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# Comorbidity and patterns of familial aggregation in attention-deficit/hyperactivity disorder and bipolar disorder in a family study of affective and anxiety spectrum disorders

Rachel F.L. Walsh [a,*], Brooke Sheppard [a,b], Lihong Cui [a], Cortlyn Brown [a], Anna Van Meter [a,c], Kathleen R. Merikangas [a]

[a] Genetic Epidemiology Research Branch, National Institute of Mental Health, Intramural Research Program, Building 35A, Room 2E410, MSC 3720, Bethesda, MD, 20892, USA
[b] Department of Epidemiology, Johns Hopkins' Bloomberg School of Public Health, 615 North Wolfe Street, W6508, Baltimore, MD, 21205, USA
[c] The Feinstein Institutes for Medical Research, The Zucker Hillside Hospital, Division of Psychiatry Research, 350 Community Dr, Manhasset, NY, 11030, USA

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ABSTRACT

The aim of this study is to examine the familial aggregation of Attention-deficit/hyperactivity disorder (ADHD) and its cross-transmission with bipolar disorder (BD) in a community-based family study of mood spectrum disorders. A clinically-enriched community sample of 562 probands recruited from the greater Washington, DC metropolitan area and their 698 directly interviewed relatives were included in analyses. Inclusion criteria were English speaking and consent to contact at least two first-degree relatives. Standard family study methodology was used and DSM-IV classified mental disorders were ascertained through a best-estimate procedure based on direct semi-structured interviews and multiple family history reports. There was specificity of familial aggregation of both bipolar I disorder (BD I) and bipolar II disorder (BD II) (i.e., BD I OR = 6.08 [1.66, 22.3]; BD II OR = 2.98 [1.11, 7.96]) and ADHD (ADHD OR = 2.13 [1.16, 3.95]). However, there was no evidence for cross-transmission of BD and ADHD in first degree relatives (i.e., did not observe increased rates of BD in relatives of those with ADHD and vice versa; all *ps* > 0.05). The specificity of familial aggregation of ADHD and BD alongside the absence of shared familial risk are consistent with the notion that the comorbidity between ADHD and BD may be attributable to diagnostic artifact, could represent a distinct BD suptype characterized by childhood-onset symptoms, or the possibility that attention problems serve as a precursor or consequence of BD.

## 1. Introduction

Comorbidity between attention-deficit hyperactivity disorder (ADHD) and major mood disorders, such as major depressive disorder (MDD) and bipolar disorder (BD), has been well-established in both clinical and community-based studies of adults and children (Angold et al., 1999; Blackman et al., 2005; Kalaydjian and Merikangas, 2008; Karaahmet et al., 2013; Klassen et al., 2010; Larson et al., 2011; Ostrander et al., 2006). In clinical samples, rates of ADHD among adults with BD range from 9.5 to 30% (Bernardi et al., 2010; Karaahmet et al., 2013; McIntyre et al., 2010; Nierenberg et al., 2005; Perroud et al., 2014; Perugi et al., 2013; Rydén et al., 2009; Sentissi et al., 2008; Tamam et al., 2008; Wingo and Ghaemi, 2007), and rates of BD range from 5 to 47% among adults with ADHD (Faraone, 2006; McGough et al., 2005; Wilens et al., 2009; Wingo and Ghaemi, 2007). Strong associations between ADHD and BD in community samples of adults (Bernardi et al., 2012; Kessler et al., 2006; Merikangas et al., 2011, 2010) suggest that this comorbidity is not merely an artifact of the increased severity that characterizes clinical samples (Berkson, 2014; Merikangas et al., 2009). Investigation of potential explanations for ADHD-BD comorbidity has etiologic and clinical importance because comorbidity is associated with greater severity and impairment of most mental disorders (Merikangas et al., 2007).

Prospective cohort studies and family studies (Holtmann et al., 2008; Kowatch et al., 2005; West et al., 2008) have shown that BD-ADHD comorbidity may reflect a common underlying diathesis of genetic (Larsson et al., 2013; van Hulzen et al., 2017), biologic (Carlson, 1998; Holtmann et al., 2008; Kowatch et al., 2005; West et al., 2008;

* Corresponding author.
*E-mail addresses:* rachel_walsh@temple.edu (R.F.L. Walsh), merikank@mail.nih.gov (K.R. Merikangas).

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Youngstrom et al., 2010), prenatal, or early environmental (MacKinnon et al., 2018) risk factors. For example, low birth weight has been indicated as a non-specific risk factor for both conditions (Hack et al., 2004) and genome-wide association studies have identified five loci associated with both BD and ADHD (O'Connell et al., 2019). Alternatively, other research has suggested that the link between ADHD and BD could result from causal mechanisms wherein the presence of ADHD elevates the risk of development of BD, or vice versa. It is also possible this comorbidity is reflective of nosologic overlap between symptoms (e.g., impulsivity, distractibility, increased activity) of ADHD and BD (Algorta et al., 2011; Brus et al., 2014). This overlap has led to diagnostic challenges that may complicate the distinction between these two conditions. For example, attributing overlapping symptoms to one disorder may increase diagnostic specificity of BD but the inclusion of these overlapping symptoms as criteria for both disorders may lead to misclassification of one or both conditions (Goldstein and Birmaher, 2012).

Family-based study designs provide a powerful approach to discriminate between common diathesis versus causal explanations for the association between ADHD and BD (Merikangas et al., 2014). Prior work has demonstrated that ADHD, BD, and MDD each independently exhibit strong familial aggregation (Bernardi et al., 2012; Chen et al., 2017; Vandeleur et al., 2014; Wozniak et al., 2010). Heritability estimates of ADHD and BD exceed 60% (Barnett and Smoller, 2009; Craddock and Sklar, 2013; Epstein et al., 2000; Faraone et al., 2000, 1994; 1991; McGuffin et al., 2003; Song et al., 2015), while MDD estimates are slightly lower, hovering around 40% (Kendler et al., 2006; Sullivan et al., 2000; Weissman et al., 1993). Investigating patterns of coaggregation (or cross-transmission) of two disorders can be used to distinguish between common etiologic and "causal" explanations for their association (Sullivan et al., 2000). For example, if ADHD and bipolar disorder share underlying risk factors, there should be increased rates of ADHD in the families of individuals with bipolar disorder and vice versa (Faraone et al., 2012). In contrast, if comorbidity is not attributable to common underlying risk factors, the two conditions should aggregate independently in families.

The results of prior family studies examining the cooccurrence of ADHD and BD have not yielded consistent results (Faraone et al., 2012; Wozniak et al., 2010). Whereas some studies have supported independence of familial transmission of ADHD and BD, a recent meta-analysis found that there is increased risk of ADHD (RR = 2.6) in relatives of probands with BD and increased risk of BD among relatives of probands with ADHD (RR = 1.8; Faraone et al., 2012). Similarly, a population-based study of treatment-seeking individuals in Taiwan found coaggregation of BD and ADHD (Chen et al., 2019). However, many of the extant studies that are based on child participants may have underestimated rates of ADHD in adult relatives given that adult ADHD was historically overlooked as an impairing condition and the substantial occupational and functional consequences of ADHD in adulthood have recently been recognized (Chung et al., 2019; Katzman et al., 2017). Furthermore, there is limited research on patterns of familial aggregation based on family studies of adult probands with the full range of mood disorder subtypes and systematic diagnostic assessment of ADHD.

The goal of the present study is to examine the prevalence and familial transmission of ADHD in a large community-based family study of adults with mood spectrum disorders. Specifically, we seek to 1) estimate the prevalence of ADHD among people with BD (BD I, BD II) in a non-clinical sample; 2) to examine the familial aggregation of ADHD and BD; and 3) to evaluate the familial coaggregation of ADHD with BD; 4) to determine whether any familial associations were specific to BD or if ADHD co-aggregates across the spectrum of mood disorders (BD I, BD II, MDD).

## 2. Methods

### 2.1. Participants

The sample consists of 562 probands and 698 of their directly-interviewed first-degree adult relatives from the National Institute of Mental Health's Family Study of Affective Spectrum Disorders, an ongoing community-based family study examining the full range of mood and anxiety disorders (Merikangas et al., 2014). The probands were recruited through a community screen of the Washington, D.C. metropolitan area, referrals from the National Institutes of Health Clinical Center general volunteer core, and advertisements in local newspapers. To increase the number of participants with mood disorders, participants were also recruited from the NIMH Mood and Anxiety Disorder Program. Participation criteria included ability to speak English and permission to contact at least two first-degree relatives to participate in the study. Additional details regarding the recruitment procedures and sample characteristics for the NIMH Family Study are described elsewhere (Merikangas et al., 2014).

### 2.2. Procedures

Standard family study methodology was employed including direct interviews of probands and relatives by experienced clinicians, systematic enumeration of all relatives including children, and blind assessment of relatives. This study was approved by the Combined Neuroscience Institutional Review Board at the National Institutes of Health. This study was carried out in accordance with the latest version of the Declaration of Helsinki. All subjects provided written informed consent.

### 2.3. Diagnostic assessments

The NIMH Family Study Diagnostic Interview for Affective Spectrum Disorders (DIAS) was based on the adaptation of the diagnostic interview used in our earlier family studies of anxiety disorders and substance use disorders at the Yale University School of Medicine Genetic Epidemiology Research Unit based on the SADS/DIGS (Merikangas et al., 1998; Merikangas et al., 1998). The DIAS ascertains diagnostic criteria for current and lifetime DSM-IV-TR disorders, but does not adhere to strict diagnostic criteria for skip-outs based on frequency or duration at the probe level in order to capture subthreshold phenomenology across the key domains of psychopathology for multiple diagnostic systems (Angst et al., 2005, 1984). Symptoms of ADHD and BD were assessed separately within sections of the interview based on the core phenomenology of the particular condition. Of note, for a symptom to be attributed to BD it must occur exclusively during an episode or be exacerbated during an episode, whereas symptoms exhibiting a more chronic presentation were only counted towards an ADHD diagnosis. The NIMH Family Study Family History Interview (DIAS-FHX) was used to assess a family history of psychiatric disorders. The DIAS-FHX was based on modifications of the family history interview from our previous family study research (Andreasen et al., 1986; Merikangas et al., 1998; Merikangas et al., 1998).

Best estimate diagnoses for this study were based on all available information by a team of experienced clinicians (psychologists and a psychiatrist) using a best estimate procedure (Leckman et al., 1982). The current analyses assess BD I and II disorder subtypes and MDD as defined by DSM-IV-TR, and then distinguish mania and hypomania episodes and major depressive episodes independent of the bipolar disorder subtype. Anxiety disorders include generalized anxiety disorder, panic disorder and social phobia. For these analyses, we examined combinations of these conditions including BD with ADHD, BD alone and ADHD alone. A hierarchical classification of mood and anxiety disorders was applied such that mood disorders took precedence over anxiety disorders; therefore, the anxiety disorder group included probands with anxiety

disorders without a lifetime history of a mood disorder. The control group included 176 people with no lifetime history of a mood or anxiety disorder. Sensitivity estimates of direct interview versus best estimate diagnoses that also included family history information were: 67.5% for BD I, 73.5% for and 98.9% for MDD.

### 2.4. Statistical analysis

Differences between the diagnostic categories (i.e. BD I + ADHD, BD II + ADHD, MDD + ADHD) were assessed using analysis of variance (ANOVA) for continuous measures and Chi-square test for binary measures. The association between proband and relative ADHD was evaluated using mixed effects logistic regression, including both fixed and random effects. The models included a random intercept in order to account for variability of family members in each family. Included in the adjusted models were proband ADHD and mood subtype (BD I, BD II, MDD) and any anxiety disorders in probands and sex, age, and any anxiety of relatives. Analyses were completed using SAS 9.4 (SAS Institute, Cary, NC, USA).

## 3. Results

Demographic and clinical information for probands and relatives is presented in Table 1. The lifetime rates of ADHD were highest among those with BD I compared to the other mood disorder subgroups: 39% of probands with lifetime BD I also had ADHD, followed by 21% of probands with BD II and 18% of probands with MDD, compared to 4% of controls.

Table 2 shows the clinical correlates of the aggregate sample of probands and relatives with BD I, BD II, and MDD stratified by the presence or absence of comorbid ADHD. Individuals with BD I, BD II, or MDD, plus comorbid ADHD had lower lifetime Global Assessment of Functioning (GAF) scores than their counterparts without comorbid ADHD. Furthermore, compared to those with no history of ADHD, people with comorbid ADHD were more likely to have a BD or MDD rated "severe" by a clinician. The age of onset for BD or MDD was also earlier among participants with comorbid ADHD than among those without comorbid ADHD. Participants with comorbid ADHD also exhibited higher rates of anxiety and substance use disorders than participants without ADHD.

Table 3 displays lifetime rates of ADHD, BD I, BD II, MDD, and anxiety disorders among the relatives of probands classified with a hierarchy of mood disorders (i.e., BD I > BD II > MDD) in probands. Rates of ADHD were elevated in relatives of probands with BD I, MDD, and anxiety disorders (without mood disorders) compared to relatives of the controls ($p < 0.05$).

Results from the mixed model assessing familial aggregation of ADHD while controlling for age and sex of the relative and mood and anxiety disorders in both probands and relatives, are presented in Table 4. There were strong associations between ADHD with BD I (OR = 7.24 (2.68–19.6); BD II OR = 3.29 (1.43–7.55) and anxiety disorders OR = 2.82 (1.60–4.98)) within relatives, after controlling for age and sex. After controlling for these comorbid associations, sex and age, there was a strong association between ADHD in probands and relatives (OR = 2.13 (1.16, 3.95)). However, there was no evidence for increased risk of ADHD among the relatives of probands with BDI, BD II, MDD, or anxiety disorders after controlling for comorbidity within relatives.

Table 5 presents the associations between proband ADHD with relative BD I, BD II, and MDD after adjusting for comorbid BD I, BD II, MDD, anxiety disorders, age, and sex of relatives. Although there were strong associations between ADHD and BD I and BD II disorders within relatives [BD I OR = 5.03 (2.04, 12.42); BD II OR = 2.11 (1.04, 4.32)], ADHD in probands was not associated with any of the mood disorder subtypes in relatives [BD I OR = 1.03 (0.40, 2.62); BD II OR = 0.87 (0.38, 1.97) MDD OR = 0.75 (0.47, 1.19).

**Table 1**
*N* and demographic characteristics of probands ($n = 562$) and first-degree relatives ($n = 698$) by proband lifetime mood disorder subgroups.

| | Proband Diagnostic Subgroups | | | | |
|---|---|---|---|---|---|
| | Bipolar I | Bipolar II | Major Depression | Anxiety Only | Other[a]/ None[b] |
| **PROBANDS** | | | | | |
| *N* | 110 | 72 | 177 | 59 | 144 |
| Sex (% male) | 34.55 | 31.94 | 22.6 | 20.34 | 52.08 |
| **Age (years)** | | | | | |
| An | 44.7 | 47.5 | 48.6 | 48.2 | 49.8 |
| s.d. | 12.3 | 13.9 | 13.8 | 15.1 | 19.1 |
| Range | 22–73 | 19–83 | 19–80 | 22–84 | 18–90 |
| **Lifetime ADHD (%)** | 39.09 | 20.83 | 17.51 | 13.56 | 4.17 |
| **RELATIVES**[c] | | | | | |
| *N* | **144** | **83** | **226** | **69** | **176** |
| Sex (% male) | 37.5 | 32.53 | 38.5 | 42.03 | 36.93 |
| **Age (years)** | | | | | |
| Mean | 51.3 | 50.4 | 48.9 | 49.3 | 48.9 |
| s.d. | 18.5 | 17.7 | 18.7 | 18.1 | 17.0 |
| Range | 18–87 | 18–83 | 18–95 | 19–82 | 18–89 |

ADHD: Attention-deficit/hyperactivity Disorder.
[a] No mood or anxiety disorder, subthreshold mood/anx, eating disorder, or substance use disorder (n = 31).
[b] No lifetime mental disorder (n = 144).
[c] Relatives: Interviewed first degree adults (by proband mood anxiety groups).

## 4. Discussion

This study examined the comorbidity and patterns of familial aggregation and coaggregation of ADHD and BD in a large community-based family sample of adults. ADHD was highly comorbid with BD, most notably BD I. Individuals with comorbid BD and ADHD had higher rates of anxiety and substance use disorders, an earlier age of onset, and greater clinical impairment, compared to those with BD alone. Consistent with previous research (Smoller and Finn, 2003), ADHD and BD exhibited significant familial aggregation: relatives of probands with ADHD were approximately twice as likely to have ADHD, and relatives of probands with BD I were almost nine times more likely to have BD. However, there was no evidence of coaggregation of ADHD and BD. This suggests that ADHD and BD have distinct familial profiles, despite the high rates of comorbidity.

These findings add to a large body of literature examining whether ADHD and BD stem from a common underlying diathesis or have distinct etiologies. Our results were not consistent with a familial association between ADHD and BD. Furthermore, rates of ADHD among those with BD I (20.1%) were comparable to those of individuals with MDD (19.5%) and anxiety disorders (20.3%), suggesting a lack of specificity of the ADHD-BD link.

We did not replicate findings from an earlier meta-analysis of family genetic studies that found coaggregation of ADHD and BD I (i.e., 2.6-fold increased relative risk of BD I among relatives of those with ADHD, and a 1.8 increased relative risk for developing BD I among relatives of individuals with ADHD; Faraone et al., 2012). One possible explanation for the differences in our findings may be that the meta-analysis was primarily based on samples recruited from clinical settings, while the current study utilized a non-clinical sample of probands that may represent a broader spectrum of these conditions than those identified in clinical samples. Furthermore, whereas most prior studies were based on parent-child dyads, the current study was based on a sample of adults with ADHD and all first-degree relatives. Therefore, a greater proportion of the sample has passed through the risk period for onset of BD and MDD. Additionally, the meta-analysis included studies that relied on a broad definition of BD, which may have artificially increased overlap. We also did not replicate findings from a population-based study of

**Table 2**
Clinical correlates of lifetime mood disorder subtypes, stratified by ADHD in probands and relatives.

| | Mood Group | | | | | | *p*-value[b] |
|---|---|---|---|---|---|---|---|
| | Bipolar I | | Bipolar II | | Major Depression | | |
| | W ADHD | w/o ADHD | w ADHD | w/o ADHD | w ADHD | w/o ADHD | |
| **N** | **59** | **85** | **35** | **93** | **78** | **372** | |
| **Age** | | | | | | | |
| mean (s.d., range) | 43.93 (12.72, 21–69) | 45.74 (13.56, 18–73) | 39.86 (13.92, 18–69) | 45.2 (16.19, 18–83) | 42.27 (15.06, 18–74) | 49.99 (15.35, 18–95) | <.0001 |
| **GAF (Lifetime)** | | | | | | | |
| mean (s.d., range) | 50.63 (8.22, 30–68) | 54.05 (8.94, 25–72) | 59.89 (4.73, 48–70) | 62.88 (7.77, 35–85) | 61.37 (6.71, 45–78) | 65.94 (7.38, 31–85) | <.0001 |
| **Sex** | | | | | | | |
| %male | 35.59 (21) | 34.12 (29) | 54.29 (19) | 27.96 (26) | 48.72 (38) | 23.92 (89) | <.0001 |
| **Treatment (%, n)** [a] | | | | | | | |
| BD I, BD II, or MDD | 96.61 (57) | 95.29 (81) | 77.14 (27) | 66.67 (62) | 71.79 (56) | 70.7 (263) | <.0001 |
| ADHD | 57.14 (32) | NA | 62.86 (22) | NA | 43.59 (34) | NA | 0.1077 |
| **Severity (%)**[a] | | | | | | | |
| Severity of BD I, BD II, or MDD | 82.76 | 83.33 | 51.43 | 32.61 | 40.54 | 24.79 | <.0001 |
| Severity of ADHD | 46.55 | NA | 32.35 | NA | 17.95 | NA | 0.0016 |
| **Age Onset** [a] | | | | | | | |
| BD I, BD II, or MDD | | | | | | | |
| mean (sd, range) | 13.44 (7.12, 5–49) | 17.79 (9.83, 4–53) | 14.03 (9.24, 3–39) | 17.88 (11.42, 3–66) | 20.46 (11.3, 3–50) | 25.3 (13.7, 2–71) | <.0001 |
| ADHD | | | | | | | |
| mean (sd, range) | 6.24 (3.62, 3–18) | NA | 7.76 (4.41, 3–18) | NA | 7.55 (4.93, 1–35) | NA | 0.1577 |
| **Comorbidity (%, n)** | | | | | | | |
| Anxiety | 94.92 (56) | 89.41 (76) | 97.06 (33) | 76.34 (71) | 79.22 (61) | 65.5 (243) | <.0001 |
| Substance Use | 72.88 (43) | 45.24 (38) | 62.86 (22) | 39.13 (36) | 37.18 (29) | 28.03 (104) | <.0001 |

ADHD, Attention-Deficit/Hyperactivity Disorder; GAF, Global Assessment of Functioning.
[a] Only the subjects with the diagnosis have treatment, severity, and age onset available.
[b] *p*-values: from ANOVA for continuous measures, Chi-square for binary variables. Only severity for ADHD was used Fisher Exact Test due to small cells.

**Table 3**
Rates of lifetime mood disorders and ADHD in relatives by proband mood subgroups.

| | Proband Mood Disorder Subgroups (%,N)[a] | | | | | *p*-value |
|---|---|---|---|---|---|---|
| | Bipolar I | Bipolar II | Major Depression | Anxiety Disorder Only | Other/None | |
| **N** | **144** | **83** | **226** | **69** | **176** | |
| **ADHD** | 20.14 (29) | 9.64 (8) | 19.47 (44) | 20.29 (14) | 11.36 (20) | 0.0445 |
| **Bipolar I** | 13.19 (19) | 6.02 (5) | 2.21 (5) | 4.35 (3) | 1.14 (2) | <.0001 |
| **Bipolar I** | 6.94 (10) | 16.87 (14) | 7.52 (17) | 11.59 (8) | 3.98 (7) | 0.0067 |
| **Major Depression** | 43.75 (63) | 43.37 (36) | 45.13 (102) | 28.99 (20) | 29.55 (52) | 0.0045 |

ADHD, Attention-Deficit/Hyperactivity Disorder.
[a] Results of pairwise comparisons indicate rates of ADHD are significantly higher ($ps < 0.03$) in BD I and MDD, but not BD II ($p > 0.7$) or ANX ($p = 0.06$) compared to the Other/None.

**Table 4**
Association between ADHD in probands and relatives controlling for comorbid mood and anxiety disorders in probands and relatives.

| | ADHD in Adult Relatives | |
|---|---|---|
| | *p*-value | OR (95%CI) |
| **PROBANDS** | | |
| ADHD | 0.0157 | 2.13 (1.16, 3.95) |
| Bipolar I | 0.3643 | 0.69 (0.3, 1.55) |
| Bipolar II | 0.0503 | 0.35 (0.12, 1) |
| Major Depression | 0.6099 | 1.18 (0.62, 2.25) |
| Anxiety Only | 0.4103 | 1.3 (0.7, 2.4) |
| **RELATIVES** | | |
| Bipolar I | 0.0001 | 7.24 (2.68, 19.6) |
| Bipolar II | 0.0052 | 3.29 (1.43, 7.55) |
| Major Depression | 0.1031 | 1.64 (0.9, 2.97) |
| Anxiety Only | 0.0004 | 2.82 (1.6, 4.98) |
| Age | <.0001 | 0.96 (0.94, 0.97) |
| Sex (F vs M) | <.0001 | 0.26 (0.16, 0.42) |

ADHD, Attention-deficit/hyperactivity disorder.

treatment-seeking adults that found evidence supporting the coaggregation of ADHD and BD (i.e. relative risk of BD among relatives of those with ADHD 2.21; Chen et al., 2019)). These findings, however, may reflect the nature of the sample: treatment-seeking individuals tend to exhibit more severe symptomatology and report more impairment than community-based samples.

Another potential explanation for the inconsistency in findings may be that the risk of ADHD is elevated among those who experience early onset of BD symptoms, but risk of ADHD subsides if BD symptoms emerge later in life. These findings may also reflect the diagnostic misclassification of BD and ADHD that are both based on disturbances in attention and motor activity (Phillips and Kupfer, 2013; Wasserstein, 2005). In fact, the increasing recognition of the salience of activation, rather than mood changes, as a core feature of mania, may explain the apparent overlap of BD and ADHD (Merikangas et al., 2019; Scott et al., 2017).

Our results are consistent with the findings of several studies of youth at-risk for BD based on parental BD (Axelson et al., 2015; Duffy et al., 2019; Nurnberger et al., 2011; Preisig et al., 2016) It is important to note that, in some cases, studies reported elevated rates of ADHD among offspring of BD parents compared to offspring of controls, but after

**Table 5**
Associations between proband ADHD and BD I, BD II, and MDD in relatives, controlling for comorbid BD I, BD II, and MDD in probands.

| | Disorders in Relatives | | | | | |
|---|---|---|---|---|---|---|
| | Bipolar I | | Bipolar II | | Major Depression | |
| | *p*-value | OR (95%CI) | *p*-value | OR (95%CI) | *p*-value | OR (95%CI) |
| **PROBANDS** | | | | | | |
| ADHD | 0.9555 | 1.03 (0.4, 2.62) | 0.7332 | 0.87 (0.38, 1.97) | 0.2207 | 0.75 (0.47, 1.19) |
| Bipolar I | 0.0067 | 6.08 (1.66, 22.3) | 0.5845 | 0.75 (0.26, 2.14) | 0.035 | 1.81 (1.04, 3.14) |
| Bipolar II | 0.1197 | 3.35 (0.73, 15.39) | 0.0298 | 2.98 (1.11, 7.96) | 0.0625 | 1.8 (0.97, 3.33) |
| Major Depression | 0.8194 | 0.85 (0.21, 3.42) | 0.8701 | 1.07 (0.46, 2.47) | 0.0008 | 2.18 (1.38, 3.45) |
| Anxiety Only | 0.8813 | 0.92 (0.29, 2.85) | 0.6647 | 1.19 (0.54, 2.59) | 0.7024 | 0.92 (0.6, 1.41) |
| **RELATIVES** | | | | | | |
| ADHD | 0.0005 | 5.03 (2.04, 12.42) | 0.0398 | 2.11 (1.04, 4.32) | 0.5836 | 0.87 (0.54, 1.41) |
| Anxiety | 0.0038 | 5.19 (1.71, 15.77) | 0.003 | 2.88 (1.44, 5.78) | <.0001 | 2.42 (1.71, 3.42) |
| Age | 0.9904 | 1 (0.98, 1.02) | 0.0004 | 0.97 (0.95, 0.98) | 0.5376 | 1 (0.99, 1.01) |
| Sex (F vs M) | 0.4238 | 1.42 (0.6, 3.35) | 0.9504 | 1.02 (0.53, 1.97) | 0.1473 | 1.3 (0.91, 1.85) |

ADHD, Attention-Deficit/Hyperactivity Disorder; MDD, Major Depressive Disorder.

controlling for confounds such as age, socioeconomic status, and other non-BD parental psychopathology, high-risk offspring only exhibited higher rates of ADHD in comparison to the offspring of healthy controls, but not the offspring of parents with non-BD psychopathology (Birmaher et al., 2009). This suggests there may be an underlying diathesis that increases risk for psychopathology, including BD and ADHD, but that the ADHD-BD link is not specific. When taken together with the results of prospective, clinical high-risk studies (Arnold et al., 2020), one compelling alternative explanation for our findings is that comorbid ADHD and BD may index a distinct BD subtype marked by symptoms of inattention and distractibility beginning in childhood. Future studies that address these alternatives are clearly indicated.

A major strength of this study is the use of a non-clinical community-based sample of adults that includes individuals with a broad range of affective and anxiety spectrum disorders in addition to controls. While many previous studies recruited only probands with BD or probands with ADHD, this sample includes probands with both disorders, as well as with other conditions including MDD, anxiety, and substance use disorders. Unlike many previous studies, this study was sufficiently powered to investigate the specificity of the specific mood disorder subgroups including BD I, BD II and MDD. Furthermore, employing a community-based sample increases the generalizability of the findings. The comprehensive diagnostic evaluation of the full range of mental disorders and their correlates along with ancillary information derived from parental and other relative reports increases our confidence that misclassification is a potential explanation for our findings.

Several limitations of this work should be considered in the interpretation of these findings. This study only included data from directly-interviewed individuals in order to avoid underestimating the rates of BD and ADHD in adults, which has been recognized as a substantial issue in recent years (Angst, 2008; Ginsberg et al., 2014). However, retrospective recall of childhood-onset ADHD in an adult sample may still have led to diagnostic under-estimation this study because prior research has shown that adults have difficulties accurately remembering ADHD symptoms, especially milder, less impairing cases (Mannuzza et al., 2002; Miller et al., 2010). Despite these limitations, the findings appear to be consistent with those of high risk samples (Arnold et al., 2020) and extend the conclusion regarding independence of the familial risk of BD and ADHD to multigenerational families.

These findings have important clinical and etiologic implications. When coupled with longitudinal research that documents BD as a consequence of ADHD (Tillman et al., 2003), this work highlights the importance of careful monitoring of youth with ADHD for mood disorder symptoms to prevent greater impairment, disability and other consequences of ADHD (Strine et al., 2006). The significant association between BD and ADHD in adulthood is often neglected in adult clinical settings (Chung et al., 2019) and in light of the substantial impact of comorbidity on impairment and disability in adults (Chung et al., 2019) should alert clinicians to evaluate childhood-onset disorders that may complicate clinical presentation and course. Future research may assist in reconciliation of the discrepant findings with respect to the common versus independent familial diatheses underlying BD and ADHD. With the growing effort to characterize mental disorders dimensionally by core components such mood, activity, cognition, and attention, familial coaggregation of these domains may reveal that the appearance of co-morbidity, based on categorical diagnostic categories, is better described as a spectrum of presentations across a single diagnostic category.

## Author statement

Dr. Merikangas and Dr. Brown conceptualized this study. Ms. Cui analyzed the data and helped in interpretation. Ms. Walsh and Dr. Sheppard wrote the initial manuscript. Dr. Van Meter and Dr. Merikangas aided in the interpretation of the findings and contributed to the written manuscript. All authors approve the final version.

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## Declaration of competing interest

None of the authors have any potential conflicts of interest to disclose.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2020.08.017.

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