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*This thesis has not been submitted for any other degree than named above or for any other purpose. I  
certify that the intellectual content of this thesis is the product of my own work and that all the assistance  
received in preparing this thesis and sources have been acknowledged.*

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# Abstract

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Bipolar Disorder (BD) is a severe chronic mood disorder with typical onset in late adolescence to early adulthood. A large proportion of individuals with BD experience onset of symptoms prior to adulthood and it is commonly reported that an earlier onset is associated with more negative outcomes. Delays in diagnosis and appropriate treatment are also associated with poorer prognosis for patients with BD. Early identification is therefore imperative for more favourable outcomes, however, the heterogeneity of bipolar presentations mean that diagnosis remains a complicated process. The aims of this thesis were threefold: To summarise and synthesise the current empirical and theoretical research into BD; to critically evaluate the literature investigating early onset of BD to ascertain whether age of onset is indeed associated with poorer outcomes; and to examine whether individual symptoms associated with BD may be clinically useful as risk markers in childhood and adolescence.

Study one systematically evaluated and analysed data from existing research investigating outcomes associated with an early onset of bipolar disorder. Analysis included data from fifteen empirical papers that compared clinical presentation and outcomes for individuals with BD grouped according to age of onset (Total n = 7370). Results indicated there was insufficient evidence to support commonly reported associations between early onset and clinical characteristics indicative of greater severity such as psychotic symptoms or mixed episodes. Clinical features found to have the strongest relationship with an earlier age of onset were those that may potentially be amenable to intervention such as comorbid anxiety, substance use, and treatment delay. Results highlight the importance of early identification in BD and provide potential areas of focus for the development of early intervention.

In the second study, the potential clinical usefulness of individual symptoms was examined using a novel analytical approach based on Item Response Theory (IRT). The main objective of this study was to evaluate whether individual symptoms differed in their capacity to discriminate between those scoring high and low on underlying latent traits of depression and mania, and in the information they provided in relation to severity. The sample consisted of n=186 participants aged 12 – 21yrs including n = 105 with a first degree relative who has a diagnosis of BD (At Risk); n = 63 control participants (C); and n = 18 with a confirmed diagnosis of bipolar disorder (BD). Depressive symptoms found to be the most informative



were Anhedonia, Hopelessness, and Thoughts of Death. The least discriminating items were Insomnia and Irritability. From the mania scale, the most informative items were Increased Energy, Hyperactivity and Elevated Mood. Symptoms providing least information were Mood Lability and again, Irritability. Results support hypotheses from previous research that specific mood symptoms are more informative of risk in BD than general symptoms. Results are also in line with previous findings that indicate that increased energy is a core feature of mania. These findings are important in relation to ongoing controversy around diagnoses of paediatric BD and the broadening of diagnostic criteria.

Overall, the studies in this thesis provide information useful to clinicians in the identification of at risk populations that may benefit from early support, monitoring and intervention. They provide a basis for the creation of developmentally appropriate clinical screening tools that assist in differentiating normal adolescent stress from clinically relevant risk, and development of early intervention programs for individuals considered at risk. From a theoretical perspective, these studies identify key risk areas in adolescent populations and inform areas of future research important for this group.

# Chapter 1: Introduction

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Over the last two decades there has been a drive in mental health care and support services to move from a crisis care model to a more preventative approach. The aims of this approach are to use early identification to minimise diagnostic delays, allow for appropriate and timely intervention, and thus improve prognosis and outcomes. There has been some evidence of success with this approach in schizophrenia and psychotic disorders. For example, positive outcomes have been found for those with early (EOS) and very early-onset (VEOS) schizophrenia following psychosocial intervention and cognitive remediation (Armando, Pontillo, & Vicari, 2015); and specialised assertive early intervention has been found to have positive effects on positive and negative symptoms as well as comorbid substance use (Nordentoft, Rasmussen, Melau, Hjorthøj, & Thorup, 2014). Given the commonalities that have been identified by genetic and epidemiological research between schizophrenia and bipolar disorder (BD) in certain symptoms, susceptibility markers, and neurotransmitter dysfunction (Möller, 2002; Murray et al., 2004) these results may provide promise for early intervention outcomes in bipolar BD. Unfortunately, many psychological disorders, BD included, are heterogeneous in their presentations often making accurate and reliable diagnosis complex. As such, early identification when symptoms are less pronounced is very challenging. The aims of this thesis were threefold: First, to summarise and synthesise the current empirical and theoretical research relating to onset, diagnosis and prognosis in BD. Second, to systematically review and analyse empirical data specific to studies of early onset of BD and resulting outcomes; and finally, to apply a novel statistical approach to symptom measures from commonly used standardised interviews to identify individual symptoms that may be clinically useful in identifying risk of later disorder development.

The following literature review provides an overview of the relevant theoretical and empirical research as rationale for the two studies included in the thesis. This includes an introduction to the recent history of BD research; diagnostic difficulties in BD; changes to key focus areas over time; and current opinions. Also addressed are the parallels and overlap between BD and schizophrenia research, and the relevant advances in schizophrenia research that, it is argued, may inform developmental research into BD. Finally, a brief overview of Item Response Theory is provided, as background to the examination of adolescent symptoms of BD in study two.

## **Background**

Bipolar disorder (BD) is a clinically severe, chronic mood disorder with onset commonly around late adolescence and early adulthood (Joyce, 1984; Merikangas et al., 2007). It is linked with high rates of comorbidity (Oswald et al., 2007), and is a leading cause of premature mortality due to suicide and associated medical conditions such as diabetes and cardiovascular disease (Coryell et al., 1993c). BD causes widespread role impairment, and is associated with a significant economic burden, both to the individual, and to society due to the direct costs of medical expenditure, and indirect costs such as loss of productivity and increased mortality (Fagiolini et al., 2013). Although severity and course vary among individuals affected with BD, overall it is a grave psychiatric illness that is a leading cause of disability worldwide (Azorin et al., 2013; World Health Organisation, 2001).

The defining feature of BD is the occurrence of episodes of mania, or hypomania, that alternate, or occur concurrently with, episodes of depression (Fagiolini et al., 2013). A manic episode is defined by a significant, persistent, abnormal change in mood (becoming highly euphoric, elated, or irritable) accompanied by an increase in behaviours that signify an activated state (Blader & Carlson, 2013). Such behaviours may include rapid speech, increases in goal directed activity and risk taking behaviours, impulsivity, and hyper-sexuality. Hypomania also represents a marked change from an individual's standard mood and functioning, differing from mania primarily with regard to severity and level of impairment (Blader & Carlson, 2013). In BD, episodes are usually separated by periods of recovery involving a return to normal functioning. However, recurrence rates are high (Oswald et al., 2007), and residual sub-syndromal symptoms often persist between major episodes (Gitlin, Swendsen, Heller, & Hammen, 1995; Goldberg & Grossman, 1995; Keller et al., 1992).

## **Diagnosis**

The classification and diagnosis of affective disorders has had a long and eventful history (see Angst and Marneros (2001) for a detailed outline). Although all affective disturbances were originally believed to be varying presentations of the same underlying disorder, in the 1960s and 1970s key work by Perris and D'Elia (1966a), and Cadoret, Winokur, and Clayton (1970) demonstrated that unipolar and bipolar depression differed significantly across a number of characteristics including genetics (Perris, 1966a; Winokur, 1970), course (Perris & d'Elia, 1966b) and premorbid personality (Perris, 1966b).

Further support for this differentiation between unipolar and bipolar depression has also been provided by neuroimaging studies (de Almeida & Phillips, 2013). However, there remains a relationship between unipolar and bipolar disorders in depressive symptomatology, which is frequently misdiagnosed as unipolar depression in those with BD.

BD is commonly misdiagnosed. A survey study conducted by the Depression and Bipolar support alliance (Hirschfeld, Lewis, & Vornik, 2003), found that 69% of their members had experienced initial misdiagnosis, most frequently as major depression, followed by anxiety disorders, schizophrenia and substance use disorders. Moreover, a prospective longitudinal study of 550 individuals originally diagnosed with major depression (Fiedorowicz et al., 2011), found that over the course of 17.5 years approximately 20% of the sample experienced mania or hypomania, resulting in a revision of diagnosis to bipolar I disorder (7.5%) or bipolar II disorder (12.2%). Misdiagnosis can have major implications for appropriate treatment and long term clinical course for individuals with BD. For example, antidepressant medications, a common first line treatment for major depression, have been found to induce mania or hypomania in a proportion of individuals susceptible to BD if provided without accompanying mood stabiliser medication (Goldberg & Ernst, 2002c; Goldberg & Truman, 2003; Henry, Sorbara, Lacoste, Gindre, & Leboyer, 2001). Incorrect diagnosis of BD can also have negative consequences including increased risk of harm due to unnecessary treatments; stigma associated with the diagnostic label; and the inappropriate use of health care resources (Ghouse, Sanches, Zunta-Soares, Swann, & Soares, 2013).

Perhaps due to the complexities of diagnosis in BD, delays in diagnosis are also common with patients reporting up to 10 years between the onset of affective symptoms and formal diagnosis (Drancourt et al., 2013; Schneck, 2011b). This is thought to be even more pronounced in those with an earlier onset of BD (Azorin et al., 2013; Drancourt et al., 2013). Such delays in diagnosis, and therefore appropriate treatment, are associated with poorer prognosis for individuals with BD, having been linked to higher rates of suicidal behaviour, poorer social adjustment and higher hospitalisation rates (Goldberg & Ernst, 2002b). There is also evidence to suggest that patients with a greater number of affective episodes prior to the institution of lithium prophylaxis have a less favourable prognosis than those who begin prophylaxis after fewer episodes (See Coryell, Fiedorowicz, Leon, Endicott, and Keller (2013) for a review). Early identification is therefore imperative for more favourable outcomes in BD; however, due to

the heterogeneity of bipolar presentations, along with the frequent occurrence of depression as the onset episode, diagnosis remains a complicated process.

To account for the heterogeneity of bipolar disorder presentations, the Diagnostic and Statistical Manual of mental disorders (DSM) has separated BD variations into categories according to different clinical and diagnostic criteria. In the 3<sup>rd</sup> edition (DSM-III) (Drancourt et al., 2013) the category of bipolar mood disorders included: bipolar disorder, cyclothymic disorder and atypical bipolar disorder. DSM-3-revised addition (American Psychiatric Association, 1987) altered these categories slightly by removing the duration criterion for manic episodes, thereby loosening the diagnostic criteria; and replacing atypical bipolar disorder with bipolar disorder not otherwise specified (NOS). At this time, bipolar II was subsumed under bipolar NOS and was not classified as a separate disorder, and rapid cycling was not included at all (Vieta, Reinares, & Bourgeois, 2005). In DSM-IV (American Psychiatric Association, 1994) and DSM-IV-TR (American Psychiatric Association, 2000), BD was classified into the following diagnostic categories: bipolar I disorder, characterised by one or more manic or mixed episodes, usually accompanied by major depressive episodes; bipolar II disorder, characterised by one or more major depressive episodes, accompanied by at least one hypomanic episode; cyclothymic disorder, characterised by at least two years of numerous periods of hypomanic symptoms that do not meet criteria for a manic episode, and numerous periods of depressive symptoms that do not meet criteria for a major depressive episode; and bipolar disorder NOS, included for coding disorders with bipolar features that did not meet criteria for any of the specific bipolar disorders, and for bipolar symptoms about which there was inadequate or contradictory information.

In the change from DSM-III to DSM-IV, bipolar disorders were no longer recognised as a unique category unto themselves. They became grouped under the category of “mood disorders” with unipolar depressive disorders and other mood disorders such as substance induced mood disorders, and mood disorders NOS. With the recent development and release of DSM-5 (American Psychiatric Association, 2013a) bipolar disorders have again been separated from depressive disorders, presumably in recognition of the identified differences between bipolar and unipolar disorders. The diagnoses included under the category of bipolar disorders in DSM-5 include: bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance / medication-induced bipolar and related disorder, bipolar and related disorder due to

another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorder (American Psychiatric Association, 2013a).

The recent changes in BD classification have prompted both positive and negative responses from clinicians and researchers. Those who have argued previously that BD has been underdiagnosed due to overly stringent diagnostic criteria have praised some of the changes, such as the recognition / inclusion of more variations of the disorder and the removal of substance induced mania as an exclusion criteria (Angst, 2013). However, they have expressed concerns about the addition of the diagnostic specifier for mania that increased energy and activity must be included for a diagnosis. The argument is that this change excludes individuals who present primarily with symptoms of irritability, and who previously would have met criteria for diagnosis (Angst, 2013). However, others have argued that this change is an important addition to avoid over-loosening of diagnostic criteria that would impact BD treatment and research (Severus & Bauer, 2013). They argue that such loosening of diagnostic criteria can undermine the core conceptualisation of BD and result in an increase in false positive diagnoses with concerning consequences. For example, a young person presenting with a depressive episode who is suspected of having BDII may be treated with a prophylactic mood stabiliser in the absence of an observed hypomanic episode. Such treatment may then continue indefinitely as assessment of efficacy involves seeking the prevention of new manic episodes, which would be unlikely to occur if the individual is suffering from unipolar, not bipolar depression (Severus & Bauer, 2013). This kind of inappropriate and unnecessary treatment is likely to have long-term physical health effects as well as a financial impact for the individual. Moreover, it is a potential misuse of health resources. There is already concerning evidence to suggest that whereas a decade ago BD, particularly BDII, was perhaps underdiagnosed, the trend is now toward an over diagnosis with the label BDII applied incorrectly to presentations such as unipolar depression, borderline personality disorder, and impulse control disorders (Mitchell, 2013). Unfortunately, this kind of shift from under- to over-diagnosis does not address the diagnostic issues identified in BD, and may in fact create more confusion than clarity around BD diagnosis.

The concerns raised by Severus and Bauer (2013), relate primarily to the potential adverse consequences of incorrect pharmacological treatment, and rightly so. The current primary treatment for BD is pharmacological. For some this is extremely effective, however, recurrence rates for patients on active medications are unfortunately high (see Gitlin and Frye (2012) for a review). A substantial

proportion of patients treated for BD report significant levels of residual depressive symptoms despite having high levels of adherence to using prophylactic medication and being rated as euthymic by clinicians (Scott, Stanton, Garland, & Ferrier, 2000). Given that individual medications have some efficacy, when one is insufficient, the approach to treatment is often to assume a cumulative benefit will be obtained by adding additional medications. In many cases, this strategy does provide more optimal treatment. It can, however, also result in patients being treated with up to six mood stabilisers, each of which contributes to side effects and patient burden, and of which none has any demonstrated efficacy for the individual (Gitlin & Frye, 2012). Moreover, we know little about the long-term effects of many of these medications and the resulting impacts on physical health and outcomes for the individual.

It could be argued that from a psychological intervention perspective, increased sensitivity at the cost of increasing probability of false positives may be of greater benefit than concern. Appropriate application of early psychological support and interventions involves far less risk of increased harm and fewer unknown outcomes. Unfortunately, the psychological investigation of bipolar disorder has been severely neglected. It is only in the last few decades that researchers have begun to investigate the potential contribution of psychosocial factors to the onset and course of the disorder, and thus far the research has been limited. According to some researchers, the lack of strong psychological models for bipolar disorder has been a major impediment to the development of new therapeutic approaches, and also to the enhancement of current treatment options (Jones & Tarrrier, 2005). Psychological therapies have the potential to address a number of concerns in BD, particularly in conjunction with pharmacological treatment.

Support for the potential of psychological therapies for complex disorders previously treated primarily with medication again comes from schizophrenia research. For example, a meta-analysis of 26 randomised controlled trials found clear improvements in mental state and reduction of relapse risk for individuals with schizophrenia receiving psychological treatment (Bellivier, Golmard, Henry, Leboyer, & Schurhoff, 2001b). For patients with BD, psychological therapies including CBT, family-focused therapy, and interpersonal social rhythm therapy have been shown to promote treatment adherence and provide positive benefits such as reduction in symptom severity, and prolonging time to relapse (Schneck, 2011b). Moreover, a review examining outcomes from studies of psychotherapy for BD (Bellivier et al., 2003) found a range of approaches were able to provide treatment benefits, with the clearest evidence for

individual cognitive-behavioural therapy (CBT) which was found to impact social functioning, symptoms, and risk of relapse. Nevertheless, research into the effectiveness of psychological therapies for bipolar disorder is limited and improvements are needed in the quality of studies before we will have a clear picture of the treatments that provide the greatest improvements in management and prognosis.

It is, as yet, unclear whether psychological strategies can prevent, delay or minimise full expression of mood disorders, however, they do offer promise in lowering the long-term morbidity and mortality associated with this severe disorder. Current psychological strategies for reducing relapse in BD include: psychoeducation on the signs and symptoms of mood dysregulation; the protective effects of daytime routine and well-regulated sleep-wake cycles; and the importance of managing stress. Adapting core features of these treatments may also help those at heightened risk of developing BD recognise early warning signs of affective change and implement protective strategies. This has the potential to alter the trajectory and minimise the severity of impending mood disturbance, despite our current inability to definitively diagnose the disorder in early stages (Schneck, 2011b). Of course, accurate identification of individuals at increased risk is necessary before interventions can be provided. Similarly, identification of the most informative early, or high risk symptoms is needed to facilitate development of interventions that are likely to be most effective and appropriate for those identified as at heightened risk.

### **Category vs. Continuum**

Although reassessment of the categories of BD may be progressing, as with many psychological diagnoses, the argument against a categorical approach using symptom checklists persists. This discussion of whether psychological disorders are better accounted for by categorical or dimensional models is not a new one. Limitations and complications engendered by the categorical approach to diagnosis, such as excessive diagnostic comorbidity and problematic boundary disputes, are well recognised and have driven an escalation in the importance placed on developing an answer to the categorical / dimensional dilemma (Widiger & Samuel, 2005). The issues identified with the categorical approach suggest that a dimensional model may provide a more valid description of psychopathology, as it would effectively address the illusory boundaries and extensive comorbidity created by existing diagnostic categories (Widiger & Samuel, 2005).



Psychiatric symptoms have been found to be dimensional in patient populations (Goldberg, 2000), and research into a range of psychological symptomatology using population samples has shown continuous distributions. For example, using data collected prospectively in the general population of Zurich over twenty-years, Rössler et al. (2007) found expression of psychotic symptoms to be continuous and characterised by different levels of persistence and severity. A review of earlier literature conducted by Johns and Van Os (2001) also found evidence to indicate that psychosis exists as a continuum of experiences with a distribution in the general population. Further, research into personality disorders has found that the functioning represented by symptoms of these disorders is not qualitatively different to typical functioning. Rather, personality disorders appear to be maladaptive variants of the domains and facets of normal personality factors (Widiger & Samuel, 2005).

Clinical and epidemiological studies have demonstrated a continuous distribution of symptoms from normal to pathological in both depressive and hypo / manic symptoms (Angst, 2007). In a 20-year follow up study of patients with BDI and BDII, patients were found to spend approximately half the time in sub-threshold affective conditions that were found to be dimensional, involving the full range of symptom severity for both depression and hypomania (Judd & Akiskal, 2003). On the other hand, Akiskal and Benazzi (2007) found evidence for a categorical distinction between major depressive disorder and bipolar II disorder identifying features that distinguish unipolar depression from BP-II such as earlier age of onset, family history of BD, higher rate of depressive recurrences and atypical depression symptoms. It should be noted however, that the same study also found a continuous distribution of the number of atypical depressive symptoms between MDD and BP-II which they argued provided support for a dimensional view of depressive disorders (Akiskal & Benazzi, 2007).

### ***The Bipolar Spectrum***

It has been suggested that current diagnostic criteria lack the sensitivity to detect the full range of conditions in what could be seen as a bipolar spectrum (Vieta et al., 2005). Evidence for this comes from studies showing that large proportions of bipolar II patients are misdiagnosed as having unipolar depression due to stringent diagnostic criteria for mania, and failure to recognise minor related states (Ghaemi, Boiman, & Goodwin, 2000; Vieta, Gasto, Otero, Nieto, & Vallejo, 1997). Again, such incorrect diagnoses guide treatment and can have a detrimental impact on the clinical course and prognosis for individuals with BD (Vieta et al., 2005). As identified by Angst and colleagues (Angst & Gamma, 2002;

Angst et al., 2003a), individuals with BD identified by both the diagnostic criteria of DSM-IV (American Psychiatric Association, 2000) and ICD10 (World Health Organization, 1992), form only the tip of the iceberg of the bipolar spectrum. Below the surface of these diagnostic thresholds are significant numbers of individuals with unidentified BDII, hypomania, and minor bipolar disorders (Angst & Cassano, 2005).

In the 1990s Goodwin and Jamison argued that the exploration of spectrum models of BD had the potential to enhance research on genetic markers and modes of transmission, provide an approach for identifying at risk individuals, and permit the evaluation of early intervention treatments and treatments for milder forms of the disorder (Goodwin & Jamison, 1990; Vieta et al., 2005). In 1978 Wing and colleagues argued that the question of correct cut-off levels for “caseness” was raised by the dimensional nature of the mood disorders (Wing, Mann, Leff, & Nixon, 1978). Yet the attempts to address the diagnostic complications that persist in BD continue to come from a categorical perspective.

### **Importance of sub-clinical symptoms**

Sub-syndromal symptoms outside an episode are common in bipolar disorder (Fava, 1999). These are symptoms that, though not reaching the severity of an episode, can cause significant distress and disruption in patients’ lives (Lam & Wong, 2005), and can develop into prodromal symptoms that herald the onset of a full episode. Several studies report that more than 50% of bipolar patients suffer from significant sub-syndromal symptoms between episodes (Gitlin et al., 1995; Goldberg, Harrow, & Grossman, 1995; Keller et al., 1992) and amelioration of sub-syndromal symptoms is a vital component of maintenance treatment in BD (Gitlin & Frye, 2012). Sub-syndromal symptoms are associated with functional impairment for those with BD. They have also been found to be predictive of earlier relapse of both manic and depressive episodes (Frye et al., 2006; Judd et al., 2008; Perlis et al., 2006), and the psychosocial impact of relapse persists for years in a great number of bipolar patients (Coryell et al., 1995; Keck, McElroy, & Arnold, 2001). It stands to reason that such sub-clinical symptoms may have a similar impact for those aware of their own increased familial risk of BD, particularly those who have been exposed to the impact of the disorder on family members. Such individuals may be pre-disposed to anxiety around the development of BD related symptomatology in the same way that those with remittent BD may be anxious about relapse.

Symptoms that do not reach threshold for diagnosis of BD may also be useful indicators of later risk, as has been demonstrated in the depression literature. The results of studies of adults with depression suggest that subclinical symptoms are associated with a high risk of later development of full depressive episodes (Eaton, Badawi, & Melton, 1995). Moreover, a predictive relationship has been found between subclinical depressive symptoms in adolescence and major depression in adulthood (Pine, Cohen, Cohen, & Brook, 2014), and adolescents with major depression have a two to four-fold greater risk of experiencing depression as young adults (Pine et al., 2014). Some studies have found only specific sub-threshold symptoms associated with depression predict later development of major depressive disorder. For example, (Pine, Cohen, & Brook, 2001) identified anhedonia and suicidal ideation as two key predictors of later development of major depression over and above other associated symptoms. In the attempt to identify potential bipolarity in those diagnosed with major depression, it has also been suggested that sub-threshold symptoms of mania may be useful (Angst et al., 2003b; Goldberg et al., 2009; Merikangas et al., 2007). Although the predictive validity of such symptoms has not yet been established (Fiedorowicz et al., 2011), at least one recent study supports this hypothesis (Zimmermann et al., 2009). The findings outlined above highlight the potential significance of symptoms of psychopathology below the threshold of disorder. They also highlight differences in the potential utility of individual symptoms and their usefulness in identifying risk.

## **The Prodromal Phase**

There is evidence to suggest that during preadolescence or adolescence, individuals who go on to develop bipolar disorder show sub-syndromal, premorbid symptoms or signs that may be useful indicators of risk. Such a period where symptoms or behaviours that are clear changes from an individual's ordinary functioning emerge months or years prior to onset of a full disorder is known as a prodromal phase. Prodromal phases are notable in other serious disorders such as unipolar depression (Fava, Grandi, Canestrari, & Molnar, 1990; Fava & Kellner, 1991; Jackson, Cavanagh, & Scott, 2003) and schizophrenia (Cornblatt et al., 2003; Yung & McGorry, 1996) and have been found to be useful in identifying groups at high risk of later development of disorder. Once identified, these groups can be more closely monitored and provided with greater support, early targeted interventions and family education.

The word prodrome comes from the Greek word “prodromos” meaning the forerunner of an event (Lam & Wong, 2005). In mental health, the term prodrome is used to describe the symptoms that patients may experience and warning signs they may be at the early stages of an episode. Such prodromal symptoms can be strikingly different to full-blown episodes or can be similar but less intense. They tend to be idiosyncratic, and are thought to be the result of complex mixture of psychological makeup, biology and past experiences (Lam & Wong, 2005). Prodromal symptoms for individuals with BD have been identified that indicate impending relapse and can be reliably recognised and reported (Joyce, 1984; Keitner et al., 1996; Lam, Wong, & Sham, 2001; Molnar, Feeney, & Fava, 1988; Smith & Tarrier, 1992). Common depression prodromes include anhedonia, interrupted sleep, and pre-occupation with worries. Prodromal features common to mania are increased activity and decreased need for sleep, increased socialisation, and racing thoughts (Lam & Wong, 2005). The emergence of such prodromal symptoms in BD can cause distress, and level of coping with prodromal symptoms has been found to predict relapses (Lam & Wong, 2005). Further, both mania and depression have been clinically observed to fuel themselves once started. Individuals may not be completely aware that a re-emergence of feelings of confidence, decreased need for sleep and increased sociability may be part of the early stages of mania, and may be tempted to seek more stimulation, leading to further disruption of sleep and routine. Similarly, individuals at the early stage of depression, who are experiencing an increase in worrying thoughts, lack of motivation and loss of interest, may feel guilty for being “lazy” or about their decrease in functioning, which can, in turn, increase depressive symptoms (Lam & Wong, 2005).

If such sub-syndromal or subclinical symptoms have been found to infer risk of relapse in those with BD, the same subclinical symptoms may be useful risk indicators in those at heightened genetic risk of developing BD. For those with a diagnosis of BD, the identification of prodromal symptoms is hoped to offer the opportunity for early intervention to slow or prevent development of relapse into a full episode. In at risk populations, the identification of a bipolar prodrome, is hoped to provide the opportunity to slow or even prevent development of full blown bipolar illness, reduce diagnostic delay, and improve prognosis for those who do go on to develop the disorder.

## **Early identification/ intervention research**

Research reconstructing the prodromal stage of psychotic illnesses such as schizophrenia has enabled researchers to put together operational criteria that can be used prospectively to identify individuals at risk of transition to psychosis (McGorry et al., 2013). This has allowed for the development and trial of early intervention strategies that have been shown to have some impact on later outcomes for these at risk groups (Larsen et al., 2001; Stafford, Jackson, Mayo-Wilson, Morrison, & Kendall, 2013). There is hope that, in a similar way, identification of specific sub-threshold symptom clusters or patterns in BD may help predict who is at greater risk of developing the disorder and allow the development of targeted interventions that parallel those in schizophrenia research.

### ***Research with High Risk Populations***

An important factor in identifying high risk populations is of course genetic loading or predisposition. BD is highly heritable (McGuffin et al., 2003; Schneck, 2011a), and there is substantial genetic overlap with unipolar depression (McGuffin et al., 2003). It has been suggested that positive family history is in fact the most potent risk factor for mood disorders, particularly BD. As such, much of the recent research in BD has focused on the genetic contribution to the development of the disorder. It is acknowledged, however, that the specific factors transmitted in families are still unknown (Merikangas & Low, 2004) and more recently researchers have begun to investigate the contribution of other potential risk factors outside of heritability. Genes confer vulnerability to illness by impacting on an individual via biochemical, endocrinological, neuroanatomical and psychological processes that are more closely related to the onset of symptoms (Egeland, Blumenthal, Nee, Sharpe, & Endicott, 1987). Therefore, psychological characteristics associated with high risk or development of BD may serve as endophenotypic components that can assist in understanding the family transmission of the disorder through genes and gene-environment interactions (Hasler, Drevets, Gould, Gottesman, & Manji, 2006).

Awareness of the genetic contribution to BD allows for the investigation of such additional risk factors with samples of individuals identified as having increased risk due to their family history. Comprehensive prospective studies with groups of individuals such as this have been found to be useful in identifying key differences between those considered at genetic risk and those with no family history of mood disorder (Nurnberger et al., 2011; Perich et al., 2015; Perich et al., 2013). Moreover, similar

research in schizophrenia has demonstrated the interplay between genetic factors and other important areas contributing to risk and development of psychopathology (Yung et al., 2008). Important factors identified in this research include environmental and psychosocial factors, as well as subclinical psychological and behavioural symptoms such as affective changes, disturbances in thinking and perception, and decline in social functioning (Simon et al., 2006).

Research findings of poor outcomes in BD highlight the need for further exploration of the role of psychosocial factors in the development and course of the disorder (Prien & Potter, 1989; Scott, 1995). The exploration of similar factors in schizophrenia research has resulted in development of interventions aimed at prevention and improving prognoses for individuals identified as at risk or in the prodromal phases of the illness (Morrison et al., 2004). It is hoped that identification of additional key risk indicators for BD may bring us closer to prevention, early intervention, and improved outcomes.

## **Adolescence**

Although established diagnostic criteria for bipolar disorder come primarily from clinical and research data derived from affected adults, onset of bipolar disorder in adolescence is common (Kessler et al., 2005), and it is believed that the first presentation of symptoms or indicators of later disorder is often even earlier. Retrospective examination of prospectively collected data in a study by Egeland, Hostetter, Pauls, and Sussex (2000), found a number of common early symptoms experienced by children who later went on to develop bipolar disorder. These symptoms were: depressed mood, irritability, increased sensitivity, increased energy and agitation / anger. Unfortunately, as fluctuations in mood are understood to be common during this stage of development, it can be difficult to differentiate normal adolescent emotional development from early indications of later mood disorder.

Adolescence is a unique period marked by developmental change in biological, psychological and social systems. Evidence suggests that hormonal changes during adolescence are linked to disruptions in mood and behaviour that typically generates more emotional turmoil than either childhood or adulthood (Larson, Csikszentmihalyi, & Graef, 1980). Epidemiological studies have reported depression prevalence rates as high as 8% in adolescents (Fleming & Offord, 1990; Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993), and the lifetime prevalence of depression in adolescents is comparable to that in adults, at around 15 to 20% (Muris, Schmidt, Lambrichs, & Meesters, 2001). It is believed, however, that healthy

adolescents are prone to hyper-emotionality that is both normative and developmentally specific (Arnett, 1999; Casey, Jones, & Hare, 2008; Casey et al., 2010; Casey, Jones, & Somerville, 2011) and most adolescents cope successfully with the developmental demands of this period without extremes of maladaptation. Further, greater mood variability and instability does not necessarily mean greater disequilibrium or “turmoil”. A study by Larson et al. (1980) found that although adolescents experienced wider mood extremes and less mood stability than adults, this mood variability was not positively associated with social maladjustment as had been predicted. In fact, adolescents reporting wider mood variation were less alienated from their peers and more likely to be leaders in organisations. Moreover, mood variation was associated with a peer-oriented life style, and more time spent with friends and in public (Larson et al., 1980).

The fact that behaviours associated with internalizing and externalizing forms of psychopathology, such as mood disruptions and increased risk taking are not atypical during adolescence, makes it difficult during this period to clarify the boundaries between normative struggles and psychopathology (Cicchetti & Rogosch, 2002). Although the importance of early identification in mental health is clear, it is equally important not to over-pathologise what may simply be part of normal adolescent development. Unfortunately, it may be no less damaging to dismiss potential signs of risk in someone who is experiencing the beginnings of disruption and who may benefit from increased monitoring or early intervention. In fact, it is commonly reported that BD with an earlier than typical onset is associated with more severe illness course and significantly poorer prognosis although the results of research investigating this relationship are mixed (Azorin et al., 2013; Baldessarini et al., 2012; Goldstein & Levitt, 2006; Leverich et al., 2007; Post et al., 2010; Suominen et al., 2007).

## **Summary**

In summary, Bipolar disorder is a complex psychiatric illness that is a leading cause of disability worldwide (Azorin et al., 2013). Accurate diagnosis of BD is complex, and this frequently results in long delays in diagnosis (Drancourt et al., 2013; Schneck, 2011b) or misdiagnosis (Fiedorowicz et al., 2011; Hirschfeld et al., 2003). Evidence suggests, that subsequent delays to appropriate treatment for those with BD can have severe negative impacts and increase adverse outcomes (Coryell et al., 2013; Goldberg & Ernst, 2002c). This would imply that improved early identification and intervention is important for

improving outcomes in BD. Moreover, such improvements may be of particular importance for those with an earlier onset, which is often reported to be associated with especially poor prognoses. However, results of studies investigating these relationships are mixed (Azorin et al., 2013; Baldessarini et al., 2012; Goldstein & Levitt, 2006; Leverich et al., 2007; Post et al., 2010; Suominen et al., 2007) and the true relationship unclear. Identification of emerging BD is likely to be fraught with difficulties as many diagnostic indicators that may be helpful at other developmental stages are difficult to differentiate from emotional and behavioural changes typical during adolescence (Cicchetti & Rogosch, 2002). Pathologising of normal developmental processes, or shifting to over-diagnosis is unlikely to address current issues, and may create its own difficulties (Mitchell, 2012).

BD has been demonstrated to have high heritability (McGuffin et al., 2003; Schneck, 2011a) and family history is therefore a useful risk indicator in BD; however, it is not sufficient to predict later development of the disorder. In other related disorders, such as schizophrenia, sub-threshold symptoms have been found to be useful in the identification of high risk groups that are likely to benefit from early intervention. Results of this research also suggest that there are differences in the usefulness of individual symptoms in the prediction of risk.

Despite the extent and high quality of research into BD, there remain important areas of investigation that have not been addressed. Research into psychological and social factors contributing to development and outcomes in BD has been very limited and there is clear need for further exploration of psychological symptoms and other psychosocial factors in the expression of risk, development and course of the disorder (Prien & Potter, 1989; Scott, 1995). The exploration of similar factors in Schizophrenia research has proven helpful in development of early intervention and improvement of prognoses (Morrison et al., 2004). Applying these same principles to BD research may bring us closer to prevention, early intervention, and improved outcomes. In addition, although it is commonly reported that an earlier onset of BD is associated with poorer prognosis and greater adverse outcomes, the results of studies investigating these relationships have found mixed results. There are no published reviews of this research that draw together the disparate findings and assist in clarifying the relationship between age of onset and outcomes. Yet the relationship is widely reported in the research as though it were common knowledge.



## **Introduction to thesis studies**

The aims of the research conducted as part of this thesis were as follows: Chapter 2 comprises a meta-analysis designed to systematically review and analyse empirical findings that have been published to date regarding associations between age of onset of BD, prognoses and outcomes. This meta-analysis analysed existing evidence from empirical research to ascertain whether an earlier onset of BD is in fact associated with poorer prognoses and greater adverse outcomes as has commonly been reported. Further, this paper aimed to identify the specific adverse outcomes shown to have the strongest relationship to an earlier age of onset of BD. Chapter 3 comprises an empirical study based on novel data including participants with a heightened genetic risk of BD. The aims of this study were to characterize the individual symptoms of BD that may be most informative during adolescence and early adulthood regarding risk for the disorder. Using a standardised clinical interview, the endorsement of individual clinical and sub-threshold symptoms was examined in participants from three groups: those with a diagnosis of BD (BD); those with a first-degree relative with BD (At-Risk); and controls (C). Patterns of endorsement were then examined using novel analysis based on Item Response Theory (IRT) to assess whether differences could be identified in the information provided by individual symptoms in relation to discrimination and severity.

Item Response Theory (IRT) comprises a collection of mathematical models and statistical methods that explore the way in which underlying, unobserved or latent constructs manifest as observable item responses (Harvey & Hammer, 1999). IRT procedures are well established and well researched in the field of achievement and aptitude testing, however, the application of IRT models to personality and attitude measurement, and measurement of psychopathology is less well explored. In clinical research IRT has been applied to analyses using the SADS-C to identify the level of information provided by each symptom in terms of syndrome severity in bipolar mania (Cheniaux et al., 2014). It has also been used to develop understanding of comorbidity among anxiety and unipolar mood disorders (Krueger & Finger, 2001), compare measures of depressive symptomatology (Olino et al., 2012), and to identify differences in depressive symptoms between patients with unipolar and bipolar depression (Weinstock, Strong, Uebelacker, & Miller, 2009).

In the present study it was anticipated that individual symptoms from scales of depression and mania would provide varying levels of information relating to risk for, and severity of, psychopathology. Further, it was anticipated that symptoms found to be most informative at lower levels of severity would be different to those found to be most informative at higher levels of severity. The findings of this study may be useful in the identification of high risk individuals who may benefit from early support and intervention. Moreover, this information has the potential to inform areas of further research with adolescent and young adult populations. Identifying key items or patterns of endorsed responses may help inform development and assessment of early intervention treatments for youth with BD. Moreover it may also inform areas of focus for developing early interventions to ameliorate or minimise severity of later development of dysfunction / disorder.

The final chapter presents a general discussion of key findings included in this thesis. Findings of both the meta-analysis and empirical study are discussed. This chapter also covers a discussion of the clinical and theoretical implications of the findings of the present research, and recommendations for future research.

# Chapter 2: Systematic Review and Meta-Analysis

**Is age of onset associated with severity, prognosis and clinical features in bipolar disorder?**

**A meta-analytic review**

The following chapter is a replication of material published in *Bipolar Disorders* 2016

Joslyn, C., Hawes, D. J., Hunt, C. & Mitchell, P. B. (2016) Is age of onset associated with severity, prognosis and clinical features in bipolar disorder? A meta-analytic review. *Bipolar Disorders*

Cassandra Joslyn developed the review focus and took the primary lead in the writing, research and interpretation of the paper.

Signature:

Date:

A/Prof David Hawes, A/Prof Caroline Hunt, and Scientia Prof Philip B. Mitchell provided critical revisions of the manuscript.

Signature:

Date:

## **Abstract**

*Objectives:* To identify clinical characteristics and adverse outcomes associated with an earlier age of onset of bipolar disorder.

*Methods:* A comprehensive search yielded 15 empirical papers comparing clinical presentation and outcomes in individuals with bipolar disorder grouped according to age of onset (Total N: 7370). The following variables were examined to determine odds ratios (ORs) and 95% confidence intervals (CI): presence of axis 1 comorbidity, rapid cycling, psychotic symptoms, mixed episodes (DSM-IV), lifetime suicide attempts, lifetime alcohol and substance abuse, symptom severity and treatment delay.

*Results:* Early age of onset was found to be associated with longer delay to treatment (Hedges  $g = 0.39$ ,  $p = 0.001$ ), greater severity of depression (Hedges  $g = 0.42$ ,  $p < 0.001$ ), and higher levels of comorbid anxiety (OR = 2.34,  $p < 0.001$ ) and substance use (OR = 1.80,  $p < 0.001$ ). Surprisingly, no association was found between early age of onset and clinical characteristics such as psychotic symptoms or mixed episodes as defined by DSM-IV.

*Conclusions:* Earlier age of onset of BD is associated with factors that can negatively impact long term outcomes such as increased comorbidity. However, no association was found between early onset and indicators of severity or treatment resistance such as psychotic symptoms. Clinical features found to have the strongest relationship with early age of onset were those potentially amenable to pharmacological and psychological treatment. Results highlight the importance of early identification and provide potential areas of focus for the development of early intervention in BD.

**Key Words:** Bipolar disorder, Meta-Analysis, Age of onset, Prognosis, Outcomes, Severity, Comorbidity

## Introduction

Bipolar disorder (BD) is a severe, chronic mood disorder with a population prevalence of around 1-5% (Fagiolini et al., 2013; Ketter, 2010). It is associated with high rates of comorbidity and is a leading cause of premature mortality due to suicide (da Silva Costa et al., 2015; Hayes, Miles, Walters, King, & Osborn, 2015). BD often results in enduring work and social impairment (Coryell et al., 1993a), and is associated with a significant economic burden, to the individual and society, due to both direct and indirect costs such as medical expenditure, loss of productivity and increased mortality (Fagiolini et al., 2013). The typical onset of BD occurs in late adolescence to early adulthood (Joyce, 1984). However, a large proportion of adults with BD experience the onset of the disorder prior to adulthood (Chengappa et al., 2003) and, although it remains controversial, some have argued that incidences of prepubescent and childhood onset BD are increasing (Axelson et al., 2006; Birmaher & Axelson, 2006; Wozniak et al., 2011).

A strong birth cohort effect has been detected in bipolar disorder whereby higher overall rates of the disorder as well as earlier ages of onset have been found over successive generations (Bauer et al., 2015; Chengappa et al., 2003). Much of this research has focused on differences between those born prior to and after 1940 (Chengappa et al., 2003; Lasch, Weissman, Wickramaratne, & Bruce, 1990), however, several studies have also found a similar continuing trend for later decades (Bauer et al., 2015; Da Silva Magalhaes, Gomes, Kunz, & Kapczinski, 2009; Gershon, Hamovit, Guroff, & Nurnberger, 1987). At least one study using a US based community sample detected this trend for major depression but not for BD (Burke, Burke, Rae, & Regier, 1991). However, a wealth of evidence, including a large study with data from 36 international sites, supports these cohort effects (Bauer et al., 2015; Da Silva Magalhaes et al., 2009; Gershon et al., 1987). Changes in the development and detection of BD over time are perhaps not unexpected, particularly as our understanding of the disorder develops, however, whether these effects are the result of genetic, environmental or cultural / educational influences is as yet unclear.

It has been suggested that increases in the prevalence of BD in younger populations are mainly due to changes in diagnostic criteria, with claims that diagnostic rates are significantly higher in the United States compared to other countries (James et al., 2014). Studies comparing hospital discharge rates for children and adolescents (under 20years) diagnosed with BD have found significantly higher rates in

the US compared to other countries such as England, Australia, New Zealand, and Germany (Clacey, Goldacre, & James, 2015; James et al., 2014). Further, rates of diagnosis of BD in general, but particularly in children have been found to be increasing significantly within U.S. over time (Blader & Carlson, 2007; Moreno et al., 2007). There are a number of possible explanations for these discrepancies. Patient expectations and medical system differences can influence the acceptance of particular diagnoses and treatment (Stringaris & Youngstrom, 2014b). Differences in the way clinicians in different countries interpret symptoms in children, and use of non-specific symptoms such as irritability as core features can also impact rates of diagnosis (Dubicka, Carlson, Vail, & Harrington, 2008).

It is important to note here the difference between epidemiological prevalence and administrative prevalence. What is generally reported in studies where these differences between countries have been identified are numbers of diagnoses made by health care professionals during a particular period in a defined region (administrative prevalence). Epidemiologic prevalence estimates on the other hand, use standardized instruments and random population samples (Stringaris & Youngstrom, 2014b). A meta-analysis of epidemiologic studies of pediatric bipolar disorder conducted by Van Meter et al. in 2011 (Van Meter, Moreira, & Youngstrom, 2011) found no significant differences between US and non-US samples in average rates of pediatric mania and hypomania in the community. This would suggest that differences in detection rates are primarily driven by different application of diagnostic criteria (Van Meter et al., 2011). Improving accuracy of BD diagnoses is of utmost importance, and over-diagnosis is a grave concern (Mitchell, 2012). However, to deny the possibility of early onset BD is not necessarily an appropriate solution. BD has been diagnosed in children as young as 12yrs, and it is recognized that particular symptoms should be closely monitored by clinicians for early signs of mania (Kessing, Vradi, & Andersen, 2015).

The definitive diagnosis of BD is often difficult and misdiagnosis is common particularly for younger individuals. As a result, long delays in diagnosis frequently occur. Patients report up to 10 years between the onset of affective symptoms and formal diagnosis (Lish, Dime-Meenan, Whybrow, Price, & Hirschfeld, 1994) and there is evidence to suggest that an earlier age of onset is associated with the longest delays to appropriate diagnosis and treatment (Drancourt et al., 2013; Leverich et al., 2007; Post et al., 2010; Suominen et al., 2007). These delays are associated with poorer prognosis and more adverse outcomes for individuals such as more time depressed, greater severity of depression (Post et al., 2010),

elevated risk for suicidal behavior (Drancourt et al., 2013; Goldberg & Ernst, 2002a; Nery-Fernandes et al., 2012), poorer social adjustment, and greater number of hospitalizations (Goldberg & Ernst, 2002a).

One possible explanation for diagnostic difficulties in BD is the clinical heterogeneity of the disorder. As such, a great deal of research has focused on identifying a specific prodrome and key risk indicators to aid with early identification and intervention; and thereby assist in refining early diagnosis. Age at onset (AAO) has been proposed as one potential marker for more homogeneous subgroups of BD (Bellivier, Golmard, Henry, Leboyer, & Schurhoff, 2001a). It was also proposed as a course specifier for BD in the development of DSM-5 (Baldessarini et al., 2012; Colom & Vieta, 2009), however, was not incorporated in the final publication. It is often suggested that, compared to a more typical age of onset of BD, earlier age of onset is associated with a more severe clinical presentation and poorer outcomes. This appears intuitive given the potential impact that the development of BD during adolescence might have on critical developmental processes (Moor, Crowe, Luty, Carter, & Joyce, 2012), however, the nature of the relationship between age of onset and outcome in BD remains unclear.

One limitation of early studies investigating the potential for AAO to delineate more homogenous subgroups of BD was that age cut-offs for AAO groups were arbitrarily chosen to define early and late onset (Strober, 1992). More recent investigations have used admixture analysis to overcome this limitation and determine the model that best fits observed AAO distributions. These studies have identified three subgroups defined by AAO; early, with mean onset around 17 -18yrs (SD= 2); intermediate, with mean onset around 24yrs (SD=6) and late, with mean onset around 40yrs (SD=10) (Azorin et al., 2013; Bellivier et al., 2001a; Geoffroy, Etain, Jamain, Bellivier, & Leboyer, 2013; Hamshere et al., 2009; Leboyer, Henry, Paillere-Martinot, & Bellivier, 2005).

Studies of the relationship between AAO, and BD severity and prognosis have reported mixed results. For example, although many have found early age of onset to be associated with more severe clinical characteristics such as greater rates of psychotic features (Schürhoff et al., 2000; Strober et al., 1995; Suominen et al., 2007; Yildiz & Sachs, 2003), rapid cycling (Azorin et al., 2013; Cate Carter, Mundo, Parikh, & Kennedy, 2003) and mixed episodes (Patel, DelBello, Keck, & Strakowski, 2006; Schürhoff et al., 2000), others have found no difference in rates of these characteristics between EAO and Adult onset groups (Goldstein & Levitt, 2006; Tozzi et al., 2011a). Moreover, some have found the opposite relationships. For example, Patel et al. (Patel et al., 2006) reported psychotic features to be more

common in those with “typical onset” (20-30yrs) compared to those with early onset. Finally, others have found no evidence of more severe symptomatic morbidity among juvenile onset cases but have instead found differences in functional outcomes such as employment, independent living and quality of life (Baldessarini et al., 2012).

A number of studies have shown higher rates of psychiatric comorbidity such as anxiety disorders (Cassano, Pini, Sacttoni, & Dell’Osso, 1999; Cate Carter et al., 2003; Ibiloglu & Caykoylu, 2011; McElroy et al., 2001; Mick, Biederman, Faraone, Murray, & Wozniak, 2003), and alcohol or substance use disorders (Azorin et al., 2013; Bashir, Russell, & Johnson, 1987; Grunebaum et al., 2006a; Lin et al., 2014) in those with an earlier onset of BD. Others though, have found no relationship between age of onset and comorbid anxiety (Altindag, Yanik, & Nebioglu, 2006), or alcohol abuse (Schürhoff et al., 2000), or have found an association between EAO and either alcohol or substance abuse but not the other (Cate Carter et al., 2003; Lagerberg et al., 2011).

Finally, many studies have suggested that earlier onset of BD is associated with more frequent and severe depressive episodes (Slama et al., 2004), more suicidal ideation (Biffin et al., 2009), and a greater likelihood of lifetime suicide attempts (Azorin et al., 2013; Cate Carter et al., 2003; Grunebaum et al., 2006b; Slama et al., 2004; Tozzi et al., 2011a). It is difficult, however, particularly with lifetime risk indicators, to clearly differentiate risk associated with age of onset from risk associated with other factors such as duration of illness. Studies using multiple logistic regression to examine relative associations of different variables with a past history of suicide attempt in BD (Leverich et al., 2007; López et al., 2001; Slama et al., 2004; Tondo et al., 1999; Tsai, Lee, & Chen, 1999) have consistently found a number of variables to be associated with suicide attempts including: earlier age of onset, depression severity (hospitalization) and comorbid substance use. Other studies have found no significant difference in rates of suicide attempts between early and adult onset age groups (Ernst & Goldberg, 2004; Schürhoff et al., 2000). A recent meta-analysis by Schaffer and colleagues (Schaffer et al., 2015) synthesizing data on BD and suicide attempts between 1980 and 2013, found a wide range of factors to correlate with previous suicide attempts in BD such as female gender, comorbid anxiety, substance use, or alcohol use disorder and a family history of suicide in first degree relatives. This study included samples with an ages >13yrs and found a younger age at onset to be significantly associated with a history of suicide attempts.



While it is frequently stated that those with early onset BD have a more severe clinical presentation and poorer prognosis, as yet no reviews or meta-analyses have been published on this relationship. Indeed, findings on the magnitude of differences in clinical characteristics and prognosis associated with this age group have varied markedly across studies. As such, meta-analysis is a useful tool for synthesizing data to identify outcomes with more robust effects. The present study aimed to review the current evidence regarding clinical presentation and outcomes associated with early onset of bipolar disorder compared with those associated with adult onset.

## **Method**

This review included studies that investigated differences in clinical presentation and outcomes in bipolar disorder (BD) for individuals with differing ages of onset. Only studies with original data published in peer reviewed journals were included. Review articles, book chapters, commentaries and symposia were excluded. All participants were required to have a formal structured diagnosis of bipolar I disorder (BDI), bipolar II disorder (BDII) or bipolar disorder not otherwise specified (BDNOS) to be included. Samples including participants with a diagnosis of schizophrenia, schizo-affective disorder and major depressive disorder were excluded. Genetic studies investigating heritability and family history of BD were also excluded on the basis that their focus was not on differences in clinical or prognostic characteristics between onset age groups, but on factors that are outside the scope of the current paper.

Age at onset (AAO) of BD ranged from younger than 13 years to older than 40 years. For the majority of studies, AAO was defined as the age at which the person first met diagnostic criteria for an affective episode of depressive, manic, hypomanic or mixed state. Studies involving both early age at onset (EAO) and typical (or adult) age at onset groups were included. Those that focused on age of onset over 65 years were considered outside the age range of focus for this paper and were therefore excluded. Furthermore, studies that compared pre-pubertal onset alone without an older comparison group were also excluded. Consistent with the majority of prior research, EAO was defined as onset less than or equal to 18 years of age where possible, however, to account for minor differences in studies, EAO was extended to include participants up to 20 years of age where necessary. Studies that classified EAO outside of this age range were excluded.

As the focus of this paper was on the comparison between early and typical (intermediate) onset, only participants within this age range were included in the analysis. Unfortunately many of the papers included in the analysis did not categorize AAO groups according to the model suggested by admixture analysis studies. An attempt was made to recognize these recently identified AAO group cut-off ages while at the same time maintaining the integrity of the data from studies where AAO groups were not categorized according to these cut-offs. Where the original data was separated into two groups: early (<18yrs) and late (>18yrs) these groups were maintained. Where the original data was separated into three groups with early onset defined as <13yrs, adolescent 13-18yrs, and adult >18yrs the early and adolescent groups were combined to reflect the suggested cut-off range from admixture analysis studies. Where necessary, when the original data was grouped as such, the early AAO cut-off was extended as far as 21yrs. This breakdown of age groups fits within the suggested grouping identified by admixture analyses where the peak age for the EAO group is between 17 and 18yrs, and the cut-off for that range has been suggested to be 21yrs (Geoffroy et al., 2013; Hamshere et al., 2009; Leboyer et al., 2005).

Studies reporting on any of the following clinical characteristics and outcomes were included: psychotic features, rapid cycling, mixed episodes (as classified in DSM-IV), severity of depression or mania, comorbidity, suicidal ideation and / or attempts, treatment delay, and objective quality of life measures such as education, employment and independent living. Confirmation of an operationalized diagnosis of BD by semi-structured clinical interview or medical records was required for inclusion. Clinical characteristics and outcomes were also required to be established using standardized measures. Examples of acceptable diagnostic instruments included: Structured Clinical Interview for DSM-IV Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 1995); Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994); Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott & Spitzer, 1978); and the Kiddie-Schedule for Affective Disorders and Schizophrenia (KSADS) (Puig-Antich & Chambers, 1978). Acceptable rating scales for severity of symptoms included: Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979); Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978); Beck Depression Inventory (BDI) (Beck, Steer, & Brown, 1996); Beck Anxiety Inventory (BAI) (Steer & Beck, 1997); and the Hamilton Depression Rating Scale (Hamilton, 1960).

A comprehensive literature search was conducted using the databases Medline, PsychINFO, Embase and CINAHL using a combination of the following search terms: (*bipolar disorder .mp.* OR *exp bipolar disorder*) AND (*onset .mp.* OR *exp “onset (Disorders)”* OR *“Age of Onset”*) AND [(*prognosis .mp.* OR *exp prognosis*) OR (*Severity .mp.* OR *“Severity Disorders”* OR *“Disease Severity”* OR *“Severity of Illness”*) OR (*symptoms .mp.* OR *exp Symptoms* OR *exp Psychiatric Symptoms* OR *“Behavioral Symptoms”* or *“Affective Symptoms”* OR *symptomatology*) OR (*disease course .mp.* OR *exp disease course* OR *disease progression*)]. The search was limited to studies published in peer-reviewed journals in English and covered the period from the inception of the databases to March 2014. No further studies were identified via the reference lists of previously published papers review or included papers.

After duplicates were removed, a total of 2629 papers were retrieved from the original search. An initial screening by title was then conducted in order to identify relevant articles, resulting in 426 papers being retained. Papers were then screened by title and abstract resulting in the exclusion of a further 306 articles. A more detailed examination of the remaining 120 papers resulted in the removal of a further 105 papers. A proportion of the papers included at the full-text level (20%) were screened by a second reviewer to reduce bias in the selection procedure and ensure inter-rater reliability. The resulting Cohen’s Kappa score was  $k = 0.8$ . Any discrepancies in the inclusion or exclusion of papers were resolved by consensus. 15 studies comprised the final pool available for the meta-analysis (See Table 1. for study characteristics). An overview of the search strategy including exclusion criteria is presented in Figure 1.

### **Statistical Analyses**

Meta-analyses were conducted using Comprehensive Meta-Analysis (CMA) Software (Borenstein, Hedges, Higgins, & Rothstein, 2005). The mean rated event rate was estimated as proportions (number of cases / sample size), and used as effect sizes in the analyses with the exception of four outcome variables for which the standardized mean difference method was used, with Hedge’s  $g$  correction for bias. Due to expected heterogeneity, calculations were based on a random effects rather than a fixed effects model (Cooper & Lindsay, 1998). Homogeneity of weighted effect sizes was assessed using a Q-test (Higgins & Thompson, 2002) and results are reported with associated  $I^2$  (Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006) statistics in Table 2.

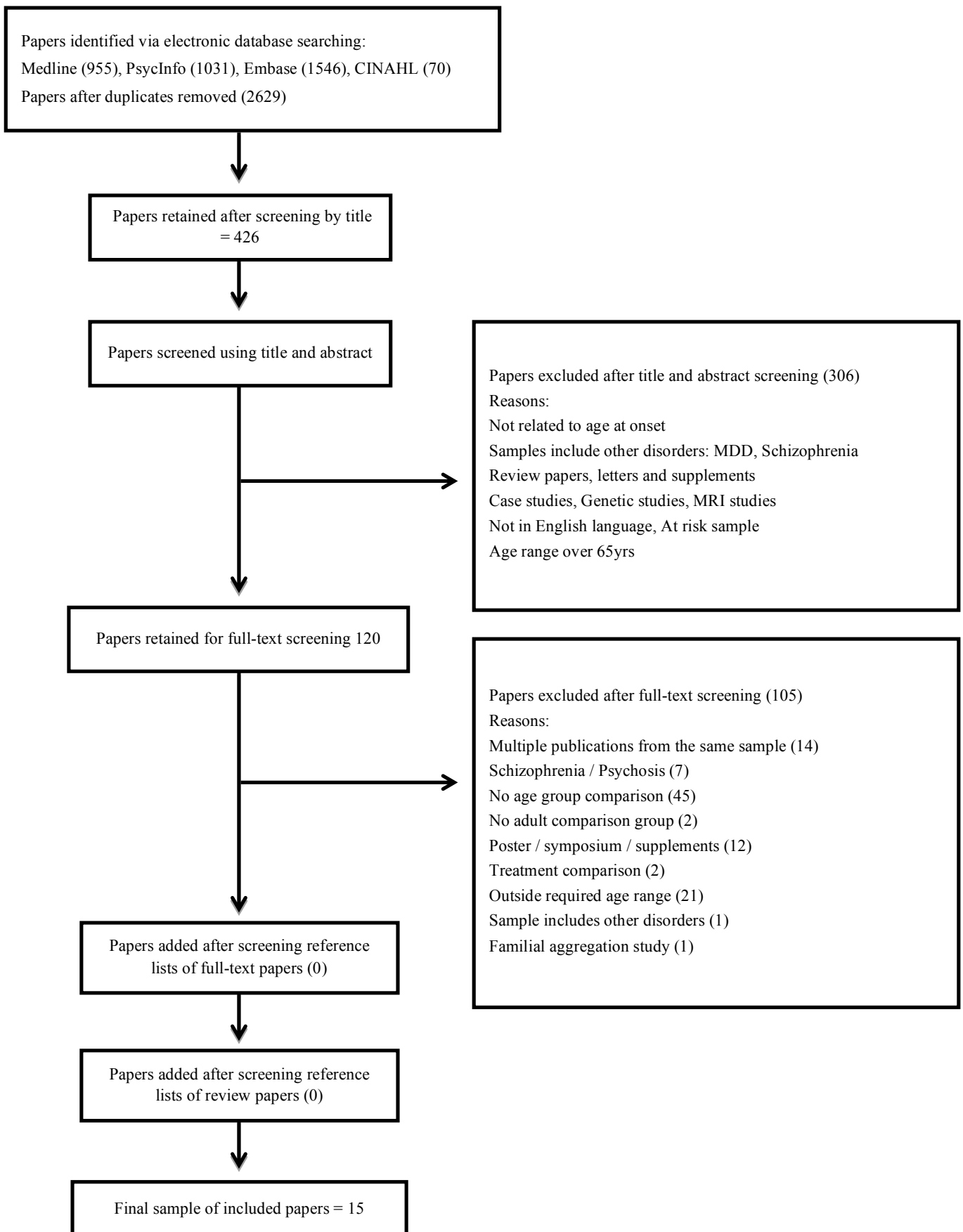


Figure 1: Study Ascertainment Diagram

**Table 1: Characteristics of Included Studies**

<b>N o.</b>	<b>Study</b>	<b>N</b>	<b>Diagnosis</b>	<b>Onset Groups</b>	<b>Meta-Analysis Groups</b>	<b>Definition of AAO</b>	<b>Included Outcome Variables</b>	<b>List of Measures Included in study</b>
1	Azorin et al. (2013) <sup>a</sup>	723	BDI	Early <= 20yrs; Intermediate 20-30yrs; Late >30yrs	<=20yrs vs. >20yrs	The age at which the participant first met the Research Diagnostic Criteria for an affective episode	Alcohol abuse / dependence; Substance abuse /dependence; Comorbid Anxiety; Mixed Episodes; Psychotic Features; Rapid Cycling; Suicidal Ideation; Suicide Attempt; Mean severity depression; Mean severity mania; Treatment Delay (years)	SCID, Medical records, MSRS, MADRS, SAPS
2	Baldessarini et al. (2012) <sup>a</sup>	1665	BDI	Childhood <13yrs; Adolescence 12-18yrs (also combined <18yrs); Adult >19yrs	<=18yrs vs. >18yrs	First clinically appreciable syndromal illness as indicated by patient history, recollections of family members and medical records	Psychotic symptoms; Suicide attempts; Any psychiatric comorbidity;	SCID; BPRS; GAF; CGI
3	Biffin et al. (2009)	162	BD	Early <=19yrs; Intermediate 20-39yrs; Late >=40yrs	<=19yrs vs. >20yrs	The age at which participants reported experiencing their first major affective episode	Alcohol abuse / dependence; Substance abuse / dependence; Comorbid anxiety; Mean severity depression; Mean severity mania ; Suicidal Ideation	MINI; HAM-D; YMRS; CGI-BP
4	Cate Carter et al. (2003) <sup>a</sup>	320	BDI; BDII	Early <=18yrs; Late >18yrs	<=18yrs vs. >18yrs	Age at which participants fulfilled diagnostic criteria for a major mood episode (depressive, manic/hypomanic or mixed) as defined by DSM-IV. Determined by best estimate procedure involving interviewer and a senior psychiatrist	Alcohol abuse / dependence; Substance abuse / dependence; Any psychiatric comorbidity; Comorbid anxiety; Psychotic features; Rapid cycling; Suicidal ideation	SCID; Medical records; FIGS
5	Coryell et al. (2013)	427	BDI; BDII	Early <=20yrs; Intermediate 21-29yrs; Late >=30yrs	<=20yrs vs. >20yrs	Age at which full criteria for disorder were first met	Alcohol abuse / dependence; Substance abuse /dependence; Comorbid anxiety; Psychotic features; Suicide attempt	SADS
6	Drancourt et al. (2013)	501	BDI; BDII	Early <=21yrs; Intermediate 22-37yrs; Late >37yrs	<=21yrs vs. >21yrs	Age at which the participant first met full syndromal DSM-IV criteria for a BD episode (manic, hypomanic, mixed or major depressive)	Treatment delay (years)	DIGS; FIGS; Medical records
7	Ernst and Goldberg (2004) <sup>a</sup>	56	BDI; BDII; BD-NOS	Early <19yrs; Typical >19yrs	<19yrs vs. >19yrs	The first distinct episode of mania, hypomania or major depression.	Substance abuse / dependence, Psychotic features, Rapid cycling, Suicide attempt	SCID; HAM-D; YMRS
8	Goldstein and Levitt (2006) <sup>a</sup>	1411	BD	Child <13yrs; Adolescent 13-18yrs; Adult >=19yrs	<19yrs vs. >19yrs	The first experience of endorsed DSM-IV mania criteria for at least one week duration.	Alcohol and substance abuse, Alcohol abuse / dependence; Substance abuse / dependence; Comorbid anxiety; Comorbid personality disorder, Mixed episodes	AUDADIS
9	Grunebaum et al. (2006a) <sup>a</sup>	146	BDI; BDII; BD-NOS	Child <=12yrs; Adolescent 13-18yrs; Adult >=19yrs	<19yrs vs. >-19yrs	Not defined	Alcohol and substance abuse, Alcohol abuse / dependence; Substance abuse / dependence	SCID; BPRS; GAS

**Table 1. (cont.) Characteristics of Included Studies**

Study	N	Diagnosis	Onset Groups	Grouping for Meta-Analysis	Definition of AAO	Included Outcome Variables	List of Measures Included in Study
<b>10</b> Leverich et al. (2007)	480	BDI; BDII	Child <=12yrs; Adolescent 13-18yrs; Adult 19-29yrs	<=18yrs vs. >18yrs	Age of onset of first depressive symptoms associated with dysfunction, first hypomanic or manic symptoms, or first treatment for mania or depression	Alcohol abuse / dependence, Substance abuse / dependence, Comorbid anxiety, Comorbid personality disorder,	SCID; NIMH-LCM
<b>11</b> Mick et al. (2003)	44	BD	Child <13yrs, Adolescent 13-18yrs, Adult >19yrs	<=18yrs vs. >18yrs	Not defined	Alcohol and substance abuse, Comorbid Anxiety, Comorbid personality disorder	KSADS
<b>12</b> Moor et al. (2012) <sup>a</sup>	100	BDI; BDII; BD-NOS	Early <13yrs; Adolescent 13-17yrs; Adult >=18yrs	<18yrs vs. >=18yrs	The first 2 week period of functionally impairing and pervasive depressive symptoms or the first 4 day hypomania or mania whichever was earlier.	Alcohol abuse / dependence, Substance abuse / dependence, Comorbid anxiety, Comorbid personality disorder,	SCID
<b>13</b> Patel et al. (2006) <sup>a</sup>	161	BDI	Early <18yrs; Typical 20-30yrs; Late >35yrs	<=18yrs vs. >18yrs	The age at which participants endorsed enough DSM-IV syndrome criteria for an affective episode (either major depressive, manic or hypomanic).	First polarity depression; First polarity mania; Alcohol and substance abuse; Mixed episodes; Psychotic features	SCID, KSADS, YMRS, HAM-D, SAPS
<b>14</b> Perlis et al. (2004) <sup>a</sup>	983	BDI, BDII, BD-NOS	Early <13yrs; Intermediate 13-18yrs; Adult >18yrs	<=18yrs vs. >18yrs	Age of onset of the first episode of depressive, manic, hypomanic or mixed type.	Alcohol dependence; Substance dependence; Comorbid anxiety; Psychotic features; Suicide attempt	MINI, ADE, GAF
<b>15</b> Suominen et al. (2007) <sup>a</sup>	191	BDI; BDII	Early <=18yrs; Adult >18yrs	<=18yrs vs. >18yrs	Age of first mood episode fulfilling DSM-IV criteria	First polarity depression; First polarity mania; Alcohol and substance abuse; Any psychiatric comorbidity; Comorbid anxiety; Comorbid personality disorder; Mean severity anxiety; Mean severity depression; Mean severity mania; Psychotic features; Rapid cycling; Suicidal ideation; Suicide attempt; Treatment delay (years)	MDQ; SCID; Medical records; YMRS; HAM-D; BDI; BAI; BHS;

ADE = Affective Disorders Evaluation; AUDADIS = Alcohol Use Disorder and Associated Disabilities Interview Schedule for DSM-IV; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BHS = Beck Hopelessness Scale; BPRS = Brief Psychiatric Rating Scale; CGI= Clinical Global Impression Scale; DIGS = Diagnostic Interview for Genetic Studies; FIGS = Family Interview for Genetics Studies; GAF = Global Assessment of Functioning; HAM-D = Hamilton Depression Scale; KSADS = Kiddie-Schedule for Affective Disorders and Schizophrenia; NIMH-LCM = National Institutes of Mental Health Life Chart Method; MADRS = Montgomery Asberg Depression Rating Scale; MDQ = Mood Disorder Questionnaire; MINI = Mini International Neuropsychiatric Interview; MSRS = Mania State Rating Scale; SADS = Schedule for Affective Disorders and Schizophrenia; SAPS = Scale for the Assessment of Positive Symptoms; SCID = Structured Clinical Interview for DSM-IV Disorders; YMRS = Young Mania Rating Scale

<sup>a</sup> indicates that multivariate analyses were included in the study

**Table 2: Summary of results for individual outcomes**

<b>Outcome</b>	<b>Studies (n)</b>	<b>Participants (n)</b>	<b>Odds Ratio</b>	<b>Hedges g</b>	<b>95% CI</b>	<b>Q</b>	<b>I<sup>2</sup> value (%)</b>	<b>Eggers Test (t)</b>	<b>Trim &amp; Fill (studies added)</b>	<b>Study references from Table 1.</b>
<b>Alcohol or Substance Abuse</b>	5	1953	0.90	-	0.50 - 1.62	18.57*	78.46	1.28	0	8; 9; 11; 13; 15
<b>Alcohol Only*</b>	9	4752	1.36	-	1.04 - 1.76	21.20*	62.26	1.07	5	1; 3; 4; 5; 8; 9; 10; 12; 14
<b>Substance Only**</b>	10	4808	1.80	-	1.39 - 2.35	18.00*	49.99	0.62	2	1; 3; 4; 5; 7; 8; 9; 10; 12; 14
<b>Any Psychiatric Comorbidity</b>	3	2176	1.62	-	0.91 - 2.87	8.10*	75.32	2.38	2	2; 4; 15
<b>Comorbid Anxiety**</b>	10	4841	1.72	-	1.34 - 2.19	25.20*	64.28	1.70	2	1; 3; 4; 5; 8; 10; 11; 12; 14; 15
<b>Comorbid Personality Disorder*</b>	4	1746	2.34	-	1.85 - 2.95	1.11	0.00	3.42	2	8; 11; 12; 15
<b>Psychotic Features</b>	8	4526	0.83	-	0.56 - 1.24	53.45*	86.90	0.27	1	1; 2; 4; 5; 7; 13; 14; 15
<b>Rapid Cycling</b>	5	1770	1.80	-	0.86 - 3.77	29.95*	86.64	1.78	1	1; 4; 7; 10; 15
<b>Mixed Episodes</b>	3	2295	1.81	-	0.70 - 4.71	20.16*	90.08	1.69	0	1; 8; 13
<b>Mean Severity Mania</b>	3	1076	-	-0.03	-0.33 - 0.26	7.86*	74.56	8.95	0	1; 3; 15
<b>Mean Severity Depression**</b>	3	1076	-	0.42	0.30 - 0.55	0.36	0.00	0.67	0	1; 3; 15
<b>Mean Severity Anxiety</b>	2	618	-	-	-	-	-	-	-	5; 15
<b>Suicidal Ideation**</b>	3	673	2.37	-	1.69 - 3.31	0.08	0.00	0.04	0	3; 4; 15
<b>Suicide Attempt**</b>	6	4045	1.68	-	1.29 - 2.18	11.79*	57.59	0.56	3	1; 2; 5; 7; 14; 15
<b>Treatment Delay (Years)**</b>	3	1415	-	0.39	0.15 - 0.63	8.24*	75.73	1.12	0	1; 6; 15
<b>First Polarity Depression</b>	2	352	-	-	-	-	-	-	-	13; 15
<b>First Polarity Mania</b>	3	1075	1.16	-	0.79 - 1.70	2.77	27.72	0.05	1	1; 13; 15

\*Significant at p=0.05

\*\* Significant at p=0.01

Meta-analytic methods accept published studies as representative of all valid studies undertaken, however, direction and significance of results can influence the chance of submission and publication of studies and this can be a source of bias in results (publication bias). In the current meta-analysis, publication bias was tested using two methods. Egger's regression test (Higgins & Thompson, 2002) and Duval and Tweedie's trim and fill (Rosenthal, 1979) were used to assess funnel plots for significant asymmetry that may indicate potential publication bias.

## **Results**

The total number of participants in the 15 studies included in the meta-analysis was 7370. A summary of the included studies, with results and assessment for bias for each outcome variable, is presented in Table 2. The particular clinical and prognostic features varied between studies, with the most common including suicide ideation and attempts, comorbid alcohol and substance abuse, comorbid psychopathology, treatment delay, and illness characteristics such as rapid cycling, mixed episodes (DSM-IV), psychotic symptoms and general severity. Participants included in the studies varied in diagnosis from BDI, for which an individual has to have experienced at least one full-blown manic episode, to BD-NOS; however, all studies included a greater proportion of BDI participants than any other bipolar disorder diagnosis. Gender representation was approximately equal across studies with a combined average of 57.2% female participants. Average age of onset across groups ranged from 9 to 37yrs with an overall average age of onset across studies of 22.79yrs. Ten of the fifteen studies used retrospective methods while five involved a prospective design. Duration of follow up ranged from one to 25 years, with a median follow up of two years.

### ***Suicide Attempts / Suicidal Ideation***

Six studies (n= 4045) reported rates of lifetime suicide attempts. Meta-analysis (see figure 2.) demonstrated that the odds of those with an earlier age of onset having attempted suicide were significantly greater than for those with later age of onset (OR = 1.68, 95% CI = 1.29-2.18, p<0.001). Egger's regression test was not significant (B = 0.94, standard error (SE) = 1.68, t = 0.56, p = 0.607). Only two studies (n=511) reported rates of suicidal ideation. These studies (Cate Carter et al., 2003; Suominen et al., 2007) both found the early onset group to have higher rates of lifetime suicidal ideation than the



adult onset group ( $\chi^2 = 12.12$ ,  $p = 0.002$ ;  $v^2(1) = 4.1$ ,  $p = 0.04$  respectively). However, results from such a small number of studies, each with small sample sizes are unlikely to be robust.

Only one paper (Moor et al., 2012) reported on Parasuicidal behaviors, having assessed whether participants had ever deliberately harmed themselves without the intent to die, but in order to relieve tension or help them to feel better. Very early onset (<13yrs) was found to predict both Parasuicidal and suicidal behaviors. However, these are the results of one study alone and as these variables were not reported by other papers, they were not able to be included in the meta-analysis.

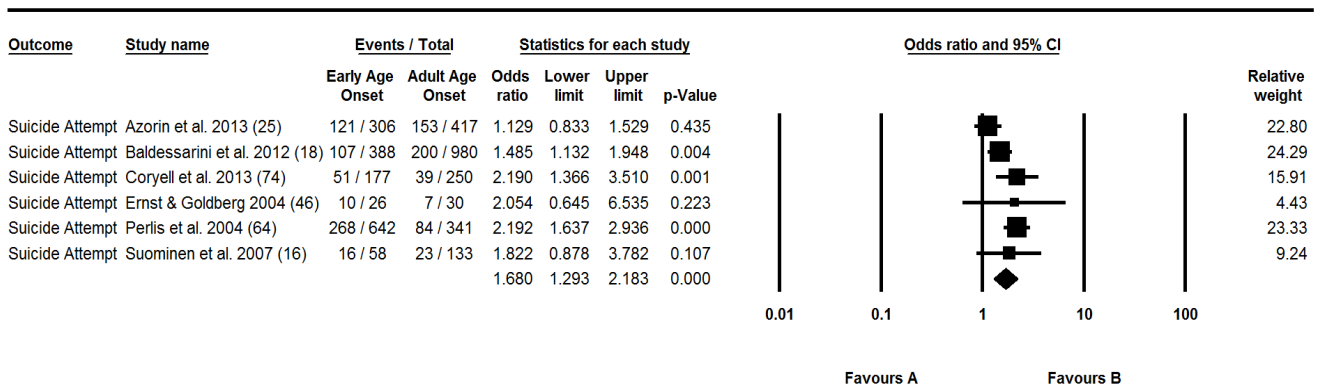


Figure 2: Forest plot odds ratios (ORs) as shaded squares proportional to study weight, with 95% confidence intervals (CIs) based on random-effects meta-analysis of lifetime suicide attempts in six studies

### Comorbidity

*Alcohol and Substance Abuse / Dependence.* Five studies (n=1953) reported on rates of combined alcohol and substance abuse or dependence, nine (n=4752) reported rates of abuse and / or dependence of alcohol alone, and 10 (n=4808) reported rates of substance abuse or dependence alone. Those with an earlier age of onset were more likely to have comorbid alcohol abuse or dependence (OR = 1.35, 95% CI 1.04-1.76,  $p=0.02$ ) (For forest plot see figure 3), and almost twice as likely to have comorbid substance abuse or dependence (OR=1.80, 95% CI 1.39-2.35,  $p<0.001$ ) (Figure 4). It should be noted, however, that assessment for publication bias suggested that the robustness of the findings relating to alcohol abuse / dependence is questionable. Results for comorbid substance abuse or dependence appeared to be robust with trim and fill of only two additional studies, and non-significant Egger's intercept ( $B = -0.56$ , standard error (SE) = 0.91,  $t = 0.62$ ,  $p = 0.55$ ). No significant difference was found between groups for combined alcohol and substance abuse.

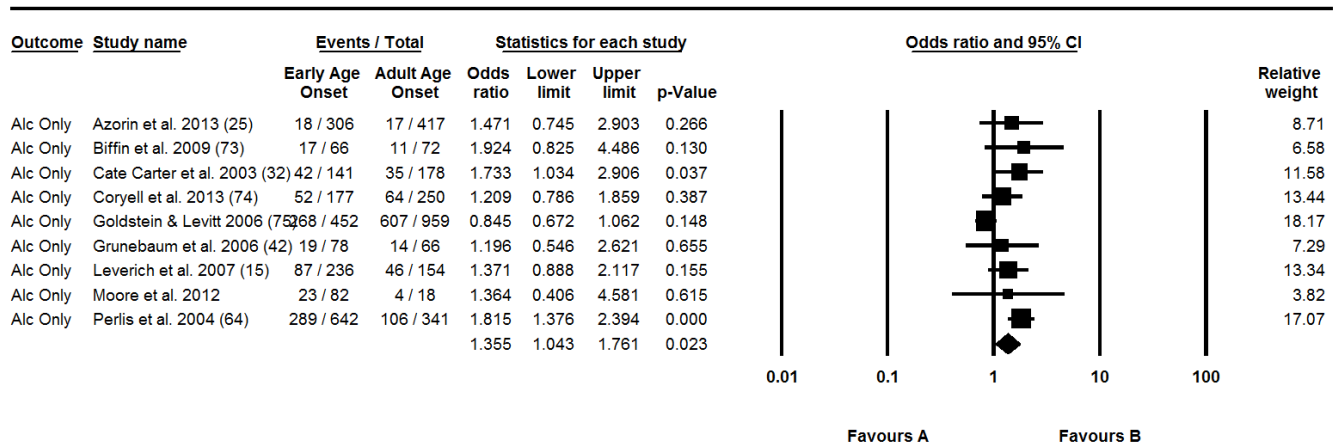


Figure 3: Forest plot odds ratios (ORs) as shaded squares proportional to study weight, with 95% confidence intervals (CIs) based on random-effects meta-analysis of comorbid alcohol abuse/dependence in nine studies

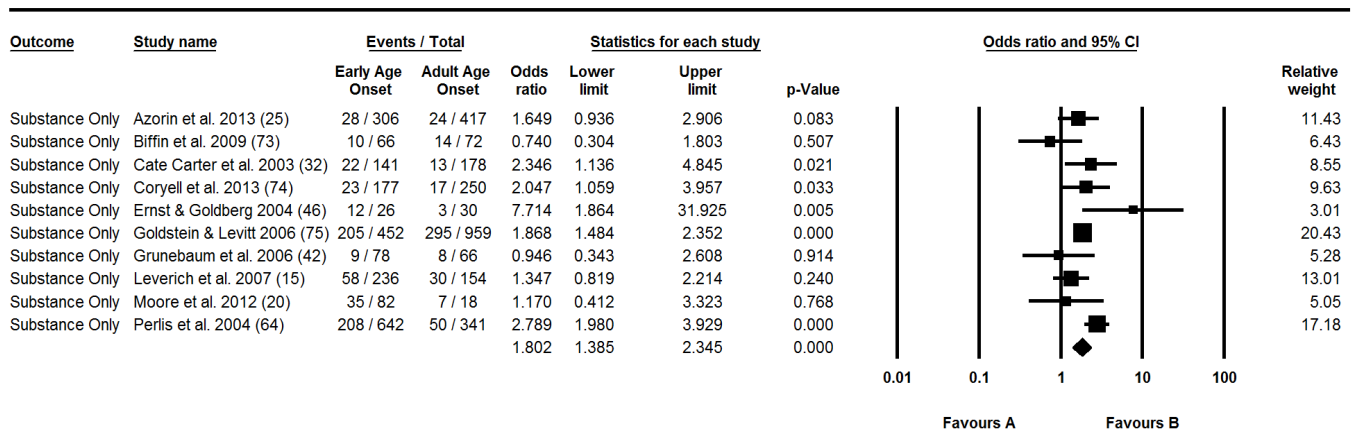


Figure 4: Forest plot odds ratios (ORs) as shaded squares proportional to study weight, with 95% confidence intervals (CIs) based on random-effects meta-analysis of comorbid substance abuse/dependence in 10 studies

**Psychiatric Comorbidity.** Rates of psychiatric comorbidity were reported in 11 studies, of which 10 (n=4841) included rates of *comorbid* anxiety disorders, 4 (n=1746) rates of comorbid personality disorder, and 3 (n=2176) ratings of any lifetime psychiatric comorbidity. The odds of having comorbid anxiety were found to be significantly higher for those with an early age of onset (OR= 1.72, 95% CI 1.34-2.19, p<0.001) (see figure 5). Egger's intercept was not significant (B = 1.76, standard error (SE) = 1.03, t = 0.62, p = 0.13) and trim and fill of only 3 studies indicate that this result is likely to be robust.

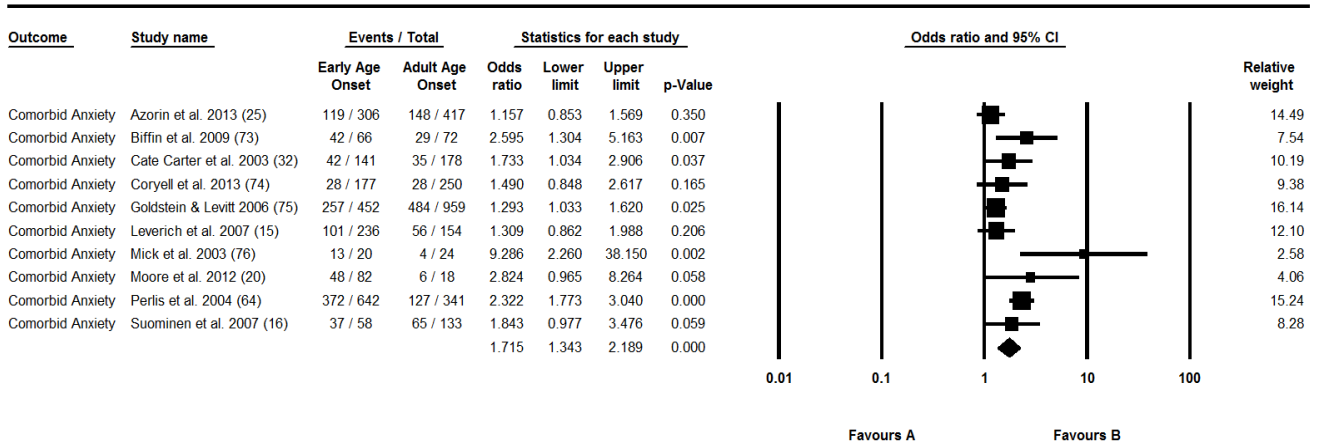


Figure 5: Forest plot odds ratios (ORs) as shaded squares proportional to study weight, with 95% confidence intervals (CIs) based on random-effects meta-analysis of comorbid anxiety in 10 studies

Comorbid personality disorders were found to be significantly more likely for those with an early age of onset (OR = 2.34, 95% CI 1.85-2.95,  $p < 0.001$ ). However, it should be noted that assessment for publication bias suggests that this result is not robust, perhaps due to the small number of studies included. No significant difference was found in rates of ‘any’ lifetime comorbidity between age of onset groups.

### Clinical Characteristics and Severity

*Psychotic Features.* Eight studies ( $n=4526$ ) reported on the presence of psychotic features or symptoms. No significant differences were found in rates of psychotic symptoms.

*Rapid Cycling and Mixed Episodes (as defined by DSM-IV).* Rates of rapid cycling were reported in five studies ( $n=1770$ ) and mixed episodes in three ( $n=2295$ ). No significant differences were found in rates of rapid cycling or mixed episodes as defined by DSM-IV.

*Severity.* A limited number of studies reported mean severity ratings for depression and mania and only two studies reported mean severity for anxiety symptoms, making this outcome unsuitable for meta-analysis. It should also be noted that variation in measurement tools may lead to pooling of data representing similar but not identical outcomes for variables such as these. For example, one study (Suominen et al., 2007) found no difference between early and adult onset groups in depression severity as measured by the clinician-rated Hamilton Depression Scale (HAM-D) (Hamilton, 1960). However, the same study found a significant difference on scores of depression as measured by the patient self-rated Beck Depression Inventory (BDI) (Beck et al., 1996) ( $t(177) = 2.1, p = 0.04$ ). As such, results should be

interpreted with caution. A total of three studies (n=1076) reported mean severity ratings for depression and mania. Mean depression severity was found to be significantly higher in the early age of onset group (Hedges  $g = 0.42$ ,  $p < 0.001$ ) (See figure 6). No significant difference was found in mean mania severity ratings.

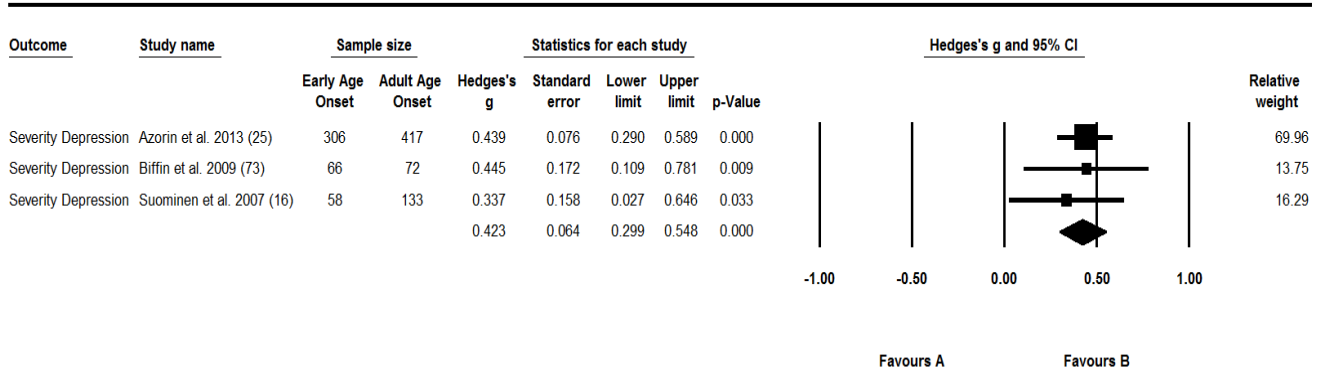


Figure 6: Forest plot standard difference in means (Hedges'  $g$ ) as shaded squares proportional to study weight, with standard error, based on random-effects meta-analysis of mean depression severity in three studies

*Treatment Delay.* Delay to first treatment in years was reported in three studies (n=1415). The mean treatment delay was found to be significantly higher for those in the early onset group (Hedges  $g = 0.39$ ,  $p = 0.001$ ) (see figure 7).

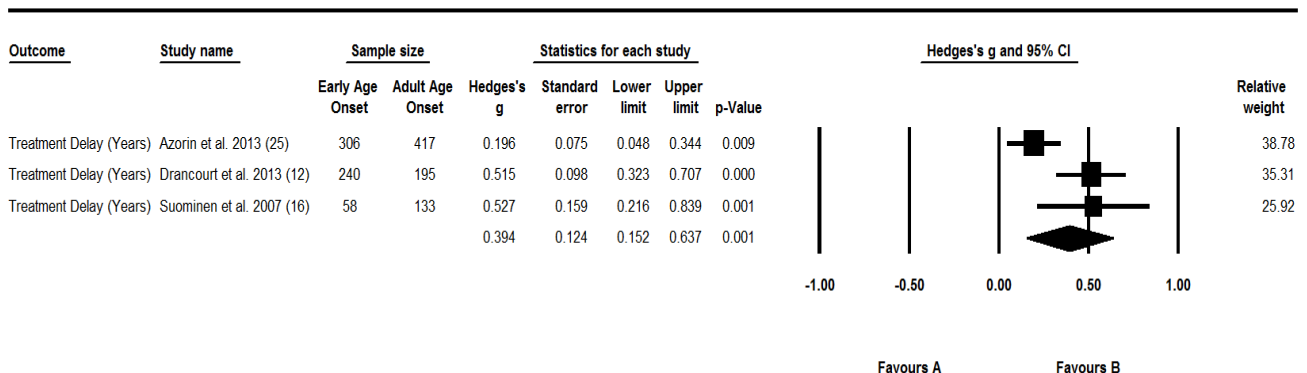


Figure 7: Forest plot standard difference in means (Hedges'  $g$ ) as shaded squares proportional to study weight, with standard error, based on random-effects meta-analysis of treatment delay (years) in three studies

Due to concerns relating to confounding bias, sensitivity analyses were conducted removing all studies that did not conduct multivariate analyses to control for potential confounds. For a number of outcomes the removal of these studies resulted in too few studies for meta-analysis. This was the case for: severity of anxiety, depression and mania; suicidal ideation; and treatment delay. However, for a number of key outcomes analyses were still viable.

The relationship between comorbid substance abuse and age of onset remained significant and appeared to be a robust finding (OR = 2.03, 95% CI: 1.51-2.72,  $p < 0.001$ ; Trim and Fill = 0; Eggers intercept not significant). The same was found for comorbid anxiety (OR = 1.64, 95% CI: 1.23-2.19,  $p = 0.001$ ) and comorbid personality disorder (OR = 2.38, 95% CI: 1.88-3.01,  $p < 0.001$ ). The relationship between previous suicide attempts and age of onset also remained significant (OR = 1.60, 95% CI: 1.20 - 2.14,  $p = 0.002$ ). A major change was found, however, in the relationship between early age of onset and rapid cycling, which became significant (OR = 2.27, 95% CI: 1.49-3.47,  $p < 0.001$ ). This may be a reflection of the high heterogeneity between studies in the original analysis ( $I^2 = 86.64$ ) and as such, the results associated with this outcome should be interpreted with caution.

## **Discussion**

Although it is often stated that an earlier onset of bipolar disorder (BD) results in poorer prognosis, investigations of this association have reported inconsistent findings. This current paper reports on the first meta-analysis of clinical characteristics and prognostic outcomes associated with earlier age of onset and has confirmed a number of adverse clinical characteristics more prevalent in those who develop BD at a younger age. Psychiatric comorbidity, particularly comorbid anxiety and substance abuse, were much higher in those with early onset. However, contrary to the findings of some individual studies, (Azorin et al., 2013; Patel et al., 2006; Suominen et al., 2007) psychotic symptoms, and mixed episodes, do not appear to be more prevalent in this group. It is important to note that the definition and use of mixed episodes has changed significantly in recent years with DSM-5 incorporating 'mixed features' as a specifier, rather than including distinct mixed episodes. The current results apply only to mixed episodes as defined in DSM-IV, and do not generalize to current understandings of the mixed states specifier in DSM-5.

Suicide prevention is currently an area of keen interest for researchers, particularly efforts to understand and interrupt processes that lead to suicide attempts in adolescents and young adults. Suicide is a significant contributor to increased mortality in BD (da Silva Costa et al., 2015; Hayes et al., 2015) and higher rates of suicide attempts have been found in BD than any other psychiatric diagnosis (Chen & Dilsaver, 1996). The current analysis found a significant and robust relationship between early age of onset in BD and occurrence of at least one suicide attempt, a finding consistent with previous research that has suggested age of onset may be a key risk factor for suicide behaviors in BD (see Hauser et al. (Hauser, Galling, & Correll, 2013) for review). The precise nature of the relationship between age of onset of BD and suicide, however, is unclear. Higher risk of suicide has been shown to be associated with comorbid anxiety and substance use disorders (Dalton, Cate-Carter, Mundo, Parikh, & Kennedy, 2003; Hayes et al., 2015) as well as severity of depression (Oquendo et al., 2000), all factors that have also been linked to earlier age of onset in BD. Further, Moor and colleagues (2012) found that in a sample of 100 individuals with BD whose ages of onset ranged from younger than 13years to over 18years, previous suicide attempts were predicted by greater comorbidity but *not* earlier age of onset (Moor et al., 2012). The association between age of onset of BD and suicidality appears to be part of a more complex picture of severity, comorbidity, and maladaptive coping mechanisms that, in combination, translate to increased risk, and for which the relationships and interactions between variables have not yet been fully investigated. Moreover, in order to separate risk associated with age of onset, from that associated with duration of illness, particularly with lifetime risk indicators prospective longitudinal data is needed.

Whereas some studies included in the meta-analysis included only data from univariate analyses, others used multivariate analyses where possible to control for any intercorrelation between variables and to adjust for potential confounds such as duration of illness. For example, Azorin and colleagues (Azorin et al., 2013) found lifetime suicide attempts to be associated with early age of onset in univariate but not multivariate analyses and suspected that this indicated intercorrelation with another variable such as duration of illness. Interestingly, Perlis et al. (Perlis et al., 2004) found that after controlling for duration of illness, a greater likelihood of making at least one suicide attempt was associated with early relative to late age of onset. Similarly, after adjusting for duration of illness, Suominen et al. (Suominen et al., 2007) found a significant higher probability of psychiatric comorbidity and suicidal ideation for the early onset age group; and Carter et al (Cate Carter et al., 2003), using logistic regression found that the most

adequate model using age of onset as the dependent variable included the following factors: lifetime suicidal ideation or attempt, axis I comorbidity, comorbid substance abuse and rapid cycling. Even with attempts to control and account for intercorrelation and confounding variables, the exact nature of the relationship between such factors and age of onset remains unclear. Future research exploring the interaction between these factors may be able to clarify the exact nature of the relationship between these variables and identify the most significant predictors of suicide ideation and attempts in this population.

A significant and robust association was found between early age of onset and comorbid substance abuse and dependence. The odds of comorbid alcohol use and dependence was also found to be significantly higher for the early age of onset group, however, assessment for potential publication bias suggested that this was not a robust finding. These findings may be impacted by the chosen cut-offs for early and later age groups. While a majority of studies have reported comorbid substance abuse to be more prevalent in the earlier onset age groups, the adolescent age group, often defined as 13 to 18yrs, has been found to have higher rates of substance and alcohol abuse / dependence than earlier onset (Wilens et al., 2004; Wilens et al., 1999). By combining the younger and adolescent groups in the current study, finer details of the relationship between onset age and alcohol or substance abuse may have been missed. Given the high rates of substance use found in BD and the association with increased risk of suicide, comorbid substance use is clearly an area of concern in BD, particularly for those with an earlier onset. It should be noted, however, that not all studies included in this meta-analysis reported age of substance use onset or whether substance use commenced prior to, or after BD onset. It is thus difficult to ascertain whether substance use is the result of an earlier age of onset of BD, or whether it is a factor that contributes to onset.

An interesting and perhaps less obvious finding of the current analysis was the relationship between comorbid anxiety and early age of onset. Those with early onset of BD were almost twice as likely to report one or more comorbid anxiety disorders. Rates of comorbid anxiety are high in BD (McElroy et al., 2001) and high rates of anxiety have also been found in high risk populations who have not developed BD themselves (Decina et al., 1983; Grigoriu-Serbănescu et al., 1989; Perich et al., 2015). However, as with other clinical features, findings of studies on the relationship between anxiety and BD are inconsistent. Moreover, as discussed previously in relation to substance use, higher rates of comorbid anxiety have also been associated with comorbid substance use and suicide attempts (Altindag et al., 2006;

Cassano et al., 1999); thus the intricacies of the inter-relationships between these three factors and early age of onset, remains to be clearly elucidated. Although a significant difference was found in rates of comorbid personality disorder (PD) between early and adult onset groups, this was based on a limited number of studies and assessment of potential publication bias suggested that the finding was not robust. Mean level of depression severity was found to be higher in the younger onset age group. This finding is consistent with previous studies suggesting that both rates and severity of depression are higher in those with an earlier onset (Leverich et al., 2007; Post et al., 2010).

The findings of this study should be interpreted with a number of limitations in mind. Many of the samples included in the meta-analysis were comprised primarily of outpatient participants and as such may not be representative of the more general population of those with BD. Further, not all individual studies incorporated the full range of diagnostic subgroups of BD which again may affect the generalizability of the results. All subgroups of BD were represented across samples, however, and thus, the synthesis of multiple studies should increase the chance of generalizability. Insufficient information on the breakdown of BD diagnoses was available in the original articles to conduct analyses stratified by diagnostic status. Given the recognized differences between BDI and BDII in terms of severity and prognostic factors, conducting the analysis in this way may have provided additional information relating to differences between ages of onset. Provided samples have sufficient power to do so, future research may benefit from breaking BD groups down further in this way for analysis. It may also be useful for future research to examine BD alongside broader neurodevelopmental phenotypes such as ADHD and early onset anxiety disorders, given the difficulty identifying a homogenous phenotype in BD. Such an approach stands to provide useful additional information regarding potentially important factors associated with specific early onset disorders.

Although the majority of studies used adequate definitions of Age at onset (AAO) (Egeland et al., 1987), differences in the measurement and definition of AAO between studies (see Table 1. for details of individual studies) may impact the synthesis of the data. More broadly,  $Q$  and  $I^2$  statistics identified significant heterogeneity for most outcome variables suggesting variability between studies that again, can influence results. Unfortunately, any attempts to synthesize data from multiple studies in this way are likely to encounter such difficulties with heterogeneity. However, this is not to suggest that the pursuit of such approaches should be abandoned. What it does suggest, as recommended by Baethge (Baethge,



2015), is that results such as those in the current study should be interpreted with this in mind and used to indicate direction, rather than exact estimates. Further, the reliability of AAO information gathered retrospectively is questionable. It should be noted, however, that many studies attempted to address this by collecting information from multiple sources and corroborating information using medical records where possible.

An EAO cut-off of 18 – 20yrs was used in this meta-analysis as this age cut-off is reflective of the broader literature. Although this method has been used in a number of previous studies (Azorin et al., 2013; Coryell et al., 2013; Drancourt et al., 2013), recent research using admixture analysis has shown that the theoretical model that best accounts for observed distributions of AAO is consistent with the existence of three AAO subgroups with average onset ages of 17years, 25years and 38years (Azorin et al., 2013; Bellivier et al., 2001a; Tozzi et al., 2011a). Further, despite the controversy surrounding early diagnosis of BD, if studies are including cases with onset as early as 12yrs, future research investigating differences between pre-adolescent and adolescent onset groups is warranted. Such research may identify severity or prognostic indicators not clearly delineated in the current study due to the compression of these age groups.

The association with AAO and mixed episodes as defined by DSM-IV was explored to ensure a comprehensive summary of the data included in the papers reviewed. Given recent changes in the definition and use of mixed features in BD, it is important to recognize that the lack of association found in the current study does not necessarily apply to mixed features as currently defined as a specifier in DSM-5. Further research would be needed to identify whether there is a relationship between AAO and BD with mixed features as currently used.

Finally, the impact of potential confounding factors such as duration of illness, particularly duration of untreated illness, should not be underestimated. A number of the factors found to be associated with earlier age of onset, such as greater comorbidity and increased likelihood of suicide attempts, have also been found to be associated with longer duration of untreated illness, which itself has been linked to earlier age of onset. As such, the true nature of many of the relationships identified in this paper is not yet clear. Follow up data from longitudinal studies may offer opportunities to investigate this more thoroughly.

## Conclusions

An earlier age of onset has long been reported to be associated with greater severity and a particularly poor prognosis in BD, yet the evidence to support many of these claims is variable. This is possibly due to difficulties differentiating the contribution of AAO over and above other factors such as length of untreated illness. The present study found that an earlier age of onset is indeed associated with features that can negatively impact long term outcomes. However, no association was found with indicators of severity and treatment resistance such as psychotic symptoms or mixed episodes (DSM-IV). Although this alone cannot rule out a possible link between AAO and these factors, it does highlight the need to for caution in drawing conclusions regarding such associations. Clinical features found to have the strongest relationship with early age of onset such as comorbid anxiety and substance use are those that may have greater potential for response to treatment. This suggests that with early identification, careful monitoring, and further development of early interventions, there may be hope for improvements in prognosis.

Whether early intervention can in fact lead to prevention and improved prognosis in mental health in general remains to be seen. However, in order to further our knowledge in this area, development and assessment of early intervention strategies is necessary. Our results contribute to growing evidence that highlights the importance of early identification and provide potential areas of focus for the development of early intervention for young people with BD. Although the relationships identified in this study are complicated by confounding factors, particularly duration of untreated illness, it could be argued that the support for early identification remains the same.

# Chapter 3: Empirical Study

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**Investigating the clinical utility of individual symptoms of depression and mania in the identification of risk of bipolar disorder: An IRT analysis**

As previously outlined, Bipolar disorder (BD) is a clinically severe, chronic mood disorder with typical onset around late adolescence, early adulthood (Leboyer et al., 2005). Diagnosis of BD is complex and delays in diagnosis are common (Drancourt et al., 2013), particularly for those with an earlier onset of the disorder (Joslyn, Hawes, Hunt, & Mitchell, 2016). Delays in diagnosis and appropriate treatment are also associated with poorer prognosis for patients with BD, having been linked to higher rates of hospitalization, and poorer social adjustment (Goldberg & Ernst, 2002c). Early identification is therefore imperative for more favourable outcomes, however, the heterogeneity of bipolar presentations mean that diagnosis remains a complicated process.

Researchers have attempted to establish a BD prodrome that reliably identifies those who will go on to develop the disorder; however, it has been difficult to delineate specific prodromal features that apply across the spectrum of BD. Genetic, neuropsychological and brain imaging studies have also attempted to identify key risk indicators for early identification in BD using high risk participants (Corry et al., 2013; Mitchell, Roberts, & Green, 2013; Nurnberger et al., 2011; Shaw, Egeland, Endicott, Allen, & Hostetter, 2005). These samples include individuals who are not symptomatic, yet have been identified as at heightened genetic risk as they have a first degree relative with a confirmed diagnosis of BD. Such 'high risk' individuals, although not meeting diagnostic thresholds, have been shown to endorse increased symptoms of psychopathology compared to control participants (Perich et al., 2015).

Accurate differentiation between those whose changes in behaviour indicates a prodromal phase and those who will not go on to develop a disorder is important for early intervention and improved prognoses. Yet the same behaviour changes may represent very different processes across individuals, particularly during different developmental periods. Importantly, during adolescence, the emotional and behavioural features that could be indicative of risk for BD may at times resemble developmental changes that are typical during this period. For example, recent epidemiological research based on both parent and youth self-report, has indicated high prevalence of brief distinct periods of euphoria and elation in adolescents (Stringaris, 2011; Stringaris et al., 2010), mood states previously thought to be primarily specific to mania (Geller et al., 2002). Irritability, also commonly associated with both manic and depressive states (Stringaris, 2011), particularly in younger individuals (Wozniak et al., 2005) has also been found to be common in adolescents (Brotman et al., 2006; Pickles et al., 2010). Moreover, evidence suggests that healthy adolescents are prone to hyper-emotionality that is normative and developmentally

specific, and is believed may intensify periods of irritability (Arnett, 1999; Casey et al., 2008; Casey et al., 2010; Casey et al., 2011).

The complexity of distinguishing atypical versus typical trajectories during adolescence has received growing attention in recent years (Cicchetti & Rogosch, 2002), and there has been an alarming shift to over-diagnosis in BD (Mitchell, 2012), particularly in young people (Blader & Carlson, 2007; Moreno et al., 2007). Over-diagnosis is as much, if not more of a concern as diagnostic delays. We know little about the long term impact psychiatric medication has for adults, let alone when it is administered at such an important developmental period as adolescence. A rapid shift such as this from one extreme to another is unlikely to be helpful. Such shifts highlight the importance of the move toward a dimensional approach in developmental research, considering not only the stark differences between typical development and disorder, but also everything in between those two extremes.

There has been growing evidence regarding the relative importance of particular sub-threshold symptoms in the prediction of various mood disorders in recent years. For example, Pine, Cohen, Cohen, and Brook (1999) found that two specific sub-threshold depressive symptoms; anhedonia, and suicidal ideation, were helpful in predicting later development of major depression over and above other symptoms. In addition, exploration of factors outside of those associated with standard diagnostic criteria may also assist in the identification of endophenotypic markers for mood disorders. In an analysis of sibling pairs, Papolos, Hennen, Cockerham, and Lachman (2007), identified five symptoms which most efficiently differentiated affected from non-affected participants in their study of childhood-onset BD. These were: fear of harm, aggression, anxiety, sensory sensitivity, sleep-wake cycle disturbances, and attention/executive functioning deficits. Results such as these suggest that threshold and sub-threshold symptoms, both those directly related to mood disturbance, and those not considered to be directly related, may have clinical utility in the prediction of risk in mood disorders.

It may also be valuable to identify whether there are differences in how informative individual symptoms are in relation to severity. Many current diagnostic tools have been developed to fit within a categorical diagnostic system. As such, they are designed to tally endorsed symptoms up to a diagnostic threshold, with little attention paid to the weight carried by each individual symptom. With clinical judgment, it seems clear that there are symptoms that are indicative of greater severity, and perhaps therefore greater potential risk than others. Clinical judgment, however, can be subjective and vary

according to level of experience. This has led to growing interest in the application of analytic methods such as Item Response Theory (IRT) that can be used to examine risk based on patterns of individual symptoms rather than total symptom clusters.

## **Aims**

The major aim of the current study was to characterize the individual symptoms of depression and mania that may be most informative during adolescence and early adulthood regarding risk for the disorder. Using novel analyses based on Item Response Theory, individual items (symptoms) included in a diagnostic clinical interview were examined to assess whether identifiable differences could be found in the information they provided in relation to discrimination and severity. It was anticipated that individual symptoms from scales of depression and mania would provide varying levels of information relating to risk for, and severity of, psychopathology among offspring of parents with BD. It was further anticipated that symptoms found to be most informative at lower levels of severity would be different to those found to be most informative at higher levels of severity.

## ***Item Response Theory***

Item Response Theory (IRT) comprises a collection of mathematical models and statistical methods that explore the way in which underlying, unobserved or latent constructs manifest as observable item responses (Harvey & Hammer, 1999). IRT provides ways to assess the extent to which individual differences in a specified latent construct can be measured by items on a scale designed to measure that construct (Thissen & Steinberg, 1988). Moreover, statistical analysis using IRT allows us to assess the degree of severity represented by each item in a measure, and the strength of the relationship between the item and the underlying construct being measured (Steinberg, Thissen, ShROUT, & Fiske, 1995). The primary assumption of IRT models is that responses to symptom queries are a function of individual variation along a single underlying dimension. All IRT models follow three essential ideas: That the variable being measured is unobserved, or latent (Stouffer et al., 1950); That items have parameters that place them on the same scale as the variable being measured (Thurstone, 1925); and that the unobserved variable accounts for the observed interrelationships among the item responses (Stouffer et al., 1950). Response probability is predicted using: (a) properties of individuals (Theta); and (b) properties of items (difficulty and discrimination). Whereas statistics associated with classic test theory often confound item

discrimination with difficulty or severity, IRT models provide information on the power of an item to discriminate between groups separately from its difficulty or severity (Steinberg et al., 1995).

Although IRT has been developed throughout the last century, it has only recently begun to gain momentum in the investigation of its application across a wide range of psychological contexts. Historically IRT analyses were believed to require substantial sample sizes in order to provide robust results (Fayers, 2004; He & Wheadon, 2013; van der Linden & Hambleton, 2013). Initially, perhaps because of these requirements, IRT methods were primarily used for the analysis of data from large scale standardised achievement and aptitude tests (Harvey & Hammer, 1999; Holman, Glas, & de Haan, 2003) and were not considered for smaller scale application. More recent research has shown that IRT analyses are possible and reliable with much smaller sample sizes than originally thought. However, it should be noted that the best methods of conducting IRT analyses with these smaller sample sizes is still being researched (Blanchin et al., 2015; Guilleux, Blanchin, Hardouin, & Sébille, 2014).

The limited range of application of IRT analyses historically may also in part be explained by the demanding computational nature of IRT models which would have limited their accessibility prior to the widespread availability of affordable computer hardware and software (Harvey & Hammer, 1999). There are now many diverse IRT models available and more readily accessible, and these models are increasingly being applied to attitude, personality and similar inventories (Embretson & Reise, 2004; Harvey & Hammer, 1999). For example, IRT has been applied to analyses using the SADS-C to identify the level of information each symptom provides in terms of syndrome severity in bipolar mania (Cheniaux et al., 2014). It has also been used to develop understanding of comorbidity among anxiety and unipolar mood disorders (Krueger & Finger, 2001), compare measures of depressive symptomatology (Olinio et al., 2012), and to identify differences in depressive symptoms between patients with unipolar and bipolar depression (Weinstock et al., 2009).

## **Method**

### ***Participants***

This study was conducted in association with a larger longitudinal study with the approval of the University of New South Wales Human Research Ethics Committee (HREC Protocol 09/104), and the South Eastern Sydney Illawarra Health Service HREC (Protocol 09/097) in Sydney, Australia. The overall

methodology of the longitudinal study and each of its components have been reported in detail elsewhere (Breakspear et al., 2015; McCormack et al., 2016; Perich et al., 2015; Perich et al., 2013; Perich et al., 2014). Methodology reported here will primarily be that relevant to the current study. A total of  $n = 186$  participants were included in the final analyses. Age of participants ranged from 12 to 22yrs, with a mean age of 17.26 (SD = 3.2). Male participants comprised 48.5% of the sample; 77% were Caucasian, 9.2% Asian, 2.6% reported mixed cultural background, and for 11.2% ethnicity was not recorded.

Participants were categorized as follows: those with a diagnosis of bipolar disorder (Bipolar Disorder group;  $n = 18$ ), those considered at genetic risk of developing bipolar disorder but without a current diagnosis (At Risk group;  $n = 105$ ), and Controls ( $n = 63$ ). Control participants were defined as those who did not have a first degree relative with current or past history of BD, recurrent major depression, schizophrenia, schizoaffective disorder; or past psychiatric hospitalisation; or a second degree relative with a history of psychosis or mood disorder related hospitalisation. Participants in the At Risk group were those with an identified first degree relative, either parent or sibling with a confirmed DSM-IV-TR diagnosis of Bipolar I or II disorder. Participants in the Bipolar Disorder group had a current diagnosis of Bipolar I or II disorder confirmed via semi-structured interview and medical records where available.

The majority of participants included in both the At Risk and Bipolar groups were recruited via distribution of print and electronic media. Recruitment also included local university and community noticeboards, mental health consumer clinicians and organisations, and families who had participated in previous research studies. Control participants were recruited primarily via local university and community noticeboards and distribution of print and electronic media. Written informed consent for participation in an ongoing longitudinal study was obtained from all participants and additional parental consent was also obtained for all participants under 16yrs of age.

Participants were included in the AR group with confirmed proband best-estimate consensus diagnosis based on information collected via the Diagnostic Interview for Genetic studies (DIGs v.4) (Nurnberger et al., 1994), The Family Interview for Genetic Studies (FIGS) (Maxwell, 1992) and medical records where available. Based on an ecological approach similar to that used in other studies involving high risk groups (Nurnberger et al., 2011), for both AR and Control groups, participants with reported lifetime or current psychiatric symptoms (with the exception of the occurrence of BD) were not excluded



from participating in the study. This approach is believed to provide greater ecological validity in the sampling and therefore improved generalisability.

### ***Materials / Measures***

The Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL)(Kaufman et al., 1997) is a semi-structured diagnostic interview designed to assess symptoms of psychopathology in children and adolescents, both current and past episodes, according to DSM-III and IV criteria. The primary diagnoses assessed with the K-SADS-PL include but are not restricted to: major depression, mania, hypomania, cyclothymia, bipolar disorders, anxiety disorders, schizoaffective disorders, and schizophrenia. The K-SADS-PL is administered by interviewing one or both parents as well as the participating child. Probes and objective criteria are provided to rate individual symptoms, and summary ratings are compiled including all sources of information collected.

The Diagnostic Interview for Genetic Studies (DIGS) is a semi-structured clinical interview developed by the National Institute of Mental Health (NIMH) Genetics Initiative, especially constructed for the assessment of major mood and psychotic disorders and their spectrum conditions (Nurnberger et al., 1994). The DIGS provides a retrospective lifetime description of BD and other axis I disorders, and is intended to be useful as part of archival data gathering for genetic studies of major affective disorders, schizophrenia, and related conditions.

The Family Interview for Genetic Studies (FIGS) is a guide developed by principal investigators in the NIMH Schizophrenia and Bipolar Disorder Genetics Initiatives for the systematic collection of diagnostic information about relatives in family / genetic studies (Maxwell, 1992). Unlike the DIGS, the FIGS does not collect self-report data but asks participants to provide information about their relatives. The diagnostic information collected using the FIGS is pooled with other data collected using the DIGS and medical records to provide more comprehensive information on each individual relative (Maxwell, 1992). There are three components of the FIGS: The general screening questions are intended to gather the most general information about all known relatives regardless of how distantly they are related; The face sheet is to collect information about first degree relatives, and any affected relatives about whom the interviewee can provide information; and symptom checklists are used to collect diagnostic details to assist with best estimate diagnoses (Maxwell, 1992).

## ***Procedure***

To determine eligibility for the study, Clinical interviews were administered to all potential adult participants, parents of younger participants, and Bipolar Disorder probands to assess family history, and confirm proband diagnoses. At least one parent of participants in the 12-21yr age group was required to be available in addition to their participating child to complete the FIGS interview and the Kiddie-Schedule for Affective Disorders and Schizophrenia – Present and Lifetime version (KSADS-PL) about their child. The KSADS-PL was administered separately to both parent and child, after which ratings from both interviews were used to determine summary ratings for each symptom measure. All clinical interviewers were extensively trained by the principal investigator or study coordinator. Each possessed a minimum of an honours level degree in psychology, some also possessing graduate level degrees in psychology and / or psychology related fields. Where possible the same interviewer conducted interviews with both parent and child for continuity of data collection.

## ***Analytic Plan***

As is consistent with previous IRT studies, factor analysis was used to test that the required assumptions for IRT analysis were met. Exploratory Factor Analysis (EFA) was conducted using Statistical Package for the Social Sciences (SPSS) software 22.0 for Windows. IRT analyses were conducted in R using the latent trait models (ltm) package (Rizopoulos, 2006) GRM function. As response options were not consistent across all scales, item responses were first re-coded to provide a consistent scale for all items that represented: No endorsement (1), Endorsement at a sub-threshold level (2), and Endorsement at threshold level (3). An EFA was conducted to identify underlying latent variables required for the IRT analysis. Participants were removed from a dataset for a particular scale if they had any missing data for that scale.

One critical component for deciding which IRT model to use for analysis is the response format of items included in the measure being analysed. Models for items with dichotomous responses include: The Rasch Model, and One and Two parameter Logistic models. As their name suggests, the logistic IRT models are based on the logistic distribution (Embretson & Reise, 2013). One-parameter and Rasch Models, estimate the probability of a response (for example, endorsement of a symptom) based on trait level and item difficulty (severity) information. Items differ only in difficulty (or severity) and the value for item discrimination is estimated as a constant. The two-parameter model adds item discrimination

parameters which allow for differences in the relationship between individual items and the latent trait. In other words, the two parameter model is more appropriate for measures where individual items may not be equally related to the latent trait. Other types of models such as the nominal model, and the Graded Response Model (Samejima, 1969, 1997) can be used for items with polytomous response data. Samejima's Graded Response Model (GRM) is a two parameter (2PL) IRT model that is often applied to the analysis of item responses such as those in Likert rating scales where the assumption of ordinal response levels is plausible (Embretson & Reise, 2004). In the GRM each item in a scale is described by one slope (discrimination) parameter  $\alpha$ , and a number of between category threshold parameters  $\beta$  equal to the number of possible response categories minus 1. The  $\beta$  threshold parameters represent the trait level necessary to respond above a given response threshold with 0.50 probability. In the current study, Samejima's two-parameter Graded Response Model (GRM), was used for all IRT analyses. The two parameters estimated in the model for each item were: (a) severity; or location along the continuum of the latent trait, and (b) discrimination; or the ability of the item to differentiate between those scoring high and low on each domain.

## **Results**

### ***Factor Analysis***

Maximum likelihood extraction with Promax Rotation (Kappa 4) was conducted on all items in the clinical interview measure, and then constrained to 5 factors and 6 factors for comparison on the basis of examination of the scree plot (Appendix B). Total variance explained for the five and six factor models was 51.15% and 54.04% respectively. For both models, KMO statistic was fair at 0.881, and Bartlett's Test of Sphericity was significant ( $p < 0.001$ ). Examination of the pattern matrices suggested that the five factor model was theoretically a better fit with factors that appeared to represent the following clusters: depression items, mania items, anxiety items, externalizing items and attention deficit hyperactivity items. Items that loaded weakly on all five factors (i.e. coefficients under 0.3) were excluded from further analyses. Excluded items were: aches and pains; psychomotor agitation, increased appetite and self-harm from the Depression scale; and hypersexuality from the Mania scale. Following removal of these items KMO statistic improved and Bartlett's Test of Sphericity remained significant (0.891,  $p < 0.001$ ). The five factor solution accounted for 52.9% of total variance with only 24% non-redundant residuals over 0.05

resulting in five separate unidimensional scales. Cronbach's Alpha was calculated for each of the symptom scales. Alpha values for Depression, Mania, Anxiety, Externalising and ADHD scales were 0.95, 0.94, 0.87, 0.85 and 0.90 respectively.

### **GRM Analysis**

Item Response Theory Analyses were performed separately for factors identified in the EFA directly relevant to BD, i.e. Depression and Mania. Three parameters were estimated for each item: two severity (between category) threshold values and one item discrimination value. The estimates for category threshold and discrimination parameters can be found in Tables 3 and 4.

The threshold parameter between item responses 1 and 2, or the level of the latent trait theta at which an individual has a 50% chance of endorsing response 2 or higher is represented by  $\beta_1$ .  $\beta_2$  represents the threshold parameter between a response of 2, endorsing subthreshold level of a symptom, and 3, endorsing a symptom at its highest, or threshold level. Alpha ( $\alpha$ ) is the discrimination parameter, which represents how well an item discriminates between someone scoring high and someone scoring low on the latent trait. Model fit was assessed by comparing the fit of the two-parameter model to that of the one-parameter model, where the discrimination parameter is held constant between items. This was conducted using the likelihood ratio test, using a p-value of  $<0.01$  as indicator of a significantly better fit of the two-parameter over the one-parameter model.

We present two types of plot to facilitate interpretation of results: *category response curves*, which show for each item the levels of the latent trait at which each response is most likely; and *item information function and test information function curves* provide information on the level of the latent trait at which the item provides the most precision of measurement (the test information function curves is the sum of the item information curves). The complete array of plots can be found in Appendices C to F with select plots provided in the main text for illustration. In the category response curves, the position of the curves on the x-axis indicates threshold locations, and discrimination is indicated by the steepness of the curves. The graphs included in Figures 8 and 10 are chosen to illustrate the differences that can be seen in these parameters between individual items on the depression and mania scales.

### ***Depression items***

Parameter estimates for depression items can be found in Table 3. Across the items in the depression scale, those with the highest discrimination parameter ( $\alpha$ ) were Anhedonia, Hopelessness, and Thoughts of Death. The least discriminating items in the depression scale were Insomnia, and Irritability. Items with the lowest location values ( $\beta_1$ ) were Depressed Mood, Irritability, Negative Self Image, and Rejection Sensitivity. Items endorsed at sub-threshold levels at higher severity of the latent trait included Leaden Paralysis, and Anorexia. Insomnia and Thoughts of death were the items most likely to be endorsed at the threshold level at higher severity of the latent trait ( $\beta_2$ ), whereas, items such as Fatigue, Depressed mood and Negative Self-image were most likely to be endorsed at the threshold level at lower severity.

***Table 3: Parameter Estimates for Depression Scale Items***

<b>Depression Items</b>	<b>Parameter Estimates</b>		
	<b><math>\beta_1</math></b>	<b><math>\beta_2</math></b>	<b><math>\alpha</math></b>
Depressed Mood	-0.64	1.57	2.74
Irritability	-0.11	2.40	1.45
Excessive Guilt	0.89	2.41	2.10
Negative Self Image	-0.24	1.60	2.70
Hopelessness	0.14	1.73	3.37
Anhedonia	0.17	1.61	3.88
Fatigue	0.26	1.46	2.74
Difficulty Concentrating	0.21	1.76	2.87
Psychomotor Retardation	0.95	2.26	2.68
Social Withdrawal	0.07	1.79	2.29
Insomnia	0.38	3.75	1.02
Hypersomnia	0.87	1.95	1.69
Anorexia	1.01	2.44	1.74
Leaden Paralysis	1.57	2.28	2.70
Rejection Sensitivity	-0.27	1.85	2.42
Thoughts of Death	0.71	2.55	3.06
Suicidal Ideation	0.98	2.43	2.63

Included in Figure 8 are category response curves that illustrate clear differences in threshold locations, and discrimination between individual depression items. For example: Although the discrimination information (steepness of curve) is very similar for Depressed Mood and Thoughts of Death, the latter is endorsed at a sub-threshold level at a higher severity of the latent trait (position of curves). In comparison, both Insomnia and Leaden Paralysis provide much less discrimination

information. Further, as perhaps could be expected, Leaden Paralysis presents almost as a dichotomous item that is either present or absent with little endorsement at the sub-threshold level (middle curve).

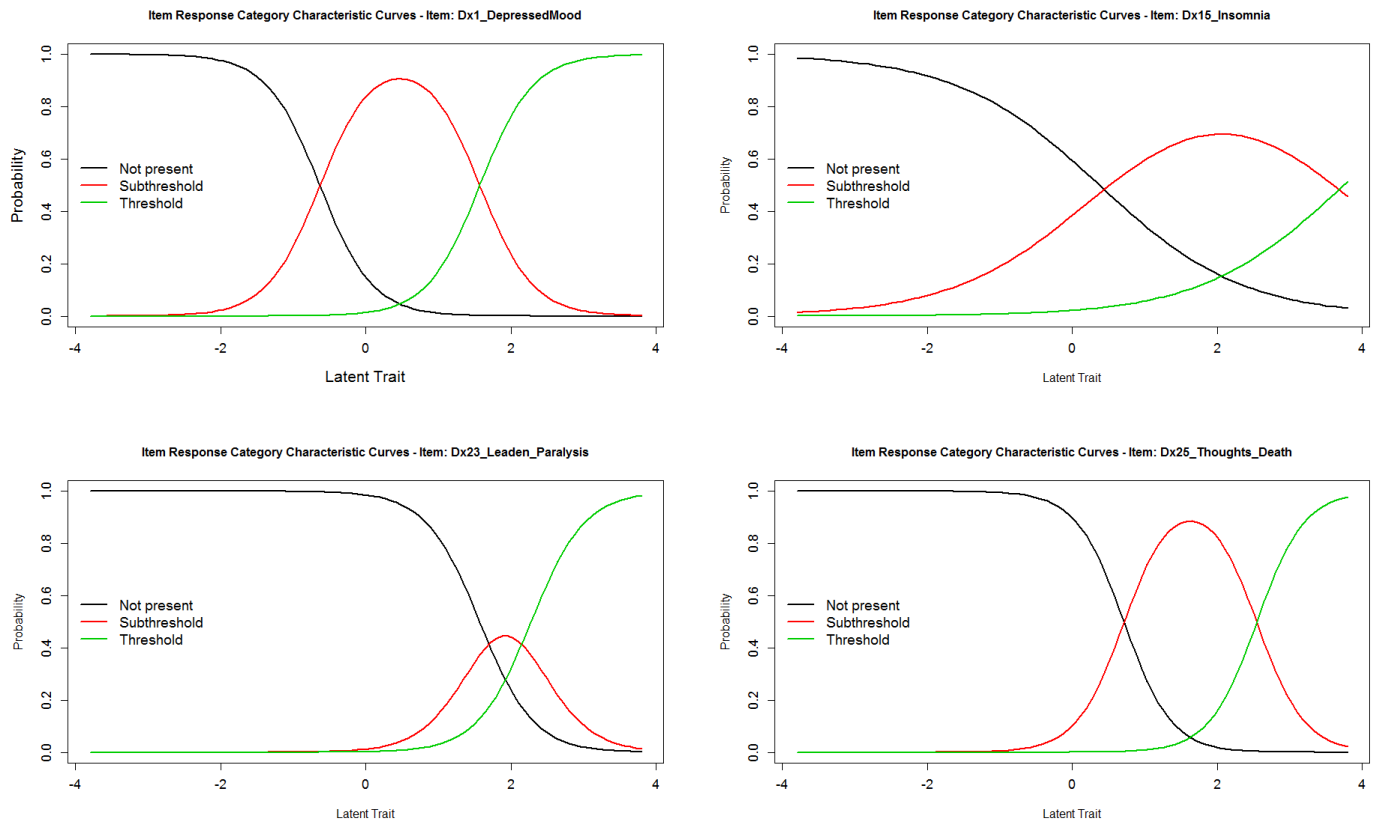


Figure 8: Response Category Curves for Depression Symptoms: Depressed Mood, Insomnia, Leaden Paralysis and Thoughts of Death.

The item information curve (see Figure 9) for depression items indicates that although symptoms such as Irritability, and Insomnia, appear to provide more consistent information across the levels of the latent trait, overall the information they provide is minimal (i.e. the curves are uniform but low). The information statistics support this, showing that these two items together provide only 5.8% of the total information provided by the scale, compared with Hopelessness, Anhedonia, and Thoughts of Death which account for 26% of the total information. Comparison of one- and two- parameter models indicate that the two-parameter model fits significantly better than the one-parameter model ( $p < 0.001$ ).

## Item Information Curves

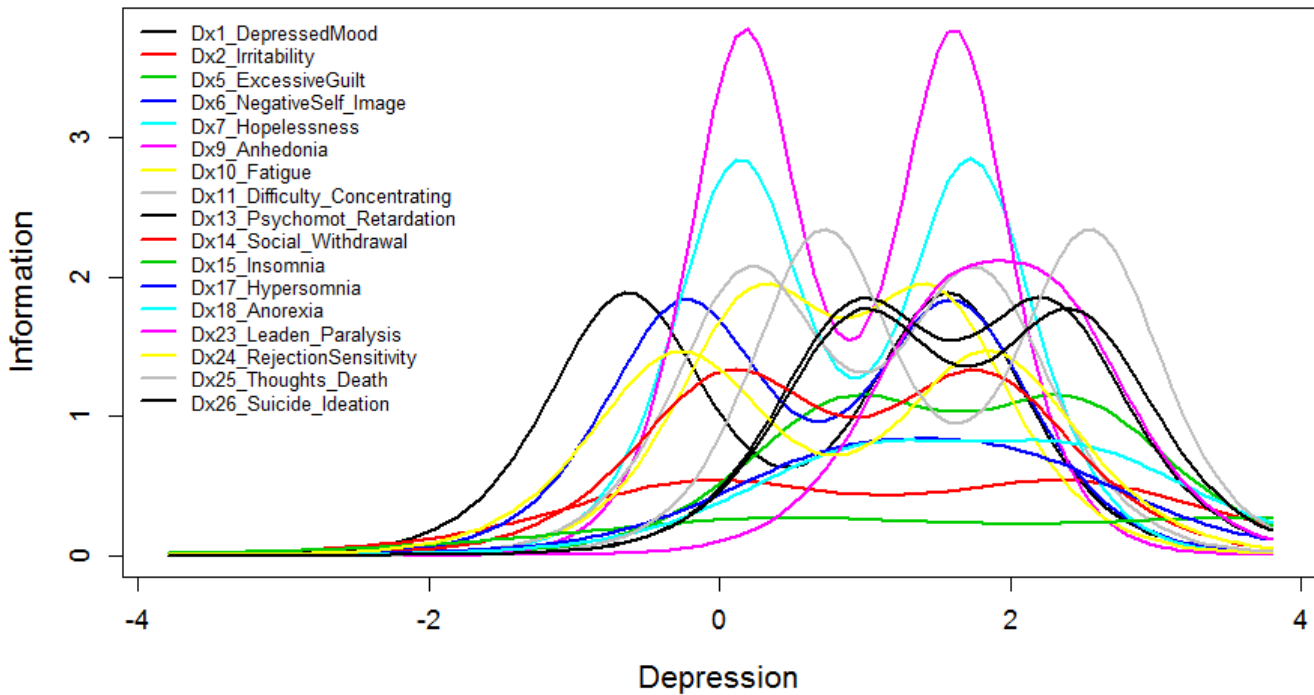


Figure 9: Information Curve for Depression Items

### Mania Items

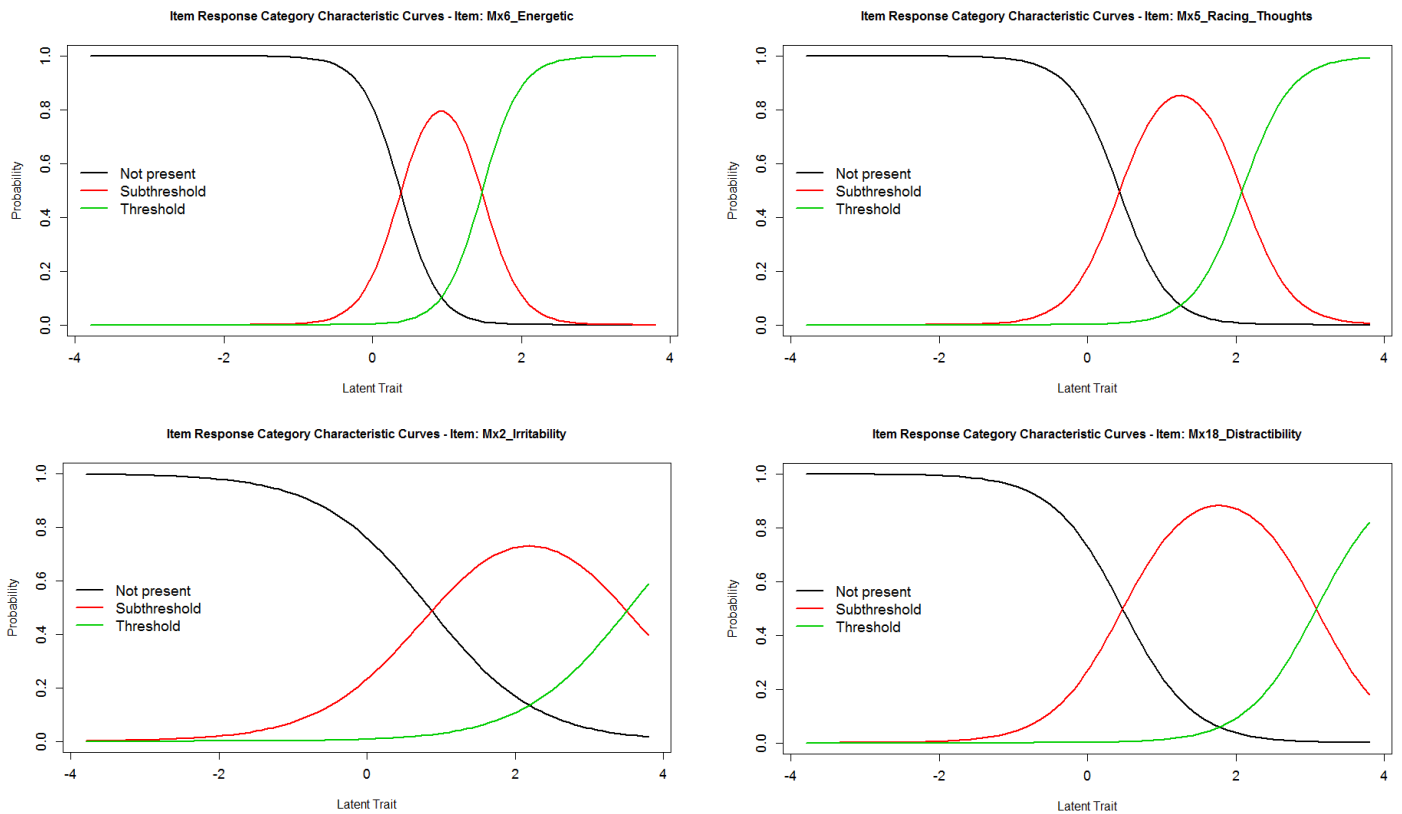
A number of the mania items included in the scale following exploratory factor analysis, were required to be removed from the IRT analysis as they had not been endorsed by participants across the full range of responses. Mania items 13 through 16 (Inappropriate Laughing, People Seeking, Increased Productivity, and, Increased Creativity) were not endorsed at the highest (threshold) level of symptoms by any participants and as a result the analysis was not able to be completed with these items included.

Parameter estimates for mania items can be found in Table 4. In the mania scale Elevated Mood, Racing thoughts, Increased Energy, Hyperactivity, and Pressured Speech showed the highest discrimination capacity. Those with the lowest discrimination capacity were Mood Lability, and, as with the depression items, Irritability. Looking at the Category response curves and parameter estimates we can see that although racing thoughts and increased energy both have steep peaks representing good discrimination, Racing thoughts is more informative at greater severity levels (i.e. has a higher second threshold), whereas increased energy is more informative at lower levels of the latent trait (see Figure 10). Interestingly, Irritability and Distractibility are items most likely to be endorsed at threshold at the highest

levels of the latent trait, whereas, items such as Increased Energy, and Hyperactivity, are more likely to be endorsed at threshold at much lower severity. This may suggest that these symptoms are more easily recognized as unusual or out of the ordinary for individuals than changes in irritability or ability to focus.

**Table 4: Parameter Estimates for Mania Scale Items**

Mania Items	Parameter Estimates		
Item	$\beta_1$	$\beta_2$	$\alpha$
Elevated Mood	0.38	1.74	3.41
Irritability	0.84	3.54	1.38
Mood Lability	0.56	2.75	1.98
Decreased Sleep	1.05	2.08	2.37
Racing Thoughts	0.43	2.09	3.06
Energetic	0.37	1.48	3.94
Increased Goal Activity	0.59	1.67	2.98
Hyperactivity	0.34	1.55	3.59
Grandiosity	0.89	2.50	2.80
Pressured Speech	0.36	2.11	3.15
Poor Judgement	0.96	2.60	2.00
Distractibility	0.47	3.09	2.12



*Figure 10: Response Category Curves for Mania Items Increased Energy, Racing Thoughts, Irritability, and Distractibility.*



Examination of the item information curve (Figure 11.) suggests that the symptom Irritability provides minimal information across the latent trait continuum (low flat curve). This is supported by the information statistics that show that Irritability accounts for only 4% of the total information accounted for by the scale whereas the most informative item, Increased Energy accounted for 12%.

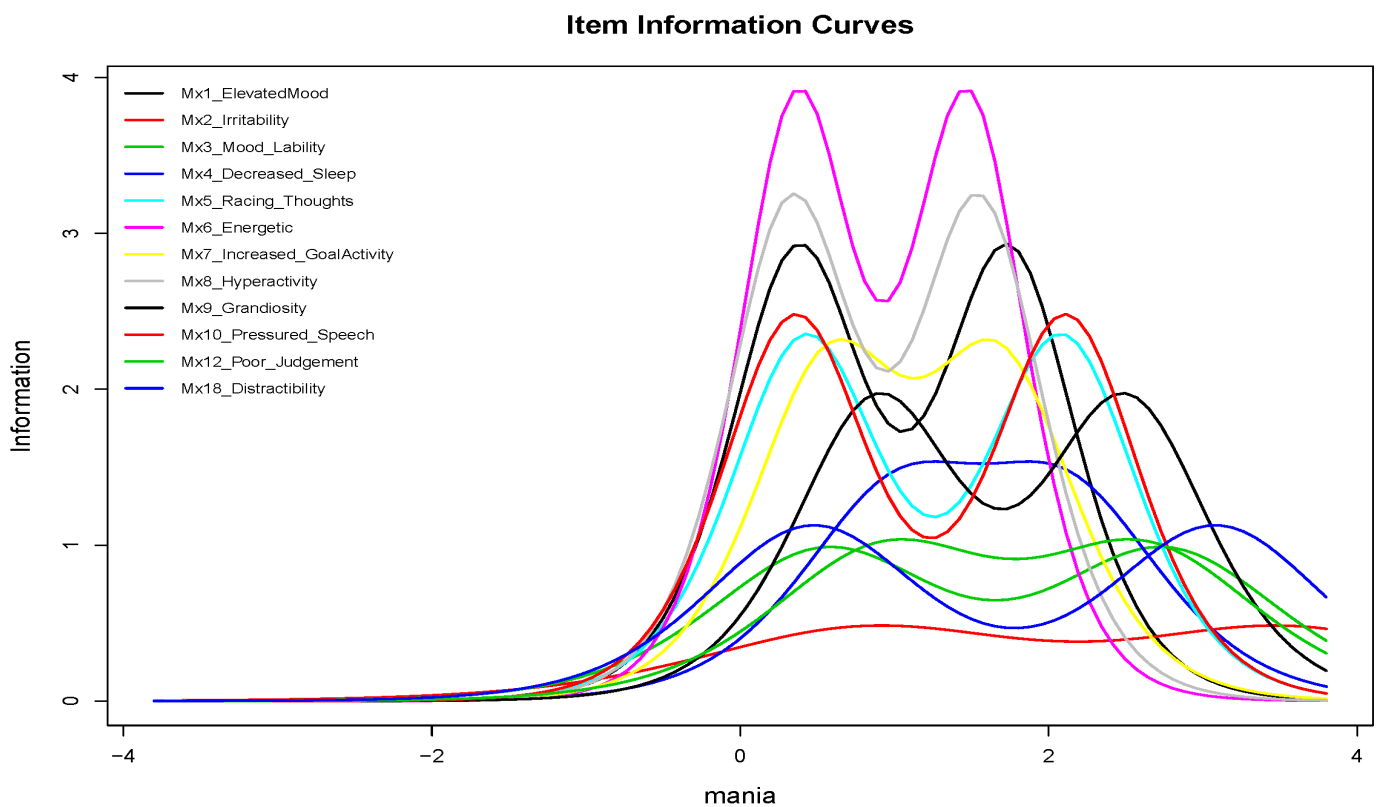


Figure 11: Information Curve for Mania Items

Comparison of constrained and unconstrained models showed that the 2 parameter GRM model demonstrated a significantly better fit than the 1PL constrained model ( $p < 0.007$ ).

## Discussion

The aim of this study was to identify the specific symptoms of BD that may be most clinically informative in the assessment of risk during adolescence and early adulthood. Diagnostic interviews were conducted with individuals with a diagnosis of BD, those considered at increased genetic risk, and those with no diagnosis of mood disorder, for endorsement of experiences of clinical and sub-threshold level symptoms. IRT analysis was then conducted on these patterns of endorsement to identify which individual symptoms were most informative with regard to discrimination and severity. As expected, individual

symptoms differed in their capacity to discriminate between individuals scoring high and low on underlying latent traits representing Depression and Mania. They also differed in the amount of information they could provide in relation to severity on these underlying traits. Moreover, symptoms found to be most informative at lower levels of severity were different to those found to be most informative at higher levels of severity.

Across both scales, symptoms commonly thought to be informative in the prediction of risk in young people, but that are also found across a variety of different presentations, for example: irritability, provided the least discriminatory information. The symptoms found to provide the most information in terms of discriminating between those scoring high and low on Depression and Mania were those more specific to the underlying trait being examined. For example, across depressive symptoms, losing interest in previously enjoyed activities, a sense of hopelessness, and thoughts of death and suicide, all symptoms highly representative of, and specific to, depression were found to have most discrimination capacity. For mania, it was increased energy and activity, elevated mood, and racing thoughts. These results support hypotheses proposed by Faedda et al. (2015) and Van Meter, Burke, Youngstrom, Faedda, and Correll (2016) that individual symptoms more specific to manic and depressive presentations would be more informative in the identification of risk than other key symptoms that are associated with more heterotypic outcomes.

These findings are also consistent with those of a previous IRT study that demonstrated the importance of energy and activity as an indicator of severity in mania (Cheniaux et al., 2014). Although the results of the study included in this thesis show a much more even distribution of information from mania items in comparison to the Cheniaux et al. (2014) study, the symptom Increased Energy still clearly stands out as the most informative item. Differences in results between the current study and that of Cheniaux and colleagues may relate to sampling differences. The Cheniaux (2014) study was restricted to include only participants with a diagnosis of BD, whereas the present study included a broader range including at risk and control participants. It is nevertheless interesting to see for both studies a similar pattern of results which may indicate that unusual increases in energy and hyperactivity are clinically meaningful at both diagnostic and lower threshold levels, and in both adolescent and young adult age groups.

These findings can be seen to have various implications for conceptualizations of childhood-onset BD. Due to the difficulties identifying and differentiating core symptoms such as elevated mood and grandiosity in younger children, irritability has been proposed as a potential key diagnostic indicator for BD in children (Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003; Wozniak et al., 1995; Wozniak et al., 2005). The results of the current study do not support this. In a sample comprised primarily of younger individuals, irritability was found to be the least informative of all symptoms across both depression and mania items. This would suggest that although irritability may be a symptom associated with both of these presentations, it does not demonstrate sufficient specificity to be a reliable indicator of clinical risk. The overall prevalence of irritability in children and adolescence, combined with this lack of specificity indicate that irritability is unreliable as a diagnostic marker. The broadening of diagnostic criteria to include irritability over and above other clinical markers in BD risks incorporating a range of heterogeneous presentations thereby risking over-diagnosis and inappropriate treatment.

The results of this study should be interpreted with certain limitations in mind. Historically, the use of IRT analyses have required large sample sizes to general accurate parameter estimates (Embretson & Reise, 2004; Embretson & Reise, 2013; Fayers, 2004). This is, however, dependent on the type of analysis conducted and number of parameters estimated. Although previous studies have demonstrated effective use of IRT analysis with sample sizes similar to that used in the current study, analysis using a larger sample size may provide more robust results. Moreover, the sample size in the current study was not sufficient to run separate analyses comparing parameter estimates between At Risk, Control and Bipolar groups. Future research using larger samples may provide further insight into whether there are identifiable patterns of differences in information provided by individual symptoms between these groups, and as such, which symptoms are most clinically useful for each group. Further, future research comparing individual symptom patterns between more restricted age groups, i.e. pre-adolescent / adolescent / early adult, may provide greater insight into which symptoms are most indicative of risk at different developmental stages.

Finally, despite the range of presentations included in the sample, it was necessary to remove certain symptoms from the IRT analysis due to a lack of endorsement across levels of the symptoms, particularly at the threshold level. This means that these items were not able to be assessed as part of the latent traits investigated, and in terms of the level of information they may have provided. However, the

fact that these items were not endorsed at the threshold level by any participants, even those with a diagnosis of BD, suggests that these items are relatively uninformative in relation to diagnosis or future risk of BD.

Despite these limitations, this is one of few studies investigating the potential of individual and sub threshold clinical symptoms to explore their usefulness as developmentally appropriate indicators of risk in adolescents and young adults. The results of this study provide information that is potentially useful for clinicians in the identification of at risk individuals who may benefit from early monitoring, support and intervention. Further, identification of the most and least informative symptoms, in conjunction with existing knowledge of genetic and environmental risk factors, provides a basis for the development of developmentally appropriate clinical screening tools which may help differentiate normal adolescent stress from clinically relevant risk. It also informs areas to target in the development of early intervention programs for young people. From a theoretical perspective, this information may be useful in informing developmentally specific models of BD in terms of symptom structure; and it identifies key risk markers that may benefit from future research with adolescent populations. Finally, this is one of a limited number of studies to apply IRT principles in a clinical context.

## **Conclusions**

The results of this empirical study support the potential usefulness of individual diagnostic symptoms, and sub-threshold level symptoms, in the identification of risk and assessment of severity in BD. Further, results indicate that not all symptoms are equal in the level of information they provide. This has implications for the application and scoring of clinical measures that simply sum the number of endorsed symptoms with little regard for differences in the level of information each symptom provides. Understanding and applying the additional information provided by individual symptoms with regard to severity and discrimination capacity may enhance the accuracy and efficacy of current diagnostic instruments. This information may also inform the development of brief screening scales including only those symptoms that provide the greatest levels of information. The results of this study support previous findings impacting the theoretical conceptualisation of core features of mania that question the focus on elevated mood over activation, and call into question the reliability of using irritability as a key symptom in the identification of BD in younger individuals. They also highlight the potential usefulness of novel

analytical approaches based on IRT in clinical research. IRT has much to offer clinical research and the development of more accessible and affordable means for conducting these types of analyses, means that there are fewer barriers for researchers wanting to apply them. Further research using similar analyses with larger samples would be helpful both to improve the robustness of results, and allow separate analyses with more cohesive groups (i.e. At Risk only, control only; specific age ranges) that may identify the most clinically meaningful symptoms for these populations.

# Chapter 4: General Discussion

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As outlined in the previous chapters, bipolar disorder (BD) is a chronic psychiatric illness associated with significant, pervasive and enduring functional impairment (Coryell et al., 1993b; Fagiolini et al., 2013; World Health Organisation, 2001). The empirical evidence suggests that there are long delays to diagnosis in BD (Drancourt et al., 2013; Schneck, 2011a), particularly for those who experience onset at an earlier age (Joslyn et al., 2016), and that these delays in diagnosis and appropriate treatment are associated with poorer long term outcomes for those with BD (Goldberg & Ernst, 2002c). Reliable early identification is imperative to improving outcomes in BD, yet may be complicated by difficulties distinguishing symptoms of BD in adolescence from the emotional difficulties that are developmentally typical during this period. Research into BD has attempted to identify a specific prodrome following the success of a similar approach in schizophrenia research. As yet, no clear prodromal features have been found that span the BD spectrum. Progress has been made in the identification of genetic markers (Adams et al., 1998; McQueen et al., 2005; Segurado et al., 2003), and structural and functional brain differences associated with BD (Strakowski, Delbello, & Adler, 2005), however, there has been limited research into the clinical utility of sub-threshold psychological symptoms that may provide useful information in the indication of risk.

The aims of this thesis were threefold. The first aim was to synthesise, summarise and critically evaluate current empirical and theoretical literature related to BD, with a focus on difficulties in diagnosis, and impact on outcomes. The second was to systematically review and analyse empirical research into the impact of age of onset on prognosis and outcomes for those with BD; and the final aim was to empirically investigate the potential clinical utility of individual symptoms from a standard clinical interview in the assessment of risk of BD.

## **Summary of Findings**

Chapter 2 comprised a published systematic review and meta-analysis that examined existing empirical research investigating the adverse outcomes associated with an early onset of BD. Of 2629 Papers identified, fifteen met inclusion criteria and were entered into the meta-analysis. Results confirmed that there are a number of adverse clinical characteristics more prevalent for those with an earlier onset of BD. However, not all characteristics previously believed to be associated with early onset were supported.

There was insufficient evidence to support commonly reported associations between an early onset of BD and clinical characteristics indicative of greater severity of illness. These characteristics, such as psychotic symptoms and mixed episodes (as defined by DSM-IV) have been thought to result in greater treatment resistance in BD and, as such, particularly poor long term outcomes. Contrary to popular belief, the results of the current meta-analysis indicated that such poor outcomes are not inevitable with earlier onset of BD.

The clinical features that were found to have the strongest relationship with an earlier age of onset were those that may potentially be amenable to intervention, for example: comorbid anxiety, substance use, and treatment delay. Awareness of these relationships may provide promise for recognising comorbidity early and providing appropriate intervention to minimise negative outcomes. Moreover, these results emphasise the need for continued efforts to find clear indicators of BD and BD risk in younger individuals to reduce delays to appropriate treatment. The results of this meta-analysis provide a hopeful message for those who develop BD at an earlier age and provide potential areas of focus for the development of early intervention. They also highlight the importance of early identification for improved prognoses.

As reported in Chapter 3, an empirical study was conducted that was designed to investigate the potential clinical usefulness of relevant individual symptoms in the assessment of risk of psychopathology, particularly BD. The main objective of the study was to evaluate whether individual symptoms differed in their capacity to discriminate between individuals scoring high and low on underlying latent traits representing Depression and Mania. It also investigated differences in the amount of information individual symptoms could provide in relation to severity on these underlying traits.

In both depression and mania scales, the symptoms that were found to be most informative were those that could be considered most representative of the underlying trait being examined. For example, of depressive symptoms, losing interest in previously enjoyed activities, a sense of hopelessness, and thoughts of death and suicide, all symptoms highly representative of, and specific to, depression were found to have most discrimination capacity. Similarly, for mania, increased energy and activity, elevated mood, and racing thoughts showed the greatest capacity for discrimination. Perhaps understandably, symptoms that could be considered more common to a variety of presentations e.g. irritability, provided the least discriminatory information on both scales. These results support hypotheses proposed by (Faedda et al., 2015; Van Meter et al., 2016) that individual symptoms more specific to manic and depressive

presentations would be more informative in the identification of risk than other key symptoms that are associated with more heterotypic outcomes.

Interestingly, Irritability and Distractibility were symptoms most likely to be endorsed by individuals as meeting clinical threshold at much higher levels of severity in the mania scale. On the other hand, items such as Increased Energy, Hyperactivity, and Elevated Mood were more likely to be endorsed at much lower levels of severity. This may suggest that changes in mood and energy levels are more easily recognized by individuals as a departure from the norm than changes in irritability or ability to focus. Alternatively, it may be that changes in mood, energy and activity levels are more easily identified at lower levels of severity and more difficult to identify at higher levels. A recent study by da Silva and colleagues investigating insight in bipolar mania, found that individuals with BD demonstrated less insight into changes in their own activity and energy levels (da Silva, Mograbi, Bifano, Santana, & Cheniaux, 2016) compared to their overall insight about their illness, and the consequences of previous episodes. This lower level of insight into specific symptoms was significantly correlated with greater severity of agitation and increased energy. However, it also appeared to be associated with greater severity of illness overall.

The results of the current empirical study also fit with previous research findings to indicate that although irritability is highly correlated with BD, it is by no means specific to BD, and that chronic irritability does not appear to be pathognomonic for BD (Stringaris et al., 2010). Findings such as this are important in the context of the controversial argument in favour of paediatric BD. Given the difficulties in recognizing or identifying particular key diagnostic indicators of BD such as grandiosity and elated mood in children, chronic irritability has been proposed as a more appropriate indicator for paediatric BD (Leibenluft et al., 2003; Wozniak et al., 1995; Wozniak et al., 2005). When taken with the findings of previous studies, the results of the current study suggest that irritability is not an appropriate symptom on which to base a diagnosis of BD. As a diagnostic indicator, irritability has high sensitivity and low specificity, and as previously suggested by Stringaris and Youngstrom (2014a), using such a non-specific symptom as a core diagnostic indicator for BD is likely to lead to over-diagnosis.

Over several decades researchers have argued that variables related to activation rather than mood states are more central in the phenomenology of mania (Bauer et al., 1991; Beigel & Murphy, 1971; Johnson, Gershon, & Starov, 2015). For example, in their 1971 study, Biegel and Murphy identified



several symptoms they believed to be representative of core characteristics of mania (Beigel & Murphy, 1971). These included increased motor behaviour, increased verbal production and increased rapidity of thought processes. Similarly, the results of a study by (Bauer et al., 1991) led them to conclude that mania was primarily a disorder of activation rather than mood. Results of the French multi-site EPIMAN study (Akiskal et al., 2001) prompted recommendations that activation should be included as one of the stem criterion for the diagnosis of mania, a change that was integrated into the development of DSM-5 (American Psychiatric Association, 2013b). More recently, a study by Perry, McIlwain, Kloezeman, Henry, and Minassian (2016) found increased energy to be a distinguishing feature of bipolar mania, particularly energy related to specific and goal directed exploration activity. Interestingly, a study published last year by Johnson et al. (2015) found that high energy in BD was not associated with high mood, leading them to suggest that general shifts in activation may be problematic to use as an indicator of impending mania. It should be noted, however, that the researchers themselves identified a number of significant limitations to this study and highlighted the need for replication of results in a more robust design.

The findings of the current empirical study provide further support for the theory that symptoms of increased energy and activation may be more clinically useful in the identification of mania than changes in mood. These findings are also consistent with those of a previous IRT study that demonstrated the importance of energy and activity as an indicator of severity in mania (Cheniaux et al., 2014). It is interesting to note the consistency in these findings, particularly given the age of the sample included in the current study, and the high proportion of sample participants identified as “At Risk”. This may indicate that unusual increases in energy and activity are clinically useful in the identification of risk of BD, particularly for younger individuals. However, results of longitudinal follow up studies would be necessary to support this.

### **Theoretical implications**

With the development of DSM-5 (American Psychiatric Association, 2013b), there has been a shift in the structure of diagnostic classification of BD to include increased energy and activation along with elevated and expansive mood as core diagnostic criteria. The results of the current empirical study support the importance of increased energy and activation in identifying and assessing the severity of

manic symptoms. Further, they suggest that such increases in activation and energy may even be more informative than mood variability in the assessment of risk of later psychopathology in adolescents and young adults.

Moreover, results of the IRT analysis highlight the fact that individual symptoms do not all provide the same level of information with regard to discriminating between groups and levels of severity of disorder. This has important implications for development and use of standardized diagnostic instruments. Many current diagnostic tools have been designed to fit within a categorical diagnostic system whereby numbers of endorsed symptoms are summed to assess whether an individual reaches a diagnostic threshold. The results of the empirical study included in this thesis show that all individual symptoms are not equal in the information they provide and therefore should not necessarily be equally weighted in diagnostic assessments. To do so risks minimizing the potential information garnered from these assessments and may result in a trend toward over or under-diagnosis.

Further, results of the empirical paper do not support the use of irritability as a key diagnostic indicator for BD in younger populations. Despite the difficulties identifying clinical levels of other core criteria such as grandiosity and elevated mood in younger individuals, the prevalence of increased irritability in these populations, combined with the lack of specificity associated with such symptoms indicate that it is unreliable as a diagnostic marker. The broadening of diagnostic criteria to include irritability over and above other clinical markers in BD risks incorporating a range of heterogeneous presentations thereby risking over-diagnosis and inappropriate treatment.

## **Clinical Implications**

The outcomes of studies included in this thesis also have potentially important clinical implications. Despite mixed evidence in the empirical literature, it has commonly been reported that an earlier onset of BD is an indicator of greater severity of illness and poorer prognosis, offering little hope for those who develop BD at an earlier age and their treating clinicians. However, there have previously been no published reviews or meta-analyses critically evaluating whether the evidence is in support of these reports. The review included herein is the first published meta-analysis investigating this relationship, the results of which support some, but not all, of the commonly reported claims. Although adverse outcomes associated with an earlier onset of BD were identified, these outcomes do not suggest as

poor prognosis as previously believed. Clinical features associated with greater severity of illness in BD, and often thought to increase treatment resistance, were not found to be associated with an earlier onset. Features found to have the strongest association with an earlier age of onset were those that may be amenable to intervention if reliably identified and treated appropriately. For example, evidenced based psychological treatment targeting anxiety and substance abuse may be helpful in addressing identified comorbidities that add to the burden of illness and often result in poorer outcomes.

The results of the empirical study provide information useful to clinicians working with young people in mental health and other clinical settings relating to identification of at risk populations. The recognition of key symptoms, particularly in combination with a positive family history, may help identify individuals who are likely to benefit from early support, increased monitoring, and implementation of early intervention strategies. Moreover, areas of focus for the development of early intervention programs for individuals considered at risk are identified. Psychological strategies that have been found to be helpful in identifying early warning signs, minimising severity of mood episodes, and reducing anxiety around relapse for those with BD, with some adaptation, may also be useful for those considered at risk. Of course, whether early intervention can lead to prevention and improved prognoses in mental health remains to be seen. However, the benefit of psychologically based interventions as opposed to early pharmacological treatment is the reduce risk of harm in the case of false positives. The information included in this thesis provides a more hopeful outlook and supports the need for development and evaluation of early intervention strategies for youth at risk of psychopathology. It provides the beginning of a basis for the creation of developmentally appropriate clinical screening tools to assist in differentiating normal adolescent stress from clinically relevant risk.

### **Strengths, Limitations, and Future Directions**

The results of the studies included in this thesis should be interpreted with certain limitations in mind. Many of the samples included in the meta-analysis were comprised primarily of outpatient participants and as such may not be representative of the more general population of those with BD. Moreover, not all individual studies included in the meta-analysis incorporated the full range of diagnostic subgroups of BD which again may affect the generalizability of the results. Unfortunately, insufficient information on the breakdown of BD diagnoses was available in the original articles to conduct analyses

stratified by diagnostic status. Given the recognized differences between BDI and BDII in terms of severity and prognostic factors, conducting the analysis in this way may have provided additional information relating to differences between ages of onset. Provided samples have sufficient power to do so, future research may benefit from breaking BD groups down further in this way for analysis. Moreover, despite the controversy surrounding early diagnosis of BD, if studies include cases with onset as early as 12yrs, future research investigating differences between pre-adolescent and adolescent onset groups is warranted. Such research may identify severity or prognostic indicators not clearly delineated in this meta-analysis due to the compression of these age groups.

Although the majority of studies included in the meta-analysis used adequate definitions of Age at onset (AAO) (Egeland et al., 1987), differences in the measurement and definition of AAO between studies may have impacted the synthesis of the data. An EAO cut-off of 18 – 20yrs was used as this age cut-off is reflective of the broader literature. Although this method has been used in a number of previous studies (Coryell et al., 2013; Drancourt et al., 2013), recent research using admixture analysis has shown that the theoretical model that best accounts for observed distributions of AAO is consistent with the existence of three AAO subgroups with average onset ages of 17years, 25years and 38years (Azorin et al., 2013; Bellivier et al., 2001b; Tozzi et al., 2011b). In addition, the impact of potential confounding factors such as duration of untreated illness on the results of the meta-analysis should not be underestimated. A number of the factors found to be associated with earlier age of onset, such as greater comorbidity and increased likelihood of suicide attempts, have previously been found to be associated with longer duration of untreated illness, which itself has been linked to earlier age of onset. As such, the true nature of many of the relationships identified in the meta-analysis is not clear. Follow up data from longitudinal studies may offer opportunities to investigate this more thoroughly.

In the empirical study, due to the large number of items included in the factor analysis, the sample included was not large enough to conduct exploratory and then confirmatory factor analyses as one might do in a factory analytic study. As the primary purpose of the factor analysis for this study, was to test the assumption of unidimensionality for the IRT analyses, however; and as the procedure followed in the study is in line with previous empirical research using IRT analyses, it was felt that using exploratory factor analysis alone was appropriate.

In order to generate accurate parameter estimates using IRT analyses, large sample sizes are typically required. This is, however, dependent on the type of analysis conducted and number of parameters estimated. Although previous studies have demonstrated effective use of IRT analysis with sample sizes similar to that used in the current study, analysis using a larger sample size may provide more robust results. Moreover, the sample size in the current study was not sufficient to run separate analyses comparing parameter estimates between At Risk, Control and Bipolar groups. Future research using larger samples may provide further insight into whether there are identifiable patterns of differences between these groups, and as such, which symptoms are most clinically useful for each group. Further, future research comparing individual symptom patterns between more restricted age groups, i.e. pre-adolescent / adolescent / early adult, may also provide greater insight into which symptoms are most indicative of risk at different developmental stages.

Despite the limitations highlighted, the papers included in this thesis also carry significant strengths. The Meta-Analysis included in chapter 2 is the first published paper that has critically evaluated and statistically analysed the evidence for what is often reported as “common knowledge” in the bipolar disorder literature. By investigating the specifics of the relationship between earlier onset of BD and outcomes, this paper has provided a more positive message for those who develop BD at a younger age, and the clinicians who work with them. Moreover, it identifies specific areas that warrant further research in younger ‘at risk’ populations and that may be useful in informing development of early intervention programs.

The empirical study is one of few studies investigating the potential of individual and sub threshold clinical symptoms to explore their usefulness as developmentally appropriate indicators of risk in adolescents and young adults. It is also one of the few studies to apply a novel statistical approach based on IRT principals in a clinical context. The results of this study provide information that is potentially useful for clinicians in the recognition of at risk individuals who may benefit from increased monitoring and support, the first step toward early identification and intervention. This study also identifies key risk markers that may benefit from future research with adolescent populations and provides information that may be useful in informing developmentally specific models of BD in terms of symptom structure. The identification of the most clinically relevant symptoms, in conjunction with existing knowledge of genetic and environmental risk factors, provides a basis for the creation of developmentally appropriate screening

tools which may help differentiate normal adolescent stress from clinically relevant risk. Finally, these results inform areas to target in the development and trial of early intervention programs for young people who may be at risk of later psychopathology.

## **Conclusions**

This thesis explored and presented a range of evidence supporting the importance of early identification in bipolar disorder. In addition, it identifies areas of potential usefulness for further investigation with adolescent and young adult populations; and for development of early intervention strategies for individuals identified as at increased risk of later psychopathology. The results of the empirical study support the potential usefulness of individual diagnostic symptoms, and sub-threshold level symptoms, in the identification of risk and assessment of severity in BD. Further, results indicate that not all individual symptoms are equal in the level of information they provide. This has implications for the scoring methods of clinical measures that simply sum the number of endorsed symptoms in a scale with little regard for differences in the level of information provided by each symptom. Understanding and making use of the additional information provided by individual symptoms with regard to severity and discrimination capacity may enhance the accuracy and efficiency of current diagnostic instruments. In addition, this information may help inform the development of brief screening scales including only those symptoms that provide the greatest levels of information. These results also support previous findings that question the focus on elevated mood over activation as core features of mania and call into question the reliability of using irritability as a key symptom in the identification of BD in younger individuals. Finally, the empirical study highlights the potential usefulness of novel analytical approaches based on IRT in clinical research. IRT has much to offer clinical research. Moreover, the development of more accessible and affordable means for conducting these types of analyses means that there are fewer barriers for researchers wanting to apply them. Further research using similar analyses with larger samples would be helpful both to improve the robustness of results. In addition, it would allow for separate analyses with more cohesive, homogenous samples that may identify the most clinically meaningful symptoms for these populations.

# References

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- Adams, L. J., Mitchell, P. B., Fielder, S. L., Rosso, A., Donald, J. A., & Schofield, P. R. (1998). A susceptibility locus for bipolar affective disorder on chromosome 4q35. *The American Journal of Human Genetics*, *62*(5), 1084-1091.
- Akiskal, H., Hantouche, E., Bourgeois, M., Azorin, J., Sechter, D., Allilaire, J., . . . Lancrenon, S. (2001). Toward a refined phenomenology of mania: combining clinician-assessment and self-report in the French EPIMAN study. *Journal of Affective Disorders*, *67*(1), 89-96.
- Akiskal, H. S., & Benazzi, F. (2007). Continuous distribution of atypical depressive symptoms between major depressive and bipolar II disorders: dose-response relationship with bipolar family history. *Psychopathology*, *41*(1), 39-42.
- Altindag, A., Yanik, M., & Nebioglu, M. (2006). The comorbidity of anxiety disorders in bipolar I patients: prevalence and clinical correlates. *Israel Journal of Psychiatry and Related Sciences*, *43*(1), 10.
- American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders: Dsm-3-R*: American Psychiatric Assoc.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders (DSM)*. Washington, DC: American psychiatric association, 143-147.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders, text revision (DSM-IV-TR)*: American Psychiatric Association.
- American Psychiatric Association. (2013a). *Diagnostic and statistical manual of mental disorders, (DSM-5®)*: American Psychiatric Pub.
- American Psychiatric Association. (2013b). *DSM 5*: American Psychiatric Association.
- Angst, J. (2007). The bipolar spectrum. *The British Journal of Psychiatry*, *190*(3), 189-191.
- Angst, J. (2013). Bipolar disorders in DSM-5: strengths, problems and perspectives. *International Journal of Bipolar Disorders*, *1*(1), 1-3.
- Angst, J., & Cassano, G. (2005). The mood spectrum: improving the diagnosis of bipolar disorder. *Bipolar Disorders*, *7*, 4-12. doi:10.1111/j.1399-5618.2005.00210.x
- Angst, J., & Gamma, A. (2002). Prevalence of bipolar disorders: traditional and novel approaches. *Clin Appr Bipol Disord*, *1*, 10-14.
- Angst, J., Gamma, A., Benazzi, F., Ajdacic, V., Eich, D., & Rössler, W. (2003a). Diagnostic issues in bipolar disorder. *European neuropsychopharmacology*, *13*, 43-50.
- Angst, J., Gamma, A., Benazzi, F., Ajdacic, V., Eich, D., & Rössler, W. (2003b). Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. *Journal of Affective Disorders*, *73*(1), 133-146.
- Angst, J., & Marneros, A. (2001). Bipolarity from ancient to modern times: conception, birth and rebirth. *Journal of Affective Disorders*, *67*(1), 3-19.

- Armando, M., Pontillo, M., & Vicari, S. (2015). Psychosocial interventions for very early and early-onset schizophrenia: a review of treatment efficacy. *Current opinion in psychiatry*, 28(4), 312-323.
- Arnett, J. J. (1999). Adolescent storm and stress, reconsidered. *American psychologist*, 54(5), 317.
- Axelson, D., Birmaher, B., Strober, M., Gill, M. K., Valeri, S., Chiappetta, L., . . . Iyengar, S. (2006). Phenomenology of children and adolescents with bipolar spectrum disorders. *Archives of General Psychiatry*, 63(10), 1139-1148.
- Azorin, J.-M., Bellivier, F., Kaladjian, A., Adida, M., Belzeaux, R., Fakra, E., . . . Golmard, J.-L. (2013). Characteristics and profiles of bipolar I patients according to age-at-onset: findings from an admixture analysis. *Journal of Affective Disorders*, 150(3), 993-1000.
- Baethge, C. (2015). A bold meta - analysis on suicidality in bipolar disorder. *Bipolar Disorders*, 17(1), 17-18.
- Baldessarini, R. J., Tondo, L., Vazquez, G. H., Undurraga, J., Bolzani, L., Yildiz, A., . . . Tohen, M. (2012). Age at onset versus family history and clinical outcomes in 1,665 international bipolar-I disorder patients. *World Psychiatry*, 11(1), 40-46.
- Bashir, M., Russell, J., & Johnson, G. (1987). Bipolar affective disorder in adolescence: a 10-year study. *Australian and New Zealand Journal of Psychiatry*, 21(1), 36-43.
- Bauer, M., Glenn, T., Alda, M., Andreassen, O., Angelopoulos, E., Ardu, R., . . . Belmaker, R. (2015). Influence of birth cohort on age of onset cluster analysis in bipolar I disorder. *European Psychiatry*, 30(1), 99-105.
- Bauer, M. S., Crits-Christoph, P., Ball, W. A., Dewees, E., McAllister, T., Alahi, P., . . . Whybrow, P. C. (1991). Independent assessment of manic and depressive symptoms by self-rating: Scale characteristics and implications for the study of mania. *Archives of General Psychiatry*, 48(9), 807-812.
- Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Manual for the beck depression inventory-II: San Antonio, TX: Psychological Corporation.
- Beigel, A., & Murphy, D. L. (1971). Assessing clinical characteristics of the manic state. *American Journal of Psychiatry*, 128(6), 688-694.
- Bellivier, F., Golmard, J. L., Henry, C., Leboyer, M., & Schurhoff, F. (2001a). Admixture analysis of age at onset in bipolar I affective disorder. *Archives of General Psychiatry*, 58(5), 510-512. doi:DOI 10.1001/archpsyc.58.5.510
- Bellivier, F., Golmard, J. L., Henry, C., Leboyer, M., & Schurhoff, F. (2001b). Admixture analysis of age at onset in bipolar I affective disorder [2]. *Archives of General Psychiatry*, 58(5), 510-512.
- Bellivier, F., Golmard, J. L., Rietschel, M., Schulze, T. G., Malafosse, A., Preisig, M., . . . Leboyer, M. (2003). Age at onset in bipolar I affective disorder: Further evidence for three subgroups. *American Journal of Psychiatry*, 160(5), 999-1001.
- Biffin, F., Tahtalian, S., Filia, K., Fitzgerald, P. B., De Castella, A. R., Filia, S., . . . Berk, L. (2009). The impact of age at onset of bipolar I disorder on functioning and clinical presentation. *Acta neuropsychiatrica*, 21(4), 191-196.



- Birmaher, B., & Axelson, D. (2006). Course and outcome of bipolar spectrum disorder in children and adolescents: A review of the existing literature. *Development and Psychopathology*, *18*(4), 1023-1035.
- Blader, J. C., & Carlson, G. A. (2007). Increased rates of bipolar disorder diagnoses among US child, adolescent, and adult inpatients, 1996–2004. *Biological Psychiatry*, *62*(2), 107-114.
- Blader, J. C., & Carlson, G. A. (2013). Bipolar Disorder. In S. P. Hinshaw, T. P. Beauchaine, & P. S. P. Hinshaw (Eds.), *Child and Adolescent Psychopathology*. Somerset, USA: Wiley.
- Blanchin, M., Guilleux, A., Perrot, B., Bonnaud-Antignac, A., Hardouin, J.-B., & Sébille, V. (2015). Power and sample size determination for the group comparison of patient-reported outcomes using the Rasch model: impact of a misspecification of the parameters. *BMC medical research methodology*, *15*(1), 21.
- Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. (2005). *Comprehensive meta-analysis version 2*. Englewood, NJ: Biostat, 104.
- Breakspear, M., Roberts, G., Green, M. J., Nguyen, V. T., Frankland, A., Levy, F., . . . Mitchell, P. B. (2015). Network dysfunction of emotional and cognitive processes in those at genetic risk of bipolar disorder. *Brain*, awv261.
- Brotman, M. A., Schmajuk, M., Rich, B. A., Dickstein, D. P., Guyer, A. E., Costello, E. J., . . . Leibenluft, E. (2006). Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biological Psychiatry*, *60*(9), 991-997.
- Burke, K. C., Burke, J. D., Rae, D. S., & Regier, D. A. (1991). Comparing age at onset of major depression and other psychiatric disorders by birth cohorts in five US community populations. *Archives of General Psychiatry*, *48*(9), 789-795.
- Cadoret, R. J., Winokur, G., & Clayton, P. J. (1970). Family history studies: VII. Manic depressive disease versus depressive disease. *The British Journal of Psychiatry*, *116*(535), 625-635.
- Casey, B. J., Jones, R., & Hare, T. (2008). The adolescent brain. *Annals of the New York Academy of Sciences*, *1124*(1), 111-126.
- Casey, B. J., Jones, R., Levita, L., Libby, V., Pattwell, S. S., Ruberry, E. J., . . . Somerville, L. H. (2010). The storm and stress of adolescence: insights from human imaging and mouse genetics. *Developmental psychobiology*, *52*(3), 225-235.
- Casey, B. J., Jones, R. M., & Somerville, L. H. (2011). Braking and accelerating of the adolescent brain. *Journal of Research on Adolescence*, *21*(1), 21-33.
- Cassano, G. B., Pini, S., Sacttoni, M., & Dell’Osso, L. (1999). Multiple anxiety disorder comorbidity in patients with mood spectrum disorders with psychotic features. *American Journal of Psychiatry*.
- Cate Carter, T. D., Mundo, E., Parikh, S. V., & Kennedy, J. L. (2003). Early age at onset as a risk factor for poor outcome of bipolar disorder. *Journal of Psychiatric Research*, *37*(4), 297-303.
- Chen, Y.-W., & Dilsaver, S. C. (1996). Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. *Biological Psychiatry*, *39*(10), 896-899.

- Chengappa, K. N. R., Kupfer, D. J., Frank, E., Houck, P. R., Grochocinski, V. J., Cluss, P. A., & Stapf, D. A. (2003). Relationship of Birth Cohort and Early Age at Onset of Illness in a Bipolar Disorder Case Registry. *American Journal of Psychiatry*, *160*(9), 1636-1642. doi:doi:10.1176/appi.ajp.160.9.1636
- Cheniaux, E., Filgueiras, A., Silva, R. d. A. d., Silveira, L. A. S., Nunes, A. L. S., & Landeira-Fernandez, J. (2014). Increased energy/activity, not mood changes, is the core feature of mania. *Journal of Affective Disorders*, *152–154*, 256-261. doi:<http://dx.doi.org/10.1016/j.jad.2013.09.021>
- Cicchetti, D., & Rogosch, F. A. (2002). A developmental psychopathology perspective on adolescence. *Journal of consulting and clinical psychology*, *70*(1), 6.
- Clacey, J., Goldacre, M., & James, A. (2015). Paediatric bipolar disorder: international comparisons of hospital discharge rates 2000–2010. *British Journal of Psychiatry Open*, *1*(2), 166-171. doi:10.1192/bjpo.bp.115.001933
- Colom, F., & Vieta, E. (2009). The road to DSM-V. *Psychopathology*, *42*(4), 209-218.
- Cooper, H. M., & Lindsay, J. (1998). *Research synthesis and meta-analysis*: Sage Publications.
- Cornblatt, B. A., Lencz, T., Smith, C. W., Correll, C. U., Auther, A. M., & Nakayama, E. (2003). The schizophrenia prodrome revisited. *Schizophrenia Bulletin*, *29*(4), 633-651.
- Corry, J., Green, M., Roberts, G., Frankland, A., Wright, A., Lau, P., . . . Mitchell, P. B. (2013). Anxiety, stress and perfectionism in bipolar disorder. *Journal of Affective Disorders*, *151*(3), 1016-1024.
- Coryell, Scheftner, W., Keller, M., Endicott, J., Maser, J., & Klerman, G. L. (1993a). The enduring psychosocial consequences of mania and depression. *Am J Psychiatry*, *150*(5), 720-727.
- Coryell, W., Endicott, J., Maser, J. D., Mueller, T., Lavori, P., & Keller, M. (1995). The likelihood of recurrence in bipolar affective disorder: the importance of episode recency. *Journal of Affective Disorders*, *33*(3), 201-206.
- Coryell, W., Fiedorowicz, J., Leon, A. C., Endicott, J., & Keller, M. B. (2013). Age of onset and the prospectively observed course of illness in bipolar disorder. *Journal of Affective Disorders*, *146*(1), 34-38.
- Coryell, W., Scheftner, W., Keller, M., Endicott, J., Maser, J., & Klerman, G. L. (1993b). The enduring psychosocial consequences of mania and depression. *American Journal of Psychiatry*, *150*, 720-720.
- Coryell, W., Scheftner, W., Keller, M., Endicott, J., Maser, J., & Klerman, G. L. (1993c). The enduring psychosocial consequences of mania and depression. *The American Journal of Psychiatry*.
- da Silva Costa, L., Alencar, Á. P., Neto, P. J. N., dos Santos, M. d. S. V., da Silva, C. G. L., Pinheiro, S. d. F. L., . . . de Lima, M. A. P. (2015). Risk factors for suicide in bipolar disorder: A systematic review. *Journal of Affective Disorders*, *170*, 237-254.
- Da Silva Magalhaes, P. V., Gomes, F. A., Kunz, M., & Kapczinski, F. (2009). Birth-cohort and dual diagnosis effects on age-at-onset in Brazilian patients with bipolar i disorder. *Acta Psychiatrica Scandinavica*, *120*(6), 492-495.

- da Silva, R. d. A., Mograbi, D. C., Bifano, J., Santana, C. M. T., & Cheniaux, E. (2016). Insight in bipolar mania: evaluation of its heterogeneity and correlation with clinical symptoms. *Journal of Affective Disorders*, *199*, 95-98. doi:<http://dx.doi.org/10.1016/j.jad.2016.04.019>
- Dalton, E. J., Cate - Carter, T. D., Mundo, E., Parikh, S. V., & Kennedy, J. L. (2003). Suicide risk in bipolar patients: the role of co - morbid substance use disorders. *Bipolar Disorders*, *5*(1), 58-61.
- de Almeida, J. R. C., & Phillips, M. L. (2013). Distinguishing between unipolar depression and bipolar depression: current and future clinical and neuroimaging perspectives. *Biological Psychiatry*, *73*(2), 111-118.
- Decina, P., Kestenbaum, C. J., Farber, S., Kron, L., Gargan, M., Sackeim, H. A., & Fieve, R. R. (1983). Clinical and psychological assessment of children of bipolar probands. *American Journal of Psychiatry*, *140*(5), 548-553.
- Drancourt, N., Etain, B., Lajnef, M., Henry, C., Raust, A., Cochet, B., . . . Zanouy, L. (2013). Duration of untreated bipolar disorder: missed opportunities on the long road to optimal treatment. *Acta Psychiatrica Scandinavica*, *127*(2), 136-144.
- Dubicka, B., Carlson, G. A., Vail, A., & Harrington, R. (2008). Prepubertal mania: diagnostic differences between US and UK clinicians. *European Child & Adolescent Psychiatry*, *17*(3), 153-161. doi:10.1007/s00787-007-0649-5
- Eaton, W. W., Badawi, M., & Melton, B. (1995). Prodromes and precursors: epidemiologic data for primary prevention of disorders with slow onset. *The American Journal of Psychiatry*.
- Egeland, J. A., Blumenthal, R. L., Nee, J., Sharpe, L., & Endicott, J. (1987). Reliability and relationship of various ages of onset criteria for major affective disorder. *Journal of Affective Disorders*, *12*(2), 159-165.
- Egeland, J. A., Hostetter, A. M., Pauls, D. L., & Sussex, J. N. (2000). Prodromal symptoms before onset of manic-depressive disorder suggested by first hospital admission histories. *Journal of the American Academy of Child & Adolescent Psychiatry*, *39*(10), 1245-1252.
- Embretson, S., & Reise, S. (2004). Item response theory for psychologists.
- Embretson, S. E., & Reise, S. P. (2013). *Item response theory*: Psychology Press.
- Endicott, J., & Spitzer, R. L. (1978). A diagnostic interview: the schedule for affective disorders and schizophrenia. *Archives of General Psychiatry*, *35*(7), 837-844.
- Ernst, C. L., & Goldberg, J. F. (2004). Clinical features related to age at onset in bipolar disorder. *Journal of Affective Disorders*, *82*(1), 21-27.
- Faedda, G. L., Marangoni, C., Serra, G., Salvatore, P., Sani, G., Vázquez, G. H., . . . Koukopoulos, A. (2015). Precursors of bipolar disorders: a systematic literature review of prospective studies. *The Journal of clinical psychiatry*, *76*(5), 614-624.
- Fagiolini, A., Forgione, R., Maccari, M., Cuomo, A., Morana, B., Dell'Osso, M. C., . . . Rossi, A. (2013). Prevalence, chronicity, burden and borders of bipolar disorder. *Journal of Affective Disorders*, *148*(2), 161-169.

- Fava, G. A. (1999). Subclinical symptoms in mood disorders: pathophysiological and therapeutic implications. *Psychological Medicine*, 29(01), 47-61.
- Fava, G. A., Grandi, S., Canestrari, R., & Molnar, G. (1990). Prodromal symptoms in primary major depressive disorder. *Journal of Affective Disorders*, 19(2), 149-152.
- Fava, G. A., & Kellner, R. (1991). Prodromal symptoms in affective disorders. *Am J Psychiatry*, 148(7), 823-830.
- Fayers, P. (2004). Item response theory for psychologists. *Quality of Life Research*, 13(3), 715-716.
- Fiedorowicz, J. G., Endicott, J., Leon, A. C., Solomon, D. A., Keller, M. B., & Coryell, W. H. (2011). Subthreshold hypomanic symptoms in progression from unipolar major depression to bipolar disorder. *American Journal of Psychiatry*, 168(1), 40-48.
- First, M., Spitzer, R., Gibbon, M., & Williams, J. B. (1995). Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). New York, New York State Psychiatric Institute. *Biometrics Research*.
- Fleming, J. E., & Offord, D. R. (1990). Epidemiology of childhood depressive disorders: A critical review. *Journal of the American Academy of Child & Adolescent Psychiatry*, 29(4), 571-580.
- Frye, M. A., Yatham, L. N., Calabrese, J. R., Bowden, C. L., Ketter, T. A., Suppes, T., . . . Thompson, T. R. (2006). Incidence and time course of subsyndromal symptoms in patients with bipolar I disorder: an evaluation of 2 placebo-controlled maintenance trials. *The Journal of clinical psychiatry*, 67(11), 1721-1728.
- Geller, B., Zimmerman, B., Williams, M., DelBello, M. P., Frazier, J., & Beringer, L. (2002). Phenomenology of prepubertal and early adolescent bipolar disorder: examples of elated mood, grandiose behaviors, decreased need for sleep, racing thoughts and hypersexuality. *Journal of Child and Adolescent Psychopharmacology*, 12(1), 3-9.
- Geoffroy, P. A., Etain, B., Jamain, S., Bellivier, F., & Leboyer, M. (2013). [Trouble bipolaire à début précoce: validation par les études de mélange et les biomarqueurs.]. *Canadian Journal of Psychiatry/Revue Canadienne de Psychiatrie*, 58(4), 240-248.
- Gershon, E. S., Hamovit, J. H., Guroff, J. J., & Nurnberger, J. I. (1987). Birth-cohort changes in manic and depressive disorders in relatives of bipolar and schizoaffective patients. *Archives of General Psychiatry*, 44(4), 314-319.
- Ghaemi, S. N., Boiman, E. E., & Goodwin, F. K. (2000). Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. *J Clin Psychiatry*, 61(10).
- Ghouse, A. A., Sanches, M., Zunta-Soares, G., Swann, A. C., & Soares, J. C. (2013). Overdiagnosis of bipolar disorder: a critical analysis of the literature. *The Scientific World Journal*, 2013.
- Gitlin, M., & Frye, M. A. (2012). Maintenance therapies in bipolar disorders. *Bipolar disorders*, 14(s2), 51-65.
- Gitlin, M. J., Swendsen, J., Heller, T. L., & Hammen, C. (1995). Relapse and impairment in bipolar disorder. *The American Journal of Psychiatry*.
- Goldberg, D. (2000). Plato versus Aristotle: categorical and dimensional models for common mental disorders. *Comprehensive psychiatry*, 41(2), 8-13.

- Goldberg, J. F., & Ernst, C. L. (2002a). Features associated with the delayed inhibition of mood stabilizers at illness onset in bipolar disorder. *Journal of Clinical Psychiatry*, 63(11), 985-991.
- Goldberg, J. F., & Ernst, C. L. (2002b). Features associated with the delayed initiation of mood stabilizers at illness onset in bipolar disorder. *Journal of Clinical Psychiatry*, 63(11), 985-991.
- Goldberg, J. F., & Ernst, C. L. (2002c). Features Associated With the Delayed Initiation of Mood Stabilizers at Illness Onset in Bipolar Disorder [CME]. *The Journal of clinical psychiatry*, 63(11), 985-991.
- Goldberg, J. F., & Grossman, L. S. (1995). Course and outcome in bipolar affective disorder: a longitudinal follow-up study. *Am J Psychiatry*, 152(3), 379-384.
- Goldberg, J. F., Harrow, M., & Grossman, L. S. (1995). Recurrent affective syndromes in bipolar and unipolar mood disorders at follow-up. *The British Journal of Psychiatry*, 166(3), 382-385.
- Goldberg, J. F., Perlis, R. H., Bowden, C. L., Thase, M. E., Miklowitz, D. J., Marangell, L. B., . . . Sachs, G. S. (2009). Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD.
- Goldberg, J. F., & Truman, C. J. (2003). Antidepressant - induced mania: an overview of current controversies. *Bipolar disorders*, 5(6), 407-420.
- Goldstein, B. I., & Levitt, A. J. (2006). Further evidence for a developmental subtype of bipolar disorder defined by age at onset: results from the national epidemiologic survey on alcohol and related conditions. *The American Journal of Psychiatry*, 163(9).
- Goodwin, F., & Jamison, K. (1990). *Manic. Depressive Illness*. New York, NY: Oxford University Press.
- Grigoriu-Serbănescu, M., Christodorescu, D., Jipescu, I., Totoescu, A., Marinescu, E., & Ardelean, V. (1989). Psychopathology in children aged 10–17 of bipolar parents: psychopathology rate and correlates of the severity of the psychopathology. *Journal of Affective Disorders*, 16(2), 167-179.
- Grunebaum, M. F., Galfalvy, H. C., Nichols, C. M., Caldeira, N. A., Sher, L., Dervic, K., . . . Oquendo, M. A. (2006a). Aggression and substance abuse in bipolar disorder. *Bipolar Disorders*, 8(5p1), 496-502.
- Grunebaum, M. F., Ramsay, S. R., Galfalvy, H. C., Ellis, S. P., Burke, A. K., Sher, L., . . . Oquendo, M. A. (2006b). Correlates of suicide attempt history in bipolar disorder: a stress - diathesis perspective. *Bipolar Disorders*, 8(5p2), 551-557.
- Guilleux, A., Blanchin, M., Hardouin, J.-B., & Sébille, V. (2014). Power and sample size determination in the Rasch model: evaluation of the robustness of a numerical method to non-normality of the latent trait. *PloS one*, 9(1), e83652.
- Hamilton, M. (1960). A rating scale for depression. *Journal of neurology, neurosurgery, and psychiatry*, 23(1), 56.
- Hamshere, M. L., Gordon-Smith, K., Forty, L., Jones, L., Caesar, S., Fraser, C., . . . Jones, I. (2009). Age-at-onset in bipolar-I disorder: mixture analysis of 1369 cases identifies three distinct clinical subgroups. *Journal of Affective Disorders*, 116(1), 23-29.

- Harvey, R. J., & Hammer, A. L. (1999). Item response theory. *The Counseling Psychologist*, 27(3), 353-383.
- Hasler, G., Drevets, W. C., Gould, T. D., Gottesman, I. I., & Manji, H. K. (2006). Toward constructing an endophenotype strategy for bipolar disorders. *Biological psychiatry*, 60(2), 93-105.
- Hauser, M., Galling, B., & Correll, C. U. (2013). Suicidal ideation and suicide attempts in children and adolescents with bipolar disorder: A systematic review of prevalence and incidence rates, correlates, and targeted interventions. *Bipolar Disorders*, 15(5), 507-523.
- Hayes, J., Miles, J., Walters, K., King, M., & Osborn, D. (2015). A systematic review and meta - analysis of premature mortality in bipolar affective disorder. *Acta Psychiatrica Scandinavica*, 131(6), 417-425.
- He, Q., & Wheadon, C. (2013). The effect of sample size on item parameter estimation for the partial credit model. *International Journal of Quantitative Research in Education*, 1(3), 297-315.
- Henry, C., Sorbara, F., Lacoste, J., Gindre, C., & Leboyer, M. (2001). Antidepressant-induced mania in bipolar patients: identification of risk factors. *Journal of Clinical Psychiatry*, 62(4), 249-255.
- Higgins, J., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta - analysis. *Statistics in Medicine*, 21(11), 1539-1558.
- Hirschfeld, R. M., Lewis, L., & Vornik, L. A. (2003). Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. *The Journal of clinical psychiatry*(64), 161-174.
- Holman, R., Glas, C. A., & de Haan, R. J. (2003). Power analysis in randomized clinical trials based on item response theory. *Controlled clinical trials*, 24(4), 390-410.
- Huedo-Medina, T. B., Sánchez-Meca, J., Marín-Martínez, F., & Botella, J. (2006). Assessing heterogeneity in meta-analysis: Q statistic or I<sup>2</sup> index? *Psychological methods*, 11(2), 193.
- Ibiloglu, A. O., & Caykoylu, A. (2011). The comorbidity of anxiety disorders in bipolar I and bipolar II patients among Turkish population. *Journal of Anxiety Disorders*, 25(5), 661-667.
- Jackson, A., Cavanagh, J., & Scott, J. (2003). A systematic review of manic and depressive prodromes. *Journal of Affective Disorders*, 74(3), 209-217.
- James, A., Hoang, U., Seagroatt, V., Clacey, J., Goldacre, M., & Leibenluft, E. (2014). A comparison of American and English hospital discharge rates for pediatric bipolar disorder, 2000 to 2010. *Journal of the American Academy of Child and Adolescent Psychiatry*, 53(6), 614-624.
- Johns, L. C., & Van Os, J. (2001). The continuity of psychotic experiences in the general population. *Clinical Psychology Review*, 21(8), 1125-1141.
- Johnson, S. L., Gershon, A., & Starov, V. (2015). Is energy a stronger indicator of mood for those with bipolar disorder compared to those without bipolar disorder? *Psychiatry Research*, 230(1), 1-4. doi:<http://dx.doi.org/10.1016/j.psychres.2015.06.016>
- Jones, S. (2004). Psychotherapy of bipolar disorder: a review. *Journal of Affective Disorders*, 80(2), 101-114.

- Jones, S. H., & Tarrrier, N. (2005). New developments in bipolar disorder. *Clinical Psychology Review*, 25(8), 1003-1007.
- Joslyn, C., Hawes, D. J., Hunt, C., & Mitchell, P. B. (2016). Is age of onset associated with severity, prognosis, and clinical features in bipolar disorder? A meta - analytic review. *Bipolar disorders*.
- Joyce, P. R. (1984). Age of onset in bipolar affective disorder and misdiagnosis as schizophrenia. *Psychological Medicine*, 14(01), 145-149. doi:doi:10.1017/S0033291700003147
- Judd, L. L., & Akiskal, H. S. (2003). The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *Journal of Affective Disorders*, 73(1), 123-131.
- Judd, L. L., Schettler, P. J., Solomon, D. A., Maser, J. D., Coryell, W., Endicott, J., & Akiskal, H. S. (2008). Psychosocial disability and work role function compared across the long-term course of bipolar I, bipolar II and unipolar major depressive disorders. *Journal of Affective Disorders*, 108(1), 49-58.
- Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., . . . Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child & Adolescent Psychiatry*, 36(7), 980-988.
- Keck, P. E., McElroy, S. L., & Arnold, L. M. (2001). Bipolar disorder. *Medical Clinics of North America*, 85(3), 645-661.
- Keitner, G. I., Solomon, D. A., Ryan, C. E., Miller, I. W., Mallinger, A., Kupfer, D. J., & Frank, E. (1996). Prodromal and residual symptoms in bipolar I disorder. *Comprehensive psychiatry*, 37(5), 362-367.
- Keller, M. B., Lavori, P. W., Kane, J. M., Gelenberg, A. J., Rosenbaum, J. F., Walzer, E. A., & Baker, L. A. (1992). Subsyndromal symptoms in bipolar disorder: a comparison of standard and low serum levels of lithium. *Archives of General Psychiatry*, 49(5), 371-376.
- Kessing, L. V., Vradi, E., & Andersen, P. K. (2015). Diagnostic stability in pediatric bipolar disorder. *Journal of Affective Disorders*, 172, 417-421.
- Kessler, R. C., Demler, O., Frank, R. G., Olfson, M., Pincus, H. A., Walters, E. E., . . . Zaslavsky, A. M. (2005). Prevalence and treatment of mental disorders, 1990 to 2003. *New England Journal of Medicine*, 352(24), 2515-2523.
- Ketter, T. (2010). Diagnostic features, prevalence, and impact of bipolar disorder. *The Journal of clinical psychiatry*, 71(6), e14-e14.
- Krueger, R. F., & Finger, M. S. (2001). Using item response theory to understand comorbidity among anxiety and unipolar mood disorders. *Psychological Assessment*, 13(1), 140.
- Lagerberg, T. V., Sundet, K., Aminoff, S. R., Berg, A. O., Ringen, P. A., Andreassen, O. A., & Melle, I. (2011). Excessive cannabis use is associated with earlier age at onset in bipolar disorder. *European Archives of Psychiatry and Clinical Neuroscience*, 261(6), 397-405.

- Lam, D., & Wong, G. (2005). Prodromes, coping strategies and psychological interventions in bipolar disorders. *Clinical Psychology Review, 25*(8), 1028-1042.
- Lam, D., Wong, G., & Sham, P. (2001). Prodromes, coping strategies and course of illness in bipolar affective disorder—a naturalistic study. *Psychological Medicine, 31*(08), 1397-1402.
- Larsen, T. K., Friis, S., Haahr, U., Joa, I., Johannessen, J., Melle, I., . . . Vaglum, P. (2001). Early detection and intervention in first - episode schizophrenia: a critical review. *Acta Psychiatrica Scandinavica, 103*(5), 323-334.
- Larson, R., Csikszentmihalyi, M., & Graef, R. (1980). Mood variability and the psychosocial adjustment of adolescents. *Journal of Youth and Adolescence, 9*(6), 469-490.
- Lasch, K., Weissman, M., Wickramaratne, P., & Bruce, M. L. (1990). Birth-cohort changes in the rates of mania. *Psychiatry Research, 33*(1), 31-37.
- Leboyer, M., Henry, C., Paillere - Martinot, M. L., & Bellivier, F. (2005). Age at onset in bipolar affective disorders: a review. *Bipolar disorders, 7*(2), 111-118.
- Leibenluft, E., Charney, D. S., Towbin, K. E., Bhangoo, R. K., & Pine, D. S. (2003). Defining clinical phenotypes of juvenile mania. *American Journal of Psychiatry, 160*(3), 430-437.
- Leverich, G. S., Post, R. M., Keck Jr, P. E., Altshuler, L. L., Frye, M. A., Kupka, R. W., . . . Luckenbaugh, D. (2007). The Poor Prognosis of Childhood-Onset Bipolar Disorder. *Journal of Pediatrics, 150*(5), 485-490.
- Lewinsohn, P. M., Hops, H., Roberts, R. E., Seeley, J. R., & Andrews, J. A. (1993). Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. *Journal of Abnormal Psychology, 102*(1), 133-144.
- Lin, P.-I., McInnis, M. G., Potash, J. B., Willour, V., MacKinnon, D. F., DePaulo, J. R., & Zandi, P. P. (2014). Clinical correlates and familial aggregation of age at onset in bipolar disorder. *American Journal of Psychiatry*.
- Lish, J. D., Dime-Meenan, S., Whybrow, P. C., Price, R. A., & Hirschfeld, R. M. A. (1994). The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. *Journal of Affective Disorders, 31*(4), 281-294. doi:[http://dx.doi.org/10.1016/0165-0327\(94\)90104-X](http://dx.doi.org/10.1016/0165-0327(94)90104-X)
- López, P., Mosquera, F., de Leon, J., Gutiérrez, M., Ezcurra, J., Ramírez, F., & González-Pinto, A. (2001). Suicide attempts in bipolar patients. *Journal of Clinical Psychiatry, 62*(12), 963-966.
- Maxwell, M. E. (1992). Family Interview for Genetic Studies (FIGS): a manual for FIGS. *Clinical Neurogenetics Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD*.
- McCormack, C., Green, M., Rowland, J., Roberts, G., Frankland, A., Hadzi-Pavlovic, D., . . . Levy, F. (2016). Neuropsychological and social cognitive function in young people at genetic risk of bipolar disorder. *Psychological medicine, 46*(04), 745-758.
- McElroy, S. L., Altshuler, L. L., Suppes, T., Keck Jr, P. E., Frye, M. A., Denicoff, K. D., . . . Rochussen, J. R. (2001). Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *American Journal of Psychiatry*.



- McGorry, P. D., Nelson, B., Phillips, L. J., Yuen, H. P., Francey, S. M., Thampi, A., . . . Kelly, D. (2013). Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: twelve-month outcome. *The Journal of clinical psychiatry*, *74*(4), 349-356.
- McGuffin, P., Rijdsdijk, F., Andrew, M., Sham, P., Katz, R., & Cardno, A. (2003). The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Archives of General Psychiatry*, *60*(5), 497-502.
- McQueen, M. B., Devlin, B., Faraone, S. V., Nimgaonkar, V. L., Sklar, P., Smoller, J. W., . . . Laird, N. M. (2005). Combined Analysis from Eleven Linkage Studies of Bipolar Disorder Provides Strong Evidence of Susceptibility Loci on Chromosomes 6q and 8q. *The American Journal of Human Genetics*, *77*(4), 582-595. doi:<http://dx.doi.org/10.1086/491603>
- Merikangas, K. R., Akiskal, H. S., Angst, J., Greenberg, P. E., Hirschfeld, R. M., Petukhova, M., & Kessler, R. C. (2007). Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Archives of General Psychiatry*, *64*(5), 543-552.
- Merikangas, K. R., & Low, N. C. (2004). The epidemiology of mood disorders. *Current psychiatry reports*, *6*(6), 411-421.
- Mick, E., Biederman, J., Faraone, S. V., Murray, K., & Wozniak, J. (2003). Defining a developmental subtype of bipolar disorder in a sample of nonreferred adults by age at onset. *Journal of Child and Adolescent Psychopharmacology*, *13*(4), 453-462.
- Mitchell, P. B. (2012). Bipolar disorder: the shift to overdiagnosis. *The Canadian Journal of Psychiatry*, *57*(11), 659-665.
- Mitchell, P. B. (2013). Bipolar disorder. *Australian family physician*, *42*(9), 616.
- Mitchell, P. B., Roberts, G., & Green, M. J. (2013). Studying young people at high genetic risk of bipolar disorder: preparing the ground for future prevention and early intervention. *Neuropsychiatry*, *3*(4), 357-361.
- Möller, H.-J. (2002). Bipolar disorder and schizophrenia: distinct illnesses or a continuum? *The Journal of clinical psychiatry*, *64*, 23-27; discussion 28.
- Molnar, G., Feeney, M. G., & Fava, G. A. (1988). Duration and symptoms of bipolar prodromes. *The American Journal of Psychiatry*.
- Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *The British journal of psychiatry*, *134*(4), 382-389.
- Moor, S., Crowe, M., Luty, S., Carter, J., & Joyce, P. R. (2012). Effects of comorbidity and early age of onset in young people with Bipolar Disorder on self harming behaviour and suicide attempts. *Journal of Affective Disorders*, *136*(3), 1212-1215.
- Moreno, C., Laje, G., Blanco, C., Jiang, H., Schmidt, A. B., & Olfson, M. (2007). National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Archives of General Psychiatry*, *64*(9), 1032-1039.

- Morrison, A. P., French, P., Walford, L., Lewis, S. W., Kilcommons, A., Green, J., . . . Bentall, R. P. (2004). Cognitive therapy for the prevention of psychosis in people at ultra-high risk Randomised controlled trial. *The British Journal of Psychiatry*, *185*(4), 291-297.
- Muris, P., Schmidt, H., Lambrichs, R., & Meesters, C. (2001). Protective and vulnerability factors of depression in normal adolescents. *Behaviour Research and Therapy*, *39*(5), 555-565.
- Murray, R. M., Sham, P., Van Os, J., Zanelli, J., Cannon, M., & McDonald, C. (2004). A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophrenia research*, *71*(2), 405-416.
- Nery-Fernandes, F., Quarantini, L. C., Guimarães, J. L., de Oliveira, I. R., Koenen, K. C., Kapczinski, F., & Miranda-Scippa, Â. (2012). Is there an association between suicide attempt and delay of initiation of mood stabilizers in bipolar I disorder? *Journal of Affective Disorders*, *136*(3), 1082-1087.
- Nordentoft, M., Rasmussen, J. Ø., Melau, M., Hjorthøj, C. R., & Thorup, A. A. (2014). How successful are first episode programs? A review of the evidence for specialized assertive early intervention. *Current opinion in psychiatry*, *27*(3), 167-172.
- Nurnberger, J. I., Blehar, M. C., Kaufmann, C. A., York-Cooler, C., Simpson, S. G., Harkavy-Friedman, J., . . . Reich, T. (1994). Diagnostic interview for genetic studies: rationale, unique features, and training. *Archives of General Psychiatry*, *51*(11), 849-859.
- Nurnberger, J. I., McNnis, M., Reich, W., Kastelic, E., Wilcox, H. C., Glowinski, A., . . . Gershon, E. S. (2011). A high-risk study of bipolar disorder: childhood clinical phenotypes as precursors of major mood disorders. *Archives of General Psychiatry*, *68*(10), 1012-1020.
- Olino, T. M., Yu, L., Klein, D. N., Rohde, P., Seeley, J. R., Pilkonis, P. A., & Lewinsohn, P. M. (2012). Measuring depression using item response theory: an examination of three measures of depressive symptomatology. *International Journal of Methods in Psychiatric Research*, *21*(1), 76-85.
- Oquendo, M. A., Waternaux, C., Brodsky, B., Parsons, B., Haas, G. L., Malone, K. M., & Mann, J. J. (2000). Suicidal behavior in bipolar mood disorder: clinical characteristics of attempters and nonattempters. *Journal of Affective Disorders*, *59*(2), 107-117.
- Oswald, P., Souery, D., Kasper, S., Lecrubier, Y., Montgomery, S., Wyckaert, S., . . . Mendlewicz, J. (2007). Current issues in bipolar disorder: a critical review. *European Neuropsychopharmacology*, *17*(11), 687-695.
- Papoulos, D., Hennen, J., Cockerham, M. S., & Lachman, H. (2007). A strategy for identifying phenotypic subtypes: Concordance of symptom dimensions between sibling pairs who met screening criteria for a genetic linkage study of childhood-onset bipolar disorder using the Child Bipolar Questionnaire. *Journal of Affective Disorders*, *99*(1-3), 27-36.
- Patel, N. C., DelBello, M. P., Keck, P. E., & Strakowski, S. M. (2006). Phenomenology associated with age at onset in patients with bipolar disorder at their first psychiatric hospitalization. *Bipolar Disorders*, *8*(1), 91-94.

- Perich, T., Lau, P., Hadzi-Pavlovic, D., Roberts, G., Frankland, A., Wright, A., . . . Radlinska, B. (2015). What clinical features precede the onset of bipolar disorder? *Journal of Psychiatric Research*, *62*, 71-77.
- Perich, T., Mitchell, P. B., Loo, C., Hadzi-Pavlovic, D., Roberts, G., Frankland, A., . . . Wright, A. (2013). Clinical and demographic features associated with the detection of early warning signs in bipolar disorder. *Journal of Affective Disorders*, *145*(3), 336-340.
- Perich, T., Mitchell, P. B., Loo, C., Hadzi - Pavlovic, D., Roberts, G., Green, M., . . . Corry, J. (2014). Cognitive styles and clinical correlates of childhood abuse in bipolar disorder. *Bipolar disorders*, *16*(6), 600-607.
- Perlis, R. H., Miyahara, S., Marangell, L. B., Wisniewski, S. R., Ostacher, M., DelBello, M. P., . . . Investigators, S.-B. (2004). Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biological Psychiatry*, *55*(9), 875-881.
- Perlis, R. H., Ostacher, M. J., Patel, J. K., Marangell, L. B., Zhang, H., Wisniewski, S. R., . . . Gyulai, L. (2006). Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *American Journal of Psychiatry*, *163*(2), 217-224.
- Perris, C. (1966a). A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. I. Genetic investigation. *Acta Psychiatrica Scandinavica. Supplementum*, *194*, 15.
- Perris, C. (1966b). A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. IV. A multidimensional study of personality traits. *Acta Psychiatrica Scandinavica. Supplementum*, *194*, 68.
- Perris, C., & D'Elia, G. (1966a). IX. Therapy and prognosis. *Acta Psychiatrica Scandinavica*, *41*(s194), 153-171.
- Perris, C., & d'Elia, G. (1966b). A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. X. Mortality, suicide and life-cycles. *Acta Psychiatrica Scandinavica. Supplementum*, *194*, 172-189.
- Perry, W., McIlwain, M., Kloezeman, K., Henry, B. L., & Minassian, A. (2016). Diagnosis and characterization of mania: Quantifying increased energy and activity in the human behavioral pattern monitor. *Psychiatry Research*, *240*, 278-283. doi:<http://dx.doi.org/10.1016/j.psychres.2016.04.078>
- Pickles, A., Aglan, A., Collishaw, S., Messer, J., Rutter, M., & Maughan, B. (2010). Predictors of suicidality across the life span: the Isle of Wight study. *Psychological medicine*, *40*(09), 1453-1466.
- Pine, D. S., Cohen, E., Cohen, P., & Brook, J. (1999). Adolescent depressive symptoms as predictors of adult depression: moodiness or mood disorder? *American Journal of Psychiatry*.
- Pine, D. S., Cohen, E., Cohen, P., & Brook, J. (2014). Adolescent depressive symptoms as predictors of adult depression: moodiness or mood disorder?

- Pine, D. S., Cohen, P., & Brook, J. (2001). Adolescent fears as predictors of depression. *Biological psychiatry*, 50(9), 721-724.
- Post, R. M., Leverich, G. S., Kupka, R. W., Keck Jr, P. E., McElroy, S. L., Altshuler, L. L., . . . Grunze, H. (2010). Early-onset bipolar disorder and treatment delay are risk factors for poor outcome in adulthood. *Journal of Clinical Psychiatry*, 71(7), 864.
- Prien, R., & Potter, W. (1989). NIMH workshop report on treatment of bipolar disorder. *Psychopharmacology bulletin*, 26(4), 409-427.
- Puig-Antich, J., & Chambers, W. (1978). The schedule for affective disorders and schizophrenia for school-age children (Kiddie-SADS). *New York: New York State Psychiatric Institute*.
- Rizopoulos, D. (2006). ltm: An R package for latent variable modeling and item response theory analyses. *Journal of statistical software*, 17(5), 1-25.
- Rosenthal, R. (1979). The file drawer problem and tolerance for null results. *Psychological bulletin*, 86(3), 638.
- Rössler, W., Riecher-Rössler, A., Angst, J., Murray, R., Gamma, A., Eich, D., . . . Gross, V. A. (2007). Psychotic experiences in the general population: a twenty-year prospective community study. *Schizophrenia research*, 92(1), 1-14.
- Samejima, F. (1969). Estimation of latent ability using a response pattern of graded scores. *Psychometrika monograph supplement*.
- Samejima, F. (1997). Graded response model *Handbook of modern item response theory* (pp. 85-100): Springer.
- Schaffer, A., Isometsä, E. T., Tondo, L., H Moreno, D., Turecki, G., Reis, C., . . . Kessing, L. V. (2015). International Society for Bipolar Disorders Task Force on Suicide: meta - analyses and meta - regression of correlates of suicide attempts and suicide deaths in bipolar disorder. *Bipolar Disorders*, 17(1), 1-16.
- Schneck, C. (2011a). Bipolar phenomenology: have we learned all we can learn? *American Journal of Psychiatry*.
- Schneck, C. (2011b). Bipolar Phenomenology: Have We Learned All We Can Learn? *American Journal of Psychiatry*, 168(1), 4-6. doi:doi:10.1176/appi.ajp.2010.10101482
- Schürhoff, F., Bellivier, F., Jouvent, R., Mouren-Siméoni, M.-C., Bouvard, M., Allilaire, J.-F., & Leboyer, M. (2000). Early and late onset bipolar disorders: two different forms of manic-depressive illness? *Journal of Affective Disorders*, 58(3), 215-221.
- Scott, J. (1995). Psychotherapy for bipolar disorder. *The British Journal of Psychiatry*, 167(5), 581-588.
- Scott, J., Stanton, B., Garland, A., & Ferrier, I. (2000). Cognitive vulnerability in patients with bipolar disorder. *Psychological Medicine*, 30(02), 467-472.
- Segurado, R., Detera-Wadleigh, S. D., Levinson, D. F., Lewis, C. M., Gill, M., Nurnberger, J. I., . . . Gershon, E. S. (2003). Genome scan meta-analysis of schizophrenia and bipolar disorder, part III: Bipolar disorder. *The American Journal of Human Genetics*, 73(1), 49-62.

- Severus, E., & Bauer, M. (2013). Diagnosing bipolar disorders in DSM-5. *International journal of bipolar disorders, 1*(1), 1.
- Shaw, J. A., Egeland, J. A., Endicott, J., Allen, C. R., & Hostetter, A. M. (2005). A 10-year prospective study of prodromal patterns for bipolar disorder among Amish youth. *Journal of the American Academy of Child & Adolescent Psychiatry, 44*(11), 1104-1111.
- Simon, A. E., Dvorsky, D. N., Boesch, J., Roth, B., Isler, E., Schueler, P., . . . Umbricht, D. (2006). Defining subjects at risk for psychosis: a comparison of two approaches. *Schizophrenia research, 81*(1), 83-90.
- Slama, F., Bellivier, F., Henry, C., Rousseva, A., Etain, B., Rouillon, F., & Leboyer, M. (2004). Bipolar patients with suicidal behavior: toward the identification of a clinical subgroup. *The Journal of clinical psychiatry, 65*(8), 1035-1039.
- Smith, J., & Tarrrier, N. (1992). Prodromal symptoms in manic depressive psychosis. *Social psychiatry and psychiatric epidemiology, 27*(5), 245-248.
- Stafford, M. R., Jackson, H., Mayo-Wilson, E., Morrison, A. P., & Kendall, T. (2013). Early interventions to prevent psychosis: systematic review and meta-analysis. *Bmj, 346*, f185.
- Steer, R. A., & Beck, A. T. (1997). Beck Anxiety Inventory.
- Steinberg, L., Thissen, D., ShROUT, P., & Fiske, S. (1995). Item response theory in personality research. *Personality research, methods, and theory: A festschrift honoring Donald W. Fiske*, 161-181.
- Stouffer, S. A., Guttman, L., Suchman, E. A., Lazarsfeld, P. F., Star, S. A., & Clausen, J. A. (1950). Measurement and prediction.
- Strakowski, S., Delbello, M., & Adler, C. (2005). The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Molecular psychiatry, 10*(1), 105-116.
- Stringaris, A. (2011). Irritability in children and adolescents: a challenge for DSM-5. *European Child & Adolescent Psychiatry, 20*(2), 61-66. doi:10.1007/s00787-010-0150-4
- Stringaris, A., Baroni, A., Haimm, C., Brotman, M., Lowe, C. H., Myers, F., . . . Towbin, K. (2010). Pediatric bipolar disorder versus severe mood dysregulation: risk for manic episodes on follow-up. *Journal of the American Academy of Child & Adolescent Psychiatry, 49*(4), 397-405.
- Stringaris, A., & Youngstrom, E. (2014a). Unpacking the differences in US/UK rates of clinical diagnoses of early-onset bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*(6), 609-611.
- Stringaris, A., & Youngstrom, E. (2014b). Unpacking the differences in US/UK rates of clinical diagnoses of early-onset bipolar disorder. *Journal of the American Academy of Child & Adolescent Psychiatry, 53*(6), 609-611.
- Strober, M. (1992). Relevance of early age-of-onset in genetic studies of bipolar affective disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 31*(4), 606-610.
- Strober, M., Schmidt-Lackner, S., Freeman, R., Bower, S., Lampert, C., & DeAntonio, M. (1995). Recovery and relapse in adolescents with bipolar affective illness: a five-year naturalistic,

- prospective follow-up. *Journal of the American Academy of Child and Adolescent Psychiatry*, 34(6), 724-731.
- Suominen, K., Mantere, O., Valtonen, H., Arvilommi, P., Leppamaki, S., Paunio, T., & Isometsa, E. (2007). Early age at onset of bipolar disorder is associated with more severe clinical features but delayed treatment seeking. *Bipolar Disorders*, 9(7), 698-705.
- Thissen, D., & Steinberg, L. (1988). Data analysis using item response theory. *Psychological Bulletin*, 104(3), 385.
- Thurstone, L. L. (1925). A method of scaling psychological and educational tests. *Journal of educational psychology*, 16(7), 433.
- Tondo, L., Baldessarini, R. J., Hennen, J., Minnai, G. P., Salis, P., Scamonatti, L., . . . Mannu, P. (1999). Suicide attempts in major affective disorder patients with comorbid substance use disorders. *Journal of Clinical Psychiatry*.
- Tozzi, F., Manchia, M., Galwey, N. W., Severino, G., Del Zompo, M., Day, R., . . . McGuffin, P. (2011a). Admixture analysis of age at onset in bipolar disorder. *Psychiatry Research*, 185(1), 27-32.
- Tozzi, F., Manchia, M., Galwey, N. W., Severino, G., Del Zompo, M., Day, R., . . . Muglia, P. (2011b). Admixture analysis of age at onset in bipolar disorder. *Psychiatry Research*, 185(1-2), 27-32.
- Tsai, S.-Y., Lee, J.-C., & Chen, C.-C. (1999). Characteristics and psychosocial problems of patients with bipolar disorder at high risk for suicide attempt. *Journal of Affective Disorders*, 52(1), 145-152.
- van der Linden, W. J., & Hambleton, R. K. (2013). *Handbook of modern item response theory*: Springer Science & Business Media.
- Van Meter, A. R., Burke, C., Youngstrom, E. A., Faedda, G., & Correll, C. U. (2016). The Bipolar Prodrome: Meta-Analysis of Symptom Prevalence Prior to Initial or Recurrent Mood Episodes. *Journal of the American Academy of Child & Adolescent Psychiatry*.
- Van Meter, A. R., Moreira, A. L. R., & Youngstrom, E. A. (2011). Meta-analysis of epidemiologic studies of pediatric bipolar disorder. *The Journal of clinical psychiatry*, 72(9), 1,478-1256.
- Vieta, E., Gasto, C., Otero, A., Nieto, E., & Vallejo, J. (1997). Differential features between bipolar I and bipolar II disorder. *Comprehensive psychiatry*, 38(2), 98-101.
- Vieta, E., Reinares, M., & Bourgeois, M. L. (2005). Bipolar I and bipolar II: a dichotomy? *This page intentionally left blank*, 88.
- Weinstock, L. M., Strong, D., Uebelacker, L. A., & Miller, I. W. (2009). Differential item functioning of DSM - IV depressive symptoms in individuals with a history of mania versus those without: An item response theory analysis. *Bipolar disorders*, 11(3), 289-297.
- Widiger, T. A., & Samuel, D. B. (2005). Diagnostic categories or dimensions? A question for the Diagnostic and statistical manual of mental disorders. *Journal of Abnormal Psychology*, 114(4), 494.
- Wilens, T. E., Biederman, J., Kwon, A., Ditterline, J., Forkner, P., Moore, H., . . . Wozniak, J. (2004). Risk of substance use disorders in adolescents with bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 43(11), 1380-1386.

- Wilens, T. E., Biederman, J., Millstein, R. B., Wozniak, J., Haheesy, A. L., & Spencer, T. J. (1999). Risk for Substance Use Disorders in Youths With Child-and Adolescent - Onset Bipolar Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 38(6), 680-685.
- Wing, J., Mann, S., Leff, J., & Nixon, J. (1978). The concept of a 'case' in psychiatric population surveys. *Psychological Medicine*, 8(02), 203-217.
- Winokur, G. (1970). Genetic findings and methodological considerations in manic depressive disease. *The British Journal of Psychiatry*, 117(538), 267-274.
- World Health Organisation. (2001). *The World Health Report 2001: Mental health: new understanding, new hope*: World Health Organization.
- World Health Organization. (1992). *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*: Geneva: World Health Organization.
- Wozniak, J., Biederman, J., Kiely, K., Ablon, J. S., Faraone, S. V., Mundy, E., & Mennin, D. (1995). Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *Journal of the American Academy of Child & Adolescent Psychiatry*, 34(7), 867-876.
- Wozniak, J., Biederman, J., Kwon, A., Mick, E., Faraone, S., Orlovsky, K., . . . van Grondelle, A. (2005). How Cardinal are Cardinal Symptoms in Pediatric Bipolar Disorder? An Examination of Clinical Correlates. *Biological Psychiatry*, 58(7), 583-588. doi:<http://dx.doi.org/10.1016/j.biopsych.2005.08.014>
- Wozniak, J., Petty, C. R., Schreck, M., Moses, A., Faraone, S. V., & Biederman, J. (2011). High level of persistence of pediatric bipolar-I disorder from childhood onto adolescent years: a four year prospective longitudinal follow-up study. *Journal of Psychiatric Research*, 45(10), 1273-1282.
- Yildiz, A., & Sachs, G. S. (2003). Age onset of psychotic versus non-psychotic bipolar illness in men and in women. *Journal of Affective Disorders*, 74(2), 197-201.
- Young, R., Biggs, J., Ziegler, V., & Meyer, D. (1978). A rating scale for mania: reliability, validity and sensitivity. *The British journal of psychiatry*, 133(5), 429-435.
- Yung, A. R., & McGorry, P. D. (1996). The prodromal phase of first-episode psychosis: past and current conceptualizations. *Schizophrenia bulletin*, 22(2), 353-370.
- Yung, A. R., Nelson, B., Stanford, C., Simmons, M. B., Cosgrave, E. M., Killackey, E., . . . McGorry, P. D. (2008). Validation of "prodromal" criteria to detect individuals at ultra high risk of psychosis: 2 year follow-up. *Schizophrenia research*, 105(1), 10-17.
- Zimmermann, P., Brückl, T., Nocon, A., Pfister, H., Lieb, R., Wittchen, H.-U., . . . Angst, J. (2009). Heterogeneity of DSM-IV major depressive disorder as a consequence of subthreshold bipolarity. *Archives of General Psychiatry*, 66(12), 1341-1352.



**Human Research Ethics Committee (HREC)**

30-Apr-2014

Dear Scientia Professor Mitchell,

HREC Ref: # **HC14128**

**Identifying the determinants and early manifestations of bipolar disorder**

The Human Research Ethics Committee considered the above protocol at its meeting held on 29-Apr-2014 and is pleased to advise it is satisfied that this protocol meets the requirements as set out in the National Statement on Ethical Conduct in Human Research\*. Having taken into account the advice of the Committee, the Deputy Vice-Chancellor (Research) has approved the project to proceed.

Would you please note:-

- approval is valid from 29-Apr-2014 to 28-Apr-2019;
- you will be required to provide annual reports on the study's progress to the HREC, as recommended by the National Statement;
- you are required to immediately report to the Ethics Secretariat anything which might warrant review of ethical approval of the protocol (National Statement 3.3.22, 5.5.7: <http://www.nhmrc.gov.au/files/nhmrc/publications/attachments/e72.pdf>) including:
  - serious or unexpected outcomes experienced by research participants (using the Serious Adverse Event proforma on the University website at <http://research.unsw.edu.au/human-ethics-forms-and-proformas> ;
  - proposed changes in the protocol; and
  - unforeseen events or new information (eg. from other studies) that might affect continued ethical acceptability of the project or may indicate the need for amendments to the protocol;
- any modifications to the project must have prior written approval and be ratified by any other relevant Human Research Ethics Committee, as appropriate;
- if there are implantable devices, the researcher must establish a system for tracking the



participants with implantable devices for the lifetime of the device (with consent) and report any device incidents to the TGA;

- if the research project is discontinued before the expected date of completion, the researcher is required to inform the HREC and other relevant institutions (and where possible, research participants), giving reasons. For multi-site research, or where there has been multiple ethical review, the researcher must advise how this will be communicated before the research begins (National Statement 3.3.22, 5.5.7:  
<http://www.nhmrc.gov.au/files/nhmrc/publications/attachments/e72.pdf>);
- consent forms are to be retained within the archives of the PSYCEN - Sch of Psychiatry and made available to the Committee upon request.

**\*\*\* Please Note: As your application has now been approved, a new reference number has been issued: HC14128. Please use this number in all future correspondence in relation to Project Title: Identifying the determinants and early manifestations of bipolar disorder. Project number HC09097 has been deactivated. \*\*\***

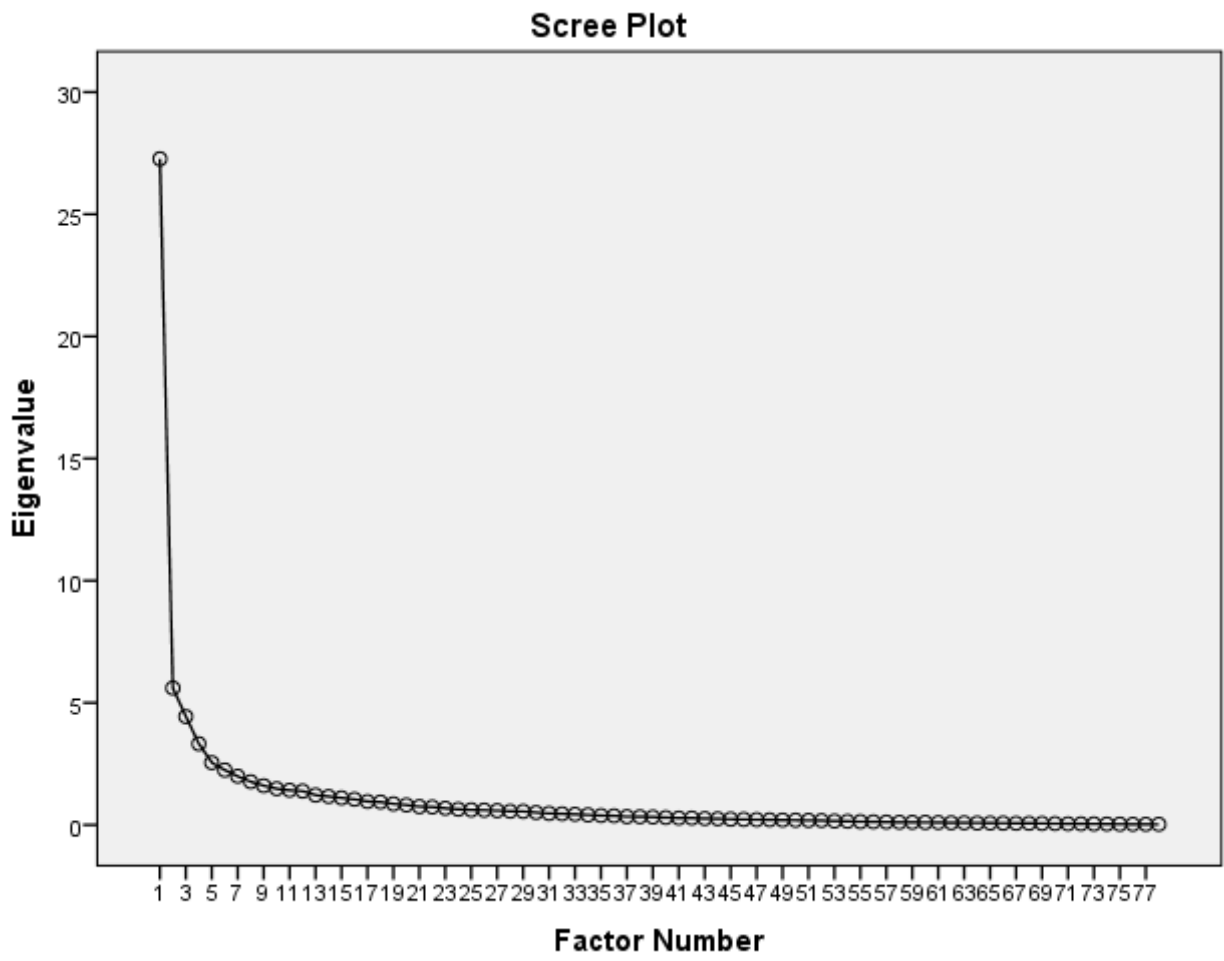
Sincerely,



Professor  
Heather  
Worth  
Presiding  
Member  
Human Research Ethics Committee

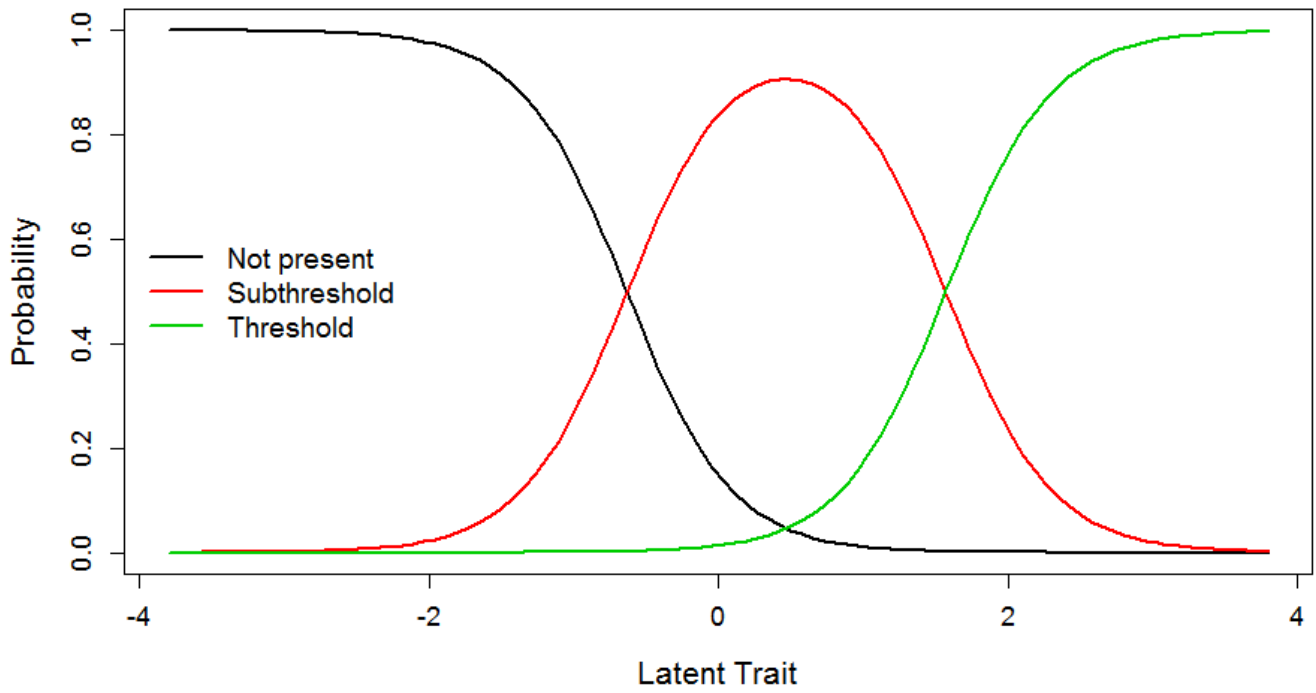
\* <http://www.nhmrc.gov.au>

**APPENDIX B: Scree Plot – Exploratory Factor Analysis**

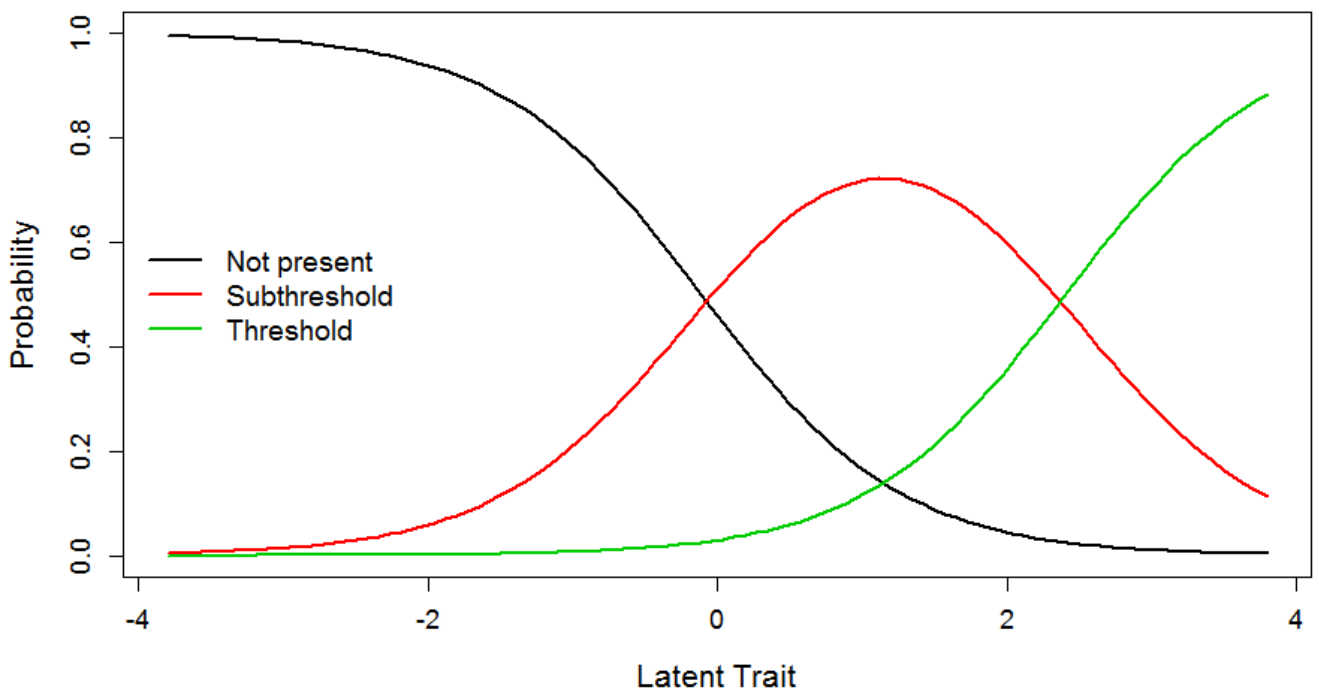


**APPENDIX C: Category Response Curves Depression**

**Item Response Category Characteristic Curves - Item: Dx1\_DepressedMood**

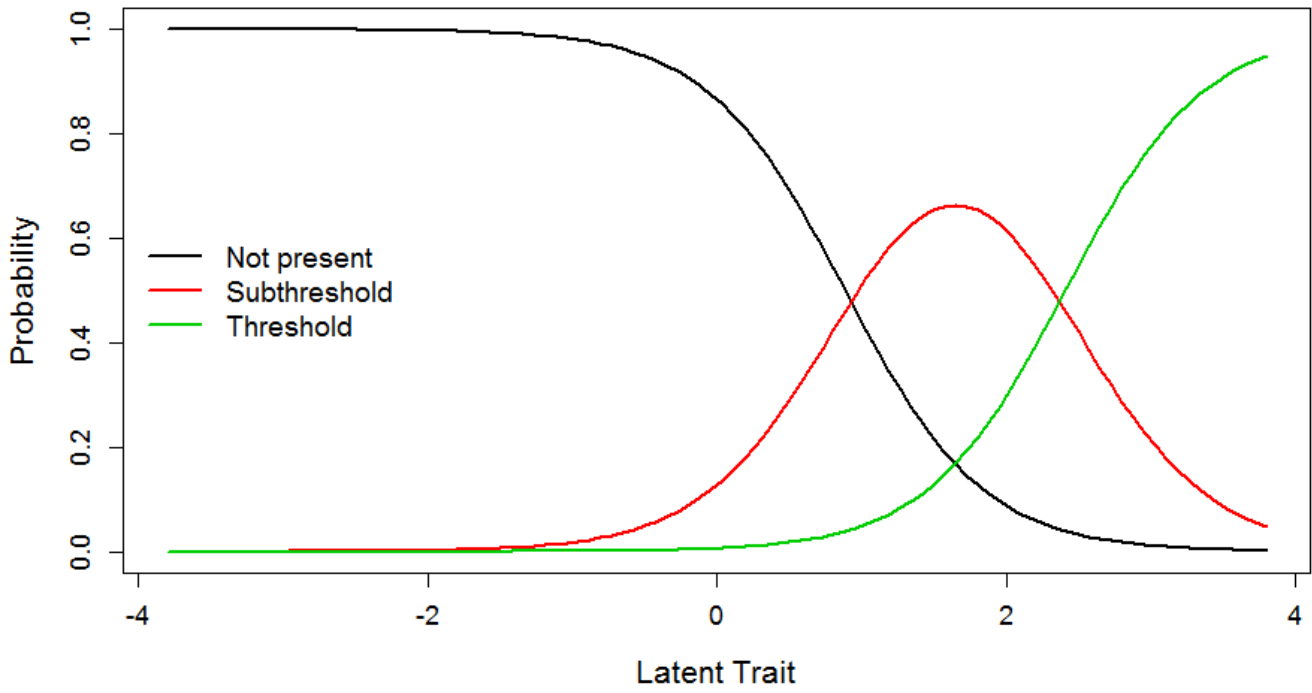


**Item Response Category Characteristic Curves - Item: Dx2\_Irritability**

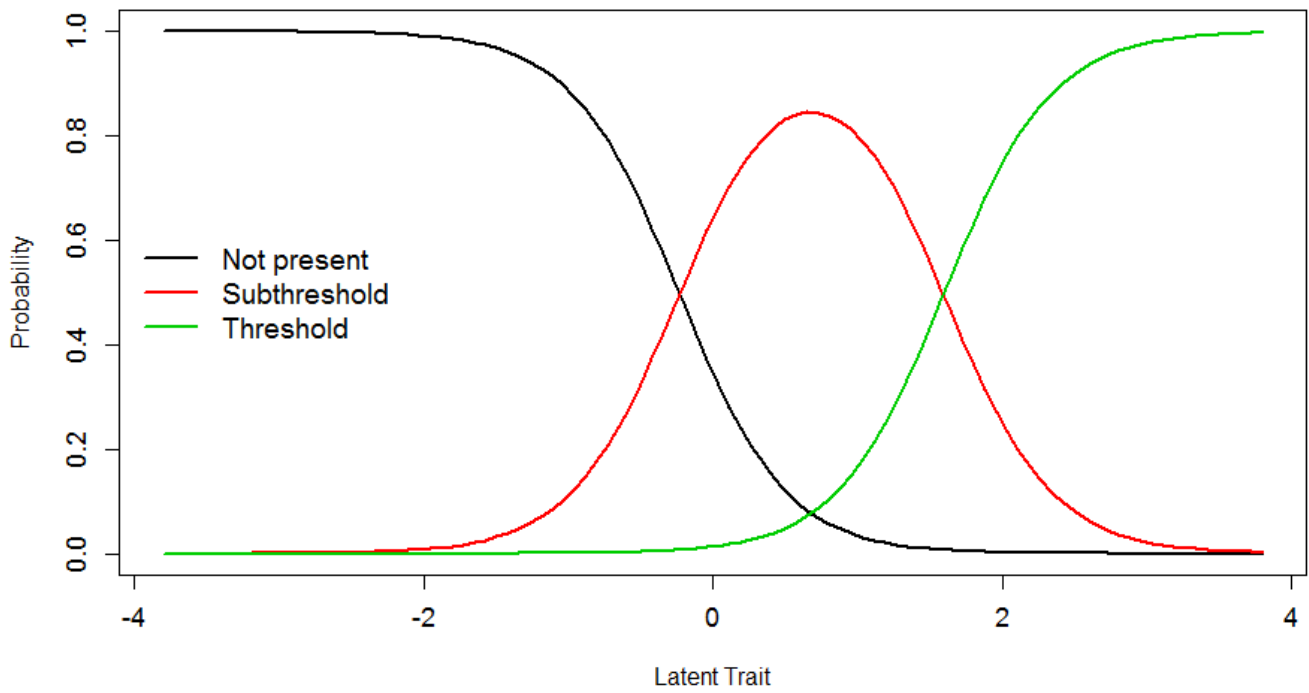


**APPENDIX C: Category Response Curves Depression continued**

**Item Response Category Characteristic Curves - Item: Dx5\_ExcessiveGuilt**

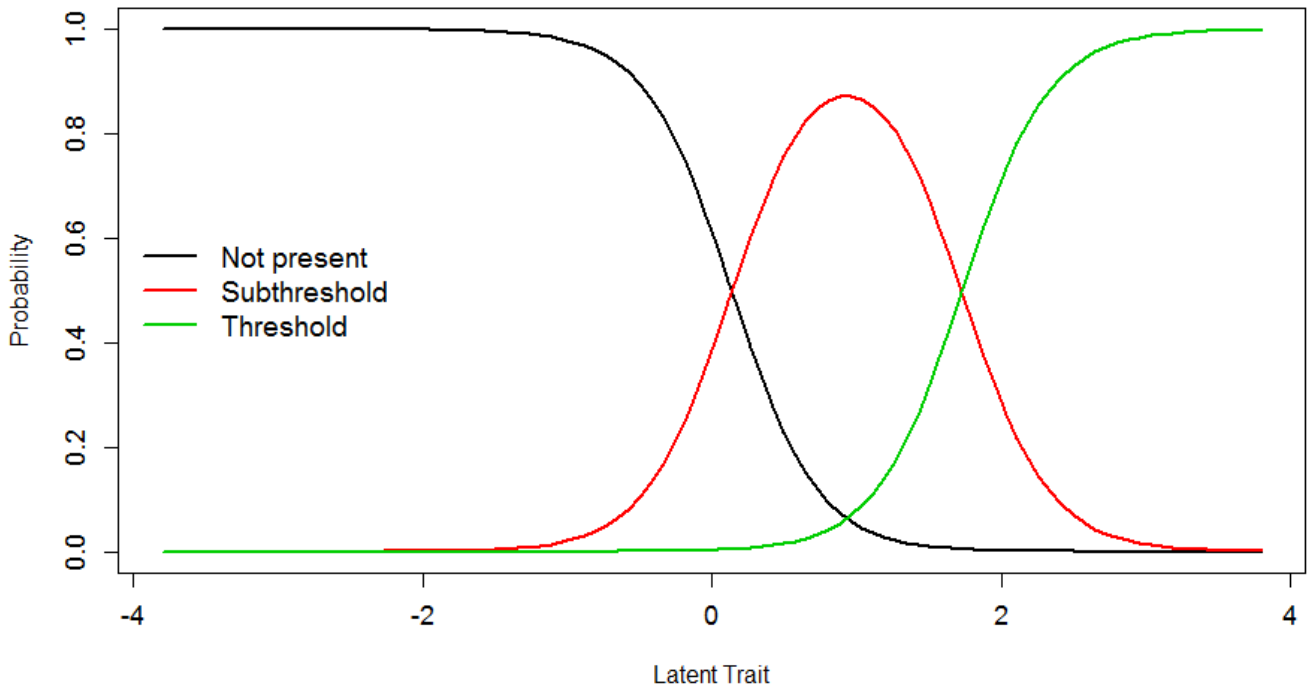


**Item Response Category Characteristic Curves - Item: Dx6\_NegativeSelf\_Image**

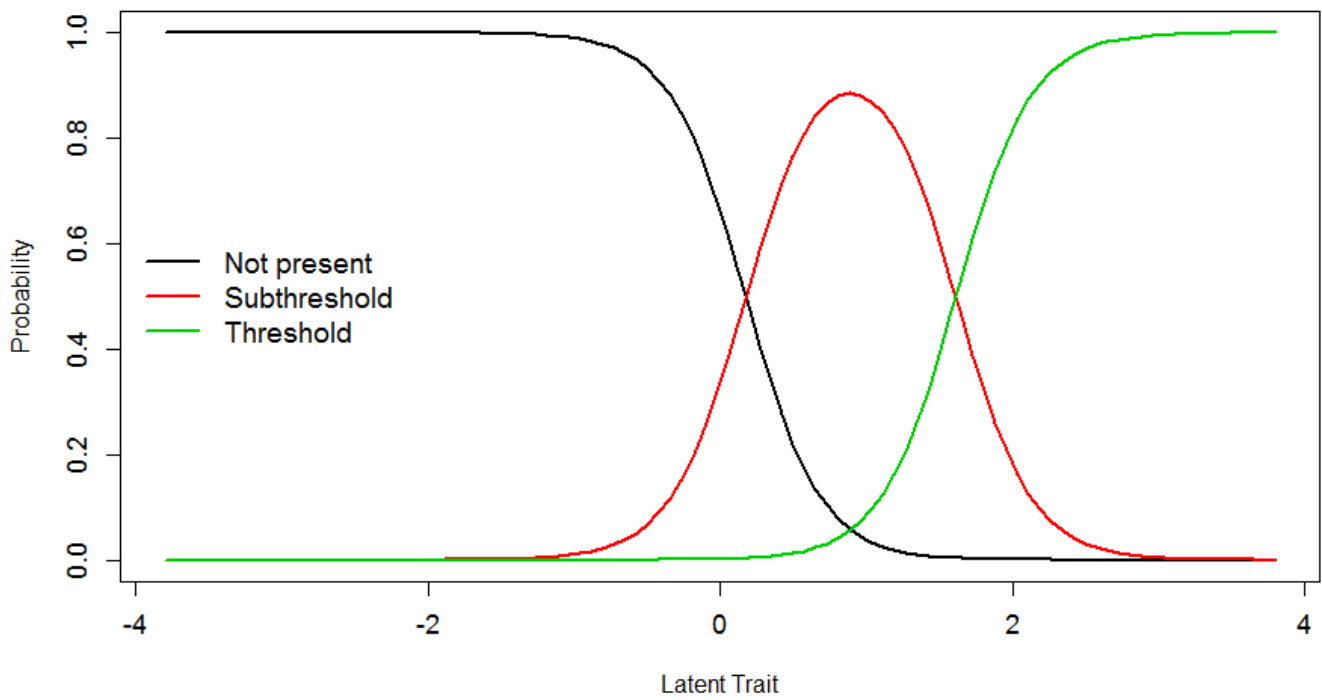


**APPENDIX C: Category Response Curves Depression continued**

**Item Response Category Characteristic Curves - Item: Dx7\_Hopelessness**

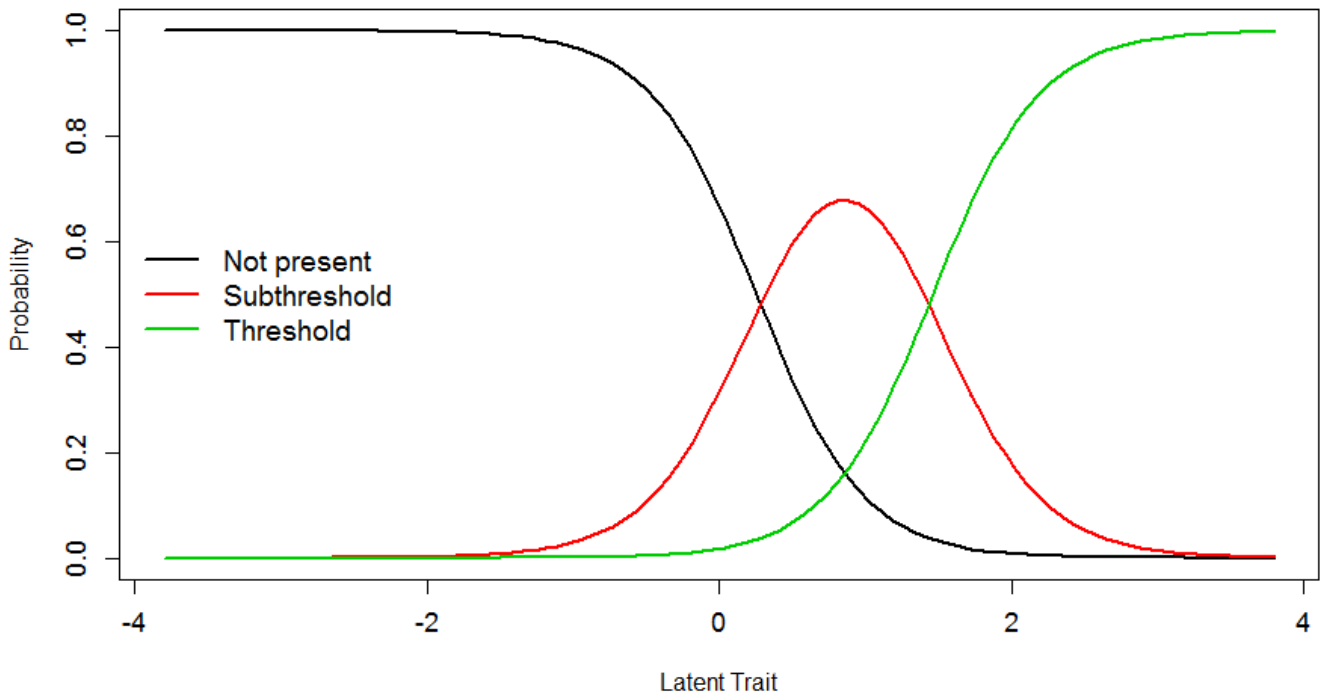


**Item Response Category Characteristic Curves - Item: Dx9\_Anhedonia**

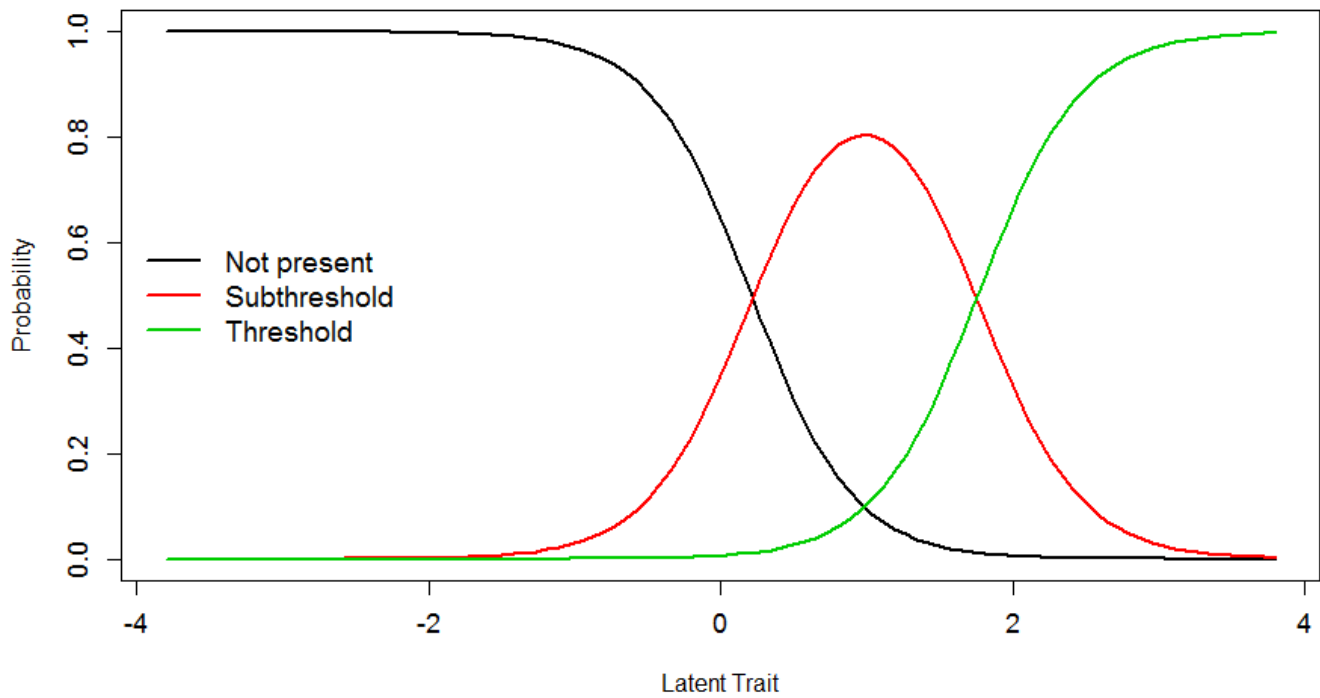


**APPENDIX C: Category Response Curves Depression continued**

**Item Response Category Characteristic Curves - Item: Dx10\_Fatigue**

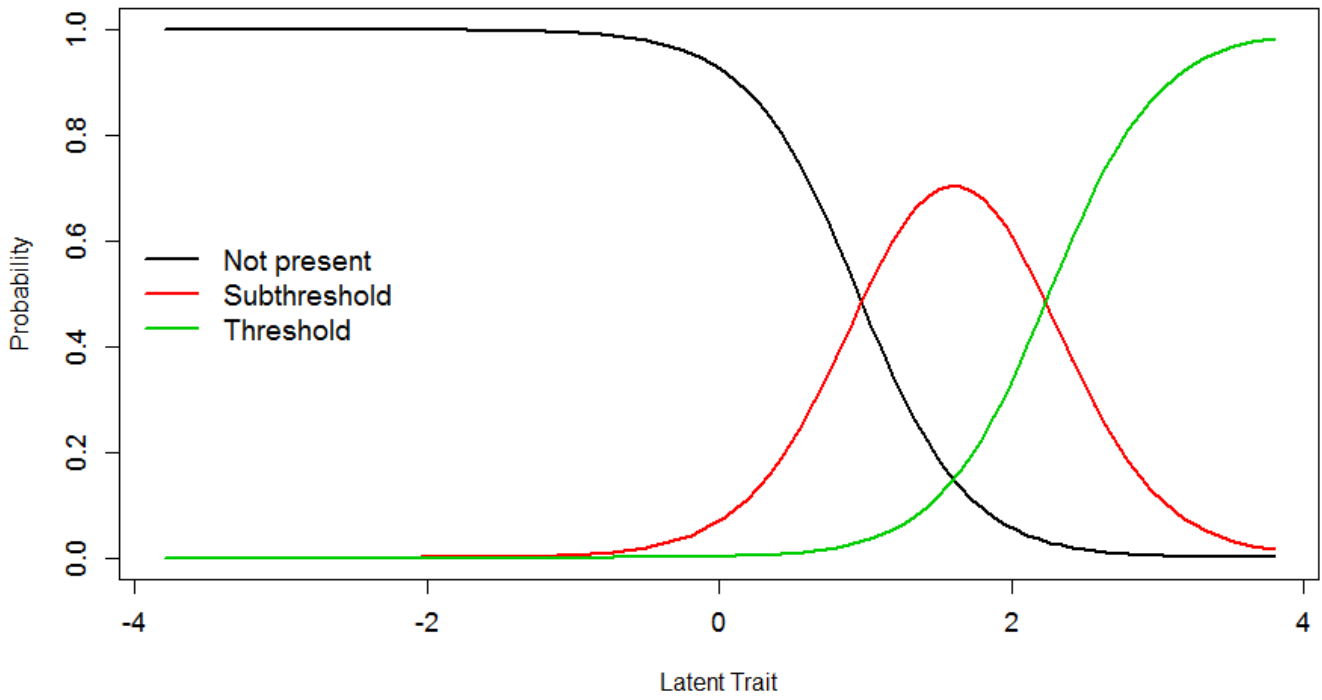


**Item Response Category Characteristic Curves - Item: Dx11\_Difficulty\_Concentrating**

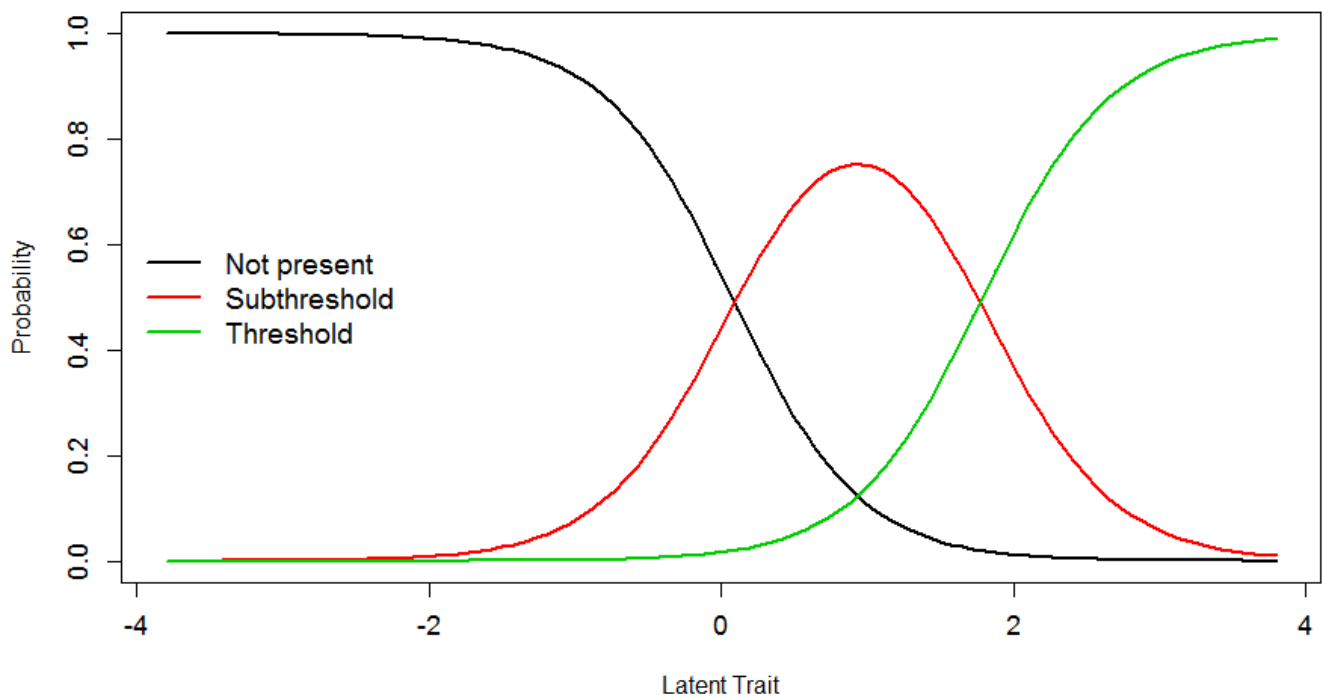


**APPENDIX C: Category Response Curves Depression continued**

**Item Response Category Characteristic Curves - Item: Dx13\_Psychomot\_Retardation**

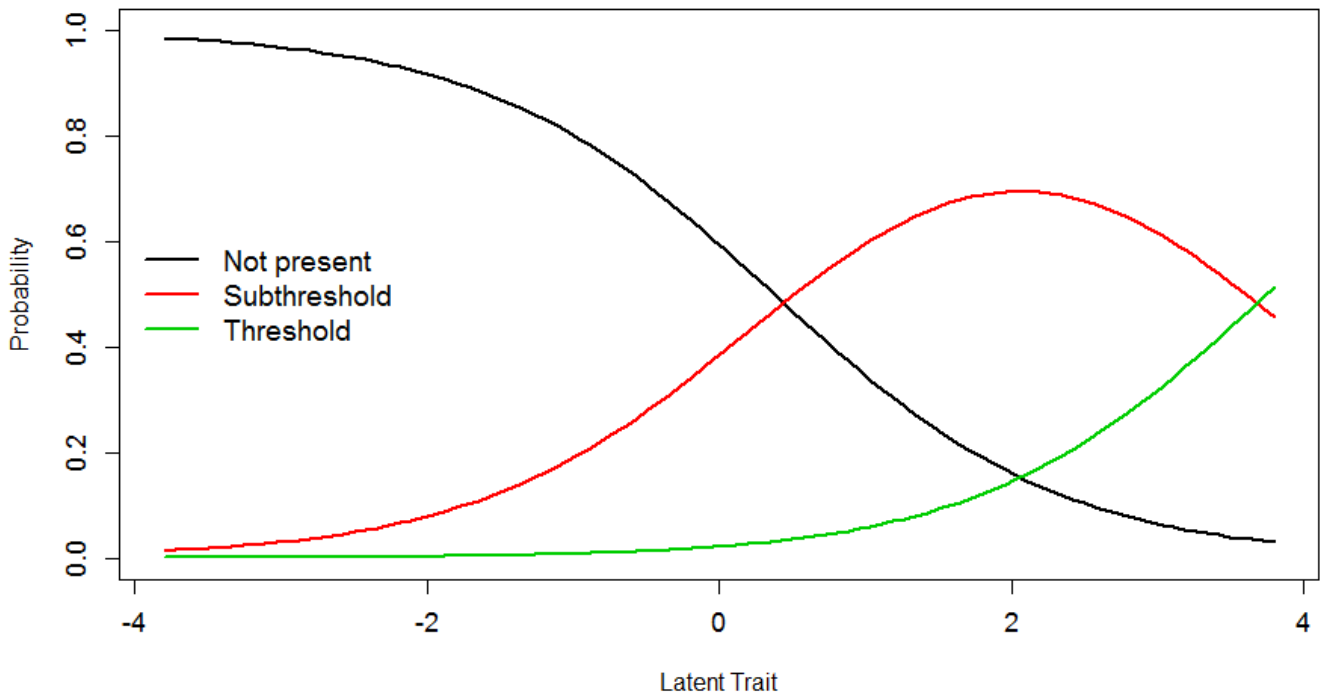


**Item Response Category Characteristic Curves - Item: Dx14\_Social\_Withdrawal**

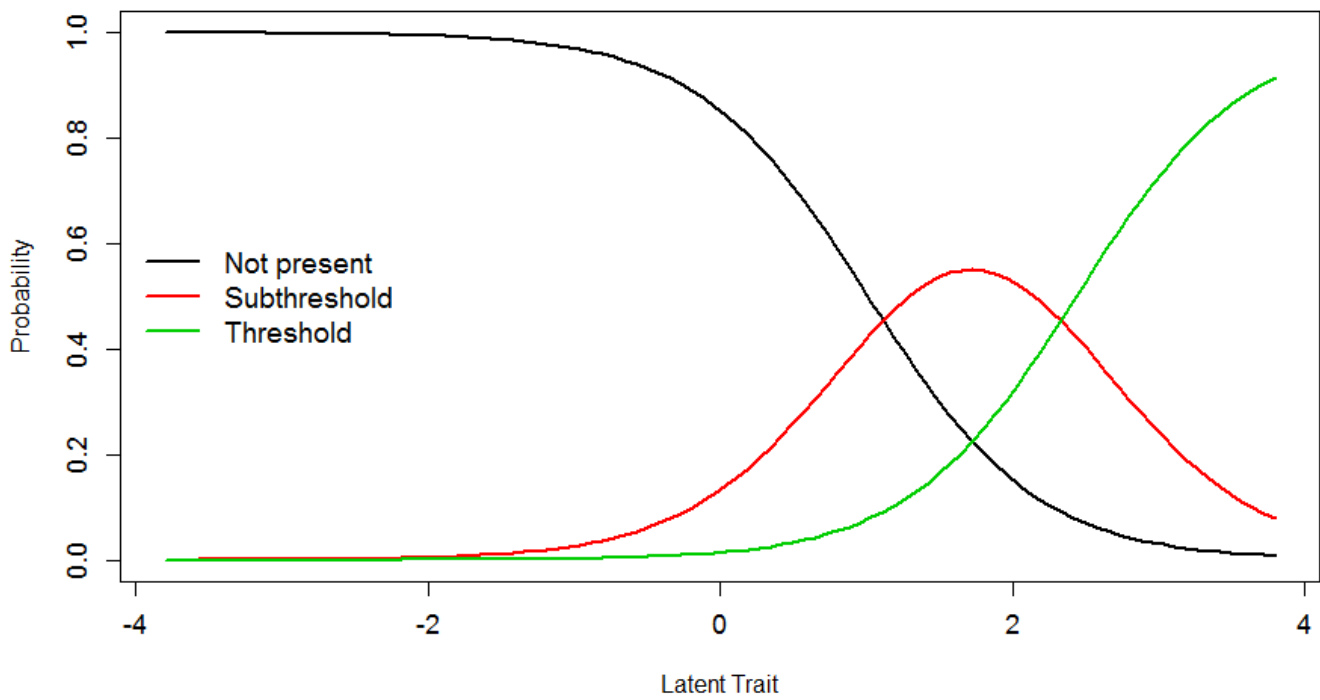


**APPENDIX C: Category Response Curves Depression continued**

**Item Response Category Characteristic Curves - Item: Dx15\_Insomnia**



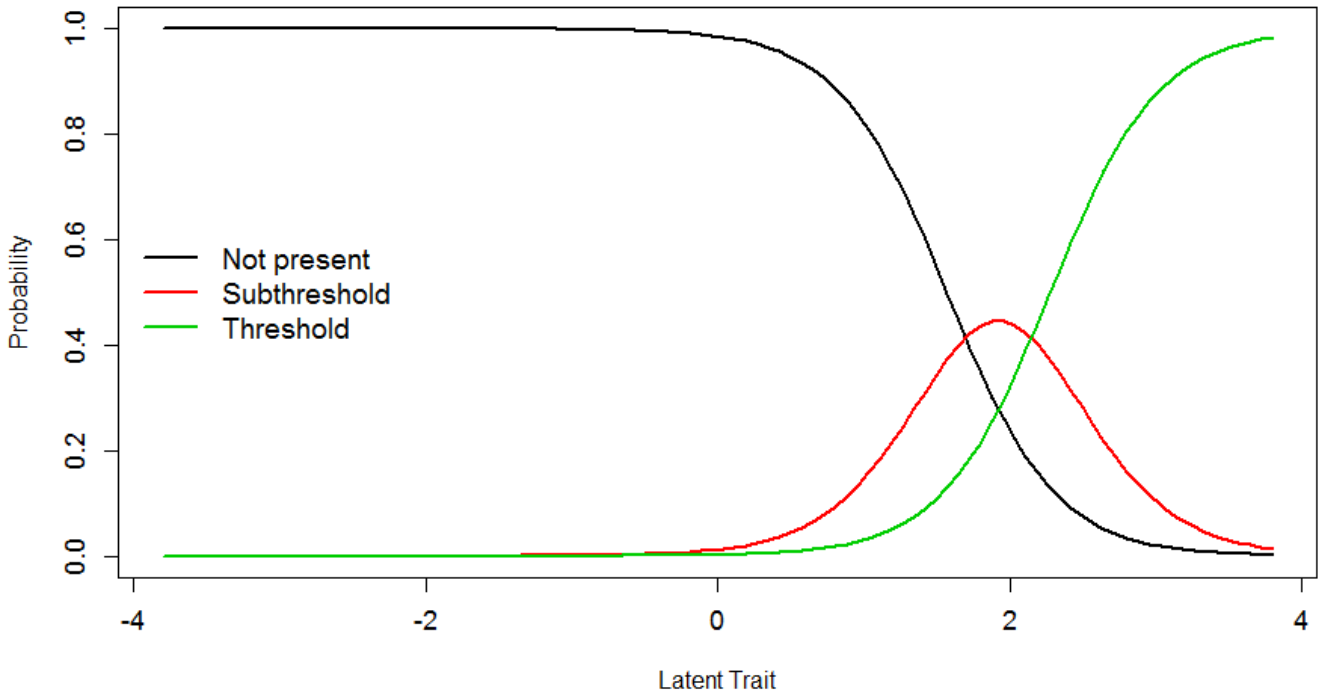
**Item Response Category Characteristic Curves - Item: Dx18\_Anorexia**



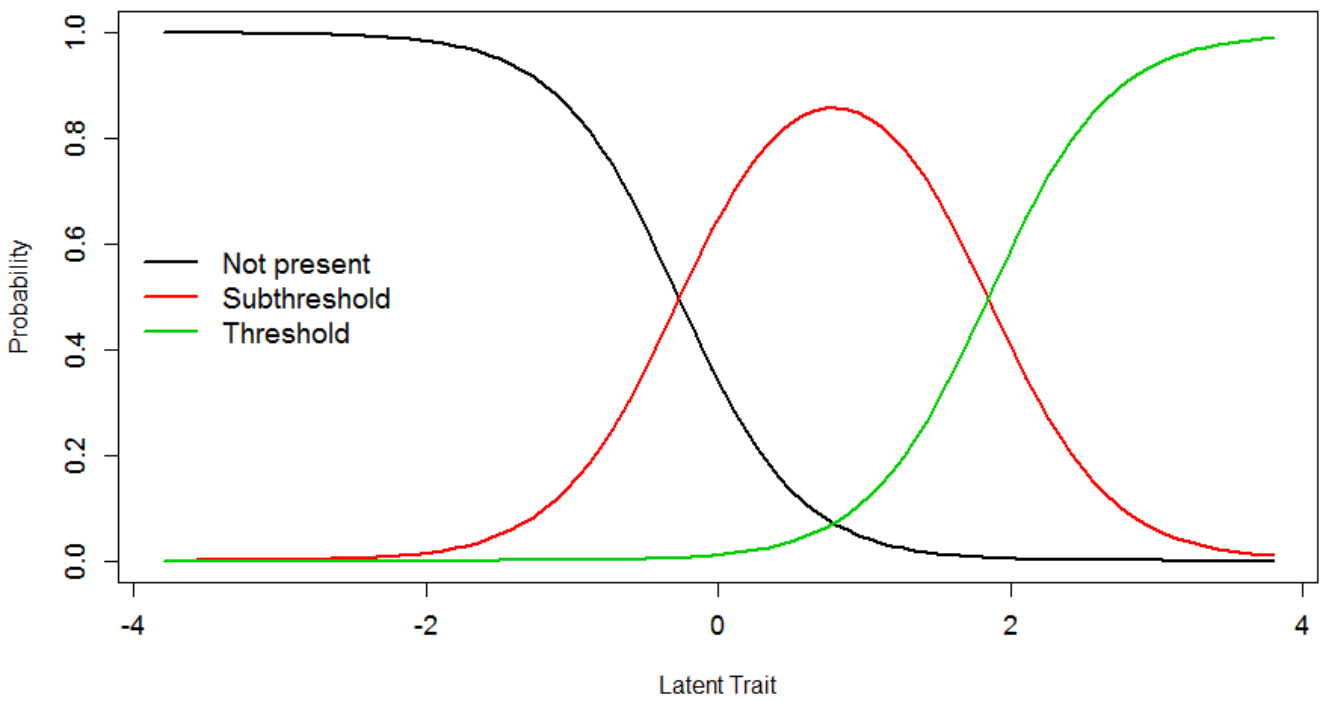


**APPENDIX C: Category Response Curves Depression continued**

**Item Response Category Characteristic Curves - Item: Dx23\_Leadene\_Paralysis**

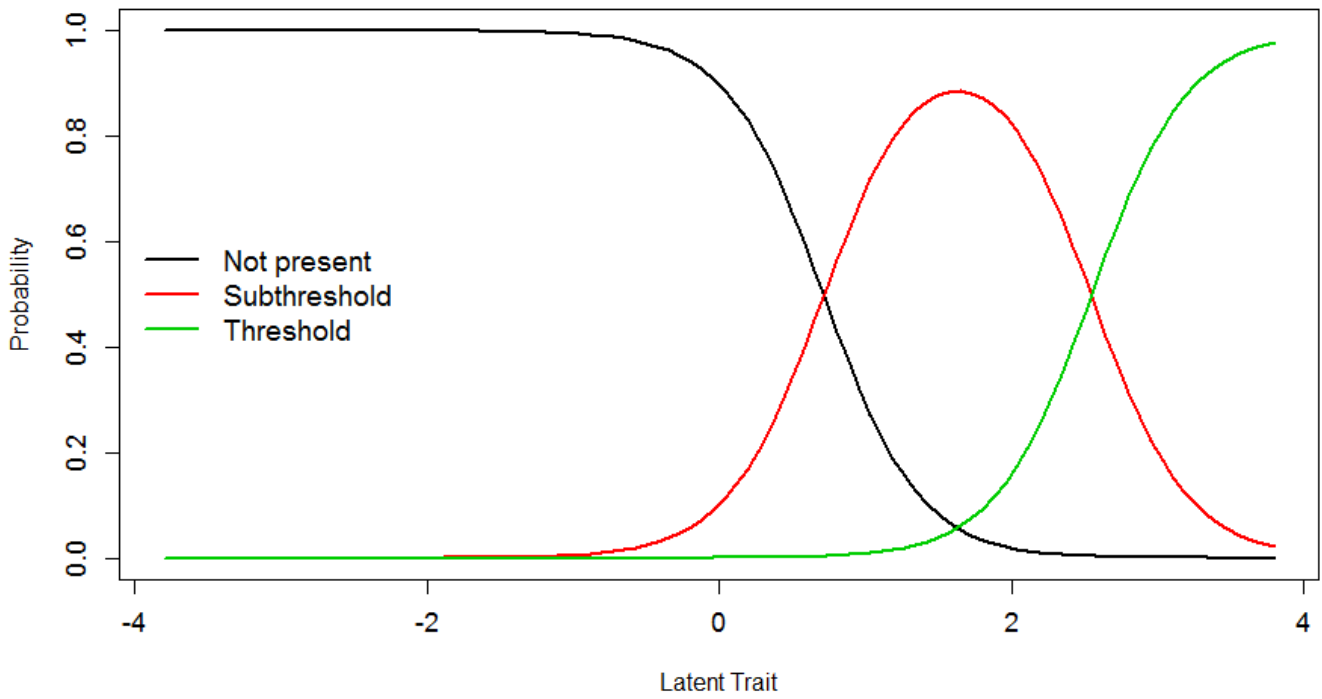


**Item Response Category Characteristic Curves - Item: Dx24\_RejectionSensitivity**

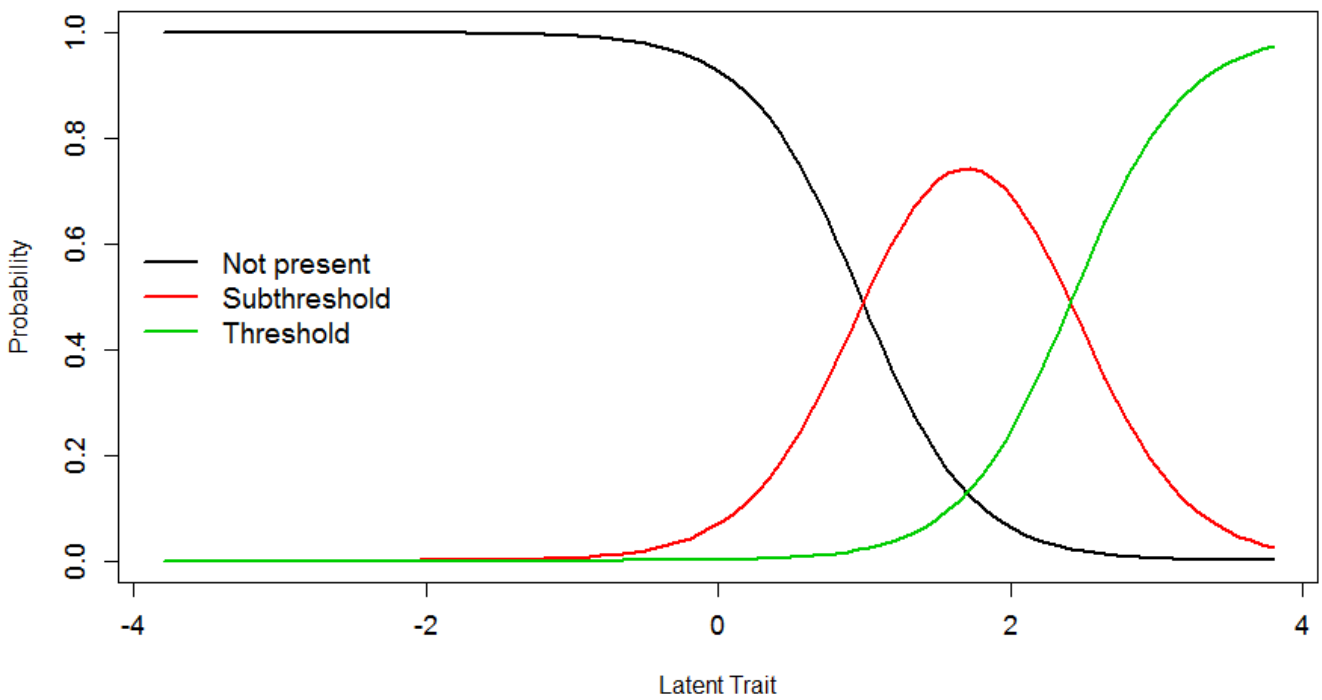


**APPENDIX C: Category Response Curves Depression continued**

**Item Response Category Characteristic Curves - Item: Dx25\_Thoughts\_Death**

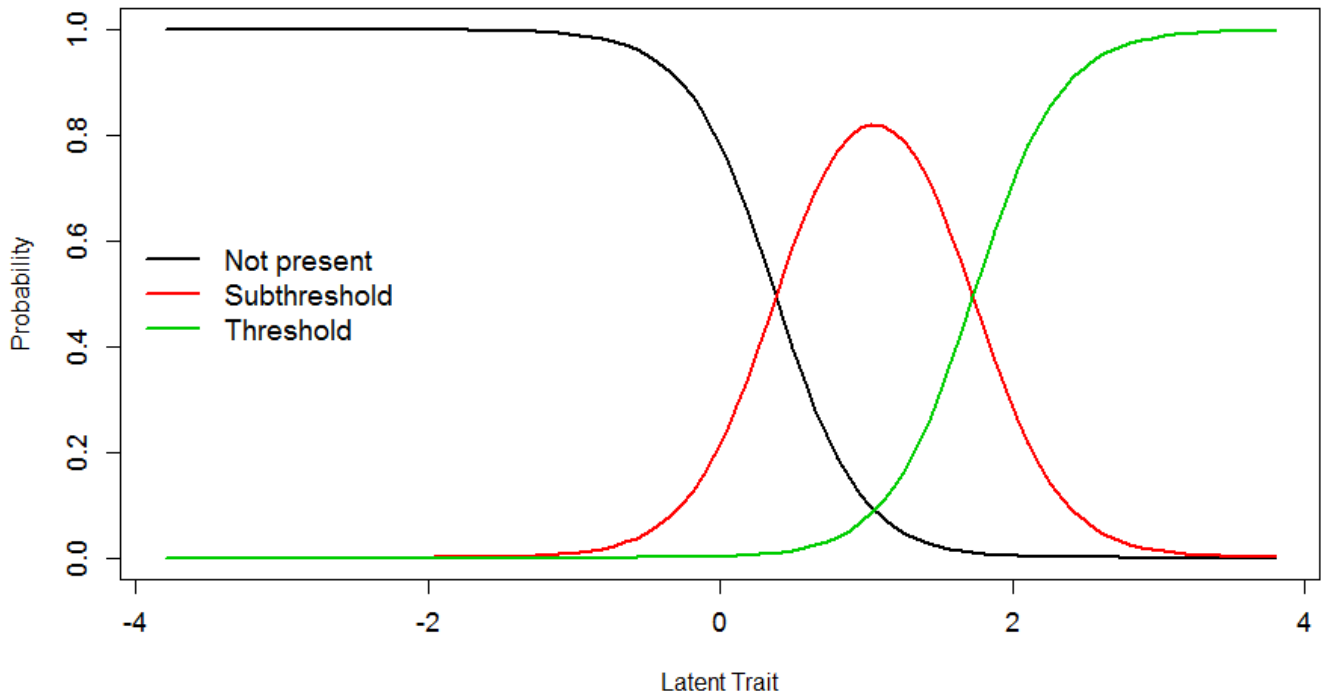


**Item Response Category Characteristic Curves - Item: Dx26\_Suicide\_Ideation**

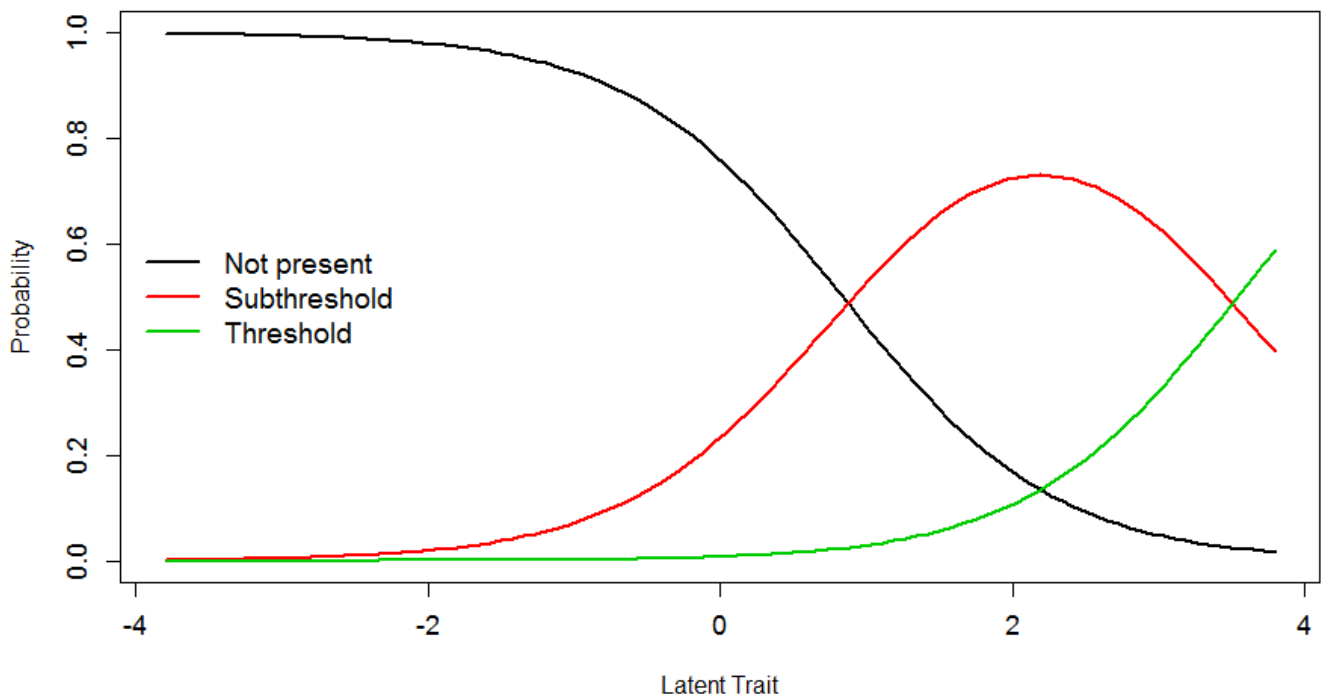


**APPENDIX D: Category Response Curves Mania**

**Item Response Category Characteristic Curves - Item: Mx1\_ElevatedMood**

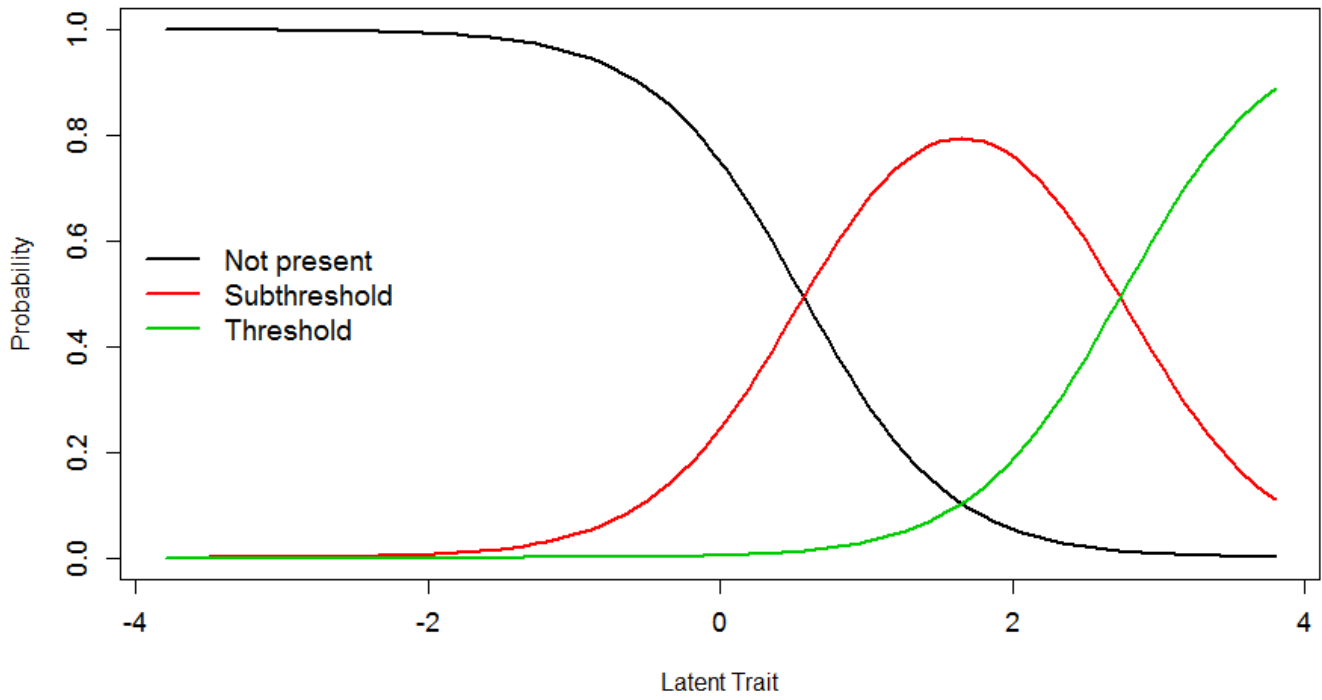


**Item Response Category Characteristic Curves - Item: Mx2\_Irritability**

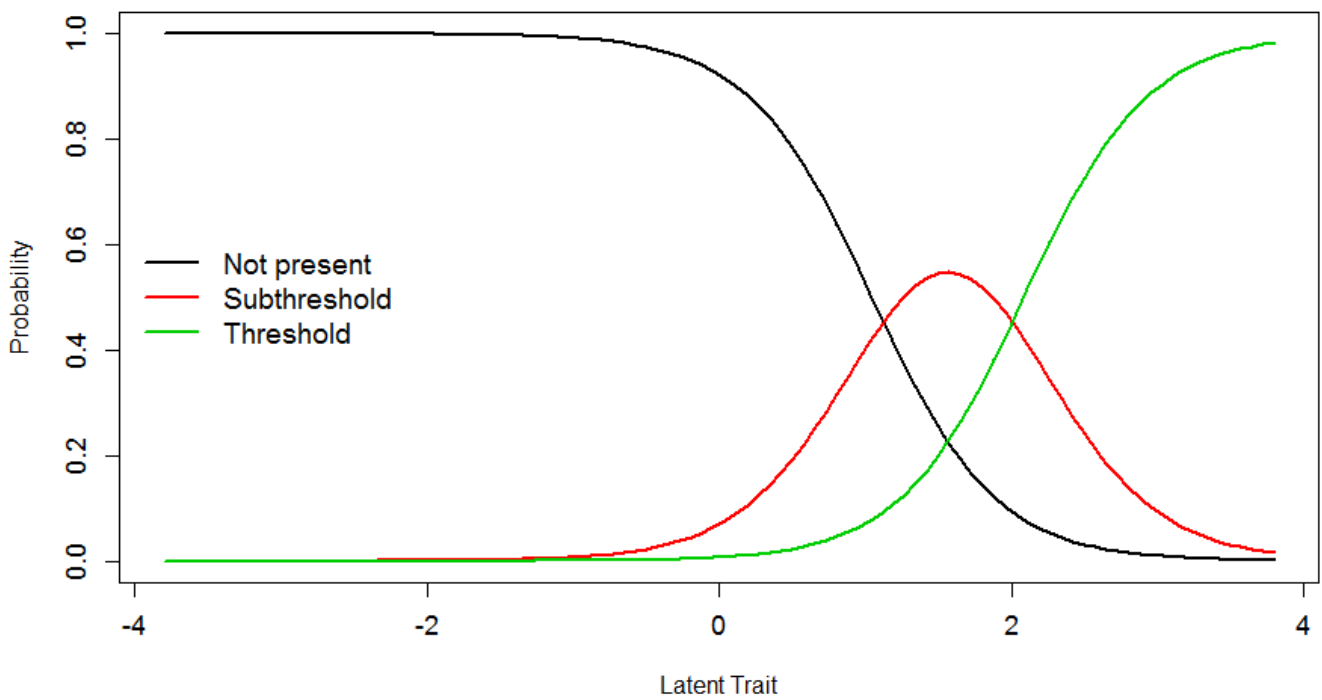


**APPENDIX D: Category Response Curves Mania continued**

**Item Response Category Characteristic Curves - Item: Mx3\_Mood\_Lability**

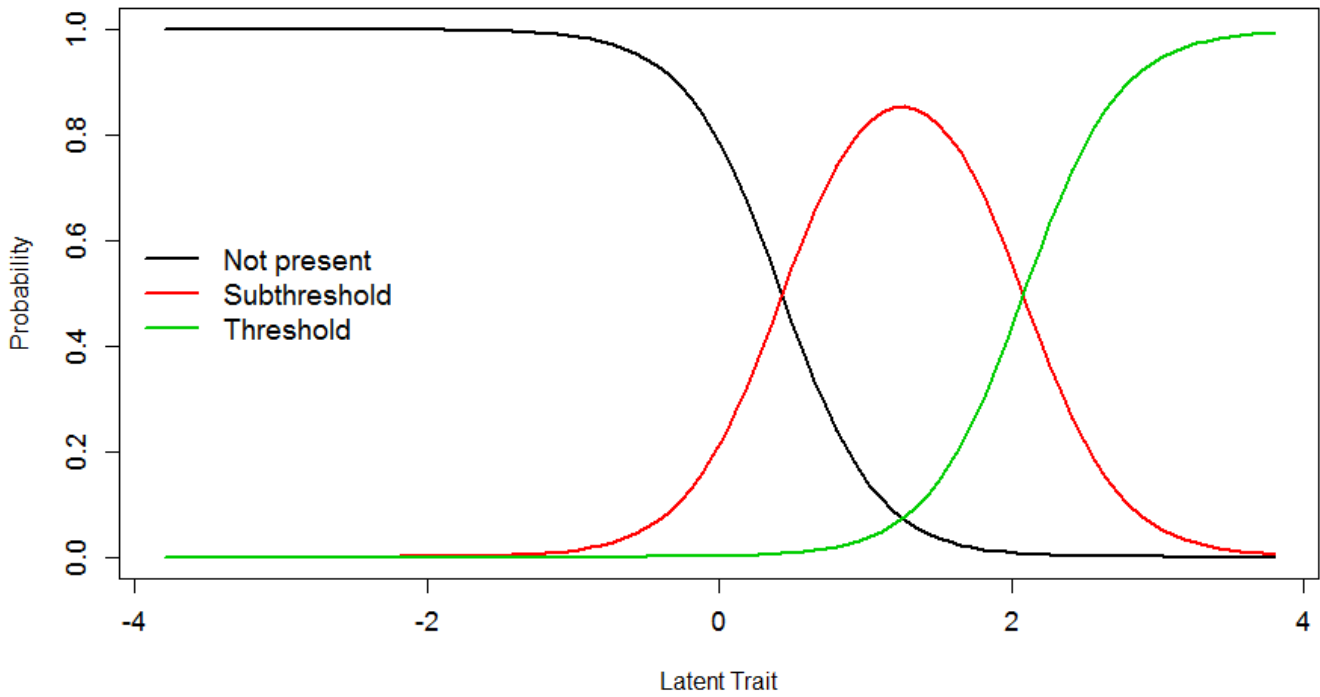


**Item Response Category Characteristic Curves - Item: Mx4\_Deceased\_Sleep**

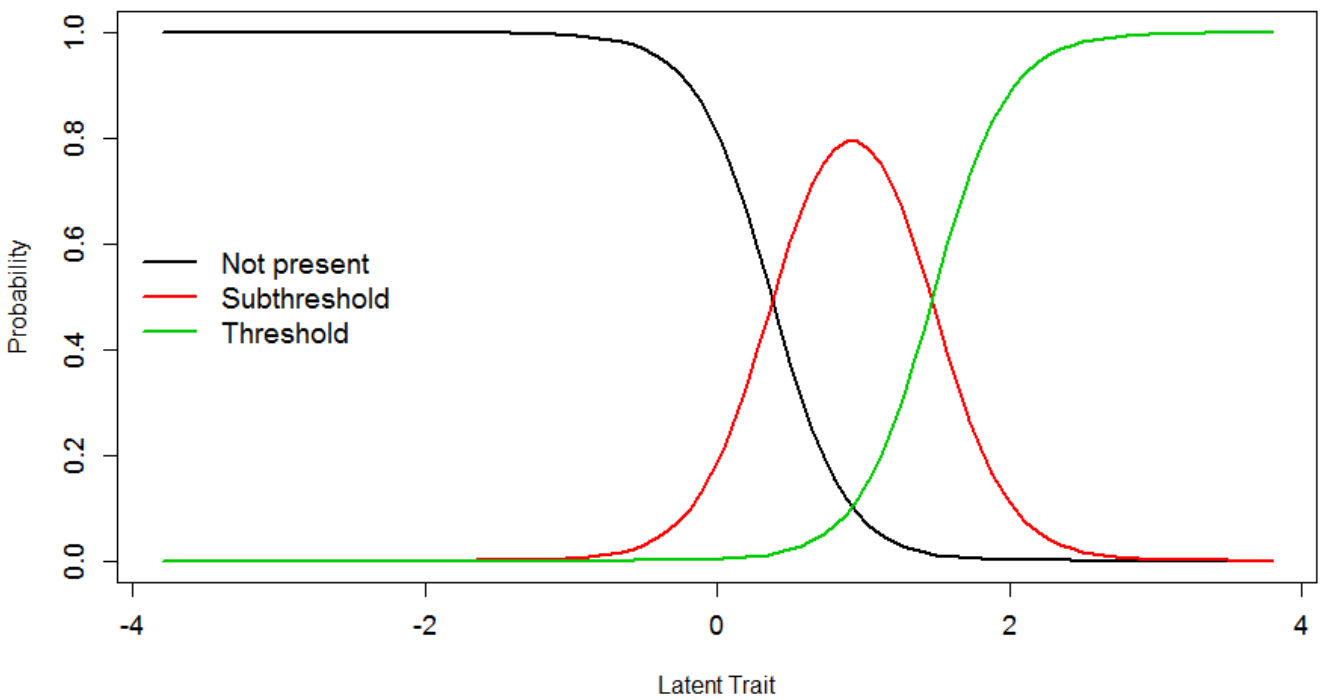


**APPENDIX D: Category Response Curves Mania continued**

**Item Response Category Characteristic Curves - Item: Mx5\_Racing\_Thoughts**

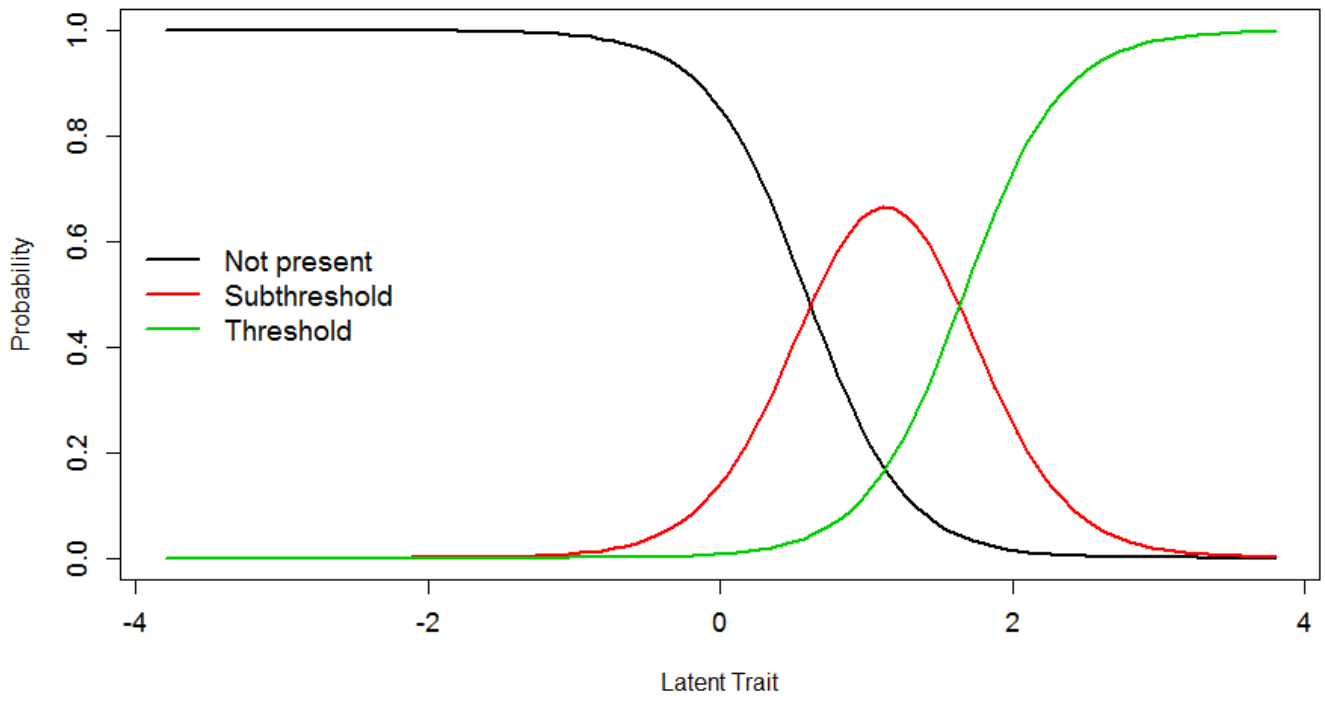


**Item Response Category Characteristic Curves - Item: Mx6\_Energetic**

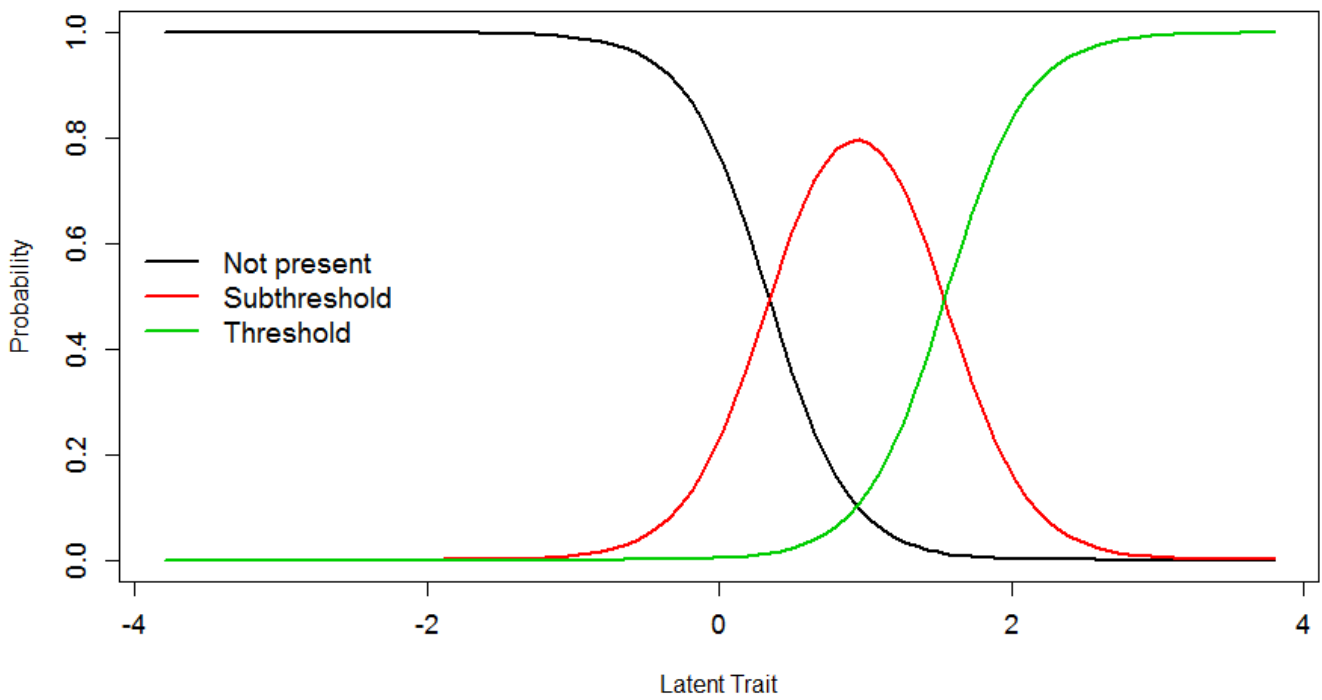


*APPENDIX D: Category Response Curves Mania continued*

Item Response Category Characteristic Curves - Item: Mx7\_Increased\_GoalActivity

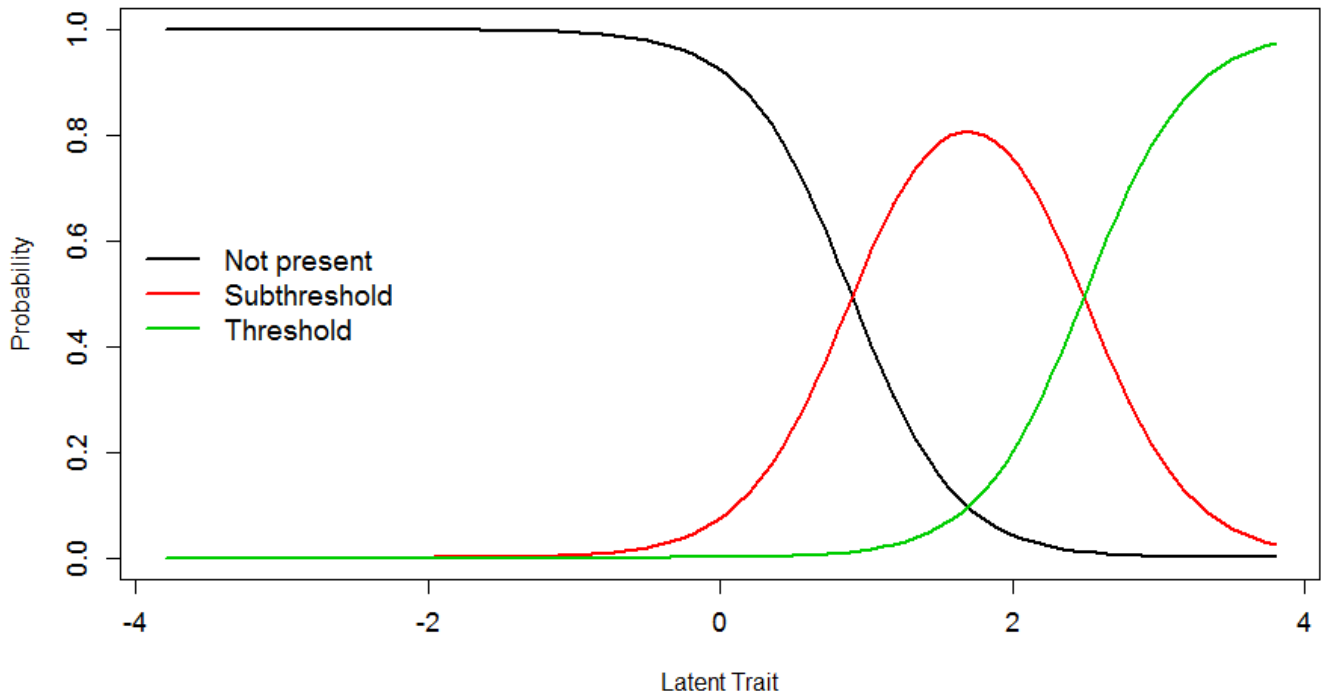


Item Response Category Characteristic Curves - Item: Mx8\_Hyperactivity

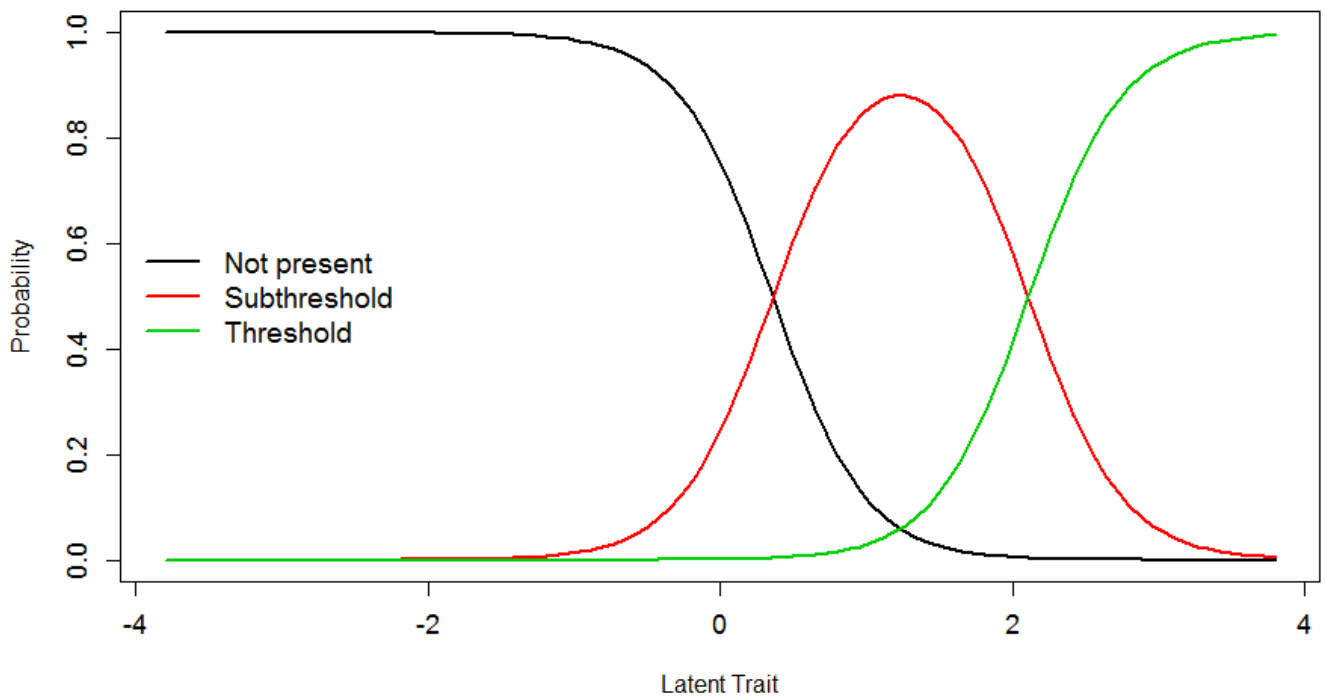


**APPENDIX D: Category Response Curves Mania continued**

**Item Response Category Characteristic Curves - Item: Mx9\_Grandiosity**

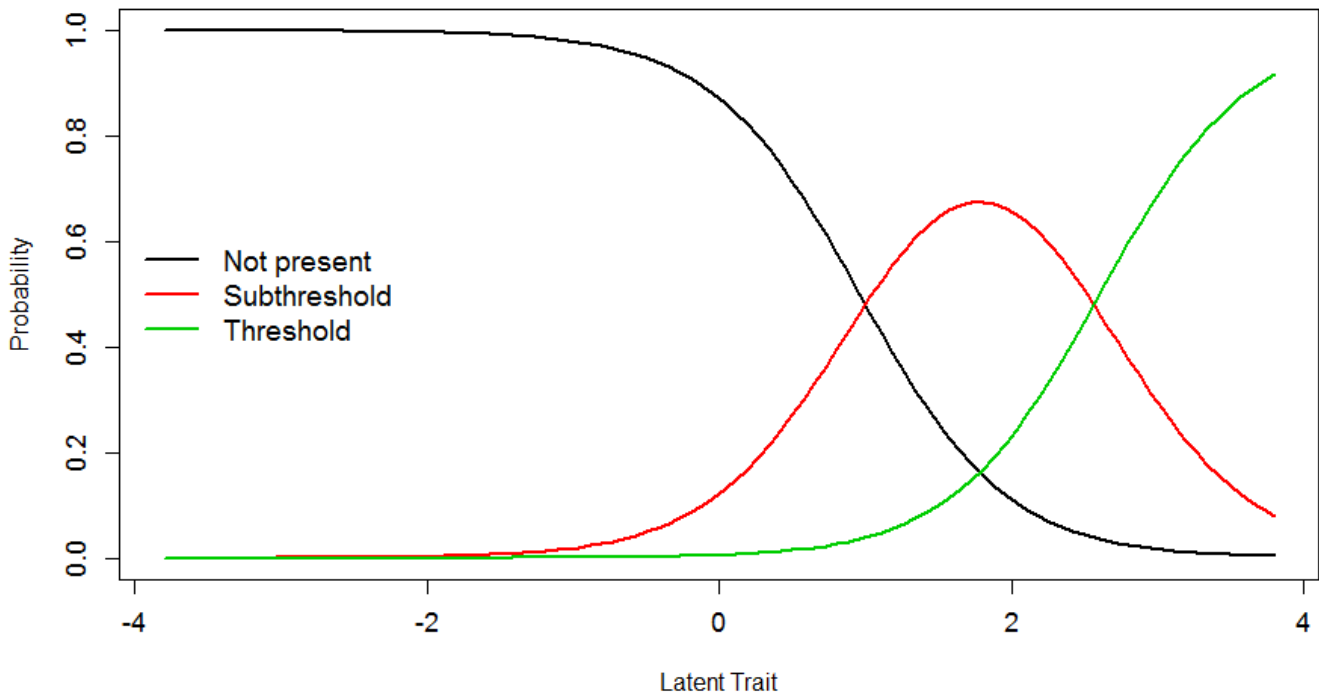


**Item Response Category Characteristic Curves - Item: Mx10\_Pressured\_Speech**

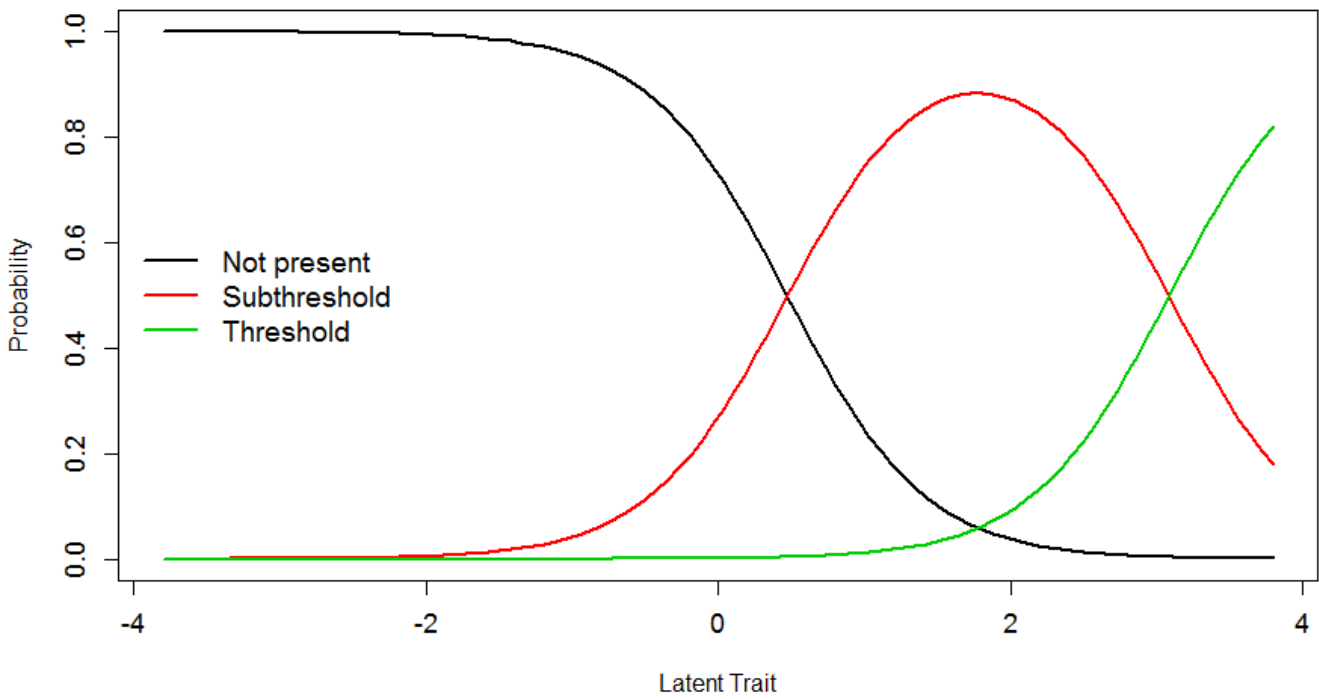


**APPENDIX D: Category Response Curves Mania continued**

**Item Response Category Characteristic Curves - Item: Mx12\_Poor\_Judgement**



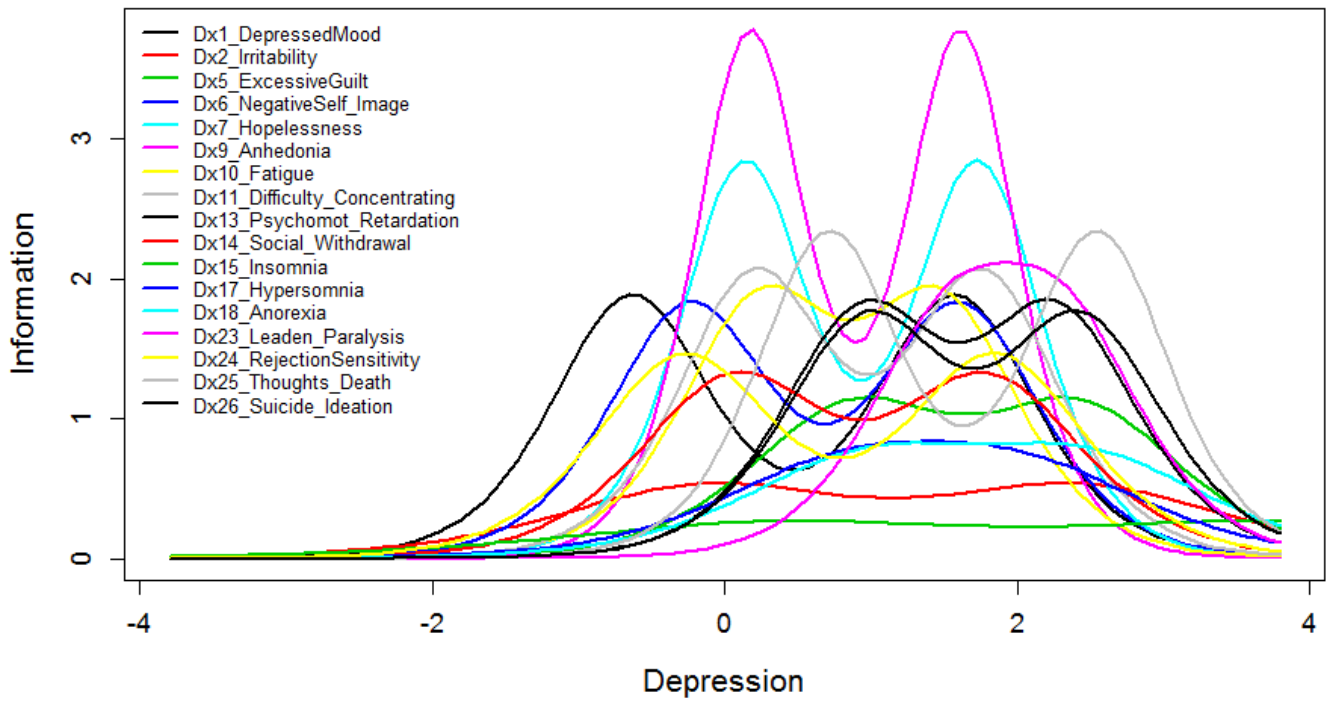
**Item Response Category Characteristic Curves - Item: Mx18\_Distractibility**



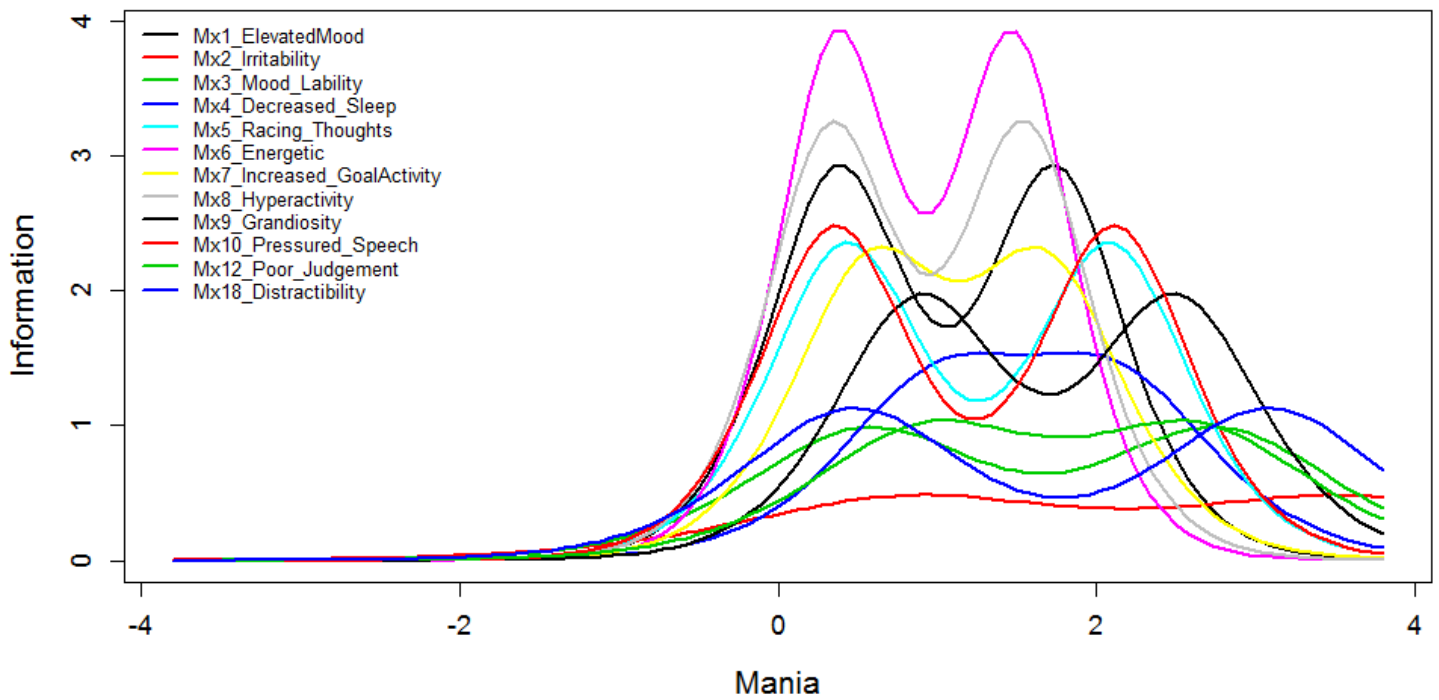


**APPENDIX E: Item Information Curves**

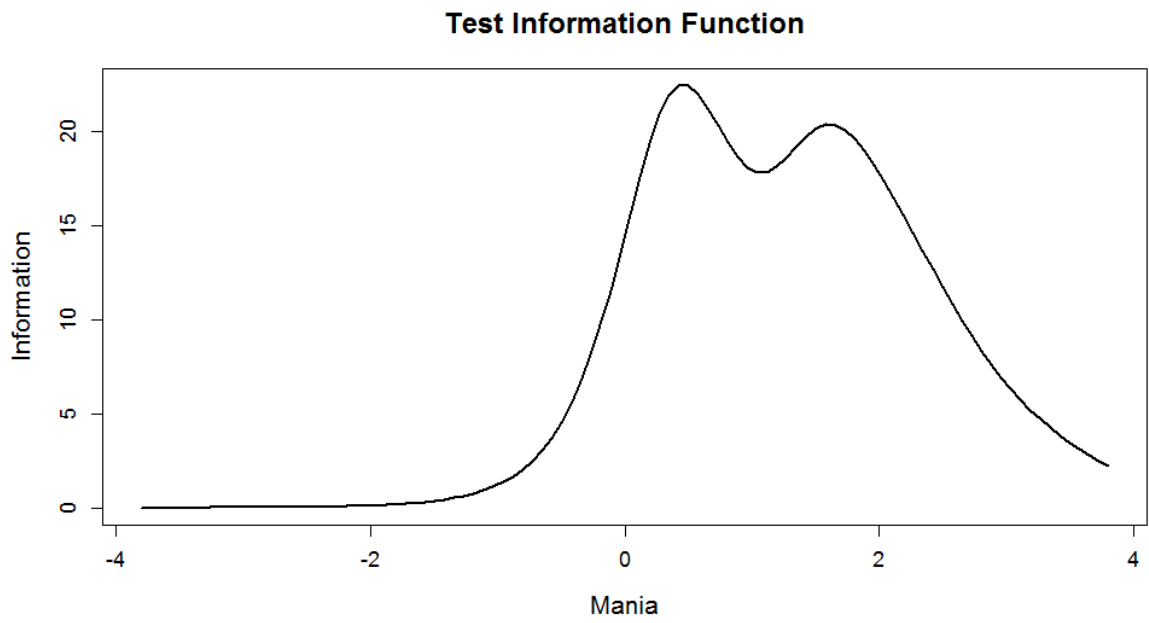
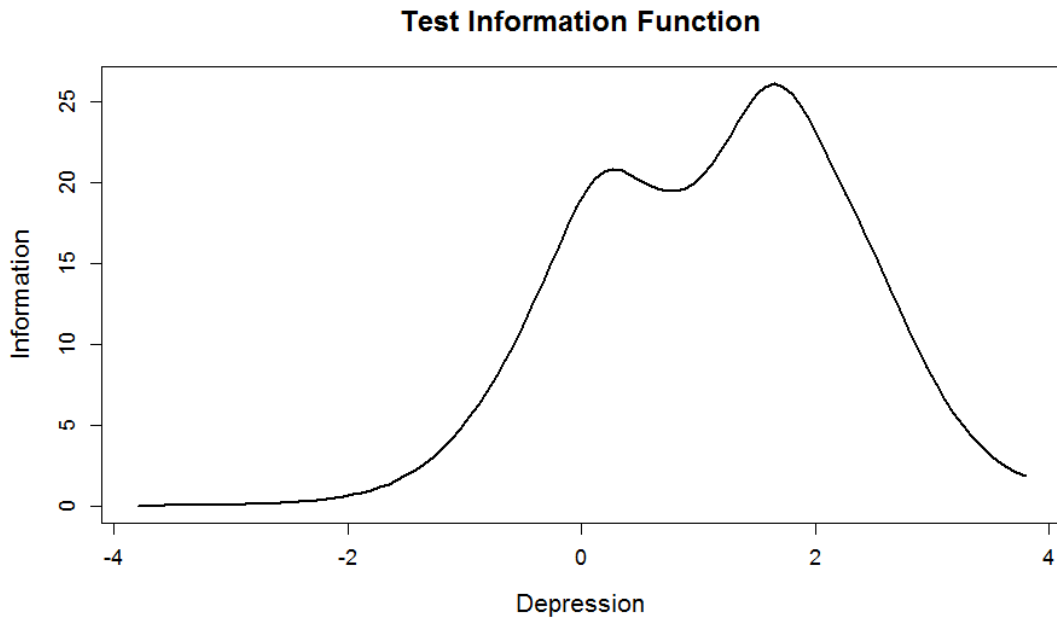
**Item Information Curves**



**Item Information Curves**



**APPENDIX F: Test Information Curves**



## ***APPENDIX G: Example Script for IRT analysis – Depression variables***

(# denotes description of what the subsequent script does)

```
# open library for read command
```

```
library(foreign)
library(ltm)
```

```
#read the spss file to access data
```

```
KSADS <- read.spss("R:\Data\SPSS Files\Separated Data Files for IRT\KSADS_IRT_Depression.sav", use.value.labels = TRUE,
to.data.frame = TRUE)
```

```
#create a dataset using chosen variables
```

```
Myvars_depression <- KSADS[c("Dx1_DepressedMood", "Dx2_Irritability", "Dx5_ExcessiveGuilt", "Dx6_NegSelf_Image",
"Dx7_Hopelessness", "Dx9_Anhedonia", "Dx10_Fatigue", "Dx11_DiffConcentrate", "Dx13_PsychomotRetardation",
"Dx14_SocialWithdrawal", "Dx15_Insomnia", "Dx17_Hypersomnia", "Dx18_Anorexia", "Dx23_LeadParalysis",
"Dx24_RejectionSensitive", "Dx25_ThoughtsDeath", "Dx26_Suicidal_Ideation", "Dx30_SelfHarm")]
```

```
#fit GRM to that dataset
```

```
Fit1 <- grm(Myvars_depression)
```

```
#Show coefficients / results of grm analysis
```

```
Fit1
```

```
#Produce graphics and information statistics from GRM analysis
```

```
par(mfrow = c(1, 1))
```

```
plot(Fit1, type = "IIC", lwd = 2, cex = 1.2, legend = TRUE, cx = "topleft", xlab = "Depression", cex.main = 1.5, cex.lab = 1.3, cex.axis = 1.1)
```

```
plot(Fit1, type = "IIC", items = 0, lwd = 2, xlab = "Depression", cex.main = 1.5, cex.lab = 1.3, cex.axis = 1.1)
```

```
plot(Fit1, lwd = 2, cex = 1.2, legend = TRUE, cx = "left", xlab = "Latent Trait", cex.main = 1.5, cex.lab = 1.3, cex.axis = 1.1)
```

```
info1 <- information(Fit1, c(-4, 0))
```

```
info2 <- information(Fit1, c(0, 4))
```

```
text(-1.9, 8, labels = paste("Information in (-4, 0):", paste(round(100 * info1$PropRange, 1), "%", sep = ""), "\n\nInformation in (0, 4):", paste(round(100 * info2$PropRange, 1), "%", sep = "")), cex = 1.2)
```

```
information(Fit1, c(-4, 4), items = c(1))
```

```
information(Fit1, c(-4, 4), items = c(2))
```

```
information(Fit1, c(-4, 4), items = c(3))
```

```
information(Fit1, c(-4, 4), items = c(4))
```

```
information(Fit1, c(-4, 4), items = c(5))
```

```
information(Fit1, c(-4, 4), items = c(6))
```

```
information(Fit1, c(-4, 4), items = c(7))
```

```
information(Fit1, c(-4, 4), items = c(8))
```

```
information(Fit1, c(-4, 4), items = c(9))
```

```
information(Fit1, c(-4, 4), items = c(10))
```

```
information(Fit1, c(-4, 4), items = c(11))
```

```
information(Fit1, c(-4, 4), items = c(12))
```

```
information(Fit1, c(-4, 4), items = c(13))
```

```
information(Fit1, c(-4, 4), items = c(14))
```

```
information(Fit1, c(-4, 4), items = c(15))
```

```
information(Fit1, c(-4, 4), items = c(16))
```

```
information(Fit1, c(-4, 4), items = c(17))
```

```
information(Fit1, c(-4, 4), items = c(18))
```



**UNSW**  
AUSTRALIA

Psychiatry  
Medicine

PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM

***Bipolar Kids and Sibs Study***

Approval No (HREC 09097)

THE UNIVERSITY OF NEW SOUTH WALES

**PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM**

Below are some questions that you might like to ask about the study. We will happily explain further or answer any other questions that you might have.

*What is the study about?*

- ▶ You are being invited to take part in a longitudinal study to examine the genetic and environmental risk factors for bipolar disorder.
- ▶ We hope to learn about risk factors for bipolar disorder and use this data to develop better ways to intervene early in those at risk for bipolar disorder.

*Why have I been asked to take part?*

You were selected as a possible participant in this study because either you or a member of your family has a history of bipolar disorder.

*How long does the study last?*

Identifying risk factors requires information to be collected over many years and so we would like to keep in contact with you for 5 – 10 years. Over that period we will get in touch every 12 months and ask you some questions.

*What are you asking me to do?*

- ▶ We will be interviewing you to find out about symptoms you experience now and also those you may have experienced when you were younger.
- ▶ You will also be asked to undertake a mood interview, fill in some self-report questionnaires (you will be given the option of completing these questionnaires online), complete a series of simple neuropsychological computerised tasks, give some blood, and undertake a brain scan.
- ▶ After the initial interview we would like to contact you every 12 months to do shorter assessments.
- ▶ So the first thing we need is your permission to use these assessments in our research.

### *How long will it take?*

- ▶ The initial assessment will be conducted in a morning and afternoon session over the course of a day, or over two days if preferred.
- ▶ The questions to be done every 12 months will take approximately 3-4 hours.

### *Genetic testing*

- ▶ The genetic testing will only be done once. We will take 20 ml of blood from a vein in your arm.
- ▶ The blood will be used to look for genes that may increase your risk of developing bipolar disorder. As it is now considered likely that many genes – which each individually play a small role – are involved together in causing bipolar disorder, we will test for many genes at once when we analyse your blood sample.
- ▶ When researchers understand how genes are involved in the development of bipolar disorder they have a better chance of designing better methods to diagnose, treat or cure that disease.

### *Brain imaging*

- ▶ We will be inviting some of the participants to be involved in a brain imaging study. If you are asked to be involved in this, you will be provided with a separate information sheet and consent form.

### *What will you be asking me every 12 months?*

There will be an interview asking you about any symptoms you have experienced over the previous twelve months. You will also complete some self-report questionnaires and sometimes a series of neuropsychological tests. The questions are a lot like the ones you are answering for the first assessment.

### *What are the advantages and disadvantages of being involved in the study?*

- ▶ We don't anticipate any risks to you from being involved in the study. However, we acknowledge that the assessments are lengthy and that involvement in the study will mean setting aside time to complete them.
- ▶ The main advantage is early detection of any symptoms of bipolar disorder or psychosis. If we notice symptoms we can help you get the appropriate treatment.
- ▶ The blood draw may cause some mild discomfort or bruising.

### *How is the blood sample used?*

- ▶ The blood sample will be submitted to Genetic Repositories Australia (GRA), a research resource located at Neuroscience Research Australia, for subsequent processing. Your sample will be de-identified and only be tracked by a code number.
- ▶ Genetic material will be extracted from your blood sample. In order to ensure ongoing source of DNA, white blood cells (lymphocytes) are cultured and kept growing in the laboratory as a cell line, which allows a source of genetic material without having to obtain another blood sample. These cell lines can be stored indefinitely.
- ▶ GRA collects, stores, and distributes DNA samples and cell lines. All researchers wishing to access the genetic material stored by GRA must first have approval from the relevant Human Research

Ethics Committee for their projects. Those researchers must then apply in writing to the GRA Management Committee, describing the intended use for the samples for approval for access to the samples. Researchers may be from non-profit research institutes, universities, etc or from commercial organisations from Australia or overseas.

- ▶ Research using your blood, in combination with samples from many other people, may result in discoveries that could lead to commercial developments. These developments may include new understanding about the cause of the disease, new diagnostic tests, new treatments, and new ways to prevent diseases. In this respect, it should be noted that it is the whole collection of many samples that is of value and that each individual sample probably has no commercial value on its own. You agree to waive any future claim to ownership rights for financial benefit through participation in this research.

#### *Issues about online data entry for self-report questionnaires*

- ▶ The security of your personal information is important to us. We use a third party web-based service operated by QuestionPro in the USA for conducting surveys. The data remains controlled by us. QuestionPro follows generally accepted industry standards to protect personal information and uses secure socket layer technology. More information on QuestionPro and their Privacy Policy is available on their website at [www.questionpro.com](http://www.questionpro.com). However, no method of transmission over the internet, or method of electronic storage is 100% secure. Therefore, while we strive to use commercially acceptable means to protect your personal information, we cannot guarantee its absolute security.
- ▶ By using this service you understand that we use the QuestionPro service and consent to the transfer of relevant data to the USA based system. We also encourage you to take responsibility for the security of your own computer system.

#### *Who gets told how I answer the questions?*

- ▶ The researcher who asks you questions will know, but they will keep all information confidential.
- ▶ When we do our research your name and your answers are kept apart, so no one except the researcher responsible for you can find out.
- ▶ Apart from that we don't tell anyone else (unless the law requires us to).

#### *What if I change my mind and don't want to go on with the study?*

- ▶ That's OK. You can pull out of the study at any time — just sign the form and tell us.
- ▶ If you decide to withdraw from the study, GRA will follow the directions of the Chief Investigator to either destroy your sample or to allow your sample to continue to be used based on your decision as detailed in the attached revocation of consent form.

#### *So it is all confidential?*

- ▶ Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission, except as required by law.
- ▶ All clinical details — and any other confidential information we collect — will be available only to the member of the research team responsible for you.
- ▶ Blood samples will be given a unique identification number to protect your privacy. Genetic Repositories Australia will not give out any personal information that can identify you to the scientists who are approved to receive the samples.

► If you give us your permission by signing this document, we plan to discuss/publish the results at scientific conferences and in scientific journals. In any discussion or publication, information will be provided in such a way that you cannot be identified.

*Can I complain about the study?*

Complaints may be directed to the:

Ethics Secretariat,  
The University of New South Wales,  
SYDNEY 2052 AUSTRALIA  
Phone 9385 4234, Fax 9385 6648, email [ethics.sec@unsw.edu.au](mailto:ethics.sec@unsw.edu.au).

Any complaint you make will be treated in confidence and investigated, and you will be informed of the outcome.

*What if the questions upset me?*

If you find that the questioning is upsetting or if you just want to talk about the questions, please call Gloria Roberts on 1800 352 292. So that we can ensure your usual GP or psychiatrist is urgently informed on your condition we will need you to provide us with emergency contact details for these doctors.

*Why do I have to sign a consent form?*

It is important that no research is done without your permission — and we have to be able to prove that you said “yes.”

*Tell me again what I am consenting to.*

By signing the **Consent Form** you are giving us permission to

1. Use the answers from your assessment in our research; **and**
2. Contact you every 12 months over the next 5-10 years, ask you some more questions, and use those answers in our research.

### **Your consent**

Your decision whether or not to participate will not prejudice your future relations with The University of New South Wales. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without prejudice.

If you have any questions, please feel free to ask us. If you have any additional questions later Gloria Roberts will be happy to answer them (Ph 1800 352 292, email [bipolar-kidsandsibs@unsw.edu.au](mailto:bipolar-kidsandsibs@unsw.edu.au) ).

You will be given a copy of this form to keep.

**Please tick and initial each part of the study procedures to show your agreement to participate. If you do not wish to participate in a specific procedure simply do not tick or initial it.**

	Yes	No	Initials
I consent to my information being entered as part of the study records	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
I consent to provide a blood sample for genetic testing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
I consent to be contacted every 12 months for a period of 5-10 years	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
I consent to be contacted regarding future studies of bipolar disorder	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

*Sharing data across studies of bipolar disorder and mental illness allows for researchers to pool resources and make the most of our data, maximising the benefits of the research. Research studies conducted by the Australian Schizophrenia Research Bank (ASRB) or the Sydney Bipolar Disorders Clinic at the Black Dog Institute, use the same cognitive and genetic analyses that we are conducting. Do you give us permission to share your de-identified data (i.e. no name, address or other identifying information will be provided) with these researchers?*

	Yes	No	Initials
I consent to have my de-identified (cognitive/genetic/MRI) data, made available for use in research by other studies approved by the UNSW human research ethics committee.		<input type="checkbox"/>	<input type="text"/>
I would be interested in receiving information via mail or email about other potential mental health research studies. I understand that this would not oblige me to take part in these studies.		<input type="checkbox"/>	<input type="text"/>

**In providing a blood sample, I understand that the following is involved:**

- Blood samples will be collected for DNA extraction and/or generation of cell lines for research, and that my sample will be processed and stored by Genetic Repositories Australia
- My samples will be stored indefinitely
- My non-identifiable samples may be shared with approved researchers from academic institutions or companies from Australia or internationally
- Data gathered from my sample may be published, provided that I cannot be identified
- I will not receive any routine results
- I will not receive any financial benefit from my participation
- I will not receive or be able to claim any payment, compensation, royalty or any other financial benefit which may result from this research
- Should I wish to withdraw from the study and have my samples destroyed, I may do so by contacting Professor Mitchell
- In the event that any clinically significant result is found that has a significant probability of impacting on my health or that of my children, I wish to be advised how to access that information through established medical channels which will include genetic counselling and information provision via an appropriate clinical specialist:.....

YES	NO	Initials
<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>



**PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM (continued)**

***Bipolar Kids and Sibs Study***

**You are making a decision whether or not to participate. Your signature indicates that, having read the Participant Information Statement, you have decided to take part in the study.**

.....

Signature of Research Participant

.....

Signature of Witness

.....

(Please PRINT name)

.....

(Please PRINT name)

.....

Date

.....

Nature of Witness

.....

Signature(s) of Investigator(s)

.....

Please PRINT Name



**REVOCAION OF CONSENT**

***Bipolar Kids and Sibs Study***

I hereby wish to **WITHDRAW** my consent to participate in the research proposal described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with The University of New South Wales.

I hereby wish to withdraw my consent to participate in the study.

Tick and initial which aspects of the study you wish to withdraw from:

	Yes	No	Initials
1. I request that I no longer be contacted regarding this research but I agree that the data and samples already collected to continue to be used	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
2. I request that my data and blood sample be destroyed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

.....

Signature

.....

Date

.....

Please PRINT Name

The section for Revocation of Consent should be forwarded to **Professor Philip Mitchell**, The Black Dog Institute, Prince of Wales Hospital, RANDWICK NSW 2031.



**UNSW**  
AUSTRALIA

Psychiatry  
Medicine

PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM

***Bipolar Kids and Sibs Study***

Approval No (HREC 09097)

THE UNIVERSITY OF NEW SOUTH WALES

**INFORMATION STATEMENT AND CONSENT FORM**

**For parents to consent for 12-16 year old children**

*What is the study about?*

- ▶ Your child is being invited to take part in a longitudinal study to examine the genetic and environmental risk factors for bipolar disorder.
- ▶ We hope to learn about risk factors for bipolar disorder and use this data to develop better ways to intervene early in those at risk for bipolar disorder.

*Why has your child been asked to take part?*

Your child has been selected as a possible participant because your child has been diagnosed with bipolar disorder, or a parent or sibling of your child has been diagnosed with bipolar disorder.

*How long does the study last?*

Identifying risk factors requires information to be collected over many years and so we would like to keep in contact with your child for 5-10 years. Over that period we will get in touch every 12 months and ask your child some questions.

*What are you asking my child to do?*

- ▶ We will be interviewing your child to find out about symptoms they are currently experiencing and also any they may have experienced when they were younger. We may also ask you to participate in the interview.
- ▶ Your child will be asked to undertake a mood interview, fill in some self-report questionnaires (you will be given the option of completing these questionnaires online), complete a series of simple neuropsychological computerised tasks, give some blood, and undertake a brain scan.
- ▶ After the initial interview we would like to contact your child every 12 months to do shorter assessments.
- ▶ So the first thing we need is your permission to use these assessments in our research.

*How long will it take?*

- ▶ The initial assessment will be conducted in a morning and afternoon session over the course of a day, or over two days if preferred.

- ▶ The assessment to be conducted every 12 months will take approximately 3-4 hours.

### *Genetic testing*

- ▶ The genetic testing will only be done once. We will take 20 ml of blood from a vein in their arm.
- ▶ The blood will be used to look for genes that may increase your child's risk of developing bipolar disorder. As it is now considered likely that many genes – which each individually play a small role – are involved together in causing bipolar disorder, we will test for many genes at once when we analyse your blood sample.
- ▶ When researchers understand how genes are involved in the development of bipolar disorder they have a better chance of designing better methods to diagnose, treat or cure that disease.

### *Brain imaging*

- ▶ We will be inviting some of the participants to be involved in a brain imaging study. If your child is asked to be involved in this, you will be provided with a separate information sheet and consent form.

### *What will you be asking my child every 12 months?*

- ▶ The interview asks them about any symptoms they have experienced over the previous twelve months. They also fill in some self-report questionnaires and sometimes complete some neuropsychological tests.

### *What are the advantages and disadvantages of my child being involved in the study?*

- ▶ We don't anticipate any risks to your child from being involved in the study. However, we acknowledge that the assessments are lengthy and that involvement in the study will mean setting aside time to complete them.
- ▶ The main advantage is early detection of any symptoms of bipolar disorder or psychosis. If we notice symptoms we can help your child get the appropriate treatment.
- ▶ The blood draw may cause some mild discomfort or bruising.

### *How is the blood sample used?*

- ▶ The blood sample will be submitted to Genetic Repositories Australia (GRA), a research resource located at Neuroscience Research Australia, for subsequent processing. Your child's sample will be de-identified and only be tracked by a code number.
- ▶ Genetic material will be extracted from your child's blood sample. In order to ensure ongoing source of DNA, white blood cells (lymphocytes) are cultured and kept growing in the laboratory as a cell line, which allows a source of genetic material without having to obtain another blood sample. These cell lines can be stored indefinitely.
- ▶ GRA collects, stores, and distributes DNA samples and cell lines. All researchers wishing to access the genetic material stored by GRA must first have approval from the relevant Human Research Ethics Committee for their projects. Those researchers must then apply in writing to the GRA Management Committee, describing the intended use for the samples for approval for access to the samples. Researchers may be from non-profit research institutes, universities, etc or from commercial organisations from Australia or overseas.

- ▶ Research using your child’s blood, in combination with samples from many other people, may result in discoveries that could lead to commercial developments. These developments may include new understanding about the cause of the disease, new diagnostic tests, new treatments, and new ways to prevent diseases. In this respect, it should be noted that it is the whole collection of many samples that is of value and that each individual sample probably has no commercial value on its own. You agree to waive any future claim to ownership rights for financial benefit through participation in this research.

*Issues about online data entry for self-report questionnaires*

- ▶ The security of your personal information is important to us. We use a third party web-based service operated by QuestionPro in the USA for conducting surveys. The data remains controlled by us. QuestionPro follows generally accepted industry standards to protect personal information and uses secure socket layer technology. More information on QuestionPro and their Privacy Policy is available on their website at [www.questionpro.com](http://www.questionpro.com). However, no method of transmission over the internet, or method of electronic storage is 100% secure. Therefore, while we strive to use commercially acceptable means to protect your personal information, we cannot guarantee its absolute security.
- ▶ By using this service you understand that we use the QuestionPro service and consent to the transfer of relevant data to the USA based system. We also encourage you to take responsibility for the security of your own computer system.

*Who sees the information my child provides?*

- ▶ The researcher who asks your child the questions will know, but they must keep all information confidential.
- ▶ When we do our research your child’s name and answers are kept apart, so no one except the researcher responsible for them can find out.
- ▶ Apart from that we don’t tell anyone else (unless the law requires us to).

*What if I change my mind and don’t want them to go on with the study?*

- ▶ That’s OK. You can pull your child out of the study at any time — just sign the form and tell us.
- ▶ If you decide to withdraw your child from the study, GRA will follow the directions of the Chief Investigator to either destroy your child’s sample or to allow your child’s sample to continue to be used based on your decision as detailed in the attached revocation of consent form.

*So it is all confidential?*

- ▶ Any information that is obtained in connection with this study and that can be identified with you and your child will remain confidential and will be disclosed only with your permission, except as required by law.
- ▶ All clinical details — and any other confidential information we collect — will be available only to the member of the research team responsible for your child.
- ▶ Blood samples will be given a unique identification number to protect your child’s privacy. Genetic Repositories Australia will not give out any personal information that can identify you or your child to the scientists who are approved to receive the samples.
- ▶ If you give us your permission by signing this document, we plan to discuss/publish the results at scientific conferences and in scientific journals. In any discussion or publication, information will be provided in such a way that you and your child cannot be identified.. However, we cannot and do not guarantee or promise that your child will receive any benefits from the study directly.

*Can I complain about the study?*

Complaints may be directed to the

Ethics Secretariat,

The University of New South Wales,

SYDNEY 2052 AUSTRALIA

Phone 9385 4234, Fax 9385 6648, email [ethics.sec@unsw.edu.au](mailto:ethics.sec@unsw.edu.au).

Any complaint you make will be treated in confidence and investigated, and you will be informed of the outcome.

*What if the questions upset me or my child?*

If you find that the questioning is upsetting or if you just want to talk about the questions, please call Gloria Roberts on 1800 352 292. So that we can ensure your usual GP or psychiatrist is urgently informed on your condition we will need you to provide us with emergency contact details for these doctors.

*Why do I have to sign a consent form?*

It is important that no research is done without your permission — and we have to be able to prove that you said “yes.”

*Tell me again what I am consenting to:*

By signing the **consent form** you will be giving us permission to:

1. Use the answers from your child’s assessment and your questions in our research; **and**
2. Contact you and your child every 12 months over the next 5-10 years, ask your child some more questions, and use those answers in our research.

### **Your consent**

Your decision whether or not to participate will not prejudice your future relations with The University of New South Wales. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without prejudice.

If you have any questions, please feel free to ask us. If you have any additional questions later Gloria Roberts will be happy to answer them (Ph 1800 352 292, email [bipolar-kidsandsibs@unsw.edu.au](mailto:bipolar-kidsandsibs@unsw.edu.au) ).

You will be given a copy of this form to keep.

**Please tick and initial each part of the study procedures to show your agreement to participate. If you do not wish to participate in a specific procedure simply do not tick or initial it.**

	Yes	No	Initials
I consent to my child's information being entered as part of the study records	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
I consent to my child providing a blood sample for genetic testing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
I consent to be contacted every 12 months for a period of 5-10 years	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
I consent to be contacted regarding future studies of bipolar disorder	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

*Sharing data across studies of bipolar disorder and mental illness allows for researchers to pool resources and make the most of our data, maximising the benefits of the research. Research studies conducted by the Australian Schizophrenia Research Bank (ASRB) or the Sydney Bipolar Disorders Clinic at the Black Dog Institute, use the same cognitive and genetic analyses that we are conducting. Do you give us permission to share your de-identified data (i.e. no name, address or other identifying information will be provided) with these researchers?*

	Yes	No	Initials
I consent to have my child's de-identified (cognitive/genetic/MRI) data, made available for use in research by other studies approved by the UNSW human research ethics committee.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
I would be interested in receiving information via mail or email about other potential mental health research studies. I understand that this would not oblige me to take part in these studies.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

**In providing consent for my child to provide a blood sample, I understand that the following is involved:**

- Blood samples will be collected for DNA extraction and/or generation of cell lines for research, and that my child's sample will be processed and stored by Genetic Repositories Australia
- My child's samples will be stored indefinitely
- My child's non-identifiable samples may be shared with approved researchers from academic institutions or companies from Australia or internationally
- Data gathered from my child's sample may be published, provided that my child cannot be identified
- My child will not receive any routine results
- My child will not receive any financial benefit from my participation
- My child will not receive or be able to claim any payment, compensation, royalty or any other financial benefit which may result from this research
- Should I wish to withdraw my child from the study and have my child's samples destroyed, I may do so by contacting Professor Mitchell
- In the event that any clinically significant result is found that has a significant probability of impacting on my health or that of my children, I wish to be advised how to access that information through established medical channels which will include genetic counselling and information provision via an appropriate clinical specialist:.....

YES	NO	Initials
<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

**PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM (continued)**

***Bipolar Kids and Sibs Study***

**You are making a decision whether or not to permit your child to participate.**

**Your signature indicates that, having read the attached Parental (or Guardian) Information Statement and Participant Information Statement, you have decided to take part in the study and you have decided to permit your child to take part in the study.**

.....

Signature of Parent/Guardian

.....

Signature of Witness

.....

(Please PRINT name)

.....

(Please PRINT name)

.....

Date

.....

Nature of Witness

.....

Signature(s) of Investigator(s)

.....

Please PRINT Name





Approval No (HREC 09097)

**REVOCATION OF CONSENT**

***Bipolar Kids and Sibs Study***

I hereby wish to **WITHDRAW** my consent for my child/ward and myself to participate in the research proposal described above and understand that such withdrawal **WILL NOT** jeopardise any treatment, or my child/ward’s relationship, with The University of New South Wales.

I hereby wish to withdraw my child’s consent to participate in the study.

Tick and initial which aspects of the study you wish to withdraw from:

	Yes	No	Initials
1. I request that my child no longer be contacted regarding this research but I agree that the data and samples already collected to continue to be used	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
2. I request that my child’s data and blood sample be destroyed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

.....

Signature of Parent/Guardian

.....

Date

.....

Please PRINT Name

The section for Revocation of Consent should be forwarded to **Professor Philip Mitchell**, Black Dog Institute, Prince of Wales Hospital, RANDWICK NSW 2031.



**UNSW**  
AUSTRALIA

Psychiatry  
Medicine

**PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM**

***Bipolar Kids and Sibs Study***

Approval No (HREC 09097)

THE UNIVERSITY OF NEW SOUTH WALES

**PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM**

Below are some questions that you might like to ask about the study. We will happily explain further or answer any other questions that you might have.

*What is the study about?*

- ▶ You are being invited to take part in a study that will take part at different time points to examine the genetic and environmental risk factors for bipolar disorder.
- ▶ We hope to learn about risk factors for bipolar disorder and use this data to develop better ways to provide early help to those at risk for bipolar disorder.

*Why have I been asked to take part?*

You were selected as a possible participant in this study because you or a member of your family have a history of bipolar disorder.

*How long does the study last?*

Identifying risk factors requires information to be collected over many years and so we would like to keep in contact with you for 5 – 10 years. Over that period we will get in touch every 12 months and ask you some questions.

*What are you asking me to do?*

- ▶ We will be interviewing you to find out about symptoms you experience now and also those you may have experienced when you were younger.
- ▶ You will also be asked to undertake a mood interview, fill in some self-report questionnaires (you will be given the option of completing these questionnaires online), complete a series of simple neuropsychological computerised tasks, give some blood, and undertake a brain scan.
- ▶ After the initial interview we would like to contact you every 12 months to do shorter assessments.
- ▶ So the first thing we need is your permission to use these assessments in our research.

*How long will it take?*

- ▶ The initial assessment will be conducted in a morning and afternoon session over the course of a day, or over two days if preferred.

- ▶ The questions to be done every 12 months will take approximately 3-4 hours.

#### *Genetic testing*

- ▶ The genetic testing will only be done once. We will take 20 ml of blood from a vein in your arm.
- ▶ The blood will be used to look for genes that may increase your risk of developing bipolar disorder. As it is now considered likely that many genes – which each individually play a small role – are involved together in causing bipolar disorder, we will test for many genes at once when we analyse your blood sample.
- ▶ When researchers understand how genes are involved in the development of bipolar disorder they have a better chance of designing better methods to diagnose, treat or cure that disease.

#### *Brain imaging*

- ▶ We will be inviting some of the participants to be involved in a brain imaging study. If you are asked to be involved in this, you will be provided with a separate information sheet and consent form.

#### *What will you be asking me every 12 months?*

There will be an interview asking you about any symptoms you have experienced over the previous six months. You will also complete some self-report questionnaires and sometimes a series of psychological tests. The questions are a lot like the ones you are answering for the first assessment.

#### *What are the advantages and disadvantages of being involved in the study?*

- ▶ We don't anticipate any risks to you from being involved in the study. However, we acknowledge that the assessments are lengthy and that involvement in the study will mean setting aside time to complete them.
- ▶ The main advantage is early detection of any symptoms of bipolar disorder or other mental disorders. If we notice symptoms we can help you get the appropriate treatment.
- ▶ The blood draw may cause some mild discomfort or bruising.

#### *How is the blood sample used?*

- ▶ The blood sample will be submitted to Genetic Repositories Australia (GRA), a research resource located at Neuroscience Research Australia, for subsequent processing. Your sample will be de-identified and only be tracked by a code number.
- ▶ Genetic material will be extracted from your blood sample. In order to ensure ongoing source of DNA, white blood cells (lymphocytes) are cultured and kept growing in the laboratory as a cell line, which allows a source of genetic material without having to obtain another blood sample. These cell lines can be stored indefinitely.
- ▶ GRA collects, stores, and distributes DNA samples and cell lines. All researchers wishing to access the genetic material stored by GRA must first have approval from the relevant Human Research Ethics Committee for their projects. Those researchers must then apply in writing to the GRA Management Committee, describing the intended use for the samples for approval for access to the samples. Researchers may be from non-profit research institutes, universities, etc or from commercial organisations from Australia or overseas. Research using your blood, in combination with samples from many other people, may result in discoveries that could lead to commercial developments. These developments may include new understanding about the cause of the disease, new diagnostic tests, new treatments, and new ways to prevent diseases. In this respect, it

should be noted that it is the whole collection of many samples that is of value and that each individual sample probably has no commercial value on its own. You agree to waive any future claim to ownership rights for financial benefit through participation in this research.

#### *Issues about online data entry for self-report questionnaires*

- ▶ The security of your personal information is important to us. We use a separate web-based service operated by QuestionPro in the USA for conducting surveys. The data remains controlled by us. QuestionPro does what is accepted business practice to protect personal information, using what is called ‘secure socket layer technology’. More information on QuestionPro and their Privacy Policy is available on their website at [www.questionpro.com](http://www.questionpro.com). However, no method of answering questions over the internet, or method of storing data electronically is 100% secure. Therefore, while we strive to use acceptable means to protect your personal information, we cannot guarantee that it’s absolutely safe.
- ▶ By using this service you understand that we use the QuestionPro service and consent to the transfer of relevant data to the USA based system. We also encourage you to take responsibility for your own computer system’s safety and protection.

#### *Who gets told how I answer the questions?*

- ▶ The researcher who asks you questions will know, but they will keep all information private.
- ▶ When we do our research your name and your answers are kept apart, so no one except the researcher responsible for you can find out.
- ▶ Apart from that we don’t tell anyone else (unless the law requires us to).

#### *What if I change my mind and don’t want to go on with the study?*

- ▶ That’s OK. You can pull out of the study at any time — just sign the form and tell us.
- ▶ If you decide to withdraw from the study, GRA will follow the directions of the Chief Investigator to either destroy your sample or to allow your sample to continue to be used based on your decision as detailed in the attached revocation of consent form.

#### *So it is all private?*

- ▶ Any information that is obtained in connection with this study and that can be identified with you will remain private, except as required by law.
- ▶ All the information we collect — will be available only to the member of the research team responsible for you.
- ▶ Blood samples will be given a unique identification number to protect your privacy. Genetic Repositories Australia will not give out any personal information that can identify you to the scientists who are approved to receive the samples.
- ▶ If you give us your permission by signing this document, we plan to discuss/publish the results at scientific meetings and in scientific journals. In any discussion or publication, information will be provided in such a way that you cannot be identified.

#### *Can I complain about the study?*

Complaints may be directed to the

Ethics Secretariat,

The University of New South Wales,

SYDNEY 2052 AUSTRALIA

Phone 9385 4234, Fax 9385 6648, email [ethics.sec@unsw.edu.au](mailto:ethics.sec@unsw.edu.au).

Any complaint you make will be treated in confidence and investigated, and you will be told about the outcome.

*What if the questions upset me?*

If you find that the questioning is upsetting or if you just want to talk about the questions, please call Gloria Roberts on 1800 352 292. So that we can ensure your usual GP or psychiatrist is urgently informed on your condition we will need you to provide us with emergency contact details for these doctors.

*Why do I have to sign a consent form?*

It is important that no research is done without your permission — and we have to be able to prove that you said “yes.”

*Tell me again what I am consenting to.*

By signing the **Consent Form** you are giving us permission to

3. Use the answers from your assessment in our research; **and**
4. Contact you every 12 months over the next 5-10 years, ask you some more questions, and use those answers in our research.

### **Your consent**

Your decision whether or not to participate will not affect your future relations with The University of New South Wales. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without any consequences.

If you have any questions, please feel free to ask us. If you have any additional questions later Gloria Roberts will be happy to answer them (Ph 1800 352 292, email [bipolar-kidsandsibs@unsw.edu.au](mailto:bipolar-kidsandsibs@unsw.edu.au) ).

You will be given a copy of this form to keep.

**Please tick and initial each part of the study procedures to show your agreement to participate. If you do not wish to participate in a specific procedure simply do not tick or initial it.**

	Yes	No	Initials
I consent to my information being entered as part of the study records	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
I consent to provide a blood sample for genetic testing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
I consent to be contacted every 12 months for a period of 5-10 years	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
I consent to be contacted regarding future studies of bipolar disorder	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

*Sharing data across studies of bipolar disorder and mental illness allows for researchers to pool resources and make the most of our data, maximising the benefits of the research. Research studies conducted by the Australian Schizophrenia Research Bank (ASRB) or the Sydney Bipolar Disorders Clinic at the Black Dog Institute, use the same cognitive and genetic analyses that we are conducting. Do you give us permission to share your de-identified data (i.e. no name, address or other identifying information will be provided) with these researchers?*

	Yes	No	Initials
I consent to have my de-identified (cognitive/genetic/MRI) data, made available for use in research by other studies approved by the UNSW human research ethics committee.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
I would be interested in receiving information via mail or email about other potential mental health research studies. I understand that this would not oblige me to take part in these studies.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

**In providing a blood sample, I understand that the following is involved:**

- Blood samples will be collected for DNA extraction and/or generation of cell lines for research, and that my sample will be processed and stored by Genetic Repositories Australia
- My samples will be stored indefinitely
- My non-identifiable samples may be shared with approved researchers from academic institutions or companies from Australia or internationally
- Data gathered from my sample may be published, provided that I cannot be identified
- I will not receive any routine results
- I will not receive any financial benefit from my participation
- I will not receive or be able to claim any payment, compensation, royalty or any other financial benefit which may result from this research
- Should I wish to withdraw from the study and have my samples destroyed, I may do so by contacting Professor Mitchell
- In the event that any clinically significant result is found that has a significant probability of impacting on my health or that of my children, I wish to be advised how to access that information through established medical channels which will include genetic counselling and information provision via an appropriate clinical specialist:.....

YES	NO	Initials
<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

**PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM (continued)**  
*Bipolar Kids and Sibs Study*

**You are making a decision whether or not to participate. Your signature indicates that, having read the Participant Information Statement, you have decided to take part in the study.**

.....  
Signature of Research Participant

.....  
Signature of Witness

.....  
(Please PRINT name)

.....  
(Please PRINT name)

.....  
Date

.....  
Nature of Witness

.....  
Signature(s) of Investigator(s)

.....  
Please PRINT Name



**REVOCATION OF CONSENT**

***Bipolar Kids and Sibs Study***

I hereby wish to **WITHDRAW** my consent to participate in the research proposal described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with The University of New South Wales.

I hereby wish to withdraw my consent to participate in the study.

**Tick and initial which aspects of the study you wish to withdraw from:**

	Yes	No	Initials
1. I request that I no longer be contacted regarding this research but I agree that the data and samples already collected to continue to be used	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>
2. I request that my data and blood sample be destroyed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/>

.....  
Signature

.....  
Date

.....  
Please PRINT Name

The section for Revocation of Consent should be forwarded to **Professor Philip Mitchell**, The Black Dog Institute, Prince of Wales Hospital, RANDWICK NSW 2031.





**UNSW**  
AUSTRALIA

Psychiatry  
Medicine

PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM

***Bipolar Kids and Sibs Study***

Approval No (HREC 09097)

THE UNIVERSITY OF NEW SOUTH WALES

**INFORMATION STATEMENT AND CONSENT FORM**

**For parents to consent for themselves.**

Below are some questions that you might like to ask about the study. We will happily explain further or answer any other questions that you might have.

*What is the study about?*

- ▶ You are being invited to take part in a longitudinal study to examine the genetic and environmental risk factors for bipolar disorder.
- ▶ We hope to learn about risk factors for bipolar disorder and use this data to develop better ways to intervene early in those at risk for bipolar disorder.

*Why have I been asked to take part?*

You were selected as a possible participant in this study because a parent or sibling of your child has been diagnosed with bipolar disorder.

*How long does the study last?*

Identifying risk factors requires information to be collected over many years and so we would like to keep in contact with you for 5 – 10 years. Over that period we will get in touch every 12 months and ask you some questions.

*What will I be asked for?*

- ▶ As a parent we will be interviewing you to find out about symptoms experienced by your child now and also those that he/she may have experienced at a younger age.
- ▶ For the initial assessment you will undertake a mood interview about your child, fill in some questionnaires about yourself in addition to questionnaires about your children who are participating in this study (you will be given the option of completing these questionnaires online), and give some blood. You will also be asked will undertake a mood interview about yourself. After the initial interview we would like to contact the parent every 12 months to do shorter assessments.

*How long will it take?*

- ▶ The initial assessment about your child will be conducted in a morning or afternoon session, or over two days if preferred. The questionnaires can be completed during this

session or else online prior to mood interviews. If you are also undertaking a mood interview about yourself this will take an additional morning or afternoon session that will be conducted prior to the interview about your child.

- ▶ The questions and mood interviews to be done every twelve months will take approximately 3-4 hours.

#### *Genetic testing*

- ▶ The genetic testing will only be done once. We will take 20 ml of blood from a vein in your arm.
- ▶ The blood will be used to look for genes that may increase your risk of developing bipolar disorder. As it is now considered likely that many genes – which each individually play a small role – are involved together in causing bipolar disorder, we will test for many genes at once when we analyse your blood sample.
- ▶ When researchers understand how genes are involved in the development of bipolar disorder they have a better chance of designing better methods to diagnose, treat or cure that disease.

#### *What will you be asking every 12 months?*

- ▶ There will be an interview asking you about any symptoms your child may have experienced over the previous twelve months. You will also complete some self-report questionnaires. The questions are a lot like the ones being answered for the first assessment.

#### *What are the advantages and disadvantages of being involved in the study?*

- ▶ We don't anticipate any risks to you from being involved in the study. However, we acknowledge that the assessments are lengthy and that involvement in the study will mean setting aside time to complete them.
- ▶ The main advantage is early detection of any symptoms of bipolar disorder or psychosis in your child. If we notice symptoms we can help your child get the appropriate treatment.

#### *How is the blood sample used?*

- ▶ The blood sample will be submitted to Genetic Repositories Australia (GRA), a research resource located at Neuroscience Research Australia, for subsequent processing. Your sample will be de-identified and only be tracked by a code number.
- ▶ Genetic material will be extracted from your blood sample. In order to ensure ongoing source of DNA, white blood cells (lymphocytes) are cultured and kept growing in the laboratory as a cell line, which allows a source of genetic material without having to obtain another blood sample. These cell lines can be stored indefinitely.
- ▶ GRA collects, stores, and distributes DNA samples and cell lines. All researchers wishing to access the genetic material stored by GRA must first have approval from the relevant Human Research Ethics Committee for their projects. Those researchers must then apply in writing to the GRA Management Committee, describing the intended use for the samples for approval for access to the samples. Researchers may be from non-profit research institutes, universities, etc or from commercial organisations from Australia or overseas.
- ▶ Research using your blood, in combination with samples from many other people, may result in discoveries that could lead to commercial developments. These developments may include new understanding about the cause of the disease, new diagnostic tests, new treatments, and new ways to prevent diseases. In this respect, it should be noted that it is the whole collection of many samples that is of value and that each individual sample

probably has no commercial value on its own. You agree to waive any future claim to ownership rights for financial benefit through participation in this research.

*Issues about online data entry for self-report questionnaires*

- ▶ The security of your personal information is important to us. We use a third party web-based service operated by QuestionPro in the USA for conducting surveys. The data remains controlled by us. QuestionPro follows generally accepted industry standards to protect personal information and uses secure socket layer technology. More information on QuestionPro and their Privacy Policy is available on their website at [www.questionpro.com](http://www.questionpro.com). However, no method of transmission over the internet, or method of electronic storage is 100% secure. Therefore, while we strive to use commercially acceptable means to protect your personal information, we cannot guarantee its absolute security.
- ▶ By using this service you understand that we use the QuestionPro service and consent to the transfer of relevant data to the USA based system. We also encourage you to take responsibility for the security of your own computer system.

*Who gets told how I answer the questions?*

- ▶ The researcher who asks you questions will know, but they will keep all information confidential.
- ▶ When we do our research your name and your answers are kept apart, so no one except the researcher responsible for you can find out.
- ▶ Apart from that we don't tell anyone else (unless the law requires us to).

*What if I change my mind and don't want to go on with the study?*

That's OK. You can pull out of the study at any time — just sign the form and tell us.

*So it is all confidential?*

- ▶ Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission, except as required by law.
- ▶ All clinical details — and any other confidential information we collect — will be available only to the member of the research team responsible for you.
- ▶ If you give us your permission by signing this document, we plan to discuss/publish the results at scientific conferences and in scientific journals. In any discussion or publication, information will be provided in such a way that you cannot be identified.

*Can I complain about the study?*

Complaints may be directed to the

Ethics Secretariat,

The University of New South Wales,

SYDNEY 2052 AUSTRALIA

Phone 9385 4234, Fax 9385 6648, email [ethics.sec@unsw.edu.au](mailto:ethics.sec@unsw.edu.au).

Any complaint you make will be treated in confidence and investigated, and you will be informed of the outcome.

*What if the questions upset me?*

If you find that the questioning is upsetting or if you just want to talk about the questions, please call Gloria Roberts on 1800 352 292. So that we can ensure your usual GP or psychiatrist is

urgently informed on your condition we will need you to provide us with emergency contact details for these doctors.

*Why do I have to sign a consent form?*

It is important that no research is done without your permission — and we have to be able to prove that you said “yes.”

*Tell me again what I am consenting to.*

By signing the **Consent Form** you are giving us permission to

5. Use the answers from your assessment in our research; **and**
6. Contact you every 12 months over the next 5-10 years, ask you some more questions, and use those answers in our research.

### **Your consent**

Your decision whether or not to participate will not prejudice your future relations with The University of New South Wales. If you decide to participate, you are free to withdraw your consent and to discontinue participation at any time without prejudice.

If you have any questions, please feel free to ask us. If you have any additional questions later Gloria Roberts will be happy to answer them (Ph 1800 352 292, email [bipolar-kidsandsibs@unsw.edu.au](mailto:bipolar-kidsandsibs@unsw.edu.au) ).

You will be given a copy of this form to keep.

**PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM (continued)**  
*Bipolar Kids and Sibs Study*

**You are making a decision whether or not to participate. Your signature indicates that, having read the Participant Information Statement, you have decided to take part in the study.**

.....  
Signature of Research Participant

.....  
Signature of Witness

.....  
(Please PRINT name)

.....  
(Please PRINT name)

.....  
Date

.....  
Nature of Witness

.....  
Signature(s) of Investigator(s)

.....  
Please PRINT Name

Do you agree to be contacted every 12 months for a period of 5-10 years?  
yes  no

Sharing data across studies of bipolar disorder and mental illness allows for researchers to pool resources and make the most of our data, maximising the benefits of the research. Research studies conducted by the Australian Schizophrenia Research Bank (ASRB) or the Sydney Bipolar Disorders Clinic at the Black Dog Institute, use the same cognitive and genetic analyses that we are conducting. Do you give us permission to share your de-identified data (i.e. no name, address or other identifying information will be provided) with these researchers?

I consent to have my de-identified (cognitive/genetic/MRI) data, made available for use in research by other studies approved by the UNSW ethics committee.

I would be interested in receiving information via mail or email about other potential mental health research studies. I understand that this would not oblige me to take part in these studies.



**UNSW**  
AUSTRALIA

Psychiatry  
Medicine

**REVOCACTION OF CONSENT**

***Bipolar Kids and Sibs Study***

I hereby wish to **WITHDRAW** my consent to participate in the research proposal described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with The University of New South Wales.

I hereby wish to withdraw my consent to participate in the study.

I do not want to be contacted in the future.

.....  
Signature

.....  
Date

.....  
Please PRINT Name

The section for Revocation of Consent should be forwarded to **Professor Philip Mitchell**, The Black Dog Institute, Prince of Wales Hospital, RANDWICK NSW 2031.



**UNSW**  
AUSTRALIA

Psychiatry  
Medicine

PARTICIPANT INFORMATION STATEMENT AND CONSENT FORM

***Bipolar Kids and Sibs Study***

Approval No (HREC 09097)

THE UNIVERSITY OF NEW SOUTH WALES

**INFORMATION STATEMENT AND CONSENT FORM**  
**For parents to consent for themselves.**

Below are some questions that you might like to ask about the study. We will happily explain further or answer any other questions that you might have.

*What is the study about?*

- ▶ You are being invited to take part in a longitudinal study to examine the genetic and environmental risk factors for bipolar disorder.
- ▶ We hope to learn about risk factors for bipolar disorder and use this data to develop better ways to intervene early in those at risk for bipolar disorder.

*Why have I been asked to take part?*

You were selected as a possible participant in this study because your child has been diagnosed with bipolar disorder or a parent or sibling of your child has been diagnosed with bipolar disorder.

*How long does the study last?*

Identifying risk factors requires information to be collected over many years and so we would like to keep in contact with you for 5 – 10 years. Over that period we will get in touch every 12 months and ask you some questions.

*What will I be asked for?*

- ▶ As a parent we will be interviewing you to find out about symptoms experienced by your child now and also those that he/she may have experienced at a younger age.
- ▶ For the initial assessment you will undertake a mood interview about your child, fill in some questionnaires about yourself in addition to questionnaires about your children who are participating in this study (you will be given the option of completing these questionnaires online). You will also be asked will undertake a mood interview about yourself. After the initial interview we would like to contact the parent every 12 months to do shorter assessments.

*How long will it take?*

- ▶ The initial assessment about your child will be conducted in a morning or afternoon session, or over two days if preferred. The questionnaires can be completed during this session or else online prior to mood interviews. If you are also undertaking a mood interview about yourself this will take an additional morning or afternoon session that will be conducted prior to the interview about your child.
- ▶ The questions and mood interviews to be done every twelve months will take approximately 3-4 hours.

#### *Genetic testing*

- ▶ The genetic testing will only be done once. We will take 20 ml of blood from a vein in your arm.
- ▶ The blood will be used to look for genes that may increase your risk of developing bipolar disorder. As it is now considered likely that many genes – which each individually play a small role – are involved together in causing bipolar disorder, we will test for many genes at once when we analyse your blood sample.
- ▶ When researchers understand how genes are involved in the development of bipolar disorder they have a better chance of designing better methods to diagnose, treat or cure that disease.

#### *What will you be asking every 12 months?*

- ▶ There will be an interview asking you about any symptoms your child may have experienced over the previous twelve months. You will also complete some self-report questionnaires. The questions are a lot like the ones being answered for the first assessment.

#### *What are the advantages and disadvantages of being involved in the study?*

- ▶ We don't anticipate any risks to you from being involved in the study. However, we acknowledge that the assessments are lengthy and that involvement in the study will mean setting aside time to complete them.
- ▶ The main advantage is early detection of any symptoms of bipolar disorder or psychosis in your child. If we notice symptoms we can help your child get the appropriate treatment.
- ▶

#### *How is the blood sample used?*

- ▶ The blood sample will be submitted to Genetic Repositories Australia (GRA), a research resource located at Neuroscience Research Australia, for subsequent processing. Your sample will be de-identified and only be tracked by a code number.
- ▶ Genetic material will be extracted from your blood sample. In order to ensure ongoing source of DNA, white blood cells (lymphocytes) are cultured and kept growing in the laboratory as a cell line, which allows a source of genetic material without having to obtain another blood sample. These cell lines can be stored indefinitely.
- ▶ GRA collects, stores, and distributes DNA samples and cell lines. All researchers wishing to access the genetic material stored by GRA must first have approval from the relevant Human Research Ethics Committee for their projects. Those researchers must then apply in writing to the GRA Management Committee, describing the intended use for the samples for approval for access to the samples. Researchers may be from non-profit research institutes, universities, etc or from commercial organisations from Australia or overseas.
- ▶ Research using your blood, in combination with samples from many other people, may result in discoveries that could lead to commercial developments. These developments may include new understanding about the cause of the disease, new diagnostic tests, new



treatments, and new ways to prevent diseases. In this respect, it should be noted that it is the whole collection of many samples that is of value and that each individual sample probably has no commercial value on its own. You agree to waive any future claim to ownership rights for financial benefit through participation in this research.

#### *Issues about online data entry for self-report questionnaires*

- ▶ The security of your personal information is important to us. We use a third party web-based service operated by QuestionPro in the USA for conducting surveys. The data remains controlled by us. QuestionPro follows generally accepted industry standards to protect personal information and uses secure socket layer technology. More information on QuestionPro and their Privacy Policy is available on their website at [www.questionpro.com](http://www.questionpro.com). However, no method of transmission over the internet, or method of electronic storage is 100% secure. Therefore, while we strive to use commercially acceptable means to protect your personal information, we cannot guarantee its absolute security.
- ▶ By using this service you understand that we use the QuestionPro service and consent to the transfer of relevant data to the USA based system. We also encourage you to take responsibility for the security of your own computer system.

#### *Who gets told how I answer the questions?*

- ▶ The researcher who asks you questions will know, but they will keep all information confidential.
- ▶ When we do our research your name and your answers are kept apart, so no one except the researcher responsible for you can find out.
- ▶ Apart from that we don't tell anyone else (unless the law requires us to).

#### *What if I change my mind and don't want to go on with the study?*

That's OK. You can pull out of the study at any time — just sign the form and tell us.

#### *So it is all confidential?*

- ▶ Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission, except as required by law.
- ▶ All clinical details — and any other confidential information we collect — will be available only to the member of the research team responsible for you.
- ▶ If you give us your permission by signing this document, we plan to discuss/publish the results at scientific conferences and in scientific journals. In any discussion or publication, information will be provided in such a way that you cannot be identified.

#### *Can I complain about the study?*

Complaints may be directed to the

Ethics Secretariat,

The University of New South Wales,

SYDNEY 2052 AUSTRALIA

Phone 9385 4234, Fax 9385 6648, email [ethics.sec@unsw.edu.au](mailto:ethics.sec@unsw.edu.au).

Any complaint you make will be treated in confidence and investigated, and you will be informed of the outcome.

#### *What if the questions upset me?*

If you find that the questioning is upsetting or if you just want to talk about the questions, please call Gloria Roberts on 1800 352 292. So that we can ensure your usual GP or psychiatrist is urgently informed on your condition we will need you to provide us with emergency contact details for these doctors.

*Why do I have to sign a consent form?*

It is important that no research is done without your permission — and we have to be able to prove that you said “yes.”

*Tell me again what I am consenting to.*

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