Journal of Affective Disorders 248 (2019) 185–197

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review article

Risk of autistic spectrum disorder in offspring with parental mood disorders: A systematic review and meta-analysis

Getinet Ayano[a,*], Joemer Calderon Maravilla[a], Rosa Alati[a,b]

[a] School of Social Sciences, The University of Queensland, 80 Meiers Rd, Indooroopilly, Queensland 4068Australia
[b] School of public Heath, Curtin University, Western Australia, Australia

ARTICLE INFO

Keywords:
Autism
Offspring
Parent
Mood disorder
Systematic review
Meta-analysis

ABSTRACT

Background: The association between mood disorders in parents and autism spectrum disorder (ASD) risk in offspring has been investigated in several studies, but the evidence is inconclusive. This systematic review and meta-analysis will explore whether an association exists between parental mood disorders and ASD risk in offspring.

Methods: A literature search was performed using the electronic databases PubMed, EMBASE, PsycINFO, and Scopus. We also reviewed reference lists from retrieved articles. Meta-analysis was conducted, and combined effect values and their 95% confidence intervals were calculated. Study-specific risk ratios (RRs) were pooled using a random effect model. The risk of publication bias was assessed by funnel plot and Egger's regression asymmetry test.

Results: Nine observational studies (two cohort and seven case-control studies) were included for analysis. Our meta-analysis found a greater risk of ASD in children exposed to parental affective, depressive, and bipolar disorders [(RRs 1.65 (95%CI 1.45–1.88); 1.37 (95%CI 1.04–1.81) and 1.87; 95%CI 1.69–2.07) respectively]. We also found increased ASD risk in children of mothers who experienced affective and depressive disorders [(RRs 1.67 (95%CI 1.34–2.09) and 1.62 (95%CI 1.32–1.99) respectively]. We found no increased risk of ASD in children exposed to paternal affective and depressive disorders. Subgroup and sensitivity analysis confirmed the robustness of our main analysis.

Conclusion: The evidence from the present study suggests parental affective, depressive and bipolar, as well as maternal affective and depressive disorders increased the risk of ASD in offspring. Exposure to affective and depressive disorders in fathers only was not linked with ASD risk in children.

1. Introduction

Autism spectrum disorder (ASD) is a group of neurodevelopment disorders characterized by persistent deficits in social communication and interaction as well as by restricted, repetitive, and stereotyped patterns of behavior interests, or activities (American Psychiatric Association, 2013). Symptoms of ASD start to emerge in early childhood and persist over the life course of affected individuals (Newschaffer et al., 2007; Baxter et al., 2015).

According to a recent meta-analysis, the pooled estimates for the worldwide prevalence of autism was 0.62–0.70% (Elsabbagh et al., 2012; Hill et al., 2015), whereas, reported prevalence estimates range from 1–2% in large-scale surveys (Mattila et al., 2011; Kim et al., 2011; Baron-Cohen et al., 2009; Hsu et al., 2012; Idring et al., 2012; Blumberg et al., 2013; Russell et al., 2014; Saemundsen et al., 2013).

Although the etiology of autism spectrum disorder (ASD) remains largely unknown, it is currently believed that ASD is the result of complex gene-environment interactions, with a strong genetic component (Ronald and Hoekstra, 2011; Rosenberg et al., 2009; Lichtenstein et al., 2010; Kim and Leventhal, 2015). A review of seven primary studies by Ronald and Hoekstra in 2011(Ronald and Hoekstra, 2011), found that the heritability estimates of ASD were high and largely comparable across the published studies. The median estimated concordance rates were 88% in monozygotic twins and 31% in dizygotic (DZ) twins. More recently it has been argued that over 50% of the risk of developing ASD is attributed to genetic variation (De Rubeis and Buxbaum, 2015; Hallmayer et al., 2011).

Evidence from a recent study using genome-wide single-nucleotide polymorphism data from the Psychiatric Genomics Consortium (PGC) for cases and controls, suggests that ASD and affective disorders, such

* Corresponding author.
E-mail addresses: g.ayano@uqconnect.edu.au (G. Ayano), j.maravilla@uq.edu.au (J.C. Maravilla), r.alati@uq.edu.au (R. Alati).

https://doi.org/10.1016/j.jad.2019.01.038
Received 9 May 2018; Received in revised form 18 January 2019; Accepted 22 January 2019
Available online 01 February 2019
0165-0327/ © 2019 Elsevier B.V. All rights reserved.

as bipolar and depressive disorders may have a shared etiology (Lee et al., 2013b). This is supported by other research which suggest that the risk of ASD is higher in children of parents with mood disorders compared with children of parents with no mood disorders (Sullivan et al., 2012a; Dean et al., 2010; Hammen et al., 1987; Daniels et al., 2008b; Fairthorne et al., 2016; Harrington et al., 2014; Sørensen et al., 2013; Hviid et al., 2013; Jokiranta et al., 2013; Gidaya et al., 2014; Daniels et al., 2008a; Rasic et al., 2013). Epidemiological studies have also found that children of parents with bipolar and depressive disorders have a 20–90% increased risk of developing ASD in later life (Sullivan et al., 2012a; Rai et al., 2013).

Even though the above studies identified an increased risk of ASD in offspring of parents with mood disorders, these findings are not consistent throughout the literature; there are also studies that have found no increased risk of ASD in offspring of parents with mood disorders including bipolar (Goetz et al., 2017a; Birmaher et al., 2010), depression (Daniels et al., 2008a; Rai et al., 2013) as well as affective disorders (Sørensen et al., 2013). Therefore, this study aims to meta-analyse observational studies that investigated the risk of ASD in offspring with parental mood disorders; to better establish the strength of evidence and formulate recommendations for future research.

2. Methods

2.1. Research design and methods

This systematic review and meta-analysis was conducted and reported in adherence to standards of quality for reporting a meta-analysis of observational studies in epidemiology (MOOSE) (Reviews and Dissemination, 2009) and the preferred reporting items for systematic review and meta-analysis guidelines (PRISMA) (Moher et al., 2009). Search strategy, study selection, data extraction, and analysis were performed according to a pre-defined protocol.

2.2. Data source and searches

The electronic databases EMBASE, PubMed, PsychINFO, and Scopus were systematically searched for published studies that investigated the association between ASD in children and mood disorders in parents. No date limit was applied. The search terms and keywords included: autism OR autistic OR spectrum OR autistic disorder OR autistic spectrum disorder OR developmental OR disorder OR developmental disorder OR psychopathology OR pervasive OR pervasive developmental disorder OR cognition OR cognitive OR developmental disability OR disability OR psychology OR psychiatry OR behavior) AND (pregnant OR pregnancy OR pregnant women OR maternal OR parental OR women OR family OR antenatal OR prenatal or mother OR postpartum) AND (epidemiology OR risk OR exposure OR factor OR risk factor OR determinant OR antecedent) AND (depressive OR depression OR depressive disorder OR disorder OR mood OR mood disorder OR bipolar OR bipolar disorder OR affect OR affective disorder OR mental illness OR illness OR mental health OR emotional stress OR stress OR problems OR mania OR manic OR unipolar) AND (offspring OR child OR children OR adolescent OR toddler OR young adult OR childhood OR youth). Additional studies were identified through a manual search of bibliographic references in relevant articles and reviews.

2.3. Eligibility criteria

Studies were included if they satisfied the following criteria: (1) The study design was observational, including case-control or cohort study designs; (2) the exposure of interest was mood disorders (Overall or specific types) in parents; (3) the outcome of interest was ASD; (4) measured outcomes using odds ratio (OR) or relative risks (RR) estimates with 95% confidence intervals (CIs) or data to calculate these were reported. We excluded case reports, reviews, editorials, comments, letters without sufficient data, abstracts of meeting presentations, animal studies and studies not published in the English language.

2.4. Data extraction

Data were extracted independently by two reviewers according to a standardized data extraction form. The following data were extracted from each study: The first author's name, year of publication, study design, study period, measurement of ASD and mood disorders, number in case and control groups, source of data, country in which the study was conducted, source of comparison groups, confounders adjusted for, parental sex, inclusion criteria, risk estimate (OR) or hazard ratio (HR) and their 95% confidence interval as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015). Disagreements were resolved by consensus.

2.5. Study quality

The quality of all selected studies was assessed using the Newcastle-Ottawa quality assessment scale (NOS) (Wells et al., 2011) and the assessment was performed independently by two reviewers. The NOS grading standard, including case-control or cohort study, was calculated based on three categories: Group selection (four items), comparability between the groups (one item), and outcome and exposure assessment (three items). A maximum of one star could be awarded for each item in the group selection and outcome and exposure assessment categories. A maximum of two stars could be awarded for comparability. Thus, the maximum possible score was nine stars, which represented the highest methodological quality. A score above the median on a 0-to-9- point scale indicated high methodological quality. Discrepant scores between the two reviewers were resolved by discussion and consensus by looking the selected studies together. In addition, a thorough description of the included observational studies was provided. While we report on the results of this quality assessment, studies were not excluded on the basis of quality alone

2.6. Diagnostic definitions

In the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV) mood disorders included disorders that have a disturbance in mood as the predominant feature. DSM-IV defines mood disorders as syndromes consisting of a group of signs and symptoms sustained over weeks to months that represent pervasive alterations of this experience that have a significant functional impact on a variety of areas ranging from cognition to occupational performance and quality of life (American Psychiatric Association, 2000).

According to the DSM-IV definition, mood disorders are divided into depressive disorders ("unipolar depression"), bipolar disorders and other disorders in this category, such as mood disorder due to a general medical condition, substance-induced mood disorder and mood disorder not otherwise specified (American Psychiatric Association, 2000).

In this study, the definition of our exposure variable (mood disorders, including depressive and bipolar disorders), were based on DSM-IV or DSM-5(American Psychiatric Association, 2000, 2013). We defined 'parental mood or affective disorders' as the presence of any mood or affective disorders (bipolar or depressive or affective disorders as a diagnosis) in any parents. We defined 'maternal mood or affective disorders' when mothers only had a diagnosis of mood or affective disorders (bipolar or depressive or affective disorders) and 'paternal mood or affective disorders' when fathers only had been diagnosed with mood or affective disorders (bipolar or depressive or affective disorders).

2.7. Data synthesis and analysis

Data from all studies were pooled using Comprehensive Meta-Analysis (CMA) software version3(Borenstein et al., 2005). If multiple estimates were presented, the estimate with the most extensive adjustment was selected. RR and 95% CI were taken as the magnitude of association for all studies, and OR (or hazard ratios) were considered equivalent to RR. Any results stratified by gender were treated as separate reports. Those articles which stratified parental depressive, bipolar or overall affective disorders in both parents as exposure and reported ASD in children were also treated as separate reports. To estimate the association between parental mood disorders and ASD in children, the results of included studies were combined using random effect models (Borenstein et al., 2010) to account for heterogeneity among the studies. Heterogeneity was evaluated using Q and the I^2 statistics (Borenstein et al., 2010). Q test indicates us about the presence or the absence of heterogeneity, but it does not report on the degree of such heterogeneity. However, the $I2$ statistics quantifies the degree of heterogeneity in a meta-analysis. The values of 25, 50 and 75% were considered to represent low, moderate and high heterogeneity respectively (Higgins et al., 2003). The p-value for statistical significance was set at 0.05. Meta-regression was performed to explore the potential source of heterogeneity, including the covariates parental sex, types of mood disorders, study design (cohort study or case-control study) and source of comparison groups. A leave-one-out sensitivity analysis was carried out to evaluate the key studies that exerted a major impact on between-study heterogeneity (Patsopoulos et al., 2008). Publication bias was assessed by funnel plot and Egger's test (Egger et al., 1997). A significant result in Egger's test indicates that small studies (i.e., with smaller precision) show larger effect sizes. This makes it likely that publication bias has occurred: small studies with insignificant findings (small effect sizes) are not published and not included in the meta-analysis. All reported probabilities were two-sided.

3. Results

3.1. Study selection

4308 articles were identified by our literature search. Twenty-five additional relevant references were found through a manual search of the reference lists. Of these, 4107 were excluded after reviewing duplicate and titles that did not meet the inclusion criteria. The review of abstracts and keywords resulted in the exclusion of a further 176 articles. A full text of 50 articles were retrieved for further screening and 41 of these were excluded. The main reasons for the exclusion include: not assessed ASD as an outcome (21 studies), the exposure was not mood disorders (8 studies), and the risk of exposure was not evaluated (5 studies). Thus, nine studies were found to be suitable for the present meta-analysis (Fig. 1).

3.2. Characteristics of included studies

Characteristics of the included studies are provided in Table 1. Selected studies were published between May 2008 (Daniels et al., 2008a) and August 2017 (Goetz et al., 2017b). Three studies were conducted in Sweden (Rai et al., 2013; Daniels et al., 2008a; Sullivan et al., 2012a), two in Denmark (Hviid et al., 2013; Sørensen et al., 2013), one in the Czech Republic, one in the USA (Birmaher et al., 2010), one in Australia (Fairthorne et al., 2016), and one in Finland (Jokiranta et al., 2013). Six studies recruited participants from population registers (Jokiranta et al., 2013; Rai et al., 2013; Hviid et al., 2013; Sørensen et al., 2013; Sullivan et al., 2012a; Birmaher et al., 2010) and three recruited participant from hospitals (Fairthorne et al., 2016; Daniels et al., 2008a; Goetz et al., 2017b). Seven were case-control studies (Jokiranta et al., 2013; Rai et al., 2013; Daniels et al., 2008a; Fairthorne et al., 2016; Sullivan et al., 2012a; Goetz et al., 2017b; Birmaher et al., 2010)and two were prospective cohort studies (Hviid et al., 2013; Sørensen et al., 2013). Six studies assessed the risk of ASD in children of mothers with mood disorders (Jokiranta et al., 2013; Rai et al., 2013; Daniels et al., 2008a; Sørensen et al., 2013; Hviid et al., 2013; Fairthorne et al., 2016), three in children of mothers with maternal depression (Rai et al., 2013; Daniels et al., 2008a; Hviid et al., 2013), three in children of fathers with mood disorders (Jokiranta et al., 2013; Rai et al., 2013; Daniels et al., 2008a), three in children of parents with bipolar disorder (Sullivan et al., 2012a; Goetz et al., 2017b; Birmaher et al., 2010), and two in children of fathers with unipolar depression (Rai et al., 2013; Daniels et al., 2008a). All studies used a diagnostic instrument (ICD or DSM) to ascertain ASD in children. Two studies used hospital records for confirmation of cases in exposed or control groups (Jokiranta et al., 2013; Sørensen et al., 2013), while the remaining studies used diagnostic instrument (ICD) (Rai et al., 2013; Daniels et al., 2008a; Fairthorne et al., 2016; Hviid et al., 2013; Sullivan et al., 2012a; Goetz et al., 2017b; Birmaher et al., 2010)

3.3. Quality assessment

The Newcastle-Ottawa scale (NOS), a 9-point scoring system was used to assess the study quality. Five studies which scored higher or equal to eight were considered of high quality. Two studies with a score above the 25th percentile (6.5) were considered of moderate quality. The remaining two studies were ranked as low quality (**See supplementary material Table 1**).

3.4. Parental mood disorder and risk of ASD

The forest plot shows the relative risk and 95% CI of each study and the pooled relative risk (**Fig. 2**). Our meta-analysis identified moderate heterogeneity among the studies (I^2 = 55.24%; Q = 29.04; df = 13; p = 0.006), so the random effect model was adopted. The pooled relative risk (RR) demonstrated that ASD risk was significantly higher in children exposed to parents who experienced affective disorders [RR 1.65 (95%CI 1.45–1.88)]. When we stratified the analysis by type of study design, the combined RR in the case-control studies was 1.69 (95%CI 1.47–1.95)), whereas the pooled RRs for cohort studies was 1.47 (95%CI 1.07–2.02).We observed moderate heterogeneity among case-control studies (I^2 = 59.79%; Q = 24.87; df = 10; p < 0.0001), but no apparent heterogeneity among cohort studies (I^2 = 14.48%; Q = 2.34; df = 2; p = 0.31).

In addition, our stratified meta-analysis showed an increased risk of ASD in children of parents with depressive (RR 1.37 (95%CI 1.04–1.81)) and bipolar disorders (RR 1.87 (95%CI 1.69–2.07)). There was no heterogeneity for both parental depressive (I^2 = 50%; Q = 8; df = 4; p = 0.09) and bipolar disorders (I^2 = 0%; Q = 1.07; df = 3; p = 0.78). (See Fig. 3)

In our subgroup analysis we found that ASD risk was significantly higher in children with maternal affective and depressive disorders [RR 1.67 (95%CI 1.34–2.09) and 1.62 (95%CI 1.32–1.99) respectively] but we observed no apparent association in offspring of fathers who had affective and depressive disorders [RR 1.32 (95%CI 0.87–2.01) and 0.88 (95%CI 0.49–1.59) respectively]. (Fig. 4 and 5). Moderate heterogeneity was observed among studies reporting ASD risk by maternal affective (I^2 = 65.05%; Q = 17.17; df = 6, p = 0.009) and paternal affective disorders (I^2 = 73.49%; Q = 7.54; df = 2, p = 0.023), but no heterogeneity was observed among studies reporting offspring's ASD risk by depressive disorders in mothers (I^2 = 0%; Q = 0.42; df = 2, p = 0.81) and fathers (I^2 = 46.65%; Q = 1.87; df = 1, p = 0.17).

In studies that recruited participants from the general population, the parental affective disorder was associated with an increased risk of ASD [RR 1.75 (95%CI 1.57–1.95)]. This elevated risk was not seen when participants were recruited from hospital-based samples [RR 1.49 (95%CI 0.86–2.58)]. (See Fig. 6). We observed heterogeneity among studies recruiting inpatient groups (I^2 = 79.61%; Q = 14.72; df = 2,

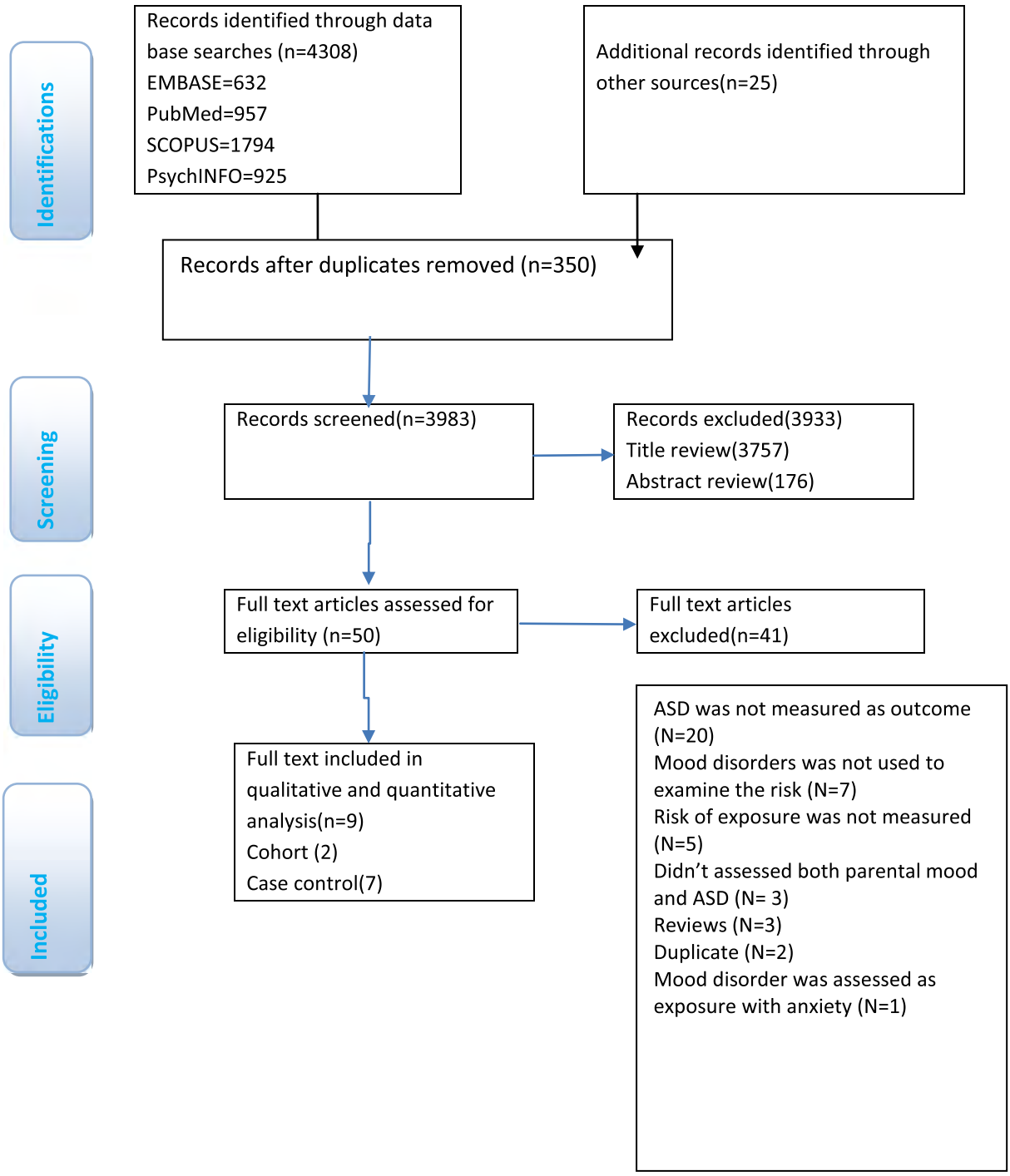

Fig. 1. PRISMA flowchart of review search.

$p = 0.002$) but not in studies with population-based comparison groups ($I^2 = 33.74\%$; $Q = 13.58$; df $= 9$ $p = 0.158$)

3.5. Publication bias

The funnel plot and Egger's regression tests (B $= -1.34$, SE $= 0.57$, $P = 0.037$) provided evidence of substantial publication bias for the affective disorder (Fig. 7). However, when the analysis was stratified by research design, the results of the Egger's test varied: Prospective cohort studies (B $= -1.98$, SE $= 0.62$, $P = 0.19$), population-based case-control studies (B $= -1.32$, SE $= 0.72$, $P = 0.124$) and inpatient control studies (B $= -0.98$ SE $= 2.78$, $P = 0.757$) were unaffected by publication bias. In addition, when we further stratified by sex the results of the Egger's test were not significant for both analysis: B $= -2.6$, SE $= 1.05$, $P = 0.056$ and B $= -3.71$, SE $= 0.66$, $P = 0.11$ for maternal affective and paternal affective disorders respectively. Furthermore, after stratifying by disorder type, Egger's test results showed that parental depression (B $= -3.81$, SE $= 1.5$, $P = 0.85$) and maternal depression (B $= 0.67$, SE $= 2.14$, $P = 0.81$) were unaffected by publication bias. (Table 2)

3.6. Sensitivity analysis

For the purpose of further investigating the potential source of

Table 1
Characteristics of included studies in systematic review and meta-analysis.

Author, year	Country	Sex of parent	Data source	Type of control or exposed	Study design and duration	Confirmation of outcome(ASD)
Jokiranta et al. (2013)	Finland	Women	The Finnish hospital discharge register (FHDR), the Finnish Medical Birth register (FMBR), and the Finnish central population register(CPR)	Population based	NESTED-Case control (1987–2005)	ICD-9(299X) and ICD-9(F84X)
Jokiranta et al. (2013)	Finland	Men	The Finnish hospital discharge register (FHDR), the Finnish Medical Birth register (FMBR), and the Finnish central population register(CPR)	Population based	NESTED-Case control (1987–2005)	ICD9(299X) and ICD-9(F84X)
Rai et al. (2013)	Sweden	Women (*P*)	The stockholm youth cohort, record linked with national and regional healthcare, social and administrative registries	Population based	Nested-Case control (2001–2007)	ICD-9(299), ICD-10(F84),DSM-IV (299)
Rai et al. (2013)	Sweden	Men	The Stockholm youth cohort, record linked with national and regional healthcare, social and administrative registries	Population based	Nested-Case control (2001–2007)	ICD-9(299), ICD-10(F84),DSM-IV (299)
Fairthorne et al. (2016)	Australia	Women	Mental health information system (MHIS), the midwife notification system(MNS) and the intellectual disability exploring answers(IDEA) in WA	Institution based	Case control (1983–1999)	DSM-4
Daniels et.al. (2008a,b)	Sweden	Women	Swedish hospital discharge data linked with Swedish medical birth registry, Swedish multi- generation register, Swedish statistics registry, Swedish national registry	Institution based	Nested Case control (1977–2003)	ICD-10(F84, F84.5, F84.2, F84.3, ICD-9(299)
Daniels et. al (2008a,b)	Sweden	Women	Swedish hospital discharge data linked with Swedish medical birth registry, Swedish multi- generation register, Swedish statistics registry, Swedish national registry	Institution based	Nested Case control (1977–2003)	ICD-10(F84, F84.5, F84.2, F84.3, ICD-9(299)
Daniels et.al., (2008a,b)	Sweden	Men	Swedish hospital discharge data linked with Swedish medical birth registry, Swedish multi- generation register, Swedish statistics registry, Swedish national registry	Institution based	Nested Case control (1977–2003)	ICD-10(F84, F84.5, F84.2, F84.3, ICD-9(299)
Daniels et. al. (2008a,b)	Sweden	Men	Swedish hospital discharge data linked with Swedish medical birth registry, Swedish multi- generation register, Swedish statistics registry, Swedish national registry	Institution based	Nested Case control (1977–2003)	ICD-10(F84, F84.5, F84.2, F84.3, ICD-9(299)
Hviid et.al. (2013)	Denmark	Women(p)	The Danish civil registration system, the Danish national registration system, the Danish national hospital register and the Danish psychiatric center register	Population based	COHOTRT (1996–2005)	ICD-10(F840.0, F84.1, F84.5, F94.8, and F84.9)
Hviid et. al. (2013)	Denmark	Women(p)	The Danish civil registration system, the Danish national registration system, the Danish national hospital register and the Danish psychiatric center register	Population based	COHOTRT (1996–2005)	ICD-10(F840.0, F84.1, F84.5, F94.8, and F84.9)
Sørensen et. al. (2013)	Denmark	Women(p)	The Danish civil registration system, the Danish national registration system, the Danish national hospital register and the Danish psychiatric center register	Population based	COHOTRT (1996–2006)	ICD-10(F840.0, F84.1, F84.5, F94.8, and F84.9)
Sullivan et.al. (2012), study 1	Sweden	Both	Swedish hospital discharge data linked with Swedish medical birth registry, Swedish multi- generation register, Swedish statistics registry, Swedish national registry	Population based	Case control (1973–2009)	*ICD-9*(299) *and ICD-10* (F84).
Sullivan et.al. (2012), study 2	Sweden	Both	The Stockholm youth cohort, record linked with national and regional healthcare, social and administrative registries	Population based	Case control (1984 −2007)	*ICD-9*(299) *and ICD-10* (F84).
Birmaher et al. (2010)	USA	Both	From the community via the university center for social and urban research of the Pittsburgh	Population based	Case control study	*DSM-IV*
Goetz et al. (2017)	Czech republic		Offspring of age 6 to 17 years from the clinical register (CZ-BDCR) of the national institute of mental health, Klecancy the Czech republic	Institution based	Case control (2012 −2015)	*DSM-5*

Author, year	Parental diagnosis	Number of participants (exposed or cases)	Number of events (in exposed or cases)	Confirmations of cases and controls or exposed /unexposed	Inclusion criteria
Jokiranta et al. (2013)	Affective disorder	Not available	211	Medical record(FHDR)	All singleton live births born in Finland between January 1, 1987 and December 31, 2005
Jokiranta et al. (2013)	Affective disorder	Not available	183	Medical record(FHDR)	All singleton live births born in Finland between January 1, 1987 and December 31, 2005
Rai et al. (2013)	Depression	4429	44	ICD	All children 0–17 years old in Stockholm country during the study period with ASD
Rai et al. (2013)	Depression	4429	19	ICD	All children 0–17 years old in Stockholm country during the study period with ASD
Fairthorne et al. (2016)	Affective disorder	4225	52	ICD	All mothers of a live child born in WA between 1983 and 1999 inclusisve
Daniels et. al. (2008a,b)	Affective disorder	204	42	ICD	Children born between 1977 and 2003 and had a diagnosis of autism disorder, Asperger syndrome, or pervasive developmental disorder not-otherwise- specified at or before 10 years of age that was recorded in the registry between 1987 and 2003
Daniels et. al. (2008a,b)	depression	204	22	ICD	Children born between 1977 and 2003 and had a diagnosis of autism disorder, Asperger syndrome, or pervasive developmental disorder not-otherwise- specified at or before 10 years of age that was recorded in the registry between 1987 and 2003
Daniels et. al. (2008a,b)	depression	177	7	ICD	Children born between 1977 and 2003 and had a diagnosis of autism disorder, Asperger syndrome, or pervasive developmental disorder not-otherwise- specified at or before 10 years of age that was recorded in the registry between 1987 and 2003

(*continued on next page*)

Table 1 (*continued*)

Author, year	Parental diagnosis	Number of participants (exposed or cases)	Number of events (in exposed or cases)	Confirmations of cases and controls or exposed /unexposed	Inclusion criteria
Daniels et. al. (2008a,b)	Affective disorder	177	28	ICD	Children born between 1977 and 2003 and had a diagnosis of autism disorder, Asperger syndrome, or pervasive developmental disorder not-otherwise- specified at or before 10 years of age that was recorded in the registry between 1987 and 2003
Hviid et. al. (2013)	depression	3482	37	ICD	Live singleton births in Denmark during the study period with known gestational age
Hviid et. al. (2013)	affective disorders (excluding depression)	577	3	ICD	Live singleton births in Denmark during the study period with known gestational age
Sørensen et.al. (2013)	Affective disorder	Not available	Not available	medical record	Antidepressant drug with ATC code NO6A with exposure window from 30 days before conception to the day of birth; time of conception n after February 1996
Sullivan et. al. (2012), study 1	Bipolar disorder	Not available	Not available	ICD	Children born between1973 and 2009 and had a diagnosis of autism disorder
Sullivan et. al. (2012), study 2	Bipolar disorder	Not available	Not available	ICD	Children age 0 to 17 and registered in cohort 1984 and 2007 and had a diagnosis of autism disorder
Birmaher et al. (2010)	Bipolar disorder	121	2	DSM-IV	All children 2–5 years old in Pittsburgh during the study period
Goetz et al. (2017)	Bipolar disorder	43	1	DSM-5	Offspring of age 6 to 17 years

Author, year	Number of participants(unexposed or controls)	Number of events (in unexposed or controls)	Exposer to affective disorder window
Jokiranta et al. (2013)[1]	Not available	405	Diagnosis at any time
Jokiranta et al. (2013)[1]	Not available	416	Diagnosis at any time
Rai et al. (2013)[2]	43,277	272	Diagnosis before the birth of the child
Rai et al. (2013)[2]	43,277	155	Diagnosis before the birth of the child
Fairthorne et al. (2015)[3]	204,317	950	During pregnancy
Daniels et. al. (2008a,b)[5]	2856	631	diagnosis at any time
Daniels et. al. (2008a,b)[5]	2856	239	diagnosis at any time
Daniels et. al. (2008a,b)[5]	2856	187	diagnosis at any time
Daniels et. al. (2008a,b)[5]	2856	480	diagnosis at any time
Hviid et.al (2013)[6]	623,393	3855	Diagnosis ofdepressionat any time
Hviid et.al, (2013)[6]	626,298	3889	diagnosis of depressionat any time
Sørensen et. al. (2013) [7]	Not available	Not available	Affective disorder at any time from record
Sullivan et.al. (2012a)(8)1	Not available	Not available	diagnosis at any time
Sullivan et.al. 2012(8)2	Not available	Not available	diagnosis at any time
Birmaher et al., 2010	102	1	diagnosis at any time
Goetz et al., 2017	43	0	diagnosis at any time
Author, year	Crude OR(95% CI)	Adjusted OR(95% CI)	Adjusted for
Jokiranta et al., 2013	Not available	OR 2.1(1.8–2.5)	Maternal age, paternal age, smoking during pregnancy, weight for age
Jokiranta et al., 2013	Not available	OR 1.8(1.5–2.2)	Maternal age, paternal age, smoking during pregnancy, weight for age
Rai et al., 2013	OR 1.61(1.17–2.23)	OR 1.49(1.08–2.08)	Age, income, education, occupations, migration status, parity, other psychiatric disorders, personality and drug and alcohol use disorders
Rai et al., 2013	OR 1.21(0.75–1.96)	0R 1.12(0.69–1.82)	Age, income, education, occupations, migration status, parity, other psychiatric disorders, personality and drug and alcohol use disorders
Fairthorne et al., 2016	OR 2.68(2.0–3.5)	OR 2.45(1.8–3.2)	SES, maternal age, parity and index birth year group
Daniels et. al. (2008a,b)	OR 0.91(0.64–1.30)	OR1.2(0.8–1.7)	Age, gender, hospital birth and parents birth at delivery, country of birth, SES, and psychiatric disorder in opposite parents
Daniels et. al. (2008a,b)	OR 1.33(0.83–2.10)	OR 1.7(1.0–2.6)	Age, gender, hospital birth and parents birth at delivery, country of birth, SES, and psychiatric disorder in opposite parents
Daniels et. al. (2008a,b)	OR 0.59(0.27–1.27)	OR 0.6(0.3–1.4)	Age, gender, hospital birth and parents birth at delivery, country of birth, SES, and psychiatric disorder in opposite parents
Daniels et. al. (2008a,b) [5]	OR 0.93(0.61–1.41)	1.0(0.6–1.5)	Age, gender, hospital birth and parents birth at delivery, country of birth, SES, and psychiatric disorder in opposite parents
Hviid et. al. (2013)	1.72(95%CI 1.25–2.37)	RR 1.8(**95%CI** 1.32–2.52)	maternal parity, age at the onset of pregnancy, country of origin, place of residence at the start of the pregnancy, and smoking status during pregnancy, employment status and the, mother's level of education, use of SSRIs during pregnancy, psychiatric diagnosis
Hviid et. al. (2013)	0.84(95%CI 0.27–2.59)	RR 0.89(95%CI O.29–2.76)	

(*continued on next page*)

Table 1 (*continued*)

Author, year	Number of participants(unexposed or controls)	Number of events (in unexposed or controls)	Exposer to affective disorder window
			maternal parity, age at the onset of pregnancy, country of origin, place of residence at the start of the pregnancy, and smoking status during pregnancy, employment status and the, mother's level of education, use of SSRIs during pregnancy, psychiatric diagnosis
Sørensen et. al. (2013)	Not available	HR 1.2(95%CI O.7–2.1)	Maternal age at conception, paternal age at conception, parental psychiatric history(except maternal affective disorder), gestational age, birth weight, sex, and parity
Sullivan (et.al. 2012a), study 1	Not available	OR 1.9(95%CI 1.7–2.1)	Not available
Sullivan et.al. (2012b), study 2	Not available	OR 1.6(95%CI 1.1–2.1)	Not available
Birmaher et al. (2010)	Not available	Not available	Not available

heterogeneity in the analysis of parental mood disorder and risk of ASD in children, we performed leave-one-out sensitivity analysis. Our pooled estimated relative risk (RR) varied between 1.59 (95% CI 1.36–1.54) and 1.73 (95% CI 1.83–1.95) after deletion of a single study which suggests that our findings were robust and not dependent on a single study **(see supplementary material Table 2).**

Moreover, to identify the possible effects of other comorbid psychiatric disorders we restricted the analysis to studies that included an adjustment for other comorbid psychiatric disorders. An increased risk of ASD in offspring of parents with mood disorders was apparent in these studies [RR 1.24 (95%CI 1.03–1.49)] as it was in the studies with no adjustment [RR 1.92 (95%CI 1.78–2.07)]. We found a significant heterogeneity between studies which adjusted and those that did not adjust for comorbid psychiatric disorders ($Q = 18.34$, df = 1, $P < 0.001$).

Furthermore, we restricted the analysis to studies that contained an adjustment for confounding by antidepressant medications. We found an increased risk of ASD in offspring of parents with mood disorders in studies that accounted for the effect of antidepressant use [RR 1.50 (95%CI 1.22–1.85)]. Studies that did not account for such confounding also reported an increased risk of ASD in children [RR 1.71 (95%CI 1.48–1.99)]. We found no significant heterogeneity between the studies that adjusted and studies that did not adjust for the use of antidepressants ($Q = 1.01$, df = 1, $P = 316$).

Finally, we restricted our analysis to high-quality studies. We found a considerably increased risk of ASD in high [RR 1.60 (95%CI 1.32–1.94] as well as moderate [RR 1.72 (95%CI 1.39–2.12)] quality studies. There were no significant associations in low-quality studies [RR 2.08 (95%CI 0.31–13.98)]. Heterogeneity among the groups was not significant ($Q = 0.294$, df = 2, $P = 0.863$). When we excluded the low-quality studies, the associations remained (RR = 1.65 (95%CI 1.44–1.89)). (Table 3)

4. Discussion

4.1. Main findings

The present systematic review and meta-analysis examined the risk of ASD in children with parental mood disorders across seven case-control and two cohort studies. Our review indicated a higher risk of ASD in offspring with parental affective (64%), depressive (37%), bipolar disorders (87%), as well as maternal affective (67%), and depressive disorders (62%).

The epidemiological evidence was highly diverse by subtype of mood disorder, study design, timing, the source of controls or exposed groups, study location, sample size and degree of adjustment for confounding factors. The studies included parents with different types of affective disorders and settings, and some studies included only female or male parents. For the ascertainment of the outcome, all studies used recognized diagnostic criteria as described in the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM), meaning disorder measurement were derived from structured clinical interviews that provided well-validated assessments of both ASD and mood disorders.

Numerous interpretations of the association between parental mood disorders and ASD in offspring are plausible. One of the possible explanation is that autism spectrum and affective disorders, such as bipolar and depressive disorders may have a shared genetic etiology (Lee et al., 2013a). Epigenetic modifications may also lead to greater risk of ASD in offspring of parents with mood disorders. Prenatal adversity including in-utero exposure to stress, mental health problems and/or substance use may affect offspring neurodevelopment and increase the risk of ASD in later life possibly through epigenetic mechanisms. These may affect DNA expression through modifications of the DNA methylations and remodeling of the chromatin that occur without a change in the DNA sequence (Klose and Bird, 2006;

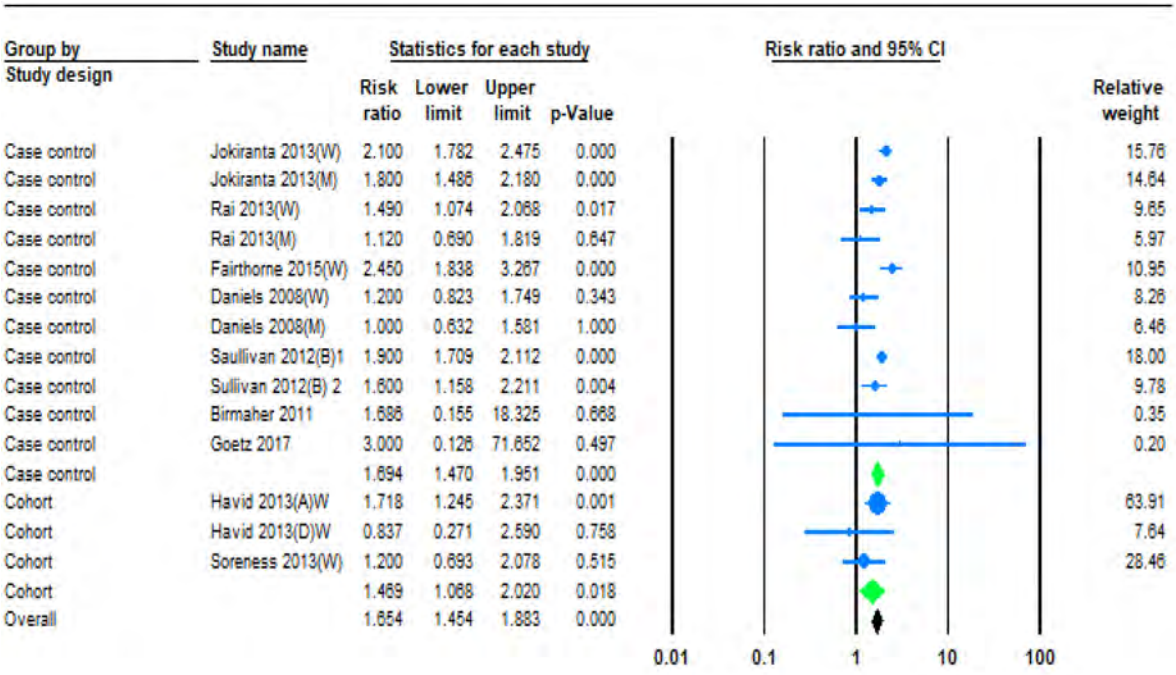

Fig. 2. Forest plot of parental affective disorder and risk of ASD in offspring: A meta analysis.

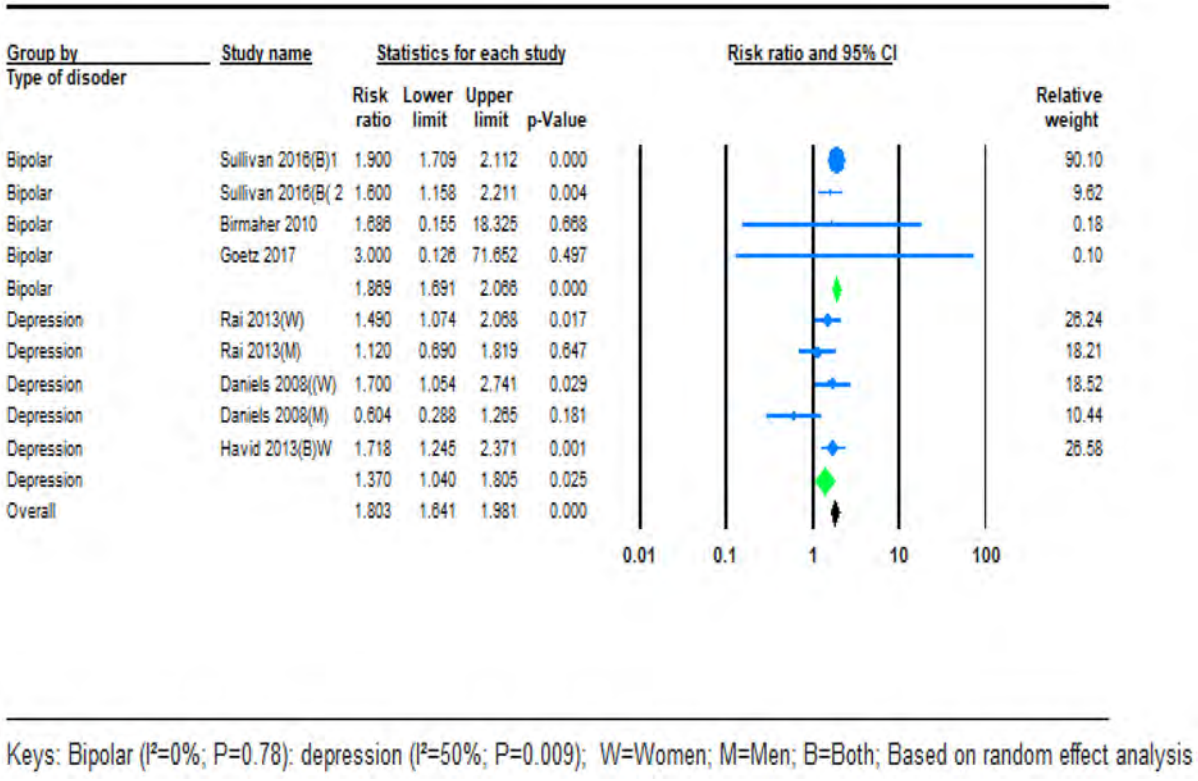

Fig. 3. Forest plot of parental affective disorders and ASD in offspring: Subgroup analysis by type of disorder.

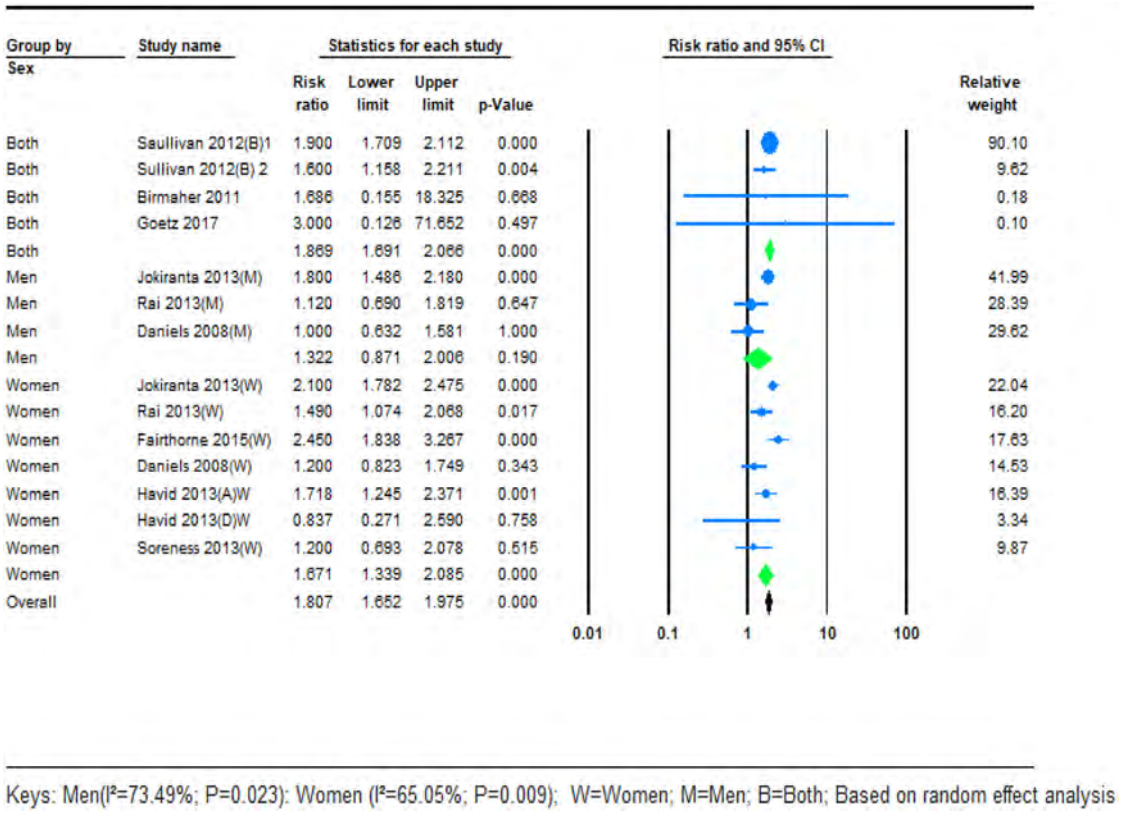

Fig. 4. Forest plot of parental affective disorders and ASD in offspring: Subgroup analysis by gender of parent.

Talbert and Henikoff, 2006; Richards, 2006).

In support of the above explanations, the pooled RR showed a positive association between parental mood disorders such as parental affective, depressive, bipolar, as well as maternal affective, and depressive disorders and the risk of ASD in offspring. However, the included case-control studies, the sample sizes, and adjustment for confounding must be considered. In the seven case-control studies, adjustment factors were inconsistent. The most common potential confounders taken into account were parental age (4 studies), substance use (smoking, drugs, and alcohol) (2 studies), socioeconomic status or income (2 studies), antidepressant (3 studies), and other psychiatric disorders (3 studies). In one of the cohort study (Sørensen et al., 2013) where maternal age at conception, paternal age, psychiatric history, gestational age, sex, birth weight, and parity were adjusted for no

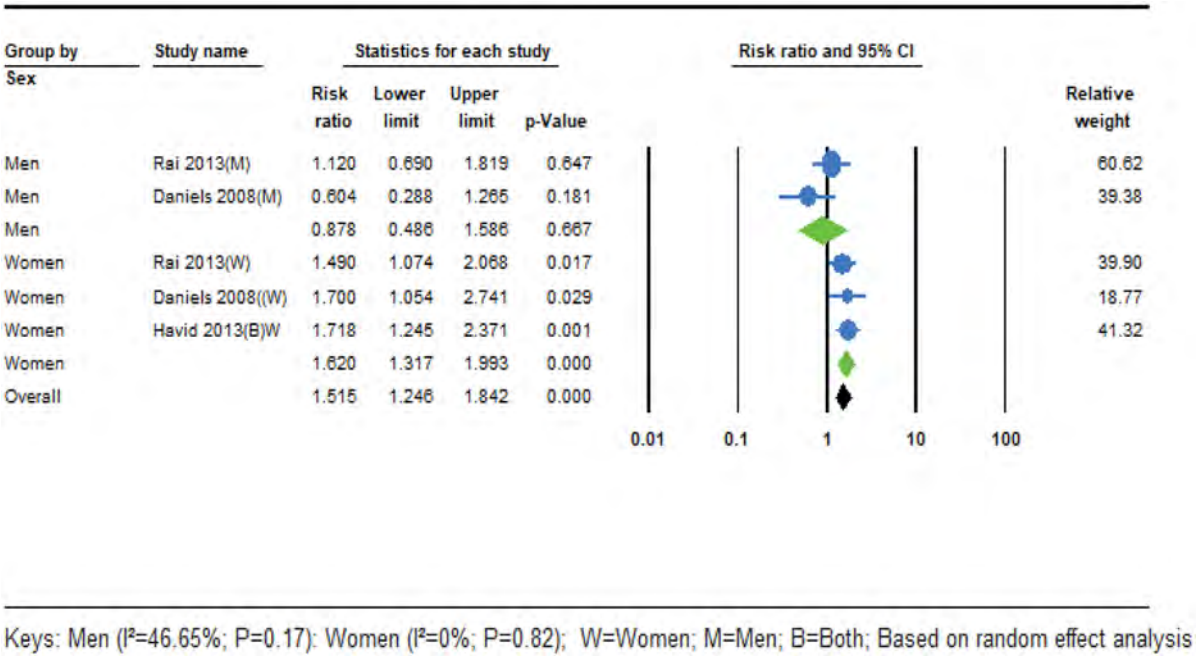

Fig. 5. Forest plot of parental depressive disorder and ASD in offspring: Subgroup analysis by gender of parent.

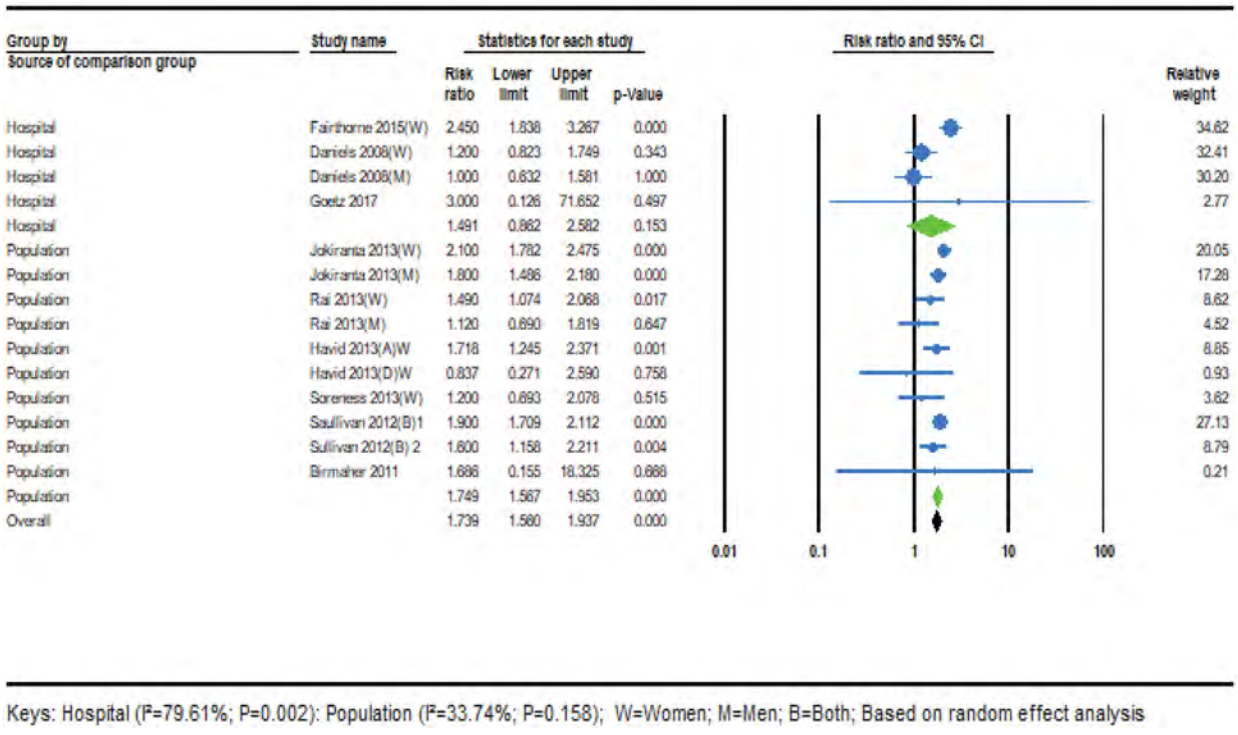

Fig. 6. Forest plot of parental affective disorder and ASD in offspring: Subgroup analysis by source population.

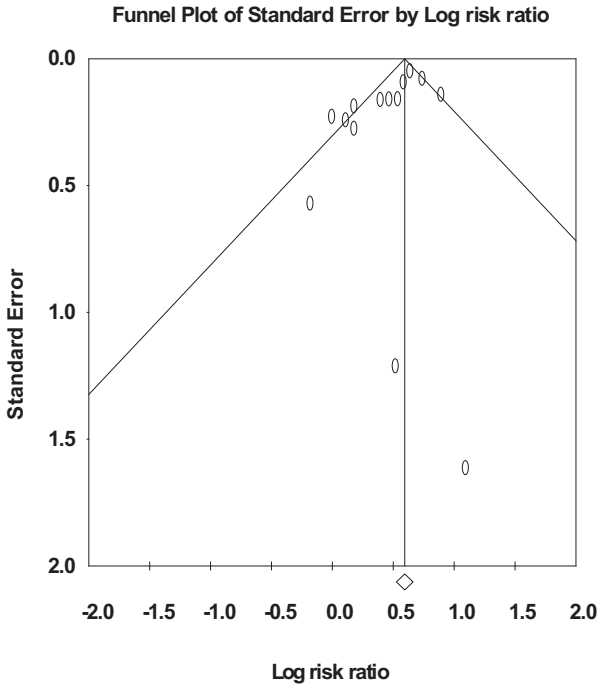

Fig. 7. Funnel plot of publication bias for parental affective disorder and ASD risk in offfspring.

increased risk of ASD was observed (RR 1.2; 95%CI 0.7 to 2.1).

So since this study included an adjustment for a range of important confounding factors, it is possible that the association seen in studies with lower level of adjustment may be due to chance or to the effect of unmeasured factors (Birmaher et al., 2010; Goetz et al., 2017a). Epidemiologic studies shown that factors such as alcohol, psychotic disorders, anxiety disorders, and paternal age are associated with an increased risk of ASD in offspring. For example, a recent epidemiological

Table 2
Summary of results of publication bias (the results of the Egger's test).

Characteristics of the studies	Studies, n	B	SE	*P* value
Overall affective disorder	14	−1.34	0.57	0.037
Cohort studies	4	−1.98	0.62	0.190
Population-based case-control studies	4	–1.32	0.72	0.124
Inpatient control studies,	3	−0.98	2.78	0.757
Maternal affective disorders	7	−2.6	1.05	0.056
Paternal affective disorders	3	−3.71	0.66	0.110
Parental depression	5	−3.81	1.5	0.85
Maternal depression,	3	0.67	2.14	*P* = 0.81

study showed that parental alcohol consumption before and during pregnancy was linked to ASD in offspring (RR, 1.39; 95% CI 1.34–1.44) (Sundquist et al., 2014). It has been shown that parents with mood disorders are more likely to use legal and illegal drugs including alcohol which in turn increase ASD risk (Henderson et al., 2007; Olds, 1997; Fried and Smith, 2001; Polanska et al., 2017). So, in studies which did not control the effect of substance use including alcohol and nicotine, the observed association between parental mood disorders and greater risk of ASD in offspring might be due to the confounding effect of unmeasured substance use in parents.

In another recent systematic review and meta-analysis that evaluated advanced parental age and autism risk in children, a positive association between advanced parental age and ASD in children has been reported (Wu et al., 2017). This study found that the highest parental age category was associated with an increased risk of autism in the offspring, with adjusted ORs of 1.41 (95% CI 1.29–1.55) and 1.55 (95% CI 1.39–1.73) for mother and father respectively. Similarly, there is also evidence of a positive association between exposure to other psychiatric disorders such as schizophrenia in parents and ASD in children. A recent case-control study found that schizophrenia in parents was linked to nearly three times the odds of ASD in offspring. This was seen in both in a Swedish national cohort (OR, 2.9; 95% CI, 2.5–3.4) and a Stockholm County cohort (OR, 2.9; 95% CI, 2.0–4.1) (Sullivan et al., 2012b). Studies have also found that anxiety and

Table 3
Summary of results of subgroup and sensitivity analysis.

Subgroups	Diagnosis in parents	Studies, n	OR	95% CI	Heterogeneity between the studies I^2	Heterogeneity between the studies *P* value	Heterogeneity among the groups *P* value
Study design							0.423
Cohort	Any	2	1.47	1.47–1.95	14.48	0.31	
Case control	Any	7	1.69	1.07–2.02	59.79	<0.001	
Disorder type							0.215
Affective	Paternal		0.88	0.49–1.59	73.49	0.023	
Depression	paternal		1.32	0.87–2.01	46.65	0.170	
Study setting				1.57–1.95			0.577
Community	Any		1.75	0.86–2.58	33.74	0.158	
Institution	Any		1.49		79.61	0.002	
Adjusted for comorbid psychiatric disorders				1.03–1.49			<0.001
yes	Any	9	1.24	1.78–2.07	0.00	0.687	
no	Any	5	1.92		2.624	0.413	
Adjusted for antidepressant							0.136
Yes	Any	4	1.50	1.22–1.85	0.00	0.504	
No	Any	10	1.71	1.48–1.99	61.29	0.006	
Quality of the study							0.863
High	Any	9	1.60	1.32–1.94	68.41	0.001	
Moderate	Any	3	1.84	1.67–2.03	41.17	0.183	
low	Any	2	2.08	0.31–13.98	0.00	0.776	

personality disorders in parents may be associated with a greater risk of ASD in the offspring. For example, a study conducted in 2008 in Sweden found an increased risk of ASD in the offspring of parents with maternal neurotic and personality disorders and other nonpsychotic disorders (OR, 1.7; 95% CI, 1.3–2.2) (Daniels et al., 2008b). There are many explanations for these findings. Firstly, ASD and other psychiatric disorders may have a commonly shared etiology (Lee et al., 2013a). Secondly, there may be a poor interaction between the parent and children in offspring of parents with psychiatric disorders due to their illness (Mattejat and Remschmidt, 2008). Thirdly, epigenetic changes may occur via different mechanisms including DNA methylations and histone alterations (Kubota et al., 2013; Nardone et al., 2014). Also, there may be a greater chance of comorbid substance use in people with psychiatric disorders (Assanangkornchai and Edwards, 2012). Finally, mental disorders are linked with a higher risk of negative birth outcomes which may indirectly lead to ASD in later life (Männistö et al., 2016; Abel et al., 2010)

On the other hand, the robustness of an increased risk of ASD in offspring with parental mood disorders was supported by the sensitivity analyses that we conducted, where we restricted our analysis to studies that adjusted for comorbid psychiatric disorders. We found the increased risk of ASD in offspring of parents with mood disorders was apparent in both studies which accounted for the possible effects of other psychiatric disorders [RR 1.24 (95%CI 1.03–1.49)] as well as those studies that did not adjust for other psychiatric disorders [RR 1.92 (95%CI 1.78–2.07)].

In this study, no significant association was observed between ASD in offspring and paternal affective and depressive disorders. Among the three studies which evaluated the risk of ASD in offspring whose fathers only had a diagnosis of affective disorders one study (case-control study) identified an increased risk of ASD in offspring (OR, 1.8; 95% CI, 1.5–2.2) (Jokiranta et al., 2013) but no increased risk was reported in the other two studies (one based on a cohort study design and one based on a nested-case control study design) (Rai et al., 2013; Daniels et al., 2008a). Furthermore, in two studies that also assessed the risk of ASD in offspring with paternal depressive disorders no significant association was found between ASD in children and depressive disorders in fathers (Rai et al., 2013; Daniels et al., 2008a). These findings suggest a stronger association between ASD risk in offspring and mood disorders in mothers than in fathers.

This greater risk of ASD in offspring of mothers with mood disorders than fathers with mood disorders may point to specific intrauterine exposure to maternal mood disorders during pregnancy. One of the possible explanation is that mood disorders during pregnancy play a causal role in the etiology of ASD through epigenetic mechanisms. The prenatal and early postnatal periods are critical periods for brain development which are characterized by extensive and rapid changes in neuronal and synaptic organization and epigenetic modifications. Exposure to stress and mood disorders during pregnancy can alter the epigenetic status of genes that are important to brain development and lead to neurobehavioral problems and psychiatric disorders including ASD in offspring (Jirtle and Skinner, 2007; Prickett and Oakey, 2012; Kundakovic and Jaric, 2017).

4.2. Differences among the studies included in the meta-analysis

Despite our meta-analysis found associations between parental affective disorder and ASD in children, it is worth noting that differences between the nine studies led to a moderate level of heterogeneity in our meta-analysis. The type of mood disorders, the setting, and exposed population differed on a number of characteristics which may have contributed to the variance in the risk of ASD in offspring of parents with mood disorders. However, our leave-one-out sensitivity analysis showed estimates from our main analysis remained virtually unchanged, which suggests our findings were robust and not heavily influenced by a single study. In addition, subgroup analysis and sensitivity analysis by level of adjustment to a range of confounding factors appeared to support the robustness of our findings.

4.3. Strength and limitations

Our study has several strengths: first, to minimize possible reviewer bias we used a predefined search strategy and data extraction and quality assessment was performed by two independent reviewers; Second, we performed sensitivity and subgroup analysis based on source of controls, sex, and type of specific mood disorder to identify the small study effect and the risk of heterogeneity in analyses of the risk of ASD and maternal affective disorders; third, we evaluated the quality of the included studies based on a standard evaluation tool (NOS) and the result from the assessment indicated that the methodological quality was generally good. This study also has some limitations: Although our meta-analysis results showed significant associations between ASD and parental and maternal affective disorders, (including overall affective disorders, depressive and bipolar disorders),

adjustments were inconsistent and relevant confounders such other mental disorders, licit and illicit substance use were not adjusted in most studies. Also, we only included articles published in English, so it is possible that relevant studies published in a language other than English may have been missed; We detected significant heterogeneity across the studies for overall affective disorders. The difference among the studies may not be a major concern because in our subgroup analysis we found an increased risk of ASD in offspring of parents with mood disorder in both case-control and cohort studies with stronger effect among case-control studies (RR = 1.68 (95%CI 1.45 to 1.95)) than cohort studies (RR = 1.47 (95%CI 1.07 to 2.02)). We further conducted analyses among specific types of mood disorders and we found a significantly higher risk of ASD in offspring in both parents with bipolar and depressive disorders with strong risk in parents with bipolar disorder (RR = 1.87 (95%CI 1.69–2.07)).

In our study, most of the evidence came from case-control studies, therefore the possibility that ASD diagnosis in children may lead to rather than precede, a parental increased risk of mood disorders needs to be acknowledged. In order to address this limitation, we restricted our analysis to cohort studies where the diagnosis of mood disorders in parents was likely to precede the diagnosis of ASD in offspring. We found the relationship between mood disorders in parents and ASD in offspring was still seen after these exclusions [RR,1.47 (95%CI 1.07–2.02).

Further, two of the nine studies included in our meta-analysis were poor in quality. When we excluded them, our results remained the same (RR = 1.65 (95%CI 1.44–1.89)).

The other limitation of this study is the relatively low number of studies included in the meta-analysis. Our subgroup analysis comprised a small number of studies which reduced the precision of the estimate; Finally, the possibility of publication bias is always a concern, because studies with null results are less likely to be published than those reporting positive associations

4.4. Implications for future research

Our study identified some implications for future research; our meta-analysis identified parental sex difference in risk of ASD and mood disorders in parents, which require further investigation to better assess the robustness of our findings. We identified significant associations between exposure to specific mood disorders, such as bipolar and depressive disorders and ASD risk in offspring. However, due to the small number of studies in subgroup analysis, the small sample size and inconclusive findings, further studies are warranted to replicate our findings and further investigate which specific mood disorder is most likely to be associated with ASD in offspring. Also, the majority of the studies included in our meta-analysis were case-control studies and the cohort studies included in this systematic review and meta-analysis were not originally designed to estimate the risk of ASD in offspring of parents with mood disorders; therefore, future studies based on large population-based cohort studies are needed to confirm our findings. Furthermore, future studies need to control for possible confounding factors impacting ASD in parents such as other psychiatric disorders, substance and medication use as well as sociodemographic characteristics including parental age. Future studies should also account for the risk of developing ASD in offspring with both parents having mood disorders as a diagnosis. Finally, studies focusing on shared factors between ASD and mood disorders are warranted.

5. Conclusions

Even though the etiology of ASD remains largely unknown, results from this systematic review and meta-analysis suggest that parental affective, depressive and bipolar, as well as maternal affective and depressive disorders increased the risk ASD in offspring. Paternal affective and depressive disorders were not associated with ASD risk in children. Further well-designed cohort studies are needed to confirm the present findings. If these results are replicated, early screening for ASD in offspring of parents who experience mood disorders may be warranted.

Contributors

GA conceived the hypothesis, developed the methodology, identified all potential studies, extracted the data, assessed quality, conducted the analysis, and wrote the first draft of the manuscript. JCM reviewed abstracts, extracted the data, and assessed the quality. RA, reviewed the protocol, reviewed data extraction, and synthesis and contributed to subsequent drafts of the manuscript. All authors read and approved the final manuscript.

Funding

No external funding obtained for this systematic review and meta-analysis.

Conflict of interest

No conflict of interest declared.

Acknowledgment

We are grateful to the University of Queensland for providing us a wide range of available online databases.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.01.038.

References

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders-IV-TR. American Psychiatric Association, Washington, DC.
American Psychiatric Association, 2013. Diagnostic Stastistical Manual of Mental Disorder, Fifth ed. American Psychiatric Association, Wahington, DC.
Abel, K.M., Wicks, S., Susser, E.S., et al., 2010. Birth weight, schizophrenia, and adult mental disorder: is risk confined to the smallest babies? *Arch. Gen. Psychiatry* 67, 923–930.
Assanangkornchai, S., Edwards, J.G., 2012. Clinical and epidemiological assessment of substance misuse and psychiatric comorbidity. *Curr. Opin. Psychiatry* 25, 187–193.
Baron-Cohen, S., Scott, F.J., Allison, C., Williams, J., Bolton, P., Matthews, F.E., Brayne, C., 2009. Prevalence of autism-spectrum conditions: UK school-based population study. *Br. J. Psychiatry* 194, 500–509.
Baxter, A., Brugha, T., Erskine, H., Scheurer, R., Vos, T., Scott, J., 2015. The epidemiology and global burden of autism spectrum disorders. *Psychol. Med.* 45, 601–613.
Birmaher, B., Axelson, D., Goldstein, B., Monk, K., Kalas, C., Obreja, M., Hickey, M.B., Iyengar, S., Brent, D., Shamseddeen, W., 2010. Psychiatric disorders in preschool offspring of parents with bipolar disorder: the Pittsburgh Bipolar Offspring Study (BIOS). *Am. J. Psychiatry* 167, 321–330.
Blumberg, S.J., Bramlett, M.D., Kogan, M.D., Schieve, L.A., Jones, J.R., Lu, M.C., 2013. Changes in Prevalence of Parent-Reported Autism Spectrum Disorder in School-Aged US children: 2007 to 2011-2012. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics.
Borenstein, M., Hedges, L., Higgins, J., Rothstein, H., 2005. Comprehensive Meta-Analysis Version 2. Biostat, Englewood, NJ, pp. 104.
Borenstein, M., Hedges, L.V., Higgins, J., Rothstein, H.R., 2010. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res. Synth. Methods* 1, 97–111.
Daniels, J.L., Forssen, U., Hultman, C.M., Cnattingius, S., Savitz, D.A., Feychting, M., Sparen, P., 2008a. Parental psychiatric disorders associated with autism spectrum disorders in the offspring. *Pediatrics* 121, e1357–e1362.
Daniels, J.L., Forssen, U., Hultman, C.M., Cnattingius, S., Savitz, D.A., Feychting, M., Sparen, P., 2008b. Parental psychiatric disorders associated with autism spectrum disorders in the offspring. *Pediatrics* 121, e1357–e1362.
De Rubeis, S., Buxbaum, J.D., 2015. Genetics and genomics of autism spectrum disorder: embracing complexity. *Hum. Mol. Genet.* 24, R24–R31.
Dean, K., Stevens, H., Mortensen, P.B., Murray, R.M., Walsh, E., Pedersen, C.B., 2010. Full spectrum of psychiatric outcomes among offspring with parental history of mental disorder. *Arch. Gen. Psychiatry* 67, 822–829.
Egger, M., Smith, G.D., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by

a simple, graphical test. BMJ 315, 629–634.
Elsabbagh, M., Divan, G., Koh, Y.J., Kim, Y.S., Kauchali, S., Marcín, C., Montiel-Nava, C., Patel, V., Paula, C.S., Wang, C., 2012. Global prevalence of autism and other pervasive developmental disorders. *Autism Res.* 5, 160–179.
Fairthorne, J., Hammond, G., Bourke, J., De Klerk, N., Leonard, H., 2016. Maternal psychiatric disorder and the risk of autism spectrum disorder or intellectual disability in subsequent offspring. *J. Autism Dev. Disord.* 46, 523–533.
Fried, P., Smith, A., 2001. A literature review of the consequences of prenatal marihuana exposure: an emerging theme of a deficiency in aspects of executive function. *Neurotoxicol. Teratol.* 23, 1–11.
Gidaya, N.B., Lee, B.K., Burstyn, I., Yudell, M., Mortensen, E.L., Newschaffer, C.J., 2014. In utero exposure to selective serotonin reuptake inhibitors and risk for autism spectrum disorder. *J. Autism Dev. Disord.* 44, 2558–2567.
Goetz, M., Sebela, A., Mohaplova, M., Ceresnakova, S., Ptacek, R., Novak, T., 2017a. Psychiatric disorders and quality of life in the offspring of parents with bipolar disorder. *J. Child Adolesc. Psychopharmacol.* 27, 483–493.
Goetz, M., Sebela, A., Mohaplova, M., Ceresnakova, S., Ptacek, R., Novak, T., 2017b. Psychiatric disorders and quality of life in the offspring of parents with bipolar disorder. *J. Child Adolesc. Psychopharmacol.* 27, 483–493.
Hallmayer, J., Cleveland, S., Torres, A., Phillips, J., Cohen, B., Torigoe, T., Miller, J., Fedele, A., Collins, J., Smith, K., 2011. Genetic heritability and shared environmental factors among twin pairs with autism. *Arch. Gen. Psychiatry* 68, 1095–1102.
Hammen, C., Gordon, D., Burge, D., Adrian, C., Jaenicke, C., Hiroto, D., 1987. Maternal affective disorders, illness, and stress: risk for children's psychopathology. *Am. J. Psychiatry* 144, 736–741.
Harrington, R.A., Lee, L.-C., Crum, R.M., Zimmerman, A.W., Hertz-Picciotto, I., 2014. Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay. *Pediatrics* 133, e1241–e1248.
Henderson, J., Gray, R., Brocklehurst, P., 2007. Systematic review of effects of low—moderate prenatal alcohol exposure on pregnancy outcome. *BJOG* 114, 243–252.
Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. *BMJ* 327, 557.
Hill, A.P., Zuckerman, K., Fombonne, E., 2015. Epidemiology of autism spectrum disorders. Translational Approaches to Autism Spectrum Disorder. Springer.
Hsu, S.-W., Chiang, P.-H., Lin, L.-P., Lin, J.-D., 2012. Disparity in autism spectrum disorder prevalence among Taiwan National Health Insurance enrollees: age, gender and urbanization effects. *Res. Autism Spectr. Disord.* 6, 836–841.
Hviid, A., Melbye, M., Pasternak, B., 2013. Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism. *N. Engl. J. Med.* 369, 2406–2415.
Idring, S., Rai, D., Dal, H., Dalman, C., Sturm, H., Zander, E., Lee, B.K., Serlachius, E., Magnusson, C., 2012. Autism spectrum disorders in the Stockholm Youth Cohort: design, prevalence and validity. *PLoS One* 7, e41280.
Jirtle, R.L., Skinner, M.K., 2007. Environmental epigenomics and disease susceptibility. *Nat. Rev. Genet.* 8, 253.
Jokiranta, E., Brown, A.S., Heinimaa, M., Cheslack-Postava, K., Suominen, A., Sourander, A., 2013. Parental psychiatric disorders and autism spectrum disorders. *Psychiatry Res.* 207, 203–211.
Kim, Y.S., Leventhal, B.L., 2015. Genetic epidemiology and insights into interactive genetic and environmental effects in autism spectrum disorders. *Biol. Psychiatry* 77, 66–74.
Kim, Y.S., Leventhal, B.L., Koh, Y.-J., Fombonne, E., Laska, E., Lim, E.-C., Cheon, K.-A., Kim, S.-J., Kim, Y.-K., Lee, H., 2011. Prevalence of autism spectrum disorders in a total population sample. *Am. J. Psychiatry* 168, 904–912.
Klose, R.J., Bird, A.P., 2006. Genomic DNA methylation: the mark and its mediators. *Trends Biochem. Sci.* 31, 89–97.
Kubota, T., Miyake, K., Hirasawa, T., 2013. Epigenetics in neurodevelopmental and mental disorders. *Med. Epigenetics* 1, 52–59.
Kundakovic, M., JARIC, I., 2017. The epigenetic link between prenatal adverse environments and neurodevelopmental disorders. Genes 8, 104.
Lee, S.H., Ripke, S., Neale, B.M., Faraone, S.V., Purcell, S.M., Perlis, R.H., Mowry, B.J., Thapar, A., Goddard, M.E., Witte, J.S., 2013a. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat. Genet.* 45, 984.
Lee, S.H., Ripke, S., Neale, B.M., Faraone, S.V., Purcell, S.M., Perlis, R.H., Mowry, B.J., Thapar, A., Goddard, M.E., Witte, J.S., 2013b. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat. Genet.* 45, 2711 ng.
Lichtenstein, P., Carlström, E., Råstam, M., Gillberg, C., Anckarsäter, H., 2010. The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *Am. J. Psychiatry* 167, 1357–1363.
Männistö, T., Mendola, P., Kiely, M., O'loughlin, J., Werder, E., Chen, Z., Ehrenthal, D.B., Grantz, K.L., 2016. Maternal psychiatric disorders and risk of preterm birth. *Ann. Epidemiol.* 26, 14–20.
Mattejat, F., Remschmidt, H., 2008. The children of mentally ill parents. *Deutsches Ärzteblatt Int.* 105, 413–418.
Mattila, M.-L., Kielinen, M., Linna, S.-L., Jussila, K., Ebeling, H., Bloigu, R., Joseph, R.M., Moilanen, I., 2011. Autism spectrum disorders according to DSM-IV-TR and comparison with DSM-5 draft criteria: an epidemiological study. *J. Am. Acad. Child Adolesc. Psychiatry* 50, 583–592 e11.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 6, e1000097.
Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst. Rev.* 4, 1.
Nardone, S., Sharan Sams, D., Reuveni, E., Getselter, D., Oron, O., Karpuj, M., Elliott, E., 2014. DNA methylation analysis of the autistic brain reveals multiple dysregulated biological pathways. *Transl. Psychiatry* 4, e433.
Newschaffer, C.J., Croen, L.A., Daniels, J., Giarelli, E., Grether, J.K., Levy, S.E., Mandell, D.S., Miller, L.A., Pinto-Martin, J., Reaven, J., 2007. The epidemiology of autism spectrum disorders. Annu. Rev. Public Health 28, 235–258.
Olds, D., 1997. Tobacco exposure and impaired development: a review of the evidence. *Dev. Disabil. Res. Rev.* 3, 257–269.
Patsopoulos, N.A., Evangelou, E., Ioannidis, J.P., 2008. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. *Int. J. Epidemiol.* 37, 1148–1157.
Polanska, K., Krol, A., Merecz-Kot, D., Ligocka, D., Mikolajewska, K., Mirabella, F., Chiarotti, F., Calamandrei, G., Hanke, W., 2017. Environmental tobacco smoke exposure during pregnancy and child neurodevelopment. *Int. J. Environ. Res. Public Health* 14, 796.
Prickett, A.R., Oakey, R.J., 2012. A survey of tissue-specific genomic imprinting in mammals. *Mol. Genet. Genomics* 287, 621–630.
Rai, D., Lee, B.K., Dalman, C., Golding, J., Lewis, G., Magnusson, C., 2013. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. BMJ 346, f2059.
Rasic, D., Hajek, T., Alda, M., Uher, R., 2013. Risk of mental illness in offspring of parents with schizophrenia, bipolar disorder, and major depressive disorder: a meta-analysis of family high-risk studies. *Schizophr. Bull.* 40, 28–38.
Reviews, U. O. Y. C. F. & Dissemination, 2009. Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care. University of York, Centre for Reviews & Dissemination.
Richards, E.J., 2006. Inherited epigenetic variation — revisiting soft inheritance. *Nat. Rev. Genet.* 7, 395.
Ronald, A., Hoekstra, R.A., 2011. Autism spectrum disorders and autistic traits: a decade of new twin studies. *Am. J. Med. Genet. Part B* 156, 255–274.
Rosenberg, R.E., Law, J.K., Yenokyan, G., Mcgready, J., Kaufmann, W.E., Law, P.A., 2009. Characteristics and concordance of autism spectrum disorders among 277 twin pairs. *Arch. Pediatr. Adolesc. Med.* 163, 907–914.
Russell, G., Rodgers, L.R., Ukoumunne, O.C., Ford, T., 2014. Prevalence of parent-reported ASD and ADHD in the UK: findings from the Millennium Cohort Study. *J. Autism Dev. Disord.* 44, 31–40.
Saemundsen, E., Magnússon, P., Georgsdóttir, I., Egilsson, E., Rafnsson, V., 2013. Prevalence of autism spectrum disorders in an Icelandic birth cohort. BMJ Open 3, e002748.
Sørensen, M.J., Grønborg, T.K., Christensen, J., Parner, E.T., Vestergaard, M., Schendel, D., Pedersen, L.H., 2013. Antidepressant exposure in pregnancy and risk of autism spectrum disorders. *Clin. Epidemiol.* 5, 449.
Sullivan, P.F., Magnusson, C., Reichenberg, A., Boman, M., Dalman, C., Davidson, M., Fruchter, E., Hultman, C.M., Lundberg, M., Långström, N., 2012a. Family history of schizophrenia and bipolar disorder as risk factors for autism. *Arch. Gen. Psychiatry* 69, 1099–1103.
Sullivan, P.F., Magnusson, C., Reichenberg, A., Boman, M., Dalman, C., Davidson, M., Fruchter, E., Hultman, C.M., Lundberg, M., Langstrom, N., Weiser, M., Svensson, A.C., Lichtenstein, P., 2012b. Family history of schizophrenia and bipolar disorder as risk factors for autism. *Arch. Gen. Psychiatry* 69, 1099–1103.
Sundquist, J., Sundquist, K., Ji, J., 2014. Autism and attention-deficit/hyperactivity disorder among individuals with a family history of alcohol use disorders. Elife 3.
Talbert, P.B., Henikoff, S., 2006. Spreading of silent chromatin: inaction at a distance. *Nat. Rev. Genet.* 7, 793.
Wells, G.A., Shea, B., O'connell, D., Peterson, J., Welch, V., Losos, M., et al., 2011. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses.
Wu, S., Wu, F., Ding, Y., Hou, J., Bi, J., Zhang, Z., 2017. Advanced parental age and autism risk in children: a systematic review and meta-analysis. *Acta Psychiatr. Scand.* 135, 29–41.