A systematic review of the rates of depression in autistic children and adolescents without intellectual disability

A Systematic Review of the Rates of Depression in Autistic Children and Adolescents without Intellectual Disability

Running title: Depression and Autism in Children and Adolescents

Psychology and Psychotherapy: Theory, Research and Practice

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Abstract

Objectives: Increasing evidence suggests that Major Depressive disorder (MDD) is a highly prevalent in Autism Spectrum Disorder (ASD). The current study is a systematic review of rates of depression in autistic children and adolescents, without intellectual disability. Design: Adhering to PRISMA guidelines, a total of 14,557 studies were identified through five databases (MEDLINE, EMBASE, Cinahl, ERIC, PsycINFO, Web of Science). Methods: Articles were screened for inclusion and exclusion criteria and 10% double coded at each stage. Nineteen studies met criteria and were retained in the review. Results: The reported rates of depression in autistic children and young people varied from 0% to 83.3%. We discuss these findings in relation to method of report (self/informant, interview/questionnaire), recruitment status (clinical/community recruited) and age (pre-pubertal/adolescent). Conclusions: Rates of depression vary considerably across studies and do not show a particular pattern in relation to methodology, or age. Our research joins a crucial call to action from the research community for future research to improve the identification of depression in autism, which in turn will aid our understanding of the potentially different characterisation and manifestation of depression in autism, to ultimately improve assessment and treatment of depression in autistic children and young people.

Keywords: Autism Spectrum Disorder, Children and Adolescents, Co-occurrence, Depression

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Practitioner Points

- Rates of depression in autistic children and adolescents vary and do not show a particular pattern in relation to methodology or age.

- Our research joins the call to action from the research community for future research to improve the identification of depression in autistic children and adolescents, which in turn will aid understanding of depression in autism, and ultimately improve assessment and treatment of depression in autistic children and young people.

- The development of new measures of depression, specifically designed with, and for, children and adolescents with autism is warranted.

Autism Spectrum Disorder (ASD)[1] is a neurodevelopmental condition characterised by differences in social communication and interaction, and restricted and repetitive behaviour, with approximately 1 – 1.9% of the U.K. population estimated to have ASD (Baron-Cohen et al., 2009; Rydzewska et al., 2019). There is growing emphasis from researchers, clinicians and those with lived experience of autism that co-occurring mental ill-health is a key issue for health, well-being and mortality in autism. The American Psychiatric Association (APA, 2013) estimated that approximately 70% of individuals with ASD have co-occurring psychiatric disorders. In children and adolescents aged 10-14 years specifically, Simonoff, Pickles, Charman, Chandler, Loucas, & Baird (2008) reported that 70% of children with autism also met diagnostic criteria for one co-occurring psychiatric diagnosis and 41% met criteria for two or more. Similar findings have been reported by Leyfer et al. (2006) who reported that 72% of autistic 5-17 year olds met diagnostic criteria for at least one psychiatric disorder. These rates are much higher than the one in every four to five (20-25%) of young people in the general population who will have a psychiatric disorder in any given year (Patel, Flisher, Hetrick, McGorry, 2007). One of the most common psychiatric conditions in autism is depression (Greenlee, Mosley, Shui, Veenstra-VanderWeele, & Gotham, 2016).

Depression is a heterogeneous disorder characterised by a wide range of symptoms including either (or both) anhedonia and low mood, and a number of further symptoms including changes in sleep patterns and appetite, fatigue, cognitive difficulties and poor self-worth and suicidality (APA 2013). In the general population, depression is relatively uncommon in pre-pubertal children (1-2%), although prevalence rates begin to rise in early adolescence to around 4-5% by mid to late adolescence (Costello, Erkanli, & Angold, 2006), with rates of depression

[1] Language statement: There is no unified consensus within the autism community about how to talk about autism (e.g. Kenny et al., 2016). Out of respect to all preferences within the autism community, including the children, young people and families we work with "with autism", "autistic", "autism spectrum disorder" and "autism spectrum condition" will be used interchangeably in the current paper.

hastening considerably from early to late adolescence (a substantial six-fold from ages 15 - 18years) (Hankin & Abela, 2005). Adolescent depression, in the general population, has been shown as a risk factor for adult maladjustment, such as increased substance abuse, educational underachievement, recurrent unemployment, as well as suicidal behaviours (Fergusson and Woodward, 2002). For example, suicide attempts occur in 48% of those with early, adolescent-onset depression (DeFilippis and Wagner, 2014) and recent research has shown that young people with autism are 9 times more likely to die by suicide than the general population (Hirvikoski et al., 2016). Most research has examined depression in autistic adult populations (although still under-researched and poorly understood; Cassidy and Rodgers, 2017), whilst depression is yet to be explored in the same level of detail in the child and adolescent literature. This is surprising given the substantial rise of depression throughout adolescence in the general population (Green, McGinnity, Meltzer, Ford, & Goodman, 2007) and the little that is currently known about the developmental trajectory of depression in autistic adolescents.

Previous research has shown that depression (or anxiety) in autistic children and adolescents occurs at greater rates (38.9%) than in the general population of children and adolescents (4.2%) (Gurney et al., 2006). One previous systematic review, including studies from 1992-2015 from both adult and child and adolescent literature, reported rates of depression varied between 1% - 47.1% (Wigham, Barton, Parr, & Rodgers, 2017). The authors noted the heterogeneity in rates of depression and the clinical implications specifically in relation to case recognition and treatment effectiveness. Similarly to Wigham et al. (2017), Lai et al. (2019) reviewed depression (amongst other mental health conditions) in the autistic adult and child literature. They reported depression prevalence of 11% (across childhood to adulthood). They noted substantial levels of unexplained heterogeneity, even after accounting for, study design, age, sex, country of origin, and Intellectual Disability (ID), suggesting contributors to

heterogeneity of co-occurring mental health conditions in autism were still not well accounted for.

The disparity of depression rates between studies likely reflects the lack of psychometrically validated tools for the measurement of depression in autism as it can be= often difficult to appropriately measure depression in autism for a number of reasons. For example, autistic people can have differences in communication style (APA 2013) that can be difficult for neurotypical people to understand (Jaswal & Akhar, 2019; Sheppard, Pillai, Wong, Ropar & Mitchell, 2016). Thus, communication differences may result in interpretation and / or response differences in depression measures that have been designed for use in the general population. Indeed, Stewart, Barnard, Pearson, Hasan and O'Brein (2006) reported that it can be difficult for children and young people and their parents to answer some of the questions on scales (e.g. due to overlap of characteristics such as sleep and appetite changes) that are normed with neurotypical populations.

Furthermore, preliminary evidence suggests differences in the manifestation of depression in autistic children and young people, with the most predictive symptoms of depression having been shown to differ. Anhedonia, a loss of pleasure in everyday activities, has been reported to be the strongest predictor of depression in autism while low mood has been shown to be fourth (Bitsika & Sharpley, 2015). It is possible depression follows a different pattern in autistic young people than in the general population. These collective differences may lead to poor case recognition, increased clinical risk and likely contributes to the varying rates of depression reported in the literature. Therefore examining rates of depression in autistic children and young people separately (from adults and the general population) would be beneficial.

It is also highly likely rates of depression in autism vary between studies due to the inclusion or exclusion of co-occurringID. Rates of depression in autistic adults have been found to be greater in individuals without ID (Sterling, Dawson, Estes, & Greenson, 2008). This is similar to reports in the child and adolescent literature, where research has shown that depression in autism increases with greater IQ (Mayes, Colhoun, Murray & Zahid, 2011). It is also important to note, that research has shown that depression is characteristically different in those with ID (Hermans & Evenhuis, 2010; Magnuson & Constantino, 2011), warranting the examination of the two groups separately.

Due to the significant, but treatable, effects that depression can have, there is an urgent need to examine accurate rates of depression, specifically in autistic children and young people. Developmentally, this is a time frame associated with the onset of depression and given that depression may manifest differently in autistic children and adolescents, it is important to understand rates of depression specific to this population. Given the potentially confounding impact of ID on depression, this review examined rates of current depression (Major Depressive Disorder [MDD]) either diagnosed or in the clinical range on questionnaire based measures, with rates reported collectively and separately) in children and young people without ID (IQ >70). This also allows for the examination of measures that utilise self-report. The current systematic review sought to examine the reported rates of depression in = children and young people with autism (mean age < 18 years old) from 1992 to August 2020. Our review adds a further 14 studies to child and adolescent articles reported in Wigham et al.'s (2017) review and five years since Wigham et al.'s (2017) search for articles was conducted. Further exploration of depression in autism is warranted, to consolidate research findings, in order to inform depression treatment planning that is specific, and appropriate, for autistic children and young people.

Methodology

Reporting

To ensure transparency and appropriate reporting, this review was conducted and written in accordance to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement and guidelines (Shamseer et al., 2015).

Search strategy

Medical subject headings (MeSH) and text words related to depression and autism in childhood and adolescence were developed. Search terms were:

[Insert table 1]

Key terms were searched in six databases: Medline, EMBASE, Cinahl, ERIC, PsycINFO and Web of Science for peer-reviewed papers post 1992 and published in English. We limited our search to post 1992 when the WHO defined Asperger syndrome. The first search was conducted in October 2018 to search for papers from 1992 to October 2018 (MF). A final updated search for papers published between October 2018 to August 2020 was conducted by an additional author (JO). Endnote was used as the citation manager for the current study.

Selection, inclusion and exclusion

A 3-step model was applied to selection, inclusion and exclusion. At step 1, the search of databases returned a total of 14,557 articles. After duplicates (n = 5524) were removed, 9033 papers remained for screening. At step 2, titles and abstracts were screened at this stage by two reviewers (MF and JO) against the inclusion and exclusion criteria. A sample of 10% were screened by second reviewers (SR and AP) and there was 100% agreement across both

searches. Inclusion criteria was as follows: a diagnosis of Autism Spectrum Disorder, Asperger's Disorder or Pervasive Developmental Disorder not otherwise specified, children and young people aged 18 years or younger (studies that contained some participants over the age of 18 years were retained if the mean age of the sample was 18 years or less), clinical/community/population studies, studies reporting current rates of MDD were included, studies reporting clinical rates of depression were also included if scaled scores were specified as a numerical value and reported in the paper. Studies were only included if they used a specific measure of depression, a generic measure with a depression subscale, or assessed depression according to DSM/ICD criteria, and included participants with an individual IQ score of above 70 (see Table 4 below for means, SD, range and IQ measure). Exclusion criteria is as follows: any paper that did not satisfy inclusion criteria was excluded, i.e. those with a mean age of over 18 years, studies on subclinical depression (below clinical cut off range), and past rates of MDD (e.g. lifetime rates) were not included. Intervention studies were also excluded. Papers were excluded if they used instruments that did not report rates for depression separately (e.g. papers that included a measure of anxiety and depression combined were excluded). A total of 420 papers were retained for step 3, with 8613 not meeting inclusion and exclusion criteria. At step 3, the articles were read in their entirety and analysed for relevance by two reviewers (MF and JO) in adherence to the inclusion and exclusion criteria. In total, 401 papers were removed and 19 articles remained. The reasons for exclusion at Step 3 were: it was not always clear until the full-text screen that the mean age of the sample was <18, or that all participants with depression data had an IQ>70. Other reasons were no clinical cut off data reported, or depression rates were not reported separately (i.e. some studies examined anxiety and depression combined). The final 19 articles were read in full by the team (TS, MF, KM, JO, AP and SR) and all were deemed eligible for inclusion in the review. Figure 1 shows a flow diagram of this process.

[Insert figure 1 here]

Data extraction and quality assessment

Data was extracted from the final papers using an adapted version of a data extraction form from the Cochrane Handbook (Higgins & Green, 2011). The data extraction was performed by three reviewers separately (MF, KM and JO) and 10% were cross-screened to ensure consistency across reviewers (AP). There was 90-100% agreement across both extractions. The remaining 10% was resolved through discussion. The bias rating chart (Table 2) used in the current study was previously described in Wigham *et al* (2017), which is based on validated tools developed by Munn, Moola, Riitano and Lisy (2014) and Hoy et al. (2012). The tool assessed risk of bias in (i) diagnosis of ASD, (ii) depression measure, (iii) description of participants, (iv) description of recruitment pool, (v) the reliability and validity of depression measure in ASD and (vi) measure of IQ (see Table 2). Quality assessment was conducted by two reviewers (TS and JO) and to ensure consistency of quality assessment, 10% of papers were also screened by second reviewers (JO and AP). There was 100% agreement.

[Insert table 2 here]

Data analysis

There was significant heterogeneity in the included studies, with substantial variations in the study designs and primary outcomes. Each of the studies examined in this systematic review differed in sample size, age range, and used varying diagnostic criteria when classifying autism and depression populations. None of the included studies were deemed to have low risk of bias across all categories of the quality assessment (see Table 3) and none of the included studies

were rated as having low risk of bias for reliability and validity of depression outcome measure in autism. Given the risk of bias, particularly in the reliability/validity of depression measures in ASD, it would not be meaningful to combine articles in a meta-analysis. If bias is present in included studies, a meta-analysis will compound errors, producing misleading and erroneous findings that could be interpreted as credible (Higgins & Green, 2011). Results are therefore discussed narratively.

[Insert table 3 here]

Results

Description of included studies

As reported in Table 4, nineteen studies examined the rates of depression in autistic children and adolescents. Of the included studies, rates of depression are reported for a total of 1052 participants. From this, 853 (81%) participants were male, and 167 (19%) were female (excluding data from Salazar et al., 2015; Witwer & Lecavalier, 2010, who did not report subsample information – see Table 4). The number of autistic participants differed across studies from 20 to 150, with an age range from 4.5 to 24 years old (although all with a sample mean of < 18 years old) in all but one study. Ghaziuddin et al. (1998) reported an age range of 8 to 51 years, with a mean age of 15.1 years old. A mixture of cross-sectional (Demirkaya et al., 2016; Mattila et al., 2010; Mazefsky et al., 2011; Montazeri et al., 2020; Mukkades & Fateh, 2010; Phung et al., 2019; Vickerstaff et al., 2007; Witwer & Lecavalier, 2010), prospective designs (Bitsika et al., 2016; Ghaziuddin et al., 1998; Salazar et al., 2015) and case-control (case controls, unless comprised of an autistic group, are not reported in this review, please see individual papers for details) were included. Six studies were conducted in USA (Ghaziuddin et al., 1998; Lopata et al., 2010; Joshi et al., 2018; Mazefsky et al., 2011;

Phung et al., 2019; Witwer & Lecavalier, 2010), three in Turkey (Demirkaya et al., 2016; Mukaddes & Fateh, 2010; Sahin et al., 2019), three in Australia (Bitsika et al., 2016; Bitsika & Sharpley, 2015; Vickerstaff et al., 2007), two in the UK (Green et al., 2000; Salazar et al., 2015), two in Finland (Mattila et al., 2010; Reinvall et al., 2016), one in Canada (Orinstein et al., 2015), one in the Netherlands (Montazeri et al., 2020), and one in Italy (Mazzone et al., 2013).

Of the 19 studies included, 13 examined rates of depression in autistic children and adolescents as their (or one of) main aim. Of the remaining six, one aimed to assessed autism and suicidality (Demirkaya et al., 2016), one aimed to explore the relations between generalized anxiety, depression symptoms and social competence (Lopata et al., 2010), one explored autism and the psychometric properties of four self-report measures that screen for depression, anxiety, Attention Deficit Hyperactivity Disorder, and Obsessive–Compulsive Disorder (Mazefsky et al., 2011) and one aimed to investigate the associations between self-perceived social competence, intellectual ability, and depressive symptomatology (Vickerstaff et al., 2007). Another aimed to investigate pre-pubertal risk factors in developing developmental disorders (Sahin et al., 2019) and one aimed to explore correlates of sleep difficulties in ASD (Phung et al., 2019).

Measures of depression

The measurement of depression in autism varied across the included studies (see Table 4). Depression was determined by interview (Demirkaya et al., 2016; Green et al., 2000; Joshi et al., 2018; Mattila et al., 2010; Mazefsky et al., 2011; Mazzone et al., 2013; Mukaddes & Fateh, 2010; Orinstein et al., 2015; Reinvall et al., 2016; Sahin et al., 2019; Salazar et al.,

2015; Witwer & Lecavalier, 2010), questionnaire based measures (Bitsika et al., 2016; Bitsika & Sharpley, 2015; Lopata et al., 2010; Mazzone et al., 2013; Montazeri et al., 2020; Phung et al., 2019; Vickerstaff et al., 2007) and a mix of multiple pulled methods (Ghaziuddin et al., 1998). Multiple pulled methods included psychiatric examinations based on DSM criteria, psychiatric, school and social services records, the Kiddie-Schedule for Affective Disorders and Schizophrenia-Epidemiological Version, and supplemented telephone interviews to determine diagnosis (Ghaziuddin et al., 1998). Six studies determined diagnosis of depression via interviews, specifically a version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime (K-SADS). The K-SADS are semi-structured integrated parent-child interviews, with data from parents and children recorded and diagnoses then derived by synthesizing the parent and child data (Kaufman, Birmaher, Brent & Rao, 1997). Of these six studies who employed the K-SADS measure; one appeared to administer the K-SADS (Turkish version) to child/adolescent participants only (i.e. "...applied routinely to the follow-up patients", Demirkaya et al., 2016), one with parents and children combined (Mattila et al., 2010) andtwo with parents / guardians only (Joshi et al., 2018; Orinstein et al., 2015). In other studies it was less clear who the K-SADS was administered to. Ghaziuddin et al. (1998) noted that young people aged under 17 were examined independently by the second author with the help of the K-SADS, suggesting the K-SADS was administered to young people. Mukaddes & Fateh (2010) and Sahin et al. (2019) stated that a comorbidities were assessed using the K-SADS interview (Turkish version) but do not specificity state who it was administered to (i.e. child or parent / guardian). In these two cases, we based on our interpretation according to Kaufman et al. (1997) and assumed the K-SADS was applied to both the child and the parent / guardian.

Parent interviews were also conducted using other methods in five studies. This included the modified Isle of Wight Semi-structured Informant and Child Interviews (MDD only reported informant as parent data derived best-fit with diagnoses within ICD-10 criteria; Green et al., 2000), the Autism Comorbidity Interview-Present and Lifetime Version (Mazefsky et al., 2011), the Children's Interview for Psychiatric Symptoms-Parent Version (Witwer & Lecavalier, 2010), the Preschool Age Psychiatric Assessment Interview (Salazar et al., 2015) and the Development and Well-Being Assessment-Finish online version (Reinvall et al., 2016) to determine diagnosis. One study interviewed child and adolescent participants with the Children's Depression Rating Scale-Revised (Mazzone et al., 2013).

Clinical cut-off scores of questionnaire measures were used in seven studies. Three studies employed multiple measures of depression; this included parent and self-report on the Child and Adolescent Symptom Inventory which measures DSM-V criteria for MDD (Bitsika et al., 2016), parent and self-report on The Revised Children's Anxiety and Depression Scale (RCADS) measuring DSM-IV criteria for MDD (Montazeri et al., 2020), and self-report on, the Italian version of Children's Depression Inventory, in addition to an interview measure, as described above (Mazzone et al., 2013). Three studies used self-report questionnaires as their measure of depression rates; the Child and Adolescent Symptom Inventory's MDD subscale (Bitsika & Sharpley, 2015), the Children's Depression Inventory (Vickerstaff et al., 2007), and the Center for Epidemiological Studies Depression Scale (Phung et al., 2019). One used a parent report questionnaire as their measure of depression in their sample; Lopata et al., (2010) employed the Behaviour Assessment System for Children, Second Edition.

Measures of autism

Measures of autism varied across studies (see Table 4). Methods included prior clinical interviews with parents conducted by paediatricians / psychiatrists and confirmed by a clinical psychologist and behavioural observations (Bitsika & Sharpley, 2015) or confirmed by the Autism Diagnostic Observation Schedule (ADOS), in addition to a clinical psychologist (Bitsika et al., 2016). Autism was also confirmed by ICD-10 / DSM-IV criteria by a child psychiatrist (Ghaziuddin et al., 1998) or confirmed via child clinical interview, although it was not clear who administered the interview (Sahin et al., 2019). Autism was also assessed by a clinical interview with the child and parents (Mukaddes & Fateh, 2010), but similar to Sahin et al. (2019) it is not clear who administered the interview (see risk of bias section next for discussion). Other studies confirmed autism based on DSM-IV-TR criteria by psychiatric interview, conducted by a psychiatrist, with the child and parent / guardian(s) and included multiple sources (e.g., psychiatric records, schools, social services). Similarly, consensus on diagnosis was reached by a paediatrician & psychiatrist based on school observations (community group only for school observations), patient records and the Autism Diagnostic Interview Revised (ADI-R) and ADOS module 3 in another study (Mattila et al., 2010) and the ADOS-G and ADI-R and confirmed by a clinical psychologist in another (Mazefsky et al., 2011). Autism was established in one study from multidisciplinary neurodevelopmental and social communication assessments led by a paediatrician, where multi-source information (parents, teachers, social workers) and observation of child and the ADI-R, Developmental, Dimensional and Diagnostic Interview (DDDI), Diagnostic Interview for Social and Communication Disorders (DISCO) and ADOS was used (Salazar et al., 2015). A psychiatric interview with the child and parent / guardian(s), conducted by a psychiatrist, and included multiple sources (e.g., psychiatric records, schools, social services) to determine autism in another study (Johsi et al., 2018).

Prior diagnosis of autism was assessed by at least two different child psychiatry specialists both on admission and during follow-up (over 1-15 years) in one study and confirmed by clinical observation by psychiatrists (Demirkaya et al., 2016). Prior diagnosis was stated in one study and confirmed by the study team based on ICD-10 criteria and by the ADI and ADOS (Green et al., 2000). Other assessment of autism included parent report measured by the ADI-R and evaluation of documentation of diagnosis by the study team (Lopata et al., 2010), prior diagnosis by an experienced clinician, confirmed using the ADOS-G (Mazzone et al., 2013) or prior diagnosis confirmed by the ADOS and ADI-R with autism determined based on all diagnostic information available and on consensus of the multidisciplinary team that included psychologists and psychiatrists (Montazeri et al., 2020). Prior diagnosis of autism was noted in another study and confirmed by the ADOS-2 and / or the Social Communication Questionnaire (SCQ) (Phung et al., 2019) or the ADI-R (Witwer & Lecavalier, 2010) with autism determined by prior diagnosis and confirmation by the DISCO in one study (Vickerstaff et al., 2007). Prior diagnosis of autism by experienced child neurology professionals and/or multidisciplinary teams, confirmed by medical records and the ADI-R was noted in one study (Reinvall et al., 2016) or noted as diagnosis by Module 3 or 4 of the ADOS and according to best clinical judgement in another (Orinstein et al., 2015).

Risk of bias

All of the included studies were deemed low risk in quality in relation to diagnosis of autism and IQ level (see Table 3). All ASD diagnoses were confirmed by either a standardised test; or by a psychologist or psychiatrist and DSM or ICD criteria and an IQ score of >70 (using, e.g., The Wechsler Abbreviated Scale of Intelligence;[WAIS], Wechsler Intelligence Scale for Children [WISC], Stanford-Binet, Cattell IQ, Stanford-Binet-V). Two studies noted that participants were clinically recruited from a psychiatry outpatient clinic and diagnosis of

autism were made by clinical interviews based on DSM-5 criteria (Sahin et al., 2019) or the DSM-IV (Mukaddes & Fateh, 2010), however the authors did not state *who* confirmed autism diagnosis. We took the decision to rate this as low risk of bias given it was a clinically recruited sample and diagnoses were made on the basis of the DSM criteria, as it most closely fitted a category of low bias (see Table 2), but offer caution here to our decision. Others note a previous diagnosis, without specifying who diagnosed autism but were been rated as low risk of bias as a standardised test was confirmed during the study (e.g. Witwer & Lecavalier, 2010). Similarly, Phung et al. (2019) stated parent reports of clinical diagnosis of autism and confirmed with the ADOS, but note that some children were only screened with the SCQ and not the ADOS. We took the decision to rate this study as low risk of bias for autism diagnosis due to parent report of autism and the use of the ADOS for most children, but we highlight caution with this as while the SCQ is used in clinical practice, it is a screener measure. We note these examples to highlight the varying ways that autism was assessed in the current studies.

Bias in the measurement of depression varied across studies, with 4 of the 19 included studies showing medium risk of bias (Bitsika & Sharpley, 2015; Bitsika et al., 2016; Lopata et al., 2010; Montazeri et al., 2020), as they were depression subscales within a standardised generic measure (see Table 2) . The remaining 15 studies were deemed low risk demonstrating that the assessment of depression was a standardized depression-specific assessment or clinical interview; or diagnosis of depression according to DSM or ICD by a psychiatrist or psychologist. Only four studies described key participant characteristics (see Table 2) including mean age, age range, sex, comorbidity, medication and ethnicity (Bitsika & Sharpley, 2015; Joshi et al., 2018; Mazefsky et al., 2011; Witwer & Lecavalier, 2010), with the other 15 rated as medium risk of bias as some descriptive characteristics were

missing. The description of the recruitment pool also varied across studies, although 13 were rated as low risk of bias. The remaining 6 studies (Demirkaya et al., 201; Mattila et al., 2010; Mazzone et al., 2013; Orinstein et al., 2015; Phung et al., 2019; Sahin et al., 2019) were rated as medium risk of bias as some information on recruitment was missing. Strong reporting of recruitment methods and the inclusion of key participant information could support the validity of studies in the extent to which the findings are generalisable and represent the population.

Importantly, no study was rated as having low risk of bias for reliability and validity of depression outcome measure when measuring depression in children and adolescents with autism. Of the 19 included studies, 15 were considered to have high risk of bias, and 4 with medium risk of bias, which was deemed as showing some evidence of reliability and validity (Bitsika & Sharpley, 2015; Bitsika et al. 2016; Mazefsky et al., 2011; Witwer & Lecavalier, 2010). These measures included the Child and Adolescent Symptom Inventory MDD subscale (CASI-4; Gadow & Sprafkin, 2010; Gadow et al., 2002), the Autism Comorbidity Interview–Present and Lifetime Version (ACI-PL: Leyfer et al., 2006), and the Children's Interview for Psychiatric Symptoms-Parent Version (P-ChIPS, Weller et al., 1999). For example, Witwer, Lecavalier, & Norris (2012) examined the reliability and validity of the P-ChIPS in children and young people with ASD and results indicated that interrater reliability was high for depression, concordance between the P-ChIPS and the Child and Adolescent Symptoms Inventory (CASI) was fair for depression (although intraclass correlation coefficient which measures association between severity scores was poor) and the authors did note overlap in features which was not accounted for by the P-ChIPS. The CASI was rated as medium risk of bias as the authors note that the measure has satisfactory internal consistency,

reliability, and convergent and discriminant validity in both autistic and non-autistic populations community (Gadow, De Vincent & Schneider, 2008; Gadow & Sprafkin, 2010).

The ACI-PL (Leyfer et al., 2006) was developed as a modified version of the Modified version of K-SADS-PL to account for overlap in symptoms between depression and ASD. While preliminarily research has shown the ACI-PL to correctly diagnose depression (i.e. validity) and show good inter-rater reliability for lifetime diagnoses of MDD, it was rated as having medium risk of bias as beyond the pilot test of the measure (Leyfer et al., 2006) it has only been used in a few studies, has not been widely available for distribution due to reasons outlined elsewhere (Zainal, Magiati, Tan, Sung, Fung & Howlin, 2014), and therefore has not been extensively validated (also noted elsewhere; Oreinstein et al., 2015). It should be noted here that it was not the aim of the current study to review all measures of depression in autism, and it is possible that some psychometric properties for other measures have been noted in the literature. Nonetheless, and while some measures may show some psychometric properties, no questionnaire measure has been designed specifically for, and with, autistic young people or account for possible differences in depression manifestation or trajectory in autistic young people. Therefore, studies examining depression in autism likely have a medium to high risk of bias in accounting for rates of depression. This means that rates of depression noted below must be taken with caution.

Rates of depression

Rates of depression are shown in Table 4. Rates of depression in autistic children and young people ranged from 0% - 83.3% across all included studies.

[insert Table 4 here]

Child interview

Rates of depression from interviews with children and young people was 18% and 18.7% in one study (Demirkaya et al., 2016) and 22% in another study who used multiple methods to determine diagnosis (Ghaziuddin et al., 1998). Additionally, Mazzone et al., (2013) reported a prevalence of 83.3%, as measured by the Children's Depression Rating Scale-Revised. This measure includes interviews with children and adolescents, as well as clinician observed non-verbal behaviour.

Parent interview

Rates of depression from interviews with parents ranged from 1.7% - 68.0% across seven studies (Green et al., 2000; Joshi et al., 2018; Mazefsky et al., 2011; Orinstein et al., 2015; Rienvall et al., 2016; Salazar et al., 2015;; Witwer & Lecavalier, 2010). Two measures, the Children's Interview for Psychiatric Symptoms-Parent Version (P-ChIPS) and the Autism Comorbidity Interview-Present and Lifetime version (ACI-PL) have been shown to have some evidence of psychometric properties in autism (Leyfer et al., 2006; Witwer et al., 2012) and therefore excluding all other parent-reports, rates of depression using these measures were 15.8% - 22.7%, respectively (Mazefsky et al., 2011; Witwer & Lacavalier, 2010).

Child and parent interview

When parents and children were interviewed together, rates were 0% - 29% across three studies (Mattila et al., 2010; Mukkades & Fateh, 2010; Sahin et al., 2019).

Self-report questionnaires

Self-report questionnaire based rates ranged from 8% - 47.1% across five studies. Rates as measured by the Children's Depression Inventory (CDI) ranged from 26.6% - 29% across two studies (Mazzone et al., 2013; Vickerstaff et al., 2007). Rates as measured by the self-report version of the Revised Children's Anxiety and Depression Scale (RCADS) was 28.8% as reported by one study (Montazeri et al., 2020). Although none of the self-report measures have been developed specifically to assess depression in autism, one measure, the Child and Adolescent Symptom Inventory–4 (CASI-4) has been shown to have some evidence of psychometric properties in autism (Gadow, DeVincent, & Schneider, 2008; Gadow & Sprafkin, 2010) and therefore excluding all other self-reports, rates of depression using the CASI-4 were 8% ((Bitsika et al., 2016) and 47.1% (Bitsika & Sharpley, 2015).

Parent-report questionnaires

Rates of co-occurring current depression from parent-report questionnaire measures range from 8.7% - 40% across four studies (Bitsika et al., 2016; Lopata et al., 2010; Montazeri et al., 2020; Phung et al., 2019). Rates as measured by the Behaviour Assessment System for Children (BASC) second edition parent questionnaire was 40% in one study (Lopata et al., 2010) and 8.7% in another study when measured by the Child and Adolescent Symptom Inventory (CASI) MDD subscale questionnaire (Bitsika et al., 2016). The rate from the parent report version of the Revised Children's Anxiety and Depression Scale (RCADS) was 23.7% (Montazeri et al., 2020) and 35% when employing the Center for Epidemiological Studies Depression (CES-D) Scale (Phung et al., 2019).

Community vs clinically recruited

Of the 19 included studies, 4 studies included community recruited participants (Bitsika & Sharpley, 2015; Bitsika et al., 2016; Mazefsky et al., 2011; Phung et al., 2019) with rates

varying between 8 – 47.1%. Eleven studies included clinically recruited participants (Demirkaya et al., 2016; Ghaziuddin et al., 1998; Green et al., 2000; Joshi et al., 2018; Mazzone et al., 2013; Montazeri et al., 2020; Mukaddes & Fateh., 2010; Orinstein et al., 2015; Reinvall et al., 2016; Sahin et al., 2019; Salazar et al., 2015) with rates between 0% - 83.3%. Two studies included community and clinically recruited participants combined (Vickerstaff et al., 2007; Witwer & Lecavalier, 2010) and reported rates of 39% and 22.7% respectively One study (Mattila et al., 2010) included community and clinically recruited participants separately and reported rates of 6-8%. One study reported rates of 40% (Lopata et al., 2010) for participants who were awaiting participation in a treatment study and it was not clear if these participants were community or clinically recruited.

Age

Rates in the current study for pre-pubertal children, defined as studies with participants who had a mean age of under 13 years old, ranged from 0% - 83.3%. Three studies included an entire sample of children aged below 13 years (Montazeri et al., 2020; Sahin et al., 2019; Salazar et al., 2015) which reported rates ranging between 0 - 39% for depression. None of the studies included exclusively adolescents 13 years or above, however rates of depression in studies with a mean age of 13 – 18 years ranged from 5% - 35% (Demirkaya et al., 2016; Ghaziuddin et al., 1998; Green et al., 2000; Joshi et al., 2018; Phung et al., 2019), with rates of 22% and35% respectively for studies with a mean age of over 15 years olds (Ghaziuddin et al., 1998; Phung et al., 2019). Sex differences could not be investigated as depression rates were not reported separately in the included studies.

Discussion

The rates of depression varied considerably (0% – 83.3%) demonstrating that rates of depression are not stable across the child and adolescent literature. The wide range of rates of depression in autistic children and adolescents was found across and within measures (i.e. self-report, parent report, interviews and questionnaire methods), design (i.e. clinically vs community recruited) and age. While rates of depression vary considerably and are greater than has been reported in the general population of children and adolescents (e.g. under 13 years old, 2.8% and 13-18 years old, 5.6%; Costello et al., 2006), the current findings must be taken with caution as the depression measures in the included studies may not accurately identify depression in autistic children and young people.

Only one of the included studies used a measure of depression, an interview, which was specifically designed to measure depression in autistic children and adolescents (The ACI-P; Leyfer et al., 2006). The remaining studies that used measures to screen for depression have not been developed for use with autistic children and young people. This is problematic as the detection of depression in autism can be complicated by the phenotypic overlap between the two, with many characteristics that underpin autism also manifest themselves in depressive symptomatology (Gotham, Unruh, & Lord, 2015).. Indeed, Stewart et al. (2006) reported that it can be difficult for children and young people and their parents to answer some of the questions on scales normed with neurotypical populations (e.g. due to overlap of characteristics). It is also possible that differences in communication style between neurotypical and autistic people (APA, 2013) could lead to researcher / clinical interpretation bias as it has been shown that neurotypical people find these differences in communication difficult to understand (Jaswal & Akhar, 2019; Sheppard et al., 2016).

Furthermore, preliminary evidence suggests that depression in autistic children and young people may follow a different pattern in autistic than in the general population, with the most predictive symptoms of depression having been shown to differ. Anhedonia, a loss of pleasure in everyday activities, has been reported to be the strongest predictor of depression in autism while low mood has been shown to be fourth (Bitsika & Sharpley, 2015).. These collective differences may lead to poor case recognition and increased clinical risk. Research has also shown that, in comparison to the general population, autistic people experience and define quality of life (McConachie et al. 2018) and depression (Stewart et al. 2006) differently, and this has been shown to impact the measurement properties of tools (Cassidy et al. 2018a, b; Wigham and McConachie 2014). Similarly, in the child and adolescent literature, Hanratty et al. (2015) found only a few measurement tools that were used to measure behaviour difficulties in young children with autism were reliable or valid for use in the autistic population. These findings, taken alongside the current review, highlight that new, or adaptations to questionnaire measures that can be used with, and for, the autistic child and adolescent community are warranted.

Similar calls have been made from researchers in the area of suicidality. For example, a recent systematic review of tools used to measure suicidality among autistic children showed that no suicidality assessment tool has yet been validated specifically with autistic children and young people (Howe, Hewitt, Baraskewich, Cassidy, & McMorris, 2020). Furthermore, Cassidy et al. (2020) found that Suicide Behaviours Questionnaire—Revised; (SBQ-R; Osman et al. 2001), a widely used suicidality assessment tool which is validated for use in the general population, was not operationally equivalent for use with autistic populations given autistic people's unique experience of suicidality and the complex and sometimes abstract nature of questions and response options. More recently, Cassidy, Bradley, Cogger, Graham

& Rodgers (Preprint, 2021) highlighted that due to the overlap between autism and symptoms of depression, it can make it difficult to accurately identify depression in autistic adults. The authors developed the Autistic Depression Assessment Tool (ADAT-A), with and for autistic adults without intellectual disability. Such a tool will inform understanding of depression in autistic adults, which will ultimately facilitate appropriate assessment and depression treatment plans for autistic adults.

Research into the nature, assessment and treatment of depression in autism, particularly in the child and adolescent literature, is however limited. For example, DeFilippis (2018) highlighted that current diagnostic scales may not be suitable for diagnosing depression in children and adolescent with autism and that there are no empirical studies on psychopharmacology for depression in autistic children and adolescents. The author concludes that future research should focus on the potentially different expression of depression in autism, establishing appropriate assessments and developing safe and effective treatments for depression in autistic children and adolescents. The limited research into the nature, assessment and treatment of depression in autism is surprising as there is robust evidence that depression leads to the greatest impairment in personal health and produces the highest cost of care when all chronic diseases are considered (Moussavi et al., 2007). There is a growing emphasis from researchers, clinicians, individuals and families that mental ill-health in autism is a key issue for health, well-being and mortality. The Scottish Parliament SPICe briefing (Murphy, 2017) has recognised the mortality issue in autism , specifically for children and adolescents who are 9 times more likely to die by suicide than the general population (Hirvikoski et al., 2015). There is an evidenced and clinical need to better understand depression in autism, specifically in child and adolescent populations.

Multi-informant approaches to develop new measures of depression in autism that are tailor-made with, and for children and adolescents, alongside input from parents and multiple professionals involved in their care is needed in order to improve diagnosis and treatment of depression. Similar measures of anxiety have been developed and validated as anxiety screening tools (i.e. the Anxiety Scale for Children – ASD (ASC-ASD; Rodgers et al., 2016). The tool accounts for challenges in the assessment of anxiety in autism while aiming to capture autism specific presentation of anxiety and supports the notion for developing autism specific depression measures. The development of depression specific tools is now warranted, and once developed, will allow for large-scale epidemiological studies to provide accurate rates of depression in autistic children and adolescents.

Limitations and future directions

While the inclusion of cut-off questionnaire measures of depression may be seen as a limitation, we included these as such measures are often used in research and screening in clinical practice and therefore important to include. We acknowledge it was not our aim to review all measures of depression in autism and it is possible that some psychometric properties of measures have been noted in the literature. We also acknowledge that the inclusion of articles written in languages other than English could have resulted in a wider range of studies. While we did not exclude co-occurring conditions beyond intellectual disability, but given the high overlap of conditions (e.g. Antshel, Zhang-James, Wagner, Ledesma & Faraone, 2016; Boulet, Boyle & Schieve, 2009; Levy et al., 2010; Simonoff et al., 2008; Soke, Maenner, Christensen, Kurzius-Spencer & Schieve, 2018), future research would benefit to ascertain whether the trajectory of depression differs or manifests differently in autism alone, or whether there is shared, or increased, risk of depression with co-occurring conditions such as ADHD. Examination of sex differences is also warranted to determine

whether the depression trajectory in autism follows a similar pattern as the general population (i.e. greater in females; Salk et al., 2016). As noted elsewhere (e.g. Munn et al., 2014) future research is warranted with stratified random sampling to ensure representatives. It is also recommended that future research describes the participants in sufficient detail to determine comparability between studies.

Notwithstanding these limitations, our review highlighted that rates of depression in the autistic child and adolescent literature varied considerably, across measures, design and age. Our research joins a crucial call to action from the research community to improve the identification of depression in autism, to aid understanding of the potentially different characterisation and manifestation of depression in autistic people, to ultimately improve assessment and treatment of depression in autistic children and young people.

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Tables

Table 1. Search strategy key words and combinations

S1	"autis*" OR "asperger*" OR "asd" OR "ASC" OR "high functioning" OR "pervasive developmental disorder*" OR "PDD" OR "HFA"
S2	"depress*" OR "major depress*" OR "clinical depress*" OR "low mood" OR "affective disorder*" OR "mood disorder*"
S3	"child*" OR "adoles*" OR "youth*" OR "minor*" OR "girl*" OR "boy*" OR "teen*"
S4	S1 AND S2 AND S3

Table 2. Wigham et al. (2017) bias rating chart

Diagnosis of HF ASD

a. A diagnosis of HF ASD was made prior to the study – no details given on method
b. Individuals were recruited from an ASD research database. A diagnosis of HF ASD was made prior to the study using the methods below.
c. A diagnosis of HF ASD was confirmed at the time of the study by standardised test; or by a psychologist or psychiatrist and DSM or ICD.

2. Assessment of depression
    a. Nonstandardised
    b. Depression subscale within a standardised generic measure
    c. Standardised depression-specific assessment or clinical interview; or diagnosis of depression according to DSM or ICD by psychiatrist or psychologist.
3. Clear description of participants
    a. Key demographic information missing
    b. Some descriptive characteristics included; or reference to where further details can be found is provided

   c. Key characteristics described including: mean age, age range, gender, comorbidity, medication ethnicity

4. Description of recruitment pool provided
   a. Recruitment pool is not described
   b. Some detail provided
   c. Recruitment pool described including: geographical area, method of referral (e.g., self, database), setting (e.g., clinic or school)
5. Reliability and validity of depression outcome measure in HF ASD populations
   a. No psychometric properties reported for HF ASD
   b. Some evidence of reliability and validity
   c. The measure is standardised for the HF ASD populations
6. Measure of IQ
   a. None given
   b. IQ given or, e.g., described as all being > 70 or having Asperger
   c. IQ measured during study (e.g., Wechsler Adult Intelligence Scale [WAIS], Wechsler Intelligence Scale for Children [WISC], Standford-Binet.

Table 3. Quality assessment of included studies

Study	Diagnosis of ASD	Depression Measure	Description of Participants	Description of Recruitment pool	Reliability/Validity of depression measure in ASD	Measure of IQ
Bitsika and Sharpley (2015)	Low risk	Medium risk	Low risk	Low risk	Medium risk	Low risk
Bitsika et al. (2016)	Low risk	Medium risk	Medium risk	Low risk	Medium risk	Low risk
Demirkaya et al. (2016)	Low risk	Low risk	Medium risk	Medium risk	High risk	Low risk
Ghaziuddin et al. (1998)	Low risk	Low risk	Medium risk	Low risk	High risk	Low risk
Green et al. (2000)	Low risk	Low risk	Medium risk	Low risk	High risk	Low risk
Joshi et al. (2018)	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Lopata et al. (2010)	Low risk	Medium risk	Medium risk	Low risk	High risk	Low risk
Mattila et al. (2010)	Low risk	Low risk	Medium risk	Medium risk	High risk	Low risk
Mazefsky, Kao & Oswald (2011)	Low risk	Low risk	Low risk	Low risk	Medium risk	Low risk
Mazzone et al. (2013)	Low risk	Low risk	Medium risk	Medium risk	High risk	Low risk
Montazeri et al. (2020)	Low risk	Medium risk	Medium risk	Low risk	High risk	Low risk
Mukaddes & Fateh (2010)	Low risk	Low risk	Medium risk	Low risk	High risk	Low risk

Orinstein et al. (2015)	Low risk	Low risk	Medium risk	Medium risk	High risk	Low risk
Phung et al. (2019)	Low risk	Low risk	Medium risk	Medium risk	High risk	Low risk
Reinvall et al. (2016)	Low risk	Low risk	Medium risk	Low risk	High risk	Low risk
Sahin et al. (2019)	Low risk	Low risk	Medium Risk	Medium risk	High risk	Low risk
Salazar et al. (2015)	Low risk	Low risk	Medium risk	Low risk	High risk	Low risk
Vickerstaff et al. (2007)	Low risk	Low risk	Medium risk	Low risk	High risk	Low risk
Witwer et al. (2010)	Low risk	Low risk	Low risk	Low risk	Medium risk	Low risk

Table 4. Participant information, recruitment, method of assessments and rates of depression

Studies (year)	No. of autistic participants (% male)	Age (mean and standard deviation)	Mean FSIQ (SD); range; measurement	Medication	Recruitment (country)	Assessment of autism	Assessment of depression	Rates of MDD
Bitsika & Sharpley (2015)	ASD: 70 (100%)	ASD: 8-24yrs (M = 10.96, SD = 3.44)	ASD: 96.21 (14.21); FSIQ > 90,range not reported; measured by the WASI –II (Wechsler, 2011)	ASD: not taking antidepressant medication	Community recruited: parent support group and schools (Australia)	Confirmed prior to study by clinical interview with parents conducted by paediatrician / psychiatrist (based upon DSM-V criteria & family history) and confirmed by clinical psychologist and by behavioural observation.	Self-report: presence of at least five of the DSM-V criteria for MDD including either depressed mood or anhedonia measured by the CASI – 4R (Gadow & Sprafkin, 2010; Gadow et al., 2002)	47.1%
Bitsika et al. (2016)	ASD: 150 (100%)	6 – 18yrs (M = 11.2, SD = 3.3)	FSIQ = 94.9 (SD = 12.4); range = 73 – 132; measured by the WASI-II	Not reported	Community recruited parent support group and ASD service organisations (Australia)	Diagnosis prior to study by clinical interview with mother conducted by paediatrician / psychiatrist and confirmed by clinical psychologist (based upon	Self & parent report: Criteria for presence of a full diagnosis of MDD measured by the CASI-4R (Gadow & Sprafkin, 2010; Gadow et al., 2002)	Self-report: 8% Parent report: 8.7%

			(Wechsler, 2011)			DSM-5 criteria). Autism confirmed by the ADOS (Lord et al., 2012)		
Demirkaya et al. (2016)	ASD & suicidal: 16 (94%, n = 15) ASD & non-suicidal: 39 (87%, n = 34) Total: 55 (89%)	7-20yrs Suicidal: (M = 13.4, SD = 2.0) Non-suicidal: (M = 13.7, SD = 3.2) Total: (M = 13.56, SD = 2.9)	Total: FSIQ = 93.53 (SD = 14.52); range = 70-126; measured by the WISC-R (Wechsler, 1974), Cattell IQ (Cattell, 1949) or the Stanford Binet (version not stated)	Both groups: many taking medication for additional psychiatric disorders (type not reported)	Both groups clinically recruited: patients of the Autism Clinic of Child and Adolescent Psychiatry Department of the University hospital (Turkey)	Both groups: Assessed and established by at least two different (one junior and one senior expert in the field) child psychiatry specialists both on admission and during follow-up. Confirmed by DSM-IV-TR criteria and clinical observations by the authors, three experts of ASD (psychiatrists)	Child interview: presence of depression as measured by the K-SADS-PL (Kaufman et al., 1997)	Non-suicidal group: 18% Suicidal group: 18.7%
Ghaziuddin et al. (1998)	AS: 35 (83%, n = 29)	8-51 (M = 15.1, SD = 10.5)	FSIQ: 102.7 (SD = 18.7); range not report but FSIQ noted as >70 for each participant;	Not reported	Clinically recruited via referrals to the University of Michigan Medical Center, Arm Arbor, MI (USA)	Confirmed by ICD-IO (WHO, 1993) and DSM-IV (APA, 1994) criteria by a child psychiatrist.	Confirmed based on a combination of 1) DSM-IV criteria (APA 1994), 2) psychiatric, school and social services records, 3) a child psychiatric examination by psychiatrist,	22%

			measured by the WISC-R (Wechsler, 1974) or WAIS (Wechsler, 1981)				4) the K-SADS-E, (Puig-Antich et al. 1980), and 5) supplemented with telephone interviews and chart reviews. All available information discussed and diagnosis agreed	
Green et al. (2000)	AS: 20 (100%)	AS: 11-19yrs (M = 13.75)	AS: 92.15 (17.70); range = 71 – 141; measured by the WISC-R (Psychological Corporation, 1974) or WAIS-R (Psychological Corporation, 1986)	AS: two taking medication (one taking anticonvulsants for epilepsy, one taking imipramine for possible depression)	AS group clinically recruited via referrals by clinicians with diagnosis of AS (UK)	ASD: Clinical diagnosis of AS (pre-study) .Confirmed by study team (including psychiatrists and psychologists) based on ICD-10 criteria and by the ADI (Lord et al., 1994) and ADOS (Lord et al., 1989)	Parent (usually mother) interview: Modified (IOW-I; Institute of Psychiatry). Diagnoses referred to the 3-month period focused in the interview rather than the 6 months in some ICD-10 diagnoses	Parent interview: 5%
Joshi et al. (2018)	ASD total: 123 Split into 3 groups based on CBCL (Achenbach 1991; Samson	ASD-ED: 7 – 18yrs (M = 13.4, SD = 3.6)	ASD-ED: (M = 106.1, SD = 16.7); range = 77 – 136	Not reported	Youth clinically referred to an ASD clinic at a university hospital (USA)	Diagnosis based on DSM-IV-TR criteria by psychiatric interview with the child and parent / guardian(s) conducted by a	MDD assessed by K-SADS-E interview with parent or guardian (usually the mother)	ASD-ED: 33% ASD-DESR: 36% ASD-SED: 68%

	et al. 2014b) emotional dysregulation profile. ASD-ED: 22 (95%, n = 21) ASD-DESR: 47 (87%, n = 41) ASD-SED: 54 (81%, n = 44)	ASD-DESR: 6 – 21yrs (M = 12.0, SD = 3.5) ASD-SED: 5 - 19yrs (M = 11.7, SD = 3.2)	ASD-DESR: (M = 99.0, SD = 14.8); range = 70 – 141 ASD-SED: (M = 101.2, SD = 13.8); range = 73 – 128; measured by WISC-III (Wechsler, 1991)			psychiatrist and included multiple sources where available (e.g., psychiatric records, schools, social services)	(Orvaschel,1994) administered by trained & supervised psychometricians with bachelor's or master's degrees in psychology or a related field (on basis of DSMIII-R/IV criteria (including clinical judgement). All interviews reviewed by psychiatrists and clinical psychologists	
Lopata et al. (2010)	HFASD: 40 (90%, n = 36)	HFASD: 7-13yrs (M = 9.75, SD = 1.66)	HFASD: 110.14 (12.23); range not reported but participants noted as >70; measured by the WISC-IV	Not reported	HFASD: awaiting participation in a treatment study for children with HFASDs (USA)	HFASD: prior diagnosis and evaluation of documents and confimed by reviewing documents and parent report as measured by the ADI-R (Rutter et al. 2003)	Parent report: BASC-2 (Reynolds and Kamphaus, 2006) measured current symptoms (i.e., in the last several months)	Parent report: 40%

			(Weshler, 2003)					
Mattila et al. (2010)	AS/HFA community sample: 18 (67%, n = 12 AS/HFA clinical sample: 40 (80%, n = 32) (includes 8 also in community group) Total sample: 50 (76%, n = 38)	AS/HFA community sample: 12-13yrs (M = 12.7, SD = 0.3) AS/HFA clinical sample: 9-16yrs (M = 12.7, SD = 1.7) Combined: M = 12.7yrs	Mean, SD or range not reported but all had FSIQ > 75; measured by the WISC-III (Wechsler 1991)	Not reported	Study performed in three phases: first, AS/HFA screening and diagnosis in the community based study (Mattila et al. 2007), second, AS/HFA diagnosis in the clinic-based study (Kuusikko et al. 2008; Loukusa et al. 2007; Weiss et al. 2009), and third, comorbidity examinations (Finland)	AS/HFA community: ASSQ; Ehlers et al., 1999) and ADI-R (Lord et al., 1995), ADOS module 3 (Lord et al., 2000), patient record and school observations. DSM-IV-TR criteria (APA 2000) used to construct consensus (based on DSM-IV-TR criteria (APA 2000) by a paediatrician & psychiatrist) AS/HFA clinical: All diagnosed in psychiatric clinic or neurological department Diagnosis confirmed by ADI-R (Lord et al., 1995) and ADOS module 3 (Lord et al., 2000) and diagnosis derived based on DSM-IV-TR	Parent and child combined interview: K-SADS-PL (Kaufman et al., 1997) measured in 2005, administered by trained graduate-level interviewers and the interviewers and senior psychiatrist (study authors) confirmed diagnosis	Community and clinical combined: 6% Community based: 6% Clinical based: 8%

						criteria (APA 2000) by a paediatrician & psychiatrist)		
Mazefsky et al. (2011)	ASD: 38 (82%, n = 31)	10-17 yrs (M = 12, SD = 2)	FSIQ = 105 (SD = 17); range = 71-144; measured by the WASI (Wechsler, 1999)	42.1% (n = 16) - either form of mood stabilizer or ADHD related medication (31.6%; n = 12 for each)	Community recruited: through word of mouth/fliers, mostly within a children's hospital that has a diagnostic clinic for developmental disorders (USA)	ADOS-G (Lord et al., 2000) and ADI-R (Lord et al., 1994). All diagnoses were confirmed by the expert opinion of a licensed clinical psychologist who specializes in ASD (based on DSM-IV-TR criteria)	Parent interview: frequency of current depression as measured by the ACI-PL (Leyfer et al., 2006) administered by study first author.	15.8%
Mazzone et al. (2013)	AS/HFA = 30 (100%)	AS/HFA = 7-16 years (M = 11.06, SD: 2.59)	AS/HFA: 117.72 (SD = 17.10); range not reported but all participants >85; measured by the WISC-III (Wechsler et al., 1992)	Not reported	Clinically recruited via referral to the Child and Adolescent Neuropsychiatry Unit of the Children's Hospital Bambino Gesù of Rome (Italy)	AS/HFA: DSM-IV-TR criteria by an experienced clinician, confirmed using the ADOS-G module 2 or 3 (Lord et al., 2000)	Self-report: Italian version of the CDI (Kovacs, 1982, 1988) to measure current symptoms (i.e. last 2 weeks, 19-point cutoff Child interview: a clinician administered CDRS-R (Poznanski & Mokros, 1996) measured current depression (i.e. during the days or weeks prior to the interview and current observed non-verbal behaviour >40 cutoff)	CDI: 26.6% CDRS-R: 83.3%

Montazeri et al. (2020)	ASD: 118 (85%, n = 100)	9.5 – 13yrs (M = 11, SD = 14.6)	ASD: 101.92 (SD = 14.61);range = 72 – 132; measured by the WISC (Wechsler, 1999)	Not reported	Clinically recruited through four outpatient mental health clinics (Netherlands)	Previous diagnosis (based om DSM-IV-TR) and confirmed by the ADOS (Lord et al., 2012), and ADI-R (Rutter et al., 2003). A clinical DSM-IV-TR diagnosis was assigned based on all diagnostic information available and on consensus of the multidisciplinary team that included psychologists and psychiatrists	Parent and self-report using The Revised Children's Anxiety and Depression Scale (RCADS; Chorpita et al., 2005). It includes a subscale assessing DSM-IV MDD criteria, using a cut off T-score of 70 or above	Self-report: 28.8% Parent report: 23.7%
Mukaddes & Fateh (2010)	AD: 37 (86%, n = 32)	6-20yrs 10.9 (SD = 4.5)	FSIQ = 116 (SD = 14); range = 90-139; measured by the WISC-R	Five taking multiple medications (type not stated)	Clinically recruited from a private psychiatry clinic, located in the city centre in Istanbul (Turkey)	AS was diagnosed according to DSM-IV criteria by a psychiatric interview with children and the parents	Parent and child interview combined: present symptoms measured by Turkish version of the K-SADS-PL (Kaufman et al. 1997; Gokler et al. 2004). Psychiatric disorders emerging during follow-up were included. Final diagnosis based on data and clinical judgment	29%

Orinstein et al. (2015)	HFA: 42 (90%, n = 38)	HFA: 8.6-20.0 (M:13.9, SD: 2.7)	HFA VIQ: 105.5 (SD = 14.7); range = 81-142 HFA NVIQ:111.0 (SD = 12.5); range = 78-147 Measured by the WASI-VIQ and the WASI-NVIQ (Wechsler 1999)	Not reported	Clinically recruited via collected across multiple sites: University of Connecticut, the Institute of Living Hartford Hospital and Queens University (Canada)	HFA: met criteria for ASD on the ADOS (both Social and Communication domains and total score), measured by module 3 or 4 of the ADOS (Lord et al., 2000) and according to best estimate clinical judgment.	Parent interview: present diagnoses measured by the K-SADS-PL (Kaufman et al. 1997)	7%
Phung et al. (2019)	ASD: 20 (80%, n = 16)	11-20yrs (M = 16.74, SD = 2.52)	Range and mean not reported. All participants noted as having an IQ of 85 or above,; measured by	Not reported	20 participants were recruited from ASD-oriented community events as recruited from a previous study. 11 additional participants recruited via snowballing sampling (USA)	Prior parent-reported clinical diagnoses of ASD that were confirmed by ADOS-2 (Lord et al., 2012) delivered by trained administrators and/or the SCQ (Rutter, Bailey, & Lord, 2003)	Self-report using the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977). They used a clinical cut off of 16 to determine depression	35%

			WASI-II (Wechsler, 2011)					
Reinvall et al. (2016)	ASD:60 (80%, n = 48)	ASD: 6.5-16.7yrs (M = 11.6, SD = 2.5)	ASD: 105.5 (14.5); range not reported but all participants noted as having an IQ >70 as measured by the WISC-III (Wechsler, 1991)	Not reported	ASD group clinically recruited: department of Child Neurology, the Helsinki University Central Hospital and a private neuropsychiatric rehabilitation medical centre in Helsinki. TD group community recruited: mainstream schools in same cities (Finland)	ASD: clinical diagnosis based on standard ICD-10 (WHO, 1993) prior to recruitment by experienced child neurology professionals and/or multidisciplinary teams. Conformed by ADI-R (Lord, Rutter,& LeCouteur, 1994; Rutter, LeCouteur, & Lord, 2003) and medical records	Parent (one or both) interview: persistence of psychiatric symptoms over a 4–6 month period measured by the DAWBA (Goodman et al., 2000) – Finish online version (Goodman et al.,2000) An experienced psychiatrist assigned DSM-IV (APA,1994) or ICD-10 diagnoses (WHO, 1993) based on DAWBA results	ASD: 1.7%
Salazar et al. (2015)	ASD: 44 subsample with an IQ>70 from a total of 101 (total sample: 56%, n = 57)	4.5-9.3yrs	Mean, SD and range not provided at subsample level but FSIQ: >70; measured by either the	Not reported	Clinically recruited children born between September 2000 and August 2004 (4–8 years) with an ASD diagnosis and living in London (Bromley and	Teams, led by paediatricians, used multi-source information (parents, teachers, social workers), observation of child and ADI-R (Le Couteur et al., 1989), DDDI (Skuse et al., 2004), DISCO (Wing et al.,	Parent interview: DSM-IV symptoms and disorders present in the last 3 months assessed using the electronic version of the PAPA for preschool children aged 2–5 years (Egger and Angold 2004)	18.8%

			MSEL (Mullen (1997) the WPPSI-III-UK (Wechsler, 2004), and/or the WISC-IV-UK (Wechsler et al. 2004)		Lewisham, outer and inner London) were mailed invites to participate (UK)	2002) or ADOS (Lord et al., 2000)	administered by specialist trainee or by psychologists	
Sahin et al. (2019)	ASD: 26 (88.5%, n = 23)	Total sample: 7 – 12yrs (ASD group M = 9.5, SD = not reported).	Range and mean not reported but all participants noted as having an IQ >70; measured by WISC-R (Wechsler, 1974)	Not reported	Participants had applied to Ondokuz Mayıs University Faculty of Medicine Health Application and Research Center Child and Adolescent Psychiatry Outpatient Clinic (Turkey)	The diagnoses of ASD were made by clinical interviews based on DSM-5 criteria	Mental health co-morbidities, including MDD, were evaluated using Schedule for Affective Disorders and Schizophrenia for School-age Children-Present - Turkish Adaptation interview (SADS-P-T; Gökler et al, 2004)	ASD: 0%

Vickerstaff et al. (2007)	HFASD: 22 (86%, n = 19)	7.92-13.92yrs (M = 11.86, SD = 1.65)	105.41 (15.34); range = 82–141 as measured by the WASI (Wechsler, 1999)	Not reported	Clinically and community recruited children with HFASD participating in a pilot intervention study for social skills training (Australia)	Previous diagnosis of ASD and confirmed by the DISCO (Wing, 1999) conducted with each child's parent	Self-report: Current (i.e., last 2 weeks) symptoms for the CDI (Kovacs, 1992) were assessed. A cut-off of 19 was used to determine depression	CDI: 29%
Witwer & Lecavalier (2010)	ASD: 22 subsample with an IQ>70 from a total of 61 (total sample: 82%. n = 50)	Total sample: 6-17yrs (M = 11.2, SD = 3.8)	Total sample: 68.4 (SD = 23.3); range = 42-150 as measured by the Stanford-Binet-V (Roid 2003). Subsample of 22 included with a score of >70; range not reported for subsample	Total sample: Antipsychotic 37 (60.7%); ADHD medication 25 (41.0%); beta blocker 28 (32.8%); mood stabilizer 13 (21.3%); SSRI 12 (19.7%); anxiolytic 3 (4.9%); atypical antidepressant 3 (4.9%); antiepileptic 3 (4.9%)	Clinically and community recruited from University-based clinics, local psychiatrists' offices, local support groups, and previous database research participants (USA)	Previous diagnosis and confirmed by ADI-R (Rutter et al., 2003)	Parent interview: Current depression was measured via parent interview with the P-ChIPS (Weller et al., 1999) administered by trained study author	22.7%

AS = Asperger's Syndrome; AD = Asperger's Disorder; ASD = Autism Spectrum Disorder; HFASD = High Functioning Autism Spectrum Disorder; AS/HFA =Asperger's Syndrome/High Functioning Autism ; HFA = High Functioning Autism; ASD-ED = Autism Spectrum Disorder-Emotion Dysregulation; ASD-DESR = Autism Spectrum Disorder-Deficient Emotional Self-Regulation; ASD-SED = Autism Spectrum Disorder-Severe Emotional Dysregulation; FSIQ = Full Scale IQ; VIQ = Verbal IQ; NVIQ = Non-Verbal IQ; WISC = Wechsler Intelligence Scale for Children; WASI = The Wechsler Abbreviated Scale of Intelligence; WISC-R = Wechsler Intelligence Scale for Children Revised; MSEL = Mullen Scales of Early Learning; WPPSI-III-UK = Wechsler Preschool and Primary Scale of Intelligence; SBIS-5A = Stanford Binet Intelligence Scale 5th Edition, Abbreviated Battery; ADOS = Autism Diagnostic Observation Schedule; ADOS –G = Autism Diagnostic Observation Schedule-Generic ADI = Autism Diagnostic Interview; ADI-R = Autism Diagnostic Interview Revised;; DDDI = Developmental, Dimensional and Diagnostic Interview; DISCO = Diagnostic Interview for Social and Communication Disorders; K-SADS-PL = The Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version; K-SADS-E = The Kiddie Schedule for Affective Disorders and Schizophrenia Epidemiological Version; SADS-P-T; Schedule for Affective Disorders and Schizophrenia for School-age Children-Present - Turkish Adaptation; IOW-I = Modified Isle of Wight Semi-structured Informant and Child Interviews Informant version; BASC = The Behaviour Assessment System for Children; SCQ = Social Communication Questionnaire; CASI = Child and Adolescent Symptom Inventory; ACI-PL = Autism Comorbidity Interview-Present and Lifetime version; CBCL = Child Behaviour Checklist; CDI = Children's Depression Inventory; CDRS-R = Children's Depression Rating Scale-Revised; DAWBA = Development and Well-Being Assessment; PAPA = Preschool Age Psychiatric Assessment; P-ChIPS = The Children's Interview for Psychiatric Symptoms-Parent Version; CES-D = The Center for Epidemiological Studies Depression Scale; RCADS = Revised Children's Anxiety and Depression Scale.

Figures and Legends

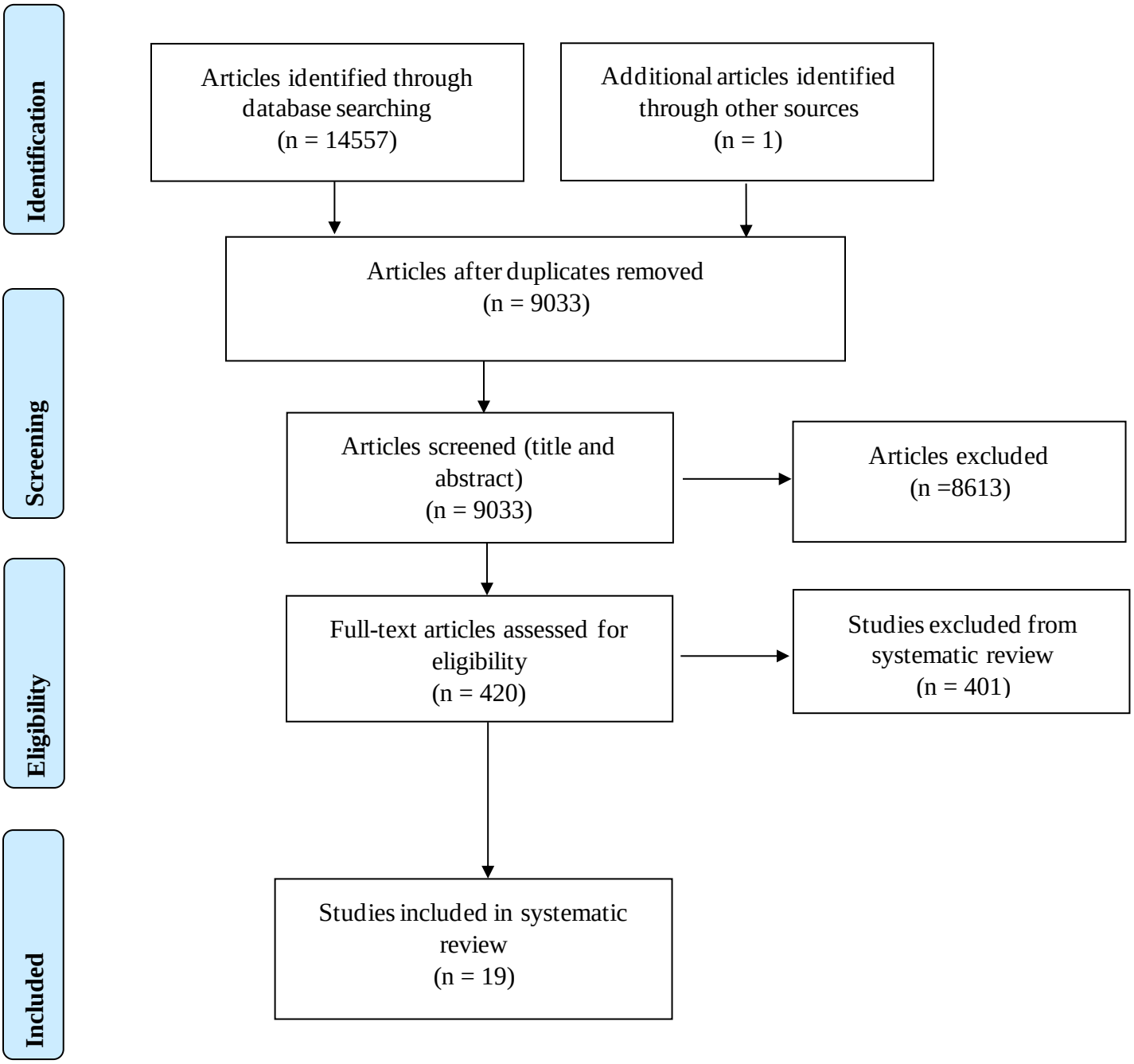

Figure 1: Flow diagram of search strategy