Genomic Guidance for Future Mental Illness Treatment

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A thesis submitted for the degree of

Doctor of Philosophy

Molecular Psychiatry

University College London

Supervised by:

Professor Andrew McQuillin

Professor Nick Bass

Declaration

I, Kai Yao, confirm that the work presented in my thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Chapter 1 of this thesis introduces how various genomic approaches can help identify potential biomarkers to enable future personalized treatments for mental illnesses. In Chapter 2, I examined how psychiatric polygenic risk scores (PRS), as an indication of genetic liabilities to different psychiatric disorders, interact with environmental factors, adverse childhood experiences (ACE) for different bipolar disorder (BD) phenotype presentations. Although no significant interaction effects were found, higher ADHD PRS correlated with increased number of ACEs and increased the likelihood of rapid cycling. Elevated BD PRS was associated with the presence of psychotic symptoms. Lithium is the gold standard for treating BD however, only about 30% of patients are excellent responders while others could experience side effects. Chapter 3 employed genome-wide association studies (GWAS) to identify good lithium response biomarkers. SNP rs116927879 (A/G) was found to be genome-wide significantly associated with good lithium response, with splicing QTL analysis suggesting that it affects *ADCY1* splicing across brain regions. Antipsychotics are widely prescribed for schizophrenia, but about 40% of patients develop extrapyramidal side effects (EPSE) such as dyskinesias, Parkinsonism, akathisia, and dystonia. Chapter 4 integrated epigenome-wide association studies (EWAS) on GWAS to identify EPSE biomarkers resulted from long-term antipsychotic use. Notably, cg12044923, which mapped to the *STK32B* gene, showed enrichment for EPSE and has been associated with movement disorders such as tremors. In Chapter 5, I explored how interventions could impact PRS predictions of cardiovascular risks in patients with severe mental illness. The findings highlighted that treatments can attenuate cardiovascular PRS predictions and warrant careful PRS

assessment timing. The results also underscored the complex interplay between BD genetic risks and cardiovascular treatment response. This thesis concludes by reflecting on the employed methods' limitations, the potential challenges with pharmacogenetic testing implementation, and how future research could address these to advance the field.

Impact Statement

While pharmacogenomic testing (PGx) is increasingly recognized as important for its potential to personalize mental illness treatments. Comprehensive genomic profiles associated with different treatments must be systematically documented and analysed to realize their potential. This thesis applies various genomic analysis methods to identify potential genetic biomarkers that can differentiate psychiatric treatment responses.

This thesis starts in Chapter 1 where I discussed how changes in views regarding mental illness have shaped the associated treatments today. Modern mental health care can benefit from PGx to provide more precise, biologically informed, and personalized treatment guidance. Thus, the field must continue refining its understanding of genetic influences on psychiatric disorders and associated treatment responses.

In Chapter 2, I employed multiple psychiatric polygenic risk scores to investigate their interactions with environmental factors like adverse childhood experiences (ACE) on the development of different BD phenotypes. The analyses used robust PRS calculation methods and the latest reference GWAS. We also made clear separation on ACE definitions. The findings provide evidence for the utility of psychiatric PRS in phenotype predictions, which can enable early risk identification.

In Chapter 3, I conducted genome-wide association study (GWAS) meta-analyses to identify lithium response genetic biomarkers. This GWAS is currently the largest to date in terms of size for lithium. We used genomic data to predict the heritability of good lithium response for the first time. The study identified *ADCY1* as a gene that may

influence the brain regions for producing different lithium response. These results pinpoint the importance of examining *ADCY1* for patients with BD in future lithium response research. Future research into its role could help optimize treatment decisions and improve outcomes for individuals with BD.

In Chapter 4, I integrated epigenome-wide association studies (EWAS) on GWAS results to identify biomarkers that can differentiate extrapyramidal side-effects (EPSE) from antipsychotic treatments. We had the largest sample size for EPSE to date in both analyses, revealing that the *STK32B* gene showed significant enrichment for EPSE. Notably, *STK32B* has been previously linked to movement disorders, such as tremors. These findings underscore the importance of examining *STK32B* in patients with schizophrenia in future antipsychotic treatment research. This may help predict and mitigate the risk of EPSE, improving treatment safety and efficacy.

Cardiovascular PRS is increasingly used in risk prediction models and has been shown to add information. However, there were very few papers examining how PRS predictions can change after interventions. In Chapter 5, I explored PRS-based predictions of 12-month cardiovascular treatment responses in patients with severe mental illness. To our knowledge, this analysis represents the first of its kind in psychiatry. The findings highlighted the instability of cardiovascular PRS predictions and warrant careful PRS assessment timing in clinical settings.

This thesis concludes in Chapter 6 where I discussed the limitations of the methods used in relation to the results from each chapter and how future research can improve on these.

Inclusion of Published Works

This paper in chapter 2 has been expanded from my previous MSc project and lead to a publication.

- Yao, K., van der Veen, T., Thygesen, J., Bass, N., & McQuillin, A. (2023). Multiple psychiatric polygenic risk scores predict associations between childhood adversity and bipolar disorder. *Journal of Affective Disorders*, *341*, 137–146. https://doi.org/10.1016/j.jad.2023.08.116

This paper in chapter 3 is currently on preprint shown at Research Square and is under review.

- McQuillin, A., Yao, K., Nadeem, A., Van Der Veen, T., Thygesen, J., Jonsson, L., ... & Bass, N. (2024). Implication of the ADCY1 Gene in Lithium Response in Bipolar Disorder by Genome-wide Association Meta-analysis.

This paper in chapter 4 is currently on preprint shown at MedRxiv and is under review.

- Yao, K., Thygesen, J. H., Lock, S. K., Pardinas, A. F., Pritchard, A. L., O'Donovan, M. C., Owen, M. J., Walters, J. T. R., Clair, D. S., Bass, N., & McQuillin, A. (2025). Integrating Genome-wide and Epigenome-wide Associations for Antipsychotic Induced Extrapyramidal Side Effects (p. 2025.02.27.25323006). medRxiv. https://doi.org/10.1101/2025.02.27.25323006

Author Contribution Statement

I led all the writing and main analyses presented in this thesis from chapter 1 to 6 under guidance of my supervisors. Other authors' contributions to each research paper presented in chapters 2 to 5 are listed in each research paper declaration form.

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   All authors participated in the design of this study. KY led the writing of the manuscript. TV and AM supported the statistical analyses. All authors contributed to revise drafts.

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   doi.org/10.21203/rs.3.rs-4000581/v1

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   KY led main analyses and manuscript writing. AN, TV, JHT, LJ, JS, and ML supported data processing. NB reviewed lithium coding. AM supported study design. All authors contributed to revise drafts.

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   doi.org/10.1101/2025.02.27.25323006

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   Psychopharmacology

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   KY led the meta-analyses and manuscript writing. JHT, IE, AL, and ZA supported UCL analyses. SKL, AFP, MCOD, MJO, and JTRW supported Cardiff analyses. ALP and DSC supported Aberdeen analyses. NB reviewed EPSE coding. AM supported UCL analyses and study design.

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Acknowledgement

I would like to express my gratitude to my supervisors for their invaluable guidance and support in helping my transition from having no prior experience in conducting genomic analyses to where I am today. I also wish to thank my parents who have always supported me emotionally and financially to the best they could.

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Abbreviations

ACE	Adverse Childhood Experience
ADHD	Attention-Deficit/Hyperactivity Disorder
AIMS	The Abnormal Involuntary Movement Scale
AUDIT-C	Alcohol Use Disorders Identification Test Score
BARS	Barnes Akathisia Rating Scale
BD	Bipolar Disorder
BMI	Body Mass Index
CLEQ	Children Life Event Questionnaire
CM	Childhood Maltreatment
CpG	Cytosine-phosphate-Guanine
CS	Continuous Shrinkage
CVD	Cardiovascular Disease
CYP	Cytochrome P450
DALY	Disability-adjusted Life Year
GTEx	Genotype-Tissue Expression
GSA	Global Screening Array
GSE	Genomic Structural equation modelling
EA	Emotional Abuse
EN	Emotional Neglect
ESRS	Extrapyramidal Symptom Rating Scale
EWAS	Epigenome-wide Association Study
EPSE	Extrapyramidal Side Effects
FDR	False Discovery Rate
FGA	First Generation Antipsychotic
FUMA	Functional Mapping and Annotation of Genome-Wide Association Studies
GLGC	Global Lipids Genetics Consortium
GWAS	Genome-wide Association Study
HDL	High-density Lipoprotein Cholesterol
IPAQ	International Physical Activity Questionnaire
IVW	Inverse-Variance Weighted
LD	Linkage Disequilibrium
LDL	Low-density Lipoprotein Cholesterol
MDD	Major Depressive Disorder
MMS	Morisky Scale of Adherence
Neff	effective sample sizes
NES	Normalized Effect Size
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OPCRIT	Operational Criteria Checklist
PA	Physical Abuse
PPD	Premorbid Personality Disorder
PGC	Psychiatric Genomics Consortium

PN	Physical Neglect
PRS	Polygenic Risk Score
SA	Sexual Abuse
SADS-L	Schizophrenia and Affective Disorder Schedule
SD	Standard Deviation
SE	Standard Error
SGA	Second Generation Antipsychotic
SSW	Sample Size Weighted
SCZ	Schizophrenia
SMI	Severe Mental Illness
SNP	Single-nucleotide Polymorphism
UCL	University College London
VIF	Variance Inflation Factor
WURS	Wender Utah Rating Scale
WGS	Whole-genome Sequencing

1. General Introduction

Mental illnesses are recognized as complex disorders that affect the mood, thought, and behaviour. Mental illnesses can be distinct from other medical conditions by their impact on cognition, particularly memory, self-awareness, and consciousness, while also being shaped by the unique life experiences and complexities that each individual carries (Malla et al., 2015).

Mental illnesses can be distinguished by their diverse forms. Varying disorders have different prevalence and impact. For instance, schizophrenia (SCZ) affects nearly 1% of the global population and is characterized by a combination of both positive symptoms such as psychotic symptoms and cognitive dysfunctions, and negative symptoms such as depressive moods and lack of motivations (Charlson et al., 2018). People diagnosed with the disorder can have a 15 year reduction in life expectancy compared with the general population (Hjorthøj et al., 2017). Meanwhile, Major Depressive Disorder (MDD) is characterized by a persistently low mood, diminished interest or pleasure in previously enjoyable activities, and recurrent thoughts of death. MDD affects about 185 million people, approximately 2.4% of the global population according to an estimate in 2019 (Marx et al., 2023). In addition, Bipolar Disorder (BD) is characterized by mood swinging between euthymia, (hypo-)mania and depressive episodes. BD has an estimated lifetime prevalence from 0.6% to 2.4% worldwide (Merikangas et al., 2011).

Mental illnesses are sometimes considered together because of overlapping symptoms. Distinguishing between SCZ and BD phenomenologically remain

challenging as they share symptoms, such as hallucinations, delusions, and mood symptoms (Yamada et al., 2020). According to a recent study, more than a third of patients with these disorders could face misdiagnosis (Ayano et al., 2021). Patients with SCZ were likely to be misdiagnosed as having BD, while patients with BD were also more likely to be misdiagnosed as having SCZ. The similar presentations of SCZ and BD might reflect the overlapping biological underpinnings. For instance, genetic findings suggest that these disorders might share a neurodevelopmental gradient of psychopathology, accompanied by shared patterns of cognitive impairments (Doherty & Owen, 2014). Meanwhile, SCZ and BD also exhibit considerable overlaps in terms of morphological brain volume changes and functional connectivity changes (O'Donoghue et al., 2017). Psychosis serves as an intermediate syndrome, bridging SCZ and BD through shared symptomatology and neurological features. Thus, SCZ, psychosis, and BD are often grouped together as severe mental illness (SMI) for their shared functional impairments, treatment needs, and biological underpinnings.

Mental illnesses together account for a growing proportion of the global health burden (Patel et al., 2018). Between 1990 and 2019, the proportion of global disability-adjusted life years (DALYs) attributed to mental disorders, which quantify the burden of a disease in terms of both premature death and disability, increased from 3.1% to 4.9% (GBD Mental Disorders Collaborators, 2022). The rise reflects population growth, aging, and improved reporting and recognition of mental illnesses globally. Such findings also highlight the chronic nature of many mental disorders, which lead to significant disability over time rather than early death and long-term treatments for

mental health are in need.

Views on mental illnesses and associated treatments have evolved significantly throughout history (George et al., 2023). In earlier stages, mental disorders were often attributed to supernatural forces, such as the Devil, with treatments like exorcisms, prayer, and physical punishment (Porter, 2003). In the 1950s, breakthroughs in psychiatric medications revolutionized mental health care and transformed treatments by targeting the biological underpinnings (Duvall & Gallicchio, 2017; Pereira & Hiroaki-Sato, 2018). In recent decades, advancements in neuroscience, genetics, and personalized medicine have further refined treatments, with a focus on tailoring interventions to an individual's psychological and biological profiles (Insel & Cuthbert, 2015). Modern mental health care prioritizes an integrative and holistic approach, combining medication, psychotherapy, community-based support, and stigma reduction efforts (George et al., 2023). However, a key challenge lies in determining the most appropriate treatment plans tailored to everyone's unique needs. The following introduction will outline key time points in the evolution of mental illness treatments and explain how genomic methods can guide future mental health care, enabling more personalized treatment planning.

1.1 A brief history of mental illness treatments

Throughout history, treatments for mental illnesses have undergone significant transformations (Farreras, 2025). During the Middle Ages, explanations of mental illnesses are dominated by the Church, attributing it to supernatural forces such as

possession by the Devil or evil spirits (Porter, 2003). Treatments were religious in nature, involving exorcisms, prayer, and rituals like chanting or using holy water. Severe cases often faced confinement, physical abuse, or execution. Medical theories, such as Hippocrates' views on the biological basis of illness, were largely dismissed. However, toward the end of the Middle Ages, the dominance of mystical explanations began to wane, giving way to a gradual reemergence of scientific and medical approaches to mental illness (Cantor, 2014).

The rise of humanism during the Renaissance further changed the situation by emphasizing human welfare and individual uniqueness. In the mid to late 1500s, physicians like Johann Weyer challenged Church dogma, arguing that many accused "witches" were mentally ill rather than demonically possessed. This shift led to the establishment of asylums where the mentally ill could be confined, as families struggled to take care of their afflicted relatives (Laffey, 2003). During the 16th century, the number of asylums increased as governments recognized that the growing population of individuals with mental illnesses could no longer be managed in private homes. However, these institutions, such as London's Bethlem Hospital, quickly became overcrowded and notorious for inhumane treatment, where patients were chained, exhibited for public entertainment, and subjected to harsh conditions (Walsh, 1907).

By the end of the 17th century and into the Age of Enlightenment, views on mental illnesses shifted further, with an increasing focus on physical causes rather than moral or spiritual ones. Harsh treatments including restraints and somatic methods persisted but, there was also an emphasis on environmental management in asylums, such as

regulating diet and exercise (Laffey, 2003). The late 18th century saw the emergence of the moral treatment movement, spearheaded by figures like Philippe Pinel in France and William Tuke in England. This approach prioritized humane and respectful treatment, emphasizing individual care, social support, and rehabilitation through structured activities. Patients were unchained, given outdoor access, and treated with kindness, leading to notable improvements in their conditions.

The success of moral treatment in the early 19th century fuelled the rapid expansion of asylums across Europe and the United States. However, overpopulation, limited resources, and discriminatory practices against immigrants led to overcrowding and a decline in care quality (Scull, 2015). By the mid-19th century, asylums had evolved into large and impersonal institutions, often prioritizing containment over therapeutic intervention. While moral treatments highlighted the importance of humane care, it became clear that additional medical advancements were needed to address more severe cases effectively (Crossley, 2006).

The turn of the 20th century marked significant developments in understanding and treating mental illnesses. Emil Kraepelin's classification system gained traction, notably distinguishing mood disorders from what would later be termed schizophrenia. This era also saw the rise of psychoanalysis, pioneered by Sigmund Freud, who emphasized the role of unconscious motives and dialogue-based therapy in mental illness (Freud, 2009). Alongside, behaviourism, introduced by John B. Watson and influenced by Ivan Pavlov’s conditioning principles, offered an alternative view, focusing on reconditioning maladaptive behaviours (Chand et al., 2023; Malone, 2014). These

theoretical frameworks laid the foundation for modern psychopathology and treatment approaches.

Institutions for mental healthcare underwent changes in both terminology and function. Asylums were rebranded as hospitals, and patients replaced the stigmatizing term "inmates." The mental hygiene movement gained momentum, advocating for preventive approaches to mental illnesses and the establishment of public health clinics. However, alongside these advances, troubling practices arose, including eugenics-driven sterilization programs targeting institutionalized patients (P. A. Lombardo & Dorr, 2006). Innovative yet controversial treatments emerged during this period. Insulin coma therapy was introduced in 1927 but later abandoned due to its risks (Wellington, 2022), while electroconvulsive therapy (ECT) became a common substitute (Suleman, 2020). Lobotomy, a drastic psychosurgical procedure, was widely performed during the mid-20th century, reflecting a lack of effective alternatives (Faria, 2013). Post-World War II, the need for standardized mental health care for veterans led to the publication of the first *Diagnostic and Statistical Manual of Mental Disorders* (DSM) in 1952. This framework evolved over time, with the DSM-III (1980) marking a shift toward diagnostic neutrality regarding the causes of mental illnesses, a position maintained in subsequent editions (Pichot, 1986). Nowadays, diagnoses tools like DSM-V and ICD-10 are still widely used although challenges in diagnoses and classifications persisted (Hirsch et al., 2016; Kawa & Giordano, 2012).

1.2 A brief history of mental illness medications

Starting in the 1950s, medications were introduced for the treatment of mental illnesses, bringing an immediate and significant impact (Braslow & Marder, 2019). The first noticeable psychiatric medication, lithium, could date back to 1949 when John Cade first used it to treat maniac patients (Duvall & Gallicchio, 2017). Lithium then became a foundational treatment for bipolar disorder, though its efficacy varies among patients. Two revolutionary drugs reserpine and chlorpromazine, were introduced into psychiatry in the early 1950s (Baumeister, 2013; Braslow & Marder, 2019). Reserpine depletes monoamines in the brain, while chlorpromazine blocks dopamine receptors, a discovery that transformed the understanding of chemical communication in the brain. Early antidepressants, such as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) were also introduced in the 1950s then dominated the field until the 1980s (Chockalingam et al., 2019).

The growing range of available drugs led to 47.2 million psychotropic drug prescriptions being dispensed under the National Health Service (NHS) between 1965 and 1970 (Haggett, 2015). However, concerns quickly arose due to inadequate training, aggressive advertising, and the simultaneous rise in prescribing, drawing significant criticism from the medical press. Meanwhile, clinicians started to notice that psychiatric medications could have significant side-effects (Evarts & Butler, 1959). Concerns about side effects have shaped the use of psychiatric medications today. Atypical antipsychotics, introduced as alternatives to typical antipsychotics, offered fewer extrapyramidal side-effects (EPSE) but introduced metabolic issues like weight gain

and glucose dysregulation (Nasrallah, 2008). Drugs like clozapine, though highly effective for treatment-resistant SCZ, remain underutilized due to concerns about agranulocytosis and other safety risks (Kendall, 2011). Over the past 70 years, antipsychotic drugs have evolved through first- (e.g., chlorpromazine and fluphenazine) and second-generation medications (e.g., olanzapine and clozapine), with a potential third generation (e.g., aripiprazole). However, there remains a critical need for the development of more effective treatments with a lower side-effect profile than existing ones (Weston-Green, 2022).

Nowadays, the use of antipsychotics and antidepressants is widespread, with up to 17% of adults being prescribed antidepressants in high-income countries (Pillinger et al., 2023). The prevalence of antipsychotic prescriptions doubled in England increased from 0.6% in 2000 to 1.2% in 2014 and continues to grow (Shoham et al., 2021). While these drugs offer relief for many individuals, around 74% of patients with chronic schizophrenia could discontinue their assigned treatment before 18 months owing to inefficacy or intolerable side effects (Lieberman et al., 2005). Around 75% of patients report experiencing side effects, which range from mild to severe (Iversen et al., 2018). Non-adherence to psychotropic medication due to concerns of inefficacy and side-effects is widespread, with an estimated overall prevalence of 49% (Semahegn et al., 2020). Non-adherence occurs in approximately 56% of individuals with SCZ, 50% with MDD, and 44% with BD. These statistics nevertheless underscore the variability in treatment response and highlight the pressing need for more robust predictive approaches to guide and improve treatment planning.

Adverse side effects can diminish quality of life, hinder daily functioning, contribute to morbidity and mortality, and foster stigma surrounding mental illness (Tandon et al., 2020). Additionally, concerns about inefficacy and side effects often lead to poor adherence, increasing the likelihood of relapse (Haddad et al., 2014). For individuals with depression and schizophrenia, the impact of side effects plays a significant role in medication decisions, often becoming a primary concern when evaluating treatment options (Hopwood, 2020; Kaar et al., 2019).

The psychiatric medication advancements provided effective treatment options for individuals with mental illnesses. However, treatment response is influenced by multiple factors (McCutcheon et al., 2015). In addition, different psychiatric medications vary widely in their side effect profiles, further complicating treatment decisions (Pillinger et al., 2023). To optimize psychiatric treatment, it is crucial to identify characteristics that distinguish patients who respond best to specific medications, allowing for more personalized and effective therapeutic strategies.

1.3 Predictions of treatment response

To increase the success of treatments, specific clinical characteristics have been identified as potential indicators of treatment response. Factors such as medication plasma levels, adherence, metabolic differences, co-prescriptions, lifestyle habits, sex, and the possibility of alternative diagnoses could all influence treatment responses (McCutcheon et al., 2015). For depression, factors such as depression subtype, symptom history, age of onset, episode duration, and recurrence all play roles in

determining treatment effectiveness. For instance, early-onset depression is linked to increased resistance to certain antidepressants, while recurrent and prolonged depressive episodes also correlate with poorer outcomes (Perlman et al., 2019). In addition, patients with severe baseline symptoms, histories of trauma, cognitive impairments, or anxious symptomatology tend to exhibit reduced antidepressant efficacy. In BD, factors predicting lithium response include the sequence of manic and depressive episodes, the absence of rapid cycling or psychotic symptoms, a family history of BD, and a shorter duration of illness before lithium treatment begins (Hui et al., 2019). Conversely, higher body mass index and a greater number of prior episodes or hospitalizations have been associated with poorer lithium response. In schizophrenia, a higher severity of positive symptoms and the use of atypical antipsychotics, particularly clozapine, are associated with the greatest likelihood of treatment response (Seppälä et al., 2021). Risk factors for extrapyramidal side-effects (EPSE) from antipsychotics include a history of prior episode and high medication dose (Hedenmalm et al., 2006) and older age (Jeste, 2004).

Given the substantial variability in individual responses to psychiatric medications, careful monitoring of physical health parameters has been recommended to optimize treatment (Hiemke et al., 2018). Taking lithium as an example, clinical guidelines emphasize the importance of tracking body mass index, kidney function, body lithium levels and thyroid activity in patients with bipolar disorder receiving lithium treatment, with ongoing dose adjustments to ensure therapeutic efficacy (Godden, 2024; NICE, 2014a). However, this process can be time-consuming, requiring extensive trial and

producing error before an optimal plan is tailored to everyone's needs. One promising alternative approach to improve this process is the integration of pharmacogenomic (PGx) testing, which examines genetic variations that affect drug metabolism and response. By guiding medication selection and dosing decisions, PGx testing can help personalize treatment, reduce adverse effects, and enhance therapeutic outcomes from the onset. The following sections will introduce how PGx testing could guide future treatments and showcase several relevant genomic methods which could enrich PGx testing.

1.4 Psychiatric genetics and application in psychiatric treatment

For centuries, observations have indicated that mental illnesses tend to run in families, a pattern that has also been confirmed by large-scale population studies (Arribas-Ayllon et al., 2019). Individuals with a first-degree relative affected by BD or schizophrenia face a significantly higher risk of developing these conditions themselves, approximately six to ten times greater (Andreassen et al., 2023; Lichtenstein et al., 2009). Furthermore, familial risk is not limited to a single disorder; relatives of individuals with psychiatric illnesses also have an increased likelihood of developing other mental health conditions, suggesting a shared underlying aetiology (Cardno & Owen, 2014). Additional complexity arises from non-inherited genetic variations that accumulate in brain tissue over time, as well as random biological processes that further shape individual risk profiles (Andreassen et al., 2023). Nevertheless, genetic variations in parents could also influence the environments they create for their offspring, adding

further complexity (Kong et al., 2018).

With the advent of molecular genetics in the 1980s and 1990s, researchers began using linkage and candidate gene studies to identify genetic variants associated with mental disorders (Owen et al., 2000). However, many early findings failed to replicate due to small sample sizes and the complex polygenic nature of psychiatric genetics (Sullivan et al., 2012). It became increasingly evident that most psychiatric conditions result from the combined effects of multiple genes, each contributing only a small increase or decrease in liability, along with environmental influences, a concept known as polygenic multifactorial causation (Owen & Cardno, 1999). The field advanced significantly in the 2000s with the introduction of genome-wide association studies (GWAS) and large-scale collaborative efforts, particularly from the Psychiatric Genomics Consortium (PGC; Sullivan et al., 2018). The PGC has played a crucial role in systematically evaluating common single-nucleotide polymorphisms (SNPs), rare variants, gene sets, and pathways, shedding light on the genetic and biological foundations of mental illnesses (Watson et al., 2020). More recently, approaches such as polygenic risk scores (PRS), whole-genome sequencing (WGS), and multi-omics integration have provided deeper insights into the genetic architecture of mental illnesses and their interactions with environmental factors (Mullins et al., 2021, 2022; O'Connell et al., 2025). These advancements continue to pave the way for a more comprehensive understanding of mental disorders and become the foundation for potential precision medicine approaches in psychiatry, guiding future psychiatric treatment medication development.

Meanwhile, the importance of applying genomic methods to predict current psychiatric medication efficacy and side effect profiles is increasingly recognized, offering new insights into personalized treatment strategies (Goetz & Schork, 2018). For instance, the cytochrome P450 (CYP) enzymes, *CYP2C19* and *CYP2D6*, hold significant clinical relevance for antidepressants (Carvalho Henriques et al., 2020). Research indicates that genetic variants in *CYP2C19* and *CYP2D6* affect antidepressant blood concentrations, adverse drug reactions, and, to an extent, clinical outcomes such as treatment discontinuation and symptom response (Bråten et al., 2020; Jukić et al., 2018). However, it is important to note that not all psychiatric medications' genetic profiles are fully documented yet, and additional investigations are needed for other components of the medication response such as side-effects (Bousman et al., 2021).

As psychiatric genetics continues to evolve, it holds the promise of transforming mental health treatments by providing more precise and biologically informed approaches. Genetic research has already shed light on the heritability and familial patterns of psychiatric disorders, and its integration with pharmacogenomics may soon truly enable personalized medication strategies. Moving forward, the field must continue refining its understanding of genetic influences on psychiatric conditions and their treatment responses, paving the way for more effective and individualized therapeutic interventions. The following sections will introduce several genomic methods that could be applied to study psychiatric medication responses.

1.4.1 Genome-wide Association Analyses

GWAS on psychiatric treatment responses stands out as a promising approach for pinpointing potential genes linked to medication response and side effects. GWAS analyses genome-wide SNP data to detect associations between genetic variants and specific phenotypes. While whole-genome and exome sequencing provide alternative approaches, most GWAS rely on genotyped SNP arrays combined with imputed variants to enhance genomic coverage (Tam et al., 2019). Imputation, based on reference haplotypes, enables researchers to infer untyped variants, reducing the need for direct genotyping while increasing cost efficiency and sample sizes (Das et al., 2016). Given that GWAS tests millions of SNPs across the genome, stringent multiple-testing correction is required. The widely accepted genome-wide significance threshold is $p<5\times10^{-8}$, accounting for approximately one to two million independent statistical tests (M. I. McCarthy et al., 2008).

With the increasing number of GWAS, researchers have realized that most psychiatric disorders could be polygenic which each SNP may only carry small to modest phenotypic effects (de Bakker et al., 2008). Meta-analysis of GWAS, which enhance detection of SNP with modest effect size through increased sample size and power from collaborative efforts, is increasingly recognized as important. Tools like METAL has been developed to efficiently meta-analyse GWAS summary statistics while using Inverse-Variance Weighted (IVW) or Sample Size Weighted (SSW) methods considering either the standard error or sample size to generate combined outputs (Willer et al., 2010).

Psychiatric genetics benefited hugely with PGC's collaborative efforts worldwide on GWAS meta-analyses. Taking BD genetics as an example, one of the first PGC BD GWAS identified 34 independent SNPs with strong evidence for replication in 4,493 independent BD cases and 42,542 independent controls (Sklar et al., 2011). Then, with an increased sample size of 41,917 BD cases and 371,549 controls of European ancestry, 64 associated genomic loci were identified (Mullins et al., 2021). More recently, by combining participants of European, East Asian, African American and Latino ancestries covering 158,036 cases with BD and 2.8 million controls, PGC reported 298 genome-wide significant loci which mapped to 36 credible genes in the aetiology of BD (O'Connell et al., 2025). Notably, one of the top SNP from the meta-analysis, rs6693503, had an odds ratio of 1.048 with a standard error of 0.007, while most other reported significant SNPs had odds ratios ranging from 0.9 to 1.1 (O'Connell et al., 2025). Such findings again highlight the polygenic nature of psychiatric disorders and emphasize the importance of larger sample size from collaborations for detecting true genetic effects.

More and more researchers have started to apply similar GWAS methods to investigate psychiatric medication responses (Li et al., 2020; Zai et al., 2023). The genes identified through GWAS provide insights into the underlying mechanisms of these medications which could be used as targets to monitor in the clinic. With clearer understanding of each psychiatric medication's metabolism and effectiveness profiles, more effective drugs could also be developed. However, most of current psychiatric medication response GWAS had limited sample size and restricted population groups.

Collaborative efforts are needed to further advance our understanding and guide future discoveries.

1.4.2 Polygenetic Risk Scores

Although GWAS could be used to investigate common SNPs, each SNP's influence is often modest with an odds ratio typically ranging from 0.7 to 1.3 (Mullins et al., 2021; Trubetskoy et al., 2022). Polygenic risk scores (PRS), could summarize the potential risk alleles from the GWAS, weighted by their respective effect sizes to produce a summary score which indicate an individual's genetic liability to the phenotype (Dudbridge, 2013). Before computing PRS, a pruning and thresholding (P + T) approach is typically applied (Purcell et al., 2007). Pruning (or clumping) removes highly correlated SNPs based on linkage disequilibrium (LD), ensuring that only independent SNPs are retained. Thresholding involves applying different p-value cutoffs to exclude SNPs with weak associations with the trait, optimizing PRS predictive power. Advanced methods for PRS computation have been developed to capture complex genetic architectures, such as those using a Bayesian framework (Ge et al., 2019; Lloyd-Jones et al., 2019).

Researchers also discovered psychiatric PRS' effectiveness in the prediction of medication responses. For instance, studies by ConLi+Gen, (2018) and Amare et al. (2021) have demonstrated that PRS for SCZ and MDD among patients with BD are negatively associated with their response to lithium. However, PRS could only explain less variance than the total genetic variance identified in GWAS, as they are constrained

by the limitations of current GWAS methodologies. Thus, more advanced GWAS may also further enhance findings from psychiatric medication response PRS.

1.4.3 Epigenome-wide Association Analyses

Epigenome-Wide Association Studies (EWAS) investigate the relationship between epigenetic modifications, primarily DNA methylation and complex disease phenotypes. Unlike GWAS, which focus on inherited genetic variants, EWAS assess modifications that are heritable and/or environmentally modifiable, providing insights into gene regulation mechanisms beyond DNA sequence variation (Campagna et al., 2021; Villicaña & Bell, 2021). The most widely studied epigenetic mechanism is DNA methylation, where methyl groups are added to cytosine-phosphate-guanine (CpG) dinucleotides, influencing gene expression. The typical significance threshold for EWAS is $p < 1 \times 10^{-7}$. This threshold accounts for the large number of CpG sites tested (~450,000 on Illumina arrays) and is similar to the multiple testing correction used in GWAS (Liu et al., 2013).

EWAS can capture dynamic, environmentally influenced epigenetic modifications, such as DNA methylation changes induced by long-term medication use, stress, or lifestyle factors. EWAS have also been applied to investigate psychiatric medication responses, offering a promising approach to understand gene-environment interactions in treatment outcomes (Engelmann et al., 2022). Despite the potential, EWAS of psychiatric medication response are often limited by smaller sample sizes, as large, well-characterized cohorts with both methylation data and detailed medication response

phenotypes remain scarce.

1.5 PhD Overview

This PhD aimed to explore the genome to identify potential biomarkers that differentiate psychiatric phenotype development and treatment responses. The findings emphasized the importance of personalized treatment approaches, which could significantly improve patient outcomes. To achieve this, the research incorporated large-scale genetic analyses, including GWAS, EWAS, and PRS predictions, while integrating significant discoveries to better understand the complex biological effects.

In my first research paper (Chapter 2), I examined how multiple psychiatric PRS interact with environmental factors, adverse childhood experiences (ACE), to influence the development of various BD phenotypes. This included age of onset, the presence of psychotic symptoms, suicide ideation, and rapid cycling. The analyses aimed to shed light on how genetic and environmental factors combine to shape the clinical presentation of BD. In Chapter 3, I used a GWAS meta-analysis approach to identify SNP associated with a positive lithium response among BD patients. I also examined if psychiatric PRS could predict positive lithium response. This investigation sought to pinpoint genetic markers that could predict which individuals are more likely to benefit from lithium treatment. In Chapter 4, I integrated an EWAS meta-analysis with associated GWAS findings to uncover biomarkers linked to extrapyramidal side effects (EPSE) in individuals with long-term exposure to antipsychotic medications. This chapter provided insights into the influence from both genetic and epigenetic factors

resulting from environmental treatment factors. In Chapter 5, I explored how genetic risk factors, assessed through PRS, could predict cardiovascular treatment responses in patients with severe mental illness (SMI). This research aimed to understand the role of genetics in shaping the effectiveness of cardiovascular treatments. These results could help patients in panning more personalized and effective health treatment. This thesis concluded in chapter 6 where I discussed the potential implications and limitations from current findings on using genomic analyses to guide PGx testing and support personalized treatment planning.

2. Multiple Psychiatric Polygenic Risk Scores Predict Associations between Childhood Adversity and Bipolar Disorder

This paper has been expanded from my previous MSc project and a version of this paper has been published at Journal of Affective Disorder (Yao et al., 2023).

2.1 Abstract

Background: It remains unclear how adverse childhood experiences (ACE) and increased genetic risk for bipolar disorder (BD) interact to influence BD symptom outcomes. Here we calculated multiple psychiatric polygenic risk scores (PRS) and used the measures of ACE to understand these gene-environment interactions.

Method: 885 BD subjects were included for analyses. BD, ADHD, MDD and SCZ PRSs were calculated using the PRS-CS-auto method. ACEs were evaluated using the Children Life Event Questionnaire (CLEQ). Participants were divided into groups based on the presence of ACE and the total number of ACEs. The associations between total ACE number, PRSs and their interactions were evaluated using multiple linear and logistic regressions. Secondary analyses were performed to evaluate the influence of ACE and PRS on sub-phenotypes of BD.

Results: The number of ACEs increased with the ADHD PRS. BD participants who had experienced ACE showed an earlier age of BD onset and higher odds of having rapid cycling. Increased BD PRS was associated with increased odds of developing psychotic symptoms. Higher ADHD PRS was associated with increased odds of having rapid cycling. No prediction effect was observed from MDD and SCZ PRS. And, we found no significant interaction between ACE numbers and any of the PRSs in

predicting any selected BD sub-phenotypes. The study was limited by sample size, ACE definition, and cross-sectional data collection method.

Conclusions: The findings consolidate the importance of considering multiple psychiatric PRSs in predicting symptom outcomes among BD patients.

2.2 Introduction

BD is recognised as a complex psychiatric disorder because of its variable clinical presentation. The first episode of mania or depression of BD commonly occurs between the ages of 18 and 24 (McMahon et al., 1994). However, early onset before age 18 is not rare and such cases are often associated with more severe or complex BD phenotypes, such as increased comorbidity and delayed treatment response (Joslyn et al., 2016). While some BD patients may experience rapid cycling of episodes within hours or days, in others, episodes are separated by months or years (Carvalho et al., 2014). BD patients may also have common comorbidities such as anxiety (Spoorthy et al., 2019), substance abuse (Jawad et al., 2018), and psychotic features (Maggioni et al., 2017). In addition, BD patients are at a higher risk of performing suicidal behaviour compared to other psychiatric patients (Jamison, 2001).

Both genetic and environmental factors are recognised to be important in the development of BD phenotypes. Environmental risk factors such as adverse childhood experiences (ACE) and childhood maltreatment (CM) have been closely associated with BD phenotype development. ACEs describe adverse events, such as the death or divorce of a caregiver, serious illness, or hospitalisation. According to the past meta-

analysis by Palmier-Claus et al., (2016), BD patients were 2.63 times more likely to have experienced ACE. ACE has also been found to play a significant role in the risk of relapse in BD patients (Hosang et al., 2010). Meanwhile, CM describes traumatic abusive events. CM is separated into emotional abuse (EA), physical abuse (PA), and sexual abuse (SA), as well as emotional neglect (EN) and physical neglect (PN) (Gilbert et al., 2009). CM is commonly recognised as a more severe form of ACE. CM has also been associated with more severe and complex BD phenotypes (Agnew-Blais & Danese, 2016). These include earlier age of onset and a higher risk of comorbidities such as anxiety disorder, substance misuse disorder, suicide attempts, and increased mood episodes.

Examining the influence of both genes and the environment is essential for understanding BD symptom outcomes (Quidé et al., 2020). It is commonly believed that existing biological vulnerabilities interact with the later experiences such ACE and lead to more complex mental health conditions. Thus, individuals who already carry a high genetic risk for BD are at even higher risk of developing BD if they have experienced ACE (Duffy et al., 2020). Recently, researchers have begun exploring such gene and environment interaction effects in predicting the development of BD sub-phenotypes (Aas et al., 2020; Anand et al., 2015; Park et al., 2020). These studies were based on the development of genome-wide association studies (GWAS) and polygenic risk score (PRS) calculations (see sections 1.4.1 and 1.4.2 for details). The calculation of polygenic risk scores generally has two primary purposes (1) to predict the likelihood of developing the outcome of interest by synthesizing existing GWAS information into

a single measure; (2) to estimate the predictive ability of known effects. Therefore, PRSs can classify the relative risk of a specific outcome for an individual within a population and have been applied in different gene-environment interaction studies.

The gene-environment interaction can be additive that the effects of genes and environment both independently contribute to the risk thus, the effects simply sum together (Rami et al., 2025). In contrast, the interaction effects can also be multiplicative that the effects of genes and environment amplify one another beyond a simple sum. Thus, the presence of both risk factors together may result in a higher risk than would be expected if their effects were additive (Lin et al., 2025).

However, there have been recent conflicts regarding how BD PRS is associated with the number of ACEs and how BD PRS interacts with ACE in the predictions of various BD sub-phenotypes (Aas et al., 2020; Park et al., 2020). For example, Aas et al. (2020) showed that BD PRS might only interact with childhood maltreatment in predicting the risk of rapid cycling. In comparison, Park et al. (2020) observed another interaction effect in predicting the age at onset (AAO) of BD. These differences between results may be due to different ACE definitions or clinical heterogeneity between sample cohorts. For instance, Aas et al.'s (2020) measures of ACE were mainly CM, while Park et al.'s (2020) measures were mainly ACE, with an additional CM item on physical abuse.

There has been ongoing debate regarding how ACEs should be defined. The original ACE framework proposed by Felitti et al. (1998) encompassed three domains: abuse, neglect, and household dysfunction (e.g. domestic violence, and parental

separation/divorce). However, following scholars have broadened the ACEs definitions to include other adversities, including discrimination, peer victimization, unsafe neighbourhoods, and socioeconomic problems further increasing conceptual inconsistency (Karatekin & Hill, 2019). It is important to distinguish between independent events (e.g. parental death, financial hardship, or divorce) and victimization experiences (e.g. neglect and abuse), as they may differ in developmental impact and intervention implications (Fitzgerald & Gallus, 2025; McLaughlin, 2017). The lack of a clear and consistent definition in past studies obscures the distinct effects of different adverse experiences.

Another major limitation of both these past studies is that they did not consider an individual's genetic liability to other psychiatric disorders (Grigoroiu-Serbanescu et al., 2020). Given that BD has a high level of overlapping clinical heterogeneity and shared genetic risk with other psychiatric disorders, it seems necessary to include multiple psychiatric PRSs and their interactions with ACE to predict phenotype development (Baldwin et al., 2022; Coombes et al., 2020).

Differentiating between attention-deficit/hyperactivity disorder (ADHD) and BD remains as a challenge for clinicians, as these two disorders have extensive symptom overlap, reciprocal comorbidity, and overlapping age of onset periods (Brus et al., 2014; Marangoni et al., 2015). ADHD and BD were proven to be genetically correlated (r_g 0.121) and share common risk variants (O'Connell et al., 2021). Children with ADHD were more likely to have higher ACE exposure than children without ADHD (Brown et al., 2017). And the higher exposure to ACE may also increase their risks to

develop ADHD (Crouch et al., 2021). The presence of ADHD symptoms can be an indication of worse depression presentation (Powell et al., 2021) and is linked to rapid cycling between BD episodes (Aedo et al., 2018).

In addition, genetic predisposition to MDD can be predictive of specific patterns of depression symptoms (Martínez-Levy et al., 2021). An additive interaction effect between genetic predisposition to depression and trauma exposure has been observed on depressive symptoms among MDD patients (Thorp et al., 2023). Meanwhile, SCZ PRS can also be predictive of schizophrenia patients' psychotic symptoms, cognition, illness severity, and diagnostic changes (K. G. Jonas et al., 2019). However, no previous study specifically examined how these different psychiatric genetic liabilities interact with environment risk factors such as ACE in predicting the development of BD sub-phenotypes.

To address these research gaps, we wanted to replicate past gene x environment (GxE) findings on ACE and BD PRS. We also wanted to explore these multiple PRSs' prediction effects of BD sub-phenotype development. Thus, our research had three main aims:

(1) to clarify the association between BD PRS and ACE;

(2) to investigate how the number of ACEs interacts with multi-PRSs in the predictions of distinct BD sub-phenotypes;

(3) to understand whether ACE could predict BD sub-phenotype development and change the interaction effect when CM items are absent.

Our objective was to use multiple linear and logistic regressions to explore the association between the PRSs and the ACE numbers, including their interaction effect in predicting the associated sub-phenotypes. We hypothesized that the multi-PRSs would interact with ACEs in predicting the sub-phenotype development. People with higher PRSs (BD/ADHD/MDD/SCZ) and more ACEs were predicted to have developed BD at a younger age and developed more severe or complex sub-phenotypes, such as psychosis symptoms, suicide ideation, and rapid cycling.

2.3 Methods

2.3.1 Participants

All BD cases received an ICD10 diagnosis of BD from a UK National Health Service (NHS) psychiatrist (World Health Organization, 1992). Ancestrally matched healthy controls (n = 1818) were recruited from the NHS blood transfusion service and from study sites where case participants were also being recruited. The controls were screened for an absence of a lifetime history of the following disorders: schizophrenia and any other psychosis, major affective or schizoaffective disorders, eating disorders, alcohol/drug addiction, and obsessive-compulsive disorders. All participants were of English, Scottish, Welsh, or Irish descent and had at least three out of four grandparents of the same descent. The study was approved by the NHS Metropolitan Multi-centre Research Ethics Committee (MREC/03/11/090). All participants read an approved information sheet and signed a physical informed consent form.

2.3.2 Study measures

Semi-structured interviews were performed with BD participants using the lifetime version of the Schizophrenia and Affective Disorder Schedule (SADS-L; Spitzer et al., 1978), the 90-item Operational Criteria Checklist (OPCRIT; McGuffin et al., 1991) and the Children Life Event Questionnaire (CLEQ; Monaghan et al., 1979). In a subset of participants, the 25-item version of the Wender Utah Rating Scale (WURS) was used to measure childhood ADHD symptoms (Grigoroiu-Serbanescu et al., 2020; M. F. Ward et al., 1993). A subset of the participants received lithium treatment prior to the assessment and their response to lithium was scored using data from clinicians and the research participant. Where these scores differed the clinician's rating was used. The data was coded in a binary format to differentiate between responders and non-responders. Participants' premorbid personality disorder (PPD) diagnosis was assessed with OPCRIT item 11. BD age of onset, presence of psychosis symptoms, presence of suicide ideation, and presence of rapid cycling were selected for analyses in the current study. These variables were chosen because of their relevance to BD according to past reviews (Escamilla & Zavala, 2008; Palmier-Claus et al., 2016). We also sought to replicate previous findings from Park et al. and Aas et al. (Aas et al., 2020; Park et al., 2020).

In this research, BD age of onset was defined as the earliest age at which symptoms began to cause subjective distress or impair functioning or at which medical advice was sought for psychiatric reasons. Age at onset was stored as a continuous variable (OPCRIT item 4). The presence of psychotic symptoms was defined as whether the

participants disclosed any symptoms of impaired reality testing (any presence of OPCRIT items 54-77; see Appendix 2.1). The presence of suicide ideation was defined as whether the participants with BD reported thoughts of death (not necessarily their own), thinking of suicide, wishing to be dead, or attempting to kill themselves (OPCRIT item 43). The presence of rapid cycling was defined as whether the patient ever had four or more mood disturbances in one year. These latter three variables were stored in binary format.

ACEs were measured separately using the CLEQ, an adaption of the children's life events inventory, which records the ACE experienced before the age of 16 (Monaghan et al., 1979). The CLEQ included 13 binary "YES" or "No" questions. The first 12 questions had content such as the death of a parent; the death of a brother or sister; serious illness; hospitalisation of a parent; teenage pregnancy; suspension from school (see CLEQ in Appendix 2.2). The last question required the participants to specify other significant adverse life events experienced as a child if they answered "YES." Due to the variability of events recorded with question 13, we only focused on the first 12 CLEQ questions. If the participant answered "Yes" to any of the first 12 questions, this indicated the experience of ACE. The number of "YES" answers to all 12 questions indicated how many ACEs each participant had been through.

2.3.3 Genotyping, imputation, and quality control

Genome-wide single nucleotide polymorphism data was available for the BD and healthy control subjects. The data was generated in two waves at the Broad Institute,

Boston, MA, US, using the Illumina PsychArray and Illumina Global Screening Array (GSA). The quality control and imputation methods used for the PsychArray had been described elsewhere (Grigoroiu-Serbanescu et al., 2020). The genotype data from the GSA underwent equivalent quality control and imputation procedures as for the PsychArray.

2.3.4 Calculation of the polygenic risk score (PRS)

Patients' multi-PRSs (BD/ADHD/MDD/SCZ) were computed using imputed data from the PsychArray and GSA with the PRS-CS-auto method which provides a single score for each sample without any thresholds (Ge et al., 2019). The PRS-CS-auto method was chosen over other methods since it outperformed other existing methods according to the simulation studies by Ge et al. (2019). Pain et al. (2021) also found PRS-CS-auto to be the best of the pseudo-validation PRS methods. PRS-CS is distinct as it utilises a high-dimensional Bayesian regression framework and places a continuous shrinkage (CS) before SNP effect size calculations. Such procedures result in substantial computational advantages and enable multivariate modelling of local LD patterns, which makes PRS-CS robust to varying genetic architectures.

The application of the PRS-CS method required an LD reference panel and reference GWAS summary statistic, which help infer the posterior effect sizes of SNPs. We chose the European sample from The 1000 Genomes Project Consortium (2010) as our LD reference panel. The BD reference GWAS came from Mullins et al. (2021) which included the PsychArray samples used in the current study. We therefore used

summary statistics generated without the overlapping samples to avoid confounding. Our ADHD reference GWAS came from the Psychiatric Genomics Consortium, a meta-analysis including 38,691 ADHD cases (Demontis et al., 2022). We used data from Howard et al. (2019) for MDD GWAS which excluded UK Biobank and 23andMe data covering 170,756 cases and 329,443 controls. The SCZ GWAS came from Trubetskoy et al. (2022) which covered 68,676 cases and 96,079 controls. We adapted all GWAS samples to be based on subjects of European ancestry and data from the samples that we had contributed to the PGC schizophrenia analyses excluded our own lab's data. The new GWAS generation followed the same procedures as described by each GWAS paper. The reference GWAS sample sizes were calculated using the effective sample size method (Neff) as 4/(1/N_cases + 1/N_controls), where N_cases is the number of cases and N_controls is the number of controls.

We used the mean and standard deviation of the PRS from the healthy controls to standardise the PRS data of the BD cases. This was performed separately for the PsychArray and the GSA data. By standardising the PRSs to a normal distribution with mean = 0 and SD = 1, the PRSs from the PsychArray and GSA could be combined directly and applied easily into regression models as continuous variables. Also, the standardisation of the PRS allowed the conversion of an individual's PRS to quantiles for risk comparison across individuals.

2.3.5 Statistical analysis

CLEQ and PRS data was available for 885 BD subjects, 640 from the PsychArray

and 245 from the GSA. The participants were first divided into two groups based on the presence of ACE and then compared for the difference in characteristics. Wilcoxon rank sum tests, chi-squared tests and independent t-tests were applied according to the variable type and distribution. To illustrate the association between ACEs and multi-PRSs, we first conducted pairwise comparisons using simple t-tests taking ACE as a categorical variable. Then we conducted linear regressions using ACE total number and multi-PRSs taking appropriate adjustments.

Next, we performed multiple linear and logistic regression analyses to assess how ACE, multi-PRSs and their interactions predict the development of selected BD sub-phenotypes. The assumptions for linear and logistic regressions were pre-checked and found to be satisfactory for each regression. Then the CLEQ total score, one PRS, or their interaction term, was each added into the model by sequence. Finally, we divided the samples into four quantile groups based on their BD/ADHD PRS values respectively. We conducted additional logistic regressions taking the lowest PRS group as reference to test if people with higher BD/ADHD PRSs would have higher odds of experiencing ACE or developing the selected sub-phenotypes. The presence of ACE was added as a moderator. We carried out additional interaction analyses to examine if there were significant differences between each PRS quantile group and the presence of ACE, and the interactions between ADHD and BD PRS were also examined.

The participants' BD age of onset and sex were included as covariates in all analyses except for age of onset where only sex was included. The genotyping chip type and the first three principal components from GWAS population stratification were

included in addition for all regression analyses involving PRS to account for chip and ancestry confounding. To further account for genotyping difference, we conducted additional sensitivity analyses using PRSs generated from only overlapping risk variants from both chips (Appendix 2.3 and 2.4). All these described analyses were done using RStudio with R version 4.1.3 (R Core Team, 2021).

To account for multiple testing, we applied False Discovery Rate (FDR) correction method (Benjamini & Hochberg, 1995) to the results obtained using the p.adjust function in R for each set of analyses. The FDR method was chosen over the others as it gives a good illustration of results and has been applied in previous studies involving PRS (Grigoroiu-Serbanescu et al., 2020).

2.4 Results

2.4.1 Sample demographics

Overall, the participants had a median age of 49 when they received the assessment. 62% of the participants experienced at least one ACE before the age of 16 (see Table 2.1). The samples contained a high proportion of females (60%) and type 1 BD patients (65%). The two groups did not differ in sex or BD type ratios. The participants also did not differ in childhood ADHD (defined using the WURS) and responses to lithium. However, the participants with any presence of ACE were more likely to have PPD (p=0.029). The participants had a median BD onset age of 19. The participants' age at interview and BD onset age was earlier in subjects who had experienced at least one ACE (See Table 2.1). The participants also differed in the presence of suicide ideation

(p=0.017) and rapid cycling (p=0.016). We found strong evidence to suggest that the presence of ACE was associated with an increase in ADHD PRS (p=0.005).

Table 2.1 Participants' Demographics and Clinical Characteristics concerning ACE Presence

Variables	N	Overall N = 885	Group without ACE N = 338 (38%)	Group with ACE N = 547 (62%)	p-values
Age at interview	728	49 (39, 59)	50 (42, 60)	48 (38, 57)	**0.003**[a]
Sex (Females)	885	532 (60%)	199 (59%)	333 (61%)	0.600[b]
BD type	885				0.400[b]
BD type 1		572 (65%)	224 (66%)	348 (64%)	
BD type 2		141 (16%)	56 (17%)	85 (16%)	
Schizoaffective BD		172 (19%)	58 (17%)	114 (20%)	
Childhood ADHD	191	37.07 (22.58)	39.00 (21.03)	35.83 (23.54)	0.333[c]
Lithium responders	418	152 (36%)	65 (38%)	87 (35%)	0.612[b]
PPD diagnosis	824	74 (9%)	19 (2%)	55 (7%)	**0.029**[b]
Age of BD onset	746	19 (16, 29)	22 (17, 29)	18 (15, 28)	**0.009**[a]
Psychotic symptoms	844	598 (71%)	222 (69%)	376 (72%)	0.400[b]
Suicide ideation	814	613 (75%)	217 (71%)	396 (78%)	**0.017**[b]
Rapid cycling	499	215 (43%)	61 (36%)	154 (47%)	**0.016**[b]
BD PRS	885	0.71 (1.05)	0.72 (1.01)	0.70 (1.08)	0.819[c]
ADHD PRS	885	0.02 (1.03)	-0.10 (1.05)	0.10 (1.01)	**0.005**[c]
MDD PRS	885	0.26 (1.00)	0.19 (0.99)	0.30 (1.00)	0.113[c]
SCZ PRS	885	0.52 (0.97)	0.59 (0.96)	0.48 (0.97)	0.101[c]

Notes. ACE, adverse childhood experience; childhood ADHD (scores from the Wender Utah rating scale); PPD, premorbid personality disorder; BD, bipolar disorder; ADHD, attention deficit hyperactivity disorder; MDD, major depressive disorder; SCZ, schizophrenia disorder; IQR, interquartile range; SD, standard deviation; PRS, polygenic risk score.

[a] Wilcoxon rank sum test; median (IQR)

[b] Pearson's Chi-squared test of independence; n (%)

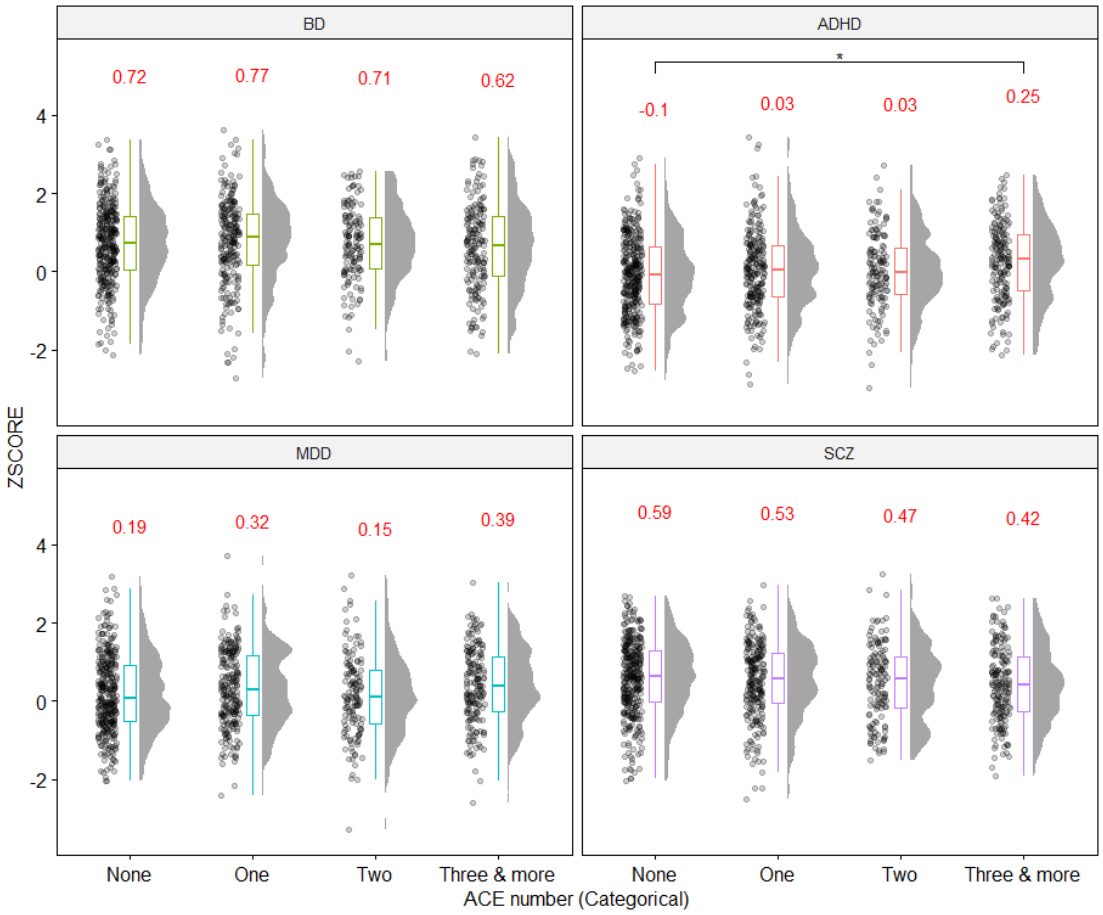
[c] Independent t-test; mean (SD)

In bold p values are below 0.05 threshold.

2.4.2 Correlations between multi-PRSs and the CLEQ scores

We found no evidence supporting any associations between BD PRS and ACE scores using pairwise comparisons (see Figure 2.1) or linear regressions with (coefficient=-0.037; 95% CI: -0.146 to 0.073, p=0.511) or without any adjustments (coefficient=-0.051; 95% CI: -0.149 to 0.046, p=0.300). However, we found strong evidence suggesting that the participants with none and three or more ACE differed in ADHD PRS (see Figure 2.1). The unadjusted linear regression results also indicated that higher ADHD PRS increased the susceptibility to ACE reporting (coefficient=0.198, 95% CI: 0.099 to 0.296, p<0.001). The association was even stronger after adding in adjustments (coefficient=0.231, 95% CI: 0.118 to 0.345, p<0.001). Weak evidence was found to suggest the association between MDD PRS and ACE scores (coefficient=0.103, 95% CI: <0.001 to 0.205, p=0.049) the evidence remained after adding in adjustments (coefficient=0.127; 95% CI: 0.012 to 0.243, p=0.031). No evidence could be found for SCZ PRS before (coefficient=-0.099, 95% CI: -0.204 to 0.006, p=0.066) or after adjustment (coefficient=-0.043, 95% CI: -0.161 to 0.074, p=0.470). And no other pair-wise comparison results survived correction for multiple testing (see Figure 2.1).

Figure 2.1 Mean Polygenic Risk Scores for ADHD, BD, MDD, and SCZ across ACE Groups



Notes. ACE, adverse childhood experience; BD, bipolar disorder; ADHD, attention deficit hyperactivity disorder; MDD, major depressive disorder; SCZ, schizophrenia disorder.
The above numbers corresponded to PRS means for each ACE group.
* in the current plot, p values survived FDR multiple testing correction for simple t-tests for pair-wise comparison.

2.4.3 ACE/BD PRS associations & interaction with phenotypes

We found substantial evidence to suggest that each unit increase in BD PRS would increase the odds of having psychotic symptoms by exp(0.258) = 1.294 (95% CI 1.093 to 1.538; *FDR_p*=0.035; See Table 2.2). We also found strong evidence that each unit increase in ACE number would increase the odds of having rapid cycling by exp(0.228) = 1.256 (95% CI 1.084 to 1.463; *FDR_p*=0.035). We found some tendency that ACE might be associated with an earlier age of onset. We carried out additional subgroup analyses to clarify the effect. We found strong evidence to suggest that only males who experienced ACE would have earlier age of onset (coefficient -1.568, 95% CI: -2.568 to -0.567, *p*=0.002).

Overall, we did not observe any interaction effect between ACE number and BD PRS in predicting any of the sub-phenotypes examined. (See Table 2.2).

2.4.4 ADHD/MDD/SCZ PRS associations & interaction with phenotypes

We found strong evidence to suggest that each unit increase in ADHD PRS led to an increase in the odds of developing rapid cycling BD by exp(0.369) = 1.45 (95% CI 1.20–1.75; *FDR_p*=0.002). No other symptoms were associated with the ADHD PRS and no significant interaction effect between ACE number and ADHD PRS in predicting these sub-phenotypes was observed (see Table 2.2).

We could not find any evidence to suggest MDD and SCZ PRS would predict any of these selected sub-phenotypes (see Table 2.3). And we observed no interaction effect.

Table 2.2 Results of Multiple Regression Analyses with Adjustments based on ACE (total score) and BD/ADHD PRS

Variables	Estimated Coefficient	Standard Error	Confidence Intervals (95%)	Reference Values	*p*	*FDR_p*
Age at onset[a]						
ACE	-0.835	0.330	-1.482, -0.188	-2.543	**0.012**	0.104
BD PRS	-0.315	0.466	-1.230, 0.600	-0.677	0.499	0.877
BD Interaction	-0.316	0.328	-0.960, 0.328	-0.963	0.336	0.765
ADHD PRS	-0.624	0.491	-1.588, 0.339	-1.273	0.204	0.717
ADHD Interaction	-0.421	0.341	-1.090, 0.248	-1.236	0.217	0.717
Presence of psychotic symptoms[b]						
ACE	0.069	0.063	-0.052, 0.195	1.091	0.275	0.761
BD PRS	0.258	0.087	0.089, 0.430	2.974	**0.003**	**0.035**
BD Interaction	-0.074	0.063	-0.197, 0.051	-1.177	0.239	0.718
ADHD PRS	-0.043	0.090	-0.221, 0.134	-0.478	0.633	0.878
ADHD Interaction	0.005	0.065	-0.122, 0.133	0.074	0.941	0.991
Presence of suicide ideation[b]						
ACE	0.178	0.074	0.037, 0.328	2.398	**0.016**	0.119
BD PRS	-0.048	0.093	-0.231, 0.134	-0.514	0.607	0.878
BD Interaction	-0.088	0.072	-0.229, 0.053	-1.229	0.219	0.717
ADHD PRS	0.055	0.098	-0.137, 0.248	0.562	0.574	0.878
ADHD Interaction	-0.007	0.077	-0.156, 0.146	-0.095	0.924	0.991
Presence of rapid cycling[b]						
ACE	0.228	0.076	0.081, 0.381	2.992	**0.003**	**0.035**
BD PRS	-0.106	0.103	-0.310, 0.095	-1.032	0.302	0.765
BD Interaction	-0.041	0.085	-0.209, 0.125	-0.479	0.632	0.878
ADHD PRS	0.495	0.121	0.262, 0.738	4.080	**<0.001**	**0.002**
ADHD Interaction	0.144	0.090	-0.30, 0.324	1.600	0.109	0.563

Notes. ACE, adverse childhood experience; PRS, polygenic risk score; BD, bipolar disorder; ADHD, attention deficit hyperactivity disorder.

[a] Multiple linear regression analyses, reference value t.

[b] Multiple logistic regression analyses, reference value z.

FDR_p = false discovery rate corrected p values for multiple testing.

In bold p values were significant before correction or survived FDR correction for multiple testing.

All results were adjusted for participants' BD age of onset and sex (except for age of onset where only sex was included).

PRS & interaction results were adjusted for chip type and the first three principal components from GWAS population stratification in addition to sex and age of onset.

Table 2.3 Results of Multiple Regression Analyses with Adjustments based on Total ACE Number and MDD/SCZ PRS

Variables	Estimated Coefficient	Standard Error	Confidence Intervals (95%)	Reference Values	*p*	*FDR_p*
Age at onset[a]						
MDD PRS	-0.472	0.494	-1.442, 0.498	-0.956	0.340	0.765
MDD Interaction	-0.070	0.331	-0.719, 0.579	-0.212	0.832	0.991
SCZ PRS	0.021	0.501	-0.961, 1.004	0.043	0.966	0.991
SCZ Interaction	-0.299	0.358	-1.001, 0.403	-0.837	0.403	0.853
Presence of psychotic symptoms[b]						
MDD PRS	-0.052	0.091	-0.232, 0.127	-0.574	0.566	0.878
MDD Interaction	-0.001	0.064	-0.128, 0.123	-0.017	0.987	0.991
SCZ PRS	0.118	0.092	-0.063, 0.299	1.280	0.201	0.717
SCZ Interaction	-0.134	0.069	-0.251, 0.021	-1.643	0.100	0.563
Presence of suicide ideation[b]						
MDD PRS	-0.041	0.098	-0.233, 0.151	-0.418	0.676	0.888
MDD Interaction	-0.002	0.074	-0.149, 0.143	-0.028	0.978	0.991
SCZ PRS	-0.001	0.100	-0.199, 0.195	-0.011	0.991	0.991
SCZ Interaction	0.021	0.086	-0.148, 0.190	0.241	0.810	0.991
Presence of rapid cycling[b]						
MDD PRS	0.086	0.111	-0.131, 0.304	0.776	0.438	0.876
MDD Interaction	0.032	0.081	-0.128, 0.193	0.397	0.691	0.888
SCZ PRS	0.052	0.109	-0.161, 0.267	0.477	0.634	0.878
SCZ Interaction	0.052	0.080	-0.105, 0.212	0.641	0.521	0.878

Notes. ACE, adverse childhood experience; MDD, major depressive disorder; SCZ, schizophrenia disorder

[a] Multiple linear regression analysis, reference value t.

[b] Multiple logistic regression analysis, reference value z.

FDR_p = false discovery rate corrected p values for multiple testing.

All results were adjusted for participants' BD age of onset and sex (except for age of onset where only sex was adjusted). PRS & interaction results were adjusted for chip type and the first three principal components from GWAS population stratification in addition to sex and age of onset.

2.4.5 PRS quantile analyses

Given that no effect could be observed from MDD/SCZ PRS, participants were only divided into quantile groups based on their BD/ADHD PRSs for ACE influence (see Table 2.4). Overall, we found strong evidence to suggest that BD patients in the highest ADHD PRS quantile group had 2.009 higher odds of having experienced ACE than those in the lowest ADHD PRS quantile group (95% CI 1.230 to 3.313, p=0.006 FDR_p=0.046; Figure 2.2A).

BD patients in the highest BD PRS quantile group had 1.917 higher odds of developing psychotic symptoms than those in the lowest BD PRS quantile group (95% CI 1.166 to 3.182, p=0.011, FDR_p=0.234; Figure 2.2B). Meanwhile, BD patients in the highest ADHD PRS quantile group had 2.642 higher odds of developing rapid cycling than those in the lowest ADHD PRS quantile group (95% CI 1.393 to 5.097, p=0.003, FDR_p=0.026; Figure 2D).

Table 2.4 Results of PRS Quantile Group Comparisons for the Odds Plot

Variables	Odds	Confidence Intervals (95%)	Reference Values	*p*	*FDR_p*
Presence of ACE					
BD Q1 vs Q2	0.889	0.558, 1.416	-0.495	0.621	1.000
BD Q1 vs Q3	1.106	0.696, 1.758	0.425	0.671	1.000
BD Q1 vs Q4	1.140	0.714, 1.821	0.548	0.584	1.000
ADHD Q1 vs Q2	0.983	0.627, 1.540	-0.073	0.942	1.000
ADHD Q1 vs Q3	1.365	0.854, 2.186	1.299	0.194	0.775
ADHD Q1 vs Q4	2.009	1.230, 3.313	2.764	**0.006**	**0.046**
Presence Psychotic Symptoms					
BD Q1 vs Q2	1.567	0.964, 2.562	1.803	0.071	0.209
BD Q1 vs Q3	1.546	0.953, 2.519	1.759	0.079	0.209
BD Q1 vs Q4	1.917	1.166, 3.182	2.547	**0.011**	0.087
ADHD Q1 vs Q2	0.922	0.560, 1.513	-0.321	0.748	1.000
ADHD Q1 vs Q3	0.696	0.421, 1.143	-1.428	0.153	0.307
ADHD Q1 vs Q4	0.925	0.547, 1.568	-0.289	0.772	1.000
Presence of suicide ideation					
BD Q1 vs Q2	0.949	0.548, 1.642	-0.187	0.852	1.000
BD Q1 vs Q3	1.008	0.583, 1.743	0.029	0.977	1.000
BD Q1 vs Q4	0.800	0.467, 1.366	-0.815	0.415	1.000
ADHD Q1 vs Q2	1.141	0.683, 1.906	0.504	0.615	1.000
ADHD Q1 vs Q3	1.054	0.618, 1.800	0.194	0.846	1.000
ADHD Q1 vs Q4	1.356	0.772, 2.409	1.052	0.293	1.000
Presence of rapid cycling					
BD Q1 vs Q2	0.785	0.427, 1.434	-0.787	0.431	0.575
BD Q1 vs Q3	0.576	0.313, 1.051	-1.789	0.074	0.196
BD Q1 vs Q4	0.727	0.397, 1.323	-1.042	0.297	0.476
ADHD Q1 vs Q2	1.702	0.901, 3.252	1.629	0.103	0.207
ADHD Q1 vs Q3	2.059	1.105, 3.893	2.254	**0.024**	0.097
ADHD Q1 vs Q4	2.642	1.393, 5.097	2.943	**0.003**	**0.026**

Notes. ACE, adverse childhood experience; PRS, polygenic risk score; BD, bipolar disorder; ADHD, attention deficit hyperactivity disorder.

Results came from multiple logistic regression analysis, reference value z.

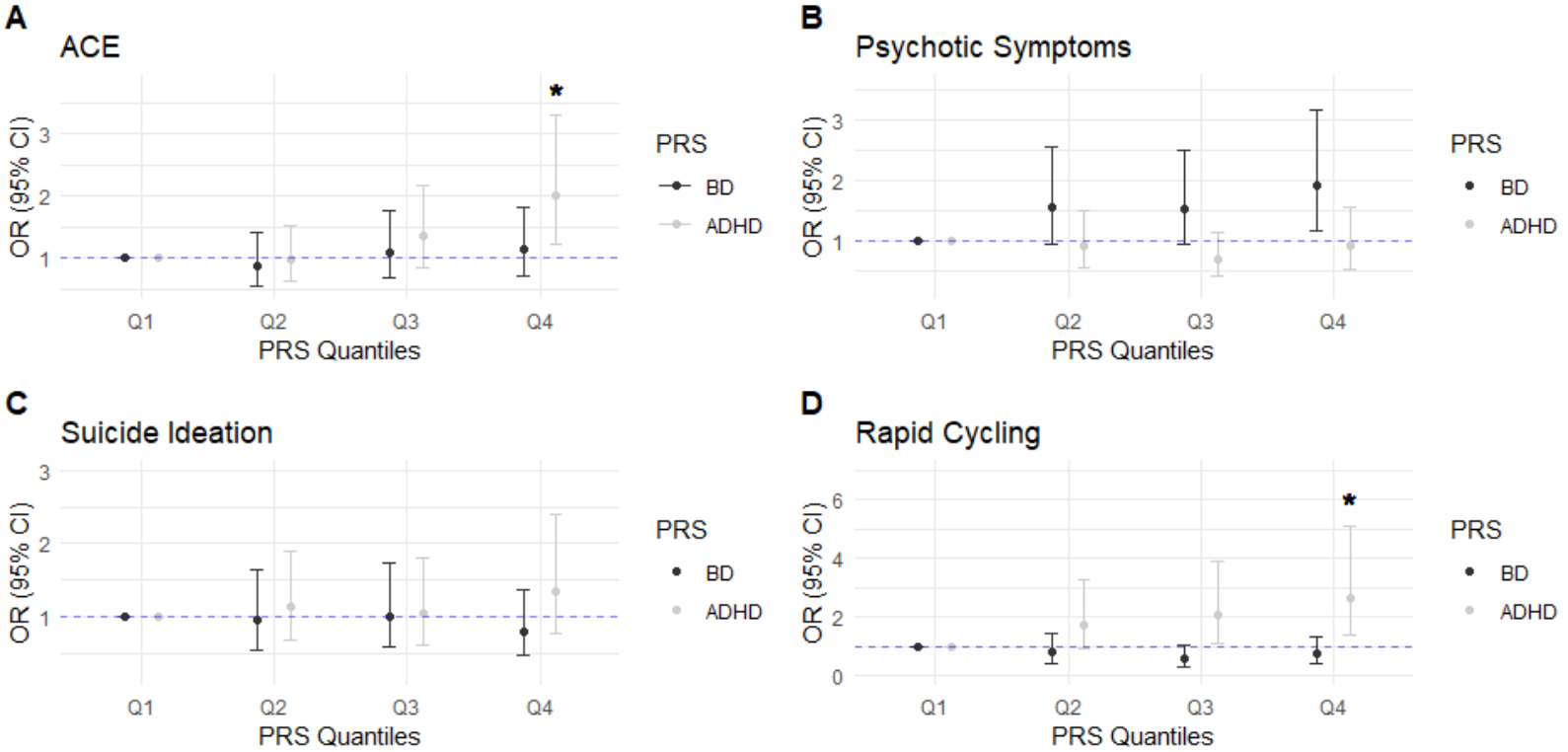
FDR_p = false discovery rate corrected p values for multiple testing.

All results were adjusted for participants' BD age of onset and sex, chip type and the first three principal components from GWAS population stratification.

The presence of ACE was included as a moderator in the PRS models for the three sub-phenotypes.

In bold p values were significant before correction or survived FDR correction for multiple testing.

Figure 2.2 The Odds Ratios of having ACE and Developing the Three Selected Sub-phenotypes with Reference to PRS Quantile Levels



Notes. OR odds ratio, CI confidence intervals, PRS polygenic risk scores

Q1, 0 - 25%; Q2, 25% - 50%; Q3, 50% - 75%; Q4 75% - 100%

The participants' sex, age of onset, the genotyping chip type and the first three principal components from GWAS population stratification were included as covariates in all analyses.

The presence of ACE was included as a moderator in the PRS models for the three sub-phenotypes.

* in the current plot, p values survived FDR multiple testing correctio

2.4.6 PRS quantile interaction analyses results

To further dissect how the presence of ACE can influence the genetic impact and if the two PRSs' associations depend on each other, we carried out additional interaction analyses (see Table 2.5). We only found weak evidence to suggest a positive interaction effect between BD and ADHD PRSs on the presence of ACE (estimated coefficient: 0.158, 95% CI: 0.018, 0.301, p=0.028, FDR_p=0.278). The positive result suggested that participant who had both high BD and ADHD PRSs are more likely to have experienced ACE than those who had both low BD and ADHD PRSs. We found no other tendency for an interaction between the two PRSs. However, such results should be interpretated with cautions because the participants' ADHD and BD PRS are highly correlated (estimated coefficient: 0.113, 95% CI: 0.047 to 0.178, p<0.001). The Variance Inflation Factor (VIF) values for the two PRS interaction variables in the models ranged from around 12 to 13 indicating potential collinearity. Further examinations in future studies are required. The other interaction analyses taking PRS quantile groups and ACE presence showed consistent results to the main analyses as no significant interaction effects could be detected.

Table 2.5 Results of Additional Interaction Analyses based on ACE Presence and BD/ADHD PRS Quantile Groups

Variables	Estimated Coefficient	Standard Error	Confidence Intervals (95%)	Reference Values	*p*	*FDR_p*
Presence of ACE						
BD ADHD interaction	0.158	0.072	0.018, 0.301	2.200	**0.028**	0.278
Presence Psychotic Symptoms						
BD ACE interaction	-0.185	0.169	-0.519, 0.144	-1.099	0.272	0.679
ADHD ACE interaction	0.059	0.171	-0.277, 0.395	0.346	0.729	0.886
BD ADHD interaction	0.011	0.076	-0.138, 0.160	0.144	0.886	0.886
Presence of suicide ideation						
BD ACE interaction	-0.296	0.180	-0.651, 0.056	-1.643	0.100	0.335
ADHD ACE interaction	-0.110	0.186	-0.478, 0.253	-0.589	0.556	0.794
BD ADHD interaction	0.020	0.082	-0.141, 0.181	0.243	0.808	0.886
Presence of rapid cycling						
BD ACE interaction	0.178	0.211	-0.234, 0.595	0.843	0.399	0.736
ADHD ACE interaction	0.384	0.220	-0.047, 0.818	1.745	0.081	0.335
BD ADHD interaction	0.072	0.094	-0.111, 0.257	0.769	0.442	0.736

Notes. ACE, adverse childhood experience; PRS, polygenic risk score; BD, bipolar disorder; ADHD, attention deficit hyperactivity disorder.

Results came from multiple logistic regression analysis, reference value z.

FDR_p = false discovery rate corrected p values for multiple testing.

All results were adjusted for participants' BD age of onset and sex, chip type and the first three principal components from GWAS population stratification.

The presence of ACE was included as a moderator in the two PRS interaction models for the three sub-phenotypes.

In bold p values were significant before correction.

2.5 Discussion

This study used multiple PRSs to dissect their association and interaction with ACE for predicting BD sub-phenotypes. Our study demonstrated that BD participants with higher ADHD PRS tended to report more ACEs, whereas BD PRS was not associated with ACEs reporting. We also found some weak evidence to suggest that BD patients with higher MDD may experience more ACE. In addition, our results suggested that the BD patients with higher BD PRS would have increased odds of developing psychotic symptoms. Although both increased ACE number and ADHD PRS were associated with increased odds of developing rapid cycling among BD patients, no additive interaction effect could be observed.

Past studies had conflicts regarding whether the increase in ACE numbers is associated with BD PRS positively (Park et al., 2020) or negatively (Aas et al., 2020). Our results still could not provide a specific answer since we could not identify any significant results between BD PRS and the reported number of ACE across multiple analyses. However, our results suggested that increased ADHD PRS was associated with more ACE reporting. These results are consistent with National Survey of Children's Health studies which observed that children with ADHD symptoms may more likely experience ACE (Brown et al., 2017; Crouch et al., 2021). We also found weak evidence for the positive association between MDD PRS and ACE. Thus, it seems more likely that BD patients' genetic liability to other psychiatric disorders together accounted for the presence of ACE. However, it should not be assumed that the exposure to ACE is entirely determined by genetic risk, given that most recorded ACE

were passive. In this case, a possible explanation could be that these participants' parents not only transmitted genetic risk variants linked to psychiatric disorders to their child but also provided adverse environments (Baldwin et al., 2022). In addition, genetically influenced behaviours in children (e.g., impulsivity, emotional dysregulation) may also evoke harsher parenting or peer rejection (Reiss et al., 2022).

Most previous research has shown that an increasing number of ACEs is associated with a lower age of BD onset (Aas et al., 2020; Anand et al., 2015; Park et al., 2020). Our study also identified the same pattern in results for ACE presence. Only the study by Park et al. (2020) found an additive interaction effect between BD PRS and ACE for predicting earlier BD age of onset. Our results and the other research did not identify such an interaction pattern (Aas et al., 2020). It should be noted that the study by Park et al. (2020) was purely based on BD type 1 patients. Our samples contained 65% BD type 1 patients, and the study by Aas et al. (2020) contained 74% BD type 1 patients. Thus, differences between study samples in the genetic liability to other psychiatric disorders may have influenced these results (Guzman-Parra et al., 2021). In addition, although another study by Anand et al. (2015) included 1995 BD type 1 patients, they still could not identify significant interaction between any single SNP and the presence of childhood traumatic events on the prediction of BD age at onset. However, they found that only SNPs in or near genes coding for calcium channel activity-related proteins (Gene Ontology: 0005262) were more likely to show an interaction effect. Thus, if the gene x environment interaction exists in predicting BD age of onset, it might be small and require large sample sizes to detect. Given that the study by Park et al.

(2020) contained 1615 BD cases, much larger than our sample size of 885 and Aas et al.'s (2020) sample size of 402. The sample sizes might explain the difference in the results. Another possible explanation for the difference on age of onset could be sex differences. Our additional sub-group analyses found that only males who experienced ACE would have earlier age of onset.

Our results on psychosis symptoms were consistent with Aas et al. (2020), which similarly recorded the psychosis variable in terms of the episode. Our results showed that people with a higher BD PRS may be more likely to show psychotic symptoms. One recent study also found that BD PRS might relate to the manic symptoms in participants with a history of psychotic episodes (Ahangari et al., 2022). However, we could not identify any significant association between ACE and psychosis symptoms or evidence for an interaction effect. Upthegrove et al. (2015) argued that the different ACE types might influence the development of psychosis symptoms differently. Childhood abuse had the strongest associations. Although Aas et al.'s (2020) study focused on CM, covering all abuse items, the associations and interaction effects were still insignificant. Thus, it seemed likely that these psychotic symptoms in BD subjects might be more genetically predetermined.

We found that the ADHD PRS in BD subjects may be highly associated with the presence rapid cycling. However, we should be careful when interpreting the findings on rapid cycling. In contrast to Aas et al. (2020), we could not find an interaction between BD PRS and ACE or between ADHD PRS and ACE on rapid cycling. Our results showed that the increase in ACE number and ADHD PRS might independently

increase the odds of rapid cycling. And they also positively associated with each other. Such results may indicate the presence of mediation effects which requires further examination.

In addition, we could not find any prediction effects from MDD or SCZ PRS. The previous studies which found these two PRSs' prediction effects were based on samples which were of the same category MDD and SCZ patients (K. G. Jonas et al., 2019; Thorp et al., 2023). Although these two disorders were also genetically correlated with BD, the current results suggest that they are underpowered to predict the development of any BD sub-phenotype symptoms.

Overall, we could not identify any significant interaction effect in any models. We anticipated that cases with more ACE and higher PRSs would develop more severe phenotypes. However, our results suggested that different levels of PRS might not significantly influence the relationship between ACE and other BD phenotypes. Meanwhile, the association between the PRS and sub-phenotypes did not significantly differ according to the number of ACE participants experienced. Such conflicts might be because past studies that found the interaction effects included more severe forms of ACE, such as CM, covering abuse and trauma (Aas et al., 2020; Park et al., 2020). However, the ACE measurement in our study only included ACE without any traumatic events such as abuse and neglect. Thus, the interaction effects may have been attenuated in our study. However, our results also showed evidence that even ACE without any CM items could be significant predictors for predicting different sub-phenotypes.

Overall, such results highlight the importance of considering different ACE definitions for future interaction studies.

Our study first used the more advanced PRS-CS-auto method and the latest reference GWAS to calculate multi-PRSs. Thus, a straightforward explanation for the difference between our results and those from past studies might be that the multi-PRSs used here were more powerful predictors of a subject's genetic liability to psychiatric disorders. We also used robust correction method for selecting results from the statistical analyses. Concerning the link between multi-PRSs and ACEs, we replicated past studies' analyses and ran additional tests. By focusing on ACE items without any CM items, our results consolidated ACE's potential in predicting different phenotype developments. Such results also highlighted that future studies should consider the ACE definition when conducting gene-environment interaction studies. In addition, our findings confirmed the importance of considering multiple psychiatric PRSs in BD subjects and their interactions with ACE for improving phenotype predictions. Future larger-scale studies with more precise separation of ACE types, more psychiatric PRSs and more of their interactions are encouraged.

This study's findings could be limited by its case-control recruitment and cross-sectional data collection methods. Retrospective data such as analysed in this study is always subject to potential recall bias. The participants had a median age of 49 at the interview assessment, but the CLEQ required them to recall life events before age 16. All data was collected directly from the participants. If the BD patients developed delusions or hallucinations regarding their childhood experiences, it would be

impossible for us to tell. Also, our study did not separate ACE severity or phenotype severity. We focused on only the ACE without any CM items. Thus, we could only make inferences but not compare ACE and CM items' different effectiveness. In addition, our findings were limited by our sample size and sample characteristics (mixed BD types). Future studies can use mixed models that deal better with missing data, characteristic differences, unequal sample sizes, and non-independence of samples. Given that all samples are Europeans, our findings might also have limited transferability. Finally, neither the PRS nor ACEs could explain a large amount of individual variation. Even though we found some links between PRS and phenotypes that might be important in the clinic, these results were still a long way from letting us predict how an individual's phenotype will develop.

BD is a complex and heterogeneous disorder. Both genetic and environmental risk factors influence its phenotypic development. In this context, future larger-scale studies with more precise separation of ACE types, more psychiatric PRSs, and more of their interactions can better illustrate the phenotype development predictions among BD patients. Together, these efforts will support better BD prognosis, risk prediction, treatment allocation, and harm prevention.

3. Implication of the ADCY1 Gene in Lithium Response in Bipolar Disorder by Genome-wide Association Meta-analysis

A version of this paper has been submitted as preprint at Research Square.

3.1 Abstract

Background: Efforts to examine the influence of genetics in the efficacy of lithium using GWAS have identified several loci. Here, we report new cases and meta-analyses to combine previous efforts.

Method: We report data from 1259 participants with BD recruited at University College London who had been treated with lithium. The data comes from three waves of genotyping on different arrays. The GWAS data from each array was analysed separately and then meta-analysed with two published lithium response GWAS datasets. Post-GWAS analyses were conducted to examine lithium response heritability and its genetic correlations with other traits. We also attempted to replicate past polygenic risk scores (PRS) results.

Results: SNP rs116927879 (A/G) was associated with lithium response at a genome-wide significance level (p=4.509×10^{-08}) with a consistent effect across all cohorts. rs116927879 is located on chromosome 7 and maps to the protein-coding gene *ADCY1* and two pseudo-genes, *GTF2IP13* and *SEPT7P2*. The sQTL results suggested that rs116927879 genotypes may influence the splicing of *ADCY1* across different brain regions. We estimated the SNP heritability (h^2) for good lithium response as 20.3% and 15.6% for subjective/objective response definitions, respectively. We did not observe any genetic correlation or PRS association between the lithium response and

schizophrenia or major depression disorder. However, we found weak evidence to suggest that males were more likely to be good responders.

Conclusions: Our GWAS identifies a genome wide significant finding, and provides updated heritability estimates for lithium efficacy.

3.2 Introduction

Lithium is a first-line treatment option for BD and has been recommended by multiple clinical guidelines (UK (NICE, 2014a); Australia & New Zealand (Malhi et al., 2015); Canada (Yatham et al., 2018)). Lithium has been found to be the most effective mood stabilizer (Joas et al., 2017), not only in controlling mania and hypomania symptoms (Cipriani et al., 2011; Yildiz et al., 2011) and reducing depression severity (J. C. Nelson et al., 2014), but also in preventing suicides and suicide attempts among BD patients (Baldessarini & Tondo, 2022; Song, Sjölander, et al., 2017). However, it has been estimated that only around 30% of patients are excellent responders while around 40% of patients do not receive any benefits (Rybakowski et al., 2001). Meanwhile, lithium can cause adverse effects on the kidneys, thyroid, and parathyroid glands (Gitlin, 2016). Exploring the genetic variability underlying heterogenous lithium response may help clinicians improve future treatment plans.

To date, GWAS of lithium response have identified several different loci. The earliest lithium response GWAS was reported in 2009 (Perlis et al., 2009). The study included samples from the US Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) cohort and a subset of the University College London (UCL)

samples. Although no SNPs reached genome-wide significance, the findings suggested that good lithium response was associated with the *GRIA2* gene which encodes glutamate ionotropic receptor AMPA type subunit 2(Perlis et al., 2009). Subsequently, a GWAS performed in a Han Chinese sample found that another protein-coding gene *GADL1* (glutamate decarboxylase-like protein 1) was highly associated with lithium response (C.-H. Chen et al., 2014). The top two SNPs (rs17026688 and rs17026651) in their combined series, had p values of 1.66×10^{-49} and 7.07×10^{-50}, respectively. However, these findings could not be replicated in subjects of European ancestry (Cruceanu et al., 2015), or in other Asian samples (Birnbaum, 2014; Kotambail et al., 2015).

In 2016, Song and colleagues (Song, Bergen, et al., 2017; Song et al., 2016) reported a GWAS meta-analysis of 3874 BD lithium users from Sweden and the UK. The researchers analysed the lithium response separately according to objective and subjective definitions. While 323 participants were objectively good responders using the clinical definition, 1639 were self-reported good lithium responders. The researchers conducted four sets of GWAS: lithium responders compared with non-responders and lithium responders compared with healthy controls using both objective and subjective measures. Overall, one SNP (rs146727601) reached genome-wide significance from the GWAS of objective measured responders versus controls (Song, Bergen, et al., 2017). rs146727601 is a two-base deletion on chromosome 11q22.4 in the gene PTS (6-pyruvoyltetrahydropterin synthase) which is a catalyst involved in the regulation of serotonin biosynthesis and nitric oxide synthase activity.

In 2016, Hou et al. (2016) also reported a GWAS for lithium response among BD-I and II participants. The data included 2343 European BD participants treated with lithium. The data was collected from 22 sites as part of the International Consortium on Lithium Genetics (ConLi^{+}Gen). Lithium response was rated on the Retrospective Assessment of the Lithium Response Phenotype Scale (Alda scale) which is a well-established measurement scale for lithium response (Scott et al., 2020). In the consortium study, the researchers reported that four linked SNPs on chromosome 21 were associated with good lithium response (rs79663003; rs78015114; rs74795342; and rs75222709) at a genome-wide level of significance. The chromosomal locus of the four SNPs contains genes for two long, non-coding RNAs (lncRNA), AL157359.3 and AL157359.4. Subsequent analyses of the ConLi^{+}Gen data provided insights into the potential genetic architecture of good lithium response. ConLi+Gen (2018) and Amare et al. (2021) reported that higher schizophrenia (SCZ) and major depression disorder (MDD) polygenic risk scores (PRS) were both associated with reduced lithium response in BD participants. These findings were further consolidated by Schubert et al. (2021), who demonstrated that a combination of the SCZ and the MDD PRSs provided improved prediction of lithium treatment response, whereas BD PRS had no impact on the prediction.

Overall, prior findings from GWAS have highlighted different loci for the mechanistic action of lithium. This may in part be due to different measures of lithium response and small sample sizes. In addition, past PRS analyses were only calculated using samples from ConLi^{+}Gen. The aim of the present study is to report a much-

enlarged University College London (UCL) sample of participants with BD taking lithium and conduct GWAS meta-analyses with other compatible European samples. We meta-analysed our GWAS results with the summary statistics from Song et al. (Song, Bergen, et al., 2017; Song et al., 2016) and Hou et al. (2016), the two largest sets of GWAS on the European population to date. We estimated SNP heritability for good lithium response and we conducted exploratory analyses based on the GWAS meta-analysis outputs as follow-up. Finally, SCZ and MDD PRSs were calculated in the samples to replicate past findings.

3.3 Methods

3.3.1 Participants

All UCL participants had received an ICD10 diagnosis of BD (World Health Organization, 1992) from a UK National Health Service (NHS) psychiatrist. A total of 1259 BD participants had a recorded lithium response. Ancestrally matched healthy control subjects (n=1782) were recruited from the NHS blood transfusion service and from study sites where case participants were also being recruited. 1323 controls were screened for an absence of a lifetime history of the following disorders: schizophrenia and any other psychosis, major affective or schizoaffective disorders, eating disorders, alcohol/drug addiction, and obsessive-compulsive disorders. 459 unscreened controls were recruited from the same sites. All participants were of English, Scottish, Welsh, or Irish descent and had at least three out of four grandparents of the same descent. The study was approved by the NHS Metropolitan Multi-centre Research Ethics Committee

(MREC/03/11/090). All participants read an approved information sheet and signed a physical informed consent form.

3.3.2 Study measures

The SADS-L (Spitzer et al., 1978) and the 90-item OPCRIT (McGuffin et al., 1991) were administered to all participants with BD by a psychiatrist or trained researcher. The participants' diagnosis with PPD was assessed with OPCRIT item 11. The assessment of lithium treatment response was determined by the interviewer based on the rate and severity of BD episodes before and after the treatment using both face-to-face and case note-derived information. Researchers were trained in the application of all the assessment measures. The rating contained a mixture of the interviewer's judgements and the participants' self-report. The lithium response was first rated on a 5-point Likert scale ranging from very good to very poor response (see Appendix 3.1). Then only subjects reporting a "very good" or "good response" were coded as "good responders" while subjects reporting "moderate response", "poor response", or "very poor response" were coded as non-responders. We chose the dichotomous conversion to differentiate excellent responders and to be consistent with the definitions used in previous GWAS of lithium response. For instance, ConLi^{+}Gen participants were classified as "responders" if had Part A score of 7 or higher (total score 10), with moderate responders excluded. These data were reviewed by a research psychiatrist (N.B.).

3.3.3 Genotyping, imputation, quality control and meta-analyses

Genome-wide single nucleotide polymorphism data was generated in three waves at the Broad Institute, Boston, MA, USA, using the Affymetrix 500K Array (Affymetrix Inc., Santa Clara, CA, US), the Illumina PsychArray (Illumina Inc., San Diego, CA, US), and the Illumina Global Screening Array (GSA; Illumina Inc.). The three waves of data underwent equivalent quality control and imputation methods which, have been described in detail elsewhere (Grigoroiu-Serbanescu et al., 2020).

We first performed three separate GWAS with imputed SNP genotypes, from each wave of genotyping using PLINK v2.00a2LM (Chang et al., 2015), with the dichotomous lithium response (responders vs non-responders) as the case-control phenotype. The first three principal components of population structure were included as covariates to control for population stratification. Sensitivity analysis including sex as a covariate was conducted, we only observed slight attenuation towards the null. Thus, to be consistent with previous studies and to avoid potential heterogeneity between studies that were to be meta-analysed, age and sex were not included as covariates in the primary analyses.

3.3.4 Lithium definition heterogeneity testing

Song et al. (Song, Bergen, et al., 2017; Song et al., 2016) reported GWAS results from their objective and subjective binary lithium response definitions. We chose to use data from Song et al.'s subjective definition GWAS because this most closely matched the definition used in the UCL sample and because this measure had the largest overall

sample size.

Data from a dichotomous coded lithium response ConLi^{+}Gen European GWAS (GCST012486) published by Hou et al. (2016) was downloaded from the NHGRI-EBI GWAS Catalog (Sollis et al., 2023) on 24/10/2023. Hou et al.'s lithium definition came from the Alda scale for the long-term treatment response to lithium (Hou et al., 2016). Thus, potential heterogeneity within the response definition existed.

We conducted binomial sign tests to compare the direction of SNP associations at three different p-value thresholds (P_T; $1x10^{-3}$, $1x10^{-4}$; and $1x10^{-5}$) with GWAS summary statistics from the Hou et al. study and from the UCL data using the Song et al.'s subjective definition GWAS as the reference study. We expected that there would be strong convergence of SNP associations between the datasets.

LD Score Regression (LDSC; Bulik-Sullivan et al., 2015) was used to further explore the genetic architecture of lithium response and to investigate the effect of differences in lithium response definition. The LDSC method requires large sample sizes, and the algorithm did not converge when all three data sets were analysed separately. We therefore performed LDSC analyses comparing data from Hou et al., with the data from a meta-analysis of data from the UCL study and the data from Song et al.'s subjective GWAS (UCL+Song^{sub}). The meta-analysis was performed using METAL (Willer et al., 2010). We also examined genetic correlation between the UCL+Song^{sub} and the Hou et al data with BD GWAS summary statistics from the PGC BD working group (Mullins et al., 2021). Next, we used Genomic Structural equation modelling (GSEM; Grotzinger et al., 2019) to fit a one-factor model to investigate

factor loadings for the UCL+Song^{sub} data and the Hou et al data on the PGC BD summary statistics.

3.3.5 GWAS meta-analysis & follow-on analyses

After we found no evidence for definition heterogeneity, the GWAS results were together meta-analysed separately with subjective and objective lithium response GWAS results from Song et al. (Song, Bergen, et al., 2017; Song et al., 2016) and with the ConLi^{+}Gen GWAS results from Hou et al. (Hou et al., 2016). We conducted fixed-effect meta-analyses with METAL (Willer et al., 2010) using each GWAS's Neff number as weights (see Table 3.1). The two sets of GWAS meta-analyses were labelled as UCL+Song^{Sub}+ConLi^{+}Gen and UCL+Song^{Ob}+ConLi^{+}Gen with corresponding data input order. The UCL+Song^{Sub}+ConLi^{+}Gen meta-analysis was used as the primary analysis, given that Song et al.'s subjective definition mostly aligns with the UCL definition, and that we found good evidence of overlap genetic association in these three datasets. Correction for multiple testing was not attempted as Song et al.'s two sets of GWAS results had highly overlapping samples. The genome-wide significance threshold was set at $P<5\times10^{-08}$.

The meta-analysis results were uploaded to Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA) for data interpretation(Watanabe et al., 2017). Single tissue Expression QTL (eQTL) and single tissue splicing QTL (sQTL) data for the top SNP was extracted from the GTEx project data V8 (dbGaP Accession phs000424.v8.p2; GTEx Consortium, 2020) on 14/12/2023 focusing on brain regions. We conducted functional fine-mapping using Polyfun+SuSiE (Weissbrod et al., 2020)

with the set number of causal variants as five per locus to identify potential causal SNPs. We took the pre-computed summary LD information from the UK Biobank as the reference and set the range to cover the start and end positions of the target locus. We estimated the heritability of good lithium response in BD cases using LDSC taking the GWAS meta-analysis results (Bulik-Sullivan et al., 2015). We examined the genetic correlation between lithium responsive BD and SCZ (Trubetskoy et al., 2022) and MDD (Howard et al., 2019). The top tissue from the MAGMA tissue expression analysis was testis. We therefore examined the genetic correlation using summary statistics of testosterone levels from Ruth et al. (2020).

Given that the lithium response phenotype was conditional on BD status, there was potential collider bias. We applied the Slope-Hunter method (Mahmoud et al., 2022) to examine if the results would be strongly influenced by the use of the PGC BD GWAS summary statistics (Mullins et al., 2021). The summary statistics that we used excluded data that the UCL group had contributed to the PGC and followed the same procedures described in the original paper. However, some additional sample overlap remained for the data from Song et al. (Song, Bergen, et al., 2017; Song et al., 2016) and ConLi^{+}Gen (Hou et al., 2016). This overlap meant that some of the statistical assumptions of the Slope-Hunter method were broken. Thus, the Slope-Hunter method was only applied to see if there would be major change in the results patterns, rather than producing adjusted results.

The meta-analysis results were uploaded to FUMA for data interpretation (Watanabe et al., 2017). Single tissue Expression QTL (eQTL) and single tissue splicing

QTL (sQTL) data for the top SNP was extracted from the GTEx project data V8 (dbGaP Accession phs000424.v8.p2) on 12/14/2023 focusing on brain regions. We conducted functional fine-mapping using Polyfun+SuSiE (Weissbrod et al., 2020) with the set number of causal variants as five per locus to identify potential causal SNPs. We took the pre-computed summary LD information from the UK Biobank as the reference and set the range to cover the start and end positions of the target locus. We also estimated the heritability of good lithium response BD cases using LDSC taking the GWAS meta-analysis results (Bulik-Sullivan et al., 2015). And we examined the genetic correlation between lithium responsive BD and the other two relevant disorders SCZ (Howard et al., 2019), MDD (Trubetskoy et al., 2022) and the top trait from the MAGMA tissue expression analysis which is testosterone using summary statistics from (Ruth et al., 2020).

Table 3.1 The Summary of Study Sample Sizes

Sources	UCL Affy	UCL Psych	UCL GSA	Song et al.'s (Subjective)	Song et al.'s (Objective)	Hou et al.'s (ConLi^{+}Gen)	UCL+Song^{Sub}+ConLi^{+}Gen	UCL+Song^{Ob}+ConLi^{+}Gen
Responders	164	247	29	1639	387	659	2738	1486
Non-responders	202	503	114	1059	792	1684	3562	3295
Total (R vs N)	366	750	143	2698	1179	2343	6300	4781
Neff (R vs N)	362	663	92	2573	1040	1895	5585	4052

Affy, Affymetrix 500K Array; Psych, Illumina PsychArray; GSA, Illumina Global Screening Array; UCL+Song^{Sub}+ConLi^{+}Gen, the meta-analysis taking Song et al.'s subjective measures with the corresponding input order; UCL+Song^{Ob}+ConLi^{+}Gen, the meta-analysis taking Song et al.'s objective measures with the corresponding input order.

Neff, the effective sample size used for METAL; R vs N, responders versus non-responders. The Neff numbers were calculated using the recommended methods as 4/(1/N cases+1/N controls), where N cases is the number of cases and N controls is the number of controls. The Neff numbers for UCL+Song^{Sub}+ConLi^{+}Gen and UCL+Song^{Ob}+ConLi^{+}Gen were calculated as the sum of corresponding samples' Neff numbers for each meta-analysis given that these were put as weights.

3.3.6 PRS calculation and analyses

PRSs for MDD and SCZ were computed using the PRS-CS-auto method (Ge et al., 2019). We chose the European samples from The 1000 Genomes Project Consortium (2010) as our LD reference panel. Once weights were produced, individual PRSs were calculated using PLINK v2.00a2LM (Chang et al., 2015). We then used the mean and standard deviation of the PRSs from the healthy controls to standardize the PRSs for the BD subjects.

We used data from Howard et al. (2019) for MDD GWAS which excluded the UK Biobank and 23andMe data. The SCZ GWAS was from Trubetskoy et al. (2022). We adapted all GWAS samples to be based on subjects of European ancestry. The summary statistics that were used excluded the data that the UCL group had contributed to the PGC SCZ analyses, but followed the same procedures as described by each GWAS paper. The effective GWAS sample sizes were calculated using the Neff equation (Willer et al., 2010). Thus, the reference GWAS sample sizes were 449,856 for MDD and 160,197 for SCZ. We performed multiple logistic regression analyses to assess how these PRSs predict lithium response in our own samples. The participants' age of BD onset, sex, genotyping chip, and first three principal components from population stratification were included as covariates in all regressions. The statistical assumptions were pre-checked and found to be satisfactory for each regression.

3.4 Results

3.4.1 Sample demographics

A total of 6300 and 4781 participants were included in the two sets of GWAS meta-analyses UCL+Song^{Sub}+ConLi^{+}Gen and UCL+Song^{Ob}+ConLi^{+}Gen respectively (see Table 3.1). Sample demographics were first combined to examine differences between lithium responders and non-responders (see Table 3.2). Overall, the participants had mean ages of 48.82 (SD 13.34) and 48.47 (SD 12.67) years. In the two meta-analyses, 43% and 31% of the participants responded well to lithium. The overall samples for the meta-analyses contained a high proportion of females (62% vs 59%) and type 1 BD patients (66% vs 68%). Responders were slightly older at the assessments (50.34 vs 47.64 & 50.60 vs 47.42; p<0.001 in both datasets). Males were overrepresented as good responders to lithium (40% vs 37%, p=0.007; 44% vs 40% p=0.005) in both meta-analyses. In the UCL+Song^{Sub}+ConLi^{+}Gen meta-analysis, there was an increased proportion of BD I participants coded as good lithium responders (68% vs 64%; p=0.016). In the UCL samples, we observed the same pattern of sex differences in lithium response (p=0.039) but not the bipolar subtype difference (p=0.189, See Table S2). The UCL non-responders more likely had diagnosis of PPD (3% vs 1%, p=0.027). To further validate the evidence for sex difference, we examined the heterogeneity across the samples. We did not observe any evidence for heterogeneity in the sex difference for the UCL+Song^{Sub}+ConLi^{+}Gen meta-analysis (Q=0.31, d.f.=2, p=0.859, I^2=0%) or the UCL+Song^{Ob}+ConLi^{+}Gen meta-analysis (Q=2.04, d.f.=2, p=0.361, I^2=1.9%). Participants who were lithium responders had risk ratios of 1.14

(UCL+Song^{Sub}+ConLi^{+}Gen, 95%CI: 1.07 to 1.22) and 1.15 (UCL+Song^{Ob}+ConLi^{+}Gen, 95%CI: 1.06 to 1.25) for being male according to the common effect model.

Table 3.2 GWAS Meta-analyses Participants' Demographics and Clinical Characteristics concerning Lithium Response

UCL+Song^{Sub}+ConLi^{+}Gen	N	Overall N = 6300	Lithium Responders N = 2738 (43%)	Lithium Non-responders N = 3562 (57%)	p-values
Age at interview	6194	48.82 (13.34)	50.34 (14.05)	47.64 (12.77)	**<0.001**[1]
Sex	6300				**0.007**[2]
Male		2408 (38%)	1082 (40%)	1326 (37%)	
Female		3892 (62%)	1656 (60%)	2236 (63%)	
BD types	3957				0.016[2]
Type 1		2607 (66%)	1406 (68%)	1201 (64%)	
Others		1350 (34%)	673 (32%)	677 (36%)	
UCL+Song^{Ob}+ConLi^{+}Gen	**N**	**Overall** N = 4781	**Lithium Responders** N = 1486 (31%)	**Lithium Non-responders** N = 3295 (69%)	**p-values**
Age at interview	3733	48.47 (12.67)	50.60 (13.09)	47.42 (12.46)	**<0.001**[1]
Sex	3839				**0.005**[2]
Male		1586 (41%)	556 (44%)	1020 (40%)	
Female		2253 (59%)	697 (56%)	1556 (60%)	
BD types	1496				0.059[2]
Type 1		1020 (68%)	429 (71%)	591 (66%)	
Others		476 (32%)	175 (29%)	301 (34%)	

UCL+Song^{Sub}+ConLi^{+}Gen, the meta-analysis taking Song et al.'s subjective measures with the corresponding input order.
UCL+Song^{Ob}+ConLi^{+}Gen, the meta-analysis taking Song et al.'s objective measures with the corresponding input order.
BD, bipolar disorder; SD, standard deviation.
[1] Two Sample t-test; mean (pooled SD)
[2] Pearson's Chi-squared test of independence; n (%)
Bold in current table for $p<0.05$.
Demographics for the ConLi^{+}Gen EUR samples were estimated from their overall samples' demographics which included 220 East Asians. And Hou et al. did not report ConLi^{+}Gen samples' BD types with the split of lithium response. The demographic information of the Swedish samples for Song et al.'s objective measures is not included because Song et al. reported a correction for the Swedish sample but did not report the updated demographics for the sample.

3.4.2 Lithium definition heterogeneity testing

Binomial sign-tests provided strong evidence for non-random convergence of SNP associations between the lithium response GWAS datasets. These findings became stronger at more stringent p-value thresholds (P_T: $1x10^{-3}$, $1x10^{-4}$, and $1x10^{-5}$; see Table 3.3). For the comparison of the $Song^{Sub}$ data with the Hou et al., $ConLi^{+}Gen$ GWAS, 58% ($p=5.58x10^{-53}$), 66% ($p=6.36x10^{-22}$), and 83% of SNPs ($p=3.30x10^{-30}$) had the same direction of effect at p-value thresholds of $1x10^{-3}$, $1x10^{-4}$, and $1x10^{-5}$ respectively. For the UCL meta-analysis, the percentages of SNPs with the same direction of effect as the $Song^{Sub}$ data were similar with 52% ($p=2.17x10^{-4}$), 70% ($p=1.51x10^{-27}$), and 86% ($p=3.04x10^{-33}$) at p-value thresholds of $1x10^{-3}$, $1x10^{-4}$, and $1x10^{-5}$ respectively.

LDSC analysis demonstrated a genetic correlation of 0.904 (SE 0.500) between $UCL+Song^{Sub}$ and $ConLi^{+}Gen$. There was low genetic correlation with BD ($UCL+Song^{Sub}$ $r^2 = 0.143$, SE 0.093; $ConLi^{+}Gen$ $r^2 = -0.045$, SE 0.139). Additionally, according to the GSEM one-factor model, the $UCL+Song^{Sub}$ and $ConLi^{+}Gen$ GWAS had high factor loadings of 0.997 and 0.907, respectively, indicating they load strongly onto the same factor, whereas BD had a low factor loading of 0.139 to that factor. These results indicated low genetic heterogeneity between lithium response GWAS datasets using clinical assessments or the Alda scale and indicate that these results were not highly related to genetic risk for BD.

Table 3.3 Binomial Sign Test Results for Response Heterogeneity

	N total	N SNP same direction	N SNP opposite direction	P
Song^{Sub} 10^{-3}	7604			
ConLi^{+}Gen	5635	3278 (58%)	2348 (42%)	**5.583x10^{-53}**
UCL	5674	2970 (52%)	2704 (48%)	**2.169x10^{-4}**
Song^{Sub} 10^{-4}	983			
ConLi^{+}Gen	832	553 (66%)	279 (34%)	**6.362x10^{-22}**
UCL	734	512 (70%)	222 (30%)	**1.509x10^{-27}**
Song^{Sub} 10^{-5}	318			
ConLi^{+}Gen	276	229 (83%)	47 (17%)	**3.303x10^{-30}**
UCL	244	211 (86%)	33 (14%)	**3.036x10^{-33}**

Song^{Sub}, Song et al.'s subjective definition of lithium response GWAS

3.4.3 GWAS results for lithium responders vs non-responders

For the UCL+Song^{Sub}+ConLi^{+}Gen meta-analysis, we observed little evidence for genomic inflation (λ=1.01, See Appendix 3.3). We found one SNP rs116927879 (A/G) reaching the genome-wide significance (p=4.509x10^{-08}) on chromosome 7 with agreement for the direction of effect in all constituent samples (see Figure 3.1 & Table 3.4). The clumping from FUMA indicated that 196 GWAS-tagged candidate SNPs fell within the genomic locus from position chr7:45697297-45869101 (hg19, see Appendix 3.5). We conducted follow-up fine mapping with Polyfun+SuSiE to identify potential causal SNPs within the region. We observed no SNP with posterior causal probability (PIP) higher than 0.10. The three SNPs with the highest PIP were rs77411260, rs1128602, and rs116927879. The SNPs rs77411260 (chr7:45823152-45823652) and rs1128602 (chr7:45762446-45762946) were close to the top SNP rs116927879 (chr7:45864477-45864977) and did not map to any additional genes.

Genotype-Tissue Expression (GTEx) data (Release V8; dbGaP Accession phs000424.v8.p2) were analysed using the SNP rs116927879 (G/A) and the genes implicated by FUMA analyses focusing on brain areas (see details in Tables S4 & S5). Single-tissue eQTL suggested that rs116927879 genotypes influence expression of *GTF2IP13* in the cortex (Normalized effect size (NES)=-0.66, p=1.4×10^{-20}), caudate (NES=-0.66, p=1.8×10^{-17}), hippocampus (NES=-0.63, p=7.5×10^{-16}), and other brain areas. The single-tissue sQTL analyses suggested that rs116927879 genotypes influence splicing of *SEPT7P2* in the cerebellum (NES=-1.3, p=3.4×10^{-25}), nucleus accumbens (NES=-1.4, p=1.1×10^{-20}), cortex (NES=-1.1, p=2.3×10^{-20}), and other

brain areas. sQTL analyses also suggested that rs116927879 genotypes influenced splicing of *ADCY1* in the cortex (NES=-0.66, $p=1.4\times10^{-10}$), and the frontal cortex (BA9) (NES=-0.66, $p=2.9\times10^{-9}$) at junction 10 (chr7:45662214:45677869, hg38) of *ADCY1*.

For the UCL+Song^{Ob}+ConLi^{+}Gen meta-analysis, we found little evidence for inflation (λ=1.03, see Appendix 3.4) but we observed no SNP reaching the genome-wide significance. We conducted the same eQTL and sQTL analyses for the top SNPs from this meta-analysis however, no significant outputs could be observed. The top four lead SNPs from the UCL+Song^{Sub}+ConLi^{+}Gen meta-analysis, rs116927879, rs4761584, rs12296932 and rs28728196 were tested for the directions of effect in the UCL+Song^{Ob}+ConLi^{+}Gen meta-analysis. The directions for all remained unchanged, suggesting consistent effect direction.

With the application of the Slope-Hunter method, the adjustment factors obtained for the two sets of meta-analyses were negative implying that variants of BD and good lithium response were of concordant net directions of effect. We observed no major change in the result patterns from the adjusted outputs but only slight attenuation towards the null. These results suggested that the identified top SNPs from the meta-analyses were distinct from BD risks.

Figure 3.1 The Manhattan Plots for Two Sets of GWAS Meta-analyses

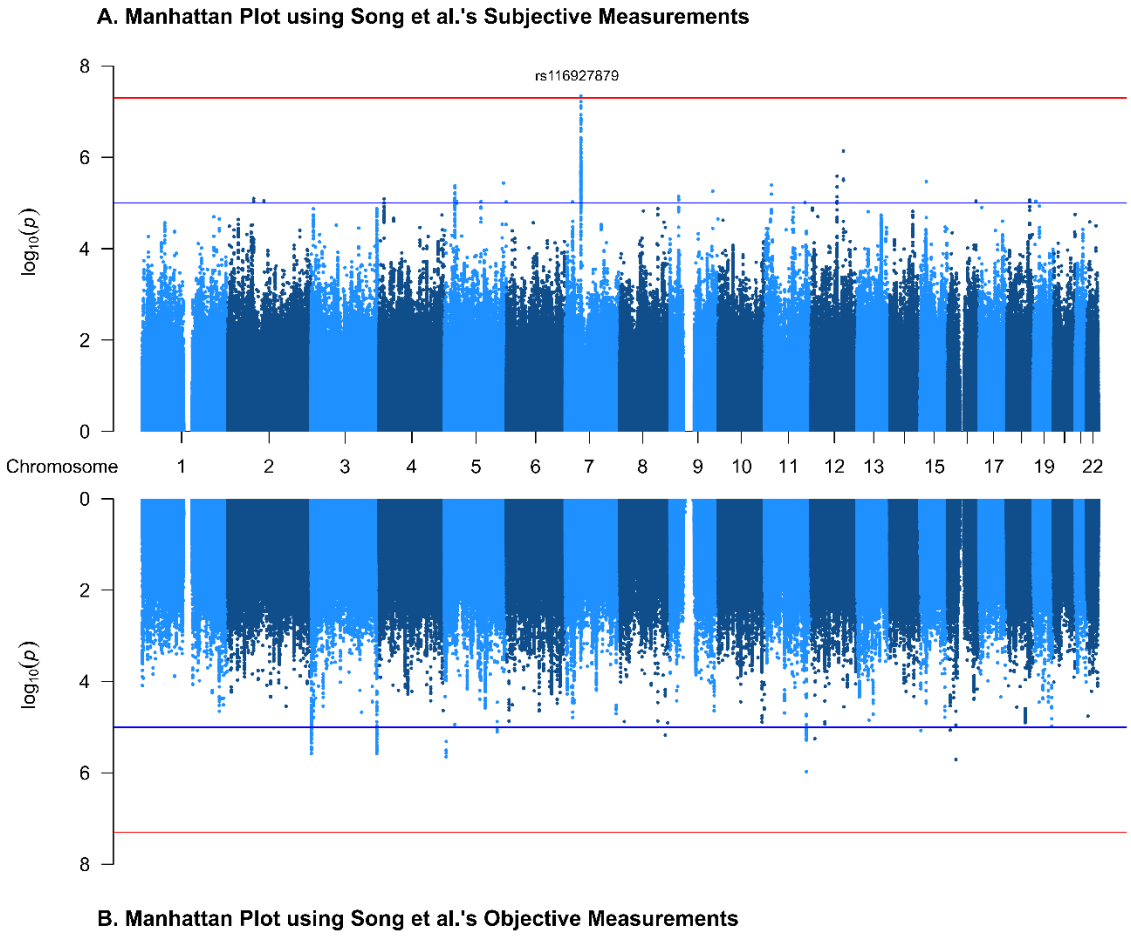


Table 3.4 Regions of the Genome showing the Strongest Association Signals with the Binary Trait

Index SNP	Chr	Position	A1/A2	EAF	Z Score	P-values	Match	Weight (Neff)	Mapped Genes
Responders vs non-responders (using Song et al.'s subjective measurements, UCL+Song^{Sub}+ConLi^{+}Gen, 2738 cases 3562 controls, max Neff 5585)									
rs116927879	**7**	**45697297-45869101**	**A/G**	**0.152**	**-5.470**	**4.509×10^{-08}**	**-----**	**5585**	***ADCY1, SEPT7P2, GTF2IP13, CICP20***
rs4761584	12	94518829-94527590	T/C	0.250	4.953	7.302×10^{-07}	+++++	5585	*RP11-1105G2.3, CCDC41, TMCC3*
rs12296932	12	76062748-76111969	T/G	0.352	-4.703	2.569×10^{-06}	-----	5585	*KRR1, PHLDA1, NAP1L1*
rs28728196	15	39533087-39562972	A/G	0.827	-4.645	3.401×10^{-06}	-----	5585	*C15orf53, C15orf54, THBS1, FSIP1*
Responders vs non-responders (using Song et al.'s objective measurements, UCL+Song^{Ob}+ConLi^{+}Gen, 1486 cases 3295 controls, max Neff 4052)									
rs78026375	11	121673147-121768986	T/G	0.082	4.879	1.066×10^{-06}	+++++	4052	*SC5D, CRTAM, ARHGEF12, BLID*
rs9933339	16	23756216-23865532	A/C	0.816	-4.758	1.957×10^{-06}	???--	2935	*PALB2, ERN2, PLK1, CHP2*
rs2913631	5	5234709-5234709	A/G	0.260	4.729	2.254×10^{-06}	?++++	3690	*ADAMTS16*
rs709122	3	191425855-191549043	T/C	0.375	4.728	2.273×10^{-06}	?++++	3690	*PYDC2, FGF12*

Index SNP, the single-nucleotide polymorphism with the strongest association in the genomic region and each is independent at $r^2<0.1$; Chr, chromosome; Position, the start and end position (UCSC hg19) of the SNP locus where near-by SNPs were clumped to with nominal associations ($p<0.05$) and LD ($r^2<0.1$) within 250-kb windows taking the 1000 genomes project phase 3 EUR as LD reference; A1/A2, effect and alternate allele; EAF, the effect allele frequency based on 1000 genomes EUR; Z-score, the meta-analysis output reference score for the SNP; P-values, the corresponding p-values to the candidate SNP; Match, the agreement across the five datasets, + means individuals who carry the A1 allele have better lithium response, - means negative, ? means missing, the orders are: three sets of GWAS from our own samples (1) Affymetrix Array, (2) Illumina PsychArray, (3) GSA, Illumina Global Screening Array, (4) Song et al.'s samples using subjective/objective measures, and (5) Hou et al.'s EUR samples (ConLi^{+}Gen) ; Weight, the overall Neff of the sample for the SNP; Mapped genes, top 4 genes mapped by positional mapping criterion with maximum distance 10 kb. In bold SNP passed genome-wide significant threshold.

3.4.4 SNP-heritability estimation & genetic correlations

SNP heritability (h^2) for good lithium response was 20.3% (SE 8.4%) for the UCL+Song^{Sub}+ConLi^{+}Gen meta-analysis and 15.6% (SE 9.1%) for the UCL+Song^{Ob}+ConLi^{+}Gen meta-analysis. We observed no genetic correlation between good lithium response and SCZ for the two sets of GWAS meta-analyses (subjective: Z=-0.625, *p*=0.532; objective: Z=-1.239, *p*=0.215). Nor did we observe any genetic correlation between good lithium response and MDD for the two sets of GWAS meta-analyses (subjective: Z=-1.753, *p*=0.080; objective: Z=-1.336, *p*=0.182). However, we found weak evidence to suggest the genetic correlation between good lithium response and total testosterone levels for both sets (subjective: 0.231 (SE 0.112); Z=2.064, *p*=0.039; objective: 0.347 (SE 0.161), Z=2.158, *p*=0.031). Importantly, there was no genetic correlation between BD and total testosterone levels (Z=0.505, *p*=0.614) suggesting the association was more relevant to lithium response.

3.4.5 PRS analyses results

We attempted to replicate previous studies, which reported that lithium response could be predicted using PRS for SCZ and MDD. We found no evidence to suggest that SCZ PRS was predictive of lithium response in the UCL sample (OR 1.040, 95%CI: 0.916 to 1.182, *p*=0.542). We also found no association between MDD PRS and lithium response (OR 0.985, 95%CI: 0.868 to 1.119, *p*=0.818).

3.5 Discussion

Here we present the largest GWAS meta-analyses of lithium response on European samples to date. By including data from the UCL study, together with Song et al.'s subjective and objective measures and ConLi^{+}Gen's European samples, our GWAS meta-analyses included 6,300 and 4,781 participants respectively. We identified one SNP, rs116927879, that reached the genome-wide significance level. The genomic interval implicated by this finding included the *ADCY1* (Adenylate Cyclase 1) gene and two pseudo-genes, *GTF2IP13* and *SEPT7P2*. While the function of *GTF2IP13* and *SEPT7P2* remain poorly understood, *ADCY1* plays roles in mediating responses to increased cellular Ca^{2+}/calmodulin levels which is relevant to regulatory processes in the central nervous system, as well as memory and learning.

Song et al. (Song, Bergen, et al., 2017; Song et al., 2016) also reported association between rs116927879 and subjective lithium response, but this finding did not achieve genome-wide significance in their original study (p=4.99×10^{-7}). With additional samples from the current UCL study and from ConLi^{+}Gen, rs116927879 became genome-wide significant with agreement for the direction of effect from all sources. Potential association with *ADCY1* and SCZ has been reported previously(Goes et al., 2015; Sundararajan et al., 2018) and it was also the only gene identified in a cross-trait GWAS meta-analysis of SCZ and lithium response (ConLi+Gen, 2018).

ADCY1 plays essential roles in the regulatory processes in the central nervous system that are critical for neurodevelopment and neuroplasticity (J. Chen et al., 2022). It has been suggested that the circadian modulation of contrast sensitivity is associated

with Dopamine D4 Receptors (D4Rs) primarily through the *ADCY1* signalling pathway (Hwang et al., 2013). Sleep disturbances and circadian rhythm dysfunction have been commonly noted among patients with BD (Takaesu, 2018). In addition, the sQTL data suggested that rs116927879 genotypes may influence expression and splicing of *ADCY1* across different brain regions.

Three main isoforms of *ADCY1* have been reported, these include the canonical longer isoform (ENST00000297323.12) and two shorter isoforms (ENST00000432715.5 and ENST00000621543.1). The sQTL data from GTEx suggests that SNP alleles associated with poor lithium led to increased splicing at junction 10 (chr7:45662214:45677869, hg38) that in turn is likely to result in the production of the shorter isoforms of *ADCY1*. The peptide encoded by the long isoform of *ADCY1* contains two adenylate cyclase domains, twelve transmembrane domains and two calmodulin interaction domains. The shorter isoforms contain the first adenylate cyclase domain and is therefore likely to have reduced activity. Further research is needed to fully elucidate the specific functions of these isoform types and their associations with response to lithium.

We estimated the SNP heritability (h^2) for good lithium response to be 20.3% (subjective meta-analysis) and 15.6% (objective meta-analysis). Inverse correlations between lithium response and PRS for SCZ and MDD have been reported for the ConLi$^+$Gen data (Amare et al., 2021; ConLi+Gen, 2018; Schubert et al., 2021). In our own subject level data, we were not able to replicate these findings. Additionally, we did not observe genetic correlation between lithium response and SCZ/MDD.

We found weak evidence to suggest a genetic correlation between lithium response and genetically predicted testosterone levels which was consistent with our finding of a sex difference in lithium response. Testosterone, together with other sex hormones have been suggested to influence the development of mood disorders (G. Lombardo et al., 2021). Lithium administration in rats has been reported to reduce male fertility parameters such as testosterone and gonadosomatic index (Abdelwahab et al., 2022). Data on the effect of sex on lithium response have been contradictory. Two large-scale meta-analytical studies did not observe sex differences in terms of lithium response (Hui et al., 2019; Rybakowski, 2014). However, a nationwide study conducted in Denmark (N=3762) found that females were more likely to be lithium non-responders (Kessing et al., 2011). Although we observed sex differences in the overall samples, the ratio differences were still quite small.

The primary limitation to the study is that we used a cross-sectional study design to collect lithium response data for our own samples which may be hampered by recall bias. Another concern could be whether to treat lithium response as binary or continuous due to potential differences in results. In addition, the lithium response coding in our and Song et al.'s samples were essentially based on clinical impression whilst the ConLi^{+}Gen group used criteria-based Alda scale. Even though we found no evidence for definition heterogeneity and a strong genetic correlation between GWAS summary statistics generated using these different approaches, differences in recording lithium response may have impacted the results. The findings from the current study suggest that sex may slightly influence lithium response and future analyses should

consider formally adjusting for it. Finally, we only included European samples in the analyses, and therefore the results presented may have limited transferability to people from different ancestries.

Overall, our GWAS meta-analyses provided new insights for lithium response among BD patients. We identified one SNP rs116927879 (A/G) reaching genome-wide significance on chromosome 7 in a region that included the genes *ADCY1*, *SEPT7P2*, and *GTF2IP13*, which could further explain lithium's bio-mechanisms. Furthermore, we first identified sex differences between lithium responders and non-responders on a genetic level. Future large-scale studies exploring lithium response among BD subjects that properly account for potential sex differences are encouraged.

4. Integrating Genome-wide and Epigenome-wide Associations for Antipsychotic Induced Extrapyramidal Side Effects

A version of this paper has been submitted as a preprint at medRxiv.

4.1 Abstract

Background: Antipsychotic medications are the first-line treatment for schizophrenia. However, around 40% of people with schizophrenia who are treated with antipsychotics could develop extrapyramidal side-effects (EPSE) including: 1) Dyskinesias, 2) Parkinsonism, 3) Akathisia, and 4) Dystonia. This study aimed to identify genetic risk factors for EPSE presence following antipsychotic treatment.

Method: We conducted Genome-wide association (GWAS) and Epigenome-wide association (EWAS) meta-analyses of EPSE, with subset analyses separating first and second generation antipsychotic (FGA/SGA) exposure. We integrated significant EWAS findings from a between-case design to a comparable GWAS for association enrichment. We investigated whether polygenic risk scores (PRS) for schizophrenia, Parkinson's disease, and Lewy-body dementia could predict EPSE.

Results: The primary GWAS top SNP rs2709733 (A/G) ($p=5.755\times10^{-07}$) mapped to a long intergenic non-protein coding RNA, *LINC01162* with consistent effects across all cohorts. Subset analyses with distinct FGA exposure indicated suggestive genes such as *NAV2, NRG3, LSAMP* and SGA exposure indicated *SHISA9* and *CNBD1* which are relevant for schizophrenia, autism, and epilepsy. In our primary EWAS, the most significant differentially methylated position (DMP) was cg05599348 (3.181×10^{-07}), located at chrX:103174718 (hg19) mapping to *TMSB15B*. Comparing EPSE cases to

healthy controls, we identified nine DMPs associated with EPSE. The DMP cg12044923 (chr2:241453995, hg19), located within the *STK32B* gene, showed significant enrichment for EPSE association (permutation p=0.010). *STK32B* is relevant to both psychiatric and movement disorders, suggesting potential shared mechanisms. *Conclusion*: Our study sheds new light on the potential biological mechanisms underlying EPSE development in schizophrenia, highlighting the importance of exploring both methylation shifts and common SNP associations. Further research with larger samples sizes and a focus on the role of *STK32B* are encouraged.

4.2 Introduction

Antipsychotic medications are the first-line treatment for schizophrenia (Sabe et al., 2022). Although many people benefit, around 70% may experience treatment failure such as psychiatric rehospitalization, suicide attempt, discontinuation or switch to other medication (Tiihonen et al., 2017). Extrapyramidal side-effects (EPSE) are common with antipsychotic treatment (Carbon et al., 2018; Huhn et al., 2019), with approximately 40% of patients treated with first-generation antipsychotics (FGA) experiencing EPSEs (Wubeshet et al., 2019). EPSEs still occur with second-generation antipsychotics (SGA), although at lower rates in comparison with FGA (Divac et al., 2014). FGAs are primarily dopamine D2 receptor antagonists, which reduce dopaminergic activity to alleviate positive symptoms of psychosis. This, however, often leads to motor side effects such as EPSE (Kapur & Remington, 2001). Meanwhile, SGA targets both dopamine D2 and other receptors such as serotonin *5-HT2A* receptors.

Serotonin modulation offsets some dopamine blockade effects thus reducing EPSE (Leucht et al., 2009; Zhang et al., 2013). EPSEs describe the movement abnormalities induced by antipsychotics including:

1) *Dyskinesia*, hyperkinetic choreiform involuntary movements of the face, extremities, and the trunk (Lim et al., 2021a). When dyskinesia persists for more than one month it is termed tardive dyskinesia which can sometimes become chronic.

2) *Parkinsonism*, symptoms of rigidity, tremor and impaired or slow movement (bradykinesia) (Keener & Bordelon, 2016).

3) *Akathisia*, characterised by subjective inner restlessness and objective increase in motor activity such as pacing (Factor et al., 2008).

4) *Dystonia*, characterised by sustained and abnormal contractions, that can result in abnormal movements and postures (van Harten & Kahn, 1999).

These movement abnormalities can lead to severe impairment and reduction in the quality of life of individuals with schizophrenia (D'Souza & Hooten, 2023), by interfering with daily living activities and social functioning (Fujimaki et al., 2012; Schouten et al., 2012). In a meta-analysis, the prevalence of spontaneous dyskinesias and parkinsonism was found to be higher in antipsychotic-naive patients with schizophrenia and in first-degree relatives of patients with schizophrenia as compared to healthy controls, indicating a heritable, non-drug induced component to these abnormalities (Koning et al., 2010).

Parkinsonism seen in EPSE can be clinically indistinguishable from the movement abnormalities seen in the neurological disorders like Parkinson's disease (PD) and

Lewy Body Dementia (LBD). Previous studies have identified shared significant loci between schizophrenia and PD (Nalls et al., 2019; Smeland et al., 2021). For example, schizophrenia and PD are both associated with the 22q11.2 deletion syndrome (R. K. Jonas et al., 2014). A duplication of the *SNCA* gene, for which pathogenic variants are associated with autosomal dominant Parkinson's and encodes α-synuclein, a major constituent of LBD, was reported in an individual diagnosed with schizophrenia nine years prior to the development of mild Parkinsonism (Takamura et al., 2016). A recent neuroimaging study on individuals with first episode psychosis found that higher iron loading in the basal ganglia correlated with greater motor abnormalities including EPSE (Cuesta et al., 2021). Similar associations were found with motor abnormalities in PD (Kim & Wessling-Resnick, 2014; R. J. Ward et al., 2014). In view of this, it is plausible that there are shared genetic features between these disorders which also contribute to the shared phenotypical features including movement abnormalities like EPSE in schizophrenia.

Genome-wide Association Studies (GWAS) are a promising approach to identify potential genes associated with development of EPSE given the often-complex biological pathways implicated in psychiatric traits (Duncan et al., 2019). However, to our knowledge, only one past study investigated antipsychotic induced EPSE using GWAS comparing EPSE cases versus EPSE controls among European schizophrenia samples (Åberg et al., 2010). The genotype data in that study had somewhat limited genomic coverage compared to contemporary studies and furthermore there was no imputation of genotypes not captured on the genotyping array. Other studies have

examined EPSE presence by comparing EPSE cases with healthy controls (Levchenko et al., 2021) and by analysing mixed ancestry cohorts (Lim et al., 2021b). Epigenome-wide Association Study (EWAS) allows for the examination of environmentally induced methylome variation which could directly result from chronic antipsychotic exposure (Murphy & Mill, 2014; Wagner et al., 2014). To date, there has been no EWAS on EPSE to examine the influence from antipsychotics.

Our understanding of the molecular mechanisms underlying EPSE may be improved using an integrated functional genomics strategy. The overall aim of this study was to conduct an integrated GWAS and EWAS meta-analysis of EPSE data from existing schizophrenia studies. We also investigated whether Polygenic Risk Scores (PRS) for schizophrenia, PD and LBD could be used to predict the risk of the development of EPSEs. The findings could provide a better understanding of the genetic underpinnings of EPSE and pave the way for the identification of informative genetic biomarkers that could allow for specific tailoring of treatments in the future.

4.3 Methods

4.3.1 Participants selection and genotyping

UCL Participants All UCL participants received an ICD10 diagnosis of schizophrenia from a UK National Health Service (NHS) psychiatrist. Details have been reported elsewhere (Trubetskoy et al., 2022; World Health Organization, 1992). The participants' PPD diagnosis was assessed with OPCRIT item 11. Ancestrally matched healthy controls were recruited from the National Health Service (NHS) blood transfusion service and from study sites where case participants were also being recruited. The

healthy controls were screened for an absence of a lifetime history of the following disorders: schizophrenia and any other psychosis, major affective or schizoaffective disorders, eating disorders, alcohol/drug addiction, and obsessive-compulsive disorders. All participants read an approved information sheet and signed a physical informed consent form. The study was approved by the NHS Metropolitan Multi-centre Research Ethics Committee (MREC/03/11/090). Genome-wide single nucleotide polymorphism data were generated in three waves at the Broad Institute, Boston, MA, US, using the, Affymetrix Array, Illumina PsychArray, and Illumina Global Screening Array (GSA). The three waves of data underwent equivalent quality control and imputation methods which had been described in details elsewhere (Grigoroiu-Serbanescu et al., 2020).

Aberdeen Participants The Aberdeen case–control sample has been described elsewhere.(Stone et al., 2008) Briefly, the cohort contains participants with schizophrenia and healthy controls who have self-identified as born in the British Isles (95% in Scotland). All participants with schizophrenia met the Diagnostic and Statistical Manual for Mental Disorders fourth edition (DSM-IV; American Psychiatric Association, 1994) and ICD-10 criteria for schizophrenia (World Health Organization, 1992). Controls were volunteers recruited through general practices in Scotland. Volunteers who replied to a written invitation were interviewed using a short questionnaire to exclude major mental illness in the individual themselves and their first-degree relatives. The study was approved by both local and multiregional academic ethical committees and all cases and controls gave informed consent. The samples were genotyped at the Broad Institute, as described for the UCL participants.

Cardiff Participants Participants were recruited from community mental health teams in Wales and England on the basis of a clinical diagnosis of schizophrenia or schizoaffective disorder (depressed sub-type) as described previously (Carroll et al., 2011). Diagnosis was confirmed following a SCAN interview (Wing et al., 1990) and review of case notes followed by consensus diagnosis according to DSM-IV criteria (American Psychiatric Association, 1994). The UK Multicentre Research Ethics Committee (MREC) approved the study and all participants provided informed consent. The samples were genotyped at the Broad Institute, as described for the UCL participants.

UK Biobank (UKB) Participants UKB is a biomedical database and research resource of approximately 500,000 individuals from across the UK aged 40 to 69 years at recruitment between 2006 and 2010 (Sudlow et al., 2015). Potential participants in UKB were selected using diagnosis of schizophrenia from ICD10, including codes from F20.0 to F20.9 and excluding participants with any primary Parkinson disorder with G20.

4.3.2 Coding of EPSE data

Participant EPSE status was derived from the data described above following: (1) prescription of antipsychotic medications (FGA or SGA); (2) recorded clinical features of EPSE side-effects; and/or recorded medications prescribed to alleviate EPSE side-effects. Medication dose information was unavailable for most participants thus, not analysed. We used key terms to classify participants with schizophrenia as cases

(having life-time EPSE) or controls (not having life-time EPSE) from all available data sources including interviews, medication, and health records. These key words covered two main areas: behavioural and pharmacological:

1) Behavioural features of the four types of EPSE, (dystonia, akathisia, parkinsonism, and dyskinesia). To compile a list of keywords for each of these EPSE types, we consulted several rating scales that are frequently employed to measure EPSE including: The Abnormal Involuntary Movement Scale (AIMS; Munetz & Benjamin, 1988) the Extrapyramidal Symptom Rating Scale (ESRS; Chouinard & Margolese, 2005), The Simpson Angus Scale (Hawley et al., 2003) and the Barnes Akathisia Rating Scale (BARS; Barnes, 1989). In addition, we searched reliable sources of clinical information for each of these abnormalities including the National Institute for Health and Care Excellence (NICE) guidelines (NICE, 2014b) and the BMJ Best Practice (BMJ Best Practice, 2021).

2) Pharmacological treatments for EPSE. To generate key words for pharmacological treatments for EPSE, we searched The NICE guidelines(NICE, 2014b) and The Maudsley Prescribing Guidelines in Psychiatry(Taylor et al., 2021) for the most recent recommendations on managing EPSE to identify a list of medications.

The UCL and Aberdeen participants' EPSE status was derived using the same list of key words described in Appendices 4.1 and 4.2. The Cardiff participants' EPSE status coding had a few minor adaptions. The keywords "dribbling" was added as it better captured other saliva-related key-words; 'shakes' was removed as it was described in the context of anxiety; "still" was removed as it referred to still doing

something not being physically still; “tap” was removed as it was in the context of ‘tapered’; “march” was removed as it referenced the month of March; “irritable” was removed as it was in the context of IBS/irritable bowel syndrome; “parkin” was removed as it referred to Parkinson’s disease not parkinsonism; ‘tropin’ was excluded as it captured atropine as opposed to benzatropine. The UKB participants were retained if they received any first or second generation of antipsychotics (See medication codes in Appendices 4.3 and 4.4), then stratified by whether participants received any medication to treat EPSE (See EPSE medication codes in Appendix 4.5); diagnosis of other drug-induced secondary Parkinsonism in G21.1; Drug-induced dystonia in G24.0 or Drug-induced tremor in G25.1 were selected as cases.

4.3.3 GWAS meta-analyses & follow-up analyses

For the main analysis, we took a within case design comparing participants with exposure to FGA or SGA with EPSE vs not having EPSE. We also conducted subset analyses separating participants who had any exposure to FGA (including those also exposed to a SGA) and participants only exposed to SGA. The Cardiff samples were only included in the SGA subset given most participants only had SGA exposure. We stratified the antipsychotic exposure into separate groups to compare their differential effects, given FGAs' higher EPSE prevalence and distinct mechanistic profiles.

We applied logistic regressions taking the participants’ EPSE status to evaluate the association between imputed SNP dosages. For UCL participants, we performed separate GWAS for data from each wave using PLINK v2.00a2LM (Purcell et al., 2007).

We conducted the same sets of analyses for Aberdeen, Cardiff, and UKB samples separately. The participants' age, sex and the first ten principal components of population structure were included as covariates to control for population stratification.

We conducted fixed-effect meta-analysis taking each GWAS's effective sample sizes (Neff) as weights using METAL (See calculation of Neff in Supplementary Table 6) (Willer et al., 2010). The genome-wide significance threshold was set at $P<5\times10^{-08}$. The output results were uploaded to FUMA for interpretation (Watanabe et al., 2017). We also conducted a binomial sign test to evaluate the SNP associations between the FGA and SGA subsets at 10^{-03} level. If there were no SNPs associations between the FGA and SGA subsets, the expectation is that 50% of the Z scores from the meta-analyses would be in the same direction.

4.3.4 EWAS methylation data

Methylation data was only available for a proportion of the UCL and Aberdeen samples. The EZ-96 DNA Methylation kit (Zymo Research, CA, USA) was used to treat 500ng of DNA from each sample with sodium bisulfite in duplicate. DNA methylation was quantified using the Illumina Infinium HumanMethylation450 BeadChip (Illumina Inc.) run on an Illumina iScan System (Illumina) using the manufacturers' standard protocol. Detailed data collection and imputation process has been described elsewhere (Hannon et al., 2016). As smoking status information was not present for all samples, we estimated a proxy based on the DNA methylation profile at sites known to be associated with smoking status following a previously described

approach (Elliott et al., 2014). Cell composition data were not available for these DNA samples, therefore these were estimated Houseman algorithm (Houseman et al., 2012; Koestler et al., 2013) for seven variables recommended in the documentation. We also estimated the participants' methylation age using the Epigenetic Clock software (Horvath, 2013).

4.3.5 EWAS analysis and meta-analyses

We employed the same design as in the GWAS to analyse the association of EPSE status on DNA methylation profiles. This included comparisons of EPSE presence among participants with any FGA/SGA exposure (111 EPSE cases, 203 EPSE controls), any FGA exposure (87 EPSE cases, 87 EPSE controls), and only SGA exposure (17 EPSE cases, 106 EPSE controls). DNA methylation values for each probe were regressed with covariates for methylation age, gender, seven cell composition scores, and smoking score. Then the results from UCL and Aberdeen were combined with fixed-effect meta- analyses.

These within-case analyses may be limited by sample size constraints, potentially reducing statistical power to detect subtle methylation changes. We also performed EPSE case with any antipsychotic exposure vs healthy control analyses to boost statistical power (111 EPSE cases, 748 healthy controls). To eliminate the influence of schizophrenia from the case control study design we included participants schizophrenia PRS as an additional covariate. Thus, the EPSE case control design may help reveal EPSE-associated methylation changes attributable to long-term

antipsychotic exposure after accounting for potential schizophrenia risks. The EWAS meta-analysis significance threshold was set at $1x10^{-07}$.

4.3.6 EWAS findings integration and permutation test

We performed separate GWAS on the same participants used in the between-case design EWAS following the same procedure described. The results were combined using METAL and clumped to represent LD independent loci in lead using the 1000 genome European samples as a reference (1000 Genomes Project Consortium et al., 2015). Any significant CpG sites from the EWAS were mapped to within 250 kb of each in the associated GWAS results to identify an enrichment in the region. To quantify significance, 5000 random permutations were generated. Empirical P values for each region were calculated by counting how many of the permutations had more significant P values than the mapped P value from GWAS and dividing by the total number of permutations performed. The CpG sites' locations were also mapped to clumped schizophrenia GWAS results within 250 kb for comparisons (Trubetskoy et al., 2022). Regional plots were produced using GWASLab (He et al., 2023).

4.3.7 PRS calculation and analyses

We calculated the participants' PRSs for schizophrenia, Lewy body dementia and Parkinson's disease using the PRS-CS method with the latest available reference GWAS (Ge et al., 2019). We chose the European samples from the 1000 Genomes Project Consortium as our LD reference panel given all samples included were of

European Ancestry (1000 Genomes Project Consortium et al., 2015). Once weights were produced, individual PRSs were calculated using PLINK v2.00a2LM.(Chang et al., 2015) We then used the mean and standard deviation of the healthy controls' PRSs from each sample to standardize their cases' PRSs. The SCZ GWAS came from Trubetskoy et al. (PGC wave 3), which were derived exclusively from European samples (Trubetskoy et al., 2022). The GWAS statistics for Parkinson's disease came from European samples of Nalls et al. excluding 23andMe data (Nalls et al., 2019). The GWAS statistics for Lewybody dementia came from Chia et al., only including European samples (Chia et al., 2021). We adapted the schizophrenia GWAS to exclude each sample's participants used in the current study to avoid sample overlap. The new GWAS generation followed the same procedures as previously described (Trubetskoy et al., 2022).

We performed multiple logistic regression analyses to assess how these various PRSs predict the presence of EPSE in each sample. Then the results were meta-analysed using a fixed effect model. The assumptions for logistic regressions were pre-checked and found to be satisfactory for each regression. The significant threshold was kept as 0.0167 (i.e. 0.05/3), for multiple testing correction.

4.4 Results

4.4.1 GWAS sample demographics

Overall, the GWAS meta-analysis included 2471 participants with schizophrenia, of whom 1178 (48%) had EPSE. The participants had a mean age of 46.57 (SD 12.22)

years old and were mostly males (70%; Table 1) as is typical of genomic studies of schizophrenia. All participants had antipsychotic exposure and most of the participants had taken at least one type of SGA (78%). The participants with and without EPSE did not differ in terms of age at assessment (46.53 vs 46.62, p=0.855) nor sex (males 71% vs 69%, p=0.213). EPSE was more prevalent in those who had taken FGA or were on both (FGA 51%, SGA 41%, both 61%; p<0.001). The participants' characteristics differed between sample sets (see Table 4.2). The participants who developed EPSE were at an older age at assessment than those who did not in the UCL (46.33 vs 42.72, p<0.001) and UKB samples (56.06 vs 53.94, p=0.020; Table 4.2). In the Cardiff sample, participants who developed EPSE had an earlier age of schizophrenia onset (24.30 vs 27.50, p=0.006). The pattern of EPSE being more prevalent in those who have taken the first generation of antipsychotics were consistent across most cohorts (UCL 60% vs 40% p<0.001; Aberdeen 64% vs 39% p<0.001; UKB 69% vs 30% p<0.001) except for the Cardiff samples where most participants only had exposure to SGA (first 18% vs second 82%). From the UCL sample, there was no evidence to suggest any association between PPD and EPSE (p=0.999) nor association between EPSE and prescriptions of any antidepressants (p=0.276).

Table 4.1 GWAS Meta-analysis Participants' Demographics and Clinical Characteristics concerning EPSE Presence

	N	Overall	EPSE Presence	EPSE Absence	p-values
Meta-Analyses	*2471*		*n = 1178 (48%)*	*n = 1293 (52%)*	
Age at assessment	2471	46.57 (12.22)	46.53 (11.82)	46.62 (12.59)	0.855[a]
Sex	2471				
Male		1727 (70%)	838 (71%)	889 (69%)	0.213[b]
Female		744 (30%)	340 (29%)	404 (31%)	
Antipsychotics	2425				
First Generation		488 (20%)	249 (22%)	239 (19%)	**<0.001**[b]
Second Generation		1436 (59%)	595 (52%)	841 (66%)	
Both Generations		501 (21%)	305 (26%)	196 (15%)	

Notes. EPSE, extrapyramidal side effects; SD, standard deviation

[a] Two Simple t-test; mean (SD)

[b] Pearson's Chi-squared test of independence; n (%)

In bold p passed significance threshold

Table 4.2 GWAS Participants' Demographics concerning EPSE Presence

	N	Overall	EPSE Presence	EPSE Absence	Neff	p-values
UCL	*1017*		*n = 587 (58%)*	*n = 430 (42%)*	*983*	
Age at assessment	1017	44.80 (12.24)	46.33 (12.10)	42.72 (12.14)		**<0.001**[a]
Age of onset	761	23.34 (8.18)	23.28 (8.07)	23.44 (8.34)		0.795[a]
Sex	1017					0.145[b]
Male		735 (72%)	435 (74%)	300 (70%)		
Female		282 (28%)	152 (26%)	130 (30%)		
Antipsychotics	973					**<0.001**[b]
First generation		102 (10%)	77 (14%)	25 (6%)		
Second generation		452 (47%)	208 (37%)	244 (59%)		
Both generations		419 (43%)	274 (49%)	145 (35%)		
Antidepressants	1020	45 (4%)	22 (2%)	23 (2%)		0.276[b]
PPD diagnosis	742	105 (14%)	60 (8%)	45 (6%)		0.999[b]
Aberdeen	*414*		*n = 90 (22%)*	*n = 324 (78%)*	*282*	
Age at assessment	414	44.40 (13.20)	45.70 (13.12)	44.03 (13.21)		0.292[a]
Age of onset	401	24.08 (8.05)	23.27 (7.76)	24.29 (8.13)		0.293[a]
Sex	414					0.426[b]
Male		311 (75%)	71 (79%)	240 (74%)		
Female		103 (25%)	19 (21%)	84 (26%)		
Antipsychotics	414					**<0.001**[b]
First generation		135 (33%)	42 (47%)	93 (29%)		
Second generation		231 (56%)	32 (35%)	199 (61%)		
Both generations		48 (11%)	16 (18%)	32 (10%)		
UKB	*507*		*n = 90 (18%)*	*n = 417 (82%)*	*296*	
Age at assessment	507	54.32 (8.08)	56.06 (7.61)	53.94 (8.14)		**0.020**[a]
Sex	507					0.322[b]
Male		335 (66%)	64 (71%)	271 (65%)		
Female		172 (34%)	26 (29%)	146 (35%)		
Antipsychotics	507					**<0.001**[b]
First generation		158 (31%)	52 (58%)	106 (25%)		
Second generation		320 (63%)	28 (31%)	292 (70%)		
Both generations		29 (6%)	10 (11%)	19 (5%)		
Cardiff	*533*		*n = 411 (77%)*	*n = 122 (12%)*	*376*	
Age at assessment	533	44.30 (11.70)	44.90 (10.90)	42.20 (14.10)		0.057[a]
Age of onset	508	25.00 (8.80)	24.30 (7.60)	27.50 (11.60)		**0.006**[a]
Sex	533					0.900[b]
Male		346 (65%)	268 (65%)	78 (64%)		
Female		187 (35%)	143 (35%)	44 (36%)		
Antipsychotics	531					0.100[b]
First generation		93 (17%)	78 (19%)	15 (12%)		
Second generation		433 (82%)	327 (80%)	106 (88%)		
Both generations		5 (1%)	5 (1%)	0 (0%)		

Notes. EPSE, extrapyramidal side effects; PPD, premorbid personality disorder; SD, standard deviation.
In bold p passed significance threshold
[a] Two Simple t-test; mean (SD); [b] Pearson's Chi-squared test of independence; n (%)
Neff, effective sample sizes, calculated as 4/(1/n_cases + n_controls)

4.4.2 GWAS results

For the main meta-analysis including all participants, we did not observe any SNP passing the genome-wide significance threshold at $5x10^{-08}$ (Table 4.3 and Appendix 4.6). We found no evidence for population inflation across the samples given the lambda value of 1, suggesting the test statistics are not inflated by population stratification or cryptic relatedness (see Appendix 4.7). We observed no evidence for excessive heterogeneity across the samples. The top index SNP rs2709733 (A/G; Z=4.999; p=5.755×10^{-07}) mapped to a long intergenic non-protein coding RNA, *LINC01162* and its effect was consistent across all cohorts (Table 4.3). The other affiliated protein-coding genes from the suggestive SNP rs11077391 (p=3.765×10^{-06}) included *USP36* and *CYTH1*.

For the subset analyses separating FGA and SGA exposures, we did not observe any SNP passing the genome-wide significance threshold (Table 4.3; Appendices 4.8 & 4.10). There was also no evidence for population inflation for these two subsets with lambda values of 1.030 and 0.992 (Appendices 4.9 & 4.11). The top suggestive SNPs from both subsets showed no excessive heterogeneity. The top affiliated genes from the FGA subset such as *NAV2, NRG3,* and *LSAMP* have been associated with autism and schizophrenia disorders (Kao et al., 2010; Must et al., 2008; Pretzsch & Ecker, 2023). In addition, one of the top affiliated protein coding genes, *SHISA9* from the SGA subset has shown associations with epilepsy and autism disorder (Pfisterer et al., 2020; Woolf et al., 2023).

Among overlapping SNPs at the 10^{-03} level, 1,463 (53%) SNPs in the SGA subset showed concordant effect directions with the FGA subset's (p=0.004), whereas 1,345 (48%) SNPs in the FGA subset aligned with the SGA subset's SNPs (p=0.995). The stronger directional agreement from SGA to FGA may reflect the broader pharmacological coverage of the FGA subset (which included mixed exposures). In contrast, the weaker concordance from FGA to SGA subset may suggest that top-associated SNP effects within the SGA subset may be more distinct given this subset included only exposure to SGA.

Table 4.3 Regions of the Genome showing the Strongest Association Signals with EPSE Presence

Index SNP	Chr	Position	A1/A2	EAF	Z Score	P-values	P-values Het	Match	Weight (Neff)	Mapped Genes
EPSEs with exposure to any antipsychotic										
rs2709733	7	20878995-20955370	A/G	0.452	4.999	5.755×10^{-07}	0.268	++++++	1937	*LINC01162*
rs12662039	6	99546454-99598593	C/G	0.057	4.948	7.492×10^{-07}	0.461	+++++?	1561	
rs11077391	17	76661207-76789754	A/G	0.311	4.624	3.765×10^{-06}	0.952	+++++?	1561	*USP36, CYTH1*
rs62530097	9	7590958-7667847	T/G	0.090	4.494	6.978×10^{-06}	0.560	++++++	1937	
EPSEs with exposure to any type of FGA*										
rs2028609	11	19918741-19933123	T/C	0.494	-5.144	2.693×10^{-07}	0.955	--?--	660	*NAV2*
rs1416851	10	84329093-84380431	T/C	0.233	-4.927	8.365×10^{-07}	0.290	-----	780	*NRG3*
rs17723244	3	117509984-117822025	A/G	0.721	-4.751	2.022×10^{-06}	0.595	-----	780	*LSAMP, LINC03051*
rs2840001	3	168714097-168862366	A/G	0.275	4.725	2.306×10^{-06}	0.563	+++++	780	
EPSEs with exposure to SGA only										
rs72800384	10	54799931-54839608	T/C	0.244	4.567	4.937×10^{-06}	0.179	-+++++	1063	
rs117545352	8	87786629-87894786	A/G	0.933	-4.522	6.117×10^{-06}	0.272	----+-	1063	*CNBD1*
rs4781355	16	13021889-13101555	A/G	0.637	4.509	6.524×10^{-06}	0.776	++++++	1063	*SHISA9*

Notes. Index SNP, the single-nucleotide polymorphism with the strongest association in the genomic region and each is independent at $r^2<0.1$; Chr, chromosome; Position, the start and end position (UCSC hg19) of the SNP locus where near-by SNPs were clumped to with nominal associations ($p<0.05$) and LD ($r^2<0.1$) within 250-kb windows taking the 1000 genomes project phase 3 EUR as LD reference; A1/A2, effect and alternate allele; EAF, the effect allele frequency based on 1000 genomes EUR; Z-score, the meta-analysis output reference score for the SNP; P-values, the corresponding p-values to the candidate SNP; P-values Het, corresponding p-values to the degree of variability in effect sizes from METAL analysis; Match, the agreement across the six datasets, + means individuals who carry the A1 allele have positive EPSE association, - means negative, ? means missing, the orders are: three sets of GWAS from UCL samples (1) Affymetrix Array, (2) Illumina PsychArray, (3) GSA, Illumina Global Screening Array, (4) Aberdeen samples, (5) UKB samples, and (6) Cardiff samples; Weight, the overall Neff of the sample for the SNP; Mapped genes, the top genes mapped by positional mapping criterion with maximum distance 10kb to the locus position. No SNP passed genome-wide significant threshold. * Includes participants who had also been exposed to SGAs.

4.4.3 EWAS sample demographics

The UCL participants who developed EPSE were younger than the healthy controls in terms of age at assessment (36.90 vs 44.48, $p<0.001$; see Appendix 4.12) and methylation age (39.54 vs 44.08, $p=0.008$). The UCL EPSE cases also had higher ratios of males (81% vs 44%, $p<0.001$). The Aberdeen participants' methylation age (54.29 vs 53.04, $p=0.473$), and males' ratio (70% vs 74%, $p=0.737$) were balanced between the EPSE and the control group.

4.4.4 EWAS meta-analysis results and permutation testing

In our primary within-case analysis including all EPSE samples, the most significant methylated position (DMP) associated with EPSE presence was cg05599348 (3.181×10^{-07}), mapping to *TMSB15B* on chromosome X (hg19 position 103174718). This DMP was also one of the top identified DMPs in the FGA exposure subset (Table 4.4). However, this DMP was only present in the UCL samples while all other top identified DMPs were present in both samples. Thus, its overall signal may have been influenced by the relatively small sample size of the UCL samples. From the FGA/SGA exposure EWAS subsets, we also did not identify any DMP passing the threshold at $1x10^{-07}$ (Table 4.4).

Comparing EPSE cases with healthy controls, we identified 9 DMPs associated with EPSE presence after controlling for schizophrenia PRS in addition (Table 4.4). Five of these identified DMPs have been implicated by past schizophrenia EWAS meta-analysis, cg12524168, $p=7.61\times10^{-20}$; cg05419385, $p=3.08\times10^{-18}$; cg22583147,

p=5.66×10^{-22}; cg12044923, p=1.32×10^{-19}; and cg20730966, p=4.90×10^{-24} (Hannon et al., 2016). The other four DMPs cg14531564, cg20647656, cg12004641, cg22845912, and their affiliated genes *SDF4*, *ANKMY1*, *TNS1*, *SLA* were not identified in past schizophrenia or smoking EWAS (Elliott et al., 2014; Zeilinger et al., 2013).

We next examined whether the locations of theses 9 DMPs could map to the corresponding GWAS of the same samples or to previously published schizophrenia GWAS. The GWAS summary statistics were first clumped so that multiple non-independent associations were collapsed into single associated loci. None of the identified DMPs were found to be associated with any genome-wide significant loci from past schizophrenia GWAS according to our regional mapping (Appendix 4.13) (Trubetskoy et al., 2022). The SNP rs7622757 within a 250kb window with cg22583147 was closest to genome-wide significance at p=4.44×10^{-07} (Appendix 13).

Our mapping of the DMPs to the GWAS of associated samples found that cg12044923 was significantly associated (permutation p=0.010) with index SNP rs13108591 which had a GWAS p value of 7.482×10^{-05}. cg20647656 was associated (permutation p=0.030) with index SNP rs75037293 which had a GWAS p value of 2.73×10^{-04}. According to the past schizophrenia GWAS (Trubetskoy et al., 2022), the SNPs rs13108591 (T/C) had p value of 0.761 and rs75037293 (G/C) had p value of 0.117 indicating minor relevance to schizophrenia (Trubetskoy et al., 2022). The SNP rs13108591 is located on chr4:5162317 (hg19), mapping to the intron of *STK32B*. SNP rs75037293 is located on chr2:241453995 (hg19) mapping to the intron of *ANKMY1*.

Table 4.4 EPSE-associated differentially Methylated Positions

Probe ID	CHR	Position	Methylation difference (%)	SE (%)	P Value	Gene Annotation
EPSEs with exposure to any antipsychotic						
cg05599348	X	103174718	-5.439	0.980	3.181×10^{-07}	*TMSB15B*
cg07679219	12	77417738	6.742	1.462	3.998×10^{-06}	*E2F7*
cg06484572	6	41605494	1.686	0.369	4.769×10^{-06}	*MDFI*
cg25194055	17	8125180	0.527	0.116	5.690×10^{-06}	
cg00145438	13	113105097	-0.991	0.220	6.620×10^{-06}	
cg26912312	20	61274254	-0.452	0.101	6.971×10^{-06}	*SLCO4A1*
EPSEs with exposure to any type of FGA*						
cg00500167	6	100841663	0.464	0.098	2.093×10^{-06}	*SIM1*
cg19185544	8	22595422	-1.748	0.371	2.418×10^{-06}	*PEBP4*
cg05599348	X	103174718	-5.340	1.156	3.854×10^{-06}	*TMSB15B*
cg05450477	6	20426845	1.654	0.369	7.293×10^{-06}	*E2F3*
cg26875877	2	133346858	-0.040	0.886	7.742×10^{-06}	*GPR39*
cg25030888	1	67156909	-3.013	0.692	1.327×10^{-05}	*SGIP1*
EPSEs with exposure to SGA only						
cg11411904	1	153935719	1.051	0.215	3.341×10^{-06}	*SLC39A1*
cg02388709	3	4910253	0.959	0.196	3.563×10^{-06}	
cg21130374	21	42734266	-1.636	0.344	5.928×10^{-06}	*MX2*
cg15977096	8	34857831	-4.410	0.965	1.268×10^{-05}	
cg09583379	16	19133877	-6.745	1.479	1.316×10^{-05}	
cg23814365	13	36429936	1.979	0.436	1.419×10^{-05}	*DCLK1*
EPSEs with exposure to any antipsychotic compared to healthy controls						
cg14531564	1	1154853	2.949	0.423	3.073×10^{-12}	***SDF4***
cg20647656	2	241439612	-1.413	0.236	2.098×10^{-09}	***ANKMY1***
cg12524168	5	76028910	1.931	0.326	3.207×10^{-09}	***F2R***
cg12004641	2	218750749	1.784	0.320	2.377×10^{-08}	***TNS1***
cg05419385	12	27352945	1.565	0.281	2.549×10^{-08}	
cg22583147	3	44331824	2.055	0.374	3.828×10^{-08}	***TOPAZ1***
cg22845912	8	134059874	1.861	0.341	4.858×10^{-08}	***SLA***
cg20730966	3	33095886	1.736	0.323	7.442×10^{-08}	***GLB1***
cg12044923	4	5207312	1.695	0.316	8.414×10^{-08}	***STK32B***

Notes. Listed are all differentially methylated positions (DMPs) associated with different sets of EPSE samples. Sample sizes were: (1) 314 (UCL 64 EPSE cases, 33 EPSE controls; Aberdeen 47 EPSE cases, 170 EPSE controls); (2) 174 (UCL EPSE 57 cases, 23 EPSE controls; Aberdeen EPSE 30 cases, 64 controls); (3) 123 (UCL only 17 samples in total thus excluded; Aberdeen 17 EPSE cases, 106 EPSE controls); and (4) 859 (UCL 64 EPSE cases, 315 healthy controls; Aberdeen 47 cases, 433 healthy controls). Results came from fixed model meta-analysis adjusted for participants' methylation age, sex, and cell compositions. The comparison between EPSE cases and healthy controls adjusted for schizophrenia polygenic risk scores in addition to alleviate schizophrenia genetic risks. Positions are in hg19. Genes in bold had p meeting threshold at $1x10^{-07}$. * Includes participants who had also been exposed to SGAs.

4.4.5 PRS results

We found no evidence to suggest any of the selected PRS could predict the development of EPSE (Table 4.5). According to the fixed model meta-analysis, the participants' genetic predisposition to Schizophrenia (p=0.566), Parkinson's disease (p=0.492), and Lewy-body dementia (p=0.765) were not associated with the presence of EPSE.

Table 4.5 Results of Multiple Regression Analyses

Variables	Estimated Coefficient	Standard Error	Confidence Intervals (95%)	Reference Values	*p*
Schizophrenia PRS					
UCL	0.013	0.017	-0.020, 0.047	0.780	0.436
Aberdeen	0.006	0.020	-0.033, 0.046	0.321	0.749
UKB	0.032	0.017	-0.036, 0.032	1.941	0.053
Fixed-effect model	0.019	0.010	-0.001, 0.039	1.828	0.566
Parkinson's disease PRS					
UCL	0.015	0.017	-0.018, 0.049	0.892	0.373
Aberdeen	0.025	0.022	-0.017, 0.068	1.162	0.246
UKB	-0.010	0.016	-0.042, 0.022	-0.637	0.525
Fixed-effect model	0.007	0.010	-0.013, 0.027	0.687	0.492
Lewy-body dementia PRS					
UCL	-0.022	0.016	-0.053, 0.009	-1.390	0.165
Aberdeen	0.017	0.023	-0.029, 0.062	0.718	0.473
UKB	0.026	0.017	-0.008, 0.060	1.481	0.139
Fixed-effect model	0.003	0.011	-0.017, 0.024	0.299	0.765

Notes. PRS, polygenic risk scores

All results were adjusted for participants' age, sex, genotyping chip-type, and the first three principal components from GWAS population stratification. UKB results were adjusted for 3 additional principal components. Reference values were t values for individual models and z values for the fixed effect model.

4.5 Discussion

In the present study, we report the largest GWAS meta-analysis of EPSE and the first EWAS meta-analysis of EPSE in European populations to date with exploration on the effects of FGA and SGA exposure. The prevalence of any type of EPSE was found to be 48% among participants who have taken either FGA or SGA. EPSEs were found to be more prevalent among those who had taken FGA or both. No SNP passed the genome-wide threshold of significance. The top index SNP rs2709733 from the GWAS of all antipsychotic exposure mapped to a long intergenic non-protein coding RNA, *LINC01162* with consistent effect across all cohorts. SNPs associated with EPSEs from exposure to FGAs at the suggestive level mapped to *NAV2, NRG3,* and *LSAMP*. SNPs associated with EPSEs from exposure to SGA mapped to *SHISA9* and *CNBD1*. The primary EWAS meta-analysis indicated suggestive gene *TMSB15*B, located on chromosome X. In addition, we identified multiple DMPs associated with EPSE passing the significance threshold comparing EPSE cases to healthy controls. The *STK32B* gene which was implicated by methylation probe cg12044923 has been associated with psychiatric and movement disorders. We found no evidence that PRSs for schizophrenia, Parkinson's, and Lewy-body dementia predict EPSE development.

The GWAS meta-analysis results may represent a false negative due to the limited sample size and power. Other factors may also be relevant. For example, our sign tests revealed weak SNP effect alignment between the FGA and the SGA GWAS results, suggesting that there may be differences in the genetic architecture of these traits. Thus, combining participants who have taken either FGA or SGA may have impacted our

ability to identify drug-specific genetic risks. Conversely, stratifying the sample by antipsychotic exposure (FGA vs SGA) substantially reduced sample sizes, compromising statistical power. However, several of the implicated genes (*NAV2, NRG3, LSAMP* and *SHISA9*) from the subset analyses were previously reported to be associated with psychiatric disorders and were and with neuronal function. Thus, these findings warrant cautious interpretation due to the suggestive nature of the associations. The results produced here are the result of a concerted effort to increase sample size as a starting point for future studies.

The limited GWAS and PRS findings lead us to speculate that EPSE may be more strongly driven by epigenetic modifications over time. Studies have suggested that methylation changes in dopaminergic or serotonergic pathway genes may impact motor control pathways more dynamically than SNP-based variations (Loke et al., 2015). This dynamic epigenetic regulation aligns with how EPSE can vary significantly among patients and change with continued antipsychotic use, whereas GWAS-derived SNPs only offer a static view of genetic risk. Therefore, integrating EWAS may provide insights into the gene-environment interactions involved in EPSE development.

Our primary EWAS analysis of EPSE status may have been again limited by modest sample size, potentially reducing statistical power to detect robust epigenetic associations. However, permutation testing in our expanded EWAS comparing EPSE cases with healthy controls identified two genes, *ANKMY1* and *STK32B*, showing significant relevance to the presence of EPSE. *ANKMY1* encodes the protein Ankyrin Repeat and MYND Domain Containing 1, which has a role for protein-protein

interactions and cellular signalling. This could indirectly influence pathways relevant to neurodevelopment or dopamine signalling. However, we have found little additional corroborating evidence directly linking *ANKMY1* to schizophrenia or EPSE. The other implicated gene *STK32B* encodes for a member of the human N-myristoylated proteins, which are involved in various cellular signalling and transduction pathways, although its exact biological function remains insufficiently defined (Takamitsu et al., 2015). A 520-kb homozygous deletion encompassing *STK32B* has been described in Ellis-Van-Creveld syndrome, which is a rare genetic disorder that primarily affects the skeletal system and other tissues (Temtamy et al., 2008).

Notably, changes in the methylation of the *STK32B* promoter region have been previously linked to both schizophrenia and anxiety disorders. This protein may play a role in executive functions such as working memory and selective attention (Ciuculete et al., 2018; Hannon et al., 2016). Moreover, *STK32B* was implicated in a GWAS of essential tremor (Müller et al., 2016), and patients with essential tremor showed increased expression of *STK32B* in the cerebellar cortex, highlighting a potential relevance to movement abnormalities.

The current study has several limitations. First, the study's EPSE classification was based on cross-sectional data from existing studies. Individuals classified as not having EPSE at the time of assessment may develop EPSE later in life with increasing exposure to antipsychotics, introducing potential pseudo-negatives. In addition, we could not differentiate between acute and chronic EPSE. Medication dose information was unavailable for most participants thus, not analysed. We used a mixed definition of

EPSE and mixed antipsychotic medications and EPSE medications, each of which may have distinct profiles of EPSE risk. Other dynamic factors such as aging, comorbid conditions and drug-drug interactions may influence the recognition of EPSE as well. Differences in sample ascertainment may have contributed to variability in EPSE detection sensitivity and the predominance of male participants could be another source of bias. These variability and potential miss-classification could impact the consistency of our findings and warrant careful consideration in future studies to clarify the effects of specific antipsychotic medications on EPSE with increased sample size to do so. Finaly, although we have implemented strategies to control for collider bias related to schizophrenia, our results may still be influenced by genetic risk to schizophrenia.

Overall, our study provides new insights into the biological mechanisms underlying EPSE development in patients with schizophrenia. Notably, our approach integrated findings from EWAS with GWAS results, allowing us to explore EPSE-associated methylation shifts using accessible SNP data. The findings of this study indicate that further investigation of the epigenetics of EPSE and the role of *STK32B* in EPSE is likely to enhance our understanding and inform future research and treatment directions.

5. Polygenic Risk and Cardiovascular Treatment Effects in Severe Mental Illness

5.1 Abstract

Background: Patients with severe mental illness (SMI) face increased cardiovascular risks, leading to reduced life expectancy. Polygenic risk scores (PRS) prediction is a promising method to assess cardiovascular risks in SMI. However, the PRS utility and the impact from interventions on these predictions were underexplored.

Methods: Using samples from the PRIMROSE, which involved longitudinal cardiovascular interventions within primary-care, we calculated 7 cardiovascular and 2 psychiatric PRS (bipolar/schizophrenia) to predict 7 corresponding cardiovascular measures (total cholesterol/HDL/LDL/triglyceride/systolic blood pressure/diastolic blood pressure/BMI) assessed at baseline and 12-month follow-up. We applied multiple linear regression models and explored the interactions between cardiovascular and psychiatric PRS on treatment outcomes.

Results: At baseline, most PRS were predictive of corresponding measures, indicating strong genetic associations. However, these associations could attenuate if the treatment effectively altered the measures, particularly for total cholesterol and systolic blood pressure. LDL measures became negatively associated with bipolar PRS after treatment, though no significant interaction effects were found. Participants in the highest bipolar PRS quartile showed 0.58 mmol/L reduction in LDL measurement on average after treatments suggesting a potential protective effect from higher bipolar genetic risks. These results were robust to potential power reduction, participants' age, sex,

medication use, smoking habits, alcohol consumption, and physical activity levels.

Conclusions: Our findings underscored the dynamic interplay between genetic risks and treatment effects and warrant careful PRS assessment timing. While the clinical application of PRS has not yet been fully realized, further research with precise BD subtype measurements is needed to clarify how BD genetic risks interact with interventions.

5.2 Introduction

Patients diagnosed with bipolar disorder (BD), schizophrenia (SCZ), or psychosis are often jointly referred to as patients with severe mental illness (SMI). Patients with SMI have a higher mortality rate leading to a 15–20 years reduction in life expectancy in comparison to the general population (Nordentoft et al., 2013). Cardiovascular disease (CVD) contributes 17.4% and 22.0% of life years lost in males and females with SMI, respectively (Jayatilleke et al., 2017; Nielsen et al., 2021). CVD was recorded as the cause of death for approximately 24% of patients with SCZ and 38% of patients with BD (Nielsen et al., 2013; Westman et al., 2013). The life expectancy gap between the general population and patients with SMI appears to be widening due to the lack of effective interventions (Hayes et al., 2017).

Multiple factors underlie the increased risks of cardiovascular events among patients with SMI (Nielsen et al., 2021). Patients with SMI are more likely to have an unhealthy lifestyle, increased sedentary time, lack of exercise, poor diet, and increased rates of smoking and heavy alcohol use (Hartz et al., 2014; Vancampfort et al., 2015,

2016, 2017). Treatments with antipsychotic drugs can lead to weight gain and higher cardiovascular mortality (Rotella et al., 2020). In addition, antidepressants and mood stabilizers can cause adverse metabolic effects (Correll et al., 2015; Pérez-Piñar et al., 2016).

People with SMI may also have a higher genetic predisposition to CVD compared with the general population (O'Sullivan et al., 2022). A meta-analysis of GWAS and candidate gene studies identified 24 potential pleiotropic genes that are likely to be shared between mood disorders and cardiometabolic disease risk (Amare et al., 2017). So et al. (2019) calculated PRS for SCZ and BD in patients with SMI, summarizing their genetic predispositions to these two disorders. These psychiatric PRS were compared with 28 additional cardiometabolic traits. The results showed that SCZ was genetically associated with several cardiometabolic abnormalities including glucose metabolism abnormalities and adverse adipokine profiles independent of medication use. In contrast, BD showed polygenic associations with an overall more favourable cardiometabolic profile, suggesting potential protective metabolic traits linked to BD genetic risks thus, cardiometabolic abnormalities in BD are more likely to be secondary. In addition, Strawbridge et al. (2021) applied multidimensional scaling to shared genetic variants between both psychiatric and cardiometabolic disorders. They found that schizophrenia patients had distinct metabolic profiles.

Various behavioural interventions have been developed to control cardiovascular risks for patients with SMI (Goldfarb et al., 2022). Most of these developed interventions were found to be effective in controlling cardiovascular risks among

people with SMI (Aschbrenner et al., 2022; Jakobsen et al., 2017). The added value from incorporating cardiovascular PRS in risk predictions is increasingly recognized (Samani et al., 2024; Sun et al., 2021). Individuals with higher cardiovascular genetic risks were found to benefit more from satin and alirocumab treatment suggesting different response profiles (Damask et al., 2020; Natarajan et al., 2017). However, genomic and clinical risk factor predictions for CVD may vary over the life course (Urbut et al., 2025). In addition, no previous studies have specifically examined how interventions or treatments can influence PRS-based predictions of cardiovascular risks in patients with SMI over time. Additionally, the impact of genetic risk for psychiatric disorders on cardiovascular treatment effectiveness remains unclear.

The PRIMROSE group developed a pragmatic intervention aimed at reducing cardiovascular disease risk factors among people with SMI in primary care in England (Burton et al., 2015). The PRIMROSE intervention had a similar effect on total cholesterol concentration reduction at 12 months as treatment-as-usual groups with decreased costs through decreased psychiatric relapses and readmissions (Osborn et al., 2018). A subset of participants provided consent for genetic data analysis to determine whether their genetic profiles can predict variations in treatment response. We used the data to explore longitudinal changes in PRS-based risk predictions.

The overall aim of this study was to use 7 cardiovascular (total cholesterol/HDL/LDL/triglyceride/systolic blood pressure/diastolic blood pressure/BMI) and 2 psychiatric (bipolar/schizophrenia) PRS to understand how genetic risks influence cardiovascular treatment effectiveness. Specifically, we wanted

to explore if these PRS predictions would change after treatments and how psychiatric genetic risks modify these predictions. We hypothesized that the cardiovascular PRS would interact with psychiatric PRSs (BD/SCZ) in predicting treatment effectiveness. People with higher genetic risks for both cardiovascular risks and psychiatric disorders were expected to have reduced treatment response given this group of patients' potential adverse metabolic profiles.

5.3 Methods

5.3.1 Participants Selection and Genotyping

Participants were recruited from GP practices across both rural and urban areas of England (see details for participant specification in Osborn et al., 2018). Participants were defined as having increased cardiovascular risk if they were aged 30–75 years, listed on the Quality and Outcomes Framework register for severe mental illness (schizophrenia, bipolar disorder, or other non-organic psychosis), with elevated cholesterol (total ≥5·0 mmol/L or total-to-HDL ratio ≥4·0) and at least one additional risk factor (hypertension, diabetes, elevated HbA1c, obesity, or smoking). Ethics approval was obtained from the City Road and Hampstead Research Ethics Committee (Reference No: 12/LO/1934, approval granted 10 January 2013). Local NHS approvals were obtained before the start of each recruitment wave. At baseline, the recruited participants were randomized into a PRIMROSE intervention group or treatment as usual group for improving cardiovascular risks. Each treatment lasted for 12 months and there were no major difference found in terms of the participants' treatment response between the two groups (see details in Osborn et al., 2018). A subset of the

participants (N=194/326) consented to provide a saliva sample for genotyping and the conduct of genetic research. These participants were included in the present study.

5.3.2 Study Measures

The participants' total cholesterol concentrations, high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL), lipid concentration (triglyceride), two blood pressures (systolic and diastolic), and BMI were included for analyses. These measures were collected at baseline using usual GP practice equipment and procedures and repeatedly taken at 12-month follow-up following the same procedure. Other health and lifestyle measures included medication use in the past 12-month (antipsychotic/antidepressant/mood stabilizer/antihypertensive/other medications); smoking habits (number of cigarettes per day); alcohol drinking habit from Alcohol Use Disorders Identification Test Score (AUDIT-C); and physical activity measures from International Physical Activity Questionnaire (IPAQ). These data were collected either directly from participant interviews, clinical measures or from the GP practice medical records (see details for all measures in Osborn et al., 2018).

5.3.3 Genetic Data Imputation and Quality Control

194 participants from the PRIMROSE gave consent for genetic analyses and provided saliva sample for genotyping. The participants' genetic data were genotyped by UCL Genomics on the Global Screening Array then received stringent quality control (QC; Anderson et al., 2010). The process focused on excluding samples with

discordant sex, missing genotype data above 10%, excessive heterozygosity (more than 3 standard deviations above the mean) and evidence of relatedness (PIHAT of > 0.2). SNPs which deviated substantially from the Hardy-Weinberg equilibrium ($P<10^{-6}$) or had a minor allele frequency < 0.5% were also excluded. All of these described quality control steps were performed using PLINK 1.9 (Chang et al., 2015).

Imputation was performed using the Sanger Imputation server. Prior to the upload, the data genotypes were prepared as instructed and checks were performed using the HRC-1000G-check-bim tool Version 4.2.3 (Rayner, W., 2015). SNPs with an MAF>0.01 were uploaded for imputation, applying the Haplotype Reference Consortium reference panel (release 1.1; McCarthy et al., 2016). Pre-phasing was done with EAGLE v.2.3.3 and imputation was done with PBWT (Durbin, 2014). Post-imputation QC repeated the prior QC procedure and further excluded all SNPs with info<0.9. A total of 188 participants' genetic data survived quality control and had complete datasets.

5.3.4 PRS Calculations

Patients' cardiovascular and psychiatric PRS were computed from the imputed genetic data with the PRS-CS-auto method which employs the Bayesian theorem to provide a single score for each sample (Ge et al., 2019). The PRS-CS-auto method was chosen over other methods since it outperformed other existing methods according to the simulation studies (Ge et al., 2019; Pain et al., 2021).

The application of the PRS-CS method required a LD reference panel and reference

GWAS summary statistic, which are used to infer the posterior effect sizes of SNPs. We chose the European sample from The 1000 Genomes Project Consortium (2010) as our LD reference panel. We used GWAS summary statistics on European samples from the Global Lipids Genetics Consortium (GLGC) for cholesterol and triglyceride PRS calculations (Graham et al., 2021). These included total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. The summary statistics for blood pressure (diastolic/systolic) came from Keaton et al. (2024). BMI European GWAS summary statistics came from Yengo et al. (2018). The GWAS summary statistics for BD came from European samples of O'Connell et al. (2025). The summary statistics for schizophrenia came from Trubetskoy et al. (2022). The calculated PRS were standardized with healthy controls before analyses.

5.3.5 Statistical analysis

The participants' demographic and summary statistics were first presented in respect to their treatment group for all variables. We conducted t and chi-square tests based on the variable type for both baseline and 12-month follow-up measures to test for group differences. Given we found little evidence for group differences in these measures, we then combined the two groups for the following analyses where the group allocation was included as an additional covariate. Before conducting the analyses, we systematically removed outliers using a 3 SD approach on the raw clinical values of the 7 selected measures at baseline and 12-month follow-up to minimize the impact of extreme values.

We conducted multiple linear regressions taking the 7 cardiovascular measures at baseline as outcome measures and their associated PRS as predictor for associations prior to any treatment. We conducted the same set of analyses on cardiovascular measures at 12-month follow-up to explore how treatments can influence PRS predictions. To address potential power reduction from participant dropout at follow-up, we calculated and compared the power of each baseline and 12-month follow-up regression model using Cohen's f^2 method at 0.05 significance level as a sensitivity check (Cohen, 2013). We then explored the interactions between cardiovascular and psychiatric PRS on the 12-month follow-up measures to test how psychiatric genetic risks can interfere with cardiovascular treatment effectiveness. In addition, we split the BD PRS into 4 quartiles for further analyses and conducted subgroup analyses for the two treatment groups as sensitivity analyses.

Covariates in all analyses included the participants' age, sex, treatment allocation, diagnosis, smoking habits, alcohol consumption, and physical activity measures. Each model was also adjusted for the corresponding medication presence recorded at baseline or 12-month assessment including antipsychotic, antidepressant, antihypertensive, mood stabilizers and other medications in binary format. Some of the 12-month analyses also included the corresponding baseline measure as an additional covariate to assess the independence of the genetic prediction. Hypotheses and assumptions for each regression were pre-checked and found to be satisfactory. We conducted sensitivity analyses including only European participants given the PRS were calculated based on GWAS of European ancestry. No significant difference in results were observed given

95% of the participants had the same ethnicity.

For multiple testing correction, we used the FDR correction methods (Benjamini & Hochberg, 1995). The FDR method was chosen over the others as it gives a good illustration of results and has been applied in previous studies involving PRS (Grigoroiu-Serbanescu et al., 2020; Yao et al., 2023). The p value threshold was set at 0.05 for adjusted p values. All reported analyses were conducted using Rstudio with R 4.3.2 (R Core Team, 2021).

5.4 Results

5.4.1 Sample demographics

Overall, 188 participants' genetic data passed quality control at baseline and had complete datasets. 92 (49%) of them received the PRIMROSE intervention while the rest received treatment as usual which was taken as the control group (See Table 5.1). The whole sample was reasonably balanced in sex (47% males) while the control group had slightly higher ratios of males (53% vs 40%), however, there was no evidence to suggest the imbalance (p=0.104). The overall sample contained mostly European (95%) participants and about half of them had diagnoses of bipolar disorder (52%) and were non/ex-smokers (53%). The overall mean AUDIT-C score of 3.52 (SD 3.47) suggested that the participants were generally at a low risk for hazardous drinking or alcohol use disorder. The overall IPAQ total score at 2133 suggested that the participants on average meet recommended activity levels for health. However, the high SD (2249) indicated that the physical activity time varied largely between individuals. The two groups of participants did not differ in ethnicity, diagnoses, smoking/drinking habits, physical

activity time or medication uses (see details in Table 5.1). The PRIMROSE intervention group's systolic blood pressure was slightly lower than the control group at the baseline (125.32 vs 130.81, p=0.027). The two groups of participants did not differ in other clinical measures including total cholesterol, HDL, LDL, triglycerides, diastolic blood pressure, and BMI.

At the 12-month follow-up, only 158 participants had complete dataset for analyses and 77 (49%) of them had the PRIMROSE intervention. We did not observe any significant difference in any of these selected measures between these two groups (See results in Table 5.2). Overall, the interventions were effective in reducing total cholesterol measures (t=2.277, p=0.024). Such results were consistent with the original PRIMROSE study suggesting that the PRIMROSE intervention had the same level of effect as the treatment as usual. Comparing these measures at the two time points, the participants' overall AUDIT-C score dropped from 3.52 to 3.04 and their IPAQ total score increased from 2133 to 3711. These indicated that the participants had positive changes in some of the life habits in general. The participants' overall systolic blood pressure dropped from 128.12 (SD 17.17) mmHg to 124.36 (SD 13.95) mmHg and their diastolic blood pressure also dropped from 81.68 (SD 10.34) mmHg to 79.68 (9.90) mmHg (see details in Table 5.1 & 5.2). These reductions were statistically significant for systolic blood pressure (t=2.243, p=0.026) and close for diastolic blood pressure (t=1.828, p=0.068). These changes further indicated the benefits from both interventions. However, changes in all the other measures were small overall considering both interventions.

Table 5.1 Participant Demographics and Clinical Characteristics by Treatment Groups at Baseline Assessment

	N	Overall	PRIMROSE	Control	p-values
Overall Samples	*188*		*n = 92 (49%)*	*n = 96 (51%)*	
Age at assessment	188	50.21 (10.22)	50.18 (10.31)	50.23 (10.19)	0.976[a]
Sex	188				0.104[b]
Male		88 (47%)	37 (40%)	51 (53%)	
Female		100 (53%)	55 (60%)	45 (47%)	
Ethnicity	188				0.693[b]
European (white)		178 (95%)	86 (93%)	92 (96%)	
Other		10 (5%)	6 (7%)	4 (4%)	
Diagnosis	188				0.263[b]
Bipolar		97 (52%)	46 (50%)	51 (53%)	
Schizophrenia		44 (23%)	26 (28%)	18 (19%)	
Other diagnoses		47 (25%)	20 (22%)	27 (28%)	
Smoking	188				0.361[b]
Heavy (⩾20 a day)		42 (22%)	24 (26%)	18 (19%)	
Moderate (10-19 a day)		28 (15%)	10 (11%)	18 (19%)	
Light (⩽9 a day)		19 (10%)	10 (11%)	9 (9%)	
Non/Ex-smoker		99 (53%)	48 (52%)	51 (53%)	
AUDIT-C Score	188	3.52 (3.47)	3.52 (3.41)	3.51 (3.55)	0.982[a]
IPAQ Total Score	188	2133 (2249)	2059 (2273)	2203 (2236)	0.663[a]
Medications	188				
Antipsychotic		117 (62%)	54 (59%)	63 (66%)	0.407[b]
Antidepressant		90 (48%)	45 (49%)	45 (47%)	0.894[b]
Mood stabiliser		55 (29%)	25 (27%)	30 (31%)	0.650[b]
Antihypertensive		40 (21%)	17 (18%)	23 (24%)	0.460[b]
Other Medications		162 (86%)	77 (84%)	85 (89%)	0.453[b]
Clinical & Blood Tests					
Total cholesterol	187	5.71 (0.85)	5.73 (0.85)	5.68 (0.86)	0.685[a]
HDL	185	1.28 (0.40)	1.30 (0.38)	1.25 (0.41)	0.405[a]
LDL	120	3.43 (0.81)	3.49 (0.84)	3.37 (0.77)	0.417[a]
Triglycerides	127	2.21 (1.22)	2.27 (1.21)	2.14 (1.23)	0.537[a]
Systolic blood pressure	188	128.12 (17.16)	125.32 (14.74)	130.81 (18.88)	**0.027**[a]
Diastolic blood pressure	186	81.68 (10.34)	81.20 (10.26)	81.68 (10.34)	0.531[a]
Body mass index (BMI)	185	31.60 (5.35)	31.86 (5.86)	31.34 (4.82)	0.510[a]

Notes. AUDIT-C, Alcohol Use Disorders Identification Test Score; IPAQ, International Physical Activity Questionnaire; HDL, high-density lipoprotein; LDL, low-density lipoprotein. In bold p met significance threshold at 0.05

Other diagnoses included schizoaffective disorder, psychosis, and persistent delusional disorder.

[a] Two Simple t-test; mean (SD); [b] Pearson's Chi-squared test of independence; n (%)

Table 5.2 Participant Demographics and Clinical Characteristics by Treatment Groups at 12 Month Follow-up

	N	Overall	PRIMROSE	Control	p-values
Overall Samples	*158*		*n = 77 (49%)*	*n = 81 (51%)*	
Age at assessment	158	51.30 (9.97)	51.21 (10.05)	51.40 (9.95)	0.907[a]
Sex	158				0.321[b]
Male		71 (45%)	31 (40%)	40 (49%)	
Female		87 (55%)	46 (60%)	41 (51%)	
Ethnicity	158				0.999[b]
White		150 (95%)	73 (95%)	77 (95%)	
Other		8 (5%)	4 (5%)	4 (5%)	
Diagnosis	158				0.435[b]
Bipolar		85 (54%)	41 (53%)	44 (54%)	
Schizophrenia		35 (22%)	20 (26%)	15 (19%)	
Other diagnoses		38 (24%)	16 (21%)	22 (27%)	
Smoking	158				0.688[b]
Heavy (⩾20 a day)		28 (18%)	16 (21%)	12 (15%)	
Moderate (10-19 a day)		25 (16%)	11 (14%)	14 (17%)	
Light (⩽9 a day)		15 (9%)	6 (8%)	9 (11%)	
Non/Ex-smoker		90 (57%)	44 (57%)	46 (55%)	
AUDIT-C Score	158	3.08 (3.34)	2.82 (3.28)	3.33 (3.39)	0.333[a]
IPAQ Total Score	158	3694 (5218)	3620 (4515)	3764 (5836)	0.863[a]
Medications	158				
Antipsychotic		94 (59%)	47 (61%)	47 (58%)	0.823[b]
Antidepressant		81 (51%)	40 (52%)	41 (51%)	0.994[b]
Mood stabiliser		40 (25%)	17 (22%)	23 (28%)	0.466[b]
Antihypertensive		48 (30%)	21 (27%)	27 (33%)	0.513[b]
Other		144 (91%)	67 (87%)	77 (95%)	0.134[b]
Clinical & Blood Tests					
Total cholesterol	158	5.46 (1.11)	5.47 (1.11)	5.45 (1.13)	0.888[a]
HDL	156	1.28 (0.42)	1.28 (0.42)	1.29 (0.42)	0.919[a]
LDL	94	3.27 (0.98)	3.25 (0.91)	3.29 (1.05)	0.840[a]
Triglycerides	102	2.20 (1.26)	2.11 (1.38)	2.28 (1.14)	0.502[a]
Systolic blood pressure	156	124.36 (13.95)	122.78 (13.52)	125.86 (14.28)	0.168[a]
Diastolic blood pressure	157	79.68 (9.90)	80.01 (9.42)	79.36 (10.39)	0.679[a]
Body mass index (BMI)	156	31.77 (5.77)	31.94 (6.26)	31.60 (5.30)	0.709[a]

Notes. AUDIT-C, Alcohol Use Disorders Identification Test Score; IPAQ, International Physical Activity Questionnaire; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Other diagnoses included schizoaffective disorder, psychosis, and persistent delusional disorder.
[a] Two Simple t-test; mean (SD); [b] Pearson's Chi-squared test of independence; n (%)

5.4.2 Cardiovascular PRS Associations Results

The PRIMROSE and control groups were combined for the following analyses with the group allocation as an additional covariate given that we did not find evidence for significant differences in measures. According to our baseline models, most cardiovascular PRSs were predictive of the actual cardiovascular measures among participants with SMI prior to any treatments except for LDL (Table 5.3). Most of the associations remained robust after interventions with only small attenuations in association coefficients (Table 5.3). After adjustment of the corresponding baseline measures, only HDL PRS remained predictive of the actual HDL measures regardless of the treatment. This might suggest that the interventions had little impact on HDL and/or HDL is more genetically modified among patients with SMI.

The interventions were most effective in reducing total cholesterol (t=2.277, p=0.024) and systolic blood pressure (t=2.243, p=0.026) measures. The longitudinal comparison revealed a clear attenuation of genetic associations after effective treatment, with the predictive effects of total cholesterol and systolic blood pressure PRS weakening towards the null at the 12-month follow-up. This trend was visually evident in Figure 5.1 (Panels A & E), where the fitted regression lines became notably flatter compared to the baseline. In contrast, measures with minimal changes maintained stable associations, as demonstrated by overlapping or near-parallel fitted lines in Figure 5.1 (Panels B, C, D, F, & G).

The association coefficients for total cholesterol PRS dropped from 0.196 at baseline to 0.155 at 12-month follow-up and the association coefficients for systolic

blood pressure PRS dropped from 4.269 at baseline to 2.093 at 12-month follow-up (Table 5.3). Formal comparison of the coefficients between the two time points using Z-score tests revealed no statistically significant differences for total cholesterol (Δ=0.041, SE=0.113, Z=0.362, p=0.717) or systolic blood pressure (Δ=2.176, SE=1.788, Z=1.217, p=0.224). However, even these modest attenuations were sufficient to substantially weaken PRS predictive accuracy following effective treatment interventions (Table 5.3).

Our sensitivity analyses comparing the baseline and 12-month regression models revealed no significant difference in model power. Therefore, the observed attenuations were more likely due to changes in participants' actual measures. In addition, our sensitivity analyses separating the PRIMROSE intervention and control group did not produce any major change in the result patterns.

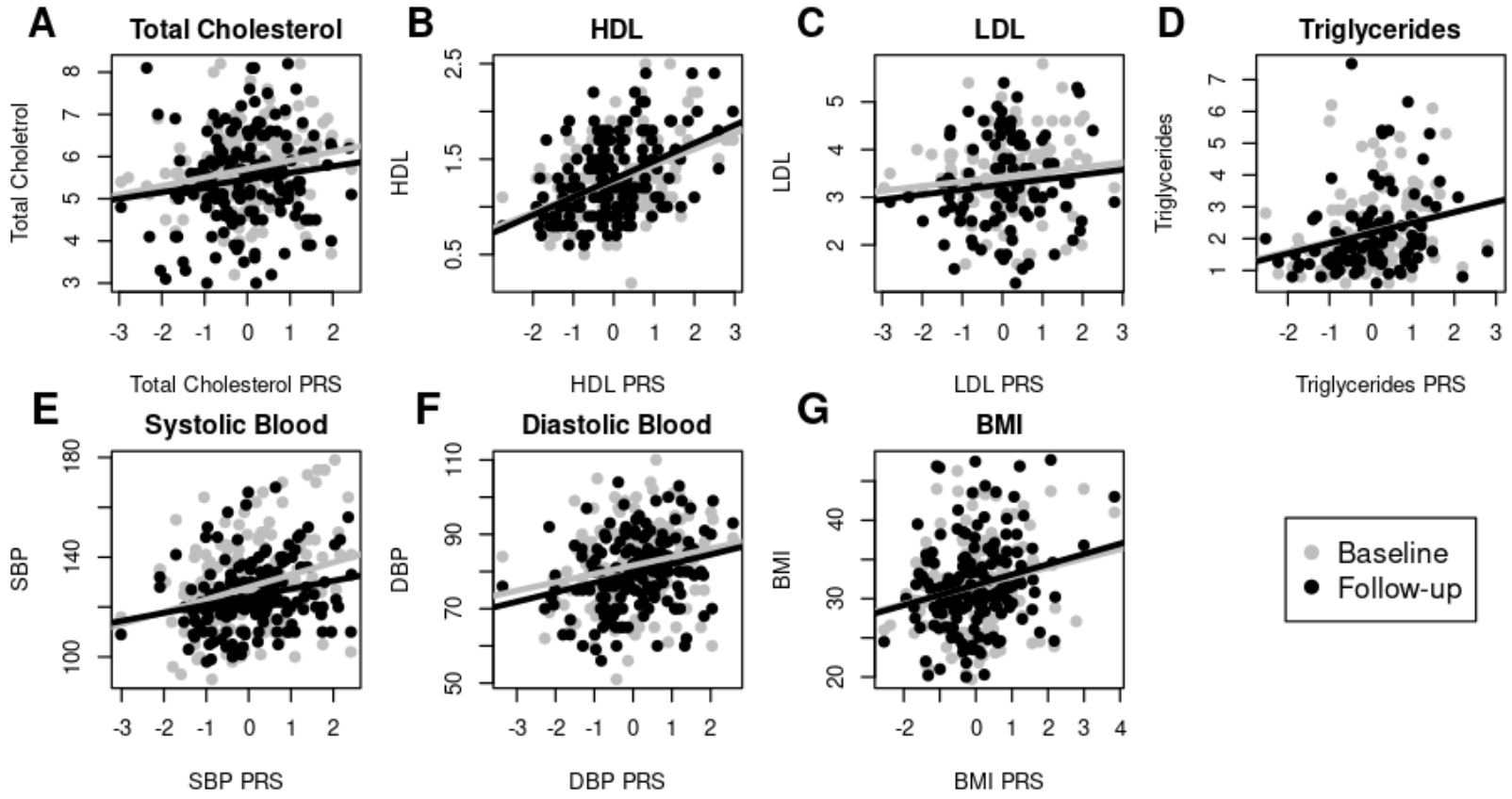
5.4.3 BD & SCZ PRS Interaction Results

We conducted multiple linear regressions taking interactions between the two psychiatric PRS (bipolar/schizophrenia) and each cardiovascular PRS on the corresponding 12-month follow-up measures to explore the impact from psychiatric genetic risk. We first examined potential collinearity between the two psychiatric PRS and each cardiovascular PRS. We only found weak associations between schizophrenia PRS and BMI PRS (coefficient=-0.171; t=-2.247, p=0.026). However, the model's variables only had the highest Variance Inflation Factor (VIF) number of 2.414 suggesting no exceptional collinearity.

From the models, we did not find any evidence to suggest that there was any significant interaction effect between BD or SCZ PRS and the corresponding cardiovascular PRS on these clinical measures (See Table 5.4). At 12-month follow-up, total cholesterol PRS was no longer predictive of the actual total cholesterol measure (*p.adj*=0.166; Table 5.3). However, for each unit increase in BD PRS, there was a decrease in total cholesterol of 0.276 mmol/L (*p.adj*=0.043). In addition, LDL PRS was not predictive of the actual LDL levels at both time points. However, for each unit increase in BD PRS, LDL decreased by 0.331 mmol/L (*p.adj*=0.043) at the 12-month follow-up, suggesting a potential protective effect from higher BD genetic risks.

To further explore BD PRS's associations with different cholesterol levels, we split BD PRS into 4 quartiles and compared its influence between baseline and 12-month follow-up where the 12-month follow-up models included the corresponding baseline measure as an additional covariate. At baseline, we found no association between BD PRS and any of these cholesterol levels (Figure 5.2 A). However, at 12-month follow-up, the associations became obvious even if controlled for the baseline measure's impact (Figure 5.2 B). If the participants were in the top BD PRS quartile group, they had 0.58 mmol/L fewer LDL measures on average (*t*=-0.860; 95% CI: -1.516, -0.204; *p.adj*=0.039). The overall model including all covariates could explain 28% of total variance in LDL measures at 12-month follow-up while BD PRS accounted for 7% of these variations. These findings further indicated BD genetic risk's potential impact on LDL treatment responses. And the relationship between LDL and BD PRS was likely to account for the association of total cholesterol levels and BD PRS.

Figure 5.1 By-group Scatter Plots comparing Baseline and 12-Month Follow-up Cnical Values against Ascciated PRS



Notes. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Fitted lines came from corresponding linear regressions.

Table 5.3 Results of Multiple Regression Analyses with corresponding Cardiovascular PRS

Variables	Coefficient	SE	t-statistics	CI (95%)	*p*	*p.adj*
Total Cholesterol						
Baseline	0.196	0.063	3.116	0.072, 0.319	**0.002**	**0.008**
12 Month	0.155	0.094	1.643	-0.032, 0.342	0.103	0.166
12 Month BA	0.001	0.091	0.011	-0.179, 0.181	0.991	0.991
HDL						
Baseline	0.166	0.024	6.822	0.118, 0.214	**<0.001**	**<0.001**
12 Month	0.198	0.030	6.604	0.139, 0.257	**<0.001**	**<0.001**
12 Month BA	0.056	0.025	2.257	0.007, 0.105	**0.026**	**0.049**
LDL						
Baseline	0.084	0.077	1.083	-0.07, 0.237	0.281	0.367
12 Month	0.119	0.117	1.022	-0.114, 0.352	0.311	0.367
12 Month BA	0.037	0.118	0.314	-0.199, 0.273	0.754	0.792
Triglycerides						
Baseline	0.440	0.139	3.171	0.165, 0.715	**0.002**	**0.008**
12 Month	0.434	0.163	2.657	0.109, 0.759	**0.010**	**0.025**
12 Month BA	0.253	0.175	1.443	-0.098, 0.604	0.154	0.216
Systolic blood pressure						
Baseline	4.269	1.339	3.187	1.624, 6.914	**0.002**	**0.008**
12 Month	2.093	1.185	1.765	-0.252, 4.438	0.080	0.140
12 Month BA	1.099	1.089	1.009	-1.055, 3.253	0.315	0.367
Diastolic blood pressure						
Baseline	1.924	0.811	2.373	0.322, 3.525	**0.019**	**0.044**
12 Month	1.890	0.829	2.280	0.25, 3.53	**0.024**	**0.049**
12 Month BA	1.126	0.745	1.513	-0.347, 2.599	0.133	0.199
Body Mass Index						
Baseline	1.451	0.416	3.486	0.629, 2.273	**0.001**	**0.004**
12 Month	1.376	0.500	2.752	0.387, 2.365	**0.007**	**0.020**
12 Month BA	0.092	0.243	0.379	-0.389, 0.573	0.705	0.780

Notes. SE, standard errors; CI, confidence interval.

Presented results are outputs from linear regressions with corresponding cardiovascular polygenic risk score regressed on each measure. Participants' sex, age, treatment allocation, diagnosis, smoking scores, alcohol scores, IPAQ scores and the first ten principal components from population stratification were added as covariates to all models. Each model was also adjusted for the corresponding medication recorded at baseline or 12-month assessment including antipsychotic, antidepressant, antihypertensive, mood stabilizers and other medications. 12 Week BA (baseline adjusted) models were further adjusted for the corresponding baseline measure.

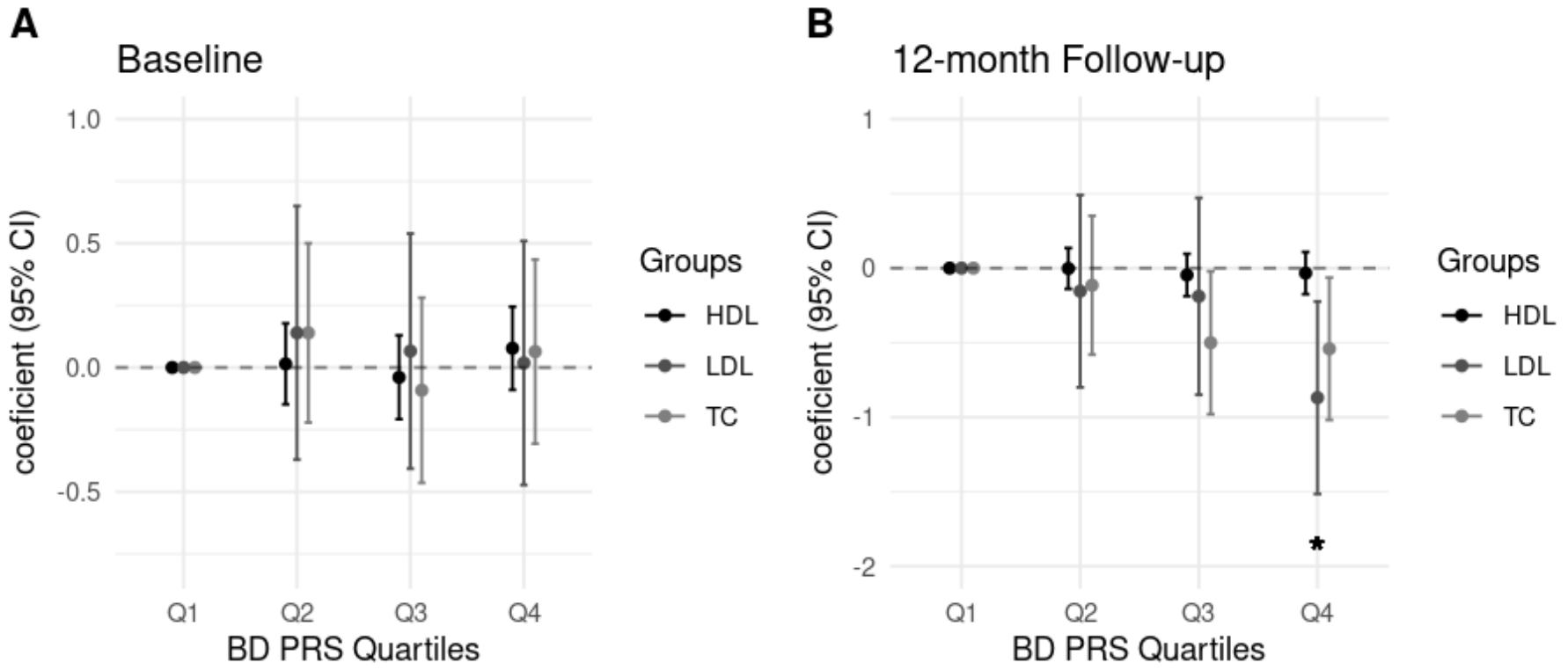
P.adj are p values corrected using FDR method. P values in bold are smaller than the threshold at 0.05.

Table 5.4 Adjusted Results of Cardiovascular and Psychiatric PRS Interactions

Variables	Coefficient	SE	t-statistics	CI (95%)	*p*	*p.adj*
Total Cholesterol						
BD PRS	-0.276	0.091	-3.016	-0.457, -0.095	**0.003**	**0.043**
BD PRS Interaction	0.138	0.097	1.422	-0.054, 0.331	0.157	0.670
SCZ PRS	-0.210	0.099	-2.117	-0.407, -0.014	0.036	0.254
SCZ PRS Interaction	0.068	0.098	0.693	-0.126, 0.262	0.490	0.940
HDL						
BD PRS	0.004	0.030	0.139	-0.055, 0.063	0.889	0.940
BD PRS Interaction	0.012	0.035	-0.352	-0.082, 0.057	0.726	0.940
SCZ PRS	-0.033	0.032	-1.028	-0.096, 0.03	0.306	0.804
SCZ PRS Interaction	-0.003	0.036	-0.075	-0.074, 0.069	0.940	0.940
LDL						
BD PRS	-0.331	0.104	-3.195	-0.539, -0.124	**0.002**	**0.043**
BD PRS Interaction	0.106	0.105	1.011	-0.103, 0.315	0.316	0.804
SCZ PRS	-0.212	0.122	-1.738	-0.456, 0.032	0.087	0.487
SCZ PRS Interaction	0.038	0.114	0.335	-0.189, 0.266	0.739	0.940
Triglycerides						
BD PRS	-0.190	0.136	-1.395	-0.461, 0.081	0.167	0.670
BD PRS Interaction	-0.093	0.156	-0.597	-0.405, 0.218	0.553	0.940
SCZ PRS	-0.161	0.149	-1.082	-0.457, 0.135	0.283	0.804
SCZ PRS Interaction	0.032	0.161	0.199	-0.29, 0.354	0.842	0.940
Systolic blood pressure						
BD PRS	1.189	1.086	1.094	-0.961, 3.338	0.276	0.804
BD PRS Interaction	-2.306	1.065	-2.165	-4.414, -0.198	0.032	0.254
SCZ PRS	-0.536	1.263	-0.424	-3.035, 1.963	0.672	0.940
SCZ PRS Interaction	0.164	0.979	0.168	-1.772, 2.101	0.867	0.940
Diastolic blood pressure						
BD PRS	-0.327	0.830	-0.394	-1.969, 1.314	0.694	0.940
BD PRS Interaction	-0.496	0.818	-0.607	-2.114, 1.122	0.545	0.940
SCZ PRS	-0.603	0.925	-0.651	-2.433, 1.228	0.516	0.940
SCZ PRS Interaction	-0.194	0.811	-0.239	-1.799, 1.411	0.812	0.940
Body Mass Index						
BD PRS	0.319	0.466	0.684	-0.603, 1.241	0.495	0.940
BD PRS Interaction	-0.049	0.505	-0.097	-1.048, 0.95	0.923	0.940
SCZ PRS	-0.063	0.520	-0.121	-1.091, 0.965	0.904	0.940
SCZ PRS Interaction	-0.057	0.460	-0.124	-0.968, 0.853	0.901	0.940

Notes. SE, standard errors; CI, confidence interval; SCZ, schizophrenia; BD, bipolar disorder
Presented results are outputs from linear regressions with corresponding cardiovascular polygenic risk scores (PRS) and their interactions with BD or SCZ PRS regressed on each measure.
Adjustments are the same as regressions in Table 3.
P.adj are p values corrected using FDR method. P values in bold are smaller than threshold at 0.05.

Figure 5.2 Comparison of Baseline and 12-Month Follow-up Cholesterol Levels Across BD PRS Quartiles



Notes. A. cholesterol measures at baseline; B. cholesterol measures at 12-month Follow-up.

TC=total cholesterol; BD=bipolar; PRS=polygenic risk scores.

The plotted values represent the estimated changes relative to the lowest bipolar PRS quartile group with 95% confidence intervals. The 12-month follow-up models were adjusted for the corresponding baseline measure in addition to all previously described covariates.

* in the current plot, p value survived FDR multiple testing correction

5.5 Discussion

In summary, we used multiple cardiovascular and psychiatric PRS to investigate how different genetic risks can impact cardiovascular behavioural treatment responses in patients with SMI within primary care. Prior to treatment, most of these selected PRSs were predictive of the actual cardiovascular measures. However, if the interventions were effective in reducing the measures, significant attenuations in the associations would be expected. For example, the total cholesterol and systolic blood pressure PRS became non-predictive at the 12-month follow-up. The interventions had little effect on HDL measures, suggesting that the HDL PRS may be independent of the baseline measures. The LDL measures were not associated with LDL PRS at both time points but became negatively associated with BD PRS after treatments even though we found no significant interaction effects. These findings collectively suggest that PRS predictions could be influenced by environmental interventions, such as treatment, particularly if the treatment was effective.

The findings of the study may provide valuable insights into the potential heterogeneity within PRS predictions when applied to variable health measures. Our sensitivity analyses comparing baseline and 12-month regression models revealed no significant difference in model power. This suggested that the attenuations in associations were more likely driven by changes in participants' actual measures rather than limitations due to sample drop at follow-up. Most of our selected cardiovascular PRS showed significant association with the corresponding measures prior to the treatments. The observed attenuations in these associations indicated that intervention

could play a substantial role in influencing outcomes over time. While individuals' genetic risks always stay stable, the changes in their prediction coefficients could reflect the treatment effects as coefficients represent the strength of associations between predictors and outcomes. For PRS coefficients which mostly remained stable or even increased after treatment such as HDL, this may suggest that the overall treatment likely had little impact. These findings underscored the importance of carefully considering the timing of PRS assessments for accurate risk predictions. Such findings also highlighted the need for more nuanced models that integrate both genetic and environmental factors to better predict individual treatment responses for patients with SMI.

For the participants' psychiatric genetic impact on the treatment outcomes, we initially hypothesized that the participants with higher both genetic risks might exhibit reduced treatment effectiveness. However, the results at the 12-month follow-up were in the opposite direction for BD PRS. While it is well-documented that patients with BD can have altered lipid profiles, previous findings have been inconsistent (Hiller et al., 2023). Notably, studies that did find associations often reported a directional trend: depressive episodes tended to correlate with increased lipid levels, whereas manic episodes were more frequently associated with decreased lipid levels (Fusar-Poli et al., 2021; Hiller et al., 2023). Using total cholesterol, triglycerides, LDL, and HDL as biomarkers is inherently complex due to numerous potential confounders, including dietary intake, comorbid somatic conditions, and medication use (Katcher et al., 2009). In this study, no prior association was observed between BD PRS and LDL levels at

baseline; however, a negative association with BD PRS emerged after treatment. Again, such findings highlighted the instability of PRS predictions.

Notably, BD does not seem to share any genetic correlation with LDL according to the most recent and largest BD GWAS to date (O'Connell et al., 2025). However, a recent comprehensive MR study covering 179 lipid species and 5 psychiatric disorders provided evidence of a potential causal relationship specifically between genetic susceptibility in the plasma lipidome and BD (Yu et al., 2025). The authors identified a protective effect in BD patients, characterized by higher levels of two sterol esters and eight phosphatidylcholines (PCs). These lipids may contribute to regulating neuroinflammation and maintaining neuronal cell membrane stability, potentially explaining their protective role (van der Veen et al., 2017). However, the role of their PCs also appeared dualistic: while some PCs exhibit protective effects, others acted as risk factors to promote the development of BD. Our findings also highlighted the complex relationship between BD and LDL levels. The observed increase in association at follow-up could be partially explained by reductions in other confounding variables, as the participants indeed showed positive changes in some lifestyle and health measures. However, environmental risk factors continue to play a role, and future studies with increased sample size and specific split on BD subtypes may provide further clarity.

The study's strengths were evident as we firstly used longitudinal behavioural treatment data to indicate how cardiovascular PRS predictions within patients with SMI could change over time. We employed robust methodologies and utilized the latest

GWAS for PRS calculations. The results presented here remained consistent and robust after accounting for the participants' age, sex, group allocation, diagnoses, medication use, smoking habits, alcohol consumption, and physical activity levels. Additionally, we conducted comprehensive sensitivity analyses to validate the results, further reinforcing the credibility and generalizability of our findings. The findings we present here may provide a solid foundation for future studies.

The study also had limitations which should be acknowledged. For instance, some of our health measures such as medication use were purely extracted from clinical records which may have been incomplete or inconsistent. The participants in the study had mixed diagnoses and lacked specific symptom measurements thus could not allow us for more in-depth investigations. It is also important to recognize that participants' cardiovascular risk profiles may evolve over time due to a range of external life factors that are independent of the intervention itself. In addition, our samples were predominantly of European ancestry which may have limited generalizability and transferability.

In summary, our findings highlighted the instability of PRS for cardiovascular risk predictions within patients with SMI. Researchers should carefully consider the measurement time points as these could produce diverse results. Future studies with increased sample size and more precise symptom measurements on BD subtypes may clarify the complex associations between BD and cardiovascular traits.

6. General discussion

6.1 PhD summary

Overall, this thesis applied different genomic methods to identify potential genomic biomarkers that could guide future mental illness treatments.

The first project (Chapter 2) investigated the interactions between environmental risk factors, ACE and psychiatric genetic risk factors predicted by multiple PRS for different BD phenotype developments. Although we could not find any significant interaction effects, ACE numbers and the PRS were associated with different phenotypes. Participants with ACEs had an earlier age of BD onset and higher odds of having rapid cycling. Higher ADHD PRS correlated with increased ACEs and could increase the likelihood of rapid cycling. Meanwhile, BD PRS was linked to psychotic symptoms and higher ADHD PRS. Thus, the results provided evidence for potential monitoring indexes which may improve phenotype management and guide treatment decisions.

In Chapter 3, I have taken a GWAS meta-analysis approach to identify SNP associated with a positive lithium response among BD patients. The SNP, rs116927879 reached the genome-wide significance level and had a consistent direction of effect from all studies. rs116927879 is located on chromosome 7 and maps to two pseudo-genes *GTF2IP13*, *SEPT7P2*, and the protein coding gene *ADCY1*. By integrating the results with expression data, we found that *ADCY1* plays a role in the regulatory processes in the central nervous system, memory, and learning. The alternative splicing of *ADCY1* could impact different brain regions. We also managed to estimate the SNP

heritability (h^2) for subjective lithium response as 20.3% for the first time using genomic data. Thus, the results provided evidence for a potential monitoring gene, *ADCY1* which may guide personalized medication allocation.

In Chapter 4, I integrated an EWAS meta-analysis with associated GWAS results to uncover biomarkers linked to EPSE in individuals with long-term exposure to antipsychotic medications. This chapter provided insights into the influence of both genetic and epigenetic factors resulting from environmental treatment factors. Among the 9 identified DMPs associated with EPSE, four of them cg14531564, cg20647656, cg12004641, cg22845912, and their affiliated genes (*SDF4, ANKMY1, TNS1, SLA*) were associated with the risk of developing EPSE and not with schizophrenia or smoking risk. One DMP (cg12044923) which maps to the *STK32B* gene, showed significant enrichment for association with the risk of EPSE and plays a role in tremor development. The results highlighted the importance of exploring both methylation shifts and common SNP associations for medication-induced side-effects.

In Chapter 5, I explored how cardiovascular and psychiatric PRS predictions can reflect treatment response using samples from the PRIMROSE trial which included participants with SMI receiving longitudinal cardiovascular treatments. At baseline, most cardiovascular PRS were predictive of corresponding measures. At 12-month follow-up, participants' total cholesterol and systolic blood pressure measures improved; however, the PRS associations weakened. LDL measures became negatively associated with BD PRS after treatment, though no significant interaction effects were found. Participants in the highest BD PRS quartile had 0.58 mmol/L lower LDL on

average after treatments suggesting a potential protective effect from higher BD genetic risks. The results showcased the insatiability of PRS predictions, underscored the dynamic interplay between genetic risks and treatment effects, and warrant careful PRS assessment timing for predictions in the future.

This thesis concludes in this chapter where I discuss potential limitations inherent in the datasets and used methods, which may impact the accuracy and generalizability of the results.

6.2 General limitations

6.2.1 Limitations in measurements

In the first three projects, the main measures were collected retrospectively through self-reports and clinician interviews. In the reporting of ACE, it has been found that the participants' current mood can impact recall (Hosang et al., 2023). Specifically, participants who reported abuse had higher depression and mania scores compared to those without such reports. The report of ACE may also relate to how individuals process and integrate adverse experiences across development (Baldwin et al., 2019). For medication responses, patients may struggle to accurately remember past treatment courses when doing the assessments. Patients with SCZ and BD can experience episodic or fluctuating symptoms (Perlis et al., 2010). The participants' subjective perception of benefit or side effects may be distorted by current mood state or long-term cognitive biases. For example, it has been shown that patients can possess a "resilience"-like period before realizing the improvements from antidepressants (Stassen et al., 2007). Thus, using retrospective recall for measurements is prone to

recall biases and may introduce inaccuracies.

In addition, the way in which the measures were recorded may also introduce inconsistencies. For instance, ACEs can be recorded in a binary format for simplicity. However, past studies have found a graded, dose-response relationship between the number of ACEs and risk for adverse mental and physical outcomes (Felitti et al., 1998). This suggests ACEs should be measured in a total number which assumes equal weighting of all adversities while neglect severity, chronicity, and timing. In contrast, more recent studies showed that individuals with at least four ACEs were at increased risks for all health outcomes compared to those with none, suggesting potential categorical measurement methods (Hughes et al., 2017). Across past studies, considerable heterogeneity (I^2 of >75%) has been observed in past ACE studies, particularly due to differences in how ACEs were defined and measured. Nowadays, how to best define and measure ACEs is still under debate. Further research is needed to quantify how each ACE should be weighted and how they cluster together (Lacey & Minnis, 2020).

Similar heterogeneity exists in the measurement of medication response. Response to medication can be treated as a binary variable for simplicity, yet it can be difficult to determine the threshold at which a person is consider as a good responder. In contrast, response can be measured as a continuous or categorical variable, ranging from excellent responders, to medium responders and non-responders. Take lithium as an example, the Alda scale is widely regarded as the gold standard for retrospective assessment of lithium response in BD (Grof et al., 2002). It is a two-part scale for

continuous response measurements. Part A (0–10) quantifies the degree of clinical improvement during lithium treatment, and part B (0–10) adjusts for confounders (e.g., adherence, duration of treatment, use of concomitant medications, number of episodes prior to lithium). Researchers have found divergent results when using a binary calcification (a total score ≥ 7 as "responders") versus taking the Alda scale as a measure (Hou et al., 2016). Such measurement differences can undermine the consistency of study findings, as other past studies defined response in binary formats and did not explore their continuous forms. However, no measure is without limitations, especially for complex traits such as medication response. Another study on Alda scale showed that the part B is vulnerable to error measurement, with some items contributing little yet may impact the overall total score (Scott et al., 2020). Thus, further research is needed to clarify how differences in measurement can impact findings.

6.2.2 Limitations in study design

The first three studies used cross-sectional collection methods, which can only provide a partial view compared to cohort designs. Cross-sectional retrospective self-report carries both advantages and limitations. Such measures are relatively inexpensive, scalable, and allow data collection from large samples across the life course (Teicher et al., 2016). However, this design assumes that retrospective reports and prospective measures identify the same, or at least similar, groups of individuals. In reality, taking ACE measurement as an example, the agreement between prospective and retrospective measures of CM is generally low ($k \approx 0.19$), suggesting that these

methods often capture different individuals. While prospective measures may capture exposure more objectively, retrospective recall may index subjective appraisal and perceived impact, both of which are relevant, but distinct dimensions of mental health outcomes (Baldwin et al., 2019).

Using cross-sectional study designs to assess medication response also be more problematic. Patients with mental illnesses often experience mood transitions from depression to manic or mixed states, many of which are not specific to treatment effects (Perlis et al., 2010). In addition, polypharmacy is common in psychiatric care (Wolff et al., 2021). Patients may frequently switch between antipsychotics or undergo dose titrations due to side effects, partial response, or non-adherence, increasing the risk for adverse effects and drug–drug interactions (Möller et al., 2014; Wolff et al., 2021). Dose effects also accumulate with increasing exposure. Longer cumulative exposure and higher lifetime dose of antipsychotics are associated with increased risk of tardive dyskinesia and parkinsonism (Correll et al., 2017). Furthermore, the pharmacokinetic and pharmacodynamic processes can change with age. Pharmacokinetic changes include reduced renal and hepatic clearance and an increased volume of distribution of lipid soluble drugs, leading to prolonged elimination half-life. Pharmacodynamic changes typically involve increased sensitivity to several drugs classes such as anticoagulants, cardiovascular and psychotropic drugs (Mangoni & Jackson, 2004). For these reasons, many drugs are considered unsuitable for the elderly (Hefner et al., 2021; Motter et al., 2018).

Given these complexities, cross-sectional designs may not be optimal. Time-

varying models can capture dynamic treatment patterns more accurately than static measures (Leucht et al., 2013). Nonetheless, cross-sectional and retrospective designs continue to dominate large-scale psychiatric genetic research due to feasibility but, findings must still be interpreted with caution.

6.2.3 Limitations in sample size

The power of GWAS to detect significant associations depends on multiple parameters, including the minor allele frequency (MAF) of SNPs, the prevalence of the trait, the effect size of genetic variants, and the sample size available (Visscher et al., 2017a). Common variants with higher allele frequencies are generally easier to detect than rare variants of similar effect size. Likewise, traits with higher prevalence provide greater statistical power, as more cases are available for comparison, whereas rare disorders often require very large sample sizes to achieve sufficient power. The increase in sample size has been the foundation for continued and increased discoveries from past GWAS as other factors are largely fixed (Abdellaoui et al., 2023). The conventional GWAS significance threshold at $5x10^{-8}$ was based on a minimum sample of roughly 5,000 cases and 5,000 controls, with SNPs having MAF of at least 5% in European population (Hoggart et al., 2008). Now, take MDD as am example, if MDD has a heritability of 0.3 with 3,000 independent significant SNPs, the sample size required to detect at least 95% of them is estimated to be a minimum of 7.56×10^7 sample (Wu et al., 2022). Comparing these numbers to our sample size of only a few thousands, it is evident that the reported samples are only the starting point for future more powered

and robust findings on the traits.

The limitations in sample also apply to PRS-based predictions. Typically, PRS studies test the associations between PRS and different traits in the target data and evaluate its potential effect. The association can be quantified using standard association or goodness-of-fit metrics such as the proportion of phenotypic variance explained (R^2). For BD, the latest PRS calculated from PRS-CS was estimated to explain a median of approximately 7.4% variance pooling from all European cohorts (O'Connell et al., 2025). For SCZ, the authors conducted leave-one-sample out PRS analyses using different p thresholds for PRS constructions (Trubetskoy et al., 2022). At a 0.05 threshold, which maximises out-of-sample prediction, the median variance in PRS liability explained was found to be 7.3%. If both testing and prediction are conducted within a single sample, allocating approximately 2000 cases and 2000 controls to the replication set is recommended to achieve reliable predictive accuracy (Dudbridge, 2013). Our PRS analyses did not achieve these sample sizes, limiting predictive performance and the ability to fully capture the PRS's potential. Moreover, even if sufficient sample sizes were reached, the variance explained would remain relatively low, particularly given that recent psychiatric GWAS with hundreds of thousands of participants report modest R^2 estimates.

6.3 Genomic method limitations

6.3.1 GWAS limitations

GWAS is a powerful method in extend to family-based linkage studies which can provide valuable genetic insights into complex psychiatric disorders. Findings from

past psychiatric GWAS have advanced our understanding of the aetiology of many different disorders and these findings continue to guide future research and medication developments (O'Connell et al., 2025). However, due to the polygenic nature of psychiatric disorders, GWAS often identify variants with small effect sizes. These identified loci may only explain a tiny fraction of the heritability and a small minority of the inferred genetic variance (Manolio et al., 2009). This is known as the "missing heritability" problem. For instance, BD is commonly estimated to have a 60% to 80% heritability from twin studies (Johansson et al., 2019; McGuffin et al., 2003). However, the most recent PGC BD multi-ancestry GWAS (excluding self-reported data), which explained the most genetic variance, could still only explain 9% of total genetic variance while other meta-analyses only explain even less variance (O'Connell et al., 2025). Such statistic is already coming from the largest study to date with 158,036 bipolar disorder cases and 2.8 million controls. Comparing these numbers with our current lithium response and EPSE GWAS meta-analysis sample sizes, we could already expect potential false positives, lack of power, and limited transferability (M. I. McCarthy et al., 2008). Thus, applying GWAS to study psychiatric medication response is still in its early stages. The data we produced here could only act as a starting point for future studies to increase the sample size for more meaningful and insightful findings.

Part of the reason why GWAS findings often had modest effect sizes was because GWAS intends to primarily focus on common genetic variants (with minor allele frequency>5%). Rare variants, which may have larger effects, are often missing or

intentionally removed (Gibson, 2012). In the two included GWAS meta-analyses, we also removed rare variants during the genetic data quality control steps leaving effects from these variants as unknown. In addition, our analyses also did not include the sex chromosomes due to complexities (e.g., dosage compensation, and hemizygosity in males, Lee et al., 2019). Although we observed potential sexual differences in lithium response which may yield findings from these sex chromosomes, we could not investigate these further.

The interpretations of GWAS findings could be another challenge. For instance, the identified loci could fall outside protein coding regions. Meanwhile, the identified loci may not provide direct information about the biological mechanisms underlying these associations. Follow-up functional studies are required (Visscher et al., 2017b). Because of LD between SNPs, identifying the most plausible causal SNP can be another challenge. Fine-mapping is required to pinpoint causal variants (Schork et al., 2013). However, as shown in our lithium response GWAS meta-analysis, even with one of the most cutting-edge fine-mapping methods Polyfun+SuSiE, pinpointing the exact causal SNP failed due to limited sample size and power (Weissbrod et al., 2020). Building on the LD problem, different ancestry groups may also have ancestry-specific patterns however, all samples reported in this thesis are of European ancestry with limited generalizability to other populations (Price et al., 2006). This is also the scenario for most reported GWAS to date (Martin et al., 2019; Sirugo et al., 2019).

6.3.2 PRS limitations

In the past decade, the numbers of PRS studies increased substantially due to the increasing number of available GWAS on different traits and diseases (Visscher et al., 2017b). PRS which provides a summary of an individual's genetic predisposition, is a promising tool for risk predictions and have been found to be associated with many heritable traits. Notably, all studies we presented here involved PRS predictions including phenotype development and treatment responses predictions. However, as we have also shown in the last project (Chapter 5), PRS predictions can be unstable.

In addition, the generation of PRS relies on the reference GWAS. As a result, the power of PRS is largely influenced by the reference GWAS quality, sample size and population structure (Choi et al., 2020). Most GWAS only focused on common variants, excluding rare variants, and used imputed data which did not capture the dosage from all SNPs for cost-effectiveness reasons. If genetic effects from GWAS could be estimated without error, and these effects were accurately aggregated by PRS, the variance in phenotype explained by PRS would be expected to equal to the SNP heritability (h^2) of the trait. However, this is often not the case is reality. With these limitations in data, PRS often only account for only a small fraction of the heritability of complex traits or diseases (Wray et al., 2013).

Although many PRS calculation methods now use Bayesian approaches to infer genetic architecture, they still do not account for non-linear interactions between genes. This limitation makes it challenging for PRS to explain more complex traits effectively (Boyle et al., 2017; Ge et al., 2019). PRS also do not account for gene-environment

interactions, which can significantly influence disease risk. For example, lifestyle factors like diet or smoking may modify the effect of genetic risk. Additionally, PRS are highly dependent on the ancestry of the training dataset. Scores derived from one population (e.g., European ancestry) often perform poorly in other populations (e.g., African or Asian ancestry), exacerbating health disparities (Martin et al., 2019). Most GWAS have been conducted in populations of European ancestry, the findings have limited generalizability to other ethnic groups, which further widen health disparities (Martin et al., 2019; Sirugo et al., 2019).

6.3.3 EWAS and integration limitations

Given the limitation that GWAS typically do not account for gene-environment interactions, EWAS is a powerful approach to identify traits' or diseases' epigenetic modifications which change over time in response to environmental exposures (Rakyan et al., 2011). In our case, we were interested in side effects from antipsychotic medication use which can accumulate epigenic changes over time. However, EWAS has similar limitation profiles like GWAS as the associations identified may not directly determine mechanisms and establish causality (Relton & Davey Smith, 2012). EWAS results do not provide direct insights into the functional consequences of epigenetic changes. Differences in ancestry or population structure can also confound EWAS results, as epigenetic patterns vary between ethnic groups. The epigenome can also vary across study populations. If any of these differences are linked to the disease of interest, confounding may be introduced (Michels, 2010). Adequately large sample sizes are

crucial for ensuring both the validity and reliability of study results. The EWAS we reported here had participants of European ancestry only and may had limited samples size and power (Michels et al., 2013). Meanwhile, the EWAS was cross-sectional which may not capture dynamic changes over time (Jones et al., 2015).

In addition to these, EWAS also suffer from its unique limitations. GWAS can use DNA from most tissue types to identify germline genetic variation, typically extracted from blood or blood-cell-derived cell lines. However, epigenetic changes can be tissue-specific, meaning that findings in one tissue (e.g., blood) may not reflect changes in other tissues (e.g., brain). As most EWAS are conducted with living individuals, DNA is generaly limited to easily accessible sources such as blood or saliva. Given our samples' data only came from blood, this may limit the generalizability of our EWAS results to understand mechanisms happening in the brain (Smith et al., 2015).

EWAS involve sensitive genetic and epigenetic data, which can also raise concerns about privacy, data security, and potential misuse of information (Heyn & Esteller, 2012). Combinations of hypermethylated DNA biomarkers have indicated high sensitivity in detecting cancer cells and predicting tumour progression (Heyn & Esteller, 2012). The key to success lies in combinatorial approaches. By integrating GWAS and EWAS, researchers can uncover the functional mechanisms underlying genetic associations and improve the translational potential of the findings. However, for biomarkers to be clinically useful, their detection sensitivity and specificity in biological fluids must be improved in the future.

6.4 Clinical implications

Personalized medicine represents one of the most promising frontiers in contemporary medicine, aiming to tailor therapies to individual patients by integrating clinical, genetic, and other molecular predictions. A patient's DNA only needs to be collected once, but it can be reanalysed over time to identify newly discovered risk genes and to calculate updated polygenic risk scores (PRS), making it a valuable and enduring resource in precision care.

GWAS findings have multiple clinical implications to strengthen future treatments. For instance, the genetic variants identified through medication response studies can help guide personalized prescriptions (Giacomini et al., 2017). Treatments could be prioritized for patients with high expression of genes associated with favourable response and reconsidered for those at high risk of adverse effects. The findings may also contribute to the development of risk prediction algorithms, enabling earlier identification of individuals at heightened risk for poor treatment response or adverse effects to facilitate more personalized intervention strategies in a timely manner. In addition, insights into the underlying medication biological pathways for good response can support the development of targeted medications to maximize treatment while minimize potential side-effects. Drugs with supporting genetic evidence are more likely to succeed in the development pipeline (M. R. Nelson et al., 2015).

PRS predictions also have multiple important clinical implications, especially for risk predictions. They may be most useful in cohorts with a higher prior probability of disease, where they can assist diagnosis or to inform treatment choices (C. M. Lewis &

Vassos, 2020). Our findings from the last study further suggest that the timing of PRS assessment is critical as predications may be more informative at specific stages of disease progression. Determining the optimal time to collect or apply this genetic information remains an important area for future research. Nevertheless, incorporating PRS into clinical workflows could enhance early intervention strategies, support personalized treatment planning, and ultimately improve patient outcomes.

6.5 Future directions

There are many ways future studies can improve on the current psychiatric treatment response GWAS. One option is to promote global collaboration to increase sample sizes and cover muti-ancestry groups. Psychiatric genetics benefited hugely through global collaborations as also discussed in Chapter 1 (O'Connell et al., 2025). Another option could be conducting a multi-trait analysis of GWAS (MTAG) which combines GWAS summary statistics of related traits using multi-trait analysis tools. By analysing schizophrenia and lithium response GWAS summary statistics together as a cross-trait meta-GWAS, ConLi+Gen (2018) identified 15 genetic loci that may have overlapping effects on lithium treatment response and susceptibility to SCZ. In addition, future research could also update genotyping arrays to include rare and structural variants and employ whole-genome/exome sequencing data for more comprehensive analyses. Large samples can be linked with electronic health records to capture more comprehensive treatment histories than using cross-sectional collection methods alone.

PRS predictions are not yet widely implemented in clinical settings due to several

challenges, including risk prediction instability, limited actionable intervention plans, and ethical concerns such as information privacy, discrimination, and stigmatization (A. C. F. Lewis & Green, 2021; Torkamani et al., 2018). Looking ahead, as GWAS sample sizes continue to grow and genotyping methods continue to advance, PRS are expected to play an increasingly central role in biomedical research and personalized medicine. However, their successful translation into clinical practice will depend on advancements in methodological development, accurate analysis, appropriate interpretation, and a thorough understanding of their strengths and limitations (Massi et al., 2023).

Even if all risk DNA variants were identified with perfect accuracy, imperfect predictions from genetics are expected. This is because genetic factors are not the only risk factors for disorders (Wray et al., 2021). Predictions can only be improved if combined with other clinical risk factors, such as sex, age, and medical histories (Hippisley-Cox et al., 2017). While no single factor is a strong predictor on its own, their combination can meaningfully guide clinical decision-making. Future progress will require developing new approaches to conceptualising and quantifying environmental risks, such as ACE, to enable more comprehensive models of risk prediction. In addition, future studies should investigate the extent to which environmental or cultural differences between populations influence specific traits (Abdellaoui et al., 2023).

6.6 Summary and conclusions

An individual's response to treatment is diverse and influenced by multiple factors. By incorporating various genomic research methods combined with environmental risk factors, projects included in this thesis tried to identify potential biomarkers that differentiate mental illness treatment responses. These findings highlight the need for further investigations to validate and expand upon the results obtained. Future research should involve larger sample sizes, meta-analyses with diverse ancestral groups, and the integration of advanced methods and technologies. These efforts will help the field move towards a more comprehensive understanding of the genetic underpinnings of mental illness treatment response and pave the way for the development of more effective prevention and more personalized treatment strategies.

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Appendices

2.1 OPCRIT Items 54 to 77

54. Persecutory delusions

Includes all delusions with persecutory ideation. (0, 1)

55. Well organised delusions

Illness is characterised by a series of well organised or well systematised delusions. (0, 1)

56. Increased self esteem

Patient believes that he is an exceptional person with special powers, plans, talents or abilities. Rate positively here if overvalued idea but if delusional in quality also score item 57 (grandiose delusions). Score '1' if duration one week and '2' if lasts two weeks. (0, 1, 2)

57. Grandiose delusions

Patient has grossly exaggerated sense of own importance, has exceptional abilities or believes that he is rich or famous, titled or related to Royalty. Also included are delusions of identification with God, angels, the Messiah etc. (See also item 56). Any duration score '1', if symptom lasts at least 2 weeks score '2'. (0, 1, 2)

58. Delusions of influence

Events, objects or other people in patient's immediate surroundings have a special significance, often of a persecutory nature. Include ideas of reference from the TV or radio, or newspapers, where patient believes that these are providing instructions or prescribing certain behaviour. (0, 1)

59. Bizarre delusions

Strange, absurd or fantastic delusions whose content may have a mystical, magical or 'science fiction' quality.(0, 1)

60. Widespread delusions

Delusions which intrude into most aspects of the patient's life and/or preoccupy the patient for most of his time. (0, 1)

61. Delusions of passivity

Include all 'made' sensations, emotions or actions. Score '1' for all experiences of influence where patient knows that his own feelings, impulses, volitional acts or somatic sensations are controlled or imposed by an external agency. (0, 1).

62. Primary delusional perception

Score '1' where the patient perceives something in the outside world which triggers a special, significant relatively non understandable belief of which he is certain and which is in some way loosely linked to the triggering perception (0, 1).

63. Other primary delusions

Includes delusional mood and delusional ideas. Delusional mood is a strange mood in which the environment appears changed in a threatening way but the significance of the change cannot be understood by the patient who is usually tense, anxious or bewildered. Can lead to a delusional belief. A delusional idea appears abruptly in the patient's mind fully developed and unheralded by any related thoughts. (0, 1)

64. Delusions & hallucinations last for one week

Any type of delusion accompanied by hallucinations of any type lasting one week. (0, 1)

65. Persecutory/jealous delusions & hallucinations

This is self explanatory But note that abnormal beliefs are of delusional intensity and quality and are accompanied by true hallucinations. (0, 1)

66. Thought insertion

Score '1' when patient recognises that thoughts are being put into his head which are not his own and which have probably or definitely been inserted by some external agency. (0, 1)

67. Thought withdrawal

Score '1' when patient experiences thoughts ceasing in his head and may experience 'thought block' which is interpreted as thoughts being removed (or 'stolen') by some external agency. (0, 1)

68. Thought broadcast

Score '1' when patient experiences thoughts diffusing out of his head so that they may be shared by others or even heard by others. (0, 1)

69. Delusions of guilt

Firm belief held by subject that they have committed some sin, crime or have caused harm to others despite absence of any evidence to support this. (0, 1)

70. Delusions of poverty

Firm belief held by subject that they have lost all or much of their money or property impoverished despite absence of any evidence to support this. (0, 1)

71. Nihilistic delusions

Firmly held belief that some part of patient's body has disappeared or is rotting away or is affected by some devastating or malignant disorder despite a lack of any objective supporting evidence. (0, 1)

72. Thought echo

Score '1' if patient experiences thoughts repeated or echoed in his or her head or by a voice outside the head. (0, 1)

73. Third person auditory hallucinations

Two or more voices discussing the patient in the third person. Score '1' if either 'true' or 'pseudo' hallucinations, i.e. differentiation of the source of the voices is unimportant. (0, 1)

74. Running commentary voices

Patient hears voice(s) describing his actions, sensations or emotions as they occur. Score '1' whether these are possible 'pseudo' hallucinations or definite ('true') hallucinations (0, 1)

75. Abusive/ accusatory/ persecutory voices

Voices talking to the patient in an accusatory, abusive or persecutory manner. (0, 1)

76. Other (non affective) auditory hallucinations

Any other kind of auditory hallucination. Includes pleasant or neutral voices and non verbal hallucinations. (0, 1)

77. Non-affective hallucination in any modality

Hallucinations in which the content has no apparent relationship to elation or depression. Score '1' if present throughout the day for several days or intermittently for One week. (0, 1)

2.2 CLEQ QUESTIONNAIRE

Did you experience as a child (up to age 16 years) any of the following life events?

		Please circle		*If yes, how old were you?*
1	**Death of parent**	Yes	No	
2	**Death of a brother/sister**	Yes	No	
3	**Death of a close friend**	Yes	No	
4	**Divorce of parents**	Yes	No	
5	**Marital separation of parents**	Yes	No	
6	**Marriage of parent to step parent**	Yes	No	
7	**Serious illness needing hospitalisation**	Yes	No	
8	**Hospitalisation of a parent**	Yes	No	
9	**Acquiring a visible deformity**	Yes	No	
10	**Prison sentence of a parent for a year or more**	Yes	No	
11	**Teenage pregnancy/fatherhood**	Yes	No	
12	**Suspension from school**	Yes	No	
13	**Are there any other significant life events you experienced as a child that are not mentioned above**	Yes	No	

Please provide brief details

Date of Completion: _____ **Completed by:** Self ☐ Interviewer ☐

2.3 Supplementary Table 1 Results of Multiple Regression Analyses with Adjustments based on ACE (total score) and BD/ADHD PRS

Variables	Estimated Coefficient	Standard Error	Confidence Intervals (95%)	Reference Values	*p*	*FDR_p*
Age at onset†						
BD PRS	-0.351	0.480	-1.294, 0.592	-0.731	0.465	0.709
BD Interaction	-0.370	0.356	-1.070, 0.330	-1.037	0.300	0.706
ADHD PRS	-0.328	0.506	-1.322, 0.665	-0.649	0.516	0.718
ADHD Interaction	-0.295	0.356	-0.993, 0.404	-0.828	0.408	0.706
Presence of psychotic symptoms‡						
BD PRS	0.254	0.090	0.079, 0.430	2.833	**0.005**	**0.074**
BD Interaction	-0.089	0.068	-0.223, 0.045	-1.300	0.194	0.706
ADHD PRS	-0.080	0.093	-0.264, 0.102	-0.863	0.388	0.706
ADHD Interaction	0.033	0.068	-0.100, 0.168	0.481	0.631	0.807
Presence of suicide ideation‡						
BD PRS	-0.029	0.096	-0.218, 0.157	-0.306	0.760	0.884
BD Interaction	-0.097	0.078	-0.250, 0.055	-1.246	0.213	0.706
ADHD PRS	0.077	0.100	-0.119, 0.275	0.770	0.441	0.706
ADHD Interaction	-0.022	0.079	-0.175, 0.135	-0.276	0.782	0.884
Presence of rapid cycling‡						
BD PRS	-0.148	0.106	-0.357, 0.058	-1.406	0.160	0.706
BD Interaction	-0.014	0.088	-0.187. 0.158	-0.157	0.875	0.884
ADHD PRS	0.471	0.124	0.232, 0.721	3.780	**<0.001**	**0.005**
ADHD Interaction	0.125	0.094	-0.056, 0.314	1.334	0.182	0.706

Notes. ACE, adverse childhood experience; PRS, polygenic risk score; BD, bipolar disorder; ADHD, attention deficit hyperactivity disorder.

† Multiple linear regression analyses, reference value t.

‡ Multiple logistic regression analyses, reference value z.

FDR_P = false discovery rate corrected p values for multiple testing.

In bold p values survived multiple testing correction in main analyses.

All results were adjusted for participants' BD age of onset and sex (except for age of onset where only sex was adjusted).

PRS & interaction results were adjusted for chip type and the first three principal components from GWAS population stratification in addition to sex and age of onset.

2.4 Supplementary Table 2 Results of Multiple Regression Analyses with Adjustments based on ACE (total score) and MDD/SCZ PRS

Variables	Estimated Coefficient	Standard Error	Confidence Intervals (95%)	Reference Values	*p*	*FDR_p*
Age at onset[†]						
MDD PRS	-1.197	0.487	-2.154, -0.241	-2.458	0.014	0.153
MDD Interaction	-0.052	0.355	-0.750, 0.646	-0.145	0.884	0.884
SCZ PRS	-0.442	0.489	-1.403, 0.518	-0.905	0.366	0.706
SCZ Interaction	-0.356	0.350	-1.043, 0.333	-1.015	0.311	0.706
Presence of psychotic symptoms[‡]						
MDD PRS	0.063	0.091	-0.115, 0.241	0.691	0.489	0.712
MDD Interaction	-0.056	0.068	-0.191, 0.077	-0.830	0.406	0.706
SCZ PRS	0.185	0.090	0.009, 0.362	2.060	0.039	0.315
SCZ Interaction	-0.072	0.068	-0.206, 0.061	-1.054	0.292	0.706
Presence of suicide ideation[‡]						
MDD PRS	0.079	0.098	-0.114, 0.272	0.802	0.422	0.706
MDD Interaction	-0.021	0.080	-0.179, 0.137	-0.260	0.795	0.884
SCZ PRS	-0.061	0.100	-0.260, 0.133	-0.610	0.542	0.722
SCZ Interaction	-0.012	0.082	-0.174, 0.148	-0.149	0.881	0.884
Presence of rapid cycling[‡]						
MDD PRS	0.116	0.112	-0.102, 0.337	1.039	0.299	0.706
MDD Interaction	0.114	0.091	-0.064, 0.292	1.231	0.218	0.706
SCZ PRS	-0.023	0.112	-0.242, 0.197	-0.203	0.839	0.884
SCZ Interaction	0.067	0.082	-0.094, 0.230	0.811	0.417	0.706

Notes. ACE, adverse childhood experience; PRS, polygenic risk score; MDD, major depressive disorder; SCZ, schizophrenia disorder.

[†] Multiple linear regression analysis, reference value t.

[‡] Multiple logistic regression analysis, reference value z.

FDR_p = false discovery rate corrected p values for multiple testing.

All results were adjusted for participants' BD age of onset and sex (except for age of onset where only sex was adjusted). PRS & interaction results were adjusted for chip type and the first three principal components from GWAS population stratification in addition to sex and age of onset.

3.1 Supplementary Table 1 UCL Samples' Lithium Response Assessment

Response to Lithium

	Investigators Opinion		Participants Opinion
☐	**Very good** - *no episodes on lithium during long-term treatment*	☐	**Very good**
☐	**Good** - *almost complete elimination of episodes, maintained well on lithium alone, episodes are due to confounding factors e.g.non-compliance*	☐	**Good**
☐	**Medium** - *a significant reduction in episode frequency or severity and/or frequent use of additional psychotropic medication*	☐	**Medium**
☐	**Poor** - *little clinical improvement, often in the presence of therapeutic lithium levels*	☐	**Poor**
☐	**Very poor** *increase in number of episodes*	☐	**Very poor**
☐	**Unknown/Unclassifiable**	☐	**Unknown/Unclassifiable**

3.2 Supplementary Table 2 UCL samples' demographics and clinical characteristics concerning lithium response

Variables	N	Overall N = 1259	Lithium Responders N = 440 (35%)	Lithium Non-responders N = 819 (65%)	p-values
Age at interview	1153	50.39 (12.84)	50.34 (13.62)	50.42 (12.40)	0.921[a]
Age of BD onset	1198	24.66 (10.62)	24.33 (10.68)	24.82 (10.60)	0.453[a]
Sex	1259				**0.039**[b]
Male		499 (40%)	192 (44%)	307 (37%)	
Female		760 (60%)	248 (56%)	512 (63%)	
BD type	1259				0.189[b]
BD type 1		827 (66%)	297 (68%)	530 (65%)	
BD type 2		169 (13%)	63 (14%)	106 (13%)	
SABP		96 (8%)	34 (8%)	62 (7%)	
No information		167 (13%)	46 (10%)	121 (15%)	
PPD diagnosis	1181	41 (3%)	7 (1%)	34 (3%)	**0.027**[b]

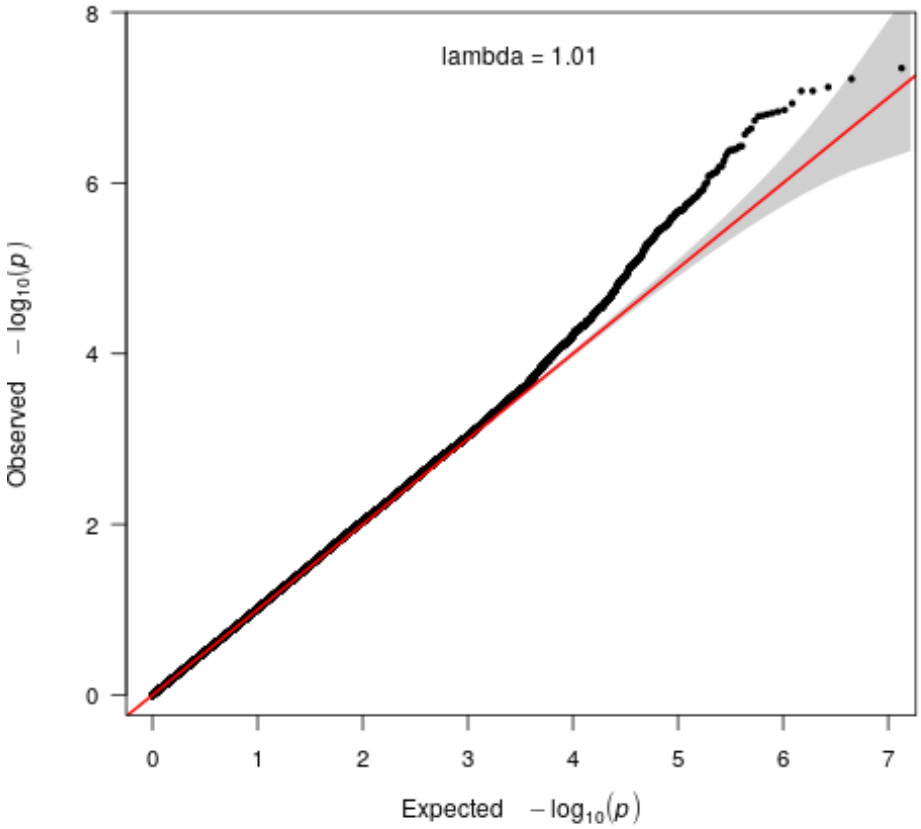
BD, bipolar disorder; SABP, schizoaffective bipolar disorder; PPD, premorbid personality disorder; SD, standard deviation

[a] Two Sample t-test; mean (SD)

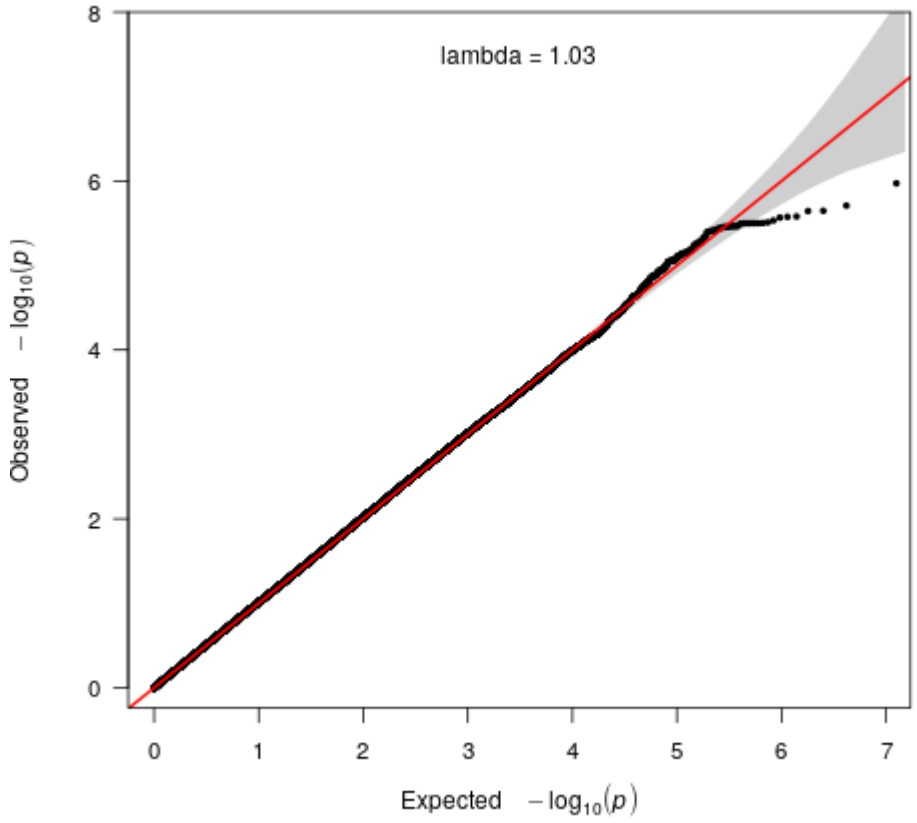
[b] Pearson's Chi-squared test of independence; n (%)

In bold, p passed significance at 0.05.

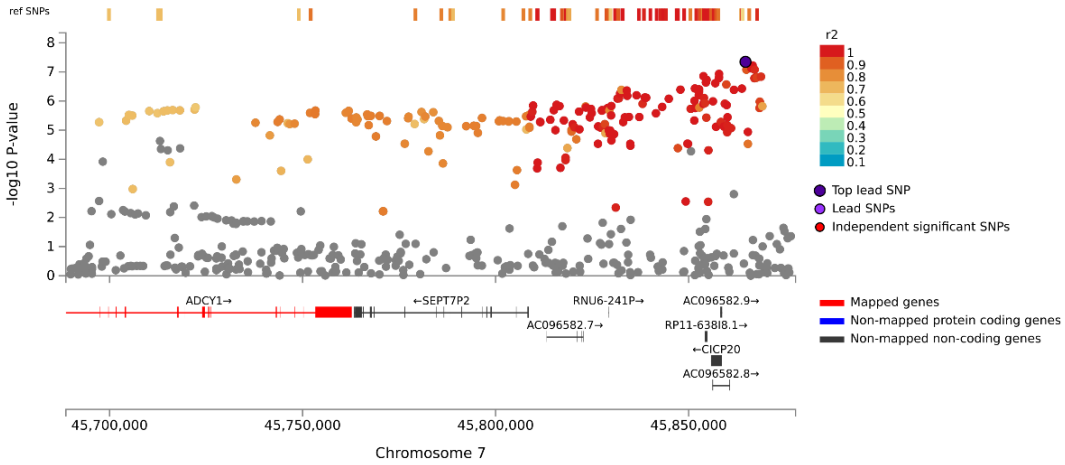
3.3 Supplementary Figure 1 The QQ plot for the UCL+Song^{Sub}+ConLi^{+}Gen GWAS meta-analysis



3.4 Supplementary Figure 2 The QQ plot for the UCL+Song^{Ob}+ConLi^{+}Gen GWAS meta-analysis



3.5 Supplementary Figure 3 Regional association plot on chromosome 7 in which the Genome-wide significant SNP is located



4.1 Supplementary Table 1 Behavioural Key Words used to Identify EPSE Cases

Symptoms	Keywords
General terms for EPSE	Extrapyramidal; extra pyramidal; epse; EPSE; movement disorder
Parkinsonism (tremor)	Tremor; tremble; shake; quiver
Parkinsonism (rigidity)	Rigid; hypertonic; stiff; inflexible; tight; tense; muscle pain
Parkinsonism (Sialorrhea)	Salivation; sialorrhea; drool
Parkinsonism (bradykinesia and hypokinesia)	Hypokinesia; bradykinesia; freeze; froze; slow; motor block; stride; reduced arm swing; blink; hypophonia; soft voice; voice volume; slurred; micrographia; handwriting
Parkinsonism (mask face)	Mask; hypomimia; expressionless
Parkinsonism (stooped posture)	Stoop; hunch; posture
Parkinsonism (parkinsonian gait)	Shuffle; festinate; parkinsonian
Parkinsonism (parkinsonian gait)	Imbalance; fall
Dystonia (general)	Dystonia; jerk; twist; twitch; spasm; lock
Dystonia (opisthotonos)	Opisthotonos; arch back; bend back; arch spine; bend spine
Dystonia (torticollis)	Torticollis; cervical dystonia; head deviation; head posturing; neck pain
Dystonia (oculogyric crisis)	Oculogyric; fix stare; fix eye; deviate eye
Dystonia (trismus)	Trismus; lock jaw; lockjaw; jawlock; jaw deviation; jaw retraction; clench; grind; mouth pain; restrict mouth; limit mouth
Dystonia (tortipelvic crisis)	Tortipelivic; bend trunk; twist trunk
Dystonia (buccolingual crisis)	Buccolingual; dysphagia; difficult swallow; grimace; protrude; protrusion; risus sardonicus; dysarthria; difficult speak; difficult speech; pseudomacroglossia; swollen tounge; tounge swell
Dystonia (laryngeal dystonia)	Laryngeal; stridor; strangled voice; breathy voice; quiet voice; whispery voice; hoarse; shaky voice; aphonia; interrupt speech; lose voice; voice loss
Tardive Dyskinesia (general)	tardive dyskinesia; dyskinesia; TD
Tardive Dyskinesia (orofacial dyskinesia)	Involuntary; tongue twist; tongue protrusion; chew; biting; bite; suck; clench; lateral jaw movement; sideway jaw movement; smack lip; lip purse; pucker; puff cheek; frown; blink; grimace; blink
Tardive Dyskinesia (limb truncal dyskinesia)	Choreiform; athetoid; choreoathetoid; purposeless; rock; twist; squirm; gyrate; thrust; knee move; tap; heel drop; writhing; rotate; nod; inversion; eversion
Akathisia	Akathisia; akathisia; restless; pace; fidget; irritable; leg cross; leg swing; foot shift; shuffle; tramp; still; march; shift weight; rock

4.2 Supplementary Table 2 Pharmacological Keywords used to Identify EPSE Cases

Medication	Keywords
Trihexyphenidyl	Trihex; benzh; artane; agitane; parkin
Benzatropine	Benza;tropin; cogentin
Procyclidine	Procy; lidin; kemad
Orphenadrine	Orphan; drine
Biperiden	Biper; akineton
Hyoscine	Hyos; kwell
Tetrabenazine	Tetrab; ranb; nitom; xenaz

4.3 Supplementary Table 3 FGA Codes used to Select Participants

Medication Name	Medication Type	Medication Code
Benperidol	anquil 250micrograms tablet; benperidol	1140867080; 1140867078
Chlorpromazine	chlorpromazine; cpz - chlorpromazine; largactil 10mg tablet; chloractil 25mg tablet	1140879658; 1140910358; 1140863416; 1140863410
Flupentixol	flupentixol; depixol 3mg tablet; fluanxol 500micrograms tablet; flupenthixol; flupentixol	1140909800; 1140867152; 1140867952; 1140867150; 1140909800
Fluphenazine	decazate 25mg/1ml oily injection; fluphenazine; fluphenazine decanoate; modecate 12.5mg/0.5ml oily injection; moditen 1mg tablet; moditen enanthate 25mg/ml injection	1140867474; 1140882098; 1140867398; 1140867456; 1140867156; 1140856004
Haloperidol	haldol 5mg tablet; haloperidol; serenace 500micrograms capsule	1140867184; 1140867168; 1140867092
Levomepromazine	levomepromazine; nozinan 25mg tablet	1140909802; 1140867122
Loxapine	loxapine; loxapac 10mg capsule	1140867406; 1140867414
Pericyazine	neulactil 2.5mg tablet; pericyazine	1140867136; 1140867134
Perphenazine	fentazin 2mg tablet; perphenazine	1140867210; 1140867208
Pimozide	orap 2mg tablet; pimozide	1140867272; 1140867218
Pipotiazine	piportil depot 50mg/1ml oily injection; pipotiazine	1140867572; 1140909804
Prochlorperazine	prochlorperazine; stemetil 5mg tablet	1140868170; 1140868172
Promazine	promazine	1140879746
Sulpiride	dolmatil 200mg tablet; sulparex 200mg tablet; sulpiride; sulpitil 200mg tablet; sulpor 200mg/5ml oral solution	1140867306; 1140917366; 1140867304; 1140882376; 1141185130
Thioridazine	thioridazine; melleril 10mg tablet	1140879750; 1140867312
Trifluoperazine	stelazine 1mg tablet; tranylcypromine+trifluoperazine 10mg/1mg tablet; trifluoperazine	1140867244; 1140867944; 1140868120
Zuclopenthixol	clopixol 2mg tablet; zuclopenthixol	1140867342; 1140882100

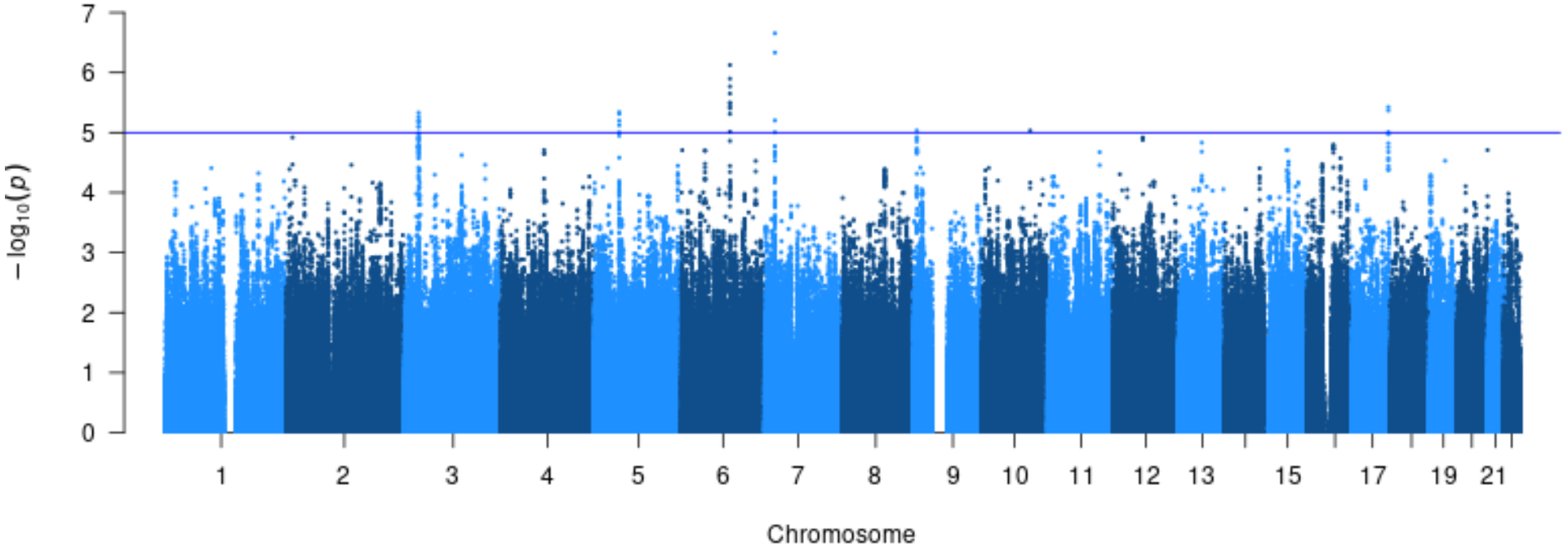
4.4 Supplementary Table 4. SGA Codes used to Select Participants

Medication Name	Medication Type	Medication Code
Amisulpride	amisulpride; solian 100mg/ml s/f oral solution	1141153490; 1141184742
Aripiprazole	abilify 5mg tablet; aripiprazole	1141202024; 1141195974
Clozapine	clozapine; clozaril 25mg tablet; denzapine 25mg tablet	1140867420; 1140882320; 1141200458
Olanzapine	olanzapine; zyprexa 2.5mg tablet	1140928916; 1141167976
Oxypertine	oxypertine; integrin 10mg capsule	1140879754; 140855978
Quetiapine	quetiapine; seroquel 25mg tablet	1141152848; 1141152860
Remoxipride	remoxipride; roxiam 150mg m/r capsule	1140879704; 1140867432
Risperidone	dozic 1mg/ml oral liquid; risperdal 0.5mg tablet; risperidone	1140867180; 1141177762; 1140867444
Sertindole	serdolect 4mg tablet; sertindole	1140927970; 1140927956

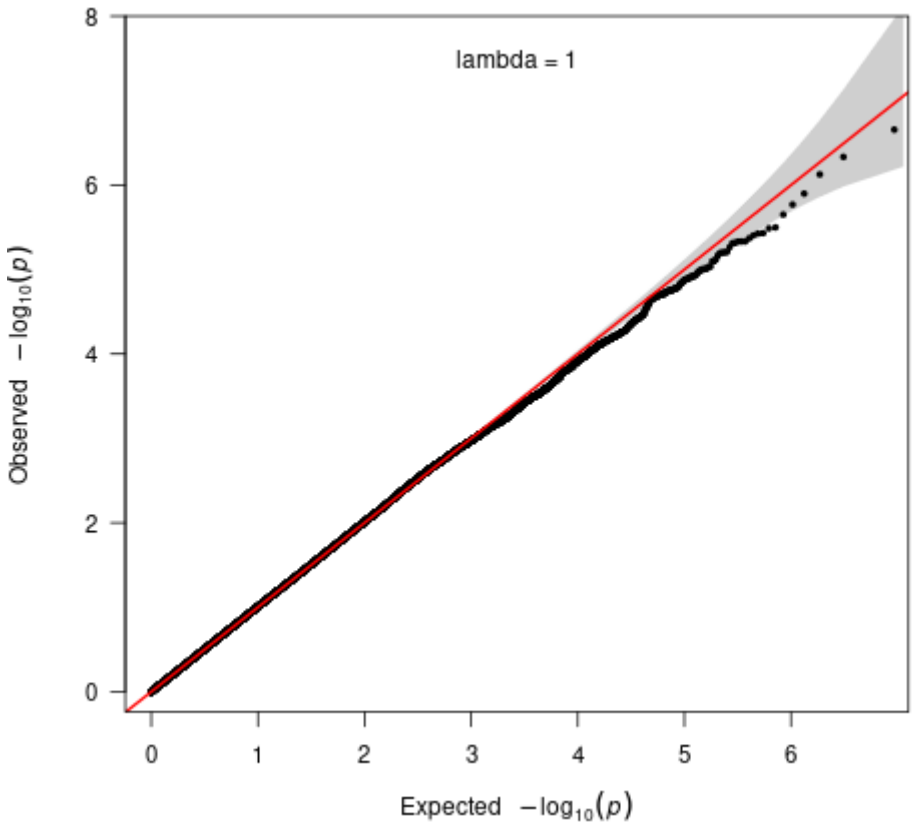
4.5 Supplementary Table 5 EPSE Medications Codes used to Select Cases

Medication Name	Medication Type	Medication Code
Akineton	akineton	1140872522
Artane	artane	1140872378
Benzatropine	benzatropine	1140909818
Benzhexol	benzhexol	1140883510
Biperiden	biperiden	1140872520
Cogentin	cogentin	1140872460
Kemadrin	kemadrin	1140872542
Orphenadrine	orphenadrine	1140883560
Procyclidine	procyclidine	1140883476
Tetrabenazine	tetrabenazine	1140872556
Tetrabenazine Product	tetrabenazine_product	1141157336
Trihexyphenidyl	trihexyphenidyl	1140909816
Xenazine	xenazine	1141171726

4.6 Supplementary Figure 1 The Manhattan Plot of EPSE GWAS Meta-analysis

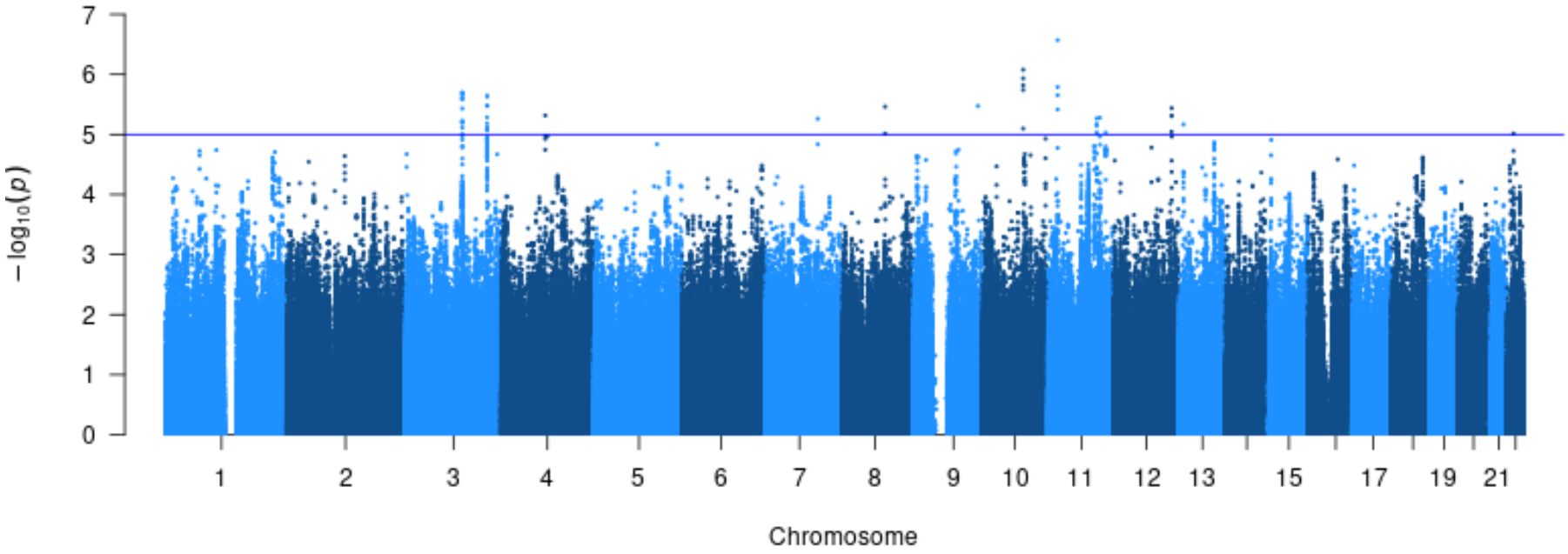


4.7 Supplementary Figure 2 The QQ Plot of EPSE GWAS Meta-analysis for FGA and SGA Combined

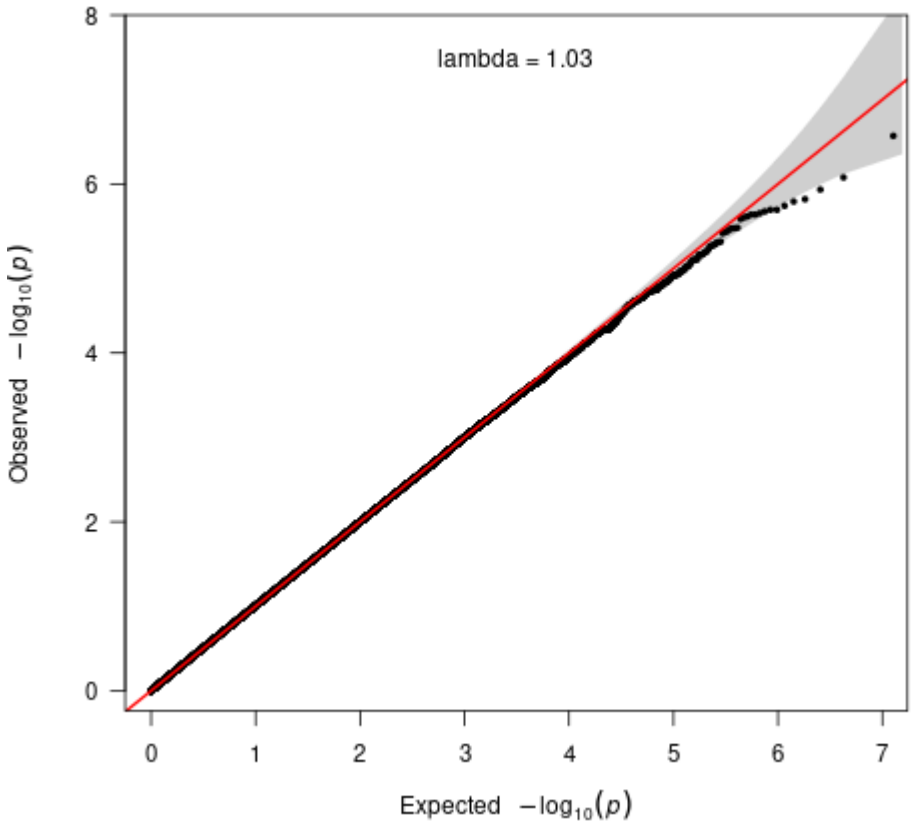


Notes. X-axis (Expected -log10(p-values)): Represents the theoretical quantiles under the null hypothesis, where p-values are uniformly distributed on a logarithmic scale; Y-axis (Observed -log10(p-values)): Shows the observed -log10(p-values) from the GWAS.

4.8 Supplementary Figure 3 The Manhattan Plot of EPSE GWAS Meta-analysis for any Exposure to FGA

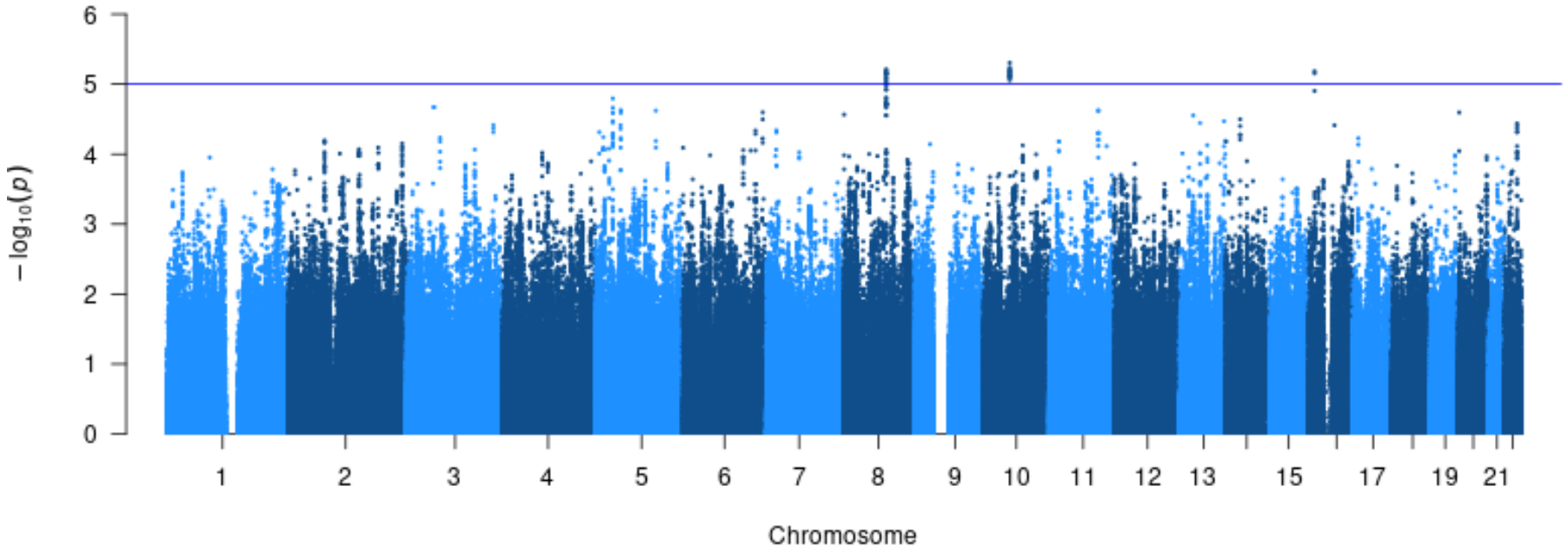


4.9 Supplementary Figure 4 The QQ Plot of EPSE GWAS Meta-analysis for any Exposure to FGA

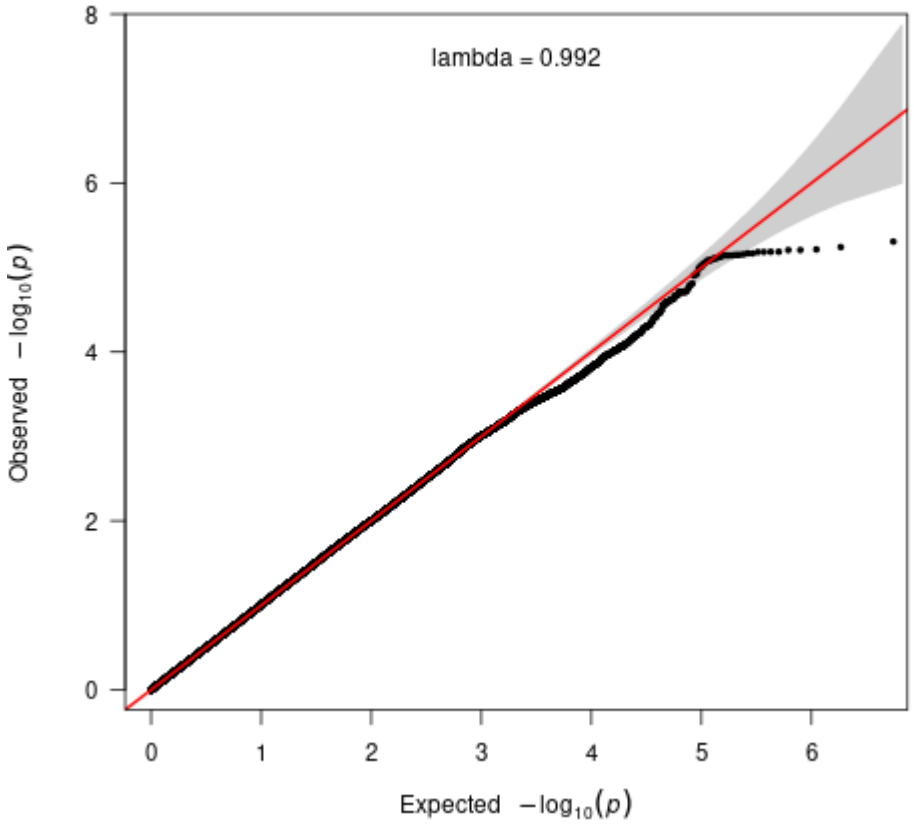


Notes. X-axis (Expected -log10(p-values)): Represents the theoretical quantiles under the null hypothesis, where p-values are uniformly distributed on a logarithmic scale; Y-axis (Observed -log10(p-values)): Shows the observed -log10(p-values) from the GWAS.

4.10 Supplementary Figure 5. The Manhattan Plot of EPSE GWAS Meta-analysis for only Exposure to SGA



4.11 Supplementary Figure 6 The QQ Plot of EPSE GWAS Meta-analysis for only Exposure to SGA



Notes. X-axis (Expected -log10(p-values)): Represents the theoretical quantiles under the null hypothesis, where p-values are uniformly distributed on a logarithmic scale; Y-axis (Observed -log10(p-values)): Shows the observed -log10(p-values) from the GWAS.

4.12 Supplementary Table 6 EWAS Participants' Demographics and Clinical Characteristics concerning EPSE Presence

		N	Overall	EPSE Presence	Controls	p-values
UCL		379		n = 64 (17%)	n = 315 (83%)	
	Age at assessment	362	38.24 (14.81)	36.90 (14.74)	44.48 (13.58)	**<0.001**[a]
	mAge (Horvath)	379	40.31 (12.46)	39.54 (12.41)	44.08 (12.13)	**0.008**[a]
	Sex					**<0.001**[b]
	Male		192 (51%)	52 (81%)	140 (44%)	
	Female		187 (49%)	12 (19%)	175 (56%)	
	Antipsychotics	64				
	First generation			57 (89%)	/	
	Second generation			50 (78%)	/	
Aberdeen		480		n = 47 (10%)	n = 433 (90%)	
	mAge (Horvath)	480	53.16 (9.88)	54.29 (11.48)	53.04 (9.70)	0.473[a]
	Sex	480				
	Male		352 (73%)	33 (70%)	319 (74%)	0.737[b]
	Female		128 (27%)	14 (30%)	114 (36%)	
	Antipsychotics	47				
	First generation			30 (64%)	/	
	Second generation			23 (49%)	/	

Notes. EPSE, extrapyramidal side effects; SD, standard deviation

[a] Two Simple t-test; mean (SD)

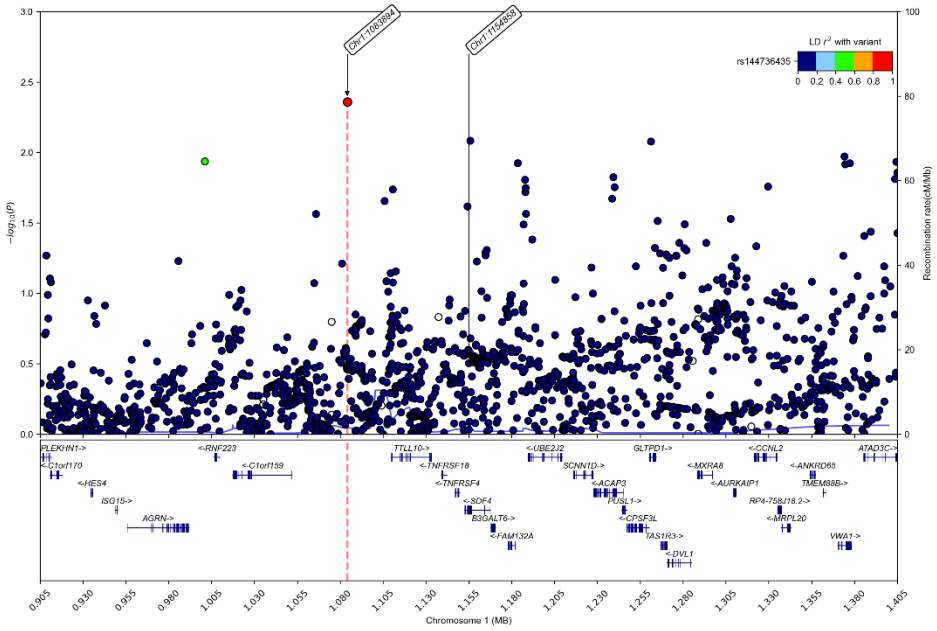
[b] Pearson's Chi-squared test of independence; n (%)

In bold p passed significance threshold

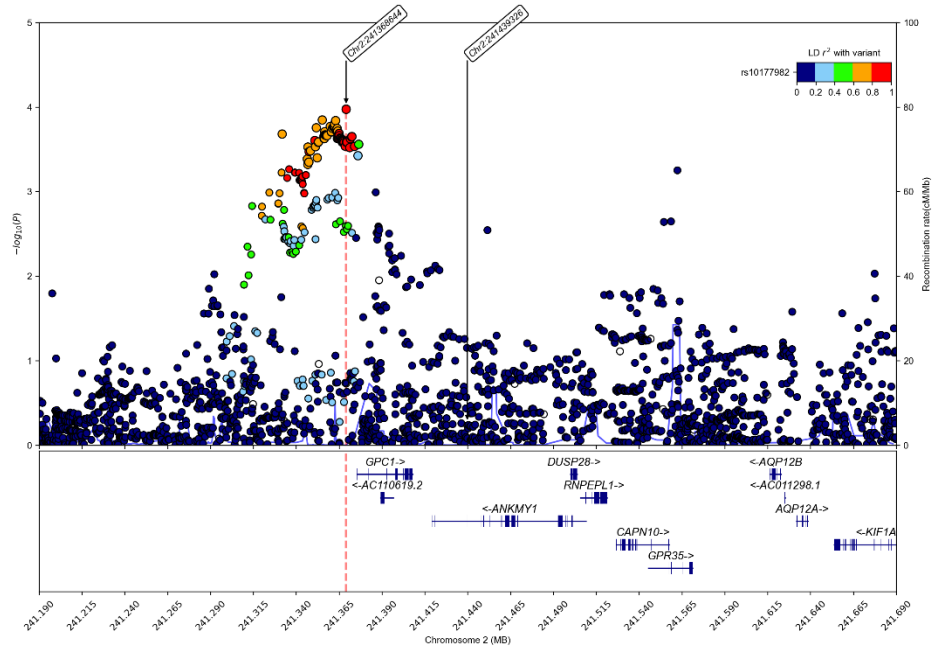
4.13 Supplementary Figures 7–15 The Mapping of CpG to the Schizophrenia GWAS Region

The figures illustrate the mapping of significant CpG sites to Schizophrenia GWAS within a 250kb window. Black line in the central mark the SNP closest to the CpG. Red dotted line marked the SNP in lead within the region and other nearby SNPs in linkage disequilibrium.

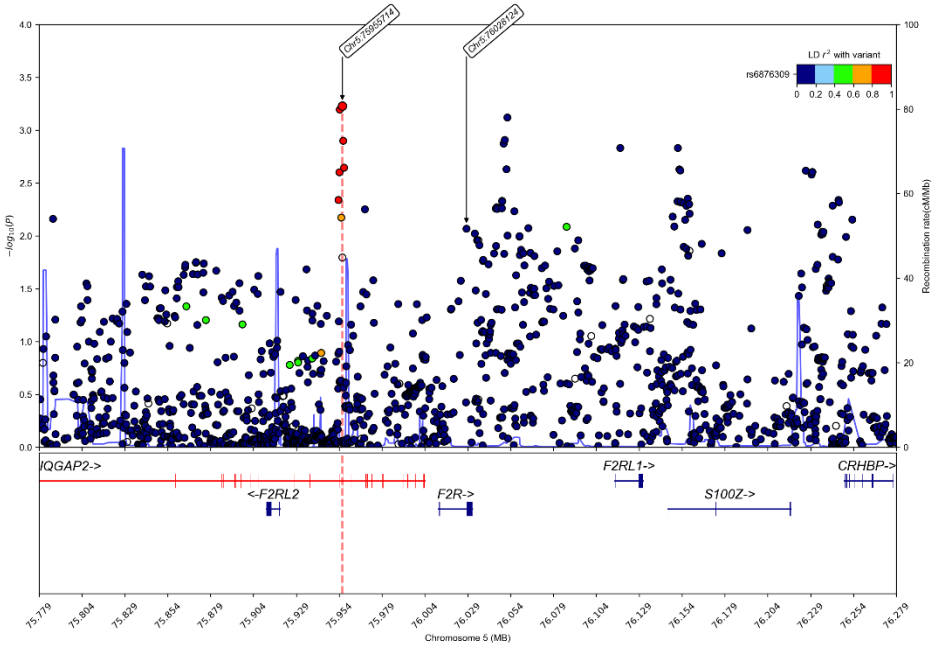
Supplementary Figure 7. The Mapping of CpG cg14531564 to the Schizophrenia GWAS Region



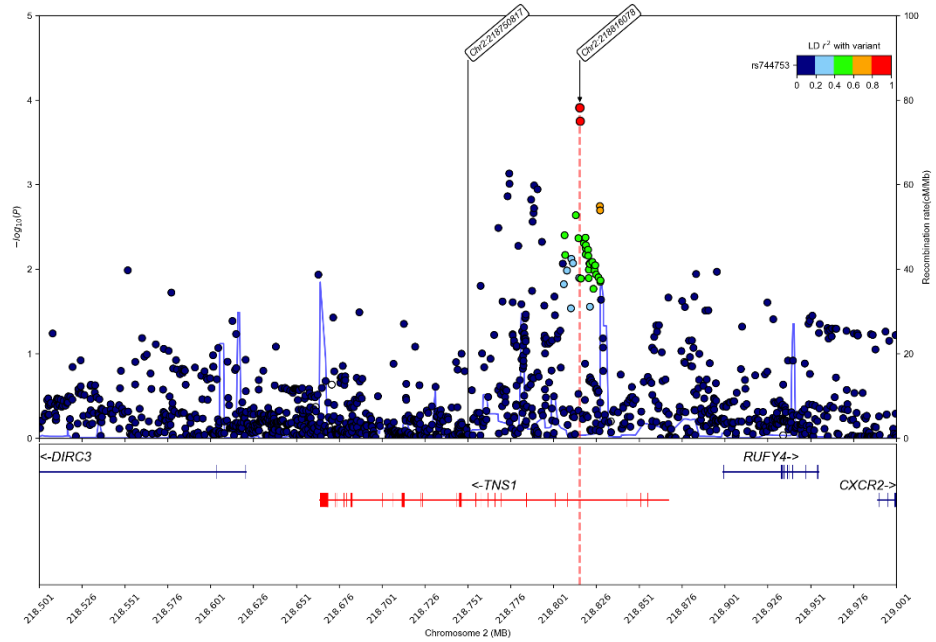
Supplementary Figure 8. The Mapping of CpG cg20647656 to the Schizophrenia GWAS Region



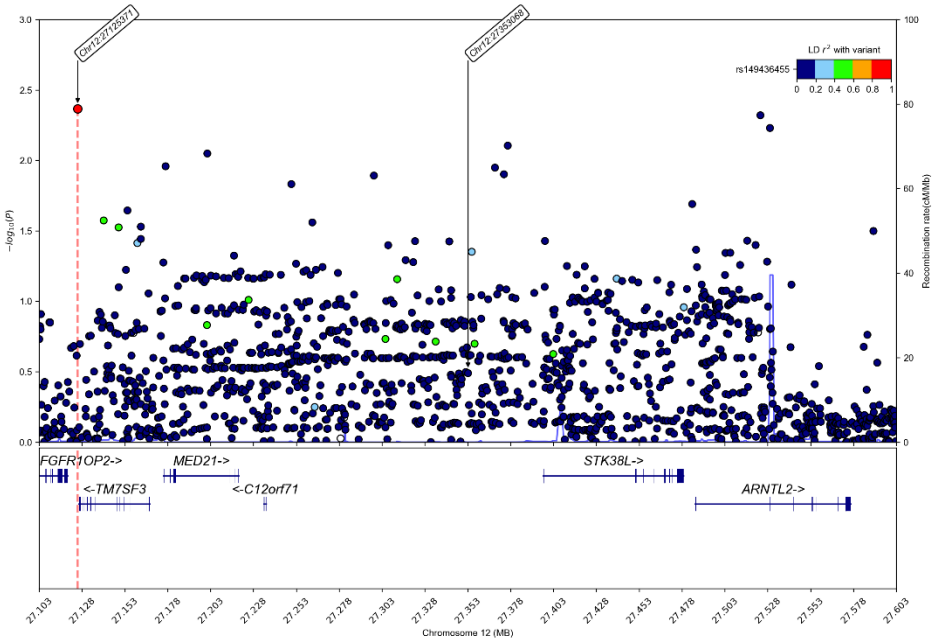
Supplementary Figure 9. The Mapping of CpG cg12524168 to the Schizophrenia GWAS Region



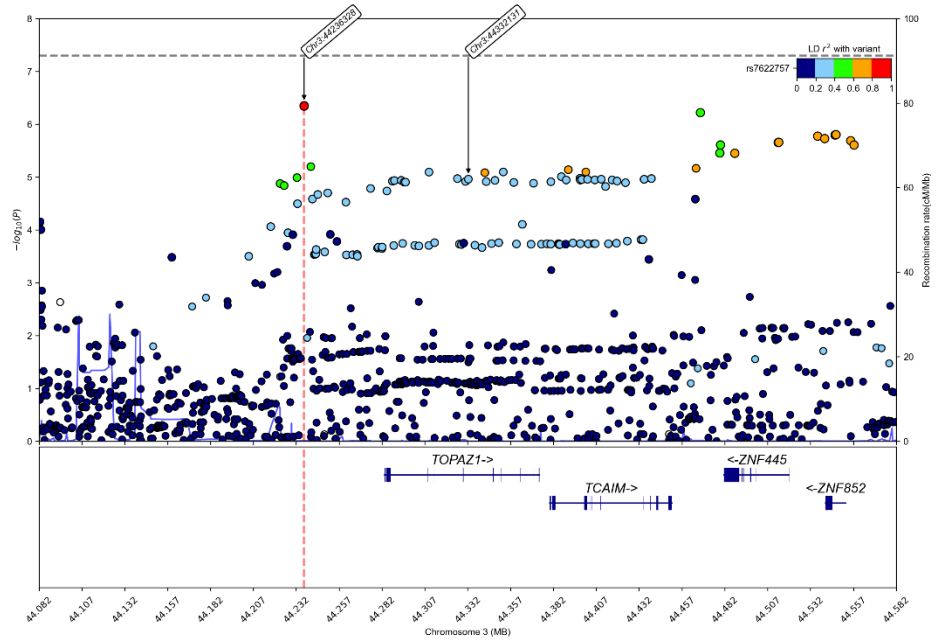
Supplementary Figure 10. The Mapping of CpG cg12004641 to the Schizophrenia GWAS Region



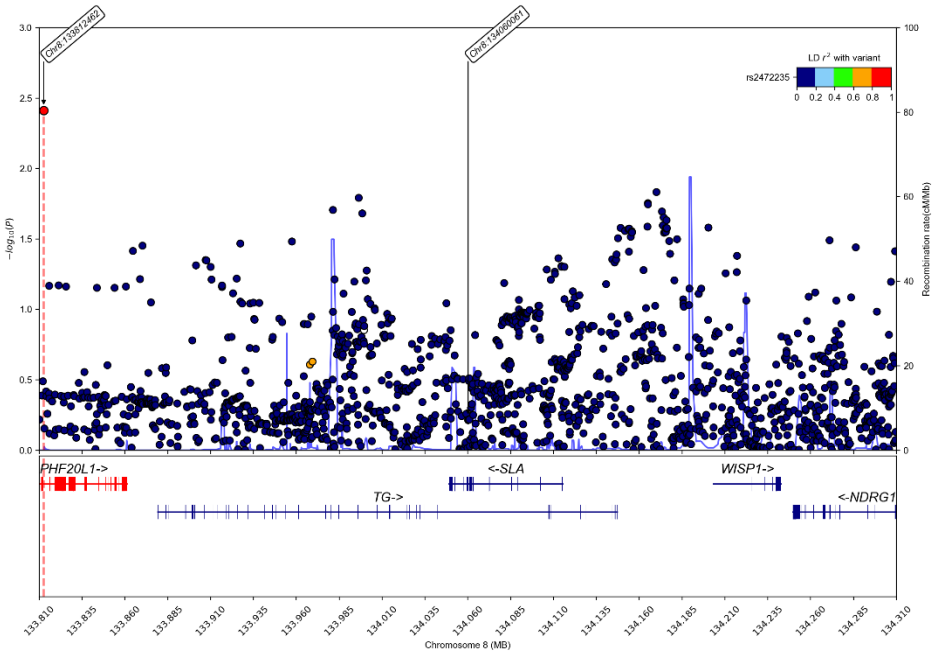
Supplementary Figure 11. The Mapping of CpG cg05419385 to the Schizophrenia GWAS Region



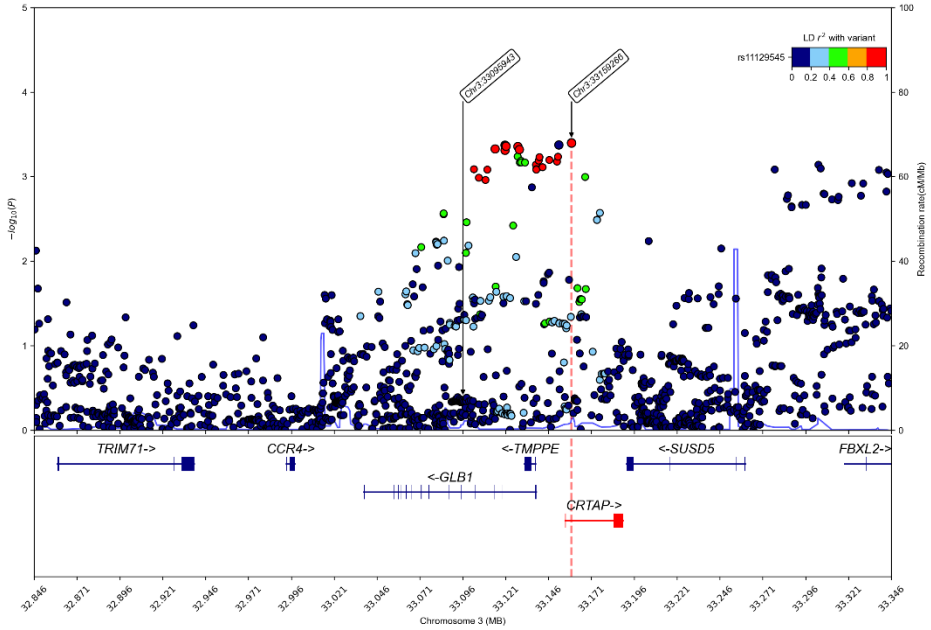
Supplementary Figure 12. The Mapping of CpG cg22583147 to the Schizophrenia GWAS Region



Supplementary Figure 13. The Mapping of CpG cg22845912 to the Schizophrenia GWAS Region



Supplementary Figure 14. The Mapping of CpG cg20730966 to the Schizophrenia GWAS Region



Supplementary Figure 15. The Mapping of CpG cg12044923to the Schizophrenia GWAS Region