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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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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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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