META-ANALYSIS

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

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Objective: To examine the risk of anxiety disorders in offspring of parents with mood disorders.

Method: We conducted a systematic review and meta-analysis. We searched 4 electronic databases (Medline, Embase, PsycINFO, and Web of Science [core collection]) to identify cross-sectional and cohort studies that examined the association between parental mood disorders (including bipolar disorder and unipolar depression) and risk of anxiety disorders in offspring. Pooled risk ratios (RRs) of overall and specific anxiety disorders were synthesized using a random effects model. Subgroup analyses and meta-regression were performed to identify moderation factors.

Results: A total of 35 studies were included in the final analysis. Our results showed higher risks of all types of anxiety disorders in the offspring of parents with mood disorders (any anxiety disorder, RR = 1.82, 95% CI = 1.47-2.26), except for agoraphobia (RR = 1.08, 95% CI = 0.56-2.08), and with an especially elevated risk of panic disorder (RR = 3.07, 95% CI = 2.19-4.32). Subgroup analysis demonstrated no significant difference between the risks of anxiety disorders across the offspring of parents with bipolar disorder as opposed to unipolar depression. The absence of anxiety disorders in control parents, younger offspring age, and specific parent/offspring sex were associated with higher RRs for some anxiety disorders in offspring of parents with mood disorders.

Conclusion: Our findings suggest a robust relationship between parental mood disorders and offspring anxiety disorders, and highlight the potential value of prevention and early intervention for anxiety disorders in this context.

Diversity & Inclusion Statement: We worked to ensure race, ethnic, and/or other types of diversity in the recruitment of human participants. One or more of the authors of this paper self-identifies as a member of one or more historically underrepresented racial and/or ethnic groups in science. While citing references scientifically relevant for this work, we also actively worked to promote inclusion of historically underrepresented racial and/or ethnic groups in science in our reference list.

Study preregistration information: Anxiety Disorders in Offspring of Parents with Mood Disorders: A Systematic Review; https://www.crd.york.ac.uk/prospero/; CRD42021215058.

Key words: affective; depressive; bipolar; parental; high-risk

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Mood disorders are common mental health problems characterized by episodic mood disturbances that interfere with daily activities. Major depressive disorder and bipolar disorder have a lifetime prevalence of 20% and are associated with increased morbidity and mortality.[1] Offspring of people with mood disorders are prone to a range of mental health problems, including sleep alterations;[2] anxiety disorders,[3] disruptive behavioral disorders, and mood disorders, [4,5] due to genetic,[6,7] biological, and environmental risk factors.[8] Anxiety disorders are the most frequent problem, affecting around 30% of these offspring.[3] Furthermore, anxiety disorders in childhood and adolescence increase the risk of major mood disorders and reduced functioning later in adulthood.[9,10] Clearly, anxiety disorders in the offspring of parents with mood disorders deserve clinical and research attention.

Although we know that there is an overall increased risk for anxiety disorder in general among offspring of parents with mood disorders,[3] little is understood about the risks of specific anxiety disorders and whether the risks differ between parental mood disorder subtypes. These 2 research questions are important, given the potential implications for prevention, early identification, and treatment.[11] Previous studies have mainly contained small sample sizes and presented inconsistent results.[12,13] To our knowledge, only 1 meta-analysis has investigated the risk of different anxiety disorders in the offspring of parents with severe psychiatric disorders,[14] including mood disorders. That meta-analysis found that parental bipolar disorder increased the risks of generalized anxiety disorder (GAD) in offspring. In contrast, parental unipolar depression increased the risk of GAD, social phobia, and separation anxiety disorder (SAD). Notably, no direct comparison of risks in offspring of

parental bipolar disorder and unipolar depression was reported. The previous meta-analysis also had a number of limitations, including a small number of studies for each anxiety disorder subtype (no more than 5), the inclusion of extended family members rather than explicitly focusing on parent−child dyads, and the use of a variety of assessment tools for identifying parental mood and offspring anxiety problems (such as symptom scales, family history tools, or registries).

It is also crucial to explore factors that might influence the risks of anxiety disorders in offspring of parents with mood disorders. To date, no meta-analyses have investigated what factors moderate risks in this population. Previous studies have indicated that parental mood disorders (depressive vs bipolar disorders),[12] study design (cohort vs case-control studies),[14] parent control conditions (healthy control vs psychiatric control),[15] parent and offspring sex,[16,17] offspring age, and anxiety disorder measures (lifetime vs current diagnosis) had an impact on certain anxiety disorders in offspring of parents with mood disorders.[18,19] Furthermore, parental anxiety disorder has been shown to increase the risk of offspring anxiety disorders.[20] Population studies have shown that different national incomes, research years,[21] and participant ethnicity were associated with varying prevalences of anxiety disorders.[22] Hence, these factors warrant further investigation to explore their moderating effects on the risk of anxiety disorders in the offspring of parents with mood disorders.

This systematic review and meta-analysis aim to do the following: (1) to identify the risk of different specific anxiety disorders in the offspring of parents with mood disorders compared with the offspring of parents without mood disorders; (2) to compare the risk in offspring anxiety disorders between the contexts of parental bipolar disorder and parental unipolar depression; and (3) to explore factors that may have an impact on the risk of offspring anxiety disorders and factors that may explain the heterogeneity of risk.

METHOD

Eligibility Criteria

The review protocol was developed in advance and registered with PROSPERO (registration number: CRD42021215058). The research question using the PICOST format is shown in Table S1, available online.[23] We performed a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Table S2, available online).[24] Eligible studies met the following criteria: (1) original data published in a peer-reviewed journal; (2) contained offspring of parents with mood disorders (at-risk offspring) and offspring whose parents did not have the mood disorder in the risk group (control offspring); (3) reported a number or percentage of anxiety disorders in offspring; (4) parental and offspring diagnoses were made by validated clinician-rated diagnostic interview tools based on the *International Classification of Diseases* (*ICD-8* to *ICD-10*) or the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III* to *DSM-5*); (5) excluded studies in which parents had physical or psychiatric conditions that could significantly influence the risk of an offspring anxiety disorder (eg, cancer or schizophrenia).

Literature Search

Systematic searches were conducted in Medline, Embase, PsycINFO, and Web of Science for relevant articles published from 1994 to January 22, 2023. We chose this time range because of the significant changes in diagnostic criteria and thresholds for anxiety disorders from *DSM-III-R* to *DSM-IV*, [25,26] which was published in 1994. The search strategy included keywords and synonyms identifying the concepts "parents," "mood disorder," "offspring," and "anxiety disorder" (detailed search terms are provided in Table S3, available online). We also searched reference lists and citation indexes of all included articles on the Web of Science website.

Data Screening

During the data screening process, authors ET and HM independently performed title and abstract screening for all the records obtained from the database search and then a thorough full-text screening to determine eligibility. Reasons for exclusion were documented at this stage (Table S4, available online). The interrater agreement rate for screening results was above 99%. Where necessary, the 2 reviewers involved the third and fourth authors, CC and KEAS, and discussed any disagreements carefully before reaching a consensus. For articles with insufficient eligibility information, the original authors were contacted to obtain additional information (Table S5, available online).

Data Extraction

The first author extracted information, including study identifier, methodology, parent and offspring characteristics, and outcome measures from each report and organized it in Microsoft Excel (Table S6, available online). CC and KEAS were consulted on queries about the extracted data. If there were multiple eligible records with data obtained from overlapping samples, for example, papers from the same cohort study, we selected studies with outcomes that could

be used independently for the data analyses based on the principle described in Figure S1, available online.

For studies looking for familial risks of parental unipolar depression, the control group could be healthy control (offspring of parents with no psychiatric disorders or axis-I mental illnesses) or parents without mood disorders (may coexist with non-mood disorders such as anxiety disorders). For studies looking for familial risks of parental bipolar disorder, the control group could be healthy control parents, parents without mood disorders, or parents without bipolar disorder (which may coexist with unipolar depression and other non-mood disorders). We grouped parents without mood disorders and those without bipolar disorder as psychiatric controls.

Anxiety disorders extracted included any anxiety disorder, SAD, GAD, social phobia, specific phobia, panic disorder, and agoraphobia. Data on obsessive-compulsive disorder and post-traumatic stress disorder were not extracted, as the 2 diagnoses were removed from the diagnostic category of anxiety disorders in *DSM-5*.[27]

Quality Assessment

ET assessed the quality of each included study by the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and discussed any questions with CC and KEAS.[28] This tool has 14 questions, but the eighth question was removed because of irrelevance to the study. Each item was rated as "yes," "no," or "other" (including "cannot determine," "not applicable," or "not reported"). The reviewers then judged each study to be of "good" (the least risk of bias), "fair" (susceptible to some bias), or "poor" (significant risks of bias) quality. If a manuscript was rated "poor," it was removed from the data analysis.

Statistical Analysis

We used the meta, metasen, and metaphor packages in the R version 4.0.5.[29,30] We performed a random-effects model meta-analysis using the exact Mantel−Haenszel method because between-study heterogeneity could be anticipated due to variations in demographics and methodologies across the included studies.[31] We calculated the overall risk ratios (RRs) for any anxiety disorder, SAD, GAD, social phobia, specific phobia, panic disorder, and agoraphobia. We estimated between-study heterogeneity using the Paule−Mandel method[32]; I^2 statistics were classified as low (<25%), low to moderate (25%-50%), moderate to high (50%-75%), and high heterogeneity (>75%).[33]

We assessed the robustness of our effect sizes using 3 methods: (1) if I^2 was over 50%, a sensitivity analysis was conducted to estimate corrected RR by removing outliers (identified via visual inspection of forest plots) or influential cases (identified by the leave-one-out analysis, Baujat plot, and influence diagnostics);[34] (2) if the Egger test indicated small study effects, a proxy for publication bias, a corrected RR using the trim-and-fill approach was calculated; and (3) studies that reported adjusted ratios (risk ratios, odds ratios, and hazard ratios) were pooled separately and together with crude RRs from the remaining studies.

Subgroup analyses and meta-regression were performed on pre-defined factors based on previous evidence in the offspring of our research focus, including parent psychopathology and control condition, parent and offspring sex, offspring age and anxiety disorder measures, and study design when there were at least 10 studies.[35] We also examined other factors that may affect the anxiety disorder risks in the general population, such as study type, national income, publication year, and ethnicity. To avoid ecological bias,[36] we analyzed offspring age using age ranges rather than mean ages and stratified offspring as children (up to 12 years), adolescents (12-18 years) and adults (19 years and above).

We performed a forced-entry meta-regression by simultaneously including 4 variables (parent control condition, offspring age, offspring sex, and parent sex) into the regression model to find the best fit. These factors were chosen and written in our pre-defined research protocol because of their clinical relevance and proven moderating roles in the offspring of parents with mood disorders.

RESULTS

Study Characteristics

This systematic review included 35 studies, 13 of which were cross-sectional studies, 3 were baseline data from cohort studies, and 19 were cohort follow-up studies. Most study populations were White in high-income Western countries. The Structured Clinical Interview for *DSM* (SCID) and Kiddle Schedule for Affective Disorders and Schizophrenia for School-aged Children (K-SADS) were the most commonly used diagnostic tools for adults and children/adolescents. A total of 23 studies recruited children under 19 years of age, and others looked mainly for offspring aged up to early adulthood. Table 1[13,15,17-19,37-66] describes the methodological and demographic characteristics of the included studies. A PRISMA flowchart for the study review process is provided in Figure 1.

Quality Assessment

All included studies consistently adopted reliable and valid diagnostic tools for exposures and outcomes and generally

TABLE 1 Characteristics of Studies Included in the Systematic Review (N = 35)

First author (year), reference	Design	Country	White (%)	Setting (risk)	Setting (control)	Adult Dx tools	C&A Dx tools	Measure	Proband sex	Exposure	control	Sample size	Age range, y	Off sex (% F)
Akdemir (2008)[37]	Cross-sectional	Turkey	NS	Clinical	Clinical	SADS-L	K-SADS	Lifetime	Parents	BD	HC	69	6-17	44.9
Axelson (2015)[15]	Longitudinal	US	78.4	Clinical	Community	SCID	K-SADS	Lifetime	Parents	BD	Not BD	639	12-24	50.9
Beidel (1997)[38]	Cross-sectional	US	82.2	Clinical	Community	SCID	K-SADS	Current	Parents	MDD	HC	101	7-12	43.6
Biel (2008)[39]	Cross-sectional	US	74.1	Clinical	Clinical	SCID	PRIS	Lifetime	Parents	MDD	HC	243	6-17	55.1
Birmaher (2010)[40]	Longitudinal (baseline)	US	79.8	Clinical	Community	SCID	K-SADS	Lifetime	Parents	BD	Not BD	223	2-5	48.0
Bushnell (2020)[41]	Longitudinal	US	100	Mixed	Community	SADS-L	K-SADS	Lifetime	Parents	MDD	HC	275	<18	52.7
Cullen (2014)[13]	Longitudinal	US	88.2	Clinical	Community	SADS-L	N/A	Current	Mothers	BD/MDD	HC	136	19-25	58.1
Duffy (2019)[42]	Longitudinal	Canada	NS	Clinical	Community	SADS-L	K-SADS	Lifetime	Parents	BD	HC	366	5-25	59.6
Eraso-Osorio (2021)[43]	Longitudinal	Columbia	NS	Clinical	Community	DIGS	K-SADS	Lifetime	Parents	BD	Not BD	192	6-30	46.3
Erkan (2015)[44]	Cross-sectional	Turkey	NS	Clinical	Clinical	SCID	K-SADS	Current	Parents	BD	HC	53	12-17	56.6
Erlenmeyer (1997)[45]	Longitudinal	US	100	Clinical	Community	SADS-L	N/A	Lifetime	Parents	MD	HC	203	32-37	N/A
Feder (2009)[46]	Cross-sectional	US	NS	Clinical	Clinical	SCID	K-SADS	Lifetime	Mothers	MDD	No MD	58	8-17	48.3
Galbally (2020)[47]	Longitudinal	Australia	89.2	Clinical	Clinical	SCID	PAPA	Current	Mothers	PND	No MD	203	3-5	43.8
Galbally (2022)[48]	Longitudinal	Australia	88.9	Clinical	Clinical	SCID	PAPA	Current	Mothers	PND	No MD	198	3-5	44.4
Gallerani (2010)[49]	Longitudinal	US	81.7	Community	Community	SCID	K-SADS	Lifetime	Mothers	MDD + DD	HC	240	16-19	54.2
Garcia-Amador (2013)[50]	Cross-sectional	Spain	NS	Clinical	Community	SCID	K-SADS	Current	Parents	BD	HC	75	6-17	40
Goetz (2017)[19]	Cross-sectional	Czech	NS	Clinical	Community	SADS-L	K-SADS	Lifetime	Parents	BD	HC	86	6-17	41.9
Hirshfeld-Becker (2006)[51]	Longitudinal (baseline)	US	88.4	Mixed	Community	SCID	K-SADS	Lifetime	Parents	BD	HC	129	5-10	44.2
Micco (2009)[52]	Longitudinal	US	NS	Mixed	Community	SCID	K-SADS	Both	Parents	MDD	HC	135	6-17	51.1
Murray (2011)[53]	Longitudinal	UK	NS	Community	Community	SCID	K-SADS	Lifetime	Mothers	PND	No MD	93	15.7-17.0	51.6

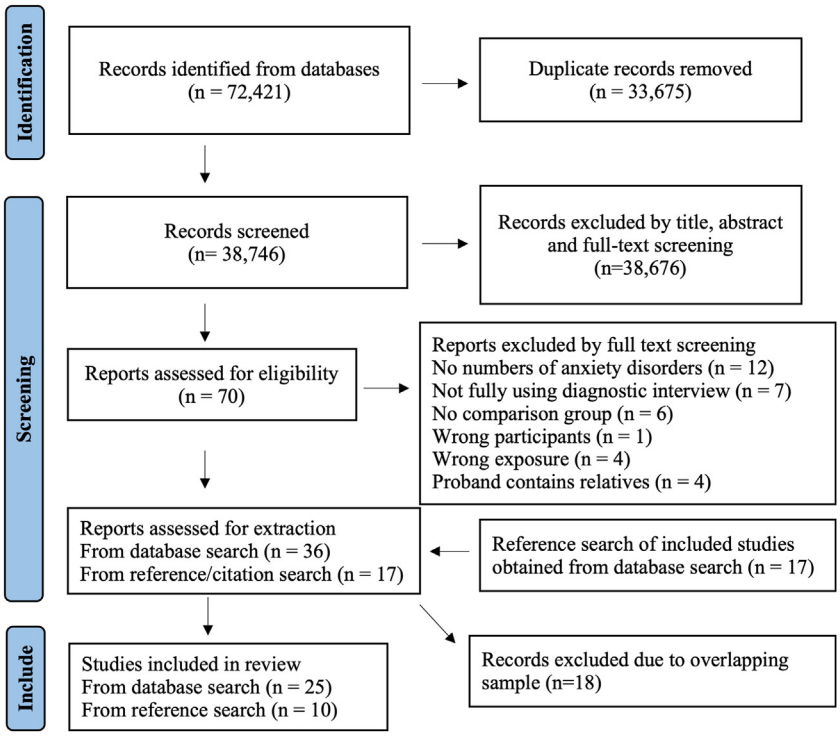
(*continued*)

TABLE 1 Continued

First author (year), reference	Design	Country	White (%)	Setting (risk)	Setting (control)	Adult Dx tools	C&A Dx tools	Measure	Proband sex	Exposure	control	Sample size	Age range, y	Off sex (% F)
Nijjar (2014)[54]	Longitudinal	Canada	NS	Clinical	Community	SCID	K-SADS	Both	Parents	BD	HC	148	14-27	43.9
Nimarko (2021)[55]	Longitudinal	US	66.3	Community	Community	SCID	K-SADS	Current	Parents	BD/MDD	HC	101	9.8-22.6	54.5
Nomura (2001)[17]	Longitudinal	US	100	Mixed	Community	SADS-L	K-SADS	Lifetime	Parents	MDD	HC	182	16-33	52.7
Pan (2017)[56]	Longitudinal	US	82	Clinical	Community	SCID	K-SADS	Current	Parents	BD	HC	350	13-18	50.3
Palacio-Ortiz (2017)[18]	Longitudinal (baseline)	Columbia	NS	Clinical	Community	DIGS	K-SADS	Lifetime	Parents	BD	Not BD	277	6-30	49.5
Pavlova (2022)[57]	Cross-sectional	Canada	NS	Clinical	Community	SCID	K-SADS	Lifetime	Parents	BD/MDD	HC	366	5-21	50.5
Petresco (2009)[58]	Cross-sectional	Brazil	59.4	Clinical	Clinical	SCID	K-SADS	Lifetime	Mothers	BD	HC	96	6-18	56.3
Pine (2005)[59]	Cross-sectional	US	NS	Clinical	Clinical	SCID	PRIS	Current	Parents	MDD	HC	120	9-19	56.7
Rudaz (2021)[60]	Longitudinal	Swiss	NS	Clinical	Clinical	DIGS	N/A	Lifetime	Parents	BD/MDD	No MD	414	19-31	50.8
Serna (2021)[61]	Longitudinal	Spain	97.0	Clinical	Community	SCID	K-SADS	Lifetime	Parents	BD	Not BD	170	8-19	46.2
Shalev (2019)[62]	Longitudinal	US	80	Clinical	Community	SCID	K-SADS	Lifetime	Parents	BD	HC	656	7-18	50.2
Singh (2007)[63]	Cross-sectional	US	87.9	Clinical	Community	SCID	K-SADS	Lifetime	Parents	BD	HC	66	8-17	54.5
Tseng (2015)[64]	Cross-sectional	US	81.6	Clinical	Community	SCID	PAPA	Current	Parents	BD	HC	38	3.5-6	39.5
Weissman (2021)[65]	Longitudinal	US	100	Mixed	Community	SADS-L	N/A	Lifetime	Parents	MDD	HC	276	36-53	53.6
Zavaleta-Ramirez (2014)[66]	Cross-sectional	Mexico	NS	Clinical	Community	MINI	K-SADS	Lifetime	Parents	BD	Not BD	62	6-18	27.4

Note: *BD = bipolar disorder; BIOS = Bipolar Offspring Study; C&A = children and adolescents; DIGS = Diagnostic Interview for Genetic Studies; DD = dysthymic disorder; Dx tools = diagnostic tools; HC = healthy control; K-SADS = Kiddle Schedule for Affective Disorders and Schizophrenia for School-Age Children; MD = mood disorders; MDD = major depressive disorder; MINI = Mini-International Neuropsychiatric Interview; Mixed = mixed clinical and community settings; N/A = not applicable; NS = not specified; Off sex = proportion of female offspring (%); SADS-L = Schedule for Affective Disorder and Schizophrenia—Lifetime version; SCID = Structured Clinical Interview for* DSM; *PAPA = Preschool Age Psychiatric Assessment; PND = post-natal depression; PRIS = Parent as Respondent Informant Schedule.*

FIGURE 1 PRISMA Flow Diagram for the Systematic Review Process



met the following quality assessment criteria: well-defined research question, study population, and eligibility criteria. Most studies measured and adjusted potential confounding variables and blinded outcome assessors to offspring's exposure status, but only about half of them described sample size justification. The main limitations of the included cross-sectional studies were that there were no data on whether the exposure was before the outcome or whether the timeframe was sufficient to analyze the association between exposure and outcome. Of the 19 cohort follow-up studies, 12 studies reported multiple assessments of exposure, and 8 described 20% or less loss of follow-up rate. The details of the quality assessment are shown in Table S7, available online.

Lifetime Rates of Offspring Anxiety Disorders

Table 2 demonstrates the lifetime prevalence of anxiety disorders in the offspring of parents with mood disorders, with a mean offspring age ranging from 16.4 to 22.3 years. Overall, 36.0% of at-risk and 20.4% of control offspring experienced anxiety disorders during their lifetime. Lifetime rates of anxiety disorders between offspring of parents with mood disorders vs control offspring were 20.4% vs 10.0% for SAD, 14.5% vs 7.16% for GAD, 15.6% vs 9.32% for social phobia, 20.2% vs 12.1% for specific phobia, 5.96% vs 1.58% for panic disorder, and 4.17% vs 4.40% for agoraphobia. The 2 groups of offspring presented a similar ordering of the rates between anxiety disorders: specific phobia and SAD were the most common, GAD and social phobia were intermediate, and panic disorder and agoraphobia were the least common anxiety disorders. Two included studies reported higher rates of 2 or more anxiety disorders in offspring of parents with major depression (22.6%) compared to controls (9.4%) and in offspring of parents with bipolar disorder (26.5%) compared to controls (10.6%). However, in the latter study, the difference lost significance after excluding children who had developed bipolar disorder (Table S8, available online).[41,51]

Risk Ratios of Offspring Anxiety Disorders: Effects of Parental Mood Disorders

Table 2 also shows pooled RRs of different anxiety disorders in the offspring of parents with mood disorders compared to control offspring. Our meta-analysis yielded an RR of 1.82 (95% CI = 1.47-2.26) for any anxiety disorder, with moderate-to-high between-study heterogeneity ($I^2 = 59.1\%$). The prediction interval ranged from 0.81 to 4.11, indicating that insignificant RR cannot be ruled out for future studies. Figure 2 provides the forest plot of this meta-analysis. According to our analysis of pooled effect size, the likelihood of a

TABLE 2 Rates and Risks of Anxiety Disorders in Offspring of Parents With Mood Disorders, Including Correction of Influential Cases for Any Anxiety Disorders

Parent Dx		Mood disorders							Bipolar disorder					Unipolar depression				
		Lifetime rates																
Off-spring	Age	Risk, %	Control, %	K (n)	RR	95%CI	I^2 (%)	Egger (*p*)	K (n)	RR	95% CI	I^2 (%)	Egger (*p*)	K (n)	RR	95% CI	I^2 (%)	Egger (*p*)
Any AD	17.6	36.0	20.4	25 (4,309)	**1.82**[a]	1.47-2.26	**59.1**[b]	**.005**[c]	17 (2,474)	**1.92**[a]	1.40-2.64	**67.2**[b]	.057	11 (1,642)	**1.54**[a]	1.27-1.87	1.3	.260
Any AD (Inf)				23[d] (4,118)	**1.75**[a]	1.49-2.05	33.9		15[d] (2,283)	**1.85**[a]	1.49-2.33	36.2						
Any AD (TF)				27	**1.71**[a]	1.43-2.05	29.9											
SAD	18.5	20.4	10.0	14 (2,736)	**1.75**[a]	1.37-2.24	5.7	.098	9 (1,965)	**1.85**[a]	1.12-3.07	32.0		7 (901)	**2.06**[a]	1.11-3.83	28.0	
GAD	19.6	14.5	7.16	17 (3,333)	**1.76**[a]	1.19-2.60	42.1	.577	11 (2,156)	1.81	0.93-3.54	**52.9**[b]	.904	8 (1,104)	1.82	0.87-3.81	33.9	
GAD (Inf)									10[e] (2,094)	**2.05**[a]	1.12-3.75	43.8						
SOC	18.4	15.6	9.32	17 (3,259)	**1.51**[a]	1.12-2.05	18.1	.323	11 (2,156)	1.70	0.93-3.09	40.9	.401	8 (1,175)	1.34	0.95-1.88	0	
SP	16.4	20.2	12.1	17 (2,979)	**1.44**[a]	1.11-1.87	24.1	**.003**[c]	10 (1,697)	1.65	0.89-3.05	46.7	**.010**[c]	8 (1,283)	**1.41**[a]	1.17-1.71	0	
SP (TF)				23	1.28	0.88-1.86	37.7		12	1.10	0.59-2.05	41.1						
PD	22.3	5.96	1.58	13 (2,913)	**3.07**[a]	2.19-4.32	0	.347	10 (2,094)	**3.27**[a]	2.06-5.19	0	.185	3 (559)	**3.39**[a]	2.18-5.25	0	
AGO	22.7	4.17	4.40	5 (1,268)	1.08	0.56-2.08	0		3 (783)	1.02	0.17-6.09	0		3 (486)	1.15	0.39-3.39	0	

Note: *AD = anxiety disorder; AGO = agoraphobia; Dx = diagnosis; Egger = Egger test (assessing publication bias); FU = a sensitivity analysis in which only follow-up data are pooled, excluding cross-sectional data; GAD = generalized anxiety disorder; Inf = correction by removing outliers and influential cases; K = number of studies; n = number of participants; PD = panic disorder; SAD = separation anxiety disorder; RR = risk ratio; SOC = social phobia; SP = specific phobia; TF = correction by trim-and-fill method for publication bias.*

[a]*The boldface RR (*p *value < .05) indicates a significant effect size.*

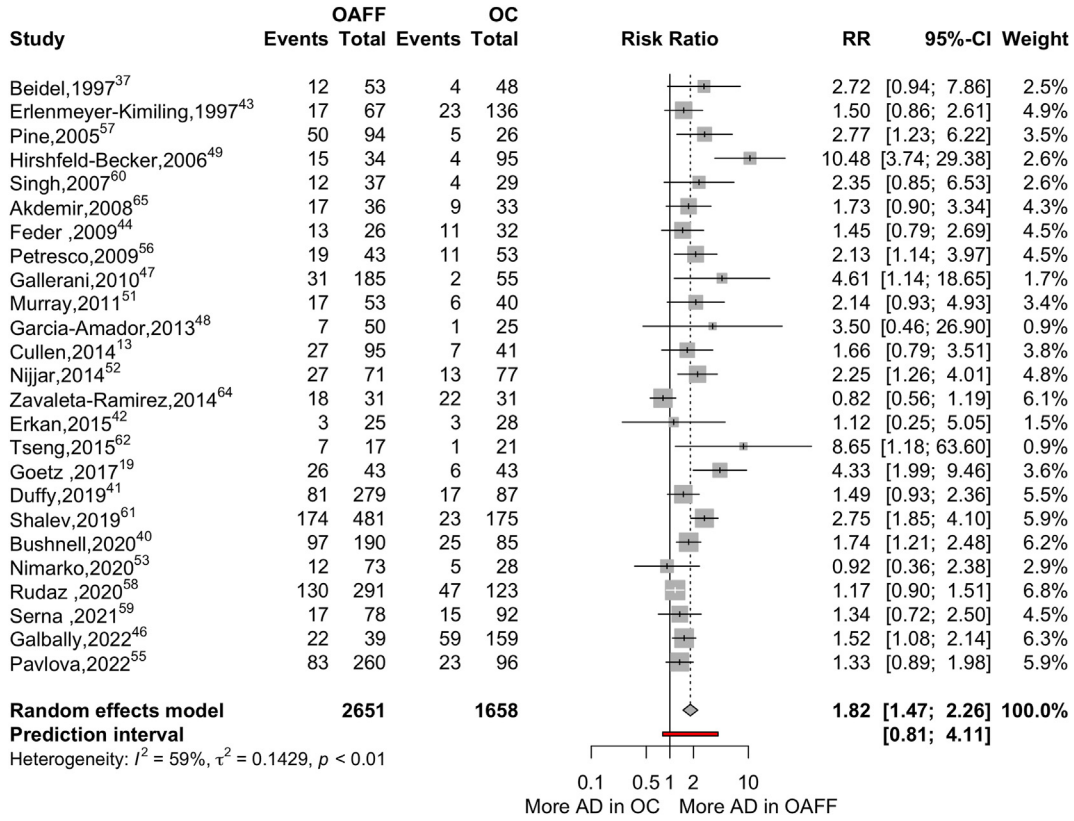
[b]*The boldface I^2 (>50) indicates significant between-study heterogeneity → Outlier/Influential cases correction (Inf).*

[c]*The boldface* p *value (<.05) for Egger test indicates a significant small study effects → trim and fill method correction (TF).*

[d]*Removed as outliers: Hirshfeld-Becker et al.,[51] Zavaleta-Ramirez et al.[66]*

[e]*Removed as an influential case: Zavaleta-Ramirez et al.[66]*

FIGURE 2 Forest Plot of the Risk of Any Anxiety Disorder in the Offspring of Parents With Mood Disorders



child having an anxiety disorder is approximately twice as high when their parents have mood disorders than when parents do not have a mood disorder. This suggests that around 1 in 8 children in this context may have an anxiety disorder, compared to the estimated prevalence of 1 in 15 children in the general population.[67]

The RRs for SAD, GAD, social phobia, specific phobia, panic disorder, and agoraphobia were 1.75 (95% CI = 1.37-2.24, I^2 = 5.7%), 1.76 (95% CI = 1.19-2.60, I^2 = 42.1%), 1.51 (95% CI = 1.12-2.05, I^2 = 18.1%), 1.44 (95% CI = 1.11-1.87, I^2 = 24.1%), 3.07 (95% CI = 2.19-4.32, I^2 = 0%), and 1.08 (95% CI = 0.56-2.08, I^2 = 0%), respectively. All pooled RRs indicated a higher risk of different anxiety disorders in at-risk offspring than in control offspring, except for agoraphobia. It is noteworthy that at-risk offspring exhibited higher RR of panic disorder than other anxiety disorders.

Risk Ratios of Offspring Anxiety Disorders by Parental Diagnosis

Offspring of parents with mood disorders were divided into 2 subgroups: offspring of parents with bipolar disorder, and offspring of parents with unipolar depression. Our meta-analysis showed that parental bipolar disorder increased risks in offspring for any anxiety disorder (RR = 1.92, 95% CI = 1.40-2.64, I^2 = 67.2%), SAD (RR = 1.85, 95% CI = 1.12-3.07, I^2 = 32%), and panic disorder (RR = 3.27, 95% CI = 2.06-5.19, I^2 = 0%), whereas no significant risks were observed for GAD (RR = 1.81, 95% CI = 0.93-3.54, I^2 = 52.9%), social phobia (RR = 1.70, 95% CI = 0.93-3.09, I^2 = 40.9%), specific phobia (RR = 1.65, 95% CI = 0.89-3.05, I^2 = 46.7%), and agoraphobia (RR = 1.02, 95% CI = 0.17-6.09, I^2 = 0%) compared with offspring of parents without bipolar disorder. On the other hand, parental unipolar depression elevated offspring's risk for any anxiety disorder (RR = 1.54, 95% CI = 1.27-1.87, I^2 = 1.3%), SAD (RR = 2.06, 95% CI = 1.11-3.83, I^2 = 28.0%), specific phobia (RR = 1.41, 95% CI = 1.17-1.71, I^2 = 0%), and panic disorder (RR = 3.39, 95% CI = 2.18-5.25, I^2 = 0%) but also not for GAD (RR = 1.82, 95% CI = 0.87-3.81, I^2 = 33.9%), social phobia (RR = 1.34, 95% CI = 0.95-1.88, I^2 = 0%), and agoraphobia (RR = 1.15, 95% CI = 0.39-3.39, I^2 = 0%).

Confirming the Strength of Risk Ratios of Offspring Anxiety Disorders

Moderate to high heterogeneity shown with RR of any anxiety disorder in offspring of parents with mood disorders

indicated the need for further sensitivity analyses removing outliers and influential cases (Figure S2, available online). The sensitivity analyses did not alter the increased risk for any anxiety disorder in offspring in the context of parental mood disorders and parental bipolar disorder (RR = 1.85, 95% CI = 1.49-2.33, I^2 = 36.2%). In contrast, the impact of parental bipolar disorder on offspring GAD emerged after sensitivity analysis (RR = 2.05, 95% CI = 1.12-3.75, I^2 = 43.8%). Possible explanations for the outliers and influential cases (Table S9, available online) implied that some variables, such as conditions of control parents and offspring age and sex, might play essential roles in accounting for the between-study heterogeneity.

Funnel plot asymmetry and significant Egger test result were shown in the RR estimates for any anxiety disorder and specific phobia in the offspring of parental mood disorders, indicating the influences of publication bias (Figure S3, available online). The trim-and-fill corrected RR for any anxiety disorder decreased but remained significant (RR = 1.71, 95% CI = 1.43-2.05, I^2 = 29.9%), whereas that for specific phobia became insignificant (RR = 1.28, 95% CI = 0.88-1.86, I^2 = 37.7%).

Although adjusted ratios can account for confounding factors, we used the raw number to calculate effect sizes because of the limited number of studies reporting adjusted ratios and to make our calculation more transparent and easier to replicate. However, we also conducted sensitivity analyses using the 6 studies reporting adjusted ratios for any anxiety disorders in the offspring of parents with mood disorders. Combining adjusted RRs and odds ratios, adjusted hazard ratios, or adjusted and crude RRs did not affect the significance of our main results (Tables S10 and S11, available online).

We also performed sensitivity analyses by excluding cross-sectional studies and baseline data from cohort studies, which did not change the increased risks in offspring of parents with mood disorders in the main analysis (Table S12, available online). It additionally indicated the potential impacts of parental bipolar disorder on GAD and social phobia among offspring. Notably, the pooled RR for panic disorder slightly decreased but remained the highest among the anxiety disorders (RR = 2.80, 95% CI = 2.00-3.91, I^2 = 0). The subgroup analysis shown in Table 3 showed no differences in RR between cross-sectional and follow-up data for all subtypes of anxiety disorders, except for panic disorder (RR = 9.14 vs 2.80, $p < .001$). Further examination for panic disorder showed that the 3 cross-sectional studies had significantly younger offspring than the 10 studies with follow-up data (mean age = 10.3 vs 22.9 years, $p = .014$). After controlling for the interaction between study design and offspring age, the risk difference for panic disorder was no longer significant.

Furthermore, diagnostic measures (lifetime vs current anxiety disorder diagnoses) and qualitative ratings ("good" vs "fair") yielded no difference in offspring anxiety disorders across at-risk and control offspring (Table S13).

Examining Factors Affecting Risk Ratios for Anxiety Disorders in Offspring

Table 3 and Tables S13 and S14, available online, provided the results of subgroup analysis and univariate meta-regression (not conducted for agoraphobia because of insufficient studies). First, there was a lack of clear differences for offspring anxiety disorders across parental mood disorders (unipolar depression vs bipolar disorder, and major depression vs bipolar disorder).

Second, separating subgroups based on healthy and psychiatric control parents yielded decreased I^2 values for any anxiety disorder, from 59.1% to 43.5% and 39.0%, respectively, suggesting that this variable can explain part of the heterogeneity. Table S15, available online, showed that control parents "without mood disorders" typically had anxiety disorders (only), except for 1 study.[53] This allowed us to estimate the effect of parental anxiety disorder by comparing the RR of anxiety disorders in the offspring of parents with mood disorders to those of parents without mood disorders. The results showed that at-risk offspring had higher risks of any anxiety disorder, social phobia, and specific phobia when compared to healthy controls than when compared to offspring of parents without mood disorders. This finding indicates that anxiety disorders among control parents decrease the RR of offspring anxiety disorders. Four studies included in our analysis showed that the presence of both major depression and anxiety disorders in parents appeared to increase anxiety symptoms but not rates of anxiety disorder diagnosis among offspring when compared with parental major depression only or parental anxiety disorder only (Table S16, available online).[38,39,52,59] These findings were supported by our meta-regression, which indicated that comorbid anxiety disorders in parents with mood disorders did not significantly increase their offspring's risk of anxiety disorder.

Third, our subgroup analysis showed children had a trend of higher risks for all types of anxiety disorders than adolescents/adults, and the risk difference achieved significance for panic disorder (RR = 8.39 vs 2.80, $p = .042$). We further analyzed the risk of anxiety disorders in different age groups of offspring using a random-effects meta-analysis presented in Table S17, available online. The results revealed that children up to 12 years old exposed to parental mood disorders had an elevated risk for any anxiety disorder (RR = 3.20, 95% CI = 1.11-9.29, I^2 = 73.0) and GAD (RR = 3.87, 95% CI = 1.71-8.78, I^2 = 0). When the age range was extended to include adolescence, the risk

TABLE 3 Summary of Subgroup Analysis and Univariate Meta-Regression

		Any AD			SAD		GAD		SOC		SP		PD	
Variable	**Subgroup**	**K**	**RR**	**I^2, %**	**K**	**RR**	**K**	**RR**	**K**	**RR**	**K**	**RR**	**K**	**RR**
Proband parent psychopathology	Unipolar depression	11	1.54	1.3	7	2.06	8	1.82	8	1.34	8	1.41	3	3.39
	Bipolar disorder	17	1.92	67.2	8	1.71	10	1.62	10	1.54	11	1.76	10	3.27
	p		.206			.515		.767		.610		.427		.882
Control parent psychopathology	Healthy control	**19**	**2.12**	**43.5**	7	1.86	10	1.55	**9**	**2.22**	**9**	**1.87**	7	2.99
	Psychiatric control	**6**	**1.24**	**39.0**	7	1.72	7	1.99	**8**	**1.22**	**8**	**1.17**	6	3.10
	p		**.001****			.771		.519		**.027***		**.035***		.929
Parent sex[a]	Parents	19	1.86	67.29	**11**	**1.70**	14	1.62	**13**	**1.61**	13	1.44	11	3.84
	Mothers	6	1.70	0	**3**	**4.45**	3	3.13	**4**	**0.91**	4	1.53	2	3.84
	p		.597			**.040***		.128		**.004****		.764		.657
Offspring age range	Children	4	2.93	79.7			4	4.00	4	1.41	5	1.81	**2**	**8.39**
	Adolescents and adults	10	1.69	28.5			9	1.99	8	1.37	6	1.08	**8**	**2.80**
	p		.252					.202		.960		.271		**.042***
AD measure	Lifetime Dx	16	1.87	70.5	11	1.81	12	1.85	12	1.53	13	1.51	11	2.99
	Current Dx	8	1.73	6.4	3	1.48	5	1.45	5	1.57	4	1.35	2	4.87
	p		.703			.543		.617		.921		.615		.591
Study design	Cross-sectional data	13	2.16	69.9	6	1.98	6	1.43	6	1.28	9	1.80	**3**	**9.14**
	Follow-up data	12	1.64	41.5	8	1.72	11	1.84	11	1.45	8	1.28	**10**	**2.80**
	p		.204			.645		.697		.804		.255		**.000*****
Variable		**K**	**β (SE)**		**K**	**β (SE)**	**K**	**β (SE)**	**K**	**β (SE)**	**K**	**β (SE)**	**K**	**β (SE)**
Offspring sex	Female offspring (%)	25	0.008 (0.014)		14	0.019 (0.024)	17	−0.009 (0.031)	17	0.013 (0.025)	**17**	**0.039 (0.016)**	13	−0.041 (0.033)
	p		.568			.442		.777		.606		**.031***		.242

Note: *Boldface data denotes significant variations between groups in subgroup analysis or significant association between the factor and RR in meta-regression. AD = anxiety disorder; **β** = estimate; C&A = children and adolescents; Dx = diagnosis of anxiety disorders in offspring; GAD = generalized anxiety disorder; K = number of studies; PD = panic disorder; RR = risk ratio; SAD = separation anxiety disorder; SE = standard error; SOC = social phobia; SP = specific phobia.*

[a]*Comparing studies that recruited offspring of parents with mood disorders to studies that recruited only offspring of mothers with mood disorders.*

*p < .05; **p < .01; ***p < .001.

differences achieved significance for any anxiety disorder (RR = 2.04, 95% CI = 1.52-2.73, $I^2 = 63.2$), SAD (RR = 1.57, 95% CI = 1.12-2.20, $I^2 = 0$), and panic disorder (RR = 4.36, 95% CI = 2.16-8.77, $I^2 = 0$). However, in studies that recruited only adults, parental mood disorder increased risks in offspring for GAD (RR = 2.28, 95% CI = 1.52-3.43, $I^2 = 0$), social phobia (RR = 1.19, 95% CI = 1.12-1.27, $I^2 = 0$), and panic disorder (RR = 2.68, 95% CI = 1.37-5.24, $I^2 = 0$).

Fourth, regarding parent sex, our subgroup analysis showed that the offspring of affected mothers presented a higher RR for SAD (RR = 4.45 vs 1.74, $p = .049$) but a lower RR for social phobia (RR = 0.91 vs 1.57, $p = .003$) compared to the offspring of affected parents (either fathers or mothers). Moreover, a study included in our analysis (Table S18, available online) also indicated that mood disorders in fathers and mothers contributed differently to offspring anxiety disorders, with higher odds ratios noted in the offspring of fathers compared to mothers. Univariate meta-regression showed a positive correlation between offspring sex (proportion of female offspring) and the RR for specific phobia ($\beta = 0.039$, $p = .03$), shown in Figure S4A, available online, indicating that parental mood disorders particularly increased the RR for specific phobia in female offspring more than in male offspring.

Table S19, available online, illustrates the results of multivariate meta-regression using the forced entry method. The parent control condition, parent and offspring sex, and offspring age were put into the regression model of any anxiety disorder. There was a significant relationship between parent control conditions and RR for any anxiety disorder ($\beta = -0.569$, SE = 0.26, $p = .046$). The overall model accounted for 55.87% (R^2) of the heterogeneity. Other results and discussions of moderation analyses are presented in Supplement 1, available online.

DISCUSSION

Key Findings

This meta-analysis comprehensively examines the relationship between parental mood disorders and offspring anxiety disorders, providing insight into a current knowledge gap. In general, our meta-analysis indicated higher risks of all types of anxiety disorders in the offspring of parents with mood disorders, except for agoraphobia. Furthermore, both parental bipolar disorder and unipolar depression were associated with a higher risk of any anxiety disorder, SAD, and panic disorder in offspring. In comparison, only parental unipolar depression contributed to a higher risk of specific phobia. However, the risk of specific phobia in the context of parental mood disorders was not robust after correcting for publication bias, and the risks of SAD and specific phobia in the context of parental unipolar depression lost significance after conducting sensitivity analysis by removing cross-sectional data, as illustrated in Figure S5, available online. Moderation analysis indicated no difference in risks for anxiety disorders between offspring of parents with bipolar disorder vs unipolar depression. In contrast, anxiety disorders in control parents, parent/child sex, child age, national income, and the publication year had significant impacts on the risks for some types of anxiety disorders.

Our study provides a more precise estimate of the overall effect of parental mood disorders on offspring anxiety disorders, with smaller effect sizes, narrower confidence intervals, and less between-study heterogeneity compared to the study conducted by Ayano *et al.*[14] We included more studies that provide data for different anxiety disorder subtypes and used more realistic pooling methods with multiple corrections. Furthermore, we adopted stricter inclusion criteria to ensure that all studies were directly relevant to our research questions and focused on the specific population of interest. Although most eligible studies had small sample sizes, this reflected the common trade-off between robust and in-depth measurement (ie, diagnostic interviews) and large sample sizes. In addition, we built on previous work by reporting the pooled risks for specific phobia and agoraphobia and what factors moderate risks.

Impacts of Parental Bipolar Disorder vs Major Depression

Our subgroup analysis found no significant difference in the risk of offspring anxiety disorders between parental bipolar disorder and major depression, highlighting the equal importance of addressing anxiety disorder in the 2 parental contexts. Previous literature has reported consistent results, with elevated anxiety symptoms and disorders in the offspring of parents with bipolar disorder and major depression, but not in offspring of parents with schizophrenia.[3,68] This pattern is interesting, given the results of a genome-wide analysis indicating that the genetic correlation between schizophrenia and bipolar disorder is more robust than that between bipolar disorder and major depression.[69] This apparent discrepancy between genetic and observational studies may reveal a shared environmental pathway across bipolar disorder/major depression in the transmission of anxiety disorders from parents to offspring.[70,71] If a common mechanism for intergenerational transmission in the offspring of parents with mood disorders can be found, this may indicate the potential utility of interventions targeting those shared risk factors.

The High Risk of Panic Disorder

The current study consistently showed a relatively high risk of panic disorder in the offspring of parents with bipolar disorder and unipolar depression, even when pooling the longitudinal follow-up data only. This finding aligns with 1 family study that indicated that panic disorder aggregated in families in which parents had bipolar disorder and in families in which parents had major depression. In contrast, specific phobia aggregated only in families in which parents had major depression, and social phobia did not show family aggregation.[72] A meta-analysis investigating comorbid anxiety disorders in people with bipolar disorder concluded that panic disorder had the highest RR among anxiety disorders compared to the control group.[73] Our meta-analysis further builds on previous studies and highlights revealing a unique relationship between parental bipolar disorder/unipolar depression and offspring panic disorder.

Factors That Influence the Association Between Parental Mood Disorders and Offspring Anxiety Disorders

Our subgroup analysis showed that anxiety disorders among control group parents were associated with higher risks of overall anxiety disorder, social phobia, and specific phobia in their offspring, which is aligned with a meta-analysis by Lawrence *et al.*[20] indicating that parental anxiety disorders are associated with offspring anxiety disorders. Notably, the RRs for overall anxiety disorder were similar in the context of parental anxiety disorders (RR = 1.76, 95% CI = 1.58-1.96) and parental mood disorder (RR = 1.82, 95% CI = 1.47-2.26). Next, we also found that anxiety disorders in parents with mood disorders did not raise the risk in their offspring beyond the effects of parental mood disorders. We should interpret the effect of mixed parental mood and anxiety disorder on offspring with caution because it was based on only 4 studies, with small samples, on parental major depression. Further research is needed to examine whether parental bipolar and anxiety disorders have additive or synergic effects on offspring anxiety disorders.

The current study also indicated sex-specific transmission from parental mood disorders to certain offspring anxiety disorders. For example, female offspring had a higher risk of specific phobia than male offspring; offspring of affected fathers had a higher risk of social phobia, whereas offspring of affected mothers had a higher risk of SAD. The findings about parent sex were possibly related to previous studies that paternal behavior was relevant to social phobia in offspring and that maternal affective disorder was significantly associated with SAD.[74,75] However, our findings are based on the subgroup of mothers vs parents (fathers or mothers) and the percentage of female offspring, so caution is warranted without individual data. Future studies should examine transmission from parents to same-sex/opposite-sex offspring. Given that parent−child research and family-based mental health services typically focus on mothers rather than fathers, our research underscores the potential importance of assessing and supporting fathers with mood disorders and their children.

Our subgroup analysis revealed that parental mood disorders had a trend of greater impact on children than on adolescents or adults, and that at-risk offspring were susceptible to developing SAD, GAD, and panic disorder during childhood and adolescence compared to control offspring. The susceptibility to specific anxiety disorders in childhood adds to the findings of previous research, which showed that youth-onset panic disorder, but not social phobia, was associated with later bipolar disorder.[76] In adulthood, the risk of GAD and panic disorder remained significant, whereas the risk of social phobia in at-risk offspring emerged. The results may be partly attributable to comorbidities of later mood disorder, where GAD, social phobia, and panic disorder were reported as the most common lifetime anxiety disorder in patients with bipolar disorder.[77] Our findings highlight the vulnerability of children to the effects of parental mood disorders, and underscore the importance of early assessment and intervention for at-risk offspring with specific anxiety disorders.

Several limitations should be considered in our meta-analysis. First, most of the included research focused on White populations in high-income Western countries, so we should be cautious about drawing conclusions regarding more diverse populations. Second, as the direction of causality cannot be established in cross-sectional studies, our results should be interpreted as indicating a correlation rather than a causal relationship. Moreover, retrospective recall of symptoms in cross-sectional studies may compromise reliability over time. Nevertheless, our sensitivity analyses, by removing the cross-sectional data, indicated the robustness of the main results. Third, because of the lack of individual-level data on potential risk factors (eg, offspring age), our regression model can explain only part of the variability in the effect sizes. Fourth, as most studies measured "lifetime" anxiety disorders before adulthood, our results are likely to underestimate adult-onset anxiety disorders. The RRs for anxiety disorders in offspring can only approximate the relationship between parental mood disorders and offspring anxiety disorders in late adolescence and early adulthood. Thus, future studies are needed to study the trajectories of different anxiety disorders across the lifespan of offspring of parents with mood disorders. Finally, caution is warranted in interpreting 5 studies using parent-reported diagnostic interviews for offspring anxiety because of the possible parent−child disagreement in reporting

anxiety symptoms and the impact of parental mood disorders on such discrepancies (detailed in Supplement 2, available online).[78]

Our meta-analysis suggests that the offspring of parents with mood disorders are vulnerable to developing anxiety disorders, especially panic disorder, starting from childhood. Furthermore, the risks of specific anxiety disorders are affected by the presence of anxiety disorders in control parents, as well as the offspring age and the sex of the affected parent and the offspring. Our study highlights the likely value of proactive prevention, early identification, and treatment strategies to reduce the risk of anxiety disorders in children of parents with mood disorders. An understanding of the mechanism underlying the increased rates of anxiety disorders in the offspring of parents with mood disorders may help to identify important targets for intervention.

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This work has been prospectively registered: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=215058.

Edoardo Ostinelli, MD, of the University of Oxford, UK, Yun-Chun Wu, PhD and Chiao-Erh Chang, PhD, of the National Taiwan University, Taiwan, served as the statistical experts for this research.

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