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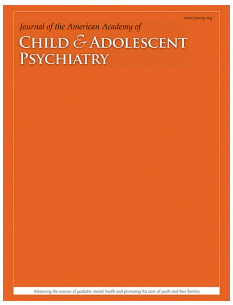

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ABSTRACT

Objective: Suicide attempts are prevalent in association with major mood disorders, and risk is greater with bipolar disorder (BD) than major depressive disorder (MDD) in adults. There may be similar relationships in juvenile mood disorders, but the evidence has not been compiled systematically and quantitatively.

Method: We searched for reports of studies comparing rates of suicide attempts in children or adolescents diagnosed with BD or MDD, and applied random-effects meta-analysis.

Results: In 6 reports from 1995 to 2017, with 2,303 participants diagnosed with mood disorder from US and South Korea, aged 3–18 years, rates of suicide attempts differed significantly by diagnosis: BD (31.5%) > MDD (20.5%) > hypomania or mania-only (8.49%). Risk of suicide attempts differed (BD > MDD) highly significantly by meta-analysis (OR=1.71 [CI = 1.33–2.20], $p<.0001$), and was very similar if a study with attempts and suicidal ideation was excluded (OR=1.64 [CI: 1.26–2.14], $p<.0001$).

Conclusion: Risk of suicide attempts in juvenile mood disorder patients ranked: BD > MDD >> hypomania or mania-only >> juvenile general population.

Key words: affective, bipolar, depression, meta-analysis, suicide attempt

INTRODUCTION

Suicide is the second leading cause of death worldwide among adolescents, and more than 80% of juveniles who have attempted suicide have had a major affective disorder.[1] In adults, suicide attempts are significantly more frequent among those with a diagnosis of bipolar disorder (BD) than of major depressive disorder (MDD).[2] However, among juveniles, the relative risk of suicidal behaviors with specific mood disorder types has not been addressed systematically.

Juvenile mood disorders are prevalent, increase risk of suicide, substance abuse and co-occurring medical illnesses, and present high rates of hospitalization and potentially severe and disabling morbidity.[3-5] Longitudinal studies have found prognosis of juvenile mood disorders to be highly unfavorable, and that their diagnosis and treatment are often delayed for more than a decade, especially BD.[5,6] Such delays probably reflect the difficulty of diagnosing BD at an early age, often starting with sub-syndromal depressive or hypomanic symptoms, mood instability, mixed features, an ultra-rapid cycling course, and occurrence of fully symptomatic hypomanic or manic episodes and a clear manic-depressive episodic pattern only later. Also, in a large proportion of cases, the first major mood episode in BD is depressive, making the diagnosis of BD and differentiation from MDD at early age even more difficult and use of potentially risky antidepressant treatment greater.[5,6]

Abundant evidence in adult patients supports the conclusion that suicide attempts are more prevalent among persons diagnosed with BD compared to MDD. In a recent meta-analysis of rates of suicide attempts among adults with a mood disorder in 101 international studies, the pooled incidence

was 31.1% (CI: 27.9–34.3), or 4.0%/year.[7] Risk was similar among patients diagnosed with types I and II BD, and two times higher in both than in MDD.[7] Among juveniles as well as adults, suicide attempts are strongly associated with major mood disorders, although relative associations with BD versus MDD remain uncertain.[8–10]

Reported risk factors for suicide attempts in juvenile mood disorder patients include relatively young onset, female sex, severe depression, functional impairment, previous suicide attempts, non-suicidal self-injurious behaviors, and a family history of suicidal acts.[11,12] Among juveniles diagnosed with MDD, the presence of psychotic symptoms and insomnia,[12,13] as well as "subthreshold" bipolar-like features, including hypomanic symptoms, cyclothymic or hyperthymic temperament, and prominent novelty-seeking behaviors[14,15] also have been associated with suicide attempts. In addition, "mixed" manic-depressive features, including irritability, psychomotor agitation, or racing thoughts with dysphoria have strongly and consistently been associated with suicidal behaviors in adults, and there are indications of similar associations among juveniles with mood disorders.[11,16–18] Given the large amount of evidence demonstrating a higher risk for suicide attempts in BD versus MDD in adults, and the strongly suggestive evidence that subsyndromal hypomanic features may increase risk of suicide attempts in juvenile MDD, we propose that, among juveniles, the risk of attempting suicide is preferentially associated with bipolar features, and that the relative risk of suicide attempts may be greater with BD versus MDD. Moreover, we propose that the clinical importance of earlier recognition of BD in juveniles and its differentiation from MDD includes the need to monitor particularly closely for emerging suicidal risk.

Given this background and remaining uncertainty about the relative risk of suicide attempts among children and adolescents diagnosed with BD versus MDD, we carried out a systematic review of the research literature on this topic. We used meta-analysis to test quantitatively for differences in suicide attempts among juveniles given these diagnoses, as well as among patients found to have hypomania or mania without depression, in an effort to evaluate the contributions of bipolar tendencies to suicidal risk in young persons.

METHOD

Literature Search

We searched PubMed/MEDLINE, CINAHL, ISI Web of Science, and PsycINFO research literature databases to identify relevant, peer-reviewed articles on suicide attempts in children and adolescents with mood disorders. The search syntax was based on combinations of the terms: (bipolar disorder OR bipolar depression OR hypomania OR mania) AND (major depressive disorder OR depression) AND (juvenile OR child* OR adolesc* OR pediatric OR youth) AND (suicid* OR suicide attempt OR suicide plan OR suicide threat OR suicide gesture OR self-harm OR self-injur*). With no lower date limit, the search was continued to 27 June 2017. We also examined references cited in included reports as well as abstracts of

recent psychiatric research conferences, and grey literature via Internet searches to find additional studies. The full search strategy is available in Supplement 1 and Table S1, available online. This systematic review accorded with PRISMA guidelines.[19]

Study Selection

We included reports of studies involving adolescents or children diagnosed with a major affective disorder (BD or MDD) by standardized criteria up to age 18 years, with at least one suicide attempt at any time. We considered a suicide attempt to be any self-injurious behavior with a non-zero level of intent to die.[20,21] We excluded: [a] review articles, editorials, letters, comments; [b] case reports; and [c] diagnosis not based on standardized criteria.

Two experienced investigators (G.S., M.U.) independently reviewed titles and abstracts of retrieved articles and applied study inclusion and exclusion criteria. These investigators then independently reviewed full-texts to confirm eligibility of studies for inclusion. Disagreements were resolved by discussion to consensus.

Data Extraction

For each included study, five authors (F.D.C., F.M., G.S., M.U., R.J.B.) collected basic information (authors, reference citation, year, country) and study characteristics, including research design, diagnostic methods, diagnoses, participant counts, proportions by sex, age range and mean, rates of suicide attempts, definition of suicide attempt, and methods of evaluating attempts. The primary outcome measure was the proportion of participants with at least one suicide attempt among those diagnosed with BD versus MDD in the same study. Secondarily, we also compared other participants with hypomania or mania only ("mM") without clinically manifest depression. Two authors (F.D.C., F.M.) independently assessed the quality of methods and potential sources of bias for each study, based on the Newcastle-Ottawa scale,[22] scored as the percentage of items considered to be of high quality among the scale's eight characteristics.

Data Analysis

We considered the number and proportion of individuals reported as having at least one suicide attempt, and compared rates of persons making suicide attempts between different mood disorders using random-effects meta-analysis. Reported analyses were carried out independently by three investigators (F.D., G.S., R.J.B.) to consensus. Meta-analytic findings are reported as pooled odds ratios (OR) with 95% CIs, based on STATA.13 statistical software (StataCorp, College Station, TX, USA). Non-quantitative data are presented descriptively. We performed a sensitivity analysis by excluding the only study[23] that included suicidal ideation as well as suicide attempts. We assessed statistical heterogeneity in each pairwise comparison with the I^2 statistic derived from Q-values provided by meta-analysis. We considered I^2 values as indicating very low (<10%), low (10%–25%), moderate (26%–50%), or high (75%–100%) heterogeneity.[24] We also performed meta-regression analysis to determine associations of

reported study characteristics (including mean age, proportion of females, reporting year, participant count, and study quality rating) on the primary meta-analytic contrast of suicide attempt rates among juveniles diagnosed with BD versus MDD.

RESULTS

Studies Selected

The literature search generated 1,364 potential records, plus 120 from the gray literature, and 6 from bibliographies of initially identified reports, leading to 1,490 records to be screened (Figure 1). Of these, 1,424 records not including information on required diagnostic categories or outcomes were excluded, to leave 66 full-text reports to be assessed for eligibility. Of these, 60 were excluded for the following reasons: [a] included adults not separated from juveniles (n=18); [b] did not include both BD and MDD cases (n=17); [c] did not differentiate BD versus MDD cases (n=16); [d] lacked data on suicide attempts (n=7); [e] duplicated data (n=2). This process yielded 6 reports (with 2,303 participants diagnosed with a mood disorder) for analyses (Figure 1).[16,23,25–28]

[Figure 1 about here]

Study Characteristics

Salient characteristics of included studies are summarized in Table 1. Their diagnostic assessments were based on structured or semi-structured diagnostic interviews, in some cases backed with validated rating scales, following *DSM-III* to *DSM-5* criteria for BD and MDD. All included studies compared participants with BD and MDD. Two involved community samples of US high school students and included individuals with hypomanic symptoms and possible unipolar mania who were not included among those diagnosed with BD and were compared separately to those with BD or MDD in the same studies.[25,27] Another study surveyed children diagnosed with putative BD versus unipolar MDD according to parental reports of symptoms and behavioral abnormalities.[26] Four studies were cross-sectional [23,26,38] or based on chart review,[16] and two included prospective follow-up to 12.0[27] or 13.8 months.[25] Participant ages averaged 15.0 (CI: 12.8–17.2) years and ranged from 3 to 18 years (Table 1).

[Table 1 about here]

Four studies considered only patients reported to have made at least one suicide attempt,[16,25,27,28] a fifth considered suicide attempts and suicidal ideation together,[23] and a sixth included suicidal and other self-injurious behaviors.[26] Quality ratings of the studies averaged 77.1% (CI: 61.8–92.4) of the maximum attainable score with the Newcastle-Ottawa scale (Table 1).[22]

Quantitative Analyses

Based on meta-analytically pooled values of reported rates of suicide attempters, participants diagnosed with BD were 1.54 times more likely to have made at least one suicide attempt than those with

MDD (31.5%/20.5%; Table 1). This difference was strongly supported by random-effects meta-analysis (OR = 1.71 [CI = 1.33–2.20]; z=4,18, p<.0001; Table 2, Figure 2), with low between-study heterogeneity (I^2 <10%; Table 2). This diagnostic difference in suicide attempt rates remained highly significant when a study including suicidal ideation [23] was excluded (OR = 1.64 [1.26–2.15]; z=3.62, p<.0001; Table 2). We also estimated number needed to harm (NNH) to differentiate the risk for suicide attempt in participants with MDD versus BD (NNH = 11.0 [7.38–31.3]), based on the reciprocal of the meta-analytically computed rate difference (1/RD) for suicide attempters between the diagnostic groups.

[Table 2 and Figure 2 about here]

Two of the studies[25,27] supported a tentative meta-analytic comparison of suicide attempts between individuals with BD or MDD versus a separate group of individuals diagnosed with only hypomania or mania (mM). Such participants were highly significantly less likely to attempt suicide than those with MDD (OR = 2.14 [1.33–3.44]; z=3.15, p=.002), and even less than others diagnosed with BD but having episodes of depression (OR = 4.68 [2.45–8.94]; z=4.68, p<.0001; Table 2).

DISCUSSION

This appears to be the first systematic review and meta-analysis to compare risks of suicide attempts in children and adolescents with different types of mood disorders. Based on a systematic literature search, we identified and pooled data from six studies meeting study criteria, with both BD and MDD cases observed under the same conditions. Juveniles with BD had a highly significantly higher risk of suicide attempt than those with MDD (OR=1.64–1.71, Table 2), and both participants with BD (31.5%; OR=4.68) and MDD (20.5%; OR=2.14) had higher rates than among those with hypomania or mania without major depression (8.49%; Tables 1 and 2). The ratio of suicide attempter rates among adults with BD versus MDD is reported to be approximately 2.4,[2,29] or greater than was found in juveniles in the present study (1.64–1.71-fold; Table 2). Nevertheless, juvenile major depressive episodes sometimes are later found to have mania or hypomania to support a diagnosis of BD, at rates ranging from 9.0% to 43%.[6,30] This tendency to change from apparent MDD to BD in juveniles might lead to underestimating the ratio of suicide attempt rates among juveniles with BD versus MDD by inflating the rate among apparent MDD cases.

Rates of suicide attempts reported here are far higher than in general population samples of children and adolescents. We found only one report that include a rate of suicide attempts among healthy control juveniles, at 1.18% [CI: 0.57–2.17] (10/845 Table 1).[25] Previously reported rates of suicide attempts between ages 9 and 18 years have ranged from about 3.3% to 7.0% (average ca. 5.2%) and to be more than twice higher among girls than boys.[9,31] Also important, the ratio of attempts to suicides (A/S, a proposed index of lethality of attempts) has averaged approximately 1000 in girls but only 300 among boys of this age group in the general population, with similarly high A/S ratios for adults in the general

population.[8,9] With samples of adult patients diagnosed with a major affective disorder, the A/S ratio is far lower than in the general population, averaging approximately 10 in MDD and 8 in BD, indicating far greater lethality in mood disorder patients than in the general population.[29] In general, in both juveniles and adults, risk of suicidal behavior appears to rank: general population << unipolar mania or hypomania << unipolar depression < bipolar disorder. Suicidal risks appear to be at least as great in highly depression-prone BP-II as in BP-I,[2,29] and in cases of BD with prominent mixed manic-depressive states, at least in adults,[2] with less certainty about relative risks among juveniles with particular subtypes of BD.[16,32]

The significance of the consistently higher risk of suicide attempts in juveniles and adults diagnosed with BD than with MDD remains to be clarified. The especially high suicidal risks associated with prominent manic-depressive mixed states, marked by agitation and increased energy and activity with prominent dysphoria, as well as the far higher risks among patients with BD with depressive as well as manic or hypomanic episodes as we found here, may offer some clues. For example, the combination of depressed or dysphoric mood with increased tendency to act, especially impulsively (as found in BD, and especially in manic-depressive mixed states), may provide particularly lethal conditions for suicide. The very low rate of suicide attempts found among young patients with mania or hypomania without obvious depression (Table 1) would seem to indicate the importance of a depressive or dysphoric component of pathological moods for risk of suicidal behavior.

The present preliminary findings in juveniles presenting mainly with mania or hypomania in two studies involving 259 participants[25,27] call for specific comment. Such cases were associated with much lower rates of suicide attempts (8.49% [CI: 5.40–12.6]) than in BD (with depression as well as mania or hypomania; 31.5% [27.5–35.9]) or MDD in the present study (20.5% [18.5–22.5]; Table 1), and only slightly higher rates than in the juvenile general population (8.49% vs. 5.20%).[8,25,26] Moreover, most juveniles presenting with early mania or hypomania without evidence of clinical depression have not developed fully expressed syndromal BD in later years.[6,32–35] These findings underscore the complexity of recognizing and evaluating the range of affective disturbances in children and adolescents and their prognostic implications for later morbidity and suicidal risks.[6,30]

The present findings have important clinical implications concerning early identification of BD, particularly in children and adolescents, as they encourage close monitoring of patients with juvenile mood disorders for potential suicidal risk. Of particular importance is uncertainty about the future course of illnesses presenting as depression in children and adolescents. Many cases of BD present with early depression and may be considered as MDD but later be identified as BD by emergence of hypomanic, manic, or mixed states, sometimes during treatment with an antidepressant or other mood-elevating medicine.[35] There are major efforts being made to improve early prediction and identification of BD in

young prople.[6] Clinical indications of increased risk of future emergence of BD include behavioral excitation, labile mood, dysphoria, or anger and insomnia, as well as a family history of BD.[6]

The present primary findings have several limitations. Notably, we found only six reports (representing a total of 2,303 participants with either BD or MDD) that met study selection criteria, and even these sometimes involved broad definitions of mood disorder diagnoses or of suicidal status or parental reports rather than direct clinical observation, perhaps with risk of over-emphasis on depression and under-recognition of hypomania or mania (Table 1). Also, variability in the assessment of suicide attempts with the use of retrospective information from chart reviews may well yield inaccurate rates, in part owing to recall bias. Nevertheless, although inaccuracies in identifying suicide attempts and in the clinical assessment of mania and depression may well occur across studies, they would be expected to arise at similar rates among both MDD and BD cases within studies. In addition, since exposure times probably varied greatly and are not defined in the studies analyzed, it was not possible to estimate time-adjusted rates (%/year). Moreover, as most of the studies included were observational and cross-sectional, long-term diagnostic and behavioral outcomes in later, more mature, years are not known.

Diagnosis of BD was associated with a higher rate of suicide attempt than of apparent unipolar MDD, and both were higher than in cases with mania or hypomania without depression in six reports involving a total of 2,303 children and adolescents diagnosed with a mood disorder. Additional studies are required to test the findings presented, to better evaluate the long-term significance of isolated mania or hypomania without depression in juveniles, and to assess the impact of mixed manic-depressive states in juveniles. Practical, clinical conclusions pertaining to the evaluation and treatment of juvenile patients include the need for close consideration of early-onset BD because of its sometimes difficult differentiation from MDD and especially high risk of suicidal behavior.

Clinical Guidance

- Juvenile mood disorders are highly prevalent psychiatric diseases with potentially severe and disabling morbidity and increased risk of suicide. The incidence of suicide attempts among adults diagnosed with a mood disorder is 31%, and is 2.4-times greater among those diagnosed with bipolar disorder (BD) than with major depressive disorder (MDD).
- In 6 reports with 2,303 participants diagnosed with mood disorder, aged 3–18 years, rates of suicide attempts were comparable to those reported in adults and differed significantly by diagnosis: BD (31.5%) > MDD (20.5%) > hypomania or mania only (8.49%).
- Risk of suicide attempts was 1.7-times greater by meta-analysis among juveniles diagnosed with BD *versus* MDD (OR=1.71 [CI = 1.33–2.20], p<.0001).
- The present findings have important clinical implications concerning the need for close monitoring of patients with juvenile mood disorders for potential suicidal risk, and the importance of early identification of BD, with accurate differentiation of juvenile BD from MDD.

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Figure 1. PRISMA flow chart of literature search to obtain six reports for analysis. Note: BD = bipolar disorder; MDD = major depressive disorder.

Figure 2. Forest plot of results of fixed-effect meta-analysis of six reports comparing risk of suicide attempts in children or adolescents diagnosed with bipolar or major depressive disorder. Note: Heterogeneity was negligible (I^2 = <10%, p=.66), supporting use of fixed-effect modeling. Pooled odds ratio (OR) = 1.17 (CI: 1.33–2.20); z-score = 4.18, p<.0001. Sensitivity analysis based on omitting the one study[29] that included participants with suicidal ideation as well as suicide attempts yielded a similar pooled OR = 1.64 (1.26–2.15); z score = 3.62, p<.0001.

Table 1. Characteristics of Studies Included in Meta-Analyses

Study	Sample, Assessment	Quality Score[a]	Age (years)[b]	Diagnoses (n)	Females (%)	Diagnostic Criteria	Suicidal History and definition of attempt	Suicidal Behavior (N, %)
Lewinsohn et al. 1995 [25]	Community; N=1,276 prospective 13.8 mos	87.5	4–18 16.6±1.2	18 BD 316 MDD 97 mM 845 HC	BD: 67 MDD: 70 (mM: 57) HC: 48	K-SADS and LIFE	"Have you ever tried to kill yourself or done anything that could have killed you?"	BD: 8/18 (44.4%) MDD: 70/316 (22.2%) mM: 14/97 (14.4%) HC: 10/845 (1.18%)
Wozniak et al. 2004 [23]	Clinical; N=152 cross-sectional	75.0	6–17 12.8±3.5	43 BD+ADHD 109 MDD+ADHD	BD: 35 MDD: 51	K-SADS-E	Self- or parent-reported suicide ideation or attempt	BD: 29/43 (67.4%) MDD: 52/109 (47.7%)
Dilsaver et al. 2005 [16]	Chart Review N=229	75.0	14.7±1.5	82 BD-Mx 147 MDD	BD: 44 MDD: 47	Chart Review	Chart Review Attempt: "a physically self-destructive act associated with the idea of terminating one's life"	BD: 42/82 (51.2%) MDD: 68/147 (46.3%)
Luby and Belden 2008 [26]	Community; N=80 cross-sectional	62.5	3–6	26 BD 54 MDD	BD: 86 MDD: 69	PAPA-1.4	Parent-reported suicidal behavior	BD: 7/26 (26.9%) MDD: 8/54 (14.8%)
Merikangas et al. 2012 [27]	Community; N=1,213 prospective 12 mos	100	13–18	246 BD 805 MDD 162 mM	BD: 68 MDD: 68 (mM: 55)	CIDI-3.0	Self-reported suicide attempt	BD: 48/246 (19.5%) MDD: 102/805 (12.7%) mM: 8/162 (4.94%)
Shon et al. 2013 [28]	Clinical; N=198 review of 16 mos	62.5	6–18 15.1±2.4	55 BD 143 MDD	BD: 54 MDD: 46	*DSM-IV* and COBY	Suicide attempt in medical record	BD: 14/55 (25.5%) MDD: 22/143 (15.4%)
Means[b]/Totals [95%CI]	**6 studies N=3,148**	**77.1 [61.8–92.4]**	**15.0 [CI: 12.8–17.2]**	**470 BD 1,574 MDD (259 mM)**	**BD: 58.0 MDD: 63.7 (mM: 55.5)**	**—**	**—**	**BD: 148/470 (31.5%) MDD: 322/1574 (20.5%) (mM: 22/259 [8.49%])**

Note: ADHD = attention-deficit/hyperactivity disorder; BD = bipolar disorder; BD-Mx = mainly mixed-states; CES-D = Center for Epidemiological Studies Depression Scale (self-reported); CIDI = Composite International Diagnostic Interview; COBY = Course and Outcome of Bipolar Youth study criteria for unspecified BD; D = depression; HC = healthy controls; K-SADS-E = Epidemiologic version of Children's Schedule for Affective Disorders and Schizophrenia; LIFE = Longitudinal Interval Follow-up Evaluation; MDD = major depressive disorder; mM = manic or hypomanic without major depression; PAPA = Preschool Age Psychiatric Assessment; SHBQ = Self-Harm Behavioral Questionnaire.

[a] Newcastle-Ottawa quality assessment score is shown as percentage of 8 characteristics considered of high quality (sampling method; sample size; controls; defined exposure; age-matching; sex-matching; outcome assessment; and statistics).

[b] Ages of diagnostic subgroups did not differ from within-study means.

[c] Means are weighted by N. For pooled rates: BD vs. MDD (χ^2 = 23.0); MDD vs. mM (χ^2 = 21.8; both p<.0001).

Table 2. Summary of Random-Effects Meta-Analyses

Comparison	Studies	OR [95%CI]	NNH [95%CI]	I^2	*z*-score	*p*-value
BD vs. MDD (all reports)	6	1.71 [1.33–2.20]	11.0 [7.38–21.5]	<10%	4.18	<.0001
BD vs. MDD (attempts only)	5	1.64 [1.26–2.15]	12.4 [7.90–28.9]	<10%	3.62	<.0001
BD vs. mM	2	4.68 [2.45–8.94]	6.01 [4.41–9.47]	<10%	4.68	<.0001
MDD vs. mM	2	2.14 [1.33–3.44]	12.9 [8.56–26.5]	<10%	3.15	.002

Note: Studies and data included are shown in Table 1. Inter-study heterogeneity (I^2) was low. Meta-regression analysis found no association of outcome with: study size, proportion of females and males, participant age, reporting year, or study quality ratings (all $p \leq .80$; not shown). *BD* = bipolar disorder; *MDD* = major depressive disorder; *mM* = hypomania or mania without depression (not included with BD); *NNH* = number needed to harm with MDD vs. BD.

SUPPLEMENT 1

PROTOCOL

The following protocol circulated internally in the review team but was not originally published.

Review question(s)

To review evidence of differences in suicide attempts in children and adolescents diagnosed with bipolar disorder (BD) versus major depressive disorder (MDD).

Searches

PubMed/MEDLINE, CINAHL, ISI Web of Science, and PsycINFO databases will be searched to identify relevant articles on suicide attempts in children and adolescents with mood disorders. The search syntax will be based on combinations of the terms: (bipolar disorder OR bipolar depression) AND (major depressive disorder OR depression) AND (juvenile OR child* OR adolesc*) AND (suicid* OR suicide attempt). Databases will be searched from the date of inception. References of studies included and of major reviews/meta-analyses will be screened as well. We will contact investigators and relevant study authors, seeking information about unpublished or incomplete studies.

Types of study to be included

Observational studies (either prospective, retrospective, or cross-sectional) on children or adolescents with a diagnosis of BD or MDD and assessing suicide attempts will be included. We will exclude editorials, letters, comments, conference proceedings, review articles, and case reports.

Participants/population

The participants consist of patients aged up to 18 years, of both sexes, with a primary diagnosis of BD, mania, hypomania, or major depression. Most recent studies are likely to have used *DSM-5,*[1] *DSM-IV,*[2] or *International Classification of Diseases – 10th Revision* (*ICD-10*)[3]

criteria. Older studies may have used *ICD-9*,[4] *DSM-III*[5]/*DSM-III-R*[6] or other diagnostic systems. *ICD-9* does not use operationalized criteria, because it has only disease names and no diagnostic criteria, so studies using *ICD-9* will be excluded. Studies using other research diagnostic criteria will be included. A concurrent primary or secondary diagnosis of another psychiatric disorder will not be considered as an exclusion criterion. Trials in patients with mood disorder and with a concurrent serious medical illness will be excluded.

Outcome(s)

Our primary outcome measure is to compare the ratio of suicide attempts between participants diagnosed with BD versus MDD. Secondarily, we will compare patients with sub-threshold BD and hypomania or only mania without depression to participants with BD or MDD.

Data extraction (selection and coding)

Two researchers will independently review titles and abstracts of retrieved articles, applying inclusion and exclusion criteria. Moreover, two reviewers will independently extract quantitative and qualitative data from the studies retrieved. We will design and use a structured data abstraction form to ensure consistency of appraisal for each study. Information extracted will include study characteristics (such as lead author, publication year), participant characteristics (gender, age range, age of onset, setting, diagnosis), number of individuals reported as having at least one suicide attempt per group, and scale or mean to measure suicide attempts.

Risk of bias (quality) assessment

We will assess risk of bias in the included studies using the Newcastle-Ottawa scale as a reference guide.[7] Where inadequate details are provided, study authors will be contacted in order to obtain further information. The quality assessment will be done by two independent raters. If the raters disagree, the final rating will be made by consensus with the involvement (if necessary) of another member of the review group.

Strategy for data synthesis

Data will be entered independently by at least two researchers into a data abstraction sheet and then analyzed by using STATA-13 (StataCorp, College Station, TX, USA). We will perform a pairwise meta-analysis using the random effects model.[8] We will compare the number of children and adolescents with BD versus MDD with at least one suicide attempt. Secondarily, we will compare the number of children and adolescents with subthreshold BD and hypomania or only mania without depression to participants with BD or MDD. We will report results as pooled odds ratios (OR) with 95% CIs. We will also perform a sensitivity analysis by comparing studies presenting pooled results on suicide attempts and suicidal ideation with those reporting specifically on suicide attempts. Heterogeneity between studies will be investigated by the I-squared statistic[9] (we will consider I-squared "low" if <25%, "moderate" from 26% to 75%, and "high" if >75%) and by visual inspection of the forest plots. Skewed data and non-quantitative data will be presented descriptively.

Analysis of subgroups or subsets

We will perform if possible a meta-regression to check for associations of suicide attempts with age or gender.

CHANGES TO THE PROTOCOL

After the final analyses, the search strategy was implemented with the inclusion of the search terms hypomania, mania, self-injury and self-harm, and conference proceedings were screened, according to specific requests from the peer review. Below we report the fully implemented search strategy and the final search output.

Search strategy

Search strategy: Medline/Pubmed

1. exp “bipolar disorders”/
2. ‘bipolar depression’.mp
3. hypomania.mp
4. mania.mp
5. ‘major depressive disorder’.mp
6. depression.mp
7. 1 OR 2 OR 3 OR 4
8. 5 OR 6
9. juvenile
10. child*.mp
11. adolesc*.mp
12. pediatric.mp
13. youth.mp
14. 9 OR 10 OR 11 OR 12 OR 13
15. suicid*.mp
16. ‘suicide attempt’.mp
17. ‘suicide plan’.mp
18. ‘suicide threat’.mp
19. ‘suicide gesture’.mp
20. ‘self-harm’.mp
21. ‘self-injur*’.mp
22. 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21
23. 7 AND 8 AND 14 AND 22

Search strategy: CINAHL

1. (MH “bipolar disorders+”)
2. “bipolar depression”
3. “hypomania”
4. “mania”
5. “major depressive disorder”
6. “depression”
7. 1 OR 2 OR 3 OR 4
8. 5 OR 6
9. “juvenile”
10. “child*”

11. “adolesc*”
12. “pediatric”
13. “youth”
14. 9 OR 10 OR 11 OR 12 OR 13
15. “suicide”
16. “suicide attempt”
17. “suicide plan”
18. “suicide threat”
19. “suicide gesture”
20. ‘self-harm’
21. ‘self-injur*’
22. 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21
23. 7 AND 8 AND 14 AND 22

Search strategy: ISI Web of Science

1. TS=‘bipolar disorders’
2. TS=‘bipolar depression’
3. TS=‘hypomania’
4. TS=‘mania’
5. TS=‘major depressive disorder’
6. TS=depression
7. #1 OR #2 OR #3 OR #4
8. #5 OR #6
9. TS=juvenile
10. TS=pediatric
11. TS=child
12. TS=adolescent
13. #9 OR #10 OR #11 OR #12
14. TS=suicide
15. TS=‘suicide attempt’
16. TS=‘self-harm’
17. TS=‘self-injury’
18. #14 OR #15 OR #16 OR #17
19. #7 AND #8 AND #13 AND #18

Search strategy: PsycINFO

1. “bipolar”
2. “bipolar depression”
3. “hypomania”
4. “mania”
5. “major depressive disorder”
6. “depression”
7. 1 OR 2 OR 3 OR 4
8. 5 OR 6
9. juvenile
10. “child”
11. “adolescent”
12. “pediatric”

13. “youth”
14. 9 OR 10 OR 11 OR 12 OR 13
15. suicid*
16. “suicide attempt”
17. “suicide plan”
18. “suicide threat”
19. “suicide gesture”
20. ‘self-harm’
21. ‘self-injury’
22. 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21
23. 7 AND 8 AND 14 AND 22

We searched for unpublished studies and gray literature via Internet searches on the following web-sites using the terms suicide, self-harm, child, adolescent, bipolar, hypomania, mania, depression, major depressive disorder.

- The New York Academy of Medicine (http://www.greylit.org).
- http://www.opengrey.eu.

We also used the following sources:

- References of the articles included.
- Conference proceedings in the last five years likely to contain studies relevant to the review. These included an unstructured search in Google Scholar, in the American Psychiatric Association (APA) website (https://www.psychiatry.org/psychiatrists/search-directories-databases/library-and-archive), and in the European Psychiatric Association (EPA) website (e.g. http://www.epa-congress.org/2018/programme-submission/2017-e-posters#.WVTa8hTFkdc).

Table S1. Numbers of Citations Retrieved by Each Database

Databases, trial registers and other sources	Citations
Databases:	
PubMed	773
Web of Science	328
CINAHL	169
PsycINFO	94
Total (databases)	**1364**
Gray Literature:	
http://www.greylit.org	84
http://www.opengrey.eu	36
Other sources:	6
Total citations:	**1490**

Note: The last update of the search was performed on June 27, 2017. The searches performed in Google Scholar and the conference proceedings were not included in the count.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (5th edition). Arlington, VA: American Psychiatric Publishing; 2013.

2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (4th edition). Washington, DC: American Psychiatric Association; 1994.

3. World Health Organisation. ICD-10 Classifications of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organisation; 1992.

4. World Health Organization. The Ninth Revision of the International Classification of Diseases and Related Health Problems (ICD-9). Geneva: World Health Organization; 1978.

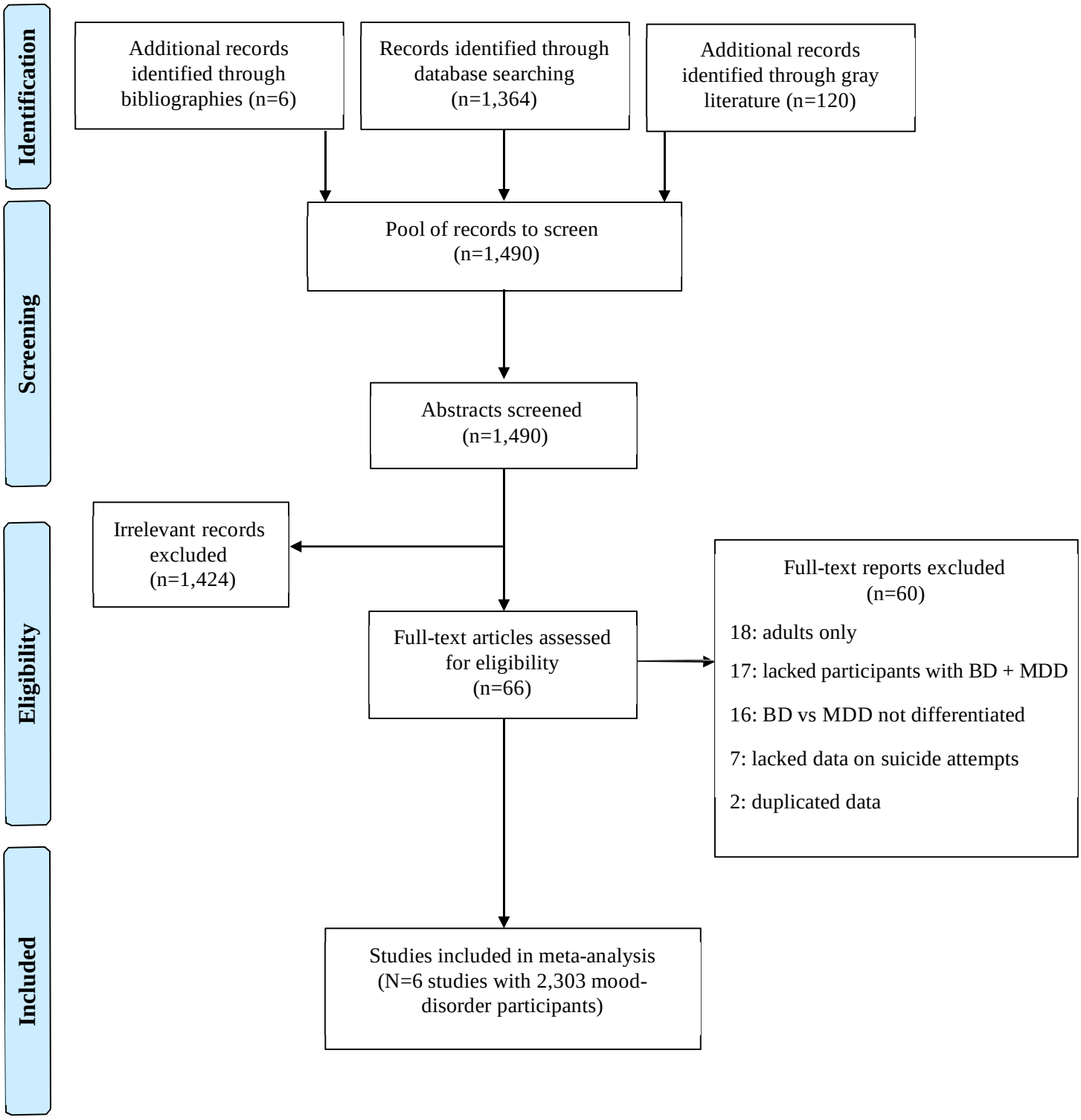
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-III). 3rd Edition. Washington, DC: American Psychiatric Association; 1980.

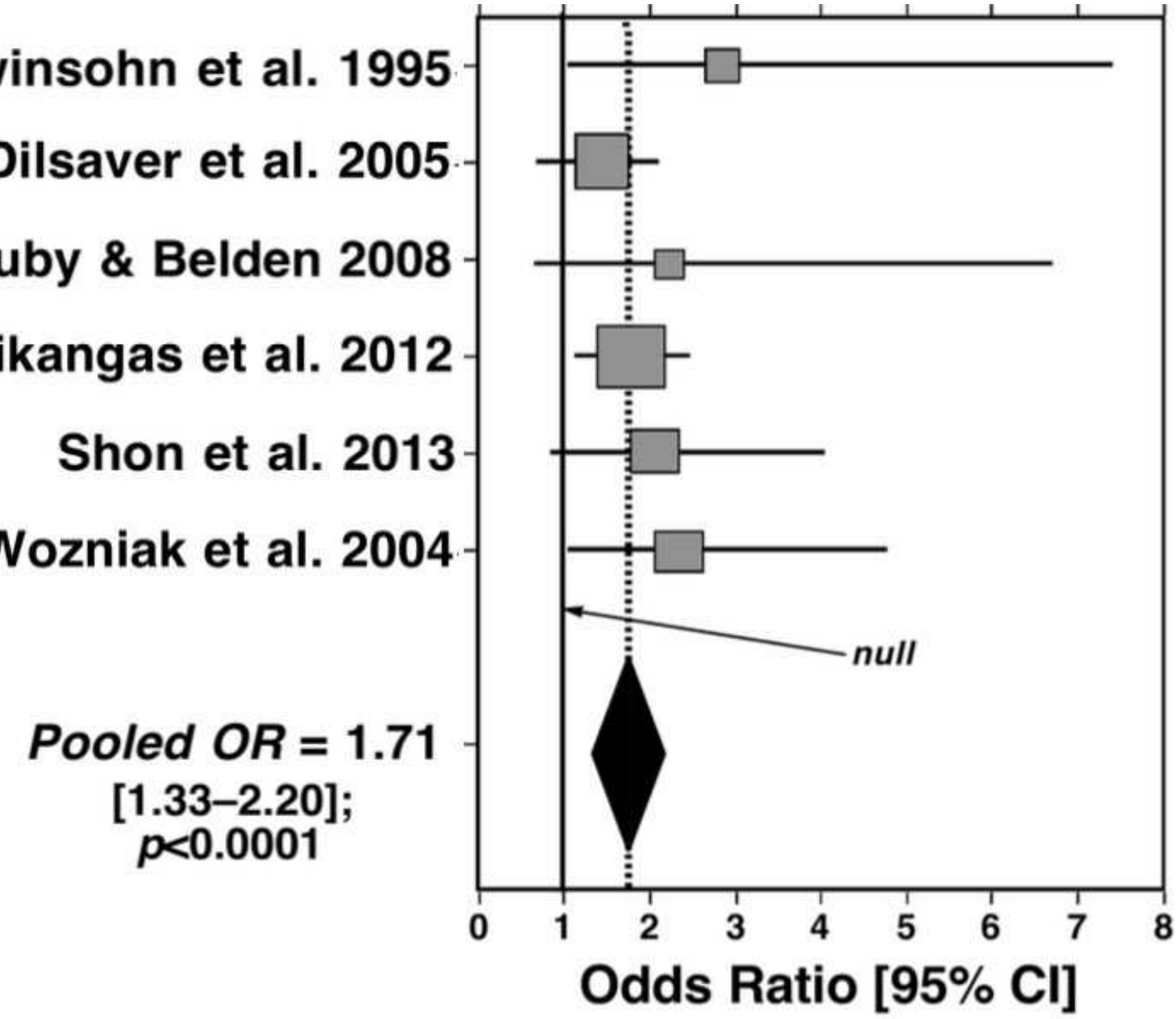
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R). 3rd Edition. Washington, DC: American Psychiatric Association; 1987.

7. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603–605.

8. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.

9. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.


Identification
Screening
Eligibility
Included
Additional records identified through bibliographies (n=6)
Records identified through database searching (n=1,364)
Additional records identified through gray literature (n=120)
Pool of records to screen (n=1,490)
Abstracts screened (n=1,490)
Irrelevant records excluded (n=1,424)
Full-text articles assessed for eligibility (n=66)
Full-text reports excluded (n=60)
18: adults only
17: lacked participants with BD + MDD
16: BD vs MDD not differentiated
7: lacked data on suicide attempts
2: duplicated data
Studies included in meta-analysis (N=6 studies with 2,303 mood-disorder participants)


vinsohn et al. 1995
Dilsaver et al. 2005
uby & Belden 2008
ikangas et al. 2012
Shon et al. 2013
Wozniak et al. 2004
null
Pooled OR = 1.71
[1.33–2.20];
p<0.0001
0
1
2
3
4
5
6
7
8
Odds Ratio [95% CI]