Genomic stratification of bipolar disorder trajectories and outcome

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Thesis Summary

The intricate interplay between disease trajectories, outcomes, and the underlying genomic structure represents a complex and significant issue within the realm of bipolar disorder. The primary objective of this thesis is to make a valuable contribution to the field by investigating and providing insights into this complex interrelationship. The thesis is organized into three distinct sections, with the first two focusing on the definition of the phenotype and the third section delving into the genomic structure that influences and predicts the observed phenotypes.

Before the three sections, the background chapter delved into the clinical presentation of bipolar disorder, mood instability, and Polygenic Risk Scoring in neuropsychiatry, with a specific focus on bipolar disorder. Integral to all subsequent analyses is a comprehensive review of existing literature, examining outcomes in bipolar disorder. The review commenced by addressing the necessity to define and individualize the selection of potential outcomes in bipolar disorder. Subsequently, all subsequent analyses were substantially influenced by the definitions and findings uncovered in this review.

In the first section, the analysis involved a longitudinal study comprising 1,020 individuals diagnosed with bipolar disorder. By examining the weekly registered data, novel phenotypic variables were derived to describe the proportion of time individuals experienced specific mood symptomatology. Notably, individuals with bipolar 2 disorder exhibited a significantly higher mean total proportion of time spent with mood symptoms and depressive symptoms compared to individuals with bipolar 1 disorder. Additionally, the retrospective assessment of episode frequency showed a significant correlation with the proportion of time spent ill during the prospective follow-up for both bipolar disorder subtypes.

Moving to the second section, disease outcomes were investigated utilizing a factor analysis approach on retrospective data from a cohort of 3,505 individuals diagnosed with bipolar disorder. The exploratory factor analysis revealed a five-factor structure for bipolar 1 disorder and a four-factor structure for bipolar 2 disorder, explaining 66% and 56.5% of the variance,

respectively. Each factor captured specific aspects of the disorder, including social functioning (e.g., employment and educational achievements), severity of the disorder, hospital admissions, and characteristics of mood episodes. The utilization of factor analysis allowed for a more comprehensive understanding of the bipolar disorder phenotype by identifying and describing these distinct dimensions of outcomes.

The third section focused on investigating the genomic structure underlying the complex phenotypes observed in the previous two sections, utilizing Polygenic Risk Scoring (PRS). Multiple PRSs for various neuropsychiatric traits were generated and analysed. In the longitudinal study, significant associations were found between the proportion of time spent ill and with depressive symptoms, and PRSs for Depression, Neuroticism, and Sleep duration. Furthermore, in the outcomes study, genetic liability to major depression exhibited significant correlations with factors explaining the severity of the disorder in terms of the number of episodes, hospitalization history, and social function. Additionally, genetic liability to schizophrenia and ADHD showed significant correlations with disease severity, while the genetic liability for Intelligence, as measured by years of education, correlated with social outcomes and the number of episodes.

This thesis contributes to the understanding of bipolar disorder by elucidating the complex interplay between disease trajectories, outcomes, and genomic structure. The findings highlight the importance of considering both clinical and genetic factors in the personalized diagnosis and treatment of bipolar disorder patients.

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Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
AIC	Akaike's information criterion
ASRMS	Altman Self-Rating Mania Scale
BD-NOS	Bipolar disorder not otherwise specified
BD1	Bipolar disorder 1
BD2	Bipolar disorder 2
BDRN	Bipolar Disorder Research Network
BIC	Bayesian information criterion
CFA	Confirmatory Factor Analysis
CFI	Comparative fit index
DALYs	Disability-adjusted life years
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
EFA	Exploratory Factor Analysis
FAST	Functional Assessment Short Test
GAF	Global Assessment of Functioning
GAS	Global Assessment Scale
GWAS	Genome Wide Association Study
HAM-D	Hamilton Depression Rating Scale
HWE	Hardy-Weinberg equilibrium
IBD	Identity-by-descent
MAF	Minor allele frequency
MDD	Major depressive disorder
MESH	Medical Subject Headings
MR1-MR5	Minimum residual
NHS	national health System
OPCRIT	Operational Criteria Checklist for Psychotic Illness and Affective Illness

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRS	Polygenic Risk Score
QC	Quality Control
QIDS	Quick Inventory of Depressive Symptomatology
QIDS-SR	Quick Inventory of Depressive Symptomatology self reported
QoL	Quality of Life
RCTs	Randomized controlled trials
RDoC	Research Domain Criteria
RMSEA	Root mean square error of approximation
SA-BD	Schizo-affective Bipolar disorder
SCZ	Schizophrenia
SNPs	Single nucleotide polymorphisms
SRMR	Standardized root mean square residual
SS	Sum squared
TC	True Colours
TLI	Tucker-Lewis index
WHO	World Health Organization
YMRS	Young Mania Rating Scale

List of my contributions to the work described in this thesis.

Work presented in Chapter 3, Longitudinal mood monitoring in bipolar disorder: I did not contribute to the recruitment or assessment of participants of the True Colours Project. I contributed to the design of the analytic plan, I cleaned the database, I created derived phenotypic variables from raw data, conducted the statistical analyses and interpreted the results.

Work presented in Chapter 4, Factor analysis of outcomes in bipolar disorder: I did not contribute to the recruitment or assessment of participants of the BDRN cohort. I contributed to the design of the analytic plan, I cleaned the database, I created derived phenotypic variables from raw data, conducted the statistical analyses and interpreted of the results.

Work presented in Chapter 5, Genomic stratification of trajectories and outcomes: I did not contribute to genotypization of subjects or QC or imputation of genomic data. I merged genomic data in one dataset selecting common SNPs to the three different platform utilized for genotypization. I did the post merging QC. I calculated PRSs for different neuropsychiatric traits. I contributed to the design of the analytic plan, I cleaned the database, conducted the statistical analyses and interpreted the results.

Chapter 1: General introduction

Bipolar disorder, also known as manic-depressive illness, is a complex psychiatric disorder characterized by recurrent episodes of mania and depression. It affects a significant portion of the global population and has a profound impact on individuals' lives. Extensive research has been conducted to understand the aetiology, clinical features, and treatment of bipolar disorder.

Genetic factors play a crucial role in the development of bipolar disorder. Family and twin studies have consistently shown a high heritability estimate for the disorder, ranging from 60% to 85% (Smoller, 2003); (Lima, Peckham, & Johnson, 2018). Genome-wide association studies (GWAS) have identified specific genetic variants associated with bipolar disorder, including ANK3, CACNA1C, and ODZ4 (Mühleisen et al., 2014); (Stahl et al., 2019). These findings have contributed to our understanding of the underlying molecular pathways and biological mechanisms involved in the disorder.

In addition to genetic factors, environmental influences also contribute to the development and course of bipolar disorder. Stressful life events, such as trauma or significant life changes, have been found to trigger episodes in susceptible individuals (Post et al., 2018). Substance abuse has also been identified as a risk factor for bipolar disorder, exacerbating symptoms and increasing the likelihood of relapse (Levin et al., 2007). Neuroimaging studies have revealed structural and functional alterations in brain regions involved in emotion regulation, reward processing, and cognitive control among individuals with bipolar disorder (Phillips & Swartz, 2014); (Hibar et al., 2018). Dysregulation of neurotransmitters, including dopamine, serotonin, and norepinephrine, has also been implicated in the pathophysiology of the disorder (Belmaker & Agam, 2008).

The clinical presentation of bipolar disorder is characterized by distinct mood episodes, including manic and depressive episodes. Manic episodes are characterized by elevated mood,

increased energy, and impulsivity, while depressive episodes are marked by profound sadness, loss of interest, and changes in sleep and appetite (American Psychiatric Association (APA), 2013). Accurate diagnosis is crucial for appropriate treatment selection and management of the disorder. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) provides standardized diagnostic criteria for bipolar disorder (American Psychiatric Association, 2013).

Treatment for bipolar disorder typically involves a combination of pharmacotherapy and psychotherapy. Mood stabilizers, antipsychotics, and antidepressants are commonly prescribed to manage symptoms and prevent relapse (Geddes et al., 2019). Psychotherapy, such as cognitive-behavioural therapy and family-focused therapy, can assist individuals in developing coping skills, improving medication adherence, and enhancing interpersonal relationships (Miklowitz, 2008). Additionally, lifestyle modifications, including maintaining regular sleep patterns, managing stress, and avoiding substance use, are important for long-term stability and overall well-being (Bauer et al., 2015).

1.1 Mood instability and Bipolar Disorder

The concept of mood instability is integral to various psychiatric conditions, necessitating a thorough examination. Characterized by frequent and abrupt fluctuations between low and high moods, as well as anxiety and irritability, mood instability exhibits unpredictability and can occur without discernible triggers. This phenomenon is well defined by the Criterion 6 of the DSM-5 criteria for borderline personality disorder, which delineates affective instability as marked mood reactivity lasting hours to a few days. “Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety, usually lasting a few hours and only rarely more than a few days)”(American Psychiatric Association (APA), 2013).

Given its prominence in bipolar disorder, mood instability has become a focal point in clinical research. Both Bipolar I and II disorders manifest varying degrees of instability between episodes or within manic or depressive phases, underscoring its clinical relevance. Notably, mood instability between affective episodes is linked to considerable functional impairment and adverse prognostic indicators, including heightened risk of hospitalization, increased rates of relapse, and compromised functioning (MacQueen et al., 2003);(Kupka et al., 2007) (MacQueen et al., 2003);(Strejilevich et al., 2013)

A significant portion of individuals diagnosed with bipolar disorder fails to achieve complete remission, enduring persistent symptoms even during inter-episode intervals, and encountering mood fluctuations exceeding those observed in individuals without psychiatric conditions (Judd et al., 2003);(Patel et al., 2015) This underscores the chronicity and severity of mood dysregulation experienced by individuals grappling with bipolar disorder.

These collective findings underscore the significance of mood instability within the realm of psychopathology, indicating the need for a more comprehensive understanding of its underlying nature, origins, correlates, and implications. However, advancing our

comprehension of mood instability necessitates addressing the lack of consensus regarding its definition. For instance, while studies rely on a single inquiry to gauge mood instability, for example “Do you have a lot of sudden mood changes?” taken from the structured interview for disease developed by the DSM curators, other study, especially in a clinical setting use one of the several mood instability rating questionnaires.

Clearly, the absence of a universally agreed-upon definition, alongside the utilization of diverse measurement approaches, may result in significantly differing prevalence rates for the phenomenon. Such variance in prevalence estimations could potentially lead to varying impacts on patients and, ultimately, contribute to the under recognition of this crucial aspect of the disorder within affected individuals.

The existing body of literature on mood instability predominantly relies on retrospective questionnaires as its primary data source. Undoubtedly, this approach has proven to be invaluable in advancing our understanding of the phenomenon. Nevertheless, it is essential to acknowledge that responses to retrospective questionnaires are susceptible to limitations, such as recall bias, which may pose challenges for studies focusing on mood instability due to its dynamic nature (Solhan, Trull, Jahng, & Wood, 2009). Momentary assessment and remote monitoring techniques offer effective solutions to mitigate these issues, providing enhanced insight and a more comprehensive quantitative depiction of mood instability in individuals' daily lives. Thanks to the True Colours (TC) tool, which allows for weekly mood state assessments of patients, a more comprehensive and robust description of mood instability can be attained. Through the utilization of True Colours, comprehensive data regarding both depressive and manic mood states can be collected from the everyday lives of enrolled subjects. Furthermore, the substantial sample size of the database, currently comprising over 1000 patients, holds promise for elucidating the multifaceted nature of the mood instability construct. In Chapter 3 of this thesis, I will propose a methodology for analysing True Colours data, aiming to gain insights into the chronicity of the disorder and its implications on disease outcomes resulting from mood instability.

2.1 Role of Polygenic Risk Scoring in Bipolar Disorder

Polygenic risk scores (PRSs) have revolutionized the field of genetic research since their introduction in 2007. These scores leverage the vast amount of data generated by genome-wide association studies (GWAS) to predict an individual's risk of developing various diseases. With advancements in genomics and the identification of single nucleotide polymorphisms (SNPs) associated with specific traits, PRSs have gained prominence as composite genomic biomarkers with potential applications in risk prediction, disease screening, early diagnosis, prognostication, and drug stratification (Lambert et al., 2021) (Offit, 2011).

A single nucleotide polymorphism (SNP) represents a prevalent form of genetic variation within populations, characterized by the substitution of a single nucleotide base at a specific genomic locus, thereby delineating allelic diversity at the individual nucleotide level(Katsonis et al., 2014). SNPs are pervasive throughout the human genome and are widely distributed across various genomic regions, including coding and non-coding regions, as well as within regulatory elements and intergenic regions. The discernible impact of SNPs on phenotypic variability and susceptibility to complex traits(Prodi et al., 2004), diseases (Dong et al., 2008), and pharmacological responses (Kimchi-Sarfaty et al., 2007) has rendered them instrumental in genetic association studies, population genetics, and personalized medicine endeavours. Notably, the allelic frequencies of SNPs can exhibit pronounced disparities across different ethnic groups, thereby underpinning their utility as genetic markers for elucidating population ancestry and evolutionary trajectories(Barreiro, Laval, Quach, Patin, & Quintana-Murci, 2008). The elucidation of SNP associations with diverse phenotypic manifestations often entails comprehensive genomic analyses, encompassing genotyping techniques, such as microarray-based platforms or high-throughput sequencing methodologies, alongside sophisticated statistical approaches for identifying significant genotype-phenotype correlations(Zhang et al., 2004).

The development of PRSs has been facilitated by the growing number of SNPs identified through large-scale GWAS analyses.

GWAS is a comprehensive and systematic investigation method employed in human genetics to identify genetic variants associated with complex traits or diseases on a genome-wide scale. GWAS endeavours involve scrutinizing the entire genome of individuals within a population or cohort, typically utilizing high-throughput genotyping technologies to assess millions of single nucleotide polymorphisms (SNPs) or other genetic markers distributed across the genome. The fundamental premise of GWAS rests on the comparison of allele frequencies between affected individuals, representing cases exhibiting the trait or disease under investigation, and unaffected controls. Through statistical analyses, GWAS aims to discern significant associations between specific genetic variants and the trait or disease phenotype. These identified genetic loci, or susceptibility loci, elucidate potential genetic determinants contributing to trait variability or disease susceptibility. Moreover, GWAS findings serve to illuminate biological pathways, molecular mechanisms, and gene-environment interactions underlying the complex trait or disease phenotype, thereby offering valuable insights into disease aetiology, pathogenesis, and avenues for targeted therapeutic interventions or personalized medicine approaches.

GWAS studies have unveiled the genetic architecture underlying numerous diseases, ranging from metabolic disorders to neuropsychiatric conditions and cancer. The inclusion of a broader set of genetic variants, including both common (minor allele frequency > 5%) and low-frequency variants, has enhanced the predictive power of PRSs by capturing the complex interplay of multiple genetic factors (Offit, 2011); (Lambert et al., 2021);(Lee, Feng, & Smoller, 2021). Furthermore, rare variants have also been recognized as contributors to disease susceptibility, as demonstrated in studies on conditions such as autism and schizophrenia (Leblond et al., 2014); (Singh et al., 2022).

In recent years, numerous clinical trials have been initiated to explore the utility of PRSs in diverse medical specialties. These trials aim to assess the value of PRSs in predicting disease risk, guiding pharmacotherapy decisions, aiding in diagnosis, and refining patient outcomes. Examples of successful integration of genetic information into clinical practice include the

identification of rare mutations in rare diseases and the use of genetic screening to guide drug prescribing (Mallal et al., 2008; Ferrell and McLeod, 2008).
In the context of bipolar disorder (BD), PRSs have emerged as a valuable tool for unraveling its genetic basis. BD is a severe mental illness characterized by recurrent episodes of mania and depression, with a heritability estimate of around 70-80% (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018). PRSs constructed for BD utilize the results of GWAS studies, which identify SNPs associated with the disorder, to estimate an individual's genetic predisposition to BD. Higher PRS scores indicate a greater genetic liability for developing BD.

The application of PRS in BD research has yielded valuable insights into the genetic architecture of the disorder. Numerous studies have demonstrated that BD PRS is significantly associated with an increased risk of developing BD (Stahl et al., 2019); (Pardiñas et al., 2018). Furthermore, BD PRS has shown associations with specific clinical features and outcomes, such as an earlier age of onset, greater illness severity, increased rates of hospitalization, and higher rates of comorbid psychiatric conditions (Stahl et al., 2019).

PRS has also proven useful in understanding the shared genetic basis between BD and other psychiatric disorders. Significant genetic overlap between BD and schizophrenia (SCZ) has been identified, with BD PRS being associated with an increased risk of SCZ and vice versa (Niarchou et al., 2019); Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). These findings support the notion of a spectrum of mood and psychotic disorders and highlight shared underlying genetic mechanisms.

Polygenic Risk Scores (PRS) hold promise as valuable tools in brain structural and functional imaging research within the context of bipolar disorder (BD), offering insights into the genetic underpinnings of neuroanatomical alterations associated with the disorder. Activation in key limbic structures, notably the anterior cingulate cortex and amygdala is positively associated with increased BD polygenic risk scores (Whalley et al., 2012). Utilising a cross-sectional design to examine the influence of BD-PRS on brain activation during negative facial emotion

processing, revealed a positive correlation with activation in the right ventrolateral prefrontal cortex (Tesli et al., 2015).

Another study explored the relationship between adolescent BD-PRS and gray matter structure and white matter integrity, revealing negative correlations with gray matter structure and fractional anisotropy (FA) in regions implicated in BD (Jiang et al., 2023). These collective findings underscore the potential utility of BD-PRS as a neuroimaging marker for BD. However, longitudinal investigations are warranted to ascertain the predictive value of BD-PRS in delineating neurodevelopmental trajectories vis-à-vis healthy controls, alongside its interaction with disease progression and long-term medication regimens.

Despite the promise of PRS in BD and other complex disorders, there are certain limitations to consider. The current PRS models have limited predictive power at the individual level, as they explain only a small proportion of the overall risk variance. This highlights the need for further research to identify additional genetic variants and improve the accuracy of PRS models. Additionally, PRSs should be interpreted in conjunction with other clinical and environmental factors to provide a comprehensive understanding of disease risk.

In conclusion, PRSs have emerged as powerful tools in the study of complex disorders such as bipolar disorder. By integrating information from GWAS studies, PRSs provide a means to estimate an individual's genetic risk for developing BD and offer insights into its genetic architecture and shared genetic basis with other psychiatric disorders. Although challenges remain, ongoing research and advancements in genomics hold the potential to enhance the clinical utility of PRSs, paving the way for personalized medicine approaches in the prevention, diagnosis, and treatment of BD and other complex diseases.

3.1 Summary and objectives

Bipolar disorder is a multifaceted disorder. Traditionally, the diagnosis has focused on the most prominent expressions of symptomatology, namely manic and depressive episodes, which guide the diagnostic criteria outlined in the DSM. When describing the natural history of the disorder, attention tends to simplify matters by referring solely to the cyclical nature of manic and depressive episodes. Less attention, however, has been given to prodromal symptoms and, more importantly, residual symptoms between episodes. The main challenge in describing and studying residual symptomatology between episodes lies in the lack of systematically collected longitudinal data. To overcome this, a study on the True Colours project is crucial (Goodday et al., 2020)

Disease outcomes, both those immediately related to patient contact such as treatment response, compliance, hospitalizations, and episode frequency, as well as those further in the patient's future life such as educational attainment and work and family aspirations like marriage, are heavily influenced not only by the patient's acute pathology, whether manic or depressive, but also by the symptoms experienced during inter-episode periods. Those who have focused on bipolar disorder outcomes have often approached the problem guided by a priori considerations of the importance and relevance of patient outcomes. This has led to studies dedicated to describing specific outcomes without considering how they may interact with each other. The comprehensive approach to studying outcomes undertaken in this thesis aims to address this knowledge gap by utilizing a statistical approach that investigates the underlying structure of various outcome variables, ranging from clinical to social domains (Sanchez-Moreno et al., 2009).

The role of genetics in bipolar disorder, starting with twin studies and now advancing to the era of genomics, can be crucial in stratifying patients and providing insights into the biological determinants of this complex phenotype. Polygenic risk scoring is particularly well-suited for this purpose due to its relative simplicity and immediate applicability (Croarkin et al., 2017). Stratifying patients based on their genetic liability for

neuropsychiatric traits can guide clinicians toward different areas of patient outcomes. By understanding the genetic underpinnings, it becomes possible to identify subgroups of patients who may have distinct clinical trajectories and may benefit from tailored treatment approaches (A. W. Charney et al., 2017).

The objectives of the present thesis are:

Chapter 2: Outcomes in Bipolar Disorder: A Review of Reviews

The primary objective of the literature review is to comprehensively understand the current landscape of outcomes in bipolar disorder. Adopting a review of reviews methodology was deemed necessary due to the extensive scope of the field, rendering it impractical to analyse each individual study for every outcome of interest. The overarching aim of this approach is to compile a comprehensive list of potential outcomes for subsequent analysis. The construction of this list will be independent of the specific database utilized and will serve as a guide to ascertain the presence of all relevant outcomes within the chosen database. In the event that certain outcomes are not adequately represented, decisions will be made regarding their inclusion or exclusion, thereby informing future investigations and patient enrolment strategies.

Chapter 3: Longitudinal mood monitoring in bipolar disorder:

The aims of this study are twofold. Firstly, it investigates and describes the course of illness in individuals enrolled in the True Colours (TC) project during a specific time window. New outcoe variables are generated to capture the proportion of time spent experiencing different symptoms (mania, depression, mixed status) based on participants' responses to mood questionnaires. This analysis provides insights into the trajectory of illness over time in bipolar disorder subjects. Secondly, the chapter explores the correlation between the course of illness variables derived from TC data and the course of illness observed in the retrospective cohort from the Bipolar Disorder Research Network (BDRN). This comparison

between different data sources aims to assess the potential utility of TC data in predicting the course of illness in individuals with bipolar disorder.

Chapter 4: Factor analysis of outcomes in bipolar disorder:

The primary objectives of this chapter are twofold. Firstly, it investigates the interrelationships among various clinical outcomes in individuals with bipolar disorder. Factor analysis is employed to uncover the underlying structure of outcome dimensions in bipolar disorder and identify how different outcomes are related to each other. Secondly, the chapter aims to explore the latent factors that contribute to both clinical and functional outcomes in bipolar disorder. The analysis identifies specific factors that play a role in determining both the clinical and functional outcomes experienced by individuals with bipolar disorder. The ultimate goal is to generate outcome factors that can be utilized in genetic association studies to better understand the genetic basis of these outcomes.

Chapter 5: Genomic stratification of trajectories and outcomes:

The objectives of this chapter encompass two key aspects. Firstly, the study utilizes polygenic risk scores (PRSs) for several neuropsychiatric traits and conditions (such as schizophrenia, major depressive disorder, neuroticism, mood instability, intelligence, and chronic pain) to investigate their predictive value for bipolar disorder (BD) phenotypes using data from both the BDRN retrospective cohort and the longitudinal TC data. This analysis assesses the potential of PRSs in predicting and understanding BD phenotypes and compares the associations between PRSs and the phenotype variables generated from TC data to evaluate the reliability and quality of the TC-generated phenotype variables. Secondly, the chapter explores the biological validity of the generated outcome factors by investigating their potential heritability and their relationship to the liability for common neuropsychiatric traits. This analysis provides insights into the genetic basis of the outcome factors and their relevance to broader neuropsychiatric conditions.

Chapter 2: Outcomes in Bipolar Disorder, a review of reviews:

1.2 INTRODUCTION

Bipolar disorder, defined as a disorder characterized by significant disturbances in mood and activity levels, presents a substantial burden on individuals and society. According to the Global Burden of Disease Study conducted by Ferrari et al. in 2016, there were approximately 49 million prevalent cases of bipolar disorder worldwide in 2013. This accounted for nearly 10 million disability-adjusted life years (DALYs), representing 0.4% of the total DALYs and 1.3% of the total years lived with disability. The prevalence and burden of bipolar disorder were relatively consistent across different regions (Ferrari et al., 2016).

Typically, the first diagnosis of bipolar disorder occurs during adolescence and continues to impact individuals throughout their lifespan (Merikangas et al., 2007). The Global Burden of Disease Study in 2013 revealed that DALYs associated with bipolar disorder were evident from as early as 10 years of age, peaked during the 20s, and subsequently declined. However, it is important to note that bipolar disorder is a heterogeneous condition, and disease trajectories and outcomes can vary significantly. While, on average, bipolar disorder is associated with reduced life expectancy and the highest risk of suicide, prognosis varies widely among individuals. Some individuals experience an episodic course with full recovery, while others face a chronic and disabling illness (Merikangas et al., 2007).

In research focused on bipolar disorder, a wide range of outcomes have been investigated. However, there is currently a lack of standardized core outcome sets specifically designed for research involving individuals with lived experience of bipolar disorder. Core outcome sets are standardized collections of outcomes that should be consistently measured and reported in all controlled trials within a particular research area (Williamson et al., 2012). These sets

represent the minimum outcomes that should be assessed to ensure comprehensive and meaningful research.

The definition and measurement of outcomes in mental health research, including bipolar disorder, pose significant challenges. Outcomes, as defined by the Oxford medical dictionary, refer to patient behaviours or attitudes that result from healthcare interventions. Assessing outcomes in clinical trials can provide valuable information for individual care and policymaking at different levels. However, the use of multiple outcome measures across different studies within the same research area can create difficulties in synthesizing research findings (Tovey, 2011); (Williamson et al., 2012). Heterogeneity in outcome measures reduces the comparability and generalizability of research results, making it challenging to establish a comprehensive understanding of bipolar disorder outcomes.

A survey of 10,000 randomized controlled trials (RCTs) conducted in the field of schizophrenia reported the use of 2,194 different measurements, with a new outcome being reported every fifth trial (Miyar & Adams, 2013). This demonstrates the vast array of outcome measures employed in mental health research, including bipolar disorder, highlighting the potential limitations in result synthesis. Moreover, many of these measures have been chosen by researchers and clinicians, which may not fully capture outcomes that are relevant to all stakeholders, including individuals with lived experience of severe mental illness and their caregivers (Keeley et al., 2015).

To address these challenges, the PARTNERS2 study at Birmingham University has aimed to establish a core outcome set specifically for effectiveness trials in bipolar disorder (Keeley et al., 2015). This study follows a three-step approach to develop a core outcome set. Initially, a comprehensive list of outcomes has been compiled through qualitative research and systematic searching of trial databases. Focus groups and one-to-one interviews have been conducted with service users, carers, and healthcare professionals to gather input. Subsequently, a Delphi study has been employed to reduce the list to a core set. Stakeholders, including service users, have scored the outcomes for relevance in a three-round Delphi process. In round two, stakeholders only saw the results of their group, while in round three,

they had access to the results of all stakeholder groups. Finally, a consensus meeting has been conducted to confirm the outcomes to be included in the core set. Following the development of the core outcome set, a systematic literature review of existing measures has allowed recommendations for how the core outcomes should be measured. Additionally, a stated preference survey has been conducted to explore the strength of people's preferences and estimate weights for the outcomes comprising the core set (Keeley et al., 2015).

The aim of this literature review was twofold. Firstly, it sought to establish a comprehensive outcome set from existing literature reviews on bipolar disorder, which we will refer to as the "research outcome set." Secondly, we aimed to compare this research outcome set with a core set of outcomes developed collaboratively with patients through the PARTNERS2 research program, which we will refer to as the "patient-reported dataset." The findings from this review have significant implications for selecting appropriate outcomes for the analyses conducted in this thesis, ensuring that the chosen outcomes align with both existing research evidence and the perspectives of individuals with lived experience of bipolar disorder (Keeley et al., 2015).

In the following sections of this literature review, we will present the methodology employed for the systematic review, the results obtained, and a comprehensive analysis and synthesis of the identified outcome sets. Through this review, we aim to contribute to the advancement of outcome measurement and reporting in bipolar disorder research, facilitating the development of more patient-cantered and comprehensive approaches to understanding and managing this complex condition. The decision to conduct a review of reviews stems from the recognition that the field of bipolar disorder outcomes is vast and multifaceted, making it impractical to comprehensively analyse each individual study. By synthesizing findings from existing reviews, this approach offers a systematic and efficient method to generate a more comprehensive list of outcomes, thereby laying the groundwork for further investigation into bipolar disorder outcomes.

2.2 METHODS

A systematic and comprehensive literature search was conducted on February 12, 2019, using multiple databases to ensure a thorough exploration of the topic. The following databases were searched: MEDLINE (1966-2019), EMBASE (the Excerpta Medica database) (1988-2019), PubMed (1967-2019), and PsychINFO (1967-2019).

To develop an effective research strategy, a MESH search string was utilized, focusing on key terms related to bipolar disorder and its outcomes. The search string employed was as follows: (cyclothymi$ or mania or manic or hypomania or hypomanic or affective psychosis or bipola).ab,kw,ti. AND ("trajector*".ab,kw,ti. OR "outcome*".ab,kw,ti.). This strategy aimed to identify relevant articles that explored the trajectories and outcomes associated with bipolar disorder.

The search results were subsequently filtered to include only English language articles. In addition, the EMBASE database underwent a deduplication process to remove any duplicate studies. Furthermore, a filter based on publication type was applied, specifically targeting reviews. This ensured that the selected articles focused on reviewing the existing literature rather than presenting original research.

Both I and my supervisor independently reviewed all the studies retrieved from the search. Notably, there was complete agreement between us in terms of the papers selected for inclusion in the review. To further augment the comprehensiveness of the literature search, the reference lists of the retrieved articles were also examined for additional relevant sources.

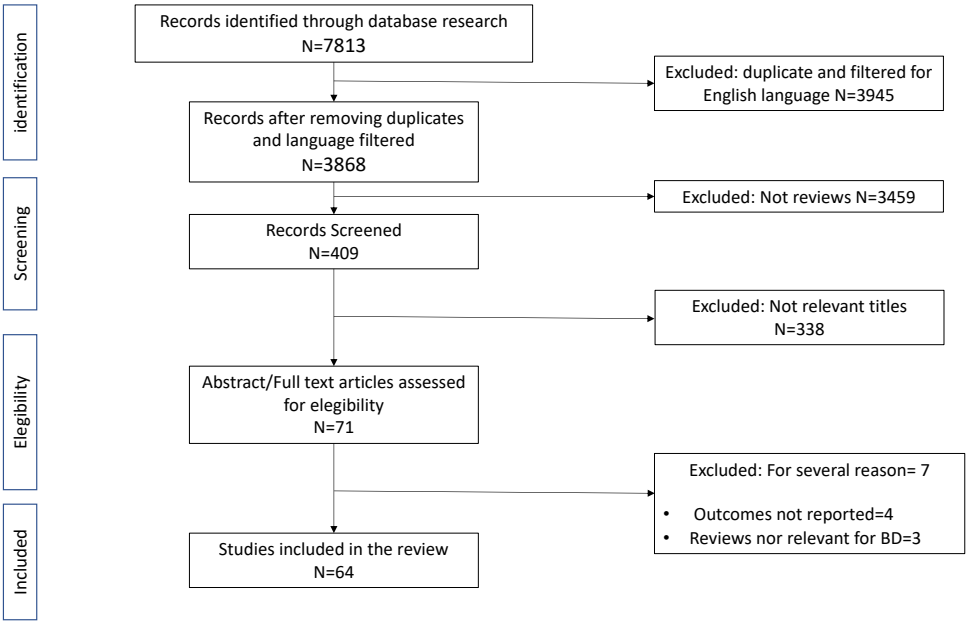
Inclusion Criteria were:

-Peer-reviewed Research Articles: Only studies published in peer-reviewed journals were considered eligible for inclusion in this review.
-Focus on Bipolar Disorder Outcomes: Studies investigating outcomes related to bipolar disorder, including but not limited to symptom severity, functional impairment, quality of life, treatment response, and relapse rates, were included social and personal outcomes.
-Diverse Study Designs: systematic and narrative reviews, were included to provide a comprehensive overview of bipolar disorder outcomes.
-Various Outcome Measures: Studies employing different outcome measures to assess bipolar disorder outcomes, such as standardized clinical rating scales, self-report questionnaires, neuropsychological tests, etc., were included.
Exclusion Criteria were:

-Non-English Publications: Studies published in languages other than English were excluded unless they provided critical insights unavailable in English-language literature.
-Non-peer-reviewed Sources: Sources such as conference abstracts, dissertations, books, and non-peer-reviewed websites were excluded due to the lack of rigorous peer-review processes.
-Irrelevant Topics: Studies not directly addressing bipolar disorder outcomes or focusing on tangential topics unrelated to the main scope of this review were excluded.
-Animal Studies: Studies conducted solely on animal models of bipolar disorder were excluded unless they offered significant insights applicable to human outcomes.

To adhere to the principles of transparency and rigor in the review process, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Welch et al., 2016) were followed. This guideline provides a structured and standardized approach to conducting systematic reviews, ensuring clarity and consistency in the reporting of methods and results.

Figure.1.2: PRISMA flow diagram for systematic review of the reviews



3.2 RESULTS

Research Outcome Set

The initial MESH terms research yielded a total of 7813 results. After removing duplicates and selecting only English language publications, 3868 entries remained. Out of these, 3459 were excluded as they were not reviews. The remaining 409 records were screened, and 338 were further excluded due to irrelevant titles. After a careful evaluation, an additional 7 reviews were removed either because they did not report outcomes or were not relevant to bipolar disorder (BD). Ultimately, a total of 64 reviews were selected and utilized for this paper, and their summarized findings are presented in Table 1.1.

In Table 1.1, each review is accompanied by a list of outcomes considered, type of review (systematic or narrative) and year considered in the papers analyzed. These outcomes are aligned with the outcome list developed in Birmingham, with the inclusion of three additional items: Suicide, Hospitalization, and Pregnancy outcomes. Among the selected reviews, the most frequently addressed outcome, featured in 38 reviews, pertained to the clinical recovery of bipolar symptoms in terms of relapse or recovery response. Quality of life, examined in 28 reviews, emerged as the second most common outcome. Connectedness, encompassing factors such as satisfaction with social networks, trust, relationships with friends, family, and others, social support via personal social contacts, social isolation, and loneliness, was present in 22 reviews. Notably, loneliness was considered a significant concept that could serve as an outcome itself or overlap with "mental health and wellbeing." Suicide and Medication Effects were recurring outcomes in 15 reviews, followed by Personal Recovery and Physical Health, which were each analysed in 14 reviews. Hospitalization appeared in 13 reviews, while Self-monitoring and Management were addressed in 12 reviews. Pregnancy outcomes and Mental Health and Wellbeing were examined in only two reviews. Notably, no reviews published at the time of the literature search explored Service outcomes, Experience of Care, or Use of Coercion.

The key finding of this literature review is the development of a new set of outcomes, comprising a total of 14 entities. This list includes the 11 outcomes identified by Keeley et al. and incorporates three additional outcomes deemed relevant in the analysed papers: Suicide, Pregnancy outcomes, and Hospitalization. When examining the integration of Research and Community-Based outcomes (Figure. 2.1), a core set of 8 outcomes was identified, along with 6 characteristic outcomes, three from each set.

Figure 2.2: Comparison of Outcome Sets. This figure illustrates the integration of research and community-based outcomes sets in the context of bipolar disorder. The two sets exhibit considerable overlap, encompassing the majority of the identified outcomes. However, each set also includes specific outcomes that are not addressed by the other.

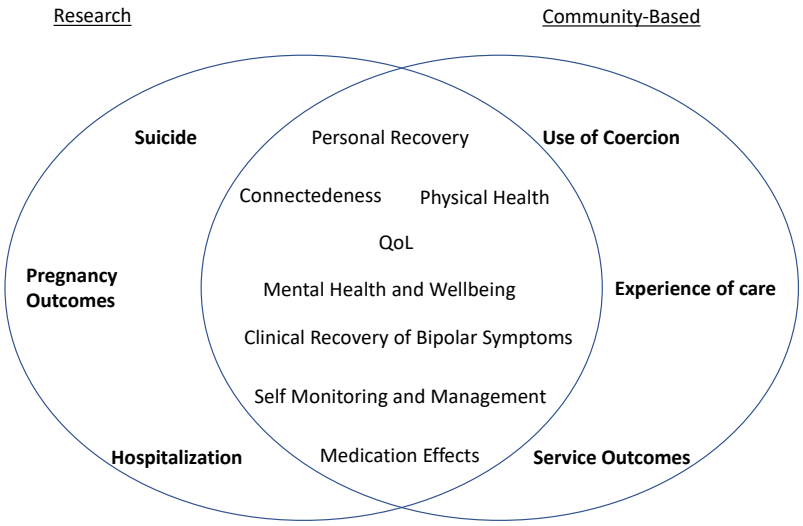


Table 1.2: Summary of papers included in the review

Progressive number	Reference	Title	Outcomes	Systematic	Period Covered
1	(Sheffield, Karcher, & Barch, 2018)	Cognitive Deficits in Psychotic Disorders: A Lifespan Perspective.	Functional outcomes	NO	1971-2018
2	(Dodd, Lockwood, Mansell, & Palmier-Claus, 2019)	Emotion regulation strategies in bipolar disorder: A systematic and critical review.	Quality of life, Suicide	YES	1980-2016
3	(Lima et al., 2018)	Cognitive deficits in bipolar disorders: Implications for emotion.	Quality of life, Suicide, Social functioning	NO	1984-2017
4	(Passos, Mwangi, Vieta, Berk, & Kapczinski, 2016)	Areas of controversy in neuroprogression in bipolar disorder.	Review the concept of neuroprogression in the following aspects: (i) clinical risk factors and outcomes associated with neuroprogression, and (ii) the environmental pathways driving neurobiological and brain changes.		1995-2016
5	(Messer, Lammers, Müller-Siechenederer, Schmidt, & Latifi, 2017)	Substance abuse in patients with bipolar disorder: A systematic review and meta-analysis.	Clarify the major risk factors of substance use among adults with BD and determine the determinant factors of SUD in people with bipolar disorder.	YES	1988-2016
6	(Lima et al., 2018)	Towards recovery-oriented psychosocial	Connectdeness hope and optimism, identity, meaning in life and	NO	1993-2016

		interventions for bipolar disorder: Quality of life outcomes, stage-sensitive treatments, and mindfulness mechanisms.	empowerment (CHIME), Quality of life, Functional outcomes		
7	(Scrandis, 2017)	Bipolar Disorder in Pregnancy: A Review of Pregnancy Outcomes.	Pregnancy complications, Preterm birth, Congenital abnormalities, Large for gestational age, Neonatal hypoglycemia, Instrumental birth, Cesarean birth, Induction of labor, Preeclampsia, Birth weight below 2500 grams, Infant death, Gestational diabetes, Placenta previa, Antepartum hemorrhage	YES	2000-2017
8	(Gitlin & Miklowitz, 2017)	The difficult lives of individuals with bipolar disorder: A review of functional outcomes and their implications for treatment.	Symptomatic/syndromal vs. functional outcomes, Working at full capacity, Strong interpersonal supports, High quality of life, Hospitalization	NO	1980-2016
9	(Lindström, Lindström, Nilsson, & Höistad, 2017)	Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis.	Discontinuation and relapses	YES	2003-2012
10	(Oud et al., 2016)	Psychological interventions for adults with bipolar disorder: Systematic review and meta-analysis.	Response, Relapse, Hospital admission, Quality of life, Suicide, Psychosocial functioning, Study discontinuation	YES	1984-2014

11	(Bond & Anderson, 2015)	Psychoeducation for relapse prevention in bipolar disorder: A systematic review of efficacy in randomized controlled trials.	Social and occupational functioning, Increased knowledge, Improved attitude to lithium, Improved mood symptoms, Quality of life, Lithium levels, Medication knowledge, Medication regularity	YES	1988-2013
12	(Baune & Malhi, 2015)	A review on the impact of cognitive dysfunction on social, occupational, and general functional outcomes in bipolar disorder.	Social function, occupational function	NO	1989-2014
13	(Manning, 2015)	Measuring patient outcomes and making the transition from acute to maintenance treatment for bipolar depression.	Symptoms response, functioning, quality of life	NO	1992-2015
14	(Miller, Dell'Osso, & Ketter, 2014)	The prevalence and burden of bipolar depression.	Socioeconomic burden, functioning and quality of life, Suicide, suicide attempts	YES	1991-2013
15	(Geoffroy et al., 2013)	Reconsideration of bipolar disorder as a developmental disorder: Importance of the time of onset.	Suicide attempts, violent behaviour, thyroid dysfunction and cardiovascular risk factors, such as diabetes (due to glucose intolerance and insulin resistance), obesity (particularly abdominal obesity) and hypertension.	NO	1990-2013

16	(Skirrow, Hosang, Farmer, & Asherson, 2012)	An update on the debated association between ADHD and bipolar disorder across the lifespan.	Response to treatment, neurobiological correlates	NO	1970-2012
17	(McMurrich et al., 2012)	Course, outcomes, and psychosocial interventions for first-episode mania.	Syndromic recovery, symptomatic recovery, functional recovery, relapse	NO	1990-2012
18	(Crowe, Wilson, & Inder, 2011)	Patients' reports of the factors influencing medication adherence in bipolar disorder - An integrative review of the literature.	Clinical outcomes, quality of life	NO	1986-2011
19	(Vega et al., 2011)	Bipolar disorder differences between genders: Special considerations for women.	Substance abuse, suicide attempts, quality of life, and psychosocial functioning	NO	1992-2011
20	(Tarr, Herbison, de la Barra, & Glue, 2011)	Study design and patient characteristics and outcome in acute mania clinical trials.	Clinical outcome, adherence, relapse	NO	1978-2011
21	(Busby & Sajatovic, 2010)	Patient, treatment, and systems-level factors in bipolar disorder nonadherence: A summary of the literature.	Psychosocial functioning, hospitalizations, suicide attempts, and completed suicides. Health outcomes, treatment outcomes.	YES	1979-2009
22	(Goodrich & Kilbourne, 2010)	A long time coming - The creation of an evidence base for physical activity prescription to improve health outcomes in bipolar disorder.	Health outcomes, cardiovascular disease, diabetes, and obesity	NO	1995-2009

23	(Beyer, 2008)	An evidence-based medicine strategy for achieving remission in bipolar disorder.	Quality of life, functional status, remission	NO	1991-2008
24	(Morriss et al., 2007)	Interventions for helping people recognize early signs of recurrence in bipolar disorder.	Measure of functioning, hospitalization, recurrence of episodes	YES	1968-2005
25	(Michalak, Murray, Young, & Lam, 2008)	Burden of bipolar depression: Impact of disorder and medications on quality of life.	Social, occupational, and/or educational functioning, rates of relapse, the number of times a patient is hospitalized, or degree of symptom reduction on clinician-rated assessment scales, social functioning	NO	1986-2008
26	(Altman et al., 2006)	Predictors of relapse in bipolar disorder: A review.	Social function, occupational function, suicide, substance abuse, relapse, adherence, recurrence	YES	1996-2006
27	(P. E. Keck, 2006)	Long-term management strategies to achieve optimal function in patients with bipolar disorder.	Psychosocial functioning	NO	1988-2006
28	(Michalak, Yatham, & Lam, 2005)	Quality of life in bipolar disorder: A review of the literature.	Quality of life	NO	1965-2004
29	(Johnson, 2005)	Life events in bipolar disorder: Towards more specific models.	Life events, suicide, hospitalization	NO	1964-2005
30	(Hawton, Sutton, Haw, Sinclair, &	Suicide and attempted suicide in bipolar disorder: A systematic review of risk factors.	Suicide	YES	1980-2003

	Harriss, 2005)				
31	(Tohen, Greenfield, Weiss, Zarate, & Vagge, 1998)	The effect of comorbid substance use disorders on the course of bipolar disorder: A review.	Substance abuse	NO	1964-1998
32	(P. E. J. Keck & McElroy, 1996)	Outcome in the pharmacologic treatment of bipolar disorder.	Quality of life, response, relapse	NO	1967-1996
33	(Morriss et al., 2007)	Interventions for helping people recognize early signs of recurrence in bipolar disorder.	Recurrence	NO	1968-2005
34	(Rusner, Berg, & Begley, 2016)	Bipolar disorder in pregnancy and childbirth: a systematic review of outcomes.	Pregnancy outcomes	YES	
35	(Fiedorowicz, Murray, Weiner, & Prabhakar, 2009)	Mania and mortality: why the excess cardiovascular risk in bipolar disorder?.	Heart disease, cardiovascular risk	NO	1986-2009
36	(Michalak et al., 2005)	Quality of life in bipolar disorder: a review of the literature.	Quality of life	YES	1965-2004
37	(Nielsen, Kessing, Nolen, & Licht, 2018)	Lithium and Renal Impairment: A Review on a Still Hot Topic.	Medical outcome, renal failure	NO	1992-2018

38	(Demissie et al., 2018)	Psychological interventions for bipolar disorder in low- and middle-income countries: Systematic review.	Number of relapses or recurrence, severity of mood symptoms, treatment adherence, quality of life, functional status, number of hospital admissions, knowledge and attitudes about bipolar disorder, and stigma and biological rhythms.	YES	2003-2017
39	(Kessing et al., 2018)	Effectiveness of maintenance therapy of lithium vs other mood stabilizers in monotherapy and in combinations: a systematic review.	Hospitalization/rehospitalization, treatment failure, recurrence, composite measure	YES	1974-2017
40	(Macritchie et al., 2003)	Valproate for acute mood episodes in bipolar disorder.	Efficacy of treatment, general health and social functioning, acceptability of valproate treatment, adverse effects, mortality rates	YES	1966-2002
41	(Vieta et al., 2018)	Early intervention in Bipolar disorder.		NO	1977-2017
42	(Cipriani, Reid, Young, Macritchie, & Geddes, 2013)	Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder.	Efficacy of valproate in preventing/attenuating further episodes of affective disorder, acceptability of treatments, adverse effects, general health and social functioning, mortality rates and deliberate self-harm	YES	1967-2013
43	(Ketter, Miller, Dell'Osso,	Treatment of bipolar disorder: Review of evidence regarding	Efficacy, safety/tolerability	NO	1999-2016

	& Wang, 2016)	quetiapine and lithium.			
44	(Prajapati, Wilson, & Maidment, 2016)	Efficacy and safety of second-generation antipsychotic long-acting injections (SGA LAIs) in maintenance treatment of bipolar disorder	Primary efficacy outcome: relapse rate or delayed time to relapse or reduction in hospitalization. Primary safety outcome: drop-out rates or all-cause discontinuation or discontinuation due to adverse events. Secondary outcomes may include changes in BDRS or YMRS, discontinuation due to hospitalization and non-adherence, safety outcomes of SGA LAIs (e.g., EPSEs and metabolic adverse effects).	YES	2000-2016
45	(Pigott et al., 2016)	Topiramate for acute affective episodes in bipolar disorder in adults	Efficacy of topiramate in the treatment of acute mood episodes in bipolar disorder, acceptability, response to treatment, remission	YES	1950-2015
46	(Li, Tang, Wang, & de Leon, 2015)	Clozapine for treatment-resistant bipolar disorder: A systematic review	Social functioning, hospital days/year, mean number of admissions	YES	1991-2015
47	(Conus, Macneil, & Mcgorry, 2014)	Public health significance of bipolar disorder: Implications for early intervention and prevention	Functional outcomes, work outcomes, social outcomes	NO	1979-2013

48	(Vita, De Peri, Siracusano, & Sacchetti, 2013)	Efficacy and tolerability of asenapine for acute mania in bipolar 1 disorder: Meta-analyses of randomized-controlled trials	Efficacy and tolerability, safety, clinical effect on mood changes	NO	1966-2013
49	(Silva, Zimmermann, Galvao, & Pereira, 2013)	Olanzapine plus fluoxetine for bipolar disorder: A systematic review and meta-analysis	Quality of life, relapse, hospitalization for psychiatric reasons, suicidal ideation/attempt, discontinuation/discontinuation due to mania, adverse effects, weight change	YES	1987-2012
50	(Bowden et al., 2012)	Aims and Results of the NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)	Suicidality, functional status, recovery, relapse, caretaker burden	NO	1990-2010
51	(Sanford & Keating, 2012)	Quetiapine: A review of its use in the management of bipolar depression	Measures of symptoms (YMRS and MADRS), global functioning (CGI-BD-S and CGI-BD-GI), cognitive functioning (MOS-COG), work functioning	NO	1999-2012
52	(Chiesa, Chierzi, De Ronchi, & Serretti, 2012)	Quetiapine for bipolar depression: A systematic review and meta-analysis	Clinical recovery, quality of life, medication side effects	YES	1999-2011
53	(McFarlane, Dixon, Lukens, & Lucksted, 2003)	Family interventions for bipolar disorder: A review of the literature	Recurrence, relapse, manic and depressive symptoms, medication adherence, problem-solving functional impairment	NO	1963-2002

54	(Vasudev, Macritchie, Rao, Geddes, & Young, 2011)	Tiagabine in the maintenance treatment of bipolar disorder	1) Efficacy of tiagabine treatment in preventing or attenuating further episodes of bipolar disorder, including its efficacy in rapid cycling disorder. 2) Acceptability of tiagabine treatment. 3) Prevalence of side effects. 4) Mortality on tiagabine treatment.	YES	1967-2011
56	(V.L., 2011)	Cognitive-behavioral therapy for comorbid bipolar and substance use disorders: A systematic review of controlled trials	Outcome measures include efficacy of treatment for manic episodes, mixed affective episodes, and depressive episodes; psychological, social, and occupational functioning; acceptability of treatment; adverse effects; mortality rates.	YES	1994-2010
57	(Ceron-Litvoc, Soares, Geddes, Litvoc, & de Lima, 2009)	Comparison of carbamazepine and lithium in the treatment of bipolar disorder: A systematic review of randomized controlled trials	Withdrawal due to adverse effects, subjects with at least one adverse effect, improvement at CGI scale, need for rescue medication	YES	1979-2008
58	(Berk et al., 2010)	Evidence and implications for early intervention in bipolar disorder	Consolidation of identity and self-confidence, development of autonomy and separation from parents, development of sexual and close peer relationships, educational and vocational achievement	NO	1987-2009

59	(Van Lieshout & MacQueen , 2010)	Efficacy and acceptability of mood stabilizers in the treatment of acute bipolar depression: Systematic review	Rates of response, remission, all-cause discontinuation, affective switching, suicidal behavior, clinically significant weight gain	YES	1999-2017
60	(Cipriani, Rendell, & Geddes, 2010)	Olanzapine in the long-term treatment of bipolar disorder: A systematic review and meta-analysis	Efficacy of olanzapine in preventing further episodes, time to relapse, admission to hospital, overall withdrawal rate, adverse effects, all-cause mortality, suicide rates	YES	1997-2008
61	(Miklowitz, 2008)	Adjunctive psychotherapy for bipolar disorder: State of the evidence	Time to recovery, recurrence, duration of episodes, symptom severity, psychosocial functioning	NO	1984-2008
62	(El-Mallakh & Hollifield, 2008)	Comorbid anxiety in bipolar disorder alters treatment and prognosis	Likelihood of recovery, social and occupational functioning, quality of life, time euthymic, suicide attempts, likelihood of substance abuse	NO	1983-2007
63	(Cipriani et al., 2006)	Lithium versus antidepressants in the long-term treatment of unipolar affective disorder	Primary outcome: relapse/recurrence of affective episodes. Secondary outcomes: quality of life, global clinical impression, social functioning, occupational functioning, adverse effects, mortality rates, acts of deliberate self-harm	YES	1968-2005

64	(Revicki, Matza, Flood, & Lloyd, 2005)	Bipolar disorder and health-related quality of life: Review of burden of disease and clinical trials	Health-related quality of life measured by the 36-Item Short-Form Survey	NO	1978-2002

Table:2.2 Comparison between outcomes set and recurrence in the literature

No.	Outcome	Recurrence in the Literature
1	Clinical Recovery of Bipolar Symptoms	38
2	Quality of Life	28
3	Connectedness	22
4	Suicide	15
5	Hospitalization	13
6	Medication Effects	15
7	Personal Recovery	14
8	Physical Health	14
9	Self-monitoring and Management	12
10	Pregnancy Outcomes	2
11	Mental Health and Wellbeing	2
12	Service Outcomes	0
13	Experience of Care	0
14	Use of Coercion	0

Discussion

The analysis of the reviewed literature revealed that the most common outcome examined is clinical recovery. Clinical recovery encompasses various aspects, such as the experience of paranoia, delusions, anxiety, depression, unusual behaviour, elevated mood, and the individual's relapse or recovery response. The substantial number of reviews focusing on clinical recovery can be attributed to the significance of clinical features and medical symptoms in trials. This prevalence may be attributed to the availability of standardized and replicable scales that primarily assess the medical aspects of the illness.

Quality of life (QoL) emerges as the second most frequently measured outcome in bipolar disorder (BD) literature. QoL, as described by the World Health Organization (WHO), refers to individuals' perception of their position in life in relation to cultural and value systems, goals, expectations, standards, and concerns (The WHOQOL Group., 1995). Although QoL has been extensively evaluated in various illnesses, there appears to be a dearth of information specifically regarding QoL in BD. The limited attention given to QoL research in BD may be due to the absence of a disease-specific QoL measure for bipolar populations, as well as concerns about the reliability and accuracy of self-report measures completed by individuals with BD, particularly during manic phases (Michalak, Yatham, & Lam, 2005).

Functional assessment has recently gained prominence in BD research. A recent review by Chen, Fitzgerald, Madera, and Tohen (2019) identified twenty-four different functional scales, including clinician-rated scales, self-reported scales, and indices based on residential and vocational data. (Chen, Fitzgerald, Madera, & Tohen, 2019) Among these, the Global Assessment of Functioning (GAS) and the Functional Assessment Short Test (FAST) were the most commonly employed global and domain-specific scales, respectively. The increasing interest in assessing functioning in BD patients, with a focus on specific domains such as work/educational, social, family, and cognitive functioning, stems from the realization that mere symptom counts or time to relapse or recurrence do not necessarily reflect functional recovery and overall patient well-being (Gitlin & Miklowitz, 2017). This review highlights the significant gap that persists in the assessment of both clinical and functional outcomes. Interestingly, more than three-quarters of the reviews considered in this analysis solely focused on the clinical aspects of BD, completely neglecting three important outcomes valued by patients and clinical professionals: service outcomes, experience of care, and the use of coercion.

Outcome research in bipolar disorder is an emerging field of study. Clinical and pharmacological outcomes have received the most attention compared to socio-functional outcomes such as connectedness, experience of care, service outcomes, and self-monitoring

and management. Quality of life has also been extensively investigated in bipolar patients. However, there is a lack of studies that simultaneously consider both functional and clinical outcomes. In recent years, Personalized Medicine has emerged as a new paradigm, facilitated by technologies like throughput genomics, which have allowed for unprecedented investigations into various aspects of illnesses. Significant efforts have been dedicated to elucidating the genetic basis of psychiatric disorders like BD. However, genomic research on outcomes in BD appears to be limited at present, with only a few genome-wide association studies (GWAS) published in the outcomes field. Of note, the only outcome that has been investigated by two GWAS is lithium treatment response (Song et al., 2016); (Hou et al., 2016).

The review sheds light on the nuanced nature of outcomes within the realm of bipolar disorder, revealing a notable lack of precise conceptual boundaries. Despite being integral to both research and clinical practice, the term "outcome" lacks definitive delineation, leading to ambiguity in its interpretation and measurement. Through its comprehensive collation of potential outcomes associated with bipolar disorder, the review represents a pioneering effort, offering a holistic perspective on the disorder's multifaceted impacts.

Within the spectrum of identified outcomes, varying degrees of robustness and clarity emerge. Outcomes related to treatment response exhibit considerable robustness, owing to the structured design of pharmacological studies focused on evaluating therapeutic efficacy. These outcomes benefit from clear operational definitions and standardized measurement tools, contributing to their reliability and comparability across studies. Similarly, symptomatic outcomes, particularly those assessed by healthcare professionals using validated rating scales endorsed by the scientific community, demonstrate high levels of robustness.

Conversely, outcomes reliant on self-reporting by patients and those embedded within community-based assessments display lower levels of robustness. The variability in terminology used to describe similar aspects of patient-reported outcomes underscores the challenges in standardizing measurement instruments and interpretation criteria. Such less robust outcomes highlight the need for ongoing efforts to validate and standardize measurement tools, thereby enhancing their utility in both research and clinical practice.

These findings carry implications for both research and clinical settings. In research, attention should be directed towards refining measurement instruments for less robust outcomes, thereby bolstering their reliability and validity. Clinically, an awareness of the varying degrees of robustness among different outcome measures can inform treatment decision-making and prognostic assessments. Moving forward, collaborative endeavours within the scientific community are essential to establishing consensus guidelines for outcome assessment in bipolar disorder research and clinical care.

As illuminated by Figure 2.1, there is not a complete overlap between the research-based and community-based outcome sets. Upon closer examination of the individual reviews incorporated in this review of reviews, it becomes increasingly apparent that research focused on the clinical-pathological aspects of the disorder and research centered on the patient's perspective and needs operate as two distinct, non-communicative compartments. This revelation serves as a catalyst for the analysis and objectives of the current thesis, aiming to provide a more comprehensive, nuanced, and holistic approach to understanding outcomes in bipolar disorder.

In conclusion, this review of reviews on outcomes in bipolar disorder offers several strengths and limitations that warrant discussion. The comprehensive overview provided by synthesizing findings from multiple reviews allows for a broader understanding of the outcomes investigated in the field. By including a diverse range of outcomes, such as clinical recovery, quality of life, and hospitalization, this review captures the multifaceted impact of bipolar disorder on individuals and the healthcare system. Additionally, the inclusion of various study designs enhances the robustness and reliability of the conclusions drawn. Moreover, the emphasis on patient-centred outcomes reflects the perspectives and needs of individuals living with bipolar disorder. Importantly, this review identifies research gaps, highlighting areas such as service outcomes, experience of care, and use of coercion that require further investigation. This review also has some limitations, such as the potential for outcome recurrence due to certain outcomes being cited more frequently in multiple reviews. With the inclusion of more recent reviews, in fact, there appears to be a trend wherein older outcomes receive increased attention simply because they are recurrent in the literature

referenced by each subsequent review. Nevertheless, the strengths of this review, including its comprehensive overview, identification of research gaps, and potential to guide future research and clinical practice, make it a valuable resource for advancing the understanding and management of bipolar disorder outcomes. Further research is warranted to address the identified limitations and to continue building on the knowledge obtained from this review.

Chapter 3: Longitudinal mood monitoring in bipolar disorder

1.3 INTRODUCTION:

Bipolar Disorder is typically considered a recurrent disorder characterized by episodes of mood elevation or depression that alternate with periods of euthymia (Grande, Berk, Birmaher, & Vieta, 2016). However, many subjects experience subsyndromal and persistent mood symptoms even during inter-episode periods. Some studies have shown that more than half of subjects report residual symptoms for both mania (68%) and depression (54%) (Keitner et al., 1996).

The presence of persistent symptoms in over 50% of subjects characterizes BD as a chronic disorder. Therefore, assessing and attempting to predict chronicity in BD is crucial for subject care.

There are contrasting and not fully consistent definitions of chronicity in BD present in the literature. Some studies define chronicity based on the total length of the disease experienced by subjects (Turvey et al., 1999), while others define it based on the number of experienced episodes (Fagiolini et al., 2013).

Identifying a phenotypic aspect that describes the chronicity and burden of bipolar disorder could be of extreme importance in improving the lives of affected individuals. Having such a diagnosis and being able to predict the onset, course, and outcomes (both clinical and social) is crucial for clinicians to better plan clinical follow-up and for subjects to have realistic expectations for their future lives.

The True Colours (TC) project is part of the Bipolar Disorder Research Network (BDRN), a large-scale research initiative that aims to improve the understanding and treatment of bipolar disorder. TC collects longitudinal data from bipolar disorder subjects by sending them weekly prompts to answer questionnaires about their mood. For each subject enrolled in TC, retrospective data about their clinical history are also available through the BDRN project. This provides a unique opportunity to compare the course of the disorder in both retrospective and prospective studies, without the bias of studying different cohorts of affected individuals.

The validity of TC data has been widely acknowledged, and it has been used to analyse and describe various clinical aspects of bipolar disorder. Previous research using the True Colours mood monitoring system focused on the phenotypic aspects of the disorder, and no genotype-phenotype associations have been described thus far.

On November 16th, 2019, a literature search yielded 19 studies that utilized TC data, spanning from 2012 to 2019, with sample sizes ranging from 8 to 5719 participants. While some studies focused on describing the system and assessing its feasibility and utility (Miklowitz et al., 2012) (Tsanas et al., 2017); (Simon, Budge, Price, Goodwin, & Geddes, 2017);(Gordon-Smith et al., 2019), others investigated various aspects of bipolar disorder. These included mood dynamics and illness course (Moore, Little, McSharry, Goodwin, & Geddes, 2014);(Kormilitzin, Saunders, Harrison, Geddes, & Lyons, 2017);(Tsanas et al., 2017);(McKnight et al., 2017), diurnal rhythms (Carr et al., 2018), psychoeducation (Bilderbeck et al., 2016), Imagery-Focused Cognitive Therapy (Hales et al., 2018), severity prediction of episodes (Vazquez-Montes, Stevens, Perera, Saunders, & Geddes, 2018) and detection of bipolar depression from geographic location data (Palmius et al., 2017).

Longitudinal data can be extremely helpful in detecting mood variations, and TC provides an ideal framework for tracking weekly mood changes in individuals with bipolar disorder.

Using TC data makes it possible to describe an aspect of bipolar disorder that is difficult to capture through retrospective evaluation of a subject's clinical history, by allowing prospective monitoring of the mood on weekly intervals. By using quantitative scales and

weekly interval, TC can capture more subtle mood variations that don’t meet the diagnostic criteria for a mood episode.

The objectives of this study were firstly to investigate and describe the course of illness in the time window in which subjects were enrolled in the TC project. To achieve this, new outcome variables were generated. These variables described the proportion of time spent with a certain symptom (mania, depression, mixed status) based on subjects' responses to the mood questionnaires.

Secondly, the study aimed to explore the correlation between the course of illness variable generated through TC data and the course of illness in the BDRN retrospective cohort. This allowed for a comparison of the course of illness between these two different data sources, and enabled researchers to evaluate the potential utility of TC data in predicting the course of illness in bipolar disorder subjects.

Overall, this study provides valuable insights into the use of TC data in understanding the course of bipolar disorder. By generating new outcome variables that describe the proportion of time spent with a certain symptom, this study offers a new perspective on the course of illness in bipolar disorder subjects. Additionally, by comparing TC data with retrospective data from the BDRN cohort, this study sheds light on the potential utility of TC data in predicting the course of illness in bipolar disorder subjects.

2.3 METHODS

1.2.3 Sample:

The present study included 653 BDRN participants, who were enrolled in the True Colour mood monitoring between March 3rd, 2015, and September 22nd, 2019, and for whom genomic data was available.

Further inclusion criteria comprised a diagnosis of Bipolar Disorder Type 1 (BD1), Bipolar Disorder Type 2 (BD2), Schizoaffective Bipolar Disorder (SA BD), or Bipolar Disorder Not Otherwise Specified (BD NOS) and a minimum disease duration of 2 years.

TC sends weekly email or message prompts to participating individuals, asking them to complete the Quick Inventory of Depressive Symptomatology (QIDS) and Altman Self-Rating Mania Scale (ASRMS), either on their mobile phone or computer. Subjects can choose the day and time to receive the prompt to respond to the questionnaires. If no response is received within 24 hours, a second prompt is sent.

-The Quick Inventory of Depressive Symptomatology (QIDS-SR) is a self-report questionnaire comprising 16 items, originally developed by (Rush et al., 2003) to assess depressive symptoms. This widely utilized rating scale aligns with DSM-IV criteria for major depressive disorder (MDD), rendering it a valuable tool for evaluating and monitoring depressive severity across diverse patient populations. While initially tailored for assessing depressive severity in MDD, the QIDS-SR has since found application across a broad spectrum of patient cohorts(Cameron et al., 2013);(Ma et al., 2015).

Internal consistency analysis yielded a Cronbach's α coefficient of 0.86 for the QIDS-SR16, indicating satisfactory reliability. Moreover, QIDS-SR16 scores demonstrated strong correlations with IDS-SR30 ($r = 0.96$) and HAM-D24 ($r = 0.86$) scores.

The questionnaire's items correspond to the nine symptom criterion domains outlined in DSM-IV, encompassing areas such as sleep disturbance (including initial, middle, and late

insomnia or hypersomnia), sad mood, changes in appetite or weight, concentration, self-criticism, suicidal ideation, interest, energy or fatigue, and psychomotor agitation or retardation.

Based on the total score, the severity of depression can be categorized as follows: scores of 1-5 indicate no depression, 6-10 indicate mild depression, 11-15 indicate moderate depression, 16-20 indicate severe depression, and 21-27 indicate very severe depression.

-The Altman Self-Rating Mania Scale (ASRM), developed by Altman et al. (1997) assesses the presence of manic symptoms.
The Altman Self-Rating Mania Scale (ASRM) comprises five distinct categories of questions, each designed to assess a particular manic symptom, including elevated mood, inflated self-esteem, decreased need for sleep, pressured speech, and psychomotor agitation. Respondents rate the severity of each item on a scale ranging from 0 (absent) to 4 (present to a severe degree).
Internal consistency analysis yielded a Cronbach's α coefficient of 0.895 indicating satisfactory reliability. ASRM is highly correlated with YMRS ($r = 0.856$, $p < 0.0005$).

The ASRM yields scores ranging from 5 to 25, with elevated scores correlating with heightened severity of manic symptoms. A threshold of 6 or above suggests a heightened likelihood of manic or hypomanic states, potentially warranting treatment intervention or additional diagnostic evaluation. Conversely, scores of 5 or lower are less indicative of pronounced manic symptomatology.

2.2.3 Outcome variables generation in TC:

Proportion of time spent with a certain mood symptom. The proportion of time spent with a certain mood symptom was used to generate outcome variables in TC. All calculated indexes were based on the ASRM (a) and QIDS (q) scores previously published in the literature. Both ASRM and QIDS scales were developed as screening tools, and the published cut-offs for these scales are based on screening studies. To select the best threshold that could describe the mood states in subjects, the following thresholds were applied: a5-q5, a10-q10, a10-q15, and a5-q10. After an initial analysis (see Appendix table A), the a10-q10 thresholds were selected for all subsequent analyses. These cut-offs were chosen for several reasons: the calculated variables using a10-q10 thresholds had a better correlation with the retrospective data in BDRN, and the time spent with a certain mood symptom by subjects in this cohort was in agreement with other studies that did similar calculations of time spent ill, last because the aim was to identify a well-defined boundary between the presence and absence of symptoms.

The following descriptors were obtained:

- Proportion of time spent with any mood symptom (as a percentage)
- Proportion of time spent without symptoms (as a percentage)
- Proportion of time spent with manic symptoms (as a percentage)
- Proportion of time spent with depressive symptoms (as a percentage)
- Proportion of time spent in mixed states (as a percentage)

To generate these indexes, a complete weekly calendar was created for each subject, and the days with symptoms were counted based on the QIDS and ASRM symptom ratings from the previous week. The percentage of time spent with any mood symptom was calculated as the ratio between the number of days with symptoms and the total number of days enrolled for each subject. All responses were included in the final count, but only the 7 days prior to the last available data were considered, and only the days between two responses were counted if a subject responded more than once a week.

It's important to note that these variables do not refer to the number of mood episodes experienced by subjects during the enrolment period. Instead, they identify periods of high or low mood based on the ASRM and QIDS scales. It is worth noting that the QIDS and ASRM scales specifically refer to the mood state experienced in the preceding seven days. Therefore, for each response, only the seven days prior to the given response are taken into account.

3.2.3 Missing data:

Participation in TC is completely voluntary, and subjects have the freedom to choose whether or not to respond to weekly prompts. In this study, a list-wise deletion approach was utilized to address the issue of missing data. As a result, only the time periods for which actual data are available were considered. If subjects do not respond every week, the days for which no data is available (NAs) are excluded from the final count.

While imputing missing data could be considered as an option, given the constraints and characteristics of the dataset, it was deemed preferable to proceed without imputation.

I chose not to impute the data for several reasons:

-The sample size was relatively small, and imputing missing data could potentially introduce bias into the analysis by relying on estimated values rather than actual observations.

-The sample exhibited heterogeneity in terms of diagnosis and sex distribution, making it difficult to accurately impute missing values that reflect the true characteristics of the population.

-The response time varied among subjects, and imputing responses based on data from participants who responded for longer periods may skew the results and lead to erroneous conclusions.

-The original study protocol specified a minimum response duration of three months, and since the analysed sample met this criterion, there was no need for imputation. Additionally, non-responders or individuals who refused enrolment were not included in the analysis.

4.2.3 BDRN variables:

In line with the previous definition of chronicity, specific retrospective variables from the BDRN were selected to describe the course of illness from various perspectives. For this analysis, the variables chosen were those that describe the length of the disease at the time of enrolment in the BDRN, the number of episodes per year, and the eventual presence or absence of rapid cycling. All these variables are defined as follows:

Disease duration: This derived variable is expressed in years and is calculated as the time elapsed between the onset of symptoms and the enrolment date.

Episode duration: Two items describe the longest episodes of both mania and depression. In the original dataset, the length of each episode is coded in weeks. The integer gives the number of weeks, and when present, the first and second decimals represent the number of days and hours.

Number of episodes: Two items provide the lifetime number of episodes of mania and depression. A derived item is the total number of episodes, which is the sum of the manic and depressive episodes lifetime.

Rapid cycling: This variable is assessed through a Likert scale comprising four classes of participants, wherein (1) rapid cycling is not present or suspected despite a period of observation of illness that includes at least 7 years from onset and at least 3 episodes of mood disorder, (2) rapid cycling is not present or suspected despite a period of observation of illness that includes less than 7 years from onset or fewer than 3 episodes of mood disorder, (3) rapid cycling predominates the course of illness and has been present for at least 5 years during the total course of the illness, and (4) there is insufficient information to allocate the subject in the previous classes. This rating is used if there has been no rapid cycling, but there have been less than 7 years from the onset of illness and/or fewer than 3 episodes of mood disorder. For this analysis, the subjects have been divided into two groups: rapid cycling YES (class 3) and rapid cycling NO (class 1-2-4).

5.2.3 Statistical analysis:

Statistical analysis was conducted using the R software environment. The Kruskal-Wallis test was utilized to evaluate differences between diagnosis groups, with p-values being reported. Kendall's tau correlation was employed to compare the descriptors derived in the therapeutic community (TC) with the total number of episode years, Rapid Cycling, Longest duration Depression, Longest duration Mania, and Disease duration in the Bipolar Disorder Research Network (BDRN). The corresponding z and p-values were also reported.

Kendall's Tau, a non-parametric statistic, serves as a measure of association between columns of ranked data. The Tau correlation coefficient ranges from 0 to 1, reflecting the strength of relationship between variables, with 0 denoting no association and 1 indicating a perfect correlation. This statistic is particularly useful in situations where the assumptions of parametric correlation measures like Pearson's correlation coefficient are not met, offering a robust alternative for assessing relationships in ranked datasets.

All of the aforementioned analyses were performed on the entire TC sample and the two primary subgroups of diagnoses: BD1 and BD2. Furthermore, the same analysis was conducted on all subgroups determined by the length of enrolment, including the total sample, responders with less than 1 year of enrolment, responders with more than 1 year of enrolment, responders with 1.5 years of enrolment, and responders with 2 years of enrolment.

3.3 RESULTS:

1.3.3 Sample description:

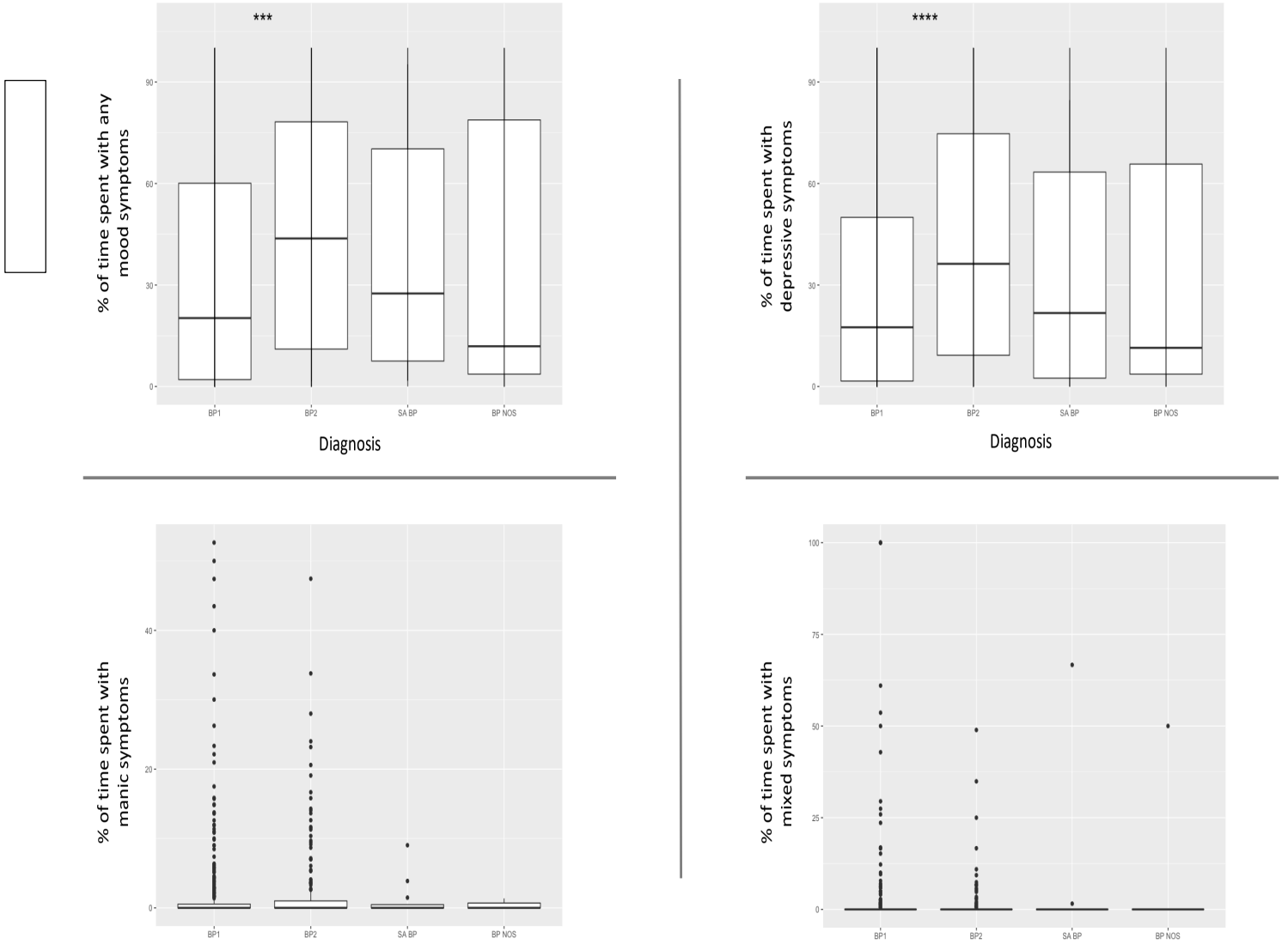
Out of the 1020 subjects recorded in the TC database, a total of 653 individuals have been genotyped and thus, were included in the current study. The sample comprises 401 subjects diagnosed with BD1 and 228 subjects diagnosed with BD2. Notably, there exists a marked difference in the distribution of sex among the participants, with 182 male and 447 female subjects. When the analysis was stratified by diagnosis, the distribution of male/female subjects was found to be 118/283 for BD1 and 64/164 for BD2.

With regards to response time, among the total sample, 285 participants responded for a period shorter than one year, 368 responded for more than one year, 294 responded for more than one year and a half, and 232 responded for more than two years. When stratified by diagnosis, the response time distribution for BD1 and BD2 was as follows: 168 and 109 for less than one year, 233 and 119 for more than one year, 183 and 98 for more than one year and a half, and 144 and 76 for more than two years, respectively.

Proportion of time spent with a certain mood symptom:
When the proportion of time spent in each mood state was analysed. The results showed that in the entire sample, most of the time was spent in euthymia (68.93%), followed by depression (28.17%), mania or hypomania (2.02%), and mixed states (0.88%). Figure 1 displays these results visually.

Further analysis was conducted to compare the two principal diagnosis groups, BD1 and BD2. The mean total proportion of time spent with mood symptoms was found to be significantly different between the two groups (33.26% vs 45.55%, p=1.8x10-4). Additionally, a significant difference was observed in the time spent in depression between BD1 and BD2 (25.08% vs 33.96%, p=1.06x10-5).

*Figure 1.3. Distribution of Percentage of Time Spent in Different Mood States (Total, Depressive, Manic, and Mixed) Across DSM-IV Diagnoses (BD1, BD2, SA BD, and BD NOS). Statistically Significant Differences are Marked as *** (P< 000.1).*



Proportion of time of time spent with a certain mood symptom and correlation with BDRN variables (Table 1.2)

When examining the correlations between the proportion of time spent with mood symptoms and temporal variables in the BDRN database, the strongest correlation is observed with the total number of episodes per year in the entire database. This correlation remains significant even when considering the two diagnoses separately, with a stronger correlation for BD1 compared to BD2 (tau=0.25 and 0.21, p=1.82xE-12 and 1.96xE-5). The strength of the association increases when subjects are stratified according to the length of response, with a weaker correlation observed in the group responding for less than one year and a stronger correlation in subjects responding for more than two years. Table 1.1 displays the correlation between the proportion of time spent in a particular mood state and the retrospective temporal items assessed in the BDRN dataset.

History of rapid cycling was also strongly correlated with prospective presence of mood symptoms. This correlation persists when the two diagnoses are considered separately, with the strongest correlation in BD1 versus BD2(tau=0.22 and 0.23, p=1,57xE-06 and 1.95E-04). This correlation was significant regardless the length of enrolment in TC, although it increases in the groups of subjects enrolled in the TC programme for a longer period. Weaker correlations are observed between the proportion of time spent with mood symptoms and the longest duration of depression, longest duration of mania, and total illness duration.

Similar patterns of correlation are observed between the proportion of time spent with mood symptoms and the total manic or depressive episodes per year which persist when the sample is stratified into the two diagnoses BD1 and BD2. Once again, the strength of correlation is higher in BD1 and increases when the analysis is conducted in the time of response subgroups. The correlation is more significant for manic episodes than for depressive ones (Appendix tables B).

Correlation of % of time spent in a mood state in TC2019 with other temporal items in BDRN	a10q10														
	Total episodes year			Rapid cycling			Longest duration Depression			Longest duration Mania			Disease duration		
	z	p	tau	z	p	tau	z	p	tau	z	p	tau	z	p	tau
Whole sample	9.22	< 2.2e-16	0.26	6.84	7.94E-12	0.21	2.15	0.03	0.06	-0.97	0.33	-0.03	-1.68	0.09	-0.05
Whole sample responders for more than 1 year	7.67	1.75E-14	0.28	4.93	8.27E-07	0.20	1.88	0.06	0.07	-1.56	0.12	-0.06	-1.47	0.14	-0.05
Whole sample responders for more than 1.5 year	7.26	3.92E-13	0.30	4.68	2.88E-06	0.21	1.99	0.05	0.08	-1.44	0.15	-0.06	-2.09	0.04	-0.08
Whole sample responders for more than 2 year	6.56	5.33E-11	0.31	3.86	0.0001146	0.20	1.45	0.15	0.07	-1.22	0.22	-0.06	-2.44	0.01	-0.11
Whole sample responders for less than 1 year	4.84	1.28E-06	0.22	4.80	1.57E-06	0.22	1.16	0.25	0.05	0.29	0.77	0.01	0.18	0.85	0.01
All BP1	7.05	1.82E-12	0.25	5.55	2.86E-08	0.22	3.35	0.00	0.13	0.95	0.34	0.04	-0.56	0.57	-0.02
BP1 responders for more than 1 year	6.43	1.29E-10	0.30	4.46	8.25E-06	0.23	2.28	0.02	0.11	-0.40	0.69	-0.02	-0.07	0.95	0.00
BP1 responders for more than 1.5 year	6.26	3.91E-10	0.33	4.25	2.10E-05	0.25	2.14	0.03	0.12	-0.07	0.94	0.00	-0.40	0.69	-0.02
BP1 responders for more than 2 year	6.09	1.10E-09	0.36	4.13	3.63E-05	0.27	1.58	0.11	0.10	-0.05	0.96	0.00	-0.33	0.74	-0.02
BP1 responders for less than 1 year	3.45	5.69E-04	0.20	3.73	0.000195	0.23	2.38	0.02	0.14	1.69	0.09	0.11	0.04	0.96	0.00
All BP2	4.27	1.96E-05	0.21	3.01	0.002585	0.16	-0.39	0.70	-0.02	-1.23	0.22	-0.06	-1.44	0.15	-0.07
BP2 responders for more than 1 year	3.18	0.001488	0.21	1.85	0.06501	0.13	0.34	0.73	0.02	-1.20	0.23	-0.08	-1.78	0.07	-0.12
BP2 responders for more than 1.5 year	3.00	0.002671	0.22	2.11	0.03521	0.17	0.40	0.69	0.03	-1.44	0.15	-0.11	-2.30	0.02	-0.16
BP2 responders for more than 2 year	2.38	0.01716	0.20	1.13	0.2589	0.10	0.39	0.69	0.03	-1.21	0.22	-0.11	-2.74	0.01	-0.23
BP2 responders for less than 1 year	2.44	1.45E-02	0.18	2.09	0.03671	0.16	-0.66	0.51	-0.05	-0.59	0.55	-0.04	0.38	0.70	0.03

Table 1.3: Correlation between the percentage of time spent in a mood state in the TC program and other temporal variables in the BDRN dataset, using Kendall's tau. Correlations are reported for the entire sample, as well as for the BD1 and BD2 subgroups based on response time.

2.3.3 Illness course using cross-sectional, lifetime variables

After finding that the variable "proportion of time spent with any mood symptom" had a stronger correlation with the BDRN variable "Total number of episodes/year," than the other temporal variables considered, the analysis was focused on the retrospective dataset, considering only those subjects who participated in TC as well. To better describe the course of the disorder, a new variable was generated in the BDRN dataset. This variable was the ratio between the number of episodes of mania and the number of episodes of depression, describing the overall mood polarity of the subject.

An inverse correlation was observed between the number of episodes per year in BDRN (expressed in log) and the disease duration, with subjects having a shorter disease duration experiencing fewer episodes than those with a longer disease duration. Neither sex nor diagnosis impacted this correlation, as shown in Figure 2.2 and Figure 3.2 The same correlation was observed when the number of manic and depressive episodes was considered separately (Appendix 2).

When comparing the number of episodes per year in BDRN with the prevalent polarity of the subject (defined as the ratio between the number of manic and depressive episodes), a similar pattern emerged regarding sex, but an opposite behaviour was observed between BD1 and BD2 subjects. BD1 subjects with more than one episode/year tended to have more depressive episodes, while BD2 subjects with more than one episode/year tended to report more episodes of hypomania (Figure 3.2, Figure 5.2).

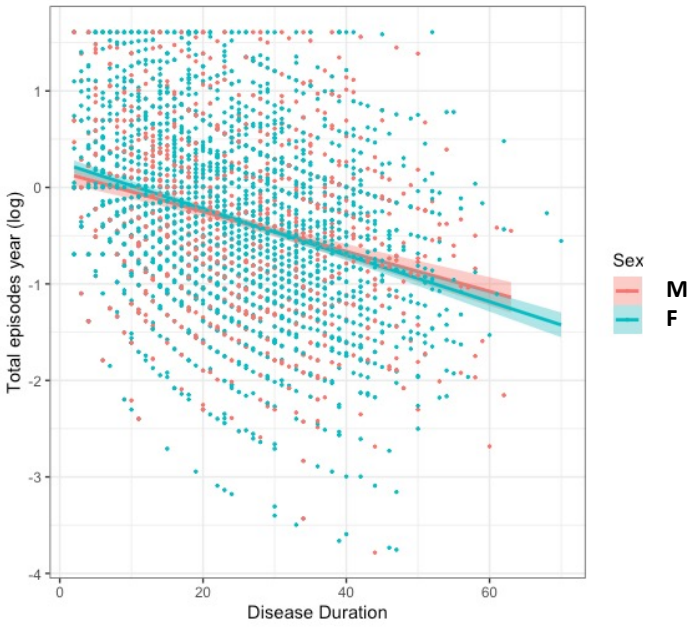


Figure 2.3 Scatter plot showing the linear correlation between two variables in the BDRN dataset, log of the total number of episodes/year and disease duration, according to sex.

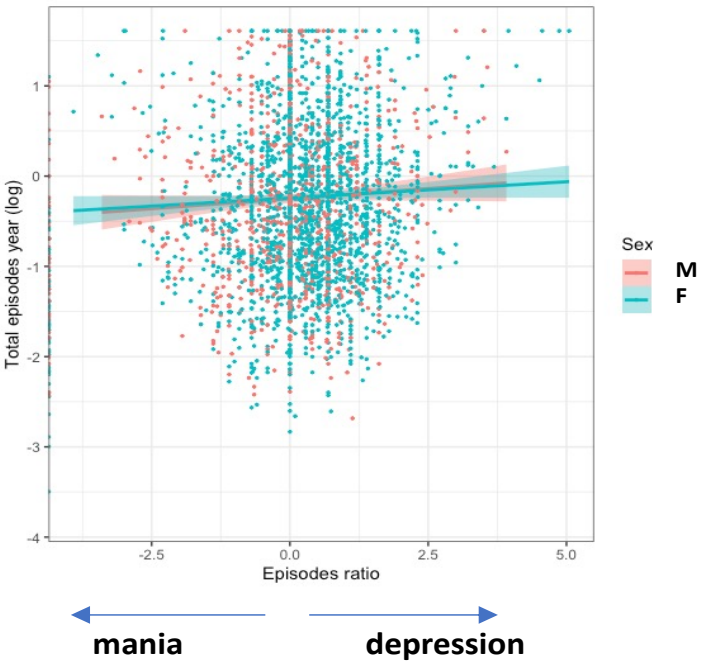


Figure 3.3 Scatter plot showing the linear correlation between the log of the total number of episodes/year in the BDRN and the episode ratio, defined as the ratio between the number of manic and depressive episodes, according to sex.

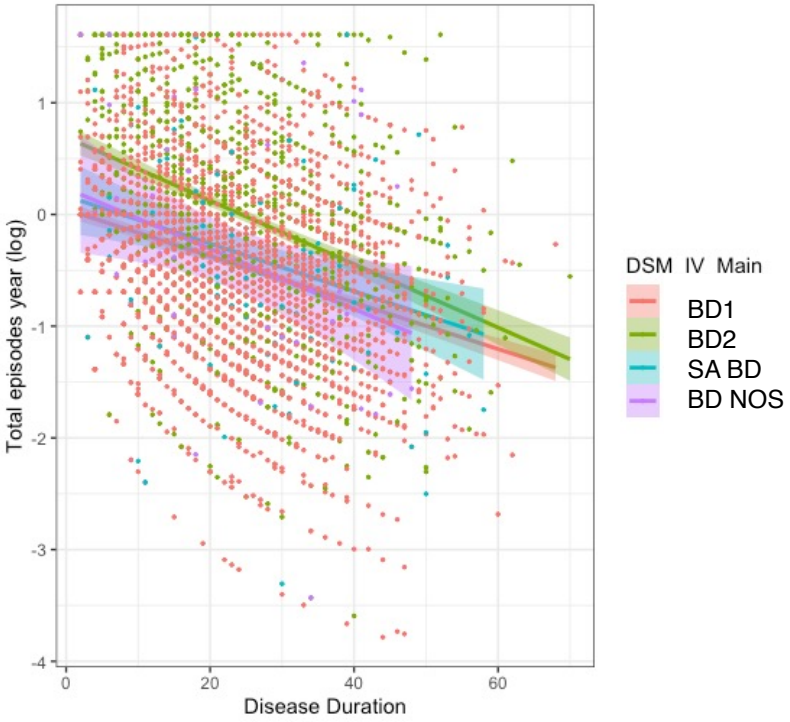


Figure 4.3 Scatter plot showing the linear correlation between two variables in the BDRN dataset, log of the total number of episodes/year and disease duration, according to diagnosis.

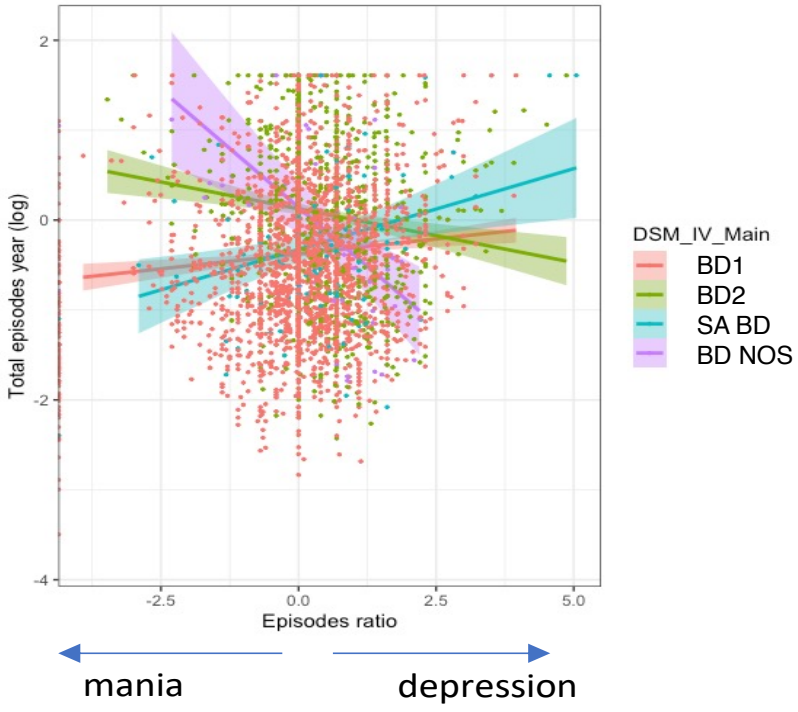


Figure 5..3 Scatter plot showing the linear correlation between the log of the total number of episodes/year in the BDRN and the episode ratio, defined as the ratio between the number of manic and depressive episodes, according to diagnosis.

4.3 DISCUSSION:

The aim of this study was to identify outcome variables that describe the illness course in a longitudinal cohort of subjects with bipolar disorder. In addition, the study explored the correlation between these identified variables and similar measures of illness course collected retrospectively on BDRN participants.

The study found that participants with different principal diagnoses (BD1 and BD2) spend different amounts of time with mood symptoms. BD2 subjects spend more time ill and especially experience depressive symptoms. Furthermore, even though the difference is not statistically significant, BD2 subjects spend more time with high mood symptoms compared to BD1 subjects. Table 2.2 shows how the results obtained in this study overlap with other published studies that have used the same TC database. To the best of my knowledge, this study analysing 653 participants is the largest to date. In agreement with already published data, this study showed that subjects with BD disorder, regardless of the diagnostic subtype, experience more depressive symptoms compared to the manic and tend to report more depressive episodes.

Table 2.3, adapted from Faurholt-Jepsen et al., compares the proportion of time spent by subjects in a specific mood state across studies that used True Colours or similar prospective data. The original follow-up lengths reported in the papers are included. In this study, medians were preferred over means due to the large variability in follow-up periods among the enrolled subjects.

refs			Percentage of time spent in mood state					
	Diagnosis	# of subjects assessed	Euthymia	depression	Hypomania or Mania	Mixed mood symptoms	Follow up	
Present Study	Whole sample	368	68.93	28.17	2.02	0.88	median 133 weeks	a10q10
	BD1		**72.53**	**25.08**	1.71	0.68		
	BD2		**61.93**	**33.96**	2.75	1.36		
McKnigth et al. 2017	Whole sample	297	40.1	35	7.5	/	mean 110 weeks	a5q10
	BD1	187	41.5	36.5	6.9	/		
	BD2	98	41.2	36.4	7.9	/		
Faurholt-Jepsen et al.,	BD1	20	**74.5**	**18.81**	5.5	12.9	mean 36 week	
	BD2	13	**51**	**45.06**	2.7	5.5		
Bopp et al., 2010	Whole sample	62	36.5	47.69	7	8.77	mean 36 weeks	
	BD1	47	**31.18**	**53.6**	7.06	8.15		
	BD2	15	**51.15**	**35.23**	6	8.62		
Kupka et al., 2007	BD1	405	47.7	36.2	12.5	/	> 1 year	
	BD2	102	50.2	36.9	10	/		
Joffe et al., 2004	BD1 & BD2	138	53.1	40.9	6	/	3 years	
Post et al., 2003	BD1 & BD2	258	52.6	33.2	10.8	/		
			Subsyndromal symptoms	Mild mood* symptoms	Syndromal mood* symptoms			
Judd et al., 2002	BD1	146	14.8	20.2	12.3			
Judd et al., 2003	BD2		15.7	25.2	13			

Prospective longitudinal assessment of illness course is the gold standard for studying the trajectories and natural history of a disease. However, one of the limitations of this type of approach, aside from the costs and complexity, is that most diseases, especially in psychiatry,

are long-life conditions that make prospective longitudinal studies hard to run. Collecting clinical information from an interview or from clinical records is easier and faster. The data that can be collected with this retrospective approach are qualitatively different from prospective data, and their meaning can be different. In the case of the number of episodes, it has been demonstrated in Bipolar Disorder that the number of episodes data must be taken very carefully because, despite the name, sometimes it is hard or impossible to obtain the actual number of mood episodes experienced by the subjects (Tremain, Fletcher, & Murray, 2020). This is because sometimes subjects tend to forget or not recognize all the episodes, and sometimes the available clinical records are incomplete.

The TC project makes it possible to have prospective data for subjects retrospectively phenotyped in the BDRN. Thanks to this opportunity, it is possible to validate these data across the two databases and see how the self-reported number of mood episodes consistently correlates with the mood episodes retrospectively assessed. This study validated the outcome variables identified in TC with the information available in BDRN. The validation was performed by identifying the variable in the retrospective database that better correlates with the outcome variable identified in TC. Because of the temporal nature of the outcome variable obtained, the proportion of time spent in a mood state, all the retrospective data chosen from the BDRN were linked to the temporal aspect of the disorder. For this reason, besides the retrospective number of mood episodes, other items such as rapid cycling and the duration of mood episodes were chosen. The results showed that the retrospectively collected variable most correlated with longitudinal course in TC is the number of episodes, followed by history of rapid cycling. No or weak correlations were found with other illness course descriptor variables such as the disease duration and the length of the longest episode of mania or depression.

The proportion of time spent with mood symptoms was defined by the degree of response to the mood symptoms rating scales. The aim of this variable was to capture chronicity and to describe even the persistence of sub-threshold symptomatology in subjects. To validate this finding in the prospective TC sample, the study looked at the association of the number of episodes and the mood state in the BDRN sample. The BDRN sample differs from TC because of its retrospective character. As shown in Graph 2d, subjects who spend more time in

depression tend to have more episodes compared to subjects who experience more manic symptoms.
TC) represents an optimal instrument for investigating mood instability in individuals with mood disorders. While TC offers valuable clinical insights into the mood states of enrolled subjects, it is imperative to recognize that it should not be construed as a diagnostic tool due to its inherent nature. TC employs two scales to assess mood symptoms, both of which were developed primarily for screening purposes rather than diagnostic assessment. Consequently, high scores on these scales do not provide diagnostic indications but rather indicate a heightened likelihood of being affected by mood disturbances. Therefore, the utilization of TC must be judiciously calibrated with this consideration in mind.

Numerous studies have employed TC to evaluate the frequency of mood episodes(McKnight et al., 2017). Given the characteristics of TC, particular caution is warranted when defining episodes. The DSM-5 provides the accepted definition of mood episodes, which necessitates precise adherence to specific criteria. Merely referencing a screening scale may not suffice for accurate diagnostic determination. Particularly during severe mood states such as profound depression or mania, patients may cease responding to TC, resulting in a lack of sufficient information to delineate well-defined episodes in accordance with DSM-5 criteria.

TC primarily serves as a tool for identifying states of mood alteration. The decision to employ a defined threshold was driven by the imperative to capture every conceivable moment of illness and effectively differentiate between normal and altered states. While this continuous approach may render the delineation of discrete episodes unfeasible, it remains well-suited for identifying and characterizing mood instability and the persistence of sub-threshold symptoms, which are occasionally overlooked by clinicians.

The findings regarding the correlation between TC measures and variables from the BDRN present intriguing implications for the utilization of longitudinally assessed versus retrospectively assessed datasets. Beyond the realm of research, these implications hold significant clinical relevance that necessitates careful consideration.

From a research standpoint, particularly in scenarios requiring large cohorts, such as genetic association studies, the utilization of a "fast phenotyping" tool like TC could expedite the recruitment process substantially. By offering a rapid phenotyping approach, TC has the potential to streamline participant enrollment. Moreover, the validation of TC against an independent dataset, as demonstrated in this study, mitigates the risk of underestimating or misinterpreting phenotypic characteristics. This validation ensures the reliability and robustness of TC as a phenotyping tool, thereby enhancing the quality and validity of research outcomes.

From a practical and clinical perspective, TC holds immense promise in predicting and intervening in symptom trajectories and patient outcomes. Clinical management often heavily relies on patients' historical data, including mood episode occurrences, hospitalization records, and responses to therapy. A validated longitudinal tool such as TC could serve as a valuable resource for clinicians, enabling them to assess and anticipate the likely clinical course of individual patients. By incorporating TC assessments at the onset of symptoms, clinicians can gain valuable insights into the probable clinical trajectories of patients, thereby facilitating more informed and personalized treatment strategies.

5.3 LIMITATIONS

Although this study provides valuable insights into the illness course of bipolar disorder subjects, there are several limitations that should be acknowledged. First, the sample size of retrospectively assessed subjects who were enrolled in the prospective study True Colours was relatively small, accounting for only one-sixth of the total BDRN sample. Increasing the number of subjects enrolled in TC could potentially lead to more consistent results.

Second, it should be noted that the TC participants may not be representative of the larger BDRN cohort. Specifically, the proportion of subjects diagnosed with bipolar 2 disorder was higher in the TC sample compared to the BDRN cohort.

Third, there was a difference in the mean disease duration between the subjects enrolled in TC and BDRN. This may have influenced the observed outcomes.

Finally, while our study identified variables that were strongly correlated between the two datasets, we did not explore the clinical or biological mechanisms underlying these correlations. Future studies could benefit from investigating these mechanisms in more detail.

To address these limitations, future studies should aim to increase the sample size of TC and enrol subjects with varying disease durations. Additionally, examining the clinical and biological mechanisms underlying the observed correlations could provide valuable insights into the illness course of bipolar disorder subjects.

To partially overcome these limitations and biologically validate the findings presented in this chapter, a polygenic risk approach applied to the phenotype descriptors analysed in the present chapter will be utilized in the fifth chapter.

Correlation of proportion of time spent with any mood symptoms in TC and Total episodes year in BDRN	a5q5			a10q15			a5q10			
	z	p	tau	z	p	tau	z	p	tau	n° of responders
Whole sample	8.2617	< 2.2e-16	0.2357889	8.6502	< 2.2e-16	0.2520099	9.2785	< 2.2e-16	0.2620725	653
Whole sample responders for more than 1 year	6.6707	2.55E-11	0.2467327	7.5588	4.07E-14	0.2876296	7.6589	1.88E-14	0.2826776	369
Whole sample responders for more than 1.5 year	6.2687	3.64E-10	0.2595396	7.0303	2.06E-12	0.2993036	7.1297	1.01E-12	0.2948167	294
Whole sample responders for more than 2 year	5.9258	3.11E-09	0.2755968	6.3206	2.61E-10	0.3040454	6.4825	9.02E-11	0.301726	232
Whole sample responders for less than 1 year	4.001	6.31E-05	0.1825603	4.1009	4.12E-05	0.187169	4.865	1.15E-06	0.2161461	285
All BP1	6.6531	2.87E-11	0.2388029	6.7935	1.09E-11	0.2518169	7.1	1.25E-12	0.253599	401
BP1 responders for more than 1 year	5.3286	9.90E-08	0.245697	6.2605	3.84E-10	0.2995371	6.505	7.77E-11	0.2995813	233
BP1 responders for more than 1.5 year	5.072	3.94E-07	0.2656523	5.9417	2.82E-09	0.3229084	6.2331	4.57E-10	0.3263292	183
BP1 responders for more than 2 year	5.1444	2.68E-07	0.3049809	5.7947	6.85E-09	0.3576596	6.0483	1.46E-09	0.3588397	144
Whole sample responders for less than 1 year	3.1859	1.44E-03	0.1861039	3.139	1.70E-03	0.1862746	3.3222	8.93E-04	0.1916898	168
All BP2	3.4627	0.0005348	0.1731774	3.7934	1.49E-04	0.1891859	4.1544	3.26E-05	0.2033359	228
BP2 responders for more than 1 year	2.8821	0.00395	0.1939097	3.2828	0.001028	0.2228911	2.886	0.003902	0.1929545	119
BP2 responders for more than 1.5 year	2.7155	0.006618	0.1991049	3.0369	0.00239	0.2246784	2.6799	0.007364	0.1956553	98
BP2 responders for more than 2 year	2.3697	0.0178	0.1966866	2.4319	0.01502	0.2057543	2.1001	0.03572	0.1743065	76
Whole sample responders for less than 1 year	1.7643	7.77E-02	0.1353429	1.8744	6.09E-02	0.1404703	2.6261	8.64E-03	0.1931373	109

***Table A**: This graph displays the Kendall correlations between the proportion of time spent with any mood symptoms and the temporal items available in TC. The number of TC responders is reported for each group based on their length of enrollment in TC. The ASRM QIDS a5q5, a10q15, and a5q10 were selected based on previously published literature.*

Correlation of proportion of time spent with any mood symptoms in TC2019 and Total manic or depressive episodes	a10q10					
	Depression			Mania		
	z	p	tau	z	p	tau
Whole sample	-2.7631	0.0057	-0.0916329	3.3711	7.49E-04	0.1135583
Whole sample responders for more than 1 year	-2.504	0.0123	-0.1050691	4.2169	2.48E-05	0.1801845
Whole sample responders for more than 1.5 year	-1.8186	0.0690	-0.0857741	3.9079	9.31E-05	0.1869137
Whole sample responders for more than 2 year	-1.0889	0.2762	-0.0584833	3.1368	0.0017	0.1697165
Whole sample responders for less than 1 year	-1.7643	0.0777	-0.0962173	0.851	0.3948	0.04688099
All BP1	-2.126	0.0335	-0.0909181	3.1146	0.0018	0.1337544
BP1 responders for more than 1 year	-2.2213	0.0263	-0.1179514	3.5513	0.0004	0.1899785
BP1 responders for more than 1.5 year	-1.6337	0.1023	-0.0986816	3.0868	0.0020	0.1861959
BP1 responders for more than 2 year	-0.83057	0.4062	-0.0570265	2.007	0.0448	0.1371828
BP1 responders for less than 1 year	-0.60661	0.5441	-0.0443568	0.96109	0.3365	0.07002901
All BP2	-1.4716	0.1411	-0.0822635	1.3694	0.1709	0.07895335
BP2 responders for more than 1 year	-0.66221	0.5078	-0.0492023	1.8224	0.0684	0.1396714
BP2 responders for more than 1.5 year	-0.65052	0.5154	-0.053649	1.8834	0.05965	0.1601752
BP2 responders for more than 2 year	-0.41096	0.6811	-0.0395953	2.0705	0.03841	0.203375
BP2 responders for less than 1 year	-1.5766	0.1149	-0.1361759	0.1887	0.8503	0.0167999

***Table B**: Correlation between the percentage of time spent with any mood symptoms symptoms in the TC program and the number of manic or depressive episodes BDRN dataset, using Kendall's tau. Correlations are reported for the entire sample, as well as for the BD1 and BD2 subgroups based on response time.*

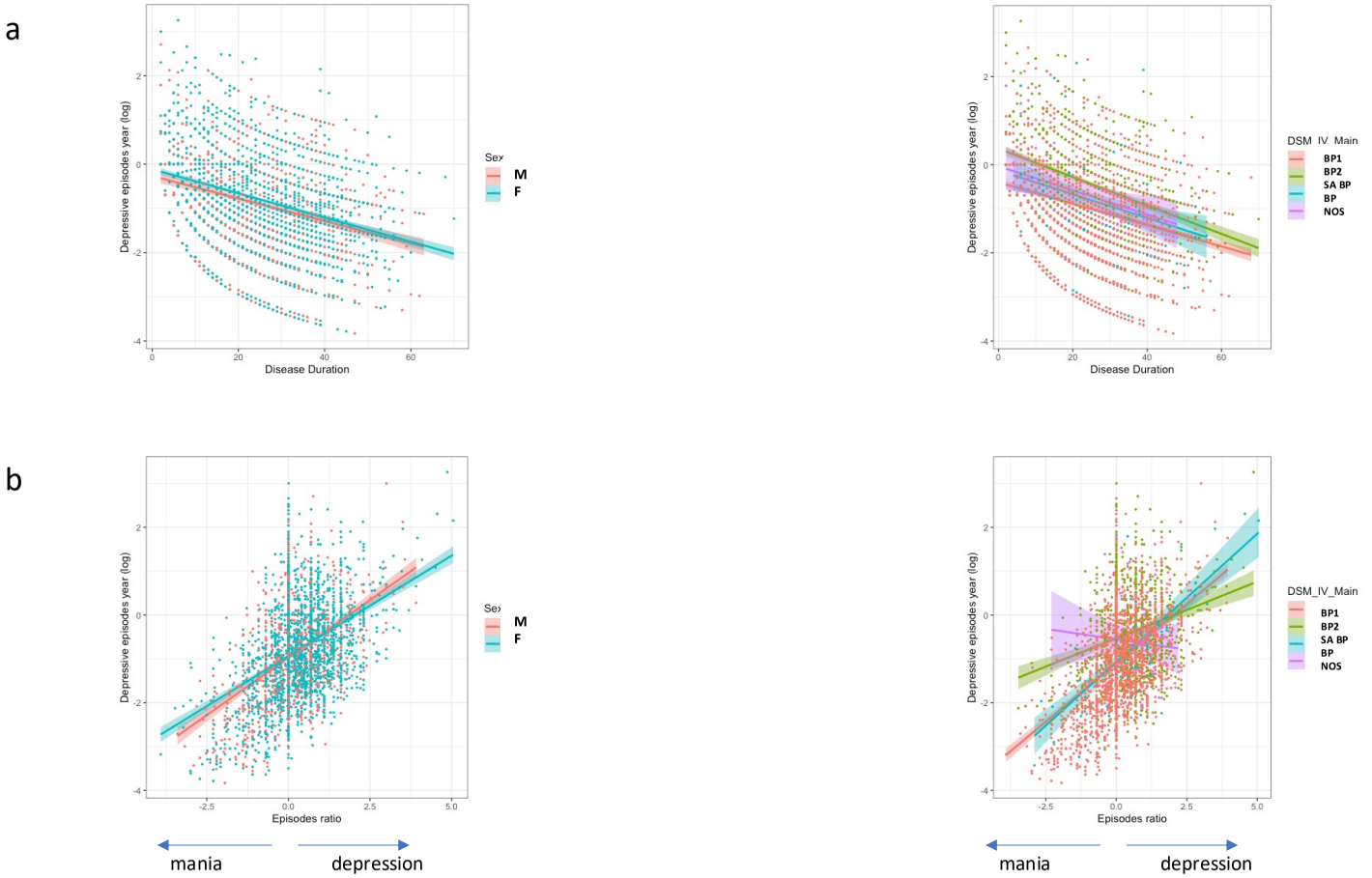


Figure A: This figure displays two scatter plots showing the linear correlation between two variables in the BDRN dataset. In the upper section (a), the log of the number of depressive episodes/year in the BDRN is plotted against the disease duration. In the lower section (b), the log of depressive number of episodes/year in the BDRN is plotted against the episode ratio, defined as the ratio between the number of manic and depressive episodes. The pink and blue colours in both scatter plots represent the sex of the subjects, while the four different colours represent the four DSM diagnoses: BD1, BD2, SA BD, and BD NOS.

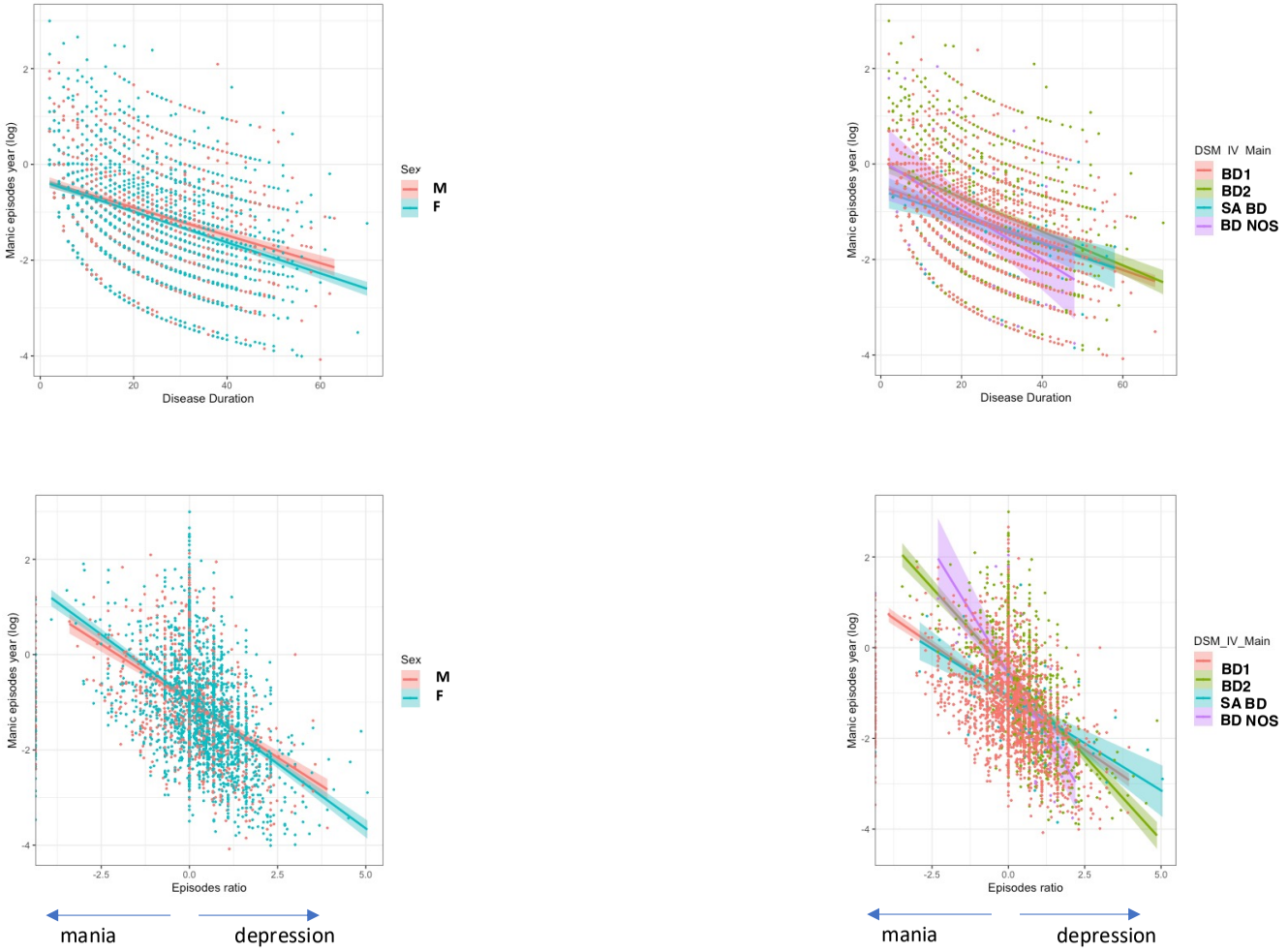


Figure B: This figure displays two scatter plots showing the linear correlation between two variables in the BDRN dataset. In the upper section (a), the log of the number of depressive episodes/year in the BDRN is plotted against the disease duration. In the lower section (b), the log of manic number of episodes/year in the BDRN is plotted against the episode ratio, defined as the ratio between the number of manic and manic episodes. The pink and blue colours in both scatter plots represent the sex of the subjects, while the four different colours represent the four DSM diagnoses: BD1, BD2, SA BD, and BD NOS.

Chapter 4: Factor analysis of outcomes in bipolar disorder

1.4 INTRODUCTION

Bipolar disorder is a psychiatric condition characterized by intricate clinical manifestations, encompassing manic episodes characterized by heightened mood, depressive episodes, and mixed states where both mania and depression co-occur. Within the current diagnostic framework of the DSM-5 (the American Psychological Association Diagnostic and Statistical Manual of Mental Disorders) (American Psychiatric Association (APA), 2013), bipolar disorder I and bipolar disorder 2 are classified as subtypes of the same disorder, with the severity of manic symptoms serving as a distinguishing factor between the two diagnoses.

In the DSM-5, bipolar disorder is positioned between psychotic disorders and depressive disorders, recognizing its unique symptomatology, familial patterns, and genetic features. This placement acknowledges bipolar disorder as a bridge between the two diagnostic categories, reflecting similarities and overlaps in terms of symptom presentation, familial inheritance, and genetic underpinnings. However, the DSM's categorical approach to diagnosis appears to be limited in capturing the intricate biological and genetic complexity of the disorder. To address this limitation, alternative classification systems such as the Research Domain Criteria (RDoC) (Insel et al., 2010) have been proposed. These novel frameworks aim to provide a more comprehensive understanding of bipolar disorder by considering multiple dimensions of psychopathology, including biological and genetic factors.

In order to comprehend the intricate nature of mental disorders like schizophrenia, depression, and bipolar disorder, numerous studies employing Factor Analysis methodologies have been conducted. Factor Analysis is a statistical technique that enables the reduction of a large number of variables into a smaller set of factors, capturing their variance and facilitating

further analysis. This approach commonly focuses on dimensions of symptoms. For instance, the classic categorization of psychotic features into positive, negative, and disorganized domains was established through Factor Analysis (Andreasen, Arndt, Alliger, Miller, & Flaum, 1995). More recently, similar techniques have been applied to bipolar disorder, revealing latent traits associated with key clinical aspects of the disorder. Notably, Factor Analysis of manic symptoms revealed clusters that extended beyond those suggested by the DSM-5 (Hanwella & de Silva, 2011).

However, most studies exploring underlying clusters and subdimensions of bipolar disorder using Factor Analysis have primarily concentrated on dimensions of symptoms. Researchers have primarily focused on assessing manic and depressive symptoms using mood rating scales such as the Young Mania Rating Scale (YMRS) or the Hamilton Depression Rating Scale (HAM-D), either individually or in conjunction (Harvey, Endicott, & Loebel, 2008). These investigations have identified subtypes of mania characterized by distinct symptom profiles, such as "irritable mania," "elated mania," and "psychotic mania." Additionally, other studies have explored the role of temperament and personality traits, revealing their association with latent traits related to comorbidity and the severity of the disorder (Qiu, Akiskal, Kelsoe, & Greenwood, 2017).

Outcome research in bipolar disorder is an emerging area of study. While clinical and pharmacological outcomes have received more attention, socio-functional outcomes have been relatively understudied. Quality of Life (QoL) is a well-investigated outcome measure in individuals with bipolar disorder. However, there is a scarcity of studies that simultaneously consider both functional and clinical outcomes. The complexity of outcomes makes them an intriguing subject of investigation. Social and clinical outcomes can be influenced by various factors such as the environment, genetics, clinical presentation, treatment, and drug response. Although disease outcomes are often examined and analysed independently for simplicity's sake, it is undeniable that many outcomes are closely interconnected. By employing Factor Analysis, researchers can explore the significance of outcomes and derive more comprehensive dimensions that can facilitate the prediction of disease prognosis.

A recent study, albeit small in scale, applied a factor analysis approach to assess QoL in 109 individuals with bipolar disorder (Charles, Branco, Shansis, & Fonseca, 2020). The analysis revealed two underlying constructs, namely "Personal" and "Social," which served as latent factors in the assessment of quality of life using the WHOQOL-BREF instrument. These latent constructs were directly influenced by the diagnosis of bipolar disorder and depressive symptomatology, in fact both aspects act negatively on the two constructs, and indirectly influenced by manic and hypomanic symptomatology.

Taking into consideration both clinical and social outcomes and utilizing factor analysis methodologies can be crucial for comprehensively understanding different aspects of the disease. Previous research has demonstrated that clinical factors, such as the number of episodes, significantly influence social outcomes such as employment status (Tse, Chan, Ng, & Yatham, 2014). Additionally, the predominant polarity of the illness, whether it is manic or depressive, has been linked to various disease outcomes (Popovic et al., 2014). For instance, a predominant manic polarity has been associated with increased suicidality and a higher number of hospitalizations, while a predominant depressive polarity has been linked to educational outcomes and substance abuse. Examining these multifaceted relationships between clinical and social outcomes can provide valuable insights into the impact of bipolar disorder on individuals' lives.

The primary objectives of this chapter were:

1. To investigate the interrelationships among various clinical outcomes in individuals with bipolar disorder. Looking at the differences according to the diagnostic groups between same outcome variables.
2. To explore the latent factors that contribute to both clinical and functional outcomes in bipolar disorder. Utilizing a factor analysis approach that permits to look at the underneath structure of outcome variables.

The sample population considered for this study was drawn from the Bipolar Disorder Research Network dataset, which encompasses data from over 9000 patients diagnosed with

bipolar disorder 1, bipolar disorder 2, schizoaffective bipolar disorder, and bipolar disorder not otherwise specified.

The selected outcome variables were categorized into three main domains related to the disease: clinical, personal, and social functioning. The clinical variables encompassed aspects such as the number of mood episodes, their characteristics, and duration. Personal level functioning variables were assessed using the Global Assessment Scale (GAS) and its subscales. Social outcomes included factors such as marital history, educational attainment, and employment status.

The overarching goals of this chapter were to gain a deeper understanding of the underlying structure of outcome dimensions in bipolar disorder and to generate outcome factors that could be utilized in genetic association studies.

2.4 METHODS

To accomplish this, I initially conducted an exploratory factor analysis (EFA) utilizing a training set comprising a random selection of 80% of participants from the Bipolar Disorder Research Network (BDRN) dataset. Subsequently, the remaining 20% of subjects' data were employed to conduct a confirmatory factor analysis (CFA) for validation purposes. These analyses were conducted on the two main diagnostics subsets, BD1 and BD2.

1.2.4 Database description and Participants selection

The dataset utilized in this analysis constitutes a subset of the Bipolar Disorder Research Network (BDRN) database. The BDRN is an extensive and ongoing research program dedicated to investigating both genetic and non-genetic factors influencing mood disorders. Recruitment of participants is conducted systematically through the UK National Health Service (NHS) Community Mental Health Teams and lithium clinics, as well as non-systematically via the BDRN website and patient support groups such as Bipolar UK.

Eligibility to participate in the BDRN research program is extended to individuals in the UK who are aged 18 years or above and have received a diagnosis of bipolar disorder, upon

providing written informed consent. Exclusion criteria encompass individuals whose affective illness is solely attributed to alcohol or substance abuse or dependence, or arises solely from medical illness, an organic brain disorder, or medication.

For the present analyses, I included participants who had available genotype data and phenotypic information in at least one of the following domains: i) current functioning, ii) current Global Assessment Scale (GAS) scores, or iii) current employment status. Out of the complete BDRN dataset, a total of 4,382 participants met the inclusion criteria and were included in the initial analyses.

The comprehensive BDRN dataset comprises over 153 variables, of which 39 variables were selected for the purpose of this analysis. Given the focus of this thesis on clinical and genetic determinants of outcomes in bipolar disorder, my approach involved identifying potential outcome variables within the dataset and exploring potential associations with other variables such as bipolar subtype.

2.2.4 Variables initially considered

The selection of variables for this analysis was informed by discussions with supervisors and the BDRN team, as well as the findings of a literature review on outcomes in bipolar disorder presented in Chapter 1. The chosen variables were chosen to represent potential outcomes experienced by individuals with bipolar disorder. The selected variables encompass:

- Clinical outcomes: These include the lifetime number of episodes, their polarity (whether they were manic or depressive), duration, the number of hospital admissions, and whether any of these admissions were compulsory. It is important to note that mixed episodes were included in the count of manic episodes.
- Global Assessment Scale (GAS) scores: These scores capture the extent of impairment in functioning experienced during the most severe manic and depressive episodes.
- Social outcomes: This category includes variables related to marital history, educational attainment, and employment status.

By including these variables, the aim was to capture a comprehensive range of potential outcomes for individuals with bipolar disorder.

Table 1.4 provides a detailed description of the selected variables, including information on missing values, data type, and coding system

Table:1.4 Description of variables initially considered

	NA	#Availables records	Type	Coding
Longest duration of mania	702	3680	Continuous	weeks
Longest duration ofdepression	557	3824	Continuous	weeks
Total episodes	399	3983	Discrete	number of episodes
Total episodes of depression	602	3780	Discrete	number of episodes
Total episodes of mania	513	3869	Discrete	number of episodes
Number of admissions	137	4245	Continuous	number of admissions
Functioning Assessment 1	1298	3084	Ordinal	No, mild moderate, severe unknown (0,1,2,3)
Functioning Assessment 2	1313	3069	Ordinal	No, mild moderate, severe unknown (0,1,2,3)
Functioning Assessment 3	1311	3071	Ordinal	No, mild moderate, severe unknown (0,1,2,3)
GAS worst in manic episode	100	4282	Interval variable	decile intervals 0-100, lowest level of functioning in the last week
GAS worst in depressive episode	322	4060	Interval variable	
OPCRIT Course of Disorder	839	3543	Ordinal	1= Single episode with good recovery 2= Multiple episodes with good recovery between 3= Multiple episodes with partial recovery between 4= Continuous chronic illness 5= Continuous chronic illness with deterioration
Ever Sectioned	203	4179	Nominal	Yes No (1,0)
Rapid Cycling	0	4382	Nominal	Yes, No, Unknown (0,1 9)
Marital History	288	4094	Nominal	Yes No (0,1)
Highest occupation	113	4269	Nominal	Unknown, Lev1, 2, 3, 4, never worked, homemaker student (0,1,2,3,4,5,6,7)
Current Occupation	807	3575	Nominal	Unknown, Lev1, 2, 3, 4, never worked, homemaker student, retired (0,1,2,3,4,5,6,7,8)
Highest educational attainment	382	4000	Nominal	Yes No
Number of admissions	137	4245	Continuous	#

3.2.4 Variables description

In this subsection, I provide a comprehensive list and definition of the variables considered in the factor analysis.

1. Episode duration: Two variables are included, one for the longest episode of mania and one for the longest episode of depression. The original dataset codes the length of each episode in weeks, with the integer representing the number of weeks and the first and second decimal places representing the number of days and hours. The episode duration was approximated to the week duration.
2. Number of episodes: Manic and depressive episodes were considered separately. The total number of episodes was calculated by summing the number of manic episodes with the number of depressive episodes. Episode was defined according to DSM-IV criteria.
3. Number of admissions: This variable captures the total number of admissions for each patient, including both inpatient admissions and day hospital or intensive home treatment. Admissions are counted separately, even if only one day separates them.
4. Current Functioning Assessment: This is a bespoke variable created for the BDRN study. It assesses difficulties in three main areas: ability to work or study (1), maintaining good relationships (2), and self-care (3). Each item is evaluated using a Likert scale ranging from 0 to 3, indicating no difficulty, mild difficulty, moderate difficulty, and severe difficulty. The Current Functioning Assessment Scale has been in use since 2005.
5. Global Assessment Scale (GAS): The GAS is a rating scale used to evaluate the overall functioning of a subject over a specified time period, ranging from psychological or psychiatric sickness to health (Endicott, Spitzer, Fleiss, & Cohen, 1976). The scale ranges from 0 to 100 with intervals of 10. The highest intervals (81-90 and 91-100) are designated for individuals who not only exhibit the absence of significant psychopathology but also demonstrate "positive mental health," such as superior functioning, a wide range of interests, social effectiveness, warmth, and integrity. A score of 85 is assigned to euthymic and well-functioning subjects. The BDRN dataset includes GAS data for the past week, the lifetime worst manic episode, and the lifetime worst depressive episode.

6. Ever sectioned: This categorical variable has five different values: (1) never been sectioned, (2) (3), NA, (4) once/minority of all admissions, and (5) majority of all admissions. It captures whether a participant has ever been subjected to involuntary psychiatric hospitalization.
7. Rapid cycling: Presence of rapid cycling was defined as having more than four episodes of mood disturbance (manic, hypomanic, or depressive) within a 12-month period.
8. Marital History: This dichotomous variable combines individuals who have ever been married with those who have ever lived as married into the same category.
9. Occupation: Two variables describe the occupation level of subjects in the BDRN dataset: Current Occupation and Highest Occupation. Occupation classifications are based on the "Standard Occupational Classification 2010." These variables are classified into four levels, and their clinical significance may differ. Current occupation is typically considered an outcome, while highest occupation can be considered an outcome if the onset is in infancy and a predictor if the onset is in adulthood.
10. Employment at enrolment: A new dichotomous variable was created based on the values of the current and highest occupation variables to capture whether the employment status at the time of enrolment is the same or worse than the highest occupation.
11. Highest educational attainment: This variable was dichotomized into low education and high education. Similar to occupation, the highest educational attainment can be considered an outcome or a predictor depending on the age of onset.
12. Course of disorder (OPCRIT item 90): This item captures the course of the disorder and includes five options: single episode with good recovery, multiple episodes with good recovery between, multiple episodes with partial recovery between, continuous chronic illness, and continuous chronic illness with deterioration. It is assessed using the Operational Criteria Checklist for Psychotic Illness and Affective Illness (OPCRIT) (McGuffin, 1991), which is a poly-diagnostic instrument used to generate diagnoses based on operational criteria.

The inclusion of these variables provides a comprehensive assessment of various aspects related to clinical outcomes and functional outcomes in bipolar disorder.

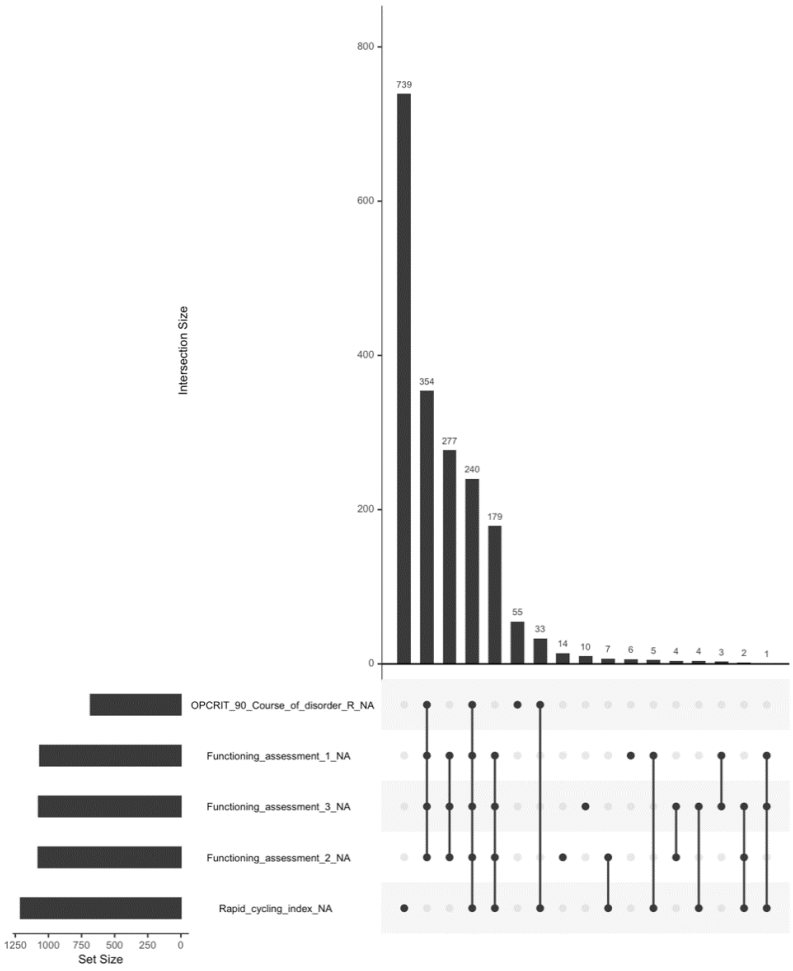
4.2.4 Variable Selection

Variables were carefully selected based on several criteria, including the number of missing values, the pattern of missingness, and redundancy. To ensure data quality, variables with a missingness rate higher than 30%, those exhibiting non-random patterns of missingness, and variables that contained redundant information with other variables but had data available for fewer participants were excluded from the analysis.

The missing values patterns among the selected variables are visually represented in Figure 1 using an "UpSet" plot. The UpSet plot is a powerful visualization technique that facilitates the quantitative analysis of sets, their intersections, and the aggregates of these intersections (Lex et al., 2014). In the plot, the bottom left bars depict the set size of the five most common missing values, while the bottom plot represents every possible intersection of variables. The occurrence of these intersections is displayed on the top bar plot.

Figure 1.4: Missing values patterns. This "Up-Set" plot shows how missing values behave across different variables. The upper part of the figure is a plot showing the

numerosity of the sample characterized by a simultaneous missingness in the variables listed in the lower part.



The missingness observed for Functioning Assessment variables 1, 2, and 3 is not random. This can be attributed to the introduction of the Functioning Assessment scale after 2005, while BDRN participant enrolment began as early as 1991. As indicated in Table 2.2, there is a statistically significant difference in the distribution of subtype diagnoses across different time periods of enrolment. Specifically, during the initial years of enrolment, a larger proportion of patients were diagnosed with Bipolar 1 (BD1), whereas in more recent years (after 2005), the difference in the proportion of BD 1 and Bipolar 2 (BD 2) diagnoses became

smaller (Table 2.2). Due to these factors, the three Functioning Assessment variables initially included in the analysis were subsequently excluded from further analysis.

Table 2.4: differences in DSM IV diagnoses according enrolment date.

DSM_IV before 2005	BP1	BP2	SA BP	BP NOS
#	534	51	23	19
%	85.17	8.13	3.67	3.03
DSM_IV after 2005				
#	2383	1183	134	55
%	63.46	31.50	3.57	1.46

Variables excluded from the analysis due to missing data proportions above 30% were the OPCRIT 90 Course of Disorder and the Rapid Cycling Index. Additionally, the total number of episodes was excluded to prevent overfitting, as it exhibited redundancy and partial overlapping with other variables that captured similar constructs.

5.2.4 Variable Discretisation

Before conducting the analysis, certain variables underwent recoding. The two Global Assessment Scale (GAS) scales, representing the worst functioning during manic and depressive episodes, were originally interval variables ranging from 0 to 100 with intervals of 10. These were transformed into nine classes (1-9) to facilitate analysis.

Furthermore, the continuous variables including the number of depressive and manic episodes, duration of the longest episode of mania and depression, and number of admissions, were recoded into five classes (1-5) based on quintiles, dividing the sample into equal quintiles.

6.2.4 Statistical Analysis

Polychoric Correlation: To address the heterogenous nature of the data, a polychoric correlation matrix was calculated using the R function "hetcor." Polychoric correlation is employed when continuous variables cannot be analyzed using Pearson correlation due to their non-continuous nature (Sammel, Ryan, & Legler, 1997).

Factor Analysis:

Exploratory Factor Analysis: This analysis was conducted on a randomly selected subset of the original dataset, representing 80% of the BDRN sample.

Factor analysis is a statistical method utilized to uncover underlying structures among variables. In the context of this study, factor analysis of outcomes aims to identify clinically meaningful subtypes of outcomes associated with bipolar disorder.

Considering the diverse data types included, a heterogeneous correlation matrix was computed. This type of matrix incorporates Pearson product-moment correlations for numeric variables, polyserial correlations for numeric and ordinal variables, and polychoric correlations for ordinal variables. The R command "hetcor" was employed to generate this matrix.

To determine the number of factors to retain, Kaiser's rules were applied, retaining factors with eigenvalues greater than 1 (Kaiser, 1960).

An exploratory factor analysis was conducted in R, utilizing the selected outcomes variables and the "fa" command from the "Psych" package. The desired number of factors to extract (in this case, 5) was specified as an argument.

To enhance interpretability of the factors and considering the interdependence of the entered variables, an oblique rotation method, specifically "promax," was employed.

Confirmatory Factor Analysis:

Confirmatory factor analysis (CFA) is a statistical technique employed to assess the relationship between observed variables and their underlying latent constructs. In this study,

CFA was conducted on a separate testing dataset, representing 20% of the BDRN sample, to validate the factor structure identified through exploratory factor analysis (EFA).
The R package "lavaan" was utilized, and the "cfa" function specifically designed for fitting confirmatory factor analysis models was employed.
In the CFA, the five-factor model was defined by including all variables (indicators) that were included in the factors identified during EFA. The "fit" function was then used to evaluate the degree of fit between the observed variables and the defined model.
Several goodness-of-fit statistics were examined to assess the model's fit, including the Overall $\chi 2$ statistic (Hooper, Coughlan, & Mullen, 2008), Akaike's information criterion (AIC), Bayesian information criterion (BIC), comparative fit index (CFI), Tucker-Lewis index (TLI) (Bentler, 1990), root mean square error of approximation (RMSEA) (Steiger, 1990), and standardized root mean square residual (SRMR) (Hooper et al., 2008).

Factor Scores Extraction:
One characteristic of factor analysis is that the factors are defined at a structural level and not at a data level. To translate the findings of the factor model to the individual subject level, factor scores were computed. The "factor.scores" function in R, available in the "Psych" package, was used for this purpose. Multiple methods with comparable reliability exist for calculating factor scores (DiStefano, Zhu, & Mîndrilă, 2009). In this analysis, the Thurstone method was employed (Thurstone, 1934). The Thurstone method utilizes a least squares regression approach for factor prediction, finding the regression-based weights: W = R^{-1} F, where R is the correlation matrix and F is the factor loading matrix.

3.4RESULTS

1.3.4 Sample description

Table 3.3 presents a summary of the demographic characteristics of the sample, consisting of 3,505 subjects who participated in the exploratory factor analysis, representing 80% of the BDRN cohort. No statistically significant differences were observed between individuals with bipolar 1 and bipolar 2 disorder when comparing age of onset impairment, age at interview, and illness duration. The distribution of sex was 32% males and 68% females.

Regarding DSM-IV diagnosis, 66.76% of the sample were diagnosed with bipolar 1 disorder, 27.99% with bipolar 2 disorder, and 3.68% and 1.57% with schizoaffective bipolar subtype and bipolar disorder not otherwise specified (NOS), respectively.

Furthermore, it was found that bipolar 1 patients were more likely to be recruited through a systematic method compared to bipolar 2 patients, who were more likely to be recruited in a non-systematic manner (χ-squared = 43.727, df = 3, p-value < 0.001).

Table 3.4: Sample Description Summary. The table provides a summary of the sample characteristics, including sex, diagnosis, age, type of recruitment, and illness duration (expressed in years).

Sex	**m**		**f**	
	1122		2383	
Diagnosis	**BD1**	**BD2**	**SA BD**	**BD NOS**
	2340	981	129	55
Illness duration	**Min.**	**Median**	**Mean**	**Max.**
	1	23	24.47	33
Age at interview	18	46	46.53	89
Age onset impairment	4	20	22.9	68
Recruitment	**Systematic**		**Not systematic**	
	1029		2417	

Table 4.4 presents the distributions of the items included in the factor analysis. For each variable, the coding system, number of available records, and the percentage of each class of response are provided.

Variable name	Variable description	Coding	Available records	%
Gas worst in manic episode	Needs some/several supervision	1	1	0.03
	Unable to function in almost all areas	2	112	3.20
	Major impairment in several areas	3	1074	30.64
	Any serious symptomatology	4	505	14.41
	Moderate symptoms	5	588	16.78
	Some mild symptoms	6	641	18.29
	Minimal symptoms	7	491	14.01
	Transient symptoms may occur	8	12	0.34
	No symptoms	9	0	0.00
		NA's	81	2.31
Gas worst in depressive	Needs some/several supervision	1	4	0.11
	Unable to function in almost all areas	2	29	0.83
	Major impairment in several areas	3	353	10.07
	Any serious symptomatology	4	558	15.92
	Moderate symptoms	5	1489	42.48
	Some mild symptoms	6	721	20.57
	Minimal symptoms	7	88	2.51
	Transient symptoms may occur	8	8	0.23
	No symptoms	9	6	0.17
		NA's	249	7.10
Marital History	Has married/lived as married	1	2780	79.32
	Has never married/lived as married	2	487	13.89
		NA's	238	6.79
Number of admissions	0	0	866	24.71
	1-5	1	1815	51.78
	6-12	2	576	16.43
	>13	3	142	4.05
		NA's	106	3.02
Ever Sectioned	No	0	2062	58.83
	Yes	1	976	27.85
		NA's	467	13.32
Highest educational attainment	Not attained higher education	0	1881	53.67
	Attained higher education	1	1308	37.32
		NA's	316	9.02

Variable name	Variable description	Coding	Available records	%
Highest Occupation*	Unknown	0	163	4.65
	Level 1	1	95	2.71
	Level 2	2	1296	36.98
	Level 3	3	655	18.69
	Level 4	4	1092	31.16
	Never worked	5	34	0.97
	Homemaker	6	12	0.34
	Student	7	61	1.74
		NA's	97	2.77
Current occupation*	Unknown	0	126	3.59
	Level 1	1	52	1.48
	Level 2	2	421	12.01
	Level 3	3	223	6.36
	Level 4	4	405	11.55
	Never worked	5	1092	31.16
	Homemaker	6	62	1.77
	Student	7	95	2.71
	Retired	8	366	10.44
		NA's	663	18.92
Number of episodes of mania	0-13	1	2405	68.62
	13-46	2	714	20.37
	47-300	3	130	3.71
		NA's	256	7.30
Number of episodes of depression	0-13	1	2083	59.43
	13-47	2	913	26.05
	48-327	3	184	5.25
		NA's	325	9.27
Longest duration of depression in weeks	0.2-44.9	1	2096	59.80
	44.9-142	2	795	22.68
	143-800	3	165	4.71
		NA's	449	12.81
Longest duration of mania in weeks	0.1-11.8	1	2084	59.46
	11.8-47.8	2	1122	32.01
	47.8-312	3	84	2.40
		NA's	215	6.13

Table 4.4: Variables Included in Factor Analysis .The table provides the names and descriptions of the variables included in the factor analysis, along with their coding systems and the number of available records represented in both absolute values (#) and percentages.

2.3.4 Differences in Outcomes Between Bipolar Disorder Subtypes

Episode Duration: Participants with bipolar 2 disorder exhibited longer duration of depression episodes compared to those with bipolar 1 disorder. Conversely, individuals with bipolar 1 disorder had longer manic episodes compared to all other diagnostic groups. Among participants with schizoaffective disorder, longer episodes of mania were observed compared to those with bipolar 2 disorder.

Number of Episodes: There was a statistically significant difference in the number of episodes between groups, with bipolar 2 patients reporting a higher number of episodes compared to other patients.

Number of Admissions and Ever Sectioned: Patients with a higher number of admissions were predominantly diagnosed with schizoaffective-bipolar disorder (SA-BD), followed by bipolar 1 (BD 1), bipolar 2 (BD 2), and bipolar not otherwise specified (BD-NOS). In terms of the ever sectioned variable, the sample can be divided into two subgroups: BD 1/SA-BD and BD 2/BD-NOS. Subjects in the first group had a higher frequency of being sectioned compared to individuals in the second group.

Global Assessment of Functioning (GAS): Patients with bipolar 1 disorder reported better actual functioning compared to those with bipolar 2 disorder and SA-BD. SA-BD patients exhibited worse functioning, with a notable association with the GAS interval 41-50, which corresponds to "Any serious symptomatology or impairment in functioning that most clinicians would think obviously requires treatment or attention (e.g., suicidal preoccupation or gesture, severe obsessional rituals, frequent anxiety attacks, serious antisocial behaviour, compulsive drinking).

Marital History: Most of the sample had either been married or lived as married. SA-BD patients had the highest percentage of never being married or living as married.

Educational Attainment: No significant differences were found in educational attainment between patients with different diagnoses.

3.3.4 Factor model in BD1

In the exploratory factor model conducted on participants with bipolar 1 disorder (BD-1) and complete information (i.e. no missing data), a polychoric correlation matrix was computed. Figure 2 displays the correlations between each item included in the analysis, with the direction of association indicated by coloured dots (red for negative association, blue for positive association).

Notably, a strong positive correlation (correlation coefficient of 0.41) was observed between two items related to hospital admission: the total number of admissions and whether the patient had been sectioned or not. Additionally, there was a strong positive correlation (correlation coefficient of 0.59) between the number of depressive and manic episodes.

On the other hand, a negative correlation (correlation coefficients of -0.63 and -0.51, respectively) was found between the Global Assessment of Functioning (GAS) subscale for the worst manic episode and whether the participant had ever been sectioned and the number of admissions. This negative correlation is expected since higher scores on the GAS subscale indicate better functioning.

These correlation findings provide insights into the relationships among different variables in the exploratory factor model within the bipolar 1 disorder subgroup.

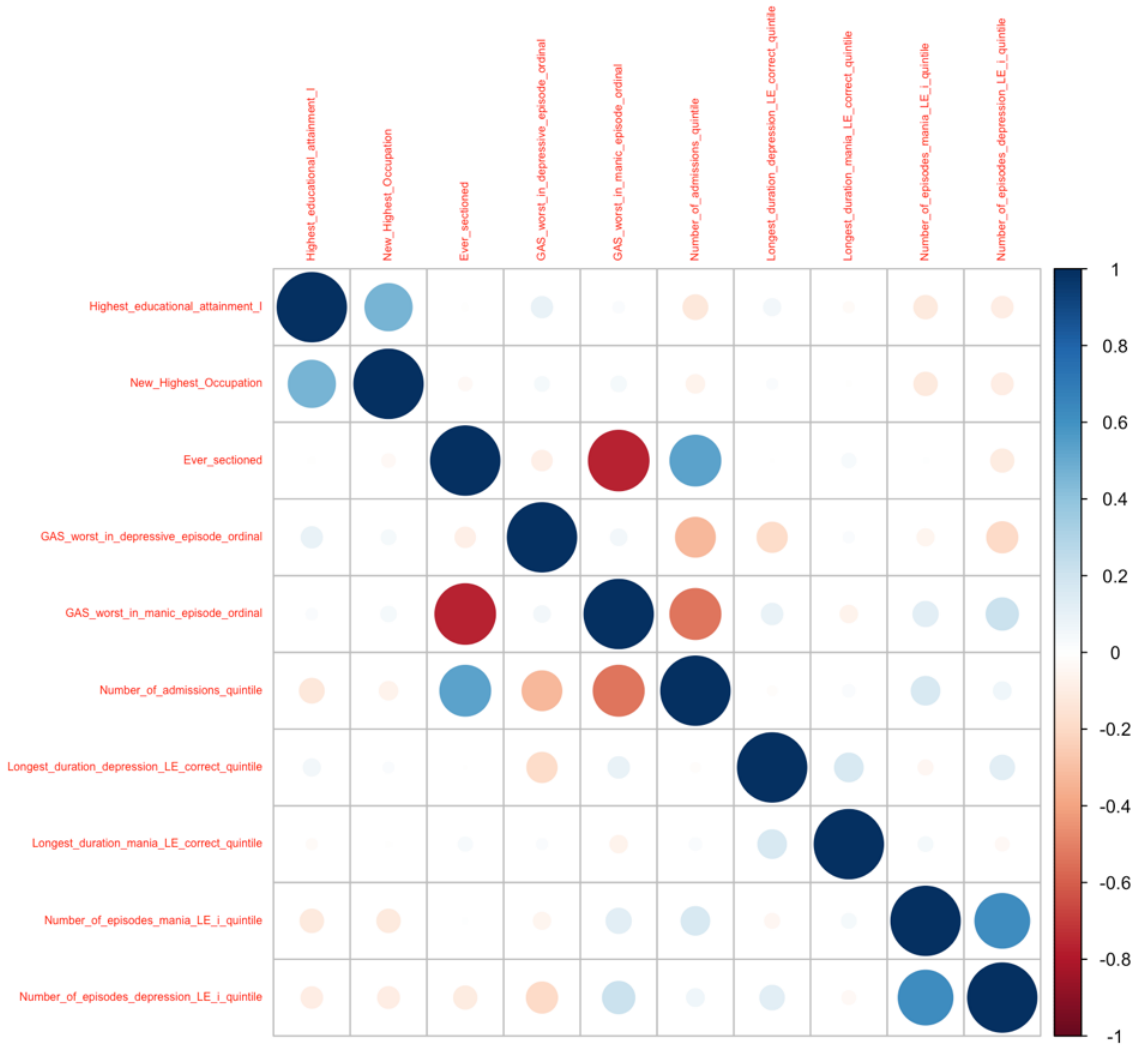
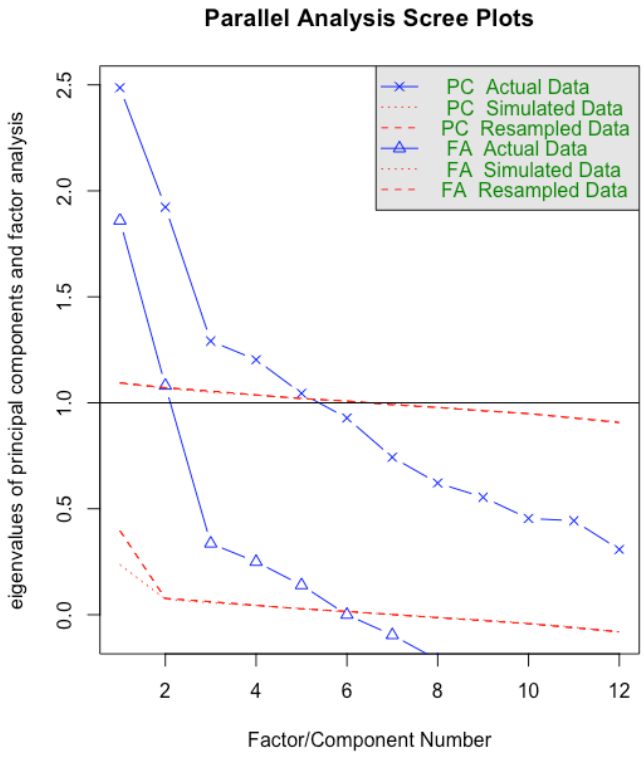


Figure2.4: Correlation plot of variables entered in factor analysis for BD1.

Determination of factors numbers:

The determination of the number of factors to retain in the factor analysis was based on Kaiser's rules. According to these rules, factors with eigenvalues greater than 1 were considered for retention. Following this criterion, the first five factors were retained for further analysis.

Figure 3.4: Scree plot of eigenvalues in BD1.



Factors loadings:

Table 5.4 presents the results of the factor analysis. In the upper section, the five factors are listed along with the loadings of each variable on each factor. The proportion of variance explained by each factor, as well as the cumulative variance explained, is also provided. The model with five factors accounts for 66% of the total variance in the bipolar 1 sample.

Factor analysis allows for the identification of latent dimensions within the set of variables considered. The first factor, labelled MR1, is associated with "Hospitalization History" and potentially reflects the severity of mania. It explains 19.4% of the observed variance. The second factor, MR2, is more focused on the clinical aspects of the disease, encompassing the number of manic and depressive episodes. It explains 14.9% of the variance and captures a dimension of disorder recurrence.

The third factor, MR3, explains 12.8% of the variance and relates to "Maximum Aspiration," combining variables such as Highest Educational Attainment and Highest Occupation. The fourth factor, MR4, explains 10.4% of the variance and pertains to another clinical aspect of the disorder, specifically the duration of the longest episode of depression and mania.

The fifth factor, explaining 8.3% of the variance, is also clinical in nature, representing functioning during the worst depressive episode.

Table 5.4 Factor analysis results in BD1: Factors structure and relative proportional and cumulative variance for the generated factors

	MR1	MR2	MR3	MR4	MR5
Highest educational attainment			1.011		
Highest Occupation			0.499		
Ever sectioned	0.842				
GAS worst in depressive episode					0.780
GAS worst in manic episode ordinal	-0.887	0.135			
Number of admissions quintile	0.61	0.115			-0.290
Longest duration depression LE quintile	-0.154	-0.125		0.993	-0.277
Longest duration mania LE quintile				0.211	
Number of episodes mania LE quintile		1.052			0.185
Number of episodes depression LE quintile	-0.152	0.581			-0.169
	MR1	**MR2**	**MR3**	**MR4**	**MR5**
SS loadings	1.938	1.493	1.281	1.044	0.842
Proportion Var	0.194	0.149	0.128	0.104	0.084
Cumulative Var	0.194	0.343	0.471	0.576	**0.660**

Upon examining communalities, it was found that eight out of ten variables have values higher than 0.4. The variables with lower communalities were Highest Occupation (0.21) and the longest duration of mania (0.04), indicating a weaker association with the underlying factors.

4.3.4 Factor model in BD2

A polychoric correlation matrix was also computed using all "complete cases" with a bipolar 2 (BD2) diagnosis. Similar to the previous analysis, Figure 3 displays the correlations between each item included in the analysis. The coloured dots indicate the direction of the association, with red representing a negative association and blue representing a positive association.

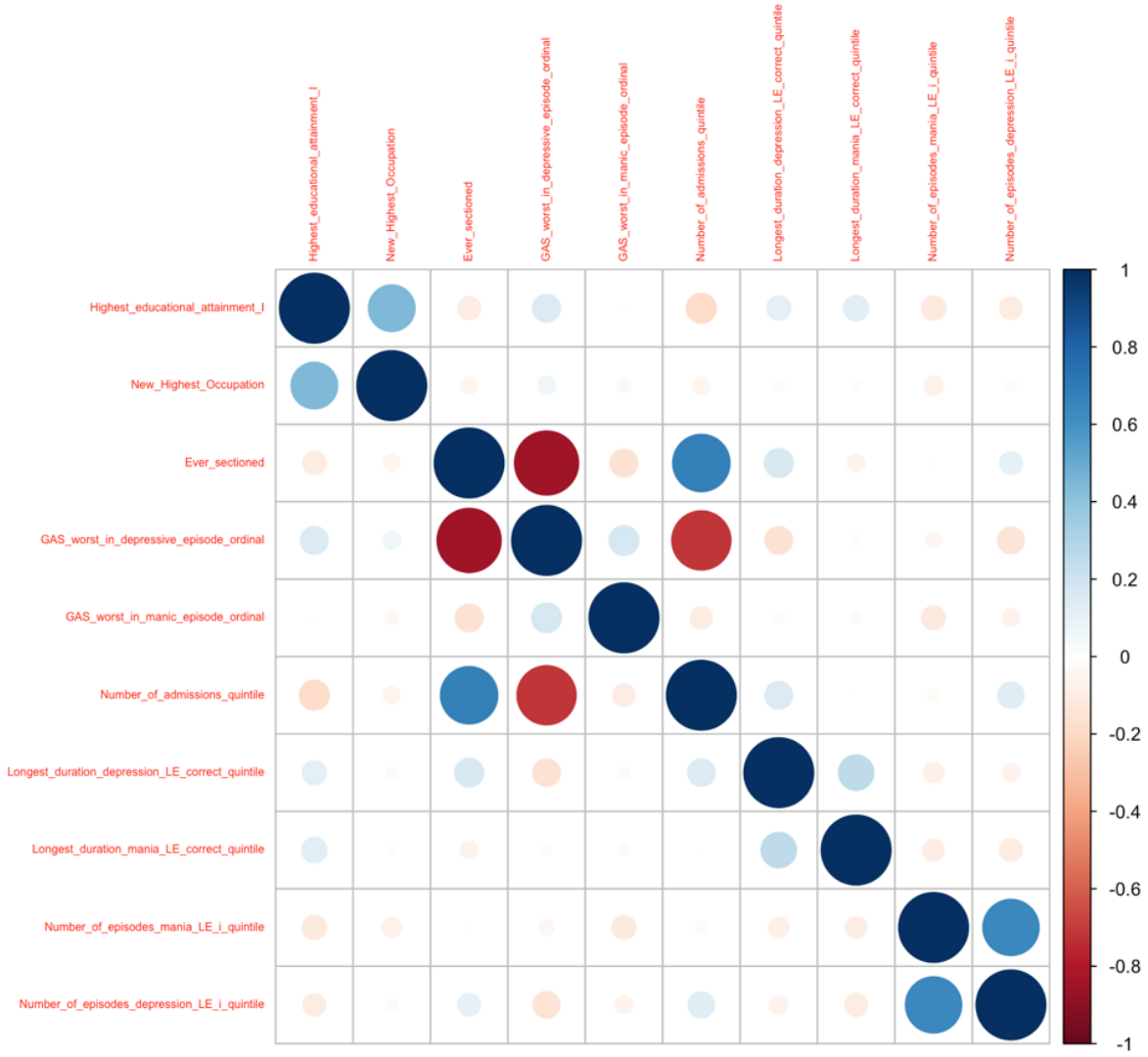


Figure 4.4: Correlation plot of variables entered in factor analysis BD2.

Similar to bipolar 1 disorder, a strong positive correlation was observed between the two items related to hospital admission in individuals with bipolar 2 disorder (correlation coefficient 0.68). Additionally, a positive correlation was found between the number of depressive and manic episodes (correlation coefficient 0.65). On the other hand, a negative correlation was identified between the GAS subscale for the worst depressive episode and both the item indicating whether the participant was ever sectioned and the number of admissions (correlation coefficients -0.84 and -0.72, respectively).

Determination of factors numbers:

To determine the number of factors to retain, Kaiser's rule was applied, resulting in the retention of the first 4 factors.

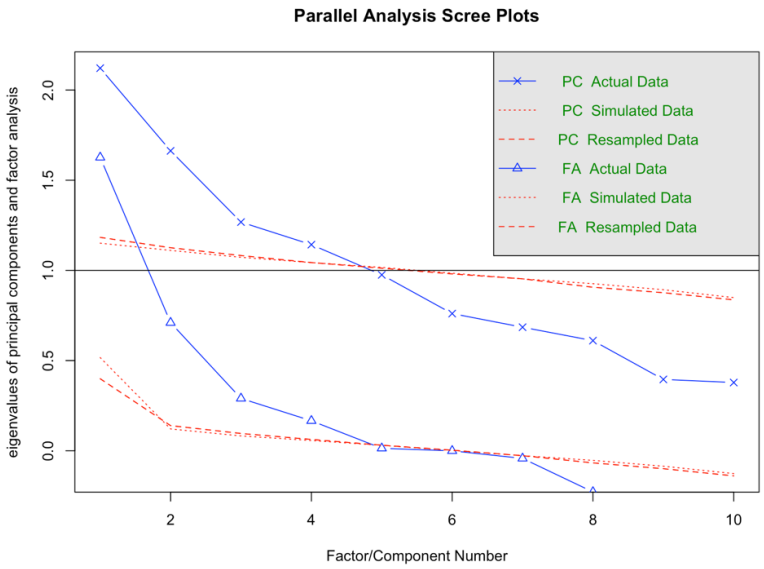


Figure 5.4: Scree plot of eigenvalues in BD2.

Factors loadings:

Table 6.3 reports the exploratory factor analysis Results for Bipolar 2 Disorder

In the upper section of Table 6.3, the 4 factors and their corresponding loadings for each variable are presented, along with the proportion and cumulative variance explained by the model. The model with 4 factors accounts for 65.6% of the total variance in the bipolar 2 sample.

The first factor (MR1), which explains 24.1% of the total variance, captures the severity of depressive symptoms and their association with hospitalization. The highest loading is observed for the GAS worst in depressive episode, followed by ever sectioned and number of admissions.

The second and third factors (MR2 and MR3) exhibit similar characteristics to those observed in the bipolar 1 sample. MR2 reflects the clinical aspect of the disorder, emphasizing its chronicity. MR3 represents the socio-personal achievements of the individuals.

Table 6.4 Factor analysis results in BD2: Factors structure and relative proportional and cumulative variance for the generated factors

	MR1	**MR2**	**MR3**	**MR4**
Highest educational attainment			0.937	0.192
Highest Occupation			0.485	
Ever sectioned	0.917	-0.103		
GAS worst in depressive episode	-0.948			
GAS worst in manic episode ordinal	-0.158			
Number of admissions quintile	0.766			
Longest duration depression LE quintile	0.127			0.535
Longest duration mania LE quintile				0.496
Number of episodes mania LE quintile	-0.174	1.042		
Number of episodes depression LE quintile		0.644		
	MR1	**MR2**	**MR3**	**MR4**
SS loadings	2.413	1.53	1.132	0.584
Proportion Var	0.241	0.153	0.113	0.058
Cumulative Var	0.241	0.394	0.508	**0.566**

Examination of communalities revealed that out of the 10 variables considered, only 6 variables had communalities greater than 0.4. The variables highest occupation (0.23), longest duration of mania (0.24), longest duration of depression (0.31), and GAS worst in manic episode (0.04) had communalities below the threshold of 0.4.

5.3.4 Confirmatory Factor Analysis in BD1

Based on the results of the exploratory factor analysis (EFA), a confirmatory factor analysis (CFA) was conducted on a sample of 578 participants with bipolar 1 disorder (BD1). The CFA confirmed a good fit of the 5-factor model (Figure 5) with the data, as evidenced by a significant $\chi 2$ statistic, a comparative fit index (CFI) greater than 0.9, a root mean square error of approximation (RMSEA) below 0.08, and a standardized root mean square residual (SRMR) of 0.05.

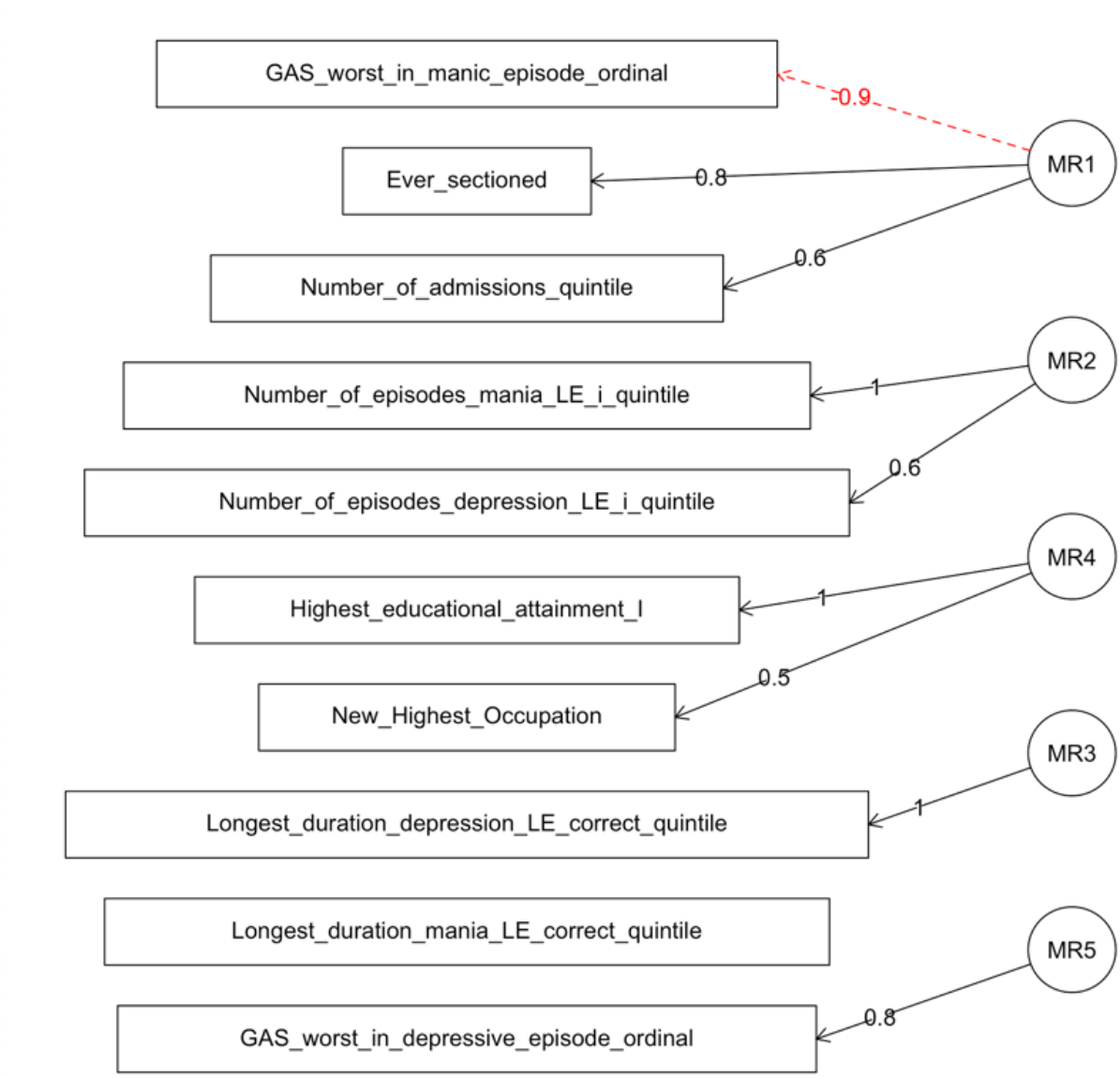


Figure 6.4: Factor model in BD1

6.3.4 Confirmatory Factor Analysis in BD2

Based on the results of the exploratory factor analysis (EFA) conducted on the subset of participants with bipolar 2 disorder (BD2), a 4-factor model (Figure 6) was suggested. However, when a confirmatory factor analysis (CFA) was performed on a sample of 245 participants with BD2, the model did not demonstrate a good fit with the data. The fit indices, such as the $\chi 2$ statistic, did not reach significance, indicating a lack of fit. Therefore, the hypothesized 4-factor model did not adequately explain the relationships among the observed variables in the BD2 sample.

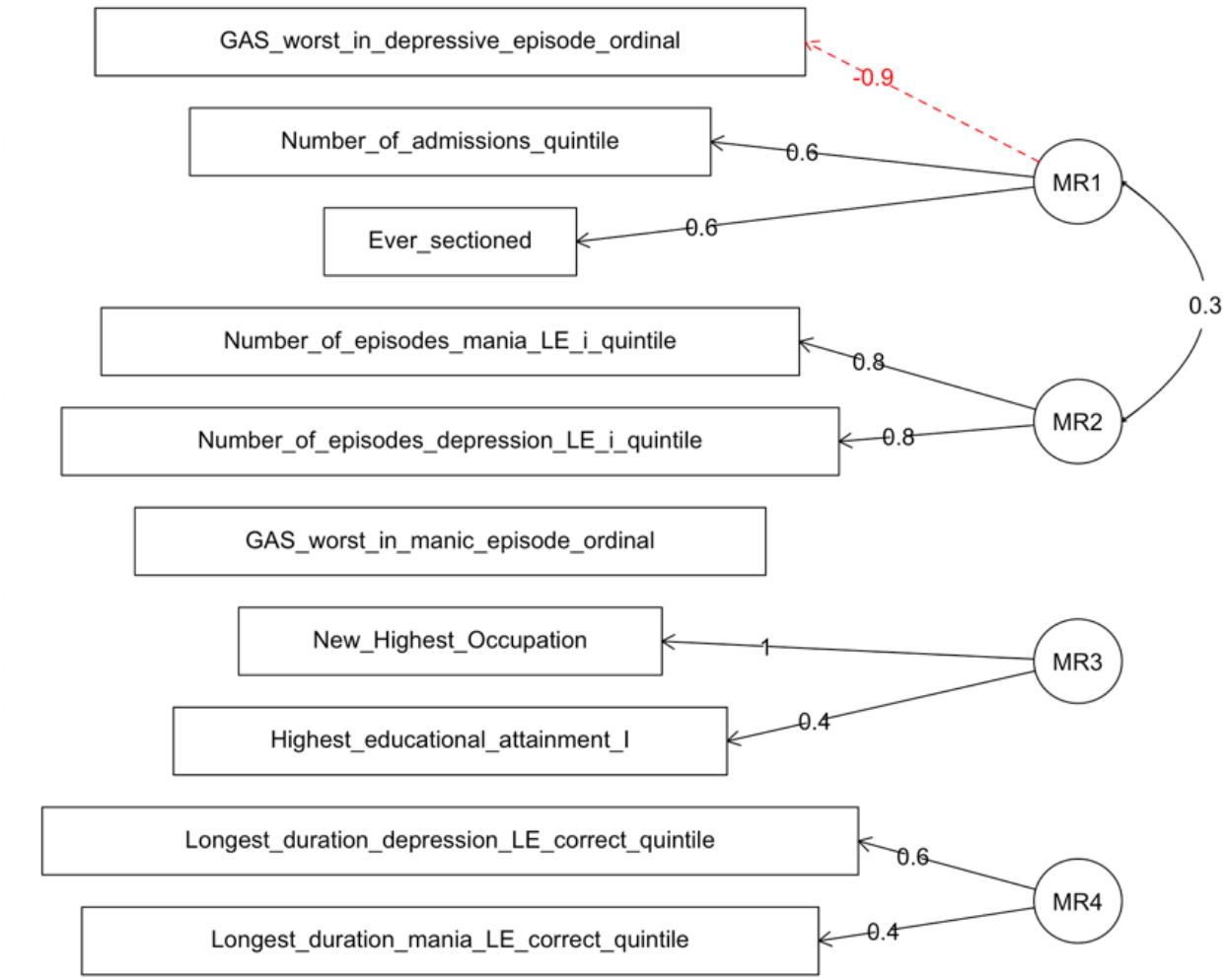


Figure 7.4: Factor model in BD2

4.4 DISCUSSION

The primary objective of this study was to provide a comprehensive description of outcomes in bipolar disorder, particularly focusing on the interactions between various domains including social, personal, and clinical aspects. To achieve this objective, a factor analysis approach was employed, which aimed to reduce the original number of outcome variables while maximizing the retained information in the generated factors.

In the BD1 sample, the exploratory factor analysis revealed a 5-factor model that accounted for 66% of the variance in the data.

This model was further validated in a replication sample, demonstrating good fit indices. The first factor in BD1, associated with the "Hospitalization History," likely reflects the severity of the disorder.

The second factor captured the number of episodes of depression and mania, representing a dimension of disorder recurrence and chronicity. This finding supports previous research indicating that the frequency of episodes significantly impacts overall well-being (Fagiolini et al., 2013) The third factor was associated with education and occupation, suggesting a potential link to socio-economic stability and the ability to achieve long-term life goals.

The fourth factor appeared also to reflect aspects of chronicity, with the longest duration of depression loading onto this factor. This suggests that the time spent by patients in a non-euthymic state may be a clinically relevant aspect to consider, beyond focusing solely on mood polarity during episodes.

The fifth factor captured a clinical aspect of the disorder, specifically pertaining to functioning during the worst depressive episode.

It is noteworthy to observe that, despite the disparity in the nature of data employed in the present Factor Analysis (FA) in contrast to a standardized scale, the outcomes, particularly the delineation of factors associated with personal functioning (such as severity of the disorder, frequency of admissions, and episodes) as well as social functioning, the third factor, parallel the findings of (Charles et al., 2020) who identified two principal factors, termed "personal" and "social," utilizing the WHOQOL-BREF instrument.

In the BD2 sample, the analysis revealed a four-factor model that partially resembled the findings obtained from the BD1 set. The first factor in the BD2 subset captured the severity

of the disorder and the hospitalization history of the subjects. As anticipated, considering depression as a predominant feature of the BD2 phenotype, the Global Assessment of Severity (GAS) scores for worst depressive episodes replaced the GAS scores for worst manic episodes observed in the BD1 analysis. Moreover, the factor loading of the phenotype variables describing depressive features was higher in the BD2 analysis, further supporting the association of this factor with depression.

However, when conducting confirmatory factor analysis on the BD2 sample, the results failed to replicate those obtained in the exploratory factor analysis. This discrepancy can be attributed to two primary factors. Firstly, the BD1 cohort had a significantly larger sample size, almost double that of the BD2 cohort. This discrepancy in sample size could have influenced the ability to replicate the factor structure in the smaller BD2 sample. Secondly, it is important to consider the variation in phenotypic heterogeneity between the two subsets. The BD1 cohort exhibited greater homogeneity in terms of phenotypic expression compared to the BD2 cohort. This may be attributed to the fact that individuals with BD2 often present with milder phenotypes that can overlap with other conditions such as depression. In contrast, the diagnosis of BD1 is primarily driven by the presence of a manic episode, resulting in a more distinct and robust diagnosis.

Even though the two-factor analysis conducted on the two diagnostic subsets yielded distinct factor structures, it is intriguing to scrutinize the arrangement and the respective contributions of the outcome variables to these different factors. Both the primary factors delineating the severity of mania and depression, respectively, manifest as "mixed" factors. Indeed, within these factors, we encounter not only purely clinical descriptors, such as the number of admissions, but also variables encompassing the overall functioning of the patients. In contrast to other factors that are either solely clinical (e.g., longest duration of episodes) or social (e.g., employment and education), the primary factors affirm the hypothesis that both social and clinical factors are intricately correlated. This underscores the imperative that, in the evaluation and treatment of patients, consideration must be given not only to clinical outcomes but also to social outcomes.

Taken together, these findings highlight the importance of considering sample characteristics, such as size and phenotypic heterogeneity, when interpreting and comparing factor structures across different subsets of bipolar disorder. Further research is warranted to replicate these findings in larger BD2 samples and to explore additional factors that may contribute to the heterogeneity within the BD2 phenotype.

5.4 LIMITATIONS

It is important to acknowledge several limitations of the present study. Firstly, participants were assessed at different stages of their illness, resulting in significant variation in the duration of illness across participants. To account for this, the length of illness was included in the analysis. Additionally, the option of incorporating the ratio between the number of episodes and the length of illness was considered but deemed inappropriate due to observed variations in episode frequency over time.

Furthermore, the study spanned over 25 years, leading to differences in enrolment rates based on diagnosis (i.e. more people with BD1 recruited in the initial years for the study) and data missingness. Moreover, certain outcomes initially considered may have different implications for different patients. For instance, personal achievements such as education and occupation can be influenced by the age of onset of the disorder, with early-onset cases potentially having a more substantial impact on educational attainment compared to adult-onset cases.

The replication study conducted in the BD2 cohort was limited by the small size of the replication sample, consisting of fewer than 300 subjects. Therefore, replication on larger and completely independent samples would be ideal for further validation.

Finally, what could have been done was to include additional clinical outcomes. For example, therapy response. It is well known that a good response and adherence to therapy significantly influence various aspects of patient outcomes. These include clinical outcomes such as the number of manic and depressive episodes (Sajatovic et al., 2018), as well as socio-functional outcomes such as socialization and employment(O'Donnell, Helmuth, Williams, McInnis, & Ryan, 2023). Unfortunately, the database I used poses problems in this regard: data missingness, as the variables describing pharmacological outcomes were not complete for all

patients, and since Factor Analysis requires complete cases to function, the sample size would have been reduced too much. Another issue is the history of sample recruitment, as recruitment lasted for more than 30 years and due to the update and development of new therapies, there was too much heterogeneity in the initially recruited sample compared to the more recent one. The last problem, despite having variables that retrospectively assessed drug response, there is no information on drug titration and blood concentration, which in the case of bipolar disorder, especially for lithium therapy, are crucial to conduct robust analyses generalizable to other patient populations and clinical databases.

In summary, this study provides valuable insights into outcomes in bipolar disorder by employing a factor analysis approach. While the findings in the BD1 sample were supported by replication, the BD2 sample demonstrated a different factor structure. It is crucial to consider the limitations outlined and encourage future research with larger and independent samples to enhance the generalizability of the findings.

Chapter 5: Polygenic Risk Scoring and Genetic Contributions to Outcomes and Trajectories in Bipolar Disorder

1.5 INTRODUCTION

Bipolar disorder, like many other psychiatric disorders, is characterized by a complex genetic architecture. Twin studies have demonstrated a high heritability of bipolar disorder, with estimates surpassing 70% (Edvardsen et al., 2008). In recent years, genome-wide association studies (GWAS) conducted by the PGC Bipolar Disorder Working Group have shed further light on the genetic basis of the disorder. This large-scale collaboration, involving 20,352 cases and 31,358 controls, identified single-nucleotide polymorphism (SNP) heritability on the liability scale ranging from 0.17 to 0.23, assuming a prevalence of 0.5-2% in the population (Stahl et al., 2019).

Despite these advancements, it is important to note that GWAS findings only account for a small proportion of the overall genetic risk associated with bipolar disorder. This limited explanatory power can be attributed to the challenge of reaching the stringent significance threshold typically set at 5×10^{-8}, owing to the issue of multiple testing. To address this limitation, researchers have employed the use of Polygenic Risk Scores (PRSs) as a viable approach. PRSs are calculated based on the theory that the heritability of a trait is determined by the collective impact of numerous common variants, each exerting a small effect size that may not reach the threshold for significance in GWAS. In the field of neuropsychiatric genetics, including studies specific to bipolar disorder, PRSs have been widely utilized and have yielded promising results.

Presently, the diagnosis and categorization of bipolar disorder (BD) subtypes predominantly rely on clinical manifestations. However, in recent years, researchers have endeavoured to integrate genetic risk factors into the diagnosis and classification of BD subtypes. For a study comparing the relative influence of rare copy number variations (CNVs) and common schizophrenia (SCZ) risk alleles on the likelihood of psychosis revealed that compared to BD-I patients without psychosis, those with schizoaffective bipolar disorder (SAB) exhibited heightened CNV burden and SCZ polygenic risk scores (PRS), with the presence of psychotic symptoms in BD-I correlating with increased SCZ-PRS (Alexander W. Charney et al., 2019). Another study corroborated these findings, demonstrating significantly elevated BD-PRS in patients with psychotic BD compared to those without psychosis (Aminoff et al., 2015). Subsequent investigations further supported these conclusions, indicating that BD-I patients experiencing manic psychosis had notably higher SCZ-PRS compared to other BD subtypes and controls. Additionally, these patients displayed lower major depressive disorder (MDD) polygenic risk scores, suggesting a genetic affinity to schizophrenia surpassing that of other BD subtypes (Markota et al., 2018);(Guzman-Parra et al., 2021).

The Efficacy Study and Prediction of Treatment Response in Bipolar Disorder Lithium, a widely utilized medication for bipolar disorder (BD) treatment, exhibits considerable variability in patient response. Polygenic risk scores (PRS) have emerged as a tool to uncover pharmacogenomic effects and potentially forecast individual drug responses. Different studies indicated that elevated polygenic risk scores for attention deficit hyperactivity disorder (ADHD) and major depressive disorder (MDD) are linked to diminished responses to lithium treatment (Coombes et al., 2021). Moreover, higher polygenic risk scores for schizophrenia (SCZ) were associated with inferior lithium treatment outcomes, while polygenic risk scores specific to BD showed no discernible correlation with treatment efficacy(Schubert et al., 2021). Given the substantial genetic overlap between BD and other psychiatric conditions, amalgamating genetic risk factors for ADHD, MDD, and SCZ with clinical risk factors may offer valuable insights into optimizing the clinical management of BD patients.

By incorporating PRSs into genetic investigations, researchers aim to enhance the understanding of the genetic underpinnings of bipolar disorder and other complex traits. This approach capitalizes on the cumulative effect of multiple variants, even those with modest individual effects, to provide a more comprehensive assessment of genetic risk. As the field

of genetics continues to advance, further exploration of PRSs and their potential utility in unravelling the complexities of bipolar disorder holds great promise for elucidating the underlying genetic mechanisms and ultimately facilitating improved diagnosis and treatment strategies.

Aims

- In the current study PRSs for several neuropsychiatric traits and condition (Schizophrenia, Major depressive disorder, Neuroticism, Mood instability, Intelligence, Chronic pain) were used first to test if these PRS are predictors of BD phenotypes coming from both retrospective and longitudinal data (BDRN and TC), moreover the comparison of association between these PRS and the phenotype variables considered will be used to test the quality and the reliability of the phenotype variables generated by TC data.

- To look at the biological validity of generated factors investigating their potential heritability and their relation to liability for common neuropsychiatric traits;

2.5 METHODS

1.2.5 Genomic Data

Participant were genotyped on Affymetrix GeneChip 500K Mapping Array Set, Illumina Omni Express Array, and Illumina PsychChip. For each platform strict quality control (QC) was performed separately. QC used PLINK 1.9 software excluding SNPs for which the minor allele frequency (MAF) was less than 0.01, deviation from Hardy-Weinberg Equilibrium (HWE) at P≤ 10-6, call rate < 98%. Individuals were excluded from the sample if they had

increased or decreased heterozygosity of |F| > 0.1, a discrepancy between their genotypic and reported sex, genotype call rate < 98%, high pairwise relatedness (pi-hat > 0.2) or did not cluster with European population samples in principal component analysis of 2000 participants from 19 populations of the 1000 Genomes Project. After QC, data for each platform were phased using SHAPEIT version 3.4.0.10233and imputed using IMPUTE24 with the 1000 Genomes Project reference panel (phase 3). Imputed data were converted to the most probable genotypes (probability ≥ 0.9) with additional SNPs excluded if the imputation INFO score was <0.8, MAF<0.01 or HWE P<1x10-6). Imputed data were then merged on common SNPs between platforms.

Merging

Subjects in BDRN where genotyped on three different platforms. The number of genotyped SNPs available is then different for the three subgroups.
Before proceeding to the analysis, the three datasets were merged retaining only the common SNPs. Relatedness, calculated as pairs of identity-by-descent (IBD) values, a pi_hat value of 0.1 was set (lower limit for first cousins).

2.2.5 PRS generation

PRSs were generated for several traits (see table 1.4) using as reference GWAS summary stats publicly available. Summary stats for Schizophrenia was modified in order to exclude subject analysed in the present study. PRSs generation using PLINK version 1.9 (Chang et al., 2015) in PRSice (Euesden, Lewis, & O'Reilly, 2015). Imputed genotypes were clumped for linkage disequilibrium (window, 250 kb; r2 = 0.1) and single-nucleotide polymorphisms most significantly associated with the different traits were retained. Table 1.4 shows for each trait the number of retained SNPs were after clumping. After clumping, PRSs were generated at different P value thresholds (PT) $P < 1.00$, $P \leq .50$, $P \leq .20$, $P \leq .10$, $P \leq .05$, $P \leq .01$, and $P \leq .001$ and converted to z scores.

Trait		GWAS reference	retained SNPs after clumping
Schizophrenia		Pardiñas et al. 2018	120379
Depression		Wray et al. 2018	123328
ADHD		Demontis et al. 2018	123414
Educational attainment		Okbay et al. 2022	123273
Mood instability		Ward et al. 2019	119747
Sleep duration		Dashti et al 2019	124424
Multisite chronic pain		Johnston et al. 2019	121094
Crohn's disease		KM de Lange et al. 2017	123436

Table 1.5: GWAS summary statistics used for PRSs generation and number of SNPs retained after clumping.

3.2.5 Statistical analysis

Factors scores for each of the 5 factors and for each patient were calculated using the R function factors.scores from the psych library. Method was set as “Thurnstone”. This method finds the regression based weights: W = R^{-1} F where R is the correlation matrix and F is the factor loading matrix.

Each factor score (1 to 5) was regressed against the 4 PRS and all analysis were corrected for the first 10 population principal components, sex, and platform on which subjects were genotyped.

4.2.5 Phenotypic data

1.4.2.5 Longitudinal mood monitoring in bipolar disorder

The phenotypic variables investigated in the True Colours (TC) study were derived from data described and analysed in Chapter 2. Two mood rating scales, namely the Quick Inventory of Depressive Symptomatology (QIDS) and the Altman Self-Rating Mania Scale (ASRM), were used to assess depressive and manic symptoms experienced by the patients. Various phenotypic descriptors were generated based on the patients' responses to these scales, focusing on the proportion of time spent in different mood states. These variables include:

Proportion of time spent with any mood symptom (in %)
Proportion of time spent without symptoms (in %)
Proportion of time spent with manic symptoms (in %)
Proportion of time spent with depressive symptoms (in %)
Proportion of time spent in mixed states (in %)
Additionally, comparative analyses were conducted between the TC study and the Bipolar Disorder Research Network (BDRN) database in this chapter. The BDRN variables considered in the comparison included the total number of episodes per year and the number of depressive episodes per year.

2.4.2.5 Factor analysis of outcomes in bipolar disorder

This section focuses on the analysis of phenotypic variables using factor scores derived from the 5-factor model specific to the BD1 subset. The five factors incorporated in the model include “Severity of Mania”, “Number of Episodes”, “Attainment”, “Episode Characteristics”, and “Severity of Depression”. It is important to emphasize that these factors are conceptualized at a structural level, providing an overarching framework for understanding the underlying dimensions of bipolar disorder, rather than being derived directly from the observed data. Consequently, it was necessary to compute factor scores for each patient, as outlined in the methodology section. The Thurstone method was employed

for this purpose, generating scores ranging from -1 to +1. Positive scores indicate a positive association with the respective factor, while scores below zero suggest no association. Furthermore, similar to the previous chapter, the BD1 sample was divided into two sets: an 80% training set and a 20% replication set, with the latter being utilized for genetic analyses to validate the findings obtained.

3.5 RESULTS

1.3.5 Longitudinal mood monitoring in bipolar disorder

Association between PRS and proportion of time spent ill assessed in TC

The analysis examining the association between Polygenic Risk Scores (PRS) and the proportion of time spent ill in the True Colours (TC) study yielded significant findings, which are presented in Tables 2.4 and 3.4. The main text includes only statistically significant associations between the phenotypic variable and the PRSs, while the non-significant associations can be found in tables 6.4 to 9.4.

In relation to the proportion of time spent ill, irrespective of the polarity of symptomatology, positive associations were identified with PRS for Depression, Neuroticism, Sleep duration, and Chronic Pain. It is important to note that patients were categorized as having depressive symptoms (low mood) when the Quick Inventory of Depressive Symptomatology (QIDS) score exceeded 10, and as having any mood symptom when the QIDS, Altman Self-Rating Mania (ASRM), or both scores were above 10.

Table 2.5, PRS association with prospective phenotypic index in TC (Proportion of time spent with depressive symptoms)

Phenotype	PRS	Estimate	Std. Error	t value	*p*
Time spent with depressive symptoms (q10) %	MDD	3.65	1.16	3.16	0.001
	Neuroticism	2.99	1.17	2.56	0.011
	Sleep duration	-3.59	1.28	-2.82	0.005
	Crohn's disease	66.25	167.50	0.40	0.693

Table 3.5, PRS association with prospective s phenotypic index in TC (Proportion of time spent with any symptoms at the defined mood rating scales thresholds ASRM 10 and QIDS 10)

Phenotype	PRS	Estimate	Std. Error	t value	*p*
Time spent with significant mood symptoms (a10q10) %	MDD	3.76	1.22	3.09	0.002
	Neuroticism	3.34	1.23	2.71	0.007
	Sleep duration	-3.81	1.34	-2.84	0.005
	Crohn's disease	45.43	168.92	0.27	0.788

To further validate the phenotypic index established in the TC study, an association analysis was conducted between the PRS and the number of total episodes and depressive episodes in the retrospective cohort of the Bipolar Disorder Research Network (BDRN). The results of this analysis can be found in Tables 4.4 and 5.4

Consistent with the TC findings, the association between the PRS for Major Depressive Disorder (MDD) and Neuroticism remained significant when examining both the total number of episodes per year and the number of depressive episodes per year in the BDRN dataset.

Table 4.5, PRS association with the retrospective phenotypic index in BDRN (total episodes year)

Phenotype	PRS	Estimate	Std. Error	t value	*p*
Total episodes year	MDD	0.04524	0.02098	2.156	0.031124
	Neuroticism	0.04188	0.02099	1.995	0.046064
	Crohn's	5.44131	3.41766	1.592	0.111438

Table 5.5, PRS association with the retrospective phenotypic index in BDRN (depressive episodes year)

Phenotype	PRS	Estimate	Std. Error	t value	*p*
Depressive episodes year	MDD	0.0325	0.01448	2.244	0.02488
	Neuroticism	0.02447	0.01448	1.69	0.09102
	Crohn's	2.97738	2.22133	1.34	0.18021

Interestingly, a comparison of the p-values and t-values for the association between similar phenotypic variables and the same PRS indicated that the prospectively assessed phenotype (i.e., the proportion of time spent with certain mood symptoms) provided a better fit for the model compared to the retrospectively assessed variable derived from interviews and available clinical records in the BDRN dataset.

Not Significant associations Between PRSs and TC variables:

Table 6.5 not significant associations between PRSs and the proportion of time spent with depressive symptoms.

Phenotype	PRS	Estimate	Std. Error	t value	*p*
Time spent with depressive symptoms (q10) %	Schizophrenia	0.63	1.13	0.56	0.58
	Mood instability	0.75	1.20	0.63	0.53
	Year of education	-0.31	1.25	-0.25	0.80

Table 7.5 not significant associations between PRSs and the proportion of time spent with significant mood symptoms.

Phenotype	PRS	Estimate	Std. Error	t value	*p*
Time spent with significant mood symptoms (a10q10) %	Schizophrenia	0.60	1.19	0.50	0.62
	Mood instability	0.88	1.26	0.70	0.49
	Years of education	-0.47	1.31	-0.36	0.72
	Multisite Chronic Pain	2.35	1.22	1.92	0.06

Table 8.5 not significant associations between PRSs and the proportion of time spent with significant mood symptoms.

Phenotype	PRS	Estimate	Std. Error	t value	*p*
Time spent with significant mood symptoms (a10q10) %	Schizophrenia	0.60	1.19	0.50	0.62
	Mood instability	0.88	1.26	0.70	0.49
	Years of education	-0.47	1.31	-0.36	0.72
	Multisite Chronic Pain	2.35	1.22	1.92	0.06

Table 9.5 not significant associations between PRSs and the proportion of time spent with manic symptoms.

Phenotype	PRS	Estimate	Std. Error	t value	*p*
Time spent with manic symptoms (q10) %	Schizophrenia	-0.21	0.21	-0.99	0.32
	MDD	-0.01	0.22	-0.04	0.96
	Neuroticism	0.25	0.22	1.13	0.26
	Mood instability	0.22	0.22	0.96	0.3359
	Sleep duration	-0.32	0.24	-1.35	0.18
	Years of education	0.06	0.23	0.26	0.79
	Multisite Chronic Pain	-0.28	0.22	-1.30	0.19
	Crohn's	21.05	32.19	0.65	0.5136

Table 10.5 not significant associations between PRSs and the proportion of time spent with manic and depressive symptoms at the same time

Phenotype	PRS	Estimate	Std. Error	t value	*p*
Time spent with mixed symptoms (a10q10) %	Schizophrenia	0.17	0.15	1.17	0.24
	MDD	0.12	0.15	0.81	0.42
	Neuroticism	0.10	0.15	0.64	0.52
	Mood instability	-0.09	0.16	-0.58	0.5595
	Sleep duration	0.11	0.17	0.63	0.53
	Years of education	-0.22	0.16	-1.36	0.17
	Multisite Chronic Pain	-0.13	0.15	-0.83	0.41
	Crohn's	2.16	23.12	0.09	0.9256

2.3.5 Factor analysis of outcomes in bipolar disorder

The present study provides a summary of the associations observed between factor scores and the genetic liability for Schizophrenia, Depression, ADHD, and Intelligence, represented as years of education. The results are presented in Table 11.4 and Table 12.4, with Table 10.4 reflecting the association results in the genotyped exploratory sample comprising 1762 subjects, and Table 11.4 presenting the same analysis in the genotyped replication sample of 578 individuals.

Table 11.5*: Genetic association in the exploratory sample. In green significant associations*

Factor	PRS	Estimate	Std. Error	t value	*p*
MR1	SCHIZOPHRENIA	0.08786	0.01662	5.287	1.32E-07
	MDD	0.04133	0.01614	2.56	0.0105
	ADHD	-0.0413	0.01598	-2.585	0.0098
	INTELLIGENCE	-0.009848	0.011572	-0.851	0.3948
MR2	SCHIZOPHRENIA	-0.017133	0.014866	-1.152	0.249219
	MDD	0.0470026	0.01408	3.338	0.000852
	ADHD	0.0364636	0.0142383	2.561	0.01048
	INTELLIGENCE	-0.014378	0.010311	-1.394	0.16331
MR3	SCHIZOPHRENIA	-0.007657	0.017897	-0.428	0.66880
	MDD	-0.03937	0.01732	-2.273	0.0231
	ADHD	0.004178	0.017155	0.244	0.8076
	INTELLIGENCE	-0.002363	0.012416	-0.19	0.8491
MR4	SCHIZOPHRENIA	-0.03065	0.01718	-1.784	0.075
	MDD	0.04904	0.01663	2.95	0.003
	ADHD	-0.05942	0.01645	-3.613	0.00031
	INTELLIGENCE	0.10135	0.0118	8.589	2.00E-16
MR5	SCHIZOPHRENIA	-0.002721	0.014902	-0.183	0.85513
	MDD	0.03087	0.01442	2.141	0.03237
	ADHD	-0.009841	0.014283	-0.689	0.49088
	INTELLIGENCE	-0.005703	0.010337	-0.552	0.58121

Factor 1, which captures the severity of mania, demonstrates a robust association with the PRS for Schizophrenia ($p < 0.0001$). Additionally, there appears to be an association with the PRS for ADHD ($p < 0.01$) and the PRS for depression ($p < 0.05$). Importantly, the replication analysis conducted in the second cohort validates these findings, confirming the associations with the liability for Schizophrenia ($p < 0.01$) and ADHD ($p < 0.05$).

Factor 2, which may reflect a dimension of disorder chronicity, exhibits a significant association with the liability for major depression ($p < 0.001$) and ADHD ($p < 0.01$). The replication analysis further corroborates this finding, confirming the significant association with the PRS for major depressive disorder ($p < 0.05$).

In contrast, no significant associations were observed between Factor 3 and Factor 5 with the genetic liability for any of the traits considered in the analysis.

Factor 4, referred to as the "social outcomes factor" or attainment, encompassing education and occupation, displays a strong positive association with the PRS for intelligence ($p < 0.001$). Moreover, it shows a negative association with ADHD ($p < 0.001$) and depression ($p < 0.01$). The replication analysis supports these findings, confirming the associations with the liability for intelligence ($p < 0.001$) and depression ($p < 0.001$).

These findings provide valuable insights into the relationships between genetic liabilities and specific factors of bipolar disorder. The associations observed suggest potential underlying mechanisms and shared genetic factors that contribute to distinct phenotypic features of the disorder. Further research, including larger-scale studies and replication analyses, is warranted to validate and expand upon these associations, enhancing our understanding of the complex aetiology of bipolar disorder.

Table 12.5: Genetic association in the replication sample in green replicated findings

Factor	PRS	Estimate	Std. Error	t value	*p*
MR1	SCHIZOPHRENIA	0.09862	0.03379	2.918	0.00361
	MDD	0.03252	0.03334	0.976	0.3295
	ADHD	-0.07051	0.032561	-2.165	0.0306
	INTELLIGENCE	-0.007434	0.022716	-0.327	0.7435
MR2	SCHIZOPHRENIA	0.0311	0.0305	1.02	0.3082
	MDD	0.0592	0.02843	2.082	0.0376
	ADHD	0.04285	0.02931	1.462	0.1442
	INTELLIGENCE	-0.01943	0.02041	-0.952	0.3414
MR3	SCHIZOPHRENIA	0.002762	0.037142	0.074	0.9407
	MDD	-0.05328	0.03643	-1.462	0.144
	ADHD	-0.01028	0.03571	-0.288	0.7736
	INTELLIGENCE	0.01707	0.02484	0.687	0.4922
MR4	SCHIZOPHRENIA	-0.02822	0.03525	-0.801	0.4236
	MDD	0.090426	0.034492	2.622	0.00891
	ADHD	-0.05191	0.03385	-1.533	0.1255
	INTELLIGENCE	0.11375	0.02326	4.89	1.21E-06
MR5	SCHIZOPHRENIA	-0.02231	0.03047	-0.732	0.46421
	MDD	0.006782	0.029931	0.227	0.82081
	ADHD	0.05615	0.02925	1.92	0.05525
	INTELLIGENCE	0.05165	0.020319	2.542	0.0112

4.5 DISCUSSION

1.4.5 Longitudinal mood monitoring in bipolar disorder

The primary objective of this chapter was to explore the genetic underpinnings of illness trajectory by examining the interplay between Polygenic Risk Scores (PRSs) calculated for various traits and the outcome variable derived in the True Colours (TC) study. In order to validate the longitudinal data obtained, an additional analysis was conducted to assess the association between the same PRSs used for the TC variables and the corresponding variable from the Bipolar Disorder Research Network (BDRN) dataset that displayed the highest correlation. Table 2.4 provides an overview of the obtained PRSs.

Remarkably, a positive association was observed between the PRS for Major Depressive Disorder (MDD) and Neuroticism with both the proportion of time spent by the patients exhibiting depressive symptoms and the overall duration of illness. These findings were consistent in the retrospective BDRN dataset, indicating that the genetic correlation between the phenotypic variables remains unchanged when considering the genetic aspect. Conversely, no significant correlations were identified between the prospectively or retrospectively assessed phenotypic variables and other common neuropsychiatric traits such as Schizophrenia, IQ, and mood instability.

The observed associations between the PRSs for MDD and Neuroticism with the duration and severity of depressive symptoms in both the TC and BDRN datasets shed light on the potential genetic influences underlying the longitudinal course of bipolar disorder. These findings contribute to a better understanding of the complex genetic architecture of the disorder and emphasize the relevance of depressive symptoms and neurotic traits in shaping the illness trajectory. However, further research is warranted to elucidate the underlying mechanisms

and explore additional genetic factors that may contribute to the multifaceted nature of bipolar disorder.

These results are consistent with previous research findings. Specifically, heightened Polygenic Risk Scores (PRS) for Major Depressive Disorder (MDD) have consistently shown associations with clinical depression across diverse populations and among individuals with various psychiatric conditions (Rabinowitz et al., 2020). Recently, there has been a focus on the association between the polarity of mood episodes and different PRS. (Hasseris et al., 2023) discovered a positive correlation between PRS for depression and the occurrence of both depressive and mixed episodes. Despite the inability to precisely define episodes in this study due to data constraints, the observed relationships between PRS for MDD and depressive episodes align with then existing literature.

2.4.5 Factor analysis of outcomes in bipolar disorder

The primary aim for the BDRN study was that to validate at a biological level the identified factor model, defined at phenotypic level, using polygenic risk scoring.

Three of the five factors identified were predicted by a polygenic risk score for a specific neuropsychiatric trait.

The factors, “Severity of Mania”, “Number of episodes” and “Attainment” were in fact strongly associated with genetic liability for schizophrenia, depression, ADHD and intelligence.

The first factor, known as "Severity of Mania," exhibited a robust association with the Schizophrenia Polygenic Risk Score (PRS). Previous research has consistently reported higher mean Schizophrenia PRSs in individuals with Bipolar Disorder Type 1 (BD-1) compared to those with Bipolar Disorder Type 2 (BD-2), as well as in BD-I with psychosis compared to BD-1 without psychosis (A. W. Charney et al., 2017). Moreover, a study by (Markota et al., 2018)demonstrated that BD-1 with manic psychosis shares greater genetic similarity with Schizophrenia (SCZ) compared to other subgroups of Bipolar Disorder.

This study employs a factor analysis (FA) approach to elucidate a factor that captures the severity of mania by not only focusing on the symptom itself but also considering its broader

effects and resulting outcomes. By incorporating these contextual elements, a more comprehensive understanding of the manifestation of mania is achieved. The findings reveal that this first factor accounts for a significant proportion (19.4%) of the overall variance in the sample. Importantly, this factor demonstrates both genetic and biological substrate linked with the Polygenic Risk Score (PRS) for schizophrenia.

The second factor identified in this study captures a dimension of chronicity within the disorder and is strongly associated with the liability for Major Depression (MDD). It is well established that a high liability for Major Depression is linked to the recurrent nature of the disorder (Wray et al., 2018) and the current findings align with previous research in this area. Notably, the use of a factor analysis (FA) approach in this study provides valuable insights. By going beyond the sole consideration of symptomatology and incorporating the number of episodes, rather than their polarity, into the phenotype manifestation of BD1, a deeper understanding of the chronic aspect of the disorder is gained. This chronicity, along with its impact on the daily lives of affected individuals, is a critical aspect to consider. The genetic associations further support the notion that this factor is more closely linked to a depressive phenotype, which may help explain the recurrence patterns and chronic features of the disorder.

Lastly, the third factor identified in this study, termed "Attainment," exhibits a strong association with the polygenic risk score (PRS) for intelligence. This finding aligns with prior research that has consistently demonstrated higher levels of educational attainment among individuals with elevated polygenic risk scores for intelligence. Additionally, it is noteworthy that this factor shows a negative association with the liability for Attention-Deficit/Hyperactivity Disorder (ADHD). These results provide further evidence for the complex interplay between genetic influences, cognitive abilities, educational achievements, and neurodevelopmental disorders. The inverse relationship between the "Attainment" factor and ADHD liability suggests that individuals with a higher genetic predisposition for intelligence may be less likely to exhibit ADHD-related symptoms or impairments.

Two out of the five identified factors showed no association with any of the considered Polygenic Risk Scores (PRS). The predominant variance within these factors was accounted

for by the duration of the longest depressive episode and the overall functioning during the most severe episode. One possible explanation for these findings could be that these descriptors are distanced from the biological underpinnings of the phenotype. Both factors encapsulate highly specific scenarios within the symptomatology of the patients. It is conceivable that the longest depressive episode coincides with the period of most impaired functioning for the patients. A limitation of the variables characterizing this phenomenon lies in their retrospective nature of recording. The information was gleaned from both subjective accounts provided by the subjects and evaluations of past medical records. The lack of robustness in these descriptors may consequently contribute to the absence of correlation with biological phenomena or processes captured by a PRS for a neuropsychiatric trait.

6.5 LIMITATIONS

The current study is not without limitations, and several factors should be taken into consideration. One notable limitation is the size of the sample. The TC study has a relatively small sample size, which can limit the generalizability of the findings. However, it is important to note that the TC project is currently the only ongoing project that has successfully enrolled and followed a deeply phenotyped cohort of individuals with bipolar disorder. The extensive duration of enrolment, utilization of mood rating scales, and comprehensive data collection make it challenging to identify similar cohorts for replication purposes in other research studies. Future studies with larger sample sizes would be beneficial to validate and extend the findings obtained from the TC project.

Given the ongoing nature of the TC project, continuous enrolment and follow-up of patients provide an opportunity for updated analyses in the coming years. Longitudinal data from the TC cohort can offer valuable insights into the dynamic nature of bipolar disorder and potentially address some of the limitations observed in the current study. Continued analysis of the TC cohort will enable researchers to explore changes in phenotypic variables, genetic associations, and further elucidate the complex nature of bipolar disorder.

Therefore, while acknowledging the limitations inherent in the current study, the ongoing nature of the TC project and the unique characteristics of the enrolled cohort provide promising avenues for future research and the potential to overcome some of the limitations observed in the present study.

The BDRN study has a larger sample size compared to the TC study, which enhances the statistical power and reliability of the findings. In order to obtain more robust and replicable results, the sample from the BDRN study was divided into two sets. This division allows for the examination of the factor structure using a different cohort with similar phenotype characteristics.
Having a separate replication sample provides an opportunity to validate and confirm the observed factor structure in large clinical datasets.

Another limitation of the study is intrinsic in the PRS approach. Polygenic risk scoring take in account the variability only in the common genetic variation of a population and only the genomic single nucleotide polymorphisms. This means that in the present study only the contribution of common variants can be investigated. Secondly the polygenic risk score relies on the availability of GWAS study investigating certain phenotype. The relative weight of each SNP considered in the polygenic score can change overtime when the sample size g GWAS will improve and even when more accurate and specific phenotype will be included in the same studies.

Another limitation of the study is inherent to the polygenic risk score (PRS) approach. The PRS methodology focuses on the common genetic variations within a population and specifically considers genomic single nucleotide polymorphisms (SNPs). Consequently, in the present study, only the influence of common variants can be investigated, while rare or structural genetic variations are not captured by this approach.

Additionally, the accuracy and reliability of the PRS rely on the availability of genome-wide association studies (GWAS) investigating the specific phenotype of interest. The weights

assigned to each SNP in the polygenic score can evolve over time as GWAS sample sizes increase and more precise and specific phenotypes are incorporated into these studies. Therefore, it is important to acknowledge that the PRS results obtained in this study are based on the current understanding and availability of genetic data, and future advancements in GWAS and phenotypic characterization may lead to updates and refinements in the PRS methodology.

Chapter 6: General Discussion

1.6 Summary of Findings: Longitudinal mood monitoring in bipolar disorder

In this study, I investigated the proportion of time spent in different mood states among individuals with bipolar disorder (BD). The findings revealed that the majority of the sample group's time was spent in euthymia, followed by periods of depression, mania or hypomania, and mixed states.

Upon further examination, I observed a significant difference in the total proportion of time spent with mood symptoms between the two principal diagnosis groups, BD1 and BD2. Individuals with BD2 tended to spend more time with mood symptoms compared to those with BD1.

To better understand the relationship between the proportion of time spent with mood symptoms and temporal variables, I explored correlations with various factors in the BDRN database. The strongest correlation was found with the total number of episodes per year, indicating that individuals with a higher number of episodes tended to spend more time experiencing mood symptoms. I observed this correlation consistently when considering BD1 and BD2 separately, although it appeared to be stronger for BD1 individuals.

Additionally, I found a significant correlation between a history of rapid cycling and the presence of mood symptoms. This correlation held true for both BD1 and BD2 individuals, and it became more pronounced for those enrolled in the treatment program for a longer duration. I also identified weaker correlations between the proportion of time spent with mood symptoms and the longest duration of depression, longest duration of mania, and total illness duration.

My analysis also explored the relationship between the proportion of time spent with mood symptoms and the total number of manic or depressive episodes per year. I observed similar patterns of correlation, with stronger associations in BD1 and among subgroups categorized by response time. Notably, the correlation was more significant for manic episodes compared to depressive episodes.

Furthermore, I examined the association between the number of episodes per year and the overall mood polarity, represented by the ratio of manic to depressive episodes. Interestingly, I found an inverse correlation, indicating that individuals with a shorter disease duration experienced fewer episodes. This correlation remained consistent across sexes and diagnoses.

2.6 Summary of Findings: Factor analysis of outcomes in bipolar disorder

The present study aimed to investigate the interrelationships among various clinical outcomes in individuals with bipolar disorder and to explore the latent factors contributing to both clinical and functional outcomes in this population.

In the analysis conducted on individuals diagnosed with Bipolar 1 disorder (BD1), five factors were identified, explaining a substantial proportion (66%) of the total variance. These factors represented distinct dimensions of the disorder, including severity of mania, clinical aspects related to the number of manic and depressive episodes, socio-personal achievements, duration of the longest episodes, and functioning during the worst depressive episode. The factor analysis allowed for the identification of these latent dimensions and provided insight into their associations with the observed clinical outcomes. Notably, communalities analysis indicated that eight out of ten variables showed strong associations with the underlying factors, while Highest Occupation and the longest duration of mania exhibited weaker associations.

To confirm the findings obtained from the exploratory factor analysis (EFA) in the BD1 sample, a confirmatory factor analysis (CFA) was conducted on a separate sample of 578 participants with BD1. The CFA results supported the 5-factor model, as indicated by significant statistical tests and fit indices, including a significant $\chi 2$ statistic, a comparative fit

index (CFI) greater than 0.9, a root mean square error of approximation (RMSEA) below 0.08, and a standardized root mean square residual (SRMR) of 0.05.

Regarding Bipolar 2 disorder (BD2), an exploratory factor analysis was performed, leading to the identification of a 4-factor solution that explained 65.6% of the total variance in the BD2 sample. These factors captured important aspects of the disorder, including the severity of depressive symptoms and their association with hospitalization, clinical aspects related to chronicity, and socio-personal achievements. Communalities analysis revealed that six out of ten variables demonstrated strong associations with the underlying factors, while Highest Occupation, longest duration of mania, longest duration of depression, and GAS worst in manic episode had weaker associations.

To validate the 4-factor model obtained from the EFA in the BD2 sample, a confirmatory factor analysis (CFA) was performed on a subsample of 245 participants with BD2. However, the results indicated that the hypothesized model did not fit well with the observed data. Statistical tests and fit indices, including the $\chi 2$ statistic, suggested a lack of fit, indicating that the relationships among the observed variables in the BD2 sample were not adequately explained by the proposed 4-factor model.

3.6 Summary of Findings: Genomic stratification of trajectories and outcomes

Longitudinal mood monitoring in bipolar disorder:

This study aimed to investigate the genetic influences on the trajectory of illness in bipolar disorder by examining the relationship between Polygenic Risk Scores (PRSs) and longitudinal outcome variables derived from the True Colours (TC) study. The findings revealed a significant positive association between PRSs for Major Depressive Disorder (MDD) and Neuroticism with the proportion of time spent by patients exhibiting depressive symptoms and the overall duration of illness. These associations were consistent when comparing the TC data with the retrospective Bipolar Disorder Research Network (BDRN) dataset. However, no significant correlations were found between the prospectively or retrospectively assessed phenotypic variables and other common neuropsychiatric traits such as Schizophrenia, IQ, and mood instability. These results provide insights into the potential genetic influences underlying the longitudinal course of bipolar disorder, highlighting the importance of depressive symptoms and neurotic traits in shaping the illness trajectory. Further research is needed to explore additional genetic factors and underlying mechanisms contributing to the complexity of bipolar disorder.

Factor analysis of outcomes in bipolar disorder:

This study aimed to validate a factor model of outcomes in bipolar disorder at a biological level using polygenic risk scoring. Three out of the five identified factors were found to be predicted by polygenic risk scores for specific neuropsychiatric traits. The first factor, named "Severity of Mania," showed a strong association with the Polygenic Risk Score (PRS) for schizophrenia. Previous research has consistently reported higher PRSs for schizophrenia in individuals with Bipolar Disorder Type 1 (BD-1) compared to Bipolar Disorder Type 2 (BD-2) and in BD-1 with psychosis compared to BD-1 without psychosis. By considering the broader effects and outcomes of mania, this study provides a comprehensive understanding of its manifestation, showing a significant contribution of genetic and biological substrates linked to the PRS for schizophrenia.

The second factor identified in this study captured a dimension of chronicity within bipolar disorder and was strongly associated with the liability for Major Depression (MDD). This finding aligns with previous research highlighting the recurrent nature of the disorder and its relationship to high MDD liability. By incorporating the number of episodes rather than their polarity, this study deepens the understanding of the chronic aspect of bipolar disorder and its impact on individuals' daily lives. The genetic associations further support the notion that this factor is closely linked to a depressive phenotype, shedding light on the recurrence patterns and chronic features of the disorder.

Lastly, the third factor identified, termed "Attainment," displayed a strong association with the polygenic risk score for intelligence. This finding aligns with previous research demonstrating higher levels of educational attainment among individuals with elevated polygenic risk scores for intelligence. Notably, this factor showed a negative association with the liability for Attention-Deficit/Hyperactivity Disorder (ADHD), suggesting that individuals with a higher genetic predisposition for intelligence may be less likely to exhibit ADHD-related symptoms or impairments. These findings contribute to our understanding of the complex interplay between genetic influences, cognitive abilities, educational achievements, and neurodevelopmental disorders in bipolar disorder.

4.6 General comment

I embarked on a comprehensive exploration and analysis of longitudinal mood monitoring, factor analysis of outcomes, and genomic stratification in individuals with bipolar disorder. By critically examining the research objectives and their corresponding results, I can assess the efficacy of my study in achieving its goals and its contributions to the scholarly understanding of bipolar disorder.

The analyses conducted in this thesis were profoundly influenced by the findings of the comprehensive literature review. Through an exhaustive examination of 64 reviews on the topic, a core set of potential outcomes for investigation was meticulously developed. This compilation encompassed outcomes characterized by their predominant clinical relevance, yet it also acknowledged the significance of exploring outcomes with a more "personal" dimension. Interestingly, the review revealed a notable gap in the literature, as outcomes with distinct characteristics had never been concurrently analysed. Thus, this thesis represented the inaugural endeavour to address this gap by integrating diverse outcome characteristics within the analytical framework.
However, it is crucial to acknowledge the inherent limitations encountered in the practical implementation of this approach. Indeed, the dataset utilized as the foundation for this analysis, derived from a research database with a predominant clinical focus, exhibited deficiencies in capturing certain identified personal outcomes.

In accordance with my objective of investigating longitudinal mood monitoring, I successfully delved into the course of illness experienced by individuals enrolled in the True Colours (TC) project. By meticulously examining the proportion of time allocated to different mood states, including euthymia, depression, mania or hypomania, and mixed states, I provided valuable insights into the temporal progression of the disorder. Moreover, through a comparative analysis of the TC project data with the retrospective Bipolar Disorder Research Network (BDRN) cohort data, I extended my investigation to encompass variations in the course of illness across different data sources. Consequently, I achieved a more comprehensive understanding of the trajectory of bipolar disorder.

I also aimed to unravel the interrelationships among various clinical outcomes in bipolar disorder through factor analysis of outcomes. By subjecting the data to rigorous factor analysis, I successfully identified distinct dimensions of the disorder in individuals with Bipolar 1 disorder (BD1) and Bipolar 2 disorder (BD2). These dimensions encompassed essential facets such as the severity of mania, chronicity, socio-personal achievements, and others. By uncovering the underlying structure of outcome dimensions, I shed light on the intricate connections among different clinical outcomes in bipolar disorder. Furthermore, the identification of specific factors contributing to clinical and functional outcomes deepened our comprehension of the factors influencing the experiences and outcomes of individuals living with bipolar disorder.

Additionally, I endeavoured to explore the genomic stratification of trajectories and outcomes in bipolar disorder. My objective was twofold: to examine the predictive value of polygenic risk scores (PRSs) for various neuropsychiatric traits on bipolar disorder phenotypes and to probe the genetic basis of the outcome factors identified in the factor analysis. I successfully established associations between PRSs for several neuropsychiatric traits, such as Major Depressive Disorder (MDD) and Neuroticism, and the proportion of time spent in depressive symptoms and the overall duration of illness. These findings offer valuable insights into the genetic influences shaping the longitudinal course of bipolar disorder, emphasizing the significance of depressive symptoms and neurotic traits in the illness trajectory. Moreover, the consistent associations observed across both the TC project and the BDRN dataset enhance the reliability and generalizability of the identified outcome factors.

By addressing my research aims, I have provided comprehensive insights into the temporal progression of the disorder, revealed the underlying structure of outcome dimensions, and elucidated the genetic influences on bipolar disorder phenotypes. These findings can have profound implications for personalized diagnosis, treatment, and prognosis in individuals with bipolar disorder, as well as for future research endeavours in the field.

5.6 LIMITATIONS

The present thesis, focusing on various aspects of bipolar disorder, provides valuable insights into the illness course and outcomes. However, it is crucial to acknowledge and address several limitations that might affect the interpretation and generalizability of the findings.

In Chapter 3, a notable limitation stems from the relatively small sample size of retrospectively assessed subjects enrolled in the prospective study True Colours (TC). This subset accounted for only one-sixth of the total sample from the Bipolar Disorder Research Network (BDRN). Expanding the number of enrolled subjects in TC could potentially enhance the consistency and reliability of the results. Furthermore, it should be noted that the TC participants may not be fully representative of the larger BDRN cohort, as the proportion of individuals diagnosed with bipolar 2 disorder was higher in the TC sample. These limitations highlight the need for larger and more diverse samples to ensure the generalizability of the findings.

Another limitation in Chapter 4 is the difference in mean disease duration between the TC and BDRN subjects. This discrepancy in illness duration might have influenced the observed outcomes. To address this limitation, future studies should aim to include subjects with varying disease durations to obtain a more comprehensive understanding of the illness course in bipolar disorder. Additionally, while the study identified variables that exhibited strong correlations between the datasets, the underlying clinical or biological mechanisms behind these correlations were not explored. Investigating these mechanisms in future studies would provide a deeper understanding of the factors contributing to clinical and functional outcomes in bipolar disorder.

Moving on to Chapter 5, one limitation to consider is the relatively small sample size of the TC study. Although the TC project successfully enrolled and followed a deeply phenotyped cohort of individuals with bipolar disorder, the small sample size limits the generalizability of the findings. It is important to note that the extensive duration of enrolment, utilization of mood rating scales, and comprehensive data collection in the TC project make it challenging

to identify similar cohorts for replication purposes in other research studies. To validate and extend the findings obtained from the TC project, future studies with larger sample sizes would be beneficial.

The ongoing nature of the TC project also offers opportunities to overcome some of the limitations observed in Chapter 3. Continuous enrolment and follow-up of patients in the TC cohort can provide valuable insights into the dynamic nature of bipolar disorder and address some of the limitations encountered in the current study. Continued analysis of the TC cohort will enable researchers to explore changes in phenotypic variables, genetic associations, and further elucidate the complex nature of bipolar disorder.

In Chapter 6, the utilization of a larger sample size from the BDRN study enhances the statistical power and reliability of the findings. However, the division of the sample into two sets, although aimed at obtaining more robust and replicable results, introduces a limitation. While this division allows for the examination of the factor structure using a different cohort with similar phenotype characteristics, replication on larger and completely independent samples would be ideal for further validation. Additionally, the polygenic risk score (PRS) approach used in Chapter 4 has inherent limitations. It focuses only on the common genetic variations within a population, neglecting rare or structural genetic variations. The accuracy and reliability of the PRS depend on the availability of genome-wide association studies (GWAS) investigating the specific phenotype of interest. The weights assigned to each SNP in the polygenic score may evolve over time as GWAS sample sizes increase and more precise and specific phenotypes are incorporated into these studies. It is important to acknowledge that the PRS results obtained in this study are based on the current understanding and availability of genetic data. Future advancements in GWAS and phenotypic characterization may lead to updates and refinements in the PRS methodology.

6.6 FUTURE PESPECTIVES

The potential research questions arising from the findings are diverse and pertain to various aspects of the thesis. The initial concern stems from the literature review, where it was observed that no studies or reviews had comprehensively analysed outcomes across different domains. Additionally, after establishing a list of outcomes deemed essential for investigation in bipolar disorder, it became evident that some of these outcomes were lacking in my dataset. Consequently, it became imperative to consider, prior to initiating new patient recruitment, a collaborative effort involving clinicians, researchers, and patient associations. This collaborative approach aims to ensure a more comprehensive examination of variables by integrating perspectives from multiple stakeholders. This strategy facilitates the inclusion of variables that may explore similar phenomena but from differing viewpoints, thereby enhancing the richness and depth of the research endeavour.

The factorial approach employed in Chapters 4 and 5 demonstrated a robustness that underscores the necessity of utilizing sophisticated statistical methods when analysing complex phenomena such as outcomes. It is overly simplistic to assume that the mere registration of a phenotype, such as education, or the mere response to rating scales or the collection and evaluation of clinical records, can provide insight into the underlying structure of isolated outcomes. While my approach was inevitably constrained by the available data, future endeavours stand to benefit from the enrichment of the database with new information. It would be particularly intriguing and fruitful to incorporate additional characteristics and outcome variables, such as drug response, adherence, and side effects, into factor analyses.

From a genetic perspective, while polygenic risk scoring can offer insights into the underlying biological mechanisms, alternative approaches may offer greater informativeness. With larger sample sizes and more precisely defined phenotypes, conducting a Genome-Wide Association Study (GWAS) and heritability analysis of factor scores could become feasible and yield valuable insights into the genetic underpinnings of outcomes.