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Luiza Borges Kampmann

Transtornos psiquiátricos em filhos de indivíduos com transtorno bipolar: uma revisão sistemática, meta-análise e meta regressão

Porto Alegre, 2026

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Dissertação apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do título de mestra em Psiquiatria e Ciências do Comportamento.

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RESUMO

Filhos de pessoas com transtorno bipolar constituem uma população de alto risco para o desenvolvimento de transtornos psiquiátricos. Entretanto, a prevalência desses transtornos e a magnitude desse risco em comparação com filhos de indivíduos sem transtorno bipolar, com transtorno depressivo maior ou com esquizofrenia permanecem incertas. O objetivo deste estudo foi investigar a ocorrência de transtornos psiquiátricos em filhos de pessoas com transtorno bipolar por meio de uma revisão sistemática, meta-análise e meta-regressão. A revisão foi conduzida conforme as recomendações do PRISMA e registrada na plataforma PROSPERO (CRD42024559671). Foram pesquisadas as bases PubMed, Embase, PsycINFO, Scopus e Web of Science e dessas, foram incluídos 59 estudos. A prevalência combinada de qualquer transtorno psiquiátrico foi de 58,05% (IC95%: 48,34–67,18), sendo transtornos do humor (29,64%), transtornos de ansiedade (28,25%), transtornos depressivos (24,0%) e transtorno de déficit de atenção/hiperatividade (21,1%) os desfechos mais frequentes. Em comparação aos filhos de indivíduos sem transtorno bipolar, observou-se aumento significativo da chance de qualquer transtorno psiquiátrico (OR = 3,15; IC95%: 2,32–4,28), bem como de transtornos do humor, transtornos do espectro bipolar, transtornos depressivos e transtornos de ansiedade. Não foram observadas diferenças estatisticamente significativas, para a maioria dos desfechos, entre filhos de pessoas com transtorno bipolar e filhos de indivíduos com transtorno depressivo maior ou esquizofrenia. Os achados demonstram que filhos de pessoas com transtorno bipolar apresentam elevada carga de psicopatologia e sugerem que parte dessa vulnerabilidade pode refletir mecanismos familiares compartilhados entre diferentes transtornos psiquiátricos graves. Esses resultados reforçam a importância do acompanhamento longitudinal e de estratégias preventivas voltadas a populações de alto risco.

Palavras-chave: transtorno bipolar; filhos; transtornos psiquiátricos; população de alto risco; revisão sistemática; meta-análise.

LISTA DE ABREVIATURAS E SIGLAS

TB- Transtorno Bipolar

TDAH- Transtorno do Déficit de Atenção com Hiperatividade

CID- Classificação Internacional de Doenças

PROSPERO- International Prospective Register of Systematic Reviews

JAACAP- Journal of the American Academy of Child & Adolescent Psychiatry

DSM- Manual Diagnóstico e Estatístico de Transtornos Mentais

NOQAS- Newcastle–Ottawa Quality Assessment Scale

OR- Odds Ratio

PRISMA- Preferred Reporting Items for Systematic reviews and Meta-analisys

REML- Restricted Maximum Likelihood

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APRESENTAÇÃO

Esta dissertação foi desenvolvida junto ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento da Universidade Federal do Rio Grande do Sul como requisito parcial para obtenção do título de Mestre em Psiquiatria e Ciências do Comportamento.

O trabalho foi elaborado no formato de dissertação baseada em artigo científico. Inicialmente, são apresentados a fundamentação teórica, a justificativa, os objetivos e os aspectos metodológicos do estudo. Em seguida, é apresentado o manuscrito intitulado *Psychiatric disorders among offspring of individuals with bipolar disorder: a systematic review and meta-analysis*, atualmente submetido para publicação no periódico *Journal of the American Academy of Child & Adolescent Psychiatry (JAACAP)*.

Ao final, são apresentadas as considerações finais da dissertação, nas quais os principais achados são discutidos à luz da literatura científica, destacando suas implicações para a pesquisa e para a prática clínica.

1 Introdução

O desenvolvimento dos transtornos psiquiátricos resulta de uma interação complexa entre fatores genéticos e ambientais ao longo da vida. Entre os fatores de risco conhecidos, a história familiar constitui um dos preditores mais robustos para o surgimento de psicopatologia, especialmente quando envolve transtornos psiquiátricos graves, como o transtorno bipolar (TB). Nesse contexto, filhos de pessoas com transtorno bipolar representam uma população de alto risco para o desenvolvimento de diferentes transtornos psiquiátricos ao longo do desenvolvimento, oferecendo uma oportunidade única para compreender como a vulnerabilidade familiar se manifesta e quais trajetórias podem culminar em diferentes desfechos psicopatológicos (Craddock & Sklar, 2013; Rasic et al., 2014; Duffy et al., 2017).

O transtorno bipolar é um transtorno mental crônico e recorrente, caracterizado pela ocorrência de episódios de depressão, mania ou hipomania, intercalados por períodos de remissão parcial ou completa dos sintomas. Embora sua prevalência seja relativamente baixa quando comparada à de outros transtornos mentais, o TB está entre as principais causas de incapacidade em todo o mundo, em razão de seu início precoce, curso recorrente e importante impacto funcional, social e ocupacional. Além disso, está associado ao aumento da mortalidade, decorrente tanto do elevado risco de suicídio quanto da maior ocorrência de doenças clínicas, como doenças cardiovasculares, obesidade e diabetes mellitus (Merikangas et al., 2011; Grande et al., 2016).

Além de sua elevada carga clínica e social, o transtorno bipolar apresenta uma das maiores herdabilidades entre os transtornos psiquiátricos, estimada entre 60% e 85%. Estudos familiares demonstram que filhos de indivíduos com TB apresentam risco aproximadamente oito a dez vezes maior de desenvolver o transtorno ao longo da vida quando comparados à população geral, reforçando a importância da agregação familiar e da contribuição de fatores genéticos para a etiologia do transtorno (Craddock & Sklar, 2013; Duffy et al., 2017).

Entretanto, a agregação familiar observada no transtorno bipolar não se restringe ao diagnóstico bipolar. Nas últimas duas décadas, estudos prospectivos conduzidos em filhos de pessoas com TB demonstraram que essa população apresenta maior risco para uma ampla gama de transtornos psiquiátricos, incluindo transtornos de ansiedade, transtornos depressivos, transtorno de déficit de atenção e hiperatividade (TDAH), transtornos

disruptivos e, posteriormente, transtorno bipolar. Esses achados sugerem que a vulnerabilidade familiar ao TB se manifesta inicialmente por meio de sintomas inespecíficos e diferentes formas de psicopatologia, que podem anteceder em vários anos o surgimento de episódios afetivos característicos (Hillegers et al., 2005; Mesman et al., 2013; Axelson et al., 2015; Duffy et al., 2017).

Os estudos realizados em populações de alto risco familiar tem contribuído significativamente para a compreensão da história natural do transtorno bipolar. Diferentemente de estudos conduzidos exclusivamente com pacientes já diagnosticados, essas coortes permitem acompanhar indivíduos desde a infância até o período de maior risco para o surgimento dos transtornos psiquiátricos, possibilitando identificar manifestações clínicas precoces, trajetórias de desenvolvimento e potenciais fatores associados à transição para diferentes desfechos psiquiátricos. Esse delineamento representa uma estratégia particularmente valiosa para compreender mecanismos de vulnerabilidade e subsidiar estratégias de prevenção e intervenção precoce (Egeland et al., 2003; Duffy et al., 2017; Axelson et al., 2015).

Evidências provenientes dessas coortes sugerem que o transtorno bipolar raramente se inicia por um episódio maníaco isolado. Ao contrário, sua trajetória costuma ser precedida por sintomas inespecíficos, como ansiedade, alterações do sono, dificuldades emocionais e episódios depressivos durante a infância e a adolescência. Esses achados reforçam a hipótese de que a psicopatologia observada em filhos de pessoas com TB representa um processo de desenvolvimento progressivo, cuja expressão clínica pode variar ao longo do tempo e culminar em diferentes diagnósticos psiquiátricos (Duffy et al., 2017; Axelson et al., 2015).

Apesar do crescente número de estudos publicados, os resultados permanecem heterogêneos quanto à magnitude do risco para diferentes transtornos psiquiátricos nessa população. Diferenças metodológicas entre os estudos, incluindo características das amostras, critérios diagnósticos, tempo de acompanhamento e grupos de comparação, dificultam uma síntese integrada das evidências disponíveis. Dessa forma, torna-se necessária uma revisão sistemática acompanhada de meta-análise capaz de sintetizar criticamente as evidências disponíveis e estimar de forma robusta a magnitude do risco para diferentes transtornos psiquiátricos em filhos de pessoas com transtorno bipolar (Lau et al., 2018).

2 Justificativa

Filhos de pessoas com transtorno bipolar constituem uma das populações de maior risco para o desenvolvimento de transtornos psiquiátricos. O reconhecimento precoce das manifestações psicopatológicas nessa população representa uma oportunidade para compreender a história natural do adoecimento mental e desenvolver estratégias de prevenção e intervenção antes do estabelecimento de quadros mais graves.

Nas últimas décadas, diversos estudos prospectivos investigaram o desenvolvimento de transtornos psiquiátricos em filhos de indivíduos com transtorno bipolar. Embora esses estudos tenham contribuído significativamente para o entendimento da evolução clínica dessa população, seus resultados permanecem heterogêneos em relação aos diferentes desfechos avaliados, à magnitude dos riscos observados e às características metodológicas empregadas. Essa variabilidade dificulta a interpretação integrada das evidências disponíveis e limita sua aplicação na prática clínica e no planejamento de novas pesquisas.

Nesse contexto, revisões sistemáticas acompanhadas de meta-análises constituem a abordagem mais adequada para sintetizar criticamente os achados da literatura, aumentando a precisão das estimativas de risco e permitindo a identificação de padrões consistentes entre diferentes estudos. A integração dessas evidências pode contribuir para o aprimoramento do conhecimento sobre a trajetória da psicopatologia em filhos de pessoas com transtorno bipolar, bem como subsidiar futuras investigações sobre fatores de risco, mecanismos envolvidos no desenvolvimento dos transtornos psiquiátricos e estratégias de rastreamento e intervenção precoce.

Assim, este estudo justifica-se pela necessidade de reunir e sintetizar as evidências disponíveis acerca da ocorrência de transtornos psiquiátricos em filhos de pessoas com transtorno bipolar, contribuindo para uma compreensão mais abrangente dessa população de alto risco e fornecendo informações que possam orientar tanto a prática clínica quanto o desenvolvimento de pesquisas futuras.

3 Objetivos

3.1 Objetivo geral

Descrever a prevalência dos transtornos psiquiátricos entre os filhos biológicos de pais com TB.

3.2 Objetivos específicos

1) Comparar a prevalência de transtornos psiquiátricos entre filhos de pais com TB e filhos de pais sem TB

2) Identificar os transtornos mais prevalentes nos descendentes de pessoas com TB;

3) Sintetizar os dados dos estudos incluídos a partir de uma metanálise;

4) Realizar meta-regressão para avaliar possível impacto das variáveis;

5) Avaliar viés de publicação.

4 Considerações éticas

Pela natureza do artigo, não foi necessário submeter o projeto para um Comitê de Ética em Pesquisa. De qualquer modo, é importante ressaltar que todo o projeto foi pautado por uma conduta ética e profissional.

Buscou-se estruturar o artigo pelos mais elevados padrões de transparência para os trabalhos desta natureza, como registro prévio do protocolo no PROSPERO https://www.crd.york.ac.uk/PROSPERO/view/CRD42024559671 e o seguimento do *Guideline* PRISMA.

5 Artigo

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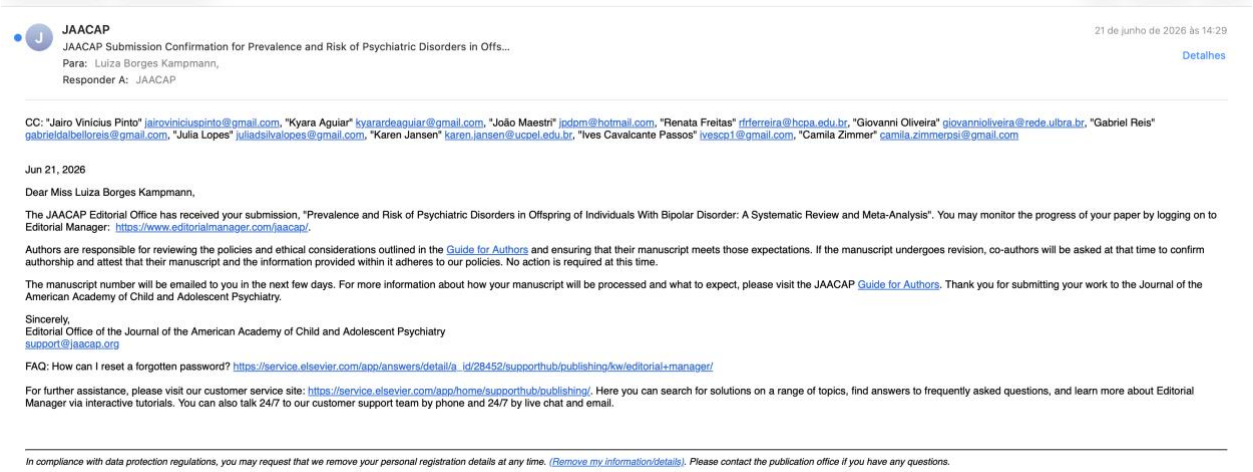

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Dear Miss Luiza Borges Kampmann,

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Title: Prevalence and Risk of Psychiatric Disorders in Offspring of Individuals With Bipolar Disorder: A Systematic Review, Meta-Analysis and Meta Regression

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ABSTRACT

Background:
Offspring of individuals with bipolar disorder (BD) are considered a high-risk population for the development of psychiatric disorders. However, the prevalence of these disorders and the extent to which this risk differs compared with that of offspring of unaffected parents, parents with major depressive disorder, or parents with schizophrenia remain unclear.

Methods:
We conducted a systematic review and meta-analysis of observational studies examining psychiatric disorders among offspring of individuals with BD, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, Embase, Web of Science, and Scopus were systematically searched through December 2025, with no date restrictions. Random-effects meta-analyses were conducted to estimate pooled prevalence rates and odds ratios (ORs) across psychiatric disorders. Heterogeneity, publication bias, sensitivity analyses, and potential moderators were also evaluated.

Results:
A total of 59 studies were included in the meta-analysis. The pooled prevalence of any psychiatric disorder among offspring of individuals with BD was 58.05% (95% CI: 48.34–67.18). The most prevalent outcomes included mood disorders (29.64%), anxiety disorders (28.25%), depressive disorders (24.0%), and attention-deficit/hyperactivity disorder (21.1%). BD showed a pooled prevalence of 9.64% (95% CI: 6.31–14.46). Compared with controls, offspring of individuals with BD had significantly higher odds of any psychiatric disorder (OR = 3.15; 95% CI: 2.32–4.28; $p < 0.0001$). Increased odds were observed for mood disorders (OR = 3.73), including bipolar spectrum disorders (OR = 7.89) and depressive disorders (OR = 3.24), as well as anxiety disorders (OR = 2.30). Sensitivity analyses yielded generally consistent results across outcomes. No statistically significant differences were observed between offspring of individuals with BD and offspring of individuals with major depressive disorder or schizophrenia. Meta-regression analyses identified publication year, offspring age, and geographic region as significant moderators for selected outcomes.

Conclusions:
Offspring of individuals with BD exhibit both a high absolute burden of psychopathology and a substantially increased risk of psychiatric disorders relative to controls. Although bipolar disorders showed the strongest relative risk estimates, mood, anxiety, and depressive disorders were more prevalent in this population. These findings support both transdiagnostic and disorder-specific models of familial vulnerability and suggest that preventive efforts should target not only emerging bipolar symptoms but also a broader range of psychiatric disorders.

INTRODUCTION

Bipolar disorder (BD) is a severe and highly disabling psychiatric condition characterized by recurrent episodes of mania, hypomania, and depression, with onset typically occurring in late adolescence or early adulthood. Prior studies indicate that first-degree relatives of individuals with BD have a markedly increased risk of developing the disorder, with estimates suggesting up to an eightfold increase compared to the general population (1,2). This increased vulnerability, however, is not restricted to BD. A

growing body of evidence supports a transdiagnostic pattern of risk, whereby offspring of affected individuals are more likely to develop a broad range of psychiatric disorders rather than a single diagnostic category (3,4). Large-scale cohort and registry-based studies further corroborate these findings, demonstrating increased incidence of mood, anxiety, and neurodevelopmental disorders among offspring of parents with BD (5,6).

From a developmental perspective, longitudinal high-risk cohort studies provide robust evidence that early, non-specific psychopathological symptoms may precede the onset of BD by several years(7,8). These findings suggest that early manifestations may represent markers of vulnerability, evolving into more structured psychiatric conditions over time. Notably, a substantial proportion of high-risk offspring develop at least one psychiatric disorder during follow-up, with estimates exceeding 50% in some cohorts (9).

To our knowledge, four previous meta-analyses have examined the risk of psychiatric disorders among offspring of parents with BD (3,4,10,11). The earliest, published nearly 30 years ago, reported a 2.7-fold increased risk for any psychiatric disorder among offspring of affected parents (10). Rasic et al. updated these findings but applied restrictive inclusion criteria, excluding studies in which the mean age of offspring was below 10 years (3). Similarly, other meta-analyses limited inclusion to English-language studies with control groups (11). More recently, a large transdiagnostic meta-analysis examined offspring across multiple parental psychiatric disorders rather than focusing specifically on BD (4). Despite these advances, important gaps remain. In particular, the prevalence and comparative risk of specific psychiatric disorders among offspring of individuals with BD has not been comprehensively updated using broad inclusion criteria. Furthermore potential sources of heterogeneity—such as offspring age, parental BD subtype, diagnostic methods, and geographic region—have not been systematically examined using meta-regression analyses.

By expanding inclusion criteria beyond those applied in previous meta-analyses, this study provides updated estimates of psychiatric disorders among offspring of individuals with BD and compares these findings with those observed in offspring of unaffected parents and those with other major psychiatric disorders. We also examine potential sources of between-study heterogeneity. We hypothesize that offspring of individuals with BD have a higher likelihood of psychiatric disorders, particularly mood disorders, compared with controls.

METHODS

This systematic review was registered in PROSPERO (CRD42024559671); https://www.crd.york.ac.uk/PROSPERO/view/CRD42024559671) and conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The flow diagram is shown in Figure 1, and the PRISMA checklist is available in Supplementary Table S1.

Information sources and search strategy

A systematic literature search was conducted in Medline (PubMed), Embase, Web of Science, and Scopus using controlled vocabulary (e.g., MeSH terms) and free-text terms related to **bipolar disorder, offspring, and psychiatric disorders**, with search strategies tailored to each database. The search strategy was designed to maximize sensitivity by including a wide range of synonyms and diagnostic terms across different classification systems. The complete search strategy, including all search terms and combinations, is provided in the supplementary material (Supplementary Table S2).

Reference lists of relevant studies were also manually screened to identify additional eligible articles. No restrictions were applied regarding language or publication year. The initial search was conducted in April 2024 and updated in December 2025 to include recent studies.

Eligibility criteria

Studies were included if they met the following criteria: original observational studies with cross-sectional, cohort, or case-control designs; studies reporting psychiatric disorders among offspring of individuals with BD; studies including offspring of parents with a primary diagnosis of bipolar I disorder, bipolar II disorder, or cyclothymic disorder; and studies in which both parental BD and offspring psychiatric diagnoses were established according to standardized diagnostic criteria, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM), International Classification of Diseases (ICD), or validated structured diagnostic interviews (e.g., MINI). No restrictions were applied regarding offspring age or language of publication.

Studies were excluded if they did not report clinical psychiatric outcomes (e.g., studies focused exclusively on genetic or biological markers) or if they were non-original publications (reviews, meta-analyses, editorials, book chapters, conference abstracts), case reports, or case series.

The primary outcome was the presence of any psychiatric disorder among offspring, and the exposure of interest was parental BD.

Selection process

After database searches, all references were imported into Rayyan for screening. Duplicate records were removed using EndNote and manually verified. Four reviewers (LK, RF, JM, GO) independently and blindly screened titles and abstracts, with disagreements resolved by a fifth investigator (CZ). Full-text screening was also performed independently and blindly by six reviewers (LK, RF, JM, GO, JL, GR), with CZ again resolving any disagreements.

Study risk of bias assessment

Study quality was assessed by five reviewers (RF, JM, GO, JL, GR) using the Newcastle-Ottawa Quality Assessment Scale (NOQAS) to evaluate the risk of bias in observational studies. Assessments were discussed with a third reviewer (LK) to ensure consistency and resolve any uncertainties in ratings. The results of the risk of bias assessment are presented in Supplementary Table S3.

Outcomes

The primary outcomes were the pooled prevalence and comparative risk of psychiatric disorders among offspring of individuals with BD. Comparative risk was estimated using pooled odds ratios (ORs) comparing offspring of individuals with BD with offspring of unaffected controls and, when available, offspring of individuals with major depressive disorder or schizophrenia. Secondary outcomes included prevalence and comparative risk estimates for specific diagnostic categories, including mood, anxiety, neurodevelopmental, disruptive behavior, and substance use disorders.

Secondary outcomes included the association between parental BD and the presence of psychiatric disorders in offspring, expressed as odds ratios (ORs) comparing offspring of individuals with BD with offspring of parents without BD or with other psychiatric disorders (MDD and schizophrenia), when available.

Additional secondary outcomes included the prevalence of specific groups of psychiatric disorders (e.g., mood, anxiety, substance use, and neurodevelopmental disorders).

Data Extraction

A standardized Excel spreadsheet was developed to extract prevalence and comparative risk data from eligible studies. The prevalence spreadsheet included the following variables: first author, year of publication, study design, total sample size, Parent's BD subtype, offspring psychiatric disorders (overall and specific diagnoses), sex distribution, skin color, ethnicity, mean age (with SD), sample type (clinical or population-based), country, and language.

The final set of included studies was divided among six reviewers (LK, RF, JM, GO, JL, GR). Each reviewer extracted data independently, and all entries were subsequently reviewed and verified by LK. When overlapping datasets were identified, the most comprehensive sample was retained. Overlap was assessed through full-text evaluation based on recruitment sites, study periods, institutional affiliations, cohort or registry names, sample characteristics, and authorship patterns. No assumptions were made regarding missing or unclear data; only explicitly reported information was extracted.

Statistical analysis

Random-effects meta-analyses using restricted maximum likelihood (REML) estimation were conducted to calculate pooled prevalence rates (PR) and pooled odds ratios (ORs) with corresponding 95% confidence intervals (95% CI). Separate models were performed for overall psychiatric disorders and for specific diagnostic categories. For prevalence analyses, prevalence estimates were transformed using a logit

transformation before pooling and back-transformed for interpretation. Comparative risk analyses were conducted using pooled ORs comparing offspring of individuals with BD with offspring of unaffected controls and, when available, offspring of individuals with major depressive disorder or schizophrenia. Between-study heterogeneity was assessed using Cochran's Q statistic and the I^2 statistic. Publication bias and small-study effects were evaluated through funnel plot inspection, Egger's regression test, and Duval and Tweedie's trim-and-fill analyses. Leave-one-out sensitivity analyses were conducted to assess the robustness of pooled estimates. Meta-regression analyses were performed to investigate potential moderators, including offspring age, publication year, geographic region, and sample type.

Meta-regression

In order to investigate potential sources of heterogeneity, we performed random-effects meta-regression analyses using REML estimation with Knapp–Hartung adjustment (12–14). Univariate models were fitted to examine the association between study-level moderators and effect sizes. Continuous moderators included publication year, offspring mean age, and proportion of male offspring in each study. Categorical moderators included offspring diagnostic criteria, parental diagnostic criteria, and the region where each study was conducted (14).

Meta-regression results are reported as regression coefficients (β), standard errors (SE), and p-values. Residual heterogeneity (τ^2) and the proportion of explained variance (pseudo-R^2) were also estimated. The significance of moderators was assessed using F-tests based on the Knapp–Hartung adjustment, reported with corresponding degrees of freedom and p-values (15).

All analyses were conducted in R (version 4.4.3 for Linux) (R Core Team, 2024), using the meta and metafor packages (15,16).

RESULTS

The initial literature search identified 3,162 records across four electronic databases. Figure 1 illustrates the full study selection process according to the PRISMA guidelines (Figure 1). After the removal of 1,172 duplicate records, 1,990 titles and abstracts were screened. Of these, 1,461 were excluded for not meeting the inclusion criteria. A total of 529 full-text articles were sought for retrieval, of which 40 could not be obtained. Consequently, 489 full-text articles were assessed for eligibility. Of these, 430 were excluded for the following reasons: ineligible outcome (n = 187), ineligible study design (n = 90), ineligible exposure (n = 85), insufficient data (n=30) and duplicate reports (n = 38). Ultimately, 59 studies met the inclusion criteria and were included in the systematic review and meta-analysis. Methodological quality, assessed using the Newcastle–Ottawa Scale, was generally moderate to high across studies. Most studies were classified as moderate- or high-quality, with detailed ratings presented in Supplementary Table S3.

Prevalence of psychiatric disorders among offspring of individuals with bipolar disorder

The pooled prevalence estimates of psychiatric disorders among offspring of individuals with BD are presented in Table 2, and a summary of disorder-specific prevalence estimates is shown in Figure 2. Overall, the prevalence of any psychiatric disorder was 58.05% (95% CI: 48.34–67.18; k = 21), although substantial heterogeneity was observed across studies.

Mood disorders were among the most prevalent diagnostic categories, with a pooled prevalence of 29.64% (95% CI: 23.02–37.24; k = 31). Bipolar disorders specifically showed a pooled prevalence of 9.64% (95% CI: 6.31–14.46; k = 16), including bipolar I disorder (5.33%; 95% CI: 3.04–9.17) and bipolar II disorder (5.37%; 95% CI: 3.91–7.34). Depressive disorders demonstrated a pooled prevalence of 24.0% (95% CI: 18.97–29.87; k = 10), while dysthymic disorder showed a lower prevalence estimate of 2.78% (95% CI: 1.62–4.73).

Anxiety disorders were observed in 28.25% of offspring (95% CI: 17.54–42.15; k = 16). Neurodevelopmental and disruptive behaviour disorders were also frequently reported across studies. Attention-deficit/hyperactivity disorder (ADHD) demonstrated a pooled prevalence of approximately 21%, while disruptive behaviour disorders showed a pooled prevalence of 11.11% (95% CI: 6.18–19.18; k = 17). Oppositional defiant disorder and conduct disorder presented prevalence estimates of 14.48% (95% CI: 9.69–21.07) and 9.69% (95% CI: 8.22–11.40), respectively. Substance use disorders showed a pooled prevalence of 13.29% (95% CI: 7.03–23.70; k = 17). Forest plots for all prevalence analyses are presented in Supplementary Figures S25–S55.

Sensitivity analyses demonstrated the overall robustness of prevalence estimates across outcomes. Leave-one-out analyses did not substantially alter pooled prevalence estimates, supporting the stability of the findings across individual studies (Supplementary Table S4). Trim-and-fill analyses suggested potential small-study effects for bipolar disorders, bipolar II disorder, conduct disorder, disruptive behaviour disorders, and other depressive disorders, resulting in modestly adjusted prevalence estimates (Supplementary Table S6). However, the overall pattern of findings remained unchanged. Funnel plots and publication bias analyses for prevalence outcomes are presented in Supplementary Figures S56–S80.

Meta-analysis - Offspring of individuals with bipolar disorder vs controls

Offspring of individuals with BD showed increased odds of presenting any psychiatric disorders compared with control offspring (OR = 3.15; 95% CI: 2.32-4.28; p < 0.0001). This increased risk was observed across a broad range of psychiatric disorders (**Figure 3**).

Increased odds were observed for multiple psychiatric outcomes, including mood disorders (OR = 3.73; 95% CI: 2.70-5.15; p < 0.0001), bipolar spectrum disorders (OR = 7.89; 95% CI: 5.22-11.93; p < 0.0001), depressive disorders (OR = 3.24; 95% CI: 2.46-4.27; p < 0.0001), anxiety disorders (OR = 2.30; 95% CI: 1.77-2.97; p < 0.0001), disruptive behavior disorders (OR = 2.37; 95% CI: 1.89-2.97; p < 0.0001), substance use disorders (OR = 2.93; 95% CI: 1.90 to 4.51; p < 0.0001), and eating disorders (OR = 1.64; 95% CI: 1.38-1.95; p < 0.0001), although with smaller effect sizes.

The subgroup analysis of BD other than bipolar I disorder also showed a large effect size (OR = 7.45; 95% CI: 3.43-16.19; p < 0.0001), although based on a smaller number of studies (k = 5) (Table 3).

At the level of specific diagnoses, offspring of individuals with BD had higher odds of major depressive disorder (OR = 2.04; 95% CI: 1.12-3.72; p = 0.0205), autism spectrum disorder (OR = 2.21; 95% CI: 1.89-2.59; p < 0.0001), ADHD (OR = 2.46; 95% CI: 1.91-3.17; p < 0.0001), oppositional defiant disorder (OR = 3.61; 95% CI: 2.57-5.07; p < 0.0001), conduct disorder (OR = 3.00; 95% CI: 2.34-3.83; p < 0.0001), and alcohol use disorder (OR = 1.98; 95% CI: 1.74-2.25; p < 0.0001) (Table 3). Forest plots for all comparative risk analyses are presented in Supplementary Figures S1–S15.

Moderate to high heterogeneity was observed for any psychiatric disorder (I^2 = 78.2%), major depressive disorder (I^2 = 79.8%), anxiety disorders (I^2 = 61.1%), and substance use disorders (I^2 = 54.7%).

Evidence of small-study effects according to Egger's regression test was observed for any psychiatric disorder (z = 3.92; p < 0.0001), mood disorders (z = 2.65; p = 0.0081), depressive disorders (z = 2.72; p = 0.0066), major depressive disorder (z = 2.64; p = 0.0082), anxiety disorders (z = 1.70; p = 0.0898), and ADHD (z = 2.98; p = 0.0029). These outcomes were further examined using trim-and-fill analyses to evaluate the potential impact of publication bias and small-study effects. No evidence of small-study effects was observed for the remaining outcomes (Table 3). A summary of effect sizes across all psychiatric outcomes is presented in Figure 3, detailed comparative risk estimates are shown in Table 3, and funnel plots assessing publication bias are presented in Supplementary Figures S16–S24.

Sensitivity analyses

Trim-and-fill analyses showed that the associations remained statistically significant for any psychiatric disorder (adjusted OR = 2.41; 95% CI: 1.68-3.46; p < 0.0001), mood disorders (OR = 2.90; 95% CI: 2.08-4.05; p < 0.0001), depressive disorders (OR = 2.72; 95% CI: 2.46-3.01; p < 0.0001), anxiety disorders (OR = 1.95; 95% CI: 1.44-2.68; p < 0.0001), ADHD (OR = 2.10; 95% CI: 1.65-2.67; p < 0.0001), and substance use disorders (OR = 2.38; 95% CI: 1.53-3.70; p < 0.0001) (Table S7). In contrast, the association with major depressive disorder was attenuated and no longer statistically significant after adjustment (OR = 1.32; 95% CI: 0.75-2.35; p = 0.3368) (Table S7).

The leave-one-out analyses showed that statistical significance was maintained for all outcomes except autism spectrum disorder and eating disorders. Following removal of Lageborn et al., 2024, the associations with autism spectrum disorders and eating disorders were no longer statistically significant ($p = 0.1827$ and $p = 0.0732$, respectively) (Supplementary Table S5).

Meta-regression analyses

Sources of heterogeneity were explored according to study-level characteristics, including offspring mean age, publication year, parents' mean age, and geographic region, using meta-regression analyses (see Table 4).

Univariate meta-regression analyses were conducted to explore potential sources of between-study heterogeneity across outcomes. For any psychiatric disorder, mood disorders, major depressive disorder, and attention-deficit/hyperactivity disorder, none of the moderators were significantly associated with effect size, and no heterogeneity was explained (Table S8).

For bipolar spectrum disorders, publication year was significantly associated with effect size ($\beta = 0.039$; SE = 0.014; $p = 0.0116$), accounting for 84.6% of between-study heterogeneity (pseudo-$R^2 = 84.6\%$), with more recent studies reporting larger effect sizes. No other moderators were statistically significant.

For anxiety disorders, offspring's mean age was significantly associated with effect size ($\beta = -0.067$; SE = 0.031; $p = 0.045$), explaining 44.0% of between-study heterogeneity. Studies including older offspring reported smaller effect sizes for anxiety disorders. No other moderators reached statistical significance.

For substance use disorders, the region where the studies were conducted was significantly associated with effect size ($F(2,10) = 7.83$; $p = 0.009$), accounting for all observed between-study heterogeneity (pseudo-R^2 = 100%). Specifically, studies conducted in Europe ($\beta = -0.892$; $p = 0.003$) and North America ($\beta = -1.016$; $p = 0.046$) reported smaller effect sizes than studies conducted in other regions. No other moderators were significant.

These findings should be interpreted cautiously, given the limited number of studies available for some meta-regression analyses.

Meta-analysis – Offspring of individuals with bipolar disorder vs offspring of individuals with major depressive disorder

When compared with offspring of individuals with major depressive disorder, no statistically significant differences were observed in the odds of any psychiatric disorder (OR = 1.27; 95% CI: 0.85 to 1.92; p = 0.2455), depressive disorders (OR = 0.95; 95% CI: 0.28-3.19; p = 0.9353), major depressive disorder (OR = 1.33; 95% CI: 0.32-5.47; p = 0.6944), anxiety disorders (OR = 1.54; 95% CI: 0.73-3.25; p = 0.2574), attention-deficit/hyperactivity disorder (OR = 0.97; 95% CI: 0.49-1.90; p = 0.9312), oppositional defiant disorder (OR = 0.99; 95% CI: 0.57-1.76; p = 0.9760), conduct disorder (OR = 1.18; 95% CI: 0.57-2.44; p = 0.6645), and substance use disorders (OR = 1.03; 95% CI: 0.66-1.63; p = 0.8863).

These analyses were based on only two studies for each outcome (k = 2), resulting in wide confidence intervals for several estimates. Accordingly, the findings should be interpreted with caution (Table 4).

Offspring of individuals with bipolar disorder vs offspring of individuals with schizophrenia

Compared with offspring of individuals with schizophrenia, no statistically significant differences were observed for any psychiatric disorder (OR = 0.63; 95% CI: 0.31-1.28; p = 0.2035), mood disorders (OR = 1.97; 95% CI: 0.97-3.99; p = 0.0601), depressive disorders (OR = 3.15; 95% CI: 0.71-13.97; p = 0.1314), anxiety disorders (OR = 1.64; 95% CI: 0.25-10.76; p = 0.6083), attention-deficit/hyperactivity disorder (OR = 0.80; 95% CI: 0.23-2.84; p = 0.7330), and disruptive behavior disorders (OR = 0.44; 95% CI: 0.11-1.80; p = 0.2526).

These analyses were based on a limited number of studies (k = 2 to 3), and several estimates were characterized by wide confidence intervals and showed substantial heterogeneity for some outcomes. Accordingly, these findings should be interpreted with caution (Table 4).

DISCUSSION

This systematic review and meta-analysis provide a comprehensive and updated synthesis of both the prevalence and comparative risk of psychiatric disorders among offspring of individuals with BD. Importantly, nearly 60% of offspring presented at least one psychiatric disorder during their lifetime, indicating that psychiatric disorders are not only relatively more common than in controls but also highly frequent in absolute terms, affecting a majority of offspring exposed to familial risk for BD. In comparative analyses, offspring of parents with BD showed an approximately threefold higher likelihood of developing psychiatric disorders compared to controls (OR = 3.15). Elevated risk was consistently observed across multiple diagnostic categories, supporting a transdiagnostic

pattern of vulnerability. Notably, the strongest associations were identified for bipolar spectrum disorders, with effect sizes approaching eightfold increases.

The broad elevation in both prevalence and comparative risk across psychiatric outcomes reinforces the notion that offspring of individuals with BD represent a high-risk population not only for mood disorders, but also for a wide range of psychopathological conditions. This pattern is consistent with longitudinal high-risk cohort studies, including those conducted by Birmaher et al. and Duffy et al., which have demonstrated increased rates of mood, anxiety, and neurodevelopmental disorders among offspring of individuals with BD (1,19–21). From a developmental perspective, early manifestations such as anxiety symptoms, attentional difficulties, and emotional dysregulation may represent non-specific markers of vulnerability that precede the onset of more structured psychiatric disorders, supporting developmental staging models of illness progression (1,21). Although bipolar spectrum disorders showed the largest relative risk estimates, the prevalence analyses indicate that broader psychopathology is substantially more common than BD itself, reinforcing the importance of transdiagnostic monitoring strategies.

The large effect sizes observed for bipolar spectrum disorders suggest the presence of disorder-specific transmission mechanisms alongside broader vulnerability. This dual pattern—combining transdiagnostic risk with disorder-specific aggregation—is consistent with evidence from genetic and epidemiological studies indicating both shared and distinct liability across psychiatric disorders. Previous work by Kendler et al. and Smoller et al. has demonstrated substantial genetic overlap across major psychiatric conditions, which may help explain the broad vulnerability observed in offspring of affected individuals (2,17).

A clinically relevant finding of the present study is the lack of significant differences in psychiatric outcomes when comparing offspring of individuals with BD to those of parents with major depressive disorder or schizophrenia. Although these analyses were based on a limited number of studies and should be interpreted with caution, they suggest that the increased risk observed in offspring may reflect a more general familial vulnerability to psychopathology rather than a disorder-specific effect. This interpretation aligns with transdiagnostic models of psychiatric disorders, such as the general psychopathology ("p factor") framework proposed by Caspi et al., 2014 and further developed by Moffitt et al., 2017 (18). Furthermore, longitudinal studies of offspring of parents with major depressive disorder have demonstrated similarly elevated risks across a range of psychiatric outcomes, supporting the notion of shared familial vulnerability (19).

Substantial heterogeneity was observed across several analyses, particularly for overall psychiatric disorders, depressive disorders, and anxiety disorders. Although heterogeneity is expected in meta-analyses of observational studies, it underscores the variability in study designs, diagnostic approaches, and sample characteristics across the literature. To investigate potential sources of heterogeneity, we conducted meta-regression analyses, which identified several noteworthy patterns. For bipolar disorders, publication year was positively associated with effect size, suggesting that more recent studies report higher risk estimates, possibly reflecting improvements in diagnostic sensitivity or increased recognition of subthreshold presentations. For anxiety disorders, offspring age was inversely associated with effect size, indicating that younger samples may exhibit higher rates of anxiety symptoms, consistent with developmental models in which anxiety represents an early manifestation of vulnerability (7,20). In addition, geographic region was significantly associated with substance use disorder outcomes,

with lower effect sizes observed in studies conducted in Europe and North America compared to other regions. These findings may reflect cultural, environmental, or methodological differences across settings. Nevertheless, a substantial proportion of heterogeneity remained unexplained, suggesting that additional methodological and clinical factors may contribute to variability across studies.

From a clinical perspective, these findings have important implications. The consistent elevation in risk across multiple psychiatric domains highlights the need for early identification and monitoring of offspring of individuals with BD. Preventive strategies and early interventions targeting emotional regulation, anxiety, and behavioral difficulties may be particularly relevant in this population. Furthermore, the coexistence of general and disorder-specific risk underscores the importance of comprehensive, developmentally informed assessment approaches, rather than focusing exclusively on early manifestations of BD. Family-focused and early intervention strategies, as proposed by Miklowitz et al., 2006, may be particularly relevant in this context.

Several limitations should be considered when interpreting these findings. First, substantial heterogeneity across studies limits the precision of pooled estimates and may reflect differences in study design, diagnostic criteria, and assessment methods. Second, the number of studies available for certain subgroup analyses—particularly comparisons with offspring of parents with other psychiatric disorders—was limited, reducing statistical power and the robustness of these findings. Third, although rigorous methods were used to assess publication bias and sensitivity analyses were conducted, the presence of small-study effects in some outcomes suggests that bias cannot be entirely excluded. Additionally, most included studies were observational, limiting causal inference. Finally, despite extensive efforts to retrieve potentially eligible reports through institutional subscriptions, interlibrary resources, and direct searches, 40 records could

not be accessed in full text and were therefore excluded from eligibility assessment. Although the impact of these unavailable studies on the pooled estimates is unknown, their exclusion may have introduced selection bias.

Despite these limitations, this study has several important strengths. It provides an updated and comprehensive synthesis of the literature, incorporates a wide range of psychiatric outcomes, and applies advanced meta-analytic techniques, including meta-regression and multiple sensitivity analyses. Additionally, by including studies across diverse age groups, settings, and geographic regions, this work enhances the generalizability of the findings and provides a broad perspective on psychiatric risk among offspring of individuals with BD

To our knowledge, this is the first meta-analysis to simultaneously synthesize prevalence estimates and comparative risk estimates across multiple psychiatric outcomes while also comparing offspring of individuals with BD to offspring of parents with other major psychiatric disorders.

Future research should aim to clarify the mechanisms underlying psychiatric vulnerability among offspring of individuals with BD by addressing important methodological limitations in the current literature. Considerable variability exists across studies regarding the definition of familial risk, including differences in the assessment of parental psychopathology, the evaluation of one versus both parents, and the characterization of comparison groups. Many studies focused primarily on the diagnostic status of a single parent, while limited attention was given to the potential influence of psychopathology in the co-parent. Similarly, control groups varied from psychiatrically healthy families to families without BD but with other psychiatric conditions. Such

differences may contribute to the heterogeneity observed across outcomes and should be systematically examined in future investigations.

Longitudinal studies are also needed to better characterize developmental trajectories from early, non-specific manifestations of psychopathology to later disorder-specific outcomes, particularly bipolar spectrum disorders. Beyond identifying risk factors, future research should investigate protective factors and resilience mechanisms that may explain why many offspring exposed to familial risk do not develop psychiatric disorders. Greater attention to family functioning, social support, environmental exposures, and other modifiable factors may help inform preventive interventions and promote adaptive developmental outcomes in this population. Finally, more standardized approaches to diagnostic assessment, reporting of parental psychopathology, and characterization of familial risk profiles would improve comparability across studies and advance understanding of the pathways linking familial BD to offspring psychopathology.

In conclusion, offspring of individuals with BD are at significantly increased risk for a wide range of psychiatric disorders, reflecting both transdiagnostic vulnerability and disorder-specific aggregation. These findings highlight the importance of early identification, longitudinal monitoring, and transdiagnostic preventive strategies in high-risk populations. A better understanding of the developmental pathways, risk modifiers, and protective factors underlying these associations may contribute to more effective and personalized approaches to prevention and intervention.

Data availability

Data supporting the findings of this study are available in the supplementary material.

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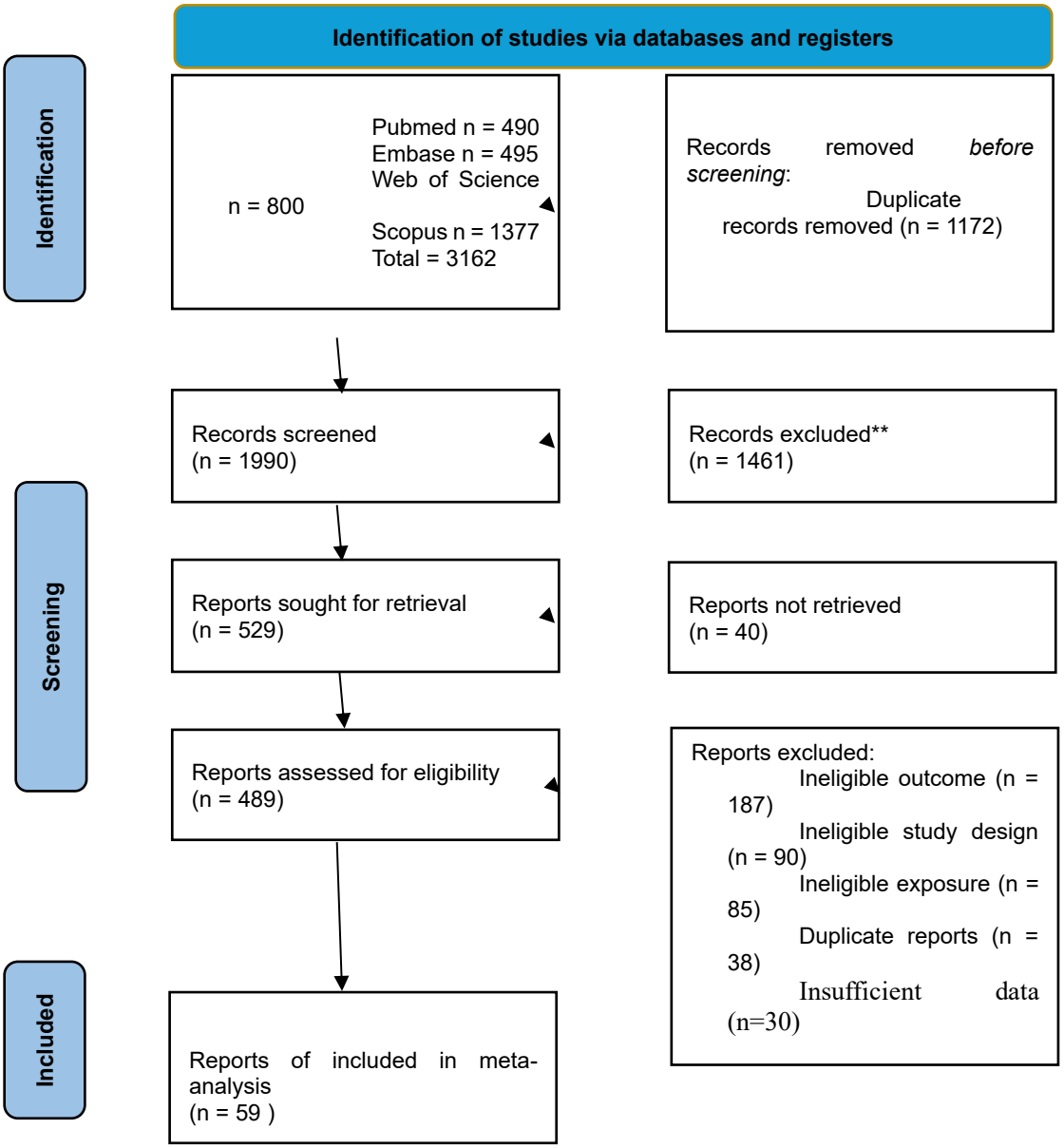
Figure S1. PRISMA 2020 flow diagram of study selection.
Flow diagram illustrating the identification, screening, eligibility, and inclusion of studies in the meta-analysis.



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Figure 2. Pooled prevalence estimates of PD among offspring of individuals with BD.

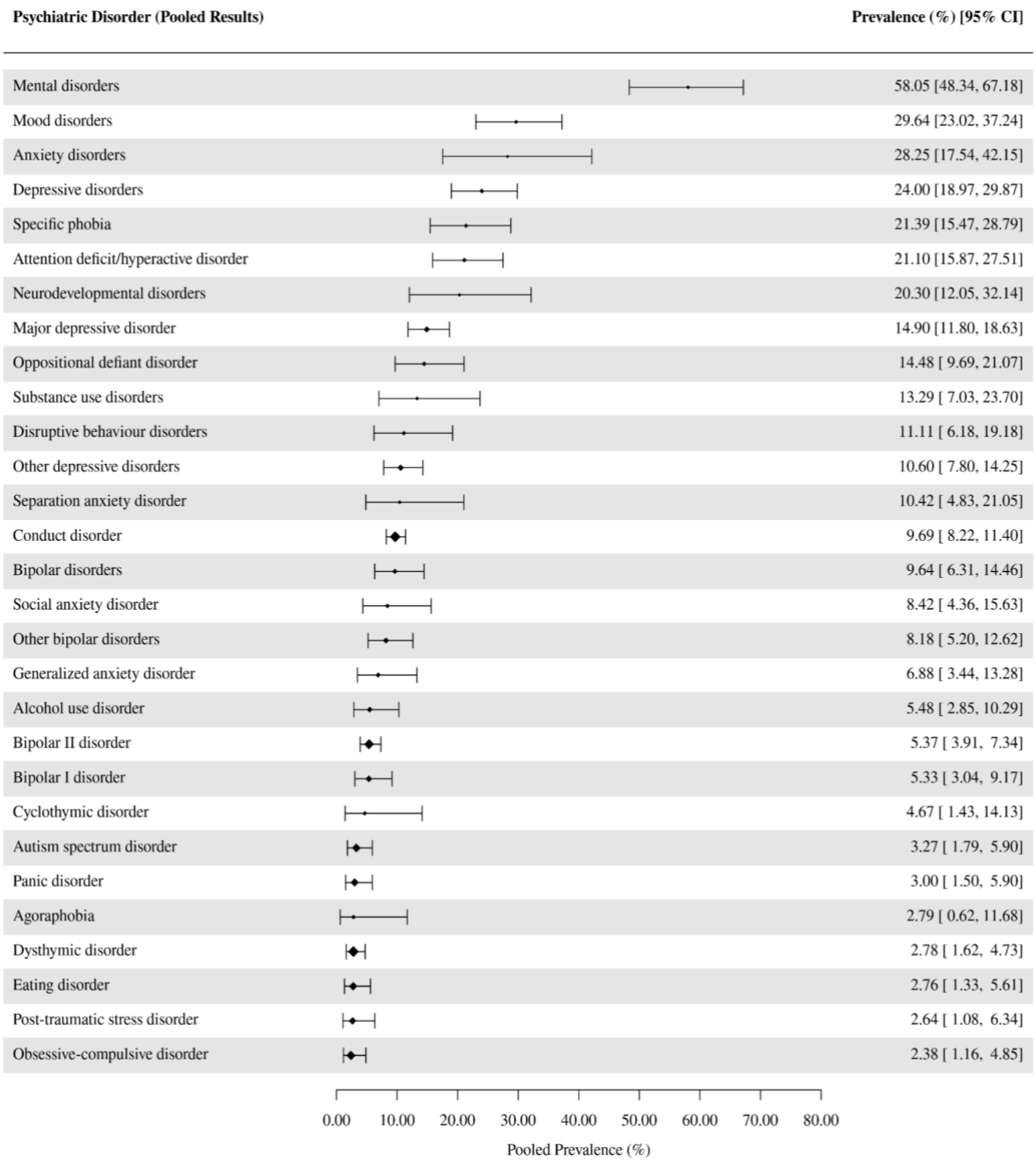


Figure 3. Summary plot of pooled odds ratios for psychiatric disorders in offspring of individuals with bipolar disorder compared with controls.

Pooled odds ratios and 95% confidence intervals are shown for each psychiatric outcome. Estimates were derived from random-effects meta-analyses.

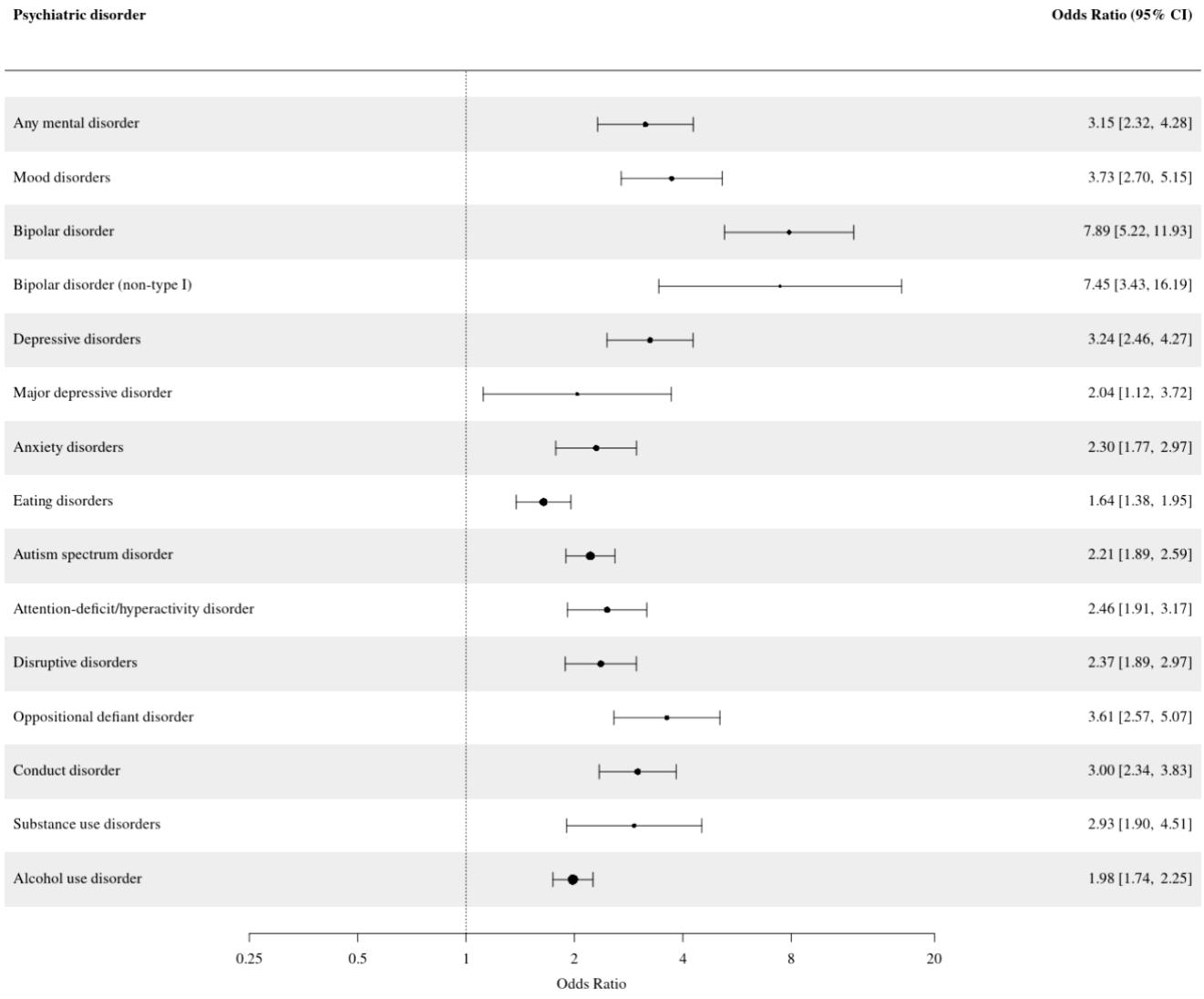


Table 1. Characteristics of studies included in the meta-analysis.

Author, Year	Study Title	Country	Study design	Parent BD diagnosis	Offspring diagnosis	Total Sample (n)	Age mean (S.D)	Male (n)	Offspring psychiatric disorder (n)
Akdemir et al., 2008	Psychopathology in the children of parents with bipolar mood disorder	Turkey	Cross-sectional Study	SADS-L	K-SADS-PL	69	12.7 (3,06)	38	27
Axelson et al., 2015	Diagnostic Precursors to Bipolar Disorder in Offspring of Parents With Bipolar Disorder: A Longitudinal Study	USA	Longitudinal Study	DSM-IV	K-SADS-PL	639	18.01 (4,8)	314	290
Bauer et al., 2015	Affective Processing in Pediatric Bipolar Disorder	USA	Cross-sectional Study	DSM-IV-TR	K-SADS-PL	57	11.83 (2,96)	21	NA
Beardslee et al., 1993	The impact of parental affective disorder on depression in offspring: a longitudinal follow-up in a nonreferred sample	USA	Longitudinal Study	SADS-L and I-SADS	K-SADS-ER	153	14.2 (3,2)	NA	NA
Birmaher et al., 2009	Lifetime Psychiatric Disorders in School-aged Offspring of Parents With Bipolar Disorder: The Pittsburgh Bipolar Offspring Study	USA	Cross-sectional Study	DSM-IV	K-SADS-PL	639	11.9 (3,6)	325	NA

Birmaher et al., 2021a	Role of Polygenic Risk Score in the Familial Transmission of Bipolar Disorder in Youth	USA	Longitudinal study	SCID and FHRDC	K-SADS-PL and SCID	745	11.1 (3.9)	119	NA
Birmaher et al., 2021b	A Longitudinal Study of Psychiatric Disorders in Offspring of Parents With Bipolar Disorder From Preschool to Adolescence	USA	Longitudinal study	K-SADS-PL and SCID	K-SADS-PL	214	13 (3.5)	56	NA
Carlson et al., 1993	Childhood behavior problems and bipolar disorder - relationship or coincidence?	USA	Longitudinal Study	K-SADS	SADS-L, SCID	434	NA	NA	66
Chang et al., 2000	Psychiatric Phenomenology of Child and Adolescent Bipolar Offspring	USA	Cohort Study	DSM-IV	K-SADS-PL	60	11.1 (3.5)	30	33
Chang et al., 2003	Temperament characteristics of child and adolescent bipolar offspring	USA	Cross-Sectional Study	DSM-IV	WASH-U-KSADS and K-SADS-PL	53	10.7 (3.3)	27	27
Cho et al., 2014	Mental disorders in offspring of parents with bipolar disorder	South Korea	Cross-sectional Study	DSM-IV	K-SADS-PL	112	12.3 (3,4)	56	NA

Cullen et al., 2014	Personality disorders in offspring of mothers with mood disorders: results from a longitudinal family study	USA	Prospective cohort study	DSM-III-R	SNAP-Y, DICA-R, SCID-II, SCID-I	146	14.6 (2,7)	36	NA
De la Serna et al., 2019	Lifetime psychopathology in child and adolescent offspring of parents diagnosed with schizophrenia or bipolar disorder: a 2-year follow-up study	Germany	Prospective cohort Study	DSM-IV (SCID-I)	K-SADS-PL	238	12.52 (3,06)	95	NA
De la Serna et al., 2025	Effects of parental characteristics on the risk of psychopathology in offspring: a 4 year follow up study	Spain	Prospective cohort Study	DSM-IV	K-SADS-PL	238	12.52 (3,06)	98	35
Diaz-Caneja et al. 2018	Psychopathology in the young offspring of parents with bipolar disorder: a controlled pilot study	Spain	Cross-sectional Study	DSM-IV (SCID-I)	K-SADS-PL	215	12.4 (3,14)	92	NA

Dienes et al., 2002	Characterization of children of bipolar parents by parent report CBCL	USA	Cohort study	DSM-IV	K-SADS-PL-K	58	11.89 (3.5)	35	40
Diler et al., 2011a	Dimensional psychopathology in offspring of parents with bipolar disorder	USA	Cross-sectional Study	DSM-IV	K-SADS-PL	589	11.8 (3,56)	361	NA
Diler et al., 2011b	Characteristics of depression among offspring at high and low familial risk of bipolar disorder	USA	Cross-sectional Study	DSM-IV	K-SADS-PL	81	14.7 (3.1)	33	61
Duffy et al., 2007	The early manifestations of bipolar disorder: A longitudinal prospective study of the offspring of bipolar parents	Canada	Longitudinal Study	DSM-IV	K-SADS-PL	188	20.4 (6,41)	75	NA
Duffy et al., 2013	Childhood anxiety: An early predictor of mood disorders in offspring of bipolar parents	Canada	Longitudinal Study	DSM-IV	K-SADS-PL	315	22.58 (6,81)	93	NA
Eraso-Osorio et al., 2021	High risk for psychiatric disorders in bipolar	Colombia	Cohort Study	DSM-IV-TR	K-SADS-PL and DIGS	281	20.5 (6,01)	108	NA

	offspring. A four years prospective study								
Findling et al., 2005	Early symptoms of mania and the role of parental risk	USA	Cross-sectional Study	SADS-LB and FH-RDC	K-SADS	400	11 (3,4)	245	148
Freed et al., 2014	EARLY RISK FACTORS FOR PSYCHOPATHOLOGY IN OFFSPRING OF PARENTS WITH BIPOLAR DISORDER: THE ROLE OF OBSTETRIC COMPLICATIONS AND MATERNAL COMORBID ANXIETY	USA	observacional transversal	SCID-I	K-SADS-E and SCID	206	13.61 (6.14)	110	159
Goetz et al., 2017	Psychiatric Disorders and Quality of Life in the Offspring of Parents with Bipolar Disorder	Czech Republic	Cross-sectional Study	SADS-L	K-SADS-PL	86	12.5 (3,1)	50	37
Hanford et al., 2016	Accuracy of emotion labeling in children of	USA	Cross-sectional Study	DSM-IV	K-SADS-PL	50	13.4 (2,8)	28	18

	parents diagnosed with bipolar disorder								
Helmink et al., 2025	Beyond the Window of Risk? The Dutch Bipolar Offspring Study: 22-year follow up	Netherlands	Prospective Longitudinal Cohort Study	DSM-IV	K-SADS-PL	100	16.1 (2.70)	46	NA
Hillegers et al., 2005	Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents	Netherlands	Prospective cohort study	DSM-IV	K-SADS-PL	129	20.54 (2.81)	69	NA
Hirshfeld-Becker et al., 2006	Psychopathology in the young offspring of parents with bipolar disorder: a controlled pilot study	USA	Cross-sectional Study	DSM-III-R	K-SADS-E	308	7.1 (2,6)	232	NA
Inal-Eiroglu et al., 2008	Mood and disruptive behavior disorders and symptoms in the offspring of patients with bipolar I disorder	Turkey	Cross-sectional Study	DSM-IV	WASH-U-KSADS	68	12.2 (3.3)	62	8
Joelsson et al., 2017	Parental psychopathology and offspring attention-deficit/hyperactivity disorder	Finland	Case-control study	ICD-9 and ICD-10	ICD-9 and ICD-10	10069	NA	NA	394

Kemner et al., 2015	The role of life events and psychological factors in the onset of first and recurrent mood episodes in bipolar offspring: results from the Dutch Bipolar Offspring Study	Netherlands	Cohort study	DSM-IV	DSM-IV, K-SADS-PL and SCID-I	140	16.1	72	NA
Keown-Stonemanan et al., 2021	Development and validation of a risk calculator for major mood disorders among the offspring of bipolar parents using information collected in routine clinical practice	Canada	Prospective cohort study	SCID and MINI	K-SADS-L and K-SADS-PL	413	NA	NA	NA
Klimes-Dougan et al., 2010	Continuity and cascade in offspring of bipolar parents: A longitudinal study of externalizing, internalizing, and thought problems	USA	Longitudinal Study	SCID, FH-RDC	CBCL, YSR	94	NA	NA	42
Küng et al., 2019	Psychiatric disorders among offspring of patients with Bipolar and	Switzerland	Cross-sectional Study	SCID-II, MINI	KSADS. DIGS	66	19.4 (3.1)	18	NA

	Borderline Personality Disorder								
Lageborn et al., 2024	Childhood and adolescence outcomes in offspring to parents with bipolar disorder: the impact of lifetime parental comorbidity, parental sex, and bipolar subtype	Sweden	Retrospective cohort study	ICD-8, ICD-9, ICD-10	ICD-9, ICD-10	272.668	NA	NA	1798
Lee et al., 2018	Differences in psychopathology between offspring of parents with bipolar I disorder and those with bipolar II disorder: A cross-sectional study	South Korea	Cross-sectional study	K-SADS-PL-K	K-SADS-PL-K	201	13.1 (3.6)	114	131
Lei et al., 2024	Circadian Rhythm dysfunction and psychopathology in the offspring of parents with bipolar disorder: a high-risk study in the chinese population	China	Case control Study	DSM-IV	K-SADS-PL	393	11.88 (4.36)	224	77

Licona-Martínez et al., 2014	Overall functioning in offsprings of parents with bipolar disorder and its association with clinical and sociodemographic variables	Finland	Cross-sectional observational study	DSM-IV-TR	K-SADS-PL	61	12.2 (3)	23	NA
Maoz et al., 2014	Dimensional psychopathology in preschool offspring of parents with bipolar disorder	USA	Cross-sectional observational study	DSM-IV	KSADS-PL, CBCL 1½–5, (ECI-4), EAS	224	3.28 (1.23)	59	NA
Palacio et al., 2017	Lifetime Psychiatric Disorders: a Comparison Study Between Offspring of Parents with bipolar disorder type I versus the Offspring of Community Controls Parents	Colombia	Cross-sectional Study	DIGS - Diagnostic Interview of Genetic Studies	K-SADS-PL + DIGS	277	17.6	140	NA
Palacio-Ortiz et al., 2015	Psychiatric disorders among offspring of patients with Bipolar and Borderline Personality Disorder	Colombia	Descriptive cross-sectional study	DIGS (DSM-IV-TR)	K-SADS-PL	110	17.3 (6)	59	NA

Park et al., 2015	Amygdalar volumetric correlates of social anxiety in offspring of parents with bipolar disorder	USA	Cross-sectional Study	Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)	WASH-UKSADS + KSADS-PL	46	13.9 (3.1)	42	29
Petresco et al., 2009	The prevalence of psychopathology in offsprings of bipolar woman from a Brazilian tertiary center	Brazil	Cross-sectional Study	DSM-IV	K-SADS-PL	43	11.2 (3.7)	18	27
Post et al., 2016	More illness in offspring of bipolar patients from the U.S. compared to Europe	USA	Cross-sectional observational study	SCID	Parent questionnaire	968	NA	NA	100
Preisig et al., 2015	The specificity of the familial aggregation of early-onset bipolar disorder: a controlled 10-year follow-up study of	Switzerland	Cohort Study	DIGS	KSADS-E	372	21.1 (5.6)	132	NA

	offspring of parents with mood disorders								
Propper et al., 2017	Disruptive mood dysregulation disorder	Canada	Cross-sectional Study l	SADS and SCID	K-SADS-PL	180	12.25 (3.6)	37	34
Propper et al., 2021	Attention-deficit/hyperactivity disorder and other neurodevelopmental disorders in offspring of parents with depression and bipolar disorder	Canada	Cross-sectional Study	SADS + SCID	SADS-PL + SCID	400	11.5 (4.6)	46	NA
Reichart et al., 2006	Social functioning of bipolar offspring	Netherlands	Cohort study	DSM-IV	K-SADS-PL + SCID	1224	21	NA	NA
Rudaz et al., 2020	Psychopathological precursors of the onset of mood disorders in offspring of parents with and without mood disorders: a result of a 13-year prospective cohort high-risk study	Switzerland	Prospective Cohort Study	DIGS	K-SADS e DIGS (digs nos offspring > 18 anos)	449	NA	NA	NA
Sánchez-Gistau et al., 2014	Environmental risk factors, prodromal	Spain	Cohort Study	DSM-IV	K-SADS-PL	237	NA	NA	33

	psychotic symptoms and psychopathology of child and adolescent offspring of parents with bipolar disorders, schizophrenia and community controls. The bipolar and schizophrenia young offspring study (basys)			(SCID-I)					
Setiaman et al., 2024	Emerging psychopathology and clinical staging in adolescent offspring in adolescent offspring of parents with bipolar disorder or schizophrenia - a longitudinal study	Netherlands	Prospective cohort Study	DSM-IV (SCID-I)	K-SADS-PL	208	13.7 (02.04)	79	50
Simonetti et al., 2025	Cognitive correlates of Borderline personality disorder features in Youth with Bipolar Spectrum Disorders and Bipolar offsprings	USA	Cross-sectional study	NA	MINI-KID	107	12.37 (2.39)	9	NA

Stapp et al., 2023	Family environment and polygenic risk in the bipolar high-risk context	USA and Australia	Cross-sectional Study	DIGS	K-SADS-BP	440	16.59 (2.84)	226	NA
Trespalacios et al., 2024	The perceived social support of parents having bipolar disorder impacts their children's mental health: a 10-year longitudinal study	Canada	Longitudinal Study	SCID-I	CAS (baseline e time 2), KSADS (menores 18) e SCID (maiores de 18)	138	20.2 (3.45)	70	46
Vandeleur et al., 2020	Mental disorders in offspring of parents with bipolar and major depressive disorders	Switzerland	Cross-sectional Study	DSM-IV	K-SADS-E	376	11.8 (3.47)	131	86
Wals et al., 2006	Prediction of change in level of problem behavior among children of bipolar parents	Netherlands	Prospective longitudinal cohort study	DSM-IV	K-SADS-PL	226	16.1 (2.7)	72	NA
Zappitelli et al., 2011	Lifetime psychopathology among the offspring of Bipolar I parents	USA	Cross-sectional case series	DSM-IV-TR	K-SADS-PL	35	12.5 (2.9)	20	25
Zavaleta-Ramírez et al.,	Estudio comparativo de psicopatología en hijos de	Mexico	Cross-sectional Study	MINI - Mini	K-SADS-PL	62	12.2	45	NA

2014	padres con trastorno bipolar			International Neuropsyatric Interview			(3.55)		
Zwicker et al., 2019	Affective lability in offspring of parents with major depressive disorder, bipolar disorder and schizophrenia	Canada	Longitudinal Study	SADS-IV and SCID-5	K-SADS-PL	320	11.66 (3.8)	77	NA

5.1.5 Table 2. Pooled prevalence estimates of psychiatric disorders among offspring of individuals with bipolar disorder

Psychiatric Disorder	Prevalence (%)	95% CI	k
Mental disorders	58.05	[48.34 to 67.18]	21
Mood disorders	29.64	[23.02 to 37.24]	31
Bipolar disorders	9.64	[6.31 to 14.46]	16
Bipolar I disorder	5.33	[3.04 to 9.17]	12
Bipolar II disorder	5.37	[3.91 to 7.34]	10
Other bipolar disorders	8.18	[5.20 to 12.62]	11
Depressive disorders	24.0	[18.97 to 29.87]	10
Dysthymic disorder	2.78	[1.62 to 4.73]	10
Other depressive disorders	10.6	[7.80 to 14.25]	10
Anxiety disorders	28.25	[17.54 to 42.15]	16
Disruptive behaviour disorders	11.11	[6.18 to 19.18]	17
Oppositional defiant disorder	14.48	[9.69 to 21.07]	19
Conduct disorder	9.69	[8.22 to 11.40]	12
Substance use disorders	13.29	[7.03 to 23.70]	17

Table 3. Meta-analysis of psychiatric disorders in offspring of individuals with bipolar disorder compared with control offspring

	Effects size			Heterogeneity			Small-study effects	Studies	Sample size
	OR	95% CI	p value	Q statistics (*df*; *p* value)	τ^2	I^2	*Egger z* (*p* value)	*k*	*n*
Mental disorders	3.15	[2.32 to 4.28]	<0.0001	56.72 (15, $p < 0.0001$)	0.22	78.20	3.92 (p <0.0001)	16	96,001
Mood disorders	3.73	[2.70 to 5.15]	<0.0001	37.64 (17, $p = 0.0028$)	0.20	63.39	2.65 (p = 0.0081)	18	96,458
Bipolar disorders	7.89	[5.22 to 11.93]	<0.0001	24.48 (16, $p = 0.0796$)	0.17	39.14	-0.18 (p = 0.3488)*	17	96,799
Bipolar disorder other than BD 1	7.45	[3.43 to 16.19]	<0.0001	0.83 (04 $p = 0.9347$)	0	0	----	05	1,004
Depressive disorders	3.24	[2.46 to 4.27]	<0.0001	10.68 (10, $p = 0.3832$)	0.03	14.57	2.72 (p = 0.0066)	11	95,430
Major depressive disorder	2.04	[1.12 to 3.72]	0.0205	64.44 (13, $p < 0.0001$)	0.85	79.83	2.64 (p = 0.0082)	14	2,962
Anxiety disorders	2.30	[1.77 to 2.97]	<0.0001	53.24 (23, $p = 0.0003$)	0.20	61.14	1.70 (p = 0.0898)	24	97,455
Eating disorders	1.64	[1.38 to 1.95]	<0.0001	3.33 (08, $p = 0.9122$)	0	0	-----	09	94,329
Autism spectrum disorder	2.21	[1.89 to 2.59]	<0.0001	1.40 (04, $p = 0.8439$)	0	0	----	05	93,929
Attention deficit hyperactivity disorder	2.46	[1.91 to 3.17]	<0.0001	30.39 (18, $p = 0.0338$)	0.10	48.35	2.98 (p = 0.0029)	19	96,597
Disruptive behaviour disorders	2.37	[1.89 to 2.97]	<0.0001	13.46 (09, $p = 0.1428$)	0.03	20.76	----	09	9,4670
Oppositional defiant disorder	3.61	[2.57 to 5.07]	<0.0001	3.05 (12, $p = 0.9952$)	0	0	0.48 (p = 0.6284)	13	2,080
Conduct disorder	3.00	[2.34 to 3.83]	<0.0001	2.71 (06, $p = 0.8438$)	0.01	1.62	----	07	93,864
Substance use disorder	2.93	[1.90 to 4.51]	<0.0001	23.02 (12, $p = 0.0275$)	0.21	54.73	1.35 (p = 0.1785)	13	96,069
Alcohol use disorder	1.98	[1.74 to 2.25]	<0.0001	5.41 (06, $p = 0.4926$)	0	0	----	07	94,936

BD: bipolar disorder; OR: odds ratio; CI: confidence interval; Q: Cochran's Q statistic for heterogeneity; τ^2: between-study variance; I^2: proportion of total variability due to between-study heterogeneity. Egger's regression test was used to assess small-study effects. k denotes the number of studies included in each meta-analysis and n the total sample size. Random-effects models were estimated using restricted maximum likelihood (REML). Each row represents a separate meta-analysis for a specific psychiatric disorder.

*The model did not converge; therefore a rank correlation test was used for testing the funnel plot asymmetry (Kendall's tau = -0.1765, p = 0.3488)

Table 4. Meta-analysis of psychiatric disorders in offspring of individuals with bipolar disorder compared with MDD Offspring

	Effects size			Heterogeneity			Studies	Sample size
	OR	95% CI	p value	Q statistics (*df*; *p* value)	t^2	I^2	*k*	*n*
Any mental disorder	1.27	[0.85 to 1.92]	0.2455	0.32 (13, $p = 0.5745$)	0	0	02	389
Depressive disorders	0.95	[0.28 to 3.19]	0.9353	6.24 (01, $p = 0.0125$)	0.64	83.96	02	400
Major depressive disorder	1.33	[0.32 to 5.47]	0.6944	8.06 (01, $p = 0.0045$)	0.92	87.59	02	462
Anxiety disorders	1.54	[0.73 to 3.25]	0.2574	3.68 (01, $p = 0.0551$)	0.21	74.83	02	462
Attention deficit hyperactivity disorder	0.97	[0.49 to 1.90]	0.9312	2.62 (01, $p = 0.1055$)	0.15	61.83	02	535
Oppositional defiant disorder	0.99	[0.57 to 1.76]	0.9760	0.67 (01, $p = 0.4129$)	0	0	02	400
Conduct disorder	1.18	[0.57 to 2.44]	0.6645	0.04 (01, $p = 0.8361$)	0	0	02	400
Substance use disorder	1.03	[0.66 to 1.63]	0.8863	0.34 (01, $p = 0.5598$)	0	0	02	375

BD: bipolar disorder; MDD: major depressive disorder; OR: odds ratio; CI: confidence interval; Q: Cochran's Q statistic for heterogeneity; τ^2: between-study variance; I^2: proportion of total variability due to between-study heterogeneity. k denotes the number of studies included in each meta-analysis and n the total sample size. Random-effects models were estimated using restricted maximum likelihood (REML). Each row represents a separate meta-analysis for a specific psychiatric disorder.

Table S1. Checklist according to the PRISMA statement.

Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review.	p. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p. 3,4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p. 5,6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p. 6,7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p. 6, Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p. 7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p. 9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were	p. 8,9

		compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p. 8, Table S3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p. 9,10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	p. 9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p. 9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p. 11-16 ; Fig 1-2 ; Tables 2-5; Fig S1-S24
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p. 9-11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	p. 10,11
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p. 10; p. 13-14

Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p. 10
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not performed.
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p. 11
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	p. 11
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p. 8 Table S3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	p. 12,13
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	p. 11-13 Table S3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	p. 11-16 Tables 2-5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	p. 13-15, Table 4
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	p. 13,14 S4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	p. 12-13, Fig S16-S24
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not performed.
DISCUSSION			

Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p.16,17
	23b	Discuss any limitations of the evidence included in the review.	p. 18,19
	23c	Discuss any limitations of the review processes used.	p. 18,19
	23d	Discuss implications of the results for practice, policy, and future research.	p. 18,19
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p.6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p.6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	p.6
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p.19,20
Competing interests	26	Declare any competing interests of review authors.	p. 20
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	p.20

Table S2. Full search strategy for each database

PubMed
("Bipolar Disorder"[Mesh] OR "Bipolar Disorder" OR "Bipolar Disorders" OR "Manic-Depressive Psychosis" OR "Manic Depressive Psychosis" OR "Manic-Depressive Psychoses" OR "Manic Depressive Psychoses" OR "Bipolar Mood Disorder" OR "Bipolar Mood Disorders" OR "Bipolar Affective Psychosis" OR "Bipolar Affective Psychoses" OR "Bipolar Affective Disorder" OR "Bipolar Affective Disorders" OR "Bipolar Disorder Type 1" OR "Type 1 Bipolar Disorder" OR "Bipolar I Disorder" OR "Bipolar II Disorder " OR "Manic Depression" OR "Manic Depressive Disorder" OR "Manic Depressive Illness" OR "Manic Depressive Psychosis" OR " Manic-Depressive Psychosis" OR "Manic Depressive Psychoses" OR "Manic-Depressive Psychoses" OR "Manic-Depressive Illness" OR "Manic-Depressive Disorder" OR "Bipolar Depression" OR "Bipolar Disorder Type 2" OR "Type 2 Bipolar Disorder" OR "Manic Disorder" OR "Manic Disorders" OR "Mania" OR "Manias" OR Mania[mh] OR "Manic State" OR "Manic States" OR "Bipolar euthymic" OR Hypomani* OR "Mixed Episode" OR "Mixed Episodes" OR Euthymi* OR Cyclothym* OR "Affective Psychoses" OR "Affective Psychosis") AND ("Offspring" OR "Offsprings" OR "descendant" OR "descendants" OR "progeny" OR "Child of Impaired Parents"[Mesh] OR "Children of Impaired Parents") AND ("Depressive Disorder, Major"[Mesh] OR "Major Depressive Disorder" OR "Major Depressive Disorders" OR "Involutional Psychosis" OR "Involutional Depression" OR "Involutional Melancholia" OR "Schizophrenia"[Mesh] OR "Schizophrenic Disorder" OR "Dementia Praecox" OR "Attention Deficit Disorder with Hyperactivity"[Mesh] OR "ADHD" OR "Attention Deficit Hyperactivity Disorder" OR "Hyperkinetic Syndrome" OR "Attention Deficit-hyperactivity Disorder" OR "ADDH" OR "Attention Deficit Hyperactivity Disorder" OR "Attention Deficit Disorder" OR "Minimal Brain Dysfunction" OR "Cocaine-Related Disorders"[Mesh] OR "Cocaine Abuse" OR "Cocaine Dependence" OR "Cocaine Addiction" OR "Alcohol-Related Disorders"[Mesh] OR "Alcohol Dependence" OR "Alcohol Addiction" OR "Chronic Alcoholic Intoxication" OR "Alcohol Abuse" OR "Ethanol Abuse" OR "Alcohol Use Disorder" OR "Marijuana Abuse"[Mesh] OR "Hashish Abuse" OR "Cannabis-Related Disorder" OR "Cannabis Abuse" OR "Cannabis Dependence" OR "Marijuana Dependence" OR "Phobia, Social"[Mesh] OR "Social Phobia" OR "Social Anxiety Disorder" OR "Sociophobia" OR "Fear of Social Evaluation" OR "Anxiety Disorders"[Mesh] OR "Anxiety Disorder" OR "Oppositional Defiant Disorder"[Mesh] OR "Schizoaffective Disorder" OR "Feeding and Eating Disorders"[Mesh] OR "Binge-Eating Disorder" OR "Anorexia Nervosa" OR "Bulimia Nervosa" OR "Borderline Personality Disorder"[Mesh])
Embase
('Bipolar Disorder'/exp OR 'Bipolar Disorder' OR 'Bipolar Disorders' OR 'Manic-Depressive Psychosis' OR 'Manic Depressive Psychosis' OR 'Manic-Depressive Psychoses' OR 'Manic Depressive Psychoses' OR 'Bipolar Mood Disorder' OR 'Bipolar Mood Disorders' OR 'Bipolar Affective Psychosis' OR 'Bipolar

Affective Psychoses' OR 'Bipolar Affective Disorder' OR 'Bipolar Affective Disorders' OR 'Bipolar Disorder Type 1' OR 'Type 1 Bipolar Disorder' OR 'Bipolar I Disorder' OR 'Bipolar II Disorder' OR 'Manic Depression' OR 'Manic Depressive Disorder' OR 'Manic Depressive Illness' OR 'Manic Depressive Psychosis' OR 'Manic-Depressive Psychosis' OR 'Manic Depressive Psychoses' OR 'Manic-Depressive Psychoses' OR 'Manic-Depressive Illness' OR 'Manic-Depressive Disorder' OR 'Bipolar Depression' OR 'Bipolar Disorder Type 2' OR 'Type 2 Bipolar Disorder' OR 'Manic Disorder' OR 'Manic Disorders' OR 'Mania' OR 'Manias' OR Mania/exp OR 'Manic State' OR 'Manic States' OR 'Bipolar euthymic' OR Hypomani* OR 'Mixed Episode' OR 'Mixed Episodes' OR Euthymi* OR Cyclothym* OR 'Affective Psychoses' OR 'Affective Psychosis') AND ('Offspring' OR 'Offsprings' OR 'descendant' OR 'descendants' OR 'progeny' OR 'Child of Impaired Parents'/exp OR 'Children of Impaired Parents') AND ('major depression'/exp OR 'Major Depressive Disorder' OR 'Major Depressive Disorders' OR 'Involutional Psychosis' OR 'Involutional Depression' OR 'Involutional Melancholia' OR 'Schizophrenia'/exp OR 'Schizophrenic Disorder' OR 'Dementia Praecox' OR 'attention deficit hyperactivity disorder'/exp OR 'ADHD' OR 'Attention Deficit Hyperactivity Disorder' OR 'Hyperkinetic Syndrome' OR 'Attention Deficit-hyperactivity Disorder' OR 'ADDH' OR 'Attention Deficit Hyperactivity Disorder' OR 'Attention Deficit Disorder' OR 'Minimal Brain Dysfunction' OR 'cocaine dependence'/exp OR 'Cocaine Abuse' OR 'Cocaine Dependence' OR 'Cocaine Addiction' OR 'alcoholism'/exp OR 'Alcohol Dependence' OR 'Alcohol Addiction' OR 'Chronic Alcoholic Intoxication' OR 'Alcohol Abuse' OR 'Ethanol Abuse' OR 'Alcohol Use Disorder' OR 'cannabis addiction'/exp OR 'Hashish Abuse' OR 'Cannabis-Related Disorder' OR 'Cannabis Abuse' OR 'Cannabis Dependence' OR 'Marijuana Dependence' OR 'social phobia'/exp OR 'Social Phobia' OR 'Social Anxiety Disorder' OR 'Sociophobia' OR 'Fear of Social Evaluation' OR 'Anxiety Disorder'/exp OR 'Anxiety Disorder' OR 'Oppositional Defiant Disorder'/exp OR 'Schizoaffective Disorder' OR 'eating disorder'/exp OR 'Binge-Eating Disorder' OR 'Anorexia Nervosa' OR 'Bulimia Nervosa' OR 'borderline state'/exp) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)
Web of Science
TS=("Bipolar Disorder" OR "Bipolar Disorders" OR "Manic-Depressive Psychosis" OR "Manic Depressive Psychosis" OR "Manic-Depressive Psychoses" OR "Manic Depressive Psychoses" OR "Bipolar Mood Disorder" OR "Bipolar Mood Disorders" OR "Bipolar Affective Psychosis" OR "Bipolar Affective Psychoses" OR "Bipolar Affective Disorder" OR "Bipolar Affective Disorders" OR "Bipolar Disorder Type 1" OR "Type 1 Bipolar Disorder" OR "Bipolar I Disorder" OR "Bipolar II Disorder" OR "Manic Depression" OR "Manic Depressive Disorder" OR "Manic Depressive Illness" OR "Manic Depressive Psychosis" OR "Manic-Depressive Psychosis" OR "Manic Depressive Psychoses" OR "Manic-Depressive Psychoses" OR "Manic-Depressive Illness" OR "Manic-Depressive Disorder" OR "Bipolar Depression" OR "Bipolar Disorder Type 2" OR "Type 2 Bipolar Disorder" OR "Manic Disorder" OR "Manic Disorders" OR "Mania" OR "Manias" OR "Manic State" OR "Manic States" OR

"Bipolar euthymic" OR Hypomani* OR "Mixed Episode" OR "Mixed Episodes" OR Euthymi* OR Cyclothym* OR "Affective Psychoses" OR "Affective Psychosis") AND
TS=("Offspring" OR "Offsprings" OR "descendant" OR "descendants" OR "progeny" OR "Children of Impaired Parents") AND TS=("Major Depressive Disorder" OR "Major Depressive Disorders" OR "Involutional Psychosis" OR "Involutional Depression" OR "Involutional Melancholia" OR "Schizophrenia" OR "Schizophrenic Disorder" OR "Dementia Praecox" OR "ADHD" OR "Attention Deficit Hyperactivity Disorder" OR "Hyperkinetic Syndrome" OR "Attention Deficit-hyperactivity Disorder" OR "ADDH" OR "Attention Deficit Hyperactivity Disorder" OR "Attention Deficit Disorder" OR "Minimal Brain Dysfunction" OR "Cocaine Abuse" OR "Cocaine Dependence" OR "Cocaine Addiction" OR "Alcohol Dependence" OR "Alcohol Addiction" OR "Chronic Alcoholic Intoxication" OR "Alcohol Abuse" OR "Ethanol Abuse" OR "Alcohol Use Disorder" OR "Hashish Abuse" OR "Cannabis-Related Disorder" OR "Cannabis Abuse" OR "Cannabis Dependence" OR "Marijuana Dependence" OR "Social Phobia" OR "Social Anxiety Disorder" OR "Sociophobia" OR "Fear of Social Evaluation" OR "Anxiety Disorder" OR "Schizoaffective Disorder" OR "Feeding and Eating Disorders" OR "Binge-Eating Disorder" OR "Anorexia Nervosa" OR "Bulimia Nervosa" OR "Borderline Personality Disorder")
Scopus
TITLE-ABS-KEY("Bipolar Disorder" OR "Bipolar Disorders" OR "Manic-Depressive Psychosis" OR "Manic Depressive Psychosis" OR "Manic-Depressive Psychoses" OR "Manic Depressive Psychoses" OR "Bipolar Mood Disorder" OR "Bipolar Mood Disorders" OR "Bipolar Affective Psychosis" OR "Bipolar Affective Psychoses" OR "Bipolar Affective Disorder" OR "Bipolar Affective Disorders" OR "Bipolar Disorder Type 1" OR "Type 1 Bipolar Disorder" OR "Bipolar I Disorder" OR "Bipolar II Disorder" OR "Manic Depression" OR "Manic Depressive Disorder" OR "Manic Depressive Illness" OR "Manic Depressive Psychosis" OR "Manic-Depressive Psychosis" OR "Manic Depressive Psychoses" OR "Manic-Depressive Psychoses" OR "Manic-Depressive Illness" OR "Manic-Depressive Disorder" OR "Bipolar Depression" OR "Bipolar Disorder Type 2" OR "Type 2 Bipolar Disorder" OR "Manic Disorder" OR "Manic Disorders" OR "Mania" OR "Manias" OR "Manic State" OR "Manic States" OR "Bipolar euthymic" OR Hypomani* OR "Mixed Episode" OR "Mixed Episodes" OR Euthymi* OR Cyclothym* OR "Affective Psychoses" OR "Affective Psychosis") AND TITLE-ABS-KEY("Offspring" OR "Offsprings" OR "descendant" OR "descendants" OR "progeny" OR "Children of Impaired Parents") AND TITLE-ABS-KEY("Major Depressive Disorder" OR "Major Depressive Disorders" OR "Involutional Psychosis" OR "Involutional Depression" OR "Involutional Melancholia" OR "Schizophrenia" OR "Schizophrenic Disorder" OR "Dementia Praecox" OR "ADHD" OR "Attention Deficit Hyperactivity Disorder" OR "Hyperkinetic Syndrome" OR "Attention Deficit-hyperactivity Disorder" OR "ADDH" OR "Attention Deficit Hyperactivity Disorder" OR "Attention Deficit Disorder" OR "Minimal Brain Dysfunction" OR "Cocaine Abuse" OR "Cocaine Dependence" OR "Cocaine Addiction" OR "Alcohol Dependence" OR "Alcohol Addiction" OR "Chronic Alcoholic Intoxication" OR "Alcohol Abuse" OR "Ethanol Abuse" OR "Alcohol Use Disorder" OR "Hashish Abuse" OR "Cannabis-Related Disorder" OR "Cannabis Abuse" OR "Cannabis Dependence" OR "Marijuana Dependence" OR "Social Phobia" OR "Social Anxiety Disorder" OR "Sociophobia" OR

"Fear of Social Evaluation" OR "Anxiety Disorder" OR "Schizoaffective Disorder" OR "Feeding and Eating Disorders" OR "Binge-Eating Disorder" OR "Anorexia Nervosa" OR "Bulimia Nervosa" OR "Borderline Personality Disorder")

Table S3. Risk of bias (Newcastle-Ottawa Scale)

Author, year	NOQAS score
Akdemir et al., 2008	******
Axelson et al., 2015	********
Bauer et al., 2015	*******
Beardslee et al., 1993	*******
Birmaher et al., 2009	********
Birmaher et al., 2021	*********
Birmaher et al., 2022	********
Carlson et al., 1993	********
Chang et al., 2001	******
Chang et al., 2003	*****
Cho et al., 2014	********
Cullen et al., 2014	********
De la Serna et al., 2019	********
De la Serna et al., 2025	********
Diaz-Caneja et al. 2018	********
Dienes et al., 2002	*****
Diler et al., 2011	******
Diler et al., 2017	*******
Duffy et al., 2007	*********
Duffy et al., 2014	*********
Eraso-Osorio et al., 2021	********
Findling et al., 2005	*****
Freed et al., 2014	*******
Goetz et al., 2017	*******
Hanford et al., 2016	*******

Helmink et al., 2025	*******
Hillegers et al., 2005	*********
Hirshfeld-Becker et al., 2006	*******
Inal-Eiroglu et al., 2008	*****
Joelsson et al., 2017	********
Kemner et al., 2015	*******
Keown-Stonemanan et al., 2021	********
Klimes-Dougan et al., 2010	*****
Küng et al., 2019	******
Lageborn et al., 2024	*********
Lee et al., 2018	*******
Lei et al., 2024	*******
Licona-Martínez et al., 2014	*******
Maoz et al., 2014	********
Palacio et al., 2017	*******
Palacio-Ortiz et al., 2015	*******
Park et al., 2015	********
Petresco et al., 2009	*********
Post et al., 2016	*******
Preisig et al., 2015	*********
Propper et al., 2017	*******
Propper et al., 2023	*********
Reichart et al., 2006	******
Rudaz et al., 2020	*********
Sánchez-Gistau et al., 2014	*****
Setiaman et al., 2024	*********
Simonetti et al., 2025	********
Stapp et al., 2023	*********
Trespalacios et al., 2024	*********

Vandeleur et al., 2012	********
Wals et al., 2006	*******
Zappitelli et al., 2011	******
Zavaleta-Ramírez et al., 2014	********
Zwicker et al., 2019	**********

Supplementary Table S4. Leave-one-out sensitivity analyses for prevalence estimates of psychiatric disorders among offspring of individuals with bipolar disorder.

Diagnostic	Original prevalence (%)	95%CI Inferior	95%CI Superior	Original I^2 (%)	Study removed	Re-estimated prevalence (%)	New 95%CI Inferior	New 95%CI Superior	Re-estimated I^2 (%)
Any mental disorder	58,05	48,34	67,18	97,25	Lageborn et al., 2024	60,14	51,03	68,61	94,4
Mood disorders	29,64	23,02	37,24	96,69	Lageborn et al., 2024	31,2	24,66	38,59	94,66
Major depressive disorder	14,9	11,8	18,63	87,73	Lageborn et al., 2024	16,1	13,14	19,59	74,52
Dysthymia	2,78	1,62	4,73	61,46	Hillegers et al., 2005	2,37	1,39	4,01	49,12
Depressive disorders	24	18,97	29,87	83,58	Preisig et al., 2015	22,91	19,95	26,16	44,15
Other depressive disorders	10,6	7,8	14,25	72,96	Kemner et al., 2015	9,93	7,89	12,43	42,33
Bipolar I disorder	5,33	3,04	9,17	85,75	Rudaz et al., 2020				0
Bipolar II disorder	5,37	3,91	7,34	39,19	Rudaz et al., 2020				0
Cyclothymic disorder	4,67	1,43	14,13	74,57	Findling et al., 2005	2,31	0,96	5,42	0
Other bipolar disorders	8,18	5,2	12,62	81,84	Findling et al., 2005	7,31	4,73	11,13	73,49
Bipolar spectrum disorders	9,64	6,31	14,46	94,94	Lageborn et al., 2024	11,53	8,28	15,82	88,47
Schizoaffective disorder	0,95	0,36	2,5	0	Nenhum	0,95	0,36	2,5	0
Attention-deficit/hyperactivity disorder (ADHD)	21,1	15,87	27,51	95,28	Lageborn et al., 2024	22,15	16,8	28,61	92,3

Substance use disorders	13,29	7,03	23,7	98,17	Hirshfeld-Becker et al., 2006	11,63	6,99	18,74	96,97
Alcohol use disorder	5,48	2,85	10,29	94,32	Lageborn et al., 2024	6,07	2,89	12,32	90,77
Anxiety disorders	28,12	20,67	36,99	94,86	Findling et al., 2005	30,78	23,91	38,64	92,89
Any anxiety disorder*	28,25	17,54	42,15	96,73	Findling et al., 2005	32,42	22,51	44,2	95,01
Generalized anxiety disorder	6,88	3,44	13,28	94,78	Lageborn et al., 2024	9,49	6,06	14,57	84,33
Social anxiety disorder	8,42	4,36	15,63	95,5	Lageborn et al., 2024	12,59	9,35	16,74	71,77
Specific phobia	21,39	15,47	28,79	64,12	Palacio et al., 2017	23,67	19,65	28,22	0
Panic disorder	3	1,5	5,9	88,6	Lageborn et al., 2024	4,45	2,77	7,07	54,63
Agoraphobia	2,79	0,62	11,68	85,32	Freed et al., 2014	1,33	0,55	3,15	0
Separation anxiety disorder	10,42	4,83	21,05	97,45	Lageborn et al., 2024	15,16	9,83	22,67	92
Obsessive-compulsive disorder	2,38	1,16	4,85	86,01	Lageborn et al., 2024	3,68	2,12	6,32	51,57
Post-traumatic stress disorder	2,64	1,08	6,34	93,22	Lageborn et al., 2024	4,04	2	7,95	80,44
Oppositional defiant disorder	14,48	9,69	21,07	91,46	Klimes-Dougan et al., 2010	13,36	9,26	18,89	88,65
Conduct disorders	9,69	8,22	11,4	0	Nenhum	9,69	8,22	11,4	0
Disruptive behaviour disorders	11,11	6,18	19,18	96,82	Lageborn et al., 2024	13,27	7,9	21,43	94,38
Neurodevelopmental disorders	20,3	12,05	32,14	89,98	Vandeleur et al., 2020	27,71	24,08	31,67	0

Autism	3,27	1,79	5,9	59,19	Lageborn et al., 2024	4,78	2,79	8,06	0
Eating disorders	2,76	1,33	5,61	71,84	Lageborn et al., 2024	2,99	1,27	6,9	61,21

For each outcome, the study exerting the greatest influence on heterogeneity was removed. The table presents the original pooled prevalence estimate and heterogeneity (I^2), together with the re-estimated prevalence and heterogeneity after exclusion of the identified study.

Table S5. Leave-one-out sensitivity analysis.

Attention-deficit/hyperactivity disorder				
	Effect size			
Study removed	OR	95% CI		p value
HirshfeldBecker et al., 2006	2.34	1.84	2.97	<0.0001
Inal-Eiroglu et al., 2008	2.45	1.9	3.16	<0.0001
Setiaman et al., 2024	2.39	1.87	3.06	<0.0001
Propper et al., 2021	2.51	1.89	3.34	<0.0001
Vandeleur et al., 2012	2.55	1.94	3.35	<0.0001
Palacio et al., 2017	2.51	1.89	3.33	<0.0001
Park et al., 2015	2.4	1.88	3.07	<0.0001
Petresco et al., 2009	2.49	1.91	3.25	<0.0001
Preisig et al., 2015	2.6	2	3.39	<0.0001
Cho et al., 2014	2.39	1.87	3.07	<0.0001
Birmaher et al., 2009	2.63	1.99	3.47	<0.0001
Duffy et al., 2007	2.42	1.88	3.11	<0.0001
Hanford et al., 2016	2.43	1.89	3.12	<0.0001
Lageborn et al., 2024	2.57	1.89	3.51	<0.0001
De La Serna et al., 2019	2.38	1.85	3.05	<0.0001
Goetz et al., 2017	2.38	1.86	3.04	<0.0001
ErasoOsorio et al., 2021	2.52	1.9	3.36	<0.0001
Lei et al., 2024	2.48	2.07	2.99	<0.0001
Zavaleta-Ramírez et al., 2014	2.44	1.87	3.17	<0.0001
Anxiety disorders				
HirshfeldBecker et al., 2006	2	2	3	<0.0001
Inal-Eiroglu et al., 2008	2.29	1.76	2.96	<0.0001

Setiaman et al., 2024	2.31	1.77	3.02	<0.0001
Zwicker et al., 2019	2.25	1.72	2.95	<0.0001
Dougan et al., 2010	2.31	1.76	3.02	<0.0001
Vandeleur et al., 2020	2.3	1.74	3.04	<0.0001
Palacio et al., 2017	2.41	1.88	3.09	<0.0001
Park et al., 2015	2.27	1.76	2.94	<0.0001
Petresco et al., 2009	2.28	1.74	2.98	<0.0001
Preisig et al., 2015	2.4	1.84	3.11	<0.0001
Findling et al., 2005	2.35	1.81	3.05	<0.0001
Cho et al., 2014	2.3	1.76	3	<0.0001
Beardslee et al., 1993	2.32	1.77	3.05	<0.0001
Birmaher et al., 2009	2.27	1.72	3	<0.0001
Duffy et al., 2013	2.29	1.74	3.02	<0.0001
Hanford et al., 2016	2.26	1.75	2.91	<0.0001
Lageborn et al., 2024	2.3	1.73	3.06	<0.0001
De La Serna et al., 2019	2.31	1.76	3.03	<0.0001
Goetz et al., 2017	2.16	1.7	2.74	<0.0001
Akdemir et al., 2008	2.3	1.76	3.02	<0.0001
ErasoOsorio et al., 2021	2.39	1.83	3.11	<0.0001
Lei et al., 2024	2.28	1.74	3	<0.0001
Trespalacios et al., 2024	2.33	1.77	3.07	<0.0001
Zavaleta-Ramírez et al., 2014	2.39	1.87	3.06	<0.0001
Autism spectrum disorders				
Setiaman et al., 2024	2.21	1.89	2.58	<0.0001
Propper et al., 2024	2.23	1.91	2.61	<0.0001
Lageborn et al., 2024	1.97	0.73	5.33	0.1827
Goetz et al., 2017	2.21	1.89	2.59	<0.0001

Lei et al., 2024	2.22	1.89	2.59	<0.0001
Alcohol Use Disorders				
Vandeleur et al., 2020	2	2	2	<0.0001
Palacio et al., 2017	1.96	1.72	2.23	<0.0001
Preisig et al., 2015	2.06	1.65	2.56	<0.0001
Beardslee et al., 1993	1.97	1.73	2.24	<0.0001
Birmaher et al., 2009	1.99	1.75	2.27	<0.0001
Lageborn et al., 2024	2.25	1.4	3.61	0.0009
ErasoOsorio et al., 2021	1.96	1.73	2.23	<0.0001
Bipolar Disorders (excluding type II BD)				
HirshfeldBecker et al., 2006	7	3	16	<0.0001
Inal-Eiroglu et al., 2008	7.89	3.55	17.55	<0.0001
Goetz et al., 2017	7.17	3.21	16.03	<0.0001
ErasoOsorio et al., 2021	6.43	2.59	15.98	<0.0001
Stapp et al., 2023	9.21	2.93	28.96	0.0001
Bipolar Disorders				
HirshfeldBecker et al., 2006	7.75	5.11	11.77	<0.0001
Inal-Eiroglu et al., 2008	7.97	5.23	12.14	<0.0001
Setiaman et al., 2024	7.96	5.22	12.13	<0.0001
Kung et al., 2019	8.01	5.26	12.19	<0.0001
Park et al., 2015	7.84	5.15	11.93	<0.0001
Petresco et al., 2009	8	5.26	12.18	<0.0001
Preisig et al., 2015	8.49	5.42	13.28	<0.0001
Findling et al., 2005	10.05	8.12	12.44	<0.0001
Birmaher et al., 2009	7.57	4.93	11.62	<0.0001

Duffy et al., 2007	7.66	5.06	11.61	<0.0001
Lageborn et al., 2024	7.24	4.51	11.62	<0.0001
Carlson et al., 1993	7.86	5.16	11.96	<0.0001
Goetz et al., 2017	7.83	5.15	11.92	<0.0001
ErasoOsorio et al., 2021	7.51	4.92	11.49	<0.0001
Lei et al., 2024	8.02	5.23	12.3	<0.0001
Stapp et al., 2023	8.1	5.11	12.83	<0.0001
Conduct disorders				
HirshfeldBecker et al., 2006	2.89	2.11	3.95	<0.0001
Propper et al., 2017	2.95	2.23	3.91	<0.0001
Birmaher et al., 2009	3.14	2.54	3.88	<0.0001
Duffy et al., 2007	3.03	2.43	3.79	<0.0001
Lageborn et al., 2024	2.15	1.11	4.15	0.0225
Goetz et al., 2017	2.97	2.27	3.89	<0.0001
ErasoOsorio et al., 2021	2.84	1.88	4.3	<0.0001
Depressive disorders				
Setiaman et al., 2024	3.38	2.46	4.65	<0.0001
Propper et al., 2017	3.02	2.4	3.81	<0.0001
Vandeleur et al., 2020	3.13	2.41	4.05	<0.0001
Birmaher et al., 2009	3.31	2.41	4.56	<0.0001
Duffy et al., 2007	2.96	2.39	3.65	<0.0001
Hanford et al., 2016	3.11	2.42	4	<0.0001
Lageborn et al., 2024	3.94	2.7	5.76	<0.0001
De La Serna et al., 2019	3.25	2.46	4.28	<0.0001
Goetz et al., 2017	3.07	2.41	3.91	<0.0001
ErasoOsorio et al., 2021	3.64	2.53	5.23	<0.0001

Lei et al., 2024	3.34	2.43	4.6	<0.0001
Disruptive behavior disorder				
HirshfeldBecker et al., 2006	2.11	1.96	2.28	<0.0001
Inal-Eiroglu et al., 2008	2.4	1.88	3.05	<0.0001
Setiaman et al., 2024	2.31	1.88	2.84	<0.0001
Vandeleur et al., 2020	2.66	1.99	3.54	<0.0001
Axelson et al.,2015	2.79	1.81	4.32	<0.0001
Birmaher et al., 2009	2.66	1.76	4.03	<0.0001
Lageborn et al., 2024	2.88	1.87	4.43	<0.0001
DiazCaneja et al., 2018	2.25	1.87	2.71	<0.0001
Goetz et al., 2017	2.28	1.87	2.79	<0.0001
Akdemir et al., 2008	2.19	1.88	2.56	<0.0001
Eating disorders				
Kung et al., 2019	1.63	1.37	1.95	<0.0001
Palacio et al., 2017	1.64	1.37	1.95	<0.0001
Cho et al., 2014	1.64	1.38	1.95	<0.0001
Duffy et al., 2007	1.65	1.38	1.96	<0.0001
Lageborn et al., 2024	2.56	0.92	7.13	0.0732
De La Serna et al., 2019	1.64	1.38	1.96	<0.0001
Goetz et al., 2017	1.63	1.37	1.94	<0.0001
ErasoOsorio et al., 2021	1.64	1.37	1.95	<0.0001
Zavaleta-Ramírez et al., 2014	1.63	1.37	1.95	<0.0001
Major Depressive Disorder				
HirshfeldBecker et al., 2006	1.95	1.05	3.65	0.0358
Zwicker et al., 2019	1.87	1	3.47	0.0485

Dougan et al., 2010	1.91	1.02	3.58	0.0444
Rudaz et al., 2020	2.23	1.16	4.3	0.0167
Kung et al., 2019	2	1.07	3.72	0.0297
Palacio et al., 2017	2.03	1.05	3.92	0.035
Petresco et al., 2009	2.11	1.12	3.98	0.0207
Preisig et al., 2015	2.25	1.17	4.31	0.0146
Findling et al., 2005	2.3	1.47	3.6	0.0003
Birmaher et al., 2009	1.98	1.03	3.81	0.0394
De La Serna et al., 2019	1.89	1.04	3.45	0.0372
Goetz et al., 2017	1.89	1.04	3.44	0.0377
ErasoOsorio et al., 2021	2.1	1.09	4.06	0.0276
Zavaleta-Ramírez et al., 2014	2.02	1.07	3.81	0.0305
Mental disorders				
Inal-Eiroglu et al., 2008	3.08	2.27	4.18	<0.0001
Setiaman et al., 2024	3.03	2.22	4.15	<0.0001
Propper et al., 2017	3.24	2.32	4.53	<0.0001
Vandeleur et al., 2020	3.25	2.3	4.59	<0.0001
Park et al., 2015	3	2.25	4.01	<0.0001
Petresco et al., 2009	3.26	2.33	4.55	<0.0001
Findling et al., 2005	3.25	2.54	4.17	<0.0001
Axelson et al., 2015	3.24	2.28	4.59	<0.0001
Hanford et al., 2016	3.03	2.25	4.07	<0.0001
Lageborn et al., 2024	3.35	2.39	4.71	<0.0001
Carlson et al., 1993	3.18	2.27	4.47	<0.0001
De la Serna et al., 2025	2.96	2.19	3.99	<0.0001
Goetz et al., 2017	2.94	2.2	3.92	<0.0001
Akdemir et al., 2008	3.13	2.27	4.33	<0.0001

Lei et al., 2024	3.34	2.4	4.65	<0.0001
Trespalacios et al., 2024	3.21	2.29	4.5	<0.0001
Mood disorders				
HirshfeldBecker et al., 2006	3.64	2.63	5.04	<0.0001
Inal-Eiroglu et al., 2008	3.72	2.69	5.16	<0.0001
Setiaman et al., 2024	3.76	2.66	5.31	<0.0001
Propper et al., 2017	3.61	2.62	4.97	<0.0001
Dougan et al., 2010	3.72	2.65	5.21	<0.0001
Vandeleur et al., 2020	3.81	2.66	5.45	<0.0001
Preisig et al., 2015	3.71	3	4.59	<0.0001
Findling et al., 2005	3.91	2.73	5.62	<0.0001
Cho et al., 2014	3.74	2.66	5.26	<0.0001
Beardslee et al., 1993	3.87	2.77	5.4	<0.0001
Birmaher et al., 2009	3.57	2.55	4.99	<0.0001
Duffy et al., 2007	3.45	2.55	4.67	<0.0001
Lageborn et al., 2024	3.93	2.72	5.69	<0.0001
De La Serna et al., 2019	3.8	2.69	5.38	<0.0001
Goetz et al., 2017	3.57	2.6	4.89	<0.0001
Akdemir et al., 2008	3.63	2.64	5.01	<0.0001
Lei et al., 2024	3.79	2.67	5.38	<0.0001
Trespalacios et al., 2024	3.8	2.68	5.38	<0.0001
Oppositional Defiant Disorder				
HirshfeldBecker et al., 2006	3.54	2.51	4.99	<0.0001
Inal-Eiroglu et al., 2008	3.68	2.62	5.19	<0.0001
Propper et al., 2017	3.67	2.59	5.19	<0.0001
Dougan et al., 2010	3.53	2.48	5.02	<0.0001

Palacio et al., 2017	3.5	2.43	5.03	<0.0001
Park et al., 2015	3.59	2.55	5.05	<0.0001
Petresco et al., 2009	3.61	2.56	5.08	<0.0001
Cho et al., 2014	3.59	2.55	5.07	<0.0001
Beardslee et al., 1993	3.58	2.54	5.04	<0.0001
Birmaher et al., 2009	3.99	2.62	6.08	<0.0001
Goetz et al., 2017	3.62	2.55	5.13	<0.0001
ErasoOsorio et al., 2021	3.52	2.45	5.06	<0.0001
Zavaleta-Ramírez et al., 2014	3.68	2.57	5.26	<0.0001
Substance Use Disorders				
Setiaman et al., 2024	2.94	1.89	4.58	<0.0001
Kung et al., 2019	2.93	1.87	4.58	<0.0001
Palacio et al., 2017	2.67	1.69	4.21	<0.0001
Preisig et al., 2015	3.29	2.03	5.33	<0.0001
Findling et al., 2005	3.08	1.98	4.8	<0.0001
Beardslee et al., 1993	2.89	1.87	4.49	<0.0001
Birmaher et al., 2009	3.25	2.03	5.2	<0.0001
Duffy et al., 2007	2.78	1.82	4.23	<0.0001
Lageborn et al., 2024	3.32	1.98	5.55	<0.0001
Goetz et al., 2017	2.84	1.84	4.37	<0.0001
ErasoOsorio et al., 2021	2.59	1.74	3.84	<0.0001
Lei et al., 2024	2.88	1.86	4.45	<0.0001
Trespalacios et al., 2024	2.85	1.76	4.6	<0.0001

Leave-one-out sensitivity analyses were performed for all outcomes by sequentially excluding each study and recalculating pooled odds ratios. The results remained largely stable across iterations, suggesting that no single study had a disproportionate influence on the overall estimates. OR: odds ratio; CI: confidence interval.

Table S6. Trim-and-fill analyses for prevalence estimates of psychiatric disorders among offspring of individuals with bipolar disorder

	Original			Adjusted			Imputed
	PR	95% CI	k	PR	95% CI	k	n
Mental disorders	58.05	[48.34 to 67.18]	21	58.05	[48.34 to 67.18]	21	0
Mood disorders	29.64	[23.02 to 37.24]	31	29.64	[23.02 to 37.24]	31	0
Bipolar disorders	9.64	[6.31 to 14.46]	16	16.33	[9.95 to 25.64]	22	6
Bipolar I disorder	5.33	[3.04 to 9.17]	12	5.33	[3.04 to 9.17]	12	0
Bipolar II disorder	5.37	[3.91 to 7.34]	10	6.19	[4.52 to 8.43]	14	4
Other bipolar disorders	8.18	[5.20 to 12.62]	11	8.18	[5.20 to 12.62]	11	0
Depressive disorders	24.0	[18.97 to 29.87]	10	24.0	[18.97 to 29.87]	10	0
Dysthymic disorder	2.78	[1.62 to 4.73]	10	2.78	[1.62 to 4.73]	10	0
Other depressive disorders	10.6	[7.80 to 14.25]	10	11.24	[8.12 to 15.37]	11	1
Anxiety disorders	28.25	[17.54 to 42.15]	16	28.25	[17.54 to 42.15]	16	0
Disruptive behaviour disorders	11.11	[6.18 to 19.18]	17	12.25	[6.71 to 21.31]	18	1
Oppositional defiant disorder	14.48	[9.69 to 21.07]	19	14.48	[9.69 to 21.07]	19	0
Conduct disorder	9.69	[8.22 to 11.40]	12	10.17	[8.66 to 11.91]	16	4

Substance use disorders	13.29	[7.03 to 23.70]	17	13.29	[7.03 to 23.70]	17	0

Table S7. Sensitivity analysis using the trim-and-fill method for outcomes with evidence of small-study effects

	Original				**Adjusted**				**Imputed**
	OR	95% CI	p value	*k*	OR	95% CI	p value	*k*	*n*
Mental disorders	3.15	[2.32 to 4.28]	<0.0001	16	2.41	[1.68 to 3.46]	<0.0001	22	06
Mood disorders	3.73	[2.70 to 5.15]	<0.0001	18	2.90	[2.08 to 4.05]	<0.0001	25	07
Depressive disorders	3.24	[2.46 to 4.27]	<0.0001	11	2.72	[2.46 to 3.01]	<0.0001	17	06
Major depressive disorder	2.04	[1.12 to 3.72]	0.0205	14	1.32	[0.75 to 2.35]	0.3368	19	05
Anxiety disorders	2.30	[1.77 to 2.97]	<0.0001	24	1.95	[1.44 to 2.68]	<0.0001	29	05
Attention deficit hyperactivity disorder	2.46	[1.91 to 3.17]	<0.0001	19	2.10	[1.65 to 2.67]	<0.0001	26	07
Substance use disorder	2.93	[1.90 to 4.51]	<0.0001	13	2.38	[1.53 to 3.70]	<0.0001	17	04

Trim-and-fill analyses were performed for outcomes showing evidence of small-study effects (Egger test $p < 0.10$). The method imputes potentially missing studies to restore funnel plot symmetry and recalculates pooled effect estimates. OR: odds ratio; CI: confidence interval.

Table S8. Univariate meta-regression analyses exploring sources of heterogeneity in any mental disorder.

Moderator	Category/unit	β	SE	*p* value	τ^2 (residual)	pseudo-R^2 (%)	$F_{(df1, df2)}$	*p* value
Offspring mean age (years)	per year	0.037	0.095	0.7022	0.36	0	$0.153_{(1,12)}$	0.7022
Proportion of male offspring (%)	per 1%	0.019	0.030	0.5369	0.40	0	$0.404_{(1,12)}$	0.5369
Offspring diagnostic criteria	DSM	0.467	0.687	0.5075	0.25	0	$0.463_{(1,14)}$	0.5075
Parental diagnostic criteria	DSM	0.467	0.687	0.5075	0.25	0	$0.463_{(1,14)}$	0.5075
Publication year	per year	0.008	0.023	0.7413	0.26	0	$0.113_{(1,14)}$	0.7413
Study region	----	----	----	----	0.27	0	$0.216_{(1,13)}$	0.8085
----	Europe	0.335	0.598	0.5846	----	----	----	----
----	North America	0.052	0.589	0.9305	----	----	----	----

β coefficients represent the change in the log odds ratio (OR) associated with a one-unit increase (continuous variables) or relative to the reference category (categorical variables). For interpretability, the proportion of male offspring was modelled per 1% increase. Random-effects meta-regression models were fitted using restricted maximum likelihood (REML) with Knapp–Hartung adjustment. τ^2 represents the residual between-study variance. Pseudo-R^2 indicates the proportion of heterogeneity explained. The F-test assesses the overall significance of each moderator. Given the limited number of studies in some analyses, results should be interpreted with caution. SE: standardized error.

Supplementary Table S9. Complete meta-regression analyses for prevalence estimates of psychiatric disorders among offspring of individuals with bipolar disorder

	Moderator	Category/unit	β	SE	*p value*	τ^2 *(residual)*	pseudo-R^2 (%)	*p value*	k
Any mental disorder	Offspring mean age (years)	per year	-0,0121	0,0865	0,8891	0,57	0	0,8891	17
	Proportion of male offspring (%)	per 1%	-0,0167	0,0114	0,1453	0,5	5,29	0,1453	17
	Parental diagnostic criteria	DSM	1,7215	0,8288	0,0378	0,65	16,14	0,0378	21
	Offspring diagnostic criteria	DSM	1,2646	0,4856	0,0092	0,57	26,33	0,0092	21
	Year	Year	-0,028	0,024	0,2435	0,76	2,64	0,2435	21
	Populational or Clinical	Populational study	-1,8425	0,4975	0,0002	0,44	43,82	0,0002	21
	Study region	----	----	----	----	0,92	0	0,9218	21
	----	USA	0,4417	0,5671	0,4361	----	----	----	----
	----	Latin America	0,4003	1,1056	0,7173	----	----	----	----
	----	Canada	0,2253	1,0927	0,8366	----	----	----	----
	----	Europe	0,0194	0,6023	0,9744	----	----	----	----

	Moderator	Category/unit	β	SE	*p value*	τ^2 *(residual)*	pseudo-R^2 (%)	*p value*	k
Any mood disorder	Offspring mean age (years)	per year	0,0562	0,0665	0,3982	0,9	0	0,3982	25

	Proportion of male offspring (%)	per 1%	-0,0113	0,0145	0,4352	0,79	0	0,4352	28
	Parental diagnostic criteria	DSM	1,8468	0,8736	0,0345	0,73	13,83	0,0345	31
	Offspring diagnostic criteria	DSM	0,0496	0,7073	0,9441	0,89	0	0,9441	31
	Year	Year	-0,0229	0,0223	0,3056	0,84	1,28	0,3056	31
	Populational or Clinical	Populational study	-1,8468	0,8736	0,0345	0,73	13,83	0,0345	31
	Study region	----	----	----	----	0,93	0	0,8121	31
	----	USA	0,5241	0,5302	0,3229	----	----	----	----
	----	Latin America	-0,0828	0,6608	0,9002	----	----	----	----
	----	Canada	0,4107	0,7091	0,5625	----	----	----	----
	----	Europe	0,2016	0,5443	0,7111	----	----	----	----

	Moderator	**Category/unit**	**β**	**SE**	***p value***	***τ² (residual)***	**pseudo -R² (%)**	***p value***	**k**
Bipolar disorders	Offspring mean age (years)	per year	0,0478	0,0734	0,5147	0,6	0	0,5147	12
	Proportion of male offspring (%)	per 1%	-0,0046	0,0472	0,9228	0,59	0	0,9228	13
	Parental diagnostic criteria	DSM	2,0689	0,6666	0,0019	0,4	46,72	0,0019	16
	Offspring diagnostic criteria	DSM	0,8867	0,6358	0,1631	0,68	10,08	0,1631	16
	Year	Year	-0,043	0,0355	0,2256	0,7	6,56	0,2256	16

	Populational or Clinical	Populational study	-0,8867	0,6358	0,1631	0,68	10,08	0,1631	16
	Study region	----	----	----	----	0,53	29,78	0,0509	16
	----	USA	0,0069	0,6511	0,9915	----	----	----	----
	----	Latin America	-0,7247	0,749	0,3333	----	----	----	----
	----	Canada	-0,1694	0,9221	0,8543	----	----	----	----
	----	Europe	-1,4063	0,6575	0,0325	----	----	----	----

	Moderator	**Category/unit**	**β**	**SE**	***p value***	***τ² (residual)***	**pseudo -R² (%)**	***p value***	**k**
Bipolar I disorder	Offspring mean age (years)	per year	-0,0651	0,1041	0,5314	1,04	0	0,5314	10
	Proportion of male offspring (%)	per 1%	-0,0008	0,0213	0,9692	0,85	0	0,9692	12
	Year	Year	-0,0583	0,0372	0,1174	0,63	20,56	0,1174	12
	Study region	----	----	----	----	0,88	0	0,5512	12
	----	USA	0,9565	0,7389	0,1955	----	----	----	----
	----	Latin America	0,4869	1,1668	0,6765	----	----	----	----
	----	Europe	0,0256	0,9516	0,9786	----	----	----	----

Bipolar II disorder	**Moderator**	**Category/unit**	**β**	**SE**	***p value***	***τ² (residual)***	**pseudo -R² (%)**	***p value***	**k**

	Proportion of male offspring (%)	per 1%	-0,0309	0,0407	0,4477	0,13	0	0,4477	10
	Year	Year	0,0396	0,0235	0,092	0,08	22,18	0,092	10
	Study region	----	----	----	----	0,1	0	0,4083	10
	----	USA	-0,4061	0,4132	0,3257	----	----	----	----
	----	Europe	0,0909	0,4568	0,8422	----	----	----	----

	Moderator	**Category/unit**	**β**	**SE**	***p value***	***τ² (residual)***	**pseudo -R² (%)**	***p value***	**k**
Other bipolar disorders	Offspring mean age (years)	per year	-0,0364	0,0605	0,5479	0,31	0	0,5479	10
	Proportion of male offspring (%)	per 1%	0,069	0,0497	0,165	0,37	21,32	0,165	11
	Year	Year	-0,0423	0,0475	0,3726	0,49	0	0,3726	11
	Study region	----	----	----	----	0,46	3,94	0,3506	11
	----	USA	1,1021	0,6796	0,1049	----	----	----	----
	----	Latin America	1,0187	0,8266	0,2178	----	----	----	----
	----	Europe	0,3742	0,8295	0,6519	----	----	----	----

Depressive disorders	**Moderator**	**Category/unit**	**β**	**SE**	***p value***	***τ² (residual)***	**pseudo -R² (%)**	***p value***	**k**
	Offspring diagnostic criteria	DSM	0,2373	0,4922	0,6297	0,2	0	0,6297	10

	Year	Year	0,0376	0,0301	0,2113	0,18	0	0,2113	10
	Populational or Clinical	Populational study	-0,2373	0,4922	0,6297	0,2	0	0,6297	10
	Study region	----	----	----	----	0,15	11,94	0,1162	10
	----	USA	-0,041	0,385	0,9152	----	----	----	----
	----	Latin America	-1,8301	0,882	0,038	----	----	----	----
	----	Canada	0,1372	0,5861	0,8149	----	----	----	----
	----	Europe	0,4771	0,4414	0,2797	----	----	----	----

	Moderator	**Category/unit**	**β**	**SE**	***p value***	***τ² (residual)***	**pseudo -R² (%)**	***p value***	**k**
	Offspring mean age (years)	per year	0,0238	0,043	0,5799	0,21	0	0,5799	17
	Proportion of male offspring (%)	per 1%	-0,0393	0,0242	0,1042	0,16	14,31	0,1042	19
	Parental diagnostic criteria	DSM	1,0655	0,4068	0,0088	0,19	34,01	0,0088	20
	Offspring diagnostic criteria	DSM	1,2149	0,4501	0,0069	0,19	34,18	0,0069	20
	Year	Year	-0,0357	0,0278	0,1995	0,26	6,96	0,1995	20
	Populational or Clinical	Populational study	-0,5274	0,4109	0,1994	0,26	9,25	0,1994	20
	Study region	----	----	----	----	0,31	0	0,696	20
	----	USA	0,491	0,4564	0,282	----	----	----	----
depressive dis	----	Latin America	-0,1365	0,4954	0,7828	----	----	----	----
	----	Canada	0,5279	0,7092	0,4567	----	----	----	----

	----	Europe	0,1688	0,3847	0,6609	----	----	----	----

	Moderator	**Category/unit**	**β**	**SE**	***p value***	***τ² (residual)***	**pseudo -R² (%)**	***p value***	**k**
Dysthymic disorder	Proportion of male offspring (%)	per 1%	0,0261	0,0847	0,7578	0,49	0	0,7578	10
	Year	Year	-0,0798	0,0542	0,1404	0,38	12,7	0,1404	10
	Study region					0,35	19,92	0,3579	10
		USA	-0,5857	0,8254	0,478				
	----	Europe	0,3341	0,71	0,6379				

	Moderator	**Category/unit**	**β**	**SE**	***p value***	***τ² (residual)***	**pseudo -R² (%)**	***p value***	**k**
depressive dis	Proportion of male offspring (%)	per 1%	-0,0306	0,0488	0,5302	0,24	0	0,5302	10
	Year	Year	-0,0313	0,0361	0,3859	0,23	0	0,3859	10
	Study region	----	----	----	----	0,31	0	0,8935	10
	----	USA	-0,2794	0,6044	0,6439	----	----	----	----
	----	Europe	-0,1867	0,513	0,7159	----	----	----	----

	Moderator	Category/unit	β	SE	*p value*	*τ² (residual)*	pseudo -R² (%)	*p value*	k
Anxiety disorders	Offspring mean age (years)	per year	0,0905	0,138	0,5121	1,71	0	0,5121	15
	Proportion of male offspring (%)	per 1%	-0,0291	0,0205	0,1558	1,36	6,36	0,1558	16
	Year	Year	0,0636	0,0473	0,1786	1,42	2,47	0,1786	16
	Study region	----	----	----	----	1,37	6,19	0,2238	16
	----	USA	-0,0776	0,9045	0,9316	----	----	----	----
	----	Latin America	2,0451	1,1305	0,0705	----	----	----	----
	----	Canada	1,6605	1,3936	0,2335	----	----	----	----
	----	Europe	0,3674	0,8935	0,681	----	----	----	----

	Moderator	Category/unit	β	SE	*p value*	*τ² (residual)*	pseudo -R² (%)	*p value*	k
	Offspring mean age (years)	per year	-0,0337	0,0942	0,7206	0,59	0	0,7206	12
	Proportion of male offspring (%)	per 1%	0,06	0,05	0,2299	0,52	2,44	0,2299	12
	Parental diagnostic criteria	DSM	2,0088	0,8705	0,021	1,04	34,39	0,021	13
lized anxiety d	Offspring diagnostic criteria	DSM	3,5664	0,798	<0.0001	0,54	66,25	<0.0001	13
	Year	Year	-0,138	0,0765	0,071	1,24	22,05	0,071	13

	Populational or Clinical	Populational study	-3,5664	0,798	<0.0001	0,54	66,25	<0.0001	13
	Study region	----	----	----	----	1,32	16,82	0,1712	13
	----	USA	1,2496	1,3382	0,3504	----	----	----	----
	----	Latin America	0,021	1,3498	0,9876	----	----	----	----
	----	Europe	-0,6567	1,3372	0,6234	----	----	----	----

	Moderator	**Category/unit**	**β**	**SE**	***p value***	***τ² (residual)***	**pseudo -R² (%)**	***p value***	**k**
Social anxiety disorder	Offspring mean age (years)	per year	0,067	0,0567	0,2376	0,2	0	0,2376	11
	Proportion of male offspring (%)	per 1%	-0,0084	0,0299	0,7791	0,23	0	0,7791	11
	Parental diagnostic criteria	DSM	3,3159	0,4945	<0.0001	0,19	85,84	<0.0001	12
	Offspring diagnostic criteria	DSM	3,3159	0,4945	<0.0001	0,19	85,84	<0.0001	12
	Year	Year	-0,1071	0,0812	0,1869	1,24	8,88	0,1869	12
	Populational or Clinical	Populational study	-1,5798	0,8034	0,0492	0,98	28,06	0,0492	12
	Study region	----	----	----	----	1,71	0	0,8024	12
	----	USA	0,8651	1,6335	0,5964	----	----	----	----
	----	Latin America	0,5869	1,5114	0,6978	----	----	----	----
	----	Europe	-0,0972	1,4779	0,9475	----	----	----	----

	Moderator	Category/unit	β	SE	*p value*	τ^2 *(residual)*	pseudo-R^2 (%)	*p value*	k
	Offspring mean age (years)	per year	0,037	0,079	0,6393	0,76	0	0,6393	13
	Proportion of male offspring (%)	per 1%	-0,0249	0,016	0,1204	0,63	13,64	0,1204	14
	Parental diagnostic criteria	DSM	5,0178	0,9482	<0.0001	0,74	70,61	<0.0001	15
	Offspring diagnostic criteria	DSM	5,0178	0,9482	<0.0001	0,74	70,61	<0.0001	15
	Year	Year	-0,1863	0,0969	0,0546	2,04	18,65	0,0546	15
	Populational or Clinical	Populational study	-1,9113	1,1479	0,0959	2,18	12,84	0,0959	15
	Study region	----	----	----	----	3	0	0,8665	15
	----	USA	0,7376	1,4757	0,6172	----	----	----	----
tion anxiety d	----	Latin America	0,9054	1,3639	0,5068	----	----	----	----
	----	Europe	0,0911	1,3063	0,9444	----	----	----	----

	Moderator	Category/unit	β	SE	*p value*	τ^2 *(residual)*	pseudo-R^2 (%)	*p value*	k
	Offspring mean age (years)	per year	-0,0578	0,064	0,3667	0,64	0	0,3667	24
eficit/hyperact	Proportion of male offspring (%)	per 1%	-0,0053	0,0154	0,7311	0,74	0	0,7311	27
	Parental diagnostic criteria	DSM	0,8438	0,6868	0,2192	0,74	4,47	0,2192	28
	Offspring	DSM	1,4407	0,8623	0,0948	0,71	8,73	0,0948	28

	diagnostic criteria								
	Year	Year	-0,0229	0,0264	0,3857	0,78	0,23	0,3857	28
	Populational or Clinical	Populational study	0,1022	0,6794	0,8804	0,82	0	0,8804	28
	Study region	----	----	----	----	0,66	15,12	0,0878	28
	----	USA	0,7809	0,4791	0,1031	----	----	----	----
	----	Latin America	0,8381	0,5683	0,1403	----	----	----	----
	----	Canada	0,7668	0,9183	0,4037	----	----	----	----
	----	Europe	-0,2231	0,4634	0,6302	----	----	----	----

	Moderator	**Category/unit**	**β**	**SE**	***p value***	***τ² (residual)***	**pseudo -R² (%)**	***p value***	**k**
	Offspring mean age (years)	per year	0,0945	0,1385	0,4953	1,5	0	0,4953	14
	Proportion of male offspring (%)	per 1%	-0,03	0,0186	0,1065	1,06	9,28	0,1065	16
	Parental diagnostic criteria	DSM	2,4707	1,125	0,0281	1,17	26,54	0,0281	17
	Offspring diagnostic criteria	DSM	2,4707	1,125	0,0281	1,17	26,54	0,0281	17
	Year	Year	-0,0054	0,0531	0,9186	1,7	0	0,9186	17
	Populational or Clinical	Populational study	-0,1596	1,0037	0,8736	1,71	0	0,8736	17
	Study region	----	----	----	----	1,85	0	0,8661	17
ve behaviour c	----	USA	0,9897	1,0501	0,3459	----	----	----	----
	----	Latin America	-1,6606	0,9198	----	----	----	----	----

			0,1672						
	----	Canada	0,7285	1,5909	0,647	----	----	----	----
	----	Europe	0,1691	0,9109	0,8527	----	----	----	----

	Moderator	**Category/unit**	**β**	**SE**	***p value***	***τ² (residual)***	**pseudo -R² (%)**	***p value***	**k**
ODD	Offspring mean age (years)	per year	-0,0175	0,0755	0,8163	0,79	0	0,8163	17
	Proportion of male offspring (%)	per 1%	0,0056	0,017	0,7392	0,86	0	0,7392	19
	Offspring diagnostic criteria	DSM	-2,024	0,8586	0,0184	0,62	26,64	0,0184	19
	Year	Year	0,0149	0,045	0,7415	0,92	0	0,7415	19
	Study region	----	----	----	----	0,64	24,21	0,0435	19
	----	USA	1,8605	0,6247	0,0029	----	----	----	----
	----	Latin America	1,5679	0,6726	0,0197	----	----	----	----
	----	Canada	1,0076	1,0286	0,3273	----	----	----	----
	----	Europe	0,993	0,6672	0,1367	----	----	----	----

	Moderator	**Category/unit**	**β**	**SE**	***p value***	***τ² (residual)***	**pseudo -R² (%)**	***p value***	**k**
Substance use disorders	Offspring mean age (years)	per year	0,0583	0,1226	0,6344	3,51	0	0,6344	12
	Proportion of male offspring	per 1%	-0,1605	0,0607	0,0082	1,81	34,25	0,0082	13

	(%)								
	Parental diagnostic criteria	DSM	1,3781	1,4627	0,3461	2	0,37	0,3461	17
	Offspring diagnostic criteria	DSM	0,9368	1,0778	0,3847	2,01	0	0,3847	17
	Year	Year	-0,0692	0,0501	0,1674	1,78	11,06	0,1674	17
	Populational or Clinical	Populational study	-0,9368	1,0778	0,3847	2,01	0	0,3847	17
	Study region	----	----	----	----	2,31	0	0,664	17
	----	USA	1,132	1,3773	0,4112	----	----	----	----
	----	Latin America	1,5485	1,5497	0,3177	----	----	----	----
	----	Canada	1,9891	1,8972	0,2944	----	----	----	----
	----	Europe	0,3401	1,2397	0,7838	----	----	----	----

Figure S1. Forest plot of attention-deficit/hyperactivity disorder (ADHD) comparing offspring of individuals with bipolar disorder and controls.

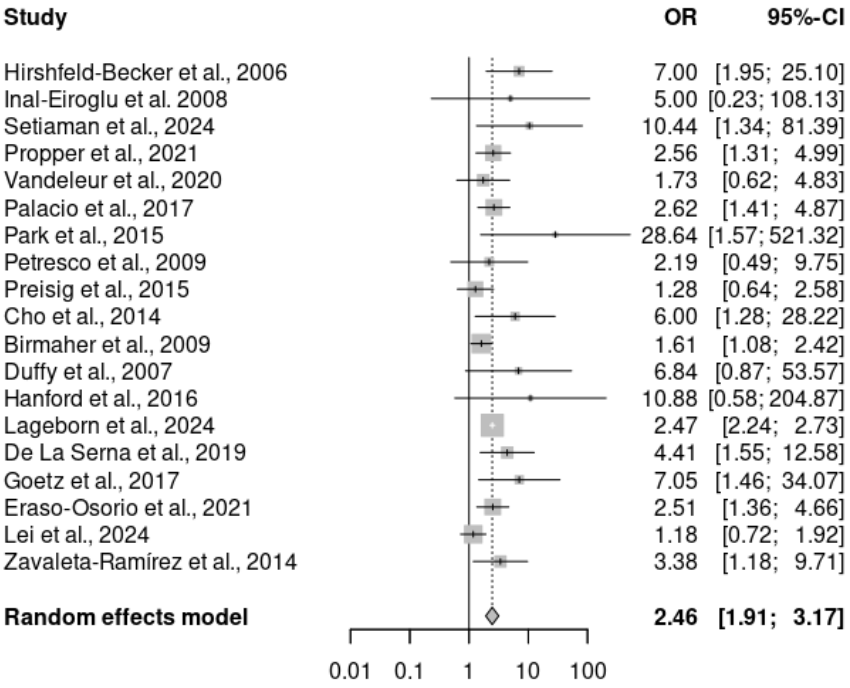


Figure S2. Forest plot of anxiety disorders comparing offspring of individuals with bipolar disorder and controls.

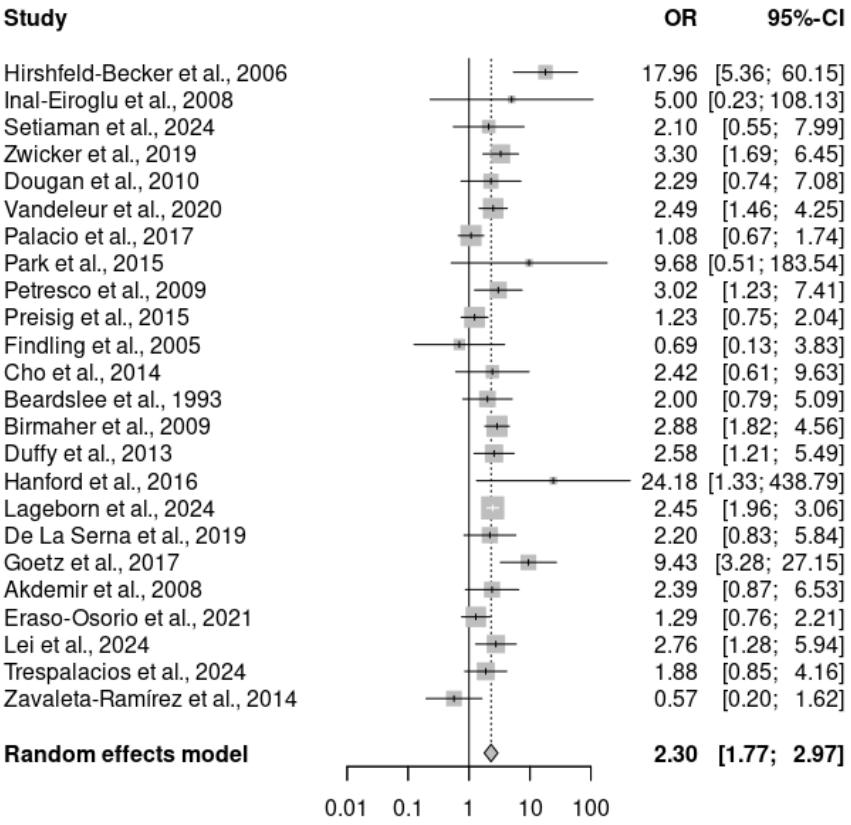


Figure S3. Forest plot of alcohol use disorder comparing offspring of individuals with bipolar disorder and controls.

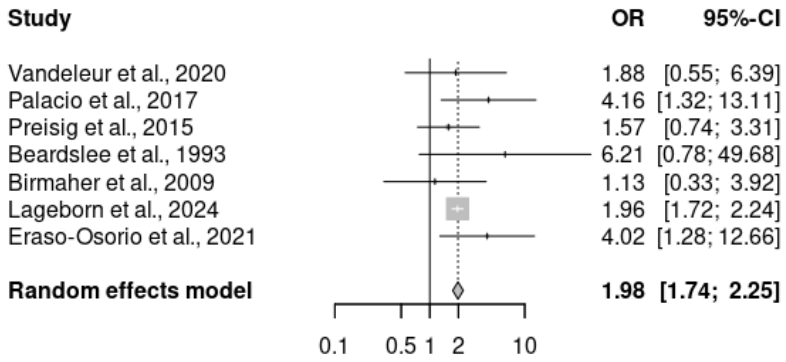


Figure S4. Forest plot of autism spectrum disorder comparing offspring of individuals with bipolar disorder and controls.

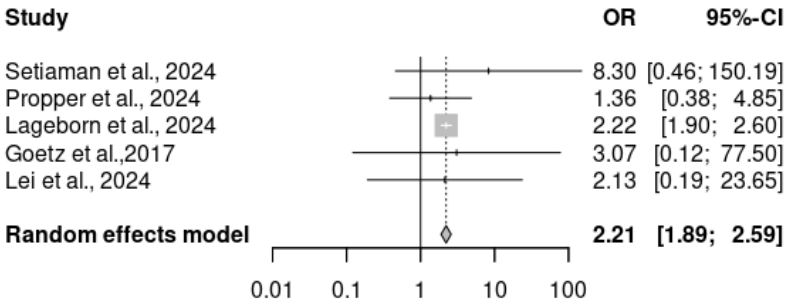


Figure S5. Forest plot of other bipolar disorders comparing offspring of individuals with bipolar disorder and controls.

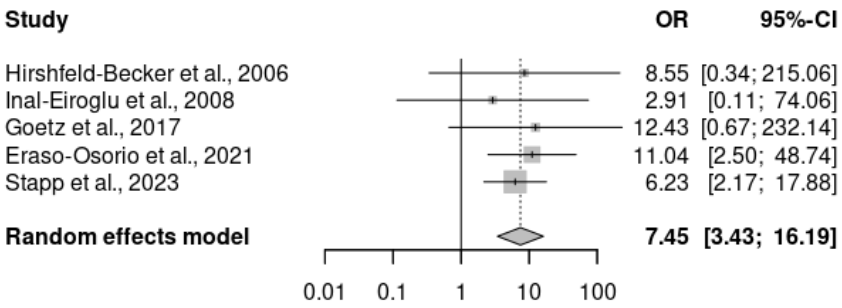


Figure S6. Forest plot of bipolar spectrum disorders comparing offspring of individuals with bipolar disorder and controls.

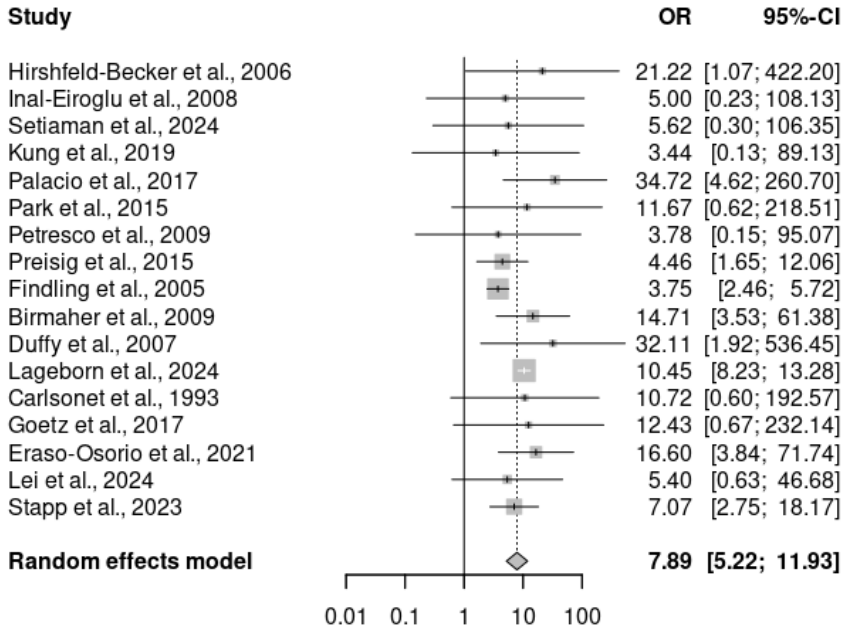


Figure S7. Forest plot of conduct disorder comparing offspring of individuals with bipolar disorder and controls.

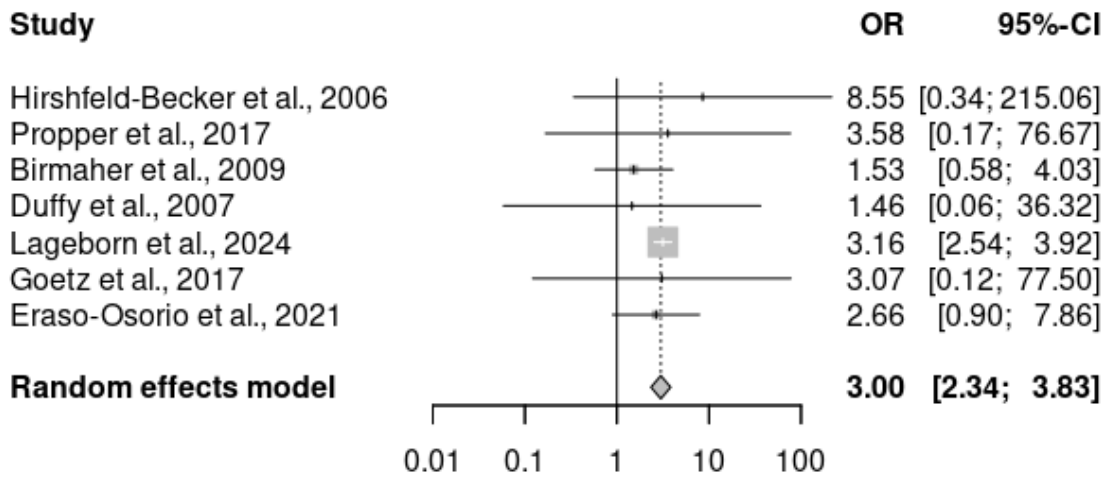


Figure S8. Forest plot of depressive disorders comparing offspring of individuals with bipolar disorder and controls.

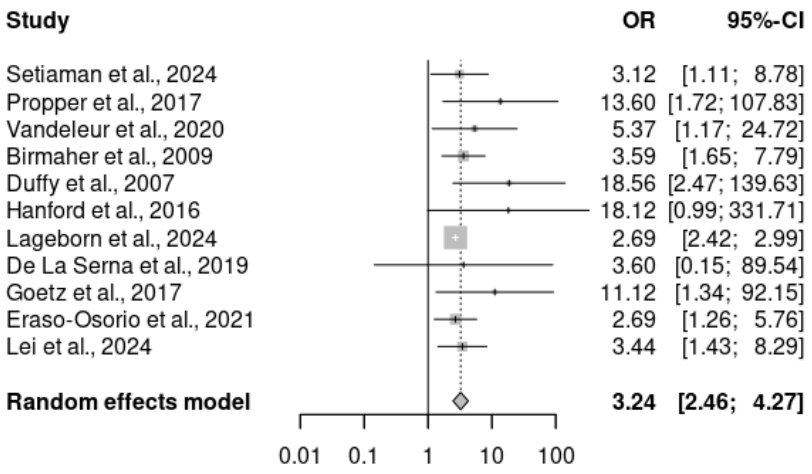


Figure S9. Forest plot of disruptive behaviour disorders comparing offspring of individuals with bipolar disorder and controls.

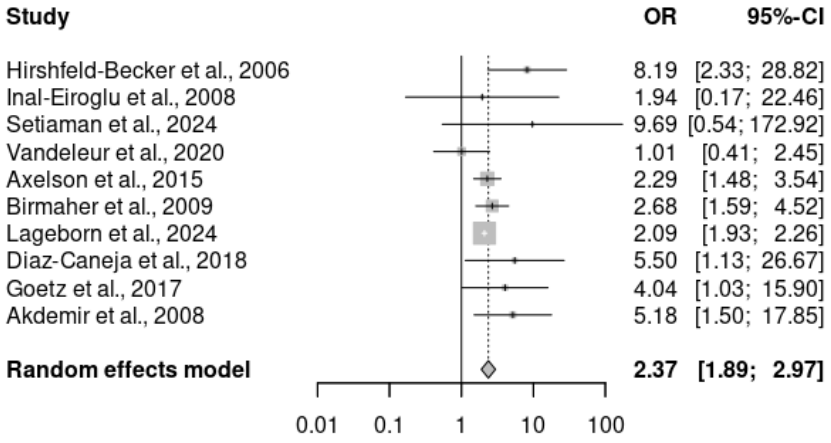


Figure S10. Forest plot of eating disorders comparing offspring of individuals with bipolar disorder and controls.

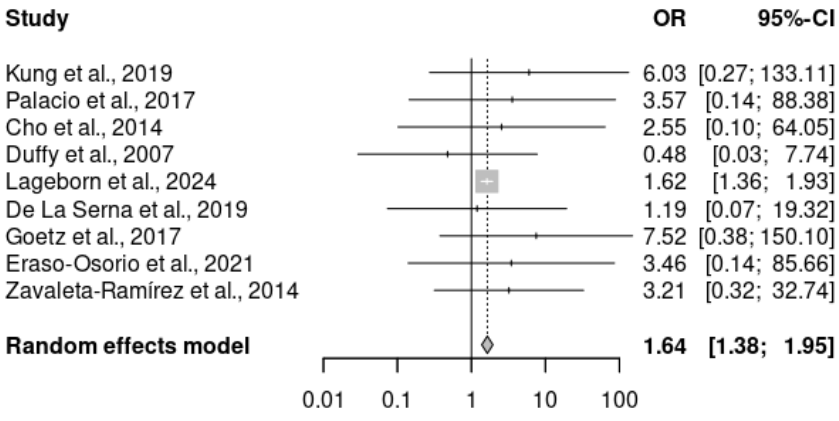


Figure S11. Forest plot of major depressive disorder comparing offspring of individuals with bipolar disorder and controls.

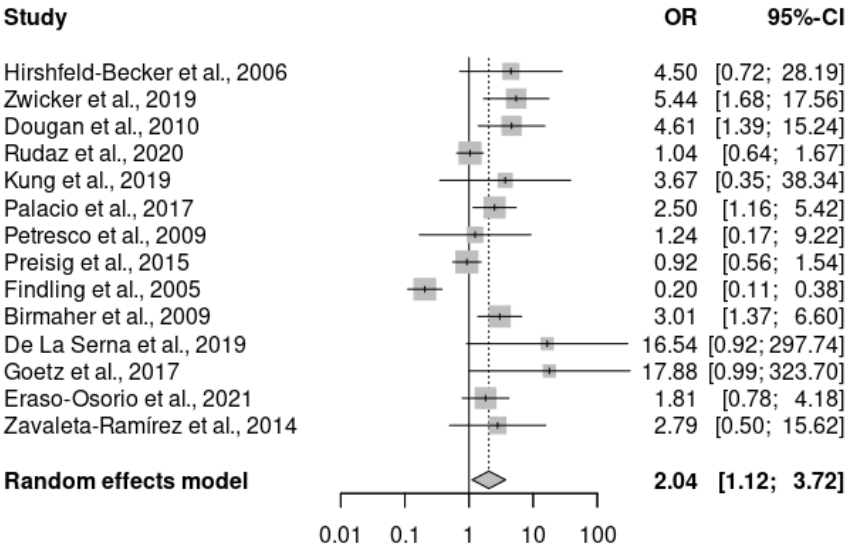


Figure S12. Forest plot of any mental disorder comparing offspring of individuals with bipolar disorder and controls.

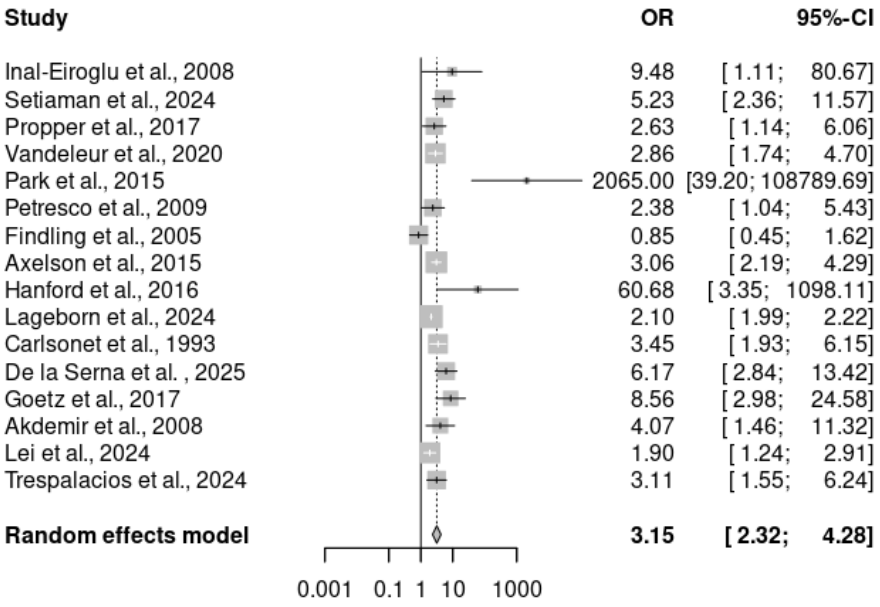


Figure S13. Forest plot of mood disorders comparing offspring of individuals with bipolar disorder and controls.

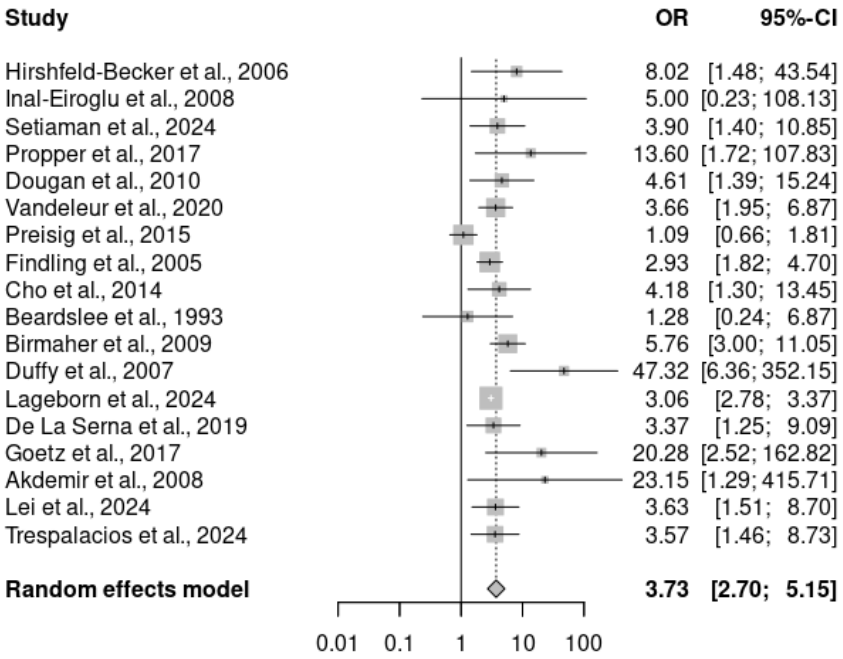


Figure S14. Forest plot of oppositional defiant disorder comparing offspring of individuals with bipolar disorder and controls.

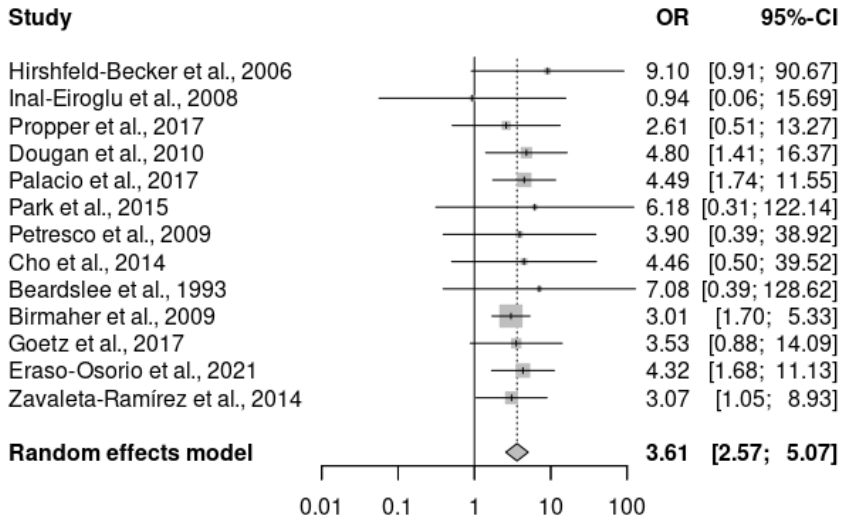


Figure S15. Forest plot of substance use disorders comparing offspring of individuals with bipolar disorder and controls.

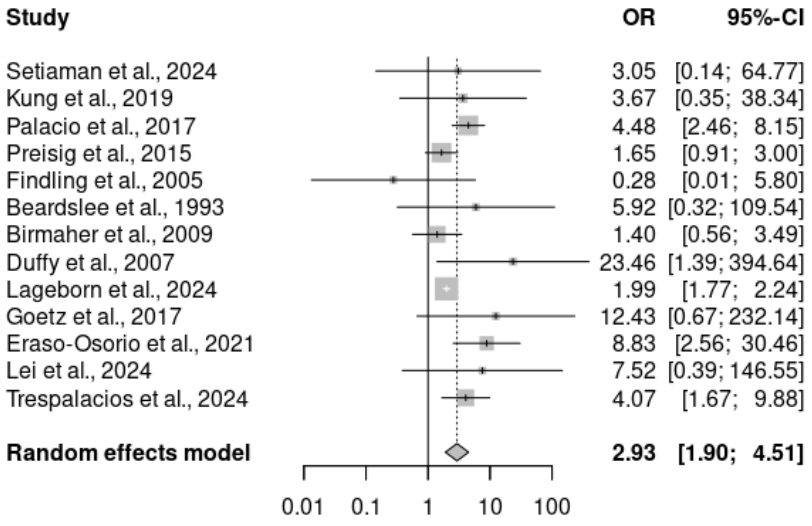


Figure S16. Funnel plot and trim-and-fill analysis for attention-deficit/hyperactivity disorder (ADHD) comparing offspring of individuals with bipolar disorder and controls.

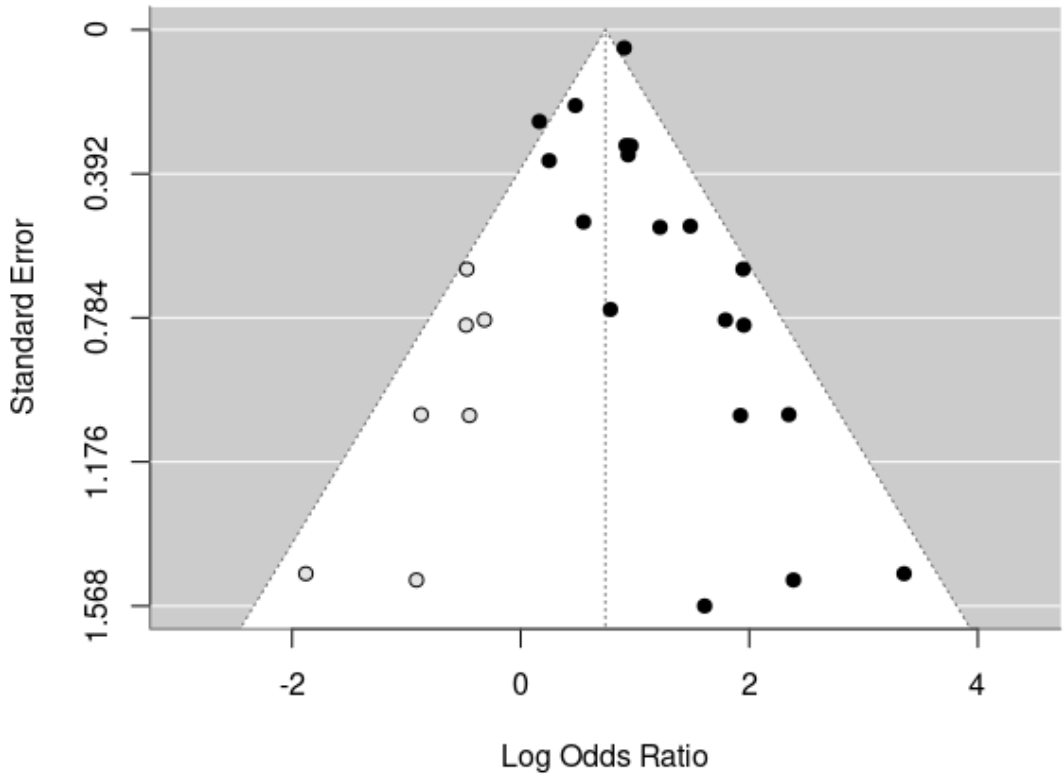


Figure S17. Funnel plot and trim-and-fill analysis for anxiety disorders comparing offspring of individuals with bipolar disorder and controls.

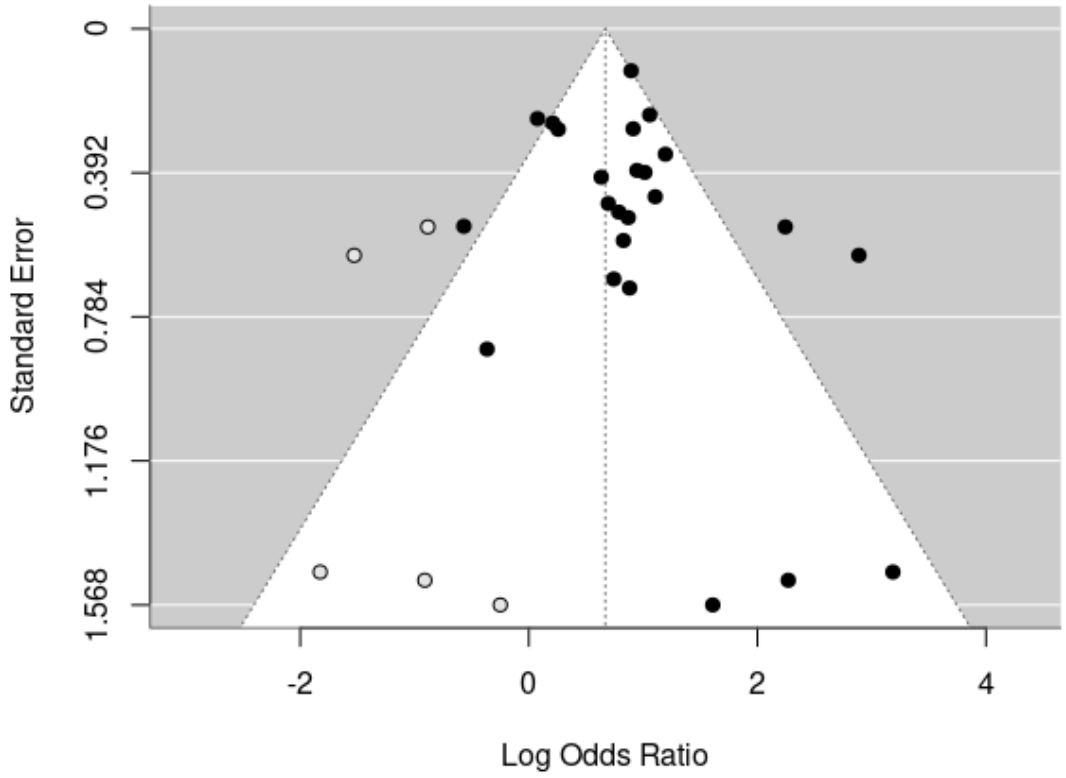


Figure S18. Funnel plot for bipolar spectrum disorders comparing offspring of individuals with bipolar disorder and controls.

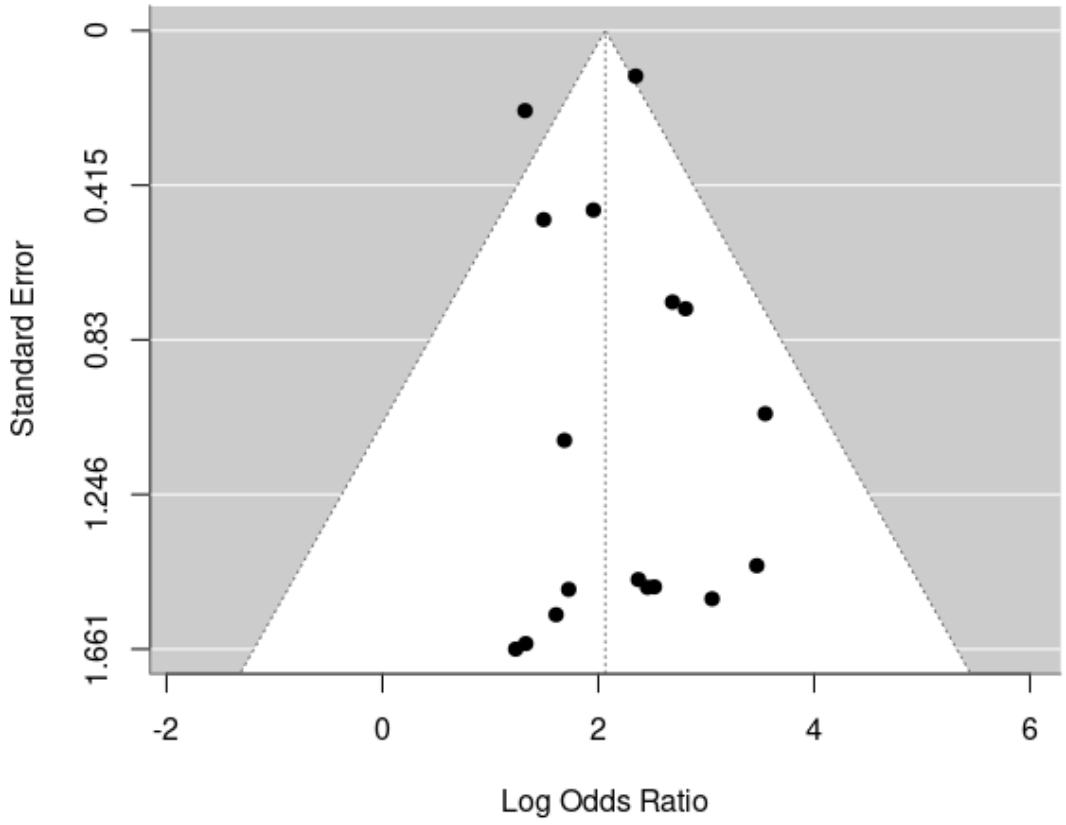


Figure S19. Funnel plot and trim-and-fill analysis for depressive disorders comparing offspring of individuals with bipolar disorder and controls.

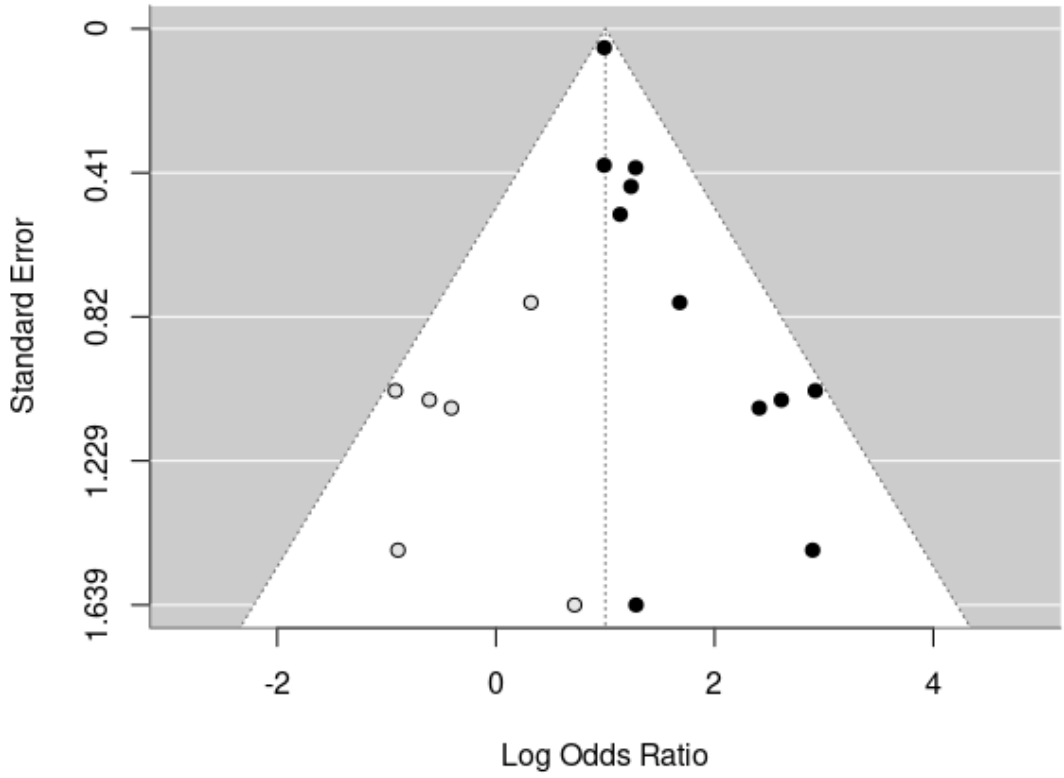


Figure S20. Funnel plot and trim-and-fill analysis for major depressive disorder comparing offspring of individuals with bipolar disorder and controls.

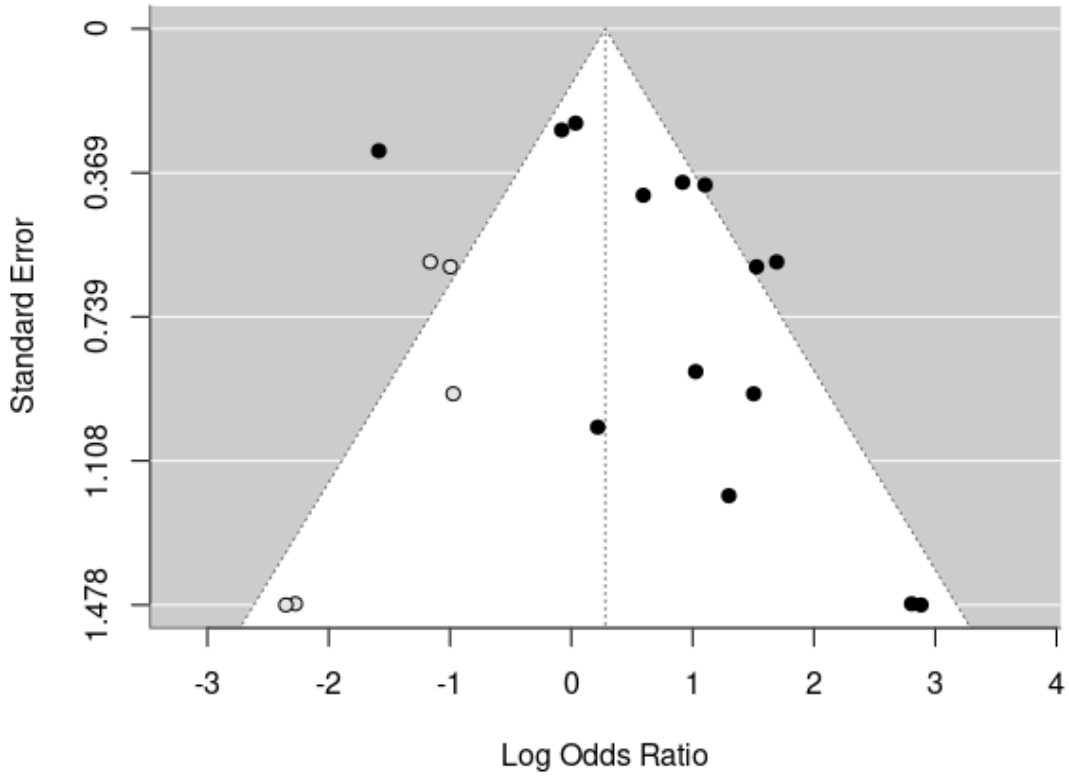


Figure S21. Funnel plot and trim-and-fill analysis for any mental disorder comparing offspring of individuals with bipolar disorder and controls.

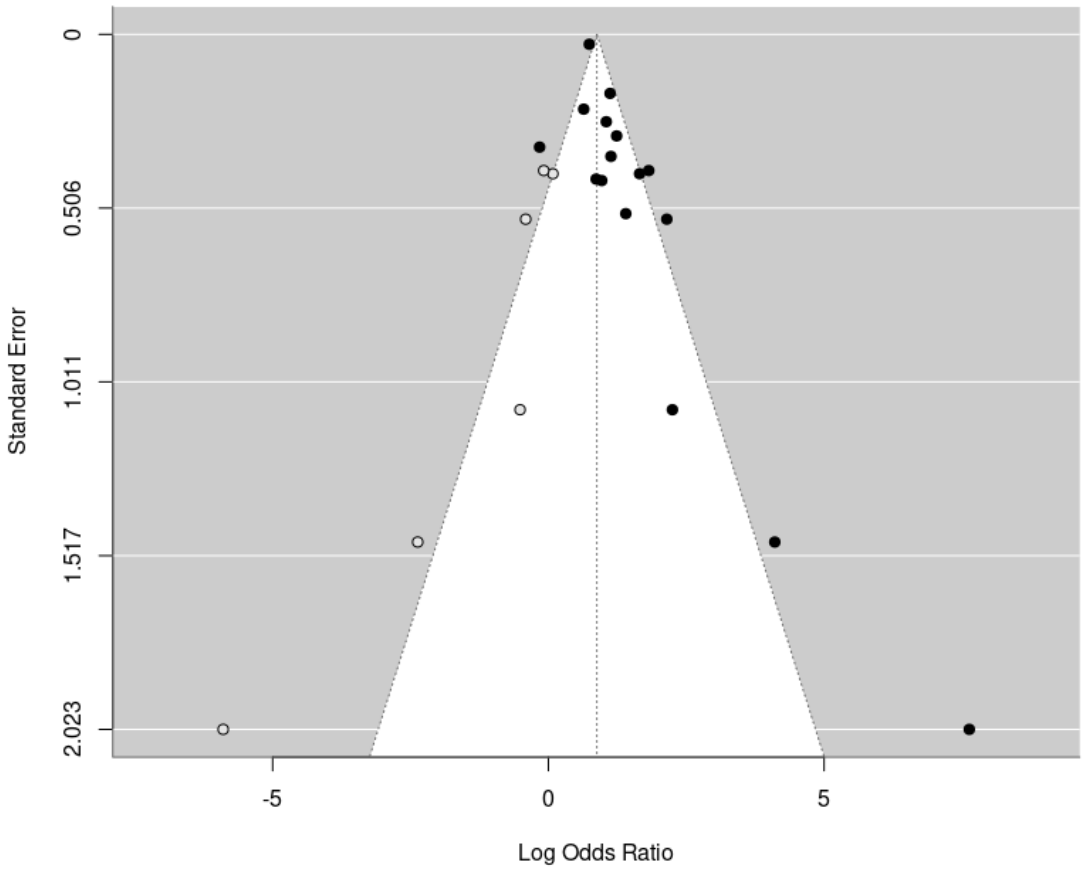


Figure S22. Funnel plot and trim-and-fill analysis for mood disorders comparing offspring of individuals with bipolar disorder and controls.

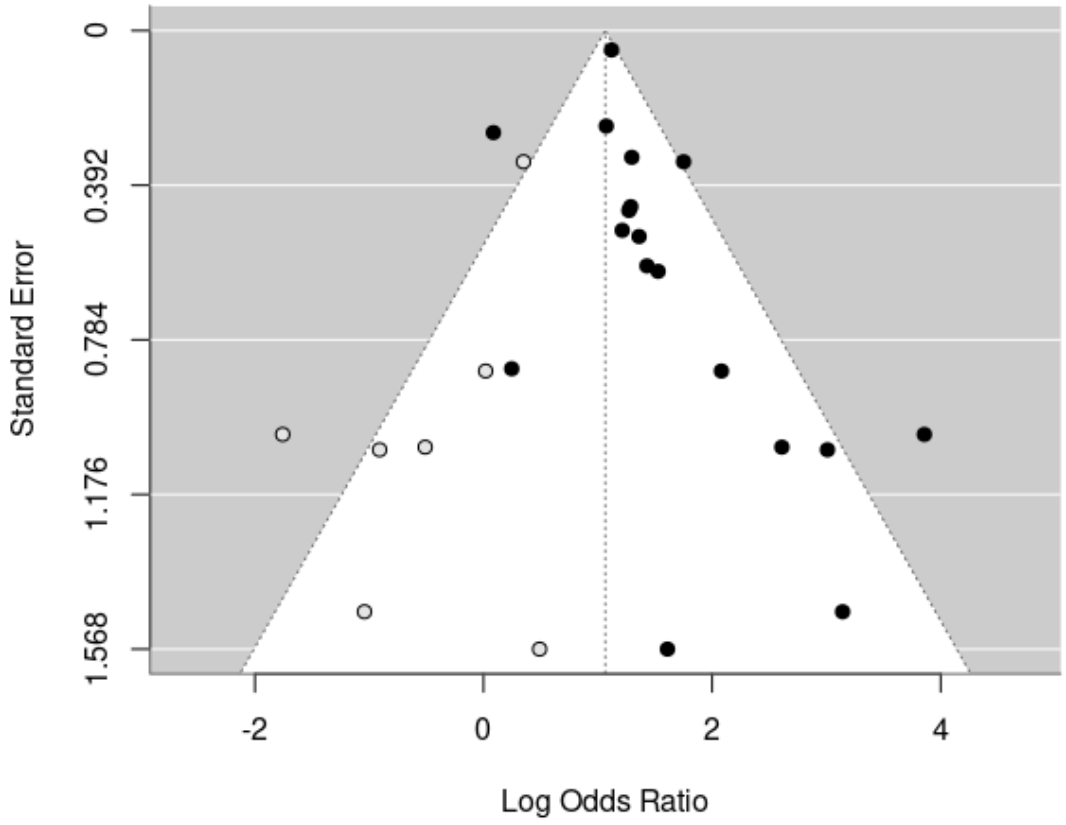


Figure S23. Funnel plot for oppositional defiant disorder comparing offspring of individuals with bipolar disorder and controls.

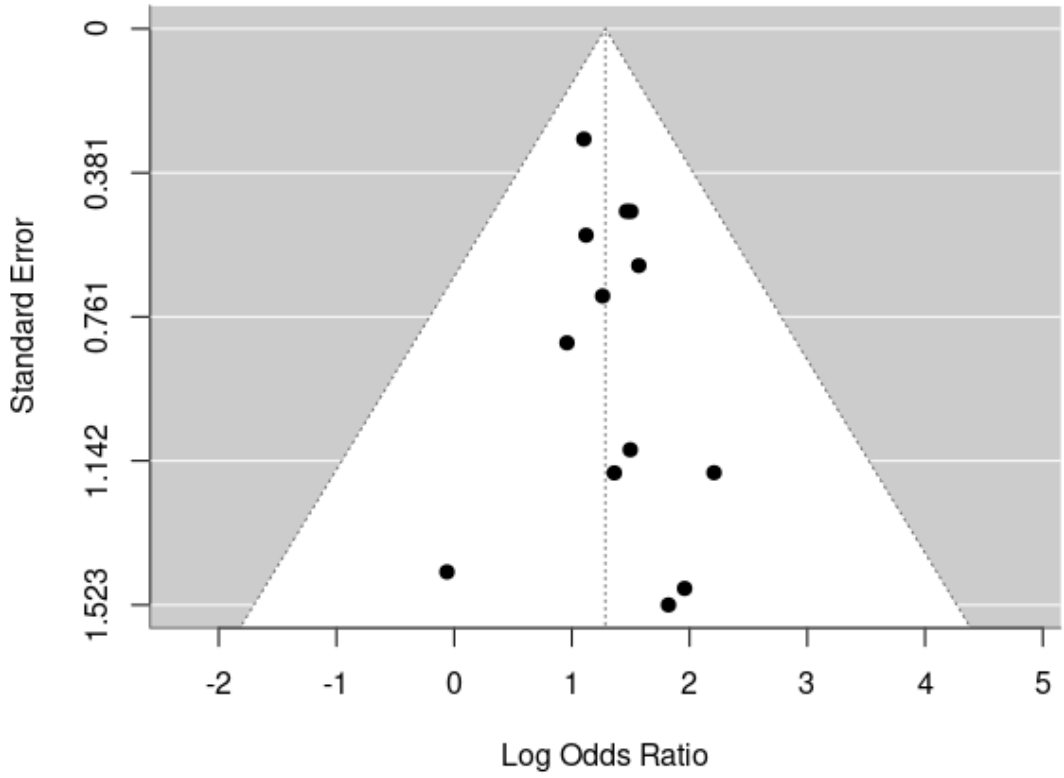


Figure S24. Funnel plot and trim-and-fill analysis for substance use disorders comparing offspring of individuals with bipolar disorder and controls.

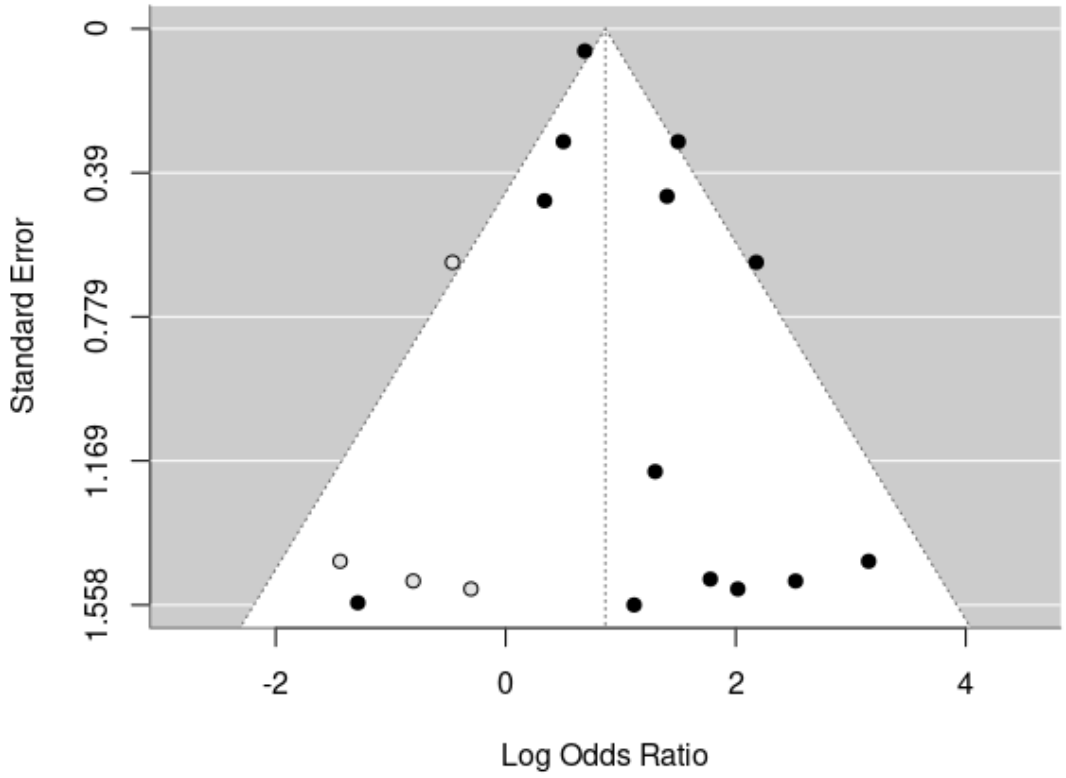


Figure S25. Forest plot of pooled prevalence estimates for any mental disorder among offspring of individuals with bipolar disorder.

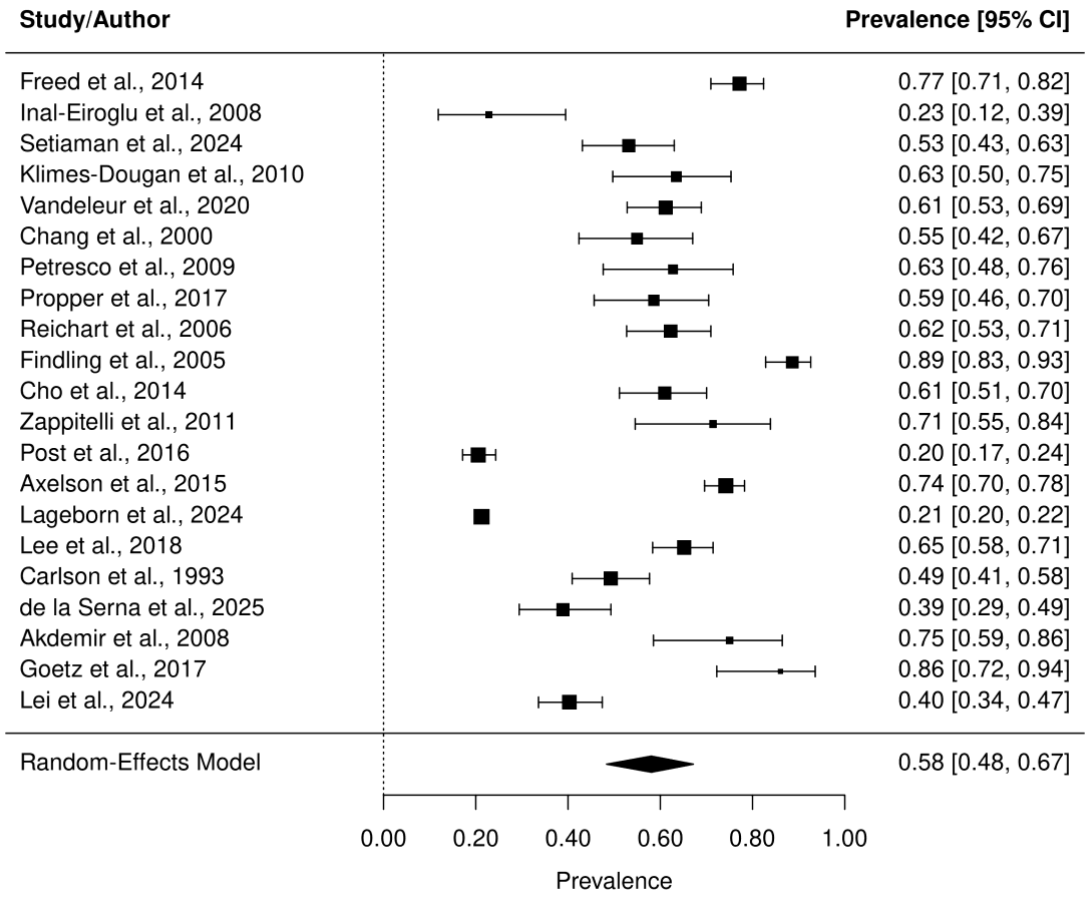


Figure S26. Forest plot of pooled prevalence estimates for mood disorders among offspring of individuals with bipolar disorder.

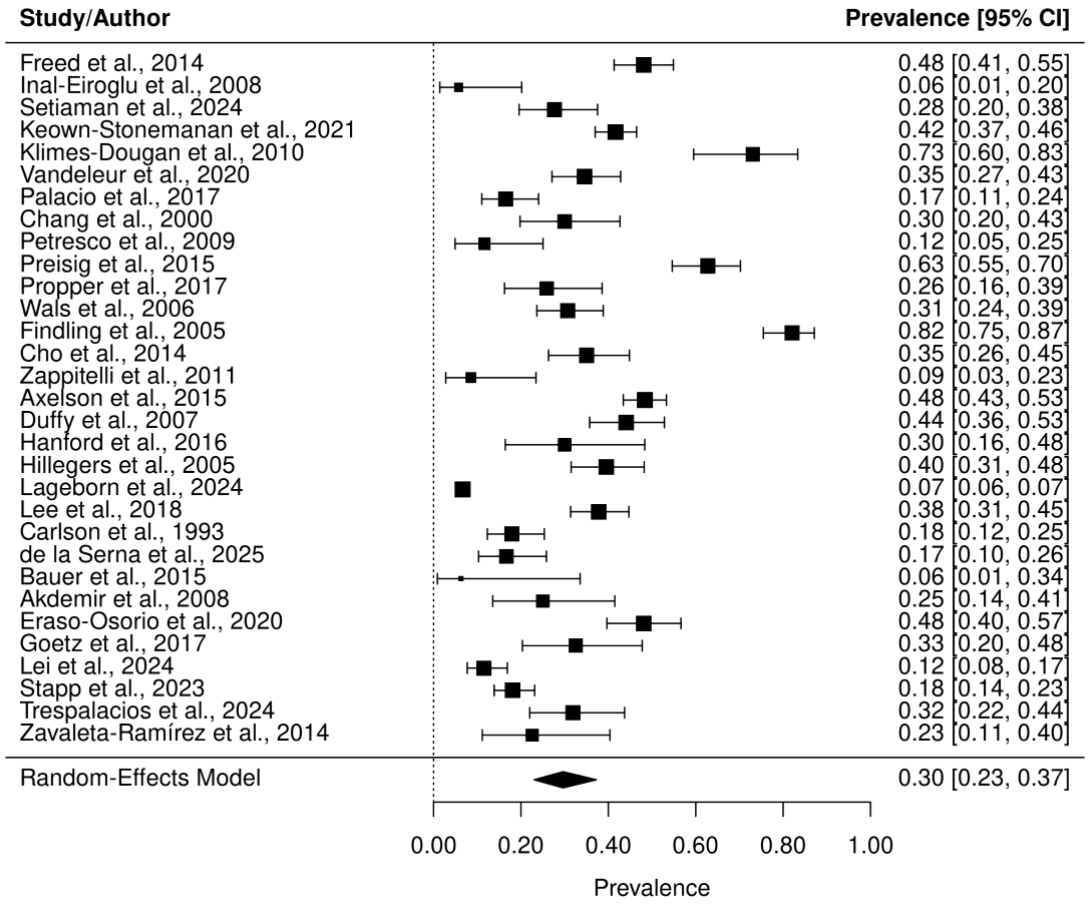


Figure S27. Forest plot of pooled prevalence estimates for anxiety disorders among offspring of individuals with bipolar disorder.

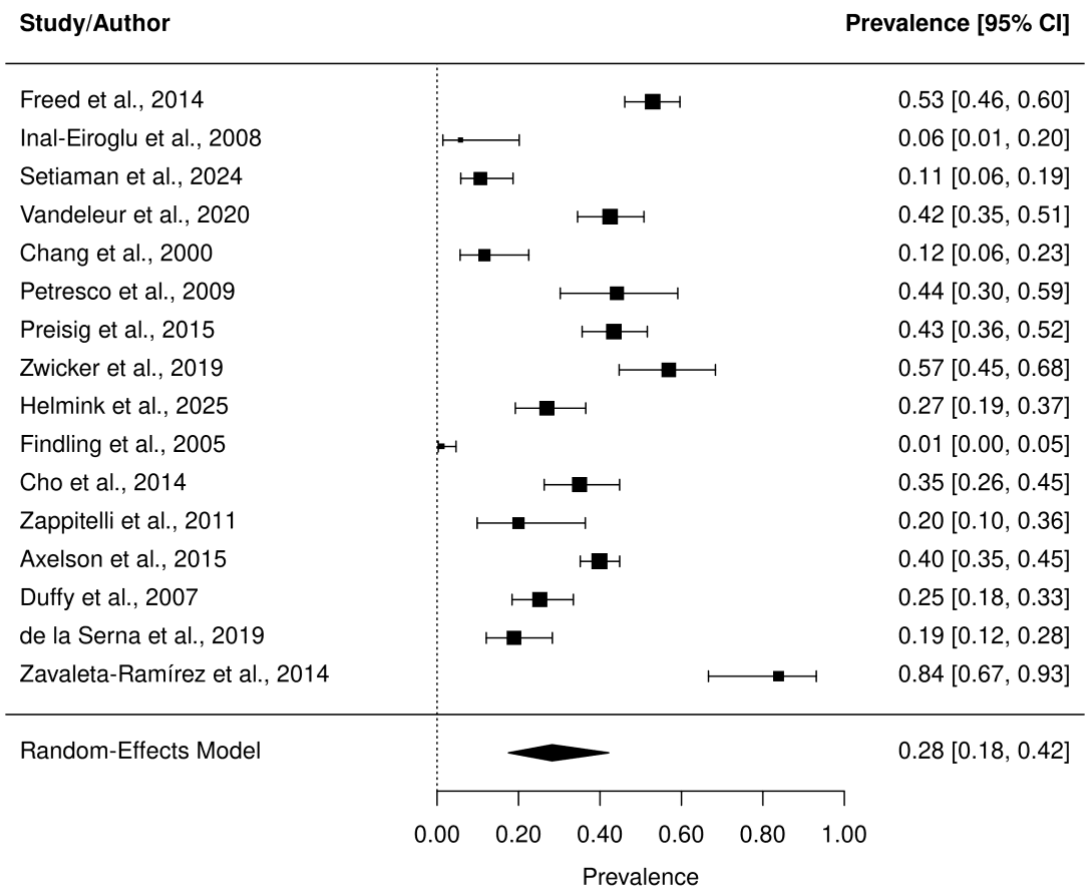


Figure S28. Forest plot of pooled prevalence estimates for depressive disorders among offspring of individuals with bipolar disorder.

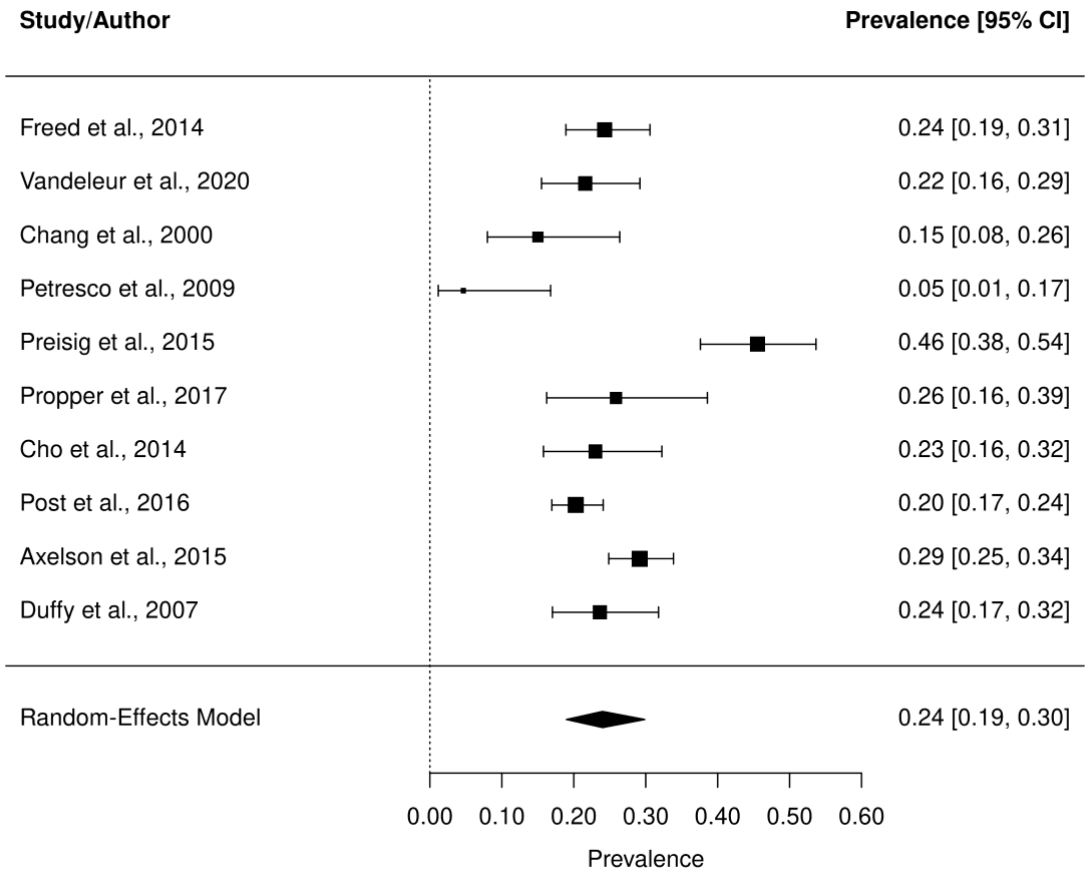


Figure S29. Forest plot of pooled prevalence estimates for attention-deficit/hyperactivity disorder (ADHD) among offspring of individuals with bipolar disorder.

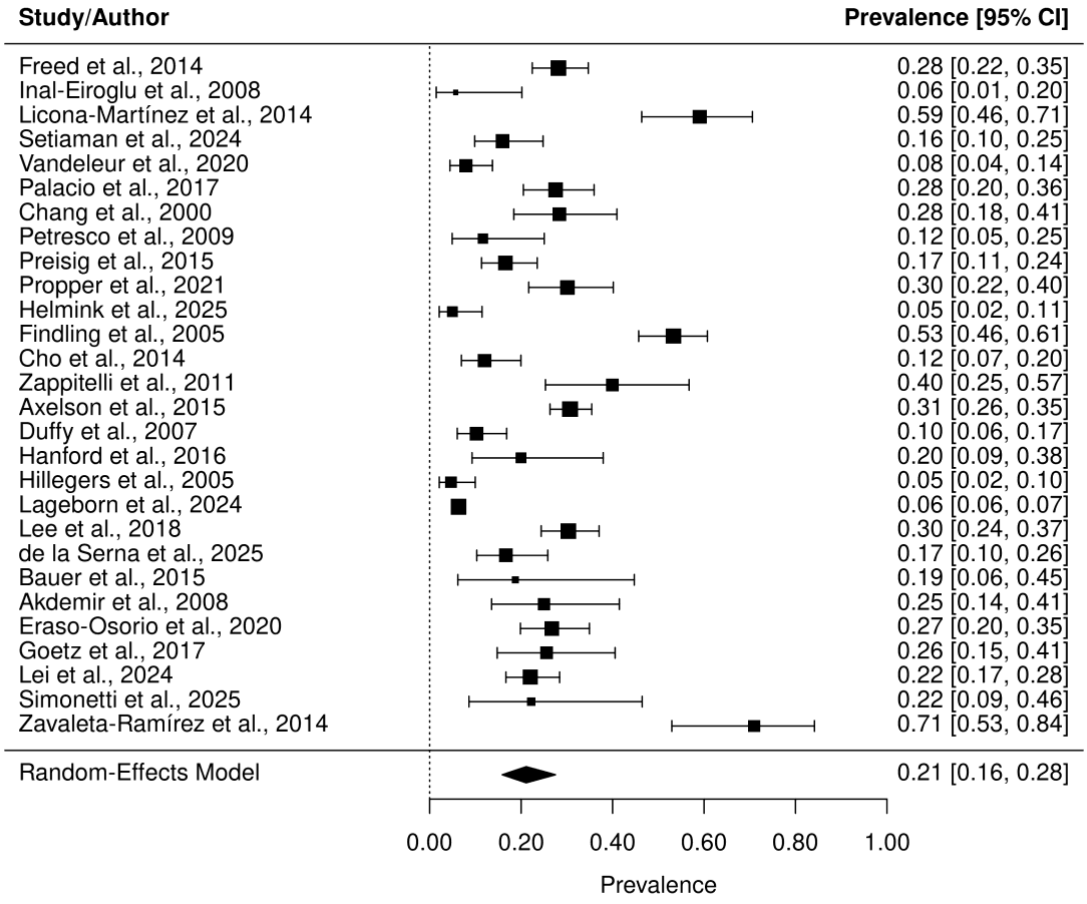


Figure S30. Forest plot of pooled prevalence estimates for major depressive disorder among offspring of individuals with bipolar disorder.

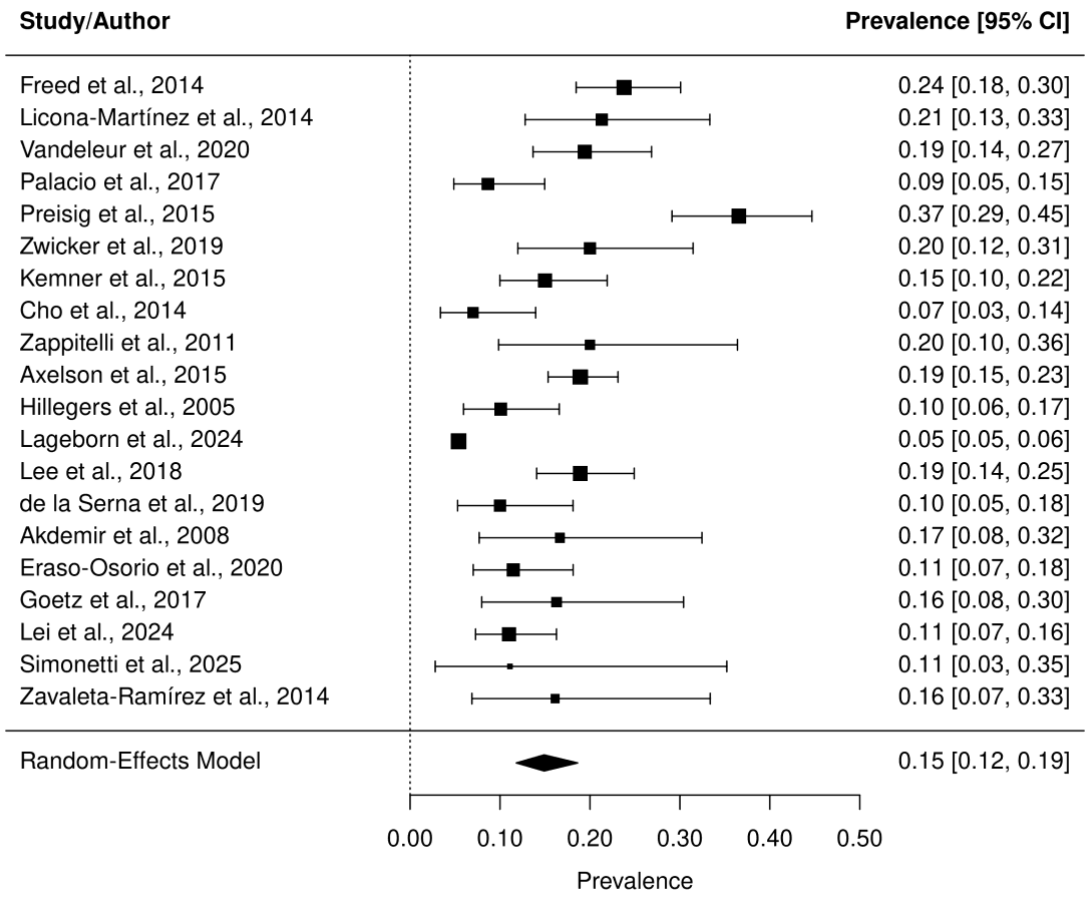


Figure S31. Forest plot of pooled prevalence estimates for disruptive behavior disorders among offspring of individuals with bipolar disorder.

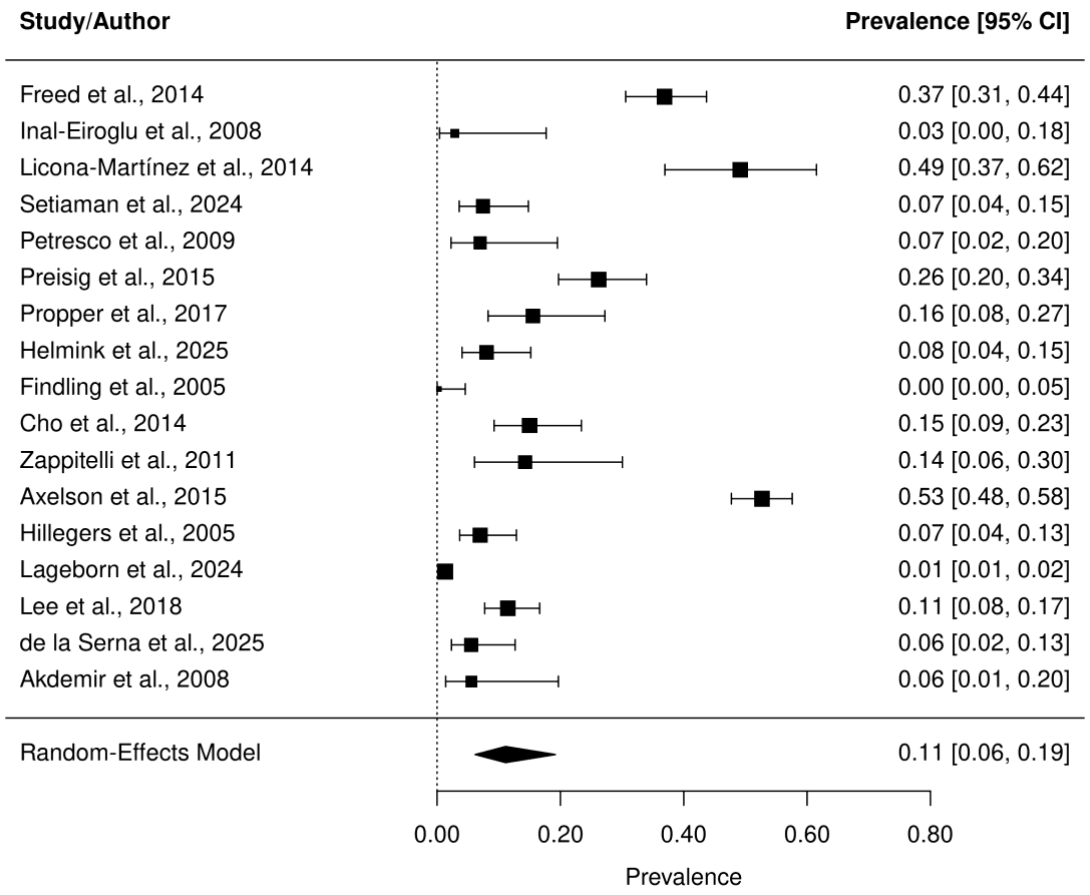


Figure S32. Forest plot of pooled prevalence estimates for alcohol use disorder among offspring of individuals with bipolar disorder.

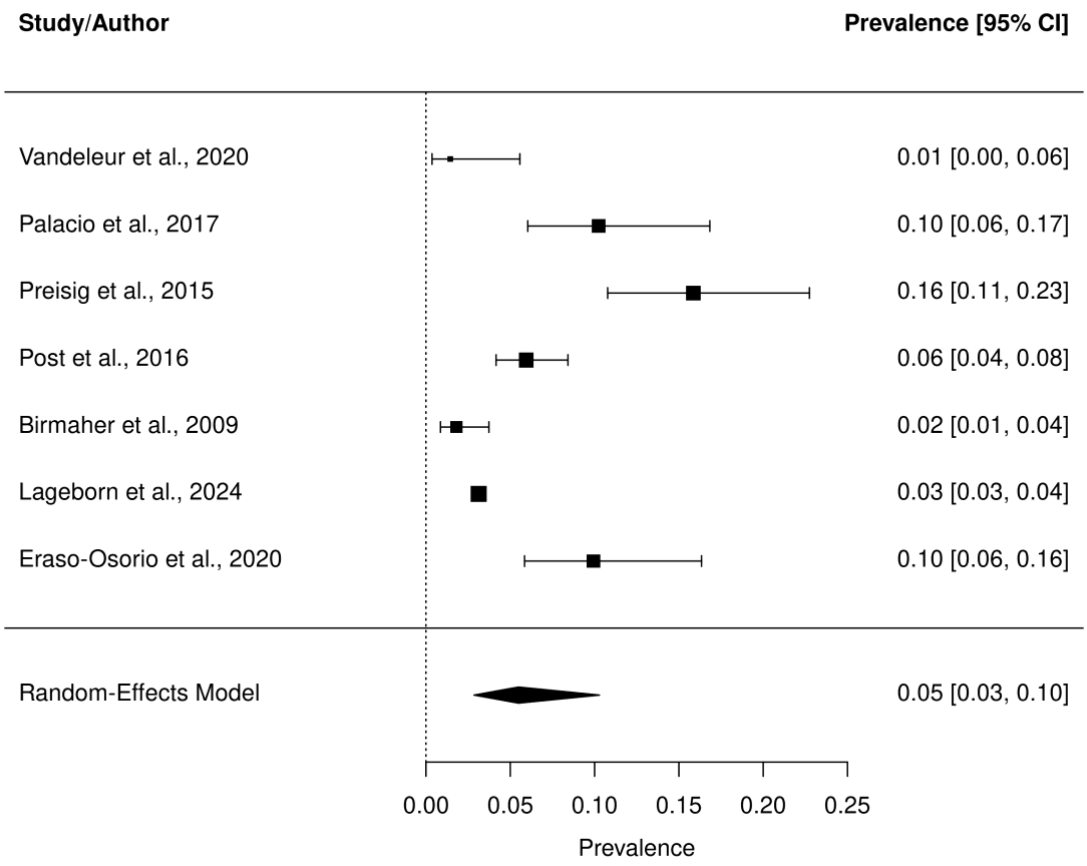


Figure S33. Forest plot of pooled prevalence estimates for bipolar spectrum disorders among offspring of individuals with bipolar disorder.

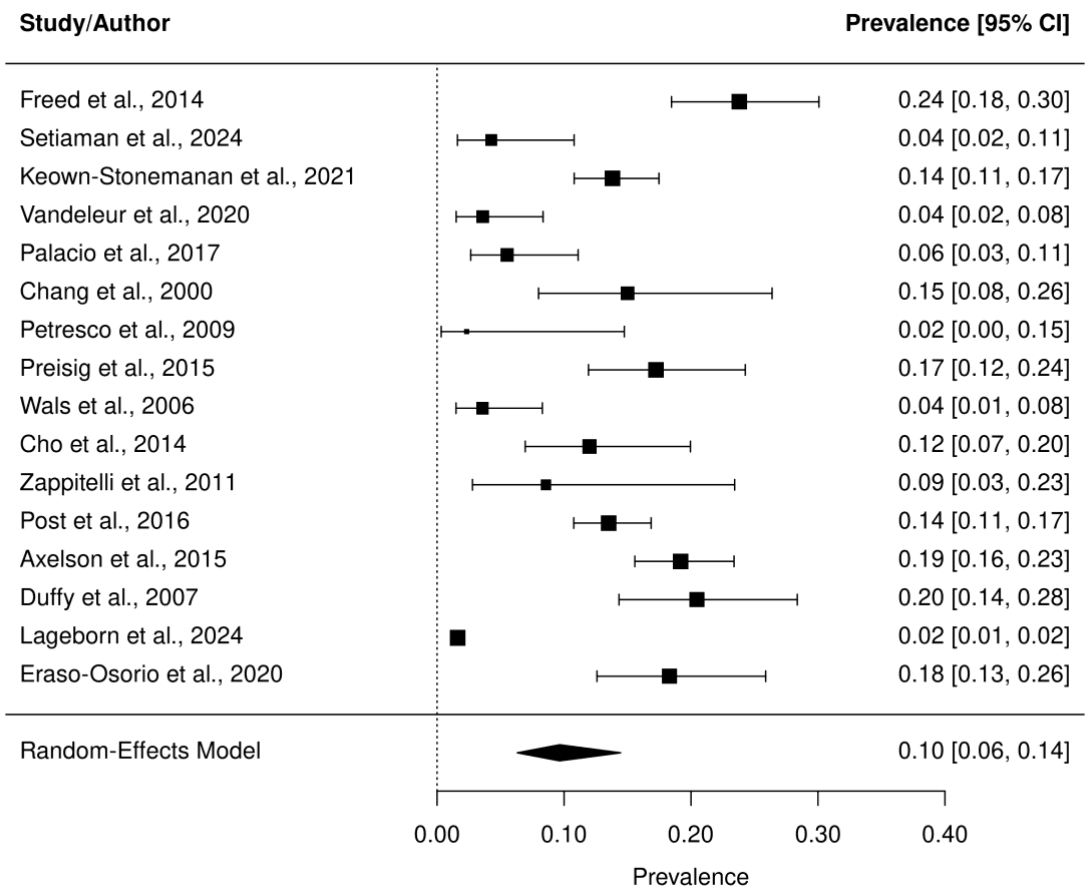


Figure S34. Forest plot of pooled prevalence estimates for generalized anxiety disorder among offspring of individuals with bipolar disorder.

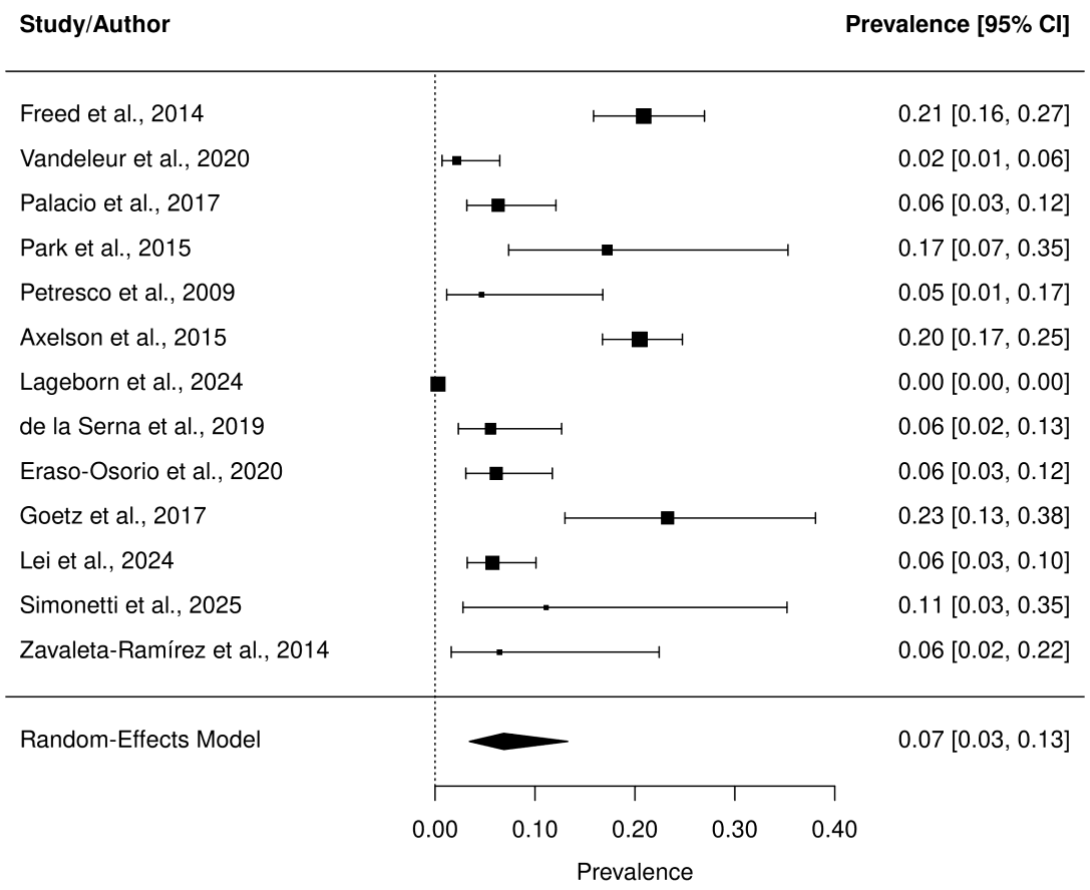


Figure S35. Forest plot of pooled prevalence estimates for conduct disorder among offspring of individuals with bipolar disorder.

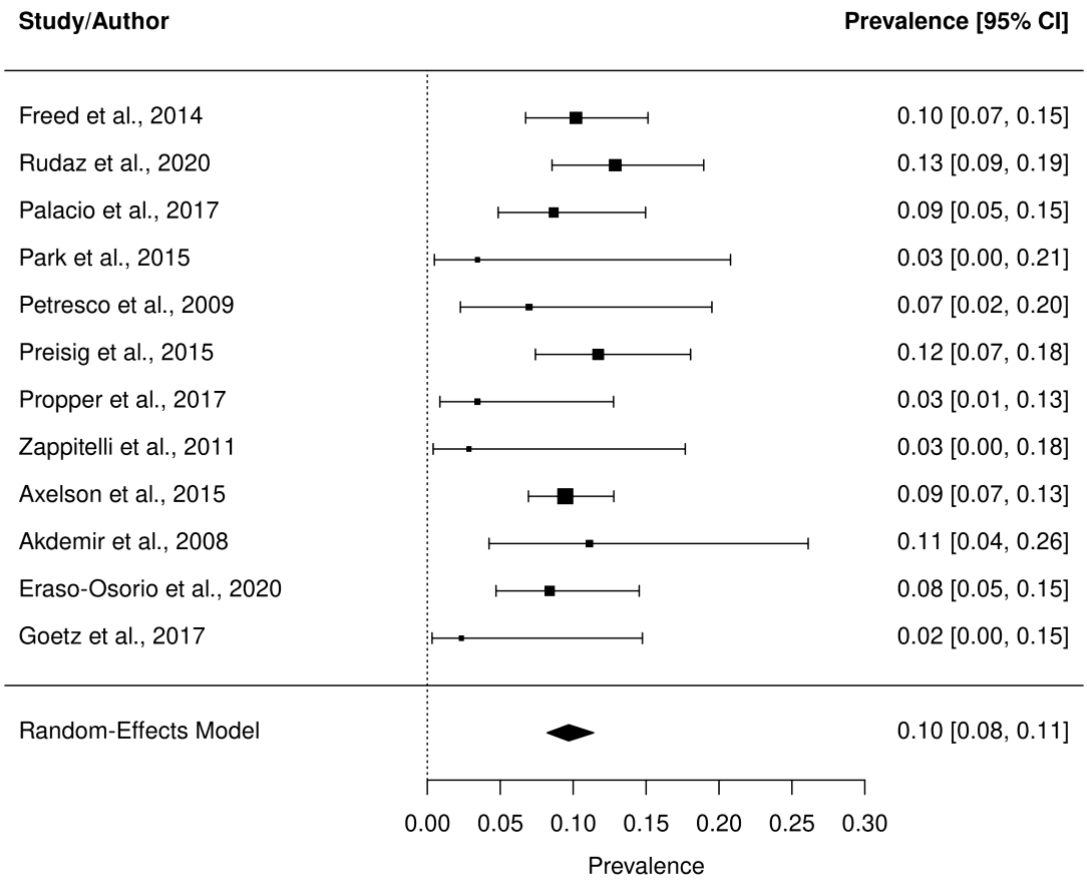


Figure S36. Forest plot of pooled prevalence estimates for autism spectrum disorder among offspring of individuals with bipolar disorder.

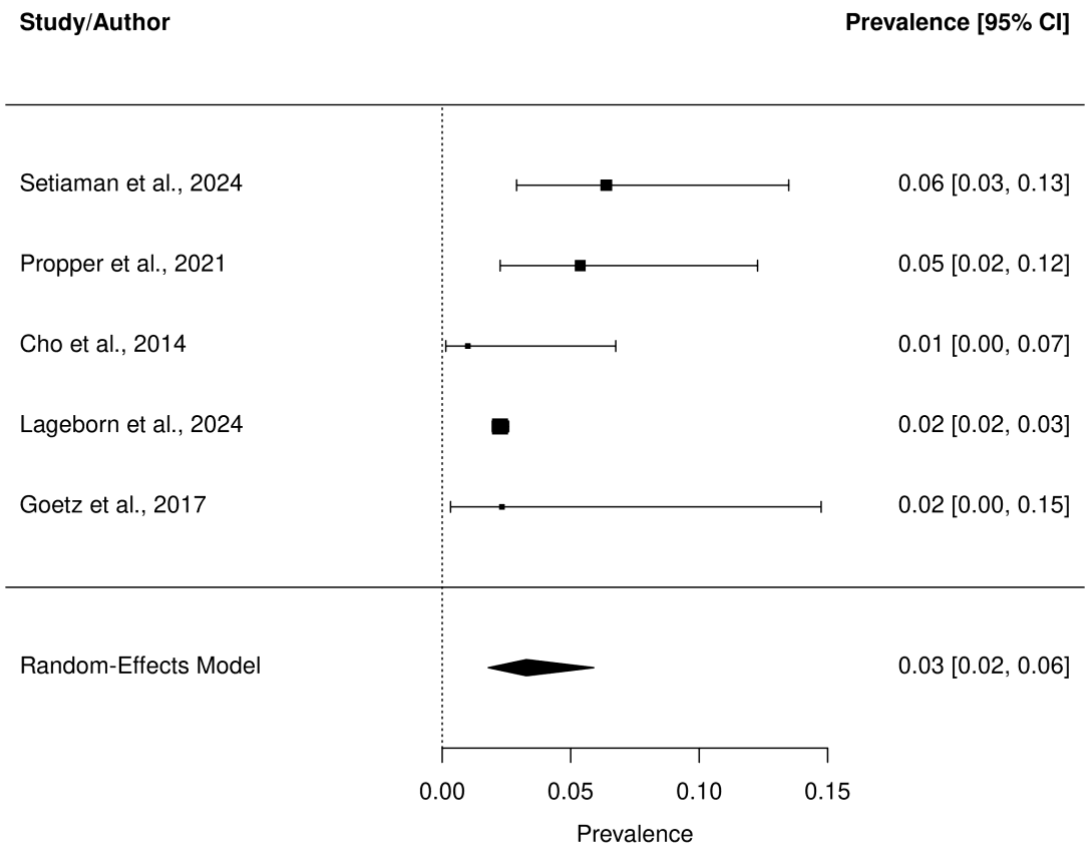


Figure S37. Forest plot of pooled prevalence estimates for bipolar I disorder among offspring of individuals with bipolar disorder.

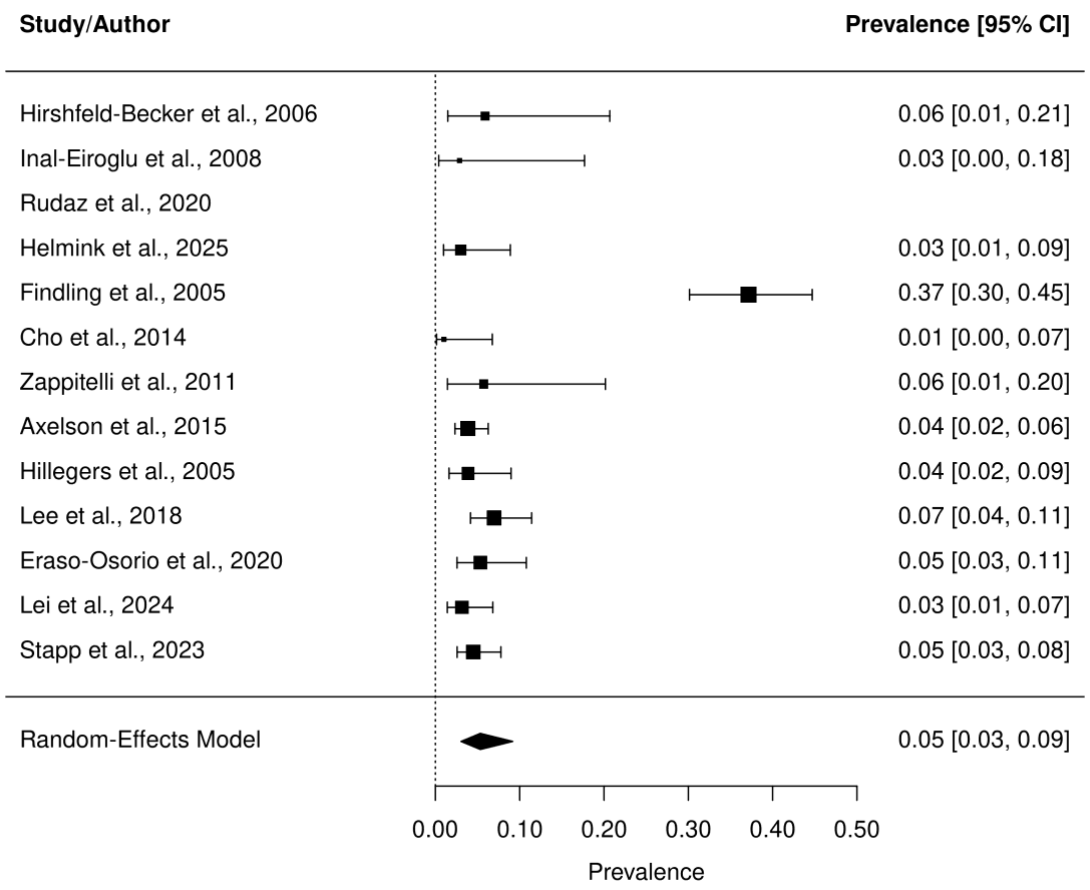


Figure S38. Forest plot of pooled prevalence estimates for bipolar II disorder among offspring of individuals with bipolar disorder.

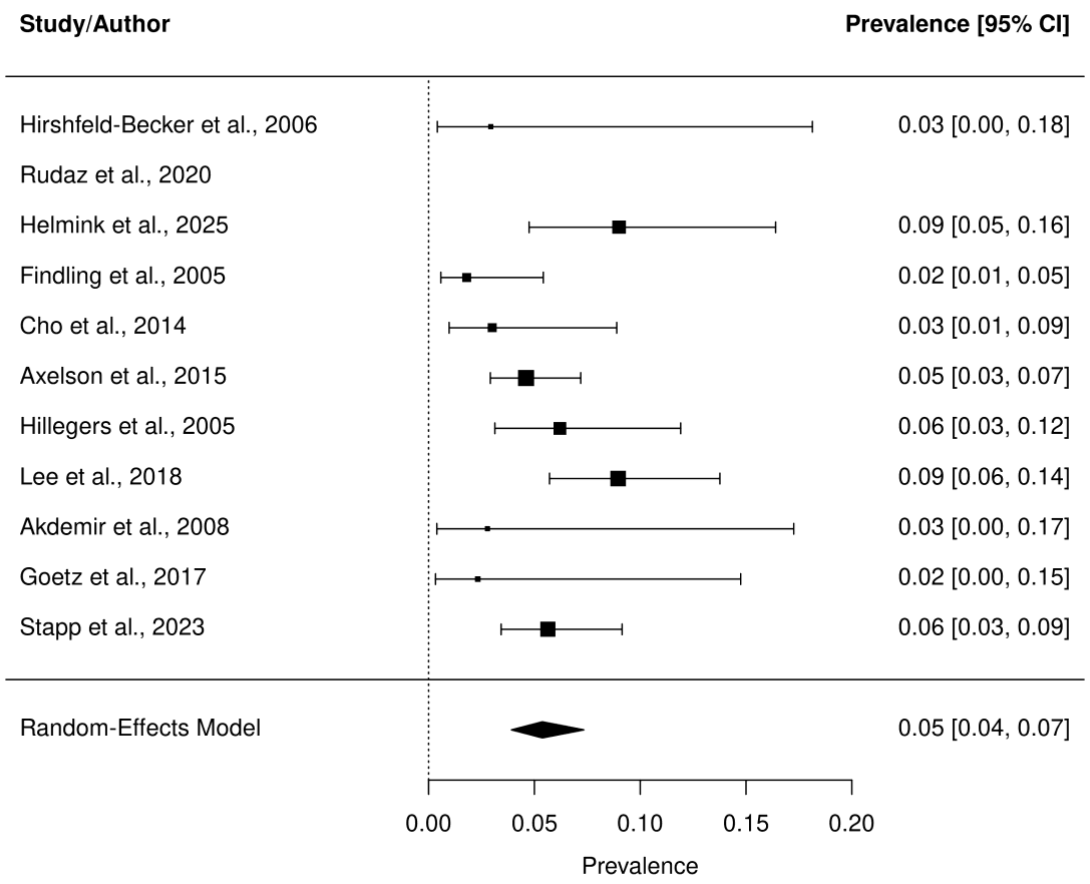


Figure S39. Forest plot of pooled prevalence estimates for bipolar disorder not otherwise specified (BD-NOS) among offspring of individuals with bipolar disorder.

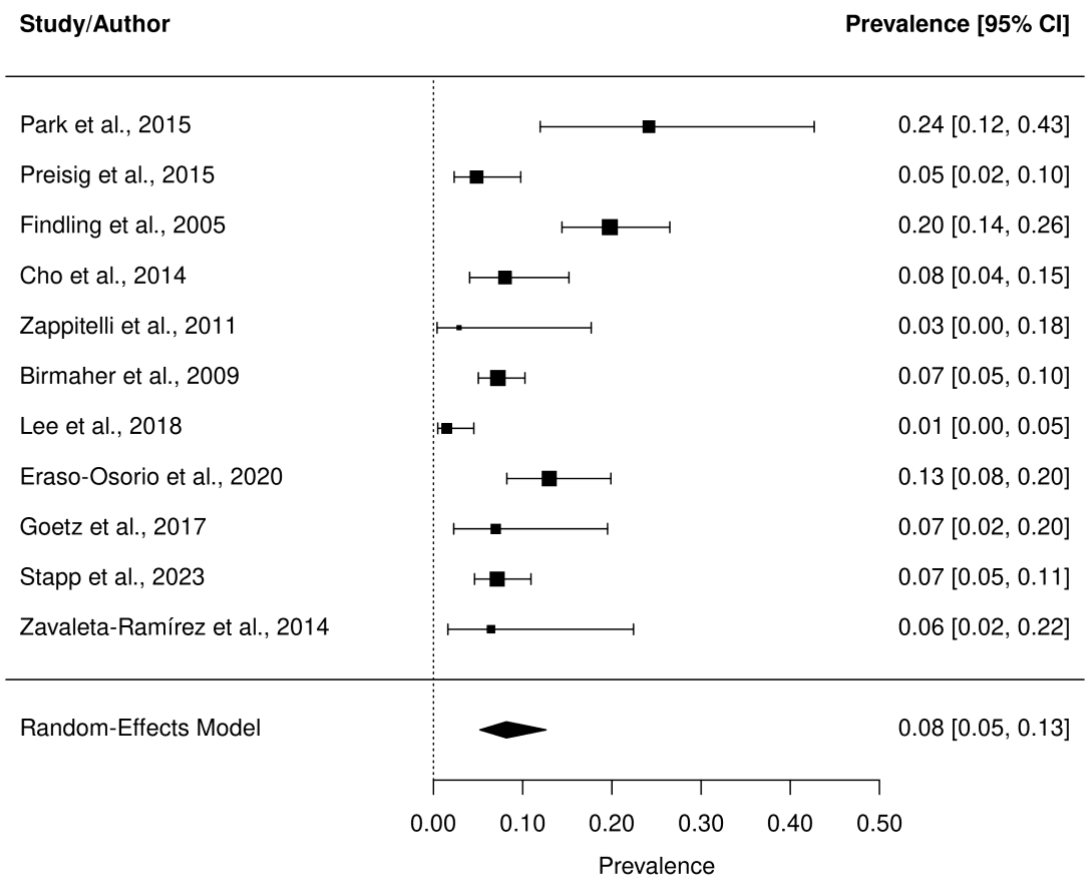


Figure S40. Forest plot of pooled prevalence estimates for cyclothymic disorder among offspring of individuals with bipolar disorder.

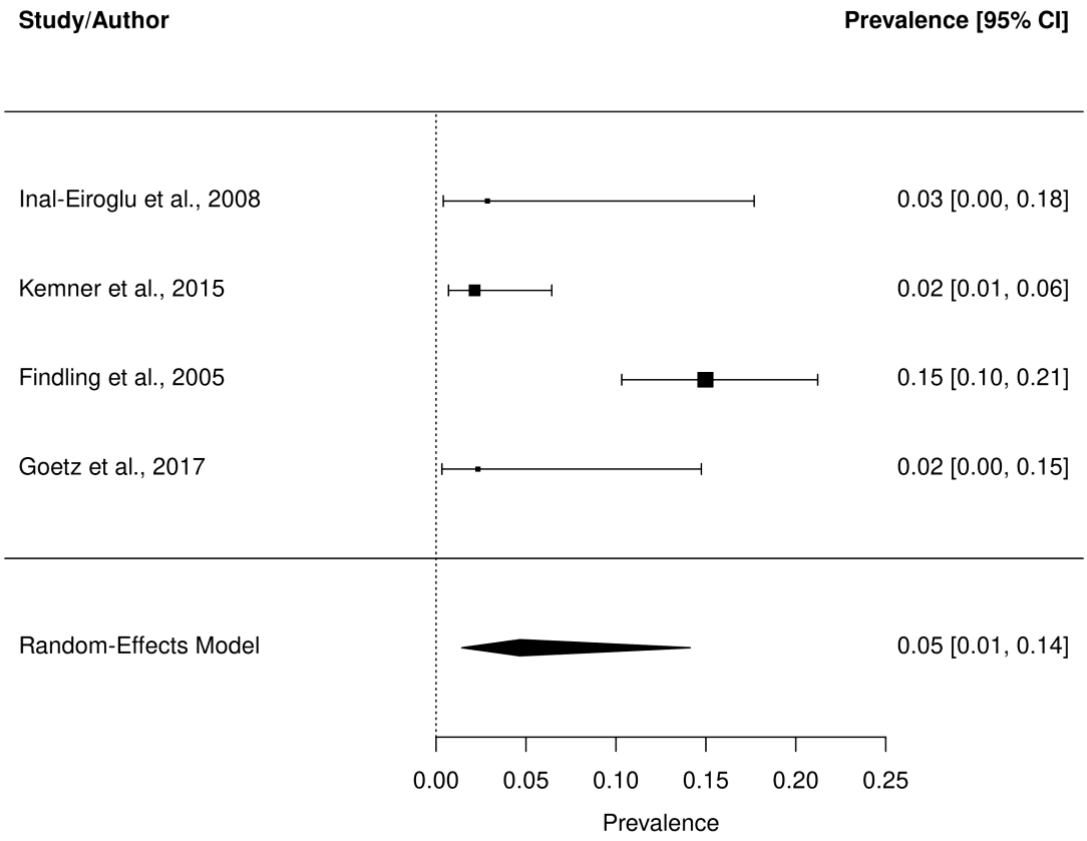


Figure S41. Forest plot of pooled prevalence estimates for dysthymic disorder among offspring of individuals with bipolar disorder.

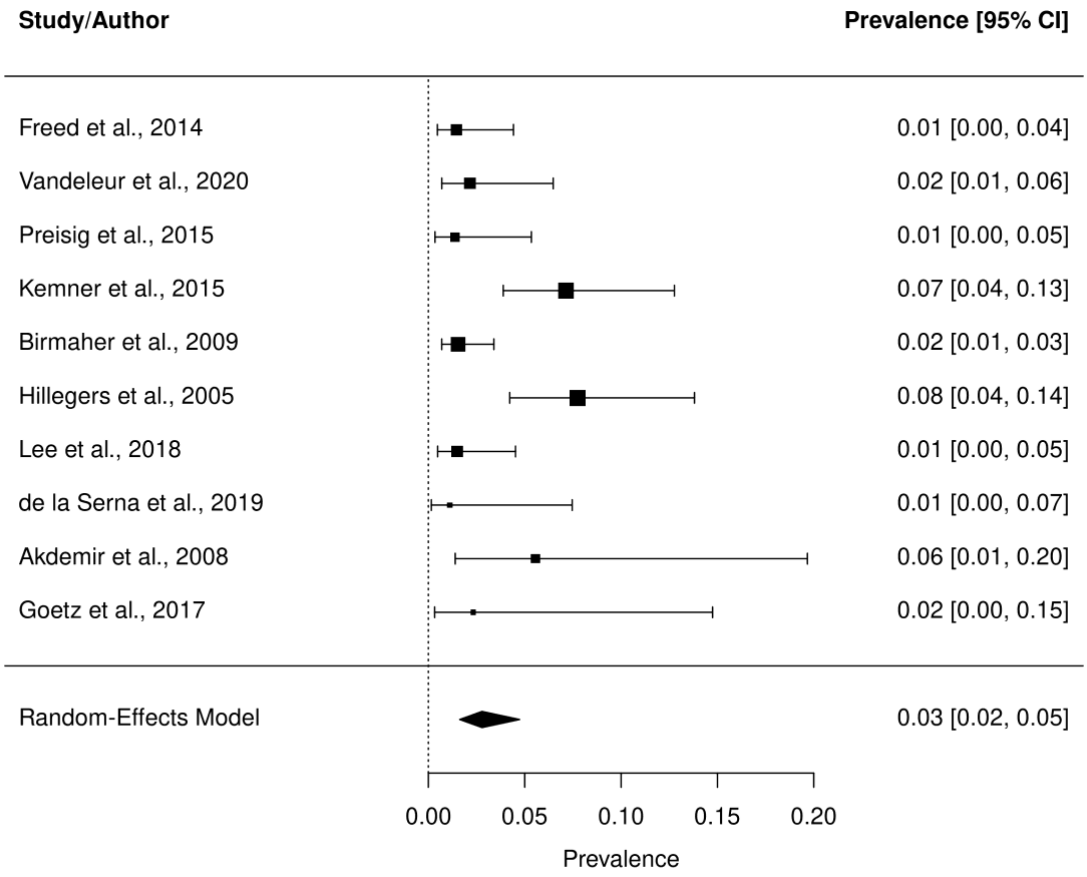


Figure S42. Forest plot of pooled prevalence estimates for eating disorders among offspring of individuals with bipolar disorder.

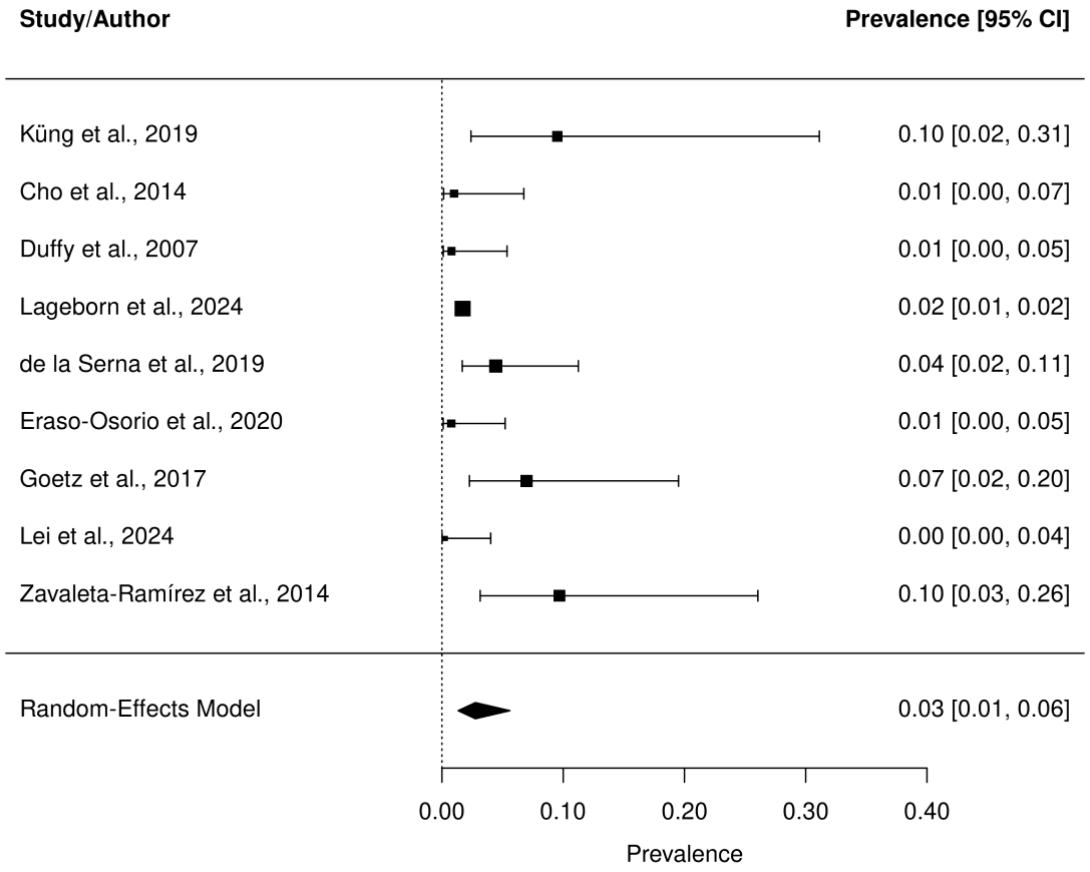


Figure S43. Forest plot of pooled prevalence estimates for agoraphobia among offspring of individuals with bipolar disorder.

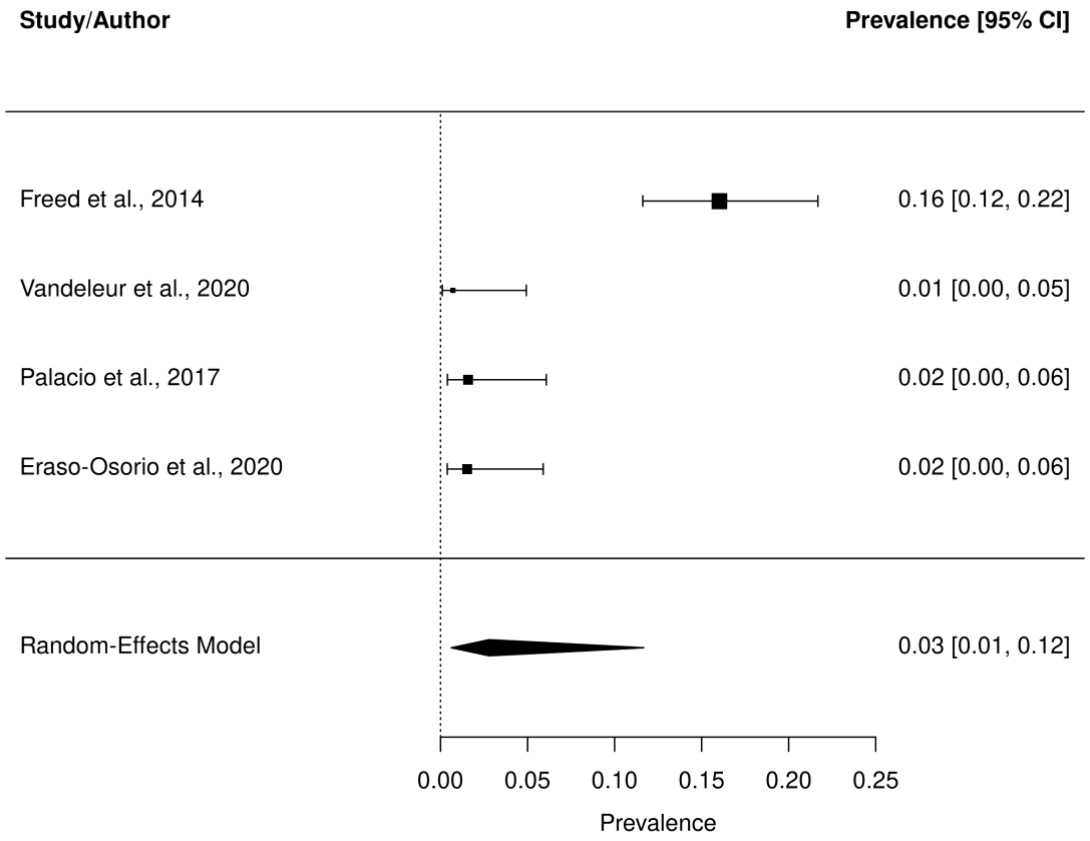


Figure S44. Forest plot of pooled prevalence estimates for anxiety among offspring of individuals with bipolar disorder.

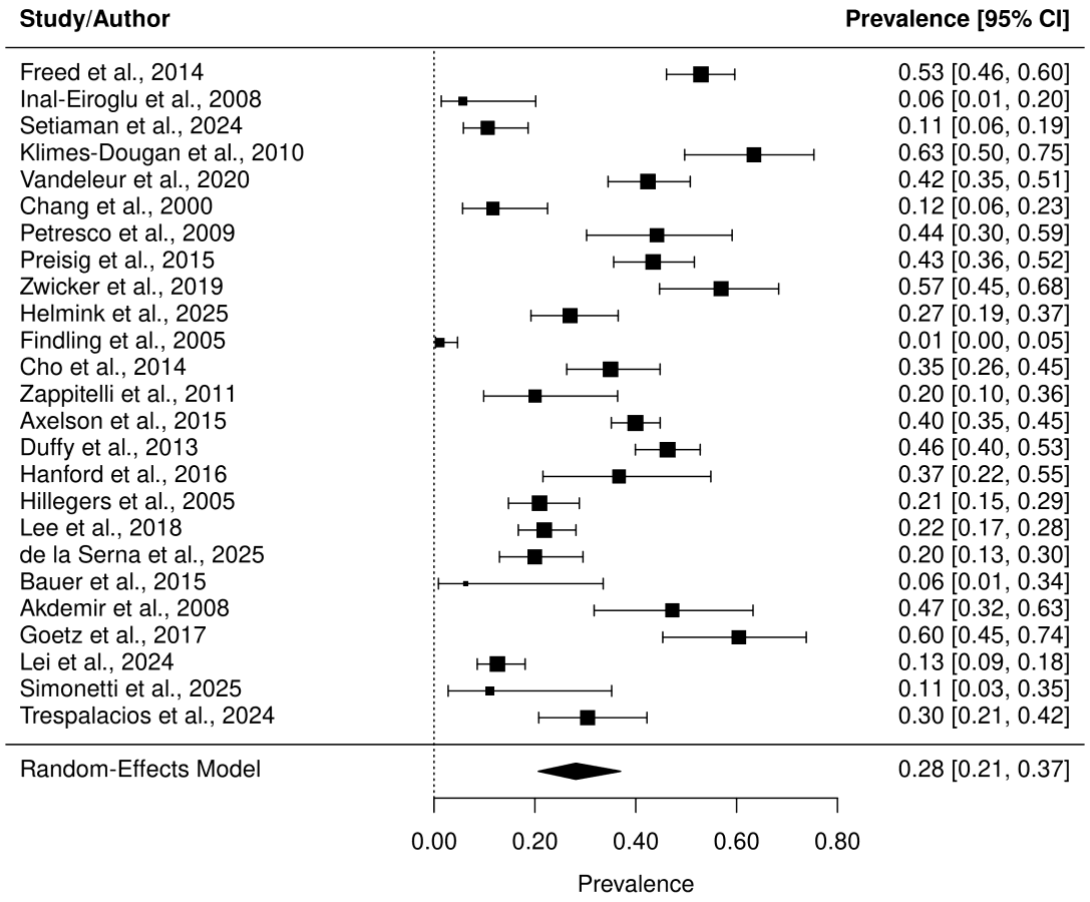


Figure S45. Forest plot of pooled prevalence estimates for neurodevelopmental disorders among offspring of individuals with bipolar disorder.

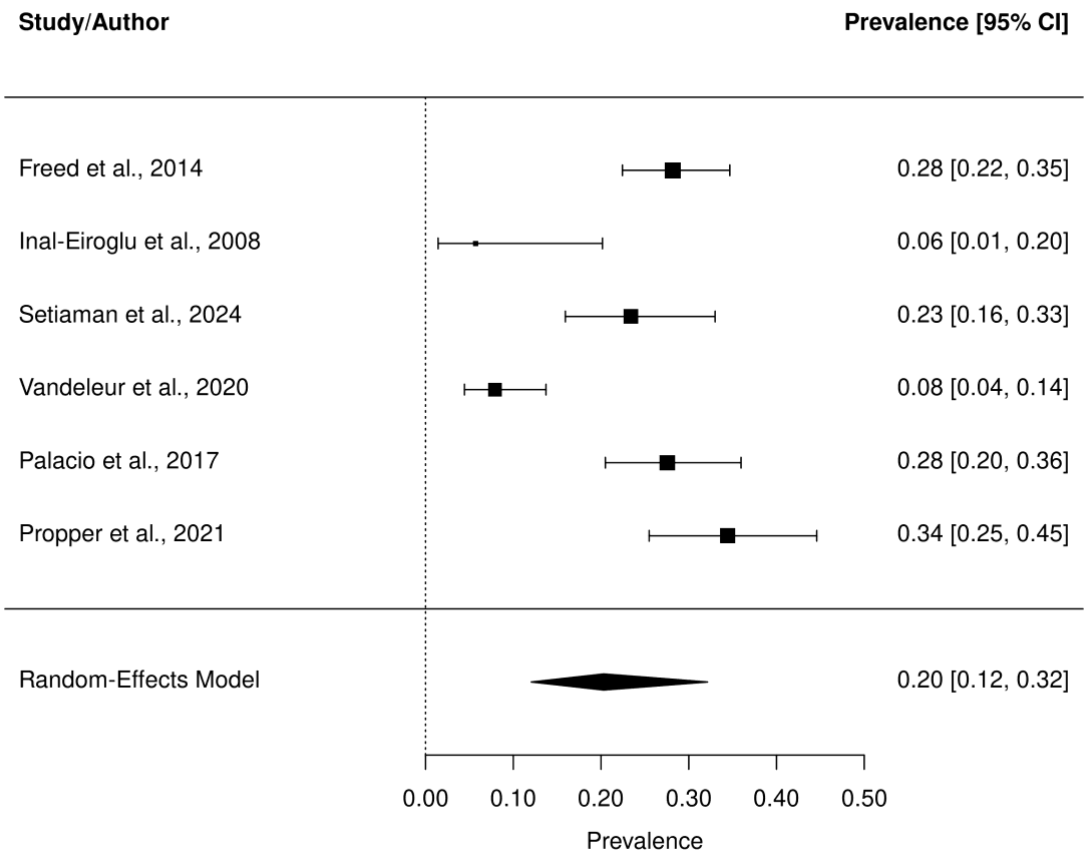


Figure S46. Forest plot of pooled prevalence estimates for obsessive-compulsive disorder among offspring of individuals with bipolar disorder.

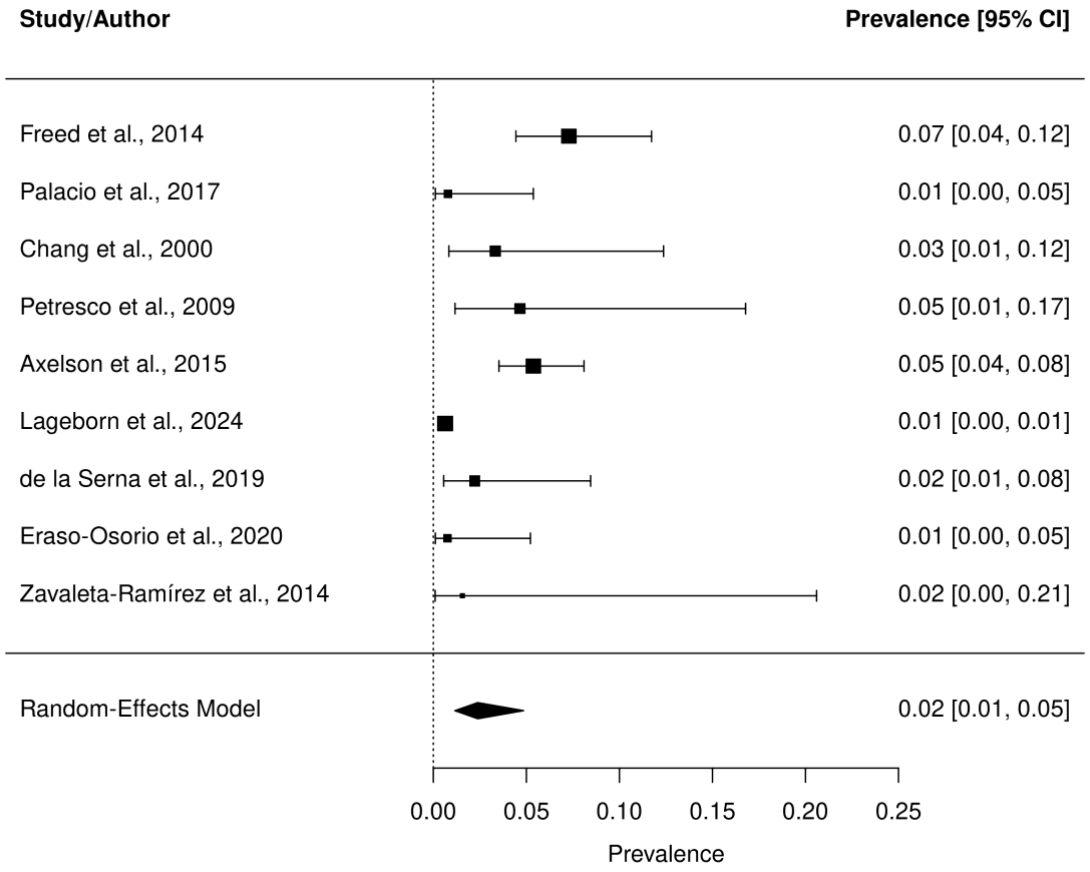


Figure S47. Forest plot of pooled prevalence estimates for oppositional defiant disorder among offspring of individuals with bipolar disorder.

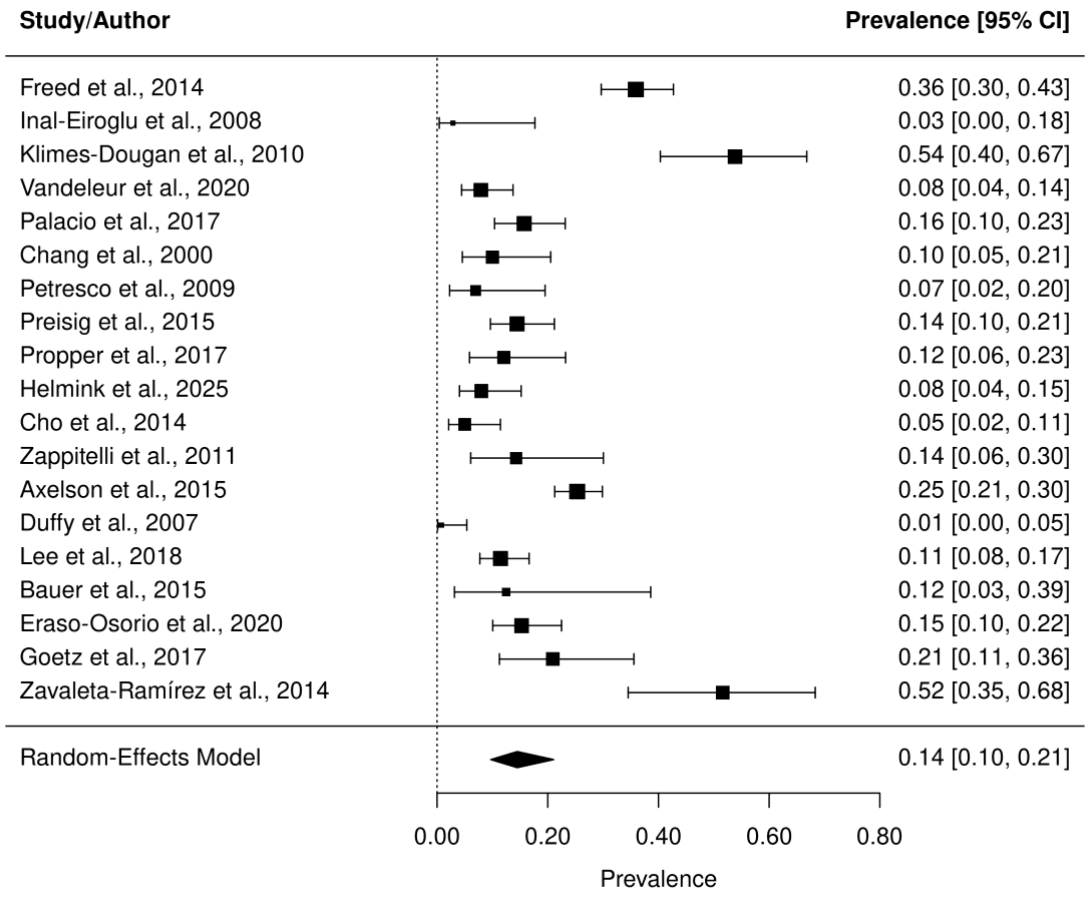


Figure S48. Forest plot of pooled prevalence estimates for other depressive disorders among offspring of individuals with bipolar disorder.

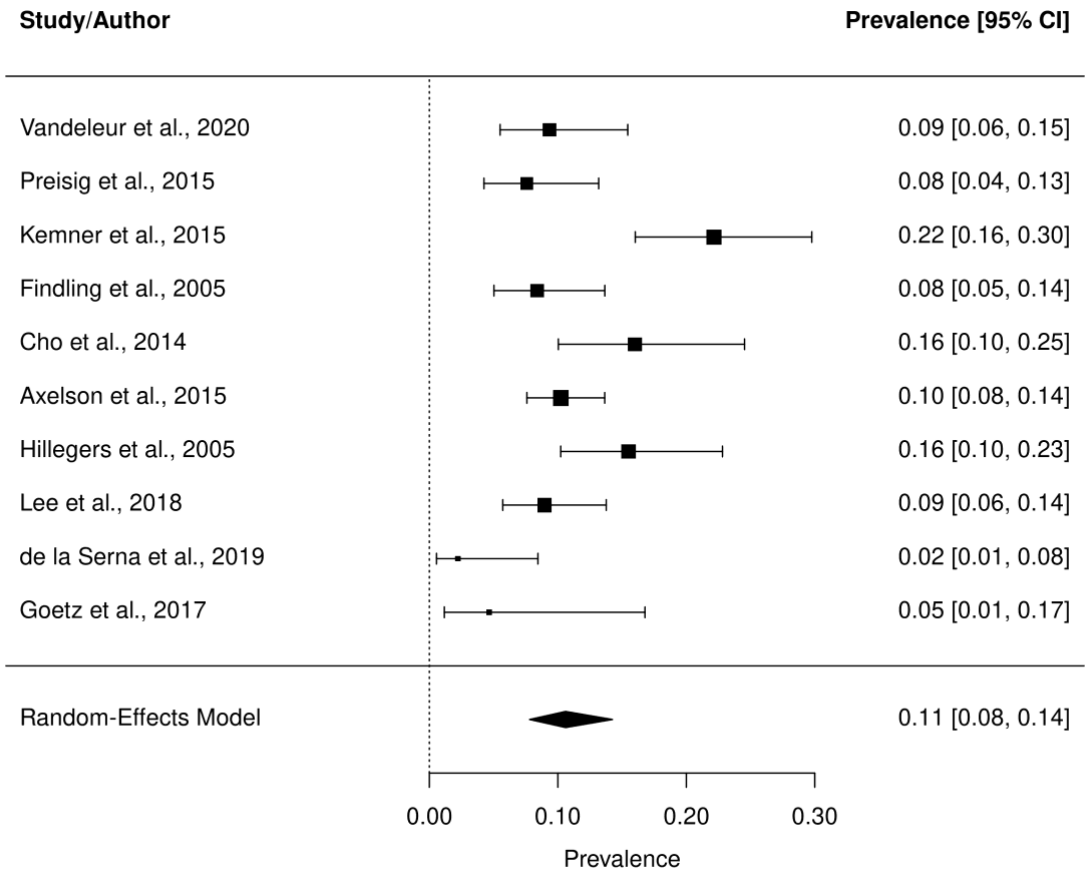


Figure S49. Forest plot of pooled prevalence estimates for panic disorder among offspring of individuals with bipolar disorder.

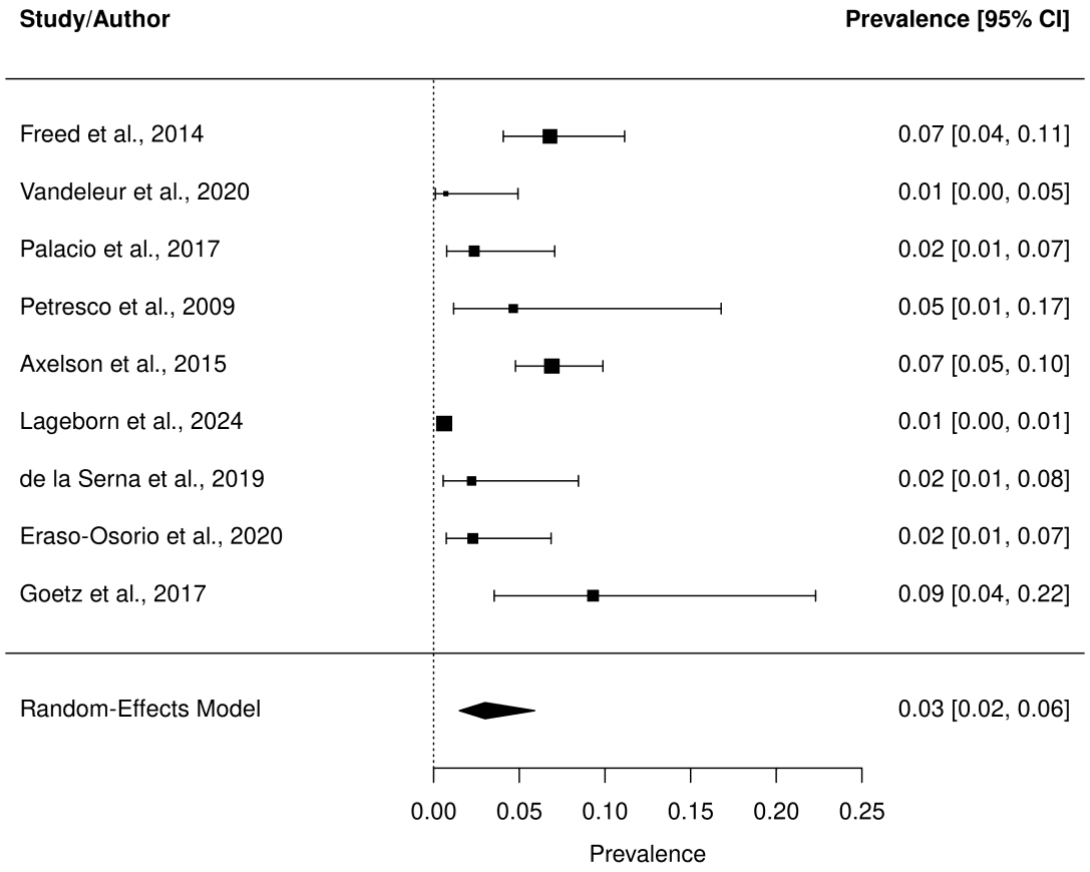


Figure S50. Forest plot of pooled prevalence estimates for post-traumatic stress disorder among offspring of individuals with bipolar disorder.

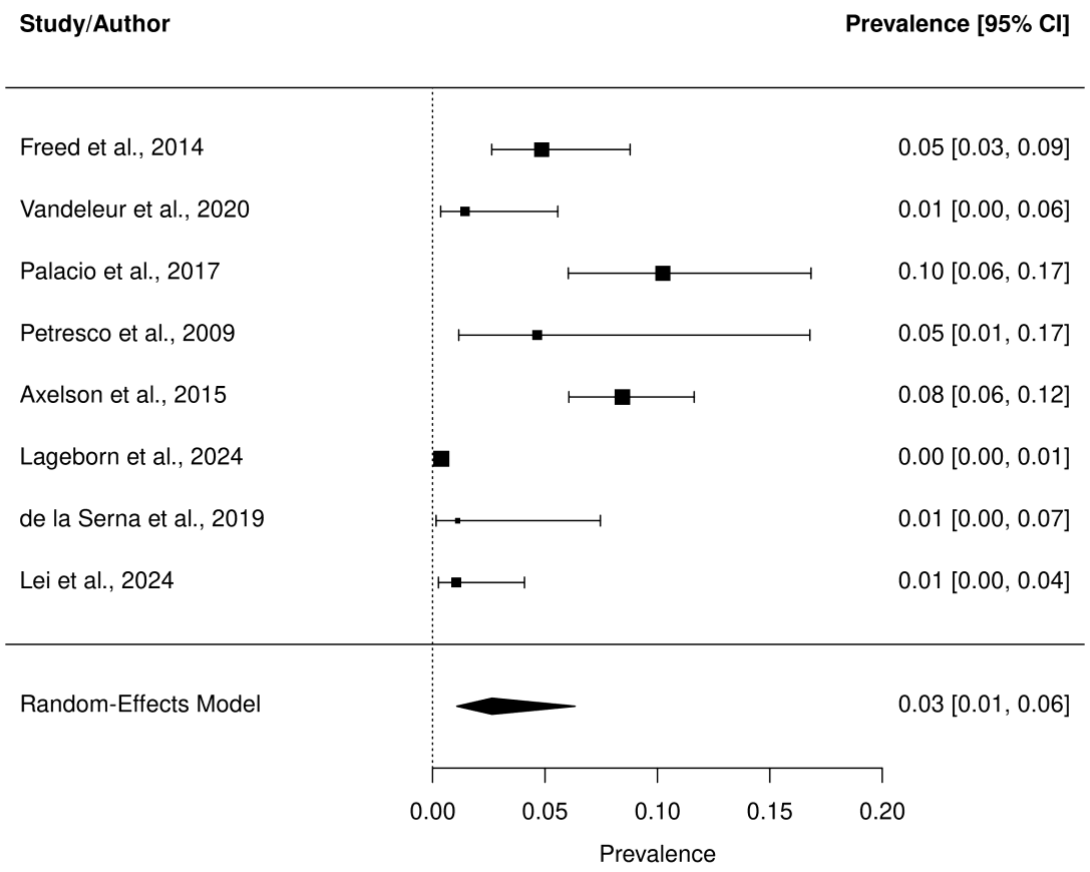


Figure S51. Forest plot of pooled prevalence estimates for schizoaffective disorder among offspring of individuals with bipolar disorder.

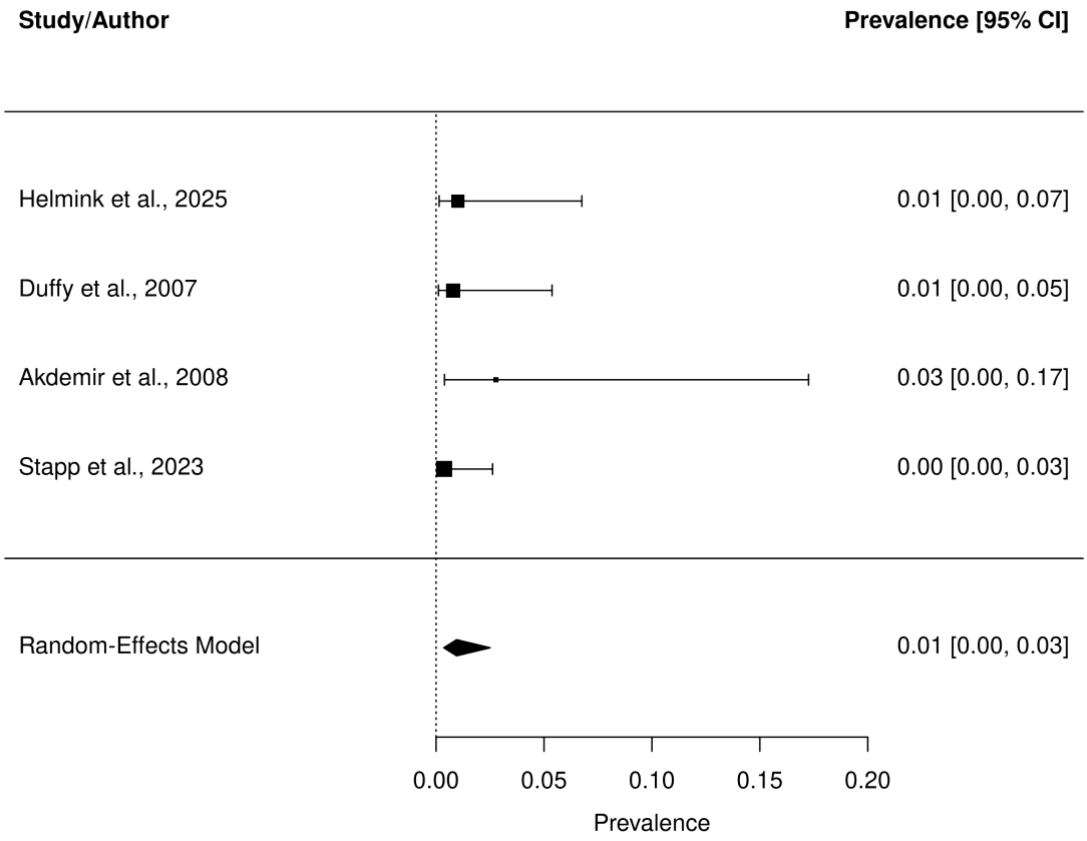


Figure S52. Forest plot of pooled prevalence estimates for separation anxiety disorder among offspring of individuals with bipolar disorder.

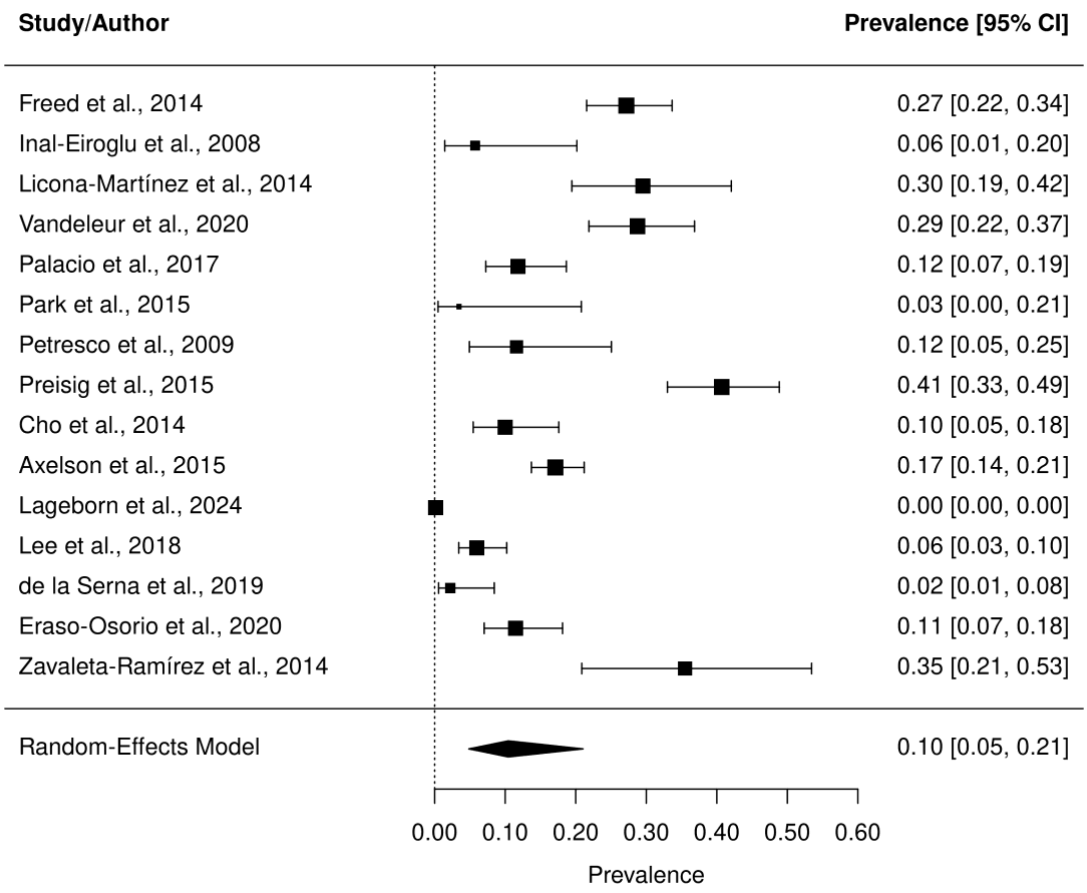


Figure S53. Forest plot of pooled prevalence estimates for social phobia among offspring of individuals with bipolar disorder.

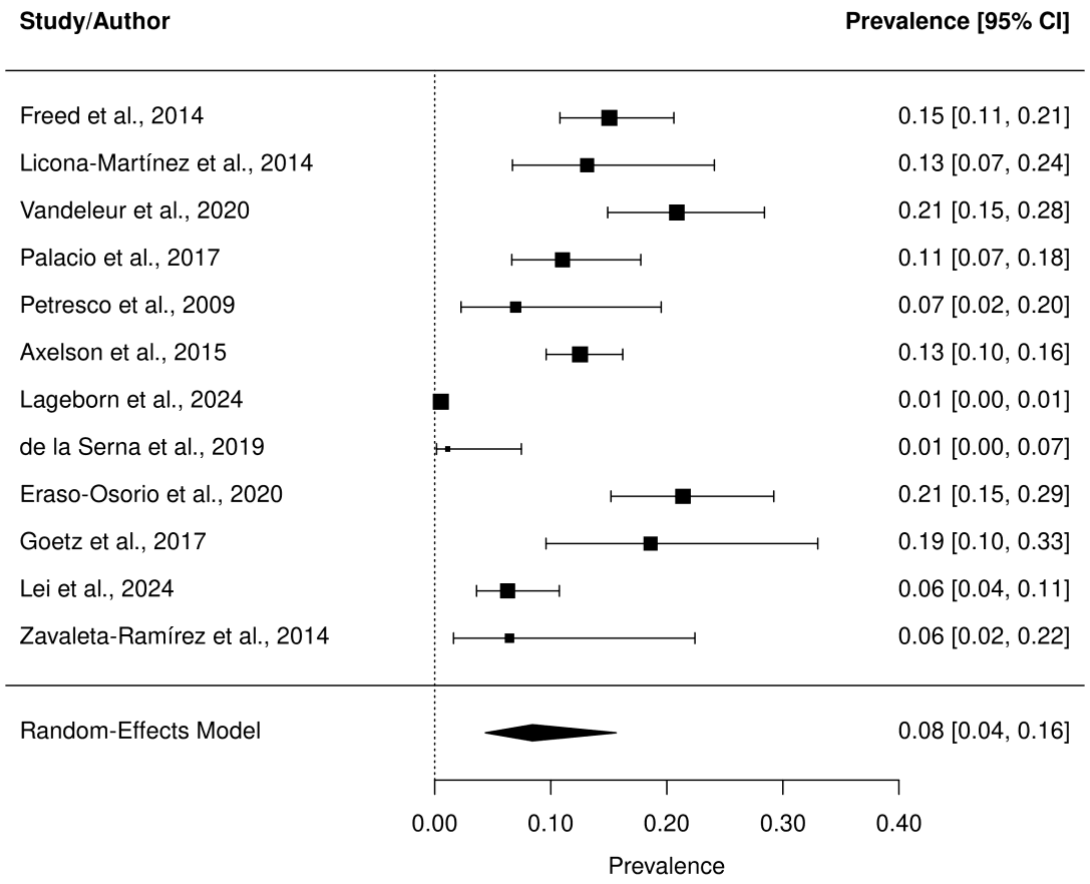


Figure S54. Forest plot of pooled prevalence estimates for specific phobia among offspring of individuals with bipolar disorder.

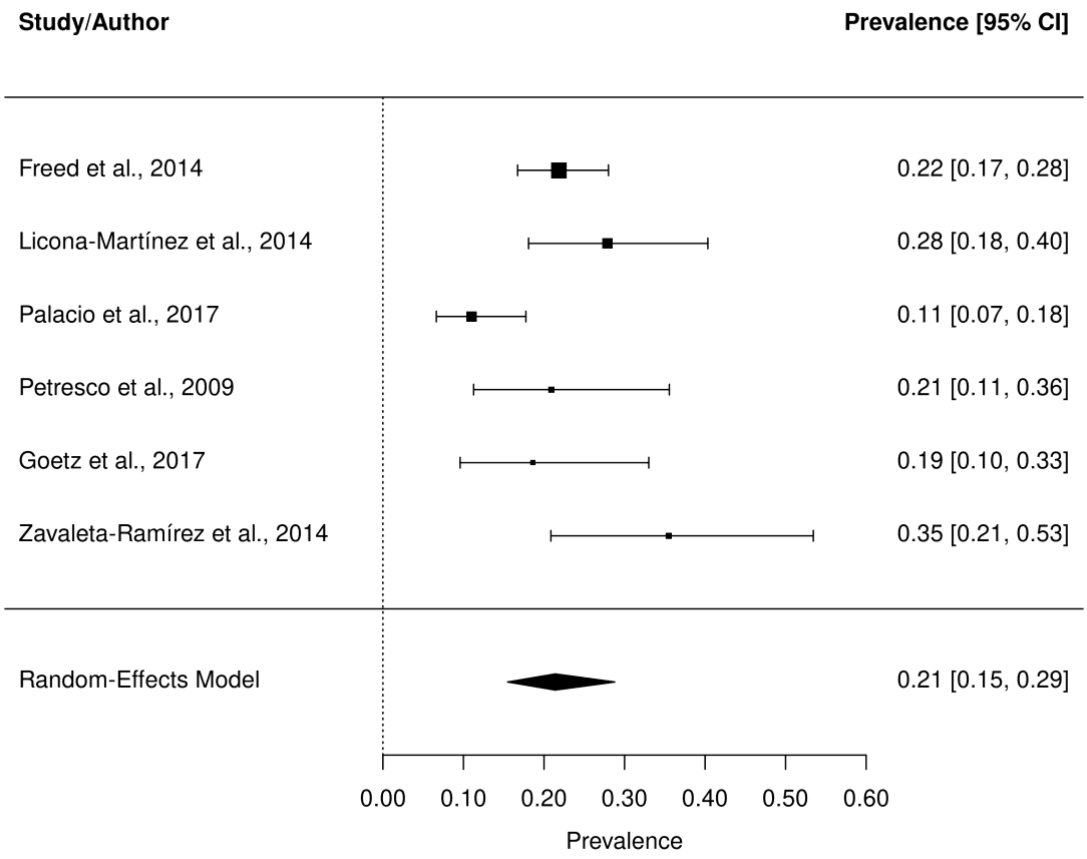


Figure S55. Forest plot of pooled prevalence estimates for substance use disorders among offspring of individuals with bipolar disorder.

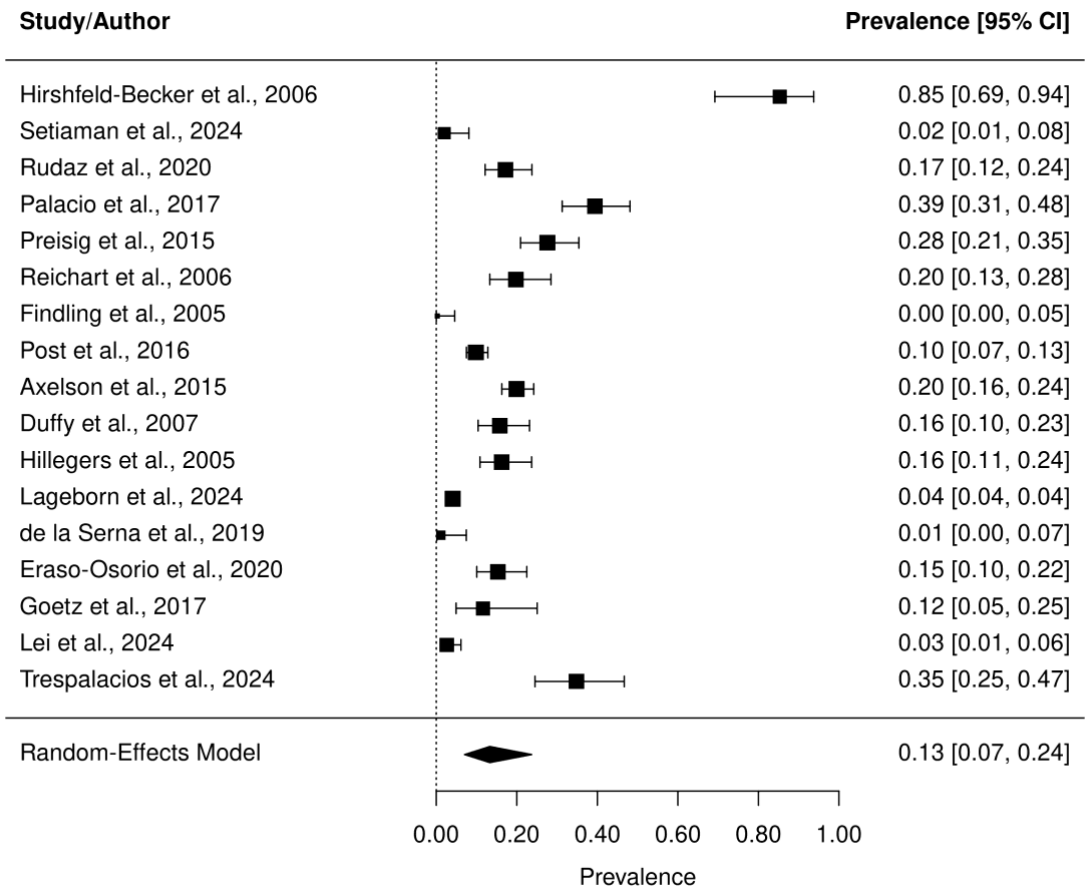


Figure S56. Funnel plot for prevalence estimates of attention-deficit/hyperactivity disorder (ADHD) among offspring of individuals with bipolar disorder.

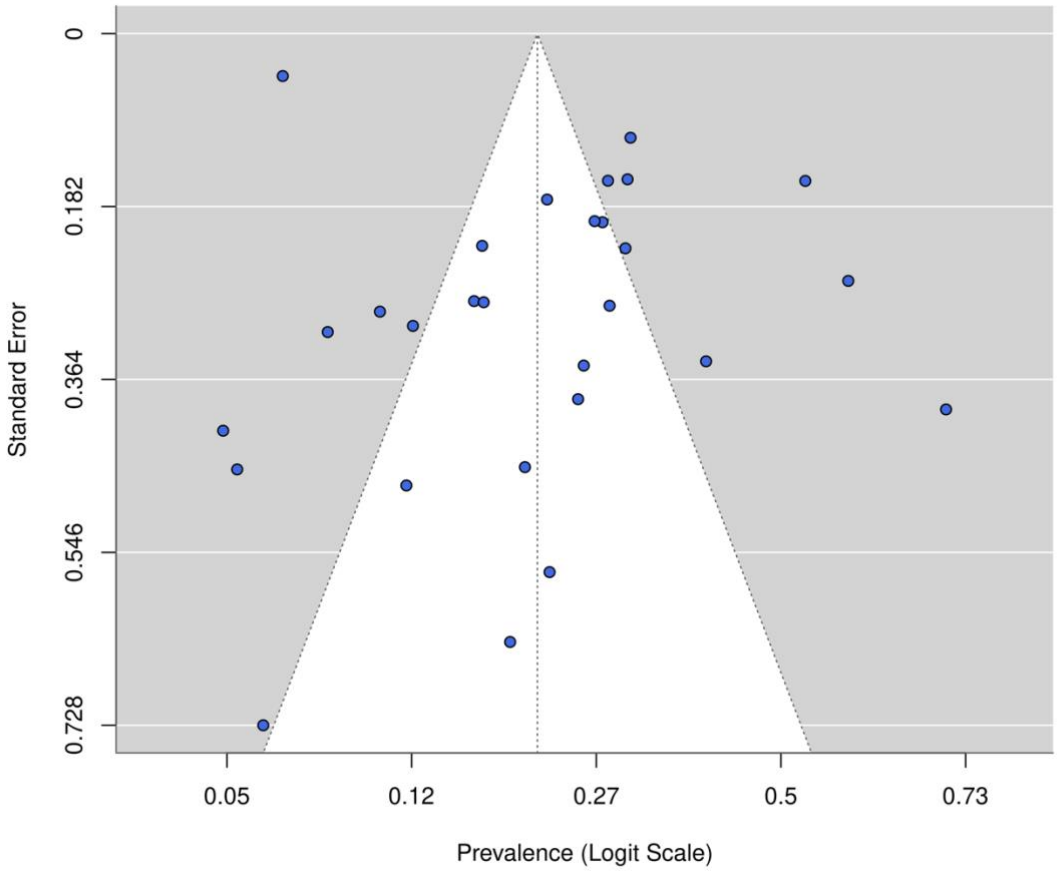


Figure S57. Funnel plot for prevalence estimates of any anxiety disorder among offspring of individuals with bipolar disorder.

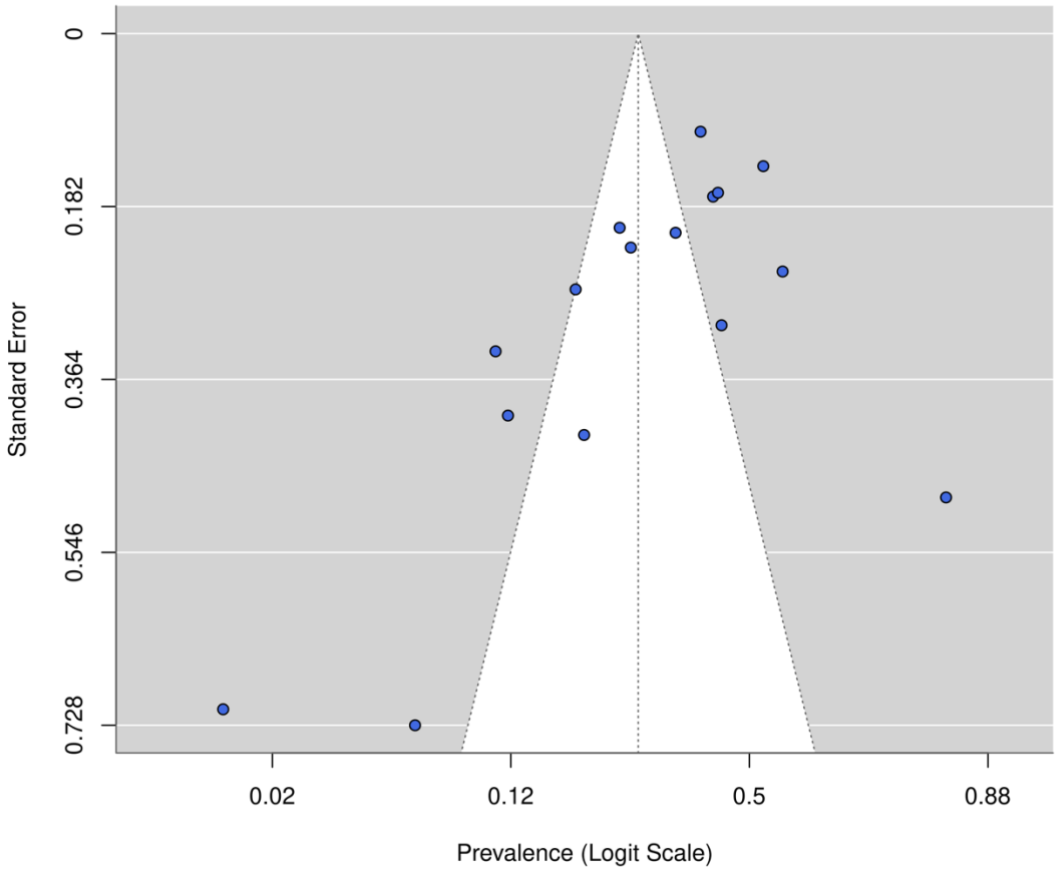


Figure S58. Funnel plot for prevalence estimates of anxiety disorder among offspring of individuals with bipolar disorder.

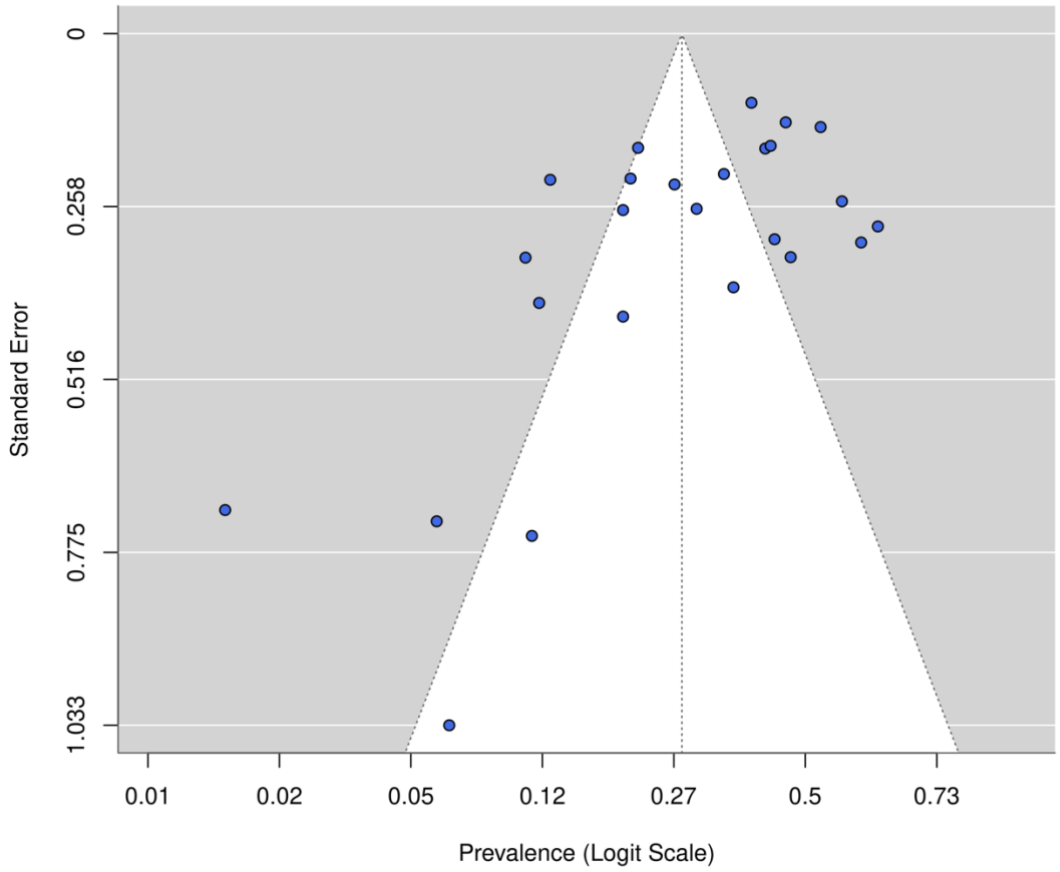


Figure S59. Funnel plot for prevalence estimates of depressive disorders among offspring of individuals with bipolar disorder.

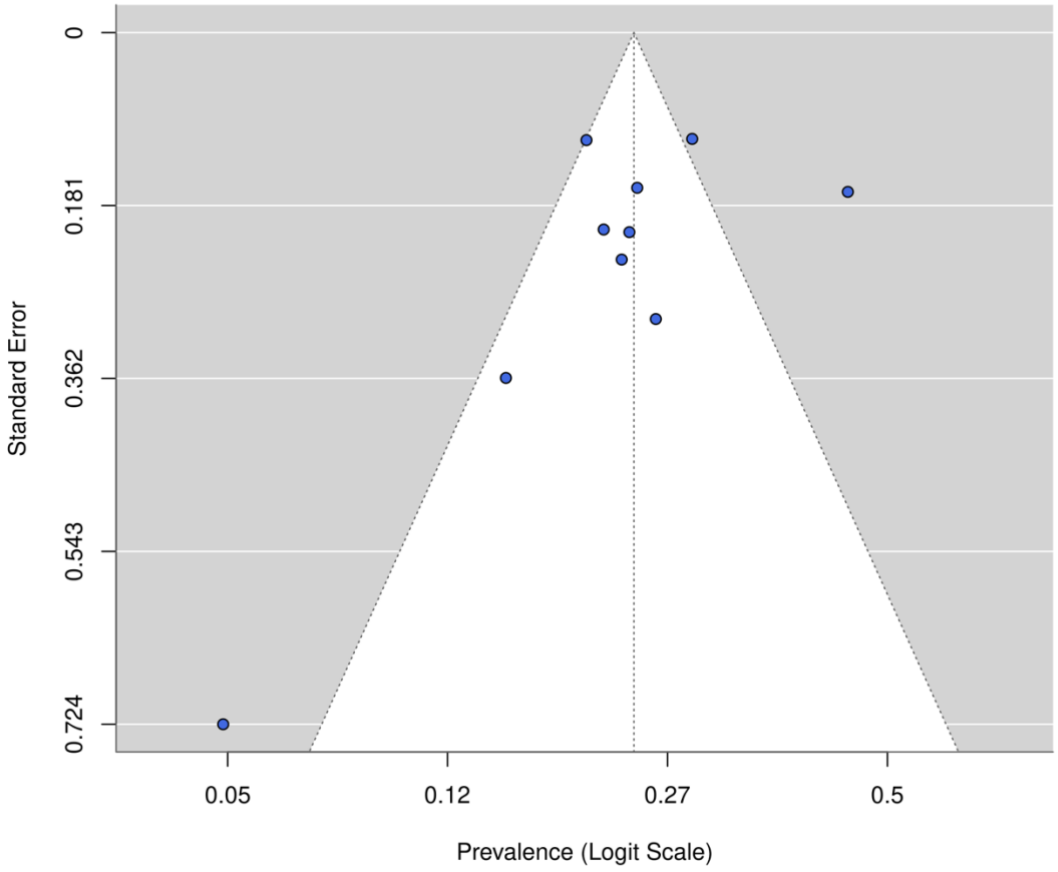


Figure S60. Funnel plot for prevalence estimates of bipolar spectrum disorders among offspring of individuals with bipolar disorder.

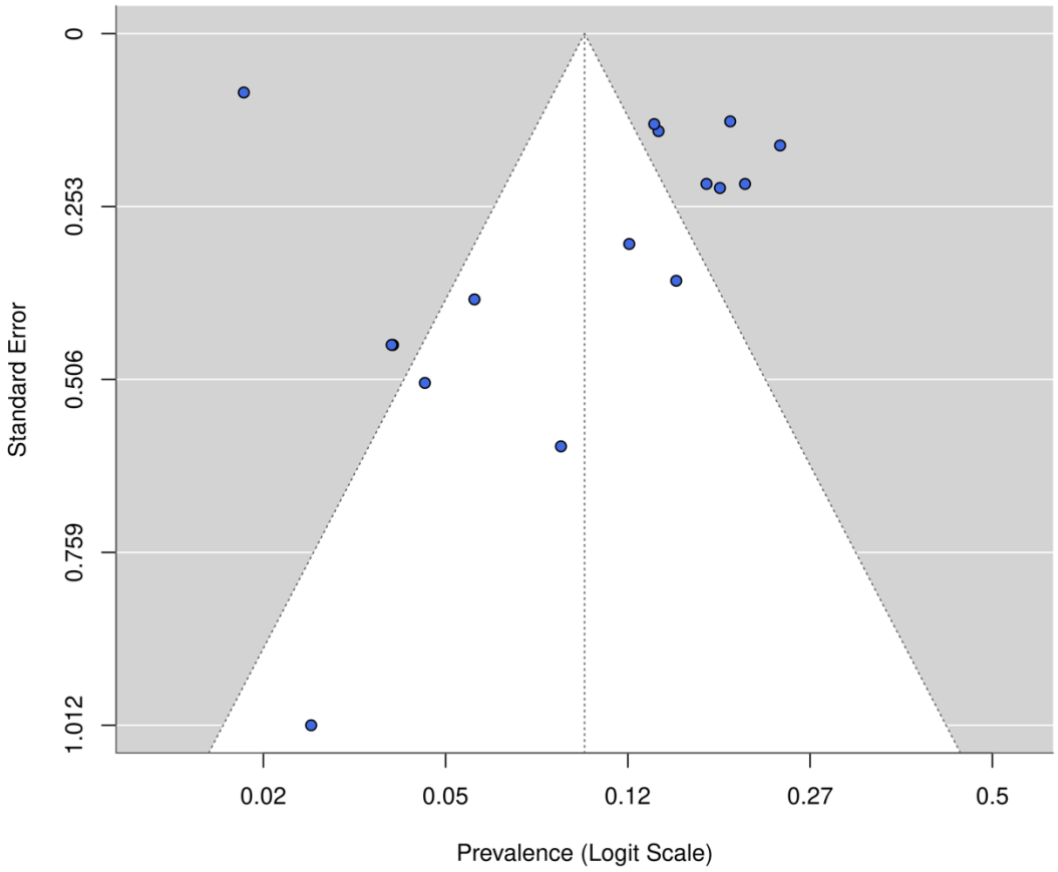


Figure S61. Funnel plot for prevalence estimates of bipolar I disorder among offspring of individuals with bipolar disorder.

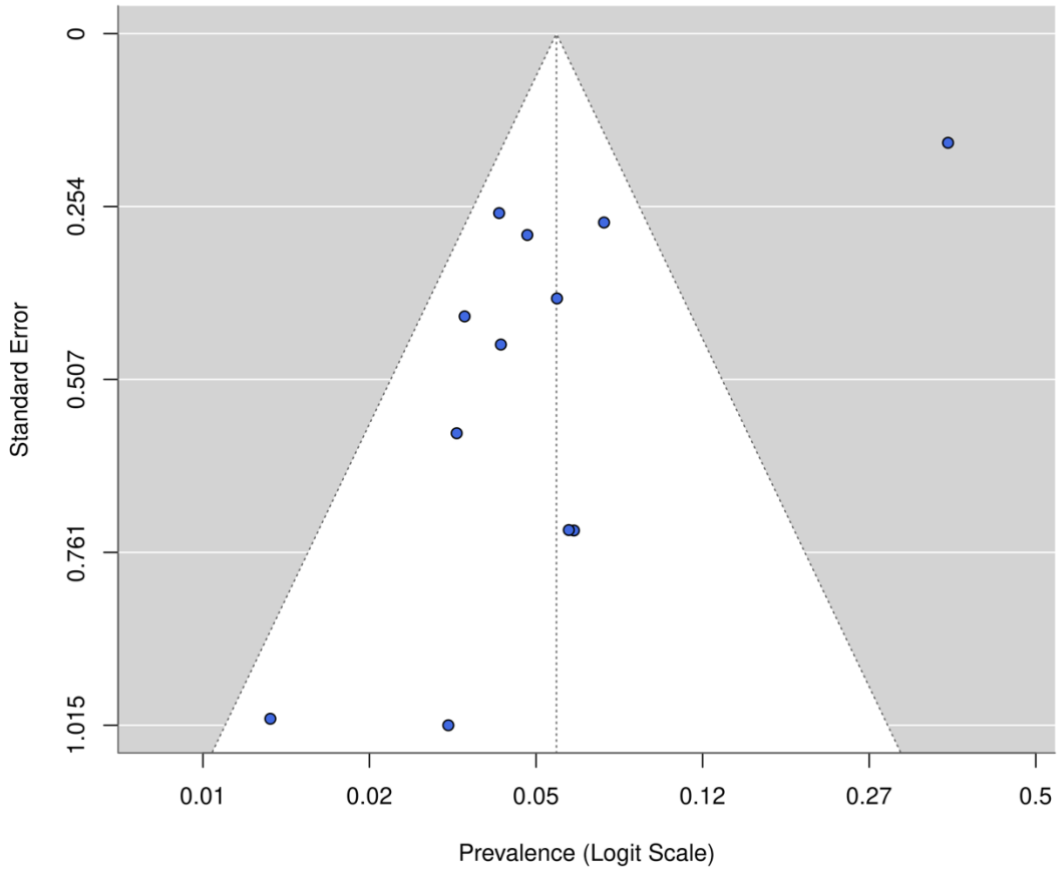


Figure S62. Funnel plot for prevalence estimates of bipolar II disorder among offspring of individuals with bipolar disorder.

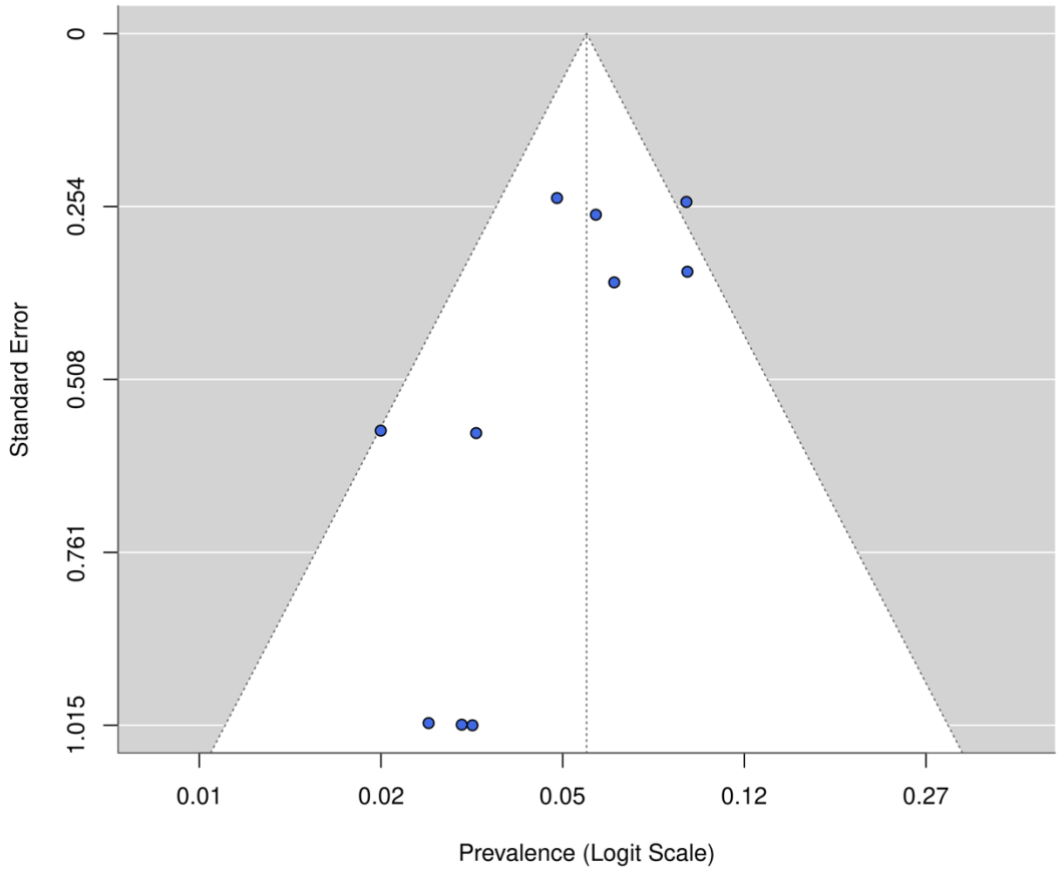


Figure S63. Funnel plot for prevalence estimates of bipolar disorder not otherwise specified (BD-NOS) among offspring of individuals with bipolar disorder.

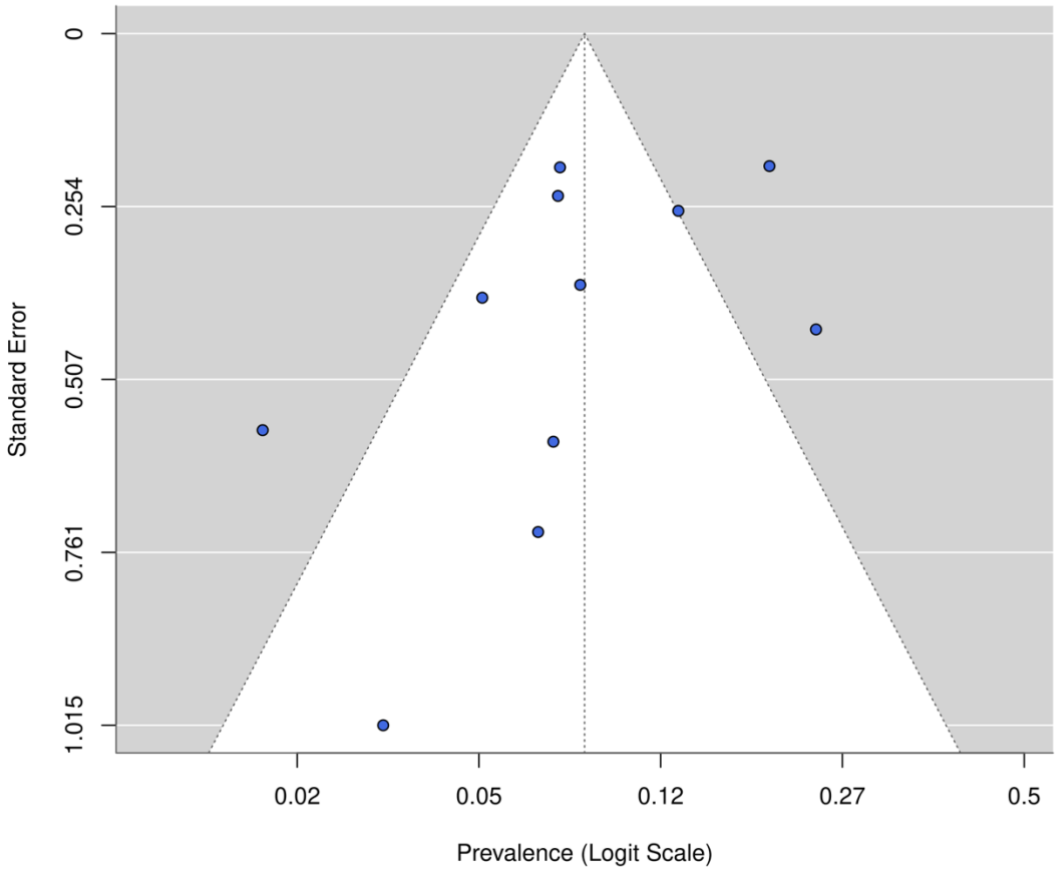


Figure S64. Funnel plot for prevalence estimates of conduct disorder among offspring of individuals with bipolar disorder.

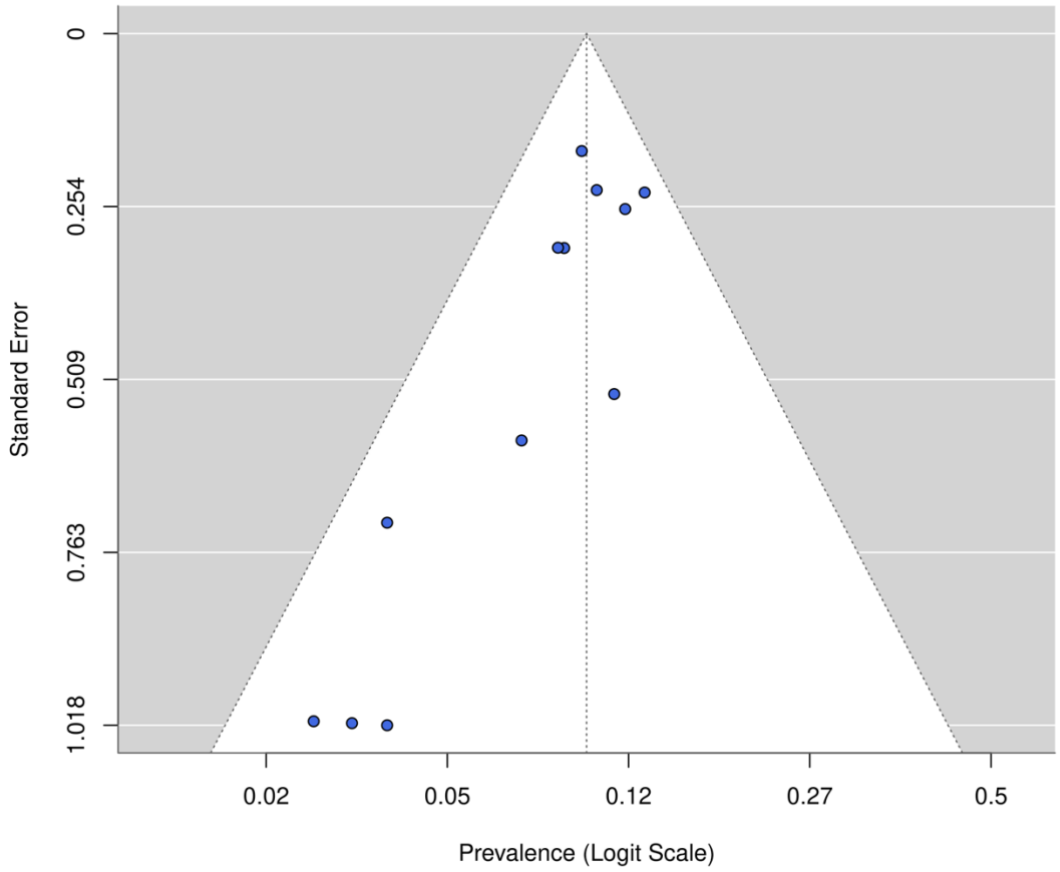


Figure S65. Funnel plot for prevalence estimates of attention-deficit/hyperactivity disorder (ADHD) among offspring of individuals with bipolar disorder.

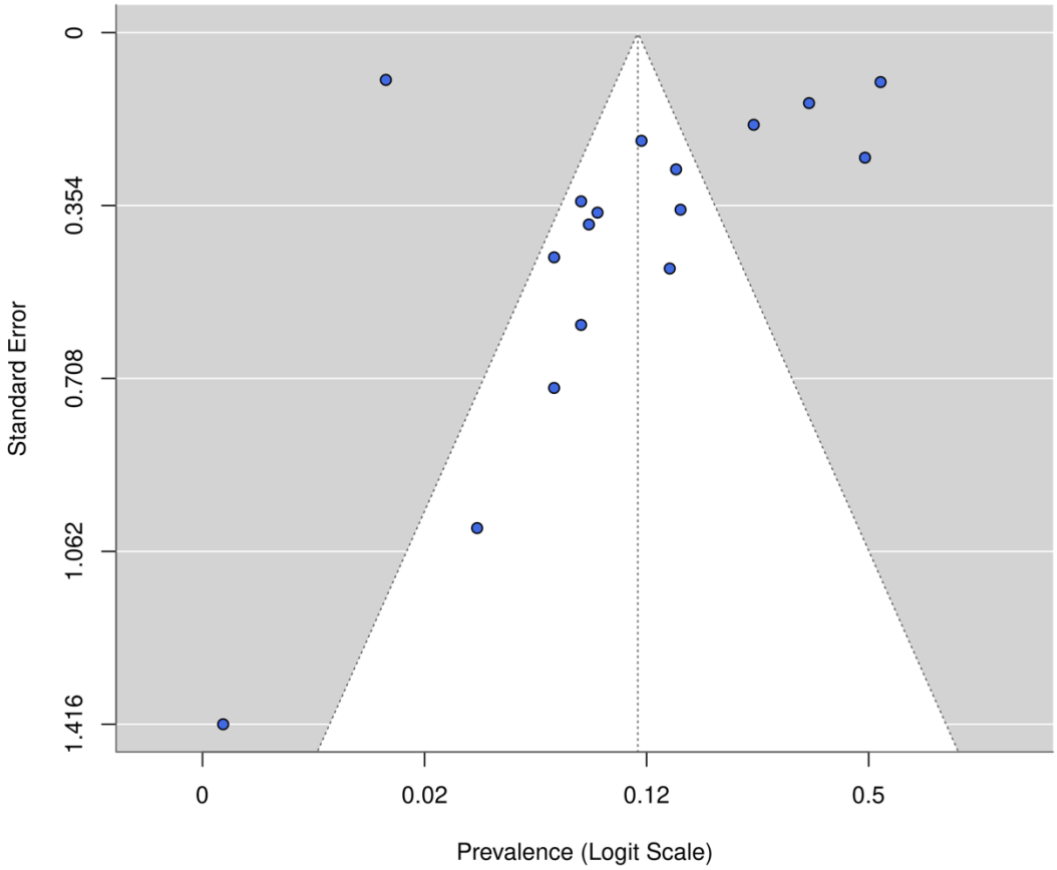


Figure S66. Funnel plot for prevalence estimates of dysthimia among offspring of individuals with bipolar disorder.

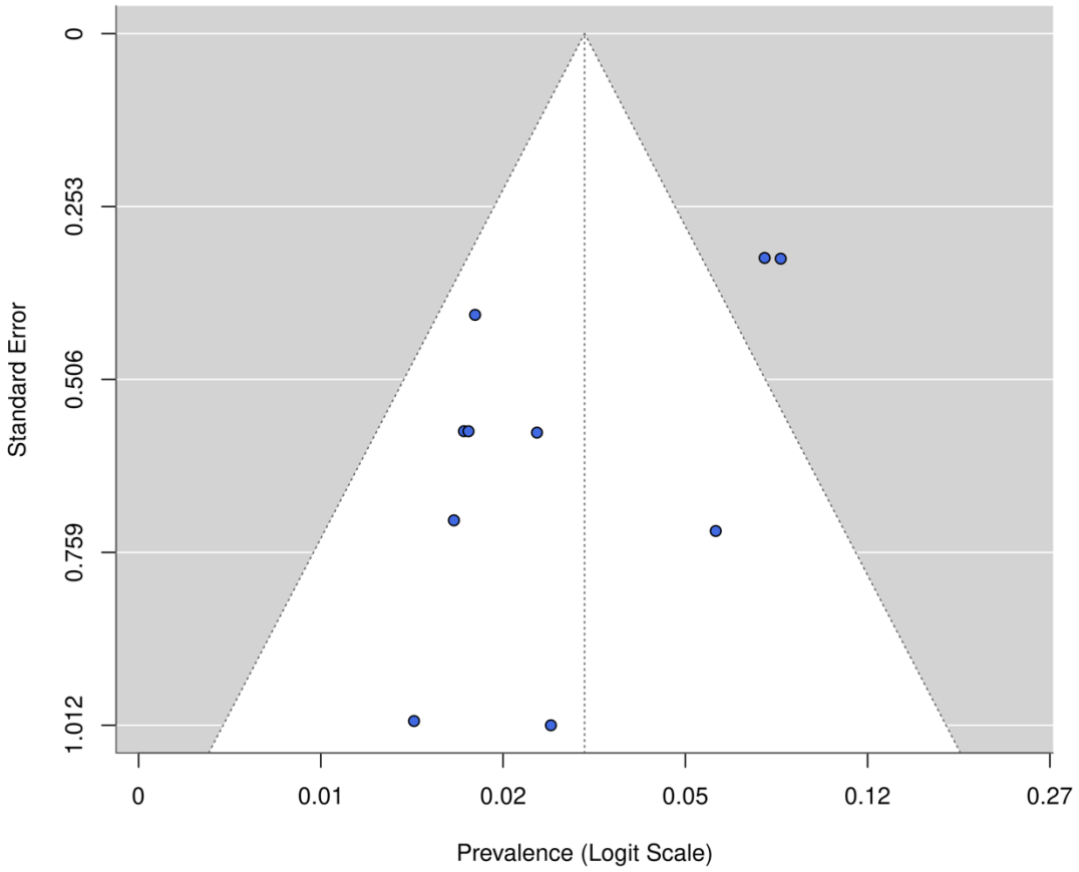


Figure S67. Funnel plot for prevalence estimates of generalized anxiety disorder among offspring of individuals with bipolar disorder.

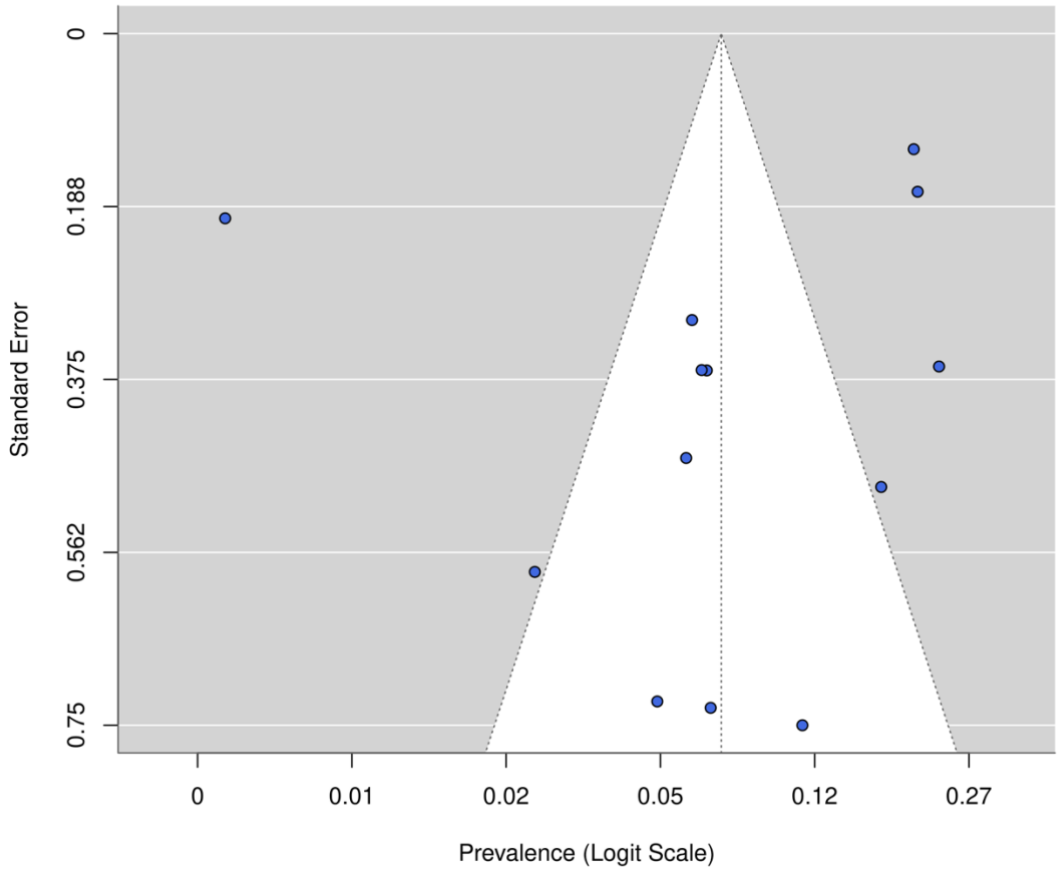


Figure S68. Funnel plot for prevalence estimates of MDD among offspring of individuals with bipolar disorder.

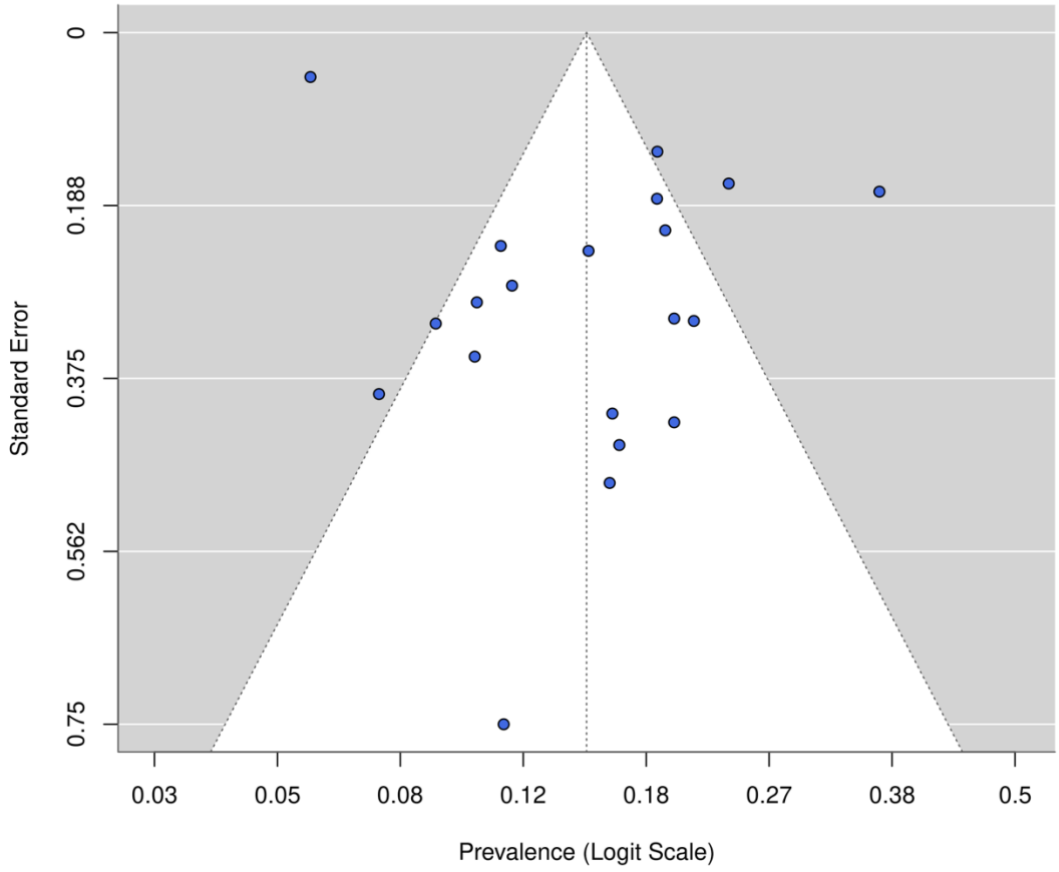


Figure S69. Funnel plot for prevalence estimates of mental disorders offspring of individuals with bipolar disorder.

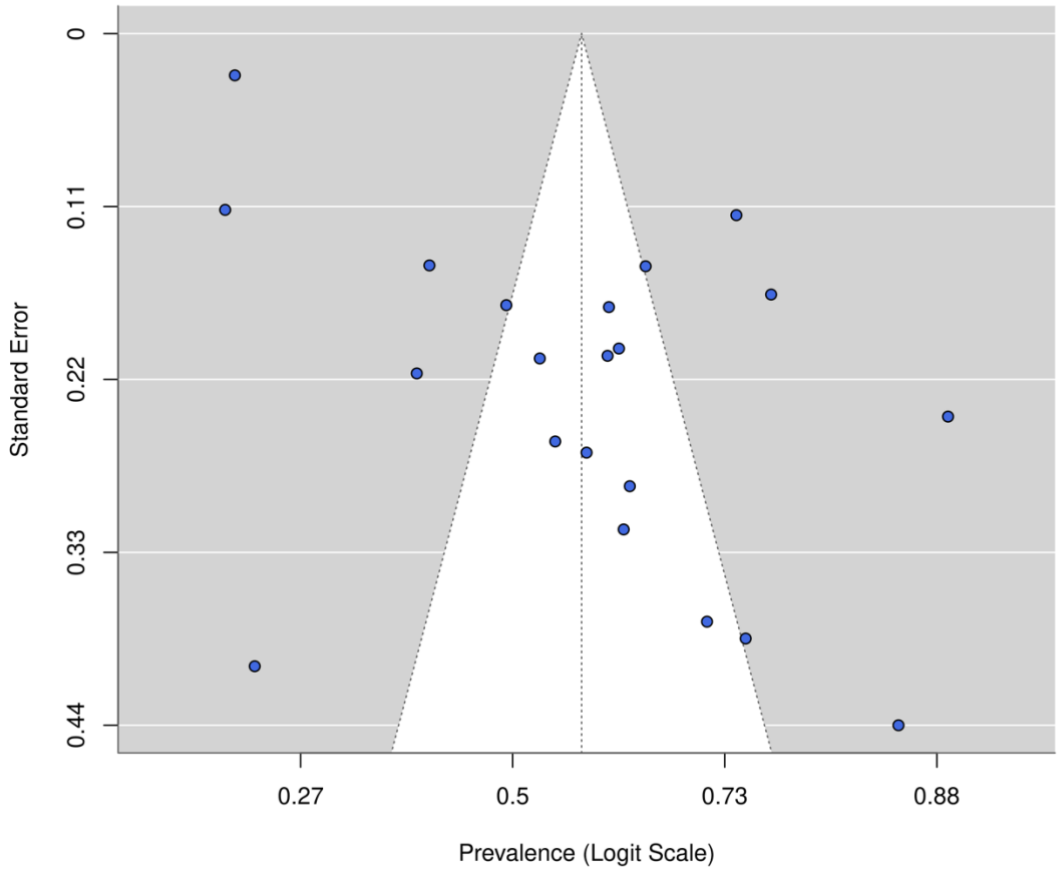


Figure S70. Funnel plot for prevalence estimates of mood disorders among offspring of individuals with bipolar disorder.

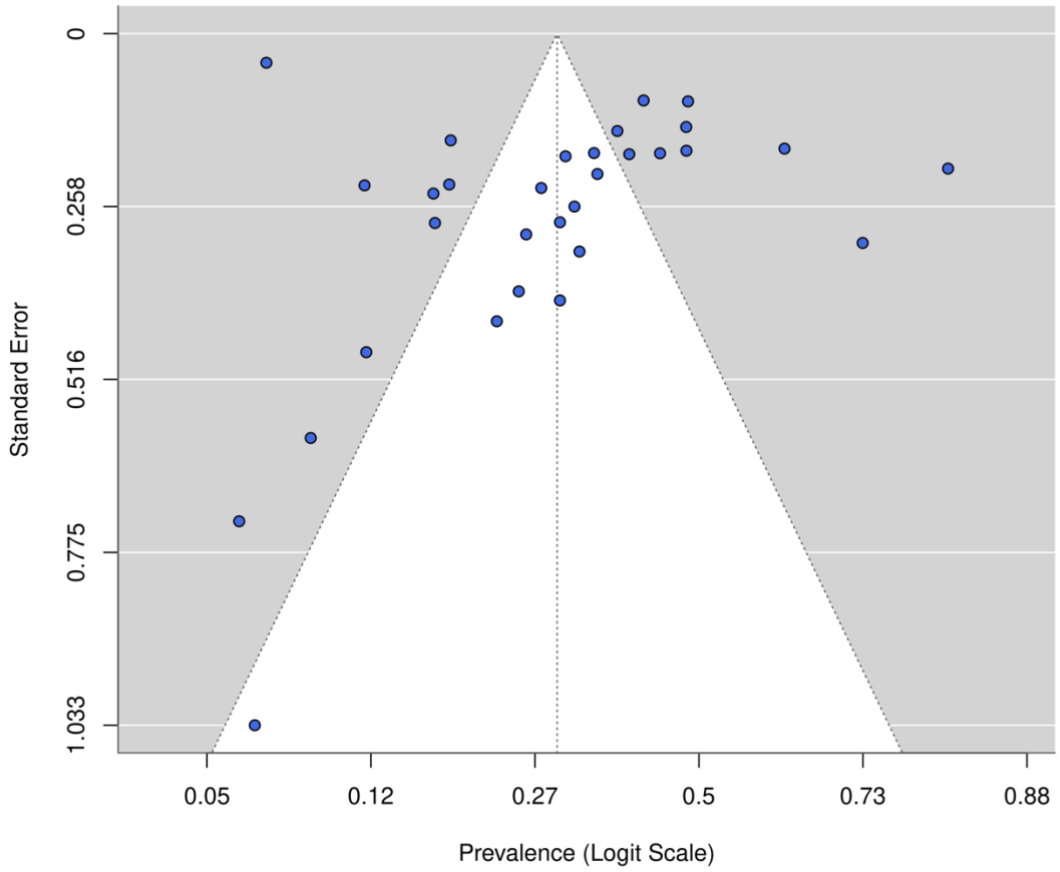


Figure S71. **Funnel plot for prevalence estimates of conduct disorder among offspring of individuals with bipolar disorder.**

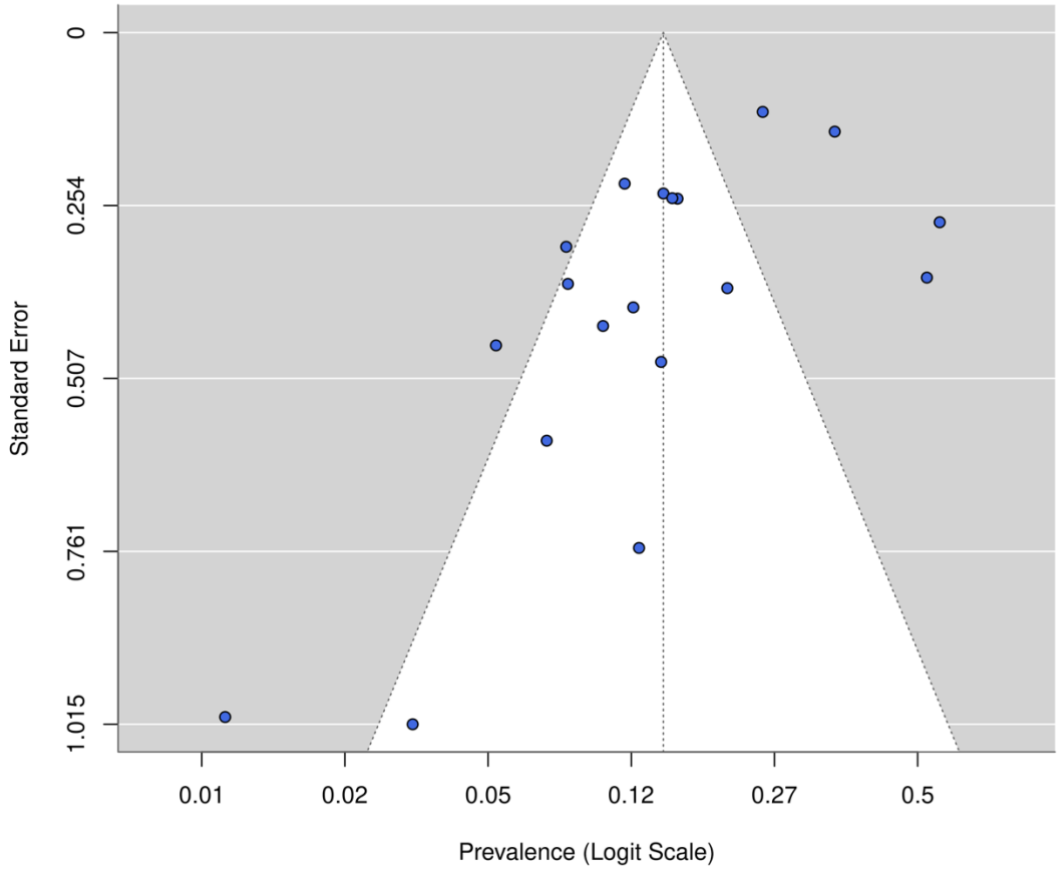


Figure S72. **Funnel plot for prevalence estimates of other depressive disorders among offspring of individuals with bipolar disorder.**

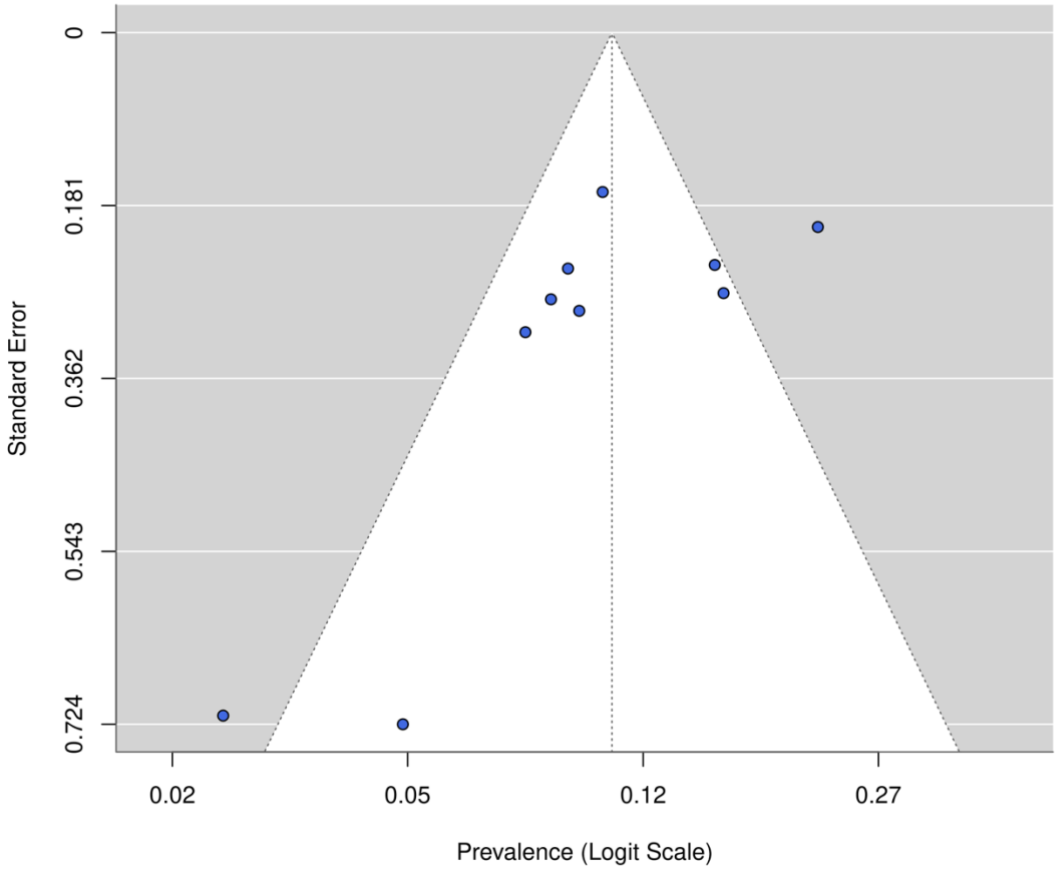


Figure S73. **Funnel plot for prevalence estimates of separation anxiety among offspring of individuals with bipolar disorder.**

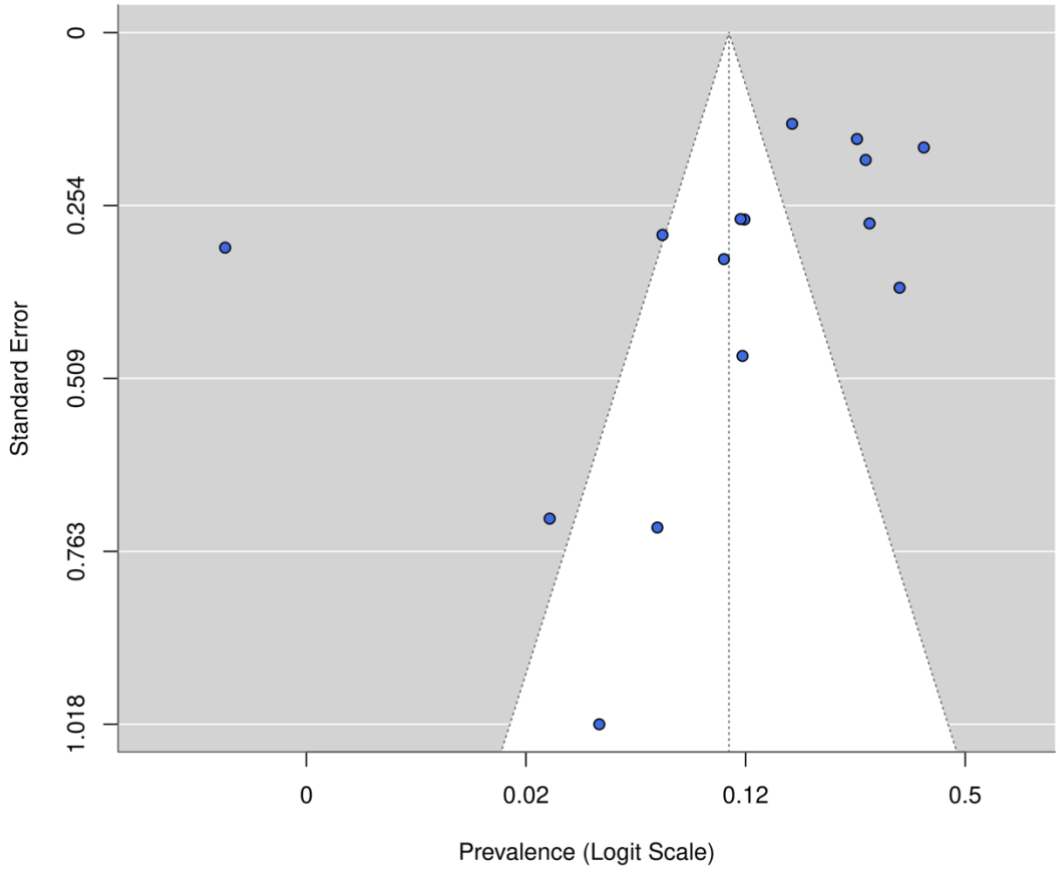


Figure S74. **Funnel plot for prevalence estimates of social phobia among offspring of individuals with bipolar disorder.**

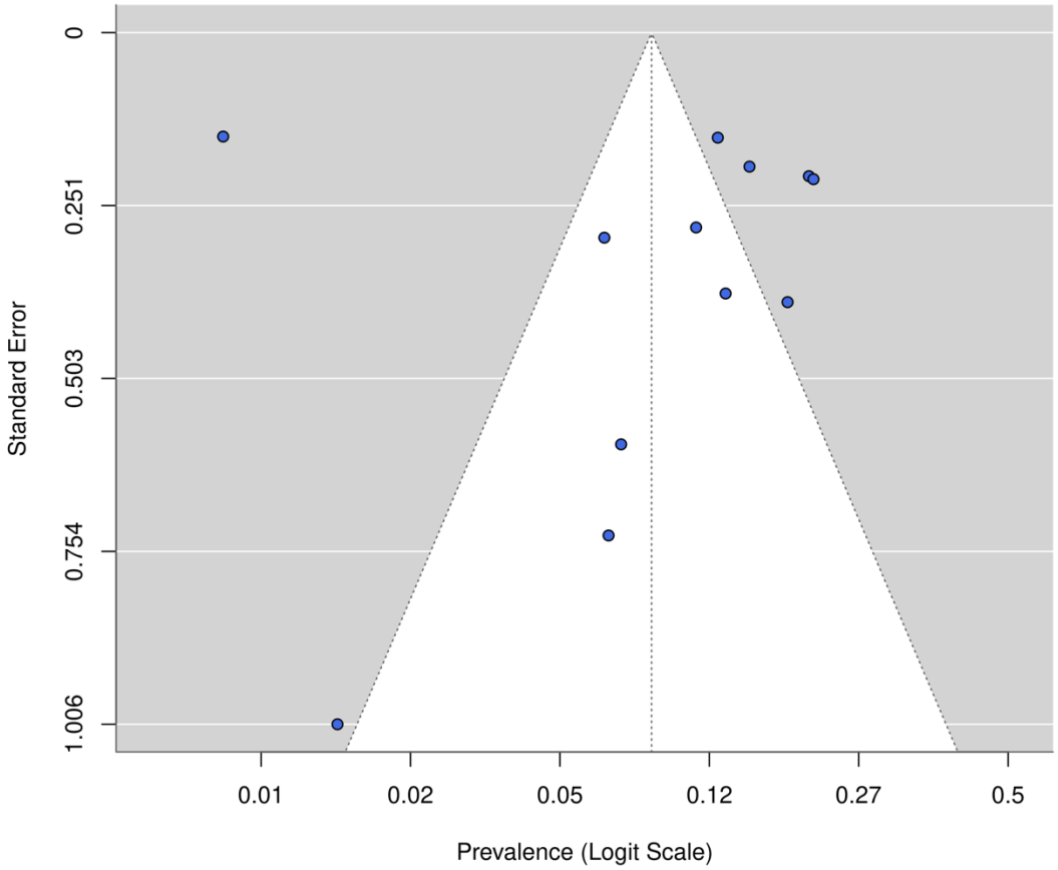


Figure S75. **Funnel plot for prevalence estimates of substance use disorders among offspring of individuals with bipolar disorder.**

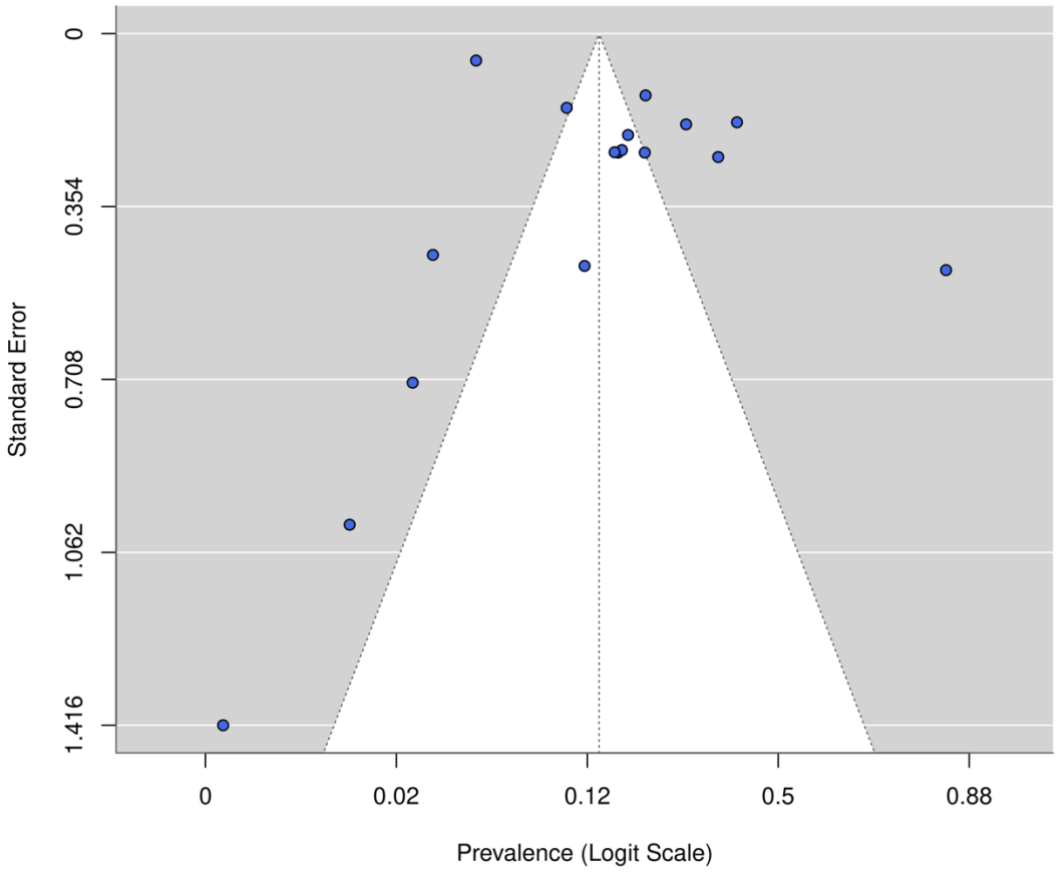


Figure S76. **Trim-and-fill funnel plot for prevalence estimates of bipolar spectrum disorders among offspring of individuals with bipolar disorder.**

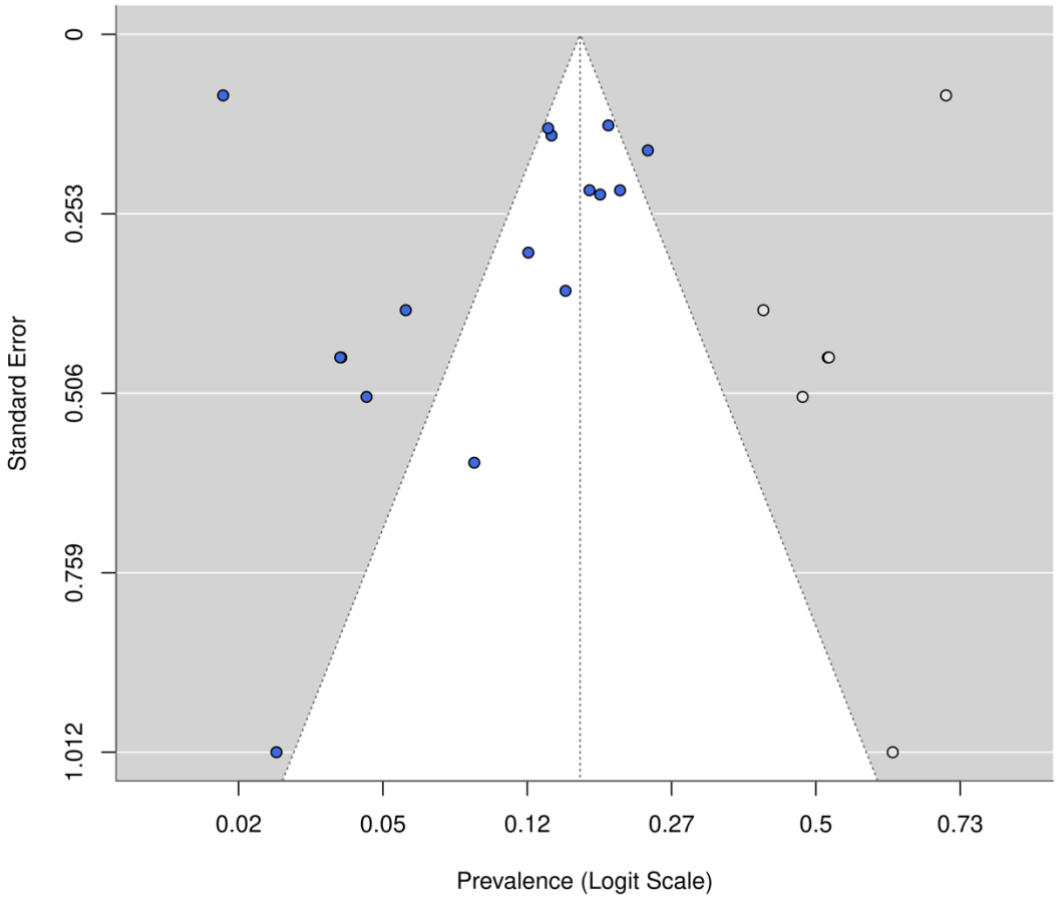


Figure S77. . **Funnel plot for prevalence estimates of BD spectrum among offspring of individuals with bipolar disorder.**

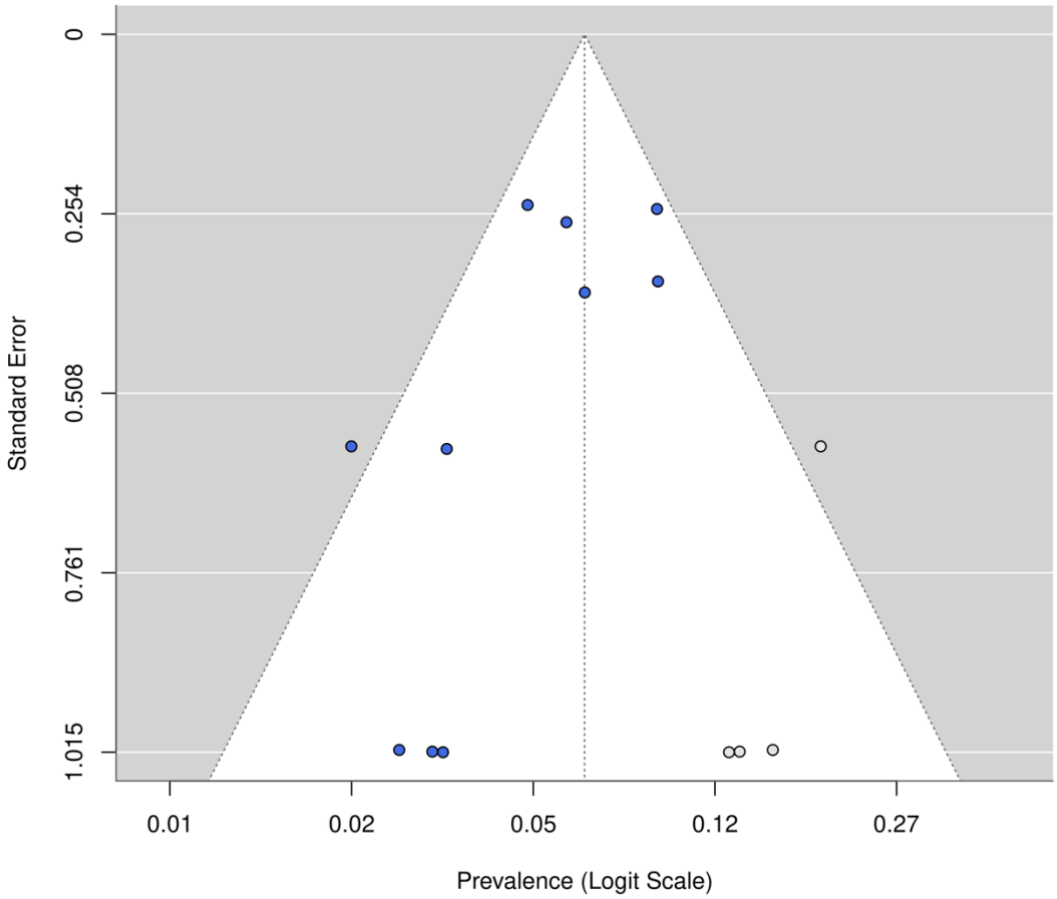


Figure S78. **Trim-and-fill funnel plot for prevalence estimates of conduct disorder among offspring of individuals with bipolar disorder.**

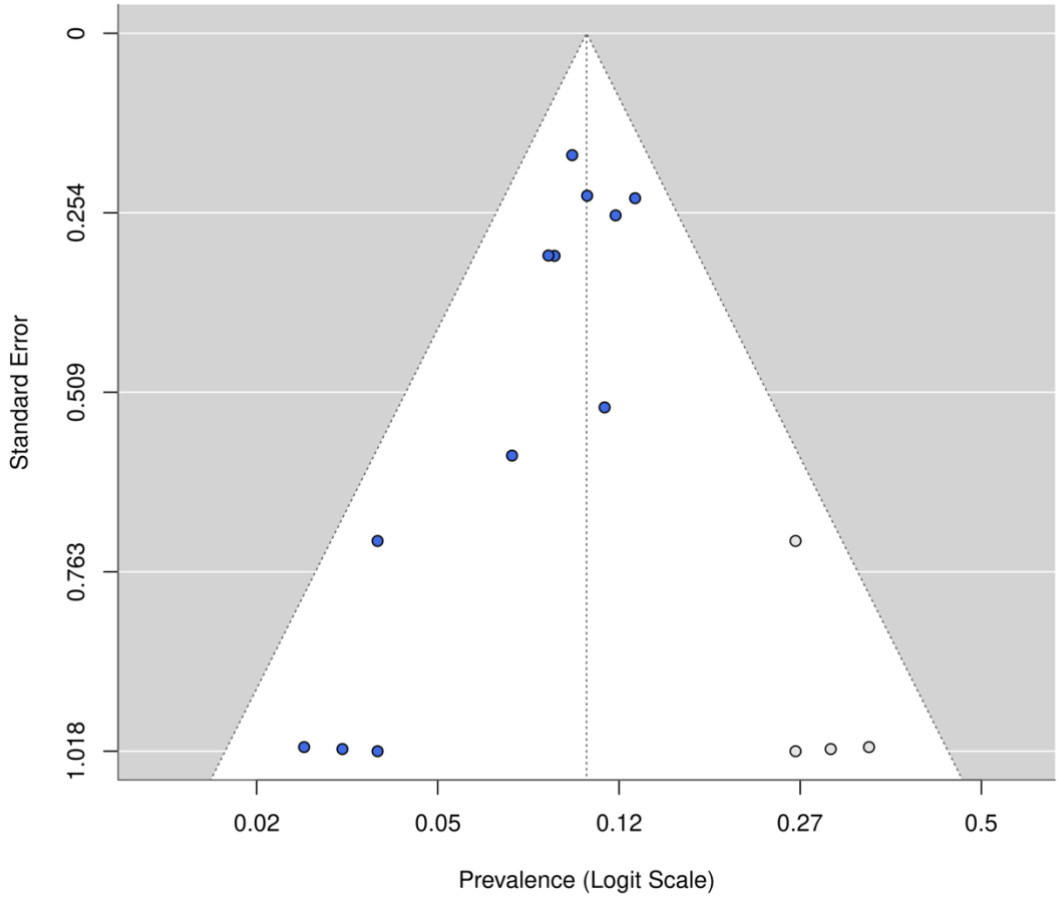


Figure S79. **Funnel plot for prevalence estimates of disruptive behavior disorders among offspring of individuals with bipolar disorder.**

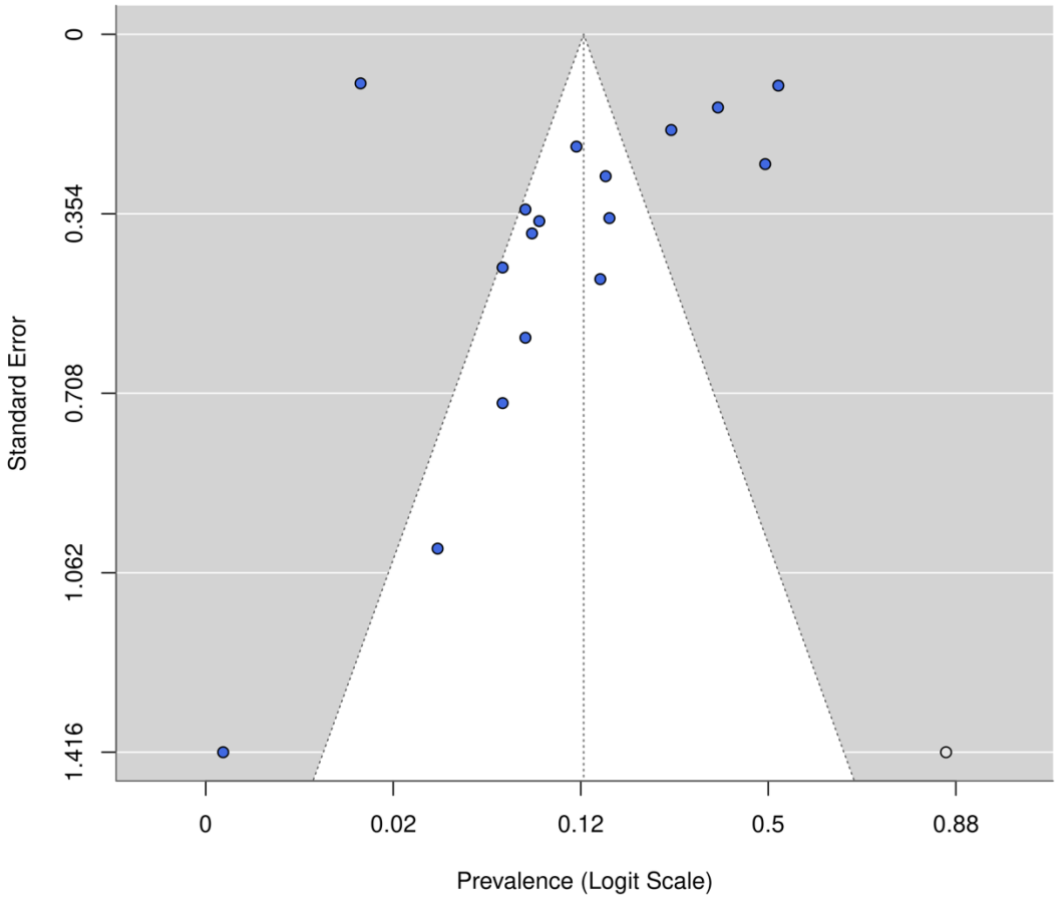
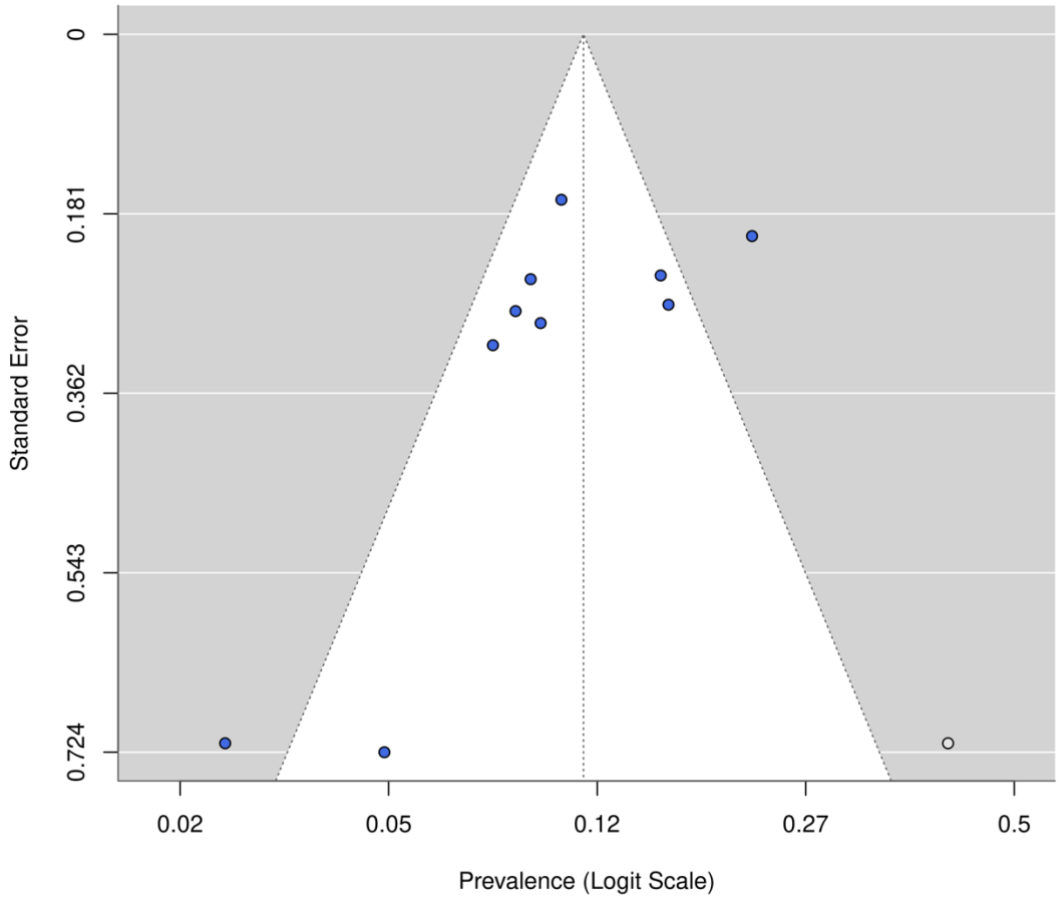


Figure S80. **Trim-and-fill funnel plot for prevalence estimates of other depressive disorders among offspring of individuals with bipolar disorder.**



6 Metodologia

6.1 Estratégia de busca e critérios de seleção

Esta revisão sistemática foi registrada no International Prospective Register of Systematic Reviews (PROSPERO; CRD42024559671) e conduzida de acordo com as recomendações do *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA).

Foi realizada uma busca sistemática nas bases de dados PubMed/MEDLINE, Embase, Web of Science, Scopus e PsycINFO, utilizando descritores e termos livres relacionados ao transtorno bipolar, filhos (*offspring*) e transtornos psiquiátricos. As listas de referências dos estudos incluídos e de revisões relevantes também foram examinadas manualmente para identificação de estudos adicionais. Não foram aplicadas restrições quanto ao idioma ou ao ano de publicação. A busca inicial foi realizada em maio de 2024 e atualizada em dezembro de 2025.

A triagem dos estudos foi conduzida de forma independente por quatro pesquisadores, em duas etapas: leitura de títulos e resumos, seguida da avaliação dos textos completos potencialmente elegíveis. Foram incluídos estudos observacionais (coorte, caso-controle ou transversais) que investigaram a ocorrência de transtornos psiquiátricos em filhos de pessoas com transtorno bipolar e que incluíram um grupo comparador composto por filhos de indivíduos sem transtorno bipolar. O diagnóstico dos transtornos psiquiátricos deveria ter sido estabelecido por meio de critérios padronizados, conforme a *Classificação Internacional de Doenças* (CID) ou o *Manual Diagnóstico e Estatístico de Transtornos Mentais* (DSM), ou por instrumentos diagnósticos validados.

Foram excluídos artigos de revisão, editoriais, capítulos de livros, relatos ou séries de casos, resumos de congressos e estudos que não apresentavam dados suficientes para extração dos desfechos de interesse.

A qualidade metodológica dos estudos incluídos foi avaliada por meio da escala Newcastle–Ottawa (Newcastle–Ottawa Quality Assessment Scale – NOQAS). Foram extraídas informações referentes às características metodológicas dos estudos, características das amostras (como tamanho da amostra, idade, sexo e características dos

grupos), critérios diagnósticos utilizados e frequência dos diferentes transtornos psiquiátricos avaliados.

6.2 Análise estatística

Inicialmente, foram realizadas meta-análises de prevalência utilizando modelos de efeitos aleatórios e o método *Restricted Maximum Likelihood* (REML), com o objetivo de estimar a prevalência combinada dos diferentes transtornos psiquiátricos em filhos de pessoas com transtorno bipolar. As proporções foram transformadas em logito antes da análise e posteriormente reconvertidas para sua escala original para apresentação dos resultados.

Posteriormente, foram conduzidas meta-análises comparativas para estimar a associação entre o histórico parental de transtorno bipolar e a ocorrência de transtornos psiquiátricos na prole. Para cada desfecho, foram calculadas estimativas combinadas de *odds ratio* (OR) e seus respectivos intervalos de confiança de 95%, comparando filhos de pessoas com transtorno bipolar com filhos de indivíduos sem transtorno bipolar.

A heterogeneidade entre os estudos foi avaliada por meio das estatísticas Q de Cochran, I^2 e τ^2. Quando observada heterogeneidade significativa, foram realizadas meta-regressões univariadas, utilizando o ajuste de Knapp–Hartung, para investigar possíveis fontes de variabilidade entre os estudos. As variáveis exploradas incluíram características metodológicas e demográficas previamente definidas, conforme disponibilidade dos dados.

O potencial viés de publicação foi avaliado por inspeção visual dos gráficos de funil e pelo teste de regressão de Egger. Quando indicado, foi aplicado o método *trim-and-fill* para estimar o impacto de possíveis estudos não publicados. Adicionalmente, foi realizada análise de sensibilidade do tipo *leave-one-out*, com o objetivo de avaliar a influência individual de cada estudo sobre as estimativas combinadas. Todas as análises estatísticas foram conduzidas no software R, utilizando os pacotes específicos para meta-análise.

7 Resultados

O presente estudo resultou em uma revisão sistemática acompanhada de meta-análise que investigou a ocorrência de transtornos psiquiátricos em filhos de pessoas com transtorno bipolar. Após o processo de seleção dos estudos, foram incluídos 59 estudos observacionais.

As meta-análises demonstraram que filhos de pessoas com transtorno bipolar apresentaram maiores prevalência de transtornos psiquiátricos e risco para o desenvolvimento de diferentes transtornos psiquiátricos quando comparados aos filhos de indivíduos sem transtorno bipolar. Foram observadas associações significativas para transtornos de ansiedade, transtornos depressivos, transtorno de déficit de atenção/hiperatividade (TDAH), transtornos disruptivos e transtorno bipolar, reforçando que essa população apresenta uma vulnerabilidade ampliada para diferentes desfechos psicopatológicos.

Por outro lado, as análises comparando filhos de pessoas com transtorno bipolar a filhos de indivíduos com outros transtornos psiquiátricos graves, como transtorno depressivo maior e esquizofrenia, não demonstraram diferenças estatisticamente significativas para a maioria dos desfechos avaliados. Esses resultados sugerem que parte do risco observado pode refletir uma vulnerabilidade familiar compartilhada entre diferentes transtornos psiquiátricos, reforçando a importância de uma perspectiva trans diagnóstica na compreensão da psicopatologia e na identificação de indivíduos em maior risco para adoecimento mental.

As análises de heterogeneidade evidenciaram variabilidade entre alguns desfechos avaliados, sendo realizadas análises adicionais para investigação de possíveis fontes dessa heterogeneidade. De maneira geral, os resultados permaneceram consistentes nas análises de sensibilidade. Também foram conduzidas análises para avaliação de viés de publicação, conforme descrito detalhadamente no manuscrito apresentado a seguir.

Os resultados completos desta revisão sistemática e meta-análise encontram-se descritos no artigo científico intitulado **"Psychiatric disorders among offspring of individuals with bipolar disorder: a systematic review and meta-analysis"**, apresentado no capítulo seguinte desta dissertação.

8 Considerações finais

O transtorno bipolar é uma condição psiquiátrica altamente hereditária, e seus filhos representam uma população particularmente vulnerável ao desenvolvimento de transtornos mentais. Compreender como essa vulnerabilidade se manifesta ao longo do desenvolvimento é fundamental para ampliar o conhecimento sobre a história natural da psicopatologia e subsidiar estratégias de prevenção e intervenção precoce.

Nesta dissertação, foi realizada uma revisão sistemática acompanhada de meta-análise com o objetivo de sintetizar as evidências disponíveis acerca da ocorrência de transtornos psiquiátricos em filhos de pessoas com transtorno bipolar. A integração quantitativa dos estudos permitiu estimar, de forma robusta, a magnitude do risco para diferentes desfechos psiquiátricos nessa população.

Os resultados demonstraram que filhos de pessoas com transtorno bipolar apresentam maior risco para o desenvolvimento de diversos transtornos psiquiátricos quando comparados aos filhos de indivíduos sem transtorno bipolar. Além do aumento do risco para o próprio transtorno bipolar, foram observadas associações significativas para transtornos de ansiedade, transtornos depressivos, transtorno de déficit de atenção/hiperatividade e transtornos disruptivos. Esses achados reforçam que a vulnerabilidade familiar ao transtorno bipolar se manifesta de forma ampla, por meio de diferentes apresentações psicopatológicas ao longo do desenvolvimento, e não exclusivamente pelo surgimento do transtorno bipolar.

Do ponto de vista clínico, esses resultados destacam a importância do acompanhamento longitudinal de filhos de pessoas com transtorno bipolar desde a infância e adolescência. O reconhecimento precoce de sintomas psiquiátricos pode favorecer intervenções oportunas, reduzir o impacto funcional associado ao adoecimento mental e contribuir para melhores desfechos clínicos. Dessa forma, estratégias de monitoramento e rastreamento devem considerar não apenas sintomas afetivos, mas também outras manifestações psiquiátricas frequentemente observadas nessa população.

Entre os principais pontos fortes deste estudo destacam-se a realização de uma busca sistemática abrangente, a inclusão de estudos provenientes de diferentes países e a utilização de métodos quantitativos para síntese das evidências disponíveis, permitindo estimativas mais precisas do risco para diferentes transtornos psiquiátricos. Entretanto, algumas limitações devem ser consideradas. A heterogeneidade metodológica entre os

estudos incluídos, diferenças nos critérios diagnósticos, nos instrumentos de avaliação e no tempo de acompanhamento podem ter influenciado parte das estimativas obtidas. Além disso, para alguns desfechos, o número reduzido de estudos disponíveis limita a precisão das análises e reforça a necessidade de novas investigações. Outra limitação importante refere-se à impossibilidade de distinguir, de forma consistente, qual genitor apresentava o diagnóstico de transtorno bipolar nos estudos incluídos. A maioria dos estudos não diferenciou se o diagnóstico estava presente na mãe, no pai ou em ambos os genitores, impossibilitando a investigação de potenciais diferenças relacionadas ao sexo do progenitor ou ao efeito da presença de transtorno bipolar em ambos os pais sobre o risco de psicopatologia na prole.

Por fim, esta dissertação contribui para consolidar as evidências acerca da psicopatologia em filhos de pessoas com transtorno bipolar e reforça a importância dos estudos em populações de alto risco para o avanço do conhecimento em psiquiatria. Espera-se que estes resultados auxiliem pesquisadores e clínicos na compreensão das trajetórias do desenvolvimento dos transtornos psiquiátricos, orientem futuras pesquisas longitudinais e subsidiem a elaboração de estratégias de prevenção e intervenção precoce voltadas a essa população.

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