REVIEW ARTICLE

Environmental factors influencing the risk of autism

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Autism is a developmental disability with age of onset in childhood (under 3 years old), which is characterized by definite impairments in social interactions, abnormalities in speech, and stereotyped pattern of behaviors. Due to the progress of autism in recent decades, a wide range of studies have been done to identify the etiological factors of autism. It has been found that genetic and environmental factors are both involved in autism pathogenesis. Hence, in this review article, a set of environmental factors involved in the occurrence of autism has been collected, and finally, some practical recommendations for reduction of the risk of this devastating disease in children are represented.

Key words: Autism, environmental factors, etiological factors

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INTRODUCTION

Autism described by Asperger (in 1938) and Kanner (in 1943)[1] is a severe neurodevelopmental disorder and belongs to autism spectrum disorders (ASDs), including autism, Asperger syndrome, Rett syndrome, unidentified pervasive developmental disorders, and childhood disintegrative disorder.[2,3] Autism is 4–5 times more common among boys than girls.[4-6] The most prominent clinical and phenotypic features of autism are extensive disabilities in social and behavioral communications, language impairment or inability to speak, and strong tendency toward stereotyped and repetitive patterns of behavior.[7,8] Regarding statistical reports, the prevalence of autism had increased from 4–5 cases per 10,000 children in 1980s to 30–60 cases in 1990s,[9] and through astonishing increase, there are about 8.0 per 1000 children aged 8 years in 2004 and 9.0 per 1000 in 2006 or 1 in every 110 children aged 8 years in 2006. In 2012, a combined ASD prevalence of 11.3 per 1000 children aged 8 years or 1 in 88 children was published by the Autism and Developmental Disabilities Monitoring Network.[7,10] With regard to its progressive increase over the last two decades,[11] and lack of effective treatment, and moreover, the difficulties imposed on the society and families of autistic children, the importance of investigation on causes of this disease and effort to prevent it become clear. There is growing body of evidence about genetic factors enrolment which is supporting autism etiology through genetic mutations (e.g., heritability and twins).[12,13] According to the important role of epigenetics in autism etiology, a lot of genes have been studied, and in some cases, opposite results obtained.[14,15] Studying identical twins and lack of complete concordance among them and excessive genetic studies with no conclusive results unveils the importance of environmental risk factors and their role in etiology of autism.[16,17] Hence, the interactions between susceptible genes and environmental factors have been proposed as the major mechanism of autism etiology.[18,19]

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Currently, epigenetic and its complex mechanisms are presented as the most momentous mediator in the environment and genome interactions.[20] Environmental factors can affect the quality and quantity of gene expression without changing the DNA sequence through epigenetic mechanisms, including DNA methylation, changes in histone proteins, and expression of noncoding RNAs. This way, they can be transferred to the next cellular generation or even the next organism generation.[20,21] As a result, exposure to harmful environmental factors can change the expression of developmental key genes in critical periods of embryo formation and increases the risk of genomic imprinting diseases such as autism.[22,23]

None of the environmental factors is sufficient to yield autism, but rather a collection of them can be involved in the incidence of autism.[24] In this article, regarding mother and child exposure time to risk factors, they are divided into prenatal, natal, and postnatal risk factors.

PRENATAL RISK FACTORS

Physical, mental, and psychological health and financial state throughout the pregnancy are important factors affecting fetal development and health. An unhealthy mother who is not mentally and physically healthy and well nourished might be unable to have a healthy neonate. A set of prenatal risk factors which increase a child's susceptibility to autism is presented in Table 1.

Parental age

Advanced parental age (particularly paternal age) has been identified as one of the most important risk factors of autism.[25-29] In many studies, maternal and paternal age older than or equal to 34 years has been found associated with increased risk of autism in their offspring; however, in other studies, the relationship between child autism and the age of both parents[30] or even the age of one parent[24,31-34] is rejected. Intriguingly, the relationship between increased risk of autism and elevated paternal age has been approved in most studies.[28,32-40] Particularly, a study was conducted among Iranian people in 2010 to explore the presence or absence of association between parental age and risk of autism. Based on this study, autism risk increases by 29% for every 10-year elevation in fathers' age. In other words, fathers aged between 34 and 39 had a nearly two-fold greater risk, and those who are older than 40 have more than two-fold (2.58) greater risk to have an affected child in comparison to who ones aged 25-29 years old.[38] In other studies in Japan[34] and China,[40] similar relationships were explored between paternal age and increased risk of autism. Lack of any correlation between maternal age and susceptibility of autism in these three mentioned studies has critical importance. The probable explanation for this phenomenon is the formation of *de novo* mutations in germline cells and modifications in DNA methylation, which can result in general epigenetic alterations in the expression of neural development genes and, finally, disorders in sperm genomic imprinting. As a result, the probability of neural impairments, such as autism, would be increased.[28,36,37] Advanced paternal age also affects immune system function and, consequently, the development of the nervous system.[35]

In studies that increase in maternal age manifests a correlation with autism,[24,30,31,41-44] chromosomal abnormalities and trinucleotide repeat expansion in the ovule,[42] and increase in the obstetric intervention[43] may be proposed as probable reasons. On the other hand, being small for gestational age can increase the risk of autism due to lack of physical maturity, inability, and poor maternal cares. Mothers who are younger than 20 may be exposed to intrauterine growth retardation of fetus and preterm birth, which both of them are potent for, associated with increased risk of autism.[30,31,41]

Maternal physical health

Metabolic syndrome, bleeding, and mother infection during pregnancy are some of mother's physical diseases which are related to child autism.[45] Maternal bleeding during pregnancy which is associated with a significant 81% elevated risk of autism,[26] and metabolic syndrome, including diabetes,[26,46,47] hypertension,[31,48] and obesity,[48,49] paves the way for hypoxia (deficiency of oxygen) *in utero*[46] which results in deficient brain development and induction of myelination changes, membrane adhesion, and deficiency in hippocampal neurons (a brain area which is highly involved in autism).[23,50] Maternal viral infections in the first trimester of pregnancy, including rubella,[51-53] measles, mumps, chicken pox,[45,51] influenza,[45,51,54] herpes,[51,55] pneumonia, syphilis, varicella zoster,[55] and cytomegalovirus[45,56] and bacterial infections in the second trimester which require hospitalization, increase the risk of autism in embryo.[51] Such relationship is due to abnormal maternal immune activation and, consequently, elevated levels of inflammatory cytokines which affect the embryonic brain development and increase the risk of autism and other neuropathophysiological status.[57,58]

Maternal mental health

According to the importance and impact of family unit, parental behavior, and their communication patterns on the formation of children's personality and emotions,[59] the association between parental psychiatric history and risk of child mental disorders, especially autism, is obvious. For example, the association of parental psychiatric history such as schizophrenia with a nearly three-fold increased risk of autism[30,60-63] or the relationship between mother's

Table 1: Prenatal risk factors

Risk factors	Positive and negative association with autism	Reference
Parental age	Positive	[25-29,114,115]
	Negative	[30]
Paternal age	Positive	[28,32-40]
	Negative	[24]
Maternal age	Positive	[24,30,31,41-44]
	Negative	[31-34]
Birth order	Positive	[24,25,40,91,118,140]
	Negative	[30,31,97,120,121]
Maternal physical diseases		
Preeclampsia	Positive	[94,141,142]
	Negative	[30]
Maternal gestational diabetes	Positive	[26,46,47]
	Negative	[31,94,143]
Hypertension/edema	Positive	[31,48]
	Negative	[26]
Nausea/vomiting	Positive	[119]
Other maternal diseases including psoriasis, asthma, hay fever, atopic dermatitis, rheumatoid arthritis, celiac disease, and mastocytosis	Positive	[57,144]
Maternal bleeding during pregnancy	Positive	[26,31,40,47,58]
Infections during pregnancy	Positive	[45,58]
Bacterial infection*	Positive	[145]
Viral infection*	Positive	
Influenza		[45,51,54]
Rubella		[45,51-53]
Cytomegalovirus		[45,56]
Measles		[45,51]
Mumps		[45,51]
Chicken pox		[45,51]
Herpes virus		[51,55]
Pneumonia		[55]
Syphilis		[55]
Varicella zoster		[55]
Maternal mental diseases		[30]
Schizophrenia	Positive	[30,60-63]
Depression	Positive	[20,30,60-63]
Anxiety and stress	Positive	[40,60,61,64-70]
	Negative	[146,147]
Personality disorders	Positive	[55]
Infant gender	Positive	[116,117]
Existence of>1 affected sibling	Positive	[116,117]
Maternal prenatal medication use	Positive	[26,45]
Antiepileptic drugs	Positive	[30,53,75,76,101,148,149]
	Negative	[95]
Psychotropic drugs	Positive	[122,150]
Antidepressant drugs	Positive	[78-80]
Beta 2 adrenergic agonist drugs	Positive	[83,84]
Paracetamol (acetaminophen)	Positive	[77,126]
Antipyretics	Positive	[151,152]
Thalidomide	Positive	[30,40,53,81,149]
Misoprostol	Positive	[82,122]
Exposure to certain chemicals heavy metals	Positive	[123,153-155]
Pesticides	Positive	[124,156,157]
Air pollutants	Positive	[123,154,158,159]
P-CB[a]	Positive	[43,53]
PBDE[b]	Positive	[160,161]

Contd...

Table 1: Contd...

Risk factors	Positive and negative association with autism	Reference
PAH[c]	Positive	[95,123,154]
Familial socioeconomic status		
Economic situation	Positive	[85,87,88,162]
	Negative	[30]
Social status	Positive	[40,65,66,70,85,86, 88-90,163]
Educational level	Positive	[85,88,91-93]
Mother born abroad	Positive	[24,31,32,42,61]
	Negative	[91]
Cigarettes or alcohol addiction of one parent	Positive	[31,40,49,129]
	Negative	[92,95,130]
Maternal iron, folate, and methionine deficiency	Positive	[50,113,131-133]
Maternal vitamin deficiency	Positive	[134-139,164]
Weight gain during pregnancy	Positive	[48,49]
Threatened abortion	Positive	[24,40,49]

[a]Polychlorinated biphenyls, [b]Polybrominated diphenyl ether, [c]Polycyclic aromatic hydrocarbons

depression,[20,60-63] anxiety,[40,61,64-70] and personality disorders[60] and susceptibility to autism has been proved in many studies.

In addition to mothers who have experienced mental illnesses throughout their lives and are recognized as mentally illness, those who undergo mental problems such as depression, anxiety, and considerable stress during 21–32 weeks of gestation, a period of heightened plasticity for fetal formation and development[71] can have irremediable effects, through epigenetic mechanism, on the expression of fetus stress response genes, the genes involved in neurobiology, metabolism, and physiology that can persist across the lifespan.[70] Mother's inappropriate psychological state, especially great and long-lasting stresses[72] which may result in some other personality disorders such as aggression in mothers,[73] can expose the fetus to elevated levels of cortisol through interrupting mother's HPA axis, amplifying adrenal steroids such as cortisol and increasing placental permeability to these hormones, basically. Consequently, fetal developmental programming (through epigenome) would be highly affected, and through interrupting the fetal stress response system, the way for different physical and mental impairments including autism would be paved.[20] On the other hand, rates of subclinical anxiety problems are increased among males and siblings in middle childhood.[74]

Maternal prenatal medication use

Maternal prenatal medication use can be associated with a 46% increased risk of fetus autism.[26] Researches about different kinds of drugs have revealed a significant 68% increased risk of autism in relation to prenatal psychiatric medication use.[26] The negative effect of prenatal medication use is caused by their placental crossing and disturbing fetal development, based on many studies. For example, use of antiepileptic drugs, as well as valproic acid, leads to fetal valproate syndrome, increases oxidative stress and varied gene expression pattern, and subsequently results in developmental delays, deficient motor activities and social behaviors, and finally, postnatal growth alterations.[45,75,76] Moreover, it is confirmed that paracetamol (acetaminophen), which is widely used as an analgesic/antipyretic drug, can induce apoptosis and necrosis that are observed in autistic brains. In addition, paracetamol (acetaminophen) induces oxidative stress and immune dysregulation in humans.[77] Furthermore, positive connection between antidepressant medications and autism has been demonstrated in many studies.[78-80] The relationship between susceptibility to autism and taking some other medications has been identified, such as thalidomide, a painkiller,[81] misoprostol, a prostaglandin analog drug for the prevention and treatment of gastric ulcers,[82] in the first trimester, and β2-adrenergic agonists such as terbutaline to treat asthma.[83,84]

Familial socioeconomic status

Considering economic, social, educational, and psychological aspects of family's life, autistic children and their families are of poor state, mainly.[85] Basically, these families inevitably experience unhealthy, inappropriate sociality and unrehabilitated life conditions because of financial problems, occupational and psychological stresses.[86-88] Inaccessibility to health care and recreational facilities represented in infection and impaired physical health.[89] Furthermore, exposure to stress and anxiety (such as shared living place with couple's families) imposes psychological tension for the parents, especially pregnant mother, and increasing susceptibility to child autism during pregnancy.[40,65,66]

On the other hand, isolation of mother and breakdown in communications and social interactions can negatively affect her psychological state and endanger both mother

and embryo's health.[90] There are numerous researches evaluating the relationship between parental education and risk of child autism and have variable conclusions which confirmed the correlation between low level of parental education and risk of autism,[85] and some others indicate strength correlation between highly educated parents and incidence of autism.[91-93]

NATAL RISK FACTORS

Table 2 suggests natal risk factors which increase the fetal risk of autism. Abnormal gestational age, preterm (<35 weeks) and postterm pregnancy (>42 weeks), is associated with a significantly increased risk of autism.[30,40,47,92,94,95] Prenatal risk factors such as bleeding during pregnancy and natal risk factors such as fetal complications including fetal distress, umbilical-cord complications such as fetal nuchal cord and cesarean delivery (26% increased risk of autism)[47] are all involved in hypoxia (lack of oxygen) and consequently increasing susceptibility to child autism.[31,42,47,95] Fetal nuchal cord occurred significantly more frequent among children with autism (23.2%) regarding the controls (6.3%) and it causes fetal deficiency in blood, oxygen, and nutrition, which would affect fetal brain development and results in damage to the newborn central nervous system if the inadequate blood flow is severe or enough long-lasting.[40] Three brain regions, including basal ganglia, hippocampus, and lateral ventricles, are highly vulnerable to hypoxia.[42] Autistic children's brain exhibit larger lateral ventricles, morphological hippocampal abnormalities, and increased dopaminergic activity (what hypoxia causes).[96]

Table 2: Natal risk factors

Risk factors	Positive and negative association with autism	Reference
Abnormal presentation		
Preterm birth	Positive	[30,40,47,92,94,99]
Postterm birth	Positive	[40]
	Negative	[47]
Cesarean delivery	Positive	[26,31,40,47,165]
Fetal complications	Positive	[24,26,31,36,42,95]
Hypoxia (lack of oxygen)	Negative	[166-168]
	Positive	[24,40,49,50,96]
	Negative	[166,169-171]
Congenital anomalies	Positive	[30,31,47,172]
Fetal respiratory distress	Positive	[24,31,42,47,95]
Natal ulcers and bleeding	Positive	[30,47]
Umbilical cord complication	Positive	[24,26,31,40,42,47, 95,97,121,170,173]
Maternal complications		
Maternal bleeding after childbirth	Positive	[24,47,95]
Venous thrombosis	Positive	[88]
Assisted conception (IVF)	Positive	[92]
Season of birth		
Winter	Positive	[99]
Summer	Positive	[30,47]

IVF = *In vitro* fertilization

Postnatal risk factors: Lesser

Postnatal risk factors have crucial roles in susceptibility to autism, and a set of them is mentioned in Table 3. Low birth weight, jaundice, and postnatal infection are some of the most significant risk factors. A neonate with birth weight, which is the result of three potential factors (genetic growth potential, duration of pregnancy and rate of fetal growth)[30] minor than 2500 g considered as low birth weight and associated with a two-fold increase in the risk of autism.[31,47,93,97,98] Postnatal jaundice is a result of high bilirubin production caused by increased breakdown of fetal erythrocytes and a low hepatic excretory capacity resulting from general immaturity of the liver and it can be associated with death during a sensitive period (around the 40 weeks of pregnancy) or susceptibility to mental disorders, especially a four-fold increase in autism if survive.[30,40,47,99,100]

Table 3: Postnatal risk factors

Risk factors	Positive and negative association with autism	Reference
Postnatal complications		
Low birth weight and size	Positive	[30,31,36,47,91,93,95,97, 98,169,174-176]
	Negative	[40,142,143,166,167,170,177]
Jaundice and hyperbilirubinemia	Positive	[30,40,42,47,99,100,168]
	Negative	[166,177,178]
Encephalopathy	Positive	[94,100,143,179]
Birth defects	Positive	[31,94,95,170,176,180,181]
	Negative	[167,173,182]
Early infant infections	Positive	[94,101-103,149,183]
	Negative	[143,177]
Meningitis	Positive	[55]
Lack of breathing and infant resuscitation	Positive	[24,40,47,166,170]
	Negative	[170,171]
Postnatal anemia	Positive	[30,47]
	Negative	[143,184,185]
Weak or no	Positive	[24,40,47,166,170,186]
Crying after birth	Negative	[170,171]
Postnatal Vitamin D deficiency	Positive	[136,138]
Feeding difficulties	Positive	[30,47]
Medical intervention	Positive	[26]
Low levels of primary maternal	Positive	[64]
Care		
Postnatal chemical exposure to trihalomethanes, tetrachloroethylene, and trichloroethylene	Positive	[101]

In addition to prenatal maternal infection during pregnancy, postnatal infections such as meningitis[55] mumps, varicella, unknown fever, and ear infections[101] on the first 30 days of life are correlated with high risk of autism.[102,103]

PROTECTIVE OR AUTISM-UNRELATED FACTORS

Among the environmental factors which are probable to cause autism, vaccines can be noted. Epidemiological studies have found no association between measles, measles, as well as mumps, vaccines (as environmental risk factors), and increased risk of autism.[101,104] Contrary to directly related or unrelated factors to autism, some factors have protective roles. Unsaturated fatty acids can be cited as these factors. The biological effects of such fatty acids, such as linoleic acid, omega-3, and omega-6, on the retinal and brain development *in utero*,[105] signal transduction, gene expression, and as components of cell membranes[106,107] in the first 2 months of pregnancy (the most critical period of embryonic physical development) are highly important to such an extent that high maternal intake of omega-6 and linoleic acid is inversely associated with ASD risk in offspring, corresponding to a 34% reduction in autism risk, and in contrary, lower than 5% of ω-3 fatty acid intake had significant increase in offspring ASD risk. Therefore, fatty acids consumption of different diets has an inverse effect on risk of autism.[108] In addition to unsaturated fatty acids, taking folic acid 3 months before pregnancy and during the 1st month of pregnancy can provide protection against autism in mothers and infants who have one copy of MTHFR 677 C>T allele at least. Maternal folic acid supplementation intake during early pregnancy is associated with less behavioral problems in offspring at 18 months age,[109] reduced risk of severe language delay at age 3,[110] improved verbal and attention competence at 4 years,[111] subordinate scores of childhood hyperactivity at age 8 years,[112] and particularly decrease the risk of autism.[113]

DISCUSSION

Autism is a multifactorial neurodevelopmental disorder which is caused by genetic and environmental factors. The prevalence of autism has been increased over the last decades. About every disorder, prevention is more important than cure. Among the risk factors of autism, environmental ones attracted the attention of most of the scientists because prevention is possible by avoiding from them.

There are a lot of environmental risk factors which influence autism pathogenesis by their epigenetic effects. These factors are divided into three categories, included prenatal, natal, and postnatal risk factors. Each category allocates to the specific period of neonate development. A collection of these factors is involved in the pathogenesis of autism. A comprehensive list of these factors is collected in this review. Regarding these factors, it would be essential to point out some requirements to prevent child autism. The following advice and suggestions are useful for parents to pass the highly significant period of pregnancy with confidence, especially those who have had experience of autistic children, and are about to prevent giving birth to another suffered infant.

Recommendations

1. Advanced parental age (particularly paternal age) has important role in autism incidence in their neonate;[25-29, 32-40, 114,115] therefore, it is suggested that the best time to have a child (especially for father) is under the age of 35
2. Families with more than one autistic child would have increased risk to have an affected infant because the presence of more than one older affected sibling causes a two-fold increase in the risk of autism in the next children. These families are further at risk regarding those who have only one autistic child (32.2% of multiplex vs. 13.5% of simplex).[116,117] Therefore, genetic consultation is strongly suggested to families with more than two autistic children who decided to have more children
3. Considering the fact that autistic children are typically the primary child of their family and there is a significant (61%) increase in risk for first-born children compared with next children; if the first child of a family is autistic and the second child is unaffected, it will be less probable to have another autistic child.[26,53,55,56,118,119] However, such a relationship has not been observed in other studies[30,31,97,120,121]
4. Although the severity of autism is higher in the female gender, the prevalence of autism in boys is 3–4 folds greater than girls.[4,6] Hence, sex determination test is highly recommended to parents who are in danger for autism, to increase the probability of having healthy baby girls
5. The investigation of families and relatives of both autistic and healthy children has revealed the fact that familial psychiatric history is more common among autistic children's families and relatives with regard to healthy children;[30,60] hence, in addition to genetic susceptibility, environmental factors are also involved in the incidence of such diseases and make mental problems appear in children differently from their parents.[61] As a result, regarding the strong association between parental psychiatric history and higher risk of autism in their children[30,62,63] and, generally, the impact of parental behavior on children's personality and mental health,[59] parents will be advised to complete their treatment and recovery periods before pregnancy

6. Due to the direct effect of maternal emotional state on fetal health, mothers must avoid occupational and mental stresses. Mothers, who tolerate mental stresses such as family problems, stressful living places, financial problems, and loneliness, expose their children to different learning and mental problems such as autism[20,40,64,86,90,93,122]
7. Mother exposure to some chemicals such as pesticides, air and water pollutants, and heavy metals and other chemicals can affect fetal health negatively through epigenetic alterations of gene expression and neurodevelopmental process such as changing neuronal migration.[20,123,124] Consequently, parents must care about where they choose to live that be far from environmental pollutions and recreational and clinical facilities must be available. Moreover, newborns must not be exposed to trihalomethane, tetrachloroethylene, trichloroethylene, and other chemicals[101]
8. The quality of mother–infant interactions during the postnatal period has great importance; that's why mothers are supposed to provide proper care for their children. The absence of such emotional mother–infant relation has a great effect on the postnatal development of neural and signaling pathways in addition to affecting secretion of some hormones such as dopamine, oxytocin, and serotonin.[64,125] They all can be involved in susceptibility to autism
9. Due to side effects of mother's prenatal medication that is mentioned previously,[26] it is highly recommended that mothers should avoid taking any medication during pregnancy. Moreover, without prescription, the children must not be given medications such as paracetamol (acetaminophen) for pain and fever management following vaccinations in early infancy[77,126,127].
10. Maternal smoking and alcohol consumption should be strictly forbidden during pregnancy, because in various studies, it has been proved that prenatal maternal smoking or even passive smoking includes polycyclic aromatic hydrocarbons, metals, and other chemicals with known adverse health effects, which may cause fetal hypoxia and affect fetal brain development.[31,40,49,128,129] Although in some studies, the connection between maternal smoking and risk of ASD has been rejected[130]
11. Natural childbirth has priority over cesarean section because cesarean is especially prevalent among mothers who give birth to autistic children[47]
12. Regarding the protective properties of unsaturated fatty acids[105-108] and folic acid[109-113], in addition, the effects of iron deficiency, folate, methionine,[50,113,131-133] and vitamins[134-139] on susceptibility to autism highlight the importance of an appropriate diet during pregnancy. Considering the profound impacts of different vitamins on physical health, the impact of Vitamin D on significant biological processes such as DNA repair and its anti-inflammatory quality on brain tissue,[134,135,137,139] and the roles of vitamin A and other vitamins in brain development,[53] it is better to eat foods enriched with different vitamins and iron in addition to taking vitamin supplements and folic acid during pregnancy. Furthermore, eating foods such as fish which is enriched with omega-3 and other unsaturated fatty acids help in the normal development of the embryo. Appropriate postnatal care prevents the problems with lack of Vitamin D and other crucial components[136,138]
13. Pregnancy obesity (>90 kg) and excessive weight gain during pregnancy are significantly associated with the incidence of autism;[48,129] therefore, mothers who are more susceptible to autism should be very careful about their dietary to prevent weight gain during pregnancy.
14. Based on some studies, prolonged exposure to elevated temperature during pregnancy and susceptibility to child autism are related.[47] Therefore, mothers must avoid taking long saunas and other forms of exposure
15. Due to the negative impacts of activation and aberrations of the maternal and fetal immune systems and increased level of cytokines on neural development of embryos and infants, mothers must care about their health during pregnancy as well as their newborn's health to stop probable infections, especially in the 1st month of infant lives.[45,49,77,99,101,108,122]

CONCLUSION

Given that autism is an epigenetic disorder in which environmental risk factors are the most momentous mediators in its pathogenesis, detection of these factors can help parents avoid the danger of autism onset in their children. By following the mentioned tips, parents can provide a lower risk condition for the outbreak of autism.

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Conflicts of interest

There are no conflicts of interest.

AUTHORS' CONTRIBUTION

- PK, EK, SMM contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work . PK contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- MK contributed in the conception of the work, conducting the study, revising the draft, approval of

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REFERENCES

1. Lyons V, Fitzgerald M. Asperger (1906-1980) and Kanner (1894-1981), the two pioneers of autism. J Autism Dev Disord 2007;37:2022-3.
2. Volkmar FR, State M, Klin A. Autism and autism spectrum disorders: Diagnostic issues for the coming decade. J Child Psychol Psychiatry 2009;50:108-15.
3. Paris P. Autism Spectrum Disorders: Phenotypes, Mechanisms and Treatments. Switzerland: 2015. DOI:10.1159/isbn.978-3-318-02602-3.
4. Kinney DK, Munir KM, Crowley DJ, Miller AM. Prenatal stress and risk for autism. Neurosci Biobehav Rev 2008;32:1519-32.
5. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcín C, *et al.* Global prevalence of autism and other pervasive developmental disorders. Autism Res 2012;5:160-79.
6. Werling DM, Geschwind DH. Sex differences in autism spectrum disorders. Curr Opin Neurol 2013;26:146-53.
7. Rapin I. The autistic-spectrum disorders. N Engl J Med 2002;347:302-3.
8. Developmental, D.M.N.S.Y. and I. Principal. Prevalence of autism spectrum disorder among children aged 8 years-autism and developmental disabilities monitoring network, 11 sites, United States, 2010. Morbidity and mortality weekly report. Vol. 63. Surveillance summaries, Washington, DC: 2002. p. 1.
9. Bertrand J, Mars A, Boyle C, Bove F, Yeargin-Allsopp M, Decoufle P. Prevalence of autism in a United States population: The Brick Township, New Jersey, investigation. Pediatrics 2001;108:1155-61.
10. Volkmar FR, Pauls D. Autism. Lancet 2003;362:1133-41.
11. Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders- autism and developmental disabilities monitoring network, 14 sites, united states, 2008. MMWR 2012;61(3):1-19.
12. Weiss LA, Arking DE; Gene Discovery Project of Johns Hopkins and the Autism Consortium, Daly MJ, Chakravarti A. A genome-wide linkage and association scan reveals novel loci for autism. Nature 2009;461:802-8.
13. Folstein SE, Rosen-Sheidley B. Genetics of autism: Complex aetiology for a heterogeneous disorder. Nat Rev Genet 2001;2:943-55.
14. Musavi SM, Kamali E, Karahmadi M, Salehi M. RORA and autism in Isfahan population: A complicated epigenetic relationship. Cell J (Yakhteh) 2016;18:540-6.
15. Nguyen A, Rauch TA, Pfeifer GP, Hu VW. Global methylation profiling of lymphoblastoid cell lines reveals epigenetic contributions to autism spectrum disorders and a novel autism candidate gene, RORA, whose protein product is reduced in autistic brain. FASEB J 2010;24:3036-51.
16. Ronald A, Hoekstra RA. Autism spectrum disorders and autistic traits: A decade of new twin studies. Am J Med Genet B Neuropsychiatr Genet 2011;156B: 255-74.
17. Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, *et al.* Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry 2011;68:1095-102.
18. Herbert MR. Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders. Curr Opin Neurol 2010;23:103-10.
19. Deth R, Muratore C, Benzecry J, Power-Charnitsky VA, Waly M. How environmental and genetic factors combine to cause autism: A redox/methylation hypothesis. Neurotoxicology 2008;29:190-201.
20. Perera F, Herbstman J. Prenatal environmental exposures, epigenetics, and disease. Reprod Toxicol 2011;31:363-73.
21. Bollati V, Baccarelli A. Environmental epigenetics. Heredity (Edinb) 2010;105:105-12.
22. Foley DL, Craig JM, Morley R, Olsson CA, Dwyer T, Smith K, *et al.* Prospects for epigenetic epidemiology. Am J Epidemiol 2009;169:389-400.
23. Wang SC, Oelze B, Schumacher A. Age-specific epigenetic drift in late-onset Alzheimer's disease. PLoS One 2008;3:e2698.
24. Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: A population study. Arch Gen Psychiatry 2004;61:618-27.
25. Durkin MS, Maenner MJ, Newschaffer CJ, Lee LC, Cunniff CM, Daniels JL, *et al.* Advanced parental age and the risk of autism spectrum disorder. Am J Epidemiol 2008;168:1268-76.
26. Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: Comprehensive meta-analysis. Br J Psychiatry 2009;195:7-14.
27. Lee BK, McGrath JJ. Advancing parental age and autism: Multifactorial pathways. Trends Mol Med 2015;21:118-25.
28. Parner ET, Baron-Cohen S, Lauritsen MB, Jørgensen M, Schieve LA, Yeargin-Allsopp M, *et al.* Parental age and autism spectrum disorders. Ann Epidemiol 2012;22:143-50.
29. Shelton JF, Tancredi DJ, Hertz-Picciotto I. Independent and dependent contributions of advanced maternal and paternal ages to autism risk. Autism Res 2010;3:30-9.
30. Larsson HJ, Eaton WW, Madsen KM, Vestergaard M, Olesen AV, Agerbo E, *et al.* Risk factors for autism: Perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol 2005;161:916-25.
31. Hultman CM, Sparén P, Cnattingius S. Perinatal risk factors for infantile autism. Epidemiology 2002;13:417-23.
32. Lauritsen MB, Pedersen CB, Mortensen PB. Effects of familial risk factors and place of birth on the risk of autism: A nationwide register-based study. J Child Psychol Psychiatry 2005;46:963-71.
33. Reichenberg A, Gross R, Weiser M, Bresnahan M, Silverman J, Harlap S, *et al.* Advancing paternal age and autism. Arch Gen Psychiatry 2006;63:1026-32.
34. Tsuchiya KJ, Takagai S, Kawai M, Matsumoto H, Nakamura K, Minabe Y, *et al.* Advanced paternal age associated with an elevated risk for schizophrenia in offspring in a Japanese population. Schizophr Res 2005;76:337-42.
35. Alter MD, Kharkar R, Ramsey KE, Craig DW, Melmed RD, Grebe TA, *et al.* Autism and increased paternal age related changes in global levels of gene expression regulation. PLoS One 2011;6:e16715.
36. Hultman CM, Sandin S, Levine SZ, Lichtenstein P, Reichenberg A. Advancing paternal age and risk of autism: New evidence from a population-based study and a meta-analysis of epidemiological studies. Mol Psychiatry 2011;16:1203-12.
37. Kong A, Frigge ML, Masson G, Besenbacher S, Sulem P, Magnusson G, *et al.* Rate of *de novo* mutations and the importance of father's age to disease risk. Nature 2012;488:471-5.
38. Sasanfar R, Haddad SA, Tolouei A, Ghadami M, Yu D, Santangelo SL. Paternal age increases the risk for autism in an Iranian population sample. Mol Autism 2010;1:2.
39. van Balkom ID, Bresnahan M, Vuijk PJ, Hubert J, Susser E, Hoek HW. Paternal age and risk of autism in an ethnically diverse, non-industrialized setting: Aruba. PLoS One 2012;7:e45090.
40. Zhang X, Lv CC, Tian J, Miao RJ, Xi W, Hertz-Picciotto I, *et al.* Prenatal and perinatal risk factors for autism in China. J Autism Dev Disord 2010;40:1311-21.
41. Hultman CM, Sparén P. Autism – Prenatal insults or an

epiphenomenon of a strongly genetic disorder? Lancet 2004;364:485-7.
42. Kolevzon A, Gross R, Reichenberg A. Prenatal and perinatal risk factors for autism: A review and integration of findings. Arch Pediatr Adolesc Med 2007;161:326-33.
43. Rosenthal AN, Paterson-Brown S. Is there an incremental rise in the risk of obstetric intervention with increasing maternal age? Br J Obstet Gynaecol 1998;105:1064-9.
44. Sandin S, Hultman CM, Kolevzon A, Gross R, MacCabe JH, Reichenberg A. Advancing maternal age is associated with increasing risk for autism: A review and meta-analysis. J Am Acad Child Adolesc Psychiatry 2012;51:477-86.e1.
45. Ornoy A, Weinstein-Fudim L, Ergaz Z. Prenatal factors associated with autism spectrum disorder (ASD). Reprod Toxicol 2015;56:155-69.
46. Eidelman AI, Samueloff A. The pathophysiology of the fetus of the diabetic mother. In: Seminars in Perinatology. Seminars in perinatology 2002;26(3):232-36. [DOI:http://dx.doi.org/10.1053/sper.2002.34215].
47. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: A comprehensive meta-analysis. Pediatrics 2011;128:344-55.
48. Krakowiak P, Walker CK, Bremer AA, Baker AS, Ozonoff S, Hansen RL, *et al.* Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics 2012;129:e1121-8.
49. Guinchat V, Thorsen P, Laurent C, Cans C, Bodeau N, Cohen D. Pre-, peri- and neonatal risk factors for autism. Acta Obstet Gynecol Scand 2012;91:287-300.
50. Georgieff MK. The effect of maternal diabetes during pregnancy on the neurodevelopment of offspring. Minn Med 2006;89:44-7.
51. Deykin EY, MacMahon B. Viral exposure and autism. Am J Epidemiol 1979;109:628-38.
52. Libbey JE, Sweeten TL, McMahon WM, Fujinami RS. Autistic disorder and viral infections. J Neurovirol 2005;11:1-10.
53. London EA. The environment as an etiologic factor in autism: A new direction for research. Environ Health Perspect 2000;108 Suppl 3:401-4.
54. Atladóttir HÓ, Henriksen TB, Schendel DE, Parner ET. Autism after infection, febrile episodes, and antibiotic use during pregnancy: An exploratory study. Pediatrics 2012;130:e1447-54.
55. Gillberg C, Coleman M. The Biology of the Autistic Syndromes. Vol. 25. London, UK: Cambridge University Press; 2000. p. 340.
56. Yamashita Y, Fujimoto C, Nakajima E, Isagai T, Matsuishi T. Possible association between congenital cytomegalovirus infection and autistic disorder. J Autism Dev Disord 2003;33:455-9.
57. Croen LA, Grether JK, Yoshida CK, Odouli R, Van de Water J. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: A case-control study. Arch Pediatr Adolesc Med 2005;159:151-7.
58. Elovitz MA, Brown AG, Breen K, Anton L, Maubert M, Burd I. Intrauterine inflammation, insufficient to induce parturition, still evokes fetal and neonatal brain injury. Int J Dev Neurosci 2011;29:663-71.
59. Karahmadi M. Parental interaction patterns in children with attention deficit hyperactive disorder and control group. J Res Med Sci 2007;12:143-6.
60. Bölte S, Knecht S, Poustka F. A case-control study of personality style and psychopathology in parents of subjects with autism. J Autism Dev Disord 2007;37:243-50.
61. Daniels JL, Forssen U, Hultman CM, Cnattingius S, Savitz DA, Feychting M, *et al.* Parental psychiatric disorders associated with autism spectrum disorders in the offspring. Pediatrics 2008;121:e1357-62.
62. Fish B, Marcus J, Hans SL, Auerbach JG, Perdue S. Infants at risk for schizophrenia: Sequelae of a genetic neurointegrative defect. A review and replication analysis of pandysmaturation in the Jerusalem Infant Development Study. Arch Gen Psychiatry 1992;49:221-35.
63. Wolff S, Narayan S, Moyes B. Personality characteristics of parents of autistic children: A controlled study. J Child Psychol Psychiatry 1988;29:143-53.
64. Gudsnuk K, Champagne FA. Epigenetic influence of stress and the social environment. Ilar J 2012;53:279-88. [doi: 10.1093/ilar.53.3-4.279].
65. Ladd CO, Huot RL, Thrivikraman KV, Nemeroff CB, Plotsky PM. Long-term adaptations in glucocorticoid receptor and mineralocorticoid receptor mRNA and negative feedback on the hypothalamo-pituitary-adrenal axis following neonatal maternal separation. Biol Psychiatry 2004;55:367-75.
66. Maccari S, Darnaudery M, Morley-Fletcher S, Zuena AR, Cinque C, Van Reeth O. Prenatal stress and long-term consequences: Implications of glucocorticoid hormones. Neurosci Biobehav Rev 2003;27:119-27.
67. Mueller BR, Bale TL. Sex-specific programming of offspring emotionality after stress early in pregnancy. J Neurosci 2008;28:9055-65.
68. O'Donnell K, O'Connor TG, Glover V. Prenatal stress and neurodevelopment of the child: Focus on the HPA axis and role of the placenta. Dev Neurosci 2009;31:285-92.
69. Sabih F, Sajid WB. There is significant stress among parents having children with autism. J Rawalpindi Med 2008;33:214-6.
70. Weinstock M. The long-term behavioural consequences of prenatal stress. Neurosci Biobehav Rev 2008;32:1073-86.
71. Beversdorf DQ, Manning SE, Hillier A, Anderson SL, Nordgren RE, Walters SE, *et al.* Timing of prenatal stressors and autism. J Autism Dev Disord 2005;35:471-8.
72. Musavi SM, Kamali E, Karimi P, Fatahi F, Chaleshtari MH, Salehi M. Autism and ENVIRONMENT in Isfahan area: Severe and Scheduled Prenatal Stresses at Spotlight! Archive of Iranian Medicine, 2016. [under review].
73. Karahmadi M, Esmaeili DN. Aggression and some of its demographic correlates in nurses of pediatric wards in hospitals affi liated to Isfahan Medical University. J Res Behav Sci 2007; 5(1):33-7.
74. Shivers CM, Deisenroth LK, Taylor JL. Patterns and predictors of anxiety among siblings of children with autism spectrum disorders. J Autism Dev Disord 2013;43:1336-46.
75. Narita M, Oyabu A, Imura Y, Kamada N, Yokoyama T, Tano K, *et al.* Nonexploratory movement and behavioral alterations in a thalidomide or valproic acid-induced autism model rat. Neurosci Res 2010;66:2-6.
76. Ornoy A. Valproic acid in pregnancy: How much are we endangering the embryo and fetus? Reprod Toxicol 2009;28:1-10.
77. Bauer AZ, Kriebel D. Prenatal and perinatal analgesic exposure and autism: An ecological link. Environ Health 2013;12:41.
78. Gidaya NB, Lee BK, Burstyn I, Yudell M, Mortensen EL, Newschaffer CJ. *In utero* exposure to selective serotonin reuptake inhibitors and risk for autism spectrum disorder. J Autism Dev Disord 2014;44:2558-67.
79. Harrington RA, Lee LC, Crum RM, Zimmerman AW, Hertz-Picciotto I. Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay. Pediatrics 2014;133:e1241-8.
80. Rai D, Lee BK, Dalman C, Golding J, Lewis G, Magnusson C. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: Population based case-control study. BMJ 2013;346:f2059.
81. Ito T, Ando H, Suzuki T, Ogura T, Hotta K, Imamura Y, *et al.* Identification of a primary target of thalidomide teratogenicity.

Science 2010;327:1345-50.
82. Bandim JM, Ventura LO, Miller MT, Almeida HC, Costa AE. Autism and Möbius sequence: An exploratory study of children in Northeastern Brazil. Arq Neuropsiquiatr 2003;61:181-5.
83. Witter FR, Zimmerman AW, Reichmann JP, Connors SL. *In utero* beta 2 adrenergic agonist exposure and adverse neurophysiologic and behavioral outcomes. Am J Obstet Gynecol 2009;201:553-9.
84. Zerrate MC, Pletnikov M, Connors SL, Vargas DL, Seidler FJ, Zimmerman AW, *et al.* Neuroinflammation and behavioral abnormalities after neonatal terbutaline treatment in rats: Implications for autism. J Pharmacol Exp Ther 2007;322:16-22.
85. Lee LC, Harrington RA, Louie BB, Newschaffer CJ. Children with autism: Quality of life and parental concerns. J Autism Dev Disord 2008;38:1147-60.
86. Adler NE, Newman K. Socioeconomic disparities in health: Pathways and policies. Health Aff (Millwood) 2002;21:60-76.
87. Durkin MS, Maenner MJ, Meaney FJ, Levy SE, DiGuiseppi C, Nicholas JS, *et al.* Socioeconomic inequality in the prevalence of autism spectrum disorder: Vidence from a U.S. cross-sectional study. PLoS One 2010;5:e11551.
88. Finegan JA, Quarrington B. Pre-, peri-, and neonatal factors and infantile autism. J Child Psychol Psychiatry 1979;20:119-28.
89. Kaczynski AT, Henderson KA. Parks and recreation settings and active living: A review of associations with physical activity function and intensity. J Phys Act Health 2008;5:619-32.
90. Samadi SA, McConkey R. Autism in developing countries: Lessons from iran. Autism Res Treat 2011;2011:145359.
91. Croen LA, Grether JK, Selvin S. Descriptive epidemiology of autism in a California population: Who is at risk? J Autism Dev Disord 2002;32:217-24.
92. Hvidtjørn D, Grove J, Schendel D, Schieve LA, Sværke C, Ernst E, *et al.* Risk of autism spectrum disorders in children born after assisted conception: A population-based follow-up study. J Epidemiol Community Health 2011;65:497-502.
93. King MD, Bearman PS. Socioeconomic status and the increased prevalence of autism in California. Am Sociol Rev 2011;76:320-46.
94. Buchmayer S, Johansson S, Johansson A, Hultman CM, Sparén P, Cnattingius S. Can association between preterm birth and autism be explained by maternal or neonatal morbidity? Pediatrics 2009;124:e817-25.
95. Maimburg RD, Vaeth M. Perinatal risk factors and infantile autism. Acta Psychiatr Scand 2006;114:257-64.
96. Previc FH. Prenatal influences on brain dopamine and their relevance to the rising incidence of autism. Med Hypotheses 2007;68:46-60.
97. Eaton WW, Mortensen PB, Thomsen PH, Frydenberg M. Obstetric complications and risk for severe psychopathology in childhood. J Autism Dev Disord 2001;31:279-85.
98. Schendel D, Bhasin TK. Birth weight and gestational age characteristics of children with autism, including a comparison with other developmental disabilities. Pediatrics 2008;121:1155-64.
99. Maimburg RD, Bech BH, Vaeth M, Møller-Madsen B, Olsen J. Neonatal jaundice, autism, and other disorders of psychological development. Pediatrics 2010;126:872-8.
100. Maimburg RD, Vaeth M, Schendel DE, Bech BH, Olsen J, Thorsen P. Neonatal jaundice: A risk factor for infantile autism? Paediatr Perinat Epidemiol 2008;22:562-8.
101. Newschaffer CJ, Fallin D, Lee NL. Heritable and nonheritable risk factors for autism spectrum disorders. Epidemiol Rev 2002;24:137-53.
102. Rosen NJ, Yoshida CK, Croen LA. Infection in the first 2 years of life and autism spectrum disorders. Pediatrics 2007;119:e61-9.
103. Li Q, Cheung C, Wei R, Hui ES, Feldon J, Meyer U, *et al.* Prenatal immune challenge is an environmental risk factor for brain and behavior change relevant to schizophrenia: Evidence from MRI in a mouse model. PLoS One 2009;4:e6354.
104. Taylor B, Miller E, Lingam R, Andrews N, Simmons A, Stowe J. Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: Population study. BMJ 2002;324:393-6.
105. Haggarty P. Effect of placental function on fatty acid requirements during pregnancy. Eur J Clin Nutr 2004;58:1559-70.
106. Casper RC. Nutrients, neurodevelopment, and mood. Curr Psychiatry Rep 2004;6:425-9.
107. Deckelbaum RJ, Worgall TS, Seo T. n-3 fatty acids and gene expression. Am J Clin Nutr 2006;83 6 Suppl: 1520S-5S.
108. Lyall K, Munger KL, O'Reilly ÉJ, Santangelo SL, Ascherio A. Maternal dietary fat intake in association with autism spectrum disorders. Am J Epidemiol 2013;178:209-20.
109. Roza SJ, van Batenburg-Eddes T, Steegers EA, Jaddoe VW, Mackenbach JP, Hofman A, *et al.* Maternal folic acid supplement use in early pregnancy and child behavioural problems: The Generation R Study. Br J Nutr 2010;103:445-52.
110. Roth C, Magnus P, Schjølberg S, Stoltenberg C, Surén P, McKeague IW, *et al.* Folic acid supplements in pregnancy and severe language delay in children. JAMA 2011;306:1566-73.
111. Julvez J, Fortuny J, Mendez M, Torrent M, Ribas-Fitó N, Sunyer J. Maternal use of folic acid supplements during pregnancy and four-year-old neurodevelopment in a population-based birth cohort. Paediatr Perinat Epidemiol 2009;23:199-206.
112. Schlotz W, Jones A, Phillips DI, Gale CR, Robinson SM, Godfrey KM. Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring. J Child Psychol Psychiatry 2010;51:594-602.
113. Schmidt RJ, Tancredi DJ, Ozonoff S, Hansen RL, Hartiala J, Allayee H, *et al.* Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. Am J Clin Nutr 2012;96:80-9.
114. Grether JK, Anderson MC, Croen LA, Smith D, Windham GC. Risk of autism and increasing maternal and paternal age in a large North American population. Am J Epidemiol 2009;170:1118-26.
115. King MD, Fountain C, Dakhlallah D, Bearman PS. Estimated autism risk and older reproductive age. Am J Public Health 2009;99:1673-9.
116. Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L, *et al.* Recurrence risk for autism spectrum disorders: A Baby Siblings Research Consortium study. Pediatrics 2011;128:e488-95.
117. Constantino JN, Zhang Y, Frazier T, Abbacchi AM, Law P. Sibling recurrence and the genetic epidemiology of autism. Am J Psychiatry 2010;167:1349-56.
118. Bolton PF, Murphy M, Macdonald H, Whitlock B, Pickles A, Rutter M. Obstetric complications in autism: Consequences or causes of the condition? J Am Acad Child Adolesc Psychiatry 1997;36:272-81.
119. Brown GE, Jones SD, MacKewn AS, Plank EJ. An exploration of possible pre- and postnatal correlates of autism: A pilot survey. Psychol Rep 2008;102:273-82.
120. Lord C, Mulloy C, Wendelboe M, Schopler E. Pre- and perinatal factors in high-functioning females and males with autism. J Autism Dev Disord 1991;21:197-209.
121. Piven J, Simon J, Chase GA, Wzorek M, Landa R, Gayle J, *et al.* The etiology of autism: Pre-, peri- and neonatal factors. J Am Acad Child Adolesc Psychiatry 1993;32:1256-63.
122. Dietert RR, Dietert JM, Dewitt JC. Environmental risk factors for autism. Emerg Health Threats J 2011;4:7111.
123. Pavanello S, Bollati V, Pesatori AC, Kapka L, Bolognesi C,

Bertazzi PA, *et al.* Global and gene-specific promoter methylation changes are related to anti-B[a] PDE-DNA adduct levels and influence micronuclei levels in polycyclic aromatic hydrocarbon-exposed individuals. Int J Cancer 2009;125:1692-7.
124. Shelton JF, Geraghty EM, Tancredi DJ, Delwiche LD, Schmidt RJ, Ritz B, *et al.* Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: The CHARGE study. Environ Health Perspect 2014;122:1103-9.
125. Curley JP, Jensen CL, Mashoodh R, Champagne FA. Social influences on neurobiology and behavior: Epigenetic effects during development. Psychoneuroendocrinology 2011;36:352-71.
126. Becker KG, Schultz ST. Similarities in features of autism and asthma and a possible link to acetaminophen use. Med Hypotheses 2010;74:7-11.
127. Schultz ST, Klonoff-Cohen HS, Wingard DL, Akshoomoff NA, Macera CA, Ji M. Acetaminophen (paracetamol) use, measles-mumps-rubella vaccination, and autistic disorder: The results of a parent survey. Autism 2008;12:293-307.
128. Wright RJ. Moving towards making social toxins mainstream in children's environmental health. Curr Opin Pediatr 2009;21:222-9.
129. Xiao R, Sorensen TK, Williams MA, Luthy DA. Influence of pre-eclampsia on fetal growth. J Matern Fetal Neonatal Med 2003;13:157-62.
130. Rosen BN, Lee BK, Lee NL, Yang Y, Burstyn I. Maternal smoking and autism spectrum disorder: A meta-analysis. J Autism Dev Disord 2015;45:1689-98.
131. James SJ, Melnyk S, Jernigan S, Pavliv O, Trusty T, Lehman S, *et al.* A functional polymorphism in the reduced folate carrier gene and DNA hypomethylation in mothers of children with autism. Am J Med Genet B Neuropsychiatr Genet 2010;153B: 1209-20.
132. Main PA, Angley MT, Thomas P, O'Doherty CE, Fenech M. Folate and methionine metabolism in autism: A systematic review. Am J Clin Nutr 2010;91:1598-620.
133. Ramaekers VT, Blau N, Sequeira JM, Nassogne MC, Quadros EV. Folate receptor autoimmunity and cerebral folate deficiency in low-functioning autism with neurological deficits. Neuropediatrics 2007;38:276-81.
134. Fernell E, Barnevik-Olsson M, Bågenholm G, Gillberg C, Gustafsson S, Sääf M. Serum levels of 25-hydroxyvitamin D in mothers of Swedish and of Somali origin who have children with and without autism. Acta Paediatr 2010;99:743-7.
135. Grant WB, Soles CM. Epidemiologic evidence supporting the role of maternal Vitamin D deficiency as a risk factor for the development of infantile autism. Dermatoendocrinol 2009;1:223-8.
136. Kalueff AV, Tuohimaa P. Neurosteroid hormone Vitamin D and its utility in clinical nutrition. Curr Opin Clin Nutr Metab Care 2007;10:12-9.
137. Kinney DK, Barch DH, Chayka B, Napoleon S, Munir KM. Environmental risk factors for autism: Do they help cause *de novo* genetic mutations that contribute to the disorder? Med Hypotheses 2010;74:102-6.
138. Levenson CW, Figueirôa SM. Gestational Vitamin D deficiency: Long-term effects on the brain. Nutr Rev 2008;66:726-9.
139. Moore M, Piazza A, Nolan Y, Lynch MA. Treatment with dexamethasone and Vitamin D3 attenuates neuroinflammatory age-related changes in rat hippocampus. Synapse 2007;61:851-61.
140. Zwaigenbaum L, Szatmari P, Jones MB, Bryson SE, MacLean JE, Mahoney WJ, *et al.* Pregnancy and birth complications in autism and liability to the broader autism phenotype. J Am Acad Child Adolesc Psychiatry 2002;41:572-9.
141. MacKinnon DP, Krull JL, Lockwood CM. Equivalence of the mediation, confounding and suppression effect. Prev Sci 2000;1:173-81.
142. Mann JR, McDermott S, Bao H, Hardin J, Gregg A. Pre-eclampsia, birth weight, and autism spectrum disorders. J Autism Dev Disord 2010;40:548-54.
143. Dodds L, Fell DB, Shea S, Armson BA, Allen AC, Bryson S. The role of prenatal, obstetric and neonatal factors in the development of autism. J Autism Dev Disord 2011;41:891-902.
144. Atladóttir HO, Pedersen MG, Thorsen P, Mortensen PB, Deleuran B, Eaton WW, *et al.* Association of family history of autoimmune diseases and autism spectrum disorders. Pediatrics 2009;124:687-94.
145. Atladóttir HO, Thorsen P, Østergaard L, Schendel DE, Lemcke S, Abdallah M, *et al.* Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. J Autism Dev Disord 2010;40:1423-30.
146. Hastings RP, Brown T. Behavior problems of children with autism, parental self-efficacy, and mental health. Am J Ment Retard 2002;107:222-32.
147. Li J, Vestergaard M, Obel C, Christensen J, Precht DH, Lu M, *et al.* A nationwide study on the risk of autism after prenatal stress exposure to maternal bereavement. Pediatrics 2009;123:1102-7.
148. Arndt TL, Stodgell CJ, Rodier PM. The teratology of autism. Int J Dev Neurosci 2005;23:189-99.
149. Rutter M. Incidence of autism spectrum disorders: Changes over time and their meaning. Acta Paediatr 2005;94:2-15.
150. Kocijan-Hercigonja D, Remeta D, Orehovac M, Brkljacic D. Prenatal, perinatal and neonatal factors in infantile autism. Acta Med Croatica 1991;45:357-62.
151. Enstrom AM, Onore CE, van de Water JA, Ashwood P. Differential monocyte responses to TLR ligands in children with autism spectrum disorders. Brain Behav Immun 2010;24:64-71.
152. Torres AR. Is fever suppression involved in the etiology of autism and neurodevelopmental disorders? BMC Pediatr 2003;3:9.
153. Adams JB, Baral M, Geis E, Mitchell J, Ingram J, Hensley A, *et al.* The severity of autism is associated with toxic metal body burden and red blood cell glutathione levels. J Toxicol 2009;2009:532640.
154. Baccarelli A, Bollati V. Epigenetics and environmental chemicals. Curr Opin Pediatr 2009;21:243-51.
155. Kern JK, Grannemann BD, Trivedi MH, Adams JB. Sulfhydryl-reactive metals in autism. J Toxicol Environ Health A 2007;70:715-21.
156. D'Amelio M, Ricci I, Sacco R, Liu X, D'Agruma L, Muscarella LA, *et al.* Paraoxonase gene variants are associated with autism in North America, but not in Italy: Possible regional specificity in gene-environment interactions. Mol Psychiatry 2005;10:1006-16.
157. Windham G, Fenster L. Environmental contaminants and pregnancy outcomes. Fertil Steril 2008;89 2 Suppl: e111-6.
158. Choi H, Rauh V, Garfinkel R, Tu Y, Perera FP. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and risk of intrauterine growth restriction. Environ Health Perspect 2008;116:658-65.
159. Salam MT, Millstein J, Li YF, Lurmann FW, Margolis HG, Gilliland FD. Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: Results from the Children's Health Study. Environ Health Perspect 2005;113:1638-44.
160. Johnson-Restrepo B, Kannan K. An assessment of sources and pathways of human exposure to polybrominated diphenyl ethers in the United States. Chemosphere 2009;76:542-8.
161. Costa LG, Giordano G, Tagliaferri S, Caglieri A, Mutti A. Polybrominated diphenyl ether (PBDE) flame retardants: Environmental contamination, human body burden and potential Adverse health effects. Acta Biomed 2008;79:172-83.
162. Luginaah IN, Lee KS, Abernathy TJ, Sheehan D, Webster G. Trends and variations in perinatal mortality and low birthweight: The contribution of socio-economic factors. Can J Public Health 1999;90:377-81.
163. Sampson RJ, Morenoff JD, Gannon-Rowley T, Assessing

"neighborhood effects": Social processes and new directions in research. Ann Rev Sociol 2002;28:443-78.
164. Currenti SA. Understanding and determining the etiology of autism. Cell Mol Neurobiol 2010;30:161-71.
165. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, *et al*. Births: Final Data for 2006. National Vital Statistics Reports. Vol. 57. Hyattsville, MD: National Center for Health Statistics; 2009.
166. Brimacombe M, Ming X, Lamendola M. Prenatal and birth complications in autism. Matern Child Health J 2007;11:73-9.
167. Bilder D, Pinborough-Zimmerman J, Miller J, McMahon W. Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. Pediatrics 2009;123:1293-300.
168. Sugie Y, Sugie H, Fukuda T, Ito M. Neonatal factors in infants with autistic disorder and typically developing infants. Autism 2005;9:487-94.
169. Burstyn I, Sithole F, Zwaigenbaum L. Autism spectrum disorders, maternal characteristics and obstetric complications among singletons born in Alberta, Canada. Chronic Dis Can 2010;30:125-34.
170. Stein D, Weizman A, Ring A, Barak Y. Obstetric complications in individuals diagnosed with autism and in healthy controls. Compr Psychiatry 2006;47:69-75.
171. Laxer G, Rey M, Ritvo ER. A comparison of potentially pathologic factors in European children with autism, Down's syndrome, and multiple physical handicaps. J Autism Dev Disord 1988;18:309-13.
172. Timonen-Soivio L, Vanhala R, Malm H, Leivonen S, Jokiranta E, Hinkka-Yli-Salomäki S, *et al*. The association between congenital anomalies and autism spectrum disorders in a Finnish national birth cohort. Dev Med Child Neurol 2015;57:75-80.
173. Juul-Dam N, Townsend J, Courchesne E. Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population. Pediatrics 2001;107:E63.
174. Haglund NG, Källén KB. Risk factors for autism and Asperger syndrome. Perinatal factors and migration. Autism 2011;15:163-83.
175. Karmel BZ, Gardner JM, Meade LS, Cohen IL, London E, Flory MJ, *et al*. Early medical and behavioral characteristics of NICU infants later classified with ASD. Pediatrics 2010;126:457-67.
176. Schendel DE, Autry A, Wines R, Moore C. The co-occurrence of autism and birth defects: Prevalence and risk in a population-based cohort. Dev Med Child Neurol 2009;51:779-86.
177. Williams K, Helmer M, Duncan GW, Peat JK, Mellis CM. Perinatal and maternal risk factors for autism spectrum disorders in New South Wales, Australia. Child Care Health Dev 2008;34:249-56.
178. Croen LA, Yoshida CK, Odouli R, Newman TB. Neonatal hyperbilirubinemia and risk of autism spectrum disorders. Pediatrics 2005;115:e135-8.
179. Badawi N, Dixon G, Felix JF, Keogh JM, Petterson B, Stanley FJ, *et al*. Autism following a history of newborn encephalopathy: More than a coincidence? Dev Med Child Neurol 2006;48:85-9.
180. Dawson S, Glasson EJ, Dixon G, Bower C. Birth defects in children with autism spectrum disorders: A population-based, nested case-control study. Am J Epidemiol 2009;169:1296-303.
181. Tripi G, Roux S, Canziani T, Bonnet Brilhault F, Barthélémy C, Canziani F. Minor physical anomalies in children with autism spectrum disorder. Early Hum Dev 2008;84:217-23.
182. Mason-Brothers A, Ritvo ER, Pingree C, Petersen PB, Jenson WR, McMahon WM, *et al*. The UCLA-University of Utah epidemiologic survey of autism: Prenatal, perinatal, and postnatal factors. Pediatrics 1990;86:514-9.
183. Atladóttir HO, Thorsen P, Schendel DE, Østergaard L, Lemcke S, Parner ET. Association of hospitalization for infection in childhood with diagnosis of autism spectrum disorders: A Danish cohort study. Arch Pediatr Adolesc Med 2010;164:470-7.
184. Bryson SE, Smith IM, Eastwood D. Obstetrical suboptimality in autistic children. J Am Acad Child Adolesc Psychiatry 1988;27:418-22.
185. Gillberg C, Gillberg IC. Infantile autism: A total population study of reduced optimality in the pre-, peri-, and neonatal period. J Autism Dev Disord 1983;13:153-66.
186. Deykin EY, MacMahon B. Pregnancy, delivery, and neonatal complications among autistic children. Am J Dis Child 1980;134:860-4.