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Long-Term Health Outcome of Adolescent Mood Disorders

Focus on Bipolar Disorder

AIVAR PÄÄREN



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Abstract

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There has recently been an intense debate about the increased rate of bipolar disorders (BPD) in children and adolescents observed in clinical settings. Thus, there is great interest in child and adolescent symptoms of hypomania and whether these symptoms subsequently will develop into BPD. More knowledge about early signs could give insight into the development of the disorder. There are also concerns that hypomanic symptoms in adolescence indicate excess risk of other health conditions. It has been reported that patients with mood disorders have a high consumption of prescription drugs in different ATC classes.

The primary objective of this thesis was to better understand the mental health outcome of adolescents with hypomania spectrum symptoms and to identify early risk factors for adult bipolar disorder among adolescents with mood disorders. In order to widen the scope and investigate health outcome of mood disorder in general psychopharmacological outcomes were included.

A community sample of adolescents (N=2 300) in the town of Uppsala, Sweden, was screened for depressive symptoms. Both participants with positive screening and matched controls (in total 631) were diagnostically interviewed. Ninety participants reported hypomania spectrum episodes, while another 197 fulfilled the criteria for major depressive disorder (MDD) without a history of a hypomania spectrum episode. A follow-up after 15 years included a blinded diagnostic interview, a self-assessment of personality disorders, and national register data on prescription drugs and health services use. Adolescent mood symptoms, non-mood disorders, and family characteristics were assessed. Univariate and multivariate analyses were used.

The results indicate that the phenomenology of the hypomania spectrum episodes during childhood and adolescence per se does not predict adult bipolar disorder. However, having both affective symptoms during adolescence and a family history of bipolar disorder increases the risk of developing bipolar disorders in adulthood. Disruptive disorder in childhood or adolescence as well as family histories of BPD emerged as significant risk factors that differentiated between the future development of BPD and MDD.

Adolescents with hypomania spectrum episodes and adolescents with MDD do not differ substantially in health outcomes in adulthood. Both groups are at increased risk for subsequent mental health problems, high consumption of prescription drugs, and high health care use, compared with the control group. The high rates of prescription drugs in many ATC classes found among the former depressed females seem to indicate a series of co-morbid somatic illnesses.

Thus, it is important to identify and treat children and adolescents with mood disorders, and carefully follow the continuing course. Characteristics such as disruptive disorders and family history warrant particular attention.

Keywords: adolescent mood disorders, bipolar disorder, long-term follow-up assessment

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To my family and my mother:
Helen, Arthur, Ander, Martha Maria,
Andreas Einar and Leili Päären

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I **Päären A**, von Knorring A-L, Olsson G, Bohman H, von Knorring L, Jonsson U. (2013). Hypomania spectrum disorders from adolescence to adulthood: A 15-year follow-up of a community sample. *Journal of Affective Disorders* 145(2): 190-9
- II **Päären A**, Bohman H, von Knorring L, Olsson G, von Knorring A-L, Jonsson U. (2014). Early risk factors for adult bipolar disorder in a community sample of adolescents with mood disorders. *BMC Psychiatry*14(12):363
- III **Päären A**, Bohman H, von Knorring A-L, , von Knorring L, Olsson G, Jonsson U. (2014). Hypomania spectrum disorders in adolescence: A 15-year follow-up of non-mood morbidity in adulthood. *BMC Psychiatry* 14(1):9
- IV **Päären A**, von Knorring L, Jonsson U, Bohman H, Olsson G, von Knorring A-L. (2012). Drug prescriptions of adults with adolescent depression in a community sample. *Pharmacoepidemiology and Drug Safety*, 2012 Feb; 21(2): 130-6

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Contents

Introduction	11
History of bipolar disorder	12
Unipolar versus bipolar syndrome.....	13
Classification of bipolar disorder in adults.....	13
Classification of bipolar disorder in children and adolescents	14
The bipolar spectrum disorders and clinical course in children and adolescents.....	16
Epidemiology of bipolar spectrum disorders.....	17
Bipolar differential diagnoses.....	18
Temperament in bipolar spectrum disorders	22
Normal vs. clinical mood lability	23
Disruptive Mood Dysregulation Disorder (DMDD)	24
Child and adolescent bipolar comorbidity.....	24
Predictors of adult bipolar disorder in adolescents with affective disorders.....	25
Genetics in bipolar spectrum disorders	26
Neuroanatomy of bipolar disorders	26
Neuroendocrine systems in bipolar spectrum disorders	27
Circadian dysfunction in bipolar disorders.....	28
Neuroplasticity and neurotrophin signaling in bipolar disorders	29
Alterations in neurotransmission in bipolar disorders.....	30
Continued mental health problems in adulthood after adolescent bipolar disorder.....	31
Neuro-immune-endocrine disturbances in mood disorders.....	32
Continued general health problems in adulthood after adolescent mood disorder	35
Aim and scope.....	36
Methods.....	37
Subjects and procedure.....	37
The original investigation	37
The follow-up assessment.....	37
The register data.....	38
Design of Paper I	40
Design of Paper II	40

Design of Paper III.....	41
Design of Paper IV.....	41
Attrition at follow-up.....	41
Statistics.....	42
Paper I.....	42
Paper II.....	42
Paper III.....	43
Paper IV.....	43
Ethics.....	43
Summary of results.....	44
Paper I.....	44
Paper II.....	45
Paper III.....	49
Paper IV.....	51
Discussion.....	52
General strengths.....	52
Paper I.....	53
Paper II.....	53
Paper III.....	54
Paper IV.....	54
Methodological considerations.....	55
Implications.....	57
Conclusion.....	58
Sammanfattning på svenska.....	59
Bakgrund och frågeställningar.....	59
Metod.....	59
Resultat.....	60
Slutsatser.....	60
Acknowledgement.....	61
References.....	63

Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
ATC	Anatomical Therapeutic Chemical classification system
BDI-C	Beck Depression Inventory-Child
BPD	Bipolar Disorder
CES-DC	Centre for Epidemiological Studies – Depression Scale for Children
CD	Conduct Disorder
CI	Confidence interval
DDDs	Defined Daily Doses, measurement units of prescription drugs
DICA	Diagnostic Interview for Children and Adolescents in the revised form according to DSM-III-R for adolescents
DIP-Q	DSM-IV – ICD-10 Personality Questionnaire
DMDD	Disruptive Mood Dysregulation Disorder
DSM	American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders
GAD	Generalized Anxiety Disorder/ Overanxiousness
ICD	World Health Organization, International Classification of Mental and Behavioural Disorders
MDD	Major Depression Disorder
MINI	Mini International Neuropsychiatric Interview
OCD	Obsessive-Compulsive Disorder
ODD	Oppositional Defiant Disorder
OR	Odds ratio
PTSD	Posttraumatic Stress Disorder
ROC curve	Receiver Operating Characteristic curve
SCI	The Somatic Checklist Instrument

Introduction

Mood disorders is the leading global cause of years of healthy life lost due to disability in middle and high-income countries, according to the World Health Organization (1, 2). Mood is a concept that refers to internal emotional experiences, whereas affect refers to external expressions of emotions. Usually they are congruent, i.e. the external affect accurately reflects the internal mood. Our mood constantly influences how we perceive the world. Abnormalities of mood changes include depressed/dysphoric mood (unpleasant sadness), elevated mood (an exaggerated feeling of well-being), expansive mood (lack of control in expressing feelings with overestimation of one's importance), and irritable mood (easily provoked to anger). Mood disorders constitute a group of heterogeneous disorders that are characterised by abnormalities of mood, drive and cognition. The typical symptoms of depression are low mood, reduced affective responsiveness, lack of drive and initiative and negative cognitive evaluation of situation and self. Somatic symptoms such as vegetative dysfunctions, weight loss, sleep disturbances and other disturbances of the circadian rhythm are frequent in major depression. The opposite condition to depression is mania, which is typically associated with elevated, expansive and irritable mood with increased drive and accelerated cognition as flight of ideas and a sense of grandiosity (3).

Prospective longitudinal studies have shown that mood disorders commonly begin early in life before adulthood (4-6). Diagnostic criteria for depressive and manic episodes that were originally created for the adult population have recently also been adapted for children and adolescents (DSM-5) (7). Mood disorders represent a large burden to the youth population worldwide, accounting for more than one-tenth of the global burden of disease among 10 to 24 year-olds (8). Major depression (MDD) is the most important source of disability in the age group 10- 24 years, corresponding to 8.2% of the disability-adjusted life-years. Early onset of bipolar disorder (BPD), with 3.8% of the disability-adjusted life-years, is associated with social, emotional and academic consequences. Comorbidity and complications like substance abuse, suicide attempts, hospitalizations and criminal behaviour are common - not only during adolescence but through the whole life span (6, 9-11). Suicide among young individuals is more common in the early onset BPD population, with twice the number of suicide attempts in comparison with individuals with unipolar depression (6, 12, 13).

There has been an intense debate during the last two decades concerning age at onset, continuity, and discontinuity of the broader spectrum of bipolar disorders (14-22). This has raised concerns regarding the accuracy of the diagnoses and also about the consequences of medication in young individuals with a central nervous system that is still physiologically developing and maturing. Surprisingly little is known about future manifestation of hypomania spectrum episodes in community samples and new data from prospective studies are needed. To increase the scientific knowledge about this, longitudinal population-based data are essential. This thesis constitutes the first Swedish attempt to describe and study a longitudinal population-based sample from the perspective of BPD and simultaneously also increase the knowledge about the general outcome of adolescent mood disorders.

History of bipolar disorder

The identification of manic and depressive symptoms traces back to ancient Greece and to Hippocrates and Aretaeus of Cappadocia (23). However the original characteristic of bipolar disorder as a cyclical disorder originates from contributions by Falret on "la folie circulaire – circular insanity" (Falret 1845), by Baillarger on "la foie a double-forme – dual-form insanity" (Baillarger 1854) and by Kraepelin's descriptions of manic-depressive insanity (24, 25). Kraepelin suggested an integrating approach to the classification of mood disorders by the concept of "manic-depressive insanity" which included circular insanity and unipolar disorders. Kleist and Leonard opposed Kraepelin's idea and collected data on family history and clinical course of patients with bipolar symptoms with the intention of supporting the hypothesis that BPD and unipolar disorders are different entities (26). Angst's monograph (1966) (27) and an article by Perris and d'Elia's (1966) suggested that genetics play an important role in the aetiology of both endogenous depression and manic-depressive illness and that these are not homogenous (28, 29). Dunner et al suggested a definition of bipolar II disorder as recurrent episodes of depression and hypomania, which were less severe than the mania of BPD I (30). The differentiation between BPD I and BPD II was based by family history, gender differences and diagnostic stability (31-34). The spectrum approach of mood disorders was initially based on the work by Angst (15), Akiskal (35), Ghaemi et al (36), Dunner (37), and others.

Several textbooks of child psychiatry during the 19th century described cases of mania and melancholia in children, i.e. Emminghaus (38). Kraepelin reported that mania occurred rarely during childhood, and that the onset of the first episode was increasingly common after puberty (24, 25). A systematic review from the 60s by Anthony & Scott concluded that manic depression in children was rare (39). In 1969, the child psychiatrist Anna-Lisa Annell was the first to report positive effects of lithium treatment in

children younger than 10 years with manic-depressive illness (40). From the 70s large retrospective studies of bipolar adults have reported that in one fifth of the patients symptoms related to the illness had started before 19 years of age (41, 42). They described childhood mania as characterized by hyperactivity with more contributions of agitation, irritability and emotional lability than in adults as well as a relative lack of symptoms like paranoia and grandiosity. Discrete episodes could only rarely be identified. A bipolar I disorder was considered rare in young ages, but bipolar II was gradually considered quite common in adolescence. During the last two decades child and adolescent BPD has been more generally acknowledged and consequently the reported prevalence has increased (43, 44).

Unipolar versus bipolar syndrome

Mixed states (manic & depressive) were Kraepelin's unitary view of mood disorders, where symptoms of opposite polarity could be present in the same episode (24, 25). According to this view mixed states were mainly temporary, transition periods appearing during the cycling, but could appear as "independent attacks".

" True bipolar and unipolar" disorders share many underlying characteristics referring to pathophysiology, genetic background, environmental risks, disturbed sleep-wake cycles and circadian function, altered neurobiology (fronto-striatal and fronto-temporal paths), neuroendocrine systems, neuroplasticity, neurotrophin signaling and alterations in monoamine, GABA and glutamate transmission (45-48). The reason is probably that both share the characteristics of the depressive phase. Further, MDD is the most common mood disorder in relatives of BPD patients (49-52).

Broadening diagnostic systems of BPD in children and adolescents during the last two decades has led to discussion about validity and defining clear-cut boundaries between these " true bipolar" and unipolar disorders.

During a mood episode, patients may live the majority of their time below the definition of the full-syndromal threshold and after that several weeks with residual subsyndromal affective symptoms. Moreover, in chronic bipolar or unipolar disorders symptoms fluctuate frequently over time during the long-term course of the illness (53-56). Thus, longitudinal studies with a developmental approach may shed light on some questions of this international debate on the problem of define the diagnoses of affective disorders.

Classification of bipolar disorder in adults

Definition of BPD in DSM was relatively similarly to description by E. Kraepelin (24, 57), with the exception of the BPD grouping (58). According

to the DSM-IV-TR (59), the classical BPD I diagnosis requires a manic (or mixed) episode with a duration of at least 7 days (unless psychosis or hospitalization occurs). The classical BPD II disorder requires at least one major depressive episode and hypomania (episode lasting at least 4 days). Rapid cycling is used to describe the course of illness, and defined as the occurrence of 4 or more episodes within 1 year (See table 1). Multiple domains (school, home) and multiple informants (parents, teachers) must be part of the diagnostic procedure. Diagnosis entails establishing not only whether criterion symptoms are present, but also whether these symptoms are stable and pervasive, and whether they can be accounted for BPD diagnoses. Also the timing, onset of symptoms, should be considered carefully in order to rule out other differential diagnoses like posttraumatic stress disorder (PTSD) or ADHD (60-62).

Table 1. Classical criteria of mania according to DSM-IV-TR

A Criteria	B Criteria
<ul style="list-style-type: none"> • Distinct period of abnormally elevated/expansive mood plus ≥ 3 B-criteria, or • Irritable mood plus ≥ 4 B-criteria • Lasting ≥ 7 days (unless hospitalization is necessary or psychosis is present) 	<ol style="list-style-type: none"> 1. Inflated self-esteem or grandiosity 2. Decreased need for sleep 3. More talkative than usual 4. Flight of ideas or racing thoughts 5. Distractibility 6. Increased goal-directed activity/psychomotor agitation 7. Excessive involvement in high-risk pleasurable activities

Classification of bipolar disorder in children and adolescents

As described above from the perspective of history, the symptoms of BPD in children have been described differently than in adults by many authors (63-67). The same authors have suggested that childhood mania might represent a specific subtype that is different from adult onset bipolar disorder. The symptom pattern in children and adolescents is often characterized by mixed mania, or ultradian-rapid cycling with very brief recurrent episodes that last from a few hours to a few days. Psychotic features like delusions and hallucinations are common and the children suffer from an overall impaired functioning (64, 68-70).

There have been many discussions concerning how BPD should be defined in children and adolescents. Two main topics concern irritability, which may be present in other psychopathologic entities as well, and the

duration of symptoms. Thus, different research groups have presented their own proposed criteria (See table 2).

Table 2. Proposed criteria for BPD in children and adolescents by different research groups

Research center	Mood	Symptoms	Duration
National Institute of Mental Health (DSM-IV-TR) (Leibenluft E, et al 2003)(70)	Elation and/or grandiosity (irritability)	3 or more (4 if irritable): grandiosity, decreased need for sleep, pressured speech, racing thoughts, distractibility, increase in activity, risky behavior	1 week (or any duration if hospitalized)
Washington University School of Medicine (Geller B, et al 2000)(65)	Elation and/or grandiosity	DSM-IV-TR + requirement of at least one cardinal manic symptom (elation and/or grandiosity); irritability is not considered alone due to its low specificity. Episodic: whole duration of illness	Cycles: mood changes lasting a minimum of 4 hours
University of Pittsburgh Medical Center (Birmaher B, et al 2006)(71)	Elation/ irritability	BPD-NOS definition: DSM-IV-TR modified in relation to the number of symptoms; if elation is present it is required more than two symptoms of the DSM-IV-TR item B; and if irritability is present, three symptoms	At least 4 hours/day for 4 days (not necessarily consecutive days)
Massachusetts General Hospital, Harvard Medical School (Biederman J, et al 2003)(72)	Elated and/or irritability	DSM-IV-TR. When severe irritability is present, there is no need for change in the usual mood pattern	No duration required

The manic episode duration in early childhood may last for years (60, 73) or only for minutes-hours. It is very difficult to differentiate from mood lability and temper tantrums. Irritability is a symptom of depression as well as of mania. In the DSM-III the criteria for a major depressive episode was dysphoria, which is characterised partly by irritability. Many longitudinal studies has shown that irritability in childhood predict depression or anxiety in adults but not BPD (6, 74, 75). The symptom of irritability has altered BPD prevalence, and therefore the diagnosis Disruptive Mood Dysregulation Disorder (DMDD) was included in DSM-5 to capture irritable, explosive youth (76, 77).

The criteria for BPD I and II in DSM-5 are relatively unchanged to those in DSM-IV-TR. Exceptions include that symptoms of mixed episodes are replaced by a mixed features specifier, that can be used with any of the mood episodes (7). This specifier is used when subjects experience full criteria for a manic episode and three symptoms of a depressive episode or when subjects experience full criteria for a depressive episode and three symptoms of a manic episode. This mixed features specifier will hopefully facilitate the diagnostic procedure in children and adolescents. As in the DSM-IV-TR (59), one or more manic episodes are mandatory for a BPD I diagnosis, just as one or more depressive episodes and one or more hypomanic episodes (but not any manic episode) are mandatory for a BPD II diagnosis.

In this project, hypomania was defined as “elevated mood” and/or “grandiosity” and 1–3 additional symptoms, or alternatively, with irritability as the only core symptom and at least four additional symptoms. The reason for this definition was that elevated mood and/or grandiosity could be considered as the “cardinal features” of mania. They have been proposed as required symptoms in children and adolescents with hypomania (64, 65). Thus, only irritable mood was not sufficient as the core symptom unless grandiosity and/or elevated mood were also present (78). This approach was adopted to avoid overlap with dimensional irritability/aggression, which is present across different child and adolescent mental disorders (e.g., ADHD, CD, ODD, MDD, PTSD, and disruptive mood dysregulation disorder).

The bipolar spectrum disorders and clinical course in children and adolescents

The different disorders of BPD spectrum are defined as a line of linked unitary disorders, where MDD is on one side and BPD on another side. The concept of whole BPD spectrum syndrome includes BPD I, BPD II, cyclothymia, and MDD mixed state. There are differences between BPD I and BPD II or between BPD II and cyclothymia or between cyclothymia and MDD, but that does not argue against spectrum construction. Identifying discrete disorder entities along spectrum of continuous variation is an important goal of medical classification. It is also important to delineate the boundaries of BPD spectrum subgroups in order to understand conversion or drug-associated switch.

Emerging data from clinical and prospective community studies indicate that the clinical course may be different in different samples. From clinical samples it is clear that child and adolescent mania often has a continuing course (17, 60, 67, 79), which might be explained by the high rates of family history of bipolar disorder in this group (55, 80, 81). When it comes to community samples, where the spectrum can be expected to be broader and

less severe, the picture is less clear. The first prospective study of early onset bipolar spectrum disorder in a community sample examined the stability from late adolescence to early adulthood (6, 82). This study reported that out of the 17 bipolar youths identified in adolescence (4 bipolar I, 11 bipolar II, and 2 cyclothymic), 9 (53%) had at least one recurrence or failure to recover by the age of 24. This indicates that a substantial proportion of adolescents who meet the criteria for bipolar disorder might not continue to have mania/hypomania disorder as young adults.

Similarly, it is not clear how subsyndromal hypomania and very brief-episodes of (hypo)mania during childhood and adolescence develop in the long-term perspective. In the community study by Lewinsohn et al (5, 83), 5.7% of the respondents reported distinct periods of mania symptoms without full-filling criteria for bipolar disorder or cyclothymia. Others have found that adolescents with subsyndromal manic symptoms experience serious functional impairment (52, 63, 66, 67, 84). To catch subsyndromal BPD manifestations in children and adolescents, the NIMH (National Institute of Mental Health) has recommended the use of the diagnosis BPD NOS (bipolar disorder not otherwise specified), for patients with bipolar features not full-filling the criteria for BPD diagnosis (85). However, the situation is complicated by high occurrence of complex comorbidity (22, 64, 86).

Broadening diagnostic systems of bipolar disorder in children and adolescents during the last decade has conveyed a more complicated picture and a non-satisfactory diagnostic validity. A more narrowly defined diagnosis, and better differentiated from the unipolar disorder, could open up for scientific and clinical development (26, 31, 32, 87). This does not necessarily mean that a spectrum concept of mood disorders should be challenged by a categorical approach. Vice versa it would help us to find more clearly defined boundaries within the mood disorder spectrum and support the evidence of valid diagnoses. Longer observation periods are needed for readjustment of the preliminary BPD NOS diagnosis. Community based long-term outcome studies of children and adolescents are needed.

Epidemiology of bipolar spectrum disorders

Bipolar disorder affects approximately 1-3% of the adult population (21, 88). The estimates of lifetime prevalence for adult bipolar I disorder is 0.4-1.6% and 0.3-2.0% for bipolar II disorder (89-92), although some authors have reported a prevalence as high as of 5-11% (5, 14, 93). Individuals with hypomania symptoms that do not full-fill all diagnostic criteria for hypomania, have been reported to have a similar disability history as those meeting a formal diagnosis (15, 88, 93). Epidemiological studies suggest that subsyndromal bipolar disorder is common, impairing, and it constitutes a continuum with bipolar I and bipolar II disorders (15, 21, 84).

About two-thirds of the adult patients diagnosed with bipolar disorder report the onset of symptoms already in childhood or adolescence (6, 94, 95). The increased rate of bipolar disorders in children and adolescents, especially observed in clinical settings, has been under debate (43, 44, 96). Several authors have reported an increase of bipolar diagnoses in children and adolescents in both inpatient and outpatient settings from 1994 to 2004. For instance, during this period the population-adjusted rate of hospital discharges with primary diagnoses of bipolar disorder increased substantially both in children and adolescents in the US (43, 44, 70). In a recent US national survey of 10148 adolescents 13-17 years of age, the 12-month prevalence was estimated to 2.1% (97). A summary of prevalence data from different countries and continents is presented in Table 3.

Bipolar differential diagnoses

The differential diagnoses of BPD above all include other mood disorders (e.g. MDD and dysthymia), other psychotic conditions (like schizophrenia and psychotic disorders), disruptive disorders (ODD, CD, ADHD) and underlying physical illnesses or primary organic states (secondary BPD). Since BPD patients are frequently depressed and have more prior depressive episodes (98-100) the differential diagnosis of MDD (Unipolar depression) may constitute a diagnostic challenge. This is also of strong clinical relevance since inadequate treatment with antidepressants may trigger mood elevation symptoms. In addition, numerous studies have demonstrated that early onset of depressive disorders in children or adolescents usually precede bipolar disorder (84, 101-103). Furthermore, distinguishing mixed MDD episodes from BPD can be crucial for the accurate diagnoses. In such cases atypical depressive symptoms such as increased sleep, increased eating, and weight gain may be markers of increased risk of bipolarity (104). Also psychomotor retardation may be a marker of increased risk of bipolarity (47, 105).

Table 3. Summary of previous prevalence data of child and adolescent bipolar spectrum studies.

Cohort	Country	Age range	Diagnoses	Participants at baseline	Diagnostic tool	Diagnostic criteria	Prevalence %
<i>Epidemiological samples</i>							
Kashani et al., 1987 (106)	USA (Missouri)	14-16	Mania	150	DICA (youth and parent)	DSM-III	0.7 (lifetime)
Lewinsohn et al., 1995 (5)	USA (Oregon)	14-24	BPD I, BPD II, BPD NOS	1710	K-SADS (youth)	DSM-III-R	0.64 (lifetime)
Andrade et al., 2006 (107)	USA (Hawaii)	13-21	Mania, Hypomania	619	DISC (youth)	DSM-III-R	1.5 (lifetime)
Costello et al., 1989 (108)	USA (Great Smoky Mountains)	7-11	BPD I, BPD II, BPD NOS	789	CAPA (child and parent)	DSM-III	0.2 (12 month)
Kessler et al., 2009 (109)	USA (NCS-A)	13-17	BPD I, BPD II, BPD NOS	347	K-SADS (youth and parent)	DSM-IV	6.3 (lifetime)
Kadri et al., 2010 (110)	Morocco (national)	15-99	BPD I, BPD II, BPD NOS	5498	MINI	DSM-IV	3.2 (point)
Wells et al., 2006 (111)	New Zealand (national)	16-99	BPD I, BPD II, BPD NOS	7435	CIDI 3.0	DSM-IV	2.2 (12 month)
Stringaris et al., 2010 (112)	UK (national)	8-19	BPD I, BPD II, BPD NOS	5326	DAWBA (youth and parent)	DSM-IV	1.2 (lifetime)
Canals et al., 1997 (113)	Spain (community)	17-18	BPD NOS (hypomania alone)	290	SCAN (youth)	ICD-10	2.4 (point)
Lynch et al., 2006 (114)	Ireland (community)	12-15	BPD I, BPD II, BPD NOS, cyclothymia	723	K-SADS (youth and parent)	DSM-IV	0.0 (lifetime)
Benjet et al., 2009 (115)	Mexico City (community)	12-17	BPD I, BPD II	3005	CIDI (youth)	DSM-IV	2.5 (12 month)
Verhulst et al., 1997 (116)	Netherlands (community)	13-18	BPD I, BPD II	780	DISC (youth and parent)	DSM-III-R	2.8 (6-month)
Kim-Cohen et al., 2003 (4)	New Zealand (community)	11-15	BPD I	973	DISC (youth and parent)	DSM-III	1.8 (12 month)
Vicente et al., 2002 (117)	Chile (community)	15-99	BPD I, BPD II, BPD NOS	2978	CIDI	DSM-III-R	1.4 (6 month)
Faravelli et al., 1990 (118)	Italy (community)	15-99	BPD I, BPD II	1000	Clinical interview	DSM-III	0.5 (point)

Abbreviations: BPD I or II: Bipolar disorder I or II; BPD NOS: Bipolar disorder not otherwise specified; DICA: Diagnostic Interview for Children and Adolescents and Parent version; K-SADS: Kiddie Schedule for Affective Disorders and Schizophrenia; DISC: Diagnostic Interview Schedule for Children; CAPA: The Child and Adolescent Psychiatric Assessment; CIDI: World Mental Health Composite International Diagnostic Interview; DAWBA: The Development and Well-Being Assessment; DSM: American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders; ICD: World Health Organization, International Classification of Mental and Behavioural Disorders

If psychotic symptoms are prominent, it is important to differentiate BPD from schizophrenia, schizoaffective disorder and other psychotic disorders. For that purpose it is useful to determine the presence and chronicity of symptoms as disorganized speech and negative symptoms; duration of one month is mandatory for a diagnosis of psychotic disorders and at least six months for schizophrenia diagnoses, also given the presence of marked deterioration of psychosocial or occupational function. However, detecting psychotic symptoms with duration of two weeks (at least subchronic) in the absence of prominent mood symptoms, where mood episodes account for substantial portion of the total illness duration makes differential diagnoses more easy.

Other differential diagnoses are pervasive developmental disorders (autism spectrum disorders) and anxiety disorders including PTSD (3, 61, 119). The possibility of underlying developmental delays should also be investigated. Culturally validated categorical and/or dimensional assessment tools should be utilized.

The differential diagnoses of hypomanic states are often quite difficult to exclude. Especially highly creative individuals may full-fill many hypomania criteria. Some personality disorders as cluster B type (e.g. Borderline type) or cyclothymic personality may mimic hypomania symptoms. Long-standing adolescent-onset symptoms of irritability, impulsivity, unstable intense interpersonal relationships, unstable self-image and recurrent suicidal behavior are more characteristic of borderline personality disorder (120-122).

It is also important to distinguish BPD from ADHD and other disruptive behavioral disorders (CD, ODD), because hyperactivity, inattention and impulsivity may be prominent symptoms. However, the onset of disruptive behavioral disorders typically occurs before age 7 years and symptoms are rather chronic than episodic. Indeed, they are commonly co-morbid with childhood onset BPD (84, 119, 123, 124).

The concept of secondary BPD means that a physical illnesses or an organic state underlies the BPD-symptoms. This may occur in the presence of any disorder or process that disrupts brain architecture or physiologic functioning, including infection, trauma, tumor, drug intoxication or withdrawal, cardiovascular disease, metabolic disturbance, endocrine dysfunction, nutritional deficiency and neurodegenerative or demyelinating disorders (3). Common factors associated with secondary BPD are presented in table 4.

Table 4. Common factors associated with secondary BPD.

General medical conditions		Substance induced (intoxication)	
Medical conditions	Examples	Category	Agents
Infections	HIV encephalopathy, Herpes simplex virus, Influenza, Neurosyphilis, St. Louis encephalitis, Q-fever, Prion disease, Creutzfeldt-Jacob disease, Cryptococcal meningitis, sepsis, meningitis, prenatal infections (toxoplasmosis, rubella, herpes simplex etc.)	Stimulants	Amphetamine, Cocaine, Diethylpropion, Ephedrine, Fenfluramine, Isoetharine, Methylphenidate, Pemoline, Phenylpropanolamine, Sympathomimetics
Cerebral neoplasms	Diencephalic glioma, hypothalamic tumors, Craniopharyngioma, Temporal glioma (right), Orbitofrontal meningioma (bilateral), Parasagittal meningioma, Intra-ventricular meningioma (right), Spheno-occipital tumor	Hallucinogens	Cannabinols, Indole hallucinogens, Phencyclidine
Cerebrovascular disorders	Basotemporal cortex (right), Binswagner disease, Cerebrovascular vasculitides, Inferofrontal cortex (right), Thalamus (right), Caudate (right)	Anti-parkinsonian drugs	Amantadine, Bromocriptine, Levodopa, Lisuride, Piribedil, Procyclidine, Selegeline
Neurodegenerative and movement disorders	Huntington disease, Idiopathic basal ganglia calcification (Fahr's disease), Postencephalitic Parkinson's, Multiple sclerosis, Neurocanthocytosis, Alzheimer's disease, Idiopathic dystonia	Anti-depressants	Tricyclic agents, Mirtazapine, Bupropion, Nefazodone, Trazodone, SSRI
Congenital disorders	Fragile X syndrome, Velo-cardio-facial syndrome, Angelman syndrome, Agenesis corpus callosum, Klinefelter's syndrome	Antimicrobial agents	Antimalarials, Cycloserine, Dapsone, Podophyllins, Isoniazid, Iproniazid, Zidovudine, Cephalosporins, Cimetidine
Seizure disorders	Temporal lobe epilepsy (right), Partial complex seizures	H2 blockers	
Endocrine disorders	Hyper- or hypothyroidism, Hyperparathyroidism, glucocorticoid disturbance	Analgesics	Tramadol, Indomethacine, NSAIDs
Metabolic disorders	Phaeochromocytoma, Wilson's disease, metachromatic leuko-dystrophy, hypo- or hyperglycemia, postictal states	Endocrine agents	Corticotrophine (ACTH), Lupon, Corticosteroids, Thyroid hormones, Dihydroepiandrosterone
Nutritional deficiency	Pellagra, vitamin B12 or folate deficiency, vitamin D deficiency	Antineoplastic drugs	Procarbazine
Traumatic head injury	Subdural hematoma, cerebral contusion	Anti-hypertensive drugs	Clonidine, Propranolol, Methyl dopa, Hydralazine, Captopril
Autoimmune disorders	Systemic lupus erythematosus, NMDA receptor encephalitis	Sedative-hypnotics	Alprazolam, Triazolam, Buspirone, Meprobamate
Withdrawal syndromes	Alcohol, Baclofen, Amphetamines, Diethylpropion, MAOs, Nicotine, Opiates, Propranolol, Tricyclic agents	Miscellaneous drugs	Interferon α , L-Glutamine, Theophylline, Tryptophan, Yohimbine, Sympathomimetics, Disulfiram, Codeine etc.

Secondary BPD begins within hours or days after the physiologic or toxic insult. This highlights the need for a carefully collected psychiatric history screening prior to the onset of BPD. In the presence of a positive family history secondary BPD is less likely. However, up to 30% of patients with a brain injury reported at least one relative with MDD. In some of these cases the brain injury may have triggered a bipolar predisposition (3, 125, 126).

Temperament in bipolar spectrum disorders

The roots of the concept of temperament can be traced back to Hippocrates' seminal description of the melancholic, phlegmatic, choleric, and sanguine temperaments in the 4th century BC (62). Modern concepts of BPD temperament originated from the work of Kraepelin (1921) (57). He described four "fundamental states": depressive, manic (hyperthymic), irritable and cyclothymic, where these states could be viewed as different modalities of sub-clinical long-term traits of mood disorders. The Kraepelin's concept of "temperament" for mood disorders in his work is a synonym for "personal disposition." This concept was encouraged in the 1960s by psychiatrists as Angst (1973)(127) and Winokur (1969) (128) and also in 1970s by authors as Akiskal et al (1977) (129). In this approach, diagnostic criteria for depressive, cyclothymic, hyperthymic and irritable temperament have been conceived as subthreshold expressions of mood disorders. They have also inspired the development of standardized diagnostic instruments (130, 131). Temperament or personality profiles may precede or predispose to BPD. They may also be of key clinical importance not only for the diagnostic process, but also for treatment and preventive approaches.

In 1983 Akiskal defined mood disorders as a clinical continuum he termed the "bipolar spectrum," extending from subclinical manifestations to full-blown bipolar I disorder and encompassing major and minor depression, dysthymia, cyclothymic disorder, and bipolar II disorder (132). After that cyclothymia remains conceptualized in the DSM and ICD classifications as a persistent personality or temperament trait, termed "cyclothymic temperament" or "cyclothymia" (133). Temperament is considered to be more constitutionally, genetically and biologically based, whereas personality is more shaped by environmental circumstances and developmental events during childhood and adolescence (3, 134, 135). DSM-IV did not define any concrete criteria for differentiating between rapid cycling bipolar II disorder, cyclothymia, or subthreshold BPD (58). The current DSM-5 classification has a similar definition of cyclothymic disorder. ICD-10 defines "cyclothymia" as a persistent instability of mood, with numerous periods of mild depression and mild elation that fails to meet criteria for bipolar or recurrent depressive disorders, is generally unrelated to life events, and is generally developing in early adult life (136).

Measures for temperament dimensions are novelty seeking (impulsive, extravagant, enthusiastic), harm avoidance (shy, worried, pessimistic), reward dependence (sentimentality, dedicated, attached) and persistence (ambitions, determined). Measures for character dimensions include self-directedness (mature, responsible, reliable), cooperativeness (social tolerance, empathy, compassion) and self-transcendence (spiritual, faith, humble) (134, 137).

The most widely used measures of temperament are TEMPS-A (Temperament Evaluation of the Memphis, Pisa, Paris and San Diego Questionnaire) (138), TCI (Temperament and Character Inventory) (139) and EAS (The Emotionality, Activity, Sociability and Shyness Temperament Questionnaire) (140, 141). The last listed measure has been developed and extensively studied in children and adolescents and has shown to be a reliable and valid measure of temperament. Explorations of temperament and personality profiles in BPD – as compared to healthy controls - have demonstrated lower levels of frustration tolerance, impulse control, social avoidance and cooperativeness as well as higher levels of novelty seeking, self-transcendence, impatience, irritability, anxious worrying, self-criticism, and interpersonal sensitivity (134, 142, 143).

Normal vs. clinical mood lability

Adolescence is expected to be a period of turbulence with mood swings and lability. It is a challenge for clinicians to distinguish between normal mood shifts and clinically significant mood changes. It should be acknowledged that there are no clear-cut boundaries between clinical mood disorders and normal mood lability in adolescence. However, clinical mood changes are more severe, persistent and to a higher degree convey impairment. They are more likely associated with other comorbid conditions as suicidality and anxiety. Clinical mood lability is characterized by strong shifts of mood changes that are not appropriate to the setting or the developmental stage. They can appear suddenly with high levels of irritability and be expressed as frequent crying spells or tantrums. But they may also be manifested as an „over-expression“ with more energetic involvement and higher excitability than what would be proportionate to the eliciting circumstances (144-147). These both positive and negative mood shifts typically last from days to weeks, which are characterised by protracted mood episodes rather than episodes that are brief in duration. The latter are typical for the emotional lability observed in relation to ADHD, in disruptive mood dysregulations (DMDD), in CD and in ODD (146, 148).

Disruptive Mood Dysregulation Disorder (DMDD)

Several authors have raised concerns about presumed over-inflated rates of BPD in children and adolescents and have questioned the accuracy and the claimed serious consequences of this diagnosis in developing youth (43, 44). This was one reason why DMDD was introduced into the DSM-5: to capture children with persistent irritability and frequent episodes of extreme explosive-behavioral dyscontrol (76, 77, 148). DMDD core symptoms are chronic, severe persistent irritability with frequent temper outburst responses to frustration or angry mood that persists most of the day, nearly every day (three or more times per week) and at a developmentally inappropriate level. These temper outbursts are out of proportion in intensity or duration to the situation or provocation. These symptoms shall be present in at least 2-3 settings for 12 or more months. Throughout that time, there must not have been symptom free periods of longer duration than three consecutive months. The onset of DMDD should be before 10 years of age and the diagnosis should be restricted to children between 7 to 18 years of age. The clinical presentation of DMDD should not be better explained by another mental disorder as pediatric bipolar disorder, MDD, dysthymia, PTSD, autism spectrum disorder or separation anxiety disorder and should not be attributable to the physiological effects of a substance or to another medical or neurological condition. A DMDD diagnosis cannot coexist with oppositional defiant disorder, intermittent explosive disorder, BPD, MDD, ADHD, CD, or substance use disorder.

Child and adolescent bipolar comorbidity

Many epidemiological studies have shown that co-morbidity is common in children and adolescents with BPD (5, 66, 83, 86, 149-151). The disorder is highly co-morbid with ADHD, anxiety disorders, OCD, CD, PTSD and substance abuse (73, 80, 86, 152). The frequency of the co-morbidity of ADHD in patients with BPD ranges from 29% to 98% (73, 124, 153, 154). Many psychiatric and behavioral symptoms overlap between ADHD and bipolarity. Among prepubertal children with bipolar disorder, lifetime co-morbid CD is reported in two thirds, and among adolescents with BPD in 40% (155-157). Rates of different anxiety disorders range from 14% to 76% (86, 152). Substance abuse disorders have been reported about one third of adolescents with bipolar disorder (156, 157).

Predictors of adult bipolar disorder in adolescents with mood disorders

The early recognition of severe mental disorders such as mood disorders is an important issue in research and of relevance for clinical work. A number of studies have shown that adolescents with mood disorders are at increased risk of continued mood disorders in early adulthood (17, 53, 60, 158-160). BPD is a severe condition associated with substantial impairment in emotional, cognitive, and social functioning already at an early stage (81, 161-163). Notably, the diagnosis is often delayed and appropriate early intervention is not delivered (47, 164, 165). Unipolar depression, on the other hand, is often recognized early, since many individuals with this condition seek treatment or are hospitalized due to a depressive episode or suicidal behavior.

However, having (hypo)manic symptoms during childhood and adolescence does not necessarily indicate a continuing course of bipolar disorder in adulthood (6, 82, 166, 167). The early signs that predict the continued course of adolescent mood disorders are not well established. Thus, we basically do not yet know which adolescents with a mood disorder later will develop bipolar disorder (BPD), major depressive disorder (MDD), or no mood disorder at all as adults.

Adolescent BPD is associated with mood lability or swings, anxiety, hyperarousal, somatic complaints, behavioral dysregulation, and attention difficulties and school problems before the first episode (64, 153, 168-170). Several studies have also investigated whether the early signs of psychopathology may predict later BPD. Numerous studies have demonstrated high rates of switching to mania among depressed children or adolescents (101, 103, 151, 171, 172). Therefore early onset depressive symptoms or major depression may be of interest to predict early signs of later BPD. Disruptive behavioral disorders in combination with mood changes have been identified as a more specific marker of early onset BPD (63, 156, 157). Additionally, some authors have found that the presence of anxiety disorders, especially panic disorder, could be a marker for early onset of BPD (149, 173). However, the best established early marker of risk for future BPD is still family history (55, 66, 167). This has been widely accepted in clinical practice, despite the fact that a majority of high-risk offspring of individuals with mood disorders do not develop BPD (174-176). The validity of the early markers/premorbidity problems remain to be proven. The generally high frequency of pre- and co-morbidity between adolescent mood disorders, externalizing and internalizing disorders raise questions about the importance of these disorders for the continued course. More knowledge about early signs could give insight into the development of the disorder. In addition, it could facilitate the identification of subjects at risk of developing BPD and enable early intervention.

Genetics in bipolar spectrum disorders

During the past three decades researchers have made great efforts in order to understand genetic and epigenetic processes involved in BPD. In the 1970-1980s, family history, twin and adoption studies demonstrated that there is a substantial heritable component involved in the development of BPD (177). In twin studies, 70% monozygotic twins vs. 30% dizygotic twins were concordant for BPD disorders (178-180). Adoption studies pointed in the same direction with an elevated rate of BPD in the biological parents (181). From mid-1980s there have been attempts to identify the particular genes and genetic variants involved. In 1986-2006 linkage studies and association studies were conducted, which first focused on isolated parts of the genome (177). The genome-wide association studies (GWAS) began in 2008 by Craddock et al (182). During the years to follow, data from large samples were collected. Recent advances have indicated an influential role of ANK3, CACNA1C, SYNE1, ODZ4, and TRANK1 in bipolar disorder genetics. Additional studies have begun to examine the biology of these genes and how risk variants influence aspects of brain and behavior that underlie BPD. For example, carriers of the CACNA1C risk variant have been found to exhibit hippocampal and perigenual anterior cingulate dysfunction during episodic memory recall. Carriers have increased left amygdala activation in response to a negative face-matching task (183-185). This risk allele CACNA1C has been associated with lower extroversion and higher harm avoidance, anxiety and paranoid ideation (186). Another BPD related gene, ANK3, has been associated with decreased signaling in the facial affect-processing network, lower levels of novelty seeking and behavioral activation (187, 188). ANK3 gene function is also important for brain development through neural proliferation in the developing cortex (189).

Georgeva et al found an increased burden of *de novo* copy number variation, 4.3%, in BPD, which was significantly greater than controls (190). A recent publication found that BPD share genetic etiology with MDD, autism spectrum disorder, ADHD and schizophrenia where SNPs explain 17-19% of the variance in liability. The genetic correlation using common SNPs was highest between BPD and schizophrenia (191). Gene-mapping studies are now providing clear results that provide insights into the pathophysiology of the disorder. Sequencing studies should extend this process further. Findings could eventually set the stage for rational therapeutic development.

Neuroanatomy of bipolar disorders

Several regions have been associated with BPD. However, all neuro-anatomical findings must be interpreted with caution, due to heterogeneous

samples with variations of gender, age, duration of illness, severity of symptoms, medication and episode states.

Diffuse abnormalities in volumetric changes in the anterior limbic network (ALN) have been found in patients with childhood BPD. These include the prefrontal regions, thalamus, striatum, amygdala, hippocampal complex and the midline cerebellum (192, 193). Some studies have found smaller volumes of the amygdala, hippocampus, caudate, and thalamus (194-197). Other studies have reported that familial bipolar disorder may have underlying abnormalities in the regulation of prefrontal-subcortical circuits. For example, during a visuospatial working memory task, the individuals with familial bipolar disorder have higher activation in their bilateral anterior cingulate cortex (ACC), left putamen, left thalamus, left dorsolateral prefrontal cortex (DLPFC), and right inferior frontal gyrus compared to controls (198, 199).

Other studies have reported changes after first episode of bipolar disorder, as reduced gray matter volume in the left DLPFC, the left accumbens and left amygdala (200) and decreased volume of the left superior temporal gyrus (201). Bilateral ACC and DLPFC are supposed to play a role for mood regulation and attention (48). Basal ganglia and hippocampal volume reductions are common for both MDD and BPD. A reduced volume of the corpus callosum is characteristic of early adolescence BPD (202, 203). The corpus callosum is the major interhemispheric commissure connecting most of the neocortical brain regions including brain networks influential for attention, memory, language and emotional stages (204, 205). Abnormal maturation process in the corpus callosum of BPD during adolescence represents reduced coherence or aberrant myelination and increasing fractional anisotropy with age (203).

Notably, the understanding of pathophysiology of bipolar disorder is based on mixed results from adult and adolescent studies and developmental issues need more attention. Thus, more work is needed.

Neuroendocrine systems in bipolar spectrum disorders

The hypothalamic-pituitary-adrenal axis (HPA) is an important system for adaptation to physiological, chemical and psychological challenges. The release of its end product, cortisol, contributes to this adaptation by giving higher priority to the mobilization of energy and lower priority to digestion, growth, reproduction and immune/inflammatory processes (206). The response to stress is regulated in a complex feedback system by – inter alia - corticotrophin-releasing hormone (CRH) secreted from the paraventricular nucleus (PVN) in the hypothalamus and adrenocorticotrophic hormone (ACTH) released by the anterior pituitary. Circulating ACTH induces increased secretion of cortisol in the adrenal cortex. Cortisol interacts with the

glucocorticoid receptors and mineralocorticoid receptors in multiple tissues. During normal conditions, glucocorticoids give feedback to their receptors in the PVN and anterior pituitary to inhibit the secretion of CRH and ACTH (207). There is also interplay between the autonomic nervous system (ANS) and the HPA axis. Further, glucocorticoids regulate tryptophan hydroxylase and expression of several serotonin receptors, by turns intracellular metabolism has been shown to mediate the action of glucocorticoids within brain cells (208).

The regulation of the HPA-axis in individuals with BPD differs from controls in certain psychiatric disorders, probably due to genetic factors (209-211), early life adversities (212), exposure to intense and continuous stressors (213) and medication (214).

HPA-axis hypoactivation has been observed in atypical depression (206), and hyperactivation has predicted the onset of depression (211, 215). Both depressive and manic episode have been associated with elevated daytime cortisol (216, 217). Moreover, increased cortisol secretion frequently persists during remission and increases the risk for relapse/recurrence of depression (215).

Circadian dysfunction in bipolar disorders

Disturbances of biological rhythms constitute the core feature of BPD and it has been hypothesized that circadian rhythm systems play a fundamental role in the etiology of the disorder. The expression of endogenous circadian rhythms is influenced by exogenous factors, like daily activities, and exogenous factors can cause alterations in the expressions of endogenous circadian rhythms (218). The hormone melatonin, produced and secreted by the pineal gland in a diurnal fashion (219), is influenced only by endogenous circadian rhythms (220) and by ocular light exposure, that inhibits the melatonin production (219).

Subjects with BPD - as compared to controls - have lower peak nocturnal melatonin levels (221, 222) and hypersensitive pineal responses to ocular light exposure (223). Interestingly, lithium and valproic acid may decrease the sensitivity of melatonin secretion to nocturnal bright light administration (224, 225). Further, lithium and valproic acid influence the rhythmic expression of circadian genes and rhythmic properties of molecular clocks through inhibition of glycogen synthase kinase-3 β (GSK3- β). This results in a modification of phosphorylation patterns in circadian proteins with subsequent lengthening circadian periods (226, 227).

An irregular and delayed sleep wake cycle has been associated with lifetime hypomanic symptoms in a non-clinical adult sample (228). Subjects with BPD have significantly delayed and reduced melatonin secretion compared to MDD subjects (229). Circulating cortisol is typically inversely regulated compared to

melatonin; higher morning cortisol levels are associated with the wakening effort. As mentioned above, some individuals with BPD have higher awakening and evening cortisol level than healthy controls (230, 231).

The secretion of several neurotransmitters appears to be altered in BPD. There are many connections between serotonergic nuclei raphe and hypothalamic suprachiasmatic nucleus (the main circadian pacemaker). Both serotonin and melatonin levels peak at night. The pace of conversion of serotonin to melatonin is regulated by hypothalamic suprachiasmatic nucleus. Serotonin has been found to influence transcription of the CLOCK genes, which is one of several circadian genes (TIMELESS, ARNTL1, PER 3, CRY1, RORA, NR1D1) established association between GWAS (“gold standard” genome-wide association study) and BPD (230-233). Ventral tegmental area dopaminergic neurons have been implicated in regulation of REM sleep and adaptation to light. On the other hands dopaminergic neurons in ventral tegmental area in the CLOCK mutants show increased firing rates and increase of expression of tyrosine hydroxylase activity and decrease of other clock genes as PER1, PER2, CRY, CK1 ϵ (234). Norepinephrine provides a regulatory influence on melatonin synthesis (230, 231).

To summarize, circadian rhythm disruption may be associated with BPD and play a significant role in the pathophysiology of the illness. Therapeutic interventions focusing on restoring proper circadian rhythmicity, such as interpersonal and social rhythms therapy, and phototherapy have received some clinical support. Manipulation of the sleep-wake cycle, as sleep deprivation, is an encouraging treatment for both unipolar and bipolar depression (235, 236).

Neuroplasticity and neurotrophin signaling in bipolar disorders

Impairment of hippocampal plasticity may have a relevant role in the pathophysiology of BPD (237). Hippocampus plays an important role in the inhibitory regulation of the HPA-axis after excessive stress in the context of mood disorders.

Neurotrophic factors, especially BDNF (brain-derived neurotrophic factor), play an important role in neuronal function, development, neuronal maturation, differentiation and survival, synaptic plasticity and long-term memory consolidation in the cerebral cortex and hippocampus (238-240). Although, BDNF is important in mood disorders because it is involved in the release of serotonin, glutamate and GABA (γ -aminobutyric acid) (241, 242).

BDNF gene may have compromised ability to normalize HPA axis activity. BDNF acts also as resilience factor, assisting the maturation and differen-

tiation of the nerve cell progenitors (243), and as immunomodulator in the periphery of the body (244). Microglia BDNF appears to have importance in learning and memory-related synaptic plasticity (245). Several clinical studies have demonstrated low levels of BDNF in bipolar patients (239) and that this is correlated with the clinical severity of depression and mania (246, 247). BDNF gene polymorphism have shown early onset of BPD, rapid cycling, suicidality and treatment response (248, 249). GDNF (glial cell-derived neurotrophic factor) plays an important role in the regulation of neuroplasticity, monoamine and GABA signaling and microglia activation (250, 251) However, in BPD depressive episodes do not seem to influence GDNF levels, opposite to reduction of GDNF in unipolar depressive episodes (250). However, GDNF may play key role in stabilizing microglia activation and peripheral inflammatory signaling in the BPD pathogenesis.

Glycogen synthase kinase-3 (GSK-3) is regulated by BDNF and is important in synaptic pruning (deconsolidation) and glutamate receptor cycling (252). GSK-3 activity is modulated by serotonin and dopamine thereby facilitating synaptic plasticity and cellular resilience (253).

Alterations in neurotransmission in bipolar disorders

Neurotransmitters regulate the communication between neurons. They are stored in vesicles in the presynaptic endings and released into the synaptic cleft by electric stimulations of the neuron. Results from research on how neurotransmitters are involved in the etiology of BPD are so far not conclusive but several preliminary observations are of potential interest. In most studies concerning mood disorders the dysregulation of dopamine, serotonin, GABA (γ -aminobutyric acid) and glutamate have been in focus.

The neurotransmitter dopamine plays an important role for movement, attention, emotional reaction as well as experiencing pleasure and pain. In depression the levels of dopamine appear to be decreased, whereas it is increased during manic states, especially in mesolimbic areas. An excess of dopamine is known to bring about disturbances concerning thought, mood, self-image and feelings about one's relationship with external world (254). During the course of mania there is excessive dopaminergic activity whereas during a depressive phase there is a dopamine receptor down-regulation (255).

The neurotransmitter serotonin is related to mood, anxiety and cognition. A decrease of serotonin levels is often expressed as exaggerated worry or tension and in depression as physical symptoms like fatigue, trembling, headaches, and nausea (254). Serotonin transporter (5HTT) binding is reduced in the midbrain, amygdala, hippocampus, thalamus, putamen, dorsal ACC and insula in depressed subjects with BPD as compared to matched controls (256, 257). There is one report of elevated 5HTT binding in the

midbrain and dopamine transporter binding in the striatum in mixed mania subjects (258).

The neurotransmitter GABA acts as an inhibitor within the synapses of the brain. One GABA system, located in the hippocampus, is thought to be involved in the memory formation, from short-term to long-term memory during a person's sleep cycles (254). There have been reports showing decreased uptake of GABA into platelets during mania and increased GABA uptake during depressive episodes in bipolar subjects. Altered platelet GABA and glutamate uptake is correlated with severity of BPD respective phase (259).

Glutamate is the most plentiful amino acid neurotransmitter in the brain. It functions as a substrate in protein metabolism, and as a precursor for glutamine, GABA and glutathione (254, 260). Glutamate stimulates the N-methyl-D-aspartate (NMDA) receptors. Overstimulation of NMDA receptors may cause nerve cell damage or death. Some of the glutamatergic abnormalities in BPD reflect functional and numerical glial abnormalities given glutamate metabolism and signaling. Altered glutamatergic signaling in cortico-limbic circuits may be reflected in various BPD symptoms. There have been reports on an association between glutamate transmission and neuroendocrine disturbances involved in memory, emotional regulation, and stress response in BPD (261). Some studies noted abnormalities of NMDA glutamate receptors in the hippocampus and a significant increase in the expression of glutamate transporter-1 in the ACC of bipolar subjects (262, 263). Neuronal NMDA and astrocytic kainate receptor-mediated glutamate signaling activity reduction by mood-stabilizing agents has been seen as antidepressant effect in bipolar disorder (264). Currently used agents with mood-stabilizing properties (lithium, valproate, atypical antipsychotics) directly and indirectly modulate the PI3K (phosphoinositide-3-kinase), GSK-3, and Wnt signaling pathways modulates apoptosis and synaptic plasticity in BPD (265, 266). Thus, genetic vulnerabilities in BPD become more evident in oligodendrocyte dysfunction in the white matter changes in cortico-limbic pathways during mood regulation, which enhances the stress and circadian dysregulation role.

Continued mental health problems in adulthood after adolescent bipolar disorder

Due to the severity of bipolar disorder (1), there is great interest in child and adolescent symptoms of hypomania and whether these symptoms subsequently will develop into bipolar disorder. Long-term follow-up studies have shown different results, depending on the sample. On the one hand, clinical samples suggest a continuity of the disorder from childhood and adolescence to adulthood (43, 52, 78, 84). On the other hand, community samples do not

suggest a clear continuity (267, 268). However, there might be concerns that hypomanic symptoms in adolescence indicate excess risk of other psychiatric disorders. For example, while the majority of the high-risk offspring of individuals with mood disorders do not develop BPD (174-176, 269), a large proportion of offspring will have other severe mental disorders (270). The risk of anxiety disorders and substance use disorders is elevated in this group. Other findings suggest that childhood onset BPD is associated with greater severity of depressive episodes in adulthood, with higher incidence of comorbidity, and suicide attempts (271-273). Individuals with childhood and adolescent onset BPD are more likely to be hospitalized for treatment or have higher health care costs.

In adults with bipolar spectrum disorder, high rates of comorbidity are reported for anxiety disorders, substance abuse and personality disorders (22, 120, 274-277). Recent data also suggest increased comorbid substance/alcohol abuse and anxiety in adults with MDD and subsyndromal hypomanic features, compared to individuals with MDD without a history of subsyndromal hypomanic features (268, 278). Further, personality disorders are frequently associated not only with mood disorders in general but also with bipolar disorder (120, 121, 279). Personality disorders are more common in individuals with an early onset of bipolar disorders than in those with a late onset (121, 280). Some studies suggest that comorbid personality disorders reduce the likelihood of recovery from early-onset forms of mood disorders (281, 282). Also ADHD and eating disorders are common comorbid disorders in adults with bipolar disorder (275, 283, 284), although ADHD seems to be more prevalent in children and adolescents than in adults (43, 285).

Neuroimmunoendocrine disturbances in mood disorders

Conditions that are associated with significant acute or chronic stress and affective disorders may suppress or potentiate autoimmune diseases or progression through modulation of the systemic or local pro/anti-inflammatory cytokine balance (286). It has been reported that patients with a history of childhood maltreatment with depression had highly elevated inflammatory levels in later life (287, 288). One explanatory mechanism is role for stress and activation of the HPA axis. Elevated cortisol level is frequent finding in depression and this may be caused by acute or /and protracted exposure to stress. Inflammation may be related to depression through neuroimmunoendocrine interactions (Figure 1): brain function regulates secretion of glucocorticoid hormones and glucocorticoids can inhibit inflammation process. On the other hand inflammation can reduce glucocorticoid signaling and reduced glucocorticoid signaling may lead to abnormal brain functioning.

Depressed persons often have impaired glucocorticoid signaling (289, 290) and may therefore be at higher risk for inflammation (291-294).

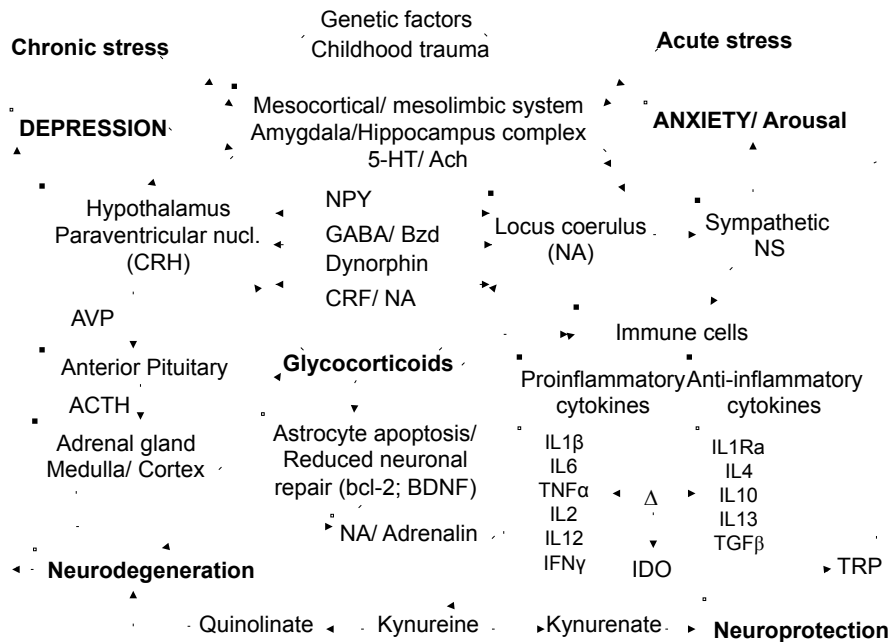


Fig. 1. Diagrammatic representation of the neuroimmunoendocrine interaction components of the stress systems modified from Leonard, Myint & Kim and Chrousos & Gold (295-297).

Abbreviations: CRH, corticotrophin releasing hormone; NPY: neuropeptide Y; NA: noradrenaline; AVP: arginine vasopressin; ACTH: adrenocorticotrophic hormone; GABA-Bzd: gamma aminobenzoic acid/ benzodiazepine receptor complex; 5HT/ACh: serotonin/ acetylcholine; IL: cytokines interleukin; TNF: tumor necrosis factor; INF: cytokine interferon; IDO: indoleamine 2,3 dioxygenase

Key: The hypothalamic-pituitary-adrenal axis is activated by both external and internal stressors, which result in the hypersecretion of adrenal glucocorticoids. In major depression the prolonged elevation of the glucocorticoid concentration leads to desensitization of the central corticoid receptors and some of the receptors located on T-cell macrophages. During depression there is an increased release of pro-inflammatory cytokines from activated macrophages in the periphery and brain. Pro-inflammatory cytokines are capable of destabilizing brain function and this makes the brain vulnerable to stress and unknown endogenous factors such as mood disturbances. Pro-inflammatory cytokines are released from monocytes, macrophages and other immune cells in the periphery and from microglia and astrocytes in the brain. Pro-inflammatory cytokines are responsible for some of the changes in the neurotransmitter (NA; 5-HT) functions occurring during depression. IDO is induced by the pro-inflammatory cytokines and inhibited by the anti-inflammatory cytokines. The metabolism of tryptophan by IDO occurs in both the microglia and astrocytes. In depression, the metabolism of tryptophan through the kynurenine pathway is increased, thereby reducing the availability of tryptophan for serotonin synthesis in the brain. Astrocytes produce kynurenic acid and metabolise quinolinic acid and thereby reduce the neurotoxic impact of microglia activa-

tion. Chronic stress and depression causes imbalance between the pro-inflammatory and anti-inflammatory arms of the system (through the inflammatory Th-1 pathway, such as INF- α , IL-6, and predominantly over the Th-2 anti-inflammatory pathway, as IL-10), which increases the vulnerability of individuals to infections, autoimmune disorders and allergic diseases, metabolic-syndrome and essential hypertension.

Studies of depressed adults report altered immunity as evidenced by reduced lymphocyte and lymphocyte subset quantities, decreased lymphocyte proliferation in response to mitogens and natural killer cell activity (298). The macrophage-T-cell theory of depression postulates an activated inflammatory response system in mood disorders and considers this activated inflammatory response system to be a driving force behind the illness, because pro-inflammatory cytokines (IL-6; IL-1 β ; TNF- α ; PGE2 and CCL2) are capable of destabilizing brain function.

This makes the brain vulnerable to stress and unknown endogenous factors, and depressions can be a consequence. In humans the low intravenous doses of endotoxin increase the level of these cytokines and induce depressive symptoms (299-301). In this case depressive symptoms can be precipitated by interferon alpha treatment.

On the other hand, various forms of stress during early life are associated with HPA axis sensitization, and occur through multiple epigenetic changes in limbic regions. However it may also sensitize proinflammatory cytokines (IL-6, CRP, TNF- α , IL-1), neurotrophins and oxidative species and impact an individual's mental and physical resilience (302). For example, in the early stages of bipolar disorder elevated serum levels of IL-6, TNF- α , and IL-10 have been reported (303), and in depressed individuals CRP appears to be elevated (304). Mood disorder increases also interferon gamma (INF- γ), which is associated with dysregulation of the tryptophan metabolite pathway via indoleamine 2, 3-dioxygenase (IDO) activation, resulting in depletion of serotonin and augmentation of quinolinic acid (QUIN) metabolism over kynurenic acid (KYNA). Tryptophan metabolites (KYNA, kynurenin, 3-hydroxykynurenine, QUIN) are neuromodulators to influence the depression by behavioral, neuroendocrine and neurochemical actions.

Women have higher systemic baseline levels of glucocorticoids than men due to the transcriptional regulation of CRH by estrogen (305, 306), which increases IL-4 levels, resulting in a greater Th2-type immune response (307). In males testosterone reduces glucocorticoid and IL-4 levels, resulting in a predominantly IFN- γ , Th1-type immune response to infection and trauma (306). This is reflected by the fact that approximately 80% of the autoimmune diseases appears in women (308-310). It is therefore possible that adolescent depression could increase prevalence of infections, inflammations and autoimmune diseases in females later in life, because they respond to similar stressful events differently than males.

To summarize, inflammatory mechanisms are associated with mood disorder pathophysiology via regulation of neuronal excitability, synaptic

transmission and plasticity and neuronal survival (311-313). Stress and inflammation inhibit brain derived neurotrophic factor (BDNF) through disrupt synaptic signaling and integrity during the early stages of mood disorder.

Continued general health problems in adulthood after adolescent mood disorder

The last sub-study of this thesis has a focus on health problems after adolescent depression, motivating an introduction also to this sub-theme. Several studies have shown a link between mood disorders and increased risk for early mortality due to general medical illnesses (314). Depression is very common in e.g. patients with hypothyroidism (315, 316), infections (287) and coronary heart disease (317).

Comorbidity between general medical illnesses and depression has been shown to be prevalent. The link between thyroid dysfunction and depression has been well established. Sub-clinical hypothyroidism is not rare among patients with episodes of major depression, and have been linked to increased risk of depression (315, 318, 319). Thyroid peroxidase antibodies and not thyroid hormone levels per se may be associated with increased depression rates in some subgroups (318). Bipolar disorder, especially rapid cycling, has also been linked to both thyroid hypofunction and to autoimmune thyroiditis (320, 321) but even here is the evidence under question (322). Administration of T3 alleviates the depressive symptoms of hypothyroidism and thyroid hormone and is an effective adjunct to antidepressant treatment in subgroups of euthyroid depressed patients.

Taylor et al (323) observed that ulcers occurs ten times more frequently in depressed persons compared with controls without depression, and depressive symptoms are more common in people with asthma than in general population (324). Individuals with any history of allergy (rhinitis; hay fever) have significantly more depression diagnoses (325). It has also been shown that elevated blood pressure and coronary heart disease are associated with depression (291, 326, 327). The link between depression and chronic pain as in osteoarthritis is also well recognized (328). Some antidepressants have been prescribed for pain treatment and chronic stress (329). Possibly, these health problems, both mental and somatic, may have a chronic course, and persist even after recognition and treatment of the mood disorder.

The psychosocial burden and the high mental health service costs in mood disorders has caused the World Health Organization to expect that this will be the leading cause of disability worldwide in 2020. The early identification and diagnoses of mood disorders can have direct and indirect impact on subsequent disability, social costs and even mortality across the lifespan.

Aim and scope

This thesis evaluated the link between mood disorder in adolescence and health outcomes during adulthood. The main objective was to increase the knowledge about the development, continuity and discontinuity of bipolar disorder. The broader health outcome of adolescents with hypomania spectrum episodes was also investigated. The final paper widens the scope and investigates health outcome of adolescents with mood disorder in general

Four main research questions were addressed:

- I. How do the symptoms of hypomania spectrum episodes in children and adolescents (<18 years of age) manifest and to what extent do adolescent hypomania spectrum episodes continue as bipolar disorder or other mood disorders in young adults (age 19-31 years of age)?
- II. What are the early risk factors for adult BPD (compared with MDD or no mood episodes in adulthood) among individuals with adolescent mood episodes?
- III. Which are the broader health outcomes (psychiatric non-mood Axis I and II disorders, utilization of health services and prescription of drugs) of adolescents with hypomania spectrum symptoms compared with adolescents with MDD and with controls without a history of adolescent mood disorders?
- IV. Do adults with a background of a depression during adolescence use more prescribed drugs than adults without mood disorders in adolescence?

Methods

Subjects and procedure

The thesis is based on a 15-year follow-up of a population-based investigation of adolescent depression. In the original investigation (Olsson et al., 1998, 1999), carried out in 1991-93 in the Swedish university town of Uppsala, all first-year students in upper secondary school (16-17 years old) during one academic year were asked to participate. School dropouts of the same age group were also invited. Fifteen years later, in 2006-2008, a second wave of data was collected including both diagnostic interviews and register data.

The original investigation

Out of a total of 2 465 adolescents in the age group, 2 300 (93%) participated in a screening with two self-evaluations of depression, the Beck Depression Inventory (BDI) (330) and the Centre for Epidemiological Studies – Depression Scale for Children (CES-DC) (331). Students with high scores ($BDI \geq 16$ or $CES-DC \geq 30 + BDI \geq 11$), or who reported a suicide attempt, were diagnostically interviewed with the Diagnostic Interview for Children and Adolescents in the revised form according to DSM-III-R for adolescents (DICA-R-A) (332, 333). For each student with high scores a same-sex classmate with low scores ($BDI < 16$ and $CES-DC < 30$) and without attempted suicide was interviewed in the same manner, in order to create a comparison group. In all, 631 adolescents were interviewed and asked for consent to be contacted for a future follow-up. 609 participants consented to a new contact, and were thereby eligible for the follow-up study.

The DICA-R-A is designed to assess mood disorders and a range of other child and adolescent mental disorders, but also included questions about adverse life events. Additional measures were completed by the participants, including the Somatic symptom Check-list Inventory (SCI) assessing various physical symptoms (334).

The follow-up assessment

At age 30-33 years of age, 409 of the original 609 participants (67%) took part in a follow-up interview. A range of axis I disorders were assessed with

the MINI International Neuropsychiatric Interview Plus (335). Episodes of major depression, hypomania and mania were rated from age 19 years to follow-up. To further enhance the participants' recall of mood episodes during the investigated period, a life-chart with questions about life-events, (hypo)mania, depressions, and treatments was used. The participants were also asked if either of their parents, grandparents, siblings or relatives had ever had any mood disorder. At the time of the follow-up interview, the participants also completed the DSM-IV – ICD-10 Personality Questionnaire (DIP-Q) (336) in order to assess personality disorder. Figure 2 shows the flow of participants from the first wave to the follow-up assessment.

The register data

The National Board of Health and Welfare keeps the official registers concerning health and illness in Sweden. The Patient Register contains data on psychiatric in-patient care on a national level since 1973, all in-patient care since 1987, and outpatient care (primary care excluded) since 2001. The purpose of this register is to follow the development of health in the population, to obtain information on health care utilization, to improve the abilities of prevention and treatment of disease and to contribute to the progress of health care.

The Prescribed Drug Register contains information on all dispensed prescribed drugs to the entire Swedish population from 1999 and onwards. The personal identity number is available since July 2005. Regular quality checks are performed and usually less than 1% of the civil registration numbers are missing or incorrect. All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Measurement units of utilization are prescriptions, Defined Daily Doses (DDDs) and expenditures. Updates are carried out monthly.

After informed consent, data were obtained on registered inpatient care (including delivery) during the years 1992 through 2009 and outpatient care during the years 2001 through 2009 with the diagnoses according to the International Classification of Diseases, 10th edition (ICD-10) (136). The diagnoses were grouped according to the chapters in ICD-10, except for chapter V, mental and behavioral disorders, where each block was grouped and analyzed separately.

Following the same procedure, data on prescription drugs during from July 1, 2005 through 2009 were obtained, categorized according to the ATC. The drugs were grouped according to the ATC main groups, with the exception of nervous system (N01-N07) in which each pharmacological/therapeutic subgroup was grouped and analyzed separately. Data from 2005 through 2006 were used in paper IV, and data from 2005 through 2009 were used in paper III.

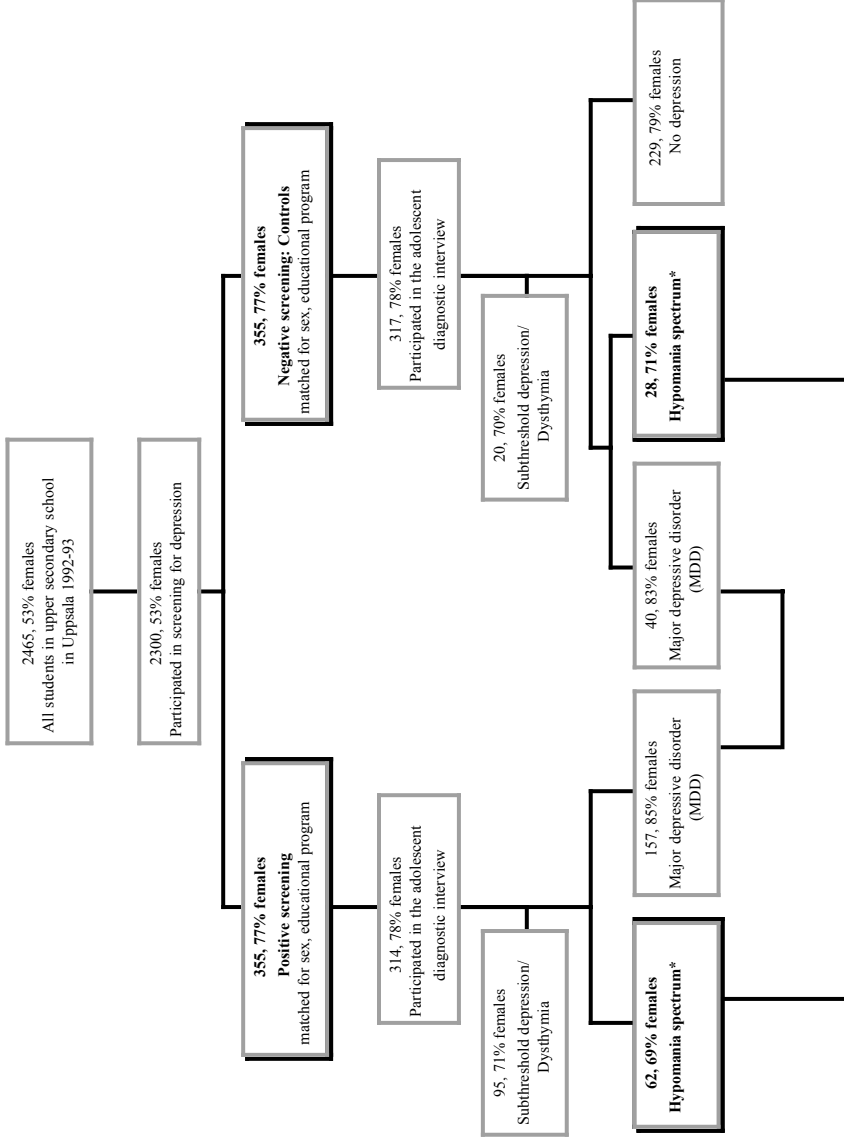


Fig. 2. Chart illustrating the selection of participants and division into groups for the present follow-up study.

Design of Paper I

This study focused on adolescent hypomania spectrum symptoms and continued mood disorders in adulthood. Subgroups of adolescents with hypomania spectrum were followed. The MINI was used to establish mood episodes in adulthood from age 19 years to follow up. Questions about suicidal ideation and suicide attempts during the period from age 19 years to follow-up were included. Participants were also asked about psychotropic medication and psychological treatment during adulthood and family history of mood disorders.

Adolescent hypomania spectrum was defined as “elevated mood” and/or “grandiosity” and 1-3 additional symptoms or alternatively irritability as the only core symptom and at least 4 additional symptoms. Elevated mood and/or grandiosity have been called “cardinal features” of mania and have been proposed as required symptoms in child and adolescent (hypo)mania (64, 65).

Based on the evaluation, the participants were divided into five subgroups as follows:

1. Full-syndromal hypomania: criteria for hypomania were fulfilled for at least 4 days duration (n=40)
2. Brief-episode hypomania: the symptom criteria for hypomania were fulfilled, but for less than 4 days (n=18)
3. Subsyndromal hypomania: 1 or 2 main symptoms and 1-2 additional symptoms were fulfilled (totally ≥ 3 symptoms). The duration was not defined, but was in most of the cases more than four days (n=32)
4. Major Depression Disorder (MDD): defined according to the DSM-IV criteria (n=197).
5. Controls: did not full-fill the criteria for MDD or dysthymia, and did not have mania spectrum symptoms according to the definitions for the subgroups 1-3 (n=229)

Design of Paper II

This study examined the early risk factors for adult BPD in adolescents with mood disorders. Adolescents with either hypomania spectrum or MDD were included in the analyses. We assessed adolescent risk factors for adult BPD compared with, first, MDD in adulthood and second, no mood episodes in adulthood. The groups with adolescent hypomania and adolescent MDD were analyzed both jointly and separately.

Several risk factors of potential relevance for the continued course of mood disorder were considered in the analyses, including child and adolescent mental disorders, adolescent mood symptoms, somatic symptoms, adverse life events during childhood and adolescence, and a family history of mood disorders in 1st and/or 2nd degree relatives.

Design of Paper III

This paper investigated the broader health outcomes of adolescents with hypomania spectrum. Adolescents with MDD without a history of hypomania spectrum episodes and controls without a history of adolescent mood disorders were used as reference groups.

Non-mood Axis I disorders and personality disorders in adulthood were assessed with the MINI and the DIP-Q. Some non-mood disorders were assessed from age 19 years to follow up (panic disorder and agoraphobia, alcohol abuse or dependence, and drug abuse or dependence), while only current status at follow-up was assessed for the other non-mood disorders and the personality disorders. In addition to these measures, register data on health care utilization and prescription drugs were used as proxy measures of disease and related health problems.

Design of Paper IV

This paper widened the scope to adolescents with mood disorders in general. The civic registration number was available for 612 of the subjects, and they were included in a long-term follow-up register study. Personal data was obtained from July 2005 through 2006 concerning the purchase of prescribed drugs.

In accordance with previous research showing that subthreshold depression in adolescents is similar to major depression with respect to both functional impairment and mental health outcome (158, 337), a broadly defined depression group was composed of subjects meeting the DICA-R-A criteria for major depressive disorder, or reporting suicide attempt, or scoring high on self-evaluation. The subjects who did not meet any of these criteria were classified as non-depressed and constituted a comparison group. The depression group included subjects meeting the criteria for major depression (72%), or dysthymia / subthreshold depression (28%). Subthreshold depression was defined as positive screening, but no depressive disorder according to the DICA-R-A. Totally 362 former depressed subjects (78% females) and 250 healthy controls (77% females) were included in this study.

Attrition at follow-up

The participant rate at the follow-up interview for the total hypomania spectrum group was 71% (64/90): 68% (27/40) for full-syndromal hypomania, 67% (12/18) for brief-episode hypomania and 78% (25/32) for subsyndromal hypomania. The participation rate was 65.9% (130/197) for the MDD group, and 64.6% (148/229) for the control group.

After informed consent, register data was linked to the full interview data for 64.4% (58/90) of the hypomania spectrum group, 64.5% (127/197) of the MDD group, and 64.2% (147/229) of the controls.

Statistics

Overall, P values less than 0.05 were regarded as significant. All statistical analyses were performed with SPSS. The specific statistics used in each paper is described below

Paper I

First, the χ^2 -test (Fisher's Exact Probability Test when applicable) was used to compare the five diagnostic subgroups (the three hypomania spectrum groups, MDD and controls) regarding both the baseline characteristics and the outcomes. Sex differences within all groups were investigated in the same manner. Baseline characteristics and outcomes of the total hypomania spectrum group were compared to the groups with MDD and controls in the same way. Comparison of age of onset was calculated with the t-test. Due to a skewed distribution the comparison of hypomania duration in childhood was calculated with the Mann-Whitney test.

Paper II

In the first set of analyses, adolescents with MDD or hypomania spectrum episodes were divided into three groups: those who developed BPD in adulthood, those who developed MDD in adulthood, and those who did not develop mood episodes in adulthood. Differences in risk factors (previous diagnoses, clinical characteristics and family characteristics) were analyzed using univariate logistic regression. In the second step, statistically significant risk factors were entered as covariates into multivariate logistic regression models. In the first model, the outcome variable was BPD versus no mood episodes in adulthood. In the second model, the outcome variable was BPD versus MDD in adulthood.

The risk factors that differed significantly between those who developed adult BPD and those who did not have mood episodes in adulthood were used to calculate a receiver operating characteristic (ROC) curve to evaluate the sensitivity and specificity for numerous risk factors. However, it was not possible to perform this for the risk factors of BPD versus MDD in adulthood due to the low number of statistically significant factors.

In the second set of analyses, univariate logistic regressions were used to identify the risk factors of adult BPD among adolescents with MDD compared with adolescents with MDD who would develop adult MDD and

compare with adolescents with MDD who would not have mood episodes in adulthood. Similarly, the risk factors for continuity between adolescent hypomania spectrum episodes and adult BPD were examined compared with the transition from adolescent hypomania spectrum episodes to adult MDD as well as the transition from adolescent hypomania spectrum episodes to no mood episodes in adulthood. Multivariate analyses were not conducted due to the small sample size of these groups.

Paper III

The baseline characteristics and outcomes in the three groups (hypomania spectrum, MDD and controls) were compared by univariate logistic regression analyses. As the hypomania spectrum group had a significantly higher proportion of males than the MDD group at baseline, all analyses were also performed with logistic regression adjusted for sex.

Due to skew distributions, differences between means were tested with the Mann Whitney U test. The subgroups of hypomania spectrum (full-syndromal, brief episode, and subsyndromal) were regarded too small to be analyzed separately. However, all background characteristics and outcomes are presented separately for the participants with full-syndromal hypomania, to increase transparency. To address the problem with loss of information and possible bias due to attrition, a multiple imputation approach was adopted for the logistic regression analyses.

Paper IV

The differences between means were tested by means of the Mann Whitney U test. When more than two groups were compared the Kruskal-Wallis test was used.

Ethics

Participants reporting current psychiatric disorders or recurrent depressions were informed of available treatment options and where to seek treatment. In some instances, a letter of referral was written to the local psychiatric outpatient clinic, after consent from the participant. The register data obtained from Statistics Sweden did not include information that could lead to identification of single participants. The studies were approved by the Ethical Committee of Uppsala University and later by The Regional Ethical Vetting Board of Uppsala, Sweden. The study was conducted in accordance with the ethical standards established in the Declaration of Helsinki.

Summary of results

Paper I

Ninety adolescents (16-17 years) with a lifetime hypomania spectrum episode (3.9% of the total sample) were identified: 40 with full-syndromal, 18 with brief-episode (<4 days), and 32 with subsyndromal (1-2 main symptoms and 1-2 additional symptoms) hypomania. The hypomania symptoms reported by the full-syndromal and the brief-episode groups were similar, whereas the subsyndromal group per definition reported fewer symptoms.

Compared to the controls, a larger proportion of the adolescents with hypomania spectrum or MDD had consulted a mental health professional such as a counselor, psychologist, psychotherapist or a child and adolescent psychiatrist. The hypomania spectrum groups and the MDD group differed significantly from the controls ($p < 0.01$ for brief episodes and $p < 0.001$ for the other groups and MDD). No participant reported psychopharmacological treatment in adolescence.

Of the 90 adolescents with a hypomania spectrum episode, 64 (71%) participated in the follow-up interview. In adulthood two participants (3%) reported mania, while an additional four (6%) reported hypomania. The majority reported at least one major depressive episode in adulthood: 67% of the full-syndromal hypomania subgroup, 67% of the brief-episode hypomania subgroup, and 48% of the subsyndromal subgroup. The participants with only MDD in adolescence reported a similar incidence of mania/hypomania and major depressive episodes (Fig. 3).

Among the adolescents with either hypomania spectrum disorder or MDD, those who also had a first and/or second degree family member with bipolar I and/or II disorder were more likely to report bipolar disorder I or II as adults compared to those without such family history (31% vs. 10%; $p < 0.01$). Adolescents with MDD and a first/second degree relative with bipolar I or II disorder ($n=9$) were more likely to have converted to bipolar disorder (33% vs. 11%; $p < 0.05$) compared to adolescents with MDD without such family history. Similarly, there was a trend for the adolescents with hypomania spectrum disorder to be more likely to continue into adulthood with (hypo)mania episode(s) if they had a first/second degree family member with bipolar disorder. A family history of suicide, depression, substance abuse, and anxiety disorder was not associated with bipolar disorder in adulthood.

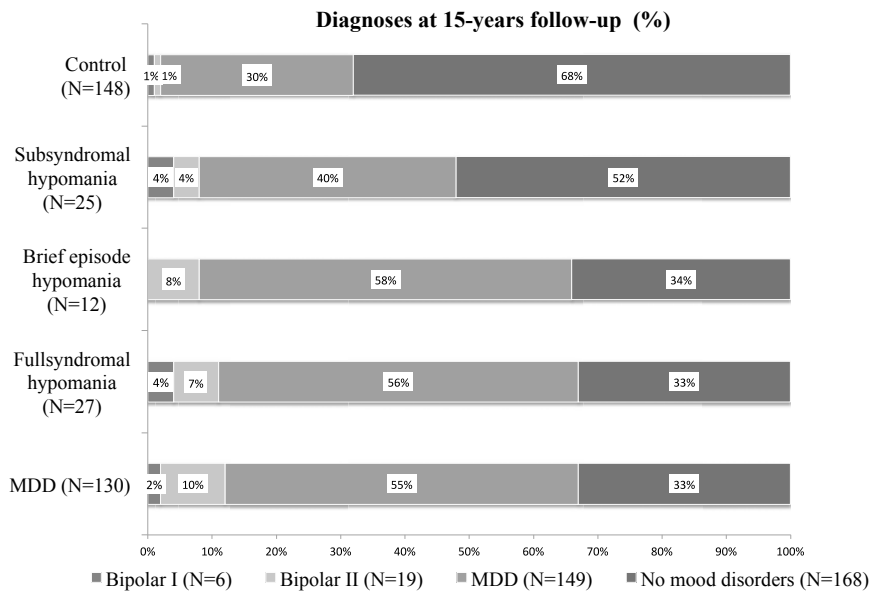


Fig. 3. Adult mood disorders in adolescents with hypomania, major depressive disorder or no mood disorder.

MINI diagnoses: BP I: Bipolar I disorder according to DSM-IV criteria; BP II: bipolar II disorder according to DSM-IV criteria; MDD: major depression disorder according to DSM-IV criteria; the group with no mood disorders did not meet the criteria for BP I or II or MDD, but some subjects met the criteria for other mental disorders. It should be noted that there are no over-lapping diagnoses.

Key: *DICA diagnoses:* Full-syndromal hypomania: criteria for hypomania were fulfilled (1 or 2 of the main symptoms and 3 or more additional symptoms) for at least 4 days duration; Brief-episode hypomania: the symptom criteria for hypomania were fulfilled, but for less than 4 days; Subsyndromal hypomania: 1 or 2 main symptoms and 1-2 additional symptoms were fulfilled (totally ≥ 3 symptoms). The duration was not defined, but was in most of the cases more than four days; Major Depression (MDD) was defined according to DSM-IV criteria in DICA; Controls (C) did not fulfill the criteria for MDD or dysthymia, and did not meet the criteria for hypomania spectrum according to subgroups 1-3.

Paper II

Of the 194 participants with adolescent mood disorders who were followed up after 15 years, 22 were diagnosed with bipolar I or II, 104 had MDD and 68 had no mood episodes in adulthood. The main finding was that among the adolescents with mood disorders, a family history of BPD was the strongest predictor of developing BPD (OR=3.53; 1.03-12.08). Disruptive disorders significantly increased the risk of developing BPD compared with developing MDD (OR=3.56; 1.38-9.21).

The risk that adolescents with MDD would develop adult BPD, versus having no mood episodes in adulthood, was elevated among those with an early disruptive disorder (OR=3.62; 1.09-12.07) or multiple somatic symptoms (OR=6.60; 1.70-25.67). Only disruptive disorders significantly predicted adult BPD among adolescents with MDD versus continued MDD in adulthood (OR=3.59; 1.17-10.97).

Out of the 130 adolescents with MDD during adolescence, 72 had developed adult MDD; furthermore, 16 had developed hypomania or mania and 42 reported no mood episodes in adulthood. The transition from adolescent MDD to adult BPD (compared with no mood episodes in adulthood) was associated with the presence of disruptive disorders (OR=3.62; 1.09-12.07) and multiple somatic symptoms (OR=6.60; 1.70-25.67, see Figure 4).

The transition from adolescent MDD to adult BPD (compared with continuing MDD in adulthood) was only significantly associated with adolescent disruptive disorders (OR=3.59; 1.17-10.97, see Figure 5).

Of the 64 adolescents with hypomania spectrum episodes during childhood, 6 had developed adult hypomania or mania, 32 developed MDD and 26 reported no mood episodes in adulthood. The continuity between adolescent hypomania spectrum and adult BPD (compared with no mood episode) was associated with panic disorder (OR=12.00; 1.39-103.48), GAD (OR=12.00; 1.39-103.48) and long-term depression (OR=12.00; 1.39-103.48). When these three factors were entered simultaneously into a logistic regression analysis, panic disorder and GAD predicted an increased risk of adult BPD, whereas long-term depression did not remain significant (Fig. 4). Continuity between adolescent hypomania spectrum and adult BPD (compared with MDD in adulthood) was associated with psychotic symptoms in adolescence (OR=15.50; 1.13-212.18, see Figure 5).

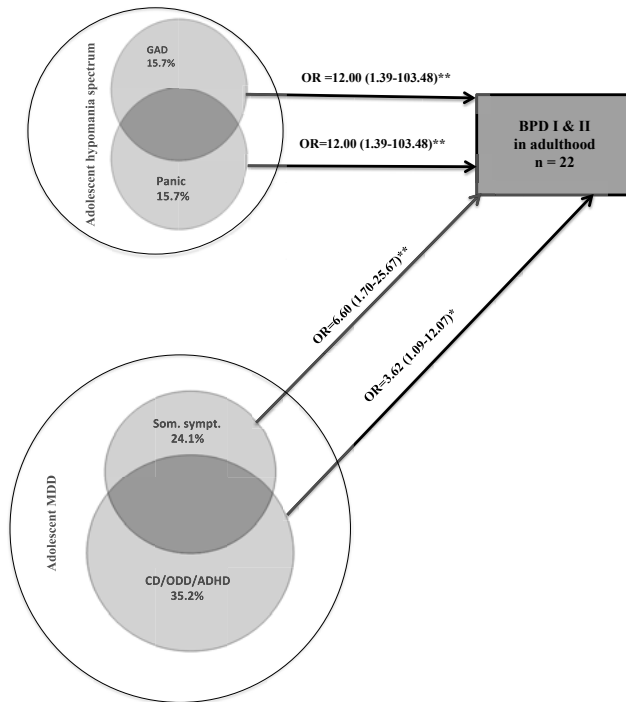


Fig. 4. Child and adolescent risk factors for developing bipolar disorder (BPD; n=22) compared with no mood episodes (n=68) in adulthood among adolescents with hypomania spectrum episodes (n=32; 6 developed adult BPD) or transition from adolescent MDD to adult BPD (n=58; 16 developed adult BPD).

Note: *p<0.05; **p<0.01

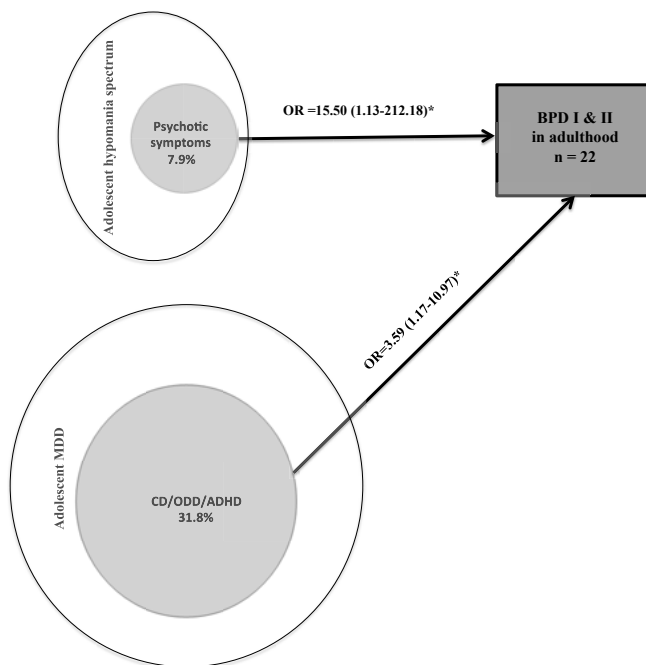


Fig. 5. Child and adolescent risk factors for developing bipolar disorder (BPD; n=22) compared with major depressive disorder (MDD; n=104) in adulthood among adolescents with hypomania spectrum episodes (n=38; 6 developed adult BPD) or transition from adolescent MDD to adult BPD (n=88; 16 developed adult BPD).

Note: *p<0.05

Paper III

The main message was that the outcomes of the hypomania spectrum group and the MDD group were similar regarding subsequent non-mood Axis I disorders in adulthood. At follow-up a non-mood disorder on Axis I was reported by 34 (53%) of the hypomania spectrum group, compared with 74 (57%) of the MDD group, and 41 (28%) of the controls.

The most prevalent disorders were anxiety disorders. There were no significant differences between the hypomania spectrum group and the MDD group regarding any of the investigated Axis I disorders in the complete case analyses. In the analyses with multiple imputations, no significant differences were found except for PTSD and bulimia nervosa, although the prevalence of these disorders was low.

A personality disorder in adulthood was reported by 18 (29%) of the participants with hypomania spectrum in adolescence, compared with 26 (20%) of those with adolescent MDD, and 12 (8%) of the controls. A statistically significant difference was reached only for obsessive-compulsive personality disorder (24 vs. 14%).

Venn diagrams were used to illustrate how anxiety disorders, substance abuse, and personality disorders overlapped in the three groups at follow up (Figure 6). The pattern of overlap was similar for the hypomania spectrum group and the MDD group. In the control group, these disorders were less common and the overlap of the disorders was less extensive. In both groups, the risk of Axis I disorders and personality disorders in adulthood correlated with continuation of mood disorder. Prescription drugs and health service use in adulthood was similar in the two groups. Compared with adolescents without mood disorders, both groups had a higher subsequent risk of psychiatric morbidity, used more mental health care, and received more psychotropic drugs.

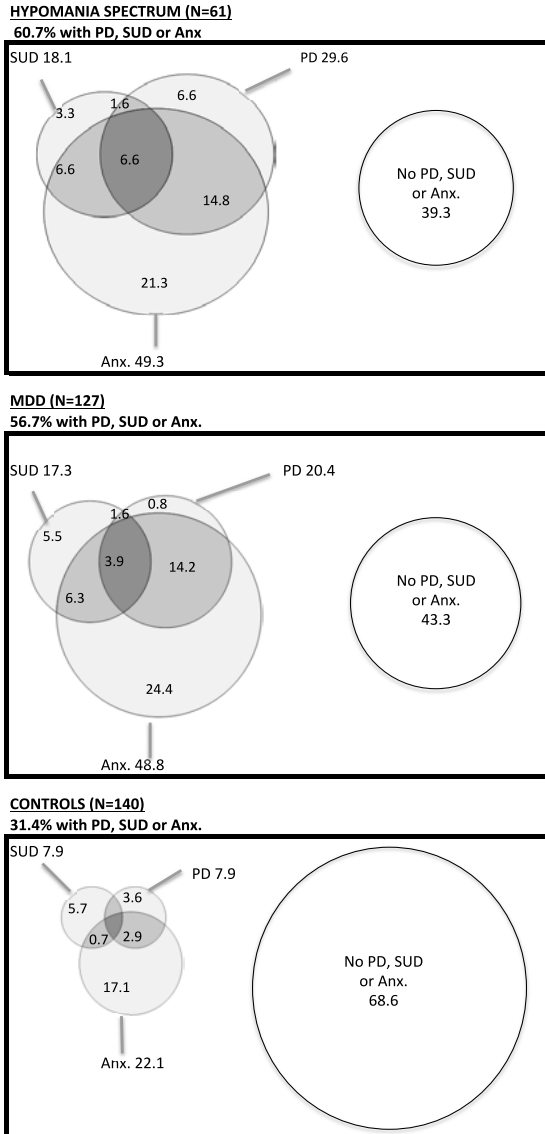


Fig. 6. Venn diagrams illustrating the overlap of adult anxiety disorders (Anx.), substance use disorders (SUD) and personality disorder (PD) in former adolescents with hypomania spectrum or major depressive disorder (MDD) and in controls. All values are shown as %.

Paper IV

The formerly depressed females received significantly more prescription drugs such as antidepressants, anticonvulsants, antibacterials, antimycotics and antihistamines for systemic use, stomatological drugs, drugs for acid related disorders, mineral supplements, vasoprotectives, corticosteroids for dermatological use, thyroid therapy, drugs for obstructive airway diseases, as well as ophthalmological and otological drugs.

Formerly depressed males, on the contrary, did not differ from non-depressed males regarding prescription drugs. The formerly depressed males had significantly lower numbers of prescription drugs as compared to the formerly depressed females ($p < 0.001$). Also among the controls, females were prescribed more prescription drugs than men ($p < 0.05$, see Figure 7).

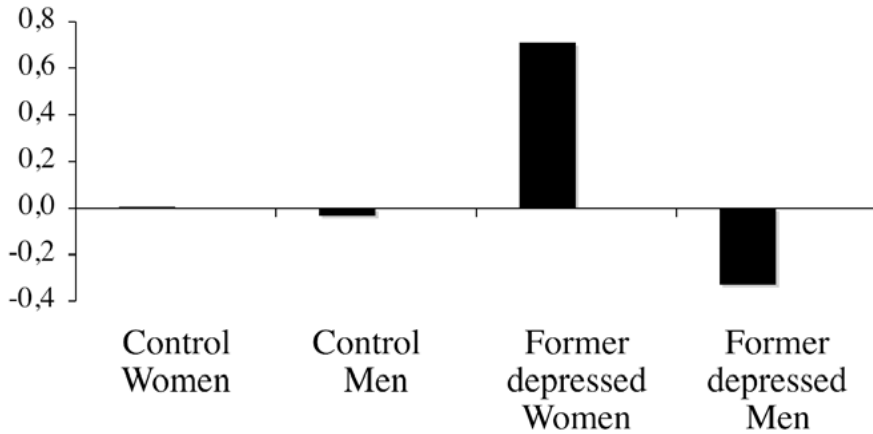


Fig. 7. Deviations in mean number of prescriptions from the mean of the total control group, expressed in SD. Kruskal-Wallis, $\chi^2=43.9$, $df\ 3$, $p < 0.001$. Post hoc analyses according to Mann-Whitney; control women vs. control men n.s., control women vs. former depressed women, $p < 0.01$, control men vs. former depressed men n.s., former depressed women vs. former depressed men $p < 0.01$

Discussion

Hypomania spectrum episodes in children and adolescents and future manifestation in adults have rarely been studied in community samples. This thesis presents the first Swedish longitudinal community based study in this field. In fact, no similar study has to date been conducted anywhere in the world. The main finding of this thesis is that adolescent hypomania spectrum disorder did only rarely develop into bipolar disorder during adulthood. Instead a substantial proportion with this condition developed major depression later in life. This thesis also sheds light upon the early signs of bipolar disorders. Early identification of individuals at risk of developing mood disorders combined with prospective follow-ups into adulthood open up for understanding mechanisms of vulnerability and resilience. This kind of studies can also contribute to improved treatment of children and adolescents with mood disorders in general. The discussion to follow will focus on some advantages of these four papers, the main findings, conclusions, methodological considerations and implications.

General strengths

The study has some advantages compared to other long-term community studies. It is a large, well-defined community sample with controls (matched for age, school class, and sex), and focused on the natural development of mood disorders. Participants were assessed during adolescence and followed up 15 years later by clinically trained interviewers blinded to their previous conditions. Both interviews and registers were used as sources of information, which broadened the scope of the investigation. Additionally, to enhance participant recall of mood episodes during the follow-up, a life-chart with questions concerning life events, mood episodes, and treatments was used. For example, information about psychotropic medication, treatment and presence of 1st - and/or 2nd - degree family histories of mood disorder was collected during follow-up. Furthermore, this investigation includes information about hypomania episodes from the whole child- and adolescent period, which makes it possible to detect new cases and probable transition or switch to BPD in the investigation period.

Paper I

The study showed, that only a smaller proportion of the adolescents with hypomania spectrum disorders reported bipolar disorder in adulthood. This is in contrast to the results from clinical samples (17, 19, 43, 52, 79, 104, 142, 338, 339), but in line with results from other community samples (5, 6, 22, 82, 340, 341). The phenomenology of the hypomania spectrum episodes during childhood and adolescence per se did not predict adult bipolar disorder in our study. However, having both affective symptoms during adolescence and a family history of bipolar disorder seemed to somewhat increase the risk of developing bipolar disorders in adulthood.

Our study also demonstrates that child and adolescent hypomania spectrum disorders exist and are quite common. The findings are in line with previously published studies regarding age of onset, duration, phenomenology, a slight female predominance, suicidal behavior, depressive disorders, help seeking, and family history (19, 51, 66, 99, 151, 342, 343). However, this study does not confirm previous findings that hypomania spectrum with “cardinal symptoms” such as elevated mood, grandiosity (64, 65) and other additional symptoms like hyperactivity (344) in children and adolescents predict the diagnosis of bipolar disorder in adults.

Paper II

The study showed that among adolescents with mood disorders numerous child and adolescent factors differed between those who subsequently developed BPD and those who did not have any mood episodes in adulthood, including family history of BPD, multiple somatic symptoms, and anxiety disorders. Disruptive disorder in childhood or adolescence and family histories of BPD emerged as significant risk factors that differentiated between the future development of BPD and MDD. Our results are in line with previous studies showing that a family history of BPD is a robust risk factor for this disorder (84, 101, 171, 345). Also several longitudinal studies have found an association between early disruptive disorders and the bipolar spectrum (4, 176, 346) and anxiety disorders in general (119, 159, 347, 348). However, no risk factor with high sensitivity or specificity was identified. Characteristics such as family histories, disruptive disorders, anxiety disorders, somatic symptoms, and family histories of mood disorders warrant particular attention.

Paper III

The results demonstrated that hypomania spectrum in adolescence is a marker of future excess risk for other mental disorders, high consumption of prescription drugs, and high health care use. The general pattern of anxiety disorders, personality disorders, and substance use disorders in adulthood was similar in the adolescent hypomania spectrum and MDD group, but clearly differed from that of the control group. The results thus seem to suggest that adolescent hypomania spectrum and MDD overlap on an affective spectrum scale. This general pattern of non-mood morbidity was rather different from the comorbidity pattern of BPD in adults. Therefore we interpreted this finding as further support of our conclusion that adolescent hypomania spectrum may only rarely be related to adult BPD. For instance, the anxiety cluster was more typical of MDD than BPD in adults and we did not find a higher prevalence of panic disorder or PTSD in the hypomania spectrum group (277, 349, 350). Further, personality disorders within cluster C (obsessive-compulsive and avoidant) were the most prevalent personality disorders in both the hypomania spectrum group and MDD group. This is in contrast to other studies, where mainly comorbidity of bipolar disorder and cluster A and B disorders such as borderline, antisocial and schizotypal have been reported (120, 121, 351).

This paper also found that health service use and prescription drugs in adults were similar in the hypomania spectrum and MDD groups, which further demonstrate that the prognostic severity of the conditions in these groups is quite similar. A continued course of adolescent mood disorders is strongly associated with non-mood morbidity in adulthood. From the clinical perspective, it is therefore important to identify and treat children and adolescents with mood disorders and to monitor their development. About two-thirds of adults with mood disorders report an onset during childhood and adolescence (343, 348), and children and adolescents are often diagnosed many years after the onset of the illness. This might lead to a longer duration of untreated illness, increased risks of chronicity and social impairment, and higher health care costs.

Paper IV

The results suggest that adult females with a history of adolescent depression have more prescription drugs in many ATC classes than their peers. This could reflect a presence of recurrent mood disorders as well as a series of comorbid somatic illnesses. At least females with adolescent depression may have an increased prevalence of infections, inflammations and autoimmune diseases later in life. Women have higher systemic baseline levels of glucocorticoids than men due to estrogen. In males testosterone reduces glucocor-

ticoid levels (306). This might explain why approximately 80% of the autoimmune diseases occur in women (308, 309, 352). Similar processes might possibly explain why our study showed high numbers of recipes for prescribed drugs such as corticosteroids for dermatological use, antibacterials for systemic use, antimycotics for systemic use, thyroid therapy, drugs for obstructive airway diseases, antihistamines for systemic use as well as ophthalmological and otological drugs.

The increased use of antidepressants and anticonvulsants probably reflects repeated episodes of mood disorders. Anticonvulsant drugs were frequently used as mood stabilizers (353, 354). Thyroid hormones might have been used to augment antidepressant therapy (355), but early onset depression might also precede thyroid disorder.

The lack of increased use of prescription drugs among former depressed males indicate a need for further studies elucidating the health status of adult men with earlier adolescent depression. The males could either be under-medicated or under diagnosed (158, 356). It has been estimated that less than half of patients with depression are properly recognized (357). Male depression is frequently masked by irritation, anger, hostile-aggressive-abusive behavior and alexithymia. Usually, the depressed males do not seek medical help (358).

Methodological considerations

Some limitations of this study must be taken into account. First, the response rate at the first investigation in adolescence was very high and the participation rate at follow-up did not differ between the subgroups. However, the subjects lost to follow-up could represent a group with more severe mood disorders. In that case, there is a risk for selection bias. However, we had access to register data on inpatient and outpatient care and purchase of prescription drugs for 97% of the original participants (337). These data show that only a small proportion was prescribed mood stabilizers, and only a few received in- or outpatient care for mood disorders. It is thus unlikely that we have missed many cases of bipolar disorder.

Second, the aim at baseline was to screen for depression and not for hypomania. However, 317 controls with negative screening were also diagnostically interviewed. In addition, numerous studies (15, 101-103, 151, 171) have demonstrated that early onset of depressive disorders in children or adolescents usually precedes bipolar disorder. Still, there are a few studies (60, 359) that have reported atypical mania-like symptoms in young children, mainly comorbid with ADHD. A fully representative sample of adolescents with hypomania spectrum episodes might show a slightly different comorbidity pattern in adulthood.

Third, lowering “cut- offs” for hypomania, as done in our study, increases the prevalence and makes the condition difficult to define operationally, which might diminish specificity and reliability (18). Thus, this procedure may have inflated the prevalence of hypomania spectrum. However, the usage of structured clinical interviews enhances the quality of diagnostic decision-making, and structured assessment of hypomania symptoms leads to high inter-rater reliability (360). Hantouche et al (361) reported that the number of bipolar diagnoses almost doubled when a systematic search for hypomania was carried out in a sample of patients with depression. Conversely, the potential lack of insight into manic symptoms may have contributed to false-negative diagnostic results, as the structured interviews DICA-III-R and MINI are based on information only from the participants. Thus, the prevalence found might also have been too low. Previous studies have found that parent reported problems in children have the strongest predictive values in self-reported problems in adulthood (74, 112, 362).

Fourth, the diagnostic accuracy can have been affected by other psychiatric symptoms like ADHD in adolescence that might mimic (hypo)mania symptoms. However, only 3 of the 90 adolescents with hypomania spectrum fulfilled the criteria for ADHD.

Fifth, data on age of onset and symptom description were obtained retrospectively. This may have caused “recall bias”, and some hypomania episodes could have been missed. Such a bias would more likely affect hypomania than mania. However, all 25 participants who reported the first episode during childhood (0-12 years) had a second episode in adolescence. In the follow-up assessment a life-chart was used to minimize the risk of recall bias. We also had information from the national patient register.

A further limitation is the general risk of type II errors because of the relatively small number of participants. Thus, it is not possible to conclude that the outcome of adolescents with hypomania spectrum and MDD is equivalent. However, the data suggest that there are no fundamental differences between the groups.

Finally, some limitations specific to paper IV should be mentioned. In this register follow-up, there was no information about the course of the depression from age 16-17 years onward. No information was available about the presence of diagnosed mental or somatic diseases. The use of non-psychotropic drugs may indicate, but does not equal diagnosed somatic disease. However, drugs prescribed by a medical doctor might indicate the presence of mental or somatic diseases. Thus, prescription drugs use can be regarded as a proxy variable for the presence of diseases. Unfortunately, only data from the one and a half year at the end of the follow up period were available in the register. The male group was quite small, which decreased the statistical power. However, as compared to the former depressed females who had high consumption of prescription drugs, the males tended to have lower consumption, although the difference versus the controls was

not statistically significant. Furthermore, significant differences were found between the former depressed females and the former depressed males and thus it is less likely that the gender differences found are due to limited power in the male group.

Implications

The findings from this thesis will hopefully contribute to an increased awareness of the early signs of mood disorders and an increased understanding the development to bipolar disorder. The findings also have implications for how hypomania spectrum symptoms should be handled in child and adolescent care. Long-term preventive or prophylactic pharmacological treatment in children and adolescents with hypomania spectrum episodes might be unnecessary and risky by provoking potentially harmful side effects. Instead, educating children with early risk factors and their parents about coping skills and a healthy lifestyle may be more promising. Mental health promotion like adequate sleep, sufficient exercise, healthy diet and avoidance of smoking and other drugs could protect against the development of mood disorders in adult life (363-366). Adaptive coping strategies (e.g. seeking social support, problem solving, positive self-control, accepting responsibilities) and social and emotional support might protect against the development and progression of bipolar disorders (367, 368). However, depressive episodes and anxiety disorders need to be identified and adequately treated. In addition, long-term psychopharmacological treatment is necessary in severe cases of mood disorders.

Overall, adolescents with mood disorders in general are at increased risk of subsequent health problems and could benefit from improved treatment, careful monitoring and support in order to facilitate adaptive development. The gender differences concerning medication in former MDD patients are of special interest. Adolescent depression in females – but not in males - seems to increase the risk of several somatic symptoms. Inflammatory processes may be influential in females, which may explain the higher risk of infections, inflammations and autoimmune diseases in females later in life.

Conclusion

A significant number of adolescents with full-syndrome, brief-episode, and subsyndromal hypomania will not develop bipolar disorder as adults. In fact, only a small proportion of adolescents with hypomania spectrum episodes seem to have (hypo)mania in adulthood. However, a substantial proportion will have major depression later in life.

Disruptive disorder in childhood or adolescence as well as family histories of BPD emerge as significant risk factors differentiating between future development of BPD and MDD. However, no predictor appears to clearly delineate the group of adolescents who subsequently develop BPD as adults.

Adolescents with hypomania spectrum episodes and adolescents with MDD do not differ substantially in health outcomes. Both groups are at increased risk for subsequent mental health problems, high consumption of prescribed drugs, and extensive use of health care services. The general pattern of anxiety disorders, personality disorders, and substance use disorders in adulthood are likely to be similar in the two groups, but clearly differ from that of the control group.

Females with adolescent depression are more often than female comparisons prescribed both psychotropic as well as non-psychotropic drugs. This seems to indicate an increased vulnerability to both mental and somatic illness. Males with adolescent mood disorders do not seem to use more drugs than their peers, demonstrating a distinct gender difference.

Sammanfattning på svenska

Bakgrund och frågeställningar

Bipolär sjukdom kännetecknas av extrema svängningar i humör, energi, tankar och beteende och förekommer hos ca 1-3 % hos vuxna befolkningen. Tillståndet förekommer även hos barn. Risken för ökad sjuklighet, dödlighet och nedsatt social funktion är stor. Epidemiologiska studier tyder på att även subsyndromala bipolära tillstånd är vanliga och medför funktionsnedsättning.

Den ökade diagnosticeringen av bipolär sjukdom hos barn och ungdomar har debatterats intensivt senaste decenniet. Tillståndets förlopp har stor betydelse för hur stöd och behandling ska läggas upp, och det finns därför ett stort intresse för hur symtomen utvecklas över tid. Kliniska studier talar för att bipolär sjukdom i barn- och ungdomsåren ofta fortsätter i vuxen ålder, medan befolkningsstudier tyder på att många med symtom på bipolaritet i barn- och ungdomsåren inte utvecklar sjukdomen som vuxna. Det är möjligt att hypomana symtom under ungdomsåren även kan innebära ökad risk för andra hälsoproblem senare i livet.

Ökad kunskap om tidiga prediktorer skulle kunna ge insikt i tillståndets utveckling, förbättra möjligheterna att identifiera personer i riskzonen och skapa bättre förutsättningar för vård, behandling och omhändertagande.

Metod

Avhandlingen bygger på en 15-årsuppföljning av en befolkningsundersökning av depression hos ungdomar. Den ursprungliga undersökningen genomfördes på gymnasieskolorna i Uppsala 1991-93. Totalt 2300 ungdomar i åldrarna 16-17 år screenades för depression. För varje ungdom som bejakat depressionssymtom rekryterades även en klasskamrat av samma kön och utan depressionssymtom till en referensgrupp. Cirka 300 ungdomar (80 % flickor) med positiv screening och lika många ungdomar (samma könsfördelning) med negativ screening intervjuades kring psykisk ohälsa.

Efter cirka 15 år (2006-2009) genomfördes en uppföljning, där 409 deltagare intervjuades angående psykiatriska diagnoser och social situation, samt besvarade skriftliga frågor om personlighet. Information om läkemedelsan-

vårdning och sjukhusvård (inom sluten- och öppenvård) inhämtades från Socialstyrelsens nationella register.

Sammanlagt 90 ungdomar hade haft hypomanispektrumtillstånd under tonåren (antingen episoder av hypomani eller subsyndromal hypomani). I den här avhandlingen har dessa ungdomars hälsa i vuxen ålder undersökts. Därtill har faktorer i tonåren som predicerar bipolär sjukdom i vuxen ålder undersökts. Slutligen har läkemedelsförskrivning i vuxen ålder jämförts mellan de som hade respektive inte hade depression som tonåringar.

Resultat

Av de 90 deltagare som hade hypomanispektrumtillstånd som tonåringar deltog 64 i uppföljningen i vuxen ålder. Majoriteten rapporterade depressionsepisoder som vuxna, men endast sex personer uppfyllde kriterierna för bipolär sjukdom. Deltagarna med hypomanispektrum i ungdomen hade även hög förekomst av generaliserad ångest, paniksyndrom, tvångssyndrom och personlighetsstörningar i vuxen ålder. Förekomsten var dock inte högre än hos de som endast hade depression i tonåren. Bland ungdomarna som hade antingen depression eller hypomanispektrum fanns en ökad risk att utveckla bipolär sjukdom hos de som även hade beteendeproblem eller familjehistoria av bipolär sjukdom.

Data från Socialstyrelsens register visade på högre konsumtion av läkemedel hos kvinnor med depression i tonåren jämfört med kvinnor utan sådan sjuklighet i tonåren. Hos män med depression under tonåren fanns inte någon ökad konsumtion av läkemedel

Slutsatser

Resultaten tyder på att de flesta barn och ungdomar som har episoder med symtom på hypomani inte utvecklar bipolär sjukdom i vuxen ålder. Även om en del riskfaktorer identifierades finns det idag inga tidiga tecken som på ett träffsäkert sätt kan predicera vilka ungdomar som kommer att utveckla bipolär sjukdom. Många ungdomar med hypomana symtom får dock andra hälsoproblem senare, som depression, ångest och kroppslig sjukdom. Det är därför viktigt att uppmärksamma dessa symtom och noggrant följa och stödja de ungas utveckling. Kännetecknen som beteendestörningar och familjehistorik av bipolär sjukdom kräver speciell uppmärksamhet.

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