# Introduction to Autism Spectrum Disorders (ASDs): Genetic and Environmental Risk Factors, Treatments

Jingran Ye(✉)

University College London, London, UK
zcbtyex@ucl.ac.uk

**Abstract.** Nowadays, autism has received extensive attention from society. The aim of this review is to summarize some common genetic and environmental risk factors that lead to autism, as well as the following effective psychotherapy for autism. Autism is a heterogeneous disorder with high heritability. Vitamin D deficiency during the gestation period increases the risk of autism in children. Meanwhile, other environmental risk factors including adverse childhood experiences, family socioeconomic status, parental and maternal age, prenatal drug uptake during pregnancy, and sleep problems (such as sleep onset delay, and night waking) lead to an increased risk of autism or more severe autism symptoms. At the same time, several intervention therapies have been reported such as neurofeedback training and speech therapy, applying zonisamide, musical therapies, and dolphin-assisted therapy. These treatments can effectively relieve autism symptoms.

**Keywords:** Autism · Adverse Childhood Experiences · Socioeconomic Status · Sleep · Therapies

## 1 Introduction

After Leo Kanner first discovered and described autism in 1943, autism spectrum disorder has gone from a rare, unclear disorder to a well-researched, widely concerned, heterogeneous disorder. Basically, autism spectrum disorder is a neurobiological abnormality. It is a complex disability caused by a variety of genetic and environmental factors. The diversity in the induced causes contributes to the diversity in autism features in different people. ASD patients usually appear repetitive behaviours and have difficulties in communication and social interactions [1]. A spectrum disorder usually refers to manifestations that defer from person to person, for example, the different patients can present different characteristics and the same patient can give different responses at different times [2]. Autism patients have a wide range of characteristics. The main features are repetitive behaviours, limited language skills, resistance to social interactions, and lack of interest; other common signs like resistance to changes, difficulties in understanding other's emotions, avoiding hugs, and increased sensitivity to sound, texture or smell


G. Ali et al. (Eds.): ISEMSS 2022, ASSEHR 687, pp. 406–413, 2022.
https://doi.org/10.2991/978-2-494069-31-2_52

[3]. Those changes hinder the patients' social ability and correct emotional expression and perception, which lead to huge differences and inconvenience in the life of ASD patients and their families. Thus, even though ASD is a mental, biological disorder, it needs educational and behavioural services as intervention treatment with medication as an adjunct.

## 2 Genetic

Genetic risk factors usually cause permanent, and incurable autism. People born with autism can be relieved to some extent but hard to be cured completely.

### 2.1 Heritability

Autism is a highly inherited genetic disorder which is proved by sibling experiments and twin studies. For instance, in a 2011 largest population-based twin study, scientists concluded that the autism heritability was estimated to be 55% [4]. This figure increased to 74–93% in a 2015 study [5]. Sibling studies reveal that 7–20% of subsequent children are diagnosed with ASD after the elder child is diagnosed with ASD [6]. As the technology develops, more genes are found to be associated with autism, most of them are coded for proteins involved in neural development and are important for neuron communications or controlling other genes' expression [7]. There are 400 genes found to be strongly linked with ASD and 200 genes weekly lined, but it is still hard to ensure the influence of each gene on ASD as the mutation that increases autism risk has not been identified. Autism is a highly heritable disorder with diverse genetic architecture. This is due to the difference in alleles frequencies. Dominant inheritance is the most common variant type, and the variant types include copy number variants (CNV), insertion, deletion, duplication, and single-nucleotide variants (SNVs) [8]. Moreover, the remarkably distinct clinical expression of autism can be explained by the genetic variation and differences in epigenetic influences [7].

### 2.2 Vitamin D

More recent research shows that Vitamin D deficiency [25(OH)D $<$ 40 ng/ml] during the gestation period leads to an increased risk of autism [9]. Vitamin D is an active neurosteroid that takes part in brain development, affecting cellular differentiation, proliferation, calcium signalling, synaptic plasticity, and neurotrophic and neuroprotective actions [9]. The relation between vitamin D and autism is proved by several studies and research, for example, in 2017, scientists investigated the association between mid-gestational vitamin D deficiency and ASD. Based on 4334 children and their mothers including 68 children being diagnosed with ASD, the subjects with vitamin D deficiency at the mid-gestational period had a more than the twofold increased risk of ASD compared with the control group [10]. Also, in 2018 International Society for Autism Research, researchers pointed out that children born with low levels of vitamin D have 33% more risks than those born with normal vitamin D levels. More similar studies reinforce the relationship between vitamin D and autism.

## 3 Environmental

Autism developed due to environmental risk factors after born is usually curable, it can be greatly relieved or completely cured by medicine and certain treatments. Those environmental factors include:

### 3.1 Adverse Childhood Experiences (ACEs)

Mounting evidence proves that negative early life experiences lead to a higher chance of developing ASD, especially the childhood experiences with families. Rigles (2016) suggested that adverse childhood experiences are negatively associated with children's mental health [11]. Adverse childhood experiences are potentially traumatic events which can cause long-lasting negative effects on mental health when the child grows up. The more adversities experienced early in life, the higher the probability to develop serious problems in mental and physical health later in life. Those Adverse Childhood Experiences (ACEs) include all types of abuse, experiencing physical or emotional neglect, experiencing the death of family members, and experiencing parent divorce after he/she was born [12]. The massive stress and trauma as well as poor self-esteem and lack of motivation caused by ACEs are the reason for developing core symptoms of autism with psychiatric comorbidities such as depression or anxiety [13]. Several studies reported the relationship between exposure to ACEs in childhood and white matter microstructural disruption. For instance, in animal studies, hypomyelination in the prefrontal cortex of mice can be induced by childhood stress like social isolation or traumatic stress [14]; in human studies, neglect in childhood is related to deteriorated frontal white matter microstructure [15], and white matter microstructural abnormality of the left arcuate fasciculus is caused by parental verbal abuse in childhood [16]. Subsequently, ACEs like exposure to neglect and emotional abuse in childhood were significantly important for the development of white matter in ASD. ACE exposures can affect the anterior thalamic radiation (ATR) easily which then affects the white matter microstructural disruption in ASD. The ATR dysconnectivity which represents cortico-thalamic network dysfunction is related to emotional dysregulation and cognitive dysfunction, which eventually lead to psychological symptoms in adults with ASD. Also, the exposure to neglect in childhood is related to white matter abnormality in the prefrontal cortex, which increases the risk of psychiatric comorbidities in ASD adults [17]. Meanwhile, recent research has shown that ASD is highly associated with one or more ACEs: the more ACEs experienced, the higher probability of developing ASD, and among the children who are exposed to four or more ACEs, the number of autistic children is twice as high compared to healthy children.

### 3.2 Socioeconomic Status (SES)

Socioeconomic status is a combination of economic and sociological aspects which used to measure an individual's or family's social position, economic access to all kinds of resources and educational achievement [18]. Scientists found that the socioeconomic status of parent-carers is also an important environmental factor affecting the development of childhood autism, but interestingly, the effect of SES on ASD prevalence varies

from geographic region and culture. In the United States, data show that higher SES and higher parental education levels lead to earlier and higher ASD [19]. The same association between higher parental education level and a higher ASD diagnosis is found in the United Kingdom, where researchers found that the probability of ASD diagnosis of children of higher education status mothers (A-level or above) is twice greater than that of children of low education mothers [20]. However, in China, children with low SES families tend to have a higher risk of developing childhood autism [21].

### 3.3 Pregnancy-Related

One of the most important risk factors is parental and maternal age. Several studies proved that parents aged older than or equal to 34 years have a higher risk of offspring autism [7]. Especially, the advanced parental age increases the risk of childhood autism. For instance, the 2010 studies revealed that for every ten-year increase in a father's age, the risk of autism increases by 29% [22]. The advanced father's age disrupts the function of immune systems, thus affecting the offspring's nervous system development, and consequently causes a high probability of neural impairments like autism [7].

Besides, the use of drugs and prenatal medications during pregnancy significantly increases the risk of developing autism, those drugs may pass through the placenta and affect fetal development. For instance, studies show that the probability of having ASD in children exposed in utero to valproate is 8 times higher than those in utero without valproate [23]. Also, paracetamol, commonly used as an analgesic drug, can cause oxidative stress, immune dysregulation, and cellular apoptosis which matches the legions observed in autistic brains [24]. The use of such psychiatric drugs gives a 68% increase in the autism risk, and the use of other medications like painkillers or thalidomide during pregnancy also shows increased susceptibility to ASD [7].

### 3.4 Sleep

Sleep problems including sleep onset delay and sleep duration are reported to be significantly associated with autism in children. A study on children aged between 3 to 5 years showed that 53% of autistic children have serious sleep problems [25]. Mounting researchers have reported the fact that autistic children experience a wide variety of sleep problems like frequent night wakings, prolonged sleep onset, and reduced sleeping time [26]. A 2012 study collecting data from 109 autistic children suggested a positive correlation between sleep problems and autism symptoms. They found out that insufficient sleep time caused by night waking and sleep onset delay lead to severe autism symptoms. The delayed sleep onset can significantly predict communication deficit, stereotyped behaviour, and autism severity [26]. Meanwhile, parasomnias can be a significant sign of communication symptoms and overall autism severity [27]. And the problem with sleep-disordered breathing was also related to communication symptoms [27]. Conversely, better sleep can effectively reduce the symptom severity of children with autism. Thus, treatment of sleep problems can be an effective intervention therapy for children with autism, improving ASD patients' quality of life as well as their families.

## 4 Treatments

Although there is no drug invented that can completely cure autism, more psychotherapy methods have been developed and used to treat autism effectively. In 2008, Dawson pointed out that intervention can improve the social engagement and reciprocity of ASD patients [28]. Enhanced parent-child interactions can improve toddlers' communication skills. Autistic children have a relatively low concentration of cysteine, methionine, and glutathione, and low levels of cystine lead to high oxidative stress, thus Ghanizadeh pointed out that applying zonisamide to ASD children can improve the influx of cystine to reduce the oxidative stress [29]. At the same time, scientists proved that musical therapies are also an effective treatment for verbal communication. Because the left inferior frontal gyrus in ASD patients is largely activated when stimulated by songs, but no reaction during speech stimulation [30]. There are few cases in which ASD patients show extraordinary talents in arts or music fields. Karimi et al. (2011) suggested neurofeedback training (NFT) and speech therapy for ASD patients, which is effective in the improvement of patients' learning and speech ability [31]. Cai et al. (2013) reported that virtual reality technology applications as an effective intervention and treatment for promoting learning and positive behaviours in ASD children [32]. They invented Dolphin-assisted therapy which teaches children to communicate through hand gestures with a virtual dolphin.

## 5 Conclusion

Continuous research enables people to have a more comprehensive understanding of autism and its pathogenesis and treatment. More details and aspects of genetic and environmental risk factors of autism are acknowledged, thus more effective therapies are invented to relieve autism. These findings have greatly improved the status and lives of people with autism. More people with autism can communicate normally, make friends and integrate into the community. The situation of ASD patients will continue to improve through more cooperation with schools, community, and families and more understanding and tolerance from the public. A world where ASD patients are no longer troubled by autism will come sooner or later.

## References

1. Szego, M. J., & Zawati, M. H. (2016). Whole Genome Sequencing as a Genetic Test for Autism Spectrum Disorder: From Bench to Bedside and then Back Again. Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l'Academie canadienne de psychiatrie de l'enfant et de l'adolescent, 25(2), 116–121.
2. Wing, L., Gould, J., & Gillberg, C. (2011). Autism spectrum disorders in the DSM-V: Better or worse than the DSM-IV? Research in Developmental Disabilities, 32(2), 768–773. https://doi.org/10.1016/j.ridd.2010.11.003
3. Public Health Agency of Canada. (2022, April 7). Autism: Signs and symptoms. Canada.Ca. https://www.canada.ca/en/public-health/services/diseases/autism-spectrum-disorder-asd/signs-symptoms-autism-spectrum-disorder-asd.html

4. Hallmayer J, Cleveland S, Torres A, et al. Genetic Heritability and Shared Environmental Factors Among Twin Pairs With Autism. Arch Gen Psychiatry. 2011;68(11):1095–1102. doi:https://doi.org/10.1001/archgenpsychiatry.2011.76
5. Tick, B., Bolton, P., Happé, F., Rutter, M., & Rijsdijk, F. (2015). Heritability of autism spectrum disorders: A meta-analysis of twin studies. Journal of Child Psychology and Psychiatry, 57(5), 585–595. https://doi.org/10.1111/jcpp.12499
6. Sandin, S., Lichtenstein, P., Kuja-Halkola, R., Larsson, H., Hultman, C. M., & Reichenberg, A. (2014). The familial risk of autism. JAMA, 311(17), 1770. https://doi.org/10.1001/jama.2014.4144
7. Styles, M., Alsharshani, D., Samara, M., Alsharshani, M., Khattab, A., Qoronfleh, M. W., & Al-Dewik, N. I. (2020). Risk factors, diagnosis, prognosis and treatment of autism. Frontiers in bioscience (Landmark edition), 25(9), 1682–1717. https://doi.org/10.2741/4873
8. De Rubeis, S., & Buxbaum, J. D. (2015). Genetics and genomics of autism spectrum disorder: Embracing complexity. Human Molecular Genetics, 24(R1), R24–R31. https://doi.org/10.1093/hmg/ddv273
9. Cannell, J. J. (2017). Vitamin D and autism, what's new? Reviews in Endocrine and Metabolic Disorders, 18(2), 183–193. https://doi.org/10.1007/s11154-017-9409-0
10. Vinkhuyzen, A., Eyles, D., Burne, T., Blanken, L., Kruithof, C., Verhulst, F., McGrath, J. (2017). Gestational vitamin D deficiency and autism spectrum disorder. BJPsych Open, 3(2), 85-90. doi:https://doi.org/10.1192/bjpo.bp.116.004077
11. Rigles B. The Relationship Between Adverse Childhood Events, Resiliency and Health Among Children with Autism. Journal of Autism and Developmental Disorders. 2016 doi: https://doi.org/10.1007/s10803-016-2905-3
12. Hoover, D. W., & Kaufman, J. (2018). Adverse childhood experiences in children with autism spectrum disorder. Current Opinion in Psychiatry, 31(2), 128–132. https://doi.org/10.1097/yco.0000000000000390
13. Brenner J, Pan Z, Mazefsky C, Smith KA, Gabriels R, Autism and Developmental Disorders Inpatient Research Collaborative (ADDIRC). Behavioral symptoms of reported abuse in children and adolescents with autism spectrum disorder in inpatient settings. J Autism Dev Disord. (2018) 48:3727–35. doi: https://doi.org/10.1007/s10803-017-3183-4
14. Liu J, Dietz K, DeLoyht JM, Pedre X, Kelkar D, Kaur J, et al. Impaired adult myelination in the prefrontal cortex of socially isolated mice. Nat Neurosci. (2012) 15:1621–3. doi: https://doi.org/10.1038/nn.3263
15. Lim L, Howells H, Radua J, Rubia K. Aberrant structural connectivity in childhood maltreatment: a meta-analysis. Neurosci Biobehav Rev. (2020) 116:406–14. doi: https://doi.org/10.1016/j.neubiorev.2020.07.004
16. Samson AC, Dougherty RF, Lee IA, Phillips JM, Gross JJ, Hardan AY. White matter structure in the uncinate fasciculus: Implications for socio-affective deficits in autism spectrum disorder. Psychiatry Res Neuroimaging. (2016) 255:66–74. doi: https://doi.org/10.1016/j.pscychresns.2016.08.004
17. Yoshikawa, H., Kitamura, S., Matsuoka, K., Takahashi, M., Ishida, R., Kishimoto, N., Yasuno, F., Yasuda, Y., Hashimoto, R., Miyasaka, T., Kichikawa, K., Kishimoto, T., & Makinodan, M. (2022). Adverse childhood experience is associated with disrupted white matter integrity in autism spectrum disorder: A diffusion tensor imaging study. Frontiers in Psychiatry, 12. https://doi.org/10.3389/fpsyt.2021.823260
18. Oakes, J. M., & Rossi, P. H. (2003). The measurement of SES in health research: Current practice and steps toward a new approach. Social Science & Medicine, 56(4), 769–784. https://doi.org/10.1016/s0277-9536(02)00073-4
19. Mazurek, M. O., Handen, B. L., Wodka, E. L., Nowinski, L., Butter, E., & Engelhardt, C. R. (2014). Age at first autism spectrum disorder diagnosis. Journal of Developmental & Behavioral Pediatrics, 35(9), 561–569. https://doi.org/10.1097/dbp.0000000000000097

20. Kelly, B., Williams, S., Collins, S., Mushtaq, F., Mon-Williams, M., Wright, B., Mason, D., & Wright, J. (2017). The association between socioeconomic status and autism diagnosis in the United Kingdom for children aged 5–8 years of age: Findings from the Born in Bradford cohort. Autism, 23(1), 131–140. https://doi.org/10.1177/1362361317733182
21. He, P., Guo, C., Wang, Z., Chen, G., Li, N., & Zheng, X. (2018). Socioeconomic status and childhood autism: A population-based study in China. Psychiatry Research, 259, 27–31. https://doi.org/10.1016/j.psychres.2017.08.046
22. Sasanfar, R., Haddad, S. A., Tolouei, A., Ghadami, M., Yu, D., & Santangelo, S. L. (2010). Paternal age increases the risk for autism in an Iranian population sample. Molecular Autism, 1(1). https://doi.org/10.1186/2040-2392-1-2
23. Rasalam, A., Hailey, H., Williams, J., Moore, S., Turnpenny, P., Lloyd, D., & Dean, J. (2005). Characteristics of fetal anticonvulsant syndrome associated autistic disorder. Developmental Medicine & Child Neurology, 47(8), 551–555. https://doi.org/10.1017/s0012162205001076
24. Bauer, A. Z., & Kriebel, D. (2013). Prenatal and perinatal analgesic exposure and autism: An ecological link. Environmental Health, 12(1). https://doi.org/10.1186/1476-069x-12-41
25. Krakowiak, P., Goodlin-Jones, B., Hertz-Picciotto, I., Croen, L. A., & Hansen, R. L. (2008). Sleep problems in children with autism spectrum disorders, developmental delays, and typical development: A population-based study. Journal of Sleep Research, 17(2), 197–206. https://doi.org/10.1111/j.1365-2869.2008.00650.x
26. Tudor, M. E., Hoffman, C. D., & Sweeney, D. P. (2012). Children with autism. Focus on Autism and Other Developmental Disabilities, 27(4), 254–262. https://doi.org/10.1177/1088357612457989
27. Hoffman, C. D., Sweeney, D. P., Gilliam, J. E., Apodaca, D. D., Lopez-Wagner, M. C., & Castillo, M. M. (2005). Sleep problems and symptomology in children with autism. Focus on Autism and Other Developmental Disabilities, 20(4), 194–200. https://doi.org/10.1177/10883576050200040101
28. Dawson, G. (2008). Early behavioral intervention, brain plasticity and the prevention of autism spectrum disorder. Dev. Psycho- pathol. 20, 775–803.
29. Ghanizadeh, A. (2011). A novel hypothesized clinical implication of zonisamide for autism. Ann. Neurol. 69, 426.
30. Lai, G., Pantazatos, S.P., Schneider, H., and Hirsch, J. (2012). Neural systems for speech and song in autism. Brain 135, 961–975.
31. Karimi, M., Haghshenas, S., and Rostami, R. (2011). Neurofeedback and autism spectrum: a case study. Procedia Soc. Behav. Sci. 30, 1472–1475.
32. Cai, Y., Chia, N.K.H., Thalmann, D., Kee, N.K.N., Zheng, J., Thalmann, N.M. (2013). Design and development of a virtual dolphinarium for children with autism. IEEE Trans. Neural Syst. Rehabil. Eng. 21, 208–217.