Prevalence of Autism Spectrum Disorder in Preterm Infants: A Meta-analysis

Sachin Agrawal, FRACP,a Shripada C. Rao, FRACP,a,b Max K. Bulsara, PhD,a Sanjay K. Patole, DrPH,a,b

CONTEXT: Evidence is emerging that preterm infants are at risk for autism spectrum disorder (ASD).

OBJECTIVES: To conduct a systematic review and meta-analysis to estimate the prevalence of ASD in preterm infants.

DATA SOURCES: Medline (via PubMed and Ovid), Embase, PsycINFO, and relevant conference proceedings were searched in May 2017.

STUDY SELECTION: Original studies in which researchers report on the prevalence of ASD using diagnostic tests in children born preterm were included. Studies in which researchers used only ASD screening tools were excluded.

DATA EXTRACTION: Relevant data were extracted independently by 3 authors.

RESULTS: Researchers in a total of 18 studies (3366 preterm infants) used ASD diagnostic tools. The median gestation, birth weight, and age at assessment were 28.0 weeks (range: 25.1–31.3 weeks), 1055 g (range: 719–1565 g), and 5.7 years (range: 1.5–21 years), respectively. Meta-analysis revealed that the overall prevalence rate for ASD was 7% (95% confidence interval: 4% to 9%). The funnel plot and Egger’s test revealed that there was probably no evidence of publication bias.

LIMITATIONS: The limitations were significant heterogeneity and a lack of studies from middle- and low-income countries.

CONCLUSIONS: The prevalence of ASD is significantly high in the preterm population. Adequate resources are needed to improve the outcomes of these children.
Advances in neonatal intensive care have improved the survival of preterm infants.\textsuperscript{1,4} It is well known that very preterm and extremely preterm infants carry a high risk of long-term neurodevelopmental morbidities.\textsuperscript{5,6} Recent literature reveals that even moderate- to late-preterm infants are also vulnerable for such adverse outcomes.\textsuperscript{6} Of late, evidence is emerging that prematurity and being of low birth weight are risk factors for later development of autism spectrum disorder (ASD).\textsuperscript{7–9} The prevailing consensus favors a multifactorial pathogenesis for ASD. It is thought that ASD develops in individuals with an underlying biologic vulnerability who experience varying degrees of exogenous stressors during a critical period of brain development during intrauterine and immediate postnatal life.\textsuperscript{10} It is also thought that whatever initiates the preterm birth process might also initiate abnormal pathways of brain development, thereby creating a “perfect storm” of interactions among genetic background and environmental exposures that initiates a fetal immune response and leads to both preterm birth and altered development of the brain and neural connectivity.\textsuperscript{11} Injury to the cerebellum in preterm infants is more common than previously thought and is known to be associated with an increased risk of ASD.\textsuperscript{12}

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), the criteria for ASD are as follows: (1) persistent deficits in social communication and social interactions in multiple contexts; (2) restricted, repeated patterns of behavior, interest, or activities; (3) symptoms must be present in the early developmental period; (4) symptoms cause significant impairment in social, occupational, and other current areas of functioning; and (5) disturbances are not explained by intellectual disability or global developmental delay.\textsuperscript{13} ASD is associated with substantial lifetime costs to individuals, their families, and the community.\textsuperscript{14} A recent study revealed that the median family cost of ASD was $34 900 (Australian dollars) per annum. For each additional symptom reported, an extra $1400 per family per annum was incurred. Delay in diagnosis was associated with a modest increase in the number of ASD symptoms, which indirectly impacts the cost of ASD.\textsuperscript{14} Researchers in multiple narrative reviews have discussed the risk factors and prevalence of ASD in the preterm population\textsuperscript{15,16}; however, there are no meta-analyses or systematic reviews. We aimed to conduct a systematic review and meta-analysis to describe the prevalence of ASD in preterm infants and analyze the relation between gestational age, birth weight, and prevalence of ASD.

\section*{METHODS}

Guidelines from the Joanna Biggs Institute were followed for conducting and reporting this systematic review.\textsuperscript{17} Ethics approval was not required.

\section*{Review Questions}

Review questions included the following:

1. What is the prevalence of ASD in preterm infants when diagnostic tools are used?
2. Is there a relation between gestational age, birth weight, and prevalence of ASD?
3. Does the prevalence of ASD decrease if children with a disability are excluded?

\section*{Inclusion Criteria}

Original studies in which researchers report on the prevalence of ASD in children who were born preterm were included. Studies in which data allowed for the calculation of prevalence were also included. Studies in which researchers described the prevalence of ASD in the general population were included if specific information on the preterm population was available (ie, the number of preterm infants with ASD, total number of preterm infants tested, and tool that was used). The studies could have been published in peer-reviewed journals or presented as conference abstracts. The diagnosis of ASD should have been based on diagnostic tests rather than screening tools. Preterm infants were defined as neonates born before 37 weeks’ gestation.\textsuperscript{18} Low birth weight was defined as birth weight <2500 g.

\section*{Exclusion Criteria}

Studies in which information regarding the number of preterm infants with ASD, total number of preterm infants tested, and tools used to diagnose ASD were not available were excluded. Studies in which researchers used only screening tools to diagnose ASD were excluded. Multiple publications from the same cohort of preterm infants were included only if any additional information was available; otherwise, they were considered to be duplicates, and information was used only once. Animal studies, letters to the editor, reviews, case reports, and series were excluded but read in detail to identify potentially eligible studies.

\section*{Search Strategy}

The databases PubMed, Embase, Medline (via Ovid), and PsycINFO were searched from inception until May 2017. Abstracts of conference proceedings (such as the Perinatal Society of Australia and New Zealand, the European Academy of Pediatric Societies, and the British Maternal and Fetal Medicine Society) were searched in Embase. Electronic abstracts from the Pediatric Academic Society and other conference proceedings were also searched. The reference lists of all included full-text articles were reviewed.
were searched to identify any studies missed in the initial search. Reviewers (S.R. and S.A.) conducted the literature search independently. No language restriction was applied. We searched Medline via Ovid using the following terminology: [Preterm infant.mp. or exp Infant, Premature/ OR low birth weight infant.mp. or exp Infant, Low Birth Weight/ OR exp Infant, Very Low Birth Weight/ or exp Infant, Premature/ or very low birth infant.mp. or exp Infant, Low Birth Weight/ or exp Infant, Premature, Diseases/] AND [asymmetry and publication bias]. The other databases were searched with similar terms. References were compiled and managed by using EndNote 8 (Thomson Reuters, Toronto, Canada), with duplicate citations being removed by using this software.

Study Selection
Two reviewers (S.R. and S.A.) screened the titles and abstracts of the potentially relevant studies. At this stage, the search was purposely broad to allow for the inclusion of all potentially relevant studies. All studies that met the inclusion criteria at this stage were reviewed by the third author (S.K.P.) to ensure appropriateness for inclusion in the final analysis. Disagreements of eligibility were reconciled by discussion among 3 authors.

Data Abstraction and Risk-of-Bias Assessment
A standardized data abstraction form was used to enter the study-related variables. Two independent reviewers (S.A. and S.C.R.) abstracted the data from each included study. The following data were abstracted: study identification (ie, author, journal, country, and year), study characteristics (participant year of birth, study population, mean age at diagnosis, exclusion of children with congenital anomalies and syndromes, and exclusion of children with major disability), method used for diagnosing ASD, number of children (former preterm infants) evaluated, number of children (former preterm infants) who tested positive on diagnostic tests, and prevalence of ASD based on diagnostic tests.

Risk of bias was assessed by using the quality assessment tool for prevalence studies from the Joanna Briggs Institute[19] by using the following criteria: (1) Was the sample frame appropriate to address the target population? (2) Was the study population sampled in an appropriate way? (3) Was the sample size adequate? (4) Were the study subjects and settings described in detail? (5) Was the data analysis conducted with sufficient coverage of the identified sample? (6) Were valid methods used for identification of the condition? (7) Was the condition measured in a standard, reliable way for all the participants? (8) Was there appropriate statistical analysis? (9) Was the response rate adequate, and if not, was the low response rate managed appropriately? The criteria were rated as either yes, no, not clear, or not applicable. When necessary, authors of the included studies were contacted, requesting additional information from their studies.

Statistical Analysis
We used the absolute number of observed events and calculated the proportions and 95% confidence intervals (CIs), assuming a binomial distribution. A logistic normal random effects model was fitted. For CIs for the pooled estimate, we used a variance stabilizing Freeman–Tukey transformation. Heterogeneity was assessed by using the standard $\chi^2$ test and the I² statistic. When data could be pooled, meta-analysis was conducted, and relevant summary statistics and 95% CIs were reported. In addition, the proportions with their 95% CI values from individual studies were also presented in a forest plot. Meta-regression analysis was conducted to find the relationship between the prevalence of ASD, gestational age, and birth weight. The results of the meta-regression analysis are given as regression coefficients with 95% CIs. Funnel plots were used for assessing publication bias. Eggers’s test was used as a formal test of funnel plot asymmetry and publication bias.[20]

For studies in which researchers reported only the median, range, or interquartile range (IQR), we used the method of Wan et al[21] to estimate the sample means. All statistical analyses were conducted by using Stata 15 SE (Stata Corp, College Station, TX). We planned 2 subgroup analyses. The first was based on the presence of disability, and the second was based on the age at assessment (<3 years versus ≥3 years). For the first subgroup analyses, the presence of either a genetic syndrome or neurodevelopmental disability or both was considered a disability. Current opinion is that early diagnosis and intervention, especially at <3 years of age, may improve the outcomes of children with autism. This is supported by the results of a recently published randomized controlled trial, in which children (2–4 years old) who were randomly assigned to receive early intervention showed significant improvements compared with those who received usual care.[22,23] Hence, we chose a cutoff of 3 years of age for the second preplanned subgroup analysis.

Tools Used to Diagnose ASD in the Included Studies
The tools used to diagnose ASD included the following:

1. The Autism Diagnostic Observational Schedule (ADOS)[24–26] is a semistructured, standardized assessment designed for use with individuals who
are referred for possible ASD. A protocol of activities or social presses is administered in ~45 minutes, and then items are scored on a 4-point scale, with 0 indicating “no abnormality of type specified” and 3 indicating “moderate to severe abnormality.” It is designed for use in the diagnostic evaluation of children (12 months to 16 years old) who are referred for suspected ASD;

2. The Autism Diagnostic Interview—Revised (ADI-R) 27,28 is a revision of the Autism Diagnostic Interview, is a semistructured, investigator-based interview for caregivers of children and adults for whom autism or pervasive developmental disorders are a possible diagnosis. It is appropriate for children with mental ages from ~18 months into adulthood and is linked to International Classification of Diseases, 10th Revision (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria;

3. The Development and Wellbeing Assessment (DAWBA) 29 is a novel package of questionnaires, interviews, and rating techniques designed to generate ICD-10 and DSM-IV psychiatric diagnoses on 5- to 16-year-old patients. Interviewers administer a structured interview to parents about psychiatric symptoms and their resultant impact. When definite symptoms are identified with the structured questions, interviewers use open-ended questions and supplementary prompts to get parents to describe the problems in their own words. These descriptions are transcribed verbatim by the interviewers but are not rated by them. A similar interview is administered to 11- to 16-year-old patients. In addition, teachers complete a brief questionnaire covering the main conduct, emotional, and hyperactivity symptoms and any resultant impairment. The different sorts of information are brought together by a computer program that also predicts likely diagnoses. These computer-generated summary sheets and diagnoses form a convenient starting point for experienced clinicians (child psychiatrists and psychologists), who decide whether to accept or overturn the computer diagnosis (or lack of diagnosis) in light of their review of all the data, including transcripts. Finally, a diagnosis is allocated in accordance with DSM-IV, DSM-V, or ICD-10 criteria. Multiple studies have revealed excellent agreement between the DAWBA and the ADOS or ADI-R for the diagnosis of ASD 30 and their use in clinical settings 31,32;

4. The Childhood Autism Rating Scale (CARS) 33-34 is used from the age of 2 years to late adulthood. It is a clinical rating scale for the trained clinician to rate items that are indicative of ASD after direct observation of the patient and to determine the symptom severity through quantifiable ratings. It is used to evaluate the following functional areas: relating to people; body use; visual response; listening response; taste, smell, and touch response; use of verbal communication and nonverbal communication; and level and consistency of intellectual response. The revised version is effective in discriminating between children with autism and those with severe cognitive deficits and distinguishing mild-to-moderate from severe autism; and

5. Team assessment (psychologist, psychiatrist, and developmental pediatrician) according to DSM-IV or DSM-V criteria for diagnosis of ASD is used. The Centers for Disease Control and Prevention recommend that child psychiatrists, psychologists, developmental pediatricians, and child neurologists are the specialists who can make comprehensive assessments to diagnose ASD. 37

RESULTS

A total of 18 studies in which researchers reported the prevalence of ASD were included. 38-55 Figure 1 provides details of the study selection process. Three authors responded and provided additional information for this systematic review 41,44,46

The total sample size was 3366 participants from 18 studies (Table 1). The median sample size in the included studies was 98 (IQR 61–177; range: 53–857). The median gestational age was 28.0 weeks (IQR: 27.2–30.3 weeks; range 25.1–31.3 weeks). The median birth weight was 1055 g (IQR: 965–1201 g; range 719–1565 g). The median age at assessment was 5.7 years (IQR: 3.7–11 years; range: 1.5–21 years). The median number of preterm infants diagnosed with ASD in individual studies was 8 (IQR 3–16; range: 1–61).

Meta-analysis

The overall prevalence rate of ASD was 7% (95% CI: 4% to 9%; Fig 2); there was significant statistical heterogeneity (I² = 84.82%; Fig 2).

Subgroup Analysis

Subgroup analysis of studies in which children with disabilities were excluded revealed a prevalence rate of 9% (95% CI: 6% to 11%). 39,45-47,50,51,55 Subgroup analysis of studies in which children with disabilities were not excluded revealed a prevalence rate of 6% (95% CI: 2% to 10%). Subgroup analysis of studies in which children were assessed at <3 years revealed a prevalence rate of 7% (95% CI: 4% to 10%).
Sensitivity Analysis

The results of the study by Verhaeghe et al. appeared to be an outlier; hence, sensitivity analysis was conducted by excluding it. The prevalence rate for ASD was then 6% (95% CI: 4% to 8%), and statistical heterogeneity decreased from 85% to 74%. Nine of 53 (17%) children in that study had significant cerebellar hemorrhage in the neonatal period, which could have contributed to the high prevalence of ASD; it is well known that cerebellar hemorrhage and anomalies are associated with an increased risk of ASD.12,56

Publication Bias

The funnel plot and Egger’s test revealed that there was probably no publication bias (P = .294; Fig 3).

Meta-regression

Meta-regression analysis revealed no significant association between gestational age (regression coefficient: −0.0075; 95% CI: −0.0234 to 0.0083; P = .315; Fig 4) or birth weight (regression coefficient: −0.0001; 95% CI: −0.0003 to 0.0001; P = .68; Fig 5) and the prevalence of ASD.

Risk of Bias

The risk of bias was low in the majority of the domains in the included studies (Table 2).

DISCUSSION

Our systematic review that included 3366 preterm infants from 18 studies revealed that when diagnostic tools were used, the overall prevalence rate of ASD was 7% (95% CI: 4% to 9%). This equates to ~900,000 additional children each year who will develop ASD given that globally, ~15 million infants are born preterm (before 37 weeks’ gestation), of whom 13 million survive.57–59 Our findings confirm that the prevalence of ASD in preterm infants is considerably higher than in the general population, in which the overall prevalence has been reported to be 0.76%.60 Researchers in another study reported a prevalence of 1.46% (range: 0.57%–2.19%) in the general pediatric population aged 8 years.61

Although there are many tests used to screen children for ASD,62 it is important not to label children who test positive on screening tests as having ASD. Such children should always be assessed with definitive tests before confirming them as having ASD. Expert committees (the Child Development and Behavior Special Interest Group of the Chapter of Community Child Health, the Pediatrics and Child Health Division, and the Royal Australasian College of Physicians) have advised to use clinical judgement when suspecting a child as having ASD and to not rely solely on screening tools.63 A recent survey of health professionals in Australia revealed inconsistencies in ASD assessment practices across the states and between the private and public service settings.64 Only half of the respondents reported that they include a standardized objective assessment tool, such as the ADOS, in ASD assessments. The study raised concerns that clinicians may not be practicing in a manner that is...
<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Study Location</th>
<th>Year of Birth</th>
<th>Study Population</th>
<th>Age at Assessment</th>
<th>Exclusion of Children With Congenital Anomaly or Syndromes</th>
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<th>Diagnostic Tool Used</th>
<th>No. Children (Former Preterm Infants) Evaluated</th>
<th>No. Former Preterm Infants Diagnosed With ASD</th>
<th>Prevalence Based on Diagnostic Tool, %</th>
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<tbody>
<tr>
<td>1</td>
<td>Indredavik et al. [30] Norway</td>
<td>1986–1988</td>
<td>Birth weight &lt;1500 g; mean BW 1174 g; SD 233 g; mean GA 28.8 wk, SD 2.7 wk</td>
<td>14 y (mean 14.1 y; SD 0.3 y)</td>
<td>Yes</td>
<td>No</td>
<td>Interview by 2 psychiatrists and conclusions drawn according to DSM-IV criteria</td>
<td>56</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Pinto-Martin et al. [31] United States</td>
<td>1984–1989</td>
<td>Birth weight &lt;2000 g; mean BW 1475.3 g; SD 353.3 g; mean GA 31.2 wk, SD 3.1 wk</td>
<td>21 y</td>
<td>Not clear</td>
<td>No</td>
<td>ADI-R, ADOS</td>
<td>623</td>
<td>14</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>Johnson et al. [32] United Kingdom and Ireland</td>
<td>1995</td>
<td>GA &lt;26 wk; mean GA 27.5 wk; SD 1.94 wk; BW &lt;1250 g; mean BW 975 g, SD 223 g</td>
<td>Median 10.9 y</td>
<td>Yes</td>
<td>No</td>
<td>The DAWBA was administered to parents via telephone interview or online version, then summary sheets and clinical transcripts of the interview were reviewed by 2 child and adolescent psychiatrists, who assigned DSM-IV and ICD-10 consensus diagnoses.</td>
<td>219</td>
<td>16</td>
<td>8</td>
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<tr>
<td>4</td>
<td>Treyvaud et al. [33] Australia</td>
<td>2001–2003</td>
<td>GA &lt;30 wk; mean GA 27.5 wk; SD 1.94 wk; BW &lt;1250 g; mean BW 975 g, SD 223 g</td>
<td>7 y</td>
<td>Not clear</td>
<td>No</td>
<td>The DAWBA was completed online by parents. Raters were 2 clinical psychologists with diagnostic experience who completed the online DAWBA rater training and assigned diagnoses according to DSM-IV criteria.</td>
<td>177</td>
<td>8</td>
<td>4.5</td>
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<td>5</td>
<td>Yaari et al. [34] Israel</td>
<td>2009–2013</td>
<td>GA 24–34 wk; mean GA 31.28 wk (SD 2.57 wk); mean BW 1541.38 g (SD 474.32 g; range: 490–2400 g)</td>
<td>18 mo</td>
<td>Yes</td>
<td>Yes</td>
<td>ADOS Toddler</td>
<td>99</td>
<td>8</td>
<td>8</td>
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<td>6</td>
<td>Mettelman et al. [35] NA</td>
<td>NA</td>
<td>GA &lt;30 wk; mean GA 31.28 wk (SD 2.57 wk); mean BW 1541.38 g (SD 474.32 g; range: 490–2400 g)</td>
<td>4 y</td>
<td>NA</td>
<td>NA</td>
<td>CARS administered by psychologist while examining the children</td>
<td>174</td>
<td>17</td>
<td>10</td>
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<tr>
<td>Serial No.</td>
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<td>7</td>
<td>Czech Republic</td>
<td>2012–2013</td>
<td>BW &lt;1500 g</td>
<td>2 y</td>
<td>Not clear</td>
<td>Yes</td>
<td>ADOS and clinical evaluation by 2 psychiatrists</td>
<td>75</td>
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<td>10.6</td>
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<td>8</td>
<td>South Korea</td>
<td>NA</td>
<td>GA &lt;36 wk</td>
<td>3–6 y (mean 3.7 y; SD 0.7 y)</td>
<td>Not clear</td>
<td>Yes</td>
<td>CARS Korean version</td>
<td>58</td>
<td>1</td>
<td>1.7</td>
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<td>9</td>
<td>Japan</td>
<td>2001–2005</td>
<td>BW &lt;1500 g</td>
<td>6–9 y</td>
<td>Yes</td>
<td>Not clear</td>
<td>Clinical evaluation by psychiatrists</td>
<td>77</td>
<td>4</td>
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<td>Japan</td>
<td>2001–2005</td>
<td>Median BW 951 g, IQR 726–1219 g, Median GA 27.4 wk, IQR 25.1–30.5 wk</td>
<td>3–6 y</td>
<td>Not clear</td>
<td>No</td>
<td>Clinical assessment by pediatric neurologist using DSM-IV criteria</td>
<td>321</td>
<td>35</td>
<td>10.9</td>
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<td>11</td>
<td>Belgium</td>
<td>1999–2000</td>
<td>GA &lt;27 wk</td>
<td>11–15 y (mean 12.6 y; SD 1.03 y)</td>
<td>Not clear</td>
<td>No</td>
<td>ADOS, ADI-R</td>
<td>53</td>
<td>21</td>
<td>40</td>
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<td>12</td>
<td>Australia</td>
<td>2007–2009</td>
<td>GA &lt;30 wk, mean GA 27.6 wk, SD 2 wk</td>
<td>2 y</td>
<td>Yes</td>
<td>No</td>
<td>Clinical by developmental</td>
<td>97</td>
<td>1</td>
<td>1</td>
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<td>13</td>
<td>Taiwan</td>
<td>1996–1998</td>
<td>Mean BW 1200.9 g, SD 218.8 g</td>
<td>13.4 y</td>
<td>Not clear</td>
<td>No</td>
<td>Diagnoses of ASD were based on combined information from diagnostic tools, observations of the subjects, and parental report and labeling according to DSM-IV Text Revision criteria</td>
<td>61</td>
<td>2</td>
<td>3.3</td>
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<td>Serial No.</td>
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<tr>
<td>14</td>
<td>Mohammed et al,54 Saudi Arabia</td>
<td>2012–2013</td>
<td>BW 620–1220 g GA 27–33 wk</td>
<td>3 y</td>
<td>Not clear</td>
<td>Not clear</td>
<td>Clinical assessment in the comprehensive autism program included a multidisciplinary team of psychologists, behavioral pediatricians, and speech therapists; ASD diagnosis was based on DSM-IV criteria.</td>
<td>107</td>
<td>5</td>
<td>4.7</td>
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<tr>
<td>15</td>
<td>Ikejiri et al,55 Japan</td>
<td>2004–2007</td>
<td>GA &lt;33 wk (mean BW 857 g; SD 367 g; mean GA 27 wk (SD 2.2 wk; range 474–1448 g)</td>
<td>30–74 mo (mean 49.1 mo; SD 15.7 mo)</td>
<td>Not clear</td>
<td>Yes</td>
<td>Clinical assessment by 2 pediatricians using DSM-IV Text Revision criteria</td>
<td>59</td>
<td>9</td>
<td>15.2</td>
</tr>
<tr>
<td>17</td>
<td>Pritchard et al,44 Australia</td>
<td>2006–2008</td>
<td>GA &lt;29 wk Mean GA 26.7 wk, SD 1.4 wk</td>
<td>2–4 y</td>
<td>Not clear</td>
<td>No</td>
<td>ADOS Generic</td>
<td>169</td>
<td>3</td>
<td>1.8</td>
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<tr>
<td>18</td>
<td>Padilla et al,47 Sweden</td>
<td>2004–2007</td>
<td>GA &lt;27 wk (mean 25.1 wk, SD 1.1 wk) Mean BW 718.8 g, SD 148.5 g</td>
<td>6.5 y</td>
<td>Yes</td>
<td>Yes</td>
<td>Clinical assessment using DSM-IV and ICD-10 criteria</td>
<td>84</td>
<td>10</td>
<td>11.9</td>
</tr>
</tbody>
</table>

ADOS 2, Autism Diagnostic Observation Schedule, Second Edition; BW, birth wt; GA, gestational age; NA, not available.

a Conference abstracts only.
consistent with international best-practice guidelines or statements from professional bodies. The use of nonstandardized methods causes difficulty in calculating the true prevalence of ASD and hence makes it difficult to allocate appropriate resources from funding agencies.

The large proportion of preterm infants who subsequently develop ASD necessitates an adequate allocation of resources to facilitate diagnosis and rehabilitation. Although there are well-established neurodevelopmental programs to manage preterm infants until at least 2 years of age, routine screening for ASD in this highly vulnerable population is not yet a standard practice even in high-income countries. Given the shortage of experts in diagnosing and managing ASD, innovative strategies will be required within existing health systems. These could include the training of neonatologists, pediatricians, and developmental psychologists in administering the screening tools at routine follow-up visits. Children who test positive on screening tools and those in whom the diagnosis is suspected on the basis of clinical judgement could be referred for further assessment by experts using definitive diagnostic tools.

The median age at assessment in our review was 5.7 years, which is considered to be late. Early diagnosis and intervention have the potential to limit the severity of symptoms and improve the outcomes of children with ASD. Children with ASD require the services of multiple specialists, including pediatricians, general practitioners, psychologists, psychiatrists, occupational therapists, behavioral therapists, nutritionists, physiotherapists, audiologists, and many more. Funding agencies should provide adequate finances to support these services.

Our meta-regression analysis revealed no significant association between gestational age, birth weight, and prevalence of ASD in preterm infants. The probable reason for not reaching statistical significance may be the small sample size. Contrary to our expectations, we found no significant difference in the prevalence of ASD when infants with disabilities were included or excluded, but the sample size was small to make firm conclusions on this.

An important observation in our review was the total absence of

FIGURE 2
Forest plot used to assess the prevalence of ASD. ES, effect size.

FIGURE 3
Diagnostic funnel plot with pseudo–95% confidence limits for publication bias. ES, effect size.
ASD studies of preterm infants from low- and middle-income countries (LMICs). Because of various barriers, children with ASD often do not receive a confirmatory diagnosis until preschool age, especially in LMICs. In a Brazilian survey, Ribeiro et al found that most mothers sought help within 3 months of first suspicion and mentioned their concerns to pediatricians, but only one-third of such children were referred for further evaluation of ASD. The authors reported that in many instances, mothers were told by their pediatricians that “children should not be compared to each other” and that “boys have a slower development rate or are more agitated than girls.” In addition, they reported that most mothers described their interactions with the pediatricians as negative experiences and felt discouraged from expressing their concerns again. \(^{66}\) In a study conducted in Vietnam, Van Cong et al\(^{68}\) found that limited resources, a lack of awareness, and a lack of official government policy were barriers to the early diagnosis of ASD. In a review of ASD studies from 9 LMICs, Samms-Vaughan\(^{69}\) identified a lack of resources as the main barrier to early diagnosis. In a comprehensive review of autism-related research from Sub-Saharan Africa, Franz et al\(^{70}\) found 53 publications, but no epidemiologic or early intervention studies were identified. Durkin et al\(^{71}\) suggested that barriers in LMICs include the high cost of proprietary tools for diagnosing ASD and the high cost of training professionals to use the tools. They recommended open-source and open-access models to facilitate global collaboration and training.\(^{71}\)

Researchers in a recent systematic review identified 28 studies from LMICs in which researchers reported on 18 different screening tools that were used to assess children for ASD. None of the included studies in that review had a specific focus on preterm infants.\(^{72}\) Given that \(\sim 90\%\) of preterm deliveries occur in LMICs\(^{57}\) and the survival of preterm infants in those countries is increasing rapidly,\(^{73-75}\) the number of children who will need assessment and management of ASD are expected to increase in the coming years. Hence, the implementation of optimal strategies in LMICs is urgently needed.

The limitations and strengths of our systematic review need to be discussed. (1) There was significant clinical and statistical heterogeneity. The heterogeneity was mainly related to the age at assessment (which ranged from 1.5 to 21 years), the type of diagnostic tool used, and the sample size (which ranged from 53 to 857). Because heterogeneity was anticipated, we used a random-effects model\(^{76}\) for the meta-analysis. The high level of statistical heterogeneity was due to the varied prevalence of ASD in the included studies. Even after removing an extreme outlier, the heterogeneity remained high; hence, caution is
CONCLUSIONS

The prevalence of ASD is significantly high in the preterm population. Adequate resources are needed to improve the outcomes of these children. Given that ASD results in an enormous burden on the patients, caregivers, health care professionals, and communities, strategies to implement a definitive diagnosis and treatment are urgently needed, especially in the preterm population.

TABLE 2 Risk of Bias in the Included Studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Was the Sample Frame Appropriate to Address the Target Population?</th>
<th>Was the Study Population Sampled in an Appropriate Way?</th>
<th>Was the Sample Size Adequate?</th>
<th>Were the Study Subjects and Settings Described in Detail?</th>
<th>Was the Data Analysis Conducted With Sufficient Coverage of the Identified Sample?</th>
<th>Were the Valid Methods Used for Identification of the Condition?</th>
<th>Was the Condition Measured in a Standard, Reliable Way for All the Participants?</th>
<th>Was There Appropriate Statistical Analysis?</th>
<th>Was the Response Rate Adequate, and If Not, Was the Low Response Rate Managed Appropriately?</th>
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</thead>
<tbody>
<tr>
<td>Indredavik et al.</td>
<td>Yes</td>
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<td>Pinto Martin et al.</td>
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</table>

* Conference-only abstract.

ABBREVIATIONS

ADQ: Autism Diagnostic Interview
ADI-R: Autism Diagnostic Interview—Revised
ADOS: Autism Observation Schedule
ASD: Autism spectrum disorder
CAR: Childhood Autism Rating Scale
CI: Confidence interval
CARS: Childhood Asperger Rating Scale
CI: Confidence interval
Dawba: Development and Wellbeing Assessment
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ICD-10: International Classification of Diseases, Tenth Revision
LMIC: Low- and middle-income country
MIDAS: Multimodal Intervention for Developmental and Health Assessment
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Because all the studies were from high-income countries, the results of this review are not generalizable.

The major strength of our review is the rigorous methodology of the primary analysis and likely absence of publication bias. Ours is probably the first systematic review in which researchers address the issue of the prevalence of ASD in preterm infants.
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Pediatrics 2018;142;
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