



Risk factors for autism spectrum disorder (ASD)

Several situations or factors are associated with increased prevalence of ASD, though direct causation is difficult to prove. The reason for many of these associations is not fully understood. However, these associations can be viewed as risks for autism, though unfortunately, there is also a lot of misinformation about these risks, particularly regarding vaccines.

Factors associated with increased prevalence of ASD
• Sibling history of autism/ASD • Parental history of schizophrenia-like psychosis or depression • Maternal use of sodium valproate in pregnancy • Male gender • Birth weight <2500gm or gestation <35 weeks • Neonatal encephalopathy • Increased prevalence of ASD in the following conditions: intellectual disability, fragile X syndrome, tuberous sclerosis, cerebral palsy, Down's syndrome, muscular dystrophy, foetal alcohol syndrome, poorly managed phenylketonuria
No evidence of association with parenting, MMR or other vaccinations.

Genetic risk factors

The genetic of autism is described elsewhere, however, it is worth mentioning here some single genes mutation conditions that have a greatly increased risk for autism. These include mutations in *FMR1* (fragile X syndrome), *MECP2* (Rett syndrome), *TSC1/TSC2* (tuberous sclerosis complex), and *CACNA1C* (Timothy syndrome), as well as chromosomal abnormalities such as maternally inherited 15q11–13 duplications (dup15q syndrome), and many others, which may collectively account for 10–15% of all ASD cases.ⁱ

Environmental factors may also interact with genetic factors; for example, patients with phenylketonuria have a high risk of developing ASD and other manifestations of the disease if they consume diets high in phenylalanine.

Environmental risk factors

Potential mechanisms

Environmental toxins can influence brain development at different stages such as cell differentiation, migration, formation of mini-columns, synaptogenesis and myelination. Their effect could be direct or through immune dysregulation or oxidative stress. The toxins could also have an impact through interactions with susceptibility genes, altering their expression or through causing DNA changes and de novo mutations.





Critical periods of susceptibility

Brain is particularly vulnerable to environmental toxins in the first half of the pregnancy. The slide below exemplifies the windows of susceptibility for some of the main groups of toxins that are correlated with a higher risk of development of ASD.

Critical periods of susceptibility indicated from studies of autism spectrum disorders.

Trimester	First									Second			Third	
Gestational Weeks	1	2	3	4	5	6	7	8	9	16	20	22	28	38
														
Brain pathology														
Neurogenesis ^{145,151,152}	Weeks 1-20													
Neuronal migration ^{145, 153}	Weeks 1-16													
Neuronal maturation ^{145,154}	Weeks 1-24													
Exposure														
Freeway proximity ³²													3 rd trimester	
Traffic-related Air Pollution ⁹³	1 st , 2 nd , and 3 rd trimesters													
Pesticides ^{106,110}	Days 26-81													
Prenatal vitamins ¹⁵⁵	1 st month and 3 months before													
Folic acid ^{4,7,29}	1 st Month ⁴													
Rubella infection ^{144, 156}	Weeks 1-8													
Fever ^{142,157}	1 st and 2 nd trimesters													
Thalidomide ¹⁵⁸			Days 20-24											
Valproic Acid ^{8,139}			Day 23-28											
SSRI ^{84,160}	1 st trimester ⁵													
Prenatal stressors ¹⁶¹													Weeks 25-28	

Kristen Lyall et al. Int. J. Epidemiol. 2014;43:443-464

Maternal nutrition

Poor maternal nutrition is an established risk factor for schizophrenia, neural tube defects and adverse developmental outcomes. Then association with ASD has not yet been established. There is weak evidence supporting a linkage of ASD with maternal fatty acid intake. The strongest evidence of a supporting link with ASD is with the lack of folic acid in maternal dietⁱⁱ.

There is some evidence to link maternal smoking, alcohol and recreational drug intake during pregnancy with ASD, but the evidence is inconsistent.

Medicines taken during pregnancy

Valproic acid, an antiepileptic drug that is also used as a mood stabiliser in bipolar disorder and schizophrenia, taken during conception and early pregnancy is linked with a higher prevalence of ASDⁱⁱⁱ.

Metals

A recent study of hazardous air pollutants found a moderate association of autism with estimated airborne metal levels at birth, most notably mercury, cadmium, and nickelⁱⁱⁱ.

Ethyl mercury has been used in medical products, most notably as a preservative (thimerosal) in multi-dose vials of vaccines. Thimerosal contributes to total mercury levels in the blood, but there is little direct evidence of health effects in humans, and expert reviews





have found that available evidence does not support a causal association between thimerosal-containing vaccines and autismⁱⁱⁱ.

Other information about thimerosal:

Information from WHO

Information from CDC (US)

Although lead is a known neurotoxin and studies have found adverse effects of prenatal exposure on growth and development, surprisingly little research has been done with respect to autismⁱⁱⁱ. As a slightly separate point, children with autism often have pica, which creates a risk for causing lead toxicity.

Environmental chemicals

Air pollution is complex to specify and measure. The review of research suggests a potential though unsubstantiated link between air pollution and ASDⁱⁱ.

Linkage with pesticides and other organic pollutants, though is possible, but yet remains unproven. ⁱⁱ

ⁱ Jason A. Chen, Olga Peñagarikano, T. Grant Belgard, Vivek Swarup and Daniel H. Geschwind. The Emerging Picture of Autism Spectrum Disorder: Genetics and Pathology. *Annual Review of Pathology: Mechanisms of Disease*. Vol. 10: 111-144

ⁱⁱ Lyall, K., Schmidt, R. J., & Hertz-Picciotto, I. (2014). Maternal lifestyle and environmental risk factors for autism spectrum disorders. *International journal of epidemiology*, 43(2), 443-464.

ⁱⁱⁱ Newschaffer CJ, Croen LA, Daniels J, Giarelli E, Grether JK, et al. 2007. The epidemiology of autism spectrum disorders. *Annu. Rev. Public Health* 28:235–58

