REVIEW

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Systematic Review and Meta-Analysis: Anxiety and Depressive Disorders in Offspring of Parents With Anxiety Disorders

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Objective: We conducted meta-analyses to assess risk for anxiety disorders among offspring of parents with anxiety disorders, and to establish whether there is evidence of specificity of risk for anxiety disorders as opposed to depression in offspring, and whether particular parent anxiety disorders confer risks for particular child anxiety disorders. We also examined whether risk was moderated by offspring age, gender, temperament, and the presence of depressive disorders in parents.

Method: We searched PsycINFO, PubMed, and Web of Science in June, 2016, and July, 2017 (PROSPERO CRD42016048814). Study inclusion criteria were as follows: published in peer-reviewed journals; contained at least one group of parents with anxiety disorders and at least one comparison group of parents who did not have anxiety disorders; reported rates of anxiety disorders in offspring; and used validated diagnostic tools to ascertain diagnoses. We used random and mixed-effects models and evaluated study quality.

Results: We included 25 studies (7,285 offspring). Where parents had an anxiety disorder, offspring were significantly more likely to have anxiety (risk ratio [RR] = 1.76, 95% CI = 1.58−1.96) and depressive disorders (RR = 1.31, 95% CI = 1.13−1.52) than offspring of parents without anxiety disorders. Parent panic disorder and generalized anxiety disorder appeared to confer particular risk. Risk was greater for offspring anxiety than for depressive disorders (RR = 2.50, 95% CI = 1.50−4.16), and specifically for offspring generalized anxiety disorder, separation anxiety disorder and specific phobia, but there was no evidence that children of parents with particular anxiety disorders were at increased risk for the same particular anxiety disorders. Moderation analyses were possible only for offspring age, sex, and parental depressive disorder; none were significant.

Conclusion: Parent anxiety disorders pose specific risks of anxiety disorders to offspring. However, there is limited support for transmission of the same particular anxiety disorder. These results support the potential for targeted prevention of anxiety disorders.

Key words: anxiety disorders, depression, risk factors

J Am Acad Child Adolesc Psychiatry 2019;58(1):46–60.

Anxiety disorders are the most common psychiatric disorders among children and adolescents,[1] with a median age of onset of 11 years.[2] They are associated with increased risk for other psychiatric disorders, including mood disorders, substance abuse, and psychosis,[3-5] and carry a significant global economic burden.[6] Prevention of these common and serious disorders will advance with an improved understanding of risk factors.

One risk factor for anxiety disorders in children, examined in family aggregation studies, is anxiety disorders in parents.[7] In the first study to examine this risk, Turner *et al.* reported the odds of anxiety disorders to be more than seven times greater in children of parents with anxiety disorders than in children of psychiatrically healthy parents.[8] Other studies examining risks posed by parent anxiety disorders have also found an increased risk of depression in offspring.[9,10] However, some studies of parents with anxiety disorders have found lower, and some insignificant, odds of offspring anxiety disorders and/or depression, relative to offspring of healthy parents[9,11] and to offspring of parents without anxiety disorders but with other psychiatric disorders.[12,13] These discrepant findings regarding risk for anxiety and depressive disorders in offspring of parents with anxiety disorders have been addressed in a single previous meta-analysis of 9 studies, including 972 offspring.[14] Children of parents with anxiety disorders were found to be at increased risk for anxiety disorders generally (odds ratio [OR] = 3.91, 95% CI = 2.51–6.1), depressive disorders (OR = 2.67, 95% CI = 1.69–4.23) and agoraphobia, generalized anxiety disorder (GAD), panic disorder, separation anxiety disorder, social phobia, and specific phobias, relative to offspring of parents without psychiatric disorders. Here, we update our understanding of the issues examined by Micco *et al.*[14] regarding risks posed by parent anxiety disorders generally for research question (RQ) 1, offspring anxiety disorders generally; RQ 2, offspring

depressive disorders; and RQ 3, offspring particular anxiety disorders. Furthermore, we address 3 questions (RQ 4–RQ6) not previously addressed in the literature regarding specific risks posed by parent anxiety disorders generally and particular parent anxiety disorders.

First, regarding disorder class, Murray *et al.*[15] raised the question of whether parent anxiety disorders are associated uniquely with offspring anxiety disorders or with child internalizing disorders more broadly. Rates of anxiety and depressive disorders have both been found to be raised in the offspring of parents with anxiety disorders, with greater odds of anxiety than of depressive disorders.[14] However, the previous meta-analysis did not directly compare the rates from studies in which offspring were assessed for both anxiety and depressive disorders. So, what has not been addressed meta-analytically is whether parent anxiety disorders pose a greater risk to offspring of anxiety disorders or of depressive disorders. Thus, we ask RQ 4, which is whether offspring whose parents have anxiety disorders are at greater risk for anxiety disorders or for depressive disorders (in studies in which both are assessed).

Our second novel question focuses on whether particular parent anxiety disorders place offspring at increased risk for anxiety disorders. Longitudinal cohort studies have examined this for parent panic disorder[10,16,17] in the Massachusetts General Hospital at-risk study, and for parent Social Anxiety Disorder in the Reading Longitudinal Study[18-20] and the German Early Developmental Stages of Psychopathology study, in which parental GAD was also examined.[21-24] Thus, we ask: RQ 5: are the rates of anxiety disorders higher in offspring of parents with particular anxiety disorders compared to offspring of nonanxious parents?

Third, there is evidence of increased risk of first-degree relatives (for example, sibling or avuncular relatives) having the same particular anxiety disorder as each other, including social anxiety disorder[25-27] and specific phobia.[28] More specifically, particular parent anxiety disorders, including social anxiety disorder and separation anxiety disorder, have been found to pose a specific risk for the same particular anxiety disorder to offspring.[10,23] Thus, we ask RQ 6: where parents have a particular anxiety disorder, are offspring more likely to have that same particular anxiety disorder, or only different anxiety disorders?

Longitudinal studies have shown the importance of risk factors other than parent anxiety disorder for the development of offspring anxiety disorders, of which we examine four. First, rates of anxiety disorders have repeatedly been found to be greater in females than in males.[29,30] Second, the temperamental style of behavioral inhibition has been implicated in the development of anxiety disorders,[31,32] including in the context of parent anxiety disorders.[33] Third, age is associated with different rates of particular anxiety disorders.[34,35] Fourth, parental depressive disorders have been associated with an increased risk of offspring anxiety disorders.[14,36] Here, we examine whether the presence of parental depressive disorders moderates risks to offspring of particular outcomes from different parent risk groups. In particular we ask: in nonanxious parents, as the rate of parent depressive disorder increases, does the risk of offspring anxiety disorder increase; and, in anxious parents, as the rate of depressive disorder increases, does this modify the relative risk of anxiety versus depressive disorders in offspring? Thus, we set out to sharpen the focus of our meta-analysis by examining these four potential moderators for each of the risk relationships specified in questions 1 to 6, below.

In summary, we examine the risks posed by parent anxiety disorders generally (ie, any, but no specific, "anxiety disorder") for (1) offspring anxiety disorders generally and (2) offspring depressive disorders. We clarify issues of specificity by asking (3) whether parent anxiety disorders place offspring at greater risk for particular anxiety disorders, and (4) whether offspring whose parents have anxiety disorders are at greater risk for anxiety disorders or for depressive disorders (in studies in which both are assessed). We examine the risk posed by particular parent anxiety disorders to offspring for (5) anxiety disorders generally and (6) the same particular anxiety disorder (see Figure 1 for diagrams of the relationships in questions 1−6). Finally, we examine whether these relationships are weaker or stronger in the presence of other risk factors.

METHOD

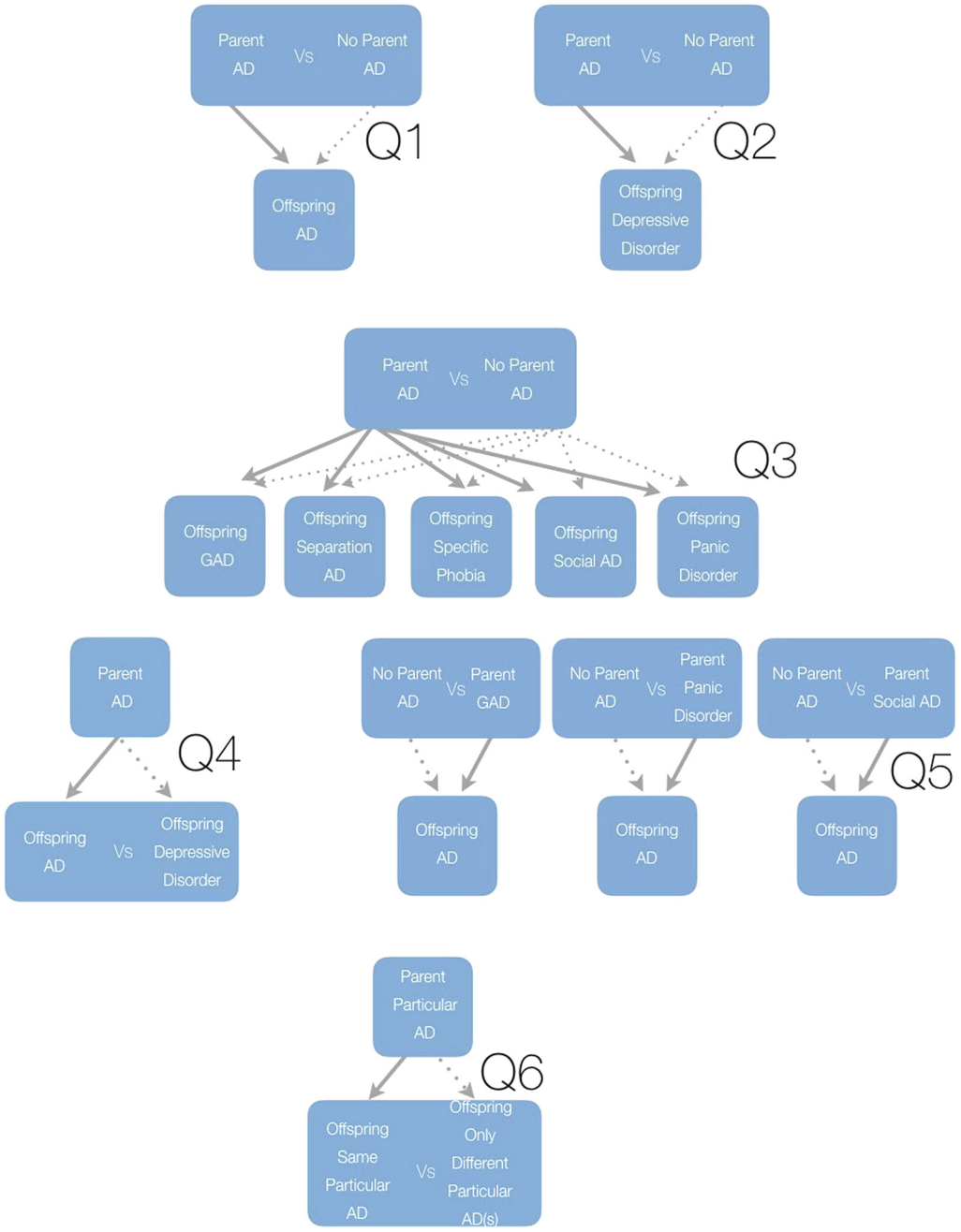
Protocol

We specified methods, inclusion and exclusion criteria, and analyses in advance, and registered them in a protocol on the International Prospective Register of Systematic Reviews (PROSPERO; protocol number: CRD42016048814). We adapted the original protocol to account for the narrower scope of this systematic review. Specifically, this report focuses only on studies reporting diagnostic outcomes for anxiety. Examining the risks of continuous features of anxiety is conceptually separate from our focus here, so those studies that met the criteria in our registered protocol but reported only continuous outcomes will be reported separately.

Eligibility Criteria

We included articles that met the following inclusion criteria: published in peer-reviewed journals[37]; contained at least one group of parents with anxiety disorders and at least one comparison group of parents who did not have anxiety

FIGURE 1 Diagrams to Show Directions of Expected Risk Relationships Examined in Research Questions (RQ) 1 to 6



Note: *Solid lines show greater risk and dotted lines shower lower risk. AD = anxiety disorder; GAD = Generalized Anxiety Disorder. Please note color figures are available online.*

disorders; reported rates of anxiety disorders in offspring; and used validated diagnostic tools to ascertain diagnoses.

We excluded articles that met the following exclusion criteria: participants were identified in light of issues other than parent psychiatric disorder (eg, child anxiety disorder, parental cancer, diabetes, dental surgery); and parents had no anxiety disorder classified in *DSM 5* (where neither posttraumatic stress disorder nor obsessive compulsive disorder is classified as an "anxiety disorder").

Information Sources and Search Terms

The electronic databases: PsycINFO (1967 onward), PubMed (no date restriction), and Web of Science Core Collection (1970 onward) were searched in the second week

of June 2016 and third week of July 2017 (this rerun yielded a single extra paper[38]) for reports published in English in a peer-reviewed journal. The search strategies and syntax for each database are contained in the Supplement 1, available online. We also completed a hand search of references from previous reviews and papers included in this review. We contacted study authors when data in a paper were reported in a format that we could not analyze.

Outcome Measures

The primary outcomes for this review were offspring anxiety disorder diagnoses and depressive disorder diagnoses.

Study Selection

P.L. retrieved references, which were all independently screened and rated by P.L. and one of two research assistants. There was 100% agreement between raters.

Study Quality Assessment

P.L. and a research assistant both assessed study quality of all papers using an adapted version of the Standard Quality Assessment Criteria for Evaluating Primary Research Papers for quantitative studies.[39] Items on the checklist that were irrelevant to studies included in this review were removed (for example, "If interventional and random allocation was possible, was it described?"), and other items' wording was modified for the purpose of this review (for example, from "Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias?" to "anxiety disorder diagnostic interviews clearly defined?"). We kept items regarding study design, sample selection, sample description and the methods of assessment of anxiety disorders. The items were as follows:

I. Is the study design evident and appropriate?
II. Is the method of participant selection described and appropriate?
III. Are the participant characteristics sufficiently described?
IV. Are the anxiety disorder diagnostic interviews clearly defined?
V. Are the anxiety disorder diagnostic tools of high quality/robust?

For all studies, each item was rated as:

0. No—study did not resolve this item.
1. Partial—study addressed query partially.
2. Yes—study addressed query to high standard.

Data Extraction and Statistical Analyses

We extracted data for each outcome as well as relevant information about the participants, as summarized in Table 1.[8,10-12,18,22,32,40-56,62] All data were extracted by both P.L. and a research assistant. Any disagreement was resolved by CC. A full list of data extracted is available from the authors.

We used the R statistical environment, with the metafor package for meta-analysis[57] and its "weightr" package for weighted sensitivity analyses.

We calculated risk ratios (RR) for diagnostic outcome reports using random effects meta-analyses.[37] We used the Knapp and Hartung adjustment because random-effects modeling meta-analysis is known to increase the type I error rate, especially when there is heterogeneity of variance or a small number of studies.[58] We used the I^2 statistic to calculate the impact of heterogeneity of effect sizes between studies.[59] We conducted meta-regressions (mixed effects meta-analyses) to assess for moderation of effects by continuous variables (rate of depressive disorders in parents, offspring age, proportion of female to male offspring participants).

Publication Bias

We used funnel plots and Egger tests to assess the risk of publication bias and used a priori weight functions for sensitivity analyses.[60]

RESULTS

In total, 53 papers met our inclusion criteria. Table 1 provides characteristics of studies retained in the analyses. (Table S1, available online, provides characteristics of studies that met inclusion criteria but did not provide data for analysis.) Figure 2 presents the PRISMA flowchart. Of these, 26 were reports from follow-up studies. We removed multiple reports from the same cohorts to retain the most recent reports. We were unable to extract analyzable data from two papers.[42,61] Two papers reporting results from the same sample were retained because we could extract data for offspring anxiety disorders from only one of them[62] and data for offspring depressive disorders from only the other.[52] Thus, we retained 25 papers from 24 studies with 7,285 unique offspring. Table 2 contains a summary of the results.

Regarding RQ 1, children of parents with anxiety disorders were at significantly greater risk for anxiety disorders (1.76, 95% CI = 1.58−1.96, k = 22, n = 6,674), with low heterogeneity between studies (I^2 = 0.01%) (Figure 3); and, regarding RQ 2), were at greater risk of depressive disorders (RR: 1.31, 95% CI = 1.13−1.52, k = 17, n = 5,009) with low heterogeneity (I^2 = 28%) (Figure 4) than children of parents without anxiety disorders. Regarding RQ 3, offspring of parents with anxiety disorders were at risk for GAD (RR = 2.19, 95% CI = 1.58−3.04, k = 5, n = 3,330, I^2 = 0%), separation anxiety disorder

TABLE 1 Characteristics of Studies Included in Meta-Analysis

Study	Offspring (n)	Age Range (mean)	Sex (% F)	Ethnicity	Parent Dx Tool	AD Parent Dxs	Control Parent Dxs	Offspring Dx Tool	Recruitment
Beesdo *et al.*, 2010[22,a]	3,021	21–34	—	German sample	CAPI DIA-x / M-CIDI	Phobias or PD; GAD	Depression; Substance Use; No Psychiatric Disorder	CAPI DIA-x / M-CIDI	Community
Beidel and Turner, 1997[40]	129	7–12 (9.6)	44	83% European Am 15% African Am; 2% E Indian	SCID (DSM III)	PD, social phobia, OCD; MDD + GAD; MDD + OCD	Depression; No Psychiatric Disorder	K-SADS	Clinical and community
Bhat and Srinivasan, 2006[41,a]	117	11–16	46	100% Indian	CIDI	PD	Depression; No Psychiatric disorder	MAGIC	Clinical
Biederman *et al.*, 1991[18]	121	(9.2)	41.3	100 White	NIMH-DIS	PD W Ag; PD + MDD	MDD; Other Psych; No Psychiatric disorder	DICA-P	Clinical and community
Biederman *et al.*, 2006[62]	319	7–18	46	95 White	SCID	PD/AG; PD/AG + MDD	MDD; No PD/AG or MDD	K-SADS E	Clinical and community
Biederman *et al.*, 2007[52]	233	7–18 (10.9)	—	95 White	SCID	PD/AG; PDD + MDD	MDD; No PD/AG or MDD	K-SADS-E (<18 y) SCID (>17 y)	Clinical and community
Breslau *et al.*, 1987[43]	331	8–23	—	80 White	DIS	GAD; GAD + MDD	No GAD or MDD	DISC	Probands from control group in study of children with disabilities
Buckley and Woodruff-Borden, 2006[44]	49	6–12 (8.4)	55	80 White	ADIS-IV	GAD, PD, social + specific phobia	Never psychiatrically ill	ADIS-IV-P/C	Community
Capps *et al.*, 1996[45]	32	8–14	67	69 White 13 African Am; 13 Asian Am; 6 Latino	ADIS-R	PD/AG	Never psychiatrically ill	DISC-2.1	Clinical and community
Chapman *et al.*, 2012[46]	100	6–17	51	100 African Am	ADIS-IV	PD/AG, social phobia, GAD, OCD, specific phobia (various); PTSD; MDD	No Psychiatric Diagnosis	ADIS-IV-P/C	Community
Cox *et al.*, 2012[47a]	352	10+ (18)	49	66 White	SCID; SCID-II	Not specified	Mood Disorder	KSADS-PL	Clinical
Hudson and Dodd, 2012[32,a]	160	8–9	50	64 Oceanic; 20 European; 10 Asian	ADIS	AD	No anxiety disorder	ADIS-P-IV	Community

(*continued*)

TABLE 1 Continued

Study	Offspring (n)	Age Range (mean)	Sex (% F)	Ethnicity	Parent Dx Tool	AD Parent Dxs	Control Parent Dxs	Offspring Dx Tool	Recruitment
Kaplan *et al.*, 1996[11]	50	6–18 (9.5)	67	—	SADS-L	AG; MDD; SUD; bipolar disorder, OCD	No anxiety disorder	DICA-P	Clinical and community
Klein *et al.*, 2005 [48,a]	775	24	—	—	K-SADS; LIFE	Any anxiety disorder	MDD, Alcohol dependence, Drug dependence	SCID-NP	Community
Kujawa *et al.*, 2014[49,a]	407	(9)	45	89.7 Causcasian; 7.6 African Am; 2.7 Asian	SCID	AD; AD + MDD	MDD; No maternal anxiety or depression	K-SADS-PL	Community
Manelis *et al.*, 2015[50,a]	81	7–17 (13.8)	58	—	SCID-IV	AD; AD + bipolar disorder	Bipolar disorder; no family history of any major psychiatric diagnosis	K-SADS-PL	Clinical and community
McClellan *et al.*, 1990[51]	163	7–17	51	—	DIS	PD	MDD; no major psychiatric diagnosis,	DICA; DICA-P	Clinical and community
Merikangas *et al.*, 1998[10]	192	7–18	49	100 White	SADS	PD/AG; Soc and / or GAD	substance abuse, or dependence; never psychiatrically ill	K-SADS-E	Clinical and community
Mogg *et al.*, 2012[52]	119	9–14 (11.8)	100		SCID	PD	No psychiatric diagnosis	ADIS-P	Clinical and community
Mufson *et al.*, 1992[53]	214	6–23	53	—	SADS	PD + MDD	MDD; never psychiatrically ill	K-SADS-E	Community
Murray *et al.*, 2014[21]	136	4–5	56.7	>99 White	SCID	Social Phobia	No anxiety disorder	ADIS?	Community
Pine *et al.*, 2005[12]	142	9–19	—	—	SCID	PD; PD+MDD	MDD; Psychiatrically healthy parents	PARIS	Clinical, dental, community
Schneider *et al.*, 2009[54]	107	13–23	—	German sample	Mini-DIPS	PD/AG	No psychiatric disorder	F-DIPS	Clinical and community

(*continued*)

TABLE 1 Continued

Study	Offspring (n)	Age Range (mean)	Sex (% F)	Ethnicity	Parent Dx Tool	AD Parent Dxs	Control Parent Dxs	Offspring Dx Tool	Recruitment
Schrock and Woodruff-Borden, 2010[55]	158	3—12	44.3	76 White; 16 African Am; 3 Hispanic; 1 Asian; 1 Native Am; 3 other	ADIS	PD/AG; Social Phobia; GAD; Specific Phobia	No anxiety disorder, no diagnoses	ADIS-P (3—5 y) ADIS/PC (6—12 y)	Clinical and community
Turner *et al.*, 1987[8]	59	7—12	42	93 White; 7 African Am	ADIS	AG; OCD	Dysthymic disorder; no *DSM-III* diagnoses	CAS	Clinical and community
Whaley *et al.*, 1999[56]	36	7—14 (10.3)	44	78 White; 11 Latino; 6 Asian Am; 6 other	ADIS-IV	AD (inc PD/AG, OCD, GAD, social phobia, specific phobia, hypochondriasis, MDD	Psychologically healthy	K-SADS	Clinical and community

Note: AD = anxiety disorder; AD Parents Dxs = diagnoses in parents with anxiety disorders; ADIS(-R) = Anxiety Disorders Interview Schedule (for DSM III-R); ADIS-IV = Anxiety Disorders Interview Schedule (for DSM-IV); Am, American; ASPD = Antisocial personality disorder; CAPI = computer-assisted personal interview; version of the (DIA-X / M-CIDI) Munich—Composite International Diagnostic Interview; CAS = Children's Assessment Schedule; CD = conduct disorder; CIDI = Composite International Diagnostic Interview; Control Parent Dxs = psychiatric disorders in parents without anxiety disorders; DIA-X = Munich-Composite International Diagnostic Interview; DICA-P = Diagnostic Interview for Children and Adolescents–Parent Version; DIPS = German version of ADIS-R; DIS = Diagnostic Interview Schedule; DISC = Diagnostic Interview Schedule for Children; F-DIPS = German version of ADIS for DSM-IV; F = female; GAD = generalized anxiety disorder; Kinder DIPS = German Child version of ADIS-R; Kinder-DIPS = German version of Child ADIS-R; LIFE = Longitudinal Interval Follow-up Evaluation; MAGIC = Missouri Assessment of Genetics Interview for Children; M-CIDI = Munich—Composite International Diagnostic Interview; MDD = major depressive disorder; Mini-DIPS = German translation of ADIS-IV-L; NIMH-DIS = National Institute of Mental Health Diagnostic Interview Schedule; NYHRSFHI = New York High Risk Study Family History Interview; Offspring Dx Tool = tool used to assess psychiatric disorders in offspring; PAPA = Preschool Age Psychiatric Assessment; Parent Dx Tool = tool used to assess psychiatric disorders in parents; PARIS = Parent As Respondent Informant Schedule; SADS-L = Schedule for Affective Disorders and Schizophrenia—Lifetime Version; SCID = Structured Clinical Interview for DSM (NP—nonpatient version); SUD = substance use disorder.

[a]*Data provided by authors.*

(RR = 2.94, 95% CI = 1.26−6.86, k = 7, n = 424, I^2 = 39%), and specific phobia (RR = 2.29, 95% CI = 1.11−4.75, k = 4, n = 269, I^2 = 0%) compared to offspring of parents without an anxiety disorder, but there were no significant differences in risks for offspring panic disorder (RR = 2.17, 95% CI = 0.97–4.87, k = 6, n = 400, I^2 = 0%) and social anxiety disorder (RR = 2.98, 95% CI = 0.80–11.08, k = 5, n = 295) where heterogeneity was moderate (I^2 = 49%). Regarding RQ 4, where studies assessed for both anxiety and depressive disorders, the risk for anxiety disorders was significantly greater than the risk for depressive disorders (RR = 2.50, 95% CI = 1.50–4.16, k = 13, n = 3,220) with high heterogeneity (I^2 = 88 %) (Figure 5). Regarding RQ 5, there was significant risk for anxiety disorders in offspring of parents with panic disorder (RR = 1.82, 95% CI = 1.30–2.55, k = 6, n = 773) with high heterogeneity (I^2 = 76%) or GAD (RR = 2.54, 95% CI = 1.86−3.45, k = 2, n = 3,614) with moderate heterogeneity (I^2 = 50%), but not social anxiety disorder (RR = 3.49, 95% CI = 0.27–45.67, k = 2, n = 3,157), where heterogeneity between studies was high (I^2 = 72%) compared to that in offspring of parents without an anxiety disorder. We could not examine the risk to offspring associated with parental specific phobia or separation anxiety disorder because there were no eligible studies. Finally, regarding RQ 6, for which offspring had at least one anxiety disorder and their parents had a particular anxiety disorder, there was no evidence that children were at greater risk for the same particular anxiety disorder than for all other anxiety disorders. For GAD (RR = .39, 95% CI = 0.19−0.83, k = 3, n = 792), although heterogeneity was high (I^2 = 85%), and panic disorder (RR = 0.26, 95% CI = 0.18−0.39, k = 4, n = 530, I^2 = 0%) there was a greater chance that offspring would have a different disorder to their parents than have the same disorder, and for social anxiety disorder there was not a significant difference in the risk of same versus other anxiety disorder (RR = 0.61, 95% CI = 0.35–1.09, k = 3, n = 730), although heterogeneity was high (I^2 = 75%).

Regarding rating study quality, interrater reliability was good (Cohen's κ = 0.779, 95% CI = 0.632−0.925). Studies were generally highly rated in four domains: evident and appropriate designs; descriptions of participant characteristics; definitions of anxiety disorder diagnostic tools; and quality of diagnostic tools (Figure S1, available online). The main area of concern was that 11 studies were scored as only "partially addressing" their methods of participant selection.

Funnel plots (Figures S2 and S3, available online) and Egger test results were consistent with publication bias for studies reporting offspring anxiety (z = 3.36, p < .0001) and for those reporting offspring depressive disorders (z =2.15, p = .003). The bias appears to reflect studies with medium or larger standard errors (ie, those with a smaller n), with null results being underreported in the published literature. We used Vevea and Woods' weight-function model to analyze sensitivity.[60] The estimates for offspring anxiety (RR = 1.75–1.78) and depressive disorders (RR = 1.26–1.32) proved robust. This is consistent with publication bias being an unlikely influence on results.

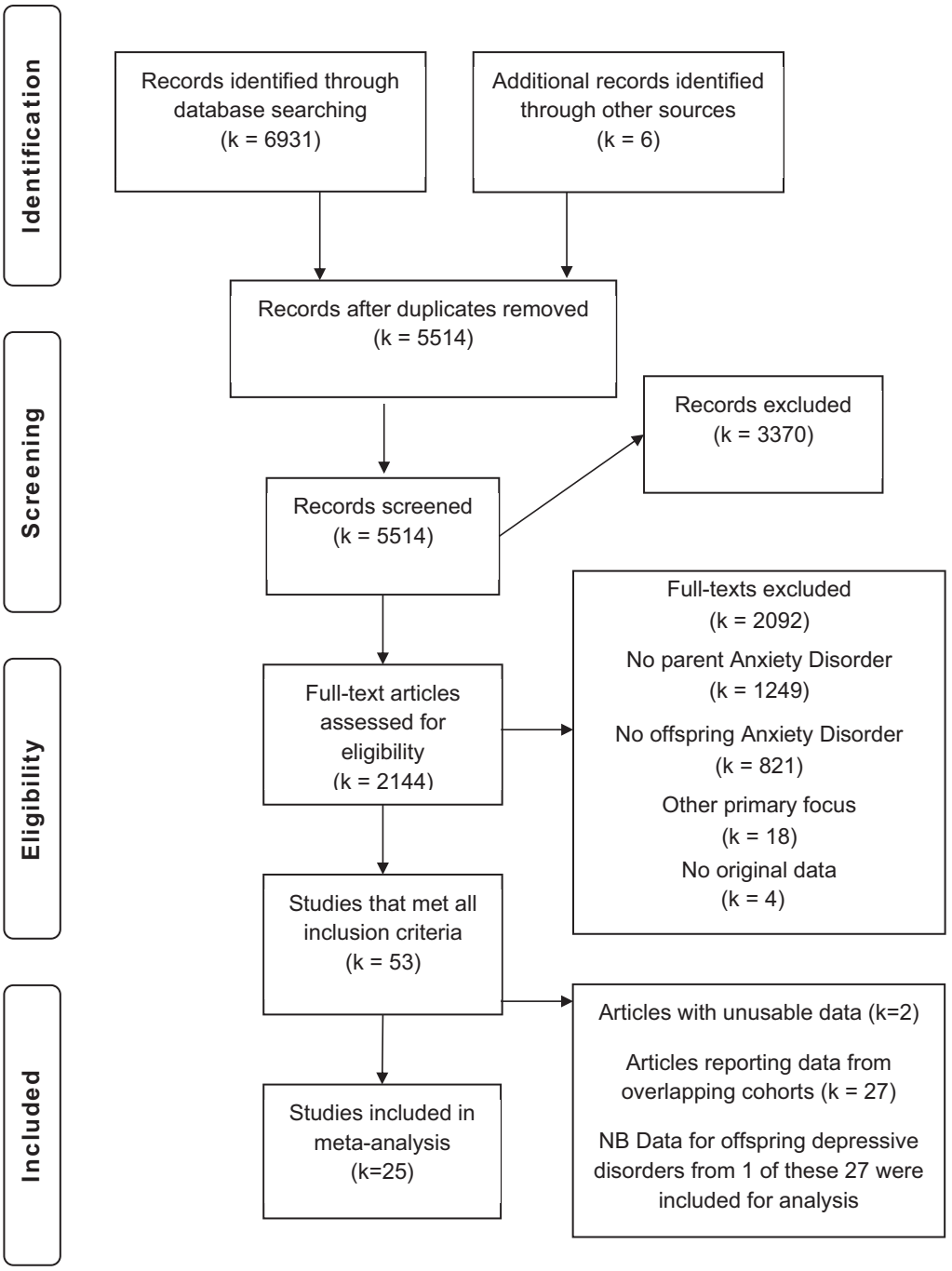
There was no support for offspring mean age moderating the risk for any outcome. Temperament was reported in too few studies to examine it as a moderator. There was limited evidence of moderation by (1) offspring gender of the risk posed by parent anxiety disorders for offspring anxiety disorders, and (2) the presence of parent depressive disorders of the risk posed by parent anxiety disorder for offspring separation anxiety disorder in particular (Figures S4 and S5, available online). The association between anxiety disorders in parents and offspring was higher when there was a greater proportion of female offspring in the study (QM_1 = 5.63, p = .02). This finding appeared to be accounted for by one study with only female participants,[63] and the moderation effect was no longer significant when this study was excluded (QM_1 = 2.93, p = .09). The relationship between anxiety disorders in parents and separation anxiety disorder in offspring was weaker when parents also had depressive disorders. However, when two outlying studies, which included no psychiatrically healthy parents, were removed, the moderation effect became nonsignificant (p = .20).

DISCUSSION

Consistent with the previous meta-analysis by Micco *et al.*,[14] we found that children of parents with anxiety disorders are at increased risk for both anxiety and depressive disorders. We extended the findings of the previous meta-analysis by demonstrating that the risk for offspring anxiety disorders is higher than the risk for offspring depression (RR = 2.50). The effect sizes that we obtained for risk for offspring anxiety (RR = 1.76) and depressive disorders (RR = 1.31) are smaller than those reported in the previous meta-analysis (anxiety; OR = 3.91; depression; OR = 2.67). This is likely to reflect the greater number of included studies (an additional 11 studies with 5,393 offspring). Indeed the effect sizes reported in many of these more recent studies are smaller than those in earlier studies, consistent with Ioannidis' concept of the "decline effect."[64]

As well as identifying this general risk, it is scientifically and clinically important to examine the specific risks posed

FIGURE 2 PRISMA Flow Diagram of Selection of Studies



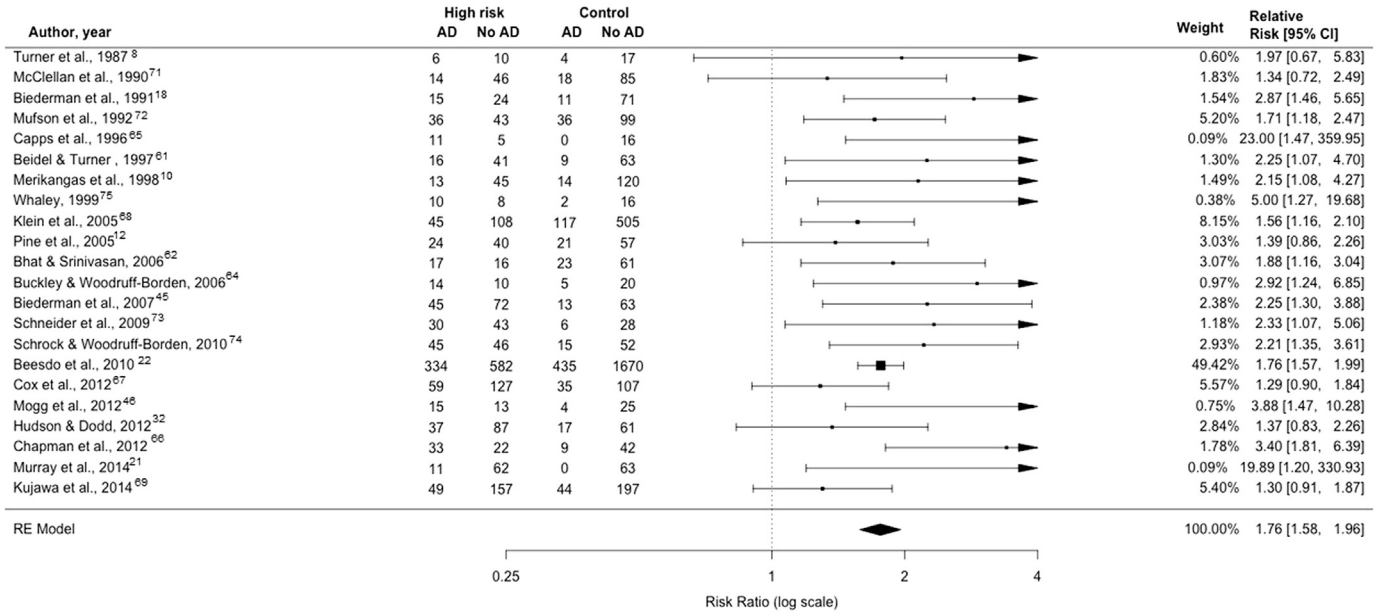
Note: *AD = anxiety disorder; GAD = generalized anxiety disorder.*

TABLE 2 Summary of Results

Offspring Outcome	Parent Risk Group	Parent Gontrol Group	Studies, k		Risk			Heterogeneity
					RR	95% CI	p	I^2 %
AD	AD	Without AD		22	1.76	1.58–1.96	<.0001	0
			Sensitivity analyses	21	Lowest 1.74	1.57–1.93	<.0001	0
				21	Highest 1.84	1.55–2.18	<.0001	26
Depressive disorder	AD	Without AD		17	1.31	1.13–1.52	.001	0
			Sensitivity analyses	16	Lowest 1.29	1.10–1.52	.004	0
				16	Highest 1.54	1.05–2.25	.03	24
GAD	AD	Without AD		15	2.19	1.58–3.04	<.0001	0
			Sensitivity analyses	4	Lowest 2.03	0.88–4.68	.09	0
				4	Highest 2.25	1.59–3.19	<.0001	0
Panic disorder	AD	Without AD		6	2.02	0.87–4.67	.1	0
			Sensitivity analyses	5	Lowest 1.87	0.81–4.35	.24	0
				5	Highest 3.31	0.87–12.6	.18	0
Separation anxiety disorder	AD	Without AD		7	2.94	1.26–6.86	.01	39
			Sensitivity analyses	6	Lowest 4.32	1.56–11.96	.01	44
				6	Highest 2.16	1.07–4.36	.03	22
Social anxiety disorder	AD	Without AD		5	2.98	0.80–11.08	.1	49
			Sensitivity analyses	4	Lowest 2.17	0.56–8.40	.26	47
				4	Highest 4.74	1.83–12.29	.001	0
Specific phobia	AD	Without AD		4	2.29	1.11–4.75	.03	0
			Sensitivity analyses	3	Lowest 1.62	0.67–3.9	.28	0
				3	Highest 2.83	1.27–6.29	.01	0
AD vs. depressive disorder	AD	—		10	2.50	1.50–4.16	.004	88
			Sensitivity analyses	9	Lowest 2.16	1.32–3.51	.002	84
				9	Highest 2.77	1.69–4.54	.005	79
AD	GAD	Without AD		2	2.54	1.86–3.45	<.001	99
			Sensitivity analyses	—	—	—	—	—
AD	Panic Disorder	Without AD		6	1.82	1.30–2.56	<.0001	95
			Sensitivity analyses	5	Lowest 1.54	1.24–1.91	<.0001	6
				5	Highest 2.05	1.37–3.06	.005	55
AD	Social AD	Without AD		3	3.49	0.27–45.7	.34	99
			Sensitivity analyses	2	Lowest 1.29	1.1–1.53	.002	0
				2	Highest 19.9	1.12–330	.037	0
GAD vs. AD without GAD	GAD	—		2	.39	0.19–0.83	.015	99
			Sensitivity analyses	—	—	—	—	—
Panic disorder vs. AD without panic disorder	Panic Disorder	—		4	.25	0.17–0.36	<.0001	76
			Sensitivity analyses	3	Lowest .23	0.13–0.39	<.0001	0
				3	Highest .26	0.17–0.39	<.0001	0
Social AD vs. AD without social AD	Social AD	—		3	.61	0.35–1.09	.09	75
			Sensitivity analyses	2	Lowest .46	0.31–0.69	.0002	0
				2	Highest .82	0.55–1.24	.035	0

Note: Sensitivity analyses used the leave-one-out method. Significant results shown in boldface type. AD = anxiety disorder; GAD = generalized anxiety disorder; RR = risk ratio.

FIGURE 3 Forest Plot for Meta-Analysis of Risk Posed by Parent Anxiety Disorder for Offspring Anxiety Disorder

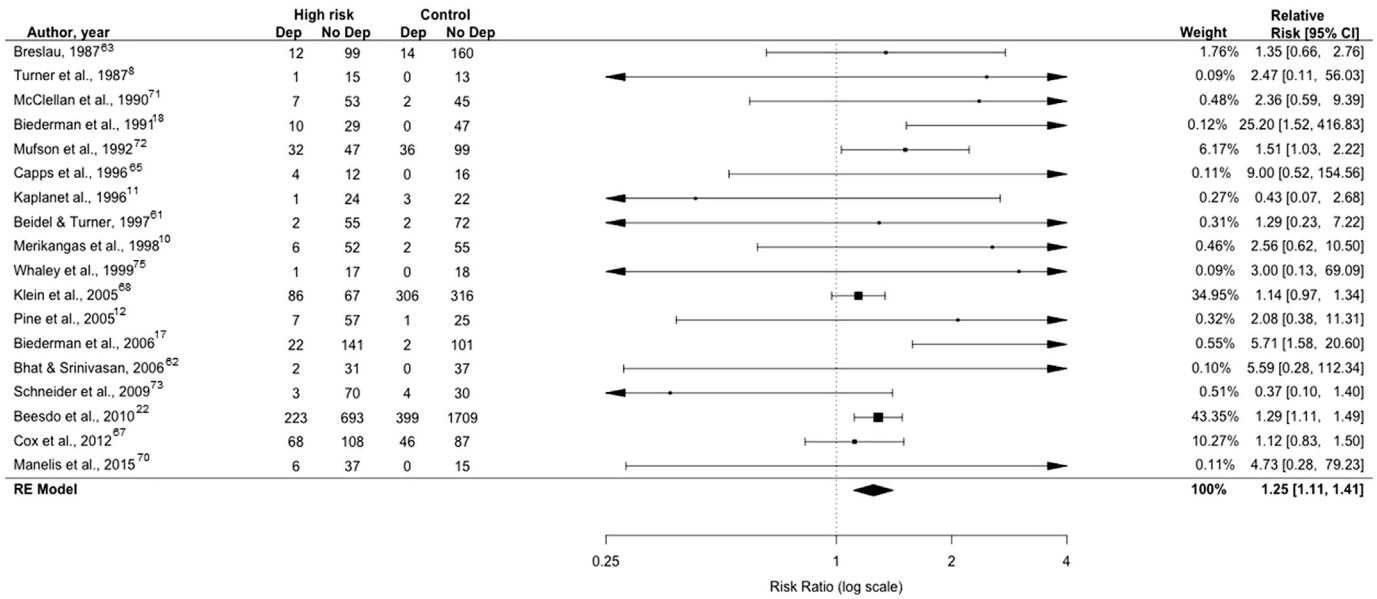


Note: AD = anxiety disorder.

(1) for particular child anxiety disorders, and (2) by particular parent anxiety disorders, to inform prevention programs for at-risk offspring. Regarding particular child anxiety disorders, Micco *et al.* found that, compared to children of psychiatrically healthy parents, children of parents with anxiety disorders were at increased risk for all particular anxiety disorders. However, when compared to children of psychiatric control parents, children of parents with anxiety disorders were at increased risk for no particular anxiety disorders.[14] We found that offspring of parents with anxiety disorders, compared to offspring of parents without anxiety disorders, were at increased risk for GAD, separation anxiety disorder, and specific phobia, but not social anxiety disorder or panic disorder, irrespective of whether the parents had depressive disorders. The important implication for prevention of anxiety disorders in offspring at risk in light of parent anxiety disorders generally is that prevention programs could focus on targeting specific mechanisms implicated in the development of GAD, separation anxiety disorder, and specific phobia, but may not necessarily need to focus specifically on the prevention of social anxiety disorder or panic disorder.

In terms of the risks posed by particular parent anxiety disorders rather than parent anxiety disorders generally, we were able to examine the risks posed by three particular parent anxiety disorders: GAD, panic disorder, and social anxiety disorder. Our meta-analyses indicated that two of these, parent GAD, and panic disorder, when compared to no parent anxiety disorder, place offspring at increased risk for anxiety disorders in general, whereas parent social anxiety disorder did not significantly increase this risk. This is surprising, because previous studies of familial aggregation of anxiety disorders have found increased rates of anxiety disorders in first-degree relatives of probands with social phobia.[25-27,65] We could include data from only two studies in this analysis, yielding a large confidence interval around the point risk estimate of 3.49, which may explain this discrepancy. (Although many more than two studies included parents with social phobia in their high risk groups, we were unable to ascertain the rates of anxiety disorders in their offspring, so we could not calculate the risk associated with parent social phobia in these studies.) Furthermore, for parent GAD and panic disorder, offspring were significantly less likely to have the same particular anxiety disorder as their parent (ie, GAD or panic disorder) than to have different anxiety disorders. For parent social anxiety disorder, offspring were not significantly more likely to have any of the other anxiety disorders than to have social anxiety disorder. These results are also surprising, given the significant associations found between particular parent anxiety disorders and the same particular anxiety disorders in their offspring in some previous studies.[10,20,66] It is possible that we failed to find a significant risk for the same particular disorder in offspring and parents because we had to set a higher bar for conclusions to be drawn about this than in individual studies. We required the risk for the same particular anxiety disorder

FIGURE 4 Forest Plot for Meta-Analysis of Risk Posed by Parent Anxiety Disorder for Offspring Depressive Disorder



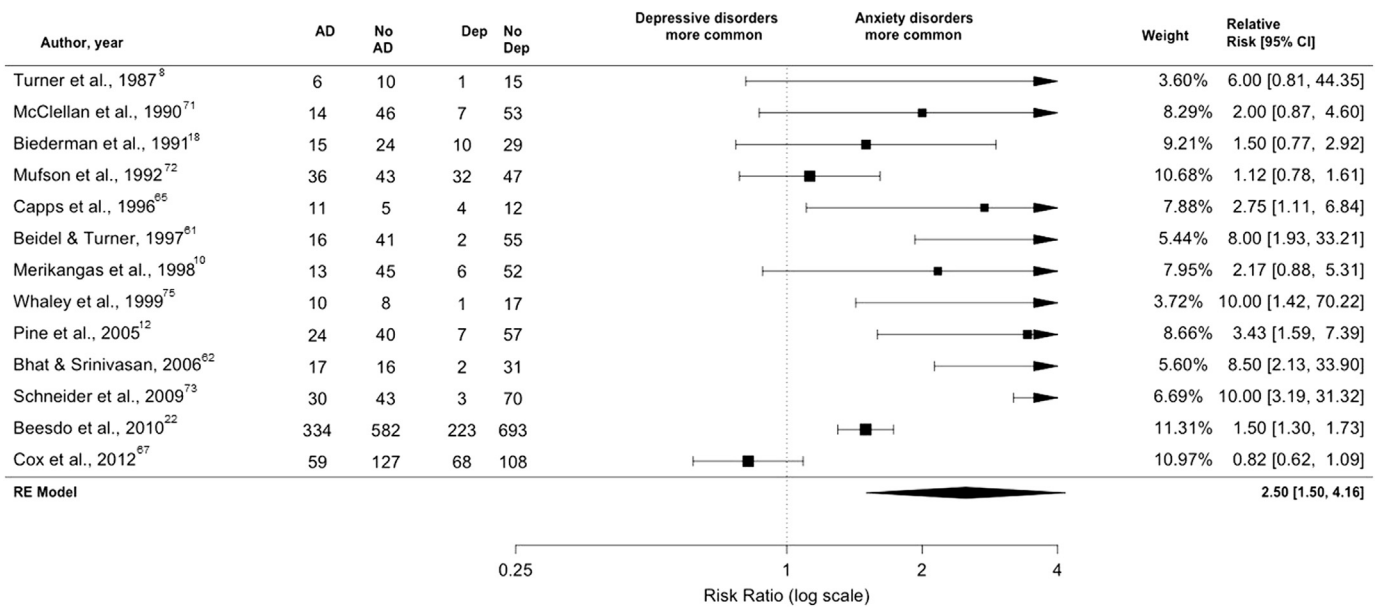
Note: *Dep = depressive disorder.*

in offspring to be greater than the combined risk for all other anxiety disorders. This is a higher bar than is typically set in individual studies in which the risk for having the same particular anxiety disorder as a parent is compared to the risk for having another individual particular anxiety disorder. We were unable to assess for specificity of risk in this same way, because we had only group level data, not individual participant level data. As highlighted by Bloch,[67] such individual participant level data are essential to clarifying meta-analyses, allowing finer-grained analyses to be conducted. Without these data, we cannot conclude whether or not particular parent anxiety disorders increase the risk for the same particular anxiety disorder in their offspring compared to any other particular anxiety disorder.

Our findings must be considered in light of the following limitations. The included studies did not report the age of onset of anxiety disorders in offspring, but the age of participation at the time of assessment. In particular, our analyses of risks for particular anxiety disorders could have failed to identify true moderation effects, because particular anxiety disorders have different median ages of onset.[35] Second, few studies have reported the rates of diagnoses of the full range of anxiety disorders so we were unable to examine which particular anxiety disorder is most commonly seen in the offspring of parents with a given particular anxiety disorder. Third, samples varied in terms of whether one or multiple children and one or two parents per family were included in study samples. This is problematic, because including siblings or more than one parent might lead to increased estimates of risk, due to both sibling and parent similarities.[68] Furthermore, where only one parent was included, we were not always able to establish whether this was a mother or a father. Although studies have found anxiety disorders in mothers and fathers to be equally important in explaining transmission of toddlers' observed anxious behaviors,[69] to our knowledge, top-down studies have not reported differential risks for offspring anxiety disorders posed by maternal versus paternal anxiety disorders. Fourth, we were unable to assess whether offspring temperament moderated risk because it was reported in too few studies. Fifth, although we examined four particular moderators of the associations between parent and child disorders, we did not examine potential influences of a broader range of environmental factors (eg, adversity, trauma, cultural factors). Furthermore, none of the studies that we identified reported parent physical illness, so we were unable to examine how this context may influence risks to offspring. The generalizability of our findings is limited by differences among studies in whether families were recruited from clinics or the community, what diagnostic system was used, and whether current or lifetime disorder was assessed. Where lifetime anxiety disorders were not assessed, this would likely make our effects sizes more conservative estimates of the risks.

We chose to examine risk for anxiety disorders based on studies using a family design, not twin designs, so we

FIGURE 5 Forest Plot for Meta-Analysis of Risk Posed by Parent Anxiety Disorder for Offspring Anxiety and Depressive Disorders



Note: *AD = anxiety disorder; Dep = depressive disorder.*

are unable to conclude anything about the extent to which transmission of risk for anxiety disorders from parents to offspring might be genetically or environmentally mediated. However, notably, a recent and pioneering children of twins study found that the transmission of risk for anxiety symptoms in adolescents was mediated solely by environmental factors.[70] This is consistent with other studies that have found shared and nonshared environmental factors to be important in the development of anxiety disorders.[71]

We focused here on categorical diagnoses of anxiety and depression, as predictor, moderator, and outcome variables. Anxiety and depression can also be examined via dimensional constructs, such as symptom/trait measures and broader domains as highlighted by the United States of America National Institute for Mental Health Research Domain Criteria (RDoC).[72] It will be important to establish whether the patterns of risk that we have found here for categorical diagnoses are similar for dimensional features of anxiety and depression. Further investigation of specific dimensions will be important, because evidence currently suggests that different dimensional features of anxiety and depression might be explained by different mechanisms. For example, twin studies examining dimensional features of anxiety and depression have found that stable genetic effects account for the stability of anxiety sensitivity, fear, and negative affect from childhood to adolescence, whereas environmental factors account for changes in anxiety and depression symptoms over time.[73-75]

In summary, our meta-analyses found that parent anxiety disorders pose a greater risk for anxiety than depressive disorders to offspring; and that the risk was significant for some particular anxiety disorders in offspring (GAD, separation anxiety disorder, and specific phobia), but not others (panic disorder or social anxiety disorder). Parent GAD and panic disorder, but not social anxiety disorder, posed a risk for anxiety disorders in offspring, but not for the same particular anxiety disorder. These findings build on those from a recent meta-analysis[76] in which the only prevention program that effectively lowered the rate of onset of child anxiety disorders was one in which at-risk offspring were targeted in light of parent anxiety disorders.[40] Although this does not establish a causal mechanism, it does demonstrate that targeting children at risk for anxiety disorders in light of parent anxiety disorders can be effective. Our findings suggest that there may be value in developing prevention programs that identify offspring in light of particular parent anxiety disorders, and that target the prevention of particular anxiety disorders in offspring.

Accepted August 15, 2018.

Drs. Lawrence, Murayama, and Creswell are with the School of Psychology and Clinical Language Sciences, University of Reading, UK.

Drs. Lawrence and Creswell are supported by a National Institute for Health Research (NIHR) Research Professorship to Dr. Creswell (NIHR-RP 2014-04-018).

The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health. The NIHR had no involvement in any aspect of this paper.

Dr. Murayama served as the statistical expert for this research.

The authors thank Chloe Williams, BSc, Caitlin Thompson, BSc student, of the University of Reading, and Lucy Feighery, MSc, of Berkshire Healthcare NHS Foundation Trust, for help with abstract screening, data extraction, and quality rating; and Sally Smith, MLS, of the University of Reading, for help with bibliographic / literature search issues. They also thank Joseph Biederman, MD, of Harvard Medical School; David Brent, MD, of the University of Pittsburgh; Helen Dodd, PhD, of the University of Reading; Daniel Klein, PhD, of Stony Brook University; Susanne Knappe, PD Dr.Dipl-Psych, of Technische Universitat Dresden; Autumn Kujawa, PhD, of Vanderbilt University; Anna Manelis, PhD, of the University of Pittsburgh; Daniel Pine, MD, of the National Institute of Mental Health; Krishnamachari Srinivasan, MD, of St John's Medical College, Bangalore, India; Lisa Starr, PhD, of Stony Brook University; and Erin Tone, PhD, of Georgia State University, for responding to our requests for data.

Disclosure: Drs. Lawrence, Murayama, and Creswell report no biomedical financial interests or potential conflicts of interest.

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https://doi.org/10.1016/j.jaac.2018.07.898

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