Berkson's bias and the mood dimensions of bipolar disorder

E. J. REGEER,¹ L. KRABBENDAM,² R. DE GRAAF,³ M. TEN HAVE,³ W. A. NOLEN⁴ & J. VAN OS^{2,5}

1 Altrecht Institute for Mental Health Care, Utrecht, The Netherlands

2 Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University, Maastricht, The Netherlands

3 Netherlands Institute of Mental Health and Addiction (Trimbos Institute), Utrecht, The Netherlands

4 Department of Psychiatry, University Medical Center Groningen, Groningen, The Netherlands

5 Division of Psychological Medicine, Institute of Psychiatry, London, UK

Key words

bipolar disorder, Berkson's Bias, comorbidity, mood dimensions

Correspondence

E.J. Regeer, Altrecht GGZ,
Lange Nieuwstraat 119, 3512 PG
Utrecht, The Netherlands.
Telephone (+31) 30 2308600
Fax (+31) 30 2308678
Email: e.regeer@altrecht.nl

Received 31 July 2007;
revised 11 December 2007;
accepted 22 January 2008

Abstract

In this paper we examined whether manic and depressive dimensions independently contribute to mental health service use and determined the degree of comorbidity between manic and depressive dimensions in individuals with and without mental health service use. If both depressive and manic episodes independently influence help-seeking behaviour, a higher level of comorbidity between these dimensions would be found in clinical as compared to non-clinical samples (i.e. Berkson's Bias). Data were derived from the Netherlands Mental Health Survey and Incidence Study (NEMESIS), a prospective epidemiological survey in a representative sample of the Dutch population ($N = 7076$). Dimensions of depression and mania and mental health service use (MHSU) were assessed with the Composite International Diagnostic Interview (CIDI) at baseline, and prospectively one and three years later. Logistic regression was used to test whether depressive and manic dimensions both had independent effects on mental health service use. The degree of mania-comorbidity given the presence of depressive dimension was assessed as a function of MHSU, both retrospectively and prospectively. Manic and depressive dimensions contributed independently to mental health service use. Mania-comorbidity given the presence of depressive dimension was significantly higher in individuals with mental health service use than in those without, both retrospectively (16.7% versus 7.1%, $p = 0.000$) and prospectively (10.8% versus 6.6%, $p = 0.017$). We conclude that the bipolar phenotype consists of manic and depressive dimensions that may be much more loosely associated than (Berkson) biased clinical observations suggest. A dimension-specific approach may be more productive in clarifying the aetiology of mood dysregulation. Copyright © 2009 John Wiley & Sons, Ltd.

Introduction

Bipolar disorder is characterized by the occurrence of one or more manic or hypomanic episodes, usually alternating with more or less severe depressive episodes. Several studies have shown that the broad expression of mania and depression occurs at a much higher rate than narrowly defined bipolar disorder, and can also be measured in non-clinical severity at the level of the general population (Angst and Merikangas, 1997; Angst *et al.*, 2003; Cuijpers and Smit, 2004; Cuijpers *et al.*, 2004; Judd *et al.*, 2002; Judd and Akiskal, 2003). Therefore, it can be questioned whether the current concept of bipolar disorder reflects the true nature of mood dysregulation. According to Berkson (1946), high rates of comorbidity seen in clinical practice, such as the apparent cross-sectional or sequential clustering of depressive and manic episodes within the same patient with bipolar disorder, may in part be an artefact if both depressive and manic episodes independently influence help-seeking behaviour and need for care. Since the concept of bipolar disorder is essentially based on observations of help-seeking individuals who have come to the attention of clinicians, the observed association between depressive and manic episodes in these individuals with the most comorbid expressions may rise accordingly, obscuring the fact that depressive and manic dimensional phenotypes may be much more loosely associated with each other in the general population of non-help seeking individuals.

If treatment-seeking bias accounts in part for the high correlation between manic and depressive symptoms in patient populations (Berkson, 1946), correlations should be much lower in the general population than in clinical populations (Maric *et al.*, 2004). This hypothesis was tested, both cross-sectionally and prospectively, in the current paper, by examining whether manic and depressive dimensions independently contribute to mental health service use and determining the degree of mania-comorbidity given the presence of depressive dimensions in individuals with and without mental health service use in a general population sample.

Methods

Sample

The Netherlands Mental Health Survey and Incidence Study (NEMESIS) is a prospective study with three measurement points over a period of three years (Bijl *et al.*, 1998a; Bijl *et al.*, 1998b). A multistage, stratified, random sampling procedure was used to first select 90 municipalities, then a sample of private households, and finally a

Dutch-speaking individual aged 18–64 years within each household. Selected households were sent an introductory letter by the Minister of Health, inviting them to participate. A total of 7076 individuals was interviewed at baseline, representing a response rate of 69.7%. At T_1 , one year post-baseline, 5618 respondents participated for the second time; at T_2 , three years post-baseline, 4848 respondents participated. At T_1 and T_2 , the presence of symptoms between respectively baseline and T_1 and between T_1 and T_2 was assessed.

The sample was found to be representative of the Dutch population in terms of gender, marital status and level of urbanization (Bijl *et al.*, 1998b), with the exception of a slight under-representation of individuals in the age group 18–24 years. Examination of attrition suggested that, after adjustment for influences of demographic variables, this had occurred largely independently of the variable of interest: mental health (de Graaf *et al.*, 2000). As this was a study of relative rather than absolute risk, no post-stratification weightings were applied to the data. NEMESIS was conducted with the approval of the Internal Review Board of the Trimbos Institute and after oral explanation of the study, in addition to the introductory letter, all respondents gave informed consent to participate in the study as required by Dutch law at the time of the investigation.

Instruments

Respondents were interviewed at home. The Composite International Diagnostic Interview (CIDI) version 1.1 (Robins *et al.*, 1988; Smeets and Dingemans, 1993; WHO, 1990) was used, yielding the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) diagnoses. The CIDI was designed for trained interviewers who are not clinicians and has been found to have high interrater reliability (Cottler *et al.*, 1991; Wittchen *et al.*, 1991), and high test–retest reliability (Semler *et al.*, 1987; Wacker *et al.*, 1990; Wittchen, 1994). Ninety interviewers experienced in systematic data collection collected the data, having received a three-day training course in recruiting and interviewing, followed by a four-day course at the World Health Organization (WHO)-CIDI training centre in Amsterdam. Extensive monitoring and quality checks took place throughout the entire data collection period (Bijl *et al.*, 1998b).

Assessment of depressive and manic mood symptoms at baseline and follow-up

At baseline, the presence of any lifetime depressive or manic symptom and the total number of lifetime

depressive and manic symptoms were assessed with the 28 items of the CIDI depression and dysthymia section (E) and the 11 items of the CIDI mania section (F). All these items can be rated either 'yes' (1) or 'no' (0). The depressive symptom has to be present for at least two weeks and the manic symptom has to be present for at least two days. The depression and dysthymia section starts with assessing the presence of depressive mood and/or anhedonia, the mania section starts with assessing the presence of abnormally and persistently elevated, expansive or irritable mood. Secondly, all other associated depressive and (hypo)manic symptoms are assessed. In order to establish a DSM-III-R diagnosis of a mood disorder, the CIDI assesses to what degree the mood symptoms and the other symptoms were experienced in the same time period. As a result of this procedure, the minimum number of depressive symptoms was two and the minimum number of mania symptoms was three. For the purpose of the analyses, depression and mania were expressed dichotomously as 'present' (1) and 'absent' (0) in case of two or more lifetime depressive and three or more lifetime manic symptoms, respectively. The lifetime measures of depression and mania at baseline are referred to hereafter as depression-lifetime and mania-lifetime, respectively.

Similarly, a dichotomous variable indicating three or more mania symptoms at baseline and/or T_1 and/or T_2 was constructed (hereafter: mania-total) as well as a similar measure of two or more depression symptoms at baseline and/or T_1 and/or T_2 (hereafter: depression-total). These definitions (depression-lifetime, mania-lifetime, depression-total and mania-total) thus also included the milder forms of minor depression and hypomania.

Mental health service use (MHSU)

Mental health service use (MHSU) rated at baseline (hereafter: MHSU-lifetime) was defined as a dichotomous variable 'yes' (1) or 'no' (0). The rating covered lifetime history of mental health service use up to the moment of baseline. Mental health service use was rated 'yes' if respondents reported any lifetime contact with: a community mental health centre, a psychiatric outpatient clinic, a private psychiatrist, a psychologist, a psychotherapist, psychiatric admission or day treatment.

In addition, a variable indicating mental health service use at T_1 and/or T_2 was constructed (hereafter: MHSU-follow-up). MHSU-follow-up was scored 'yes' if respondents reported receiving mental health service use as

defined earlier for any kind of mental health problems between baseline and T_2 .

The risk set for MHSU-follow-up was 4902, consisting of the individuals who had valid data on mental health service use at either T_1 or T_2 .

Statistical analysis

Association between mania, depression and MHSU

A logistic regression analysis, yielding odds ratios (ORs), was conducted in which MHSU-lifetime was modelled as a function of depression-lifetime and mania-lifetime, entered together, in order to test whether both had independent effects on mental health service use. Similarly, a prospective analysis was also conducted in which MHSU-follow-up was modelled as a function of depression-total and mania-total entered simultaneously in the model, whilst controlling for MHSU-lifetime.

Rate of mania-comorbidity in the presence of depression as a function of MHSU

The degree of comorbidity between mania-lifetime and depression-lifetime was assessed as a function of MHSU-lifetime, in order to assess the hypothesis that comorbidity would be higher in respondents with a history of help-seeking (i.e. in those with MHSU-lifetime). This was calculated as the difference in the rate of lifetime mania in individuals with depression-lifetime who (i) did and (ii) did not have MHSU-lifetime, and testing for statistical significance of this risk difference using the MFX procedure in STATA (StataCorp., 2005), which assesses marginal effects and their standards errors after estimation, in this case the STATA LOGISTIC procedure. The same analyses were repeated prospectively using the total measures of symptoms (mania-total and depression-total) and the follow-up of mental health service use (MHSU-follow-up). Thus, the difference in the rate of mania-total in those with presence of depression-total was assessed as a function of first-ever mental health service use occurring between baseline and T_2 (i.e. MHSU-follow-up in those without MHSU-lifetime). The depressive state was fixed because bipolar disorder starts in the majority of the cases with symptoms of depression or a depressive episode as illustrated by a prospective study among children aged 16–26 years of parents with a bipolar disorder, almost all children with bipolar disorder (92%) debuted with a depressive episode (Hillegers *et al.*, 2005).

Results

Percentages and number of respondents with mania, depression and MHSU

The mean age of the respondents was 41.2 years, 46.6% were men. The percentages and number of respondents with depression-lifetime, mania-lifetime, depression and mania-lifetime, depression-total, mania-total, depression and mania-total, MHSU-lifetime and MHSU-follow-up, are presented in Table 1.

Association between mania, depression and MHSU

Table 2 presents the association between mania and depression, on the one hand, and MHSU, on the other hand, expressed as ORs. Depression-lifetime was strongly associated with MHSU-lifetime [OR 7.6, 95% confidence interval (CI) 6.7–8.7], and so was mania-lifetime (OR 2.6, 95% CI 2.0–3.4), albeit with a lower effect size. For MHSU-follow-up similar associations were found with

Table 1 Percentages and number of respondents with depression, mania and mental health service use (MHSU) (*N* = 7076)

	Percentage (<i>N</i>)
Depression-lifetime	31.5 (2225)
Mania-lifetime	4.1 (293)
Mania + depression-lifetime	3.52 (249)
Depression-total	36.5 (2585)
Mania-total	5.0 (356)
Mania + depression-total	4.4 (311)
MHSU-lifetime	19.1 (1352)
MHSU-follow-up ¹	21.7 (1065)

¹ *N* = 4902.

Table 2 Association between mania and depression, on the one hand, entered together in the model, and mental health service use (MHSU), on the other hand, expressed as odds ratio (95% CI)

	Mania-lifetime	Depression-lifetime	Mania-total	Depression-total
MHSU-lifetime (95% CI)	2.6 (2.0–3.4)*	7.6 (6.7–8.7)*		
MHSU-follow-up (95% CI) ¹			2.8 (2.1–3.8)*	9.3 (7.9–11.0)*
MHSU-follow-up (95% CI) ¹ corrected for MHSU-lifetime			2.5 (1.9–3.4)*	7.5 (6.3–9.0)*

* *p* = 0.000.

¹ *N* = 4902.

mania-total and depression-total. Both depression-total (OR 9.3, 95% CI 7.9–11.0) and mania-total (OR 2.8, 95% CI 2.1–3.8) were significantly associated with MSHU-follow-up. These associations remained significant when controlling for MSHU-lifetime indicating that the prospective (follow-up) associations were not merely repetitions of previous mental health service use.

Rate of mania-comorbidity given the presence of depression as a function of MHSU

Table 3 shows the degree of mania-comorbidity given the presence of depression in respondents with and without mental health service use. In respondents with MHSU-lifetime, the rate of mania-lifetime given the presence of depression-lifetime was 16.7%, which was considerably higher than the rate among respondents without MHSU-lifetime (7.1%). The comorbidity difference of 9.6% (95% CI 6.8–12.3) for mania-lifetime given the presence of depression-lifetime between respondents with and without MHSU-lifetime, was highly significant (*z* = 6.82, *p* = 0.000). In respondents with first-ever mental health service use (i.e. MHSU-follow-up in those without MHSU-lifetime) the rate of mania-total given the presence of depression-total was 10.8%, which was considerably higher than the rate of mania-total given the presence of depression-total among respondents without MHSU-follow-up (6.6%). The comorbidity difference of 4.2% (95% CI 0.8–7.7) for mania-total given the presence of depression-total between respondents with and without MHSU-follow-up, was again significant (*z* = 2.39, *p* = 0.017).

Discussion

This study examined the association between manic and depressive dimensions and mental health service use, and the degree of comorbidity of the mania dimensional phenotype given the presence of the depression dimensional

Table 3 Mania-comorbidity rate (%) and mania-comorbidity differences (%) given the presence of depression as a function of mental health service use (MHSU)

	MHSU-lifetime	No MHSU-lifetime	MHSU-follow-up	No MHSU-follow-up	Comorbidity difference (95% CI)
Mania-lifetime comorbidity rate (risk set: $N = 2225$) ¹	16.7	7.1			9.6 (6.8–12.3)*
Mania-total comorbidity rate (risk set: $N = 1143$) ²			10.8	6.6	4.2 (0.8–7.7)**

* $p = 0.000$.** $p = 0.017$.¹Risk set of 2225 respondents with depression-lifetime.²Risk set of 1143 respondents with depression-total and without MHSU-lifetime.

phenotype in individuals with and without mental health service use in a general population sample. The ORs we found illustrate that both manic and depressive dimensions contributed independently to retrospective and prospective mental health service use. As a result, mania-comorbidity given the presence of depressive dimension was significantly higher in individuals with mental health service use, both retrospectively and prospectively in contrast to individuals without mental health service use.

These results, therefore, suggest that the current concept of bipolar disorder is in part the result of Berkson's Bias. The association between both dimensions in clinical samples appears to be high due to the fact that both manic and depressive dimensions contribute to help-seeking behaviour and need for care. These independent effects of both dimensions on help-seeking will lead to an increase in the number of patients in clinical samples with manic-depression comorbidity. Consequently, manic and depressive dimensions are much more loosely associated with each other in the general population of non-help seeking individuals. Recent evidence suggesting that the bipolar phenotype is continuous in the general population (Angst and Merikangas, 1997; Angst *et al.*, 2003; Cuijpers and Smit, 2004; Cuijpers *et al.*, 2004; Judd *et al.*, 2002; Judd and Akiskal, 2003; Regeer *et al.*, 2006) taken together with the current results, strongly support a dimensional rather than a categorical approach of the bipolar phenotype in which an individual can have more or less psychopathology rated on several dimensions such as severity and polarity of mood dysregulation.

The theoretical implications of the findings are that it may be rewarding in the search for the aetiology of bipolar disorder to look for separate risk factors for manic and

for depressive dimensions. This is in line with the two-illness model of bipolar disorder proposed by Joffe *et al.* (1999). These authors hypothesized that bipolar disorder constitutes two separate but related disorders, depression and mania. This hypothesis has face validity given the fact that bipolar depression is no different from unipolar depression. Although criticized (Bowden, 1999; Dunner, 1999; Swann, 1999) the model is theoretically interesting to re-evaluate the concept of bipolar disorder because research to date has not provided a clear picture of the aetiology of mood dysregulation. The relatively independent variation identified in the present study reflects the fact that mania and depression are syndromes not specific to bipolar disorder but also arise in a variety of neuro-medical and toxicological conditions (Baldessarini, 2000; Swann, 1999). Among the latter groups is mania during the use of corticosteroids, withdrawal or abuse of drugs and encephalitis (Krauthammer and Klerman, 1978) and depression as a comorbid disorder in other psychiatric disorders, chronic somatic conditions (Schweitzer *et al.*, 2005), or as a result of the use or withdrawal of drugs or medication. Therefore, mania and depression may be better seen as syndromes with at least partial different aetiologies and underlying pathophysiologies (Kelsoe, 2003). More recently, Schweitzer *et al.* (2005) argued that bipolar disorder is more appropriately viewed as a manic disorder with or without comorbid depression because the syndrome of mania is the central distinguishing feature of bipolar disorder. Most psychiatric disorders are commonly complicated by comorbid depression. Depression in bipolar disorder has been viewed as an integral part of the disorder, whereas in other psychiatric disorders depression has been viewed as a complicating and co-existing comorbid disorder.

The observation of relatively separate manic and depressive dimensions in the general population contrasts with the phenomenon of mixed episodes seen in clinical samples. The co-occurrence of manic and depressive symptoms in the same mood episode is common in clinical practice. A recent study among 441 treated individuals with bipolar disorder showed occurrence of clinically significant depressive symptoms (two or more symptoms) in 94.1% of those with a (hypo)mania; similarly, 70.1% of those in a depressive state episode had clinically significant manic symptoms (Bauer *et al.*, 2005). In addition, another study with 908 treated individuals found that in over 57% hypomania co-occurs with depression (Suppes *et al.*, 2005). The present study suggests that these observations may be influenced by Berkson's Bias.

Probably many different genes contribute to the aetiology of most if not all major psychiatric syndromes (Kendell and Jablensky, 2003). Some syndromes and symptom dimensions may share the same genes and some genes may be specific for a symptom dimension (Cardno *et al.*, 2001; Kendell and Jablensky, 2003). For example, the same regions on chromosome 13 and 22 are linked with psychotic symptoms during affective episodes and schizophrenia (MacQueen *et al.*, 2005). A recent study by Williams *et al.* (2006) suggests that variation at the DAOA/G30 locus on chromosome 13 influences susceptibility to major mood episodes (depression and mania) in individuals with schizophrenia and in individuals with bipolar disorder. Another study investigated the involvement of variations at the Brain-derived Neurotrophic Factor (BDNF) gene locus in major depressive disorder, bipolar disorder and schizophrenia. The results of this study suggest that BDNF may be a susceptibility gene for major depressive disorder and schizophrenia with lifetime depressive symptoms (Schumacher *et al.*, 2005). Variations in the genes DISC1 and neuregulin 1 (NRG1) may confer susceptibility to a form of illness with mixed features of psychosis and mania (Craddock *et al.*, 2006). These studies support the possibility of relatively specific relationships between genotype and symptom-dimensions.

In addition, a dimensional approach may also contribute to improvements in the treatment of mood disorders by focussing more on dimension-specific treatments, as indeed appears to be becoming more the case.

Limitations

The data were based on retrospective recall. This approach can be problematic in recording lifetime symptoms and

disorders due to difficulties of accurate recall. However, interview techniques such as reading the questions slowly, instructing the respondents to take their time and think carefully before answering, facilitate active memory search. Therefore, the use of intensively trained interviewers, which was the case in NEMESIS, increases accurate reporting of lifetime symptoms (Kessler *et al.*, 1998). A recent reappraisal study of the NEMESIS (Regeer *et al.*, 2004) among respondents with a CIDI diagnosis of bipolar disorder at any of the assessment points, showed that compared to clinical diagnoses made by the SCID (administered approximately two years later), the CIDI may represent both false positive and false negative results compared to the SCID. However, the reappraisal study assessed clinical diagnosis and was not designed to assess at the level of symptoms. Therefore, the presents results based on symptom dimensions has face validity. The CIDI assessment of mood symptoms does not include the degree of distress or disability associated with symptoms. Therefore the CIDI probably yields higher prevalence rates of manic and depressive symptoms than an instrument which requires that each symptom must be distressing (Krabbendam *et al.*, 2004). However, these milder expressions of depressive or manic symptoms determined by the CIDI should not be seen as false positive, as there is evidence that these less severe phenotypes of mood disorder are a risk factor for developing a major depressive disorder or bipolar disorder (Regeer *et al.*, 2006).

Another limitation is that mixed episodes were not assessed by the CIDI in the present sample of the general population. Therefore the influence of Berkson's Bias on the clinical concept of mixed episodes was not tested.

Declaration of interests statement

W.A. Nolen has received grants from the Netherlands Organisation for Health Research and Development, the European Union, the Stanley Medical Research Institute, Astra Zeneca, Eli Lilly, GlaxoSmithKline and Wyeth; has received honoraria/speaker's fees from Astra Zeneca, Eli Lilly, Pfizer, Servier and Wyeth; and has served in advisory boards for Astra Zeneca, Cyberonics, Pfizer and Servier.

References

- Angst J., Merikangas K. (1997) The depressive spectrum: diagnostic classification and course. *Journal of Affective Disorders*, **45**, 31–40.
- Angst J., Gamma A., Benazzi F., Ajdacic V., Eich D., Rössler W. (2003) Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. *Journal of Affective Disorders*, **73**, 133–146.

- Baldessarini R.J. (2000) A plea for integrity of the bipolar disorder concept. *Bipolar Disorders*, **2**, 3–7.
- Bauer M.S., Simon G.E., Ludman E., Unützer J. (2005) 'Bipolarity' in bipolar disorder: distribution of manic and depressive symptoms in a treated population. *British Journal of Psychiatry*, **187**, 87–88.
- Berkson J. (1946) Limitations of the application of the four-fold table analysis to hospital data. *Biometrics*, **2**, 47–53.
- Bijl R.V., Ravelli A., van Zessen G. (1998a) Prevalence of psychiatric disorder in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Social Psychiatry and Psychiatric Epidemiology*, **33**, 587–595.
- Bijl R.V., van Zessen G., Ravelli A., de Rijk C., Langendoen Y. (1998b) The Netherlands Mental Health Survey and Incidence Study (NEMESIS): objectives and design. *Social Psychiatry and Psychiatric Epidemiology*, **33**, 581–586.
- Bowden C.L. (1999) 'A two-illness model of bipolar disorder' – by R.T. Joffe, L.T. Young, G.M. MacQueen: a commentary. *Bipolar Disorders*, **1**, 31–35.
- Cardno A.G., Sham P.C., Murray R.M., McGuffin P. (2001) Twin study of symptom dimensions in psychoses. *British Journal of Psychiatry*, **179**, 39–45.
- Cottler L.B., Robins L.N., Grant B.F., Blaine J., Towle L.H., Wittchen H.U., Sartorius N. (1991) The CIDI-core substance abuse and dependence questions: cross-cultural and nosological issues. The WHO/ADAMHA Field Trial. *British Journal of Psychiatry*, **159**, 653–658.
- Craddock N., O'Donovan M.C., Owen M.J. (2006) Genes for schizophrenia and bipolar disorder? Implications for psychiatric nosology. *Schizophrenia Bulletin*, **32**, 9–16.
- Cuijpers P., de Graaf R., van Dorsselaer S. (2004) Minor depression: risk profiles, functional disability, health care use and risk of developing major depression. *Journal of Affective Disorders*, **79**, 71–79.
- Cuijpers P., Smit F. (2004) Subthreshold depression as a risk indicator for major depressive disorder: a systemic review of prospective studies. *Acta Psychiatrica Scandinavica*, **109**, 325–331.
- Dunner D. (1999) 'A two-illness model of bipolar disorder' – by R.T. Joffe, L.T. Young, G.M. MacQueen: a commentary. *Bipolar Disorders*, **1**, 31–35.
- Graaf de R., Bijl R.V., Smit F., Ravelli A., Vollebergh W.A. (2000) Psychiatric and sociodemographic predictors of attrition in a longitudinal study: the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *American Journal of Epidemiology*, **152**, 1039–1047.
- Hillegers M.H.J., Reichart C.G., Wals M., Verhulst F.C., Ormel J., Nolen W.A. (2005) Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. *Bipolar Disorders*, **7**, 344–350.
- Joffe T.R., Young L.T., MacQueen G.M. (1999) A two-illness model of bipolar disorder. *Bipolar Disorders*, **1**, 25–30.
- Judd L.L., Akiskal S.A. (2003) The prevalence and disability of bipolar disorder 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 L.L., Schettler P.J., Akiskal H.S. (2002) The prevalence, clinical relevance and public health significance of subthreshold depressions. *Psychiatric Clinics of North America*, **25**, 685–698.
- Kelsoe J.R. (2003) Review: Arguments for the genetics basis of the bipolar spectrum. *Journal of Affective Disorders*, **73**, 183–197.
- Kendell R., Jablensky A. (2003) Distinguishing between the validity and utility of psychiatric diagnoses. *American Journal of Psychiatry*, **160**, 4–12.
- Kessler R.C., Wittchen H.U., Abelson M.A., McGonagle K., Schwarz N., Kendler K.S., Knäuper B., Zhao S. (1998) Methodological studies of the Composite International Diagnostic Interview (CIDI) in the US National Comorbidity Survey (NCS). *International Journal of Methods in Psychiatric Research*, **7**, 33–55.
- Krabbendam L., Myin-Germeys I., de Graaf R., Vollebergh W., Nolen W.A., van Os J. (2004) Dimensions of depression, mania, and psychosis in the general population. *Psychological Medicine*, **34**, 1177–1186.
- Krauthammer C., Klerman G.L. (1978) Secondary mania: manic syndromes associated with antecedent physical illness or drugs. *Archives of General Psychiatry*, **35**, 1333–1339.
- Maric N., Myin-Germeys I., Delespaul P., de Graaf R., Vollebergh W., van Os J. (2004) Is our concept of schizophrenia influenced by Berkson's bias? *Social Psychiatry and Psychiatric Epidemiology*, **39**, 600–605.
- MacQueen G.M., Hajek T., Alda M. (2005) The phenotypes of bipolar disorder: relevance for genetic investigations. *Molecular Psychiatry*, **10**, 811–826.
- Regeer E.J., Krabbendam L., de Graaf R., ten Have M., Nolen W.A., van Os J. (2006) A prospective study of the transition rates of subthreshold (hypo)mania and depression in the general population. *Psychological Medicine*, **36**, 619–628.
- Regeer E.J., ten Have M., Rosso M.L., Hakkaart-van Roijen L., Vollebergh W., Nolen W.A. (2004) Prevalence of bipolar disorder in the general population: a reappraisal study of the Netherlands Mental Health Survey and Incidence Study. *Acta Psychiatrica Scandinavica*, **110**, 374–382.
- Robins L.N., Wing J., Wittchen H.U., Helzer J.E., Babor T.F., Burke J., Farmer A., Jablenski A., Pickens R., Regier D.A. (1988) The Composite International Diagnostic Interview. An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Archives of General Psychiatry*, **45**, 1069–1077.
- Schumacher J., Jamra R.A., Becker T., Ohlraun S., Klopp N., Binder E.B., Schulze T.G., Deschner M., Schmäler C., Höfels S., Zobel A., Illig T., Propping P., Holsboer F.,

- Rietschel M., Nother M.M., Cichon S. (2005) Evidence for a relationship between genetic variants at the Brain-Derived Neurotrophic Factor (BDNF) locus and major depression. *Biological Psychiatry*, **58**, 307–314.
- Schweitzer I., Maguire K., Hg C.H. (2005) Should bipolar disorder be viewed as manic disorder? Implications for bipolar depression. *Bipolar Disorders*, **7**, 418–423.
- Semler G., Wittchen H.U., Joschke K., Zaudig M., von Geiso T., Kaiser S., von Cranach M., Pfister H. (1987) Test–retest reliability of a standardized psychiatric interview (DIS/CIDI). *European Archives of Psychiatry and Neurological Sciences*, **236**, 214–222.
- Smeets R.M.W., Dingemans P.M.A.J. (1993) *Composite International Diagnostic Interview (CIDI) Version 1.1*, World Health Organization.
- StataCorp. (2005) *STATA Statistical Software: Release 9.0*, StataCorp..
- Suppes T., Mintz J., McElroy S.L., Altshuler L.L., Kupka R. W., Frye M.A., Keck P.E. Jr, Nolen W.A., Leverich G.S., Grunze H., Rush A.J., Post R.M. (2005) Mixed hypomania in 908 patients with bipolar disorder evaluated prospectively in the Stanley Foundation Bipolar Treatment Network: a sex-specific phenomenon. *Archives of General Psychiatry*, **62**, 1089–1096.
- Swann A.C. (1999) 'A two-illness model of bipolar disorder' – by R.T. Joffe, L.T. Young, G.M. MacQueen: a commentary. *Bipolar Disorders*, **1**, 31–35.
- Wacker H.R., Battegay R., Mullejans R., Schlosser C. (1990) Using the CIDI in the general population. In: *Psychiatry: A World Perspective* (eds Stefanis C.N., Rabavilas A.D., Soldatos C.R.), Elsevier Science Publishers.
- Williams N.M., Green E.K., Macgregor S., Dwyer S., Norton N., Williams H., Raybould R., Grozeva D., Hamshire M., Zammit S., Jones L., Cardno A., Kirov G., Jones I., O'Donovan M.C., Owen M.J., Craddock N. (2006) Variation at the DAOA/G30 locus influences susceptibility to major mood episodes but not psychosis in schizophrenia and bipolar disorder. *Archives of General Psychiatry*, **63**, 366–373.
- 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., Robins L.N., Cottler L.B., Sartorius N., Burke J.D., Regier D. (1991) Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The multi-centre WHO/ADAMHA field trials. *British Journal of Psychiatry*, **159**, 645–653.
- World Health Organization (WHO). (1990). *Composite International Diagnostic Interview (CIDI), Version 1.0*, World Health Organization.