ORIGINAL ARTICLE

Evidence that bipolar disorder is the poor outcome fraction of a common developmental phenotype: an 8-year cohort study in young people

M. J. A. Tijssen[1], J. van Os[1,2], H.-U. Wittchen[3,4], R. Lieb[4,5], K. Beesdo[3], R. Mengelers[1], L. Krabbendam[1] and M. Wichers[1]*

[1] *Department of Psychiatry, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University, Maastricht, The Netherlands*
[2] *Division of Psychological Medicine, Institute of Psychiatry, London, UK*
[3] *Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany*
[4] *Max Planck Institute of Psychiatry, Clinical Psychology and Epidemiology Unit, Munich, Germany*
[5] *Institute of Psychology, Epidemiology and Health Psychology, University of Basel, Switzerland*

Background. Reported rates of bipolar syndromes are highly variable between studies because of age differences, differences in diagnostic criteria, or restriction of sampling to clinical contacts.

Method. In 1395 adolescents aged 14–17 years, DSM-IV (hypo)manic episodes (manic and hypomanic episodes combined), use of mental health care, and five ordinal subcategories representing the underlying continuous score of (hypo)manic symptoms ('mania symptom scale') were measured at baseline and approximately 1.5, 4 and 10 years later using the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI).

Results. Incidence rates (IRs) of both (hypo)manic episodes and (hypo)manic symptoms (at least one DSM-IV core symptom) were far higher ($714/10^5$ person-years and $1720/10^5$ person-years respectively) than traditional estimates. In addition, the risk of developing (hypo)manic episodes was very low after the age of 21 years [hazard ratio (HR) 0.031, 95% confidence interval (CI) 0.0050–0.19], independent of childhood disorders such as attention deficit hyperactivity disorder (ADHD). Most individuals with hypomanic and manic episodes were never in care (87% and 62% respectively) and not presenting co-morbid depressive episodes (69% and 60% respectively). The probability of mental health care increased linearly with the number of symptoms on the mania symptom scale. The incidence of the bipolar categories, in particular at the level of clinical morbidity, was strongly associated with previous childhood disorders and male sex.

Conclusions. This study showed, for the first time, that experiencing (hypo)manic symptoms is a common adolescent phenomenon that infrequently predicts mental health care use. The findings suggest that the onset of bipolar disorder can be elucidated by studying the pathway from non-pathological behavioural expression to dysfunction and need for care.

Introduction

The World Health Organization (WHO) identified bipolar disorder as the sixth leading cause of disability-adjusted life years in the world among people aged 15–44 years (Murray & Lopez, 1996). The true prevalence and incidence rates (IRs) of (hypo)manic disorder remain unclear. Lifetime prevalence estimates vary from around 1–2% (Regier *et al.* 1988; Kessler *et al.* 1994; Weissman *et al.* 1996) to 5–8% (Carlson &

Kashani, 1988; Lewinsohn *et al.* 1995; Angst, 1998; Szádóczky *et al.* 1998; Judd & Akiskal, 2003) whereas IRs vary between 4 and $33/10^5$ per year (Bebbington & Ramana, 1995).

　The reported variability in bipolar population morbidity rates may be caused by several factors. First, nearly all incidence studies on bipolar disorder are based on participants in clinical care, which probably results in a substantial underestimation of rates (Spicer *et al.* 1973; Leff *et al.* 1976; Rasanen *et al.* 1998; Lloyd *et al.* 2005; Kennedy *et al.* 2005*b*) because many cases either have not sought help or are not diagnosed correctly (Ghaemi *et al.* 2002).

　Second, previous work suggests that the age of the study population may be crucial, as there are

---

　* Address for correspondence : Dr M. Wichers, Department of Psychiatry, Maastricht University, PO Box 616 (Vijverdal), 6200 MD Maastricht, The Netherlands.

　(Email: m.wichers@sp.unimaas.nl)

indications that much of the population lifetime risk for bipolar disorder is consumed in adolescence. Thus, Lewinsohn *et al.* (2003) showed that, in a population sample stratified by the age categories <9, 19–23 and 24–29 years, the first lifetime onset of bipolar disorder and subthreshold bipolar disorder almost always occurred in adolescence. Therefore, a young study population as used in the Early Developmental Stages of Psychopathology (EDSP) Study is most appropriate (Wittchen *et al.* 2003). The issue of age is also important in view of the considerable psychopathological, longitudinal and familial/genetic overlap between bipolar disorder and childhood disorders, in particular attention deficit hyperactivity disorder (ADHD), but also oppositional–defiant disorder (ODD) and conduct disorder (CD) (Nierenberg *et al.* 2005; Henin *et al.* 2007). Studying the onset of (hypo)manic symptoms in adolescents allows for quantification of the amount of the bipolar population morbidity rate that can be traced to childhood disorders.

Third, diagnostic criteria used have a major impact on population rates (Akiskal *et al.* 2000; Angst *et al.* 2003). Many people in the general population display subthreshold bipolar disorder (Merikangas *et al.* 2007). Therefore, widening criteria for bipolar disorder will naturally increase the number of cases.

An informative way of describing the bipolar population morbidity rate is to replace dichotomous criteria with dimensional measures; the possible use of dimensional measures in bipolar disorder is currently being examined in DSM-V (First, 2006). Angst & Marneros (2001) suggest that a natural continuum may exist on which all (hypo)manic manifestations of varied length, frequency and severity can be represented. This dimensional approach may be more sensitive and informative in the search for determinants of onset and change, making it easier to monitor onset and progression of psychiatric phenotypes (Cougnard *et al.* 2007; van Os *et al.* 2009). Furthermore, it allows for fuller examination of the impact of symptoms on well-being and functioning, severity and distress (Regeer *et al.* 2006), and may facilitate recognition of at-risk states and early intervention (Egeland *et al.* 2000; Hanssen *et al.* 2005; Birmaher & Axelson, 2006). For bipolar disorder, it has the additional advantage of allowing for the separate study of manic and depressive dimensions, the co-occurrence of which in the same mood episode is common in clinical practice and therefore represents an important parameter for study in epidemiological and taxonomic investigations. Finally, it can increase statistical power without loss of clinical utility.

Therefore, the aim of the current study was to investigate dimensional (hypo)manic categories, independent of receipt of mental health care, in a large representative cohort of adolescents followed over a period of up to 10 years.

Method

Sample

This examination is part of the EDSP study, a prospective longitudinal cohort study. Detailed information about the design, sample, instruments, procedures and statistical methods of the EDSP study is presented elsewhere (Wittchen *et al.* 1998*b*; Lieb *et al.* 2000). Data were collected in a representative population sample of adolescents and young adults living in the Munich area (Germany), aged 14–24 years at baseline. The study sample was drawn randomly from the 1994 government population registers. Fourteen to 15-year-olds were sampled at twice the rate of 16- to 21-year-olds, and 22- to 24-year-olds were sampled at half this rate.

Study design

The present study is based on a subset of EDSP respondents, aged 14–17 years at baseline (T0, $n = 1395$, response rate 75%), thus ensuring a population at risk of developing incident bipolar disorder. Participants completed a baseline survey (T0, $n = 1395$) and three follow-up investigations (T1, T2, T3), covering a time period of approximately 1.6 (T0–T1, S.D. = 0.2), 3.4 (T0–T2, S.D. = 0.3) and 8.3 years (T0–T3, range 7.4–10.6 years, S.D. = 0.7) respectively. Response rates (conditional on T0 completion) were 88% at T1 ($n = 1228$), 83% at T2 ($n = 1169$) and 73% at T3 ($n = 1022$).

Instruments

Interviews were conducted using the computerized version of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI; Wittchen & Pfister, 1997), an updated version of the WHO's CIDI version 1.2 (WHO, 1990). The DIA-X/M-CIDI is a comprehensive, fully standardized diagnostic interview and assesses symptoms, syndromes and diagnoses of various mental disorders in accordance with definitions and criteria of the DSM-IV. Its features have been developed and tested in several methodological studies with the CIDI or modifications thereof, including the deletion of many of the CIDI's skipping rules to allow for the study of subthreshold conditions. High inter-rater and test–retest reliability of the CIDI have been established (Wittchen *et al.* 1991; Wittchen, 1994), in addition to validity (Reed *et al.* 1998). Test–retest reliability (κ) of the DIA-X/M-CIDI was reported to be 0.68 ($p < 0.001$) for major depressive disorder and 0.64 ($p < 0.001$) for bipolar disorder

(Wittchen *et al.* 1998*a*). To ensure reliability of the assessments, fully trained and experienced psychologists who were allowed to probe with follow-up questions conducted the interviews. At baseline, the lifetime version of the DIA-X/M-CIDI was used, and the interval version for subsequent investigations. By using the lifetime version of the DIA-X/M-CIDI at baseline, which includes questions regarding the time period from birth until the interview, it was possible to take into account the possible onset of bipolar disorder before the baseline interview.

Mania categories based on DSM-IV algorithms

Using M-CIDI/DSM-IV diagnostic algorithms (Pfister & Wittchen, 1995), participants were divided into four groups, those experiencing: (1) neither hypomanic nor manic episodes; (2) DSM-IV manic episodes; (3) DSM-IV hypomanic episodes; and (4) either manic or hypomanic episodes [hereafter: (hypo)manic episodes]. The last three groups were subsequently subdivided into participants (*a*) with lifetime co-morbid depressive episodes and (*b*) without lifetime co-morbid depressive episodes.

Mania categories based on symptom score

(Hypo)manic symptoms were assessed using 11 items of the DIA-X/M-CIDI mania section, and concerned items regarding an increase in goal-directed activity, psychomotor agitation, spending sprees, sexual indiscretions, increased talkativeness, flight of ideas, increased self-esteem or grandiosity, decreased need for sleep, and distractibility. These items were rated yes (1) or no (0) and were only rated if: (*a*) at least one of the core symptoms 'unusual happiness or excitement' or 'unusual irritability' was present; (*b*) core symptoms were either noticed by others or caused participants problems; (*c*) symptoms were present for at least four successive days; (*d*) symptoms were not a result of alcohol/drugs use. Guided by previous work (Regeer *et al.* 2006), a sum score of symptom ratings was formed (range 0–11 symptoms). Five progressively stricter and overlapping subcategories of this sum score were created (I, no symptoms; II, $\geqslant 1$ symptom; III, $\geqslant 4$ symptoms; IV, $\geqslant 7$ symptoms; V, $\geqslant 10$ symptoms), which represented the underlying continuous score of (hypo)manic symptoms.

Mania categories based on distress

In participants with $\geqslant 4$ (hypo)manic symptoms, a division was made based on the level of distress, as reported in the DIA-X/M-CIDI mania section. Distress was assessed by asking participants if, at the moment the symptoms were at their worst, they interfered with life, work or leisure activities, and was coded (1) no interference, (2) some interference, (3) considerable interference and (4) much interference.

Grouping by mental health care

In participants fulfilling criteria for at least one of the above categories, grouping was applied based on whether or not mental health care had been received at the respective assessment. First, participants were asked if they had ever been treated in a hospital or had spoken to a professional because of (hypo)manic symptoms. Second, participants were shown a list on which several types of out-patient, in-patient or day-patient institutions for mental health problems were mentioned, after which they were asked if they had ever sought help at any of these institutions because of mental health problems. All participants who responded positively to either one of these questions were considered to have received mental health care.

Childhood disorders

Between T0 and T1, face-to-face interviews were carried out with respondents' parents to collect information regarding ODD, CD and ADHD (hereafter collectively referred to as 'childhood disorders'). These childhood disorders were assessed with questions covering the criteria defined by the DSM-IV. Information was mostly based on maternal responses (97.4%). The response rate of parents was 86% ($n = 1053$).

Statistical analysis

Cumulative lifetime incidence (CLI) and person-year IRs

Weighting occurred to account for differences in sampling probabilities and also systematic non-response at baseline according to age, gender and geographical location (Lieb *et al.* 2000). Cumulative lifetime incidence up to T3 (CLI) of the (hypo)manic categories was calculated at T3.

Survival analysis was conducted to determine IRs between T0 and T3 using the ST commands in Stata, version 9.2 (StataCorp, 2005). CLI and IR estimates were calculated, grouping by receipt of mental health care. The IR is defined as the number of new cases of disease during a given time period divided by the sum of time that each person remains under observation and is free from disease (the total person-time of observation). After defining appropriate risk sets, IRs were calculated for each category. The risk set is defined as the set of individuals at risk of belonging to a certain category for the first time during the study. Therefore, participants with past or current evidence

Table 1. *Cumulative lifetime incidence up to T3 and incidence rates (T0–T3) of (hypo)manic episodes, stratified by care*

(Hypo)manic group	Restriction	CLI up to T3[a]			IR (T0–T3)[b]		
		Total[c]	DEP+	DEP−	Total[c]	DEP+	DEP−
DSM-IV manic episode	None	3.3 (45)	1.3 (18)	2.0 (27)	308.9 (28.7/9277)	103.8 (9.8/9403)	201.9 (18.9/9358)
	MHC+	1.2 (17)	0.6 (9)	0.6 (8)	113.9 (10.7/9419)	50.6 (4.8/9448)	62.9 (5.9/9454)
DSM-IV hypomanic episode	None	4.5 (62)	1.4 (20)	3.1 (43)	409.5 (37.6/9184)	165.9 (15.6/9410)	237.6 (22.0/9258)
	MHC+	0.6 (8)	0.3 (4)	0.3 (4)	27.5 (2.6/9437)	24.5 (2.3/9467)	2.9 (0.3/9453)
DSM-IV (hypo)manic episode[d]	None	7.6 (106)	2.7 (37)	4.9 (69)	713.5 (64.1/8982)	262.3 (24.5/9334)	433.7 (39.6/9131)
	MHC+	1.8 (25)	0.8 (12)	0.9 (13)	132.6 (12.4/9376)	65.8 (6.2/9436)	66.0 (6.2/9424)

CLI, Cumulative lifetime incidence; IR, incidence rate; MHC+, episodes in combination with mental health care; DEP+, with depressive episode; DEP–, without depressive episode.

[a] Values are expressed as percentage (number) of cases.

[b] Values are expressed as number of cases per 100 000 person-years (denominator is population of person-years).

[c] Total group, independent of having lifetime depressive episodes.

[d] (Hypo)manic episode: either hypomanic or manic episode.

of this category at baseline were excluded from analysis, in which the strictest possible exclusion criteria were used [e.g. all participants experiencing ⩾1 symptom were excluded for analyses of incidence of (hypo)manic symptoms]. The total person-times of observation of the individual risk sets thus defined are presented in Table 1.

Childhood morbidity sensitivity analyses

To assess how much of the incidence of bipolar categories could be traced to childhood morbidity, co-morbidity with childhood disorders was assessed and childhood morbidity sensitivity analyses (CMSAs) performed. First, lifetime co-morbidity between T0 lifetime (hypo)manic episodes and childhood disorders was assessed using logistic regression. Second, Cox regression was used to calculate associations between childhood disorders and incidence of new (hypo)manic episodes between T0 and T3. Third, CLI and IRs for (hypo)manic episodes were recalculated with exclusion of individuals with these childhood disorders. Similar sensitivity analyses were performed for other (hypo)manic categories.

Demographic risk factors

IRs were calculated stratified by age group as a time-varying variable (15–16, 17–18, 19–21, 22–24 and 25–28 years; age = age during any moment of the study), sex and urbanicity [living in city or rural area at baseline; city area = city of Munich (population density 4061 persons per square mile) and rural area = the Munich surrounding area (population density 553 persons per square mile)] (Spauwen *et al*. 2006). Statistical differences in IRs within age, sex or urbanicity categories

were tested using Cox regression analysis yielding hazard ratios (HRs), using the 15-year age group, male sex, and rural area as reference categories (Table 2). To assess whether any association with demographic factors was independent of the others and unconfounded by co-morbid current or childhood psychopathology, HRs of all categories were adjusted for age, sex, urbanicity, presence of depression (diagnosis of a lifetime DSM-IV depressive episode) and presence of childhood disorders (diagnosis of either ODD, CD or ADHD according to DSM-IV criteria) using the Stata STRATA option for adjustment by stratification in Cox regression. HRs of the distress categories were additionally adjusted for number of (hypo)manic symptoms (as indexed by the continuous sum score of symptom ratings). As part of the CMSA, HRs were calculated similarly after exclusion of participants suffering from childhood disorders.

Results

Analyses are based on 1395 adolescents (51% male). The mean age at baseline was 15.1 years (S.D. = 1.1). Four-hundred and fifteen adolescents (30%) were living in a rural area. Of the 1395 adolescents, 1022 completed T3. Attrition rates were almost equal for sex (28.8% females *v*. 24.8% males), urbanicity (25.3% rural *v*. 27.3% city), and age (22.4% 13-year-olds *v*. 23.8% 14-year-olds *v*. 29.6% 15-year-olds *v*. 25.7% 16-year-olds *v*. 29.5% 17-year-olds).

Incidence of DSM-IV (hypo)manic episodes

CLI rates varied between 1.3% and 7.6% for the different DSM-IV episodic groups, declining after restriction to episodes plus mental health care (Table 1).

Table 2. *Predictors of incident (hypo)manic categories*

	Risk of incident (hypo)manic category, HR (95% CI)[b]			
	Age (RC: 15-year age group)	Female *v.* Male (RC: male sex)	City *v.* Rural (RC: rural)	Childhood disorder (ODD, CD or ADHD)
Manic episode	0.74 (0.50–1.10)	0.07 (0.065–0.79)*	1.55 (0.37–6.57)	3.65 (0.92–14.45)
Hypomanic episode	0.65 (0.50–0.85)**	1.55 (0.62–3.85)	1.08 (0.42–2.77)	7.82 (1.94–31.60)*
(Hypo)manic episode[a]	0.67 (0.54–0.84)**	0.75 (0.36–1.56)	1.21 (0.55–2.66)	5.29 (2.01–13.91)**
⩾1 symptom	0.63 (0.55–0.72)**	1.40 (0.94–2.08)	1.15 (0.75–1.77)	0.83 (0.36–1.92)
⩾4 symptoms	0.60 (0.51–0.72)**	1.46 (0.88–2.43)	1.10 (0.64–1.89)	1.06 (0.38–2.92)
⩾7 symptoms	0.61 (0.45–0.85)*	0.40 (0.13–1.18)	4.51 (0.94–21.72)	2.38 (0.50–11.31)
⩾10 symptoms	0.34 (0.11–1.06)	0.60 (0.05–6.79)	5.44 (0.28–107.42)	N.A.
Some distress	0.66 (0.49–0.89)*	0.99 (0.38–2.61)	1.10 (0.43–2.80)	0.95 (0.24–3.71)
Much distress	0.69 (0.43–1.10)	N.A.	0.56 (0.07–4.46)	1.23 (0.19–8.16)
Considerable distress	0.87 (0.34–2.21)	N.A.	0.93 (0.03–26.96)	N.A.
Psychiatric help	0.34 (0.13–0.86)*	2.73 (0.20–36.77)	N.A.	N.A.

HR, Hazard ratio; CI, confidence interval; RC, reference category; ODD, oppositional–defiant disorder; CD, conduct disorder; ADHD, attention deficit hyperactivity disorder; N.A., not applicable.

[a] (Hypo)manic episode: either hypomanic or manic episode.

[b] Results adjusted for age, sex, urbanicity, depression and childhood disorders. In case of distress/psychiatric help category: results also adjusted for number of (hypo)manic symptoms.

* $p \leqslant 0.05$, ** $p \leqslant 0.001$.

Table 3. *Cumulative lifetime incidence up to T3 and incidence rates (T0–T3) of (hypo)manic symptoms, stratified by care*

(Hypo)manic category	Restriction	CLI up to T3[a]	IR (T0–T3)[b]
⩾1 symptom	None	37.9 (528)	1720.0 (153.2/8909)
	MHC+	6.3 (87)	363.7 (32.9/9054)
⩾4 symptoms	None	26.5 (370)	1112.2 (101.0/9080)
	MHC+	4.8 (67)	225.6 (21.0/9145)
⩾7 symptoms	None	8.5 (119)	377.9 (35.4/9379)
	MHC+	2.4 (34)	94.7 (8.8/9328)
⩾10 symptoms	None	1.0 (13)	77.9 (7.4/9455)
	MHC+	0.5 (7)	27.7 (97.3/9075)

CLI, Cumulative lifetime incidence; IR, incidence rate; MHC+, episodes in combination with mental health care.

[a] Values are expressed as percentage (number) of cases.

[b] Values are expressed as number of cases per 100 000 person-years (denominator is population of person-years).

Approximately a third of participants had co-morbid depressive episodes. IRs ranged from $104/10^5$ to $714/10^5$ person-years, declining after restriction to episodes plus mental health care (Table 1).

Incidence of (hypo)manic symptoms

The number of participants steadily declined with increasing level of symptoms (Table 3). For participants experiencing ⩾1 symptom, the CLI was six times higher before restriction of the group to participants with symptoms plus mental health care (Table 3). This discrepancy between CLI rates decreased as the number of symptoms increased.

Incidence of distress

CLI and IRs are presented in Table 4. Higher rates of distress were experienced by fewer people. The majority of people with 'some distress' remained outside care, and the majority of people with 'much distress' were in care.

Table 4. *Cumulative lifetime incidence up to T3 and incidence rates (T0–T3) of distress, stratified by care[a]*

(Hypo)manic category	Restriction	CLI up to T3[b]	IR (T0–T3)[c]
Some distress	None	10.8 (151)	1072.7 (97.3/9075)
	MHC+	1.8 (25)	167.0 (15.6/9358)
Much distress	None	4.1 (58)	267.0 (25.0/9371)
	MHC+	1.0 (14)	96.2 (9.1/9436)
Considerable distress	None	0.8 (12)	51.4 (4.9/9468)
	MHC+	0.2 (3)	18.4 (1.7/9464)

CLI, Cumulative lifetime incidence; IR, incidence rate; MHC+, episodes in combination with mental health care.

[a] In participants with ⩾4 (hypo)manic symptoms.

[b] Values are expressed as percentage (number) of cases.

[c] Values are expressed as number of cases per 100 000 person-years (denominator is population of person-years).
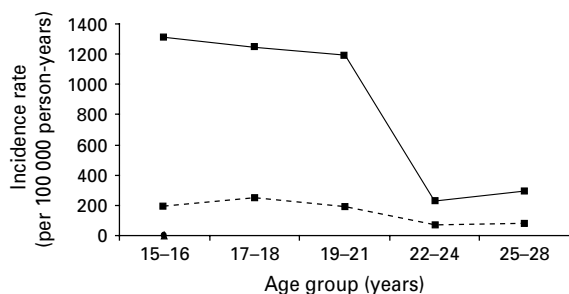
Fig. 1. Incidence of (hypo)manic disorder, stratified by age and care. —■—, (Hypo)manic episode[a,b]; - -■- -, (hypo)manic episode[a,b], MHC+. MHC+, episodes in combination with mental health care. [a] (Hypo)manic episode: either hypomanic or manic episode. [b] Independent of having lifetime depressive episodes.

Fig. 2. Hazard ratios of incident (hypo)manic categories, stratified by age group. —■—, (Hypo)manic episode[a,b,d]; ···△···, ⩾1 symptom[d]; - -◆- -, some distress[c,e]. Reference category: the 19–21 years age group. [a] (Hypo)manic episode: either hypomanic or manic episode. [b] Independent of having lifetime depressive episodes. [c] In participants with ⩾4 (hypo)manic symptoms. [d] Results adjusted for sex, urbanicity, depression and childhood disorders [oppositional–defiant disorder (OD), conduct disorder (CD) or attention-deficit/hyperactivity disorder (ADHD)]. [e] Results adjusted for sex, urbanicity, depression, childhood disorders (ODD, CD or ADHD) and number of (hypo)manic symptoms.

Association with childhood disorders

Seventy-six participants (7.2%) were diagnosed with any childhood disorder, mostly with ADHD (4.1%). Being diagnosed with a childhood disorder did not increase the risk of belonging to any (hypo)manic category at T0 (for detailed results see Tables 1-B, 1-D and 1-E at www.mania.homestead.com). The association between the incident (hypo)manic categories and childhood morbidity was large and significant [HR 5.29, 95% confidence interval (CI) 2.01–13.91, $p = 0.001$ for (hypo)manic episode] (Table 2). Thus, CMSAs reduced incidence rates (at most) by a factor of 2 according to the (hypo)manic category (see Table 1-C at www.mania.homestead.com).

Age, sex and urbanicity

A strong association existed between age and IRs for all (hypo)manic categories (Table 2, Figs 1–3), with IRs decreasing as age increased. *Post-hoc* analyses showed
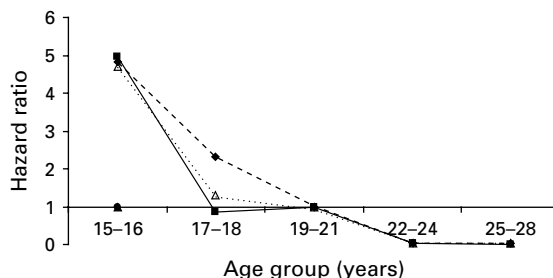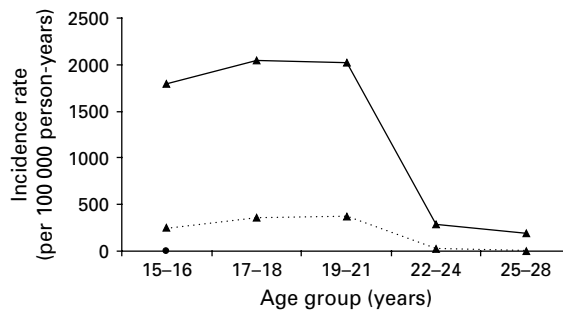

Fig. 3. Incidence of experienced distress in participants with ⩾4 (hypo)manic symptoms, stratified by age and care. —▲—, Some distress; ···▲···, some distress, MHC+. MHC+, distress in combination with mental health care.

that the IRs of episodic categories, compared to the age group 15–21 years, decreased very strongly after the age of 21 years [HR 0.021, 95% CI 0.0024–0.18, $p=0.000$ for hypomanic episode; HR 0.031, 95% CI 0.0050–0.19, $p=0.000$ for (hypo)manic episode], with a similar decline (albeit statistically inconclusive) after restriction to episodes plus mental health care. Subsequent CMSAs showed a similar pattern of associations (see Table 1-C, Figs 2-B and 3-B at www.mania.homestead.com).

The incidence of manic episodes was 14 times lower in women compared to men (HR 0.072, 95% CI 0.065–0.79, $p=0.031$). However, no sex differences were present for other (hypo)manic categories and there was no association with urbanicity. In the CMSA, a male preponderance in incidence of manic episodes remained (HR 0.08, 95% CI 0.070–0.86, $p=0.037$), whereas a female preponderance was seen in the category with $\geqslant 1$ symptom (HR 1.51, 95% CI 1.01–2.26, $p=0.045$).

Discussion

Findings

In this large prospective study of over 1000 adolescents and young adults, the results show that IRs of both (hypo)manic episodes and (hypo)manic symptoms are much higher than those reported previously, and that the risk of developing a disorder is very low after the age of 21 years, independent of childhood disorders such as ADHD. In addition, the results demonstrate a continuous distribution of (hypo)manic symptoms and distress, thus supporting the hypothesis that a dimensional representation may usefully describe the (hypo)manic phenotype (Allardyce *et al.* 2007). Only a small fraction of adolescents and young adults experiencing these phenomena were receiving psychiatric care and the co-occurrence of (hypo)manic episodes with depression was low compared to most of the literature. The incidence of the (hypo)manic categories, in particular categories at the level of clinical morbidity, was strongly associated with previous childhood disorders and male sex. In conclusion, this study showed, for the first time, that experiencing (hypo)manic symptoms is a common adolescent phenomenon that infrequently predicts mental health care use. The findings suggest that the onset of bipolar disorder can be elucidated by studying the pathway from non-pathological phenotypic expression to disability.

Limitations

Several limitations need to be considered. First, although a prospective design was used, the study became partly retrospective by implementing questions regarding time intervals between waves. Therefore, the possibility of recall bias cannot be excluded, although arguably this would be likely to contribute more to false negatives than false positives (Simon & VonKorff, 1995).

Second, exclusion of individuals at T0 and exclusion of the older cohort means that the results are based on a limited age range with an associated decrease in statistical power. This could have caused the incidence to fall after the age of 21 years. However, similar results were found after the oldest two age groups were collapsed, thus increasing statistical power.

Third, the age range of participants was limited as follow-up of participants did not begin until the age of 14 years. Future studies should examine whether adolescent bipolar symptoms, relevant to adult clinical morbidity, are present also in younger samples.

Fourth, the analyses of childhood disorders were all based on retrospective parental report. This may have influenced the reliability of the results. However, Faraone *et al.* (1995) have shown that maternal reports of their children's psychopathology by 1-year recall provided a reliable and accurate means of assessment. In addition, the rates found for the childhood disorders analysed in this study are comparable to the rates found in other studies (Costello *et al.* 2003), which likewise attests to their validity.

Fifth, the predictive validity of the broad category of (hypo)manic symptoms may be enhanced by testing whether (hypo)manic symptoms can also predict depression. Testing this in a *post-hoc* analysis revealed that participants who had at least two (hypo)manic symptoms once at T0, T1 or T2 had a nearly twofold higher risk of ever experiencing a depressive episode compared to participants with less than two (hypo)manic symptoms at T0/T1/T2.

Cumulative incidence and person-year incidence rates

IRs in this study are much higher than those reported previously (Bebbington & Ramana, 1995). A partial explanation for this discrepancy may be the use of clinical samples in previous work. The effect of sample type on observed IRs is clearly shown in the current data, in which grouping for mental health care decreased IRs. However, the elevated IRs cannot be explained entirely by sample type because even for participants receiving mental health care, IRs were still higher than previously reported estimates, whereas CLI estimates did yield estimates comparable to those in previous reports (Lish *et al.* 1994). One reason for the higher IRs may be that the current sample consisted of adolescents, who display the highest risk of developing mental disorders (Kessler *et al.* 2005).

The focus on clinical samples might also explain the low co-occurrence of depressive episodes with (hypo)manic episodes because both types of episodes, independently of each other, increase need for care and help-seeking, resulting in more 'co-morbid' psychopathology at the level of mental health care ('Berkson's bias') (Regeer *et al.*, in press). Accordingly, the co-occurrence of depressive episodes in the current study was higher in participants receiving mental health care.

Bipolar disease as a developmental disorder

The greatest risk of developing (hypo)manic episodes was before age 22 years, after which it decreased to the point of almost disappearing. This finding is supported by other studies in which the most common age of onset for bipolar disorder was reported to be between 15 and 19 years (Szádóczky *et al.* 1998). Findings similarly concur with studies in which substantial numbers of adult patients retrospectively reported first experiencing symptoms in childhood or adolescence (Joyce, 1984). The findings in the current sample show low levels of cross-sectional comorbidity of childhood disorders with (hypo)manic categories at T0, but very high longitudinal comorbidity with new, incident bipolar categories, in particular at the level of clinical morbidity, over time. The CMSA in which childhood disorders were excluded did not change the pattern of association with age. The pattern of findings therefore suggests that the ontogenesis of (hypo)manic symptoms and (hypo)manic disorder may be traced to the adolescent developmental period and that expression of certain childhood disorders may increase the risk for later expression of bipolar morbidity.

Continuity

The current results suggest that (hypo)manic symptoms may represent a common phenomenon in the general population. Symptoms and clinical morbidity showed dose–response relationships, in that more cases of clinical morbidity arose as the number of symptoms increased, supporting continuity between subclinical and clinical categories. Evidence for continuity has been provided by others (Angst *et al.* 2003; Lewinsohn *et al.* 2003; Regeer *et al.* 2006). However, as evidenced by findings in the current study, the vast majority of these individuals with symptomatic expression never develop bipolar disorder. Thus, (hypo)manic symptoms may be conceived partially as pertaining to normal adolescent development. If, however, symptoms persist over time, individuals may be at risk of transition to bipolar disorder

(Cougnard *et al.* 2007). Thus, future work should investigate whether adolescents with persistent (hypo)manic symptoms are at risk of making the transition to bipolar disorder, and which factors drive such transitions. Possible factors are symptom factors (intrusiveness, frequency and co-morbidity of symptoms), personal and cultural factors (coping, illness behaviour, societal tolerance and the development of functional impairments), and known bipolar risk factors (a positive family history, exposure to life events, or an interaction between these factors) (Lapalme *et al.* 1997; van Os & Verdoux, 2003; Hillegers *et al.* 2004; van Os *et al.* 2009).

Risk factors

Male sex was a risk factor for the onset of manic episodes. This is inconsistent with studies finding equal sex distributions (Lloyd *et al.* 2005). However, the finding does concur with several studies in which it was suggested that male sex is associated with earlier onset of mania (Carlson *et al.* 2000; Kennedy *et al.* 2005*a*). Male preponderance in incidence was not seen for subclinical bipolar categories, suggesting that male sex specifically increases the risk for clinical morbidity. The link between male sex and poor outcome is well known for other types of psychotic illness, in particular schizophrenia (Castle & Murray, 1991).

Urbanicity generally did not increase the risk for (hypo)manic categories. This concurs with previous findings (Krabbendam & van Os, 2005). A recent study showed any association between (hypo)manic disorder and urbanicity is probably mediated by positive psychotic symptoms (Kaymaz *et al.* 2007).

Clinical implications

Several clinical implications are suggested by this study. First, given the possible wide distribution of low-grade bipolar experiences, the suggested specific developmental phase of expression and evidence that subclinical expression of bipolarity increases the risk for later bipolar disorder in a dose–response fashion (Regeer *et al.* 2006), a public health approach focusing on targeted early identification may merit further investigation. Second, work focusing on psychotic disorder has indicated that subclinical phenotypes may be more likely to make the transition to the fully developed disorder if there is persistence over time (Cougnard *et al.* 2007; Dominguez *et al.*, in press). Thus, examining patterns and determinants of persistence of subclinical expression of bipolar experiences may be similarly instructive. Third, the findings suggest that greater symptom load and greater levels

of distress are associated with a higher probability of the outcome of mental health care. Understanding the dynamics between symptoms, distress and help-seeking is necessary to develop early interventions. Fourth, the findings suggest that only a minority of those with bipolar experiences are in care, similar to findings in depression and anxiety disorders. Given that, in depression, subsyndromal expression is associated with a substantial amount of disability (Judd *et al.* 2002), individuals with subclinical bipolar experiences not receiving care may similarly have a considerable degree of disability that could be reduced if recognized and treated.

Declaration of Interest

J. van Os is/has been an unrestricted research grant holder with, or has received financial compensation as an independent symposium speaker from, Eli Lilly, BMS, Lundbeck, Organon, Janssen-Cilag, GSK, Astra-Zeneca, Pfizer and Servier. H.-U. Wittchen is in receipt of research support from Eli Lilly and Company, Novartis, Pfizer and Schering-Plough, and is a consultant for Eli Lilly, GlaxoSmithKline Pharmaceuticals, Hoffmann–La Roche Pharmaceuticals, Novartis, Pfizer and Wyeth. Speaking honoraria have been received by H.-U. Wittchen from Novartis, Schering-Plough, Pfizer and Wyeth, by R. Lieb from Wyeth, and by K. Beesdo from Pfizer.

References

Akiskal HS, Bourgeois ML, Angst J, Post R, Möller H-J, Hirschfeld R (2000). Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *Journal of Affective Disorders* **59**, S5–S30.

Allardyce J, Suppes T, van Os J (2007). Dimensions and the psychosis phenotype. *International Journal of Methods in Psychiatric Research* **16** (Suppl. 1), S34–S40.

Angst J (1998). The emerging epidemiology of hypomania and bipolar II disorder. *Journal of Affective Disorders* **50**, 143–151.

Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rössler W (2003). Diagnostic issues in bipolar disorder. *European Neuropsychopharmacology* **13** (Suppl. 2), S43–S50.

Angst J, Marneros A (2001). Bipolarity from ancient to modern times: conception, birth and rebirth. *Journal of Affective Disorders* **67**, 3–19.

Bebbington P, Ramana R (1995). The epidemiology of bipolar affective disorder. *Social Psychiatry and Psychiatric Epidemiology* **30**, 279–292.

Birmaher B, Axelson D (2006). Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. *Development and Psychopathology* **18**, 1023–1035.

Carlson GA, Bromet EJ, Sievers S (2000). Phenomenology and outcome of subjects with early- and adult-onset psychotic mania. *American Journal of Psychiatry* **157**, 213–219.

Carlson GA, Kashani JH (1988). Manic symptoms in a non-referred adolescent population. *Journal of Affective Disorders* **15**, 219–226.

Castle DJ, Murray RM (1991). The neurodevelopmental basis of sex differences in schizophrenia. *Psychological Medicine* **21**, 565–575.

Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A (2003). Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry* **60**, 837–844.

Cougnard A, Marcelis M, Myin-Germeys I, de Graaf R, Vollebergh W, Krabbendam L, Lieb R, Wittchen HU, Henquet C, Spauwen J, van Os J (2007). Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness-persistence model. *Psychological Medicine* **37**, 513–527.

Dominguez MDG, Wichers M, Lieb R, Wittchen HU, van Os J (in press). Evidence that onset of clinical psychosis is the outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. *Schizophrenia Bulletin*.

Egeland JA, Hostetter AM, Pauls DL, Sussex JN (2000). Prodromal symptoms before onset of manic-depressive disorder suggested by first hospital admission histories. *Journal of the American Academy of Child and Adolescent Psychiatry* **39**, 1245–1252.

Faraone SV, Biederman J, Milberger S (1995). How reliable are maternal reports of their children's psychopathology? One-year recall of psychiatric diagnoses of ADHD

children. *Journal of the American Academy of Child and Adolescent Psychiatry* **34**, 1001–1008.

First MB (2006). Beyond clinical utility: broadening the DSM-V research appendix to include alternative diagnostic constructs. *American Journal of Psychiatry* **163**, 1679–1681.

Ghaemi SN, Ko JY, Goodwin FK (2002). 'Cade's disease' and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. *Canadian Journal of Psychiatry* **47**, 125–134.

Hanssen M, Bak M, Bijl R, Vollebergh W, van Os J (2005). The incidence and outcome of subclinical psychotic experiences in the general population. *British Journal of Clinical Psychology* **44**, 181–191.

Henin A, Biederman J, Mick E, Hirschfeld-Becker DR, Sachs GS, Wu Y, Yan L, Ogutha J, Nierenberg AA (2007). Childhood antecedent disorders to bipolar disorder in adults: a controlled study. *Journal of Affective Disorders* **99**, 51–57.

Hillegers MHJ, Burger H, Wals M, Reichart CG, Verhulst FC, Nolen WA, Ormel J (2004). Impact of stressful life events, familial loading and their interaction on the onset of mood disorders: study in a high risk cohort of adolescent offspring of parents with bipolar disorder. *British Journal of Psychiatry* **185**, 97–101.

Joyce PR (1984). Age of onset in bipolar affective disorder and misdiagnosis as schizophrenia. *Psychological Medicine* **14**, 145–149.

Judd LL, Akiskal HS (2003). The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *Journal of Affective Disorders* **73**, 123–131.

Judd LL, Schettler PJ, Akiskal HS (2002). The prevalence, clinical relevance, and public health significance of subthreshold depressions. *Psychiatric Clinics of North America* **25**, 685–698.

Kaymaz N, van Os J, de Graaf R, ten Have M, Nolen W, Krabbendam L (2007). The impact of subclinical psychosis on the transition from subclinical mania to bipolar disorder. *Journal of Affective Disorders* **98**, 55–64.

Kennedy N, Boydell J, Kalidindi S, Fearon P, Jones PB, van Os J, Murray RM (2005*a*). Gender differences in incidence and age at onset of mania and bipolar disorder over a 35-year period in Camberwell, England. *American Journal of Psychiatry* **162**, 257–262.

Kennedy N, Everitt B, Boydell J, van Os J, Jones PB, Murray RM (2005*b*). Incidence and distribution of first-episode mania by age: results from a 35-year study. *Psychological Medicine* **35**, 855–863.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **62**, 593–602.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen H-U, Kendler KS (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry* **51**, 8–19.

Krabbendam L, van Os J (2005). Schizophrenia and urbanicity: a major environmental influence – conditional on genetic risk. *Schizophrenia Bulletin* **31**, 795–799.

Lapalme M, Hodgins S, LaRoche C (1997). Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. *Canadian Journal of Psychiatry* **42**, 623–631.

Leff JP, Fischer M, Bertelsen A (1976). A cross-national epidemiological study of mania. *British Journal of Psychiatry* **129**, 428–442.

Lewinsohn P, Klein DN, Seeley JR (1995). Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *Journal of the American Academy of Child and Adolescent Psychiatry* **34**, 454–463.

Lewinsohn PM, Seeley JR, Klein DN (2003). Bipolar disorders during adolescence. *Acta Psychiatrica Scandinavica. Supplementum* **108**, 47–50.

Lieb R, Isensee B, von Sydow K, Wittchen H-U (2000). The Early Developmental Stages of Psychopathology study (EDSP): a methodological update. *European Addiction Research* **6**, 170–182.

Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RMA (1994). The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. *Journal of Affective Disorders* **31**, 281–294.

Lloyd T, Kennedy N, Fearon P, Kirkbride J, Mallett R, Leff J, Holloway J, Harrison G, Dazzan P, Morgan K, Murray RM, Jones PB (2005). Incidence of bipolar affective disorder in three UK cities: results from the AESOP study. *British Journal of Psychiatry* **186**, 126–131.

Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC (2007). Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **64**, 543–552.

Murray CJL, Lopez AD (1996). *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020*. Harvard School of Public Health: Cambridge, MA.

Nierenberg AA, Miyahara S, Spencer T, Wisniewski SR, Otto MW, Simon N, Pollack MH, Ostacher MJ, Yan L, Siegel R, Sachs GS (2005). Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. *Biological Psychiatry* **57**, 1467–1473.

Pfister H, Wittchen H-U (1995). *M-CIDI Computer Program*. Max-Planck-Institut für Psychiatrie, Klinisches Institut: Munich.

Rasanen P, Tiihonen J, Hakko H (1998). The incidence and onset-age of hospitalized bipolar affective disorder in Finland. *Journal of Affective Disorders* **48**, 63–68.

Reed V, Gander F, Pfister H, Steiger A, Sonntag H, Trenkwalder C, Hundt W, Wittchen H-U (1998). To what degree does the Composite International Diagnostic Interview (CIDI) correctly identify DSM-IV disorders? Testing validity issues in a clinical sample. *International Journal of Methods in Psychiatric Research* **7**, 142–155.

Regeer E, Krabbendam L, de Graaf R, ten Have M, Nolen W, van Os J (in press). Berkson's bias and the mood

dimensions of bipolar disorder. *International Journal of Methods in Psychiatric Research*.

Regeer EJ, Krabbendam L, de Graaf R, ten Have M, Nolen WA, van Os J (2006). A prospective study of the transition rates of subthreshold (hypo)mania and depression in the general population. *Psychological Medicine* **36**, 619–627.

Regier DA, Boyd JH, Burke JDJ, Rae DS, Myers JK, Kramer M, Robins LN, George LK, Karno M, Locke BZ (1988). One-month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. *Archives of General Psychiatry* **45**, 977–986.

Simon GE, VonKorff M (1995). Recall of psychiatric history in cross-sectional surveys: implications for epidemiologic research. *Epidemiologic Reviews* **17**, 221–227.

Spauwen J, Krabbendam L, Lieb R, Wittchen H-U, van Os J (2006). Evidence that the outcome of developmental expression of psychosis is worse for adolescents growing up in an urban environment. *Psychological Medicine* **36**, 407–415.

Spicer CC, Hare EH, Slater E (1973). Neurotic and psychotic forms of depressive illness: evidence from age-incidence in a national sample. *British Journal of Psychiatry* **123**, 535–541.

Statacorp (2005). *STATA Statistical Software*. Stata Corporation: College Station, TX.

Szádóczky E, Papp Z, Vitrai J, Ríhmer Z, Füredi J (1998). The prevalence of major depressive and bipolar disorders in Hungary: results from a national epidemiologic survey. *Journal of Affective Disorders* **50**, 153–162.

van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological Medicine* **39**, 179–195.

van Os J, Verdoux H (2003). Diagnosis and classification of schizophrenia: categories versus dimensions, distributions versus disease. In *The Epidemiology of Schizophrenia* (ed. R. M. Murray, P. Jones, E. Susser, J. van Os and M. Cannon), pp. 364–410. Cambridge University Press: Cambridge.

Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu H-G, Joyce PR, Karam EG, Lee C-K, Lellouch J, Lepine J-P, Newman SC, Rubio-Stipec M, Wells JE, Wickramaratne PJ, Wittchen H-U, Yeh E-K (1996). Cross-national epidemiology of major depression and bipolar disorder. *Journal of the American Medical Association* **276**, 293–299.

WHO (1990). *Composite International Diagnostic Interview (CIDI), Version 1.0*. World Health Organization: Geneva, Switzerland.

Wittchen H-U (1994). Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. *Journal of Psychiatric Research* **28**, 57–84.

Wittchen H-U, Lachner G, Wunderlich U, Pfister H (1998*a*). Test–retest reliability of the computerized DSM-IV version of the Munich-Composite International Diagnostic Interview (M-CIDI). *Social Psychiatry and Psychiatric Epidemiology* **33**, 568–578.

Wittchen H-U, Mühlig S, Pezawas L (2003). Natural course and burden of bipolar disorders. *International Journal of Neuropsychopharmacology* **6**, 145–154.

Wittchen H-U, Perkonigg A, Lachner G, Nelson CB (1998*b*). Early Developmental Stages of Psychopathology study (EDSP): objectives and design. *European Addiction Research* **4**, 18–27.

Wittchen H-U, Pfister H (1997). DIA-X-Interviews: Manual for the screening procedure and interview; Longitudinal Interview (DIA-X-Lifetime); Additional Book (DIA-X-Lifetime); Cross-sectional Interview (DIA-X-12 monthly version); Additional Book (DIA-X-12 monthly version); Computer program to execute the interviews (longitudinal and cross-sectional studies). Analysis program. Swets & Zeitlinger: Frankfurt, Germany.

Wittchen H-U, Robins LN, Cottler LB, Sartorius N, Burker JD, Regier D (1991). Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *British Journal of Psychiatry* **159**, 645–653, 658.