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Declarations of interest

All authors declare no conflict of interest regarding the present work.

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Abstract

Objectives: Although clinical evidence suggests important differences between unipolar mania and bipolar-I disorder (BP-I), epidemiological data are limited. Combining data from 9 population-based studies, we compared subjects with mania (M) or mania with mild depression (Md) to those with BP-I with both manic and depressive episodes with respect to demographic and clinical characteristics in order to highlight differences.

Methods: Participants were compared for gender, age, age at onset of mania, psychiatric comorbidity, temperament and family history of mental disorders. Generalized Linear Mixed Models with adjustment for sex and age as well as for each study source were applied. Analyses were performed for the pooled adult and adolescent samples, separately.

Results: Within the included cohorts, 109 adults and 195 adolescents were diagnosed with M/Md and 323 adults and 182 adolescents with BP-I. In both adult and adolescent samples, there was a male preponderance in M/Md, whereas lifetime generalized anxiety and/panic disorders and suicide attempts were less common in M/Md than in BP-I. Furthermore, adults with mania revealed bulimia/binge eating and drug use disorders less frequently than those with BP-I.

Conclusions: The significant differences found in gender and comorbidity between mania and BP-I suggest that unipolar mania, despite its low prevalence, should be established as a separate diagnosis both for clinical and research purposes. In clinical settings, the rarer occurrence of suicide attempts, anxiety and drug use disorders among individuals with unipolar mania may facilitate successful treatment of the disorder and lead to a more favorable course than that of BP-I disorder.

Key words: Mania; Bipolar-I disorder; Epidemiology; Gender; Comorbidity, family history

1. Introduction

The affective spectrum as conceptualized by Akiskal (1) originally comprised depression, bipolar-II and bipolar-I disorders. It was later extended to include mania with mild depression (Md) and pure mania (M) as separate diagnostic subgroups (2). The international diagnostic manuals, however, do not reflect the full affective spectrum. Mania – in contrast to depression – does not currently have the status of a separate disorder. Although the international classification of diseases of 1978 (ICD-9) (3) provided a separate coding 296.0 for monopolar mania, since ICD-10 (1993) (4) a manic episode has only been codable within mood disorders (F30). Similarly in successive editions of the diagnostic and statistical manual, DSM-III (1980) (5), DSM-IV-TR (2000) (6) and DSM-5 (2013) (7), a single manic episode (296.0) is coded within bipolar-I (BP-I) disorder.

From a clinical perspective, there is strong evidence that some patients suffer from pure unipolar mania or mania with mild (not major) depression although it is relatively rare. Notable differences between unipolar mania and BP-I disorder have been reported in literature reviews and single studies on mania (8-11), including a more frequent premorbid hyperthymic temperament (8-10), less suicidality (8, 10-13), a lower likelihood of developing comorbid anxiety disorders (8-10, 12), more psychotic features and more cannabis abuse (12) for subjects with unipolar mania. In addition, with some exceptions (14), there is evidence that individuals with pure mania are less likely to have a positive family history for major depressive disorder (MDD) (15) and family studies have found evidence for independent familial aggregation of manic and depressive episodes (16, 17).

Although evidence from population samples has been limited owing to the relative infrequency of M/Md, the first large-scale study of unipolar mania in adults in the community based on the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) found a prevalence of unipolar mania of approximately 0.2% and significant differences between mania and bipolar in a range of demographic and clinical characteristics (18). Those with mania were more likely to be male and non-white, to have an earlier age at onset of

manic episodes, to experience shorter episodes and to have a lower lifetime comorbidity with Generalized Anxiety Disorder (GAD), panic disorder and social and specific phobia. The authors concluded that unipolar mania is an infrequent but clinically distinct valid subtype of bipolar disorder (18).

Aims of the study:

Our analysis sought to provide further evidence for the independence of unipolar mania from BP-I disorder with both manic and depressive episodes. In order to overcome the problem of limited sample size related to the low prevalence of unipolar mania, we pooled data from nine community studies in five countries to compare mania with or without mild depression and BP-I disorder with respect to sociodemographic and clinical characteristics, comorbid disorders, temperamental features and family history in order to highlight differences.

2. Material and methods

2.1. Community samples and diagnoses

The data, which were collected through semi-structured or structured interviews, unbiased by the hypothesis of this paper, derived from the following nine epidemiological studies:

1) The Zurich Study, conducted in the Canton of Zurich, used a stratified sample enriched by risk cases (N=591 representing weighted 2600 subjects). The sample was screened in 1978 at age 19 (males) or 20 (females) and interviewed 7 times (1979–2008) until the probands were 49/50 years old. The interviews, administered by psychiatrists and psychologists, were based on the Structured Psychopathological Interview and Rating of the Social Consequences of Psychological Disturbances for Epidemiology (SPIKE) (19). Major depressive episodes were diagnosed according to DSM-IV/DSM-5 criteria and mania according to modified DSM-5 criteria (i.e. criterion A modified: presence of increased activity/energy or elated mood or irritable mood required). All other diagnoses were based on

the DSM-IV. Temperament was assessed by the General Behavior Inventory (20) and by direct SPIKE interview questions.

2) The ZInEP Epidemiology Survey, designed in congruence with the Zurich Study, was carried out between August 2010 and September 2012 (21). A representative sample of 9829 participants living in the canton of Zurich was screened by a Computer Assisted Telephone Interview (CATI) using the Symptom Checklist-27 (SCL-27) (22). A total of 1500 participants were selected from this sample following a stratified sampling procedure, which included 60% high-scorers and 40% low-scorers (the cut-off criterion being the 75th percentile of the Global Severity Index of the SCL-27). The subsamples corresponded exactly in age to the assessment points of the Zurich Study from 1979 (20 years) to 1999 (40 years). They were interviewed by extensively trained psychologists using a shortened version of the SPIKE (19). Diagnoses of common mental disorders were computed as 12-month prevalence rates based on DSM-IV criteria. In mania / hypomania and bipolar disorders, the criteria of the Bridge Study were adopted (23). This definition includes not only elated or irritable mood in criterion A, but also increased activity/energy and tentatively shortens the minimum duration of a hypomanic episode from four days to one day. It also eliminates all the exclusion criteria.

3) São Paulo Megacity Mental Health Survey is a cross-sectional household population-based survey conducted in the São Paulo Metropolitan Area (SPMA, the city of São Paulo and its 38 surrounding municipalities), Brazil. At the time of data collection (2005–2007), around 11 million inhabitants aged 18 years or older lived in the SPMA, from which a representative stratified multistage area probability sample of 5037 respondents was selected. Respondents were assessed by trained professional lay interviewers using the World Mental Health Survey Composite International Diagnostic Interview (CIDI 3.0), a fully structured lay interview that generates diagnoses according to the DSM-IV criteria, translated and adapted to the Brazilian-Portuguese language. Weights were applied to adjust for differences in the probability of selection, differential non-response, and post-stratifying the

final sample to approximate the year 2000 population census regarding gender and age distribution. The overall response rate was 81.3%. Further details regarding the methodology have been published elsewhere (24).

4) Pelotas Study: N=1560 is a cross-sectional population-based study including subjects 18 to 24 years old living in the urban area of Pelotas (Brazil). The sample selection was performed by clusters considering the population of 39 667 in the age range according to the current census of 448 sectors in the city (www.ibge.gov.br). In order to ensure the necessary sample size, 89 census-based sectors were randomly selected. The home selection in the sectors was performed according to a systematic sampling, the first one being the house at the corner pre-established by the Brazilian Geographical and Statistical Institute (IBGE) as the beginning of the sector; the interval of selection was determined by skipping two houses. Respondents were assessed by trained undergraduate students in the field of health sciences using the Mini International Neuropsychiatric Interview (MINI), a structured clinical interview according to DSM-IV criteria. Further details regarding the methodology have been published elsewhere (25).

5) The National Comorbidity Survey Replication (NCS-R) is a national study of English speakers of the conterminous United States. Part I comprised subjects aged 18 to 44 (N=5692). The interviews were conducted by trained lay interviewers. Diagnoses were made according to the DSM-IV based on a WHO modified version of the Composite International Diagnostic Interview (CIDI) (26).

6) The prospective CoLaus¦PsyCoLaus Study (27, 28) included 4874 35 to 84-year-old subjects, (46.5% male, mean age = 11.2 s.d. 35.8 years), who were recruited from the general population of the City of Lausanne according to the civil register. Subjects were interviewed by trained master's level psychologists using the Diagnostic Interview for Genetic Studies (DIGS) (29); psychiatric disorders as well as mood episodes were diagnosed according to DSM-IV criteria. The diagnosis of hyperthymic temperament was assigned

according to the criteria of Gershon et al. (30), which required periods of elation or excitement lasting most of the time (chronic form) and resulted in: 1) the subject communicated with a close friend or relative on how he/she felt, or 2) someone complained or commented on some manifestation of this condition. Family history information was based on the Family History-Research Diagnostic Criteria (FH-RDC, (31); validity of the French version (e.g. (32)).

7) The Netherlands Study of Depression and Anxiety (NESDA) is a longitudinal naturalistic cohort study, consisting of 2981 persons (18–65 years) including those with lifetime anxiety and/or depressive disorders (n=2329; 78%), as well as healthy controls (n=652; 22%) (33). Participants were recruited from the community (n=564; 19%), primary care settings (n=1610; 54%) and specialized mental health care (n=807; 27%) from September 2004 to February 2007 at three study sites (Amsterdam, Groningen, Leiden). Exclusion criteria used at baseline were (1) clinically overt diagnoses of other psychiatric conditions, such as psychotic, obsessive compulsive, bipolar, or severe addiction disorder, and (2) not being fluent in Dutch.

The NESDA subsample comprised those probands who at 2-year follow-up had developed bipolar disorder. A total of 2596 persons (87.1%) participated in the 2-year follow-up interview, conducted by well-trained research staff often with a medical or psychology background, during which mania and bipolar-I were assessed. Determinants of loss to follow-up were younger age, less years of education, not being of North-European descent, being recruited in Amsterdam, no previous participation in research and having major depressive disorder (34).

The CIDI (v2.1) was used to assess the presence and age at onset of DSM-IV diagnoses of depression, anxiety, alcohol abuse/dependence (35). At the 2-year follow-up, the CIDI also included the mania section from which lifetime diagnoses were derived. Suicidality was assessed using a question that was added to the interview: 'Have you ever made a serious

attempt to end your life, for instance by harming or poisoning yourself or by getting into an accident?' . Family history in first degree relatives was assessed using the Family Tree Inventory (36).

8) The Early Developmental Stages of Psychopathology (EDSP) study conducted in Munich, Germany, used an age stratified random community sample (N=3021, response: 71%) followed up in 3 waves over 10 years (37). Adolescents and young adults, aged 14 to 24 years at study intake, participated partly with their parents and selected family members. Interviews, which were conducted by trained interviewers (clinical and non-clinical), were based on the DSM-IV/M-CIDI and family history methods on parental psychopathology were also used (38).

9) The National Comorbidity Survey Replication-Adolescent Supplement (NCS-A) used representative household and school samples of adolescents aged 13 to 18 (N=10123) in the continental United States. The interviews were also conducted by trained lay interviewers. Diagnoses were made according to the DSM-IV based on WHO modified CIDI interviews (39).

Unipolar mania was defined as the presence of at least one manic episode without a history of a major depressive episode over the lifetime.

Approval of the study protocols were granted by the respective ethical review boards of participating centers and all participants gave written informed consent prior to participation.

2.2. Statistics

The data of the 7 adult studies and those of the 2 adolescent studies were pooled in order to conduct separate analyses in adults and adolescents. Participants with unipolar mania and BP-I disorder were compared using Generalized Linear Mixed Models (GLMM) with

adjustment for sex and age as well as for each study source as a random effect. The introduction of the random effect in the analyses could remedy potential heterogeneity across samples. A GLMM explains the relation between the predictors and the response variable via a link function. For dichotomous outcome variables, we chose the logit link function; for continuous outcome variables, we chose the identity function, which results in ordinary Linear Mixed Models. The models with sex and age as outcome variables were only adjusted for age or sex, respectively, and for the study effect. Aside from age and sex, the outcome variables comprised age of onset of mania, comorbid conditions (suicide attempts, GAD/panic disorder, bulimia/binge eating and sedative, drug and alcohol use disorders), hyperthymic and anxious temperament (in adults) as well as psychiatric family history variables (mania, depression, suicide attempts, anxiety/panic, bulimia/binge eating, any substance use disorder and alcohol use disorders). These analyses were performed using the *stats* package of R language for statistical computing: URL https://www.R-project.org/.

3. Results

3.1. Mania vs. BP-I disorder in the seven adult studies

Table 1 presents the lifetime prevalence rates, gender distribution, age, age at onset of the first manic episode and the proportion of subjects with the six comorbid mental conditions in the seven adult samples. In total, 109 cases of unipolar mania versus 323 cases of bipolar-I disorder could be compared. The subsamples varied greatly in size.

The *lifetime prevalence* of unipolar mania was about a third that of BP-I disorder, except in the two studies from Zurich (Zurich Study and ZInEP Study), where the two disorders had similar prevalence rates. Moreover, the Zurich Study and the Pelotas Study identified a much higher prevalence for both unipolar mania and BP-I disorder than the other surveys. The prevalence estimate of the NESDA Study could not be compared with those of the other studies because of the enrichment of the sample with individuals with depression.

In the pooled sample, the *gender distribution* of adults with mania compared to those with BP-I disorder differed significantly according to the generalized linear mixed model with adjustment for age and the effect of the study source. Indeed, men were preponderant in the group with unipolar mania compared to the BP-I group, a finding consistent to varying degrees across the individual studies, the exception being the NCS-R study, where the distribution was about equal. In contrast, individuals with unipolar mania did not differ from those with BP-I disorder regarding *age* or the a*ge at onset of the first manic episode*.

Regarding *comorbid conditions*, the proportion of subjects with *suicide attempts, GAD/panic, eating and drug use disorders* was significantly lower in the group with unipolar mania than in the BP-I group.

- insert table 1 -

Table 2 shows the proportion of subjects with mania vs. BP-I regarding temperamental traits and a family history of seven mental disorders in the adult studies. There were no differences between the two groups regarding *hyperthymic temperament*, assessed in two studies (Zurich and PsyCoLaus), or *anxious temperament*, for which data was available from the Zurich and São Paolo studies. Similarly, there were no inter-group differences regarding the *family history* of the mental disorders assessed in the pooled analyses.

- insert table 2 -

3.2. Mania vs. BP-I disorder in the two adolescent studies

Table 3 displays the gender distribution, age, age at onset of the first manic episode and the proportion of subjects with comorbid conditions among individuals with unipolar mania and with bipolar-I disorder in the two adolescent studies. In total, there were 195 cases with unipolar mania and 182 with bipolar-I disorder. In the EDSP study, BP-I disorder was more prevalent than unipolar mania, whereas in the NCS-A the converse was true. As in the adult subsample, there were more *males* in the adolescent groups with unipolar mania than in the

BP-I groups, whereas the two groups did not differ regarding *age* or *age at onset of mania*. Both *suicide attempts* and *GAD/panic disorder* were significantly more common among the adolescents with BP-I disorder than among those with mania.

- insert table 3 -

As shown in Table 4, in the adolescent studies there were no significant differences between the two diagnostic groups in terms of the *family history* of the mental disorders assessed. Data on temperamental traits were not available for the two adolescent studies.

- insert table 4 -

4. Discussion

This paper presents the first broadly based multisite analysis of nine well-known community studies from five countries comparing the clinical and demographic characteristics of subjects with unipolar mania and bipolar-I disorder. We found significant differences in the gender ratio and patterns of comorbidity between unipolar mania and BP-I disorder, which may index important differences in the underlying risk factors and etiology of these conditions. Our paper extends an earlier review which was based mainly on clinical samples (9) to data from the community including also two studies on adolescents. This previous review supported the distinction between unipolar mania and bipolar disorder as subtypes of the affective spectrum.

The pooling of our epidemiological data involved issues of comparability, arising not only from differences between interviews, their methods of administration and diagnostic classification systems (ICD vs. DSM) but also from cultural variations. In this respect it is remarkable that two studies, the Zurich study and the Pelotas studies, established higher prevalence of both unipolar mania and BP-I. Regarding the Zurich study, the higher prevalence estimates of these disorders are likely to be attributable to the longitudinal approach with 7 interviews over more than 30 years, the use of a diagnostic interview with a

lower threshold to enter the mania section as compared to the diagnostic tools at the other sites and potentially an increased awareness of the team in identifying manic/hypomanic episodes compared to in the other centers. Nevertheless, despite methodological variance the age differences of the participants and the *gender* distribution between unipolar mania and BP-I disorder was similar across the studies. Gender is an interesting validator; the combined results of all our studies showed a clear preponderance of women with BP-I disorder and a preponderance of men with unipolar mania. This corroborates Baek et al.'s findings from the NESARC community study using a narrowly defined group (with at least 3 episodes and 10 years illness duration) of 76 subjects diagnosed with unipolar mania (M/Md) and 935 with bipolar disorders (18). However, Rajkumar's recent clinical study (13) failed to find any significant gender difference between the diagnoses, despite there being a higher percentage of women in the group with unipolar mania than in the BP-I group. It should be borne in mind, however, that 38 of the 66 patients in that study were diagnosed with unipolar mania (57%) and only 28 (43%) with BP-I disorder, an unusual distribution not often reported. A review of the literature on clinical cases by Yazici et al. (8) mentioned contradictory findings with regard to gender distribution and also stressed culture as a potentially influential variable. In this connection, Douki et al. (40) found unipolar mania to be three times more common among patients in Tunisia than in France. These high rates in Tunisia were recently confirmed by Amamou et al.(11). Both Douki et al. and Amamou et al. attributed these differences to cultural variations and seasonality. Cultural differences in the awareness and experience of depressive and manic symptoms represent a significant limitation of studies on affective disorders.

Our finding that unipolar mania in both adults and adolescents is significantly less strongly associated than BP-I disorder with *GAD and panic disorders* confirms the results of Merikangas et al. in adolescents (41) and of Baek et al. in adults (18). It also corroborates three earlier reviews of clinical studies (10, 42, 43) and the clinical studies of Andrade et al. (44) and of Grobler et al.(12).

The lower risk of *suicide attempts* among adults and adolescents with unipolar mania compared to those with BP-I disorder in our study is a striking and clinically relevant finding. Indeed, suicide attempts in all seven adult surveys showed the same trend and overall were half as frequent among those with unipolar mania as among those with BP-I disorder (19.3% vs 38.3%). This difference was even more pronounced in the two adolescent studies (5.6% vs. 22.0%). This is in agreement with a long-term follow-up study of a sample of hospital admissions in Zurich (45), with the study of Grobler et al. (12) , with the reviews of Yazici (8) and Mehta (10) as well as with the recent finding of Amamou et al. in Tunisia (11). Our observation of a lower proportion of *bulimia/binge eating disorders* among adults with unipolar mania than among those with BP-I disorder is a new finding. Indeed, to our knowledge the rate of eating disorders has not yet been studied among unipolar manic subjects and could have important implications in terms of an attenuated likelihood of developing metabolic complications as compared to typical BP-I patients.

Our finding that the proportion of *drug use disorders* is lower among adults with unipolar mania than among those with BP-I disorder conflicts with the study of Grobler et al.(12), who found more cannabis abuse among patients with unipolar mania only than in those with mania and depression. The clinical evidence of differences in the history of substance misuse among patients with unipolar mania and with bipolar disorder is mixed. In line with our findings, at least two earlier studies documented higher levels of substance abuse in those with bipolar disorder (46), (47), whereas another reported no difference (44) and yet another observed more cannabis and amphetamine use in the group with unipolar mania (48). These inconsistent findings may derive from the varying severity of unipolar mania in the different studies. It has been shown, for instance, that more severe cases of unipolar mania with more psychotic features are more prone to substance abuse (12, 48). Our analysis shows that subjects with unipolar mania are less affected overall by comorbid conditions than those with BP-I disorder although we could not test for the severity of manic episodes in terms of psychotic features. Indeed, the lower degree of severity with a lower

occurrence of psychotic features in our community samples as compared to clinical studies generally diminished our ability to assess differences in severity between unipolar mania and BP-I disorder. We hypothesize that the higher risk of anxiety, eating and drug use disorders as well as suicidality in BP-I disorder compared to in unipolar mania is predominantly linked to the depressive component of the former disorder.

Two clinical studies (15, 49) found that patients with unipolar mania more rarely reported a positive *family history* of major depressive disorder than those with bipolar disorder. This finding was corroborated by the data from the NESARC study (18) but was not confirmed in our analyses controlled for age and gender. Indeed, as in some other studies that assessed family history (8, 12), none of these variables reached the level of statistical significance in our adjusted analyses. It has been shown that family history reports are subject to multiple bias (32), which could have led to an underestimation of associations between the patient's diagnostic status and disorders in relatives. Hence, our results based on family history reports need confirmation by family studies, which rely on direct interviews of relatives.

Limitations: First, given that unipolar mania is a rare disorder in the community, the sample sizes of several of the adult studies included were small. Second, the studies included in our analyses revealed considerable methodological heterogeneity. As not all datasets comprised exactly the same variables, comparisons were sometimes made between similar but not identical comorbid conditions or family histories of psychiatric syndromes. For instance, some disorders were assessed together (e.g. GAD and / or panic disorder, or bulimia and / or binge eating) because of strong longitudinal overlap and small Ns. Although we adjusted for the study source in our analyses, methodological variance across studies bears the risk of non-differential (conservative) bias, resulting in an underestimation of the size of associations, i.e. owing to this bias we may have failed to detect more differences between unipolar mania and BP-I disorder. Third, several clinical course characteristics were not assessed in the majority of studies which limited our ability to test meaningful course differences between unipolar mania and BP-I disorder. Ultimately, future studies should

assess differences in course and treatment outcomes between unipolar mania and BP-I disorder.

Fourth, there is the likelihood of misclassification bias, as an undefined number of respondents with unipolar mania may present with a depressive episode later on in life. This applies especially to adolescents who may still develop major depressive episodes or even associated comorbid conditions at a later age. Such misclassification may have reduced the ability to distinguish specific features or comorbid conditions associated with unipolar mania. The NESARC study found the presence of GAD or ADHD to predict an increased transition from unipolar mania to bipolar disorder over a 3-year follow-up. This was however not the case for subthreshold depression (18). Fifth, it cannot be ruled out that there could have been symptom overlap among some of the conditions, such as anxiety symptoms or suicide attempts actually being more part of the depressive episodes of bipolar disorder per se.

Despite these limitations, our analysis of the pooled data from nine well-known epidemiological surveys shows that for two important validators: gender and comorbidity of mental conditions, there are considerable differences between individuals with unipolar mania and those with bipolar-I disorder. These differences suggest that the diagnostic distinction between the two disorders should be made both for research and clinical purposes, and that their merger in DSM-5 and ICD-10 should be viewed with caution as previously shown by the NESARC study (18). In research settings, the lumping together of the two disorders is likely to lead to the creation of a more heterogeneous category of bipolar disorder, which may hamper efforts to determine etiology. In clinical settings, the treatment and prevention of unipolar mania – in less severe cases at least – is potentially less complex than that of bipolar-I disorder from a pharmacological point of view, given the absence of depressive episodes. Indeed, in unipolar mania, prevention only needs to focus on mania, whereas in bipolar disorders, prevention of both manic and depressive episodes may be more difficult to achieve and frequently needs the association of more than one drug (50). Nevertheless, the particular aspects of acute and maintenance pharmacological treatment for

unipolar mania should still be better defined. Moreover, our results suggest that the rarer occurrence of suicide attempts, anxiety and drug use disorders among individuals with unipolar mania may facilitate the successful treatment of manic episodes and lead to a more favorable course of the disorder. In contrast, the diagnosis of bipolar-I disorder, with both manic and depressive episodes, should alert the clinician to the risk of suicide attempts and favor the detection and treatment of possible comorbid anxiety, eating and drug use disorders in order to improve the long-term course of this complex disorder.

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Table 1: Seven adult studies: prevalence, characteristics and comorbidity across diagnostic groups – unipolar mania (M) vs BP-I

	Study (N)														Total			
	Zurich (n=591)		ZINEP (n=1500)		São Paulo (n=5037)		Pelotas (n=1560)		NCS-R (n=5692)		PsyCoLaus (4874)		NESDA (n=2596)				Generalized linear mixed models	
Diagnosis	M	BP-I	M	BP-I	M	BP-I	M	BP-I	M	BP-I	M	BP-I	M	BP-I	M	BP-I	OR or β (95% CI)°	*p*
Prevalence %	3.1§	2.7§	0.21§	0.19§	0.21§	0.64§	2.37	5.13	0.32§	0.66§	0.18	0.74	-	-	-	-		
N	18	19	4	7	6	29	37	80	33	68	9	36	2	84	109	323		
Males (n) **%**	(9) 50.0	(8) 42.1	(2) 50.0	(3) 42.9	(4) 66.7	(13) 44.8	(18) 48.7	(24) 30.0	(13) 39.4	(25) 36.8	(9) 100	(20) 55.7	(2) 100	(36) 42.9	(57) 52.3	(129) 39.9	1.78 (1.15; 2.81)	<.05
Age: mean	49.5[a]	49.6[a]	27.8	24.7	32.7	40	20.3	20.2	33.5	37	50.7	52.3	50.5	40.7	33.1	36.3	-1.52 (-3.7; 0.66)	n.s.
Onset mania: median	23.2	16.1	26.8	22.9	20.7	28.5	-	-	-	-	30.9	37.1	41.5	24.8	25.9	26.8	1.77 (-2.53; 6.07)	n.s.
Lifetime comorbidity of mental conditions (n) %																		
Suicide attempts	(2) 11.1	(3) 15.8	(0) 0	(2) 28.6	(0) 0	(8) 27.6	(15)[b] 40.5	(39)[b] 48.8	(3) 9.1	(31) 45.6	(1) 11.1	(12) 35.3	(0) 0	(28) 33.3	(21) 19.3	(123) 38.3	0.38 (0.22; 0.65)	<.001
GAD/Panic	(7) 38.9	(11) 57.9	(2) 50	(2) 28.6	(1) 16.7	(14) 48.3	(17) 46.0	(39) 48.8	(17) 51.5	(57) 83.8	(0) 0	(6) 18.2	(0) 0	(63) 75	(44) 40.4	(192) 60	0.46 (0.28; 0.75)	<.01
Bulimia/Binge eating	(2) 11.1	(7) 36.8	-	-	(0) 0	(12) 41.4	(2)[c] 5.4	(6)[c] 7.5	(3) 9.1	(9) 13.2	(0) 0	(2) 6.1	-	-	(7) 6.5	(36) 15.3	0.38 (0.16; 0.90)	<.05
Sedative ab/dep	(4) 22.2	(4) 21.1	-	-	(1) 16.7	(7) 24.1	(1) 2.7	(10) 12.5	(2) 6.1	(9) 13.2	(0) 0	(0) 0	-	-	(8) 7.8	(30) 13.0	0.53 (0.24; 1.18)	n.s.
Drug ab/dep	(2) 11.1	(7) 36.8	(1) 25	(1) 14.3	(3) 50.0	(7) 24.1	(6) 16.2	(23) 28.8	(11) 33.3	(37) 54.4	(1) 11.1	(3) 8.6	-	-	(24) 22.4	(78) 32.8	0.50 (0.29; 0.87)	<.05
Alcohol ab/dep	(6) 33.3	(8) 42.1	(1) 25.0	(1) 14.3	(4) 66.7	(12) 41.4	(14) 37.8	(27) 33.8	(18) 54.6	(38) 55.9	(3) 33.3	(10) 28.6	(1) 50	(15) 18.1	(47) 43.1	(111) 34.6	1.05 (0.66; 1.69)	n.s.

° adjusted for sex and age as fixed effects and study source as random effect. (Sex and age variables were only adjusted for the alternate variable and for study source).

§ weighted prevalence estimate.

[a] age in 2008 (at the 7th follow-up assessment).

[b] includes attempts as well as suicide ideation.

[c] includes only current bulimia.

GAD = generalized anxiety disorder; ab/dep = abuse/dependence.

-: no data available for these variables.

Table 2: Seven adult studies: temperamental traits and family history of mental disorders – unipolar mania (M) vs BP-I

	Study														Total			
	Zurich		ZINEP		São Paulo		Pelotas		NCS-R		PsyCoLaus		NESDA				Generalized linear mixed models	
Diagnosis	M	BP-I	M	BP-I	M	BP-I	M	BP-I	M	BP-I	M	BP-I	M	BP-I	M	BP-I	OR(95% CI)°	*p*
N	18	19	4	7	6	29	37	80	33	68	9	36	2	84	109	323		
Temperament (N) %																		
Hyperthymic	(14) 77.8	(14) 73.7	-	-	-	-	-	-	-	-	(3) 33.3	(2) 5.6	-	-	(17) 63.0	(16) 29.1	2.37 (0.75; 7.51)	n.s.
Anxious	(1) 5.6	(4) 21.1	-	-	(0) 0	(13) 44.8	-	-	-	-	-	-	-	-	(1) 4.2	(17) 35.4	0.08 (0.0; 0.96)	n.s.
Family history (N) %																		
Mania	(4) 22.2	(4) 21.1	(0) 0	(1) 14.3	(4) 66.7	(15) 51.7	-	-	(15)[a] 57.7	(45)[a] 70.3	(0)[b] 0	(3)[b] 12.0	-	-	(23) 37.7	(68) 47.2	0.74 (0.37; 1.48)	n.s.
Depression	(10) 55.6	(13) 68.4	(3) 100	(4) 57.1	(3) 50	(19) 65.5	-	-	(5)[c] 21.7	(20)[c] 36.4	(6)[b] 85.7	(17)[b] 68.0	(2) 100	(71) 85.5	(29) 49.2	(144) 66.1	0.79 (0.42; 1.52)	n.s.
Suicide attempts	(5) 27.8	(8) 42.1	(1) 25	(1) 14.3	(2) 33.3	(6) 20.7	(2) 7.1	(13) 18.8	(2)[c] 10	(8)[c] 15.7	(1)[b] 14.3	(4)[b] 16.0	-	-	(13) 15.7	(40) 20	0.76 (0.38; 1.52)	n.s.
Anxiety/Panic	(8)[d] 44.4	(10)[d] 52.6	(3)[d] 75	(3)[d] 42.9	(1)[d] 16.7	(13)[d] 44.8	-	-	14[a,d] 93.3	47[a,d] 90.4	(0)[b,e] 0	(5)[b,e] 20.0	(1)[e] 50	(60)[e] 72.3	(27) 51.9	(138) 64.2	0.70 (0.33; 1.48)	n.s.
Bulimia/Binge eating	(9) 50	(7) 36.8	(1) 25	(2) 28.6	(2) 33.3	(6) 20.7	-	-	-	-	-	-	-	-	(12) 42.9	(15) 27.3	2.05 (0.77; 5.44)	n.s.
Any substance ab/dep	(1) 5.9	(5) 26.3	(2) 50	(2) 28.6	(3) 50	(8) 27.6	-	-	(16)[a] 84.2	(38)[a] 90.5	(4)[b] 57.1	(7)[b] 28.0	(1) 50	(38) 45.8	(27) 49.1	(98) 47.8	1.21 (0.56; 2.61)	n.s.
Alcohol ab/dep	(1) 5.9	(5) 26.3	(2) 50	(2) 28.6	-	-	-	-	-	-	(4)[b] 57.1	(7)[b] 28.0	(1) 50	(34) 41	(8) 26.7	(48) 35.8	0.89 (0.34; 2.32)	n.s.

° adjusted for sex and age as fixed effects and study source as a random effect.

[a] family history information was only available for subjects who entered the chapter investigating the given disorder.

[b] 13 subjects with missing information on family history.

[c] family history information was only available on the parents of subjects who entered the childhood section.

[d] includes family history of GAD and panic disorder.

[e] includes any anxiety disorder / complaint.

GAD = generalized anxiety disorder; ab/dep = abuse/dependence.

-: no data available for these variables.

Table 3: Two adolescent studies: prevalence, characteristics and comorbidity – unipolar mania (M) vs BP-I

	Study				**Total**			
	EDSP (n=3021)		**NCS-A (n=10123)**				**Generalized linear mixed models**	
Diagnosis	M	BP-I	M	BP-I	M	BP-I	OR or β (95% CI)°	*p*
Prevalence %	1.02§	1.74§	1.71§	1.08§	-	-	-	-
N	33	51	162	131	195	182		
Males (n) **%**	(21) 63.6	(21) 41.2	(89) 54.9	(43) 32.8	(110) 56.4	(64) 35.2	2.51 (1.64; 3.82)	<.0001
Age: mean	24.9[a]	25.6[a]	15.4	15.5	17.0	18.3	-0.24 (-0-78; 0.30)	n.s.
Onset mania: median	14.7	15.8	-	-	14.7	15.8	0.92 (-0.99; 2.83)	n.s.
Comorbidity of mental conditions (n) %								
Suicide attempts	(3) 9.1	(14) 27.5	(8) 4.9	(26) 19.9	(11) 5.6	(40) 22.0	0.25 (0.12; 0.51)	<.001
GAD/Panic	(6) 18.2	(21) 41.2	(65) 40.1	(81) 61.8	(71) 36.4	(102) 56.0	0.43 (0.28; 0.66)	<.001
Bulimia/Binge eating	(0) 0	(2) 3.9	(18) 11.1	(25) 19.1	(18) 9.2	(27) 14.8	0.61 (0.32; 1.17)	n.s.
Sedative ab/dep	(0) 0	(0) 0	-	-	(0) 0	(0) 0	-	-
Drug ab/dep	(14) 42.4	(14) 27.5	(34) 21.0	(43) 32.8	(48) 24.6	(57) 31.3	0.67 (0.42; 1.08)	n.s.
Alcohol ab/dep	(25) 75.8	(22) 43.1	(30) 18.5	(30) 22.9	(55) 28.2	(52) 28.6	1.08 (0.66; 1.77)	n.s.

° adjusted for sex and age as fixed effects and study source as random effect. (Sex and age variables were only adjusted for the alternate variable and for study source).

§ weighted prevalence estimate.

[a] age at the 3rd follow-up assessment.

GAD = generalized anxiety disorder; ab/dep = abuse/dependence.

-: no data available for these variables.

Table 4: Two adolescent studies: family history of unipolar mania (M) vs. BP-I

	Study				Total			
	EDSP		NCS-A				Generalized linear mixed models	
Diagnosis	M	BP-I	M	BP-I	M	BP-I	OR (95% CI)°	*p*
N	33	51	162	131	195	182		
Family history (N) %								
Mania	(2) 6.1	(4) 7.8	(93)[a] 71	(86)[a] 75.4	(95) 57.9	(90) 54.6	0.77 (0.45; 1.33)	n.s.
Depression	(14) 42.4	(29) 56.9	(9)[a] 81.8	(90)[a] 84.1	(23) 52.3	(119) 75.3	0.53 (0.25; 1.13)	n.s.
Suicide attempts	-	-	(4)[b] 2.8	(11)[b] 9.3	(4) 2.8	(11) 9.3	0.35 (0.10; 1.22)	n.s.
Anxiety/Panic	(7)[c,d] 21.2	(15)[c,d] 29.4	(48)[a,c] 98	(68)[a,c] 95.6	(55) 67.1	(80) 67.2	0.82 (0.33; 2.0)	n.s.
Any substance ab/dep	(20) 60.6	(25) 49.0	(41)[a] 87.2	(46)[a] 80.7	(61) 76.3	(71) 65.7	1.58 (0.79; 3.18)	n.s.
Alcohol ab/dep	(12) 36.4	(13) 25.5	-	-	(12) 36.4	(13) 25.5	1.85 (0.69; 5.0)	n.s.

° adjusted for sex and age as fixed effects and study source as random effect.

[a] family history information was only available for subjects who entered the chapter investigating the given disorder.

[b] family history information was only available on the parents of subjects who entered the childhood section.

[c] includes family history of GAD and panic disorder.

[d] includes information on mothers and fathers for GAD and / or panic disorder.

GAD = generalized anxiety disorder; ab/dep = abuse/dependence.

- : no data available for these variables.