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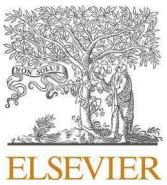

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Occurrence of psychosis and bipolar disorder in adults with autism: A systematic review and meta-analysis

Kandice J. Varcin [a,b], Sarah E. Herniman [c,d,e], Ashleigh Lin [b], Yanyu Chen [b], Yael Perry [b], Charlotte Pugh [b], Katharine Chisholm [f,g], Andrew J.O. Whitehouse [b], Stephen J. Wood [c,d,g,*]

[a] Menzies Health Institute Queensland, Griffith University, Brisbane, Australia
[b] Telethon Kids Institute, Perth, Australia
[c] Orygen, Melbourne, Australia
[d] Centre of Youth Mental Health, University of Melbourne, Australia
[e] Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Australia
[f] Department of Psychology, Aston University, Birmingham, United Kingdom
[g] Institute for Mental Health, University of Birmingham, Birmingham, United Kingdom

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ABSTRACT

Objective: Evidence suggests that individuals with autism spectrum disorder have increased rates of co-occurring psychosis and/or bipolar disorder. Considering the peak age of onset for psychosis and bipolar disorder occurs in adulthood, we investigated the co-occurrence of these disorders in adults with autism.
Methods: We conducted a systematic review and meta-analysis (PROSPERO Registration Number: CRD42018104600) to (1) examine the prevalence of psychosis and bipolar disorder in adults with autism, and (2) review potential risk factors associated with their co-occurrence.
Results: Fifty-three studies were included. The pooled prevalence for the co-occurrence of psychosis in adults with autism was 9.4 % (N = 63,657, 95 %CI = 7.52, 11.72). The pooled prevalence for the co-occurrence of bipolar disorders in adults with autism was 7.5 % (N = 31,739, 95 %CI = 5.79, 9.53).
Conclusions: Psychosis and bipolar disorder occur at a substantially higher prevalence in adults with autism compared to general population estimates. While there is an overall dearth of research examining risk factors for these disorders in autism, males had increased likelihood of co-occurring psychosis, and females of co-occurring bipolar disorder. These results highlight the need for ongoing assessment and monitoring of these disorders in adults with autism.

1. Introduction

Autism spectrum disorders (henceforth, 'autism') cover a set of chronic, neurodevelopmental disorders, lying on a spectrum of severity, typically diagnosed in childhood (Lord et al., 2018). Globally, the prevalence is estimated to be 1–1.5 % (Baxter et al., 2015). There is evidence for increased rates of psychiatric disorders in people with autism with several studies reporting co-occurring diagnoses in more than 70 % of their samples (Gillberg et al., 2016; Lever and Geurts, 2016). However, absolute prevalence rates of specific disorders are highly variable due to many factors, such as how the diagnosis was obtained, sampling differences, and the conditions studied.

Schizophrenia spectrum and other psychotic disorders (henceforth, 'psychosis') and bipolar disorders are of particular interest because of their potentially severe impact on clinical and functional outcomes, and because improving understanding of their co-occurrence with autism can inform developmental trajectories and treatments for these conditions. While conceptualised as distinct disorders, autism, psychosis and bipolar share overlapping clinical features (e.g., social difficulties and withdrawal, repetitive behaviour) (Oliver et al., 2021; Skokauskas and Frodl, 2015), genetic variants and gene expression patterns (Gandal et al., 2018), and aetiological risk factors (Sullivan et al., 2012, 2013). Likely related to the shared phenomenological and genetic overlap between these disorders, multiple reviews and meta-analyses have now reported that psychosis and bipolar disorders occur at increased prevalence in autism compared to the general population (Hossain et al.,

* Corresponding author at: Orygen, 35 Poplar Road, Parkville, VIC 3052, Australia.
E-mail address: Stephen.wood@orygen.org.au (S.J. Wood).

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2020; Lai et al., 2019). Prevalence estimates reported across reviews, however, are variable, ranging from 4% to 67% for psychosis and 5% to 21 % for bipolar disorders. Prevalence estimates from meta-analyses range from 4% to 11.8% (Lai et al., 2019; De Giorgi et al., 2019; Lugo-Marín et al., 2019; Marín et al., 2018) for psychosis and 5% for bipolar and related disorders (Lai et al., 2019).

Most commonly, these estimates have been based on studies across the lifespan (Hossain et al., 2020). Only two meta-analyses to date have examined prevalence estimates specifically for the occurrence of psychosis in adults (i.e., ≥18 years) with autism. These meta-analyses capture articles published until 2016 and report prevalence estimates (for schizophrenia spectrum disorders) of 6.4 % for adults with autism with an IQ above 70 (Marín et al., 2018) and 11.8 % for adults with autism, irrespective of IQ estimate (Lugo-Marín et al., 2019). No meta-analyses to date have specifically examined the prevalence of bipolar disorder in adults with autism. Establishing the prevalence of these disorders in adulthood is important considering the peak age of onset for psychosis and bipolar disorder occurs in adulthood (i.e., between 20–29 years; Dagani et al., 2019; Miettunen et al., 2019). As such, prevalence estimates are expected to be higher amongst adults compared to estimates in children or adolescents. Moreover, childhood/adolescent onset psychosis and bipolar disorders appear to have different outcomes, potentially because of different aetiological pathways, compared to adult-onset disorders, warranting their independent examination (Carlson et al., 2000; Ballageer et al., 2005; Frahm Laursen et al., 2019).

In the current meta-analysis and narrative synthesis, we examined the prevalence of psychosis and bipolar disorder in adults (i.e., ≥18 years) with autism. We also reviewed potential risk factors associated with the co-occurrence of psychosis and/or bipolar disorder in autism. To our knowledge, this is the first systematic review of risk factors associated with these co-occurring conditions in adults with autism.

2. Method

The review protocol was registered with PROSPERO in August 2018 (Registration Number: CRD42018104600). Amendments to the protocol were recorded with Prospero and are available from https://www.crd.york.ac.uk/prospero/display_record.php?ID = CRD42018104600. The review was initially conducted according to the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). During publication, an updated PRISMA statement was published (Page et al., 2021). As such, reporting was updated to meet the PRISMA 2020 statement.

2.1. Eligibility

Studies were eligible for inclusion if they met all the following criteria: (i) peer-reviewed journal articles; (ii) written in English or with an English translation available; (iii) study of individuals with autism that also examines any schizophrenia spectrum or other psychotic disorder and/or bipolar disorders; (iv) clinical diagnoses of autism established on the basis of diagnostic classifications in the Diagnostic and Statistical Manual for Mental Disorders (DSM) and/or the International Classification of Diseases (ICD) or standardised diagnostic instruments known to map onto DSM/ICD diagnostic criteria; (v) schizophrenia spectrum or other psychotic disorders and bipolar disorder diagnoses established on the basis of diagnostic classifications in the DSM/ICD, and/or standardised diagnostic instruments known to map onto the DSM/ICD diagnostic criteria, and/or diagnoses made by a qualified health professional; (vi) sample mean or median age of 18 years or above (or sample specified as 'adults'). Studies were eligible if they included individuals <18 years if they presented a separate analysis for individuals ≥18 years. As we were interested in both prevalence of co-occurrence *and* risk factors that may be associated with co-occurring psychosis or bipolar, studies were included for review if they reported on either of these.

Studies were excluded if they met any of the following criteria: (i) non peer-reviewed publications, systematic reviews, case studies, editorial/letter/conference abstract, dissertations, grey literature; (ii) studies that primarily focused on participants with medical conditions associated with psychosis; (iii) studies that focused on participants with psychiatric disorders due to a general medical condition; (iv) studies that did not examine co-occurrence for separate diagnostic categories (i.e., diagnoses combined into an umbrella category of "mental disorders"); (v) autism was not the primary disorder; (vi) the sample and prevalence rates or risk factors overlapped with another (published) sample included in the review. Data from overlapping samples were included if they reported on different outcomes.

2.2. Literature search strategy

The search strategy was developed by the study team and refined by a senior librarian for Health and Medical Sciences at the University of Western Australia. The initial literature search was conducted in September 2018 and updated in February 2019 and September 2021. The search was conducted in the following databases: MEDLINE, Embase, PsycInfo, CINAHL, and Cochrane Central Register of Controlled Trials (CENTRAL). The complete search strategy is provided in Supplementary 1.

The search was limited to articles published from January 1980 (when autism was first classified as distinct from psychotic disorders) to September 1 2021. A manual search was also performed by reviewing reference lists of eligible studies. The bibliographic and manual searches were conducted by a single reviewer (KV).

2.3. Study selection

All references and identification of duplicates was managed in Endnote (Version X8.2). Titles and abstracts were screened (by KV) for any potentially relevant studies. Studies were excluded at this stage (based on the title or abstract) if they met any one of the exclusion criteria. Full-text articles of all potentially relevant peer-reviewed papers were evaluated for inclusion, independently, by two reviewers (KV and either one of AL, SH or SW) against the eligibility criteria. Any disagreements regarding eligibility were resolved by a third reviewer (SW, AL). Agreement between the independent reviewers was 92 %. In two instances, authors had to be contacted to confirm the mean age of the study sample to determine eligibility for the review.

2.4. Data extraction

One reviewer (KV) extracted data for all included full-text articles into a specifically developed standardised data extraction form. A second reviewer cross-checked all data extraction for accuracy (YC, SH). Any discrepancies were then resolved by consensus or by a third reviewer (AL). Data extracted included study information (authors, country, study design, diagnostic classification systems), sample characteristics (diagnoses, age, gender ratio, intellectual quotient/intellectual disability, sample size), prevalence estimates of co-occurrence in autism, and group differences indicating potential risk factors examined. In instances where prevalence was reported as both current and lifetime diagnoses, we extracted lifetime prevalence estimates. Unless otherwise specified, information extracted was for individuals aged ≥18 years. We extracted both the numerator and denominator in which prevalence estimates could be derived for our meta-analyses. In cases where authors only reported percentages (rather than providing the original numbers in which those estimates were derived), the authors were contacted with a request to provide the numerator and denominators for the relevant prevalence estimate.

2.5. Risk of Bias assessment

Risk of bias was assessed for all studies using the Hoy Risk of Bias Tool (Hoy et al., 2012). The tool evaluates prevalence studies according to 10 items (each scored 0 or 1 for the absence or presence of bias, respectively). A summary score (out of 10) was obtained to indicate risk of bias (low [0–3], moderate [4–6], high [7–10]). In instances where information was not reported or unclear, we rated that item for the presence of bias. Risk of bias for all included studies was evaluated independently by two reviewers (KV, YC) and any discrepancies resolved by consensus. Percentage agreement between the two reviewers was 94 %. Supplementary 2 provides the risk of bias ratings for all items in each study.

2.6. Synthesis of results

2.6.1. Statistical analysis of prevalence estimates

Statistical analysis was conducted in *R* (Version 4.0.2) using the *meta* and *metafor* *R*-packages (Viechtbauer and Cheung, 2010; Schwarzer, 2007; Wang, 2018). Consistent with methods outlined in Wang (2018), random-effect models were conducted separately to estimate (i) the pooled prevalence of psychosis in autism and (ii) the pooled prevalence of bipolar disorders in autism. Publication bias was assessed using funnel plots and Egger's regression test (see Supplementary 3 for further information about the use of Egger's regression test in this context). Heterogeneity was assessed using Q and I^2 statistics. In the case of moderate-to-high statistical heterogeneity (I^2 $\geq$25 %), leave-one-out analyses were conducted to determine potential outliers or studies that were having an undue influence on prevalence estimates (Viechtbauer and Cheung, 2010; Wang, 2018; Willis and Riley, 2017). In leave-one-out analyses, each study (k) was removed in turn one at a time and the summary prevalence was re-estimated, and influential diagnostics determined, based on the remaining k-1 studies.

2.6.2. Narrative synthesis of risk factors

Due to the high variability in the range and reporting of factors examined as potential risk factors, we summarised the outcomes of these studies in the form of a narrative (rather than quantitative) synthesis. Risk factors and/or group differences indicating potential risk factors are presented separately for the co-occurrence of (i) psychosis in autism, and (ii) bipolar disorders in autism.

3. Results

After full-text screening, there were 53 eligible studies (see Fig. 1 for the PRISMA Flow Diagram). Of these, four studies reporting prevalence estimates did not include raw numbers (i.e., only percentages). For two of these studies (Supekar et al., 2017; Kohane et al., 2012), we did not receive a response from the authors following our request for their raw numbers. These two studies were excluded from the quantitative synthesis, however, as both reported on risk factors associated with the co-occurrence of psychosis in autism, the studies were retained in the review for the narrative synthesis of risk factors. Four studies (Hand et al., 2020; Fusar-Poli et al., 2019; Mouridsen et al., 2008a; Tsakanikos et al., 2006) were excluded due to overlapping samples with an already included study (Gilmore et al., 2021; Fusar-Poli et al., 2020; Mouridsen et al., 2008b; Tsakanikos et al., 2011). In these instances, the most recently published prevalence estimate was selected. For Mouridsen et al. where both papers were published in the same year (Mouridsen et al., 2008a, b), we selected the paper with the larger sample size. An additional study (Foss-Feig et al., 2019) was excluded after author confirmation that the mean age at follow-up was <18 years.

Across the 53 included studies: (i) 45 were included in the meta-analysis examining the prevalence of psychosis in autism, (ii) 27 were included in the meta-analysis examining the prevalence of bipolar disorders in autism (24 of which were also included in the psychosis prevalence meta-analysis), (iii) 14 reported on risk factors or group differences indicating potential risk factors for the co-occurrence of

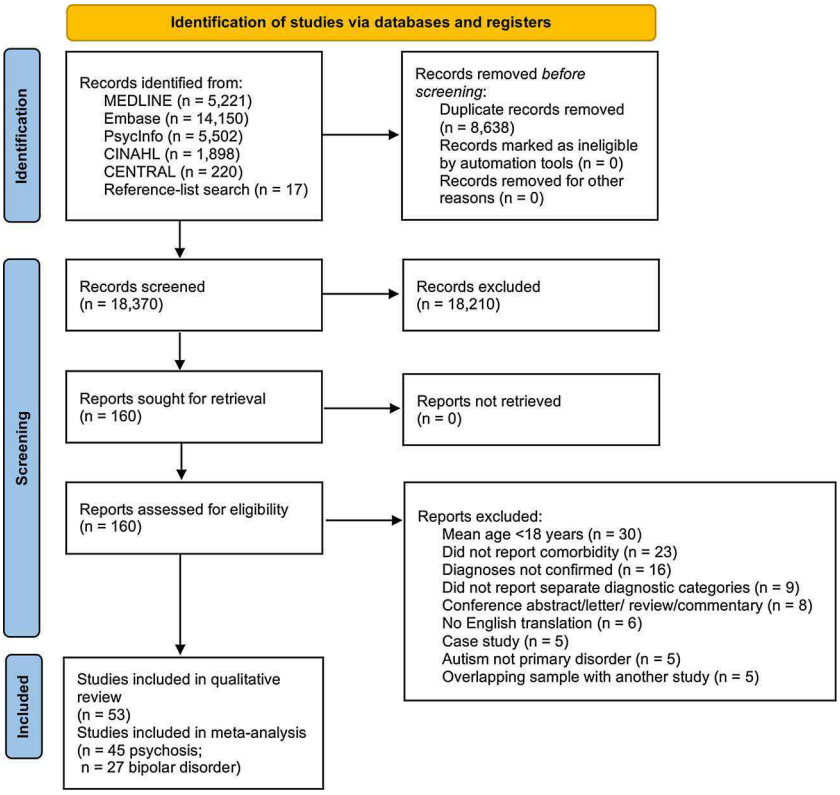

Fig. 1. PRISMA Flow Diagram.

psychosis and autism, and (iv) 6 reported on risk factors or group differences indicating potential risk factors for the co-occurrence of bipolar disorders and autism.

3.1. Study characteristics

Dates of publication ranged from 2003 to 2021 (Table 1). The USA (k = 15), Sweden (k=10), and the UK (k = 9) were the most commonly represented countries. All eligible versions of the DSM (III, IV/IV-TR, 5) and ICD (Sullivan et al., 2012, 2013; Hossain et al., 2020) were represented, with the DSM-IV/DSM-IV-TR (k = 24) and the ICD-10 (k = 18) the most commonly used classification systems for autism diagnoses. Diagnostic descriptions of autism (as reported by study authors) are outlined in Table 1.

Participant ages across studies ranged from 11 to 96 years (13 studies did not report age range, only a mean/median age). Forty-seven of the 53 studies reported on the gender distribution of participants. Of these, 45 (96 %) studies involved samples that were predominately male (i.e., >50 % of the sample). Only 32 studies (56 %) reported on the proportion of intellectual disability for participants, ranging from 0% through 100 % of the sample (typically because they were selected to not have/have comorbid intellectual disability). Characteristics of all studies are presented in Table 1.

3.2. Risk of Bias

Risk of bias scores ranged from 1 to 7, with the majority of included studies (98 %) assessed as being at low to moderate risk of bias (low: k = 22, 41 %; moderate: k = 30, 57 %; high: k = 1, 2%).

For prevalence studies examining the co-occurrence of psychosis and bipolar in autism, the most common risks of bias included: (i) a study sample that was not representative of the national population (91 % psychosis prevalence studies, 96 % bipolar prevalence studies), (ii) different modes of data collection used within the sample (62 % psychosis studies, 63 % bipolar studies), (iii) data not being collected directly from participants (62 % psychosis studies, 60 % bipolar studies), (iv) no demonstrated reliability or validity in the reporting of study measures (49 % psychosis studies, 41 % bipolar studies), and (v) a lack of random selection or census approach in sampling participants (38 % psychosis studies, 41 % bipolar studies).

3.3. Prevalence of psychosis in autism

Forty-five studies involving 63,657 individuals aged between 11–96 years (with a mean/median age of 18.3–64 years) reported on the co-occurrence of psychosis in autism (Gillberg et al., 2016; Supekar et al., 2017; Kohane et al., 2012; Gilmore et al., 2021; Fusar-Poli et al., 2020; Mouridsen et al., 2008b; Tsakanikos et al., 2011; Anckarsater et al., 2008; Billstedt et al., 2005; Buck et al., 2014; Cederlund et al., 2008; Chen et al., 2015; Croen et al., 2015; Davignon et al., 2018; Etyemez et al., 2020; Gesi et al., 2021; Geurts and Jansen, 2012; Ghaziuddin and Zafar, 2008; Haw et al., 2013; Helverschou et al., 2021, 2015; Hofvander et al., 2009; Houghton et al., 2017; Hutton et al., 2008; Isenberg et al., 2021; Ketelaars et al., 2008; LoVullo and Matson, 2009; Lugnegard et al., 2011; Lunsky et al., 2009; McCarthy et al., 2010; Melville et al., 2008; Morgan et al., 2003; Moseley et al., 2011; Mosner et al., 2019; Nahar et al., 2019; Nylander et al., 2018, 2013; Pehlivanidis et al., 2020; Raja and Azzoni, 2010; Roy et al., 2015; Russell et al., 2016; Rydén and Bejerot, 2008; Schalbroeck et al., 2019; Sheehan et al., 2021; Stahlberg et al., 2004; Tint et al., 2021; Vohra et al., 2017). Author-reported diagnostic descriptions (or categories of diagnosis) for psychosis were variable and are presented in Table 1. Prevalence rates reported across studies for the co-occurrence of psychosis in autism, ranged from 0 to 62% of the total autism sample.

As can be seen in Fig. 2, based on the results of the meta-analysis, the pooled prevalence of psychosis in autism across studies was 9.4 % (45 studies, N = 63,657, 95 %CI = 7.52, 11.72). There was evidence of publication bias (Egger's t=-3.67, p < .001) however see Supplementary 4 for further details and discussion. Heterogeneity was high (Q = 1803.57, df = 44, I^2 = 97.56 %, p < .001). Leave-one-out analyses revealed that Davignon et al. (2018) and Raja and Azzoni (2010) were having an undue influence on the prevalence estimate (see Supplementary 5). However, removal of these studies had only a negligible effect on the prevalence estimate (10.0 %, 42 studies, N = 59,508, 95 % CI = 8.06, 12.43), as they were influencing it in opposing directions, and heterogeneity remained high (Q = 1558.24, df = 42, I^2 = 97.30 %, p < .001; see Supplementary 5). This indicates that heterogeneity was not solely due to outliers and might rather be due to heterogeneity of true effects (Wang, 2018). Thus, 9.4 % appears to be a valid representation of the prevalence of psychosis in adults with autism.

3.4. Prevalence of bipolar disorders in autism

Twenty-seven studies involving 48,973 individuals aged between 11–62 years (with a mean/median age of 18.3–48 years) reported on the co-occurrence of bipolar disorders in autism (see Table 1) (Gillberg et al., 2016; Anckarsater et al., 2008; Buck et al., 2014; Cederlund et al., 2008; Chen et al., 2015; Croen et al., 2015; Davignon et al., 2018; Haw et al., 2013; Hofvander et al., 2009; Houghton et al., 2017; Hutton et al., 2008; Isenberg et al., 2021; LoVullo and Matson, 2009; Lugnegard et al., 2011; Morgan et al., 2003; Moseley et al., 2011; Mosner et al., 2019; Nahar et al., 2019; Pehlivanidis et al., 2020; Roy et al., 2015; Russell et al., 2016; Rydén and Bejerot, 2008; Schalbroeck et al., 2019; Stahlberg et al., 2004; Kirsch et al., 2020; Mazefsky et al., 2008; Munesue et al., 2008). Prevalence rates reported across studies for the co-occurrence of bipolar disorders in autism, ranged from 0 %–39 % of the total autism sample.

As can be seen in Fig. 3, the pooled prevalence of bipolar disorders in autism was 5.9 % (27 studies, N = 48,973, 95 %CI = 3.89, 8.78). There was evidence of publication bias (Egger's t=-2.19, p = .028; however see Supplementary 6 for further details). Heterogeneity was high (Q = 1240.23, df = 26, I^2 = 97.9 %, p < .001). Outlier removal of one study (Schalbroeck et al., 2019) increased the prevalence estimate to 7.5 % (26 studies, N = 31,739, 95 %CI = 5.79, 9.53), and heterogeneity decreased but remained high (Q = 305.82, df = 25, I^2 = 91.83 %, p < .001; see Supplementary 7). Thus, 7.5 % might be a more valid representation of the prevalence of bipolar disorders in adults with autism, and heterogeneity might again be primarily due to heterogeneity of true effects (Wang, 2018).

3.5. Risk factors

3.5.1. Psychosis

Fourteen studies (Gillberg et al., 2016; Supekar et al., 2017; Kohane et al., 2012; Gilmore et al., 2021; Tsakanikos et al., 2011; Buck et al., 2014; Croen et al., 2015; Isenberg et al., 2021; McCarthy et al., 2010; Raja and Azzoni, 2010; Schalbroeck et al., 2019; Stahlberg et al., 2004; Larson et al., 2015, 2017) included an examination of risk factors associated with the co-occurrence of psychosis in autism (see Table 1). As shown in Table 1, the range of variables examined in relation to co-occurring autism and psychosis was varied and included socio-demographic, clinical, IQ and other variables related to author-specified behaviours of interest (i.e., challenging behaviours, empathizing bias).

All outcomes from each study examining psychosis in autism are reported in Supplementary 8. Gender was the most examined variable, with seven studies examining the association between gender and psychosis co-occurrence in autism. Of these seven studies, six reported higher rates of psychosis diagnoses in males compared to females (Supekar et al., 2017; Tsakanikos et al., 2011; Raja and Azzoni, 2010; Schalbroeck et al., 2019; Larson et al., 2015, 2017); only one study found higher rates of psychosis in females with autism (Croen et al.,

Table 1
Characteristics, prevalence rates, and risk factors examined in included studies.

Author, Year	Country	Autism diagnoses (diagnostic system)	Co-occurring diagnoses (as specified by authors)	Sample size (N)	Mean/ median (mdn) age (years)	Age range (years)	% Male	Intellectual disability (%)	Prevalence %[a] (numerator/ denominator)	Risk factors / group differences examined
Anckarsater et al., 2008	Sweden	Autism; Asperger's syndrome; atypical autism(DSM-IV)	Psychotic disorder; schizoaffective syndrome	20	26.2 (Mdn)	18–47	Not reported for 18+ years	Not reported for 18+ years	5% (1/20)	–
			Bipolar disorder	20	26.2 (Mdn)	18–47	Not reported for 18+ years	Not reported for 18+ years	20 % (4/20)	–
Billstedt et al., 2005	Sweden	Autistic disorder; atypical autism; other ASD (DSM-IV, ICD-10)	Psychosis	108	25.5	17–40	70	>71 %	7% (8/108)	–
Buck et al., 2014	USA	Not reported (DSM-III, DSM-IV-TR)	Psychosis	129	36.4	26–54	75	73	10% (13/ 129)	Intellectual disability
			Bipolar disorder/ expansive mood	129	36.4	26–54	75	73	6% (8/129)	–
Cederlund et al., 2008	Sweden	Asperger syndrome; autistic disorder [autism, atypical autism] (DSM-IV, ICD-10)	Psychosis	140	Not reported for 18+ years	16–38	100	Not reported	4% (6/140)	–
			Bipolar disorder	140	Not reported for 18+ years	16–38	100	Not reported	1% (1/140)	–
Chen et al., 2015	Taiwan	Autism spectrum disorder (ICD-9)	Schizophrenia	725	18.3	Not reported	77	Not reported	11 % (81/ 725)	–
			Bipolar disorder	725	18.3	Not reported	77	Not reported	4% (29/725)	–
Croen et al., 2015	USA	Autism; Asperger's disorder; PDD-NOS (ICD-9)	Schizophrenic disorders; other psychoses	1507	29.0	Not reported	73	19	14% (213/ 1507)	Gender
			Bipolar disorder	1507	29.0	Not reported	73	19	11 % (159/ 1507)	Gender
Davignon et al., 2018	USA	Autism spectrum disorder (ICD-9)	Schizophrenic disorders; other psychoses	4123	18.4	14–25	81	13	2% (70/ 4123)	–
			Bipolar disorder	4123	18.4	14–25	81	13	6% (264/ 4123)	–
Etyemez et al., 2020	USA	Autism spectrum disorder (ICD-9)	Psychosis	72	23.4	18–57	Not reported	Not reported	18 % (13/72)	–
Fusar-Poli et al., 2020	Italy	Autism spectrum disorder (DSM-5)	Psychoses	161	23 (Mdn)	18–55	80	21	4% (7/161)	–
Gesi et al., 2021	Italy	Autism spectrum disorder (DSM-5)	Psychotic spectrum disorder	61	28.5	Not reported	64	0	3% (2/61)	–
Geurts and Jansen, 2012	Not reported	Autistic disorder; Asperger syndrome; PDD-NOS (DSM-IV-TR)	Schizophrenia (included dissociative disorders)	105	31.0	18–64	76	34	9% (9/105)	–
Ghaziuddin and Zafar, 2008	USA	Autism; Asperger syndrome; PDD-NOS (DSM-IV, DSM-IV-TR)	Psychosis	28	26.5	18–57	64	Not reported	7% (2/28)	–
Gillberg et al., 2016	Sweden	Autism spectrum disorder; autistic disorder; Asperger syndrome	Psychosis	50	30.2	23–43	100	Not reported	2% (1/50)	Autism diagnostic stability
			Bipolar disorder	50	30.2	23–43	100	Not reported	4% (2/50)	Autism diagnostic stability

(*continued on next page*)

Table 1 (*continued*)

Author, Year	Country	Autism diagnoses (diagnostic system)	Co-occurring diagnoses (as specified by authors)	Sample size (N)	Mean/ median (mdn) age (years)	Age range (years)	% Male	Intellectual disability (%)	Prevalence %[a] (numerator/ denominator)	Risk factors / group differences examined
Gilmore et al., 2021	USA	(DSM-IV, ICD-10, DSM-5) Autism spectrum disorder (ICD-10)	Schizophrenia/ psychotic disorders	4685	Not reported	65–84+	68	44	18 % (833/ 4685)	Intellectual disability
Haw et al., 2013	UK	Autism; atypical autism; Asperger's syndrome (ICD-10)	Schizophrenia and related disorders	45	27 (Mdn)	19–57	100	Not reported	36 % (16/45)	–
			Bipolar disorder	45	27 (Mdn)	19–57	100	Not reported	0% (0/45)	–
Helverschou et al., 2015	Norway	Asperger syndrome; other ASD including childhood autism, atypical autism, other specified PDD, PDD-NOS (ICD-10)	Psychoses	45	28.3	15–67	85	33	13 % (6/45)	–
Helverschou, 2020	Norway	Autism spectrum disorder (ICD-10)	Psychosis	132	28.6	16–66	67	100	33% (43/ 132)	–
Hofvander et al., 2009	France, Sweden	Autistic disorder; Asperger syndrome; PDD-NOS (DSM-IV)	Psychotic disorders	122	29 (Mdn)	16–60	67	0	12% (15/ 122)	–
			Bipolar disorder	122	29 (Mdn)	16–60	67	0	8% (10/122)	–
Houghton et al., 2017	USA	Autistic disorder; other specified PDDs; unspecified PDD (ICD-9)	Schizophrenia	22,253	Not reported	18–50+	Not reported for 18+ years	18–24 yrs: 22 25–49 yrs: 36 50+ yrs: 37	5% (1178/ 22,253)	–
			Bipolar disorder	22,253	Not reported	18–50+	Not reported for 18+ years	18–24 yrs: 22 25–49 yrs: 36 50+ yrs: 37	12% (2677/ 22,253)	–
Hutton et al., 2008	UK	Not reported. Diagnoses confirmed with ADI and ADOS.	Schizophrenia	135	34.9	21–57	77	Not reported	0% (0/135)	–
			Bipolar disorder	135	34.9	21–57	77	Not reported	1% (1/135)	–
Isenberg et al., 2021	USA	Autistic disorder, Asperger's disorder, PDD-NOS (DSM-IV)	Psychosis	63	ASD only: 26.2 ASD + SUD: 35.2	18–47	65	Not reported	13 % (8/63)	Substance use disorder (SUD)
			Bipolar disorder	63	ASD only: 26.2 ASD + SUD: 35.2	18–47	65	Not reported	25 % (16/63)	Substance use disorder (SUD)
Ketelaars et al., 2008	Netherlands	High functioning autism; Asperger's disorder; PDDS-NOS (DSM-IV)	Schizophrenia; psychotic disorder NOS; mood disorder with psychotic symptoms	15	22	18–24	80	0	13 % (2/15)	–
Kirsch et al., 2020	USA	Not reported (DSM-IV-TR)	Bipolar disorder	1014	22.8 (Mdn)	18–28	74	Not reported	5% (47/ 1014)	–
Kohane et al., 2012	USA	Autistic disorder; Asperger's syndrome; other PDDs (ICD-9)	Schizophrenia	Not reported for 18+ years	Not reported	18–34	Not reported for 18+ years	Not reported	Numerator/ denominator not reported	Age (0–17, 18–34)
Kurita et al., 2004	Japan	Autistic disorder; PDD-NOS (DSM-III)	Bipolar disorder (I, II, NOS)	46	Autism & bipolar disorder: 23.5	14–33	91	100	–	Family history of a mood disorder; family history of a

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Table 1 (*continued*)

Author, Year	Country	Autism diagnoses (diagnostic system)	Co-occurring diagnoses (as specified by authors)	Sample size (N)	Mean/ median (mdn) age (years)	Age range (years)	% Male	Intellectual disability (%)	Prevalence %[a] (numerator/ denominator)	Risk factors / group differences examined
					Autism only: 22.8					developmental disorder; obstetric risk factors; weight at birth; body length at birth; developmental landmarks (head control, walking, speech); CARS-TV total score; CARS-TV 15 item scores; history of epileptic EEG abnormality; epilepsy; age at onset of epilepsy
Larson et al., 2015	UK	Autistic disorder; childhood autism; Asperger's disorder; PDD-NOS (DSM-IV-TR)	Psychotic illness	135	Not reported. All 16 years+	Not reported	Autism & psychosis: 81 Autism-no psychosis: 46	Not reported	–	Gender; full scale IQ; empathizing bias
Larson et al., 2017	UK	Not reported. All had a clinical diagnosis of ASD or met criteria on the ADOS/ADI-R.	Affective psychosis; schizophrenia (including schizoaffective and schizophreniform disorders); other psychosis (non-affective psychosis)	144	Autism & psychosis: 27.7 ASD-no psychosis: 27.8	17–55	Autism & psychosis: 84 ASD-no psychosis: 46	Not reported	–	Gender; verbal IQ; Autism symptoms
LoVullo and Matson, 2009	USA	Autistic disorder; PDD-NOS (DSM-IV-TR, ICD-10)	Psychotic disorder NOS	162	48	Not reported	62	100	1% (2/162)	–
			Bipolar NOS	162	48	Not reported	62	100	6% (9/162)	–
Lugnegard et al., 2011	Sweden	Asperger syndrome. All had a clinical diagnosis and most diagnoses confirmed with DISCO-11.	Psychosis	54	27	Not reported	48	Not reported	4% (2/54)	–
			Bipolar disorder	54	27	Not reported	48	Not reported	9% (5/54)	–
Lunsky et al., 2009	Canada	Not reported (ICD-9)	Psychotic disorder	23	35.4	Not reported	74	100	26% (6/23)	–
Mazefsky et al., 2008	USA	Autistic disorder (DSM-IV)	Bipolar disorder (I, II)	16	24.8	18–32	94	71	6% (1/16)	–
McCarthy et al., 2010	UK	PDD (ICD-10)	Schizophrenia spectrum disorder	124	Not reported	18–65	Not reported for 18+ years	100	9% (11/124)	Challenging behaviour
Melville et al., 2008	Scotland	Not reported (DSM-IV-TR, ICD-10)	Psychotic disorder	77	37.8	Not reported	77	100	0% (0/77)	–
Morgan et al., 2003	UK	Autistic spectrum disorder (includes atypical autism, childhood autism) (ICD-10)	Schizophrenia; schizoaffective disorder	164	Not reported	Not reported	80	Not reported	6% (10/164)	–
			Bipolar disorder	164	Not reported	Not reported	80	Not reported	11 % (18/ 164)	–

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Table 1 (*continued*)

Author, Year	Country	Autism diagnoses (diagnostic system)	Co-occurring diagnoses (as specified by authors)	Sample size (N)	Mean/ median (mdn) age (years)	Age range (years)	% Male	Intellectual disability (%)	Prevalence %[a] (numerator/ denominator)	Risk factors / group differences examined
Moseley et al., 2011	Australia	Autistic disorder (DSM-IV-TR)	Psychotic disorders	84	19.5	11–30	82	79	0% (0/84)	–
			Bipolar I disorder	84	19.5	11–30	82	79	4% (3/84)	–
Mosner et al., 2019	USA	Not reported. All had clinical diagnoses confirmed using ADOS-2	Psychosis	32	20.19	18–25	88	0	0% (0/32)	–
			Bipolar disorder	32	20.19	18–25	88	0	0% (0/32)	–
Mouridsen et al., 2008b	Denmark	Infantile autism (ICD-8, ICD-9)	Schizophrenia spectrum disorders (schizophrenia, delusional disorders, acute psychotic disorder, unspecified non-organic psychosis)	118	40.6	25–55	72	70	7% (8/118)	–
Munesue et al., 2008	Japan	Asperger disorder; PDD-NOS (DSM-IV)	Bipolar disorder (I, II, NOS)	44	20.6	13–39	64	0	27% (12/44)	–
Nahar, 2018	India	Asperger's syndrome; PDD-NOS (ICD-10)	Psychotic spectrum disorder	33	22.8	17–37	78	0	27% (9/33)	–
			Bipolar affective disorder	33	22.8	17–37	78	0	39 % (13/33)	–
Nylander et al., 2013	Sweden	Not reported. (ICD-9, ICD-10)	Psychotic disorders	270	30.7	16–63	69	11	21 % (57/ 270)	–
Nylander et al., 2018	Sweden	Childhood autism; Asperger syndrome; atypical autism; other PDD; PDD-NOS (ICD-10)	Psychotic disorders	601	64	55–96	64	43	12% (71/ 601)	–
Pehlivanidis et al., 2020	Greece	Autism spectrum disorder (DSM-5)	Psychotic disorder	87	29	Not reported	ASD only: 81 ASD + ADHD: 66	0	8% (7/87)	–
			Bipolar disorder	87	29	Not reported	ASD only: 81 ASD + ADHD: 66	0	7% (6/87)	–
Raja and Azzoni, 2010	Italy	Asperger's disorder; autistic disorder; PDD-NOS (DSM-IV-TR)	Schizophrenia	26	30.2	18–56	96	Not reported	62 % (16/26)	Gender; age; marital status; parenthood; BPRS; SAPS; SANS; MMSE; UPDRS; BAS; CPZ-equivalents; CGI; GAF; suicidal risk
Roy et al., 2015	Germany	Asperger syndrome (DSM-IV)	Schizophrenia	50	36.5	20–62	68	Not reported	2% (1/50)	–
			Bipolar disorder	50	36.5	20–62	68	Not reported	0% (0/50)	–
Russell et al., 2016	UK	Childhood autism; Asperger's syndrome; atypical autism; PDD-NOS (ICD-10)	Psychotic disorder; schizophrenia	474	30.6	Not reported	78	0	3% (16/474)	–
			Bipolar affective disorder	474	30.6	Not reported	78	0	1% (4/474)	–
Rydén and Bejerot, 2008	Sweden	Autism; Asperger disorder; PDD-NOS (DSM-IV)	Psychosis	84	30	Not reported	54	0	6% (5/84)	–
			Bipolar disorder	84	30	Not reported	54	0	2% (2/84)	–
Schalbroeck et al., 2019	Nether-lands	Autistic disorder; Asperger's syndrome; PDD-NOS (DSM-IV)	Non-affective psychotic disorders (schizophrenia, schizophreniform disorder,	17,234	23.2	16–35	76	10	5% (845/ 17,234)	Gender; intellectual disability present before or at the moment of the

(*continued on next page*)

Table 1 (*continued*)

Author, Year	Country	Autism diagnoses (diagnostic system)	Co-occurring diagnoses (as specified by authors)	Sample size (N)	Mean/ median (mdn) age (years)	Age range (years)	% Male	Intellectual disability (%)	Prevalence %[a] (numerator/ denominator)	Risk factors / group differences examined
			schizoaffective disorder, delusional disorder, psychotic disorder NOS, brief psychotic disorder							autism diagnosis; migrant status; autism subtype; age at autism diagnosis (0–7, 8–15, 16–25, 26–35 years)
			Bipolar disorder (I, II, NOS)	17,234	23.2	16–35	76	10	1% (116/ 17,234)	Gender; intellectual disability present before or at the moment of the autism diagnosis; migrant status; autism subtype; age at autism diagnosis (0–7, 8–15, 16–25, 26–35 years)
Sheehan, 2020	UK	Autism spectrum disorder (ICD-10)	Schizophrenia spectrum disorders	315	30.5	Not reported	75	0	16% (50/ 315)	–
Stahlberg et al., 2004	Sweden	Autism; Asperger's disorder; atypical autism (DSM-IV)	Schizophrenia; other psychotic disorders	129	30.6	19–60	61	Not reported	8% (10/129)	Full scale IQ; verbal IQ; performance IQ; GAF
			Bipolar disorder with psychotic features	129	30.6	19–60	61	Not reported	7% (9/129)	Full scale IQ; verbal IQ; performance IQ; GAF
Supekar et al., 2017	USA	Not reported (ICD-9)	Schizophrenia	4790	Not reported	18–35+	Not reported for 18+ years	Not reported	Numerator/ denominator not reported	Gender; age; gender * age
Tint et al., 2021	Canada	Autistic disorder, Asperger's disorder, Childhood Disintegrative disorder, PDD-NOS (ICD-10, DSM-IV)	Psychotic mental illness	6870	23.14	15–44	0 (all female sample)	Not reported	9% (623/ 6870)	–
Tsakanikos et al., 2011	UK	PDD (ICD-10)	Schizophrenia spectrum disorders	150	28.5	16–84	67	100	17 % (25/ 150)	Gender
Vohra et al., 2017	USA	Not reported (ICD-9)	Schizophrenia and other psychotic disorders	1772	Not reported	22–64	71	Not reported	17 % (294/ 1772)	–

2015). Three studies examined age in relation to psychosis and autism co-occurrence. Two of these studies found that older age groups (18–34 years versus 0–17 years (Kohane et al., 2012), above 35 years versus 18–35 years (27)) had a higher prevalence of psychosis and autism co-occurrence compared to younger age groups. The other study found that individuals with co-occurring autism and psychosis were younger than those with psychosis only (Raja and Azzoni, 2010).

Three studies considered IQ estimates in relation to co-occurring psychosis and autism; of these, two (Larson et al., 2015, 2017) found that lower IQ was associated with co-occurrence, while one (Stahlberg et al., 2004) found no association. Similarly, three studies examined the presence of intellectual disability in autism; one study found that intellectual disability in autism was associated with increased rates of psychosis (Gilmore et al., 2021), one found less frequent co-occurrence of psychosis (Buck et al., 2014) and another found no association (Schalbroeck et al., 2019).

Other variables related to greater likelihood of autism and psychosis co-occurrence (each reported in only one study) included: stable autism diagnoses in adulthood, individuals without intellectual disability, lower full-scale IQ estimates, lower verbal IQ estimates, less stereotyped interests/behaviours, more motor side-effects from antipsychotic medication, individuals who are identified as migrants, lower global assessment of functioning scores, and an empathising (versus systemising) bias.

3.5.2. *Bipolar disorders*

Six studies (Gillberg et al., 2016; Croen et al., 2015; Isenberg et al., 2021; Schalbroeck et al., 2019; Stahlberg et al., 2004; Kurita et al., 2004) included an examination of risk factors or group differences potentially indicating risk factors associated with the co-occurrence of

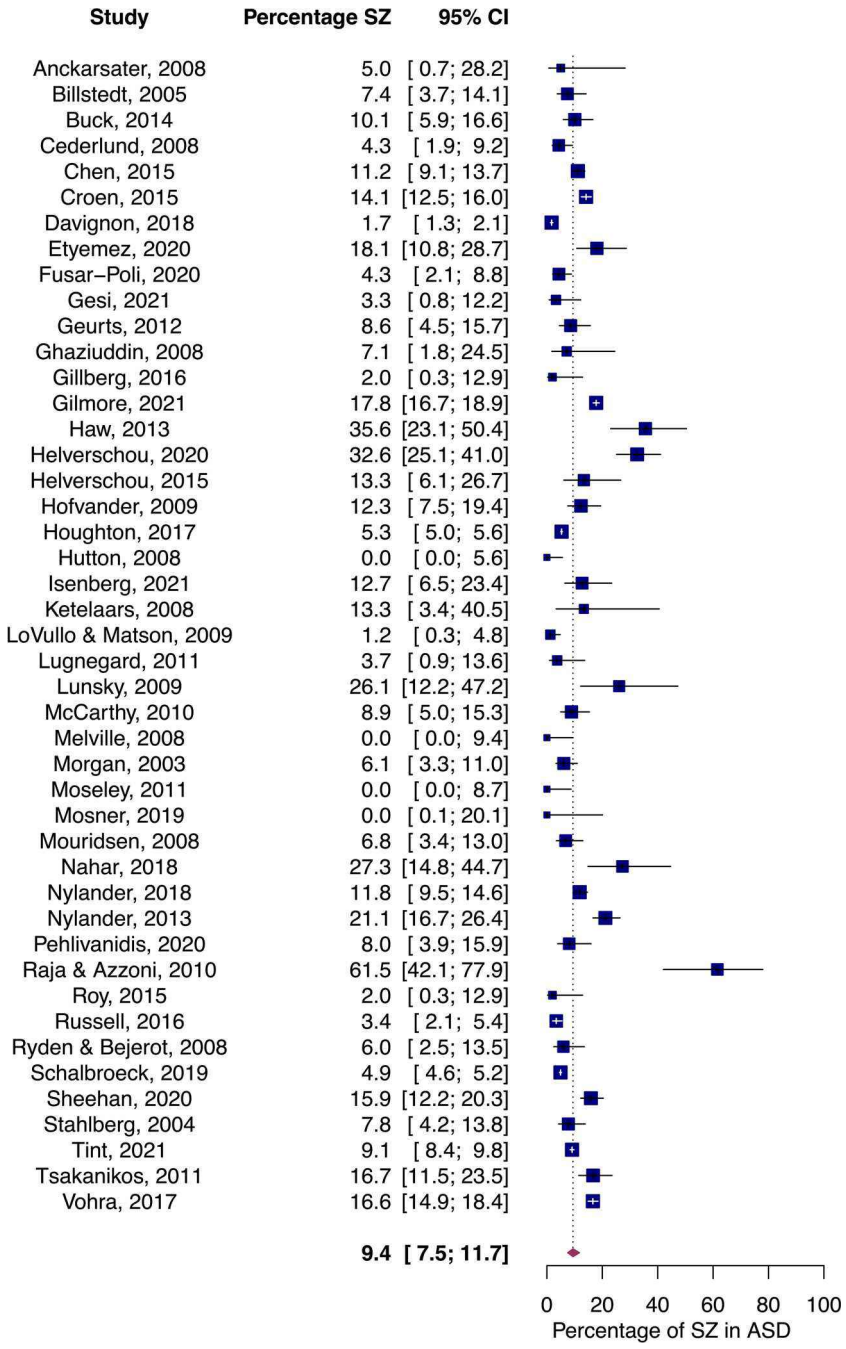

Fig. 2. Forest plot depicting the prevalence of psychosis in autism.

bipolar disorders in autism. As can be seen in Table 1, the range of variables examined in relation to co-occurring autism and bipolar disorders was varied and included demographic, clinical, IQ, developmental (milestones), and obstetric (risk factors, weight/length at birth) variables.

All outcomes from each study are reported in Supplementary 9. Gender was the only variable examined across more than one study (Croen et al., 2015; Schalbroeck et al., 2019). Both studies reporting on this variable found that females with autism had a higher likelihood of a bipolar diagnosis, compared to males with autism (Croen et al., 2015; Schalbroeck et al., 2019). Other variables with significant associations between autism and bipolar co-occurrence (each reported in only one study) included: individuals with stable autism diagnoses in adulthood, individuals with more overall behaviours associated with autism and more impairment in autism-related domains, a later age of onset of epilepsy, and individuals with a higher performance IQ compared to individuals with autism only.

4. Discussion

The current meta-analysis and narrative synthesis, based on 53 studies, examined the prevalence of co-occurring psychosis and bipolar disorders in adults with autism. The estimated pooled prevalence for psychosis in adults with autism was 9.4 %. The most valid estimate for the pooled prevalence of bipolar disorders in adults with autism was 7.5 %. Consistent with the conclusions from other meta-analyses examining the prevalence of psychosis and bipolar disorder in autism across broader age ranges, our findings suggest that these disorders each co-occur at a substantially higher prevalence in adults with autism than lifetime prevalence estimates reported from the general population: 0.75

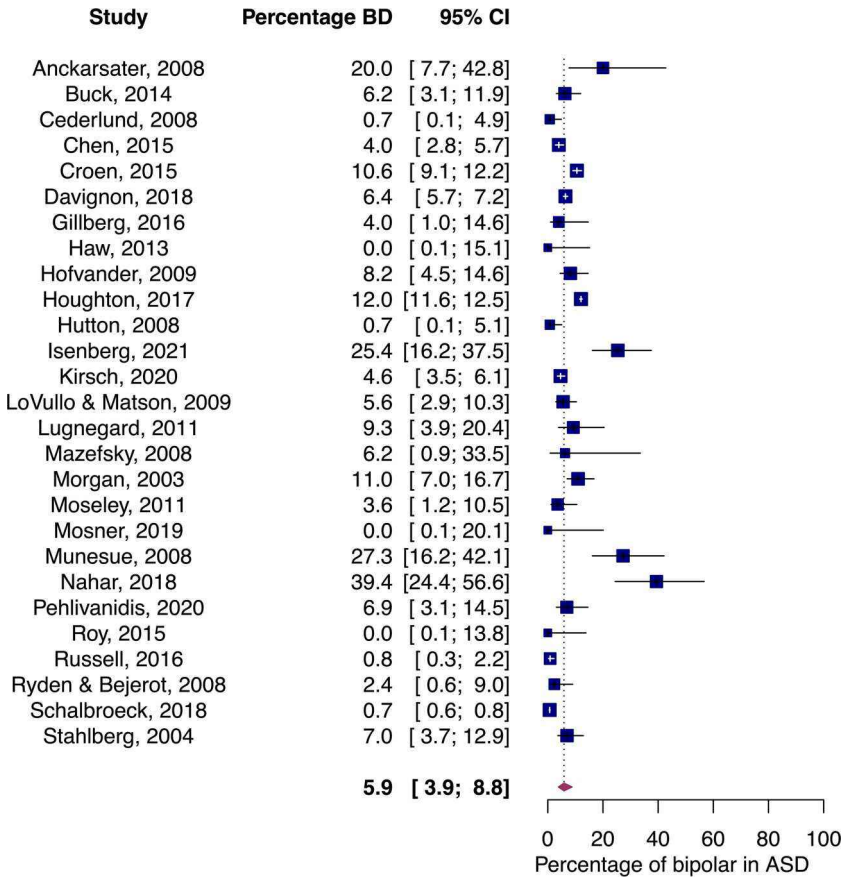

Fig. 3. Forest plot depicting the prevalence of bipolar disorder in autism.

% for psychosis (Moreno-Kustner et al., 2018), and 1.06–1.57% for bipolar disorder (Clemente et al., 2015). These prevalence rates highlight the need for clinical practice and research efforts focused on assessment, monitoring, diagnosis and intervention of these psychiatric disorders in adults with autism.

4.1. Prevalence

4.1.1. Psychosis

In terms of the comparability of our prevalence estimates of psychosis co-occurring with autism and that of other meta-analyses, our estimates fall within the range of previously reported prevalence rates (i.e., 4–11.8 %). Specifically, Marín et al. (2018) and Lugo-Marín (Lugo--Marín et al., 2019) conducted the only other meta-analyses focused specifically on adults with autism. They found prevalence estimates for the co-occurrence of schizophrenia spectrum disorders of 6.4 % for adults with an IQ above 70 (Marín et al., 2018), and 11.8 % for adults with autism, irrespective of IQ (Lugo-Marín et al., 2019). Our estimate of 9.4 % is more closely aligned with this latter estimate, consistent with our own analysis including individuals across all IQ estimates. However, our estimate is based on an increased number of studies, and includes more recent studies which may account for the slightly lower estimate. De Giorgi et al. (2019) reported a comparable prevalence estimate of psychosis in autism to our own, at 9.5 %, although their estimate included children. In a subgroup analysis focused specifically on adults with autism, they reported a similar, albeit slightly elevated estimate, of 10.1 % (De Giorgi et al., 2019). Once again, this series of meta-analyses (inclusive of the current study) converge to suggest psychosis co-occurs in adults with autism at a rate that is more than 10 times higher than the prevalence of psychosis in the general population.

Of note, these estimates of psychosis co-occurrence in autism from studies predominately focused on adults are higher than that reported by a large, recent meta-analysis involving individuals with autism across all ages – in their meta-analysis, Lai et al. (2019) reported a co-occurrence rate of 4%. There are some key points of difference as compared to the current meta-analysis. Specifically, Lai et al. (2019) estimates were based on point (rather than lifetime) prevalence. In addition, mean ages of participants were as young as 3.5 years. However, Lai et al. (2019) did report an association between age and prevalence, with older ages being associated with a higher prevalence of psychosis in autism than younger ages, consistent with the peak age of onset of psychosis in early adulthood (Miettunen et al., 2019). Therefore, it appears that both across and within meta-analyses that have examined age, the prevalence of psychosis in autism increases with age, highlighting the need for continued and ongoing clinical and research examinations of co-occurring disorders across the lifespan in autism.

4.1.2. Bipolar disorder

To our knowledge, the current meta-analysis is the first to examine the prevalence of bipolar disorder specifically in adults with autism. Lai et al. (2019) is the only other meta-analysis to date, but examined point-prevalence estimates based on all ages. This likely explains Lai et al. (2019) lower prevalence estimate of 5%. Overall, the prevalence of bipolar disorder in autism, and risk factors associated with co-occurrence, has been examined in considerably fewer studies than psychosis. This is despite evidence suggesting the likelihood for developing bipolar disorder is also substantially increased in autism compared to the general population (Lai et al., 2019; Vannucchi et al., 2014).

4.2. Risk factors

Of the studies we reviewed, the range of factors examined in relation to the co-occurrence of psychosis and bipolar disorder was highly variable across studies, with most only examined in a single study.

4.2.1. Psychosis

Of the factors examined across more than one study, only gender and age appear to show any emerging consistency in outcomes. Specifically, in six of seven studies examining the association between gender and the co-occurrence of psychosis, adult males with autism were at increased likelihood of co-occurring psychosis compared to females. Two studies examining age as a factor found that older ages were associated with increased rates of psychosis in autism (Supekar et al., 2017; Kohane et al., 2012), while one study found younger ages had higher co-occurrence rates (Raja and Azzoni, 2010). The findings from this latter study appear to be specific to this particular study population as other studies and meta-analyses examining age (Lai et al., 2019; De Giorgi et al., 2019) have all reported higher prevalence rates in older age groups. Other variables that have been examined across more than one study (IQ, intellectual disability, global assessment of functioning) have inconsistent outcomes with the co-occurrence of psychosis in autism.

4.2.2. Bipolar disorder

There were only six studies examining any potential risk factors or group differences indicating risk factors for the co-occurrence of bipolar disorder in autism. Of these, gender was the only variable examined in more than one study. Interestingly, the pattern of emerging results was the opposite to that of psychosis, whereby females with autism showed a higher likelihood of co-occurring bipolar disorder, compared to males with autism. Both studies in the current review examining the association between gender and bipolar co-occurrence in autism were large-scale register-based studies (Croen et al., 2015; Schalbroeck et al., 2019), suggesting this association between females with autism and increased prevalence of co-occurring bipolar disorder requires closer clinical and research consideration. No other variables were examined across more than one study in relation to bipolar co-occurrence, including age.

4.3. Clinical implications

The findings from the current review align with the emerging consensus from recent meta-analyses of substantially increased prevalence of psychosis and bipolar disorder in autism. In particular, our results highlight the need for assessment and monitoring of these disorders in adults with autism as part of ongoing clinical care. To support this, it is evident that screening, assessment, diagnostic tools, and interventions specifically designed and validated for adults with autism are required to facilitate the timely and accurate identification and care of individuals with these complex and heterogeneous psychiatric disorders. In addition, clinical management of adults with autism should include pathways for accessing supports for those individuals at increased likelihood of, or diagnosed with, co-occurring psychosis and/or bipolar disorder. These pathways should also take into consideration the required supports for clinical teams to deliver care to adults with autism with co-occurring disorders in standard settings, without the requirement for referral to specialised services.

4.4. Limitations

The current study should be evaluated within the context of the following limitations. While the full-text screening stage of the review was conducted in duplicate by two independent reviewers, only one reviewer conducted the initial screening (of titles and abstracts) phase of the review. The review only included published, peer-reviewed studies retrieved from database searches; we did not search or include grey literature, increasing the risk of publication bias. Only studies with an English translation available were included, increasing the potential for bias.

In terms of included studies, there was substantial variability in sampling methods, sample sizes, and diagnostic processes. The risk of bias assessment highlighted, in particular, the lack of population representativeness across most study samples and the variable data collection and sampling methods across studies (e.g., population-based, clinic-based, register). These factors, combined with heterogeneous and potentially uncertain diagnostic determinations (when using registered diagnoses), are likely to contribute to the varying prevalence estimates reported across individual studies, and point to the need for rigorous, large-scale population cohort studies to enhance the accuracy of the prevalence estimates for psychosis and bipolar disorder co-occurrence in autism.

Relatedly, we found substantial heterogeneity related to the pooled estimates of prevalence in the current meta-analysis (I^2>90 %). While we integrated leave-one-out analyses to examine the potential influence of outliers, heterogeneity remained high. Due to the substantial variability and inconsistent reporting of potential moderating variables (i.e., demographic, clinical, sampling) across studies, we did not conduct additional subgroup or meta-regression moderator analyses, so we cannot address potential sources of heterogeneity. However, it is noteworthy that other meta-analyses examining the co-occurrence of psychosis and bipolar disorder in autism have also reported significant heterogeneity in their prevalence estimates, comparable to that of the current study (Lai et al., 2019; Lugo-Marín et al., 2019; Zheng et al., 2018). Moreover, Lai et al. (Lai et al., 2019) found that while age, intellectual disability, gender, and the country of the included study were associated with heterogeneity, substantial unexplained heterogeneity remained even after subgroup moderator analyses. These sources of heterogeneity remain to be explored in future research to enhance the accuracy of prevalence estimates for the co-occurrence of psychosis and bipolar in autism.

4.5. Future research

While the field would benefit from large-scale studies of representative samples to improve the accuracy of current prevalence estimates, it is evident that psychosis and bipolar disorder co-occur with autism at a rate higher than would be expected in the general population. As such, research efforts focused on aetiological mechanisms and evidence-based clinical practices related to the co-occurrence of these disorders in adults with autism are needed. In particular, we found that there is a dearth of research examining potential risk factors associated with the co-occurrence of psychosis and bipolar disorder in autism. This is an area in need of further research, particularly due to the potential of this research to inform subgroups of individuals with autism that may be at increased likelihood of these disorders, and hence, warrant close clinical monitoring. In addition, the identification of risk factors for co-occurring psychosis and bipolar disorder in autism could inform potential causal pathways (biological or psychosocial) for their co-occurrence. Phenomenological studies of psychosis and/or bipolar in individuals with and without autism could inform the ways in which the conditions are similar or different when they co-occur in autism versus when they occur independently. Longitudinal studies of outcomes for adults with autism and co-occurring psychosis and/or bipolar disorder are also needed to assess particular domains of clinical and functional outcomes that would benefit from intervention and support in adulthood. Rigorous intervention-based clinical trials are required to identify evidence-based options for adults with autism presenting with co-occurring psychosis and/or bipolar disorder. Finally, the increased co-occurrence of psychosis in adults with autism also highlights the need for trials of early intervention specifically targeted at groups already known to be at increased likelihood for these conditions, such as individuals at clinical high risk for psychosis.

4.6. Conclusion

Psychosis and bipolar disorder occur at a substantially higher prevalence in adults with autism compared to the general population. To date, there is limited evidence informing potential risk factors or variables associated with the higher co-occurrence of psychosis and bipolar disorder in autism. Considering the impact of autism, psychosis, and bipolar disorder on clinical and functional outcomes, and now, the overwhelming consensus for their increased co-occurrence in autism, this is an area in need of clinical and research attention in order to identify and provide targeted, specific supports to those individuals at high likelihood and/or who develop co-occurring psychosis or bipolar disorder in autism.

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Declaration of Competing Interest

All authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2022.104543.

References

Anckarsater, H., Nilsson, T., Saury, J.M., Rastam, M., Gillberg, C., 2008. Autism spectrum disorders in institutionalized subjects. Nord. J. Psychiatry 62 (2), 160–167.
Ballageer, T., Malla, A., Manchanda, R., Takhar, J., Haricharan, R., 2005. Is adolescent-onset first-episode psychosis different from adult onset? J. Am. Acad. Child Adolesc. Psychiatry 44, 782–789.
Baxter, A.J., Brugha, T.S., Erskine, H.E., Scheurer, R.W., Vos, T., Scott, J.G., 2015. The epidemiology and global burden of autism spectrum disorders. Psychol. Med. (Paris) 45 (3), 601–613.
Billstedt, E., Gillberg, I.C., Gillberg, C., 2005. Autism after adolescence: population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. J. Autism Dev. Disord. 35 (3), 351–360.
Buck, T.R., Viskochil, J., Farley, M., Coon, H., McMahon, W.M., Morgan, J., et al., 2014. Psychiatric comorbidity and medication use in adults with autism spectrum disorder. J. Autism Dev. Disord. 44 (12), 3063–3071.
Carlson, G.A., Bromet, E.J., Sievers, S., 2000. Phenomenology and outcome of subjects with early- and adult-onset psychotic mania. Am. J. Psychiatry 157 (2), 213–219.
Cederlund, M., Hagberg, B., Billstedt, E., Gillberg, I.C., Gillberg, C., 2008. Asperger syndrome and autism: a comparative longitudinal follow-up study more than 5 years after original diagnosis. J. Autism Dev. Disord. 38 (1), 72–85.
Chen, M.-H., Wei, H.-T., Chen, L.-C., Su, T.-P., Bai, Y.-M., Hsu, J.-W., et al., 2015. Autistic spectrum disorder, attention deficit hyperactivity disorder, and psychiatric comorbidities: a nationwide study. Res. Autism Spectr. Disord. 10, 1–6.
Clemente, A.S., Diniz, B.S., Nicolato, R., Kapczinski, F.P., Soares, J.C., Firmo, J.O., et al., 2015. Bipolar disorder prevalence: a systematic review and meta-analysis of the literature. Braz J Psychiatry. 37 (2), 155–161.
Croen, L.A., Zerbo, O., Qian, Y., Massolo, M.L., Rich, S., Sidney, S., et al., 2015. The health status of adults on the autism spectrum. Autism 19 (7), 814–823.
Dagani, J., Baldessarini, R.J., Signorini, G., Nielssen, O., de Girolamo, G., Large, M., 2019. The Age of Onset of Bipolar Disorders. Age of Onset of Mental Disorders. Springer, Cham, pp. 75–110.
Davignon, M.N., Qian, Y., Massolo, M., Croen, L.A., 2018. Psychiatric and medical conditions in transition-aged individuals with ASD. Pediatrics 141 (Suppl 4). S335-S45.
De Giorgi, R., De Crescenzo, F., D'Alò, G.L., Rizzo Pesci, N., Di Franco, V., Sandini, C., et al., 2019. Prevalence of non-affective psychoses in individuals with autism spectrum disorders: a systematic review. J. Clin. Med. 8 (9), 1304.
Etyemez, S., Saleh, A., Hamilton, J.E., Koshy, A.J., Abraham, J.E., Salek, S., 2020. Higher prevalence of mood disorders in admitted patients with autism. Neurol. Psychiatry Brain Res. 37, 87–90.
Foss-Feig, J.H., Velthorst, E., Smith, L., Reichenberg, A., Addington, J., Cadenhead, K.S., et al., 2019. Clinical profiles and conversion rates amoing young individuals with autism spectrum disorder who present to clinical high risk for psychosis services. J. Am. Acad. Child Adolesc. Psychiatry 58 (6), 582–588.
Frahm Laursen, M., Valentin, J.B., Licht, R.W., Correll, C.U., Nielsen, R.E., 2019. Longitudinal outcomes in pediatric-and adult-onset bipolar patients compared to healthy and schizophrenia controls. Bipolar Disord. 21 (6), 514–524.
Fusar-Poli, L., Brondino, N., Rocchetti, M., Petrosino, B., Arillotta, D., Damiani, S., et al., 2019. Prevalence and predictors of psychotropic medication use in adolescents and adults with autism spectrum disorder in Italy: a cross-sectional study. Psychiatry Res. 276, 203–209.
Fusar-Poli, L., Brondino, N., Politi, P., Aguglia, E., 2020. Missed diagnoses and misdiagnoses of adults with autism spectrum disorder. Eur. Arch. Psychiatry Clin. Neurosci. https://doi.org/10.1007/s00406-020-01189-w [online ahead of print].
Gandal, M.J., Haney, J.R., Parikshak, N.N., Leppa, V., Ramaswami, G., Hartl, C., et al., 2018. Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. Science 359 (6376), 693–697.
Gesi, C., Migliarese, G., Torriero, S., Capellazzi, M., Omboni, A.C., Cerveri, G., Mencacci, C., 2021. Gender differences in misdiagnosis and delayed diagnosis among adults with autism spectrum disorder with no language or intellectual disability. Brain Sci. 11, 912.
Geurts, H.M., Jansen, M.D., 2012. A retrospective chart study: the pathway to a diagnosis for adults referred for ASD assessment. Autism 16 (3), 299–305.
Ghaziuddin, M., Zafar, S., 2008. Psychiatric comorbidity of adults with autism spectrum disorders. Clin. Neuropsychiatry 5 (1), 9–12.
Gillberg, I.C., Helles, A., Billstedt, E., Gillberg, C., 2016. Boys with asperger syndrome grow up: psychiatric and neurodevelopmental disorders 20 years after initial diagnosis. J. Autism Dev. Disord. 46 (1), 74–82.
Gilmore, D., Harris, L., Longo, A., Hand, B.N., 2021. Health status of medicare-enrolled autistic older adults with and without co-occurring intellectual disability: an analysis of inpatient and institutional outpatient medical claims. Autism 25 (1), 266–274.
Hand, B.N., Angell, A.M., Harris, L., Arstein Carpenter, L., 2020. Prevalence of physical and mental health conditions in Medicare-enrolled, autistic older adults. Autism 24 (3), 755–764.
Haw, C., Chaplin, E., Radley, J., Cooke, L., 2013. Characteristics of male autistic spectrum patients in low security: are they different from non-autistic low secure patients? J. Intellect. Disabil. Offending Behav. 4 (1/2), 24–32.
Helverschou, S.B., Rasmussen, K., Steindal, K., Sondanaa, E., Nilsson, B., Nottestad, J.A., 2015. Offending profiles of individuals with autism spectrum disorder: a study of all individuals with autism spectrum disorder examined by the forensic psychiatric service in Norway between 2000 and 2010. Autism 19 (7), 850–858.
Helverschou, S.B., Bakken, T.L., Berge, H., Bjørgen, T.J., Botheim, H., Hellerud, J.A., et al., 2021. Preliminary findings from a nationwide, multicenter mental health service for adults and older adolescents with autism spectrum disorder and ID. J. Policy Pract. Intellect. Disabil. 18 (2), 162–173.
Hofvander, B., Delorme, R., Chaste, P., Nyden, A., Wentz, E., Stahlberg, O., et al., 2009. Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. BMC Psychiatry 9, 35.
Hossain, M.M., Khan, N., Sultana, A., Ma, P., McKyer, E.L.J., Ahmed, H.U., et al., 2020. Prevalence of comorbid psychiatric disorders among people with autism spectrum disorder: an umbrella review of systematic reviews and meta-analyses. Psychiatry Res. 287, 112922.
Houghton, R., Ong, R.C., Bolognani, F., 2017. Psychiatric comorbidities and use of psychotropic medications in people with autism spectrum disorder in the United States. Autism Res. 10 (12), 2037–2047.
Hoy, D., Brooks, P., Woolf, A., Blyth, F., March, L., Bain, C., et al., 2012. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J. Clin. Epidemiol. 65 (9), 934–939.
Hutton, J., Goode, S., Murphy, M., Le Couteur, A., Rutter, M., 2008. New-onset psychiatric disorders in individuals with autism. Autism 12 (4), 373–390.
Isenberg, B.M., Woodward, D.W., Burke, C.W., Nowinski, L.A., Joshi, G., Wilens, T.E., 2021. Psychiatric comorbidity associated with co-occurring autism spectrum disorder and substance use disorder. Res. Autism Spectr. Disord. 82, 101728.
Ketelaars, C., Horwitz, E., Sytema, S., Bos, J., Wiersma, D., Minderaa, R., et al., 2008. Brief report: adults with mild autism spectrum disorders (ASD): scores on the autism spectrum quotient (AQ) and comorbid psychopathology. J. Autism Dev. Disord. 38 (1), 176–180.
Kirsch, A., Huebner, A.R.S., Mehta, S.Q., Howie, F.R., Weaver, A.L., Myers, S.M., et al., 2020. Association of comorbid mood and anxiety disorders with autism spectrum disorder. JAMA Pediatr. 174 (1), 63–70.
Kohane, I.S., McMurry, A., Weber, G., MacFadden, D., Rappaport, L., Kunkel, L., et al., 2012. The co-morbidity burden of children and young adults with autism spectrum disorders. PLoS One 7 (4), e33224.
Kurita, H., Osada, H., Shimizu, K., Tachimori, H., 2004. Bipolar disorders in mentally retarded persons with pervasive developmental disorders. J. Dev. Phys. Disabil. 16 (4), 377–389.
Lai, M.C., Kassee, C., Besney, R., Bonato, S., Hull, L., Mandy, W., et al., 2019. Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. Lancet Psychiatry 6 (10), 819–829.

Larson, F.V., Lai, M.C., Wagner, A.P., Consortium, M.A., Baron-Cohen, S., Holland, A.J., 2015. Testing the' Extreme female brain' theory of psychosis in adults with autism Spectrum disorder with or without Co-morbid psychosis. PLoS One 10 (6), e0128102.
Larson, F.V., Wagner, A.P., Jones, P.B., Tantam, D., Lai, M.C., Baron-Cohen, S., et al., 2017. Psychosis in autism: comparison of the features of both conditions in a dually affected cohort. Br. J. Psychiatry 210 (4), 269–275.
Lever, A.G., Geurts, H.M., 2016. Psychiatric Co-occurring symptoms and disorders in young, middle-aged, and older adults with autism Spectrum disorder. J. Autism Dev. Disord. 46 (6), 1916–1930.
Lord, C., Elsabbagh, M., Baird, G., Veenstra-Vanderweele, J., 2018. Autism spectrum disorder. Lancet 392 (10146), 508–520.
LoVullo, S.V., Matson, J.L., 2009. Comorbid psychopathology in adults with Autism Spectrum disorders and intellectual disabilities. Res. Dev. Disabil. 30 (6), 1288–1296.
Lugnegard, T., Hallerback, M.U., Gillberg, C., 2011. Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. Res. Dev. Disabil. 32 (5), 1910–1917.
Lugo-Marín, J., Magán-Maganto, M., Rivero-Santana, A., Cuellar-Pompa, L., Alviani, M., Jenaro-Rio, C., et al., 2019. Prevalence of psychiatric disorders in adults with autism spectrum disorder: a systematic review and meta-analysis. Res. Autism Spectr. Disord. 59, 22–33.
Lunsky, Y., Gracey, C., Bradley, E., 2009. Adults with Autism Spectrum disorders using psychiatric hospitals in Ontario: clinical profile and service needs. Res. Autism Spectr. Disord. 3 (4), 1006–1013.
Marín, J.L., Rodríguez-Franco, M.A., Chugani, V.M., Maganto, M.M., Villoria, E.D., Bedia, R.C., 2018. Prevalence of Schizophrenia spectrum disorders in average-IQ adults with Autism Spectrum disorders: a meta-analysis. J. Autism Dev. Disord. 48, 239–250.
Mazefsky, C.A., Folstein, S.E., Lainhart, J.E., 2008. Overrepresentation of mood and anxiety disorders in adults with autism and their first-degree relatives: what does it mean? Autism Res. 1 (3), 193–197.
McCarthy, J., Hemmings, C., Kravariti, E., Dworzynski, K., Holt, G., Bouras, N., et al., 2010. Challenging behavior and co-morbid psychopathology in adults with intellectual disability and autism spectrum disorders. Res. Dev. Disabil. 31 (2), 362–366.
Melville, C.A., Cooper, S.A., Morrison, J., Smiley, E., Allan, L., Jackson, A., et al., 2008. The prevalence and incidence of mental ill-health in adults with autism and intellectual disabilities. J. Autism Dev. Disord. 38 (9), 1676–1688.
Miettunen, J., Immonen, J., McGrath, J.J., Isohanni, M., Jääskeläinen, E., 2019. The Age of Onset of Schizophrenia Spectrum Disorders. Age of Onset of Mental Disorders. Springer, Cham, pp. 55–73.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J. Clin. Epidemiol. 62 (10), 1006–1012.
Moreno-Kustner, B., Martin, C., Pastor, L., 2018. Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. PLoS One 13 (4), e0195687.
Morgan, C.N., Roy, M., Chance, P., 2003. Psychiatric comorbidity and medication use in autism: a community survey. Psychiatr. Bull. 27 (10), 378–381.
Moseley, D.S., Tonge, B.J., Brereton, A.V., Einfeld, S.L., 2011. Psychiatric comorbidity in adolescents and young adults with autism. J. Ment. Health Res. Intellect. Disabil. 4 (4), 229–243.
Mosner, M.G., Kinard, J.L., Shah, J.S., McWeeny, S., Greene, R.K., Lowery, S.C., Mazefsky, C.A., Dichter, G.S., 2019. Rates of co-occurring psychiatric disorders in autism spectrum disorder using the mini international neuropsychiatric interview. J. Autism Dev. Disord. 49, 3819–3832.
Mouridsen, S.E., Rich, B., Isager, T., 2008a. Psychiatric disorders in adults diagnosed as children with atypical autism. A case control study. J. Neural Transm. 115, 135–138.
Mouridsen, S.E., Rich, B., Isager, T., Nedergaard, N.J., 2008b. Psychiatric disorders in individuals diagnosed with infantile autism as children: a case control study. J. Psychiatr. Pract. 14 (1), 5–12.
Munesue, T., Ono, Y., Mutoh, K., Shimoda, K., Nakatani, H., Kikuchi, M., 2008. High prevalence of bipolar disorder comorbidity in adolescents and young adults with high-functioning autism spectrum disorder: a preliminary study of 44 outpatients. J. Affect. Disord. 111 (2–3), 170–175.
Nahar, A., Thippeswamy, H., Shanker Reddy, M.S., Kishore, M.T., Chaturvedi, S.K., 2019. Psychiatric comorbidity in persons with high-functioning autism spectrum disorders: findings from a tertiary care neuropsychiatric hospital. Asian J. Psychiatr. 41, 50–53.
Nylander, L., Holmqvist, M., Gustafson, L., Gillberg, C., 2013. Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in adult psychiatry. A 20-year register study. Nord. J. Psychiatry 67 (5), 344–350.
Nylander, L., Axmon, A., Bjorne, P., Ahlstrom, G., Gillberg, C., 2018. Older adults with autism Spectrum disorders in Sweden: a register study of diagnoses, psychiatric care utilization and psychotropic medication of 601 individuals. J. Autism Dev. Disord. 48 (9), 3076–3085.
Oliver, L.D., Moxon-Emre, I., Lai, M.C., Grennan, L., Voineskos, A.N., Ameis, S.H., 2021. Social cognitive performance in schizophrenia spectrum disorders compared with autism spectrum disorder: a systematic review, meta-analysis, and meta-regression. JAMA Psychiatry 78 (3), 281–292.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffman, T.C., Mulrow, C.D., et al., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71.
Pehlivanidis, A., Papanikolaou, K., Mantas, V., Kalantzi, E., Korobili, K., Xenaki, L.A., et al., 2020. Lifetime co-occurring psychiatric disorders in newly diagnosed adults with attention deficit hyperactivity disorder (ADHD) or/ and autism spectrum disorder (ASD). BMC Psychiatry 20, 423.
Raja, M., Azzoni, A., 2010. Autistic spectrum disorders and schizophrenia in the adult psychiatric setting: diagnosis and comorbidity. Psychiatr. Danub. 22 (4), 514–521.
Roy, M., Prox-Vagedes, V.D., Ohlmeier, M., Dillo, W., 2015. Beyond childhood: psychiatric comorbidities and social background of adults with Asperger syndrome. Psychiatr. Danub. 27 (1), 50–59.
Russell, A.J., Murphy, C.M., Wilson, E., Gillan, N., Brown, C., Robertson, D.M., et al., 2016. The mental health of individuals referred for assessment of autism spectrum disorder in adulthood: a clinic report. Autism 20 (5), 623–627.
Rydén, E., Bejerot, S., 2008. Autism spectrum disorder in an adult psychiatric population. A naturalistic cross sectional controlled study. Clin. Neuropsychiatry 5 (1), 13–21.
Schalbroeck, R., Termorshuizen, F., Visser, E., van Amelsvoort, T., Selten, J.P., 2019. Risk of non-affective psychotic disorder or bipolar disorder in autism spectrum disorder: a longitudinal register-based study in the Netherlands. Psychol. Med. 49 (15), 2543–2550.
Schwarzer, G., 2007. Meta: an R package for meta-analysis. R news. 7 (3), 40–45.
Sheehan, R., Mutch, J., Marston, L., Osborn, D., Hassiotis, A., 2021. Risk factors for in-patient admission among adults with intellectual disability and autism: investigation of electronic clinical records. BJPsych Open 7 (1), e5.
Skokauskas, N., Frodl, T., 2015. Overlap between autism spectrum disorder and bipolar affective disorder. Psychopathology 48 (4), 209–216.
Stahlberg, O., Soderstrom, H., Rastam, M., Gillberg, C., 2004. Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and/or autism spectrum disorders. J. Neural Transm. (Vienna) 111 (7), 891–902.
Sullivan, P.F., Magnusson, C., Reichenberg, A., Boman, M., Dalman, C., Davidson, M., et al., 2012. Family history of schizophrenia and bipolar disorder as risk factors for autism. Arch. Gen. Psychiatry 69 (11), 1099–1103.
Sullivan, S., Rai, D., Golding, J., Zammit, S., Steer, C., 2013. The association between autism spectrum disorder and psychotic experiences in the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. J. Am. Acad. Child Adolesc. Psychiatry 52 (8), 806–814.
Supekar, K., Iyer, T., Menon, V., 2017. The influence of sex and age on prevalence rates of comorbid conditions in autism. Autism Res. 10 (5), 778–789.
Tint, A., Brown, H.K., Chen, S., Lai, M.C., Tarasoff, L.A., Vigod, S.N., et al., 2021. Health characteristics of reproductive-aged autistic women in Ontario: a population-based, cross-sectional study. Autism 25 (4), 1114–1124.
Tsakanikos, E., Costello, H., Holt, G., Bouras, N., Sturmey, P., Newton, T., 2006. Psychopathology in adults with autism and intellectual disability. J. Autism Dev. Disord. 36 (8), 1123–1129.
Tsakanikos, E., Underwood, L., Kravariti, E., Bouras, N., McCarthy, J., 2011. Gender differences in co-morbid psychopathology and clinical management in adults with autism spectrum disorders. Res. Autism Spectr. Disord. 5 (2), 803–808.
Vannucchi, G., Masi, G., Toni, C., Dell'Osso, L., Erfurth, A., Perugi, G., 2014. Bipolar disorder in adults with Aspergers Syndrome: a systematic review. J. Affect. Disord. 168, 151–160.
Viechtbauer, W., Cheung, M.W., 2010. Outlier and influence diagnostics for meta-analysis. Res. Synth. Methods 1 (2), 112–125.
Vohra, R., Madhavan, S., Sambamoorthi, U., 2017. Comorbidity prevalence, healthcare utilization, and expenditures of Medicaid enrolled adults with autism spectrum disorders. Autism 21 (8), 995–1009.
Wang, N., 2018. How to Conduct a Meta-analysis of Proportions in R: a Comprehensive Tutorial.
Willis, B.H., Riley, R.D., 2017. Measuring the statistical validity of summary meta-analysis and meta-regression results for use in clinical practice. Stat. Med. 36 (21), 3283–3301.
Zheng, Z., Zheng, P., Zou, X., 2018. Association between schizophrenia and autism spectrum disorder: a systematic review and meta-analysis. Autism Res. 11 (8), 1110–1119.