Symptoms and signs of the initial prodrome of bipolar II disorder

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Contents

Acknowledgements

In gratitude, I dedicate this thesis to

Isabel and Michelle,

and my late parents

Erna S. Bergh Skjelstad (specialist in clinical psychology) and Nikolai Skjelstad (attorney).

Dag Vegard Skjelstad

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Summary of the thesis

Bipolar disorder (BD) is a chronic and debilitating illness characterized by severe dysregulation of mood, energy, and activity that results in episodes of depression and (hypo)mania. Approximately 60% of patients with BD experience the onset before the end of their teens. Thus, people who develop BD are often afflicted during their most vulnerable and formative years. A delay in appropriate treatment may worsen the course and outcome of the disorder. Hence, early identification and treatment is important to improve prognosis. This thesis explores symptoms and signs and temporal aspects of the pre-onset phase (initial prodrome) of BD to investigate whether it might be possible to identify the development of BD *before* the onset of the illness based on clinical phenomena. The thesis comprises two projects: a literature review of the initial prodrome of BD and an original research study on the initial prodrome of bipolar II disorder (BD-II).

In the literature review (paper I), systematic studies addressing symptoms, signs and temporal aspects of the initial prodrome of BD were reviewed in search of potential clinical targets for early intervention. We found that irritability/aggressiveness, sleep disturbances, depression and mania symptoms, hyperactivity, anxiety, and mood swings are common symptom clusters of the initial prodrome of BD. The symptoms are not sufficiently specific to reliably identify BD prospectively. No studies have explicitly investigated the initial prodrome of BD-II.

To investigate the phenomenology of the initial prodrome of BD-II, we conducted an exploratory retrospective study using qualitative methodology supplemented by quantitative analyses. Choosing a qualitative design enabled us to pursue an in-depth exploration of an under-investigated field of research in a flexible and open fashion and to collect complex data that could be analyzed in numerous ways. Hence, we gave priority to the in-depth study of a limited sample (15 BD-II patients and 22 family member informants) to search for findings that could generate hypotheses, which could be tested on larger samples in future studies. A series of open-ended in-depth interviews covering the patients' life course from birth to the time of the study was conducted with each patient and family members. Given our interest in exploring the prodromal phase of BD-II, the time period preceding the estimated time of full diagnosable onset (hypomania and major depression) was emphasized. With the exception of certain temporal aspects, the findings presented in this thesis refer to the time period from birth to the first major affective episode (FMAE) of BD-II.

In paper II we present findings on clinically significant symptoms/behaviors, the temporal aspects of these symptoms including onset ages and time intervals, and how clinical features differ between two distinct subgroups that were identified based on prominent and enduring personal characteristics prior to the FMAE. The symptoms reported were organized into categories that mirrored the categories of the review except for the "hyperactivity" category. As in the review, we conclude that the symptoms appear to be too nonspecific to reliably predict BD-II prospectively. However, the patients in one of the identified subgroups appear to be relatively more identifiable prior to the FMAE. These patients experienced neurocognitive deficits and pronounced irritability and aggressiveness, and earlier onset of the FMAE, earlier prodromal symptom onset, and more symptoms compared to a subgroup that was described as very well-functioning. This subgroup may be of potential interest for early identification.

In paper III and IV we speculate whether the assessment of symptom instances' temporal and contextual characteristics may help identify clinical indicators with enhanced predictive power. If so, it is insufficient only to assess the types of symptoms of individuals at perceived risk of developing BD. A specific symptom may be a likely or unlikely early manifestation of a forthcoming BD depending on its' constellation of temporal and contextual characteristics. Based on theoretical reasoning, we propose that symptom instances which are characterized as episodic or chronic and as exaggerated responses to life events or inexplicable, may be the most likely early manifestations of the FMAE of BD-II. Symptom instances that were characterized as temporary, and thus, did not persist from symptom onset to the onset of the FMAE, were regarded as unrelated to the subsequent BD-II. Symptom instances characterized as episodic or chronic and as normal responses to life events were regarded as possible early manifestations. Assuming that symptom instances that emerge late in the prodrome are more likely to be early manifestations of the disorder itself, our preliminary findings support the notion that symptom instances classified as likely early manifestations may be the relatively best clinical predictors of a forthcoming BD-II. We also found that the majority of the symptom instances categorized as mood swings and irritability/aggressiveness met the criteria as likely early manifestations, and thus, may be the most prominent predictors of the FMAE of BD-II.

In sum, this thesis contributes to the knowledge of the initial prodrome of BD and is the first to explicitly investigate the initial prodrome of BD-II. Novel hypotheses about patient subgroups, intergroup differences, and symptom characteristics with enhanced predictive value are proposed. The hypotheses generated need to be tested in future studies.

List of papers

Paper I

Skjelstad, D.V., Malt, U.F., & Holte, A. (2010). Symptoms and signs of the initial prodrome of bipolar disorder: a systematic review. *Journal of Affective Disorders.* 126 (1-2), 1-13.

Paper II

Skjelstad, D.V., Malt, U.F., & Holte, A. (2011). Symptoms and behaviors prior to the first major affective episode of bipolar II disorder. An exploratory study. *Journal of Affective Disorders.* 132 (3), 333-343.

Paper III

Skjelstad, D.V., Holte, A., & Malt, U.F. (2011). Genuine clinical predictors of bipolar II disorder: An exploration of temporal and contextual characteristics. *Journal of Affective Disorders.* 135 (1-3), 419-423.

Paper IV

Skjelstad, D.V., Holte, A., & Malt, U.F. Putative early manifestations of bipolar II disorder emerge later in the initial prodrome than manifestations hypothesized to be unrelated. An exploratory study. Manuscript submitted[1st revision], 2011.

AMENDMENTS:

Shortly after the submission of my dissertation to the Faculty of Social Sciences on January 9th 2012, paper IV was accepted for publication in *Early Intervention in Psychiatry*. It is now published electronically ahead of press (DOI: 10.1111/j.1751-7893.2012.00348.x). The only differences between the version included in this thesis and the published version are a few minor linguistic alterations.

Asker, August 20th, 2012

Abbreviations

BD	Bipolar disorder
BD-I	Bipolar I disorder
BD-II	Bipolar II disorder
BD-NOS	Bipolar disorder not otherwise specified
DSM	Diagnostic and Statistical Manual for Mental Disorders
FMAE	First major affective episode
GCP	Genuine clinical predictor
(Hypo)mania	Hypomania or mania
ICD	International Classification of Diseases
IDS-C	Inventory of Depressive Symptomatology - Clinician rated
LEM	Likely early manifestation
MDD	Major depressive disorder
MDE	Major depressive episode
NEQ	Network Entry Questionnaire
PEM	Possible early manifestation
UEM	Unlikely early manifestation
YMRS	Young Mania Rating Scale

Definitions

Initial prodrome	The time interval from the onset of the first noticeable symptoms and signs that deviate from a relatively stable or normal state of being to the onset of a fully developed and diagnosable disorder.
Distal and proximal prodromes	Denominate the early and late stages of the initial prodrome, respectively.

1 Introduction

1.1 General introduction

Bipolar disorder (BD) is a chronic, pervasive, and potentially debilitating illness. BD is characterized by dysfunctional affective regulation that typically results in fluctuations between reduced (depression) and elevated (hypomania/mania) levels of mood, energy and activity compared to a normal state. The two main subtypes of bipolar affective disorders are bipolar I disorder (BD-I; formerly named manic-depressive illness) and bipolar II disorder (BD-II; see definitions below) (WHO, 1992; APA, 2000).

Approximately 60% of patients with BD experience onset before the end of their teens (Lish et al., 1994; Hirschfeld et al., 2003; Perlis et al., 2004; Post et al., 2008; Morken et al., 2009), usually between ages 15 and 19 (Goodwin and Jamison, 2007; Merikangas et al., 2007). Hence, people who develop BD are often afflicted during their most vulnerable and formative years. Adding to the burden is the lag of up to 10 years between illness onset and receiving a correct diagnosis (Suppes et al., 2001; Hirschfeld et al., 2003).

The current literature suggests that a delay in appropriate treatment may worsen the course and outcome of BD. Indeed, lack of intervention may result in more severe illness episodes (Kessing et al., 2004), deterioration of cognitive functions (Olley et al., 2005), increased rates of suicide, impaired quality of life (Yatham et al., 2004), changes in brain structure (Chang et al., 2005), worsening response to treatment (Swann et al., 1999; Ketter et al., 2006; Scott et al., 2006), increasing disability, and increased cardiovascular and other medical morbidities (Angst et al., 2002). It has been proposed that the untreated disorder may result in neurological alterations ("kindling" effects) that may worsen the prognosis (Post, 1992; Post et al., 1996). Hence, it is conceivable that early interventions might enhance both prognosis and treatment response. Pre-onset identification and interventions may even prevent the development of the full disorder.

In recent years, there has been a paradigm shift in the research and clinical approaches to severe mental disorders, from a focus on chronic established illness toward one of early detection and intervention. The focus has primarily been on non-affective psychotic disorders, predominantly schizophrenia. This shift has resulted in the establishment of specialist early detection and intervention services in many countries around the world, which have been fairly successful (Yung et al., 2007; Cannon et al., 2008; Howes and Falkenberg, 2011). By comparison, little attention has been directed toward the early recognition and prevention of

BD (Berk et al., 2007). The aim of this thesis is to contribute to the emerging knowledge in this field.

1.1.1 Diagnostic criteria of bipolar disorders

The fluctuations of mood, energy and activity that are characteristic of BD result in state-congruent alterations with heightened or lowered productivity, self-confidence, sociability, need for sleep, sexual drive, patience, risk-taking, judgment, empathy, views on self/others/the world/the future, and more. In its most classic and recognizable form, BD alternates between episodes of depression and (hypo)mania and periods of normal functioning. However, the presentation and course of BD vary widely between individuals.

The criterion for a BD-I diagnosis is at least one manic or mixed (i.e., co-occurring symptoms of depression and mania) episode, whereas a BD-II diagnosis requires both a hypomanic (a milder form of mania) and a major depressive episode (MDE) (WHO, 1992; APA, 2000). The core symptom of a (hypo)manic episode is an elated, expansive or irritable mood. In mania, but not in hypomania, symptoms need to cause clinically significant distress or impairment in social, occupational or other important areas of functioning. According to the current DSM-IV criteria, the duration criterion for mania is 7 days, unless there is a severe and rapid onset that requires hospitalization, and 4 days for hypomania. The core symptoms of a depressive episode are depressed mood and loss of interest or pleasure in activities lasting for at least 2 weeks. The intensity of a major depressive episode may be categorized as mild, moderate or severe. Symptoms should not be the result of the acute effects of substance use or a medical condition. Some patients may experience psychosis during a severe MDE or a manic episode (BD-I).

Cyclothymia and bipolar disorder not otherwise specified (BD-NOS) are the two other diagnostic categories within the bipolar spectrum (broad definition). A diagnosis of cyclothymia requires a history of hypomanic episodes with periods of depression that do not meet the MDE criteria. The BD-NOS category is used when disabling bipolar symptoms do not fulfill the specific criteria of the three above-mentioned subtypes. A disorder labeled BD-NOS is often referred to as a "subthreshold bipolar disorder" or a "bipolar spectrum disorder" (narrow definition).

1.1.2 Is BD-II a milder version of BD-I?

According to the diagnostic criteria, BD-I and BD-II are distinguished only by a more severe manifestation of (hypo)manic symptoms in BD-I, which may be of a psychotic nature. Thus,

it might seem that BD-II is a milder version of BD-I. Some studies suggest that the frequency of (hypo)mania symptoms is distributed along a spectrum (Angst et al., 2011) and that the severity and the duration of (hypo)mania symptoms determines whether the threshold for BD-II or BD-I is reached. Other findings suggest differences in clinical features, comorbidity, and course of the two illnesses. It has been demonstrated reasonably well that a chronic course with more episodes and rapid cycling are more common in BD-II than in BD-I (Vieta et al., 1997; Judd et al., 2003; Baek et al., 2011). Findings suggest that the ratio of depressive to manic features is 3:1 in BD-I, in contrast to as much as 47:1 for depression to hypomania in BD-II (Berk et al., 2009). Although the (hypo)manic symptoms are less pronounced in BD-II, the more constant presence of symptoms underscores that BD-II is an equally severe or even a more severe disorder than BD-I in some respects. A higher incidence of comorbid psychiatric illnesses (e.g., phobia and eating disorder), suicidality (Rihmer and Pestality, 1999; Valtonen et al., 2008; Baek et al., 2011), and more atypical symptoms during depressive episodes (Brugue et al., 2008) have been found in BD-II compared to BD-I. However, these findings are inconclusive (Vieta et al., 1997; Mantere et al., 2006).

Other data that may indicate that BD-II is a distinct nosological category are from genetic epidemiological studies. The morbidity risk of BD-II is shown to be much higher in relatives of BD-II probands (i.e., individuals with the disorder) than in those of BD-I probands, which might suggest a somewhat different genetic liability between BD-I and BD-II (Coryell et al., 1984; Endicott et al., 1985; Andreasen et al., 1987; Heun and Maier, 1993). Furthermore, in the evaluation of long-term diagnostic stability, only a small portion of BD-II individuals seem to convert to BD-I, i.e., 5% in 5 years (Joyce et al., 2004) and 7.5% in 10 years (Coryell et al., 1995).

1.1.3 The prevalence of bipolar disorder

Family studies of the first-degree relatives of individuals with BD-I and BD-II show that 11.9% (weighted mean) of people in this group have BD, compared to 1% in the general population (Goodwin and Jamison, 2007). Based on their review of the literature, Goodwin and Jamison (2007) demonstrated that there is a relative risk for BD of 10.7 in first-degree relatives of BD probands. The risk, however, varies according to different parameters, such as the number of first-degree relatives with BD and the age of the at-risk individual. For instance, if both parents have BD, a child's chance of developing BD increases to approximately 50%. Large, recent studies estimate that the lifetime prevalences for BD-I and BD-II are 1.0% and 1.1%, respectively (Merikangas et al., 2007). The prevalence for all

bipolar spectrum disorders (broad definition) is reported to vary between 4.5-8.5% (Angst, 1998; Judd and Akiskal, 2003; Merikangas et al., 2007) depending on the criteria and severity measures used for a BD-NOS diagnosis.

1.1.4 The etiology of bipolar disorder

Bipolar disorder is among the most heritable mental disorders, and heritability is the best documented risk factor for BD (McGuffin et al., 2003; Smoller and Finn, 2003; Tsuchiya et al., 2003; Kieseppa et al., 2004). The heritability of BD has been found to be approximately 85% in twin studies (Bienvenu et al., 2011). However, as reported above, the majority of individuals with BD do not have a known family history of the disorder. Although current data support this notion, the actual prevalence of BD individuals who have a first-degree relative with BD is unclear. It is likely that this prevalence is underestimated in Goodwin and Jamison (2007) because their review includes earlier studies that only assessed BD-I. Although large variations exist, recent clinical studies, including studies that assess relatives directly, often find that one quarter to one third of BD patients have a first-degree relative with (hypo)mania (Rybakowski et al., 2005; Othmer et al., 2007; Angst et al., 2011). Still, it is unclear if and to what extent BD individuals without a family history of BD have a genetic susceptibility for the disorder, and if they do, how genetic factors interact with environmental factors to produce BD. Investigators claim that an interaction of genes and environmental factors is the most likely cause of BD (Kendler, 2005; Hunter, 2005; Caspi and Moffitt, 2006; Rutter et al., 2006). In general, they state that the modulation of gene expression by environmental factors in complex disorders is likely, given the multiple pathways leading to disease and the probabilistic rather than deterministic effect of almost all risk factors, whether genetic or environmental. Environmental risk factors that may trigger BD may include stressful life events (Alloy et al., 2005; Garno et al., 2005), substance use (Strakowski and Delbello, 2000; Henquet et al., 2006), and an emotional or vegetative-labile personality style (Angst et al., 2003c). In sum, the etiology of BD is likely multifactorial and complex.

1.2 Clinical predictors of bipolar disorder

1.2.1 Overview of three research strategies

Different research strategies may be used to identify pre-onset clinical predictors of BD. The preferable approach from a scientific point of view is to study a representative sample of the general population prospectively (epidemiological studies). This approach may yield reliable data about the pre-onset phase in individuals who subsequently develop BD. However, such

studies are expensive and lengthy. Because of the relatively low base rate of BD in the general population, a large number of study subjects are required to obtain a sizable sample of individuals with BD. Additionally, numerous follow-up assessments are needed to cover the most common onset ages of BD.

A more feasible option is to study individuals prospectively who are perceived to be at risk for developing BD. The most obvious approach, given the elevated heritability of BD, is to study offspring of BD parents (hereafter called high-risk offspring). The major limitation of this design is that the findings only apply to a minority of individuals with a BD family history, and potential differences in pre-onset phenomenology between those with and without a family history of BD cannot be explored.

Having experienced a depressive episode is another risk factor for BD (i.e., for a subsequent episode of (hypo)mania). However, many more people will experience a MDE in their lifetime than will experience (hypo)mania, which may produce false positives. A Norwegian epidemiological study found the lifetime prevalences of BD-I and MDD to be 1.6% and 17.8%, respectively, and the 12-month prevalences to be 0.9% and 7.3%, respectively (Kringlen et al., 2001). Thus, MDE alone is approximately 11 times more common than MDE with mania. If this study had included BD-II subjects, it is likely that the odds ratio would have been approximately 5.

Studying potential clinical differences in the MDEs of those who develop BD versus those who do not may provide important information about the relative risk of developing BD in depressed patients, thus enhancing the positive predictive power. The major limitations of this design are the relatively late entry point of studying the pre-onset phase and the fact that this strategy cannot provide information regarding the pre-onset phase in individuals who experience (hypo)mania before their first MDE. However, studies suggest that approximately four fifths of individuals with BD experience a MDE before a (hypo)manic episode (Othmer et al., 2007).

A third major strategy is retrospective exploration of the pre-onset phase in individuals with confirmed BD. The major advantages of this design are that it is less time consuming and demands fewer resources than prospective studies. This design allows for exploration of the prodromal phase in individuals both with and without a family history of BD. It also allows for the exploration of individuals' entire life history from birth to the present. The obvious disadvantage is the questionable validity and reliability of retrospective studies. The study of prodromal symptoms in BD-II that is presented in this thesis utilized a retrospective approach.

1.2.2 Symptoms and signs of the initial prodrome of BD

Little was known about the symptoms and signs of the pre-onset phase of BD when this research project was conceived of during the autumn of 2006. At the time, there had only been six published systematic studies that we regarded as informative of the pre-onset phase of BD (Lish et al., 1994; Carlson et al., 2000; Egeland et al., 2000; Fergus et al., 2003; Hirschfeld et al., 2003; Faedda et al., 2004). However, not all of these were explicit about the aim of investigating the initial prodrome. In 2008 and 2009, my supervisors and I wrote a systematic review (paper I) on the topic (Skjelstad et al., 2010). By the time of the most recent literature search update in January 2009, two more relevant articles had been published (Correll et al., 2007; Rucklidge, 2008). The search methodology and study selection criteria applied in the review are described in the methods section of the thesis. Since January 2009, four more articles meeting the criteria of the review article have been published, including ours (Luckenbaugh et al., 2009; Ozgurdal et al., 2009; Conus et al., 2010; Skjelstad et al., 2011b).

Because the review article constitutes one of the four papers of this thesis, I have chosen not to repeat the details of the individual studies here. Below, I summarize the main findings of the reviewed articles and indicate some of their limitations. The three above-mentioned studies that were published after January 2009 are introduced in the discussion section of the thesis.

Seven of the eight reviewed studies were purely retrospective, whereas one utilized admission interview data recorded prior to the onset of BD (Egeland et al., 2000). Three of the studies had pure BD-I samples (Carlson et al., 2000; Egeland et al., 2000; Correll et al., 2007), two specified the makeup of mixed-phenotype samples (Faedda et al., 2004; Rucklidge, 2008), and three had unspecified BD samples (Lish et al., 1994; Fergus et al., 2003; Hirschfeld et al., 2003). None of the studies presented explicit data on the pre-onset symptoms of subjects with BD-II. The percentage of subjects with a family history of BD ranged from 29.4% to 56% in the five studies in which this figure was specified (Lish et al., 1994; Fergus et al., 2003; Hirschfeld et al., 2003; Correll et al., 2007; Rucklidge, 2008).

Irritability and aggressiveness was the most common cluster of symptoms reported, followed by sleep disturbances, mania-type symptoms, depression-type symptoms, anxiety-related symptoms, mood swings, hyperactivity, and other symptoms. There were large variations in the frequencies of comparable symptoms across the studies.

Some of the studies investigated how the symptoms and the symptom load evolved throughout the initial prodrome (Egeland et al., 2000; Rucklidge, 2008) and at the final

(proximal) stage (Correll et al., 2007). As time to full BD onset decreases, symptoms of mania and depression seem to increase gradually in strength and prevalence, and the overall symptom load increases. One study also reported attenuated positive psychotic symptoms (in BD-I patients) at the final stage before the first manic episode (Correll et al., 2007). Only two studies reported on the mean time interval between the first symptom and BD onset. Both studies included pure BD-I samples, and the time interval was found to be 7.3 years in one study[1] (Egeland et al., 1987) and 1.8 years in the other (Correll et al., 2007).

In addition to the above-mentioned studies, a prospective US study of Amish high-risk offspring (Shaw et al., 2005) collected data at the symptom/behavior level, which could produce detailed and reliable findings. Shaw et al. (2005) compared 110 at-risk children with a BD-I parent with 112 children with well parents and found a higher frequency of episodic symptoms and signs in the former group. These signs and symptoms included anxiety/worry, poor attention/distraction in school, excitability, hyperalertness, mood changes/lability, role impairment in school, somatic complaints, and stubbornness/determination. At 10-year follow-up, five additional manic-like behaviors became more evident among the at-risk adolescents: high energy, decreased sleep, problems with thinking/concentration, excessive talking, and loud talking. However, none of the at-risk offspring met diagnostic criteria for BD-I or BD-II at 10-year follow-up. Hence, it is unclear if these features turn out to be prodromal of BD.

In sum, our review shows that few studies have investigated the symptoms and signs of the initial prodrome of BD. There are many unresolved questions and under-investigated aspects of the initial prodrome for future studies to explore, as we discuss in greater detail in paper I. A major limitation of the reviewed studies is that only two of them appear to have a satisfactory operationalization of the cut-off point that marks the end of the prodrome, and conversely, the onset of BD. Carlson et al. (2000) and Correll et al. (2007) applied the actual time of the first manic episode, and hence, the time of first meeting the criteria for a BD-I diagnosis, as the transition point. Five studies (Lish et al., 1994; Egeland et al., 2000; Hirschfeld et al., 2003; Faedda et al., 2004; Rucklidge, 2008) explicitly or implicitly defined time of BD onset as the time of diagnosis, which may occur many years after the actual time of first meeting the diagnostic criteria for BD. One study did not specify an onset definition (Fergus et al., 2003). Hence, many of the symptom instances reported in these studies may actually be syndromal rather than prodromal. The scarcity of studies with adequate definitions

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[1] The BD-I subjects in Egeland et al. (1987) are included in Egeland et al. (2000).

of the transition point between the prodrome and syndrome underscores the newness of this field of research and the need for more studies that can produce data with enhanced validity. The retrospective nature of the studies is another major limitation, as mentioned earlier.

None of the studies reported explicitly on prodromal symptoms of BD-II. However, as mentioned earlier, two studies had mixed samples with specified phenotypes that included BD-II subjects. It is likely that the studies that did not specify the BD phenotypes of their samples included both BD-I and BD-II subjects, and possibly also subjects with cyclothymia and BD-NOS.

1.2.3 Diagnosable psychopathology prior to BD onset

A few prospective studies perform diagnostic assessments of individuals perceived to be at risk for BD. These studies do not report the occurrence of individual symptoms. Hence, some of the individuals included in these studies may experience clinically significant prodromal symptoms that are too few and/or of insufficient severity to meet the diagnostic criteria for certain mental disorders.

To our knowledge, there are two high-risk offspring studies that assessed diagnostic status and documented conversions to BD in the follow-up period: one Dutch study by Hillegers et al. and one Canadian study by Duffy et al. In the study by Duffy et al. (Duffy et al., 2007; Duffy et al., 2010; Duffy et al., 2011), offspring of one parent with a bipolar spectrum disorder and one well parent were followed up until age 30. The offspring were 8 to 25 years old at inclusion. The investigators compared the age-adjusted risks of lifetime psychopathology between high-risk and control subjects (with two well parents) and assessed the conditional probability of developing a mood disorder given a history of non-mood disorders. In subjects meeting full DSM-IV criteria for BD, they assessed the sequence of psychopathology against a clinical staging model. At the time of their most recent publication (Duffy et al., 2011), some of the subjects had been followed up for 15 years, and 8.6% (19/220) of the high risk offspring had met lifetime DSM-IV criteria for BD-I or BD-II, with an additional 5.5% (12/220) and 1.8% (4/220) meeting criteria for BD-NOS and schizoaffective BD, respectively. No one in the well comparison group developed BD. High-risk offspring manifested higher rates of anxiety and sleep disorders (with onset prior to the FMAE) compared to controls. Antecedent anxiety increased the age-adjusted risk of mood disorder from 40% to 85% (hazard ratio of 2.6). They found that the evolution of psychopathology follows a predictable clinical sequence over development for high-risk offspring who develop BD: from nonspecific non-mood disorders, including anxiety and sleep

problems in childhood, to adjustment disorders (sensitivity to stress) and minor depressive disorders starting in early adolescence, followed several years later by major mood episodes, most often initially in the depressive polarity (85.7%). Interestingly, only offspring of lithium non-responders had elevated rates of antecedent ADHD, learning disabilities and Cluster A traits compared to the control group. High-risk offspring with no lifetime psychopathology at the time of enrollment remained well.

At five-year follow-up, Hillegers et al. (2005) found that the lifetime prevalence of BD increased from 3% at baseline to 10% in a sample of 129 high-risk adolescents. Unipolar depression was found to be a risk factor for, and the first sign of, the subsequent development of BD-I (n=5) and BD-II (n=8) in 12 of 13 subjects (Hillegers et al., 2005).

Also of interest with regard to features of the initial prodrome of BD are studies of course and outcome in which subjects are observed to convert to BD-I or BD-II during follow-up. These are naturalistic studies, which also include subjects without a known family history of BD. Typically, subjects are included when affective problems are evident and they are admitted to assessment and treatment. Thus, these subjects are included at a relatively late stage of what may turn out to be an initial prodrome of BD-I or BD-II. Birmaher et al. found that 25% of 92 children and adolescents with BD-NOS had converted to BD-I or BD-II at two-year follow-up (Birmaher et al., 2006). At four-year follow-up, 38% of 141 BD-NOS subjects had converted to BD-I or BD-II (Birmaher et al., 2009). This study demonstrates that a subgroup of BD-NOS youth who subsequently develop BD-I or BD-II experience a prodromal illness state that is episodic, with subsyndromal and, less frequently, syndromal episodes with mainly depressive and mixed symptoms and rapid mood changes.

1.2.4 Depression features suggestive of forthcoming BD

Findings suggest that certain characteristics of those who later develop a BD, and certain features of their depressive episodes, may help distinguish these individuals from those who experience MDD without subsequent (hypo)mania. Studies have indicated that these characteristics and features (including a family history of BD) can be detected, if looked for carefully, in the initial depressive episodes of approximately one quarter of patients diagnosed with BD (Manning et al., 1997; Benazzi, 1997; Hantouche et al., 1998). The most frequently noted signs associated with the switch to mania are an early age at onset of depression (prior to age 25) and the presence of psychotic symptoms (Othmer et al., 2007). Less commonly identified indicators include atypical symptoms, such as hypersomnia with psychomotor retardation, and increased appetite; melancholic symptoms, such as a combined agitated and

retarded depression, and marked guilt; postpartum depression; antidepressant-induced mania; multiple episodes of depression (prior to the onset of the first mania); a premorbid hyper- or cyclothymic personality; abrupt onset of depressive episodes; seasonal vulnerability; and marked self-reproach (Akiskal et al., 1983; Winokur and Wesner, 1987; Akiskal et al., 1995; Mitchell et al., 2001; Rybakowski et al., 2005; Bowden, 2005; Perlis et al., 2006; Othmer et al., 2007; Muzina et al., 2007; Angst et al., 2009). Although these depression features may be suggestive of subsequent BD, none is useful as an early indicator of the FMAE of BD-II, which is explored in this thesis.

In sum, the findings presented in this section suggest a number of clinical signs that may be predictive of BD. These features may alert clinicians that an individual should be monitored. However, none of them are pathognomonic for BD, and the risk for false positives is substantial when they are used to identify at-risk individuals. For instance, the depression features reported also occur in individuals who never develop BD and do not occur in many individuals who develop BD. The symptoms identified during the bipolar prodrome are even more nonspecific and may occur in a number of disorders or simply be manifestations of a normal developmental process during childhood and adolescence that may subside with increased maturity. Thus, it remains challenging to reliably identify at-risk individuals and prospectively predict BD.

1.3. Are true prodromes predictors of forthcoming bipolar disorder?

The term "true prodrome" has been used in the psychosis and schizophrenia literature to characterize all pre-onset symptoms that are verified retrospectively after the disorder has become manifest (Kane et al., 2003). However, many of the true prodromes found in psychosis/schizophrenia and BD research are highly nonspecific and not necessarily early manifestations of the subsequent disorder (evolution of one illness over development and time). Hence, they may not be genuinely related to the subsequent BD and thus may be of little use as prospective predictors of the disorder. Instead, the symptoms may represent independent or separate conditions or disorders (including passing responses to adverse life events) or secondary symptoms of such conditions, a general vulnerability to non-specific psychopathology (partially shared diathesis), or even normal developmental dysregulations of mood. These questions are unanswered in the literature and difficult to disentangle.

1.4 Aims of the thesis

The main objective of this thesis was to acquire more knowledge about symptoms and signs (behaviors) of the initial prodrome of BD in general and BD-II in particular. The overarching aim was to contribute knowledge to the field of early detection and prevention of BD. The following research questions were addressed in the individual papers.

Paper I:

Main question:

1) What is the current status of the literature on symptoms, signs and temporal aspects of the initial prodrome of BD?

Subquestions:

1.1) Are there symptoms and signs that characterize the distal prodrome of BD?

1.2) Is there a developmental progression of symptoms and signs throughout the prodrome?

1.3) How specific to BD are the prodromal symptoms and signs?

1.4) Are there any differences in prodromal expressions between subtypes of BD?

1.5) Are there any differences in prodromal expressions associated with age at full BD onset?

1.6) Are there any differences in prodromal expressions associated with presence or absence of a family history of BD?

1.7) How common is it to experience a prolonged prodromal phase?

1.8) What is the typical duration of the prodrome?

Paper II:

2) What types of clinically significant symptoms and behaviors do patients with BD-II experience prior to the first major affective episode?

3) What is the duration of the prodrome from the first clinically significant symptom to the onset of the FMAE?

4) Do different symptoms or categories of symptoms emerge in a certain sequential order throughout the prodrome?

5) Are there subgroups of BD-II patients who differ in how they function during the initial prodrome, the type and extent of symptoms they experience, and onset ages?

Paper III:

6) To what extent might the prodromal symptom instances of different symptom categories be regarded as genuine clinical predictors of the first major affective episode of BD-II?

Paper IV:

7) To what extent do the instances of the three symptom classes hypothesized to be "likely", "possible" and "unlikely" early manifestations of the FMAE of BD-II, respectively, emerge within the last three years and the last year before the FMAE?

8) What is the duration between the onset of symptom instances and the onset of the FMAE for the three classes of symptoms?

2 Position within the philosophy of science paradigms

All researchers approach their studies with a certain paradigm or worldview that guides their inquiries. These assumptions may or may not be conscious and articulated. A paradigm can be defined as a "set of interrelated assumptions about the social world which provides a philosophical and conceptual framework for the organized study of that world" (Filstead, 1979)(p.34). These assumptions or beliefs are "… basic in the sense that they must be accepted simply on the faith (however well argued); there is no way to establish their ultimate truthfulness" (Guba and Lincoln, 1994) (p. 107).

In an attempt to clarify my position, I discuss below different aspects of my research project in light of the philosophical and practical differences between the postpositivist and constructivist approaches. To this end, I will utilize three of the four undergirding philosophical assumptions with implications for practice presented by Guba and Lincoln (Guba and Lincoln, 1988): the ontological, epistemological, and methodological assumptions. To avoid making this lengthy section even longer, I will not discuss their fourth assumption, called axiological (researcher values), nor a fifth added by Creswell (Creswell, 2007) called rhetorical (concerning the language style of the published research).

The positivist/postpositivist (standard) approach has its origin in the natural sciences, aiming at generalizing findings (nomothetic perspective), whereas the constructivist approach associated with the social/human sciences is concerned with specifying phenomena (ideographic perspective). Dilthey claimed that the goal of *Naturwissenschaft* (natural science) is scientific explanation (*Erklaren*), whereas the goal of *Geisteswissenschaft* (human science) is understanding (*Verstehen*) of the meaning of social phenomena (Schwandt, 2000). The postpositivist-constructivist positions are often portrayed as a dichotomy representing two mutually exclusive paradigms: "Realism and relativism, value freedom and value boundedness, cannot coexist in any internally consistent metaphysical system (…)" (Guba and Lincoln, 1994) (p. 116). It is claimed that adherence to one position implies that other assumptions and choices, e.g., type of methodology, automatically follow. However, others disagree with this notion and have sought to develop qualitative methods more in line with the postpositivist paradigm (Glaser and Strauss, 1968). I find that both the postpositivist (critical realism) and the constructivist (relativism) positions resonate with my worldview and with different aspects of my research project.

2.1 Ontology

Ontology concerns the nature of reality and being. More specifically, ontology addresses the following questions: What is the form and nature of reality? What can be known about that reality?

Popper's postpositivism arose out of dissatisfaction with some aspects of the logical positivist/empiricism stance (e.g., Carnap; the Vienna school). Whereas the positivists accept an (observable) objective, verifiable reality ("naïve realism"), the postpositivists acknowledge an objective reality that is only imperfectly apprehendable. The critical realist is *critical* of our ability to know reality with certainty (Guba and Lincoln, 1994). The ontological differences between the two positions are reflected in the positivists' emphasis on "theory verification," whereas the postpositivist position emphasizes "theory falsification" (Hacking, 1999) (p. 3-4). Both paradigms operate from both nomothetic and etic perspectives. Nomothetic research and assessment focus on uncovering general patterns of behavior that have a normative base. Their primary goals are prediction and causal explanation of phenomena. Etic refers to universal laws and behaviors that transcend nations and cultures and apply to all humans. Positivism and postpositivism serve as the primary foundation and anchor for quantitative research (Ponterotto, 2005).

Constructivism adheres to a relativist position that assumes multiple apprehendable and equally valid realities. Essentially, constructivists hold that reality is constructed in the mind of the individual rather than being an externally singular entity. Knowledge and truth are contingent on convention, human perception, and social experience, are a product of inter-subjectivity instead of the classical objectivity, and focus on viability instead of absolute truth. The goals of constructivism are both idiographic and emic. Idiographic research focuses on understanding the individual as a unique, complex entity. Emic refers to constructs or behaviors that are unique to an individual or a sociocultural context and are not generalizable (Ponterotto, 2005).

Reflections on my ontological assumptions: Basically, I adhere to the position put forward by Ian Hacking that there exist "objects" that are "in the world" in a commonsensical way (Hacking, 1999) (p. 21). These "objects" are not socially constructed. In the context of my project, this means that I believe that the symptoms that people experience are real, worldly "objects". The same is true for signs observed by relatives. I believe that there is some core of truth and universality determined by our common biology that leads to interpersonal

similarities in how BD symptoms and signs are experienced and manifested. However, these phenomena might only be studied by means of some kind of representations: e.g., the way in which symptomatic experiences are conveyed by language in an interview setting with a researcher, as responses to questionnaires, or using other approaches. In line with the postpositivist position, I believe that it is possible to study the nature or phenomenology of symptoms of BD in an imperfectly apprehendable way. I do not believe in one fixed and absolute truth about reality, or in an extreme version of relativism, but in approximate truths: that some prodromal symptoms are commonly experienced in at least some people with BD, and hence that there exist regularities that are true and universal in a limited sense given the context of BD. That said, I must emphasize that I do not think that the challenges regarding measuring or assessing reality (representations) are only a matter of imperfect methodologies, but also that the perception of reality and truth in humans has an approximate or unstable quality to it. The ways in which symptoms are experienced and communicated are to a certain degree contextual and changeable, and thus somewhat constructed (more discussion on the nature of knowledge appears in the epistemology section below).

I consider the *diagnosis* of BD to be a social construction. The diagnosis denotes a cluster of symptoms and signs that are repeatedly observed and appear to be in conjunction to some degree. However, the construct of BD is not "inevitable", to quote Hacking (1999). It is decided upon by a process of consensus among experts in the field. The construct and borders (inclusion criteria) of BD are a reflection of the current knowledge status and the matrix (e.g., social/professional cultures and events) from which it originates and in which it is situated, and hence, they are subjected to changes over time. For instance, although manic-depressive illness was previously synonymous with BD-I, the concept of BD has subsequently been expanded to include BD-II as a separate disorder.

I think it is difficult to take a clear stance adopting either a postpositivist or constructivist position regarding how to conceive reality and what can be known about reality. The philosophical foundations of the two positions raise a lot of questions. Additionally, I find it difficult to know how the two paradigms are delimited in relation to each other in practical terms. Theoretically, they are conceived of as being sharply delimited, reciprocally excluding categorical positions, at least by some, as previously mentioned. Pragmatically, I think such a sharp division is unhelpful and unrealistic. Therefore, if the two paradigms are instead conceptualized as representing opposite poles on a continuum, where does one end and the other begin? Do they overlap at some point? Regarding the nature of reality, I believe that reality is essentially impermanent, but that certain aspects of reality are more stable than

others. The physical aspects of human biology are relatively invariant across millennia, whereas human ideas (mental content) may result in the construction of social cultures or subjective perceptions that are rather short-lived. Hence, considering the question of what can be known about reality, I think that the period of validity of scientific findings is hugely variable. Some findings are highly transient and contextual glimpses of a momentary reality, whereas others are more durable. I also think that all aspects of our knowledge of reality are contextual to a certain degree and hence never verifiable as ultimate and universal truths in the strictest sense. However, some aspects of reality are closer to the universal end of the continuum, whereas other aspects are more context sensitive and closer to the specific or ideographic end of the continuum. I agree with the constructivist notion of multiple realities regarding subjective experiences. It is always possible to create different perspectives on something, depending on which aspects one chooses to emphasize. This does not mean that every imaginable interpretation is equally plausible or true, which implies that I disagree with the constructivist notion that all of the multiple realities are equally valid. Hence, given the context of BD, there may exist a limited set of prodromal typologies that may be universally true in an approximate sense. This does not mean that every individual within one typology has had the exact same experiences or that their experiences are completely stable. After all, typologies or categories are abstractions and rough oversimplifications of reality.

Although it is beyond the scope of this particular study, I regard the ultimate aim in my field of research to be "enabling the prediction and control of phenomena", namely full BD, which is a postpositivist position according to Cuba and Lincoln (1994, p. 113). Based on my current reflections on the topic, I tentatively define my ontological position to lean toward postpositivism while at the same time acknowledging elements of the constructivist position when it comes to contextualism, especially regarding certain social and subjective aspects of reality.

2.2 Epistemology

Epistemology, or the theory of knowledge, is concerned with the nature and scope of knowledge. Epistemology primarily addresses questions such as: "What is knowledge?" and "How is knowledge acquired?" In this section, I will focus on the latter question first, and more specifically on the relationship between the "knower" (the research participant) and the "would-be knower" (the researcher).

Postpositivists advocate for a modified version of the positivists' objectivism/dualism. They acknowledge that the researcher may have some influence on the topic being

researched, but objectivity and researcher-subject independence remain important guidelines for the research process to avoid influencing the data and introducing biases that will weaken the validity and reliability of the findings.

The constructivist position espouses a hermeneutic approach, which maintains that meaning is hidden and must be brought to the surface through deep reflection (Schwandt, 2000). This reflection can be stimulated by the interactive researcher-participant dialogue. Thus, a distinguishing characteristic of constructivism is the centrality of the interaction between the investigator and the object of investigation. The researcher and the study participants jointly create (co-construct) findings through their transactional dialogue and interpretations. Only through such transactions can rich descriptions and understandings of the deeper meaning of lived experience evolve (Ponterotto, 2005).

Reflections on my epistemological assumptions: I think that my practical position on the relationship between the researcher and the study participant depends on the aim of each particular study and the level of detail and complexity of the information that one wishes to acquire. I think that certain topics in the social sciences necessitate that researchers interact with study participants to elicit complex knowledge. Given my position that there exists a core of experiential truth, operating within certain boundaries, I view the role of the research interviewer to be more like that of a facilitator than like that of a co-constructor. The interviewee is the "owner" of the information. The interviewer and the interaction affect what the interviewee reveals or constructs. The researcher must therefore adopt a cautious attitude. The postpositivists' critique regarding "enmeshment" should be taken seriously. There is a risk of introducing unnecessary and exaggerated researcher biases. Although I think it is impossible to be value-free when interacting with study participants, I think it is important to strive to be as neutral as the particular research project permits. Such neutrality may be in line with the postpositivists' modified version of the positivists' dualism/objectivism.

Another attitude that I hold that may tend more towards the constructivist position is that I find it acceptable to suggest how the interviewee might connect or understand phenomena. This approach may clarify and validate the ideas being conveyed by the informant, both spontaneously as a response to open questions and as a response to more specific probing by the interviewer. Such hermeneutic/dialectical processes (circles) of questions/suggestions and answers may facilitate a more detailed, differentiated and concise account of the interviewees' experiences and interpretations, yielding more informed insights. However, I think that suggestions should only be given for the purpose of clarification and that it is of vital

importance that suggestions always be actively verified (or rejected) by the interviewee before they can be counted as research data.

What is the nature of the knowledge acquired through my research interviews? I find that my position on this question overlaps with my ontological view to a certain degree. All collected information is retrospective. The data are reconstructed from memory traces in the mind of the interviewee. The end result is affected and facilitated by the interplay of contextual cues of the past, associations of various kinds, and the interpersonal exchanges occurring in the interview situation. I believe that insights (and memories) are constantly moving targets in the process of reflection (and remembering). Insight is not a static phenomenon. For instance, it is known that a memory is somewhat altered every time it is contemplated, and thus, it is a reconstruction rather than a perfect reproduction of an experienced event (Baddeley, 1999). Hence, findings should not be reified as expressions of a final or ultimate ideographic truth. Rather than being perceived as the end station of a reflective process, they represent views about a topic at a particular point in time. This view implies that methodological attempts at triangulation and reliability checks may yield divergent findings at different points in time. This process of reflection is externally and actively stimulated to a larger extent in research interviews compared to when participants are given, e.g., a questionnaire. In my view, the interview approach increases the likelihood of acquiring information that is more valid.

As with ontology, I find it difficult to present myself as either a postpositivist or a constructivist. I think my notion of the nature of knowledge and my pragmatic view on how to generate valid information somewhat favor the constructivist position. Simultaneously, I feel anchored in the postpositivist position. I do not think the information acquired from the participants is the final version of their truth. I believe that the participants may construct and communicate a range of somewhat different versions of their experiences depending on the interview process, contextual factors, and other influences. However, I think that all versions are usually related to a common source of personal truth delimited by more or less clearly defined boundaries. I also believe that the hermeneutic process taking place in in-depth interviews leads to a version that the participants experience as more coherent and convincing, at least at the time.

2.3 Methodology

Methodology refers to the process and procedures of the research. As mentioned, some claim that research methods should flow from one's position on ontology and epistemology.

Postpositivists attempt to simulate, as closely as possible, strict scientific methods and procedures in which variables are carefully controlled or manipulated. Experiments are the ideal, and research in non-experimental settings is designed to imitate the methodology of experiments as closely as possible. A postpositivist researcher may use brief, semi-structured interviews and may use multiple raters in an attempt to identify a single approximate reality through either calculations of inter-rater reliability or consensual agreement upon identified themes (Lincoln & Guba, 1985; Ponterotto 2005).

In marked contrast, constructivists, given their stance on the centrality of intense researcher-participant interaction and on the need to be immersed in the participants' world over longer periods of time, more often embrace naturalistic designs. Naturalistic inquiry involves qualitative research methods, such as in-depth interviewing and participant observation. A constructivist researcher may interview only a handful of individuals for longer periods of time and, when analyzing the transcript data, will not seek other researchers' consensus on the identified themes. The point here is that there are multiple meanings of a phenomenon in the minds of people who experience it, and there are also multiple interpretations of the data (multiple realities); the researcher neither attempts to unearth a single truth from the realities of the participants nor tries to achieve outside verification of his or her analysis. Thus, it is irrelevant whether a different researcher reading the same typed interview transcripts arrives at different themes. The reader should judge the rigor of the study based on its thick description (Lincoln and Guba, 1985; Ponterotto, 2005; Creswell, 2007).

Reflections on my methodological assumptions: My methodological approach is qualitative, which is typically regarded as constructivist. My reason for choosing a qualitative methodology might not be self-evident given my partial adherence to the postpositivist assumptions about ontology and epistemology. However, I supplement the qualitative analyses with quantitative analyses to generate hypotheses about aspects that might have some validity or generalizability beyond the experiences of the study participants. First and foremost, I chose in-depth interviews as a means of exploring an under-investigated area of research and to collect experiential descriptions of prodromal phenomena and the context in which they were situated. To this end, I regard inductive qualitative methods to be superior to deductive quantitative methods (e.g., questionnaires).

Regarding reliability or trustworthiness, I think it would be preferable from a scientific point of view to have other researchers examine at least some parts of the data to reach some level of consensus. Primarily, I think this step is important for diagnostic classifications given the existence of official criteria.

2.4 Conclusions

In this chapter, I have tried to clarify my current position on the philosophy of science. I realize that my leaning toward the postpositivist stance on ontology is quite prominent in some respects. I do not believe in the positivist notion of a static, objective reality when it comes to how humans perceive, recollect and understand experiences. On the other hand, I do not believe in absolute relativism and contingency. I believe that there exist multiple potential and changeable versions of ideographic truth, but that they usually depart from some common source of subjective experiential reality. This leads me to my epistemological assumptions, which I think tilt towards constructivism. In my project, I essentially ask participants to reconstruct past experiences and construct a narrative based on available historic information. In general, I think the process of reflection leads to informed insight, where bits and pieces gradually fall into place aided by the interaction with the interviewer and information provided by family members (and psychiatric or medical records when available). To attain the most reliable and valid information possible, I think it is necessary for the researcher to engage in a relatively extensive interaction with the participants. My choice of qualitative methodology, associated with constructivism, follows as a natural consequence. To conclude, I think I favor the ontological position of postpositivism, but with special attention to contextual factors.

3 Methodology

3.1 Paper I

Paper I is a systematic review of the symptoms and signs of the initial prodrome of BD (Skjelstad et al., 2010).

3.1.1 Study acquisition

The databases PsycINFO (from 1806 to January 2009), PubMed (from 1950 to January 2009), EMBASE (from 1980 to January 2009), and British Nursing Index (from 1985 to January 2009) were searched for original studies that investigated and systematically reported on individual symptoms and signs of the initial prodrome of subjects later diagnosed with BD. The following search profile was performed: ["bipolar disorder" OR "manic–depressive illness"] AND ["symptoms" OR "phenomena"] AND ["initial" OR "early" OR "prodromal" OR "prodrome" OR "premorbidity/premorbid" OR "prediction/predictors" OR "antecedents" OR "precursors" OR "early identification" OR "early recognition"]. All journals (peer-reviewed, non-peer-reviewed, peer-reviewed status unknown) that were searchable in the databases were included. Publications had to be written in English, Norwegian, Danish or Swedish. This search yielded 2274 studies, including duplicates. The search was performed by a librarian in collaboration with the first author.

3.1.2. Study selection

Hits from the search were assessed for relevance according to the following inclusion and exclusion criteria. Studies that reported on symptoms and signs of the initial prodrome of BD were included. Given the perceived arbitrariness of the current duration criterion for diagnosing hypomania (Angst et al., 2003b; Kowatch et al., 2005; Phelps et al., 2008), studies with subjects who did not meet the four-day criterion were included. We excluded: 1) studies that reported only diagnostic status prior to the development of BD (high-risk offspring studies and studies on clinical course and outcome) (Geller et al., 2001; Hillegers et al., 2005; Birmaher et al., 2006; Duffy et al., 2007); 2) case studies (Thompson et al., 2003); 3) studies on relapse prodromes (Jackson et al., 2003; Lam and Wong, 2005; Sierra et al., 2007); and 4) studies that included a mixture of subjects with initial and relapse prodromes without reporting the two categories separately (Gupta et al., 2004). The articles that were included were selected based on their title and abstract and, when necessary, examination of the full

text to assess relevance. Finally, reference lists from the included studies and other relevant articles were searched manually to identify additional studies.

3.1.3. The analyses of the findings

To reduce the symptoms reported into comprehensible units, we made a list of all of the symptoms that are presumed to be initial or early symptoms of the prodrome (distal prodromes) across the studies and organized them into seven clinically meaningful categories and one other category. Some studies clearly distinguished between symptoms in early versus later stages of the prodrome. In these studies, the symptoms of the earliest stage were regarded as distal prodromes. Other studies did not distinguish between stages or age at symptom onset, which represented a challenge. In these cases, for lack of a better way to organize the findings, we chose to include all symptoms reported in these studies as early symptoms. We then ranked the categories according to the number of studies that reported symptoms within each category (see Table 2, paper I). Due to the methodological diversity of the studies, it was not possible to conduct a meta-analysis of the prevalences of various symptoms.

In Table 3, we present the frequencies of symptoms across age groups reported by two of the studies. Individual symptoms are ranked from most to least frequent. In addition, Table 3 displays the findings of a study that only investigated symptoms of the late stage of the prodrome (proximal prodrome). Despite variations in which symptoms were found to be most common, the table illustrates a progressive development of the types and frequencies of symptoms with age. To answer the other research questions posed in paper I, we simply explored the content of the reviewed articles for relevant data and reported these under different headings in the text.

3.2 Papers II, III and IV

Papers II, III, and IV present findings from an original research project on clinical phenomenology prior to the first major affective episode (FMAE) of BD-II (Skjelstad et al., 2011a; Skjelstad et al., 2011b).

3.2.1. Design

This project was an exploratory retrospective study that utilized a qualitative methodology supplemented by quantitative analyses. Using a qualitative design enabled us to pursue an in-depth exploration of an under-investigated field of research in a flexible and open manner without being restricted by predefined concepts and questionnaires. Additionally, a qualitative

approach made it possible to collect complex data that could be analyzed in numerous ways. Hence, we gave priority to the in-depth study of a limited sample to search for findings that could generate hypotheses to be tested on larger samples in future studies. Furthermore, a qualitative approach allowed us to be mindful of the limitations of earlier studies (Skjelstad et al., 2010).

Due to the purpose and nature of our study, we did not adhere to one specific qualitative method. Our approach may best be considered as a multiple-case study in which within-case analyses were followed by thematic analyses across cases, often called cross-case analyses (Creswell, 2007). In addition to following basic qualitative principles, we were also inspired by and incorporated elements from different qualitative approaches (Glaser and Strauss, 1968; Charmaz, 2006; Kvale and Brinkmann, 2008; Smith et al., 2009).

3.2.2. Recruitment procedures

Patients with BD-II (WHO, 1992; APA, 2000) were recruited from outpatient clinics and psychoeducation courses on BD at Buskerud Hospital, Norway. Together with three other hospitals in the region, Buskerud Hospital merged into Vestre Viken Hospital Trust in 2009. The recruitment procedure was nonprobabilistic but purposive in the sense that relatively young patients (initially < 30 years) with a clinical diagnosis of BD-II were recruited. In addition, at least one family member or other person with first-hand knowledge of the patient's life history was required to participate.

Potential patient participants from the outpatient clinics were identified through anonymous lists of BD patients containing each patient's identification number, diagnoses, age, and therapist's name. These lists were produced by the staff at the hospital administration at my request to ensure that the patients' identity was not revealed to me. I then contacted each therapist by phone who identified their patient through his/her identification number without revealing the patient's identity to me. I inquired about the correctness of the registered diagnoses. If the patient was a candidate for the study, I asked the therapist to ask the patient for oral consent to a phone call from me providing information about the study. Appointments were then made with patients who were interested in participating and had at least one suitable family member who was willing to participate.

BD-II patients that I evaluated for participation in psychoeducation courses on BD were informed about the study and asked to participate. Occasionally, my course collaborators referred potential study participants to me.

The study's youngest and only minor-aged participant was recruited from the child and adolescent outpatient clinic at the hospital, where she was diagnosed while participating in another research project on BD.

Another patient, who was also participating in another research project on BD, was recruited from the Oslo University Hospital (Rikshospitalet) because of the eventual exhaustion of potential study participants at Buskerud Hospital.

Patients who were approached were generally willing to participate. Because most patients had only recently been diagnosed with BD, they were eager to have their diagnosis reassessed and to learn more about BD.

3.2.3. Participants

The final sample was composed of 15 BD-II patients (11 females; 4 males). Twenty-two family member informants (15 mothers, 4 fathers, 2 spouses, and 1 sibling) participated. At least one parent of each patient participated.

All patients fulfilled the duration criterion of four days of hypomania, with the exception of one (ID 8), who had only experienced two consecutive days of hypomania. Recent research suggests that the hypomania of subjects experiencing recurrent two-day episodes does not differ significantly from the hypomania of subjects experiencing four days of such symptoms (Benazzi, 2001; Angst et al., 2003a; Angst et al., 2003b). We decided to include this patient in the final sample because of the distinctiveness and recurrence of his hypomanic symptoms.

Another patient (ID 6) was diagnosed with BD-NOS at the time of referral, having experienced only recurrent episodes of hypomania lasting for a few hours. Nonetheless, the interviews were performed. At diagnostic reassessment one year and eleven months later, the patient met the duration criterion for hypomania and was kept in the final sample. The remaining patients were enrolled in the study at a median of 8.5 months (range: 1 to 45 months) after being diagnosed with BD-II.

The final sample includes two patients aged 30+ at inclusion (ID 13, aged 35; and ID 15, aged 41). This was a consequence of the eventual exhaustion of potential participants at the hospital. Thus, to recruit more patients, I relaxed my original inclusion criteria of age less than 30 years at inclusion. The reason for setting this age limit was, first, that most individuals who develop BD experience onset before age 30, which would enhance the likelihood of being able to recruit enough patients within a relatively small hospital setting, and second, and more importantly, that including relatively young and newly diagnosed patients might reduce recall biases somewhat compared to older patients with a longer history of syndromal BD.

Furthermore, I reasoned that relatively young patients would be more likely to have living parents who would be willing and able to participate.

Twenty-one patients were initially recruited. Of these, four were reassessed as having other disorders: schizophrenia (n=1); schizoaffective disorder (n=1); BD-I (n=1); and unstable personality disorder (n=1). Two patients withdrew from the study during data collection.

The decision on the number of BD subjects to include in the study was based on, and restricted by, the available resources. I would have preferred to include 20-30 BD subjects to strengthen the data on which the hypotheses are based. Thus, I did not adhere to the "theoretical/data saturation" principle (i.e., to discontinue recruitment when no new information or themes are observed in the data) that is utilized in many qualitative studies (Guest et al., 2006; Creswell, 2007).

3.2.4. Assessments

Clinical BD diagnoses were reassessed and Axis I comorbidities were examined via semi-structured diagnostic interviews that I performed. Professor Malt or other senior clinicians/researchers were consulted in unclear cases. Fourteen patients were assessed with the Mini International Neuropsychiatric Interview (MINI) version 5.0 according to DSM-IV criteria (Sheehan et al., 1998). Modules A-D of the MINI-PLUS were utilized for a more comprehensive assessment of BD. One patient who was 14 years old at inclusion was assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime versions (Kaufman et al., 1997). Demographic and clinical characteristics were obtained using a modified version of the Stanley Network Entry Questionnaire (Suppes et al., 2001). The clinician-rated version of the 30-item Inventory of Depressive Symptoms[2] (Rush et al., 1996) and Young's Mania Rating Scale (Young et al., 1978) were used to ensure that the patients were relatively euthymic at inclusion. If not, or if a patient experienced mood episodes during the interview series, further interviews were postponed until the patient had recovered.

Blood samples and standard electroencephalography (EEG) were used to exclude other possible causes of BD symptomatology. Professor Malt evaluated the blood tests and EEG reports for deviations that could produce symptoms that had incorrectly been interpreted as manifestations of BD. No patients were excluded from the study based on such findings. The

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[2] I completed an 18-hour training course in the use of IDS (and MADRS). The reliability coefficients (single measure) based on 9 interviews are as follows: IDS: ICC = 0.99 (95% CI: 0.94 – 0.99); MADRS: ICC = 0.94 (95% CI: 0.76 – 0.99)

test results were provided to the patients' physicians, and recommendations were given when relevant.

3.2.5. Exploratory life-course interviews

I conducted a series of in-depth interviews with each patient and his/her family members covering the patient's life course from fetal development/birth to the present. Typically, the patients were first interviewed alone and then again with family members. Between interviews with a patient, the audio/video recording of the previous interview was reviewed to recapitulate important information, take notes, reassess the patient (e.g., regarding diagnoses), and prepare follow-up questions on topics and phenomena that required further elaboration. Occasionally, I transcribed interviews during ongoing interview series. Because of the large amount of labor involved, most interviews were transcribed later by hired transcribers. An event history chart was used during and after the interviews to register and keep track of the patient's life history data, such as important milestones, life events, changes in functional level, onset and duration of symptoms, how the emergence of symptoms was interpreted in relation to life events and circumstances at the time, and so on. The chart data evolved as new information appeared. The interview series was open-ended, and the exploration continued in repeated question-and-answer cycles until no new information of significance was obtained. The mean total duration of the interviews was approximately 10 hours per patient.

The in-depth interviews were loosely structured to elicit 1) descriptions of clinically significant changes (e.g., symptomatic and behavioral); 2) the context in which the changes took place; 3) how the participants understood the changes; 4) how the symptoms evolved from emergence to the onset of the FMAE; 5) the patient's functionality in different contexts (e.g., at home, school, and among friends); and 6) the patient's self-perceptions and others' perceptions of the patient during different developmental periods.

Given our interest in exploring the prodromal phase of BD-II, the time period preceding the estimated time of full onset (MDE + hypomania) was emphasized. Efforts were made to accurately pinpoint the patient's age at onset of symptoms/behaviors and at the time of the FMAEs of both polarities. These were dated based on a best estimate obtained from dialogue with and between the patient and his/her family members. Repeated elaborations were often needed to optimize precision. Rare cases of disagreement were resolved between the participants. Other sources were consulted when possible (e.g., medical and school records, reports, and personal diaries). A phenomenon was regarded as present if it was described by either the patient or a family member and was assessed to be of clinical significance. Not

surprisingly, parents provided the most specific information about early childhood years, whereas the patients were the better source of information concerning the time period from adolescence onwards. When a symptom was recalled by both the patient and family members, they typically reconstructed a narrative together and reached a common understanding about the symptom's temporal and contextual characteristics.

3.2.6. Qualitative analyses

Data were analyzed case by case and then compared across cases. The qualitative data software QSR NVivo 8 was used as the main tool for coding and organizing transcribed textual data. In addition, a variety of tables and figures/charts were developed in the process of exploring and analyzing the data.

Using NVivo, segments of text were coded thematically and labeled according to the phenomenon being described by the participants (open coding), e.g., "intense anger" (paper II). Codes were then categorized according to common features, e.g., "irritability and aggressiveness." Throughout the analysis, codes and categories were created and elaborated in a bottom-up (inductive) fashion through a continual and flexible dialogue with the data. The final hierarchical structure took multiple variables into account, including whether symptoms preceded depressive or hypomanic episodes and whether prodromal phenomena were reported by the patient or by family members.

We also approached the data from other angles in search of patterns that could generate hypotheses. We profiled the patients according to the participants' descriptions of the patient's prominent and enduring characteristics prior to the FMAE (paper II). These included temperament, personality traits, and stable abilities/functions. Continuous neurocognitive symptoms, such as attention difficulties associated with attention-deficit/hyperactivity disorder (ADHD) and specific learning difficulties (dyslexia and dyscalculia) with onset early in childhood ($\leq$ age 7), were also regarded as enduring characteristics and were not included in the observations of symptoms and behaviors. We regarded the neurocognitive symptoms as manifestations of an underlying and stable dysfunction that were more trait-like than the other reported symptoms. Characteristics were tentatively rated on a five-point scale from "markedly low level" to "markedly high level" with "average" at the midpoint. Seven characteristics were chosen based on their ability to differentiate between patients and, hence, form distinguishable subgroups. One of these characteristics ("neurocognitive deficits") was dichotomously recorded as present or not present. After identifying meaningful patient subgroups, we explored potential group differences.

In an attempt to disentangle the symptoms that were most likely to be intrinsically related to the subsequent FMAE (cfr. 1.3), which we named "genuine clinical predictors" (GCPs), we approached the reported symptoms as follows (paper III). First, we coded each symptom according to its temporal presentation in the interim between symptom onset and the onset of the FMAE. Three temporal codes were used. Symptoms labeled "temporary" were only present for a limited time period and did not reappear before the onset of the FMAE. However, if the same symptom occurred for a limited time period at two contextually independent occasions (e.g., sadness after the parents' divorce at age 4 and again after the grandfather's death at age 10), we regarded it to be temporary and only counted it once. Symptoms labeled "episodic" were recurrent before the onset of the FMAE. Symptoms labeled "chronic" were present almost constantly (e.g., multiple daily mood swings/temper tantrums) or were elicited repeatedly by special situations or circumstances (e.g., the presence of a phobic object). If the temporal characteristic of a symptom changed during the pre-FMAE phase (e.g., chronic mood swings that became episodic), we coded the characteristic that developed later.

Second, symptoms were coded according to whether life events at the time of symptom onset were recalled by the participants as having precipitated or elicited the symptom. If so, the symptom intensity was coded as appropriate or exaggerated in relation to the life event. Three contextual codes were used. A symptom viewed as an understandable reaction of appropriate intensity in relation to a specific life event (e.g., sadness following parents' divorce) was labeled a "normal response". A symptom assessed as having disproportionally strong intensity in relation to the eliciting life event (e.g., violence toward others when not getting one's way) was labeled an "exaggerated response". A symptom that appeared to be unrelated to the context or to a specific life event, such as the onset of mood swings for no apparent reason, was labeled "inexplicable". Symptoms coded as normal or inexplicable responses were fairly easy to categorize according to the participants' descriptions. Some codes of exaggerated responses were based on the authors' judgments.

As an analytic model, we tentatively outlined three theoretically derived and alternative sets of criteria for defining GCPs, which are based on the six above-mentioned temporal and contextual characteristics. The inclusion criteria for definitions A, B, and C are successively narrowing. Hence, symptoms meeting the stricter criteria also meet the broader criteria.

Definition A (broad) includes symptoms characterized as episodic or chronic, which implies that all temporary symptoms are excluded. Definition B (intermediate) includes episodic and chronic symptoms that are characterized as exaggerated or inexplicable. This

stricter definition considers contextual characteristics of symptoms in addition to temporal characteristics. In contrast to definition A, normal responses to life events are excluded from definition B. Definition C (strictest) includes episodic and chronic symptoms characterized as inexplicable. Hence, in contrast to definition B, exaggerated responses are excluded from definition C (Figure 1).

Figure 1

The inclusion criteria of the tentative "genuine clinical predictor" definitions A, B, and C. The criteria are successively narrowing.
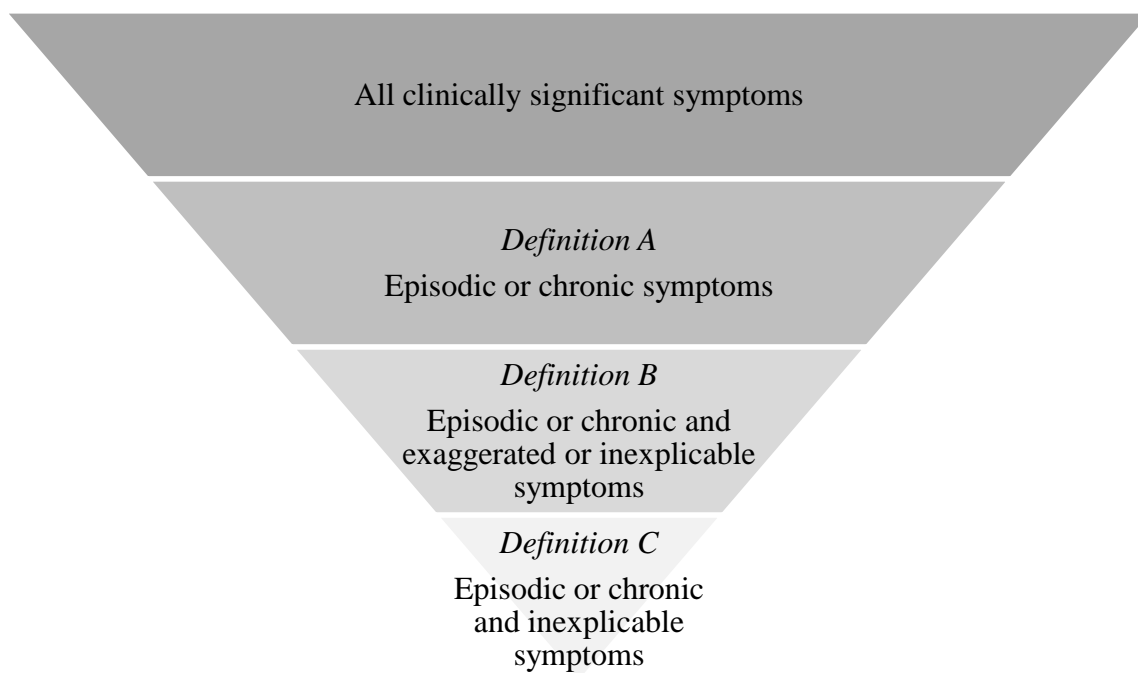
In an attempt to validate the GCP criteria we hypothesized to be the most likely, the definition B criteria, we explored and compared the time of onset and duration of symptom instances that met these criteria, which we labeled "GCPs", with those of two other symptom classes. However, because the journal to which we submitted paper IV did not approve of the term "genuine", even though this term had been accepted by and published in *Journal of Affective Disorders*, we had to substitute the term "genuine clinical predictors" with the term "likely early manifestations" (LEMs). The two other symptom classes to which LEMs were compared were: "possible early manifestations" (PEMs; symptom instances characterized as episodic/chronic and normal responses to life events, which we regarded as less likely to be early manifestations of the FMAE of BD-II) and "unlikely early manifestations" (UEMs; symptom instances characterized as temporary, which we hypothesized to be unrelated to the

FMAE). If the LEMs emerged in closer proximity to the FMAE compared to the PEMs and the UEMs, this might support the validity of the LEMs based on the assumption that it is more likely for symptom instances that are early manifestations of BD itself to emerge in proximity to the FMAE.

3.2.7. Quantitative analyses

Descriptive statistics were calculated and statistical tests performed using the Statistical Package for the Social Sciences (SPSS), version 16.0. No quantitative analyses using SPSS were performed in paper I.

In addition to descriptive statistics on the demographic and clinical characteristics of the sample, the following tests were performed in SPSS for findings presented in paper II. Categorical variables were analyzed using Pearson's chi-squared test with Fisher's exact test. Continuous variables in two independent groups were analyzed using the Mann-Whitney U test with exact significance. Continuous variables in three independent groups were analyzed using the Kruskal-Wallis test. To test the sequential order of two related samples, we used the sign test for onset of superordinate symptom categories and the Wilcoxon signed-ranks test for onset of the first episodes of major depression and hypomania, both with exact significance. We adopted a significance level of $p \leq 0.05$, two-tailed, for all analyses.

In paper III, no statistics were calculated utilizing SPSS. The frequencies of patients with symptom instances meeting the criteria for the three alternative GCP definitions A, B, and C, were calculated using a calculator.

In paper IV, we calculated descriptive statistics in SPSS to determine the mean number of years from symptom onset to the onset of the FMAE for the symptom instances within the three symptom classes, "LEMs", "PEMs", and "UEMs". The extent to which the instances of the three symptom categories emerged within the last three years and the last year before the FMAE were calculated using a calculator.

3.2.8. Ethical aspects

The project was approved by the Regional Committee for Medical Research Ethics and Norwegian Social Science Data Services (NSD). All participants gave oral and written consent prior to participation. The study was carried out in accordance with the Helsinki and Madrid declarations.

The patients were thoroughly informed of the study both orally and in writing. They were informed of the opportunity to withdraw from the study at any time without this having any consequences for the treatment offered them at the hospital.

Patients that have experienced severe distress or trauma may experience reactivation of painful memories during life-course interviews. As a specialist in clinical psychology I was acutely aware of this possibility and sought to balance the interests of the project and the need of the patients to be protected from unnecessary distress. If I sensed that a topic caused distress I thematized this in order to help the patient regulate his/her emotions. Ultimately, I let the patient decide if we should abandon the topic in question. Given that the context of the interactions with the patients was research interviews, not therapy sessions, I was especially conscious of not exploring sensitive areas in too much detail. Since I met each patient a few times I had the opportunity of monitoring delayed reactions subsequent to the prior interview. Also, the patients had the opportunity of contacting me by phone in between interviews, and most of the patients had a therapist they could consult. In some cases extra care and adjustments had to be taken, e.g., due to patients undergoing bipolar episodes during the interview series. In a few cases I contacted the patients' therapists to inform about the current state of the patients and to ensure that proper follow-up measures were taken. Hence, the clinician in me was constantly present along with the researcher.

At the end of the interview-series many of the patients expressed that participating in the study had given them better knowledge of and more insight into their own and their families' developmental history and their BD. Others were more neutral concerning personal benefits, but were glad to be able to contribute to science. Although many patients experienced strong emotions during the interviews, I am not aware of any patients that experienced the participation as harmful.

EEG and blood tests were optional because these examinations may elicit strong anxiety or discomfort in some patients.

Sensitive physical research data were stored in archives at the Department of Mental Health Research and Development at Vestre Viken Hospital Trust. Sensitive digital data were stored in files on hospital data servers with enhanced restricted access. Other data, including interview transcripts, were anonymized.

4 Results

4.1 Summary of paper I

Background: Systematic studies addressing symptoms, signs and temporal aspects of the initial bipolar prodrome are reviewed to identify potential clinical targets for early intervention.

Methods: The databases PsycINFO, PubMed, EMBASE and British Nursing Index were searched for original studies.

Results: Eight studies were identified. Irritability and aggressiveness, sleep disturbances, depression and mania symptoms/signs, hyperactivity, anxiety, and mood swings are clusters representing common symptoms and signs of the distal prodrome of bipolar disorder (BD). As time to full BD onset decreases, symptoms of mania and depression seem to increase gradually in strength and prevalence. The specificity of prodromal symptoms and signs appears to be low. Two studies compared subtypes of BD. One study found that grandiose symptoms, risk taking and problems with concentration were significantly more common before BD onset among BD-NOS patients than among BD-I/BD-II patients. Another study found attenuated positive psychotic symptoms and increased energy/goal-directed activities to be significantly more common in patients with later psychotic mania compared to those with subsequent nonpsychotic mania. Two studies reported differences associated with age at BD onset. These suggest that patients with early onset may experience more pre-onset problems than those with later onset. Only one study investigated prodromal differences between patients with and without a family history of BD, finding no differences. Findings regarding the onset pattern of BD are contradictory but suggest that not every person who develops BD experiences a prolonged initial prodrome to the full illness. Current data on the mean duration of the prodrome vary widely, ranging from 1.8 to 7.3 years. No qualitative studies were found.

Limitations: Because of the scarcity of data, studies that did not explicitly investigate the bipolar prodrome were included when thematically relevant. The selected studies are methodologically diverse, and the validity of some findings is questionable. Findings must be interpreted cautiously.

Conclusions: The initial prodrome of BD is characterized by dysregulation of mood and energy. Because of the apparently low specificity of prodromal symptoms and signs of BD, it is currently neither possible nor advisable to predict the development of BD based solely on early phenomenology. More well-designed in-depth studies, including qualitative approaches, are needed to characterize the initial bipolar prodrome.

4.2 Summary of paper II

Background: Few studies have investigated the initial prodrome of bipolar disorders, and none has explicitly addressed bipolar II disorder (BD-II). We explored symptoms and behaviors preceding the first major affective episode (FMAE) of BD-II to generate hypotheses concerning possible clinical targets for early intervention.

Methods: In-depth interviews of 15 BD-II patients and 22 family informants were performed. Patients' existing clinical diagnoses were reassessed. The textual data of transcribed interviews were analyzed using qualitative methodology supplemented by quantitative analyses.

Results: All patients experienced clinically significant symptoms and behaviors prior to the onset of BD, and their first symptom appeared, on average, more than a decade before the FMAE. Anxiety and depression-type symptoms were the most common, followed by irritability/aggressiveness, mood swings, sleep disturbances, and mania-type symptoms. A majority of the patients also experienced other symptoms not included in the six above-mentioned categories. Mood swings and mania-type symptoms typically appeared within the last few years prior to the FMAE. Of the 11 patients experiencing both "general" and "affective" symptoms, it was significantly more common to experience general symptoms before affective ones (sign test, p=0.031). The most common (n=5) illness developmental trajectory was: well → general symptoms → affective symptoms → major depressive episode → hypomania. Of the seven patients who experienced irritability and aggressiveness, it is noteworthy that the five patients who experienced aggressiveness (intense anger and/or violence) experienced their FMAE significantly earlier than the rest of the sample (mean age 13.1 vs. 17.5 years; p=0.028). Two distinct subgroups were identified based on prominent and enduring personal characteristics prior to the FMAE. The individuals in one of the subgroups ("superior profile group"; n=5) were described as functioning very well, whereas the individuals in the other subgroup ("neurocognitive deficit profile group"; n=5) were characterized by neurocognitive deficits, relatively low academic and social functioning, and pronounced irritability and aggressiveness. Furthermore, it is possible that these individuals experienced earlier prodromal symptom onset, earlier FMAEs, and more symptoms than individuals with a "superior" profile.

Limitations: This is a retrospective qualitative study designed to generate hypotheses. The hypotheses generated need to be tested in future studies.

Conclusions: Prodromal clinical phenomenology is not sufficiently specific to predict the occurrence of the FMAE of BD-II. However, identifiable subgroups may exist. We hypothesize that neurocognitive deficits together with pronounced irritability and aggressiveness may constitute a vulnerability marker for a subgroup of individuals who subsequently develop BD-II. This subgroup may be of potential interest for early identification.

4.3 Summary of paper III

Background: Symptoms of the initial prodrome of bipolar disorder (BD) are too nonspecific for reliable prospective prediction of BD. An assessment of symptoms' temporal and contextual characteristics may help to identify clinical indicators with enhanced predictive power.

Methods: Fifteen bipolar II disorder (BD-II) patients and 22 family members were interviewed about characteristics of symptom instances that emerged before the first major affective episode (FMAE). The textual data of transcribed interviews were analyzed utilizing qualitative methodology. To identify genuine clinical predictors (GCPs), we outlined three alternative definitions and investigated the extent to which the reported symptom instances in different symptom categories survived successively narrower inclusion criteria.

Results: Most of the reported symptom instances met the broadest GCP criteria as episodic or chronic. Mood swings and irritability/aggressiveness were the only symptom categories out of seven in which most of the reported instances met our intermediate strict criteria as episodic/chronic and exaggerated/inexplicable. The mood swings were mainly characterized as episodic and occurred for no apparent reason; conversely, irritability and aggressiveness were typically characterized as episodic and exaggerated responses to life events. Few symptom instances met the definition C criteria as episodic/chronic and inexplicable. Mood swings was the only symptom category in which most of the reported symptom instances met the criteria.

Limitations: This is a retrospective and hypothesis-generating study.

Conclusions: Recurrent mood swings and irritability/aggressiveness are characterized as inexplicable and exaggerated responses, respectively, and may be the most prominent genuine clinical predictors of the FMAE of BD-II. Future studies need to investigate the extent to which the presence of different characteristics of the same symptoms discriminates between individuals who later develop BD and those who do not.

4.4 Summary of paper IV

Aim: Symptom instances characterized as episodic or chronic, and as exaggerated responses to life events or inexplicable, may be the most likely early manifestations of the first episode of bipolar II disorder. Mood swings and irritability/aggressiveness characterized as likely early manifestations may be the most prominent clinical predictors of the first episode. Instances characterized as episodic/chronic, and as normal responses to life events were considered to be possible early manifestations. Symptom instances characterized as temporary, and thus, did not persist until the onset of the first episode, were regarded as unlikely early manifestations. Assuming that symptoms that emerge late in the prodrome are more likely to be early manifestations of the disorder itself, we explore the time of onset and duration of symptom instances classified as likely, possible, and unlikely early manifestations.
Methods: Information was collected retrospectively from 15 bipolar II disorder patients and 22 family members. Interviews were analyzed utilizing qualitative methodology supplemented by quantitative analyses.
Results: Likely early manifestations did to a larger extent than other symptom instances emerge within the last three years and last year before the first episode. However, two-fifths of the likely early manifestations emerged before the last three years. The mean time interval between symptom onset and the first episode is shorter for the "likely" than for the "unlikely" early manifestations, but similar to the "possible" ones.
Conclusions: Symptom instances classified as likely early manifestations may be the most useful to predict bipolar II disorder prospectively. However, to capture all putative likely early manifestations in future retrospective studies it is insufficient to only investigate the final phase of the prodrome. This is a hypothesis-generating study. Future studies need to evaluate the validity of the proposed classes of symptom instances.

5 Discussion

5.1 Discussion of the main findings

5.1.1 Paper I

The main focus of this section is to review the three relevant studies that have been published since the final literature search for the review article in January 2009 and to compare the findings of these studies with those included in paper I.

Conus et al. (2010) retrospectively investigated symptoms that emerged within the 12 months preceding the first psychotic mania episode. Fifteen BD-I and 7 schizo-affective disorder – bipolar type patients (18 males; mean age 23 years) were included. Only 3 (13.6%) had a first-degree relative with BD. To explore the occurrence of prodromal symptoms, they used their own newly developed Initial Mania Prodrome Questionnaire (IMPQ). A total of 18 patients completed the IMPQ. They found three different patterns of phenomenological manifestations: (a) 9 patients (50%) displayed progressive development of attenuated manic symptoms, culminating in mania; (b) 5 patients (30%) first developed depressive symptoms and then attenuated manic symptoms, culminating in mania; and (c) 3 patients (18%) developed attenuated manic symptoms and then went through a phase of successive depressive and hypomanic stages before developing full-blown mania. In line with the findings of the studies reviewed in paper I, Conus et al. categorized the reported symptoms as manic and depressive mood symptoms, symptoms of disordered sleep, and general symptoms. Given their sample of patients with psychotic mania, they also found prodromal sub-syndromal psychotic symptoms. A comparison of the prevalence of individual symptoms with the psychotic manic patients (n=34) of Correll et al. (2007) revealed few significant differences. The symptoms listed in the IMPQ and the BPSS-R used by Correll et al. overlap to a large extent. Because of the similar designs of the two studies, the findings of Conus et al. in general confirm those of Correll et al. (see Table 3 in paper I).

A recent study by Luckenbaugh et al. (2009) used similar methods to the reviewed study by Fergus et al. (2003), which was conducted by many of the same investigators. The main differences are that Fergus et al. included some subjects who were diagnosed by community clinicians and that the early clinical manifestations of BD subjects were compared to those of a group of subjects with different non-bipolar conditions, whereas Luckenbaugh et al. (2009) compared the early symptoms of formally diagnosed outpatients with BD and ADHD. The 14 children younger than 9 years of age with BD in the Luckenbaugh et al. study (age of BD

onset: 4.6 ± 2.3 years; 71% had BD-I; 79% had comorbid ADHD) and the 22 ADHD children were similar in age and gender distribution and age of onset. As in the study by Fergus et al., the parents retrospectively rated 37 symptoms for each year of the child's life. A symptom was considered present only if it was rated as moderate or severe based on the degree of functional impairment in the child's usual family, social, or educational roles. Brief and extended periods of mood elevation were present in the bipolar group as early as age 3, and, together with decreased sleep, constituted a strong early differentiator of the BD and ADHD children that increased in magnitude over the following years. Irritability, poor frustration tolerance and night terrors were found to be weak early discriminators. Changing appetite and physical complaints were strong discriminators from ages 8-10, whereas bed wetting was a strong discriminator across the age span. Periods of sadness, inappropriate sexual behavior and suicidal thinking were weak discriminators during the late phase. If the analysis included all children with a BD diagnosis (total n=27), including those with adolescent onset, main effects or interactions were significant for only four symptoms (elevated mood, decreased sleep, physical complaints, and bed wetting), compared to the 12 significant group differences between the more carefully matched very early childhood BD and ADHD groups. This result suggests that it may be easier to distinguish children with BD and ADHD during the early childhood years compared to the late childhood and early adolescence years. However, because the majority of the BD children also had comorbid ADHD, the classic symptoms of ADHD (hyperactivity, impulsivity, and decreased attention) did not distinguish between the groups.

Because the findings of Fergus et al. and Luckenbaugh et al. were analyzed and presented differently, it is difficult to compare how and to what extent the early symptoms of children with BD differ from the early symptoms of children with various non-bipolar conditions (Fergus et al., 2003) and children with ADHD (Luckenbaugh et al., 2009). Fergus et al. reported that the four symptom components, irritability/dyscontrol, depression, mania, and psychosis/suicidality, explained 10-14% of the variance between the BD and non-BD groups. Nevertheless, these two studies suggest that it is possible to distinguish children's early symptoms of BD from symptoms of non-bipolar conditions and ADHD on a group level on some clinical measures. However, the major limitation of applying these findings in attempts at identifying BD prior to onset is that these studies did not explicitly aim at exploring the initial prodrome of BD. Thus, it is unclear to what extent the reported symptoms occurred and if the discriminators are valid before the onset of BD.

A third recently published study is by Ozgurdal et al. (2009). Out of 20 BD-I patients (mean age: 43.85 ± 9.38; mean age at BD onset: 32.61 ± 7.09), they found that a subset of 6 subjects retrospectively reported mood swings prior to the onset of the disorder in a semi-structured interview for mood swings. These subjects reported a significantly higher occurrence of a positive family history of affective disorders. Additionally, they scored higher on cyclothymic and irritable temperament on the auto-questionnaire Temps-M, which the authors suggest may represent markers of vulnerability to BD. The duration of illness was defined as the time period between the first hospitalization due to a manic or depressive episode and the date of the interview. Thus, the first hospitalization was used as a transition point between the prodrome and the syndrome. As for many of the other studies reviewed, it is unclear whether the subjects of this study would have met the criteria for BD-I or BD-II before the first hospitalization, and hence, if the reported mood swings occurred before or after the actual onset of BD. Another limitation is that this study only investigated mood swings, not other prodromal symptoms.

To summarize, knowledge concerning the phenomenology of the initial prodrome of BD remains limited. Although the studies together suggest a variety of general and affective symptoms, and attenuated psychotic symptoms for those who subsequently experience psychotic mania, the methodological limitations make it unclear to what extent these symptoms occur prior to the actual time of the BD onset.

5.1.2 Papers II, III and IV

5.1.2.1 Symptoms, behaviors, and temporal aspects (paper II)

Our observations of symptom/behavior types are similar to findings from previous studies (see the introduction, paper I, and section 5.1.1), with a few exceptions. In our sample, none of the patients was reported to have experienced psychotic symptoms or clinically significant grandiosity, as has been found in some previous studies (Lish et al., 1994; Egeland et al., 2000; Correll et al., 2007; Rucklidge, 2008; Conus et al., 2010). This difference is likely because most of the patients in the above-mentioned studies had BD-I, and hence, experienced a mania prodrome, and because the studies used the first mania or time of diagnosis as the BD onset criteria. Moreover, our data pertain to the period preceding the FMAE rather than to a full diagnosable BD. This, and the use of different methods for data collection, may also explain the rather large variations in the frequencies of symptoms observed between studies.

Another difference between our findings and the findings of some earlier studies (e.g., Fergus et al., 2003; Faedda et al., 2004) is that we did not report any instances of hyperactivity. The main reason for this difference is that we chose not to include enduring symptoms associated with ADHD among the reported symptoms (see more on this in paragraph 5.2.2.). Another reason is that we, based on the participants' descriptions, used more specific terms, such as "more talkative" and "hours of increased energy", for hyperactive/excessive behavior.

It is worth mentioning that we did not encounter any phenomena indicating severe disturbances of the basic sense of self, as are observed during the initial prodrome of schizophrenia (Moller and Husby, 2000). Such disturbances have not been reported in other studies on the initial prodrome of BD. Based on our review of the literature, it seems unlikely that this aspect of the prodrome has been systematically investigated. However, despite our vigilance, we did not identify any potentially relevant phenomena.

We found that the average onset of the first clinically significant symptoms occurred approximately 11 years prior to the FMAE and 14 years prior to the onset of full BD-II. To our knowledge, only one study has used comparable indicators. In that study, a median duration of 9.5 years between the first symptoms and the time of meeting diagnostic criteria for BD-II was observed (Egeland et al., 1987).

A staging model of BD has been proposed (Berk et al., 2007). Berk et al. argue that specifying a sequence of common stages that individuals pass through on the path to full BD may have clinical utility in determining likely courses and useful treatments at each stage. This is a new area of research, and we only identified one comparable study of 21 patients with BD-I, BD-II, and schizoaffective BD (Duffy et al., 2010). These were high-risk offspring (one parent with BD) assessed prospectively. Duffy et al. found that most patients progressed through the same sequence of stages that we found: well → general symptoms → affective symptoms → major depressive episode (mild intensity) → (hypo)mania. However, we also found the following sequence to be quite common: well → general and affective symptoms → major depressive episode → hypomania. It is interesting that our sample of mainly non-high-risk patients progressed through the same (36%) or roughly the same (64%) sequence of stages as the high-risk offspring (71%) studied by Duffy et al. Together, these findings suggest that individuals who subsequently develop BD frequently experience general symptoms first and that most experience a MDE of mild intensity prior to the first episode of (hypo)mania. If supported, these findings have the potential to contribute to the early identification of BD.

5.1.2.2 Two distinct subgroups (paper II)

We identified two distinct subgroups based on enduring and prominent characteristics prior to the FMAE. The presence of markedly high levels of the five characteristics of scholastic achievements, socially popular/well-adjusted, positive/agreeable attitude, sense of social justice, and stable mood defined the superior profile group (n=5). All patients in this group were female and were described as functioning very well. They learned new things quickly and were top achievers at school. Their strong sense of social justice caused them to intervene when peers were bullied. In addition to their defining characteristics, all were highly energetic and active, which is a characteristic of a hyperthymic temperament, and most had a markedly high level of decisiveness (including stubbornness) and were self-secure. Together, these characteristics made them respected by their peers.

The other group was defined by the presence of neurocognitive deficits (NCDs; n=5). The patients in this group had either symptoms associated with ADHD (n=3; e.g., distractibility/poor concentration; impulsivity; fidgeting; problems with motor coordination/clumsiness; and hyperactivity) or specific learning difficulties (n=2; dyslexia and dyscalculia). The symptoms became apparent before or shortly after starting school. All patients in the NCD profile group (2 males, 3 females), with the exception of one, were described as average to markedly low on the five characteristics defining the superior profile group.

A third profile group ("other") consists of 5 patients (2 males; 3 females) who did not meet the inclusion criteria of either group 1 or group 2. As a group, they had a mixed profile regarding the five characteristics that defined the superior group and the characteristic "energy-activity". Despite variability, four of the five patients could be characterized as average, whereas one patient (ID 13) clearly deviated by being mostly below average on the six characteristics and by having an irritable temperament.

Compared to the rest of the sample, significantly more patients in the NCD profile group experienced prodromal symptoms of irritability and aggressiveness. Aggressiveness was associated with a significantly younger age at the FMAE. The patients with NCDs experienced the FMAE at a non-significantly younger age than the patients with a "superior" profile. They also experienced non-significantly earlier symptom onset and more symptoms before the FMAE compared to the superior group.

We hypothesize that the combination of NCDs and aggressiveness may constitute a vulnerability marker for earlier age at FMAE. However, it is unclear if and how NCDs and aggressiveness are related to each other. Severe aggressiveness was present in two of the

patients from the very early years of life, and thus, seemed to have co-occurred with the NCDs. In two other patients, the NCDs were present before the emergence of severe aggression at age 13, which the patients understood at least in part as a consequence of the NCDs. The subjective and bodily stress related to struggling with NCDs and severe aggression may constitute a toxic combination that may lead to earlier onset of the FMAE in vulnerable individuals. If our hypotheses are supported by future studies, this finding might facilitate pre-onset identification of a subgroup of individuals who may go on to develop full BD-II. In contrast, it may be difficult to identify individuals with a "superior" profile prior to their FMAE because of their supernormalcy and inconspicuousness. It could be speculated that these patients' pre-onset characteristics may be protective factors that delay the onset of the disorder.

Although our findings are tentative, we found some support in the literature regarding the NCD group. It has been proposed that BD-ADHD comorbidity may represent a distinct clinical phenotype of BD (Faraone et al., 2001; Doyle and Faraone, 2002; Masi et al., 2006; Bernardi et al., 2010) with earlier onset than that seen in BD patients without ADHD (Sachs et al., 2000; Nierenberg et al., 2005; Bernardi et al., 2010). However, the findings of a distinct BD-ADHD phenotype may be due to symptom overlap between the disorders (Geller et al., 1998). Hence, the validity of the phenotype is uncertain. Recently, it has been suggested that the proposed BD-ADHD phenotype may only pertain to patients with a persistent ADHD diagnosis in adulthood (Bernardi et al., 2010).

It is also interesting to note that Duffy et al. (Duffy et al., 2007; Duffy et al., 2010; Duffy et al., 2011) found that only high-risk offspring of lithium non-responders had elevated rates of antecedent ADHD, learning disabilities and Cluster A traits compared to the offspring of two well parents. Although we have no data to support the notion, there may be some potentially interesting associations between the characteristics of the lithium non-responder offspring group of Duffy et al. and our NCD group. None of our NCD patients had first-degree relatives diagnosed with BD, and thus, had no first-degree relatives who had used lithium. However, based on the participants' descriptions, three of the NCD patients had a first-degree relative with possible BD (ID 6, 9, and 10). The remaining two patients had at least one first-degree relative with recurrent depression (ID 7 and 8). One of these (ID 7) had a second-degree relative with possible BD. Duffy et al. did not provide any subgroup data regarding age at BD onset.

Others have demonstrated a relationship between ADHD and learning difficulties in girls, suggesting that these two disorders might share some underlying familial risk factors (Doyle et al., 2001).

No clear distinctions were found between the profile groups regarding social class or affective disorders in first-degree relatives.

5.1.2.3 Symptom characteristics with enhanced predictive power (papers III and IV)

Approximately two fifths of the reported symptom instances were temporary (occurred only once). Because of their transitory nature and, thus, their lack of temporal relation to the FMAE, we consider these symptom instances to be unrelated to the BD-II. These symptom instances typically emerged many years before the onset of the FMAE. Furthermore, most of the temporary symptoms were characterized as normal responses to life events; this result suggests that similar clinical manifestations would be expected in children and adolescents in the general population. Interestingly, most of the instances of depression-type symptoms were temporary. The number of patients with depressive-type symptoms was reduced from 11 (73.3%) to 6 (40%) when excluding temporary symptoms. In other studies, a depressed mood was experienced by 55.6% (Correll et al., 2007) and 66.7% (Conus et al., 2010) of patients before their first manic episode of BD-I. However, these studies did not consider the symptoms' clinical features, and the differences in methodology and samples make it difficult to compare these findings with ours. Sleep disturbances was the other symptom category in which the majority of the symptom instances were temporary.

Second, we found that the majority of the reported symptom instances across the five remaining symptom categories (mood swings, irritability and aggressiveness, mania-type symptoms, anxiety, and other symptoms) had an episodic or chronic presentation in the interim between the symptom onset and the onset of the FMAE; hence, these symptom instances met our broadest "genuine clinical predictor" (GCP) definition A criteria in paper III. Although episodic and chronic symptoms have different temporal presentations, both classes of symptoms persist from symptom onset to the onset of the FMAE and are therefore more likely than temporary symptoms to be early manifestations of BD. Given the episodicity of BD, recurrent symptoms may be potential early manifestations. Whether chronic symptoms should be regarded as early manifestations is less self-evident. Chronic symptoms may be manifestations of other mental disorders that precede the BD, such as anxiety disorders, which may or may not be related to the subsequent FMAE of BD-II. However, based on findings suggesting that bipolar symptoms often have a more chronic presentation during childhood

(e.g., rapid and severe mood cycling and chronic irritability) than they do from mid-adolescence onwards (Pavuluri et al., 2005), we tentatively decided to regard chronic symptoms as GCPs.

Third, a minority of the symptom instances were characterized as episodic or chronic *and* exaggerated or inexplicable (GCP definition B). Mood swings and irritability/aggressiveness were the only symptom categories in which most of the initially reported symptom instances survived these criteria.

Symptoms characterized as normal responses to life events were excluded from definition B because exposure to life events may elicit understandable and appropriate reactions that may become chronic with the continuation or recurrence of difficult life circumstances (e.g., reports of insomnia during periods of being bullied). Hence, these responses are contingent on and presumably more related to exogenous factors than to the subsequent FMAE.

Symptoms characterized as exaggerated responses to life events were included in definition B because they might be manifestations of an underlying and possibly biological impairment or immaturity of a mood-regulating system that may be associated with the mood dysregulation characteristic of BD. If so, they may be early vulnerability markers of BD. The patients with irritability/aggressiveness meeting the definition B criteria were hyper-reactive to provocations from symptom onset, which occurred in either early childhood or early adolescence, onwards. It appeared unlikely that their temper could be explained only by life events, which suggests underlying and enduring mood regulation vulnerability.

The other onset characteristic included in definition B is inexplicability. Similar to exaggerated responses, inexplicable symptoms, which by definition are not elicited by identifiable exogenous factors, might be early expressions of endogenous or biological vulnerability factors of BD that manifest during bipolar episodes. Few symptom instances met the definition C criteria as episodic or chronic and inexplicable. "Mood swings" was the only symptom category in which most of the reported symptom instances survived the criteria. These mood swings were characterized by an automaticity that made the oscillations unpredictable to the patients and appeared to precipitate other symptoms, such as irritability and aggressiveness. The latter implies that being in a trough made these patients more reactive to irritants.

Because of the lack of studies on the pre-FMAE prodrome of BD-II and the scarcity of reports of prodromal symptom characteristics in studies on BD-I, there are few findings that can be compared with those of the present study. Interestingly, however, the 6 BD-I patients (30% of the sample) who experienced prodromal mood swings in Ozgurdal et al. (2009) all

reported that the mood changes occurred for "no reason". Additionally, from their study of the BD-I prodrome, Egeland et al. (2000) concluded that "early episodic mood and energy symptoms/behaviors are perhaps at the core of the emerging bipolar syndrome" (p. 1251). Luckenbaugh et al. (2009) found elation and euphoria during the early years of mostly BD-I juveniles to be episodic and "out-of-context". Their findings are comparable to the inexplicable mania-type symptoms of ID 6 in the present study (see Table 4 in paper II: "age 9"), who was the youngest patient in our study. At age 14, she was retrospectively assessed in a clinical setting as having had a BD-NOS condition since age 12 ½. She met the criteria for BD-II at age 16 years, 3 months, as assessed during follow-up. These above-mentioned studies provide some preliminary support for the "inexplicable" and "episodic" criteria of our GCP definitions.

Based on our three proposed alternative GCP definitions, we hypothesize that symptom instances meeting the definition B criteria (which include symptom instances that meet the definition C criteria) may be the most genuine and useful candidates for the prospective prediction of the FMAE of BD-II. Hence, any symptoms with these characteristics across the seven symptom categories may be potential GCPs. Our findings suggest that recurrent mood swings and irritability/aggressiveness characterized as inexplicable and exaggerated responses, respectively, may be the most prominent GCPs of the FMAE of BD-II. It is noteworthy that all 7 patients who had a first-degree relative with diagnosed (n=1), probable (n=1) or possible (n=5) BD (mostly based on descriptions by parents during interviews) had symptoms meeting the definition B criteria.

We then explored if the symptom instances that met the GCP criteria of definition B (labeled "likely early manifestations", LEMs, in paper IV) emerged in closer proximity to the FMAE than the "unlikely early manifestations" (UEMs; symptom instances characterized as temporary) and the "possible early manifestations" (PEMs). The latter category is composed of symptom instances that are characterized as episodic or chronic and normal responses to life events. As mentioned before, we consider this as an in-between category because exposure to life events may elicit understandable and appropriate responses that may become persistent with the continuation or recurrence of difficult life circumstances. However, because of the PEMs' temporal persistence, we regard these as more likely than the UEMs, but less likely than the LEMs, to be early manifestations of the later FMAE of BD-II.

We found that the distribution of symptom instances that emerged within the last three years and last year of the FMAE of the BD-II is in line with our assumption that the putative LEMs, to a larger extent than PEMs and UEMs, respectively, emerge later in the pre-FMAE

prodrome. Second, the mean duration between the onset of symptom instances and the onset of the FMAE is shorter for the LEMs than for the UEMs, which also concurs with our expectations. The only finding deviating from our expectations was the nearly identical time interval for the symptom instances categorized as LEMs and PEMs. It is unclear whether this result is coincidental due to the low number of symptom instances and patients or if it challenges our basic assumptions about the characteristics of the LEMs.

Based on the assumption that LEMs to a larger extent emerge in closer temporal proximity to the FMAE, which is an underlying assumption in studies that investigate the proximal prodrome of BD-I (Conus et al., 2010; Correll et al., 2007), our findings generally suggest that symptom instances characterized as episodic or chronic and exaggerated or inexplicable responses (LEMs) may be the most likely and the best clinical predictors of subsequent BD-II. However, two fifths of the LEMs emerged before the last three years of the FMAE, which suggests that, to capture all putative LEMs in future retrospective studies, it is insufficient to investigate only the final phase of the pre-FMAE prodrome.

The mean ages at the onsets of the first LEMs, PEMs, and UEMs are not reported in the papers. It is worth mentioning that the mean age at the first LEM symptom was 9.8 years (range: 1-21 years), compared to the mean age at the first symptom of 5.1 years when all symptoms were included, as reported in paper II. The mean ages at the first UEM and PEM symptoms were 5.4 years (range: 0-13 years) and 8.8 years (range: 5-14 years), respectively. Thus, our findings suggest that the symptoms experienced at the youngest ages to a larger extent are transient, whereas symptoms that emerge later more often endure. It is unclear whether these findings are coincidental artefacts. It is possible that there is a bias toward having experienced relatively more adverse or stressful life events at an early age for the patients in our sample that may explain the earlier emergence of temporary symptoms. For instance, the seven patients that experienced the divorce of their parents were on average approximately 6 years old (range: 3-10 years) at the time. Five of these patients experienced temporary symptoms of a depressive and/or anxious nature that were perceived to be related to the difficult life circumstances at home and ultimately the divorce of their parents.

We are not aware of any studies that have presented findings comparable to those reported in paper IV.

5.2 Methodological considerations

5.2.1 Paper I

Our search for relevant studies to review was quite extensive. We have not subsequently identified any additional studies that we believe should have been included in the review. A major limitation of our selection of studies is the inclusion of studies with an insufficient (e.g., time of diagnosis) or even no operationalization of the cut-off point between the prodromal and syndromal phases of BD. If we had applied stricter inclusion criteria and only included those studies that clearly stated that the phenomenology reported took place during the period preceding the actual time when the diagnostic criteria of BD were first met, only two studies would have qualified (Correll et al., 2007; Egeland et al., 2000). However, because of the scarcity of published studies on the symptoms and signs of the initial prodrome of BD, we chose to include studies with a less than optimal design in this respect that were nevertheless assessed to be informative of the early years of BD subjects. Due to the various limitations of the reviewed studies in the context of the phenomenology of the initial prodrome of BD (see paper I for more details), our findings should be interpreted with caution.

5.2.2 Papers II, III and IV

Several limitations and strengths regarding the reliability and validity of the study's findings must be considered. First, recall bias is a general hurdle in all retrospective studies. We tried to minimize this effect by also interviewing family members and by revisiting the initially reported information numerous times during the interview series of each patient. This was an attempt to optimize the precision of the data provided. In general, the participants seemed to become more confident about the correctness of what they conveyed as a function of these revisits. Although the quality of the data seemed to increase until the final version given during the interviews, the reconstruction of past events is a dynamic process that might have yielded somewhat different answers at another point in time. This may be especially salient regarding temporal aspects such as the age of emergence of specific symptoms, which is difficult to pinpoint in retrospect. Although retrospective studies have also been shown to produce reliable and valid accounts of past events (Egeland et al., 1987; Brewin et al., 1993; Henry et al., 1994; Widom and Shepard, 1996; Hardt and Rutter, 2004), our findings should be interpreted cautiously.

Another consequence of the challenges of recollection in retrospective studies is that a retrospective design is likely to produce fewer and less detailed descriptions of phenomena than prospective studies can, which likely results in more false negatives than false positives.

Furthermore, negative emotions may be easier to recall as deviations than positive emotions, such as elation. However, the recalled aspects are likely to have been more poignant and of clinical significance.

Second, the diagnosis of BD might bias patients' and families' recollections and attributions. However, the patients in our study were recently diagnosed, and most patients and family members had little specific knowledge of BD that could have biased them toward "recalling" bipolar-type symptoms during childhood. We did not observe any such obvious biases. Actually, the opposite was more striking in some cases, especially regarding the patients whose functioning was categorized as "superior". In sum, these patients seemed to have had a rather normal childhood. Overall, the participants appeared to be trustworthy and did not seem to over-pathologize the early history of the patients.

Third, using interviews as a data-collection method required the participants to actively recall and produce information. In general, one would expect this approach to produce less data about specific symptoms than more structured data-collection methods such as questionnaires, in which suggestions are provided in the form of questions or statements. However, we chose not to use structured data-collection methods in this investigation for two reasons. First, it was necessary to collect data in a bottom-up fashion to broaden our understanding of the potential complexities of an under-explored topic. Second, we reasoned in advance that a thorough approach would produce rich contextual data including the participants' opinions about the relative importance of the phenomena. As expected, this approach helped us to understand the meaning and clinical significance of phenomena and to make choices based on them, both during the data-collection period and in the subsequent analysis. Thus, it is likely that our findings are more valid than the results we could have obtained from questionnaires only, in which the participants are not held accountable for their responses, e.g., by being asked to provide examples. It is likely that our approach also produced more reliable data.

Fourth, in contrast to some earlier studies, we did not include the occurrence of enduring personal characteristics (e.g., stubbornness, oppositionality) or trait-like symptoms associated with specific learning difficulties and ADHD (neurocognitive deficits) in our list of symptoms and behaviors. These features became evident at a very early age (before or shortly after the patients began school) and were more stable, pervasive, and enduring than symptoms such as chronic anxiety or chronic irritability that had a more erratic presentation and sometimes a later age of onset. For instance, the patients who experienced symptoms of chronic anxiety from an early age experienced anxiety in relation to certain demarcated areas of live (e.g.,

simple phobias). The anxiety symptoms were not a reflection of an anxious personality. Furthermore, we wanted to avoid duplicating the trait-like features included in the differentiation of profile groups by also including them among the reported prodromal symptoms and behaviors. However, if we had done so, the consequence would have been that the NCD profile group would have had an even higher mean frequency of symptoms before the FMAE compared to the superior profile group. Moreover, there would have been a shift toward even more symptoms emerging at a younger age for the NCD group compared to the superior group. Hence, the differences between these two profile groups would have been augmented. However, our decision to differentiate enduring personal characteristics and neurocognitive deficits from other symptoms, and chronic symptoms in particular, was a difficult one. The categorization of phenomena into trait-like characteristics/symptoms and more fluctuating prodromal symptoms involved extensive consideration. Although we recognize that others might have chosen to solve this problem in another way, we think our tentative approach is preferable to the alternative, which is to regard all clinical phenomena as symptoms.

Fifth, our definitions of LEMs, PEMs, and UEMs are highly tentative, hypothesis driven, and speculative. Thus, it is unclear whether or to what degree our definitions are valid. Because of the lack of research and debate on the concept and definition of symptoms as LEMs, our definitions must be viewed as an initial attempt at stimulating a broader interest in this perspective. A weakness of our model of temporal characteristics should be mentioned. At the final stage of the pre-FMAE prodrome, temporary symptoms are "favored" in the sense that a symptom that only occurred once before the FMAE might have become episodic and hence might have been regarded as a LEM if the FMAE had been delayed. Thus, symptoms that emerge late in the prodrome might need to be considered as LEMs regardless of their temporal characteristics. This approach may be even more sensible if the symptom is phenomenologically similar to the subsequent symptoms of the FMAE and is not perceived to be a normal response to a life event. We encountered one such instance in our study. If we had introduced an additional criterion in line with these suggestions, two additional mania-type symptoms would have been regarded as LEMs and thus made mania-type symptoms an additional putative LEM category.

Sixth, our study is based on a small convenience sample. Our aim was to explore and generate hypotheses. Hence, no efforts were made to strengthen the generalizability of the findings. However, our sample appears relatively representative compared to findings from larger clinical studies. The mean age of full BD-II onset of 19.3 years is within the age range

commonly observed in other studies (Perlis et al., 2004). Rapid cycling was reported by 53% of our patients, a proportion consistent with the values of 42-56% reported in earlier studies assessing lifetime history of rapid cycling (Cowdry et al., 1983; Baldassano et al., 2005). A lifetime history of atypical depression symptoms was reported by 73% of our patients. Atypical features have been found to be present in 40% to 53.5% of BD-II patients (Benazzi, 1999; Benazzi, 2004; Akiskal and Benazzi, 2005; Brugue et al., 2008). All except one patient (93%) reported three or more melancholia symptoms during a lifetime MDE, which is significantly higher than the 12-25% prevalence found in other studies (Akiskal and Benazzi, 2005; Brugue et al., 2008). Most of the patients in our sample were women (73%). One large study found BD-II to be twice as common among females as males (Baldassano et al., 2005), whereas other studies have found a non-significant gender difference (Hendrick et al., 2000). Although it is likely that females are overrepresented in our sample, it is unclear how a more even gender distribution would have affected our findings. For instance, one might expect males to be more aggressive than females are. However, among the seven patients who reported experiencing irritability/aggressiveness, five were females, which means that approximately half of the females and males reported this symptom. Similarly, anxiety and depression-type symptoms were almost equally distributed among males (both n=3; 75%) and females (both n=7; 64%). The finding that stands out as disproportional regarding gender is that the superior profile group only consists of females. It is unknown whether this observation is coincidental or if it would be supported in a larger sample with a more proportional gender distribution. It is possible that some of the personal characteristics that define the superior group, such as scholastic achievements, favor the female gender.

Finally, it is unknown whether some patients may develop BD-I at a later stage, which has been shown to be relatively common in some studies (Birmaher et al., 2006; Birmaher et al., 2009), but not in others (Coryell et al., 1995; Joyce et al., 2004). Technically, all reported phenomena and symptoms of hypomania episodes might then be viewed as prodromal to the first mania episode. This result illustrates the different premises for the delimitation of the initial prodromes of BD-I and BD-II.

5.3 Implications

5.3.1 Clinical implications

The prodromal clinical presentation of BD is highly nonspecific. For instance, only a minority of youth with enhanced levels of aggression (Carlson et al., 2009) or (hypo)mania or depression symptoms (Lewinsohn et al., 2003; Angst et al., 2003a; Regeer et al., 2006;

Tijssen et al., 2010a) go on to develop BD. It has been suggested that elevated scores on the attention problems, aggressive behavior, and anxious/depressed subscales of the Child Behavior Checklist predict subsequent pediatric BD (Faraone et al., 2005; Biederman et al., 2009). However, other researchers have either failed to find this association (Volk and Todd, 2007) or found that these symptoms are also associated with other disorders (Meyer et al., 2009). Hence, it is currently neither possible nor advisable to identify BD prior to full onset based on the presence of certain types of symptoms.

Longitudinal monitoring of symptoms for persistence (episodicity and chronicity) might enhance the symptoms' positive predictive value. Indeed, a large epidemiological study recently demonstrated that the risk of transition to BD, for a subset of individuals, is dependent on the level of persistence of affective symptoms in a dose-dependent fashion (Tijssen et al., 2010b). Similarly, the identification of exaggerated responses by evaluating the intensity of episodic and chronic symptoms in relation to preceding life events, as well as identifying inexplicable responses, may enhance the symptoms' specificity and predictive power. Nevertheless, the predictive power is likely too low to be of clinical use when based solely on phenomenology. Persistent exaggerated responses to life events, such as irritability and aggressiveness, are common in mental disorders. Inexplicable responses and mood swings in particular might be more specific to and predictive of BD. Clinical practice and research have long shown that syndromal symptoms of bipolar episodes may have abrupt onsets (Winokur, 1976; Molnar et al., 1988; Keitner et al., 1996) that can appear to be inexplicable. This may also apply to prodromes. However, inexplicability is a matter of subjective interpretation, attribution, and self-awareness, and neither inexplicable prodromal nor syndromal onsets are likely to be exclusive to BD, although data on BD and other mental disorders are scarce.

To reliably identify BD prior to onset, phenomenological data (including the assessment of symptom characteristics and enduring personal characteristics, as proposed in this thesis) must be combined with other sources of data. Heritability is the best-documented risk factor for BD (Tsuchiya et al., 2003). However, as previously mentioned, utilizing family history in identifying at-risk individuals is complicated because only a minority of the individuals who develop the disorder have a known first-degree relative with BD. Furthermore, many of those relatives who are identified as having BD in research studies are likely to be undiagnosed in real-life settings, which we also suspect may be the case for some first-degree relatives of the patients in our sample. Molecular-genetic, neuropsychological and biological markers are other potential sources of information that may contribute to enhanced predictive accuracy.

However, currently there are few useful endophenotypic markers (Luby and Navsaria, 2010a), and prospective studies of at-risk individuals are lacking. In sum, the bipolar pre-FMAE prodrome may only be reliably identified in retrospect, not prospectively. However, clinicians should consider carefully monitoring the developmental progression of high-risk offspring who display multiple prodromal symptoms (and possibly LEMs in particular).

5.3.2 Implications for future research

To expand our knowledge of the prodromal phase of bipolar disorders, more studies using diverse methods are needed. Due to the lack of explicit studies on the initial prodrome of BD-II, more studies should explore the early ontogenesis of the disorder in these patients. Given the low specificity of the observed prodromal symptoms, it might be sensible to further investigate developmental trajectories of symptoms, characteristics of potential subgroups that are more identifiable at an early age, and subtle qualities that may differentiate prodromal symptoms of BD from prodromal and syndromal symptoms of other mental disorders. To inquire about the validity and utility of temporal and contextual symptom characteristics, future studies should investigate the extent to which different characteristics of the same symptoms discriminate between individuals who later develop BD and those who do not. Pending prospective studies, findings of retrospective case-control studies may provide some preliminary suggestions.

Eventually, large, well-designed prospective studies, preferably using epidemiological approaches, are needed to provide reliable answers. Longitudinal studies have the unique advantage of observing the continuity or discontinuity of symptoms and psychopathology within individuals over time. However, such studies are expensive and lengthy. Because of the low base rate of BD-II in the general population, large samples are required to capture the initial prodrome of individuals who do not have a family history of BD. Moreover, the onset age of BD varies greatly, requiring a lengthy follow-up period.

By utilizing staging models (Berk et al., 2007; Kapczinski et al., 2009b) and combining knowledge of clinical phenomena, prominent and enduring personal characteristics (Skjelstad et al., 2011b) and family history of BD with molecular-genetic, neuropsychological and biological markers (Cannon and Keller, 2006; Berk et al., 2009; Kapczinski et al., 2009a; Luby and Navsaria, 2010b), researchers may eventually develop algorithmic risk models that may enhance predictive accuracy.

6 Conclusions

The aim of this PhD thesis was to contribute to the research on the initial prodrome of BD. Pre-onset identification of at-risk individuals may enable early interventions that may improve prognosis. To the best of our knowledge, the present study is the first to explicitly address the symptoms and behaviors of the initial prodrome of the first major affective episode (FMAE) of bipolar II disorder (BD-II).

The most important finding of this thesis is the identification of a subgroup of individuals with neurocognitive deficits and pronounced irritability and aggressiveness prior to the FMAE. Our findings suggest that these individuals may experience earlier onset of the FMAE and earlier symptom onset and more prodromal symptoms compared to a subgroup that was described as very well-functioning. Neurocognitive deficits and severe aggression may constitute a vulnerability marker for the development of BD-II. Although these features are not specific to BD, this subgroup may be of potential interest for early identification.

We found that it was most common for BD-II patients to experience general symptoms (irritability/aggressiveness, anxiety, sleep disturbances, and other symptoms) before affective symptoms (mood swings, mania-type symptoms, and depression-type symptoms) during the pre-FMAE prodrome. Thus, relatively more affective symptoms become apparent as the time to the FMAE decreases.

Due to the apparent low specificity of the identified prodromal symptoms, we explored the temporal and contextual characteristics of the reported symptom instances in an attempt to identify symptom features and symptom types that may be relatively more predictive of a forthcoming FMAE of BD-II. Although highly tentative and speculative, we found some preliminary support for our hypothesis that symptom instances characterized as episodic or chronic and as exaggerated responses to life events or inexplicable may be the best predictors of subsequent BD-II. For a subset of individuals who later develop BD-II, certain groups of symptoms in combination with certain characteristics, such as episodic mood swings that occur for no apparent reason, and recurrent exaggerated manifestations of irritability and aggressiveness may have higher predictive power than other symptoms. However, it is unlikely that BD can be reliably identified prior to onset based solely on phenomenology.

As a final note of caution, we emphasize that our findings are based on a retrospective and hypothesis-generating study of a small group of BD-II patients and that the validity of our findings needs to be tested in future studies.

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