Journal of Affective Disorders 158 (2014) 37–47

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

A meta-analysis of the risk of major affective disorder in relatives of individuals affected by major depressive disorder or bipolar disorder

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ARTICLE INFO

Article history:
Received 30 September 2013
Received in revised form
19 January 2014
Accepted 20 January 2014
Available online 5 February 2014

Keywords:
Meta-analysis
Incidence
Major depressive disorder
Bipolar disorder
First-degree relatives

ABSTRACT

Background: To conduct a meta-analysis to estimate the incidence of major depressive disorder (MDD) and bipolar disorder (BD) in first-degree relatives (FDRs) of probands affected by MDD or BD. The risk for MDD in FDR of BD probands and vice versa is also investigated.
Methods: A systematic review of case-control and cohort studies, which were published between 1977 and 2012; reported relative risks (RR) or odd ratios (OR) or equivalent raw data; made an explicit distinction between MDD and BD; used operational diagnostic criteria; and reported systematic proband recruitment and ascertainment of relatives. Studies were obtained by electronic MEDLINE and EMBASE searches and hand-searching. Estimates were derived from pooled data using random effects methods.
Results: Of an initial sample of 241 articles, 22 were eligible for inclusion. For FDRs of one proband with MDD compared to healthy control probands, estimates for MDD were OR=2.14 (95% CI 1.72–2.67), increasing to OR=3.23 (95% CI 2.11–4.94) for two MDD probands. For FDRs of one BD proband compared to healthy control probands, estimates for BD were OR=7.92 (95% CI 2.45–25.61), and OR=6.58 (95% CI 2.64–16.43) for FDRs of two BD probands.
Conclusions: These findings support previously published data indicating strong familiality for both MDD and BD. Data will be useful in providing individuals with a family history of MDD or BPD with tailored risk estimates.

1. Introduction

Evidence from family studies conducted over 20 years strongly suggests that both major depressive disorder (MDD) and bipolar disorder (BD) are strongly familial (Merikangas et al., 2002). Having a proband with either MDD or BD increases the likelihood of first-degree relatives (FDRs) developing an affective disorder themselves. Increasing evidence that family history is a major risk factor for affective disorders (Sullivan et al., 2000; Valdez et al., 2010) highlights the potential utility of family history as a predictive tool in the prevention of affective disorders, in the current absence of clinically validated molecular genetic testing (Yoon et al., 2002). Indeed, the utility of family history in determining individuals who may benefit from preventive interventions has been demonstrated in common chronic medical disorders such as diabetes, cardiovascular disease and certain types of cancer and cancer syndromes (Yoon et al., 2002). Family history has been advocated as a surrogate risk assessment for complex disorders with a polygenetic component (Wilde et al., 2013; Yoon et al., 2002). Individuals with a strong family history of MDD have shown a interest in having a genetic test, if such a test were available (Wilde et al., 2010), especially when the perceived risk of developing the disorder is high (Wilde et al., 2011).

Evidence for a genetic component for affective disorders arises primarily from heritability estimates for MDD (33–48%) (Kendler and Prescott, 1999; McGuffin et al., 1996) and BD (79–83%) (Kieseppa et al., 2004; McGuffin et al., 2003), derived from twin studies. However, heritability estimates provide an approximation of the proportion of phenotypic variance that can be attributed to

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http://dx.doi.org/10.1016/j.jad.2014.01.014
0165-0327

genetic influences in a given population, rather than an individual. In recent years, Genome Wide Association Studies (GWAS) have identified a growing number of genetic variants associated with affective disorders (Psychiatric Gwas Consortium Coordinating Committee, 2009), and it is commonly accepted that their additive effects and/or their interaction with environmental factors contributes to the development of MDD and BD (Khoury et al., 2000). Separating genetic factors from familial loading due to shared environment presents difficulties (Smith and Blackwood, 2004), and risk estimation from familial loading is further complicated because adolescents and young adults with MDD are also at risk of developing as yet unapparent BD (Smith and Blackwood, 2004). The genetic loading for risk of affective disorders may also vary among affected individuals, with some individuals' symptoms arising from a greater genetic loading. For example, earlier age at onset in MDD in parents has been strongly associated with higher genetic loading in offspring (Smith and Blackwood, 2004).

The effect size for risk of developing affective disorders has been estimated in case-control and cohort studies of the FDRs of adult probands (i.e., children and siblings) and FDRs of child probands (i.e., parents and siblings), with both types of family study converging to support an elevated risk of MDD and BD among families with these disorders. The adult lifetime risk of MDD has been usually estimated at 11.6% (Slade et al., 2009), while the lifetime risk of conservatively diagnosed BD is estimated at 1.3% (Mitchell et al., 2009); international figures report a total lifetime risk of BD type I and type II at 1% (Merikangas et al., 2011). However, variation in methodology of family studies has complicated interpretation of published effect sizes for MDD and BD, wherein some studies the clinical diagnostic outcome measures have not been derived from direct interviews with probands or FDRs, [e.g. (Henin et al., 2005; Mortensen et al., 2003)] and where an explicit diagnostic distinction between MDD and BD has not been made (i.e., reporting of effect sizes that relate to 'any mood disorder' [e.g. (Wals et al., 2003)]). The issue of more complex familial heritability patterns is of increasing interest in light of recent GWAS findings that MDD and BD share genetic characteristics that do not necessarily map to diagnostic categories (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013).

Risk assessment on the basis of family history, leading to preventive intervention for MDD and BD, can potentially achieve a greater reduction in the prevalence of depression than measures designed to eliminate risk factors post onset (i.e. secondary and tertiary preventive interventions) (Bottomley et al., 2010). Family history is currently the best predictor for the development of affective disorders; it is usually assessed by collecting categorical information (i.e. dichotomous data) on the presence or absence of MDD or BD in members of a proband's family, which alone may yield insufficient predictive power for risk to that individual. Scores of the number of relatives with the disorder in a family, and the population prevalence of the disorder, improve predictive power and the estimation of likely age of onset of psychopathology in a FDR. 'Malignancy' of the disorder – i.e. severity, recurrence and degree of impairment – appears to indicate an even greater familial risk (Lieb et al., 2002).

Relatively few studies have investigated familial loading for BD and published effect sizes have not been subject to meta-analysis. Two previous meta-analyses (Rice et al., 2002; Sullivan et al., 2000) assessed familial loading of MDD; however, neither of these studies included data to allow analysis of shared genetic vulnerability for MDD and BD or data on risk of MDD in more than one proband (Rice et al., 2002; Sullivan et al., 2000). Sullivan et al. (2000) reported summary odd ratios (ORs) of 2.84 for adult MDD, while Rice et al. (2002) reported ORs of 1.70–3.98 for childhood MDD in affected families, with this range reflecting methodological variation between meta-analytic methods.

The present meta-analysis aims to quantify familial loading of affective disorders (MDD and BD) in association with diagnosis type and age-of-onset in FDRs. This meta-analysis examines the risk for MDD or BP in FDRs of probands with (i) both MDD and BD; (ii) only MDD; (iii) only BD; (iv) more than one proband with MDD or BD; and estimates (v) the risk for MDD or BD in FDRs of affected probands in relation to age of the FDR.

We hypothesized that (i) there would be greater risk of MDD and/or BD in FDRs of probands with *like* diagnoses (i.e., increased risk of MDD in families with MDD; increased risk of BD in families with BD); (ii) an increased risk of MDD and BD in FDRs of probands with *either* of these diagnoses (i.e., increased risk of MDD or BD in families with MDD and/or BD); and (iii) that the risk of developing either disorder for any FDR of any proband would decrease with increasing age, relative to the general population (or individuals with no family history of MDD or BD where possible).

2. Methods

2.1. Literature search

A systematic review of studies published between 1977 and July 2011 was conducted using the MEDLINE and EMBASE databases, and duplicate records removed. Keyword searches were: (depress* or major depressive disorder or major depression or unipolar or bipolar disorder or affective disorder or psychiatr* disorder or mental illness or mania or manic depression) AND (family history or famil* or herit* or inherit* or genet* or vulnerab* or susceptib*) AND (proband* or sibling* or mother or father or brother or sister or mat* or pat* or child* or FDR or first degree or second degree or relative) AND (risk or risk factor* or high risk or increased risk or at risk).

The search was updated in January 2012 to locate new studies published following the initial search. The reference lists of prior reviews of MDD and BD were hand-searched to identify any additional papers that were not retrieved in the electronic searches.

2.2. Selection of studies

Included studies: (i) were published in a peer-reviewed journal in English; (ii) reported systematic proband recruitment and ascertainment of relatives; (iii) were case-control (including family studies), cohort, cross-sectional or epidemiological studies of MDD and/or BD in FDRs or SDRs; (iv) reported a relative risk (RR) or OR, or one could be estimated from the data published; (v) made an explicit distinction between MDD and BD and use diagnostic criteria (such as DSM or ICD); and (vi) compared one of the outcomes of interest (incidence of MDD or BD in FDRs and/or SDRs of probands affected by MDD or BD) to *either* the population incidence rates (to allow the calculation of a recurrence risk ratio and associated standard error), *or*, in the case of family studies, the incidence rates in FDR and SDR of unaffected comparison subjects. Probands were parents and FDRs were first-degree relatives of probands.

We excluded: (i) twin and adoption studies, single case reports, letters, commentaries or conference abstracts; (ii) studies that did not report outcome of interest; (iii) studies that did not report separate data for MDD and BD; (iv) studies that were not case controlled; (v) studies that did not report data point estimates of the effect measure, or were reported without *p* values, CIs or raw data, from which the effect measure could be calculated; (vi) studies that reported earlier data from same sample cohort in follow-up studies that were included in the analysis; (vii) studies

that did not diagnose MDD or BD according to DSM or ICD criteria; and (viii) studies that did not derive data from direct interviews.

When multiple publications reported longitudinal results from the same population with the same study design, we used the most recent publication of that study. A single investigator (AW) inspected the search results and excluded articles that, on the basis of their title, were clearly not relevant. The same investigator inspected abstracts of the remaining studies and excluded articles where the abstract showed clearly that the article was not relevant. For the remaining articles, a final decision on inclusion or exclusion was made on the basis of the full text.

3. Data extraction

The decision to include or exclude studies, data extraction of both qualitative and quantitative information and quality assessment were completed by two independent investigators (AW and HNC). A third reviewer (BM) reviewed three papers that required consensus. The two investigators (AW and HNC) independently extracted the following qualitative items: general information (i.e. publication year and geographic area), population characteristics (i.e. population size and ethnic label), patient characteristics (i.e. number and mean age at diagnosis), and assessment method of family history (i.e. direct interview or questionnaire administered to relatives). For cohort studies we extracted RRs or hazard ratios (HRs) and, for case-control studies, ORs as the effect estimates.

4. Quality assessment

Study quality was assessed using the STROBE checklist, which outlines a preferred means of reporting observational studies (http://www.strobe-statement.org). Quality assessments and data extraction were completed independently by AW and HNC, who were not masked to study authors; any discrepancies were resolved through discussion until consensus was achieved. The following variables were extracted: Strobe reporting score (maximum 20); whether controls were matched; whether outcome assessors were blind; as well as data on reliability of raters, and validity of instruments.

5. Statistical analysis

All statistical analyses were carried out in STATA Version 12. We considered each family study as a two-by-two contingency table of relative diagnosis (MDD cases or non-cases) versus proband diagnosis (MDD or non-psychiatric control) with the odds ratio as a summary statistic, as detailed by Sullivan et al. (2000). Risk of an FDR developing an affective disorder is typically reported as ORs, RRs or sometimes HRs. ORs are considered to be a good estimate of RRs in most situations, unless the outcome is very infrequent. The effect estimates from individual studies were pooled using the inverse-variance weighted random effects methods described by DerSimonian and Laird (1986). Effect sizes are presented on a log scale. Between-studies heterogeneity was quantified with the I^2 statistic, which describes the proportion of total variation in study estimates due to heterogeneity (Higgins et al., 2003).

A meta-regression of the logs of the effect measures, weighted by the inverse of their variances, on the mean age of the FDR was undertaken to assess the possible impact of age on the effect measures. These regressions fitted a random effects model with two additive variance components (within and between studies). The influence of each study on the combined risk estimate was examined by consecutively omitting each study from the meta-analysis. Finally, we tested for possible publication bias using Begg's and Egger's tests and by visual inspection for asymmetry of funnel plots of the natural logarithms of the effect estimates against their standard errors (Egger et al., 1997; Begg and Mazumdar, 1994).

6. Subgroup analyses

Five separate meta-analyses were carried out. Quantitative data were extracted to calculate RRs in cohort studies or ORs in case-control studies, including the associated standard errors, to estimate the risk for MDD or BD for relatives associated with having: (i) one FDR with MDD or BD (two analyses); (ii) more than one FDR with MDD or BD (two analyses); and (iii) pooled data for FDRs and probands with either MDD or BD. Too few papers reported effect sizes for SDRs so this data was not analysed. The BD subgroup combined effect sizes for studies reporting BD diagnoses as BDI, BDII, 'BD forms' and 'manic disorder'. The sample did not include diagnoses of bipolar disorder not otherwise specified.

7. Results

7.1. Search results

The MEDLINE and EMBASE searches resulted in 241 records. Two additional reports were identified by hand search. After removal of 28 duplicates, 215 records remained. An initial screen of titles based on relevance, 140 records remained. On reading the abstract, 70 reports were excluded because they did not examine familial tendency of affective disorder compared to healthy controls. Of the remaining 70 studies screened in full, a further 45 were excluded because they did not meet inclusion criteria, and a further three were subsequently removed because they did not report clear outcome data (see Section 7.2 and Fig. 1).

7.2. Excluded studies

(i) Of the 48 studies excluded after full review, four were excluded on the grounds that they were review or twin studies (Brooks et al., 2003; Centers for Disease Control and Prevention, 2000; Kendler et al., 2009, 2001). (ii) A further nine studies did not report outcome of interest (Eley et al., 2004; Ferro et al., 2000; Grove et al., 1987; Marazita et al., 1997; Martinez-Devesa et al., 2010; McGuffin et al., 1988; Mojtabai, 2005; Murray et al., 2011; Tozzi et al., 2008). (iii) Eight studies did not provide separate data for MDD and BD or stratify proband and FDR data according to inclusion criteria (Beardslee et al., 1996; Brent et al., 2004; Chang et al., 2000; Dierker et al., 1999; Gershon, 1982; McMahon et al., 1995; Orvaschel, 1990; Singh et al., 2007).

(iv) Two studies did not compare incidence of MDD or BD in FDRs and/or SDRs of probands affected by MDD or BD to population incidence rates or controls (Hillegers et al., 2005; Schreier et al., 2006). (v) Forty-one publications did not report data point estimates of the effect measure, or were reported without p values, CIs or raw data, from which the effect measure could be calculated (Andreasen et al., 1987; Brent et al., 2004; Chang et al., 2000; Dienes et al., 2002; Dierker et al., 1999; Eley et al., 2004; Ferro et al., 2000; Gershon, 1982; Giovanni et al., 2010; Grigoroiu-Serbanescu et al., 1989; Grove et al., 1987; Hillegers et al., 2005; Kaufman et al., 1998; Kendler et al., 1997; Kessler et al., 1998; Lavori et al., 1987; Levinson et al., 2003; Li et al., 2008; Lieb et al., 2002; Marazita et al., 1997; Martinez-Devesa et al., 2007; McGuffin et al., 1988; McMahon et al., 1995; Merikangas et al., 1988; Mitchell et al., 1989; Moberg, 1991; Mojtabai, 2005; Murray et al., 2011;

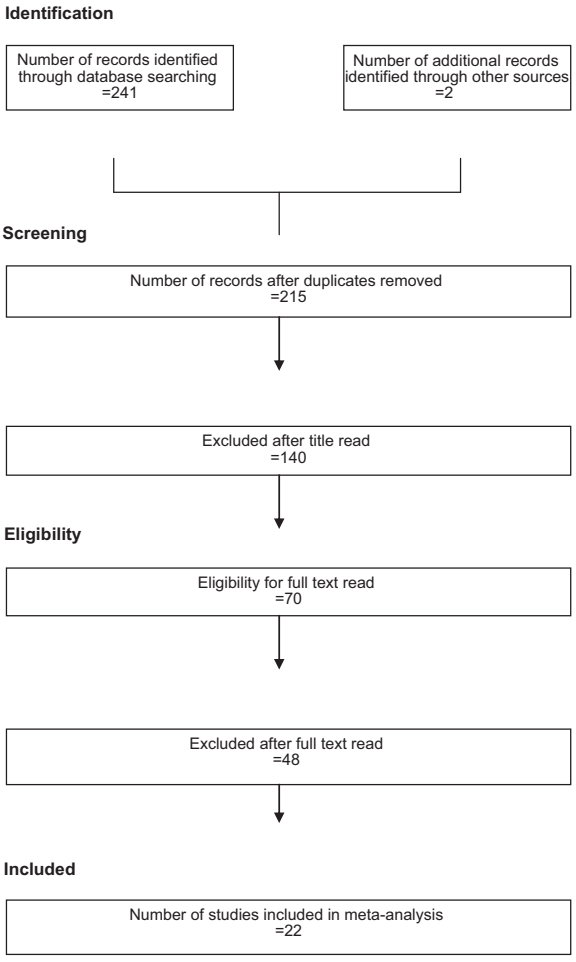

Fig. 1. Flow diagram showing the flow of information through the different phases of this review.

Olino et al., 2008; Orvaschel, 1990; Peterson et al., 1982; Ryan et al., 1992; Singh et al., 2007; Stevenson et al., 2010; Thorndike et al., 1996; Todd et al., 1994; Tozzi et al., 2008; Wals et al., 2003; Wals et al., 2004; Weissman et al., 1984a; Wickramaratne and Weissman, 1998). (vi) Wickramaratne and Weissman (1998) duplicated cases reported in two later studies, respectively (Beardslee et al., 1996; Wickramaratne et al., 2000), which were subsequently excluded because they did not report the outcomes of interest. A further two studies (Weissman et al., 1992, 1982) duplicated cases reported in longitudinal data published in a later study (Weissman et al., 2006); only the latter study was included in the meta-analysis. One other study was excluded (Nomura et al., 2002) because it duplicated data that was reported in a later study that was included in the meta analysis (Pilowsky et al., 2006). (vii) Two studies did not diagnose MDD or BD according to DSM or ICD criteria (Grove et al., 1987; Hammen et al., 1987). (viii) Finally, five studies were excluded because they did not derive diagnostic data from direct interviews with participants, (e.g. by using hospital clinical diagnoses (Hammen et al., 1987; Harrington et al., 1997; Henin et al., 2005; Mortensen et al., 2003; Olino et al., 2008). Data required for meta-analysis were extracted from the remaining 22 studies.

7.3. Included studies

Summary of the pooled sample of 10,859 FDRs of probands (median FDR sample was 494 individuals) is shown in Table 1.

Table 1
Summary of meta-analysis sample (some studies contribute to more than one subgroup).

Characteristics	*N*
Number of studies	22
Total sample size	10,859
Median sample size	494
Mean age at onset in FDR (SD)	13.7 (2.39)

All studies had a low probability of reporting bias as determined by the STROBE checklist, with a median STROBE score of 19. All studies reported proband/FDR data including 15 studies reporting effect sizes for the risk for MDD in FDRs of one proband with MDD (Hammen et al., 1990; Klein et al., 1985, 2005; Lewinsohn et al., 2000; Lieb et al., 2002; Maier et al., 1993; Marmorstein, 2011; Nomura et al., 2001; Reinherz et al., 2003; Todd et al., 1994; Tsuang et al., 1980; Warner et al., 1995; Warner et al., 1999; Weissman et al., 2006; Winokur et al., 1982). Four studies reported the risk for BD in FDRs of one proband with BD (Hirshfeld-Becker et al., 2006; Klein et al., 1985; Todd et al., 1996; Tsuang et al., 1980), five studies reported the risk for MDD in FDRs of two probands (parents) with MDD (Biederman et al., 2001; Lieb et al., 2002; Maier et al., 1993; Nomura et al., 2001; Pilowsky et al., 2006), and two studies reported the risk for BD in FDRs of two probands with BD, one involving two parents (Birmaher et al., 2009) and one a mixture of parents/siblings (Maier et al., 1993). The quality of included studies is summarised in Table 2.

Where possible, raw data were obtained from corresponding authors of individual studies to enable calculation of ORs and age of onset sub-analysis, where data were not published or could not be derived (10 studies in total) (Biederman et al., 2001; Birmaher et al., 2009; Lieb et al., 2002; Maier et al., 1993; Marmorstein et al., 2004; Nomura et al., 2002; Pilowsky et al., 2006; Reinherz et al., 2003; Tsuang et al., 1980; Weissman et al., 1984a). Age of onset was determined to be the age at which the studies stated that the individual first experienced symptoms of a disorder or age at first presentation. Characteristics of the 22 studies included in this main analysis are summarized in Table 3.

7.4. Meta-analyses for MDD or BD in FDRs of probands with either MDD or BP

The pooled OR estimates for MDD or BD in FDRs of either one or two probands with either MDD or BD were OR=2.59 (95% CI 2.09–3.21) (all studies). The pooled OR estimate for FDRs of one proband with either BD or MDD was 2.25 (95% CI 1.80–2.80), (15 studies (Hammen et al., 1990; Hirshfeld-Becker et al., 2006; Klein et al., 1985, 2005; Lewinsohn et al., 2000; Lieb et al., 2002; Marmorstein et al., 2004; Nomura et al., 2001; Reinherz et al., 2003; Todd et al., 1996; Tsuang et al., 1980; Warner et al., 1995, 1999; Weissman et al., 2006; Winokur et al., 1982) increasing to 4.10 (95% CI 2.56–6.57) for two probands with either diagnosis, six studies (Biederman et al., 2001; Birmaher et al., 2009; Lieb et al., 2002; Maier et al., 1993; Nomura et al., 2001; Pilowsky et al., 2006).

7.5. Meta-analysis by diagnosis and number of affected probands

For FDRs of one proband with MDD compared to healthy control probands, pooled estimates for MDD were OR=2.14 (95% CI 1.72–2.67) compared to FDRs of healthy control probands from 13 studies (Hammen et al., 1990; Klein et al., 2005; Lewinsohn et al., 2000; Lieb et al., 2002; Marmorstein et al., 2004; Nomura et al., 2001; Reinherz et al., 2003; Todd et al., 1996; Tsuang et al., 1980; Warner et al., 1995; Warner et al., 1999; Weissman et al.,

Table 2
Quality of studies included in the meta-analysis.

Paper	Year	Strobe score	Kappa	Alpha	Agreement %	Not reported	Controls matched	Outcome assessors blind	Validity of instruments
Biederman (Biederman et al., 2001)	2001	19	0.86	–	–	–	No	Yes	Yes
Birmaher (Birmaher et al., 2009)	2009	21	0.8–0.9	–	–	–	Yes	Yes	Yes
Birmaher (Birmaher et al., 2009)	2009	21	0.8–0.9	–	–	–	Yes	Yes	Yes
Hammen (Hammen et al., 1990)	1990	16	0.84	–	–	–	No	Yes	Yes
Hammen (Hammen et al., 1990)	1990	16	0.84	–	–	–	No	Yes	Yes
Hirsfield-Becker (Hirshfeld-Becker et al., 2006)	2006	20	0.86	–	–	–	No	Yes	Yes
Hirsfield-Becker (Hirshfeld-Becker et al., 2006)	2006	20	0.86	–	–	–	No	Yes	Yes
Klein (Klein et al., 1985)	1985	18	0.86	–	–	–	No	Yes	Yes
Klein (Klein et al., 1985)	1985	18	0.86	–	–	–	No	Yes	Yes
Klein (Klein et al., 2005)	2005	21	0.86	–	–	–	N/A	No	Yes
Klein (Klein et al., 2005)	2005	21	0.86	–	–	–	N/A	No	Yes
Lewinsohn (Lewinsohn et al., 2000)	2000	19	0.86	–	–	–	No	Yes	Yes
Lieb (Lieb et al., 2002)	2002	20	–	–	–	Not reported	No	Yes	Yes
Lieb (Lieb et al., 2002)	2002	20	–	–	–	Not reported	No	Yes	Yes
Lieb (Lieb et al., 2002)	2002	20	–	–	–	Not reported	No	Yes	Yes
Lieb (Lieb et al., 2002)	2002	20	–	–	–	Not reported	No	Yes	Yes
Lieb (Lieb et al., 2002)	2002	20	–	–	–	Not reported	No	Yes	Yes
Lieb (Lieb et al., 2002)	2002	20	–	–	–	Not reported	No	Yes	Yes
Maier (Maier et al., 1993)	1993	20	–	> 0.8	–	–	Yes	Yes	> 80
Maier (Maier et al., 1993)	1993	20	–	> 0.8	–	–	Yes	Yes	> 80
Maier (Maier et al., 1993)	1993	20	–	> 0.8	–	–	Yes	Yes	> 80
Maier (Maier et al., 1993)	1993	20	–	> 0.8	–	–	Yes	Yes	> 80
Marmorstein (Marmorstein, 2011)	2004	18	0.75–0.95	–	–	–	No	Not reported	Yes
Nomura (Nomura et al., 2001)	2001	19	–	–	–	Not reported	No	Yes	Yes
Pilowsky (Pilowsky et al., 2006)	2006	19	–	–	–	Not reported	No	Yes	Yes
Reinherz (Reinherz et al., 2003)	2003	19	–	–	98–99%	–	N/A	Not reported	Yes
Todd (Todd et al., 1996)	1996	19	–	–	–	Not reported	N/A	Yes	Yes
Tsuang (Tsuang and VanderMey, 1980)	1980	18	–	–	–	Not reported	Yes	Yes	Reported
Warner (Warner et al., 1999)	1999	21	–	–	–	Not reported	N/A	Yes	Yes
Warner (Warner et al., 1995, 1999) (recurrent)	1995	19	0.85	–	–		N/A	Yes	Yes
Weissman (Weissman et al., 2006)	2006	20	0.82	–	–	–	No	Yes	Yes
Winokur (Winokur et al., 1982)	1982	16	–	–	–	Not reported	Not reported	Not reported	DSMII

Table 3
Summary of studies included in the meta-analysis.

Paper	*Year*	*Outcome*	*Exposure type*	*Probands affected (N)*	*Exposed cases*[a]	*Exposed non-cases*[b]	*Non-exposed cases*[c]	*Non-exposed non-cases*[d]	*Effect size*	*CI (ll)*	*CI (ul)*	*Age of onset in FDR*
Biederman (Biederman et al., 2001)	2001	MDD	MDD	2					9.0	1.9	4.3	–
Birmaher (Birmaher et al., 2009)	2009	BD	BD	2	41	347	2	249	13.4	2.9	61.6	–
Birmaher (Birmaher et al., 2009)	2009	MDD	BD	2	5	383	1	250	2.1	0.9	4.9	–
Hammen (Hammen et al., 1990)	1990	MDD	MDD	1	10	11	4	34	7.7	1.7	39.2	13.0
Hammen (Hammen et al., 1990)	1990	MDD	BD	1	1	21	0	38	–	–	–	11.1
Hirsfield-Becker (Hirshfeld-Becker et al., 2006)	2006	MDD	BD	1	3	31	2	93	–	–	–	–
Hirsfield-Becker (Hirshfeld-Becker et al., 2006)	2006	BD	BD	1	3	31	0	95	–	–	–	–
Klein (Klein et al., 1985)	1985	BD	BD	1	10	27	0	21	–	–	–	–
Klein (Klein et al., 2005)	2005	MDD	MDD (maternal)	1	–	–	–	–	1.5	1.2	2.0	–
Klein (Klein et al., 2005)	2005	MDD	MDD (paternal)	1	–	–	–	–	1.1	0.8	1.6	–
Lewinsohn (Lewinsohn et al., 2000)	2000	MDD	MDD	1	–	–	–	–	3.6	1.5	8.6	–
Lieb (Lieb et al., 2002)	2002	MDD	MDD	1	–	–	–	–	2.5	1.9	3.2	–
Lieb (Lieb et al., 2002)	2002	BD 1	MDD	1	–	–	–	–	3.2	1.4	7.1	–
Lieb (Lieb et al., 2002)	2002	BD 2	MDD	1	–	–	–	–	1.7	0.3	7.7	–
Lieb (Lieb et al., 2002)	2002	MDD	MDD	2	–	–	–	–	2.8	2.0	3.9	–
Lieb (Lieb et al., 2002)	2002	BD 1	MDD	2	–	–	–	–	5.7	2.6	12.8	–
Lieb (Lieb et al., 2002)	2002	BD 2	MDD	2	–	–	–	–	8.6	1.9	38.0	–
Maier (Maier et al., 1993)	1993	MDD	MDD	2	21	178	7	117	–	–	–	–
Maier (Maier et al., 1993)	1993	BD	BD	2	5	123	1	123	–	–	–	–
Maier (Maier et al., 1993)	1993	MDD	BD	2	12	116	7	117	–	–	–	–
Maier (Maier et al., 1993)	1993	BD	MDD	2	3	196	1	123	–	–	–	–
Marmorstein (Marmorstein, 2011)	2004	MDD	MDD	1	–	–	–	–	2.5	1.7	3.6	15.7
Nomura (mother only) (Nomura et al., 2001)	2001	MDD	MDD	1	–	–	–	–	3.4	1.3	8.3	17.9
Nomura (father only)	2001	MDD	MDD	1	–	–	–	–	2.2	0.7	6.2	15.2
Nomura (both probands) (Nomura et al., 2001)	2001	MDD	MDD	2	–	–	–	–	6.6	1.9	25.0	–
Pilowsky (Pilowsky et al., 2006)	2006	MDD	MDD	2	–	–	–	–	6.0	0.7	50.7	–
Reinherz (Reinherz et al., 2003)	2003	MDD	MDD	1	–	–	–	–	1.8	1.0	3.4	–
Todd (Todd et al., 1996)	1996	BD I	BD	1	3	11	1	26	–	–	–	11.0
Todd (Todd et al., 1996)	1996	BD II	BD	1	1	13	1	26	–	–	–	–
Todd (Todd et al., 1996)	1996	MDD	BD I	1	2	12	1	26	–	–	–	–
Todd (Todd et al., 1996)	1996	BD I	BD	1	0	2	0	27	–	–	–	–
Todd (Todd et al., 1996)	1996	BD II	BD	1	0	2	0	27	–	–	–	–
Todd (Todd et al., 1996)	1996	MDD	BD II	1	0	2	0	27	–	–	–	–
Todd (Todd et al., 1996)	1996	BD I	MDD	1	1	6	2	25	–	–	–	–
Todd (Todd et al., 1996)	1996	BD II	MDD	1	0	7	2	25	–	–	–	–
Todd (Todd et al., 1996)	1996	MDD	MDD	1	1	6	2	25	–	–	–	–
Tsuang (Tsuang et al., 1980)	1980	MDD	MDD	1	41	426	25	516	–	–	–	–
Tsuang (Tsuang et al., 1980)	1980	MDD	BD	1	18	198	25	516	–	–	–	–
Tsuang (Tsuang et al., 1980)	1980	BD	MDD	1	3	464	1	540	–	–	–	–
Tsuang (Tsuang et al., 1980)	1980	BD	BD	1	3	213	1	540	–	–	–	–
Warner (Warner et al., 1999)	1999	MDD	MDD	1	–	–	–	–	0.9	0.1	5.4	–
Warner (recurrent) (Warner et al., 1995)	1995	MDD	MDD	1	–	–	–	–	3.0	0.9	9.7	12.9
Warner (non-recurrent) (Warner et al., 1995)	1995	MDD	MDD	1	–	–	–	–	1.8	0.4	8.2	12.9
Weissman (Weissman et al., 2006)	2006	MDD	MDD	1	–	–	–	–	3.3	2.0	5.6	–
Winokur (Winokur et al., 1982)	1982	MDD	MDD	1	34	382	25	516	–	–	–	–
Winokur (Winokur et al., 1982)	1982	BD	MDD	1	25	242	25	516	–	–	–	–

[a] Number of offspring/FDRs with MDD or BP (case) with affected proband/parent (exposure).
[b] Number of offspring/FDR without MDD or BP (control) with affected proband/parent (exposure).
[c] Number of offspring/FDR with MDD or BP (case) with unaffected proband/parent (control).
[d] Number of offspring/FDR without MDD or BP (control) with unaffected proband/parent (control). CI (ll) = confidence interval lower limit. CI (ul) = confidence interval upper limit.

Table 4
Summary of effect sizes by number of probands (some studies contribute to both subgroups and separate data within subgroups).

Diagnosis in first degree relatives	Diagnosis in affected probands (probands, siblings)					
	Pooled MDD* and BD**		MDD*		BD**	
	OR	95% CI	OR	95% CI	OR	95% CI
Pooled MDD* and BD**	2.59[a]	2.09–3.21				
1 Proband	2.25[b]	1.80–2.80				
2 Probands	4.10[c]	2.56–6.57				
MDD*						
1 Proband			2.14[d]	1.72–2.67		
2 Probands			3.23[e]	2.11–4.94		
BD						
1 Proband					7.92[f]	2.45–25.61
2 Probands					6.58[g]	2.64–16.43
Pooled probands						
MDD					2.48[h]	1.56–3.99
BD			3.42[i]	2.22–5.25		

* Major depressive disorder or unipolar depression.
** Bipolar disorder 1 or 2, 'bipolar forms' or 'manic disorder'.
[a] 22 Studies.
[b] 15 Studies.
[c] 6 Studies.
[d] 13 Studies.
[e] 5 Studies.
[f] 4 Studies.
[g] 2 Studies.
[h] 6 Studies.
[i] 5 Studies.

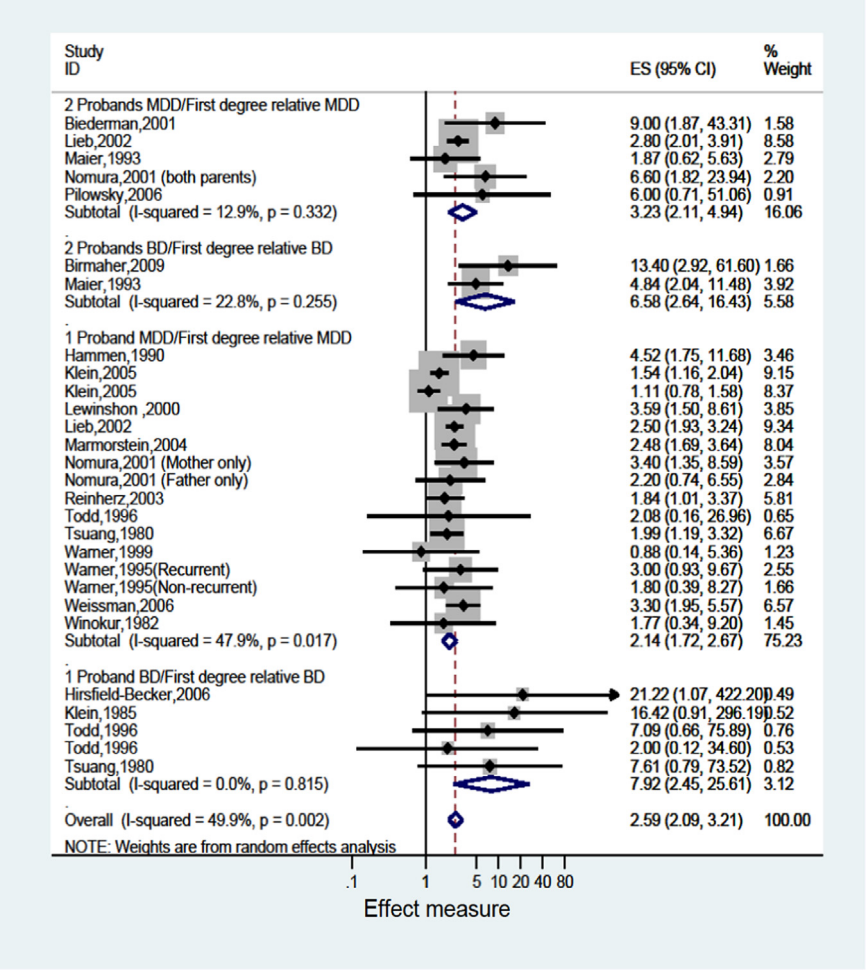

Fig. 2. Forest plot for all studies using a random effects model.

2006; Winokur et al., 1982). The effect size increased to OR=3.23 (95% CI 2.11–4.94) for two MDD probands with data from five studies (Biederman et al., 2001; Lieb et al., 2002; Maier et al., 1993; Nomura et al., 2001; Pilowsky et al., 2006). For FDRs of one BD proband compared to FDRs of healthy control probands, BD estimates were OR=7.92 (95% CI 2.45–25.61): four studies (Hirshfeld-Becker et al., 2006; Klein et al., 1985; Todd et al., 1996; Tsuang et al., 1980) and OR=6.58 (95% CI 2.64–16.43) for FDRs of two BD probands from two studies (Birmaher et al., 2009; Maier et al., 1993). Sensitivity analysis showed these results were not significantly influenced by any single study. Publication bias was not evident. Effect sizes by number of probands are summarised in Table 4. Fig. 2 shows a forest plot of effect sizes by number of probands and diagnosis.

7.6. Meta-analyses for MDD in FDRs of probands with BD

The pooled OR estimates for MDD in FDRs of at least one proband with BD were approximately two and a half-fold (OR=2.49, 95% CI 1.56–3.99) compared to FDRs of healthy control probands as seen in six studies (Birmaher et al., 2009; Hammen et al., 1990; Hirshfeld-Becker et al., 2006; Maier et al., 1993; Todd et al., 1996; Tsuang et al., 1980).

7.7. Meta-analyses for BD in FDRs of probands with MDD

The pooled OR estimates for BD in FDRs of probands with MDD were approximately three-and-a-half fold (OR=3.42, 95% CI 2.22–5.25) compared to FDRs of healthy control probands in three studies (Lieb et al., 2002; Maier et al., 1993; Todd et al., 1996).

7.8. Meta-regression on effect of age of onset

The mean (SD) age at onset of MDD in FDRs of affected probands from five studies (Hammen et al., 1990; Marmorstein et al., 2004; Nomura et al., 2001; Todd et al., 1996; Warner et al., 1995) was 12.3 (2.4) years. Only one study (Hammen et al., 1990) reported age of onset for BD (11.0 years). A meta-regression showed no significant effect of increasing age on the likelihood of FDRs developing MDD or BD ($\beta = -0.08$, 95% CI 0.25–0.07).

8. Discussion

This is the first meta-analysis investigating familial loading for BD, and the first meta-analysis of shared genetic vulnerability for MDD and BD, and risk of MDD in more than one proband. The present meta-analysis includes data from 22 case-control and cohort studies, which investigated odds of MDD or BD in 10,859 relatives of probands with diagnoses of MDD or BD.

8.1. Meta-analyses for all FDRs and probands with MDD or BD

The pooled meta-analysis revealed good quality statistically significant evidence of increased odds of any affective disorder (MDD or BD) in FDRs of probands with any affective disorder (MDD or BD) compared to controls (FDRs of probands without an affective disorder). Analysis with diagnoses reversed (MDD probands/BD FDRs and vice versa) yielded a similar outcome consistent with our first and second hypotheses.

8.2. Meta-analysis by MDD diagnosis in FDRs with one affected proband

The sub-analysis revealed increased familial risk of MDD approximately two-fold amongst FDRs of one proband with MDD compared to controls. This OR is lower than that reported in Sullivan et al. (2000), which reported summary ORs of 2.84 for MDD in adults of one proband with MDD compared to normal controls. However Sullivan et al. included a total of five studies only, while the present meta-analysis included 13 studies to estimate MDD risk in FDRs of one proband with MDD. Rice et al. (2002) reported an even higher effect size for 'high-risk' FDRs (FDRs of MDD probands, mainly depressed mothers) and 'low-risk' controls (FDRs of never psychiatrically ill probands). They found that high-risk FDRs of one affected proband had an approximately three-fold increased risk of developing first-onset MDD compared to low-risk FDRs (OR=3.21) (Rice et al., 2002).

While the present and the Rice et al. (2002) meta-analyses followed the methodology of Sullivan et al. (2000), there are some fundamental differences in the included studies between the meta-analyses. Almost all participants in the studies included in Rice et al. (2002) and Sullivan et al. (2000) meta-analyses were recruited from clinical sources, while the majority of participants in the studies included in the present meta-analysis were recruited from community sources. Recruitment from clinical settings may potentially increase the OR due to increased likelihood of referral due to familial MDD.

ORs reported by Sullivan et al. (2000) reflect MDD familial risk in adult FDRs of MDD probands, whilst those of Rice et al. (2002) reflect MDD familial risk amongst child FDRs of MDD probands. The present meta-analysis did not include age of FDRs as part of the inclusion criteria and includes data for both child and adult FDRs. These differences suggest that the magnitude of familial risk for MDD, as shown by meta-analysis, varies between children/adolescents and adults, and it could be that effect sizes for familial MDD risk in children and young people reflect a higher familial loading compared to adults. This would be consistent with the view that, with increasing age, the risk of developing MDD as a result of significant, stressful life events interacting with (perhaps modest) genetic risk, also increases.

8.3. Meta-analysis by MDD diagnosis in FDRs with two affected probands

Few family studies involving two probands diagnosed with MDD have been subject to meta-analysis. The present study found that the magnitude of familial risk of MDD increased approximately three-fold (OR=3.23, 95% CI 2.11–4.94) in FDRs with two probands affected by MDD compared to controls. Two of the five included studies reported ORs of more than six (Nomura et al., 2001; Pilowsky et al., 2006), and one more than nine (Biederman et al., 2001). However, the Begg's and Egger's tests did not show undue influence of these studies on the combined risk estimate. The findings of the present sub-analysis support a prospective longitudinal study of adolescent and young adults with two MMD affected probands, which yielded an OR of 3.00 compared to normal controls (Lieb et al., 2002).

The sensitivity analysis conducted on the present study did not find between-study heterogeneity, which suggests that the findings are comparable to Sullivan et al. (2000), and other meta-analyses using the same robust methodological approach.

8.4. Meta-analysis by BD diagnosis in FDRs with one or two affected probands

Family studies reported effect sizes for BD in FDRs of BD probands have not been subject to meta-analysis. Family studies have consistently shown increased risks for BD among FDRs of affected probands in comparison to control groups, with higher ORs for individuals with two affected probands (Birmaher et al., 2009). The present sub-analysis found an almost eight-fold

increased risk of BD in FDRs of one proband with BD compared to controls (OR=7.92, 95% CI 2.45–25.61). The effect size did not increase for BD in FDRs of two BD probands (OR=6.58, 95% CI 2.64–16.43), compared to healthy controls.

Only two studies met the inclusion criteria of the sub-analysis of BP for FDRs with more than one BD proband, which may explain the lower than expected effect size due to two BD probands. The two included studies reported ORs of 13.4 (95% CI 2.90–61.69) (Birmaher et al., 2009), and 4.84 (95% CI 2.04–11.48) (Maier et al., 1993). A large population-based cohort study that reported effect sizes for familial loading of BD due to two BD probands, reported an OR of 13.63 (95% CI 11.81–15.71) (Mortensen et al., 2003). This study was excluded from the meta-analysis because it did not differentiate between parent and sibling probands and did not undertake direct interviews with relatives. The small sample of the two BP proband analysis limits comparison. However, the finding supports a significant familial loading for BD, and that the familial loading for BD is higher than for MDD.

8.5. Meta-analyses for MDD in FDRs of probands with BD and vice versa

The sub-analysis showed evidence for increased liability of MDD in individuals with at least one proband with BD and of BD in individuals with at least one proband with MDD. These findings support a previous meta-analysis and review paper that found evidence for the contribution of proband BD to any FDR psychopathology (Lapalme et al., 1997). Lapalme et al. (1997) reported that FDRs of probands with BD were 2.7 times more likely to develop any mental disorder and four times more likely to develop an affective disorder, compared to children of probands with no psychiatric disorder (Lapalme et al., 1997). Delbello and Geller (2001) found increased rates of affective disorders in child and adolescent FDRs of probands with BD, compared to normal controls (5–67% versus 0–38%). These findings show clear evidence of increased risk of psychopathology, especially for affective disorders, in BD families. The evidence suggests genetic counselling and provision of genetic risk estimates to individuals with familial loading should include estimates of risk for affective disorders beyond the proband diagnosis. This is especially relevant in cases where individuals initially diagnosed with MDD may subsequently be diagnosed with BD (Smith and Blackwood, 2004).

8.6. Meta-regression on effect of age of onset

The analysis of age-of-onset of MDD or BD in adolescent FDRs of affected probands was non-significant, contrary to our third hypothesis. Previous studies have shown that age-of-onset of affective disorders varies with familial loading (Lieb et al., 2002; Weissman et al., 1984b). Familial loading has been shown to significantly increase likelihood of an earlier age-of-onset of MDD, compared to controls, with a larger association in cases where MDD develops prior to the age of 20 years (Tozzi et al., 2008). A prospective longitudinal study showed that MDD among FDRs of probands with MDD was associated with an earlier onset and a more severe course of illness compared to FDRs without an affected proband, and reported that MDD occurred even earlier in FDRs with two affected probands (Lieb et al., 2002). Schreier et al. (2006) did not demonstrate familial aggregation of earlier onset of MDD when using age-of-onset cut-off of 15 years in offspring and 30 years in probands, respectively. They suggest that age-of-onset might be less important in familial aggregation of MDD than previously assumed (Schreier et al., 2006). A limitation to the current meta-analysis is the variation in cut-off points used to define the age of early-onset of MDD between and within studies.

In addition, Weissman et al. (1984b) noted that studies demonstrating an association between age-at-onset of MDD and increased familial loading lacked direct assessment of FDRs' diagnosis or did not use retrospective information to assess age at onset in adults. The present meta-analysis attempted to overcome this limitation by restricting included studies to those that undertook direct interviews with probands and FDRs and which based diagnoses on operational criteria. Conversely, early age-of-onset of MDD in adult probands has been reported to be related to earlier age at onset of MDD among FDRs (Weissman et al., 1984b). The present study did not perform this sub-analysis due to lack of availability of bi-generational age-of-onset data in the included studies. Further meta-analysis is required to systematically analyze age-of-onset data for affective disorders matched in both probands and FDRs.

8.7. Familial loading: genetic factors and shared environments

Familial loading provides evidence for increased liability of affective disorders in FDRs. A review of twin and adoption studies is consistent with substantial genetic factors in familial transmission, showing high concordance rates in diagnoses between relatives even when shared familial environments were taken into account (Sullivan et al., 2000). As concordance rates between monozygotic twins for MDD and BD are not 100%, some of the contribution to effect sizes seen in family studies may be due to shared family environment and interaction with familial loading (Finn, 2007).

The present meta-analysis confirms the consistently reported familial liability for MDD and BD with a higher magnitude of risk for individuals with more than one affected proband with either MDD or BD. Comparisons with previously reported effect sizes can be made, but factors that underlie differences in effect sizes between meta-analyses as outlined here should be noted. Understanding how genotype interacts with environmental triggers in the development of psychiatric disorders presents an opportunity to improve accuracy of risk assessment and selectively target genetically vulnerable individuals for preventive interventions.

Strengths of the present study include the requirement for operational diagnostic criteria for outcome measures to minimise effect size variability due to measurement differences with other meta-analyses. There was little evidence of heterogeneity, impact of study quality, study selection bias or publication bias on the results. The inclusion of studies that used the same sample cohort as part of separate analyses may have increased the possibility of effect sizes being weighted by the specifics of a single study. However sensitivity analysis showed the results were not significantly influenced by any single study. Due to the limited availability of studies reporting effect sizes for SDRs, data for SDRs were not included in the analysis. Investigation into the contribution of SDRs to familial loading of affective disorders warrants further investigation.

9. Conclusions

The present meta-analysis confirms that elevated family loading remains the best predictive risk factor for MDD and BD (Birmaher et al., 2009). It updates the previous reports of Sullivan et al. (2000) and Rice et al. (2002) from five to 22 studies and the sample from which estimates were obtained to 10,859 individuals. Furthermore, the present study suggests that ORs for familial risk of MDD and BD should be interpreted with caution given that the ORs may be derived from child FDRs, adult FDRs or both with associated variation in magnitude of familial loading. The development of a vulnerability index tailored to family history of affective disorders would thus require the capacity to account

for differential contributions to risk from multiple family members, with respect to their specific relationship to the individual whose risk is being estimated. Such a tool could enable the triage of individuals in primary care who may benefit the most from preventive intervention. These interventions should target individuals at elevated risk due to a family history of affective disorders and should be offered with counseling and education about the contribution of genetic factors, familial factors (e.g. childhood environment), environmental factors (e.g. chronic stress) to vulnerability to affective disorders and the interaction of genetic and environmental risk factors.

Role of funding source

This research was supported by the National Health and Medical Research Council (Program grant 1037196) and the Australian Research Council (FT0991511). These sponsors had no further role in the development of ideas conveyed in the manuscript, the writing of the paper, or in the decision to submit the paper for publication.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

This project was supported by research funding from the Australian National Health and Medical Research Council (NHMRC) Program grant no. 1037196 and the University of New South Wales. BM was supported by an NHMRC Career Development Award, Level 2 (1003921). MJG was supported by a Future Fellowship (FT0991511) from the Australian Research Council (2009–13) and an NHMRC R.D. Wright Biomedical Research Fellowship (2014–17). We thank the following authors who generously provided raw data for inclusion in the meta-analysis: Professor Roselind Lieb, Universitat Basel, Switzerland; Professor Wolfgang Maier, University of Bonn, Germany; A/Professor Naomi Marmorstein, Rutgers University, US; Assistant Professor Yoko Nomura, Queens College, US; Assistant Professor Daniel Pilowsky, Columbia University, US; Professor Helen Reinherz, Simmons College, US; Professor Ming Tsuang, University of California, US and Professor Myrna Weissman, Columbia University, US.

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