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Functional outcomes across development in offspring of parents with bipolar disorder

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ABSTRACT

Objective: Whereas the risk and course of psychopathology in offspring of parents with bipolar disorder (BD) have been the primary focus of high-risk offspring studies to date, functional outcomes have not been given much attention. We present a systematic review of functional outcomes and quality of life (QoL) across development in offspring of parents with BD and aim to explore the role of offspring psychopathology in these outcomes.
Method: We searched Embase, MEDLINE, PsycINFO, Web of Science, Cochrane Central, and Google Scholar from inception to June 24, 2022, for studies referring to functional outcomes (global, social, academic or occupational) or QoL in offspring of parents with BD.
Results: From the 6470 records identified, 39 studies were retained (global = 17; social = 17; school = 16; occupational = 3; QoL = 5), including 13 studies that examined multiple domains. For all domains, high heterogeneity was found in study methods and quality. Only 56 % of studies adjusted for offspring psychopathology, impeding interpretation. Global and social functioning generally seemed to be impaired among older offspring (>16 years). Academic performance appeared to be unaffected. School behavior, occupational functioning, and QoL showed mixed results. Offspring psychopathology is associated with social functioning, but the relationship of offspring psychopathology with other domains is less clear.
Conclusion: Studies on functional outcome in offspring of parents with BD show predominantly mixed results. Inconsistent adjustment of psychopathology and age limits conclusive interpretation. Functional outcomes should be prioritized as research topics in high-risk studies and the potential associations between familial risk status, offspring psychopathology, and age may inform prevention strategies.

1. Introduction

Bipolar disorder (BD) is often a severe mood disorder with lifetime prevalence estimated between 0.2 and 2.2 % (Clemente et al., 2015). A positive family history of BD is the most robust predictor for the development of BD (Lau et al., 2018; Merikangas et al., 2014; Vandeleur et al., 2014; Wilde et al., 2014) and studies that have focused on offspring of parents with BD (i.e., high-risk offspring studies) have allowed us to study the familial risk and the mechanisms of intergenerational transmission (Branje et al., 2020). Traditionally, high-risk studies of BD have focused on the risk to develop BD and on the early trajectories of BD (Duffy et al., 2017; Raouna et al., 2018; Rasic et al., 2014; Rudaz et al., 2021; Sandstrom et al., 2019). To date, prospective studies in offspring of parents with BD with at least one follow-up into adolescence have shown high rates of BD (ranging from 10 to 13 %), lifetime mood disorders (ranging from 48.3 to 62.8 %), and general psychopathology (ranging from 70 to 75 %), with most studies showing that psychopathology starts before reaching adulthood (i.e., ≤24 years) (Axelson et al., 2015; Duffy et al., 2019; Lau et al., 2018; Mesman et al., 2013; Preisig et al., 2016).

Another line of research that focuses on functional outcomes has shown that childhood psychopathology, even subsyndromal, is associated with an adverse transition into adulthood in terms of health, legal and personal finances, as well as social functioning (Copeland et al.,

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2015; Oerlemans et al., 2020; Ormel et al., 2017). This negative association between childhood psychopathology and functional outcomes emerges regardless of current psychopathology or the presence of psychiatric disorders in adulthood (Copeland et al., 2015; Oerlemans et al., 2020; Ormel et al., 2017). To put prior findings of high rates of psychopathology in offspring of parents with BD into perspective, it is essential to expand our knowledge on the functional outcomes of this group to lower the consequences of both parental and offspring psychopathology using adequate prevention strategies.

From a developmental perspective, functioning is viewed as the ability to adapt to the developmental tasks presented at home (i.e., getting along with parents and siblings), at school (i.e., academic performance and school behavior), and within the community (i.e., relating to community activities and peers) (Hoagwood et al., 2012; World Health Organization, 2007). Functional outcomes exist on a continuum, ranging from competencies on the higher end to functional impairment on the lower end in which functioning is not completely lost, but rather operates on a lower level at which "normal" or "expected" adaption is not possible (Canino, 2016; Canino et al., 1999; Hoagwood et al., 2012). Developmental tasks vary by developmental stage, making age important when putting functional outcomes into context (Rapee et al., 2012). In addition, a subjective view on life and of one's own functioning can be provided by examining quality of life (QoL) (Rapee et al., 2012). By studying the combination of functional outcomes with QoL, one can integrate objective measures and a subjective view within one perspective.

Given that high-risk offspring often develop psychopathology themselves, it is no surprise that patients, relatives, and healthcare professionals often wonder how this risk translates into daily functioning as well as functional outcomes for later life. However, functional outcomes in high-risk offspring studies have not been a prominent topic in the field of BD and a comprehensive overview is lacking. Recently, two reviews examined family functioning in particular in offspring of parents with BD. They showed that families of parents with BD reported lower family cohesion than families without parental psychopathology (Stapp et al., 2020), whereas parental rejection and low perceived parental care have been associated with the development of mood disorders in offspring of parents with BD (Menculini et al., 2020). Yet, aside from this specific functional domain, there is still scant research on psychosocial functioning in the offspring of parents with BD.

Here we present a systematic review on functional outcomes, other than family functioning, in offspring of parents with BD. We aim to summarize the scattered literature and gain insight into its strengths, challenges, and gaps. We consider functional outcomes in terms of global functioning, social functioning, academic functioning, occupational functioning, and QoL. We also reviewed the included studies on aspects related to parental BD characteristics (i.e., parental BD subtype, biological sex) and the description of the presence of offspring psychopathology and offspring age.

2. Methods

The protocol for this systematic review was registered with PROSPERO, ID: CRD42020169930. Deviations from the pre-registration are described in Supplement 1 (available online). As a systematic review on family functioning in offspring of parents with BD was published by Stapp et al. (2020) during the review process, we therefore excluded studies on this topic. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) and the checklists are provided in Tables S1 and S2 (available online).

2.1. Selection criteria

We used the following inclusion criteria: 1) Part or all of the study sample had to include offspring of parents with a diagnosis of bipolar I disorder (BD-I), bipolar II disorder (BD-II), or bipolar disorder not otherwise specified (BD-NOS); 2) Studies had to examine one of the included domains of functioning (global, social, academic, or occupational) or QoL; 3) Studies had to be originally published studies (we excluded reviews, book chapters, editorials, and commentaries); 4) Grey literature, such as conference abstracts (since 2017) could also be included; 5) In case of treatment studies, only baseline data was included. 6) Studies had to be in English. All studies were grouped into the functional domain they covered. Studies that covered multiple domains were grouped into all applicable domains.

2.2. Search strategy

The search strategy was created in collaboration with an experienced information specialist (S.G.). We searched the databases from inception until June 24, 2022. The description of syntax per database is provided in Table S3 (available online). The Embase search strategy served as the basis and was then applied to five other literature databases: MEDLINE via Ovid, PsycINFO via Ovid, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, and Google Scholar. For conference abstracts, we limited the publication date from January 1, 2017 to June 24, 2022. A backward chasing procedure on the reference lists of all included studies was used to screen for any additional relevant studies.

2.3. Screening process and data extraction

Two reviewers (F.H. and E.M.) independently assessed the titles and abstracts of studies retrieved by the search strategy. Discrepancies between the two reviewers were discussed and resolved. Next, all full texts were screened by two independent reviewers (F.H., and C.V. or E.M.) and discussed when they raised doubt about their eligibility for inclusion. When necessary, we contacted the corresponding authors for further information ($k = 6$, response rate: $k = 2$).

To extract data from the included studies, we adapted the Cochrane Public Health Group (CPHG) Data Extraction and Assessment Template. The following data were extracted: study details (e.g., sample size, demographic characteristics, method), the presence of offspring psychopathology, information on BD type of proband parent, type of controls, and all reported functional outcomes were noted, including effect sizes (r, R^2, Beta or another estimate, OR, RR, and Cohen's d) when reported. Data was extracted by two independent reviewers (F.H., and C.V. or E.M.), discrepancies were discussed and resolved.

2.4. Methodological quality

Studies with a control group were assessed by two independent reviewers (F.H., and C.V. or E.M.) regarding their methodological quality using the Newcastle-Ottawa Scale (NOS) (Deeks et al., 2003). The NOS was specifically developed to assess the quality of non-randomized studies. The scale consists of 3 subscales including 8 items (selection, comparability, and exposure), the total maximum score is 9 stars. Studies without a control group were not assessed on methodological quality.

2.5. Data synthesis

As we expected the number of studies on the reviewed outcomes to be low, and the statistical indices and methods to vary substantially, we used a descriptive synthesis without meta-analysis as our main method of recording data.

We synthesized data of all outcome variables of interest and categorized those results into four groups: lower functioning for the high-risk offspring group, no differences in functioning between the groups, higher functioning for the high-risk offspring group, and studies without a control group. In the case of mixed results, studies were coded in

several groups. This could lead to a higher sum of results than the total of the included studies for that domain. When reported, effect sizes were also taken into account. The presence of offspring psychopathology and offspring age were also documented.

2.5.1. Psychopathology

When reported, offspring psychopathology was categorized as follows: any psychiatric disorder (hereafter referred to as: any disorder), any mood disorder, BD, and any anxiety disorder. Individuals could be in more than one category as BD is nested within any mood disorder, and any mood disorder and any anxiety disorder are nested within any disorder. We referred to affected offspring when offspring of parents with BD developed any type of psychopathology themselves, whereas unaffected offspring means that offspring did not develop any psychopathology themselves.

2.5.2. Age

In order to gain insight into the different developmental stages and functional outcomes, the mean age of study samples was used as a proxy for developmental stages. We created five age categories: preschool children (0 to 5 years old), primary school-aged children (6 to 11 years old), adolescents (12 to 17 years old), young adults (18 to 23 years old), and adults (24 years and older).

3. Results

3.1. Study characteristics

Our search provided 6470 possible studies after removing duplicates, of which 6299 were excluded after title/abstract screening. We excluded 132 additional studies after full-text review, justifications for exclusion per article can be found in Table S4 (available online). We could finally include 39 studies (global functioning = 17, social functioning = 17, academic functioning = 16, occupational functioning = 3, and QoL = 5) of which 13 studies examined more than one functional outcome. The study selection process is presented in Fig. 1. Characteristics per study are presented in Table 1 and a summary of findings per age category can be found in Fig. 2.

From all included studies, two focused on preschool children (0 to 5 years), nine studies examined primary school-aged children (6 to 11 years), twenty studies focused on adolescents (12 to 18 years), five on young adult samples (18 to 23 years), and three studies investigated adults (24 years and older). A total of 32 studies included a control group (offspring of parents without any disorders = 14, unaffected offspring of parents without any disorders = 5, community controls = 5, offspring of parents without affective disorders = 4, offspring of parents without affective or psychotic disorders = 4). In five studies, a longitudinal design was used (Conrad and Hammen, 1993; De la Serna et al., 2021; Kim et al., 2015; Ostiguy et al., 2012; Zahn-Waxler et al., 1984a), one study was a registry study (Ranning et al., 2018), and all other studies were cross-sectional. Parental BD subtype was reported in 51 % of the studies (BD-*I* = 53 %, BD-II = 29 %, BD-NOS = 5 %). Parental biological sex was reported in 36 % of the studies (mothers and fathers = 26 %, mothers only = 11 %). With the exception of global functioning, measurement of functional outcomes across all domains was highly heterogeneous. Detailed information on measures used can be found in Table S5 (available online).

3.2. Study quality assessment

Assessment of the quality of the included studies can be found in Table S6 (available online). The mean score on the NOS was 5.81 stars (SD = 1.53, range = 2 to 8). None of the studies reached the maximum of 9 stars. Biological sex and age distributions were similar between the two groups for all studies. A total of 22 out of 39 studies (56 %) adjusted their analyses for offspring psychopathology, and 17 studies (44 %) adjusted for other covariates, such as biological sex or age. A total of 8 studies (21 %) showed response rates for both the familial risk and control groups.

3.3. Global functioning

A total of seventeen studies focused on global functioning (Bella et al., 2011; De la Serna et al., 2021; Ellersgaard et al., 2018; Goetz et al., 2017; Gregersen et al., 2022; Henin et al., 2005; Kim et al., 2015; Licona-Martínez et al., 2014; Lin et al., 2015; Linnen et al., 2009; McNamara et al., 2020; Miklowitz et al., 2011; Morón-Nozaleda et al., 2017; Ostiguy et al., 2012; Palacio-Ortiz et al., 2017; Pandina et al., 2020; Petresco et al., 2009). Thirteen out of seventeen studies compared offspring of parents with BD to a control group, four did not (Licona-Martínez et al., 2014; McNamara et al., 2020; Miklowitz et al., 2011; Pandina et al., 2020). Ten studies reported lower functioning in offspring of parents with BD (Bella et al., 2011; Ellersgaard et al., 2018; Goetz et al., 2017; Gregersen et al., 2022; Henin et al., 2005; Lin et al., 2015; Linnen et al., 2009; Morón-Nozaleda et al., 2017; Ostiguy et al., 2012; Palacio-Ortiz et al., 2017), and five studies did not find any differences (De la Serna et al., 2021; Gregersen et al., 2022; Kim et al., 2015; Morón-Nozaleda et al., 2017; Petresco et al., 2009). Three studies reported effect sizes and demonstrated small (Morón-Nozaleda et al., 2017), medium (Bella et al., 2011), and large (Licona-Martínez et al., 2014) effects.

3.3.1. Psychopathology

Five out of seventeen studies adjusted for offspring psychopathology in their analyses (Bella et al., 2011; Goetz et al., 2017; Gregersen et al., 2022; Lin et al., 2015; Morón-Nozaleda et al., 2017). Three studies showed lower functioning regardless of offspring psychopathology status (Bella et al., 2011; Goetz et al., 2017; Lin et al., 2015). Gregersen et al. (2022) reported lower global functioning in offspring of parents with BD in general and when only unaffected offspring were compared. However, when only affected offspring of parents with BD were compared to affected offspring of parents without any psychopathology, no differences in global functioning were found. Bella et al. (2011) showed lower global functioning after adjustment for offspring psychopathology in the BIOS cohort. Interestingly, in a later study of the same group, no differences were found between the groups on global functioning in offspring and controls with ADHD (Kim et al., 2015), suggesting type of psychopathology may affect findings.

It should be noted that most of the studies (k = 15/17, 88 %) used the CGAS and GAF to asses global functioning. These instruments assess social, occupational, and psychological functioning within one score The CGAS and GAF scores might provide a global overview of functioning, but the use of these instruments, especially without adjustment for offspring psychopathology, complicates interpretation of functional outcome in itself.

3.3.2. Age

Studies with a mean age below 16 years ($k = 12$) showed high heterogeneity in global functioning. Six studies demonstrated lower functioning in offspring of parents with BD when compared to controls (Bella et al., 2011; Ellersgaard et al., 2018; Goetz et al., 2017; Gregersen et al., 2022; Henin et al., 2005; Morón-Nozaleda et al., 2017) and five studies did not find any differences between the groups (De la Serna et al., 2021; Gregersen et al., 2022; Kim et al., 2015; Morón-Nozaleda et al., 2017; Petresco et al., 2009). Three studies did not include a control group and found poor to average global functioning among offspring younger than 16 years (Licona-Martínez et al., 2014; McNamara et al., 2020; Miklowitz et al., 2011). From age 16 and older ($k = 5$), results on global functioning were more consistent and global functioning was shown to be lower in offspring of parents with BD when compared to controls ($k = 4/5$) (Lin et al., 2015; Linnen et al., 2009; Ostiguy et al., 2012; Palacio-Ortiz et al., 2017).

In sum, the interpretation of global functioning in offspring with

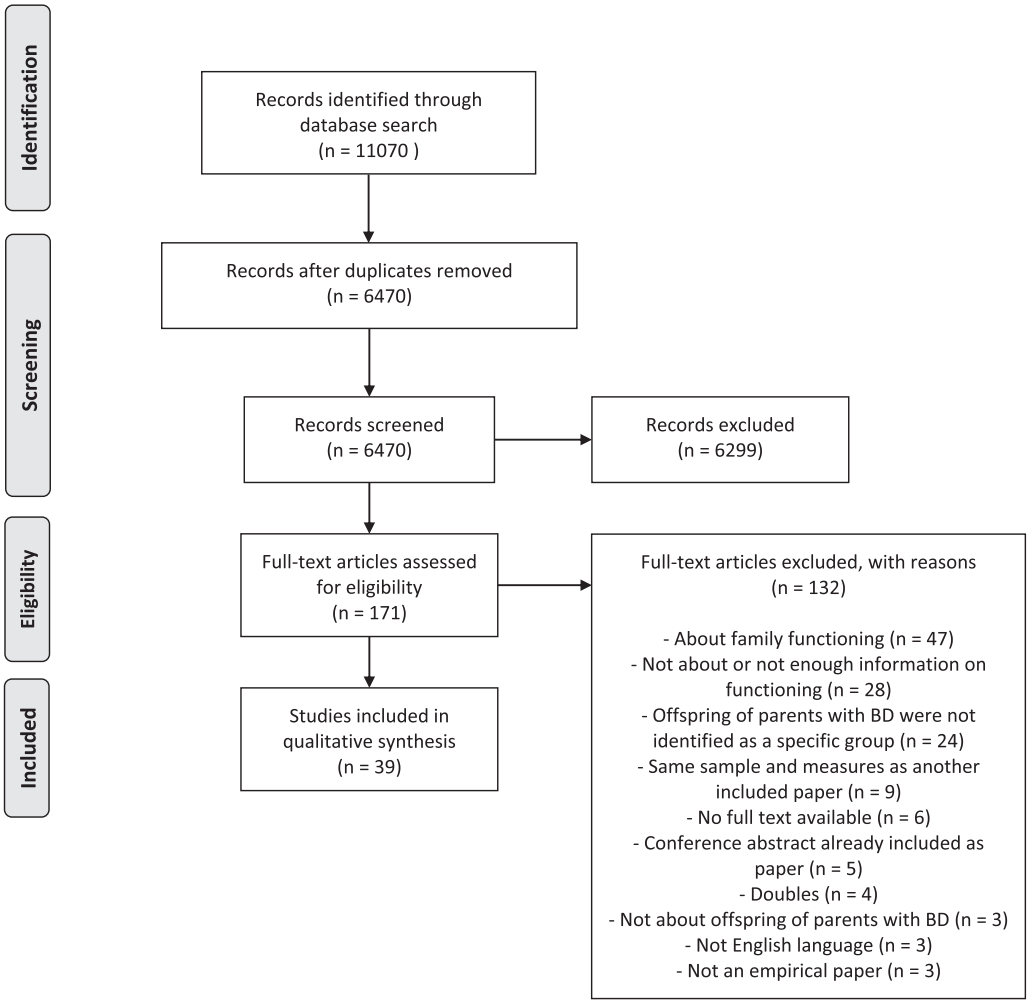

Fig. 1. PRISMA flow diagram of literature search and search process.

common measures like the CGAS and GAF scores is hampered by design as psychopathology is often part of the outcome. Offspring in their late adolescence and young adulthood show lower global functioning, but it is unclear whether the emergence of offspring psychopathology affects this.

3.4. Social functioning

Within the domain of social functioning, we included seventeen studies (Anderson and Hammen, 1993; Bella et al., 2011; Christiani et al., 2019; Conrad and Hammen, 1993; Crandall et al., 2014; Emery et al., 1982; Giles et al., 2007; Klein et al., 1986; Linnen et al., 2009; Ostiguy et al., 2012; Pellegrini et al., 1986; Petresco et al., 2009; Petti et al., 2004; Reichart et al., 2007; Whitney et al., 2013; Zahn-Waxler et al., 1984a, 1984b). All studies implemented a control group. The assessment of social functioning outcomes was heterogeneous, including diverging concepts: social functioning (Bella et al., 2011; Christiani et al., 2019; Ostiguy et al., 2012; Zahn-Waxler et al., 1984a, 1984b), social responsiveness (Christiani et al., 2019; Whitney et al., 2013), social adjustment (Crandall et al., 2014; Klein et al., 1986), social problems (Giles et al., 2007; Linnen et al., 2009; Petresco et al., 2009), social competence (Anderson and Hammen, 1993; Bella et al., 2011; Conrad and Hammen, 1993; Reichart et al., 2007), social support (Pellegrini et al., 1986; Petti et al., 2004), social interactions (Linnen et al., 2009), and likability by peers (Emery et al., 1982). The most commonly used instruments to measure social functioning were the Achenbach behavior questionnaires, such as the Children's Behavior Checklist, Youth Self Report, Young Adult Self Report, and Teacher Report Form (k = 7, 41 %).

Overall, twelve studies showed lower social functioning in offspring of parents with BD compared to controls (Bella et al., 2011; Crandall et al., 2014; Emery et al., 1982; Giles et al., 2007; Klein et al., 1986; Linnen et al., 2009; Ostiguy et al., 2012; Pellegrini et al., 1986; Petresco et al., 2009; Whitney et al., 2013; Zahn-Waxler et al., 1984a, 1984b). Nine studies did not show any differences on social functioning between the groups (Anderson and Hammen, 1993; Bella et al., 2011; Christiani et al., 2019; Conrad and Hammen, 1993; Linnen et al., 2009; Pellegrini et al., 1986; Petresco et al., 2009; Petti et al., 2004; Reichart et al., 2007), and one study revealed better social functioning in the offspring of parents with BD compared to controls (Petti et al., 2004). None of the social functioning concepts as introduced above showed unanimous results. Six studies reported effect sizes, of which three showed small effect sizes (Bella et al., 2011; Christiani et al., 2019; Reichart et al., 2007), one a medium effect size (Giles et al., 2007), and three demonstrated large effect sizes (Crandall et al., 2014; Giles et al., 2007; Whitney et al., 2013).

3.4.1. Psychopathology

Nine of the seventeen studies adjusted for offspring psychopathology in their analyses (Bella et al., 2011; Conrad and Hammen, 1993; Crandall et al., 2014; Giles et al., 2007; Klein et al., 1986; Linnen et al., 2009; Pellegrini et al., 1986; Petti et al., 2004; Reichart et al., 2007). After adjustment for offspring psychopathology, six studies demonstrated lower social functioning in high-risk offspring compared to controls

Table 1
Results of included studies of global functioning, social functioning, academic functioning (academic performance and school behavior), occupational functioning, and Quality of Life.

1A: Global functioning

Study	BD parent type	% BD parent female	Parent control offspring	Age range offspring	Measure	Offspring of parent with BD			Control offspring			Main findings	Effect size	Summary
						n (% female)	Mean age ± SD	Psychopathology %	n (% female)	Mean age ± SD	Psychopathology %			
(Bella et al., 2011), *USA*	NR	NR	w/o any Dx	6-18	CGAS	338 (48.5)	11.9±3.6	*Lifetime* Any: 59.8 BD: 10.3 Mood: 20.9 Anx: 25.8	118 (54.2)	11.7±3.4	*Lifetime* Any: 24.6 BD: 0.8 Mood: 1.6 Anx: 7.6	Offspring of parents with BD showed lower global functioning than controls. This effect remained when controlling for current offspring psychopathology and when only unaffected offspring of both groups were compared.	η2 = 0.07-0.10	↓*
(De la Serna et al., 2021), Spain	I, II	NR	w/o mood or psychotic Dx	6-19	CGAS	T1: 90 (44.4) T2: 78 (46.2)	T1: 12.5±3.1 T2: 14.6±3.2	*T1 Lifetime* Any: 37.8 Mood: 16.7 Anx: 13.3 *T2 Lifetime* Any: 42.2 Mood: 21.1 Anx: 18.9	T1: 107 (55.1) T2: 92 (54.3)	T1: 11.7±3.2 T2: 13.9±3.3	*T1 Lifetime* Any: 17.8 Mood: 5.6 Anx: 6.5 *T2 Lifetime* Any: 27.1 Mood: 8.4 Anx: 14	No differences in global functioning were found over time between offspring of parents with BD and controls nor within offspring of parents with BD.	NR	=
(Ellersgaard et al., 2018), *Denmark*	NR	55.2	community based	7	CGAS	119 (46.2)	7.9±0.2	*Lifetime* Any: 54.2 Mood: 4.2 Anx: 11.9	200 (46.5)	7.8±0.2	*Lifetime* Any: 37.1 Mood: 1.0 Anx: 4.6	Offspring of parents with BD showed lower global functioning than controls.	NR	↓
(Goetz et al., 2017), Czech Republic	I, II	44.1	w/o any Dx	6-17	GAF	43 (41.9)	12.5±3.1	*Lifetime* Any: 86 BD: 11.6 Mood: 32.5 Anx: 60.5 *Current* Any: 76.7 BD: 11.6 Mood: 28 Anx: 51.2	43 (41.9)	12.4±3.1	*Lifetime* Any: 41.9 BD: 0 Mood: 2.3 Anx: 14 *Current* Any: 23.3 BD: 0 Mood: 0 Anx: 11.6	Offspring of parents with BD showed lower global functioning than controls. This effect remained when controlling for current offspring psychopathology. Current offspring mood disorders were associated with the lowest scores in global functioning.	NR	↓*
(Henin et al., 2005), *USA*	NR	NR	w/o mood Dx	NR	GAF	117 (49.2)	13.6±5.3	*Lifetime* Mood: 42 Anx: 36	171 (48)	13.4±6.4	*Lifetime* Mood: 14 Anx: 14	Offspring of parents with BD showed lower global functioning than controls.	NR	↓
(Kim et al., 2015), *USA*	I, II	NR	w/o any Dx	6-18	CGAS	122 (42.6)	11.0±3.4	*Lifetime* Any: 100 BD: 29.5 Mood: 61.5 Anx: 50	48 (37.5)	11.2±3.5	*Lifetime* Any: 100 BD: 4.2 Mood: 18.8 Anx: 8.3	In offspring with ADHD, no differences in global functioning were found over time between offspring of parents with BD and controls, nor within offspring of parents with BD.	NR	=
(Gregersen et al., 2022), *Denmark*	NR	NR	community based	11	CGAS	104 (44.2)	11.9±0.2	*Lifetime* Any: 52.9 Mood: 10.6 Anx: 23.1	175 (46.9)	11.9±0.2	*Lifetime* Any: 28.6 Mood: 2.3 Anx: 9.1	Offspring of parents with BD showed lower global functioning than controls. When only offspring without psychopathology were compared, offspring of parents with BD still showed lower global functioning. However, when only offspring with current psychopathology were compared, no differences were found between the offspring groups.	NR	↓, ↓*, =*
(Licona-Martínez et al., 2014), *Mexico*	I, II	NR	-	6-17	CGAS	61 (62.3)	NR	*Lifetime* Mood: 21.3	-	-	-	Female offspring of parents with BD had lower global functioning than male offspring. When offspring had MDD, the chance to have lower global functioning compared to higher global functioning was 10 times higher.	OR = 5-11	○
(Lin et al., 2015), *China*	I, II	NR	w/o any Dx	8-28	GAF	44 (55)	17.1±6.1	*Lifetime* BD: 14 Mood: 39	33 (55)	15.9±4.4	*Lifetime* BD: 0 Mood: 0	Affected offspring of parents with BD showed lower global functioning than unaffected offspring of parents with BD and controls.	NR	↓*
(Linnen et al., 2009), *Canada*	NR	NR	w/o any Dx	15-25	GAF	25 (52)	18±2.5	*Lifetime* BD: 12 Mood: 24 *Current* BD: 4 Mood: 4	23 (48)	18±2.5	*Lifetime* BD: 0 Mood: 4 *Current* BD: 0 Mood: 4	Offspring of parents with BD showed lower global functioning than controls.	NR	↓
(McNamara et al., 2020), *USA*	I	NR	-	9-21	CGAS	56 (80)	14.1±3.0	*Current* Any: 100 Mood: 100 Anx: 27	-	-	-	Offspring of parents with BD and a current diagnosis of MDD/Depression NOS themselves scored poorer on global functioning.	NR	○

Study	BD parent type	% BD parent female	Parent control offspring	Age range offspring	Measure	Offspring of parent with BD			Control offspring			Main findings	Effect size	Summary
						n (% female)	Mean age ± SD	Psychopathology %	n (% female)	Mean age ± SD	Psychopathology %			
(Miklowitz et al., 2011), *USA*	I, II	53.8	-	9-16	A-LIFE	13 (69.2)	13.4±2.7	*Lifetime* BD: 38.5 Mood: 100	-	-	-	Offspring of parents with BD scored poor to average on global functioning.	NR	○
(Morón-Nozaleda et al., 2017), *Spain*	I, II	NR	w/o mood or psychotic Dx	6-17	CGAS	90 (44.4)	12.5±3.1	*Lifetime* Any: 63.3 Mood: 22.2 Anx: 30 *Current* Any: 46.7	107 (55.1)	11.7±3.2	*Lifetime* Any: 50.5 Mood: 8.4 Anx: 17.8 *Current* Any: 34.6	Offspring of parents with BD showed lower global functioning than controls (driven by post-pubertal offspring). This effect did not remain when controlled for sex, age, and current offspring psychopathology.	r = 0.15	↓, =*
(Ostiguy et al., 2012), *Canada*	NR	NR	w/o any Dx	15-25	UCLA LSI	64 (46)	20.3±3.2	*Current* Any: 34 Mood: 4.7 Anx: 29.7	59 (54)	19.3±2.8	*Current* Any: 22 Mood: 1.7 Anx: 13.6	Offspring of parents with BD showed lower global functioning than controls.	NR	↓
(Palacio-Ortiz et al., 2017), *Colombia*	I	NR	w/o mood or psychotic Dx	6-30	CGAS, GAF	127 (44.9)	17.6±NR	*Lifetime* BD: 5.5 Mood: 12.8	150 (47.3)	17.7±NR	*Lifetime* BD: 0 Mood: 1.13-4.5	Offspring of parents with BD showed lower global functioning than controls.	NR	↓
(Pandina et al., 2020), *USA*	NR	NR	-	15-25	GAF	233 (62.9)	18.6±NR	*Lifetime* BD: 0	-	-	-	Offspring with a lower GAF score (<70) reported more clinical symptoms themselves (as well as symptoms reported by a clinician), a higher number of weeks with subthreshold or diagnostic level symptoms of MDD, but not of mania/hypomania, and more serious psychiatric adverse events when compared to a higher functioning group.	NR	○
(Petresco et al., 2009), *Brazil*	I, II, NOS	100	w/o any Dx		CGAS	43 (58.1)	11.2±3.7	*Lifetime* Any: 62.8 BD: 2.3 Mood: 11.6 Anx: 44.2	53 (54.7)	12.4±3.2	*Lifetime* Any: 41.5 BD: 0 Mood: 5.7 Anx: 20.8	No differences on global functioning were found between offspring of parents with BD and controls.	NR	=

1B: Social functioning

Study	BD parent type	% BD parent female	Parent control offspring	Age range offspring	Measure	Offspring of parent with BD			Control offspring			Main findings	Effect size	Summary
						n (% female)	Mean age ± SD	Psychopathology %	n (% female)	Mean age ± SD	Psychopathology %			
(Anderson and Hammen, 1993), *USA*	NR	100	w/o any Dx	8-16	CBCL	18 (55)	13.8±2.9	NR	38 (50)	11.9±2.3	NR	No differences on social functioning were found between offspring of parents with BD and controls.	NR	=
(Bella et al., 2011), *USA*	NR	NR	w/o any Dx	6-18	A-LIFE; CBCL	338 (48.5)	11.9±3.6	*Lifetime* Any: 59.8 Mood: 20.9 BD: 10.3 Anx: 25.8	118 (54.2)	11.7±3.4	*Lifetime* Any: 24.6 Mood: 1.6 BD: 0.8 Anx: 7.6	Offspring of parents with BD showed lower social functioning than controls. This effect remained when controlling for current offspring psychopathology but not when only unaffected offspring of both groups were compared.	η2 = 0.02 - 0.03	=*, ↓*
(Christiani et al., 2019), *Denmark*	NR	55.2	community based	7	SRS; Vineland II	120 (46.7)	7.9±0.2	NR	200 (46.5)	7.8±0.2	NR	No differences on social responsiveness and social functioning were found between offspring of parents with BD and controls.	cohen's d = -0.2 - -0.3	=
(Conrad and Hammen, 1993), *USA*	NR	100	w/o any Dx		CBCL	18 (52)	12.5±2.5	4 point severity scale (0-3) T1: 0.72±1.13; T2: 1.27±1.22	38 (52)	12.5±2.5	4 point severity scale (0-3) T1: 0.47±1.06; T2: 0.31±0.90	Affected offspring of parents with BD showed lower social competence than unaffected offspring of parents with BD and controls.	NR	=*
(Crandall et al., 2014), *USA*	NR	NR	w/o mood Dx		SACQ	27 (77.8)	21.1±2.5	*Lifetime* BD: 18.5 Mood: 40.7 *Current* Mood: 11.1	32 (75)	20.9±3.2	*Lifetime* BD: 3.1 Mood: 37.5 *Current* Mood: 3.1	Offspring of parents with BD showed lower social adjustment than controls.	cohen's d = -.74	↓*
(Emery et al., 1982), *USA*	NR	NR	w/o any Dx	7-15	DESB, PEI	47	NR	NR	57	NR	NR	Offspring of parents with BD were reported to be less likeable by peers than controls.	NR	↓
(Giles et al., 2007), *USA*	I	NR	w/o any Dx	10-18	CBCL	HR: 31 (58); BD: 28 (43)	HR: 13.8±0.4; BD: 14.2±0.4	*Lifetime HR* Any: 34 BD: 23 Mood: 39 *Lifetime BD-I* BD: 100	44	13.9±0.3	*Lifetime* Any: 0 BD: 0 Mood: 0	Offspring of parents with BD showed more social problems than controls.	cohen's d = 0.6 – 1.4	↓*

Study	BD parent type	% BD parent female	Parent control offspring	Age range offspring	Measure	Offspring of parent with BD			Control offspring			Main findings	Effect size	Summary
						n (% female)	Mean age ± SD	Psychopathology %	n (% female)	Mean age ± SD	Psychopathology %			
(Klein et al., 1986), *USA*	I	54	w/o any Dx	15-21	LAI	41 (49)	18±2.0	*Lifetime* BD: 27	26 (38)	17.7±2.1	NR	Affected offspring of parents with BD showed lower social adjustment than unaffected offspring of parents with BD and controls.	NR	↓*
(Linnen et al., 2009), Canada	NR	NR	w/o any Dx	15-25	Event-contingent recording of social interactions; YSR	25 (52)	18±2.5	*Lifetime* BD: 12 Mood: 24 *Current* BD: 4 Mood: 0	23 (48)	18±2.5	*Lifetime* BD: 0 Mood: 4 *Current* BD: 0 Mood: 4	No differences on social problems were found between offspring of parents with BD and controls. Female offspring of parents with BD scored lower on quarrelsomeness and higher on agreeableness than male offspring of parents with BD and controls. No differences on dominant or submissive behaviour were found between offspring of parents with BD and controls.	NR	=*, ↓*
(Ostiguy et al., 2012), *Canada*	NR	NR	w/o any Dx	15-25	UCLA LSI	64 (46)	20.3±3.2	*Current* Any: 34 Mood: 4.7 Anx: 29.7	59 (54)	19.3±2.7	*Current* Any: 22 Mood: 1.7 Anx: 13.6	Offspring of parents with BD showed lower social functioning than controls.	NR	↓
(Pellegrini et al., 1986), *USA*	I	NR	w/o any Dx	7-18	social network structure	23 (NR)	12.7±NR	*Lifetime* Any: 70	33 (NR)	12.7±NR	*Lifetime* Any: 45	Offspring of parents with BD reported less support by residing kin supporters, nonkin adult supporters, and reciprocal supporters than controls, but more support by nonresiding kin supportersthan controls. No differences were found in peer supporters by offspring of parents with BD and controls.	NR	=*, ↓*
(Petresco et al., 2009), *Brazil*	I, II, NOS	100	w/o any Dx		CBCL; YSR	43 (58.1)	11.2±3.7	*Lifetime* Any: 62.8 BD: 2.3 Mood: 11.6 Anx: 44.2	53 (54.7)	12.4±3.2	*Lifetime* Any: 41.5 BD: 0 Mood: 5.7 Anx: 20.8	Offspring of parents with BD reported themselves to have more social problems than controls, but no differences on social problems were found between offspring of parents with BD and controls when the parent reported.	NR	=, ↓
(Petti et al., 2004), USA	I	NR	w/o any Dx	6-17	Harter social support scales	23 (52)	11.1±3.1	*Lifetime* Mood: 39	27 (52)	11.1±3.1	*Lifetime* Mood: 11	Affected offspring of parents with BD reported more support by classmates than unaffected offspring of parents with BD and controls, but this was not reported by teachers nor parents.	NR	=*, ↑*
(Reichart et al., 2007), *The Netherlands*	I, II, NOS	NR	community based	11-26	CBCL, YSR, TRF, YASR	11-17: 102 (NR); 18-26: 106 (NR)	NR	*Lifetime 11-17 years* Any: 43 Mood: 29 *Lifetime 18-26 years* Any: 62 BD: 9 Mood: 42	11-17: 1122 (NR); 18-26: 1175 (NR)	NR	NR	No differences on social functioning were found between offspring of parents with BD and controls.	< 1%	=*
(Whitney et al., 2013), *USA*	NR	NR	w/o any Dx	9-18	SRS	24 (46)	12.7±2.9	*Lifetime* Any: 100 BD: 23 Mood: 37 *Current* Mood: 56	27 (60)	13.3±2.6	*Lifetime* Any: 0 BD: 0 Mood: 0 *Current* Mood: 0	Affected offspring of parents with BD showed lower social functioning than controls.	cohen's d = 1.7	↓
(Zahn-Waxler et al., 1984a), *USA*	NR	57	w/o mood Dx	1-2	Agent Use Task	7 (0)	T1: 12-14 months, T2: 18 months, T3: 2 years	NR	20 (50)	T1: 12-14 months, T2: 18 months, T3: 2 years	NR	Offspring of parents of BD showed more self-oriented play and less other-oriented play than controls.	NR	↓
(Zahn-Waxler et al., 1984b), *USA*	NR	57	w/o mood Dx	2	lab test of social interaction	7 (0)	2±NR	NR	20 (50%)	2	NR	Offspring of parents with BD showed less social interaction and sharing with playmates than controls.	NR	↓

1C: Academic functioning – academic performance

Study	BD parent type	% BD parent female	Parent control offspring	Age range offspring	Measure	Offspring of parent with BD			Control offspring			Main findings	Effect size	Sum-mary
						n (% female)	Mean age ± SD	Psycho-pathology %	n (% female)	Mean age ± SD	Psycho-pathology %			
(Anderson and Hammen, 1993), *USA*	NR	100	w/o any Dx	8-16	TRF; CTRS	19 (55)	13.8±2.1	NR	39 (50)	11.9±2.4	NR	No differences on academic performance were found between offspring of parents with BD and controls.	NR	=
(Bella et al., 2011), *USA*	NR	NR	w/o any Dx	6-18	CBCL	338 (48.5)	11.9±3.6	*Lifetime* Any: 59.8 BD: 10.3 Mood: 20.9 Anx: 25.8	118 (54.2)	11.7±3.4	*Lifetime* Any: 24.6 BD: 0.8 Mood: 1.6 Anx: 7.6	Offspring of parents with BD showed lower academic performance than controls.	η2 = 0.02	↓*
(Conrad and Hammen, 1993), *USA*	NR	100	w/o any Dx	NR	CBCL	18 (52)	12.5±2.5	4 point severity scale (0-3) T1: 0.72±1.13; T2: 1.27±1.22	38 (52)	12.5±2.5	4 point severity scale (0-3) T1: 0.47±1.06; T2: 0.31±0.90	No differences on academic performance were found between offspring of parents with BD and controls.	NR	=*
(Henin et al., 2005), *USA*	NR	NR	w/o mood Dx	NR	placement in special classes, years repeated, receiving extra help in school	117 (49.2)	13.6±5.3	*Lifetime* Mood: 42 Anx: 36	171 (48)	13.4±6.4	*Lifetime* Mood: 14 Anx: 14	Offspring of parents with BD were more often placed into special classes than controls. No differences were found between offspring of parents with BD and controls on school years repeated and on receiving extra help in school.	OR = 3.9	↓, =
(Lin et al., 2015), *China*	I, II	NR	w/o any Dx	8-28	years of education	44 (55)	17.1±6.1	*Lifetime* BD: 14 Mood: 39	33 (55)	15.9±4.4	*Lifetime* BD: 0 Mood: 0	No differences on academic performance were found between offspring of parents with BD and controls.	NR	=
(Lin et al., 2017), *Australia*	NR	100	w/o any Dx	12	WALNA	766 (49.9)	12.2±0.4	NR	88,353	12.1±0.3	NR	Offspring of parents with BD showed lower general academic performance than controls. No differences were found on any particular domain between offspring of parents with BD and controls.	OR 1.1-1.3	↓, =
(McDonough-Ryan et al., 2002), *USA*	I	NR	w/o any Dx	8-12	WRAT-3	28 (53.6)	10.2±2.7	NR	24 (54.2)	10±1.3	NR	Offspring of parents with BD showed lower academic performance than controls. No differences were found on reading and arithmethic disabilities between offspring of parents with BD and controls.	NR	↓, =
(Palacio-Ortiz et al., 2017), *Colombia*	I	NR	w/o mood or psycho-tic Dx	6-30	grades + years repeated	127 (44.9)	17.6±NR	*Lifetime* BD: 5.5 Mood: 12.8	150 (47.3)	17.7±NR	*Lifetime* BD: 0 Mood: 1.13-4.5	No differences on academic performance were found between offspring of parents with BD and controls.	NR	=
(Petresco et al., 2009), *Brazil*	I, II, NOS	100	w/o any Dx	NR	mean years education	43 (58.1)	11.2±3.7	*Lifetime* Any: 62.8 BD: 2.3 Mood: 11.6 Anx: 44.2	53 (54.7)	12.4±3.2	*Lifetime* Any: 41.5 BD: 0 Mood: 5.7 Anx: 20.8	No differences on academic performance were found between offspring of parents with BD and controls.	NR	=
(Ranning et al., 2018), *Denmark*	NR	NR	w/o mood or psycho-tic Dx	18	registries	3806 (48.3)	18±NR	*Lifetime before age 16* Any: 12.1	676,141 (48.7)	18±NR	*Lifetime before age 16* Any: 5.06	Having a bipolar mother (but not a bipolar father) was associated with a higher chance of receiving lower grades and not completing school. When offspring of parents with BD were placed into care, they had a higher chance of receiving a higher grade, and a lower chance of receiving a lower grade and not completing school.	OR 0.5-2.6	↓, ↑*, ↓*
(Reichart et al., 2007), *The Netherlands*	I, II, NOS	NR	com-munity based	11-26	CBCL, YSR, TRF, YASR	11-17: 102 (NR); 18-26: 106 (NR)	NR	*Lifetime 11-17 years* Any: 43 Mood: 29 *Lifetime 18-26 years* Any: 62 BD: 9 Mood: 42	11-17: 1122 (NR); 18-26: 1175 (NR)	NR	NR	No differences on academic performance were found between offspring of parents with BD and controls.	< 1%	=*
(Tempelaar et al., 2019), *The Netherlands*	I, II		-	NR	LEDS	92 (45.2)	28±NR	*Lifetime* Any: 73 BD: 14 Mood: 57	-	-	-	13% declined to a lower educational level, 26.1% repeated a grade, and 43.5% (temporarily) discontinued school without	NR	

Study	BD parent type	% BD parent female	Parent control offspring	Age range offspring	Measure	Offspring of parent with BD			Control offspring			Main findings	Effect size	Summary
						n (% female)	Mean age ± SD	Psychopathology %	n (% female)	Mean age ± SD	Psychopathology %			
												completion. There was overlap between these groups. Educational achievement was not related to development of any mental disorder or age at onset in offspring.		
(Waters et al., 1981), *Canada*	NR	47	-	28	records	55 (55)	28±NR	*Lifetime* Mood: 43	-	-	-	No differences were found between affected and unaffected offspring of parents with BD on academic performance.	NR	

1D: Academic functioning – school behavior

Study	BD parent type	% BD parent female	Parent control offspring	Age range offspring	Measure	Offspring of parent with BD			Control offspring			Main findings	Effect size	Summary
						n (% female)	Mean age ± SD	Psychopathology %	n (% female)	Mean age ± SD	Psychopathology %			
(Anderson and Hammen, 1993), *USA*	NR	100	w/o any Dx	8-16	TRF; CTRS	19 (55)	13.8±2.1	NR	39 (50)	11.9±2.4	NR	No differences on school behavior were found between offspring of parents with BD and controls.	NR	=
(Crandall et al., 2014), *USA*	NR	NR	w/o mood Dx	NR	SACQ	27 (77.8)	21.1±2.5	*Lifetime* BD: 18.5 Mood: 40.7 *Current* Mood: 11.1	32 (75)	20.9±3.2	*Lifetime* BD: 3.1 Mood: 37.5 *Current* Mood: 3.1	Offspring of parents with BD showed lower school behavior than controls.	cohen's d = -.74	↓*
(Emery et al., 1982), *USA*	NR	NR	w/o any Dx	7-15	DESB; PEI	47	NR	NR	57	NR	NR	Offspring of parents with BD showed lower school behavior than controls.	NR	↓
(Reichart et al., 2007), *The Netherlands*	I, II, NOS	NR	community based	11-26	CBCL, YSR, TRF, YASR	11-17: 102 (NR); 18-26: 106 (NR)	NR	*Lifetime 11-17 years* Any: 43 Mood: 29 *Lifetime 18-26 years* Any: 62 BD: 9 Mood: 42	11-17: 1122 (NR); 18-26: 1175 (NR)	NR	NR	No differences on school behavior were found between offspring of parents with BD and controls.	< 1%	=*
(Shaw et al., 2005), *USA*	I	NR	w/o any Dx	17-18	CARE Interview	110 (53)	NR	*Lifetime* high risk rating: 41	112 (50)	NR	*Lifetime* high risk rating: 16	Offspring of parents with BD showed lower school behavior than controls.	NR	↓

1E: Occupational functioning

Study	*BD parent type*	*% BD parent female*	*Parent control offspring*	*Age range offspring*	*Measure*	*Offspring of parent with BD*			*Control offspring*			Main findings	Effect size	Summary
						n (% female)	*Mean age* ± SD	Psychopathology %	n (% female)	Mean age ± SD	Psychopathology %			
(Bella et al., 2011), *USA*	NR	NR	w/o any Dx	6-18	A-LIFE, CBCL	338 (48.5)	11.9±3.6	*Lifetime* Any: 59.8 BD: 10.3 Mood: 20.9 Anx: 25.8	118 (54.2)	11.7±3.4	*Lifetime* Any: 24.6 BD: 0.8 Mood: 1.6 Anx: 7.6	Offspring of parents with BD showed lower occupational functioning than controls. This effect remained when controlling for current offspring psychopathology and when only unaffected offspring of both groups were compared.	η2 = 0.03	↓*
(Reichart et al., 2007), *The Netherlands*	I, II, NOS	NR	community based	11-26	CBCL, YSR, TRF, YASR	11-17: 102 (NR); 18-26: 106 (NR)	NR	*Lifetime 11-17 years* Any: 43 Mood: 29 *Lifetime 18-26 years* Any: 62 BD: 9 Mood: 42	11-17: 1122 (NR); 18-26: 1175 (NR)	NR	NR	No differences on occupational functioning were found between offspring of parents with BD and controls.	< 1%	=*
(Verdoux and Bourgeois, 1995), *France*	I, II	84	-	NR	INREE categories	60 (55)	NR	NR	-	-	-	There was an overrepresentation of offspring of parents with BD in the lowest occupational level compared to higher occupational levels.	NR	

1F: QoL

Study	BD parent type	% BD parent female	Parent control offspring	Age range offspring	Measure	Offspring of parent with BD			Control offspring			Main findings	Effect size	Summary
						n (% female)	Mean age ± SD	Psychopathology %	n (% female)	Mean age ± SD	Psychopathology %			
(Bella et al., 2011), *USA*	NR	NR	w/o any Dx		A-LIFE, CBCL	338 (48.5)	11.9±3.6	*Lifetime* Any: 59.8 BD: 10.3 Mood: 20.9 Anx: 25.8	118 (54.2)	11.7±3.4	*Lifetime* Any: 24.6 BD: 0.8 Mood: 1.6 Anx: 7.6	Offspring of parents with BD showed lower QoL than controls. This effect remained when controlling for current offspring psychopathology and when only unaffected offspring of both groups were compared.	η2 = 0.05	↓*
(Crandall et al., 2014), *USA*	NR	NR	w/o mood Dx		ZBI	27 (77.8)	21.1±2.5	*Lifetime* BD: 18.5 Mood: 40.7 *Current* Mood: 11.1	32 (75)	20.9±3.2	*Lifetime* BD: 3.1 Mood: 37.5 *Current* Mood: 3.1	No differences on QoL were found between offspring of parents with BD and controls. Offspring of parents with BD showed a greater burden with respect to their parents than controls.	NR	=, ↓
(Ellersgaard et al., 2020), *Denmark*	NR	54.8	community based	7	Kidscreen-27	119 (46.2)	7.9±0.2	*Current* Any: 27.1	199 (46.2)	7.8±0.2	*Current* Any: 11.7	Offspring of parents with BD showed lower QoL in social acceptance and bullying than controls. No differences on QoL in physical well-being, psychological well-being, autonomy and parent relations, social support and peers, or school environment were found between offspring of parents with BD and controls.	NR	↓, =
(Goetz et al., 2017), *Czech Republic*	I, II	44.1	w/o any Dx	6-17	Kidscreen-52	43 (41.9)	12.5±3.1	*Lifetime* Any: 86 Mood: 32.5 BD: 11.6 Anx: 60.5 *Current* Any: 76.7 Mood: 28 BD: 11.6 Anx: 51.2	43 (41.9)	12.4±3.1	*Lifetime* Any: 41.9 Mood: 2.3 BD: 0 Anx: 14 *Current* Any: 23.3 Mood: 0 BD: 0 Anx: 11.6	Offspring of parents with BD showed lower QoL in social support and relationships with peers, parent relationships and home life, and self-perception than controls. No differences on QoL in physical and psychological well-being, satisfaction with moods and emotions, autonomy, school environment, social acceptance and bullying, and financial resources were found between offspring of parents with BD and controls.	cohen's d - 0.5- - 0.9	↓*, =*
(Giles et al., 2007), *Brazil*	I	NR	w/o any Dx	10-17	Youth Quality of Life Instrument-Research	17 (35.3)	14.4±2.9	*Lifetime* Any: 0 *Current* Any: 0	24 (66.7)	14.2±2.2	*Lifetime* Any: 0 *Current* Any: 0	No differences on QoL were found between offspring of parents with BD and controls.	NR	=

Note: NR = not reported; w/o = without; Dx = disorders; Any = any psychiatric disorder; BD = bipolar disorder; Mood = any mood disorder, including bipolar disorder; Anx = any anxiety disorder; MDD = Major Depressive Disorder; ↓ = lower functioning in offspring of parents with BD when compared to controls; ↑ = higher functioning in offspring of parents with BD when compared to controls; = = no differences were found between offspring of parents with BD and controls; ○ = no control group involved; * = statistically adjusted for offspring psychopathology; QoL = Quality of Life; CGAS = Children's Global Assessment Scale; GAF = Global Assessment of Functioning; A-LIFE = Adolescent Longitudinal Interval Follow-up Evaluation; UCLA LSI = University of California, Los Angeles Life Stress Interview; CBCL = Child Behavior Checklist; SRS = Social Responsiveness Scale; SACQ = Student Adaption to College Questionnaire; DESB = Devereux Elementary School Behavior; PEI = Pupil Evaluation Inventory; LAI = Life Activities Inventory; YSR = Youth Self Report; TRF = Teacher Report Form; YASR = Young Adult Self Report; CTRS = Conners Teacher Rating Scale; WALNA = Western Australian Literacy and Numeracy Assessment; WRAT-3; Wide Range Achievement Test 3; LEDS = Life Events and Difficulties Schedule; CARE Interview = Children and Adolescent Research and Evaluation Interview; INREE = Institut de Recherche sur les Expériences Extraordinaires; ZBI = Zarit Burden Interview; YQOL-R = Youth Quality of Life Instrument – Research.

(Bella et al., 2011; Crandall et al., 2014; Giles et al., 2007; Klein et al., 1986; Linnen et al., 2009; Pellegrini et al., 1986). In contrast, studies comparing unaffected offspring with unaffected controls found no differences in social functioning (Bella et al., 2011; Klein et al., 1986). In addition, another six studies showed no differences on social functioning between groups after adjustment for psychopathology (Bella et al., 2011; Conrad and Hammen, 1993; Linnen et al., 2009; Pellegrini et al., 1986; Petti et al., 2004; Reichart et al., 2007). One study demonstrated better social functioning (Petti et al., 2004). Despite the mixed results, these results suggest that social functioning is related to the emergence of psychopathology in offspring and is perhaps not only due to familial risk per se.

3.4.2. Age

Regarding age, two studies on preschool children showed lower social functioning in the offspring of parents with BD compared to controls (Zahn-Waxler et al., 1984a, 1984b). In primary school-aged children, results were mixed. Studies reported lower (Bella et al., 2011; Emery et al., 1982; Petresco et al., 2009), equal (Bella et al., 2011; Christiani et al., 2019; Petresco et al., 2009; Petti et al., 2004), and better (Petti et al., 2004) social functioning in offspring of parents with BD compared to controls. This mixed pattern was also observed during adolescence, with four studies showing lower social functioning in offspring of BD parents (Giles et al., 2007; Klein et al., 1986; Pellegrini et al., 1986; Whitney et al., 2013) and four studies showing no differences between the two groups (Anderson and Hammen, 1993; Conrad and Hammen, 1993; Pellegrini et al., 1986; Reichart et al., 2007). In young adulthood, studies predominantly showed lower social functioning among offspring of parents with BD compared to controls (Crandall et al., 2014; Linnen et al., 2009; Ostiguy et al., 2012).

Overall, studies showed that social functioning seems affected by offspring psychopathology and age, in addition to their familial risk and its consequences.

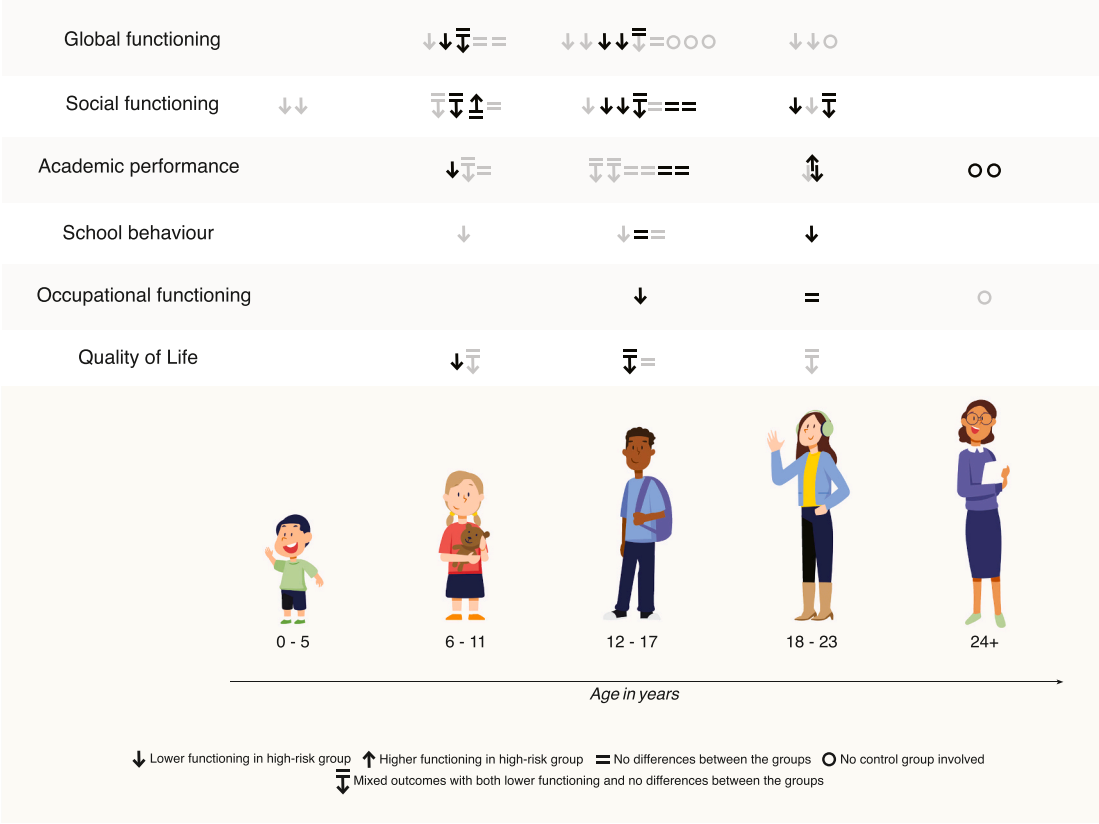

Fig. 2. Summary of findings of the included studies on global functioning, social functioning, academic functioning (academic performance and school behavior), occupational functioning, and Quality of Life. The color black indicates findings adjusted for offspring psychopathology, and the color grey indicates unadjusted findings. Findings are grouped by type of result.

3.5. Academic functioning

Sixteen studies assessed academic functioning in offspring of parents with BD. Academic functioning can be organized into two sub-domains: academic performance (Anderson and Hammen, 1993; Bella et al., 2011; Conrad and Hammen, 1993; Henin et al., 2005; Lin et al., 2017, 2015; McDonough-Ryan et al., 2002; Palacio-Ortiz et al., 2017; Petresco et al., 2009; Ranning et al., 2018; Reichart et al., 2007; Tempelaar et al., 2019; Waters et al., 1981) and school behavior (Anderson and Hammen, 1993; Crandall et al., 2014; Emery et al., 1982; Reichart et al., 2007; Shaw et al., 2005). Academic performance refers to objective measures, such as school grades, years of education, repeating a grade, school level downgrading, dropping-out or discontinuation of school, and educational level attainment. School behavior mainly includes subjective measures, such as coping with educational demands and behavior in the classroom.

3.5.1. Academic performance

Twelve studies examined academic performance, including ten studies that implemented a control group. From these ten studies, four studies showed lower academic performance (Bella et al., 2011; Henin et al., 2005; McDonough-Ryan et al., 2002; Ranning et al., 2018), nine studies did not find different results in academic performance (Anderson and Hammen, 1993; Conrad and Hammen, 1993; Henin et al., 2005; Lin et al., 2017, 2015; McDonough-Ryan et al., 2002; Palacio-Ortiz et al., 2017; Petresco et al., 2009; Reichart et al., 2007), and one study showed better academic performance in the offspring of parents with BD as compared to controls (Ranning et al., 2018). Five studies reported effect sizes ranging from small (Bella et al., 2011; Lin et al., 2017; Ranning et al., 2018; Reichart et al., 2007) to medium (Henin et al., 2005).

3.5.1.1. Psychopathology. Only four out of 12 studies adjusted for offspring psychopathology, resulting in mixed findings (Bella et al., 2011; Conrad and Hammen, 1993; Ranning et al., 2018; Reichart et al., 2007). Two studies demonstrated lower academic performance (Bella et al., 2011; Ranning et al., 2018), and two studies showed no differences in academic performance (Conrad and Hammen, 1993; Reichart et al., 2007) in offspring of parents with BD when compared to controls. The Danish registry study showed that having a bipolar mother (but not a bipolar father) was associated with a higher risk of receiving lower grades and not completing school (Ranning et al., 2018). Interestingly, when offspring of parents with BD were placed into out-of-home care, they had a higher chance of receiving higher grades, and a lower risk of not completing school, even after adjusting for offspring psychopathology (Ranning et al., 2018). Two studies that did not implement a control group but examined offspring psychopathology showed that educational achievement in adulthood was not related to psychopathology in the offspring of bipolar parents (Tempelaar et al., 2019; Waters et al., 1981).

3.5.1.2. Age. Three studies focused on primary school age, showing lower (Bella et al., 2011; McDonough-Ryan et al., 2002) to no difference (McDonough-Ryan et al., 2002; Petresco et al., 2009) in academic performance in offspring of BD parents. In adolescence, all studies found no differences in academic performance between the groups (Anderson and Hammen, 1993; Conrad and Hammen, 1993; Henin et al., 2005; Lin et al., 2017, 2015; Palacio-Ortiz et al., 2017; Reichart et al., 2007). Among these studies, two studies also reported findings of lower academic performance in offspring of BD parents than in control offspring (Henin et al., 2005; Lin et al., 2017). Only one study focused on young adulthood, and it showed both lower and higher academic performance outcomes (Ranning et al., 2018).

In sum, studies do not indicate differences in academic performance between the offspring of parents with and without BD through primary school age and adolescence. Moreover, in the limited studies that accounted for offspring psychopathology, offspring psychopathology did not seem to be associated with academic performance.

3.5.2. School behavior

All five studies that examined school behavior implemented a control group. Compared to controls, three studies found lower scores on school behavior in offspring of parents with BD (Crandall et al., 2014; Emery et al., 1982; Shaw et al., 2005), and two studies did not find any differences (Anderson and Hammen, 1993; Reichart et al., 2007). Crandall et al. (2014) reported a large effect size, suggesting a strong relationship between familial risk status and school behavior.

3.5.2.1. Psychopathology. Only two out of five studies adjusted for offspring psychopathology, resulting in either lower scores in offspring of BD parents (Crandall et al., 2014) or no differences on school behavior between the groups (Reichart et al., 2007). The adjustment for offspring psychopathology did not change the overall findings regarding school behavior.

3.5.2.2. Age. No studies reported on primary school age. Four of the five studies focused on adolescence (Anderson and Hammen, 1993; Emery et al., 1982; Reichart et al., 2007; Shaw et al., 2005), and one study included a young adult sample of college students (Crandall et al., 2014).

Overall, the few studies on school behavior show mixed results varying from lower functioning to no differences in levels of functioning. No definite conclusions can be drawn regarding school behavior in association to age and psychopathology.

3.6. Occupational functioning

Three studies examined occupational functioning in offspring of parents with BD (Bella et al., 2011; Reichart et al., 2007; Verdoux and Bourgeois, 1995). One study showed lower occupational functioning (Bella et al., 2011), another study did not find any differences between affected offspring, unaffected offspring, and controls (Reichart et al., 2007), and another study did not implement a control group (Verdoux and Bourgeois, 1995). Offspring psychopathology did not alter findings (Bella et al., 2011; Reichart et al., 2007). Verdoux and Bourgeois (1995) showed a skewed distribution of occupational level with an overrepresentation of offspring of parents with BD in the lowest occupational level compared to higher occupational levels, but no demographic or psychiatric characteristics of the offspring were reported. Due to limited studies and overlap in age range no further evaluation on age was possible.

3.7. Quality of life

A total of five studies examined QoL in children of parents with BD and all studies implemented a control group (Bella et al., 2011; Crandall et al., 2014; Ellersgaard et al., 2020; Goetz et al., 2017; Gomes et al., 2016). Four studies showed findings with lower QoL in offspring of BD parents (Bella et al., 2011; Crandall et al., 2014; Ellersgaard et al., 2020; Goetz et al., 2017) and another four studies reported no differences in QoL (Crandall et al., 2014; Ellersgaard et al., 2020; Goetz et al., 2017; Gomes et al., 2016). Two of the studies that revealed mixed results showed lower QoL of the offspring of BD parents compared to controls in the social domains, but not in other domains, such as physical well-being, autonomy, or school environment (Ellersgaard et al., 2020; Goetz et al., 2017). Two studies reported effect sizes ranging from medium (Bella et al., 2011; Goetz et al., 2017) to large (Goetz et al., 2017) effect sizes.

3.7.1. Psychopathology

Only two out of five studies adjusted for offspring psychopathology (Bella et al., 2011; Gomes et al., 2016), both reporting contrasting results. Indeed, Bella et al. (2011) showed that satisfaction with life was lower in offspring of parents with BD when compared to controls, even after controlling for current offspring psychopathology, and when only unaffected offspring of both groups were compared. Whereas another study where only unaffected offspring of both groups were compared found no differences for QoL (Gomes et al., 2016).

3.7.2. Age

Two studies were performed in primary school-aged offspring (Bella et al., 2011; Ellersgaard et al., 2020), two studies in adolescence (Goetz et al., 2017; Gomes et al., 2016), and one study with young adult college students (Crandall et al., 2014). As shown in Fig. 2, results are mixed across all age categories.

Overall, the few studies focusing on QoL revealed mixed results ranging from lower QoL to no differences in QoL. QoL experiences in the social domain are potentially affected. Information on offspring psychopathology and age is limited.

3.8. Cross-disorder comparison

We examined the generalizability of our results in terms of offspring of parents with other severe mental illnesses (see Table S7, available online). From the studies included in this systematic review, thirteen studies implemented one or two additional control group(s) of offspring with parents with schizophrenia ($k = 8$), unipolar depression ($k = 4$), or unspecified non-BD psychopathology ($k = 3$). Compared to offspring of parents with schizophrenia, offspring of parents with BD scored similar (Gregersen et al., 2022), or higher on global (De la Serna et al., 2021; Ellersgaard et al., 2018), social (Christiani et al., 2019), academic functioning (Lin et al., 2017; Ranning et al., 2018), and QoL (Ellersgaard et al., 2020). When compared to offspring of parents with unipolar depression, studies reported higher academic performance among offspring of BD parents (Anderson and Hammen, 1993; Lin et al., 2017) but no differences in social functioning, school behavior, and QoL (Crandall et al., 2014; Emery et al., 1982). Compared to offspring of parents with unspecified non-BD psychopathology, offspring of parents with BD scored lower (Bella et al., 2011) or showed no differences (Klein et al., 1986; Petresco et al., 2009) on all domains of functional outcomes.

In sum, findings suggest better functioning in offspring of parents with BD as compared to offspring of parents with schizophrenia, but whether the effect of familial BD differs from familial unipolar depression or unspecified non-BD psychopathology is less clear.

4. Discussion

With this review, we aimed to present a comprehensive overview of the functional outcomes and QoL in offspring of parents with BD throughout development and explore associations among functional outcomes, offspring psychopathology, and offspring age. A synthesis of the review findings can be found in Fig. 2. The main findings were that: 1) high heterogeneity was found in study methods and study quality in all functional domains; 2) global and social functioning seemed to be impaired in older offspring (>16 years) of parents with BD; 3) academic performance in offspring of parents with BD appeared to be unaffected by their familial risk status throughout the lifespan; 4) school behavior, occupational functioning, and QoL showed mixed results; 5) offspring psychopathology and age are highly related to social functioning, but the relationship of offspring psychopathology and age with other domains is less clear; 6) inconsistent adjustment for offspring psychopathology often impeded interpretation; and 7) information on parental characteristics (i.e., parental BD subtype, biological sex) was not systematically reported. This review highlights the complex relationships (e.g., overlap, bidirectional interactions) between functional outcomes,

offspring psychopathology, and age in offspring of parents with BD.

We investigated functional outcomes in offspring of parents with BD in the light of offspring psychopathology, as these two concepts are highly related. For example, this can be seen within the impaired functioning criterion of the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) and onwards, which states that a DSM diagnosis requires distress or clinically significant functional impairment at school, work, or within any other important domains to determine most of the psychiatric disorders (American Psychiatric Association, 2013; American Psychiatric Association et al., 2000). This review shows that studies on social functioning show at least a partial effect of offspring psychopathology on functional outcomes. Nonetheless, for the other domains, our review did not yield a clear relationship between functional outcomes and offspring psychopathology. One of the main challenges is that the relationship between offspring psychopathology and functional outcomes was not specifically addressed within many of the included studies, for example by omitting to measure psychopathology in the offspring or by using functional measures that include psychopathology within the scales. Indeed, offspring psychopathology may be an independent pathway that affects functioning beyond the fact that being a child of a parent affected by BD may already confer a risk for functional outcomes. Hence, if no adjustment for the offspring's own psychopathology is made, it becomes difficult to establish whether impaired functioning is associated with the effects of the parental disorder per se or is rather associated with the offspring's own psychopathology. To understand the relationship between high-risk status, offspring psychopathology, and functional outcomes, the underlying mechanisms should be further elucidated in future studies.

Furthermore, recent studies showed that past psychopathology trajectories and current psychopathology have independent consequences for functioning later in life (Copeland et al., 2015; Oerlemans et al., 2020; Ormel et al., 2017). Together, past and present offspring psychopathology may represent a cumulative risk for worse functional outcomes, in addition to the effect of having a parent with BD. Offspring of parents with BD show high rates of psychopathology with often an earlier onset than psychopathology in individuals without familial risk status, but mostly during adolescence (Rudaz et al., 2021). Therefore, this cumulative risk could explain the lower global and social functioning we observed in the older offspring of parents with BD. The potential effect of the development of offspring psychopathology on global and social functioning in older offspring of parents with BD, however, has yet to be studied in detail in longitudinal research.

As functional outcomes are defined as the ability to adapt to the developmental tasks of each specific domain (World Health Organization, 2007), age or age adjusted measures should be considered when interpreting results on functional outcomes (Rapee et al., 2012). In our study, age categories that seemed to be most affected are young adulthood and adulthood, but only in global and social functioning. Social and global functioning seem to be dynamic constructs, where patterns of functional impairment potentially vary by developmental levels, requiring longitudinal research. Knowing in which developmental stages these functional impairments arise or become more pronounced might lead to more informed and targeted preventative strategies that depend on the developmental stage of the child.

Earlier offspring studies predominantly examined familial risk in the context of the development of psychopathology and early trajectories of BD (Duffy et al., 2017; Raouna et al., 2018; Rasic et al., 2014; Rudaz et al., 2021; Sandstrom et al., 2019). To support offspring of parents with BD best within all areas of their lives, a shift in paradigm is needed. One way to do this is to shift our focus towards protective factors, in addition to the already existing focus on risk factors. For example, the negative bidirectional association between social functioning and psychopathology has been widely supported (Burt et al., 2008; Burt and Roisman, 2010; Korhonen et al., 2014; Thomson et al., 2019). In accordance with the multisystem resilience theory, social functioning is crucial for social support, social buffering, and a sense of belonging, which are of significant importance for resilience (Masten et al., 2021). Our review shows that social functioning generally seems to be more greatly affected in older offspring of parents with BD. This finding offers an important opportunity to imagine preventative strategies that could be implemented to help maintain social functioning early in development among offspring of parents with BD.

Findings of this systematic review should be interpreted with the following strengths and limitations in mind. One strength of our study is the extensive search and systematically screened titles and abstracts of several databases from inception to June 2022. All these results were examined by at least two authors. However, it is possible that studies might have been missed in the selection because they did not mention functional outcomes in their title or abstract, despite touching upon these domains in the studies themselves. Another limitation could be that we qualitatively synthesized our data, rather than quantitatively, because of the wide variety of measures and domains.

Limitations within the studies themselves could also have influenced the outcomes of this review. First, the sample sizes of most studies were rather small, especially in older studies. It is possible that these studies with small samples did not always have enough statistical power to find statistical differences between groups. Second, almost half of the studies did not account for offspring psychopathology. To improve our understanding of functional outcomes in relation to offspring psychopathology, it is necessary to disentangle parental and offspring psychopathology status. Third, half of the studies did not properly report characteristics of the parents with BD. This is problematic, as we know that, for example, parental age of onset of BD is associated with offspring psychopathology (Birmaher et al., 2021; Hafeman et al., 2016; Preisig et al., 2016). It remains unclear how parental BD characteristics in the studies reviewed are related to offspring functioning. Fourth, the assessment of functional outcomes and QoL is highly heterogeneous. There is no gold standard for assessment, which impedes comparison and interpretation. Both functional outcomes and QoL are constructs that are difficult to define and assess. To improve our knowledge on functional outcomes and QoL in offspring of parents with BD, we should also improve the way we examine this topic (Canino, 2016; Wallander and Koot, 2016). Fifth, many samples were predominantly of Caucasian origin with middle to high SES and results might not be generalizable to offspring of other cultures. Sixth, most of the studies are cross-sectional, making it unclear whether reduced functioning is due to parental or offspring psychopathology, or if premorbid functioning in these offspring is already affected perhaps by the consequences of parental psychopathology. Moreover, cross-sectional studies may hinder the identification of developmental stages in which functional outcome impairments arise or become more pronounced, which is crucial for the timing of intervention programs. Seventh, studies have used different sources of information, where reports did not always coincide (van der Ende and Verhulst, 2005). When the parents with BD completed the report for offspring, this might have been influenced by the parents' own symptomatology and life experiences (Maoz et al., 2014; Müller et al., 2011) and therefore other assessment methods are needed (e.g., self-reported questionnaires, teacher reports, or assessor-rated functional outcomes in a lab or real life setting).

Further research should systematically study the relationships among parental BD characteristics, functional outcomes, offspring psychopathology, and age to better understand the essence of psychosocial functioning in offspring at high-risk for psychiatric disorders. One way to do this is by using longitudinal studies that research both the trajectories of functional outcomes as well as parental BD characteristics and the presence and course of offspring psychopathology. The identified cross-disorder similarities and differences warrant a cross-disorder approach in these future longitudinal studies. Longitudinal studies might also offer insight into the developmental stages where impairments in functional outcomes emerge, become more pronounced, or even decrease after a certain period. This information is crucial for the timing of preventative strategies and early intervention programs.

Moreover, the identification of additional protective factors may inform preventative strategies. Preventative strategies aimed at enhancing social functioning in high-risk offspring might be valuable to enhance resilience and reduce the impact of potential future mental health problems. Finally, to put the high rates of psychopathology in offspring of parents with BD into perspective and to gain more understanding of the mechanisms of functional outcomes, more studies are needed, particularly within the QoL domain and including both preschool and adult samples.

In conclusion, this systematic review provides an overview of the scattered literature on functional outcomes in offspring of parents with BD. Inconsistent adjustment for the effects of emerging psychopathology in offspring frequently impeded interpretation as to whether diminished functioning in offspring of parents with BD was attributable to offspring psychopathology or high-risk status per se. The lower global and social functioning in older adolescent offspring were the most consistent results, although most studies have revealed mixed results. This review highlights the complex relationship between functional outcomes, offspring psychopathology, and age in this high-risk population. To disentangle this complexity, functional outcomes and QoL should be prioritized as a research topic in studies of offspring at familial high risk. Ultimately, this may identify new targets for preventative strategies in offspring of parents with BD.

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CRediT authorship contribution statement

Author FH wrote the original draft of the manuscript, extracted data, assessed study quality, and reviewed and edited the manuscript. Author CV extracted data, assessed study quality, and reviewed and edited the manuscript. Author MP reviewed and edited the manuscript. Author SG created and performed the literature search. Author MH reviewed and edited the manuscript. Author EM designed the study, extracted data, assessed study quality, and reviewed and edited the manuscript. All authors contributed to and have approved the final manuscript.

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Declaration of competing interest

None of the authors declare any conflict of interest.

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