



# Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation

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**Contributions:** (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Abstract:** Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors. There have been recent concerns about increased prevalence, and this article seeks to elaborate on factors that may influence prevalence rates, including recent changes to the diagnostic criteria. The authors review evidence that ASD is a neurobiological disorder influenced by both genetic and environmental factors affecting the developing brain, and enumerate factors that correlate with ASD risk. Finally, the article describes how clinical evaluation begins with developmental screening, followed by referral for a definitive diagnosis, and provides guidance on screening for comorbid conditions.

**Keywords:** Autism spectrum disorder (ASD); prevalence; etiology; screening; evaluation; medical comorbidity

Submitted Sep 25, 2019. Accepted for publication Sep 26, 2019.

doi: 10.21037/tp.2019.09.09

View this article at: <http://dx.doi.org/10.21037/tp.2019.09.09>

## Definition

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors (1). In 2013, the *Diagnostic and Statistical Manual of Mental Disorders—5<sup>th</sup> edition (DSM-5)* was published, updating the diagnostic criteria for ASD from the previous 4<sup>th</sup> edition (DSM-IV) (*Table 1*) (1,2).

In DSM-5, the concept of a “spectrum” ASD diagnosis was created, combining the DSM-IV's separate pervasive developmental disorder (PDD) diagnoses: autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS), into one. Rett syndrome is no longer included under ASD in DSM-5 as it is considered a discrete neurological disorder. A separate social (pragmatic)

communication disorder (SPCD) was established for those with disabilities in social communication, but lacking repetitive, restricted behaviors. Additionally, severity level descriptors were added to help categorize the level of support needed by an individual with ASD.

This new definition is intended to be more accurate and works toward diagnosing ASD at an earlier age (3). However, studies estimating the potential impact of moving from the DSM-IV to the DSM-5 have predicted a decrease in ASD prevalence (4,5) and there has been concern that children with a previous PDD-NOS diagnosis would not meet criteria for ASD diagnosis (5-7). There are varying reports estimating the extent of and effects of this change. One study found that with parental report of ASD symptoms alone, the DSM-5 criteria identified 91% of children with clinical DSM-IV PDD diagnoses (8). However, a systematic review suggests only 50% to 75% of

**Table 1** Changes in ASD criteria from the DSM-IV to DSM-5

Changes	DSM-IV	DSM-5
Location in manual	Disorders usually first diagnosed in infancy, childhood, or adolescence	Neurodevelopmental disorder
Sub-criteria	3 sub-criteria Qualitative impairment in social interaction Qualitative impairments in communication Restricted repetitive and stereotyped patterns of behavior, interests, and activities	2 sub-criteria Persistent deficits in social communication and social interaction across multiple contexts Restricted, repetitive patterns of behavior, interests, or activities
Needed to diagnose	Triad: 3/3 diagnostic criteria must be met	Dyad: 2/2 diagnostic criteria must be met
Diagnostic criteria	Qualitative impairment in social interaction, manifested by at least 2 of the following: Marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction Failure to develop peer relationships appropriate to developmental level A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people Lack of social or emotional reciprocity	Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following: Deficits in social-emotional reciprocity, (including abnormal social approach and failure of reciprocal conversation, reduced sharing of interests, emotions, or affect, failure to initiate or respond to social interactions) Deficits in nonverbal communicative behaviors used for social interaction (poorly integrated verbal and nonverbal communication, eye contact and gesture/body language abnormalities) Deficits in developing, maintaining, and understand relationships (including adjusting behavior in various social contexts, difficulties in sharing imaginative play or in making friends, or lack of interest in peers) Restricted, repetitive patterns of behavior, interests, or activities, manifested by at least two of the following: Stereotyped or repetitive motor movements, use of objects, or speech Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior Highly restricted, fixated interests that are abnormal in intensity or focus

**Table 1** (continued)

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Changes	DSM-IV	DSM-5
	<p>Stereotyped and repetitive use of language or idiosyncratic language</p> <p>Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level</p> <p>Restricted repetitive and stereotyped patterns of behavior, interests, and activities, manifested by at least one of the following:</p> <p>Encompassing preoccupation with one or more stereotyped patterns of interest that is abnormal either in intensity or focus</p> <p>Apparently inflexible adherence to specific, nonfunctional routines or rituals</p> <p>Stereotyped and repetitive motor mannerisms</p> <p>Persistent preoccupation with parts of object</p> <p>Onset prior to age 3 years</p>	<p>Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment</p>
Age of development		<p>Symptoms must be present in early developmental period but may not manifest until social demands exceed limited capacities or may be masked by learned strategies</p>
Not better explained by	<p>Rett's disorder or childhood disintegrative disorder</p>	<p>SPCD</p>
Sensory symptoms	<p>Not addressed</p>	<p>Sensory symptoms are a new criterion introduced in DSM-5 under the sub-criteria of restricted, repetitive patterns of behavior, interests, or activities</p>

ASD, autism spectrum disorder; SPCD, social (pragmatic) communication disorder.

individuals maintain diagnoses (9) and other studies have also suggested a decreased rate of diagnosis of individuals with ASD under the DSM-5 criteria (10). Often those who did not meet the requirements were previously classified as high functioning Asperger's syndrome and PDD-NOS (11,12). Overall, most studies suggest that the DSM-5 provides increased specificity and decreased sensitivity compared to the DSM-IV (5,13); so while those diagnosed with ASD are more likely to have the condition, there is a higher number of children whose ASD diagnosis is missed, particularly older children, adolescents, adults, or those with a former diagnosis of Asperger's disorder or PDD-NOS (14). Nevertheless, the number of people who would be diagnosed under the DSM-IV, but not under the new DSM-5 appears to be declining over time, likely due to increased awareness and better documentation of behaviors (4).

It has yet to be determined how the new diagnosis of SPCD will impact the prevalence of ASD. One study found the new SPCD diagnosis encompasses those individuals who possess subthreshold autistic traits and do not qualify for a diagnosis of ASD, but who still have substantial needs (15). Furthermore, children who previously met criteria for PDD-NOS under the DSM-IV might now be diagnosed with SPCD.

## Epidemiology

The World Health Organization (WHO) estimates the international prevalence of ASD at 0.76%; however, this only accounts for approximately 16% of the global child population (16). The Centers for Disease Control and Prevention (CDC) estimates about 1.68% of United States (US) children aged 8 years (or 1 in 59 children) are diagnosed with ASD (6,17). In the US, parent-reported ASD diagnoses in 2016 averaged slightly higher at 2.5% (18). The prevalence of ASD in the US more than doubled between 2000–2002 and 2010–2012 according to Autism and Developmental Disabilities Monitoring Network (ADDM) estimates (6). Although it may be too early to comment on trends, in the US, the prevalence of ASD has appeared to stabilize with no statistically significant increase from 2014 to 2016 (19). Changing diagnostic criteria may impact prevalence and the full impact of the DSM-5 diagnostic criteria has yet to be seen (17).

Insurance mandates requiring commercial plans to cover services for ASD along with improved awareness have likely contributed to the increase in ASD prevalence estimates as well as the increased diagnosis of milder cases of ASD in

the US (6,20,21). While there was only a modest increase in prevalence immediately after the mandates, there have been additional increases later as health care professionals better understood the regulatory and reimbursement process. The increase in prevalence may also be due to changes in reporting practices. One study in Denmark found the majority of increase in ASD prevalence from 1980–1991 was based on changes of diagnostic criteria and inclusion of outpatient data, rather than a true increase in ASD prevalence (21).

ASD occurs in all racial, ethnic, and socioeconomic groups, but its diagnosis is far from uniform across these groups. Caucasian children are consistently identified with ASD more often than black or Hispanic children (6). While the differences appear to be decreasing, the continued discrepancy may be due to stigma, lack of access to healthcare services, and a patient's primary language being one other than English.

ASD is more common in males (22,23) but in a recent meta-analysis (24), true male-to-female ratio is closer to 3:1 than the previously reported 4:1, though this study was not done using the DSM-5 criteria. This study also suggested that girls who meet criteria for ASD are at higher risk of not receiving a clinical diagnosis. The female autism phenotype may play a role in girls being misdiagnosed, diagnosed later, or overlooked. Not only are females less likely to present with overt symptoms, they are more likely to mask their social deficits through a process called "camouflaging", further hindering a timely diagnosis (25). Likewise, gender biases and stereotypes of ASD as a male disorder could also hamper diagnoses in girls (26).

Several genetic diagnoses have an increased rate of co-occurring ASD compared to the average population, including fragile X, tuberous sclerosis, Down syndrome, Rett syndrome, among others; however, these known genetic disorders account for a very small amount of overall ASD cases (27–30). Studies of children with sex chromosome aneuploidy describe a specific social functioning profile in males that suggests more vulnerability to autism (22,23,31,32). With the increased use of chromosomal microarray, several sites (chromosome X, 2, 3, 7, 15, 16, 17, and 22 in particular) have proven to be associated with increased ASD risk (28).

Other risk factors for ASD include increased parental age and prematurity (33–35). This could be due to the theory that older gametes have a higher probability of carrying mutations which could result in additional obstetrical

complications, including prematurity (36).

## Causes

ASD is a neurobiological disorder influenced by both genetic and environmental factors affecting the developing brain. Ongoing research continues to deepen our understanding of potential etiologic mechanisms in ASD, but currently no single unifying cause has been elucidated.

Neuropathologic studies are limited, but have revealed differences in cerebellar architecture and connectivity, limbic system abnormalities, and frontal and temporal lobe cortical alterations, along with other subtle malformations (28,37,38). A small explorative study of neocortical architecture from young children revealed focal disruption of cortical laminar architecture in the majority of subjects, suggesting problems with cortical layer formation and neuronal differentiation (39). Brain overgrowth both in terms of cortical size and additionally in terms of increased extra-axial fluid have been described in children with ASD and are areas of ongoing study both in terms of furthering our understanding of its etiology, but also as a potential biomarker (40,41).

Genetic factors play a role in ASD susceptibility, with siblings of patients with ASD carrying an increased risk of diagnosis when compared to population norms, and a much higher, although not absolute, concordance of autism diagnosis in monozygotic twins (42-44).

Genome wide association studies and whole exome sequencing methods have broadened our understanding of ASD susceptibility genes, and learning more regarding the function of these genes can shed light on potential biologic mechanisms (45). For example candidate genes in ASD include those that play a role in brain development or neurotransmitter function, or genes that affect neuronal excitability (46,47). Many of the genetic defects associated with ASD encode proteins that are relevant at the neuronal synapse or that are involved in activity-dependent changes in neurons, including regulatory proteins such as transcription factors (42,48). Potential “networks” of ASD genetic risk convergence include pathways involved in neurotransmission and neuroinflammation (49). Transcriptional and splicing dysregulation or alterations in epigenetic mechanisms such as DNA methylation or histone acetylation and modification may play a role (42,49-51). A recent study describes 16 newly identified genes associated with ASD that raise new potential mechanisms including cellular cytoskeletal structure and ion

transport (52). Ultimately, ASD remains one of the most genetically heterogeneous neuropsychiatric disorders with rarer *de novo* and inherited variants in over 700 genes (53).

While genetics clearly play a role in ASD’s etiology, phenotypic expression of genetic susceptibility remains extremely variable within ASD (54). Genetic risk may be modulated by prenatal, perinatal, and postnatal environmental factors in some patients (35). Prenatal exposure to thalidomide and valproic acid have been reported to increase risk, while studies suggest that prenatal supplements of folic acid in patients exposed to antiepileptic drugs may reduce risk (55-57). Research has not confirmed if a small positive trial of folinic acid in autism can be used to recommend supplementation more broadly (58). Advanced maternal and paternal age have both been shown to have an increased risk of having a child with ASD (59). Maternal history of autoimmune disease, such as diabetes, thyroid disease, or psoriasis has been postulated, but study results remain mixed (60,61). Maternal infection or immune activation during pregnancy is another area of interest and may be a potential risk factor according to recent investigations (62-65). Both shorter and longer inter-pregnancy intervals have also been reported to increase ASD risk (66). Infants born prematurely have been demonstrated to carry a higher risk for ASD in addition to other neurodevelopmental disorders (34). In a prior epidemiologic review, obstetric factors including uterine bleeding, caesarian delivery, low birthweight, preterm delivery, and low Apgar scores were reported to be the few factors more consistently associated with autism (67). A recent meta-analysis reported several pre, peri and postnatal risk factors that resulted in an elevated relative risk of ASD in offspring (35), but also revealed significant heterogeneity, resulting in an inability to make true determination regarding the importance of these factors.

Despite the hysteria surrounding the now retracted Lancet article first published in 1998, there is no evidence that vaccines, thimerosal, or mercury is associated with ASD (68-70). In the largest single study to date, there was not an increased risk after measles/mumps/rubella (MMR) vaccination in a nationwide cohort study of Danish children (70).

Ultimately, research continues to reveal factors that correlate with ASD risk, but no causal determinations have been made. This leaves much room for discovery with investigators continuing to elucidate new variants conveying genetic risk, or new environmental correlates that require further study (52).



## Evaluation

Evaluation in ASD begins with screening of the general pediatric population to identify children at-risk or demonstrating signs suggestive of ASD, following which a diagnostic evaluation is recommended. The American Academy of Pediatrics (AAP) guidelines recommend developmental surveillance at 9, 15 and 30 months well child visits and autism specific screening at 18 months and again at 24 or 30 months (28,71). Early red flags for ASD include poor eye contact, poor response to name, lack of showing and sharing, no gesturing by 12 months, and loss of language or social skills. Screening tools for ASD in this population include the Modified Checklist for Autism in Toddlers, Revised, with Follow-up (M-CHAT-R/F) and Survey of Wellbeing of Young Children (SWYC) (72,73). Red flags in preschoolers may include limited pretend play, odd or intensely focused interests, and rigidity. School age children may demonstrate concrete or literal thinking, have trouble understanding emotions, and may even show an interest in peers but lack conversational skills or appropriate social approach. If there is suspicion of ASD in these groups, screening tools available include the Social Communication Questionnaire (SCQ), Social Responsiveness Scale (SRS), and Autism Spectrum Screening Questionnaire (ASSQ) (74-76).

If concerns are raised at screening, primary care clinicians are recommended to refer the child to early intervention if less than 3 years of age or to the public school system for psychoeducational evaluation in order to establish an individual education program (IEP) if the child is three years of age or older. Clinicians should additionally refer the child to a specialist (pediatric neurologist, developmental-behavioral pediatrician, child psychiatrist, licensed child psychologist) for a definitive diagnosis and comprehensive assessment (71). A comprehensive assessment should include a complete physical exam, including assessment for dysmorphic features, a full neurologic examination with head circumference, and a Wood's lamp examination of the skin. A parent interview, collection of any outside informant observations, and a direct clinician observation of the child's current cognitive, language, and adaptive functioning by a clinician experienced with ASD should be components of this comprehensive assessment. (28,71,77,78).

Additionally, primary care clinicians need to be aware of (and evaluate for) potential co-occurring conditions in children with ASD. According to a surveillance study of over 2,000 children with ASD, 83% had an additional developmental diagnosis, 10% had at least one psychiatric

diagnosis, and 16% at least one neurologic diagnosis (79). In the past, rates of co-morbid intellectual disability (ID) in patients with ASD were reported from 50% to 70%, with the most recent CDC estimate reported at 31.0% (26.7% to 39.4%) with ID defined as intelligence quotient (IQ)  $\leq 70$  (6,80). Other common co-occurring medical conditions include gastrointestinal (GI) disorders, including dietary restrictions and food selectivity, sleep disorders, obesity, and seizures (81-84). Studies using electronic health record (EHR) analysis revealed prevalence of epilepsy ~20% and GI disorders [without inflammatory bowel disease (IBD)] at 10-12% (82). Epilepsy has been shown to have higher prevalence rates in ASD with comorbid ID and medical disorders of increased risk such as tuberous sclerosis complex (TSC) (85-87). GI disorders or GI symptomatology, including diarrhea, constipation, restrictive eating, or reflux, have been shown to be prominent in ASD across multiple studies (81,82,88,89). Sleep problems have been reported to occur in anywhere from 50% to 73% of patients with ASD with variation in prevalence dependent on the definition of sleep symptoms or the measurement tool used (90-92). Rates of overweight and obesity in ASD are reported to be roughly 33% and 18% respectively, higher than rates in typically developing children (81-84,93).

Other behavioral or psychiatric co-occurring conditions in ASD include anxiety, attention deficit/hyperactivity disorder (ADHD), obsessive compulsive disorder, and mood disorders or other disruptive behavior disorders (81). Rates of co-occurring ADHD are reported anywhere from 25% to 81% (81,94). A recent meta-analysis of 30 studies measuring rates of anxiety and 29 studies measuring rates of depression reported a high degree of heterogeneity from the current literature, but stated pooled lifetime prevalence for adults with ASD to be 42% for any anxiety disorder and 37% for any depressive disorder, though the use of self-report measures and the presence of ID could influence estimates (95). In children with ASD seeking treatment, the rate of any anxiety disorder was found to be similar at 42% and in addition this study reported co-morbid oppositional defiant disorder at a rate of 46% and mood disorders at 8%, with 66% of the sample of over 600 patients having more than one co-occurring condition (94).

Currently no clear ASD biomarkers or diagnostic measures exist, and the diagnosis is made based on fulfillment of descriptive criteria. In light of a relatively high yield in patients with ASD, clinical genetic testing is recommended and can provide information regarding

medical interventions or work up that might be necessary and help with family planning (96). The American College of Medical Genetics and Genomics (ACMGG) guidelines currently recommend chromosomal microarray for all children, fragile X testing in males, and additional gene sequencing, including *PTEN* and *MECP2*, in certain patients as first tier genetic testing in the work up of ASD (97). High resolution G-banded karyotype, once recommended for all patients with ASD, is no longer routinely indicated based on recent consensus recommendations, but might still be performed in patients with a family or reproductive history suggestive of chromosomal rearrangements or specific syndromes such as sex chromosome anomalies or Trisomy 21 (96-98). Several professional societies recommend genetic testing for ASD, including the American Academy of Neurology, the AAP, ACMGG, and the American Academy of Child and Adolescent Psychiatry, and a child may require further referral to a geneticist and/or genetic counselor, depending on results of testing (25,28,97,99). As the field of genetics continues to advance rapidly, recent publications suggest whole exome sequencing may become the preferred method for clinical genetic testing in individuals with ASD (100,101).

Aside from genetic testing, no other laboratory work up is routinely recommended for every patient with a diagnosis of ASD. However, further evaluation may be appropriate for patients with particular findings or risk factors. Metabolic work-up should be considered in patients with any of the following concerning symptoms or signs: a history of clear developmental regression including loss or plateau of motor skills; hypotonia; recurrent episodes of vomiting, lethargy or hypoglycemia; microcephaly or poor growth; concern for other organ involvement; coarse features; or concern for seizures or ataxia. Based on the patient's history and presentation, components of a metabolic laboratory evaluation could include complete blood count (CBC), liver and renal function tests, lactate, pyruvate, carnitine, amino acids, an acylcarnitine profile, urine organic acids and/or urine glycosaminoglycans (97,102). Children with a history of pica should have a lead level measured (28,103). In a child with significantly restricted food intake, one should consider a laboratory evaluation of nutritional status. Sleep symptoms may warrant a referral for a possible sleep study, and if restless sleep symptoms are present, an evaluation for iron deficiency is not unreasonable, particularly if dietary rigidity limits iron intake (104).

Neuroimaging is not routinely recommended for every patient with ASD (28,99), but may be appropriate

in patients with a suspicion for TSC or other neurocutaneous disorders, microcephaly, or an abnormal neurologic exam (spasticity, severe hypotonia, unilateral findings). Patients with suspected seizures should have an electroencephalography (EEG) obtained (102). If accessible, it might be appropriate to immediately refer children with concern for further genetic, metabolic or neurologic conditions to a specialist who can then obtain and interpret the aforementioned testing. At this time there is inadequate evidence to recommend routine testing for celiac disease, immunologic or neurochemical markers, mitochondrial disorders, allergy testing, hair analysis, intestinal permeability studies, erythrocyte glutathione peroxidase studies, stool analysis, urinary peptides or vitamin and mineral deficiencies without a history of severe food selectivity.

### Summary

ASD is a neurodevelopmental disorder characterized by deficits in social communication and the presence of restricted interests and repetitive behaviors. Recent changes to the diagnostic criteria occurred with the transition to the new diagnostic manual (DSM-5) and will likely impact prevalence, which currently stands at 1 in 59 children in the US. ASD is a neurobiological disorder influenced by both genetic and environmental factors affecting the developing brain. Research continues to reveal factors that correlate with ASD risk and these findings may guide further etiologic investigation, but no final causal pathway has been elucidated. Clinical evaluation begins with developmental screening of the general pediatric population to identify at-risk children, followed by referral to a specialist for a definitive diagnosis and comprehensive neuropsychological assessment. Children with ASD should also be screened for common co-morbid diagnoses. While no clear biomarkers or diagnostic measures exist, clinical genetic testing is recommended as part of the initial medical evaluation. Further medical work up or subspecialist referrals may be pursued based on specific patient characteristics.

### Acknowledgments

*Funding:* None.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest

to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Cite this article as:** Hodges H, Fealko C, Soares N. Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation. *Transl Pediatr* 2020;9(Suppl 1):S55-S65. doi: 10.21037/tp.2019.09.09