IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

AUTISM SPECTRUM DISORDER

DEFINITION, EPIDEMIOLOGY, ETIOLOGY, EVALUATION.

[1]Ms.Shesware Ragini Rahul, [2]Mr. Ghagare Abhishek Dinesh, [3]Mr. Nadim Khan

[1]Student, [2]Student, [3]Assistent Professor

[1]Pharm. D, [1]K. T. Patil Collage of Pharmacy, Dharashiv, India.

***Abstract*:** Autism spectrum disorder (ASD) is a neurodevelopmental illness marked by social communication difficulties as well as restricted interests and repetitive activities. There have recently been worries regarding growing prevalence, and this article aims to expand on issues that may impact prevalence rates, such as recent revisions to diagnostic criteria. The authors examine evidence that ASD is a neurobiological condition impacted by both hereditary and environmental variables impacting the developing brain, and they list risk factors for ASD. Lastly, the article outlines how clinical assessment begins with developmental screening and progresses to referral for a conclusive diagnosis, as well as offers advice on screening for concomitant diseases.

Keywords:
Medical comorbidity, screening, evaluation, prevalence, etiology, Autism Spectrum Disorder (ASD)

DEFINITION:

A neurological illness called autism spectrum disorder (ASD) is characterised by limitations in social communication, the existence of narrow interests, and repetitive activities. Asperger's disorder, childhood disintegrative disorder, autistic disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS) were all independent pervasive developmental disorder (PDD) diagnoses in the DSM-IV. The notion of a "spectrum" ASD diagnosis was developed in the DSM-5. As Rett syndrome is regarded as a distinct neurological illness, it is no longer classified as an ASD in the DSM-5. For those who struggle with social communication but don't exhibit repetitive, constrained behaviours, a distinct social (pragmatic) communication disorder (SPCD) was created. To assist classify the type of support an ASD patient needs, severity level descriptors were also added.

This revised definition aims to be more precise and advances the early detection of ASD (3).Although there has been worry that children with a prior PDD-NOS diagnosis may not fulfil criteria for ASD diagnosis, studies predicting the possible impact of switching from the DSM-IV to the DSM-5 have indicated a drop in ASD prevalence (4,5). (5-7). The size and implications of this alteration have been estimated differently in several papers. In one research, the DSM-5 criteria identified 91% of children with clinical DSM-IV PDD diagnosis based only on parental reporting of ASD symptoms (8). However according to a comprehensive analysis, only 50% to 75% of people keep their diagnoses (9), and other research has similarly indicated a declining incidence of ASD diagnoses using the DSM-5 criteria (10). Frequently, persons who didn't fit the criteria were previously labelled as having PDD-NOS and high functioning Asperger's syndrome (11,12). While those with ASD are more likely to have the condition, there are more children whose ASD diagnosis is missed, especially older children, adolescents, adults, or those with a previous diagnosis of Asperger's disorder or PDD-NOS (5,13), as well as those who have a former diagnosis of Asperger's disorder or PDD-NOS (14).

How the new SPCD diagnosis would affect the prevalence of ASD is yet unknown. According to one research, the subthreshold autistic persons who do not meet the criteria for an ASD diagnosis but nevertheless have significant requirements are included in the new SPCD diagnosis (15). Moreover, youngsters who had previously satisfied DSM-IV PDD-NOS eligibility requirements may now be given the SPCD label.

EPIDEMIOLOGY:

The World Health Organization (WHO) estimates that there are 0.76% ASD cases worldwide, while only around 16% of children worldwide fall into this category (16). According to the Centers for Disease Control and Prevention (CDC), 1 in 59 American children aged 8 have an Autism Spectrum Disorder (ASD) diagnosis (6,17). Parent-reported ASD diagnoses in the US were somewhat higher on average in 2016 at 2.5%. (18). According to estimates from the Autism and Developmental Disabilities Monitoring Network (ADDM), the prevalence of ASD more than doubled in the US between 2000-2002 and 2010-2012. (6). Notwithstanding the possibility that it is too soon to make predictions about trends, the prevalence of ASD in the US seems to have stabilised, with no statistically significant rise from 2014 to 2016. (19). The complete effect of the DSM-5 diagnostic criteria has not yet been determined, however changing the diagnostic criteria might affect prevalence (17).

ASD prevalence estimates and the number of milder instances of ASD being diagnosed in the US have likely grown as a result of insurance laws mandating commercial plans to include therapies for ASD and increasing awareness (6,20,21). Even while there wasn't much of an increase in prevalence right away following the regulations, there have been subsequent rises as medical practitioners become more familiar with the regulatory and payment procedures. The rise in prevalence can also be brought on by modifications to reporting procedures.

According to a Danish research, changes in diagnostic criteria and the addition of outpatient data, rather than an actual rise in the incidence of ASD, were mostly responsible for the increase in prevalence from 1980 to 1991. (21).

All racial, cultural, and socioeconomic groups experience ASD, yet the diagnosis varies widely amongst them. Children who have ASD are consistently more likely to be White than Black or Latino (6). Although there still seems to be a gap, it may be because of stigma, a patient's inability to get treatment, or the fact that their native language is not English.

ASD is more prevalent among men (22,23) Nevertheless, a recent meta-analysis (24), which did not use the DSM-5 criteria, found that the real male-to-female ratio is closer to 3:1 than the previously reported 4:1. According to this study, girls who fit the criteria for ASD are more likely to go without a clinical diagnosis. Girls with autism may experience misdiagnosis, delayed diagnosis, or non-diagnosis due to the feminine phenotype. In addition to being less likely to exhibit overt symptoms, women are also more inclined to "camouflage" their social deficiencies, which makes it more difficult to make a prompt diagnosis (25). Similarly, misconceptions about ASD being a male condition and gender biases might prevent diagnosis in females (26).

Fragile X, tuberous sclerosis, Down syndrome, Rett syndrome, and other genetic illnesses all have higher rates of co-occurring ASD than the general population, although they only make up a very tiny percentage of all instances of ASD (27-30). A certain social functioning profile in men is described in studies of children with sex chromosomal aneuploidy, which predicts a greater susceptibility to autism (22,23,31,32). ASD risk has been linked to a number of locations, including those on chromosomes X, 2, 3, 7, 15, 16, and 22, thanks to the growing usage of chromosomal microarray (28).

Prematurity and older parental figures are additional risk factors for ASD (33-35). This could be because, according to the notion, older gametes are more likely to have mutations that increase the risk of preterm and other obstetrical issues (36).

ETIOLOGY:

ASD is a neurobiological disease that is impacted by environmental and genetic variables that have an impact on the developing brain. Although no one, overarching explanation for ASD has yet been identified, ongoing research is expanding our understanding of various etiologic processes that may contribute to the disorder.

Despite the paucity of these research, cerebellar architecture and connection discrepancies, limbic system abnormalities, frontal and temporal lobe cortical changes, as well as other modest anomalies, have all been identified (28,37,38). Focused disruption of cortical laminar architecture was seen in the majority of participants in a short exploratory investigation of young children's neocortical architecture, pointing to issues with cortical layer creation and neuronal differentiation (39). Children with ASD have been documented to have enlarged brains in terms of cortical size as well as an increase in extra-axial fluid; these findings are the subject of continuing research to help us better understand the genesis of the disorder as well as to identify a possible biomarker (40,41).

Siblings of individuals with ASD have a greater likelihood of diagnosis compared to the general population, and monozygotic twins have a substantially higher, but not 100%, concordance of autism diagnosis. Genetic variables play a role in ASD susceptibility (42-44).

Our understanding of ASD susceptibility genes has been expanded by genome wide association studies and whole exome sequencing techniques, and knowing the function of these genes might provide insight into probable biological pathways (45). For instance, potential genes for ASD include those that impact neuronal excitability, brain development, or neurotransmitter function (46,47). The majority of the genetic flaws linked to ASD encode regulatory proteins like transcription factors, which are important at the neural synapse or involved in activity-dependent alterations in neurons (42,48). ASD genetic risk convergence "networks" may comprise neurotransmission and neuroinflammatory signalling pathways (49). Alterations in epigenetic processes, such as DNA methylation or histone acetylation and modification, or dysregulation of transcription and splicing might be involved (42,49-51). In a recent research, 16 newly discovered genes linked to ASD were described. These genes suggest novel possible processes, such as cellular cytoskeletal organisation and ion transport (52). ASD has uncommon de novo and inherited variations in approximately 700 genes, making it one of the most genetically diverse neuropsychiatric illnesses (53).

Although genetics undoubtedly contribute to the aetiology of ASD, the phenotypic manifestation of genetic predisposition within ASD is nonetheless incredibly heterogeneous (54). Prenatal, perinatal, and postnatal environmental variables in some individuals may modify genetic risk (35). Studies show that prenatal folic acid supplementation in patients exposed to antiepileptic medicines may lower risk, although prenatal exposure to thalidomide and valproic acid have been observed to increase risk (55-57). It has not been shown by research if a modest, successful trial of folinic acid in autism may be used to suggest supplementation more generally (58). An increased chance of having a child with ASD has been demonstrated for both older mothers and fathers (59). It has been hypothesised that autoimmune diseases such as diabetes, thyroid illness, or psoriasis run in the maternal family, however research findings are still conflicting (60,61). Another area of concern is maternal illness or immunological activation during pregnancy, which may be a possible risk factor, according to recent studies (62-65). There has also been evidence that both shorter and longer inter-pregnancy intervals raise the incidence of ASD (66). Premature babies have a higher chance of developing ASD as well as other neurodevelopmental abnormalities, according to research (34). Obstetric variables such as uterine haemorrhage, caesarian deliveries, low birthweight, preterm birth, and low Apgar scores were revealed to be the few factors more consistently related with autism in a previous epidemiologic analysis (67). A recent meta-analysis showed a number of prenatal, perinatal, and postnatal risk variables that contributed to an increased relative risk of ASD in children (35), but it also revealed high heterogeneity, making it impossible to accurately assess the significance of these factors.

There is no proof that vaccinations, thimerosal, or mercury are linked to ASD, notwithstanding the panic surrounding the now-retracted Lancet paper that was initially published in 1998. (68-70). A statewide cohort study of Danish children found no evidence of an elevated risk following the measles, mumps, and rubella (MMR) vaccine, making it the biggest single research to date (70).

In the end, research will continue to identify variables that are associated with an increased risk of ASD, but no causative links have been shown. This gives a lot of potential for discovery as researchers work to identify novel genetic risk variants or new environmental factors that need additional investigation (52).

EVALUATION:

A diagnostic examination is then advised after screening the general paediatric population for children who may be at risk or who are exhibiting symptoms indicative of ASD. Guidelines from the American Academy of Pediatrics (AAP) include developmental monitoring during well-child visits at 9, 15, and 30 months, as well as autism-specific screening at 18 months and again at 24 or 30 months (28,71). Poor eye contact, inadequate name response, lack of sharing and displaying, no gestures by 12 months, and loss of language or social abilities are some early indicators of ASD. The Modified Checklist for Autism in Toddlers, Revised, with Follow-up (M-CHAT-R/F) and Survey of

Wellbeing of Young Children (SWYC) are screening instruments for ASD in this demographic (72,73). Limited pretend play, unusual or extremely concentrated hobbies, and rigidity are all warning signs in toddlers. Children of school age may think logically or literally, have difficulty comprehending emotions, and may exhibit interest in their friends, but they may lack social graces or conversational abilities. The Social Communication Questionnaire (SCQ), Social Responsiveness Scale (SRS), and Autism Spectrum Screening Questionnaire (ASSQ) are accessible screening instruments if there is a suspicion of ASD in these populations (74-76).

If issues are discovered during screening, it is advised that primary care clinicians refer the child to early intervention if they are under three years old or to the public school system for a psychoeducational evaluation in order to create an individual education programme (IEP) if they are three years old or older. Also, for a thorough evaluation and clear diagnosis, clinicians should send the child to a specialist (paediatric neurologist, developmental-behavioral paediatrician, child psychiatrist, or certified child psychologist) (71). A thorough evaluation should consist of a thorough physical examination, which should include a check for dysmorphic characteristics, a full neurologic examination with a head circumference, and a skin Wood's lamp examination. This thorough evaluation should include a parent interview, the gathering of any informant observations from the outside world, and a direct clinician observation of the child's present cognitive, linguistic, and adaptive functioning by a clinician with ASD experience. (28,71,77,78).

The possibility of co-occurring disorders in children with ASD should also be considered by primary care providers. A surveillance study of more than 2,000 ASD patients found that 83% also had a developmental diagnosis, 10% had a psychiatric diagnosis, and 16% had a neurologic diagnosis (79). The most current CDC estimate placed the rate of co-morbid intellectual impairment (ID) in patients with ASD at 31.0% (26.7% to 39.4%), with ID being defined as an IQ of less than 70. In the past, rates of co-morbid ID in individuals with ASD were reported at 50% to 70%. (6,80). GI (gastrointestinal) issues, including dietary limitations and food preferences, sleep disorders, obesity, and seizures are some other frequent co-occurring medical diseases (81-84). Epilepsy was shown to be prevalent in studies employing electronic health record (EHR) analysis at 20%, while GI illnesses [without inflammatory bowel disease (IBD)] were found to be prevalent at 10-12%. (82). It has been demonstrated that ASD with comorbid ID and medical conditions carrying a higher risk, such as tuberous sclerosis complex (TSC), have higher prevalence rates of epilepsy (85-87). Depending on how sleep symptoms are defined or the measuring method employed, persons with ASD have been reported to experience sleep issues in anywhere between 50% and 73% of cases (90-92). Overweight and obesity are more common in ASD children than normally developing children, with rates of about 33% and 18%, respectively (81-84,93). Anxiety, attention deficit/hyperactivity disorder (ADHD), obsessive compulsive disorder, mood disorders, and other disruptive behaviour disorders are additional behavioural or mental co-occurring illnesses in ASD (81) .

There have been reports of co-occurring ADHD rates ranging from 25% to 81%. (81,94). Despite the high degree of heterogeneity in the current literature, a recent meta-analysis of 30 studies measuring anxiety rates and 29 studies measuring depression rates found that the combined lifetime prevalence for adults with ASD was 42% for any anxiety disorder and 37% for any depressive disorder, though the use of self-report measures and the presence of ID may have affected estimates (95). This study indicated 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 disease. Among children with ASD seeking treatment, the prevalence of any anxiety disorder was found to be comparable at 42%. (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).

According to recent consensus recommendations, high resolution G-banded karyotyping, which was once advised for all ASD patients, is no longer routinely indicated. However, it may still be done for patients who have a family or reproductive history suggesting chromosomal rearrangements or specific syndromes like sex chromosome anomalies or Trisomy 21. (96-98). Several professional societies, including the American Academy of Neurology, the AAP, the ACMGG, and the American Academy of Child and Adolescent Psychiatry, recommend genetic testing for ASD. Depending on the results of the test, a child may need to be referred further to a geneticist and/or genetic counsellor (25,28,97,99). Recent studies indicate whole exome sequencing may replace other clinical genetic testing methods as the science of genetics continues to develop quickly in people with ASD (100,101).

No further laboratory testing, save genetic testing, is typically advised for every patient with an ASD diagnosis. More testing, however, could be necessary for people with specific results or risk factors. Patients who present with any of the following worrying symptoms or signs should be evaluated for a metabolic condition: a history of obvious developmental regression, such as loss or plateauing of motor abilities, hypotonia, repeated vomiting, lethargy, or hypoglycemic episodes, microcephaly or poor growth, concern for other organ involvement, coarse features, or worry about seizures or ataxia. A metabolic laboratory assessment may include a complete blood count (CBC), liver and renal function tests, lactate, pyruvate, carnitine, amino acids, an acylcarnitine profile, urine organic acids, and/or urine glycosaminoglycans depending on the patient's history and presentation (97,102). Lead levels in kids with a history of pica should be checked (28,103). A laboratory assessment of a child's nutritional status should be taken into consideration if their food consumption is considerably reduced. An examination for iron insufficiency is not unreasonable if restless sleep symptoms are present, especially if dietary rigidity restricts iron intake. Sleep complaints may call for a referral for a potential sleep study (104). For individuals with ASD, neuroimaging is not always advised (28,99), but it may be useful if there is a suspicion of TSC or other neurocutaneous abnormalities, microcephaly, or an abnormal neurologic exam (spasticity, severe hypotonia, unilateral findings). Electroencephalography (EEG) should be performed on patients who appear to be having seizures (102). Whenever possible, it may be best to refer children who may have further genetic, metabolic, or neurological issues very away to a specialist who can order and interpret the aforementioned testing. Without a history of extreme food selectivity, there is currently insufficient evidence to recommend routine testing for vitamin and mineral deficiencies, celiac disease, immunologic or neurochemical markers, mitochondrial disorders, allergy testing, hair analysis, intestinal permeability studies, erythrocyte glutathione peroxidase studies, stool analysis, or urinary peptides.

SUMMARY:

The neurodevelopmental condition known as ASD is marked by difficulties with social interaction, as well as by narrow interests and repetitive activities. The transition to the new diagnostic manual (DSM-5) resulted in recent revisions to the diagnostic criteria, which are expected to have an effect on prevalence, which is now estimated to affect 1 in 59 children in the US. ASD is a neurobiological disease that is impacted by environmental and genetic variables that have an impact on the developing brain. A complete causal route has not yet been identified, but research is still revealing variables that are associated with an increased risk of ASD. These findings may serve as a roadmap

for future etiologic research. Clinical examination begins with developmental screening of the general paediatric population to identify children who are at risk, then is followed by a specialist referral for a precise diagnosis and thorough neuropsychological evaluation. Moreover, prevalent co-morbid disorders should be checked for in children with ASD. The first medical examination should include clinical genetic testing even if there are no obvious biomarkers or diagnostic techniques. Based on certain patient features, additional medical testing or subspecialist referrals may be requested.

REFERANCES:

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing, 2013.
2. American Psychiatric Association. Diagnostic and statistcal manual of mental disorders. 4th ed. Washington: American Psychiatric Publishing, 1994.
3. Halfon N, Kuo AA. What DSM-5 could mean to children with autism and their families. JAMA Pediatr 2013;167:608-13. [Crossref] [PubMed]
4. Maenner MJ, Rice CE, Arneson CL, et al. Potential impact of DSM-5 criteria on autism spectrum disorder prevalence estimates. JAMA Psychiatry 2014;71:292-300. [Crossref] [PubMed]
5. Kulage KM, Smaldone AM, Cohn EG. How will DSM-5 affect autism diagnosis? A systematic literature review and meta-analysis. J Autism Dev Disord 2014;44:1918-32. [Crossref] [PubMed]
6. Baio J, Wiggins L, Christensen DL, et al. Prevalence of autism spectrum disorder among children aged 8 years — autism and developmental disabilities monitoring network, 11 sites, United States, 2014. MMWR Surveill Summ 2018;67:1-23. [Crossref] [PubMed]
7. Yaylaci F, Miral S. A comparison of DSM-IV-TR and DSM-5 diagnostic classifications in the clinical diagnosis of autistic spectrum disorder. J Autism Dev Disord 2017;47:101-9. [Crossref] [PubMed]
8. Huerta M, Bishop SL, Duncan A, et al. Application of DSM-5 criteria for autism spectrum disorder to three samples of children with DSM-IV diagnoses of pervasive developmental disorders. Am J Psychiatry 2012;169:1056-64. [Crossref] [PubMed]
9. Sturmey P, Dalfern S. The effects of DSM5 autism diagnostic criteria on number of individuals diagnosed with autism spectrum disorders: a systematic review. Rev J Autism Dev Disord 2014;1:249-52. [Crossref]
10. Hartley-McAndrew M, Mertz J, Hoffman M, et al. Rates of autism spectrum disorder diagnosis under the DSM-5 criteria compared to DSM-IV-TR criteria in a hospital-based clinic. Pediatr Neurol 2016;57:34-8. [Crossref] [PubMed]
11. de Giambattista C, Ventura P, Trerotoli P, et al. Subtyping the autism spectrum disorder: comparison of children with high functioning autism and asperger syndrome. J Autism Dev Disord 2019;49:138-50. [Crossref] [PubMed]
12. Mazurek MO, Lu F, Symecko H, et al. A prospective study of the concordance of DSM-IV and DSM-5 diagnostic criteria for autism spectrum disorder. J Autism Dev Disord 2017;47:2783-94. [Crossref] [PubMed]
13. Gibbs V, Aldridge F, Chandler F, et al. Brief report: an exploratory study comparing diagnostic outcomes for autism spectrum disorders under DSM-IV-TR with the proposed DSM-5 revision. J Autism Dev Disord 2012;42:1750-6. [Crossref] [PubMed]
14. Lai MC, Lombardo MV, Chakrabarti B, et al. Subgrouping the autism "spectrum": reflections on DSM-5. PLoS Biol 2013;11:e1001544. [Crossref] [PubMed]
15. Mandy W, Wang A, Lee I, et al. Evaluating social (pragmatic) communication disorder. J Child Psychol Psychiatry 2017;58:1166-75. [Crossref] [PubMed]
16. Baxter AJ, Brugha TS, Erskine HE, et al. The epidemiology and global burden of autism spectrum disorders. Psychol Med 2015;45:601-13. [Crossref] [PubMed]
17. Palinkas LA, Mendon SJ, Hamilton AB. Annual review of public health innovations in mixed methods evaluations. Annu Rev Public Heal 2019;40:423-42. [Crossref]
18. Kogan MD, Vladutiu CJ, Schieve LA, et al. The prevalence of parent-reported autism spectrum disorder among US children. Pediatrics 2018;142:e20174161. [Crossref] [PubMed]
19. Xu G, Strathearn L, Liu B, et al. Prevalence of autism spectrum disorder among US children and adolescents, 2014-2016. JAMA 2018;319:81. [Crossref] [PubMed]
20. Mandell DS, Barry CL, Marcus SC, et al. Effects of autism spectrum disorder insurance mandates on the treated prevalence of autism spectrum disorder. JAMA Pediatr 2016;170:887-93. [Crossref] [PubMed]
21. Hansen SN, Schendel DE, Parner ET. Explaining the increase in the prevalence of autism spectrum disorders: the proportion attributable to changes in reporting practices. JAMA Pediatr 2015;169:56-62. [Crossref] [PubMed]
22. Demily C, Poisson A, Peyroux E, et al. Autism spectrum disorder associated with 49,XYYYY: case report and review of the literature. BMC Med Genet 2017;18:9. [Crossref] [PubMed]
23. Tartaglia NR, Wilson R, Miller JS, et al. Autism spectrum disorder in males with sex chromosome aneuploidy: XXY/klinefelter syndrome, XYY, and XXYY. J Dev Behav Pediatr 2017;38:197-207. [Crossref] [PubMed]
24. Loomes R, Hull L, Mandy WPL. What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. J Am Acad Child Adolesc Psychiatry 2017;56:466-74. [Crossref] [PubMed]
25. Volkmar F, Siegel M, Woodbury-Smith M, et al. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry 2014;53:237-57. [Crossref] [PubMed]
26. Bargiela S, Steward R, Mandy W. The experiences of late-diagnosed women with autism spectrum conditions: an investigation of the female autism phenotype. J Autism Dev Disord 2016;46:3281-94. [Crossref] [PubMed]
27. Sztainberg Y, Zoghbi HY. Lessons learned from studying syndromic autism spectrum disorders. Nat Neurosci 2016;19:1408-17. [Crossref] [PubMed]
28. Johnson CP, Myers SM. Identification and evaluation of children with autism spectrum disorders. Pediatrics 2007;120:1183-215. [Crossref] [PubMed]
29. Reddy KS. Cytogenetic abnormalities and fragile-X syndrome in autism spectrum disorder. BMC Med Genet 2005;6:3. [Crossref] [PubMed]
30. Yoo H. Genetics of autism spectrum disorder: current status and possible clinical applications. Exp Neurobiol 2015;24:257. [Crossref] [PubMed]

31. Ross JL, Roeltgen DP, Kushner H, et al. Behavioral and social phenotypes in boys with 47,XYY syndrome or 47,XXY klinefelter syndrome. Pediatrics 2012;129:769-78. [Crossref] [PubMed]
32. Bardsley MZ, Kowal K, Levy C, et al. 47,XYY syndrome: clinical phenotype and timing of ascertainment. J Pediatr 2013;163:1085-94. [Crossref] [PubMed]
33. Durkin MS, Maenner MJ, Newschaffer CJ, et al. Advanced parental age and the risk of autism spectrum disorder. Am J Epidemiol 2008;168:1268-76. [Crossref] [PubMed]
34. Agrawal S, Rao SC, Bulsara MK, et al. Prevalence of autism spectrum disorder in preterm infants: a meta-analysis. Pediatrics 2018;142:e20180134. [Crossref] [PubMed]
35. Wang C, Geng H, Liu W, et al. Prenatal, perinatal, and postnatal factors associated with autism: a meta-analysis. Medicine (Baltimore) 2017;96:e6696. [Crossref] [PubMed]
36. Parner ET, Baron-Cohen S, Lauritsen MB, et al. Parental age and autism spectrum disorders. Ann Epidemiol 2012;22:143-50. [Crossref] [PubMed]
37. Skefos J, Cummings C, Enzer K, et al. Regional alterations in Purkinje cell density in patients with autism. PLoS One 2014;9:e81255. [Crossref] [PubMed]
38. Stoodley CJ, D'Mello AM, Ellegood J, et al. Altered cerebellar connectivity in autism and cerebellar-mediated rescue of autism-related behaviors in mice. Nat Neurosci 2017;20:1744-51. [Crossref] [PubMed]
39. De Rubeis S, He X, Goldberg AP, et al. Synaptic, transcriptional and chromatin genes disrupted in autism. Nature 2014;515:209-15. [Crossref] [PubMed]
40. Shen MD, Kim SH, McKinstry RC, et al. Increased extra-axial cerebrospinal fluid in high-risk infants who later develop autism. Biol Psychiatry 2017;82:186-93. [Crossref] [PubMed]
41. Hazlett HC, Gu H, Munsell BC, et al. Early brain development in infants at high risk for autism spectrum disorder. Nature 2017;542:348-51. [Crossref] [PubMed]
42. Kim H, Keifer C, Rodriguez-Seijas C, et al. Quantifying the optimal structure of the autism phenotype: a comprehensive comparison of dimensional, categorical, and hybrid models. J Am Acad Child Adolesc Psychiatry 2019;58:876-86.e2. [Crossref] [PubMed]
43. Sandin S, Lichtenstein P, Kuja-Halkola R, et al. The familial risk of autism. JAMA 2014;311:1770-7. [Crossref] [PubMed]
44. Risch N, Hoffmann TJ, Anderson M, et al. Familial recurrence of autism spectrum disorder: Evaluating genetic and environmental contributions. Am J Psychiatry 2014;171:1206-13. [Crossref] [PubMed]
45. Walsh CA, Morrow EM, Rubenstein JLR. Autism and brain development. Cell 2008;135:396-400. [Crossref] [PubMed]
46. Rubenstein JL, Merzenich MM. Model of autism: increased ratio of excitation/inhibition in key neural systems. Genes Brain Behav 2003;2:255-67. [Crossref] [PubMed]
47. McDougle CJ, Erickson CA, Stigler KA, et al. Neurochemistry in the pathophysiology of autism. J Clin Psychiatry 2005;66 Suppl 10:9-18. [PubMed]
48. Zoghbi HY. Postnatal neurodevelopmental disorders: meeting at the synapse? Science 2003;302:826-30. [Crossref] [PubMed]
49. Voineagu I, Wang X, Johnston P, et al. Transcriptomic analysis of autistic brain reveals convergent molecular pathology. Nature 2011;474:380-4. [Crossref] [PubMed]
50. Ladd-Acosta C, Hansen KD, Briem E, et al. Common DNA methylation alterations in multiple brain regions in autism. Mol Psychiatry 2014;19:862-71. [Crossref] [PubMed]
51. Sun W, Poschmann J, Cruz-Herrera Del Rosario R, et al. Histone acetylome-wide association study of autism spectrum disorder. Cell 2016;167:1385-97.e11. [Crossref] [PubMed]
52. Ruzzo EK, Pérez-Cano L, Jung JY, et al. Inherited and de novo genetic risk for autism impacts shared networks. Cell 2019;178:850-66.e26. [Crossref] [PubMed]
53. Saxena A, Chahrour M. Autism spectrum disorder. In: Ginsburg GS, Willard HF, David SP. editors. Genomic and precision medicine: primary care. Cambridge: Academic Press, 2017:301-16.
54. Veenstra-Vanderweele J, Christian SL, Cook EH Jr. Autism as a paradigmatic complex genetic disorder. Annu Rev Genomics Hum Genet 2004;5:379-405. [Crossref] [PubMed]
55. Surén P, Roth C, Bresnahan M, et al. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. JAMA 2013;309:570-7. [Crossref] [PubMed]
56. Bjørk M, Riedel B, Spigset O, et al. Association of folic acid supplementation during pregnancy with the risk of autistic traits in children exposed to antiepileptic drugs in utero. JAMA Neurol 2018;75:160. [Crossref] [PubMed]
57. Rasalam AD, Hailey H, Williams JHG, et al. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. Dev Med Child Neurol 2005;47:551-5. [Crossref] [PubMed]
58. Frye RE, Slattery J, Delhey L, et al. Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial. Mol Psychiatry 2018;23:247-56. [Crossref] [PubMed]
59. Croen LA, Najjar DV, Fireman B, et al. Maternal and paternal age and risk of autism spectrum disorders. Arch Pediatr Adolesc Med 2007;161:334-40. [Crossref] [PubMed]
60. Xiang AH, Wang X, Martinez MP, et al. Maternal type 1 diabetes and risk of autism in offspring. JAMA 2018;320:89-91. [Crossref] [PubMed]
61. Croen LA, Grether JK, Yoshida CK, et al. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. Arch Pediatr Adolesc Med 2005;159:151-7. [Crossref] [PubMed]
62. Malkova NV, Yu CZ, Hsiao EY, et al. Maternal immune activation yields offspring displaying mouse versions of the three core symptoms of autism. Brain Behav Immun 2012;26:607-16. [Crossref] [PubMed]
63. Estes ML, McAllister AK. Immune mediators in the brain and peripheral tissues in autism spectrum disorder. Nat Rev Neurosci 2015;16:469-86. [Crossref] [PubMed]
64. Choi GB, Yim YS, Wong H, et al. The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. Science 2016;351:933-9. [Crossref] [PubMed]
65. Croen LA, Qian Y, Ashwood P, et al. Infection and fever in pregnancy and autism spectrum disorders: findings from the study to explore early development. Autism Res 2019. [Epub ahead of print]. [PubMed]

66. Schieve LA, Tian LH, Drews-Botsch C, et al. Autism spectrum disorder and birth spacing: findings from the study to explore early development (SEED). Autism Res 2018;11:81-94. [Crossref] [PubMed]
67. Newschaffer CJ, Croen LA, Daniels J, et al. The epidemiology of autism spectrum disorders. Annu Rev Public Health 2007;28:235-58. [Crossref] [PubMed]
68. Taylor LE, Swerdfeger AL, Eslick GD. Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. Vaccine 2014;32:3623-9. [Crossref] [PubMed]
69. Uno Y, Uchiyama T, Kurosawa M, et al. Early exposure to the combined measles-mumps-rubella vaccine and thimerosal-containing vaccines and risk of autism spectrum disorder. Vaccine 2015;33:2511-6. [Crossref] [PubMed]
70. Hviid A, Hansen JV, Frisch M, et al. Measles, mumps, rubella vaccination and autism a nationwide cohort study. Ann Intern Med 2019;170:513-20. [Crossref] [PubMed]
71. Ellerbeck K, Smith C, Courtemanche A. Care of children with autism spectrum disorder. Prim Care 2015;42:85-98. [Crossref] [PubMed]
72. Robins DL, Casagrande K, Barton M, et al. Validation of the modified checklist for autism in toddlers, revised with follow-up (M-CHAT-R/F). Pediatrics 2014;133:37-45. [Crossref] [PubMed]
73. Smith NJ, Sheldrick RC, Perrin EC. An abbreviated screening instrument for autism spectrum disorders. Infant Ment Health J 2013;34:149-55. [Crossref]
74. Ehlers S, Gillberg C, Wing L. A screening questionnaire for Asperger syndrome and other high- functioning autism spectrum disorders in school age children. J Autism Dev Disord 1999;29:129-41. [Crossref] [PubMed]
75. Rutter M, Bailey A, Lord CM. The social communication questionnaire. Los Angeles: Western Psychological Services, 2003.
76. Constantino JN, Gruber CP. Social responsiveness scale (SRS). Los Angeles: Western Psychological Services, 2005.
77. Huerta M, Lord C. Diagnostic evaluation of autism spectrum disorders. Pediatr Clin North Am 2012;59:103-11. [Crossref] [PubMed]
78. Lord C, Rutter M, DiLavore P, et al. Autism diagnostic observation schedule, second edition. Torrance: Western Psychological Services, 2012.
79. Levy SE, Giarelli E, Lee LC, et al. Autism spectrum disorder and co-occurring developmental, psychiatric, and medical conditions among children in multiple populations of the United States. J Dev Behav Pediatr 2010;31:267-75. [Crossref] [PubMed]
80. Yeargin-Allsopp M, Rice C, Karapurkar T, et al. Prevalence of autism in a US metropolitan area. JAMA 2003;289:49-55. [Crossref] [PubMed]
81. Soke GN, Maenner MJ, Christensen D, et al. Prevalence of co-occurring medical and behavioral conditions/symptoms among 4- and 8-year-old children with autism spectrum disorder in selected areas of the United States in 2010. J Autism Dev Disord 2018;48:2663-76. [Crossref] [PubMed]
82. Kohane IS, McMurry A, Weber G, et al. The co-morbidity burden of children and young adults with autism spectrum disorders. PLoS One 2012;7:e33224. [Crossref] [PubMed]
83. Kielinen M, Rantala H, Timonen E, et al. Associated medical disorders and disabilities in children with autistic disorder: A population-based study. Autism 2004;8:49-60. [Crossref] [PubMed]
84. Curtin C, Anderson SE, Must A, et al. The prevalence of obesity in children with autism: a secondary data analysis using nationally representative data from the National Survey of Children's Health. BMC Pediatr 2010;10:11. [Crossref] [PubMed]
85. Tuchman R, Rapin I. Epilepsy in autism. Lancet Neurol 2002;1:352-8. [Crossref] [PubMed]
86. Ewen JB, Marvin AR, Law K, et al. Epilepsy and autism severity: a study of 6,975 children. Autism Res 2019;12:1251-9. [Crossref] [PubMed]
87. Amiet C, Gourfinkel-An I, Bouzamondo A, et al. Epilepsy in autism is associated with intellectual disability and gender: evidence from a meta-analysis. Biol Psychiatry 2008;64:577-82. [Crossref] [PubMed]
88. Alabaf S, Gillberg C, Lundström S, et al. Physical health in children with neurodevelopmental disorders. J Autism Dev Disord 2019;49:83-95. [Crossref] [PubMed]
89. Ibrahim SH, Voigt RG, Katusic SK, et al. Incidence of gastrointestinal symptoms in children with autism: a population-based study. Pediatrics 2009;124:680-6. [Crossref] [PubMed]
90. Reynolds AM, Soke GN, Sabourin KR, et al. Sleep problems in 2- to 5-year-olds with autism spectrum disorder and other developmental delays. Pediatrics 2019;143:e20180492. [Crossref] [PubMed]
91. Krakowiak P, Goodlin-Jones B, Hertz-Picciotto I, et al. Sleep problems in children with autism spectrum disorders, developmental delays, and typical development: a population-based study. J Sleep Res 2008;17:197-206. [Crossref] [PubMed]
92. Polimeni MA, Richdale AL, Francis AJ. A survey of sleep problems in autism, Asperger's disorder and typically developing children. J Intellect Disabil Res 2005;49:260-8. [Crossref] [PubMed]
93. Hill AP, Zuckerman KE, Fombonne E. Obesity and autism. Pediatrics 2015;136:1051-61. [Crossref] [PubMed]
94. Lecavalier L, McCracken CE, Aman MG, et al. An exploration of concomitant psychiatric disorders in children with autism spectrum disorder. Compr Psychiatry 2019;88:57-64. [Crossref] [PubMed]
95. Hollocks MJ, Lerh JW, Magiati I, et al. Anxiety and depression in adults with autism spectrum disorder: a systematic review and meta-analysis. Psychol Med 2019;49:559-72. [Crossref] [PubMed]
96. Miller DT. Genetic testing for autism: recent advances and clinical implications. Expert Rev Mol Diagn 2010;10:837-40. [Crossref] [PubMed]
97. Schaefer GB, Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med 2013;15:399-407. [Crossref] [PubMed]
98. Shen Y, Dies KA, Holm IA, et al. Clinical genetic testing for patients with autism spectrum disorders. Pediatrics 2010;125:e727-35. [Crossref] [PubMed]
99. Filipek PA, Accardo PJ, Ashwal S, et al. Practice parameter: screening and diagnosis of autism. Report of the quality standards subcommittee of the American Academy of Neurology and the Child Neurology Society. Neurology 2000;55:468-79. [Crossref] [PubMed]

100. Srivastava S, Love-Nichols JA, Dies KA, et al. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. Genet Med 2019. [Epub ahead of print]. [Crossref] [PubMed]

101. Feliciano P, Zhou X, Astrovskaya I, et al. Exome sequencing of 457 autism families recruited online provides evidence for autism risk genes. NPJ Genom Med 2019;4:19. [Crossref] [PubMed]

102. American Academy of Pediatrics. Autism – caring for children with autism spectrum disorders: a resource toolkit for clinicians. 3rd ed. Itasca: American Academy of Pediatrics, 2019.

103. Shannon M, Graef JW. Lead intoxication in children with pervasive developmental disorders. J Toxicol Clin Toxicol 1996;34:177-81. [Crossref] [PubMed]

104. Dosman C, Witmans M, Zwaigenbaum L. Iron's role in paediatric restless legs syndrome - a review. Paediatr Child Health 2012;17:193-7. [Crossref] [PubMed]