility of an overlap of participants between training and target samples when calculating PRS. However, the genetic correlation analysis, for which non-overlapping samples is not a requirement, supports the PRS findings. All of the intercepts for the genetic correlations were below 1 which is consistent with minimal sample overlap between the discovery GWAS and the target sample for PRS. Case overlap between the discovery GWAS and the target sample (UK Biobank) would lead to overestimation of the PRS effect sizes for any PRS associations that are driven by psychiatric diagnoses. As the effect sizes I observed are modest, any overestimation in effect size would not alter the conclusions.

A strength of my study is the substantial sample size, allowing greater power to detect small genetic effects. However, it is important to note that the sample is a population-based cohort and the limited number of psychiatric cases within UK Biobank means the study was underpowered to measure the influence of genetic risk in those with psychiatric illness. Individuals with mental health disorders are known to be underrepresented in the UK Biobank and those that are included tend to be a more highly functioning group than people with the disorders as a whole (Kendall *et al.*, 2017). Thus, the differences in levels of activity in individuals with psychiatric disorders could be underestimated in my study.

Obtaining accelerometer data in a sufficiently powered sample of individuals with psychiatric disorders is a notable challenge. Nevertheless, future research would benefit from the study of objectively-measured activity in individuals with mental health disorders, particularly given findings demonstrating substantial discrepancies between self-report and accelerometer measured activity (Firth *et al.*, 2018).

Furthermore, it would be valuable to further measure the contribution of non-genetic factors to activity levels in individuals with psychiatric disorders, including the impact of clinical characteristics that were unavailable in my sample, for instance symptom severity and medication side effects. Such research would further elucidate the factors contributing to reduced activity in psychiatric disorders and may advance the development of effective interventions.

4.4.4 Conclusions

Levels of physical activity were significantly reduced in UK Biobank participants with a diagnosis of schizophrenia, bipolar disorder, depression, and ASD, emphasising the need for clinical intervention to address levels of physical activity in these populations. I found novel evidence of association between schizophrenia, MDD, ADHD, and ASD PRS and accelerometer-assessed physical activity in the UK Biobank. Furthermore, several significant genetic correlations were observed with subtypes of physical activity, most notably between ASD and sedentary activity, ASD and sleep duration, and bipolar disorder and moderate activity. Overall, my findings indicate weak to modest sharing of liability to the psychiatric disorders and types of activity I have tested, suggesting that the much more substantial differences in levels of activity seen in individuals with the psychiatric disorders are mainly consequences of the disorders, rather than reflections of liability to them.

Chapter 5

Discussion

5.1 Summary of results

This thesis investigated the relationships between psychosis-spectrum disorders by analysing phenotypic and genotypic associations with categorical diagnoses and examining approaches to conceptualising and defining these disorders. In Chapter 2, I compared demographics, clinical characteristics, and polygenic risk scores between individuals with schizophrenia and schizoaffective disorder depressive-type (SA-D). I identified several differences between members of the two diagnostic groups. These included associations between a diagnosis of SA-D and female sex, lifetime alcohol dependence, experience of childhood maltreatment, and more severe clinical characteristics of depression. Furthermore, Individuals with SA-D in comparison to those with schizophrenia had elevated polygenic risk for depression, but not for schizophrenia or bipolar disorder. These findings were consistent with SA-D being a hybrid of schizophrenia and depression resulting from elevated liability to both disorders.

To examine associations between symptom dimensions and polygenic risk scores (PRS) (Chapter 3), I amalgamated data across four studies creating a cohort of individuals with schizophrenia, schizoaffective disorder, and bipolar disorder. I created five symptom dimensions relating to positive, negative, disorganised, mania, and depression symptoms, and identified numerous associations between PRS for schizophrenia, bipolar disorder, depression, and intelligence and the symptom dimensions. Many of these associations were accounted for by diagnosis but not all, indicating that dimensional models of symptoms may provide additional insights into the biology underlying liability to these disorders.

Using latent class analysis, I identified three relatively phenotypically-homogenous classes of individuals in the cross-disorder cohort (Chapter 3). The first class was

characterised by poorer premorbid functioning and worse outcomes than the other classes, and had the highest factor scores for positive, negative, and disorganised symptoms. Class two was characterised by intermediate functioning relative to the other classes, but with very high rates of having ever been detained under the mental health act. The final class was characterised by relatively good premorbid functioning and outcomes, with higher rates of having experienced a psychosocial stressor in the six months prior to onset. Class three also had the highest factor scores for mania and depression symptoms. The higher functioning class was distinguished from the other two classes by lower schizophrenia and higher intelligence PRS. Compared to the intermediate functioning class, the lower functioning class was associated with higher ADHD PRS and lower bipolar disorder PRS.

Chapter 4 examined physical activity as a possible dimensional phenotype of relevance to psychiatry, as levels of activity are altered in a range of psychiatric disorders. I examined whether genetic liability to psychiatric disorders impacts objectively-measured levels of activity. Despite substantial differences in the levels of activity between individuals with and without psychiatric disorders, I found that polygenic risk for these disorders was negligibly associated with activity in the general population. This suggests that the differences in levels of activity between cases and controls are more likely the result of aspects of the disorder itself, such as symptoms or medication, rather than resulting from genetic liability to the disorder.

5.2 Validity of schizoaffective disorder

The validity of schizoaffective disorder has been debated extensively, but progress in conceptualising it has been hindered by limited research into the disorder and specifically its individual subtypes (Heckers, 2009). Hypotheses of schizoaffective disorder include that it is a form of schizophrenia, a form of mood disorder, an expression of comorbid schizophrenia and mood disorder, an intermediate category on a spectrum of schizophrenia and affective disorders, or a distinct diagnosis separate from schizophrenia and mood disorders (Heckers, 2009).

5.2.1 Hybrid model of SA-D

The findings of Chapter 2 demonstrated that individuals with SA-D in comparison to those with schizophrenia had an elevated genetic liability to depression but not to schizophrenia. SA-D, compared to schizophrenia, was also associated with more severe depression phenotypes and risk factors for depression, including more episodes, worse functioning in depression, female sex, lifetime alcohol dependence, and childhood abuse. These findings indicate that SA-D may be characterised as a hybrid of schizophrenia and depression, resulting from co-occurring liability to both disorders. The hypothesis that SA-D is a form of schizophrenia predicts that SA-D would not substantially differ to schizophrenia in terms of clinical characteristics (except for those required to make the diagnosis of SA-D such as mood change) or genetic liability. My findings are inconsistent with this hypothesis as important phenotypic and polygenic differences were observed between the two diagnoses. However, I cannot definitively exclude this as a hypothesis as my findings do not support SA-D as being entirely independent of schizophrenia. Genetic risk factors and many environmental risk factors for schizophrenia did not significantly differ between the two groups, including urbanicity, family history of schizophrenia, premorbid social functioning, obstetric complications, and cannabis dependence. Thus, a hybrid model may better account for the differences, and similarities, observed between SA-D and schizophrenia. Previous research using twin and family study designs has observed an increased risk of schizophrenia, SA-D, and depression in relatives of individuals with SA-D (Laursen *et al.*, 2005; Cardno *et al.*, 2012), suggesting an elevated liability to both schizophrenia and depression in individuals with SA-D. My findings are consistent with these observations and extend them to identify an association for SA-D with PRS for schizophrenia and depression, which has not been demonstrated previously.

5.2.2 Differences between schizoaffective subtypes

A model in which SA-D is a form of bipolar disorder would predict a higher bipolar disorder PRS in individuals with SA-D compared to schizophrenia; my findings did not support this hypothesis. However, I observed several phenotypic differences between SA-D and schizoaffective disorder bipolar-type (SA-BP), suggesting that whilst it may be appropriate to consider SA-D as a hybrid between schizophrenia and depression, it

may not necessarily be true that SA-BP is a hybrid between schizophrenia and bipolar disorder. I was unable to examine polygenic differences between SA-BP and either schizophrenia or SA-D due to a lack of data for SA-BP at the time of analysis. Therefore, it remains possible that SA-BP may be either a form of bipolar disorder or a hybrid of schizophrenia and bipolar disorder. Previous research examining SA-BP has found that individuals with SA-BP have lower schizophrenia PRS than people with schizophrenia, but increased schizophrenia PRS than people with bipolar disorder type 1 (Charney *et al.*, 2017; Allardyce *et al.*, 2018). Individuals with SA-BP and bipolar disorder type 1 did not significantly differ in terms of bipolar disorder PRS, but bipolar disorder type 1 was associated with higher bipolar disorder and schizophrenia PRS than bipolar disorder type II (Charney *et al.*, 2017). Therefore, SA-BP may be conceptualised as an intermediary between schizophrenia and bipolar disorder on a spectrum of increasing liability to these disorders.

In Chapter 3, the majority of individuals with SA-D were assigned to the lower functioning class, as were individuals with schizophrenia, while individuals with SA-BP were divided fairly evenly over the three classes. This suggests that individuals with SA-BP may represent a relatively more heterogenous group than individuals with SA-D, and that SA-BP and SA-D together do not represent a phenotypically-homogenous group despite the frequent practice in research of combining them into one group. Thus, separate investigation of SA-D and SA-BP is needed to determine the validity and reliability of each diagnosis separately. My findings, in conjunction with the results of previous research, underscore the importance of differentiating between subtypes of schizoaffective disorder. However, ICD-11, due to be adopted into clinical practice in 2022, has retained schizoaffective disorder as a diagnosis but has removed the individual subtypes. The findings here suggest that future research should continue to consider each subtype individually in order to fully assess the validity of schizoaffective disorder and determine its future diagnostic status.

5.3 Dimensional approaches to symptoms

Criticisms of validity and utility have been made not just of schizoaffective disorder but also of the categorical nature of psychotic disorders more widely (Allardyce *et al.*, 2007). An alternative suggestion has been to adopt dimensional approaches that capture the continuous nature of the phenotypes defining these disorders (Esterberg and Compton, 2009). Dimensional approaches may be considered to have greater validity and utility than categorical approaches if they are able to provide a greater amount of information regarding aetiology, risk factors, and/or outcomes (Kendell and Jablensky, 2003). Previous research across psychotic and affective disorders has suggested that a model encompassing five dimensions of positive, negative, disorganised, mania, and depression symptoms may be an appropriate fit in the context of schizophrenia and bipolar disorder (Reininghaus *et al.*, 2016; Quattrone *et al.*, 2019), but has not examined polygenic associations with these dimensions. I applied this five-dimensional model to a cohort of individuals with schizophrenia, SA-D, SA-BP, and bipolar disorder type 1 and found several associations between symptoms and PRS for different psychiatric disorders and intelligence. Categorical diagnosis was able to explain most differences between PRS for different disorders and the symptom dimensions, indicating that existing diagnostic definitions are capturing much of the variation in the genetic aetiology of these phenotypes. However, after adjusting for diagnosis, several associations remained between symptoms and PRS, including between negative symptoms and lower intelligence PRS, disorganised symptoms and higher schizophrenia PRS, and depression symptoms and higher depression PRS. These findings suggest that dimensional approaches to symptoms may capture additional variation in genetic liability that is not captured by categorical diagnosis and therefore have the potential to provide further insights into aetiology. Previous research has found an association between disorganised symptoms and schizophrenia PRS in people with schizophrenia (Fanous *et al.*, 2012; Legge, Cardno, *et al.*, 2021); here I have extended this finding to a cross-disorder sample, indicating that the aetiology of the symptoms may be similar across diagnoses.

Depression is a common comorbidity in psychiatric disorders (Rush *et al.*, 2005), yet it remains unclear whether this is due to shared genetic and environmental risk factors for depression, a distinct genetic and non-genetic aetiology, or whether depression occurs as a secondary effect of the primary diagnosis . My finding that depression PRS is associated with increased number of depression symptoms, independent of diagnosis, suggests that these symptoms are at least in part due to elevated liability for depression that occurs outside the context of psychosis spectrum disorders, and that this mechanism is shared across those disorders. Furthermore, this finding is consistent with the finding of increased depression PRS in people with SA-D compared to schizophrenia with depression that I observed in Chapter 2.

By identifying novel associations between symptom dimensions and PRS and extending previous findings to a cross-disorder sample, I have demonstrated that some of the symptoms defining psychotic and affective disorders have a common-cross disorder aetiology, suggesting that this dimensional model may be a valid approach to conceptualising these symptoms. My findings add to a growing body of evidence suggesting that adopting a dimensional model will provide an additional level of detail and capture a wider degree of heterogeneity that is lost when collapsing these phenotypes into binary categories (Guloksuz and Van Os, 2018). This is likely to be useful in a research context, where continuous dimensions allow for greater power to examine variation in these phenotypes. However, in a clinical context, dimensional approaches are not without limitations. Difficulties in communicating dimensions to individuals with psychotic and affective disorders limit the clinical translation of these approaches. Conversely, categorical approaches facilitate decision making between clinicians and patients, and provide a point of reference for accessing services and improving understanding of these disorders in the general population.

5.4 Identification of phenotypically-homogenous classes

5.4.1 Associations with specific patterns of polygenic risk

Current diagnostic categories for schizophrenia and bipolar disorder are based on signs and symptoms that have not substantially changed since their conception. Whilst these definitions have led to advances in our understanding of the genetic aetiology of

these disorders, it has become increasingly clear that current categorical diagnoses do not neatly map onto underlying biology. A key goal of psychiatric genetics research is to identify novel treatments based on aetiology. Refining diagnostic categories so that they better reflect the aetiology should create greater power for detecting genotype-phenotype associations and advance efforts in precision medicine. Data-driven approaches offer one potential way to detect relatively more homogeneous groups. The three classes I identified were associated with clear differences in their premorbid adjustment, clinical characteristics, and outcomes, suggesting that there may be utility in incorporating a wider range of phenotypes than symptoms into diagnostic classification. Poor premorbid adjustment in people with schizophrenia has been associated with worse outcomes, including more severe negative symptoms and functional disability (Bailer, Bräuer and Rey, 1996; Ayesa-Arriola *et al.*, 2013). Consistent with this finding, I observed that poor premorbid functioning clustered with measures of poor outcome, lending further support to the view that measures of premorbid adjustment could provide prognostic insights. Moreover, these phenotypic differences may reflect variation in genetic liability. The higher functioning class had higher intelligence PRS and lower schizophrenia PRS than both the lower and intermediate functioning classes, suggesting that the better premorbid adjustment and outcomes characterising the higher functioning class partly reflects differences in genetic predisposition to these traits. Furthermore, the lower functioning class had a higher ADHD PRS than the intermediate functioning class, suggesting that the higher rates of poor premorbid adjustment and worse outcomes in the lower functioning class may reflect greater neurodevelopmental risk. Previous research has found that low educational attainment PRS is associated with a cluster defined by more severe psychotic symptoms and poorer functioning (Dwyer *et al.*, 2020; Pelin *et al.*, 2021). My findings build upon this work by demonstrating clusters defined by a variety of premorbid characteristics and outcomes, associated with varying degrees of symptom severity in a cross-disorder context, and extend this to show associations between class and PRS for several psychiatric disorders and intelligence.

A particular issue of subtyping research in psychosis-spectrum disorders is the lack of consistency and replication across studies. Dwyer and colleagues (2020) used factor

scores for psychosis, quality of life, suicide, depression, and environmental risk to cluster individuals with psychotic and affective disorders. They observed a class characterised by low educational attainment, low quality of life, and high psychosis symptoms, which may be similar to the lower functioning class I identified. However, the remaining classes identified by Dwyer and colleagues are not so consistent with the classes I have identified. This may reflect differences in the variables included for clustering and the methodology used to derive clusters. For instance, I included variables with a focus on premorbid functioning and clinical history, whilst Dwyer *et al.* (2020) included measures of quality of life with an emphasis on depression and suicide. Thus, for clusters to be replicated in separate studies and evaluated for their clinical and research utility, a comprehensive range of phenotypes that capture the range of heterogeneity in these disorders need to be used. Dwyer and colleagues were unable to validate their clusters with specific patterns of polygenic risk, with the exception of lower educational attainment PRS in their severe psychosis cluster, suggesting that they do not map onto known genetic risk for psychiatric disorders. However, they were able to replicate their clusters in an independent cohort; the lack of replication is a key limitation of my study.

5.4.2 Comparison between classes and diagnosis

Whilst there was a tendency for most people with schizophrenia to be categorised into the lower functioning class and most people with bipolar disorder into the higher functioning class, the classes were not equivalent to existing diagnostic categories. Specifically, the intermediate functioning class contained approximately a third of individuals with schizophrenia, SA-D, and SA-BP, and almost half of individuals with bipolar disorder, and thus does not neatly map onto any existing diagnosis. When examining the distribution of phenotypes and PRS associations between classes restricted to only people with schizophrenia, the pattern of lower, intermediate, and higher functioning was consistent with the full sample, suggesting that differences between the classes are not driven by diagnostic group. Additionally, individuals with schizophrenia in the higher functioning class had lower ADHD PRS than individuals with schizophrenia in the other two classes, yet schizophrenia PRS did not significantly differ between any class. Whilst the lack of a significant association with schizophrenia

PRS may reflect reduced power of the within-disorder analysis, the association with ADHD PRS indicates that heterogeneity seen within a single disorder reflects variation in genetic liability to other disorders and traits. In the PRS analysis restricted to individuals with bipolar disorder, the intermediate functioning class had higher schizophrenia PRS than the higher functioning class, further suggesting that variation with disorders may be driven by genetic liability beyond risk for that specific disorder. Within individuals with bipolar disorder, higher schizophrenia PRS has been associated with the presence and increasing severity of psychotic symptoms(Allardyce *et al.*, 2018), and I extend this finding to demonstrate that a cluster of individuals with bipolar disorder characterised by higher rates of involuntary admission and relatively lower functioning was associated with higher schizophrenia PRS than a cluster characterised by relatively higher functioning and more favourable outcomes.

5.5 Physical activity in individuals with psychiatric disorders and the general population

In Chapter 3, I demonstrated that symptom dimensions across diagnostic categories reflect underlying genetic liability to psychiatric disorders in addition to that already captured by existing categorical approaches. I sought then to extend this approach to other clinically-relevant phenotypes, i.e., measures of physical activity, to assess whether dimensional assessments could provide insights into genetic liability to psychiatric disorders in the general population. I found marked differences in levels of physical activity between people with and without a psychiatric diagnosis, confirming previous findings of altered activity in people with various psychiatric disorders (Goodwin, 2003; Janney *et al.*, 2014; Stubbs *et al.*, 2016). However, PRS for different psychiatric disorders explained a negligible amount of variation in physical activity and genetic correlations between types of activity and psychiatric disorders were small. These findings suggest that activity in the general population does not provide a measure of genetic liability to the psychiatric disorders I examined. Furthermore, significant associations between activity levels and PRS for depression and autism, which explained the most variance and had the strongest genetic correlation with

activity, respectively, were better explained by other risk factors for psychiatric disorders and activity, including smoking status, deprivation, substance use, and intelligence.

Given the strong associations between physical activity and psychiatric disorders, research has attempted to measure causal relationships between the two. Evidence from Mendelian Randomisation (MR) studies has suggested that overall levels of physical activity may be a causal factor contributing to depression and bipolar disorder, but not to schizophrenia (Choi *et al.*, 2019; Papiol *et al.*, 2020; Sun *et al.*, 2020). Whilst my methodology does not explicitly test causality, my findings suggest that in people with a psychiatric diagnosis, non-genetic factors may predominantly explain reduced levels of activity. The strongest genetic correlation I observed was a positive correlation between moderate activity and bipolar disorder, indicating that the SNPs associated with greater levels of moderate activity also increase risk of bipolar disorder. Despite this, a diagnosis of bipolar disorder was associated with reduced levels of overall activity, moderate activity, and walking, suggesting a stronger influence of the disorder itself on activity levels, rather than of genetic factors that influence physical activity. I was unable to measure the association between PRS and activity levels within individuals with a psychiatric diagnosis, due to the small number of individuals with a diagnosis and accelerometer data in UK Biobank. I was also unable to measure whether PRS for physical activity was associated with case-control status, as this would require an independent GWAS of physical activity that was not conducted in the UK Biobank sample, which is not available. Therefore, it is possible that genetic factors not examined in my study could play a role in activity levels in psychiatric disorders. Physical inactivity remains a significant public health challenge and understanding the causes of inactivity in the general population and in people with psychiatric disorders should be a key priority for future research.

5.6 Strengths and limitations

5.6.1 Sample depth and breadth

A strength of my thesis is the utilisation of various methods and samples to scrutinise categorical diagnoses as they currently exist. In Chapter 2 I examined an in-depth, well characterised sample to measure differences between people with schizophrenia and SA-D. This allowed me to examine many clinically relevant variables, including detailed information relating to medical history. The sample was also genotyped, allowing for PRS analysis, however this may have been underpowered due to the small number of individuals with SA-D. Conversely, in Chapter 4 I utilised a dataset of 100,000 people allowing for well powered genetic analysis. Whilst well-suited to polygenic analyses, individuals with severe mental illness are underrepresented in UK Biobank (Kendall *et al.*, 2017), and due to selection bias for healthier volunteers (Fry *et al.*, 2017), it is likely that individuals with psychiatric disorders that are included are not representative of people with psychiatric disorders more broadly. Furthermore, the UK Biobank dataset does not contain detailed information on clinical history and medication use, preventing examination of detailed hypothesis of the effects of these factors on levels of activity. In Chapter 3, I amalgamated data from four sources to curate a dataset that balanced power for polygenic analyses and availability of detailed phenotypic variables. Not all relevant phenotypes were available across all datasets, and thus the combined sample did not include some potentially informative variables, for instance premorbid and current cognition. Despite the inherent limitations of each sample individually, by leveraging the differences between samples I have been able to apply a range of complementary analytical methods that have a collective value in addressing the aims of my thesis.

5.6.2 Lifetime clinical ratings

The phenotypes used in Chapters 2 and 3 were derived based on lifetime presence, rather than current experience at the time of interview. This approach is advantageous in that it provides a more complete picture of the individual's illness and limits issues regarding current illness stage, particularly for an episode illness such as bipolar disorder. However, it does not eliminate the possibility that the individual could go on

to develop this phenotype later as participants could be interviewed at any stage of their illness. Furthermore, lifetime ratings here rely on retrospective recall of information. The four samples used in Chapters 2 and 3 all included assessment of medical records to support the phenotype ratings, which attenuates the impact of recall bias. Nevertheless, availability and access to these records becomes more difficult the older the records are, due to various reasons including changes from paper to digital archiving and participants moving between different health boards or trusts. Therefore, participant age and duration of illness will likely have impacted the accuracy and completeness of the data. In my analysis I took steps to account for this, including using age at interview as a covariate in all regression models. I also included duration of illness and age at interview as covariates in the latent class analysis used to derive clusters in Chapter 3.

One of the major criticisms of subtypes in schizophrenia is the lack of temporal stability. The classical subtypes of schizophrenia were based on current symptoms, meaning that changes in clinical presentation with illness progression results in increasing rates of the undifferentiated subtype over time (Pfohl and Winokur, 1983). By using lifetime ratings, I was able to include a wider array of information that may result in more stable clusters. However, I was unable to test this hypothesis as I used a cross-sectional sample. To fully evaluate the stability of the clusters I identified, it is necessary to assess a prospective longitudinal sample, where individuals can be evaluated from the first episode of their illness. Clustering on the basis of premorbid characteristics and items that emerge at onset may also protect against these effects and could reduce the need for long observational periods. Furthermore, utilising premorbid variables may also result in findings that are more clinically translatable, as they can be taken into consideration as the illness is emerging and treatment is initiated.

5.6.3 Replication and clinical utility

I was unable to assess whether the clusters I identified in Chapter 3 could be replicated in an independent sample. Some studies have divided their sample into two groups to allow for replication analyses (Dwyer *et al.*, 2020; Pelin *et al.*, 2021), I chose not to adopt this approach in order to maximise the power for polygenic associations in my

study. Replication of dimensional and cluster approaches is necessary to assess their validity and investigate the utility of these clusters in clinical practice and research. It is necessary for the clusters I have identified to be replicated in additional samples and ideally extended to a broader range of phenotypes than I was able to include. For example, cognitive impairments are seen across the psychosis-affective spectrum, to varying degrees of severity. Therefore, measuring cognitive differences across the classes could allow for additional insights into the aetiology of these impairments and exploration of the relationship between cognition and other clinically-relevant phenotypes.

The five symptom dimensions I studied have been applied in two cross-disorder cohorts previously, one in first episode psychosis (Quattrone *et al.*, 2019, 2021) and the other in a sample of people with schizophrenia, schizoaffective disorder and bipolar disorder (Reininghaus *et al.*, 2016). I extended the findings of these studies to measure the relationship between symptoms and PRS for different psychiatric disorders, with my findings indicating that the dimensions were able to capture a significant degree of variation in PRS. Thus, my study, in conjunction with the work of Quattrone *et al.* and Reininghaus *et al.* suggests that conceptualising symptoms in this manner may be a valid and appropriate method in research. Further research is necessary to understand how these dimensions can be translated into clinical practice, for instance whether they should be used to support diagnosis, as is being done in ICD-11, or whether they are an acceptable alternative to a categorical diagnosis.

5.7 Recommendations for future research

5.7.1 Large-scale phenotypic analysis

One of the major limitations facing research in psychiatric genetics is the trade-off between depth and breadth of phenotype data. Due to the logistical and funding difficulties in recruiting and interviewing high numbers of participants, there has been limited ability to ascertain large-scale datasets for genetic analysis that also contain in-depth phenotype data relating to mental health. Improvements in access to such data will allow for advances in our understanding of the influence of genetics on heterogeneity within disorders as well as homogeneity across disorders. Electronic

health records (EHRs) present one method that may allow for the harmonisation of deep-phenotype and genotype data. EHRs create a systematic method of ascertaining phenotypes that are not constrained by many of the limitations of existing methods. For instance, EHRs can be used to derive variables on everyone in a given area and thus do not exclude the most severely unwell individuals or other typically under-represented groups. However, there are many logistical and ethical issues to consider when utilising EHRs. Missing data is a significant challenge, as it is difficult to differentiate between data that is absent because an event has not occurred and data that has occurred but has been omitted, although there are analytical strategies that can limit the impact of missing data (Wells *et al.*, 2013). There are also substantial ethical issues to consider, in particular relating to anonymity and consent(Riordan *et al.*, 2015). Linking EHRs to a blood sample for DNA extraction further complicates this process, although this has been achieved by private healthcare providers and in nationwide registry data (Pedersen *et al.*, 2018; Smoller, 2018). Research is beginning to establish the reliability of ascertaining psychiatric phenotypes from EHRs, for instance negative symptoms(Patel *et al.*, 2015) and antipsychotic prescriptions (Kadra *et al.*, 2015) have both been reliably ascertained. However, further research is needed in this area to determine the reliability, validity, and utility of symptom and other clinical variables derived from EHRs, as well as how various sources of bias impact the data obtained from EHRs (Dueñas *et al.*, 2020). Nevertheless, such data is being increasingly used in the context of psychiatric genetics research and further advancements provide a prime opportunity for examining phenotype-genotype associations as well as creating retrospective and prospective longitudinal samples.

5.7.2 Research in individuals of non-European ancestry

The research in this thesis has been conducted in individuals of European ancestry recruited across the United Kingdom. For the clinical application of advances in psychiatric genetics to benefit everyone equally, a significant and sustained effort needs to be made to expand research into individuals of non-European ancestry and in non-western cultures. Incorporating diverse ancestries requires more than GWAS in non-European individuals and calculating appropriate PRS. Research examining the structure of symptoms and clinically relevant phenotypes in psychosis has

predominantly been undertaken in western cultures and thus equivalent research needs to be undertaken in a diverse range of populations. Research is needed that examines differences in the psychopathology experienced across cultures, in order to determine the validity of existing dimensional and other approaches to nosology and identify appropriate alternatives where necessary. Furthermore, it is critical that studies explore the ways in which social and economic factors affect the stage and manner in which people present to psychiatric services in different cultures. For instance, urbanicity, economic status, availability of services, attitudes towards mental health, and social acceptance of help-seeking behaviours will likely impact who presents to services and when, and in turn who is recruited into research studies. By establishing the phenotypic nature of psychosis in non-western cultures, we will then be in a position to measure genotype-phenotype relationships and ensure advances in genetics and precision medicine can benefit all patients globally.

5.7.3 Genotypically-homogenous classes

In Chapter 3 I aimed to identify homogenous clusters using a phenotype-driven approach and measure how these clusters relate to variation in genetic liability. An alternative would be to adopt a genetics-driven approach, to identify genotypically homogenous classes and measure their relation to phenotypic variation. Methods are in development that may enable this style of research and have recently been used in the context of medical research to dissect genetic liability allowing for identification of pleiotropic and unique effects (Grotzinger *et al.*, 2019; Cortes *et al.*, 2020). Further advancements in this field will allow for applications in psychiatric genetics that may inform our understanding of heterogeneity in psychosis and how we can conceptualise disorders to reflect the underlying biological processes.

5.8 Conclusions

The aims of this thesis were to investigate the relationships between psychotic and affective disorders and assess whether dimensional and other alternative approaches to nosology are advantageous compared to existing categorical diagnoses, in terms of their ability to capture phenotypic homogeneity and reflect genetic liability to

psychiatric disorders and traits. To achieve this, I examined i) phenotypic and genotypic differences between individuals with schizophrenia and SA-D, ii) PRS associations with dimensional symptoms in a cohort of individuals with schizophrenia, schizoaffective disorder, and bipolar disorder, and iii) the relationship between levels of activity and polygenic risk for psychiatric disorders in the general population.

Overall, this thesis contributes to our understanding of role of common genetic variation in clinical heterogeneity and provides evidence as to the validity of existing diagnostic categories, indicating that alternative approaches to conceptualising diagnoses may better reflect the genetic contribution to these disorders.

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