Patterns of Comorbidity Among Girls With ADHD: A Meta-analysis

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abstract

CONTEXT: Although children with attention-deficit/hyperactivity disorder (ADHD) are at elevated risk for comorbid psychopathology, the clinical correlates of ADHD in girls are far less understood relative to boys, despite ADHD being one of the most common childhood disorders in girls.

OBJECTIVE: To meta-analytically summarize rates of comorbid internalizing (anxiety, depression) and externalizing (oppositional defiant disorder [ODD], conduct disorder [CD]) psychopathology among girls with and without ADHD.

DATA SOURCES: Literature searches (PubMed, Google Scholar) identified published studies examining comorbid psychopathology in girls with and without ADHD.

STUDY SELECTION: Eighteen studies (1997 participants) met inclusion criteria and had sufficient data for the meta-analysis.

DATA EXTRACTION: Odds ratios for each comorbid disorder were calculated from available data. Demographic (eg, age, race/ethnicity) and study characteristics (eg, referral source, diagnostic method) were also coded.

RESULTS: Compared with girls without ADHD, girls with ADHD were significantly more likely to meet *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for each comorbid disorder assessed. Relative odds were higher for externalizing (ODD: 5.6×; CD: 9.4×) relative to internalizing disorders (anxiety: 3.2×; depression: 4.2×). Meta-regression revealed larger effect sizes of ADHD on anxiety for studies using multiple diagnostic methods, featuring younger children, and including clinic-referred (versus community-referred) girls; the effect of ADHD on ODD varied based on diagnostic informant.

LIMITATIONS: Findings were derived from cross-sectional studies, precluding causal inferences.

CONCLUSIONS: Girls with ADHD frequently exhibit comorbid externalizing and internalizing disorders. We discuss future research priorities and consider intervention implications for ADHD and comorbid psychopathology in girls.

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Ms Tung collected and coded studies for inclusion, supervised the acquisition of data, carried out the analyses, and drafted the initial manuscript; Dr Li conceptualized and designed the study, supervised the acquisition of data, assisted with interpretation of analyses, and critically reviewed and revised the manuscript; Ms Meza and Ms Jezior collected and coded the studies for inclusion, assisted with drafting the initial manuscript, and reviewed and revised the manuscript; Ms Kianmahd, Mr Hentschel, and Mr O'Neil collected and coded the studies for inclusion and reviewed and revised the manuscript; Dr Lee supervised the acquisition of data, assisted with interpretation of analyses, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Attention-deficit/hyperactivity disorder (ADHD) is a prevalent, childhood-onset neurobehavioral disorder with considerable public health and financial consequences.[1,2] Although ADHD is 2 to 3 times more prevalent in boys than in girls,[3] greater understanding of the clinical presentation of ADHD in girls is needed. Approximately 5.6% of girls are diagnosed with ADHD in childhood, making it among the most prevalent psychiatric disorders in girls.[1,2] Similar to boys, ADHD symptoms in girls frequently persist into adolescence and adulthood, predicting poor mental health, academic, and social outcomes.[4–8] Some studies suggest that boys and girls with ADHD are similarly impaired,[9] whereas other studies suggest that ADHD is more impairing for girls (eg, peer problems)[10] despite being less prevalent. This "gender paradox" is evident across social, academic, and familial domains, which may reflect gender-atypical behavior and marginalization of girls with ADHD.[11–13]

ADHD frequently co-occurs with oppositional defiant disorder (ODD), conduct disorder (CD), anxiety disorders (eg, generalized anxiety disorder, social anxiety), and depressive disorders (eg, major depression).[14–17] However, most studies of ADHD and comorbid psychopathology have relied on predominantly male samples. A meta-analysis of 21 mixed-gender population studies (published between 1987 and 1999) found that children with ADHD were over 10 times more likely to have CD or ODD, whereas they were over 5 times more likely to have depression and 3 times more likely to have an anxiety disorder compared with peers without ADHD.[18] Thus, studies including boys with ADHD have typically focused on comorbid externalizing disorders, such as CD and ODD. In contrast, perhaps because girls overall have higher rates of internalizing (eg, anxiety, depression) versus externalizing disorders,[3,19,20] many previous studies have somewhat narrowly emphasized the association between ADHD and internalizing problems in girls. Indeed, longitudinal studies show that girls with ADHD often experience internalizing problems,[21,22] and children with ADHD and comorbid depressive and/or anxiety disorders exhibit worse outcomes than youth with 1 disorder.[23] At the same time, however, girls with ADHD show increased ODD, CD, and aggression as well, which uniquely predicts severe adult impairments, such as risky sexual behavior, involvement in abusive relationships, and criminality.[22,24–26] Given that internalizing and externalizing psychopathology may differentially predict long-term outcomes for girls, clarifying early patterns of comorbidity in girls with ADHD is imperative to understanding the impact of childhood ADHD on adult outcomes.

To inform the clinical significance of ADHD in girls, comorbid psychopathology must be adequately characterized. Most research on girls with ADHD has compared girls (the minority group) to boys (the majority group), rather than directly comparing girls with versus without ADHD. The lack of gender-matched comparison groups potentially confounds true gender differences in the association between ADHD and comorbid disorders, which could also simply reflect gender differences in rates of psychopathology regardless of ADHD. Girls overall have higher rates of internalizing versus externalizing disorders, but it is unclear if ADHD affects these patterns; clarifying this is important for several reasons. First, because of the perception that internalizing problems are more relevant than externalizing problems for girls with ADHD, treatment of internalizing symptoms is often prioritized (eg, antidepressants), even when externalizing symptoms are present and impairing.[27] Such treatment practices assume that ADHD in girls confers more risk for internalizing than externalizing symptoms. Importantly, results from previous studies of girls with versus without ADHD are mixed, with evidence that ADHD may be particularly predictive of anxiety and depression in girls[28,29]; alternatively, other studies suggest that ADHD poses a higher risk for externalizing disorders and that girls with ADHD have higher rates of internalizing symptoms than boys simply due to the main effect of gender.[30] Similar to ADHD symptoms, externalizing behaviors in girls may reflect the gender paradox: despite its lower prevalence in girls compared with boys, externalizing symptoms are more impairing and produce worse outcomes for girls, underscoring the clinical significance of comorbid externalizing symptoms. Overall, these data suggest that narrowly focusing on internalizing disorders among girls with ADHD may undermine timely detection and treatment of externalizing problems in girls. Clarifying the relative effect of ADHD on comorbid externalizing versus internalizing disorders for girls requires direct comparison of girls with and without ADHD, the primary goal of this meta-analysis.

Given the increasing number of studies consisting of girls with and without ADHD,[24,31] meta-analysis of comorbidity among girls with ADHD is timely. Thus, this meta-analysis characterized patterns of comorbid anxiety, depression, ODD, and CD among girls with versus without ADHD and also examined potential moderators of comorbidity patterns. Group differences in comorbidity rates may be sensitive to diagnostic procedures (eg, interview versus rating scale), sample characteristics (eg, age, race/ethnicity), and referral sources (eg, clinic-referred versus community-referred).[32] For instance,

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clinic-referred samples typically exhibit elevated rates of comorbidity. Because girls with ADHD are often underreferred relative to boys, clinic-referred girls may be particularly impaired compared with nonreferred girls. Participant age is also relevant given that rates of lifetime ADHD increase from preschool to adolescence.[33] Similarly, ADHD is most prevalent in non-Hispanic white children and adolescents.[1] Given these divergent patterns of association, a secondary goal of this meta-analysis is to examine study characteristics that may affect estimates of comorbidity among girls with ADHD.

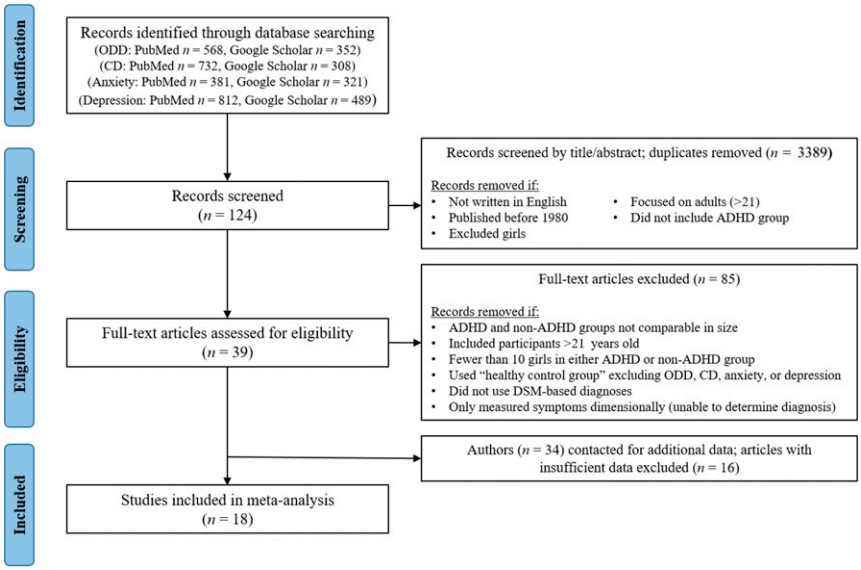

FIGURE 1
Flowchart of study inclusion.

METHODS

Search Procedure

Potential studies were identified using separate searches for each comorbid disorder (ODD, CD, anxiety, depression) in PubMed and Google Scholar. PubMed searches targeted studies with ADHD and each comorbid disorder in the title or abstract. For example, the search terms for ODD were: (ADHD OR attention-deficit hyperactivity disorder[Title/Abstract]) AND (ODD OR oppositional defiant disorder[title/abstract]). Additional PubMed filters were activated based on eligibility criteria: "Article types: Clinical Trial, Controlled Clinical Trial, Journal Article, Randomized Controlled Trial, Validation Studies; Publication dates From 1980/01/01; Species: Humans; Language: English; Sex: Female; Ages: Child: birth–18 years, Adolescent: 13–18 years, Child: 6–12 years." Similarly, Google Scholar searches targeted studies published after 1980 that included ADHD and the comorbid disorder in the title. Sample search terms for ODD were: allintitle: ("Oppositional Defiant Disorder" OR ODD) (ADHD OR ADD OR "attention deficit hyperactivity disorder"). The final search was completed in August 2014.

Study Selection and Data Extraction

Figure 1 shows the number of citations for each disorder yielded by the initial search as well as the study selection process. Following expert recommendations, 4 coders (I.T., J.I.M., K.L.J., and J.S.K.) screened these citations based on their titles and abstracts.[34] After reducing the number of studies based on broad exclusionary criteria and removing duplicates, 124 unique samples were identified and independently coded by 2 extensively trained bachelor-level coders (P.G.H. and P.M.O.) who were highly reliable (average $\kappa = 0.84$). Both in the screening and coding stages, coders met weekly with a doctoral-level supervisor (J.J.L. and/or I.T.) to resolve discrepancies. During this time, samples were additionally evaluated according to the inclusion criteria listed in Fig 1. To maximize validity, studies were required to assess ADHD and comorbid disorders using *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-based measures. Studies that produced diagnostic categories or could reasonably be recoded into diagnostic groups were considered. For studies that described comorbidity dimensionally using DSM-based measures ($n = 17$), we contacted authors to request raw data to create diagnostic groups. Given the significant variability in the number and types of anxiety disorders assessed, we included studies that assessed at least 1 DSM-based anxiety disorder. For depression, we focused on studies that assessed major depression, but we also included studies based on "any depressive disorder" (eg, including dysthymia) if depressive disorders were not reported separately.

These procedures produced 39 unique samples that were then coded for the following information: (1) number of girls with and without ADHD and (2) number of girls with ODD, CD, any anxiety disorder, and depression (separately) for the ADHD and non-ADHD groups. For the 3 longitudinal studies, variables were coded from the first available data point. Finally, because few studies exclusively focused on girls with ADHD, most studies ($n = 34$) did not directly report diagnostic rates separately for girls with and without ADHD. Thus, we contacted authors to request those data. Eighteen unique

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studies had sufficient data for the final analyses.

Moderator Variables

To explore potential moderators of the association between ADHD and each comorbid disorder, key demographic and methodological characteristics were coded for each study. Demographic factors included: (1) participant age range (child, adolescent, both) and (2) racial/ethnic composition (% white). Methodological variables included: (1) sample source (clinic-referred, community-referred, both), (2) medication status (% medicated), (3) ADHD subtypes included (any subtype, combined only), (4) informant for ADHD and comorbid disorders (parent, child, teacher), and (5) assessment method for ADHD and comorbid disorders (interview, rating scale). Finally, publication year (eg, 2003) was included as a potential moderator.

Calculation of Effect Sizes

Odds ratios (OR) were calculated from data extracted from publications or from data provided by study authors. We estimated 4 separate effect sizes of the association between ADHD (versus non-ADHD) and the following dichotomously measured disorders: (1) ODD, (2) CD, (3), any anxiety disorder, and (4) depression. For example, to estimate the OR for ADHD versus non-ADHD for ODD, we used the formula $(a + d)/(b + c)$, in which a = the number of girls with ADHD and ODD, b = the number of ADHD girls without ODD, c = the number of non-ADHD girls with ODD, and d = the number of non-ADHD girls without ODD. When cell frequencies equaled 0, we added 0.5 to each of the 4 cells to calculate the effect size.[34]

Statistical Analyses

We employed a random-effects model to estimate the OR, its 95% confidence interval (CI), and its significance. Publication bias was evaluated through visual inspection of Begg's funnel plot,[35] which plots each effect size with its SE,[35] as well as using Egger's test for funnel plot asymmetry, where significant asymmetry indicates potential publication bias.[36] To adjust for bias, we implemented Duval and Tweedie's "trim and fill" method,[37] a widely used method of addressing publication bias by first "trimming" (removing) studies causing the funnel plot asymmetry and using the trimmed funnel plot to estimate the true funnel "center," then "filling in" the funnel by replacing the removed studies and their reflected counterparts around the center to produce a new pooled estimate based on the adjusted funnel plot. Simulation studies suggest that this method improves effect size CIs and detects how much point estimates may change as a result of potentially missing studies.[38] Heterogeneity in effect sizes was estimated using the Cochran Q test; for outcomes with significant heterogeneity, we tested moderation separately for each demographic or methodological factor. All data were analyzed in Stata, version 12 (Stata Corp, College Station, TX) by using the meta, metarim, and metareg commands.

RESULTS

The final analyses included 1997 participants across 18 independent studies,[10,28,39–47] described in Table 1. Although the initial search included studies published since 1980, all of the final 18 studies were published in or after 1999, with 12 studies published since 2005. Sample sizes varied (mean n = 100 girls total) with studies being more likely to include whites (mean, 77% white) and school-aged girls (mean age range, 8.5–13.5 years). Of the 18 studies, 11 included community- and clinic-referred participants, 6 used community-referred samples, and 1 exclusively featured clinic-referred youth. Most studies (n = 14) included any ADHD subtype in the ADHD group, and diagnoses were typically based on a diagnostic interview (n = 10) or a combination of interview and rating scale (n = 4). All studies used parents as informants, although some combined parent and child (n = 5) or parent and teacher report (n = 4) to establish diagnostic status. Fifteen studies used computerized and comprehensive structured diagnostic interviews (ie, Diagnostic Interview Schedule for Children, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Diagnostic Interview for Children and Adolescents-IV) and 3 studies used standardized rating scales (ie, Swanson, Nolan and Pelham Parent and Teacher Rating Scales or ADHD Rating Scale IV) to diagnose DSM-IV ADHD. In addition to construct validity based on DSM symptoms, these widely used diagnostic tools also have superior psychometric properties, including test–retest reliability and convergent validity.[48–50] Thus, the studies included in the meta-analysis employed rigorous diagnostic procedures to ascertain ADHD.

ADHD and ODD

All 18 studies (n = 1997 participants) were included in this analysis. Among girls with ADHD, 42% were diagnosed with ODD relative to 5% of girls without ADHD. The initial pooled random effects OR estimated that girls with ADHD were >11 times more likely to have ODD than girls without ADHD (Fig 2). However, potential publication bias was indicated by Egger's test (t = 2.65, P = .02) and marginally by Begg's test (τ = 51, P = .06); the Begg's funnel plot suggested that smaller studies were more likely to yield larger ORs for ODD than larger studies. After adjusting for potential bias using the

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TABLE 1 Demographic and Methodological Characteristics of Studies Included in the Meta-analysis

Source	Girls (*N*)	Referral Source	Age Range (y)	% White	% Medicated	ADHD Subtypes	Assessment Method	Informant	Outcomes
Becker et al (39)	ADHD: 45 Control: 25	ADHD: community Control: community	7–11	71.21	Not provided	Any	Interview	Parent	Anxiety, depression, ODD, CD
Bussing et al (51)	ADHD: 29 Control: 146	ADHD: community Control: community	14–21	59.43	55.17	Any	Interview	Parent	ODD, CD
Chang et al (52)	ADHD: 63 Control: 19	ADHD: clinic Control: community	7–13	97.56	Not provided	Any	Interview	Parent	ODD, CD
Chronis et al (40)	ADHD: 18 Control: 24	ADHD: clinic/community Control: community	4–6	65.22	10	Any	Interview and rating scale	Parent and teacher	Anxiety, depression, ODD, CD
Hinshaw (41)	ADHD: 140 Control: 88	ADHD: clinic/community Control: clinic/community	6–12	52.62	50.71	Combined only	Interview	Parent	Anxiety, depression, ODD, CD
Humphreys and Lee (42)	ADHD: 32 Control: 41	ADHD: clinic/community Control: clinic/community	5–10	51.56	Not provided	Any	Interview	Parent	Anxiety, depression, ODD, CD
Hurtig et al (53)	ADHD: 29 Control: 69	ADHD: community Control: community	16–18	100	0	Any	Interview	Parent and child	Anxiety, depression, ODD, CD
Kadesjö et al (54)	ADHD: 30 Control: 16	ADHD: clinic Control: community	3–7	100	0	Any	Interview	Parent	ODD
Laucht et al (43)	ADHD: 15 Control: 144	ADHD: clinic Control: clinic	14–16	99.4	60	Any	Interview	Parent and child	Anxiety, depression, ODD, CD
Martel et al (55)	ADHD: 98 Control: 103	ADHD: clinic/community Control: clinic/community	6–17	79.1	Not provided	Combined only	Interview	Parent and child	ODD, CD
Mikami et al (44)	ADHD: 11 Control: 60	ADHD: clinic/community Control: community	6–9	87.32	4	Any	Interview and rating scale	Parent and teacher	Anxiety, depression, ODD, CD
Mikami et al (56)	ADHD: 20 Control: 20	ADHD: clinic/community Control: community	6–10	85	65	Combined only	Rating scale	Parent	Anxiety, depression, ODD, CD
Ohan and Johnston (57)	ADHD: 40 Control: 40	ADHD: clinic/community Control: clinic/community	9–12	83	Not provided	Any	Rating scale	Parent	ODD
Pheula et al (45)	ADHD: 32 Control: 32	ADHD: community Control: community	6–16	62.5	43.75	Combined only	Interview	Parent and child	Anxiety, depression, ODD, CD
Rucklidge and Tannock (28)	ADHD: 24 Control: 28	ADHD: clinic Control: clinic/community	13–16	Not provided	45.8	Any	Interview and rating scale	Parent, teacher, and child	Anxiety, depression, ODD, CD
Sciberras et al (58)	ADHD: 22 Control: 20	ADHD: clinic/community Control: community	12–18	Not provided	72.73	Any	Rating scale	Parent	ODD
Seymour et al (46)	ADHD: 12 Control: 18	ADHD: community Control: community	10–14	63.33	66.67	Any	Interview and rating scale	Parent and teacher	Depression, ODD, CD
Willcutt et al (47)	ADHD: 136 Control: 308	ADHD: community Control: community	8–18	75	Not provided	Any	Rating scale	Parent and teacher	Anxiety, depression, ODD, CD

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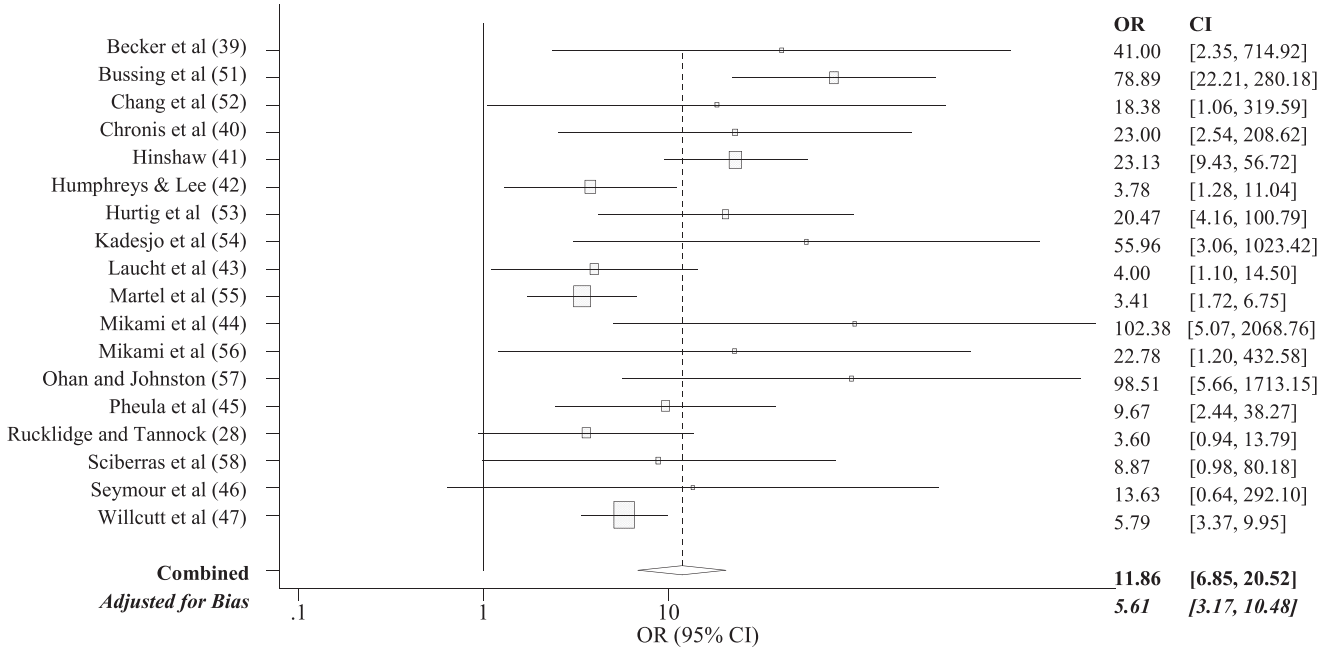

FIGURE 2

Forest plot graphing ORs for ODD among girls with versus without ADHD. Each study is represented by 1 horizontal line and box, with location of the box on the x-axis corresponding to the point estimate for each study, and the size of the box indicating the weight (inverse of variance) of the study. The diamond and dotted vertical line depict the overall effect estimate for all 18 studies, with the width of the diamond representing the CI.

trim and fill method, the re-estimated effect indicated that girls with ADHD were 5.6 times more likely to be diagnosed with ODD than girls without ADHD.

Given significant heterogeneity in effect sizes for ODD ($Q = 41.51$, $df = 17$, $P < .01$), we employed meta-regression to test potential moderators of heterogeneous effect sizes (Supplemental Table 2). Age, race, sample source, medication status, ADHD subtypes, assessment method, and publication year did not influence the association between ADHD and comorbid ODD. Only informant (parent, child, teacher) significantly moderated the effect; relative to parent-report only, studies that combined parent and child ratings for ADHD and ODD produced smaller effect sizes. However, there were no significant differences between parent-report only versus combined parent- and teacher-report.

ADHD and CD

Fifteen studies were included in the meta-analysis of ADHD and CD. A total of 12.8% of girls with ADHD were diagnosed with CD relative to 0.8% of girls without ADHD. The pooled effect revealed that girls with ADHD were >9 times more likely to be diagnosed with CD than girls without ADHD (Fig 3). Egger's ($t = -0.28$, $P = .79$) and Begg's test ($\tau = -31$, $P = .14$) did not suggest publication bias, and there was no evidence of significant heterogeneity ($Q = 8.01$, $df = 14$, $P = .89$).

ADHD and Anxiety

Eleven studies were included in the meta-analysis of ADHD and anxiety disorders. Compared with 13.9% of girls without ADHD, 37.7% of girls with ADHD met diagnostic criteria for an anxiety disorder. Girls with ADHD were 3.66 times more likely to meet criteria for an anxiety disorder than girls without ADHD (Fig 4). Begg's test ($\tau = 17$, $P = .21$) did not suggest potential publication bias, although Egger's test was marginal ($t = 1.82$, $P = .10$). Visual examination of Begg's test suggested that smaller studies may be slightly more likely to report larger effects. After adjusting for potential bias using the trim and fill method, the effect size for comorbid anxiety (OR = 3.19) was relatively similar.

Given evidence of significant heterogeneity ($Q = 22.46$, $df = 10$, $P < .01$), we employed meta-regression to examine potential moderators (Supplemental Table 3). Effect sizes were smaller for studies that included adolescents (versus children aged <13 years), and the association between ADHD and anxiety was larger in samples with clinic-referred girls (versus community-referred). Finally, multimethod assessments of ADHD (interview and rating scale) produced higher rates of comorbid anxiety compared with interview-only assessments. Participant race, medication status, ADHD subtypes, diagnostic informant, publication year, and the number of anxiety disorders assessed (varying from 1–7 disorders across studies) were not significant moderators.

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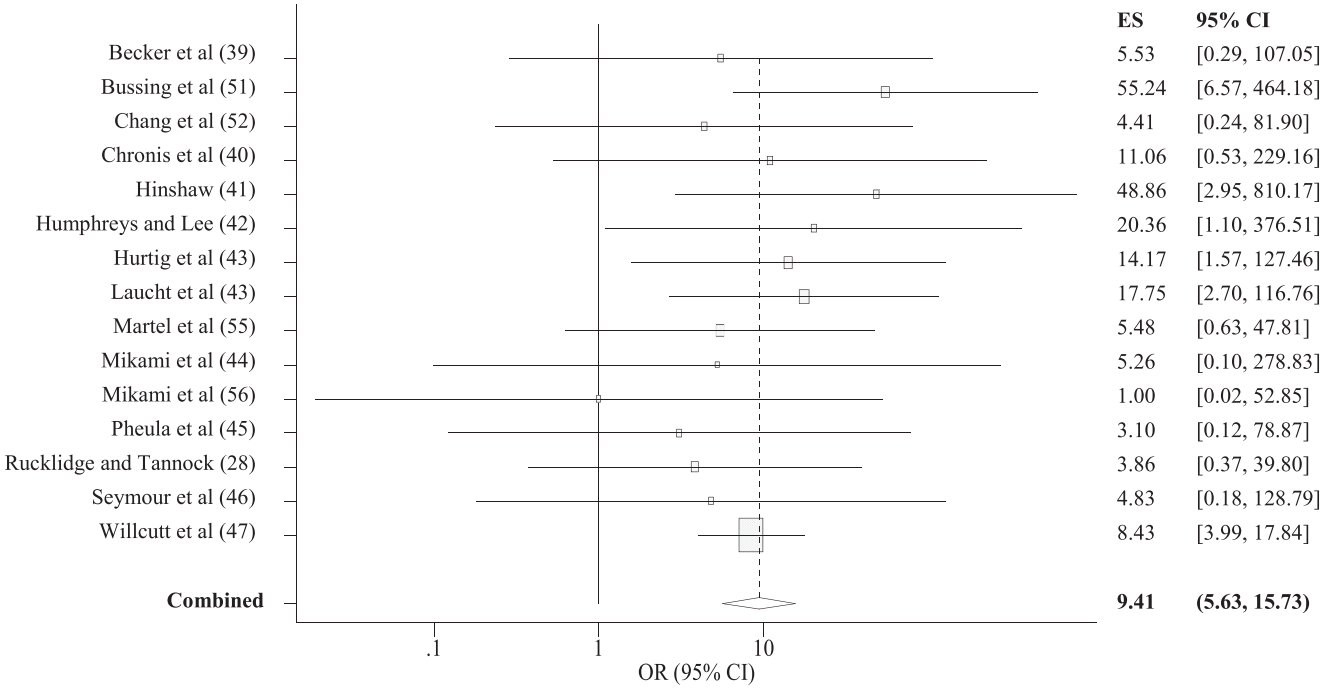

FIGURE 3

Forest plot graphing ORs for CD among girls with versus without ADHD. Each study is represented by 1 horizontal line and box, with location of the box on the x-axis corresponding to the point estimate for each study, and the size of the box indicating the weight (inverse of variance) of the study. The diamond and dotted vertical line depict the overall effect estimate for all 15 studies, with the width of the diamond representing the CI. ES, effect size.

ADHD and Depression

Twelve studies were included in the meta-analysis of ADHD and comorbid depression. A total of 10.3% of girls with ADHD were diagnosed with depression relative to 2.9% of non-ADHD girls. Girls with ADHD were >4 times more likely to be diagnosed with depression than non-ADHD girls (Fig 5). Although Begg's test for publication bias was not significant ($\tau = -10$, $P = .54$), Egger's test marginally suggested bias ($t = -2.03$, $P = .07$); examination of Begg's funnel plot suggested that smaller studies tended to report smaller effect sizes for depression. There was no evidence of significant heterogeneity ($Q = 15.05$, $df = 11$, $P < .18$).

DISCUSSION

Across 18 studies, girls with ADHD were significantly more likely to meet DSM-IV criteria for externalizing (ODD, CD) and internalizing (anxiety, depression) disorders than non-ADHD girls. Despite having generally higher rates of internalizing psychopathology relative to boys,[3,19,20] this meta-analysis indicated that girls with ADHD have significantly higher odds of having comorbid CD and ODD than either anxiety or depression. Overall, effect sizes for ADHD and comorbid CD and depression were consistent across studies, but heterogeneity was observed for ODD and anxiety. The effect of ADHD on comorbid anxiety was larger in studies with clinic-referred (versus community-referred) girls, using diagnostic methods that combined interview and rating scale, and including children aged <13 years only (versus adolescents). The effect of ADHD on ODD was moderated by informant, with smaller effects for studies employing child self-report in addition to parent-report. We observed evidence of potential publication bias where studies with smaller samples reported larger effect sizes for ODD and, to a lesser extent, anxiety.[59] Effect sizes were unaffected by sample racial/ethnic composition, ADHD subtypes, and study publication year. These findings suggest that girls with ADHD are at substantially higher odds for comorbid externalizing and internalizing disorders than girls without ADHD.

The high rate of comorbid anxiety disorders (37.7%) and relatively lower rate of comorbid CD (12.8%) among girls with ADHD is consistent with previous studies comparing girls to boys with ADHD.[30,60,61] However, compared with girls without ADHD, girls with ADHD were most likely to have comorbid CD (9.4 times) and ODD (5.6 times), followed by depression (4.2 times) and anxiety (3.2 times). The finding that ADHD posed higher odds for comorbid externalizing than internalizing disorders is consistent with a previous meta-analysis of mixed-gender studies,[18] suggesting that patterns of comorbidity in boys and girls with ADHD are comparable. Although CD is less prevalent in girls

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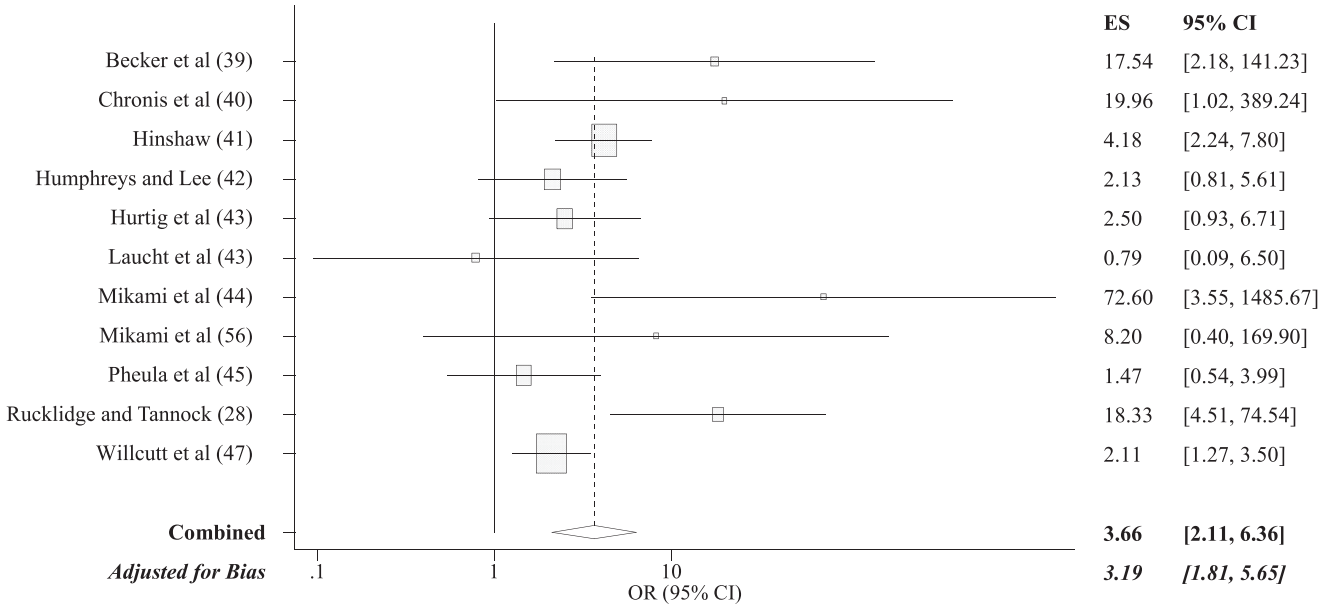

FIGURE 4

Forest plot graphing ORs for anxiety among girls with versus without ADHD. Each study is represented by 1 horizontal line and box, with location of the box on the x-axis corresponding to the point estimate for each study, and the size of the box indicating the weight (inverse of variance) of the study. The diamond and dotted vertical line depict the overall effect estimate for all 11 studies, with the width of the diamond representing the CI.

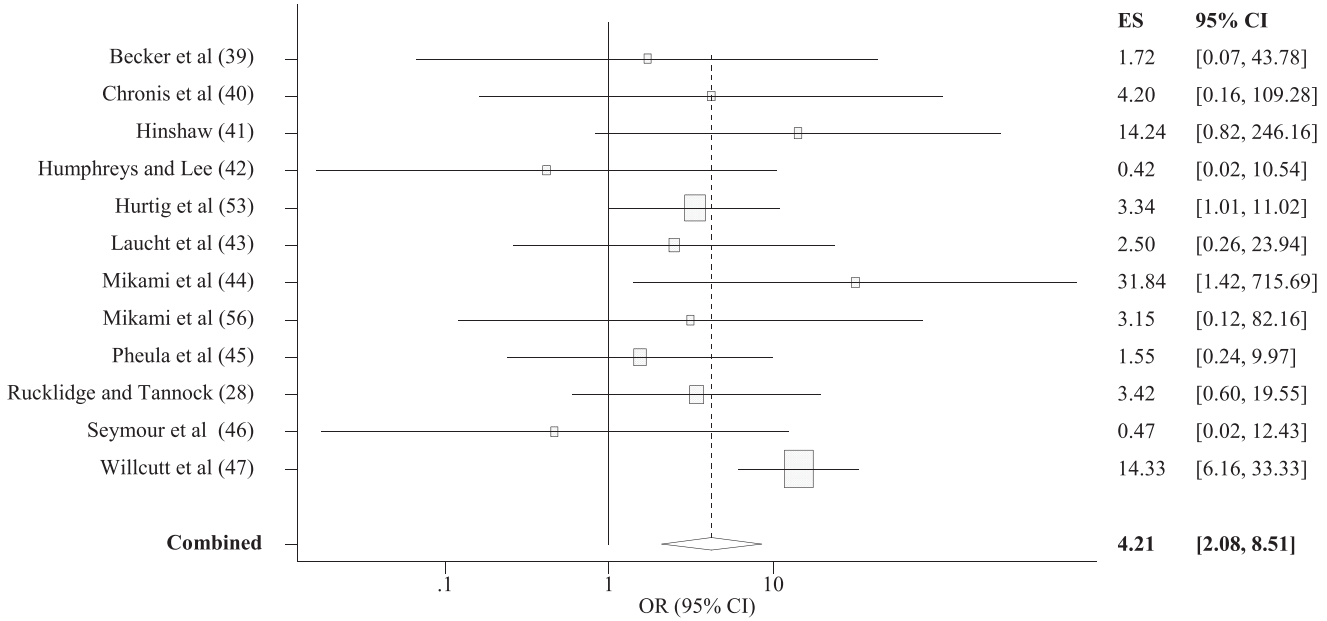

FIGURE 5

Forest plot graphing ORs for depression among girls with versus without ADHD. Each study is represented by 1 horizontal line and box, with location of the box on the x-axis corresponding to the point estimate for each study, and the size of the box indicating the weight (inverse of variance) of the study. The diamond and dotted vertical line depict the overall effect estimate for all 12 studies, with the width of the diamond representing the CI.

than boys, girls with ADHD were >9 times more likely to be diagnosed with CD than non-ADHD girls. Importantly, compared with girls with ADHD only, girls with ADHD and comorbid ODD and/or CD symptoms have particularly poor health and behavioral outcomes (eg, risky sexual behaviors).[6,62,63] Furthermore, because of the perception that girls with ADHD exhibit fewer behavior problems than boys, girls who are clinic-referred for ADHD are often treated for their internalizing symptoms, even when externalizing symptoms are also evident.[27] Given the substantial odds that ADHD poses to girls for externalizing problems

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in this meta-analysis, careful assessment of early ADHD and ODD/CD in girls should be emphasized in clinical settings to facilitate early intervention of ADHD and comorbid externalizing symptoms to prevent later negative outcomes.

These meta-analytic results suggest that, compared with girls without ADHD, girls with ADHD have significantly higher odds of having a comorbid externalizing disorder than an internalizing disorder. The pathways of risk for developing internalizing disorders among girls with ADHD may be due to individual and environmental factors that are independent of their ADHD, such as cognitive factors (eg, perceived control), temperament (eg, inhibition), and unique family factors (eg, parental overprotectiveness).[64–66] Thus, future studies should focus on understanding the factors that independently contribute to anxiety and depression for girls beyond those associated with ADHD. In addition to the direct treatment of ADHD symptoms in girls, reduction of comorbid internalizing psychopathology likely necessitates more complex treatment plans that separately target anxiety/depression symptoms (eg, cognitive behavioral therapy).[67]

Significant variability in effect sizes was observed across studies for ADHD with ODD and anxiety disorders. No single moderator explained the heterogeneity in effect sizes for ODD and anxiety; moderators were disorder-specific. Compared with studies relying on parent-report only, studies that combined parent and child reports yielded smaller effect sizes of the association between ADHD and ODD, but no differences were observed between parent and teacher reports. This is consistent with lower rates of youth self-reported psychopathology compared with parent- and teacher-report.[68] Studies including clinic-referred girls reported stronger associations between ADHD and anxiety, whereas combined diagnostic methods (interview and rating scale) yielded higher effect sizes for anxiety than interview-only methods. Finally, girls with ADHD in samples including adolescents (versus children aged <13 years) had lower rates of comorbid anxiety, which is somewhat surprising given that anxiety generally increases with age.[69] The present findings may reflect that samples exclusively focused on childhood assess different types of anxiety disorders (eg, separation anxiety, specific phobia) compared with other forms of anxiety (eg, generalized anxiety); however, the number of anxiety disorders assessed among studies did not influence effect sizes of ADHD and anxiety.

These findings were derived from cross-sectional studies, thus precluding causal inferences. It is unclear how variability in ADHD symptoms across development prospectively affects adult psychopathology, an important area of inquiry given the frequent persistence of ADHD. For example, rates of depression and CD were less prevalent in the non-ADHD groups compared with epidemiologic samples, which likely reflects the relative youth of study participants (versus adolescents or adults). Given that the median age of onset for CD and depression is in early adolescence and young adulthood,[70] respectively, studies must include a full range of development to clarify how patterns of comorbidity change over time. Especially for girls, ADHD may be particularly salient in initiating cascading effects that lead to long-term impairments because of the elevated stigma associated with the disorder.[10,11] Thus, longitudinal studies are necessary to describe the developmental outcomes of girls with and without ADHD.

Importantly, an accurate estimation of comorbidity in girls with ADHD depends on knowing the true prevalence of ADHD in girls, a critical issue that remains largely unresolved.[29,71] Some studies suggest that ADHD may be underdiagnosed in girls,[27,72] whereas others suggest that ADHD is overdiagnosed in boys.[73] The assumption of underdiagnosis of ADHD in girls may suggest that the comorbidity estimates derived in this study are inflated, because they are based on girls with particularly severe (ie, impairing) ADHD symptoms. Alternatively, it is also possible that rates of psychopathology in girls without ADHD were underestimated because these girls were more likely to be drawn from community versus clinical samples compared with girls with ADHD. Furthermore, relative to girls, boys with ADHD are more likely to be referred for treatment, reflecting a general delay in recognizing, diagnosing, and treating ADHD in girls that contributes to more severe symptoms among referred girls.[74] This is consistent with the present findings that clinic-referred samples reported higher rates of comorbid anxiety than community-referred samples, although this was not the case for comorbid ODD, CD, or depression. Thus, despite our findings that indicate substantially higher odds for comorbidity among girls with versus without ADHD, securing the true estimates of comorbidity for girls with ADHD demands first improving diagnostic accuracy of childhood ADHD in girls.

Furthermore, although this meta-analysis included any subtype of ADHD, and studies did not consistently report subtype differences for girls, the number of children with the inattentive subtype may be higher in community samples, whereas combined type cases are more common in clinic-referred samples.[60,75] Because inattention may

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be specifically linked to separation anxiety,[76] whereas hyperactivity predicts more externalizing problems,[77] generalized anxiety disorder,[76] and suicide attempts and self-injury,[5] clarifying these differential associations has important implications for the assessment of ADHD and prevention of psychopathology. Future studies that directly explore ADHD subtypes and comorbidity patterns will elucidate how inattention and hyperactivity may differentially relate to comorbid psychopathology in girls.

This meta-analysis provides the first formal characterization that girls with ADHD are at substantially higher odds for comorbid CD, ODD, depression, and anxiety disorders compared with girls without ADHD. Given the rising prevalence and significant impairment of ADHD among girls,[78] these findings attest to the need for increased scientific and clinical efforts to improve the diagnosis and treatment of girls with ADHD. Furthermore, these meta-analytic findings suggest that ADHD poses particularly higher odds for comorbid externalizing compared with internalizing disorders in girls. Careful assessment of early ADHD and ODD/CD in girls should be emphasized in clinical settings to facilitate early intervention and to prevent later negative outcomes associated with externalizing behaviors. Future longitudinal studies that investigate the developmental course of these associations are necessary to identifying the putative mechanisms underlying pathways between ADHD and other psychopathology in girls.

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ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
CD: conduct disorder
CI: confidence interval
DSM: *Diagnostic and Statistical Manual of Mental Disorders*
ODD: oppositional defiant disorder
OR: odds ratio

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