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Are parents with bipolar disorder at higher risk of having offspring with ADHD? A systematic review

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Are parents with bipolar disorder at higher risk of having offspring with ADHD? A systematic review

Short Title: Parents with bipolar disorder and ADHD offspring

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ABSTRACT

Background: The offspring of parents with bipolar disorder (BD) and with attention deficit hyperactivity disorder (ADHD) have a higher risk of having the same condition. Both disorders also share psychopathological symptoms; however, little is known about their genetic overlap. To examine whether the offspring of parents with BD have a greater chance of being affected by ADHD, we conducted a systematic review.

Methods: From inception to August 12, 2024, we searched the PubMed, SciELO, PsycInfo and Cochrane databases. We included studies if they investigated the association of parental bipolar disorder with offspring outcomes and made a proper investigation of disorders using validated instruments based on the Diagnostic Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) criteria. Studies were excluded if: parents were under 18 years old or over 70; did not report original data; systematic reviews; in vitro studies; with an animal model; offspring older than 17 years of age or with any comorbid diagnosis with ADHD. To assess risk of bias, two authors independently used the Newcastle-Ottawa Scale quality assessment tool. **Results**: 23 articles met the inclusion criteria. The majority of the studies reported that the offspring of parents with BD were at higher risk for ADHD. Particularly, in

all case–control studies, the risk of ADHD was higher in the case group than the control group.

Conclusion: The current studies are yet heterogeneous and literature did not uncover the biological correlation of these disorders regarding genetic, biochemical, neuroimaging and neuropsychological aspects.

Keywords: bipolar, attention, hereditary, offspring, intergenerational.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a highly hereditary, neurodevelopmental disorder that is associated with the risk of other mental disorders later in life, such as anxiety, substance use and depressive disorders[1,2,3]. Bipolar disorder (BD) is a mood disorder that is frequently associated with mental comorbidities but is rarely diagnosed in childhood[4.]

Various studies have already shown that bipolar disorder is also highly hereditary[5,6]; some have reported a seemingly higher chance of individuals with ADHD being diagnosed with BD later in life[7], but few have focused on the risk of mental disorders other than BD, especially neurodevelopmental disorders, among the offspring of parents with BD.

Both BD and ADHD present some psychopathology similarities, such as mood lability, psychomotor agitation and distractibility[8]. The neurobiology and neural circuitry deficiencies associated with bipolar disorder onset are not yet fully known, but the common symptomatology could indicate that these two disorders have some neurobiological correlation. Furthermore, evidence from genome-wide association studies have already identified significant single nucleotide polymorphism-based genetic correlation between these disorders and risk loci with shared effects on the two of them consistent with the existence of genetic overlap between BD and ADHD.

To the best of our knowledge, this is the first review intended to investigate whether parents with bipolar disorder may have a greater chance of having offspring with ADHD. Positive findings may reinforce perspectives that suggest ADHD symptoms might be an initial phase of a longitudinal development of bipolar disorder[7,8].

METHODS

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[9] and was conducted following an a priori established protocol on PROSPERO[10] (CRD42023431438).

Database selection and search strategy

From inception to August 12, 2024, PubMed database was searched using the following terms: “bipolar disorder”, “offspring”, “progeny”, “inheritance”, “family history”, “familial history”, “attention deficit hyperactivity disorder” and “ADHD”. SciELO, PsycInfo and Cochrane databases were also searched using these terms: “bipolar disorder”, “manic depression”, “bipolar affective disorder”, “children” “descendants”, “parents”, “genetic”, “family background, “family history”, “familial history”, “attention deficit hyperactivity disorder”, “hyperactivity disorder”, “attention deficit disorder” and “ADHD”. To avoid publication bias, non-English language studies and grey literature (for example, conference abstracts) were included. A structured search strategy based on the PICOS framework was used[11]. Studies were included if they met the following criteria: a) enrolled adult parents with bipolar disorder and their offspring; b) investigated the association of parental bipolar disorder with offspring outcomes; c) conducted a proper investigation of bipolar disorder among parents made by a psychiatrist or using validated instruments based on the Diagnostic Statistical Manual of Mental Disorders (DSM-IV, DSM-IV TR, DSM-5) or the International Classification of Diseases (ICD-9 and ICD-10) criteria; d) conducted a proper investigation of ADHD among the offspring of parents with BD made by a psychiatrist or using validated instruments based on DSM-IV, DSM-IV TR, DSM V, ICD-9 or ICD-10 criteria; e) used any study design; f) a comparison group was preferable, but not mandatory. When reported in the study, both parents and offspring should have the control group. Studies were excluded if: enrolled parents who were adolescents under 18 years of age and elderly people (over 70); systematic reviews; studies that did not report original data; studies with an animal model; in vitro studies; enrolled offspring who were not under 18 years of age or had any comorbid diagnosis with ADHD.

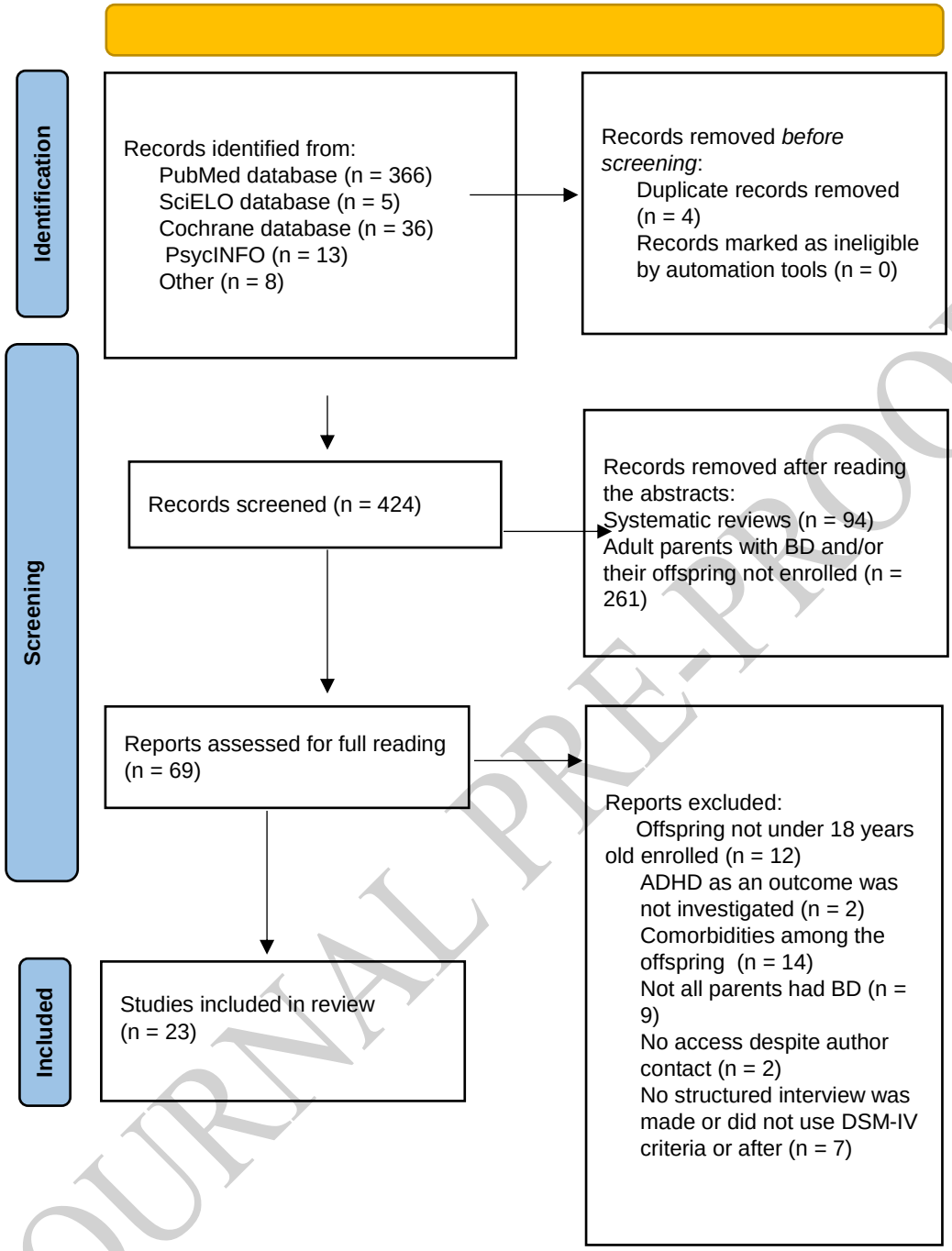
Two reviewers working independently considered the potential eligibility of each of the abstracts retrieved via the search strategy. Full-text articles were obtained unless both reviewers decided that an abstract was ineligible, with disagreements resolved by a third reviewer. The overall interobserver agreement of abstract selection was *K* = 0.70, which is deemed good to excellent agreement. Each full-text report was assessed independently by two reviewers for final study inclusion, and the agreement for final texts inclusions was *K* = 0.90.

Data abstraction and risk of bias assessment

Data on study-, parent-, and offspring-related characteristics were abstracted using a standardized form, and conducted independently by 2 researchers, with disagreements resolved by a third researcher. The following variables were extracted from all studies: authors, year of publication and subject characteristics of the parent and offspring groups. The risk of bias assessment of the individual studies was conducted independently by two authors (LLF and LAQ) using the Newcastle-Ottawa Scale quality assessment tool[12]. The overall interobserver agreement of methodological quality assessment was *K* = 0.64, which is deemed good to excellent agreement. Any disagreements were settled following discussion with a third reviewer (AEN). The details of the quality assessment are reported in the Supplemental Material.

RESULTS

366 studies were found using the previously described strategy. Four duplicate records were removed. 424 records were screened, and after reading the abstracts, 94 systematic reviews and 261 reports which did not meet the inclusion criteria of enrolling adult parents with BD and/or their offspring were excluded. 69 studies were then assessed for full reading, and 46 of them were disqualified based on this article's inclusion and exclusion criteria. Finally, a total of 23 papers representing individual studies were included. A PRISMA diagram is shown in Figure 1.



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Figure 1 - Legend: PRISMA Flow Diagram.

Study characteristics

The key study characteristics are presented in Table 1. We obtained results from studies published between 2000 and 2023. This was reflected in the categorical measurement used: the DSM-IV or DSM-IV-TR and adaptations of both. The most commonly used diagnostic tools were the Structured Clinical Interview for DSM Disorders (SCID) for the parents and the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS) for their offspring.

Table 1. Study characteristics

Study	Sample size (affected parents)	Sample size (offspring - proband)	Sample size (non-affectedparents)	Sample size (offspring - control)	Affected parents gender (%, F)	Offspring gender - Proband (%, F)	Country	ADHD scale	BD scale	Parent comorbidities	Positive correlation between BD in parents and ADHD in offspring?
Birmaher B et al. [2022][13]	156	251	180	158	-	-	-	K-SADS/ DSM-IV	SCID	None	Yes
Propper L. et al. [2021][14]	-	93	-	125	-	51%	Canada	K-SADS-PL/SCID-5	SADS/ SCID	None	Yes
Yeh TC et al. [2021][15]	5669	430	5699	272	100%	-	Taiwan	ICD-9 criteria	ICD-9 criteria	None	Yes
Solberg BS et al. [2021][16]	66211	3477	2381348	-	-	-	Norway	ICD-10 criteria	ICD-10 criteria	None	Yes

Goetz, M. et al. [2017][17]	34	43	33	43	44,1%	41,9%	Czech Republic	K-SADS-PL	SADS-L	None	Yes
Neslihan Inal-Eiroglu F et al. [2008][18]	29	35	29	33	-	48%	Turkey	T-DSM-IV-S	K-SADS	None	Yes
Sanchez-Gistau V et al. [2015][19]	54	90	65	107	55,6%	44,4%	Spain	K-SADS-PL	SCID-I	~33.3% any Axis I disorder	Yes
Axelson D et al. [2015][20]	236	391	141	248	80,5%	48,9%	USA	K-SADS-PL	SCID	any Axis I disorder + likely < control	Yes
Garcia-Amador M et al. [2012][21]	34	50	25	25	55%	42%	Spain	K-SADS-PL	SCID-I/II	Cluster A:2 B:3 C:6	Yes
Singh MK et al. [2008][22]	-	31	-	21	-	48%	USA	K-SADS	SCID	None	Yes
Birmaher B. et al. [2021][7]	78	116	79	98	80,8%	51,7%	USA	K-SADS-PL	SCID	DBD:44,9/ADHD:21.8/ANX:80.8/MDD:96,2	Yes
Sparks GM et al. [2014][23]	233	375	143	241	-	49%	USA	K-SADS-PL	SCID	ANX:84/ADHD:56/ODD:5	Yes

										2/SUD:80/	
Duffy A. et al. [2007][24]	63	127	41	61	47%	59,7%	Canada	K-SADS-PL	SADS-L	None	Yes
Oquendo MA et al. [2013][25]	86	177	234	502	86%	45,7%	USA	K-SADS-PL	SCID	None	No
Birmaher B et al. [2010][26]	83	121	65	102	90,4%	51,2%	USA	K-SADS-PL	SCID	100% any Axis I disorder	Yes
Palacio-Ortiz JD et al. [2017][27]	65	127	94	150	-	44,9%	Colombia	K-SADS-PL	DIGS	SUD:46%/ANX: 13,8%	Yes
Flinding R. L. et al. [2015][28]	185	167	571	233	57,8%	40,7%	USA	K-SADS	SADS-LB	None	No
Chang KD et al. [2000][29]	37	60	-	-	83,7%	42%	USA	K-SADS-PL	DSM-IV criteria	ADHD: 20%	Yes
Zappitelli MC et al. [2011][30]	-	35	-	-	82,9%	42,9%	USA	K-SADS-PL	SCID	None	Yes
Liang CS et al. [2023][31]	39278	-	6324048	-	57%	47,8%	Taiwan	ICD-10 criteria	ICD-10 criteria	None	Yes

Parvaresh N et al. [2010][32]	100	100	100	48	-	46%	Iran	DSM-IV-TR criteria	DSM-IV-TR criteria	None	Yes
Chen MH et al. [2021][33]	105	-	932,544	-	100%	-	Taiwan	ICD-9 criteria	ICD-9 criteria	None	Yes
Hirshfeld-Becker DR et al. [2006][34]	23	34	170	179	56%	61%	USA	K-SADS	SCID	SUD:85/ ANX:79/ DBD:50	Yes

Abbreviations: M: male; F: female; ICD: International Classification of Diseases; BD: Bipolar Disorder; ADHD: Attention Deficit Hyperactivity Disorder; ANX: Anxiety Disorder; MDD: Major Depressive Disorder; K-SADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version; SUD: Substance Use Disorder; T-DSM-IV-S: Turgay DSM-IV-Based Child and Adolescent Disruptive Behavioral Disorders Screening and Rating Scale; DIGS: Diagnostic Interview for Genetics Studies; ODD: Oppositional Defiant Disorder; DBD: Disruptive Behavior Disorder.

Parent results

The age of the parents ranged from 24 to 47 years old among the total sample. Thirteen studies identified the sex of the parents. In two of them, only female patients were included. All of the others identified the sex from a randomized sample selection, and noted the mother as being the most affected parent. Six studies identified substance use disorder as a comorbidity among parents, and five of them provided the percentage, which varied from 8% to approximately 85% among the investigated parents. Other comorbidities were also found, with one study pointing out that all parents had an associated Axis I disorder in addition to BD[26]. In two studies, 21.8%[7] and 20%[29] of the parents were also diagnosed with ADHD. A study comparing comorbidities between parents in the bipolar and control groups found that any Axis I disorder was more common among parents with bipolar disorder[20]. Anxiety disorders were also found to be highly correlated with bipolar disorder, especially in two studies that identified an association between both disorders with proportions of 84%[23] and 80.8%[7]. Two studies reported the duration of disease among the parents, varying from 19[25] to 21 years[23]. Only two studies presented the current mood episode of the parents, and they all were euthymic at the time of the study[29, 30].

Offspring results

Among the nineteen studies that identified the sex of the offspring, fourteen showed a higher prevalence among males. Nine studies reported the most common school grade among the offspring: in five of them, the majority of the participants were of school age; in three of them, they were of preschool age; one study showed high school as the most common school grade, while another identified the majority of participants as having already graduated.

The majority of the studies found that parents with bipolar disorder had a higher risk of having offspring who developed ADHD. In three of these studies, this correlation was highly positive (OR = 2.67)[14], (OR = 1.51)[15], (OR = 2.88)[19]. Three other studies also confirmed that there was an association between bipolar disorder in parents and a higher prevalence of ADHD in offspring (OR = 0.19)[13], (OR = 2.6)[18], (OR = 1.63)[20]. Seven case-control studies compared the prevalence of comorbidities among parents with bipolar disorder and healthy controls, also reporting that the offspring of parents with bipolar disorder were more affected by

ADHD than the offspring of control parents[7,21,22,24,25,26,34]. In one of these studies, this correlation even reached 39% of the sample[22]. In the study conducted by Hirshfeld-Becker DR et al., the control group was formed by patients with panic disorder and major depressive disorder (MDD), which had a prevalence of occurrence of ADHD of 8.4% among the offspring meanwhile offspring of parents with BD had 23.5%[34]. Two longitudinal studies also identified a significant prevalence of ADHD among parents with bipolar disorder of 28% and 40%, respectively[29,30]. Specifically, maternal bipolar disorder was linked to a higher risk of ADHD in offspring in two studies[31,33]. In the study conducted by Chen MH et al., women who developed bipolar disorder after giving birth and their children were followed for investigation and among those patients the prevalence of having offspring with ADHD in the follow-up was significant (OR = 4.18)[33].

A study comparing the frequency of ADHD, conduct disorder (CD) and emotional disorders among children of parents with BD, drug dependence and control found that the prevalence of ADHD among the offspring of parents with BD was higher than control. However, it was equivalent to the group of parents with drug dependence, suggesting that ADHD may be more frequent among parents with psychiatric disorders in general than control (OR = 0.2)[32]. Two studies found a meaningful correlation only before controlling for comorbid parental diagnoses and demographic variables[17,23]. In the study conducted by Goetz et al. to investigate quality of life (QoL) in offspring of a parent with BD using the self-report questionnaire KIDSCREEN, between-group differences in parental and self-assessment were controlled for co-occurring conditions (DSM-5 disorders) with the use of logistic regression. Cross-informant (parent–child) agreement in the assessment of symptoms of mood and anxiety disorders was calculated as Kendall's rank correlation coefficient (tau) and concordance correlation coefficient (CCC) for an ordinal rating and Cohen's kappa for a dichotomous rating. To compare the KIDSCREEN (QoL) between groups, the raw scores were converted to the T scores (The KIDSCREEN Group Europe 2006) and unpaired t-tests were conducted followed by Cohen's d calculation and least-square multiple regression to control for between-group differences for current psychopathology and family status[17]. Sparks et al. used Odds Ratios (ORs) to estimate the risk of disruptive mood dysregulation disorder based on status as offspring of bipolar parents or community control parents were calculated using

generalized linear mixed models with family of origin used as a random effect variable. The model was initially constructed as a univariate model. Subsequently, demographic variables (age, gender, race, SES, and offspring living with both biological parents) and proband parent non-BD lifetime diagnoses (ADHD, depressive disorder, anxiety disorder, ODD/CD, and substance use disorder) were entered as potential covariates. Models were constructed with backward model selection procedures, removing demographic variables and parental diagnoses with p>0.10 iteratively in order of magnitude until all variables remaining in the model were significant[23].

One study did not find a higher prevalence of ADHD among the offspring of parents with bipolar disorder in comparison to control parents. In this study, this correlation was definitely negative[28]. A study evaluating psychopathology in offspring of both parents with bipolar disorder and major depressive disorder (MDD) reported ADHD as being no more likely among the offspring of parents with bipolar disorder than among those of parents with MDD[25]. In a 2021 case–control study comparing the most prevalent mental disorders among the offspring of parents with bipolar disorder, parents with ADHD and control parents, it was found that ADHD was more prevalent among offspring of parents with bipolar disorder than among offspring of control parents; however, it was not more prevalent among offspring of parents with ADHD[16].

DISCUSSION

This systematic review shows that many studies in the literature point to a higher risk for parents with bipolar disorder of having offspring predisposed to ADHD. The majority of the investigated studies reported that, in comparison to control parents, parents with bipolar disorder had a higher prevalence of having children being affected by ADHD. The follow-up of the longitudinal studies that investigated only the offspring of parents with bipolar disorder indicated a high risk of ADHD among their children as well.

It is well known that a family history of bipolar disorder is associated with a higher risk for the condition[5]. In addition, ADHD symptoms in childhood are commonly discussed as possible prodromes for adult bipolar disorder[7,8], conduct disorders[35] and substance use disorders[36]. Identifying epidemiological findings that suggest that ADHD could also be a significant outcome for the offspring of parents with

BD may help to improve knowledge about the chances of children to have ADHD being in fact higher if their parents have BD.

Some studies have already demonstrated that ADHD shares a positive genetic correlation with major depressive disorder, insomnia and depressive symptoms in general[37], which are not uncommon among BD patients. A meta-analysis of family genetic studies examining the comorbidity between ADHD and BD type I found a significantly higher prevalence of ADHD among relatives of bipolar I probands and a significantly higher prevalence of bipolar I disorder among relatives of ADHD probands[38]. An analysis of shared heritability in common disorders of the central nervous system searching to understand the joint effect exerted by a pool of several small effect genomic variants which are in turn used to estimate the heritability that seems to be shared in between disorders pointed out that a common variant risk for psychiatric disorders was shown to correlate significantly especially among attention deficit hyperactivity disorder, bipolar disorder, major depressive disorder and schizophrenia[39]. Moreover, genome-wide association studies (GWAS) have already found overlapping genes among the two disorders. In a cross-trait meta-analysis of GWAS on schizophrenia, bipolar disorder, autism spectrum disorder, attention deficit hyperactivity disorder and depression, the SORCS3 gene was highlighted due to the fact that it was involved in all the five conditions of study[40]. In an analysis of genome-wide single-nucleotide polymorphism (SNP) data from the Psychiatric Genomics Consortium for the same five disorders, SNPs at four loci —regions on chromosomes 3p21 and 10q24, and SNPs in two L-type voltage-gated calcium-channel subunits, CACNA1C and CACNB2—exceeded the cutoff for genome-wide significance ($p<5\times10(-8)$) in the primary analysis[41].

Besides the genetic evidence, according to the current DSM-5 diagnostic criteria for ADHD, it also shares a psychopathology overlap with BD, such as talkativeness, hyperactivity and distractibility presented as manic episodes, in addition to emotional features seen in mood instability and irritability, which are also common in both disorders. The common overlap of psychopathology alterations between BD and ADHD could be related to shared neurocircuitry alterations[42].

Another similar neurobiological alteration between these disorders was found in a cerebrospinal fluid (CSF) monoamine metabolite concentrations analysis of

ADHD and BD patients, which identified that both disorders were associated with higher CSF homovanillic acid (HVA) concentration in that sample[43].

These previous findings suggest that these two mental disorders are somewhat correlated despite the present lack of robust information about the neurobiological mechanisms of BD. Regardless, clinical and epidemiological studies have shown rates of BD in subjects with ADHD are proportionally more elevated than other psychiatric conditions, and previous results from family studies show increased incidence of ADHD in offspring of probands with BD[8]. Given that several staging models of bipolar disorder have been proposed over time, including an initial prodromal phase where mild symptoms of mood disorder similar to ADHD such as overactivity and impulsivity could happen before culminating in a first threshold episode of illness, it is possible that many ADHD symptoms that correlate with BD psychopathology may be involved in the first stage of a longitudinal development of bipolar disorder[44].

The present review had a number of limitations. Performing a meta-analysis was not possible due to the heterogeneity of the results. Given that only a few studies were not originally from America, the cross-cultural validity and applicability of the findings of this review to the global youth population is limited. It is worth noting that since ADHD is the most prevalent psychiatric disorder in children, it could also be that the results which show a higher prevalence of this disorder among the offspring of parents with bipolar disorder only represent the well-known higher prevalence of disorders in general among offspring of individuals with psychiatric disorders. Eight studies have indicated that parents with bipolar disorder also have comorbidities such as anxiety disorders, MDD or ADHD, which might represent confounders. Despite these limitations, our analysis of the evidence showed a methodologically robust corpus of studies.

While it is well established that BD and ADHD might have a neurobiological and genetic linkage, the current studies are yet heterogeneous and literature did not uncover the biological correlation of these disorders regarding gene expression, biochemical pathways, neuroimaging aspects and neuropsychological processes. Therefore, more studies are needed in order to elucidate these aspects and improve knowledge about these disorders.

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Appendix 1: Search Protocol

Systematic Search Protocol

Written based on the WHO Review Protocol Template, 2011

1. Background: Bipolar disorder (BD) is a mental disease defined by the occurrence of mood change episodes known as depression and mania. Studies have shown that this condition can be related to attention deficit hyperactivity disorder (ADHD), a mental disorder characterized by psycomothor agitation and distractibility, symptoms that are also commonly present in BD patients. Therefore, the aim of this systematic review is to investigate if bipolar parents might have an increased rate of having ADHD offspring.

2. Objective: This review outcome is to evaluate if current literature findings support evidence of a higher risk of parents with bipolar disorder having offspring with ADHD

3. Review Question (Population Intervention Comparison Outcome)
Population: genitors with bipolar disorder and included their offspring
Intervention: analyze the risk of ADHD heritability
Comparison: a comparison group was preferable, but not mandatory
Outcome: ADHD psychopatology in offspring

Evidence Gathering and Study Selection: PubMed, SciELO, PsycINFO and Cochrane databases will be searched. Full search terms for each database and results found per database are listed in the Appendix 2.

Reference searches: Bibliographies of papers deemed eligible for this review will be hand searched to identify any additional eligible references, which will then be screened for title, abstract or full text as appropriate.

4. Eligibility Criteria

The results of these searches will be combined and deduped using Rayyan. They will then be screened for title and abstract, and then full text using the following eligibility criteria.

i) Type of study included: any

ii) Types of participants: Genitors with bipolar disorder, which included an offspring

iii) Types of outcome measures: behavior, neurodevelopment or psychopatology in offspring were reported

7. Exclusion Criteria

Reviews, studies that did not report original data, studies with an animal model, and in vitro studies will be excluded.

8. Data extraction

Data extracted will include: Title, name of the first author, year of publication, parent age, parent gender, offspring gender, offspring age, parent use of substance, parent disease time, current parent mood episode, offspring grade and parent comorbidities.

9. Data Synthesis

Narrative synthesis is planned. The systematic review will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). We anticipate that there will be limited scope for meta-analysis because of the possible heterogeneity of the results.

10. Dissemination

A manuscript will be prepared for submission to a peer reviewed journal in the neuroscience field.

11. Results

The quality appraisal of the 23 studies is summarised in Supplementary table 1. The overall average stars achieved through the 23 included studies was 7.0 stars (range = 3–9), which is considered as moderate quality.

Appendix 2: Search terms

Pubmed:

("Bipolar Disorder"[MeSH] OR "bipolar disorder") AND (offspring*[tiab] OR progen*[tiab] OR parent*[tiab] OR herit*[tiab] OR inherit*[tiab] OR "family history" OR "familial history") AND ("Attention Deficit Disorder with Hyperactivity"[MeSH] OR "ADHD")

Scielo, Cochrane and PsycINFO:

("Bipolar Disorder" OR "manic depression" OR "bipolar affective disorder") AND (children OR descendants OR parents OR genetic OR inheritance OR "family background" OR "family history") AND ("Attention Deficit Hyperactivity Disorder" OR "ADHD" OR "hyperactivity disorder" OR "attention deficit disorder").

Appendix 3: Supplementary table 1. Quality score.

Case control studies

Authors	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate
Boris Birmaher [2022]	*		*	*	**	*	*	*
Propper, L. [2021]	*	*	*	*	**	*		*
Y Teh et al [2021]		*	*	*	**		*	*
Goetz, M. et al [2017]	*	*	*	*	**	*	*	*
Neslihan Inal-Eiroglu F et al [2008]	*	*		*			*	*
Sanchez-Gistau V [2015]	*	*	*	*	**	*	*	
Axelson D et al [2015]	*	*	*	*	**	*	*	*
Garcia-Amador M et al [2012]	*	*	*	*	*		*	*

Singh MK et al [2008]	*	*	*	*	*	*	*	
Birmaher B. et al [2021]	*	*	*	*		*	*	
Sparks GM et al [2013]	*	*	*	*	**	*	*	
Oquendo MA et al [2013]	*	*		*	**	*	*	
Birmaher B et al [2010]	*	*	*	*	**	*	*	
Palacio-Ortiz JD et al [2017]	*	*	*	*	**	*	*	
Findling R. L. et al [2005]				*	**	*	*	
Parvaresh N et al [2010]	*	*	*	*			*	*
Hirshfeld-Becker DR et al [2006]	*	*	*	*	**	*	*	*

Cross-sectional studies

Authors	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of exposure	Comparability	Assessment of the outcome	Statistical test
Chang KD et al [2000]		*	*	*		**	
Zappitelli MC et al [2011]				*		**	

Cohorts

Authors	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start	compara bility	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts
Solberg BS et al [2021]	*	*			*	*	*	
Duffy, A. et al [2007]	*	*	*	*		*	*	*
Liang CS et al [2023]	*	*		*	**	*	*	
Chen MH et al [2021]	*	*	*	*	**		*	*

Appendix 4: Supplementary table 2. PRISMA 2020 checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pages 4,5
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.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4
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.	Page 5
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.	Page 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were 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.	Pages 5,6
	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.	Pages 5,6
Study risk of bias	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.	Pages 5,6

assessment			
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.	NA
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)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	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.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
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.	Page 6, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 6, Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 3 (Supplementary Material)
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.	NA
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its	NA

		precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 11, 12
	23b	Discuss any limitations of the evidence included in the review.	Pages 13, 14
	23c	Discuss any limitations of the review processes used.	Pages 13, 14
	23d	Discuss implications of the results for practice, policy, and future research.	Page 14
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.	Page 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 1 (Supplementary Material)
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 1
Competing interests	26	Declare any competing interests of review authors.	Page 1
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.	NA