Annals of Pediatric Research

Review Article
Published: 17 Mar, 2020

Role of Vitamin D and Calcium in Autism Spectrum Disorder: Overview

*Eman Refaat Youness**

Department of Medical Biochemistry, National Research Centre, Egypt

Abstract

Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental condition that cause common problems in communication and social interactions among children. Beyond the role of vitamin D in bone metabolism, also has a critical role in brain development. Deficiency of vitamin D is related to augmented risk of neurodevelopmental complaints such as (ASD). Vitamin D could maintain the phenotypic stability of both the Ca2_ and redox signaling pathways that play such a key role throughout development.

Introduction

Autism Spectrum Disorder (ASD) is considered as a heterogeneous neurodevelopmental situation, influencing about 1% of kids [1,2]. The ASD is classified *via* social communication shortfalls and the existence of restricted or repetitive interests or behavior (American Psychiatric Association 2013). There are shared difficulties in social interactions and communication among children having ASD as subjects linked to behavioral challenges, comprising aggression, non-compliance and self-injury (American Psychiatric Association 2013). There is no medication can cure ASD; but selected drugs can aid address some of the symptoms related to ASD, especially certain behaviors (American Psychiatric Association 2013). Some ASD intrusions were based on behaviors, while others were deliberated food therapies that relatives trust may enhance behavioral outcomes, as minerals, vitamins, Gluten-Free & Casein-Free (GFCF) diet and essential fatty acids [3-5]. The communal criticisms of ASD individuals are abdominal pain, chronic constipation and diarrhea [6]. Certain foods cause gastrointestinal and allergies symptoms, in addition to behavioral symptoms [7]. Given the early onset and chronic nature of ASD, dietary supplements can determine the need for families, because they can be administered early or for a long time for younger children [8,9]. Autism Spectrum Disorder (ASD) is the term for a variety of circumstances, counting Asperger syndrome, that influence a person's social communication, interaction, behavior and interests. The Centers for Disease Control and Prevention (CDC) evaluates autism's propagation as 1 in 68 children in the United States. Autism is the greatest common in girls (1 in 42 boys *vs.* 1 in 189 girls). In UK, it is probable that one in every 100 persons has autism. Previously around 700,000 children in UK have autism. When Australia is painstaking, it is estimated that almost 230,000 Australians reanimate with ASD that is around four times more frequent in boys than in girls. Astonishingly, India, one of the largest countries in the World, had no exact data of prevalence of autism [10]. Symptoms are expressed in autistic children earlier the age of three. Sometimes diagnosis can be made at age of three or later. Early intrusion in those patients may progress outcomes only. ASD causes are numerous; one of them is gene influence for sure. Nevertheless, no exact genes are related with ASD. Apart of genes, definite impact can be referred to environmental influences. The greatest supposed environmental complexes registered in epidemiology that can have impact on ASD, are pesticides, tetrachlorodibenzodioxin, benzo (a) pyrene, valproate, heavy metals, bisphenol A, cocaine, acetaminophen, polyhalogenated biphenyls, diesel constituents, phthalates, etc. Also, there are listed endocrine disruptors (over 100) including paraquat, atrazine and other pesticides not yet studied in autism and many compounds used in food, cosmetics or household products (including aspartame, tretinoin, soy phytoestrogens, titanium dioxide, and sodium fluoride). Some researchers have shown that dense contact to pesticides and air pollution (especially particulate matter <2.5 and 10 μm in diameter) throughout pregnancy is also related to ASD [11]. Numerous polluting chemical materials can affect Thyroid Hormone (TH) metabolism that might lead to irregularities in the neurological development of the child or the fetus. There was connection between autism development and thyroid gland dysfunction [12]. Investigators also observed other likely related factors. They found that maternal infections (CMV and rubella with fetal brain injuries, and possibly

OPEN ACCESS

Correspondence:
Eman Refaat Youness, Department of Medical Biochemistry, Medical Division, National Research Centre, Giza, Egypt, E-mail: hoctober2000@yahoo.com

Received Date: *11 Feb 2020*
Accepted Date: *13 Mar 2020*
Published Date: *17 Mar 2020*

Citation:
Youness ER. Role of Vitamin D and Calcium in Autism Spectrum Disorder: Overview. Ann Pediatr Res. 2020; 4(1): 1033.

Influenza with fever), maternal inflammation and prolonged fever, particularly with modifications in assortment of antibodies and inflammatory cytokines that cross the placenta may lead to ASD by affecting the brain of fetus. Some drugs as: Valproic acid, misoprostol, thalidomide, etc. paracetamol and β2-adrenergic receptor agonists have also latterly been related to augmented rate of ASD however the data is too in conclusive and preliminary [13]. Forward-looking parental age is also related to higher risk of ASD. Birth complications that are associated with ischemia or trauma and hypoxia have also shown strong relations to ASD. On the other side, other pregnancy related factors as diabetes maternal & obesity, and caesarian section have shown a less strong (but significant) relationship with ASD risk. Food allergies are frequently correlating with ASD. In one case report, peanut and milk allergies were conveyed in 13 months old child [14]. There is mounting attention in the oxytocin system role in social behavior & cognition. The neuropeptide oxytocin and its receptor have been prophesied to be implicated in organizing social functioning in autism spectrum disorders. Some researchers inspected the Oxytocin level (OT) in people suffering from ASD. They found that individuals with ASD may exhibit an OT dysregulation on the basis of changes in OT receptor gene expression [15]. OT can be liberated from brain throughout stressful circumstance [16].

Nurture and Nature

Although there is varied recognition that ASD has double reasons, both environmental and genetic in origin, lacking of accurate conception of the precise technique supporting strange neurodevelopment. Autistic broader phenotypes and characters (subclinical) of ASD are inherited and ceaselessly dispersed in the general population, through etiologies overlapping with clinical phenotypes [17]. Genome sequencing data mentions there are hundreds of genes related to ASD, both rare and common (*de novo* and inherited), with several common with another psychiatric, neurodevelopmental, and neurological conditions [18]. However the clinical service of genetic proof is currently restricted, it is improving, enabling in some cases estimation of the likelihood of familial recurrence, genetic explanations of ASD, and identification of other related genetic risks [19]. Whereas heritability assessments for ASD range from 38% to 55% and upwards to 95%, some twin and family researches proposed heritability had a lesser role than supposed before, indicating a greater part for environmental factors [20-23]. While one twin study found shared environment plays a major role in ASD etiology, the majority of family and twin studies suggest non shared environmental factors, or factors unshared between family members that make them dissimilar, are more influential [23]. But, classifying exact non-shared environmental reasons is interesting given they out spread behind features of nurturing, to factors with measurement fault, random biological noise, social chance, neuroinflammation & immune reaction, also genetic and epigenetic differences in identical twins [24]. Evidence of non-shared environmental impacts has been found through the life span and autism spectrum, from autistic characters to extreme clinical phenotypes of ASD. Complicating the decoding of the impact of non-shared environmental factors in the ASD etiology is the point that their key mechanism is likely collective frequency, rather than lone causative agents [25]. As monozygotic twins share 100% of their genetic variation at a DNA sequence level and dizygotic twins share on average 50%, twin researches offer a lone prospect for designing the relative influence of genetics and environmental factors to ASD phenotypes. Comparing dizygotic and monozygotic twin pairs and their phenotypic discordance and concordance enables examination of the environmental and genetic contributions (non-shared and shared) to ASD presentations (ACE model) [26]. The environment can be both causal if it influences the causal chain between a genetic predisposition and ASD, mediating if it is harmful and precedes ASD, protective if it decreases the risk of ASD and moderating if it influences the severity of autism. The biological environment encompasses all bacterial, viral, chemical, or physical environmental exposures and influences, directly and primarily acting on the individual physiology. Psychosocial environmental factors indicate the social, psychological, and cultural environments that mainly act on mental functions and secondarily on physiology. Understanding of the causative part of environmental factors in the ASD etiology can possibly inform both primary banning and evidence-based interventions. Although the environment is obviously key in med interposing unnecessary negative outcomes and of overriding significance in secondary and tertiary interventions and rein forcing autistic individuals in their life. While research has examined the role of environmental factors in increasing the risk of autism, developing research balances this emphasis, reassessing the environment as a possibly etiological protective factor of ASD [27]. The environmental and genetic contributions to the etiology of ASD have broadly surveyed factors in isolation, rather than considering the role of gene environment relations *via* processes as changes. Epigenetic mechanisms amend gene expressions organized by factors other than DNA sequencing and are reversible. Epigenetic mechanisms, as DNA methylation, play a historic role in ASD etiology in merging environmental and genetic factors that alter neurodevelopmental processes [28-30]. A body of developing indications to various success and onset models, integrating both environmental and genetic contributions like the Trigger Threshold Target model and the three-hit concept of resilience and vulnerability, as fruitful approaches in understanding the development & etiology of the phenotype of autism [31,32].

Environmental Factors

Investigated biological environmental risk factors in ASD include maternal and paternal age, fetal environment (e.g. Sex steroids, maternal infections/immune activation, obesity, diabetes, hypertension, or ultrasound examinations), perinatal and obstetric events (e.g., hypoxia), medication (valproate, selective serotonin reuptake inhibitors), smoking and alcohol use, nutrition (e.g. short inter-pregnancy intervals, e.g. vitamin D, iron, zinc, and copper), vaccination, and toxic exposures (air pollution, heavy metals, pesticides, organic pollutants). Astonishingly, the role of protective factors as fatty acid and folic acid intake and examine their level at frequent times. While there are many postulated mechanisms through which these environmental factors might generate autistic behaviors and clinical variants of ASD, inflammation and immune activation, oxidative stress, hypoxia, and endocrine disruptions are likely the most pivotal in contributing to atypical neurodevelopment. Although the relevance of these factors may not be directly causal, but confounded by genetic factors, understanding is limited by the paucity of research examining gene environment interactions [27].

Parental Age

The advanced parental age importance is a well-proven risk factor for chromosomal aberrations, as advanced maternal age in Down syndrome. There was amassing evidence of the importance of older parental age in the neurodevelopmental and etiology of psychiatric conditions counting schizophrenia, bipolar disorder, ADHD, and

ASD substance use disorders [33,34]. While numerous hypotheses have been posed as to the biological mechanisms of an association between advanced parental age paternal and maternal age effects, and increasing likelihood of malign *de novo* mutations has been suggested [35]. This was most likely elucidated by mutations accumulating risk during spermatogenesis through the life span [36]. Certainly, *de novo* mutations linked with ASD are more overwhelmingly paternal than maternal [37]. It was found that linked autism risk in offspring of older fathers was detected with age-related DNA methylation changes in their sperm [38]. Stimulatingly, these impacts might even be intergenerational, with advanced grandparent paternal age on both father's and mother's side linked to ASD, proposing that parental age-related risk might accumulate over generations [22]. In neurobiology, augmented paternal age has been allied with reduced cortical thickness of the right ventral posterior cingulate cortex [39]. It has also been hypothesized that the increased risk of ASD with advancing age is elucidated by males with autism risk, in the form of a subclinical broader autism phenotype. If this is the case, the increasing risk of ASD with advancing paternal age might be elucidated by genetic tendency, rather than biological aging. However, this hypothesis was reinforced [40]. Contradicting this theory is evidence that young parental aged is linked to some neurodevelopmental disorders, for instance ADHD, a complaint often comorbid to ASD [41,42]. Parental age-related risk in ASD has been found in cohorts across multiple geographic regions; with evidence those parental age-related risks for ASD offerings independently for paternal and maternal age. There is evidence that parental age-related risk is at its maximum in offspring where both the father and mother are advanced in age, and that there is a high risk of ASD for couples with greater age differentials [43]. Also it is probable that advanced paternal age causes higher maternal age for male offspring and a higher risk for female offspring [44].

Fetal Environment

Numerous environmental prenatal exposures present within the immediate environment of the developing fetus such as sex hormone alterations, maternal obesity, diabetes, hypertension, infections and immune activity, and ultrasound exposure have been considered in the context of ASD etiology. While the origins of these risks might be in genetic disposition, environmental interactions involving both them other and fetus with the potential to compromise the fetal maternal placental system cannot be ignored. Plenty of these factors could be the output of the amalgamation of numerous underlying pathophysiological procedures, as the negative effects of imbalanced fetal sex hormone contact throughout critical time openings on gene transcription and expression, and subsequent neuropeptide, neurotransmitter, or immune pathways [45,46]. Obesity endures an independent risk for diabetes, being overweight, coronary heart disease, obstetric problems and several other medical situations in the offspring [47]. Also maternal obesity is presupposed to influence the cognitive functions and brain development of offspring [48]. High-fat diet and severe maternal obesity might affect offspring and fetal neurodevelopment, through processes comprising low-grade increased oxidative stress, neuroinflammation, glucose, insulin resistance & leptin signaling, dopaminergic signaling and dysregulated serotonergic, altered DNA methylation patterns and perturbations in synaptic plasticity [49,50]. All these and extra risks for neurodevelopment are augmented in the existence of co-occurring diabetes [51]. Hypertension during pregnancy contributes substantially to mortality perinatal and morbidity of both the mother and her child [48]. Hypertension may lead to sequelae of untoward utero conditions, increasing the risk of long-term vascular and potentially altering fetal development, psychiatric outcomes and cognitive in the offspring.

Increased blood pressure is the chief driver of these adverse consequences. This is mainly problematic when it is correlating with preeclampsia, which exists with significant quantities of protein in the urine and risks of low blood platelet count, red blood cell breakdown, kidney dysfunction, impaired liver function, shortness of breath, swelling, due to fluid in the lungs, and visual disturbances [52]. Infection throughout pregnancy stimulate the maternal immune system, generating cytokine signaling, passing through the placenta, and possibly producing plentiful adverse neural effects in the developing fetal brain [53].

Vitamin D and Its Metabolism

Vitamin D is a steroid hormone that is provided through exposure to sunlight or from food sources; nevertheless, the diets consumed by most humans contain slight quantities of vitamin D, unless it is rich in fatty fish [54]. This vitamin is made from 7-dehydro-cholesterol in the skin through UVB radiation. Whether vitamin D enters the body through dermal synthesis or dietary intake, it is converted to 25-hydroxy cholecalciferol by the 25α-hydroxylase enzyme in the liver and then is activated to 1,25-dihydroxy cholecalciferol by the enzyme 1α-hydroxylase in the kidneys [55]. More than 85% of vitamin D in the circulation is strongly bound to vitamin D Binding Protein (DBP), and freeform & the fraction bound to albumin, are only the active biological forms [56]. Serum levels of 25(OH) D are the finest indicator for vitamin D status determination [57]. Regardless of sex and age, vitamin D deficiency has been reported worldwide, and according to global estimates, more than one billion people worldwide suffer from vitamin D deficiency [58]. In addition to calcium/phosphorus and bone metabolism, vitamin D plays role in regulation of immune and hormonal responses, metabolic processes, antioxidant activity, cellular differentiation & proliferation. It also has a critical role in brain development. Vitamin D affect neuroprotective and neurotrophic processes in the brain, and also potentially affects synaptic plasticity and neurotransmitters [54,59]. Vitamin D deficiency might disturb the nervous system function and possibly increases the occurrence of neurological diseases as Autism Spectrum Disorder (ASD). Vitamin D appears to have the strongest impact on the nervous system in the perinatal period. It is also associated with alterations in the mental status of adults, so that its insufficiency has been listed in neurological diseases such as depression, ASD, Multiple Sclerosis (MS), Parkinson disease, Alzheimer's disease and Attention Deficit Hyperactivity Disorder (ADHD) [54,59].

Vitamin D and Autism Spectrum Disorder

Several hypotheses have been proposed for the relationship between vitamin D and autism. Serum levels of vitamin D are lower than normal [57,60]. In 2012, it was found the lower serum levels of vitamin D in children with autism (mean serum levels of 15 ng/ml in children with autism compared to 30 ng/ml in healthy children), and also a significant correlation between serum vitamin D level and severity of ASD grading was listed [61]. It is not clear whether children with ASD are born with low levels of vitamin D, or limited exposure to sunshine leads to lower levels of vitamin D in ASD patients. Researchers suggested that low levels of vitamin D in children with ASD have a genetic basis [60,62]. Kocovska et al. [59] found that children with ASD have significantly lower levels of vitamin D

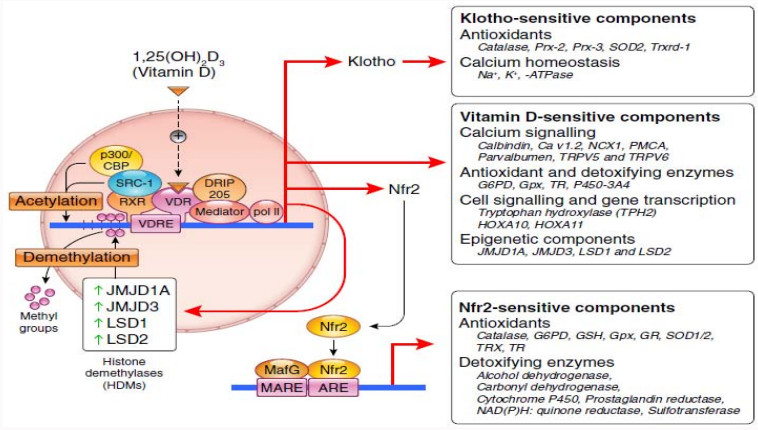

Figure 1: When vitamin D (1,25-dihydroxyvitamin D3 [1,25(OH)$_2$D3]) binds to the Vitamin D Receptor (VDR) it then interacts with the Retinoid X Receptor (RXR) and this complex binds to the Vitamin D Response Element (VDRE) that begins to induce the expression of a number of different genes. Many of these genes act to control many different cellular control mechanisms. In addition, vitamin D controls the expression of both Nrf2 and Klotho that contribute many of the vitamin D homeostatic functions.

compared to their siblings whom all live in an environment with low sun shine [63]. Also, Fernell et al. [64] analyzed 58 pairs of siblings, one of them with ASD and the other was healthy, and concluded that the serum levels of vitamin D at the birth time were lower in children with ASD. Schmidt et al. [65] examined the association between common vitamin D polymorphisms in charge Cohort & ASD and found that polymorphisms related to lower levels of vitamin D, were more common in children with ASD. Dissimilar opinions about the disease have proposed that oxidative stress is a possible cause of ASD. In autism, oxidative stress markers are elevated, while the level of glutathione, one of the most significant antioxidants in the body, diminished [66]. It was found that vitamin D is important in regulating the production of antioxidants as superoxide dismutase, glutathione and thioredoxin reductase [54]. So, it can exert protective effects against ASD.

Vitamin D and ASD Mechanism

The biological active form of vitamin D, 1,25(OH)2D, suppresses production of inducible nitric oxide synthase, that catalyzes nitric oxide, a free radical that might damage cells. Furthermore, 1,25(OH)2D stimulates gamma-glutamyl transpeptidase activity, that causes the synthesis of glutamine, an antioxidant that scavenges free radicals [54]. Vitamin D also stimulates brain cells to yield a number of growth factors such As Glial Cell Line-Derived Neurotrophic Factor (GDNF), Neurotrophin-3 (NT3) and Nerve Growth Factor (NGF). Regarding neuroprotective and neurotrophic activities of vitamin D, it is suggested that this vitamin may stimulate neuronal growth, so vitamin D decreased in the progression of neurodegenerative diseases [54]. Three possible implications of vitamin D in ASD have been indicated including (i) Vitamin D is associated with DNA repair genes and it repairs mutated genes in individuals, thereby reducing the risk of ASD [67], (ii) Vitamin D plays an important role in the immune system. Vitamin D is important in regulating the production of antioxidants as thioredoxin reductase, superoxide dismutase and glutathione. Therefore, considering the role of vitamin D in regulating the production of antioxidants, vitamin D can reduce the activity of neuroglial cells and reduce neuroinflammation [68], and (iii) there are reports of autoimmune conditions in people with ASD, which includes the presence of maternal antibodies in the brain tissue of the fetus [69]. Vitamin D plays an important role in inducing T regulatory cells that these cells regulate the control of antibodies associated with auto-immune. Therefore, vitamin D induces T regulatory cells to reduce the risk of auto-immunity and protect the fetus [60,70]. Three different independent findings point towards a role for vitamin D in the development of ASD including (1) Increasing the risk of ASD in migrant children, especially from countries where their populations have darker skin color, as well as cultures in which women use covering clothing and do not benefit from other ways to take vitamin D, (2) Low levels of 25(OH)D in newborns who later got advanced ASD, as well as in children and adults with ASD, and (3) The relationship between the season and the ASD [71].

Phenotypic Stability Hypothesis of Vitamin D Action

During development, each cell type has a differentiation program that selects out those genes responsible for its particular function. This differentiation program also determines that each cell type expresses the signaling system that is appropriate for its particular function. It is essential that the transcription of those components that make up the signaling phenotype of each specific cell type be maintained. There are a large number of vitamin D sensitive target genes that are regulated by vitamin D binding to the Vitamin D Receptor (VDR), which interacts with the retinoid X receptor before binding to the vitamin D response element (Figure 1). The action of vitamin D is markedly enhanced by its ability to control the expression of Nrf2 and the anti-aging protein Klotho, which are also important regulators of multiple cellular signaling systems that occur in all cells [72,73]. Many of the genes that are controlled by the vitamin D/Klotho/Nrf2 regulatory network function to maintain both Ca_2^- and redox homeostasis [74]. For instance, vitamin D augments the expression of Ca_2^- pumps, buffers and exchangers. It also acts to reduce the expression of the L-type Ca_2^- channel to maintain low levels of Ca_2^- [75]. Likewise, vitamin D together with Nrf2 and Klotho elevate cellular antioxidants to maintain the normal within the cell so, preventing oxidative stress by scavenging Reactive Oxygen Species (ROS). For instance, the expression of the γ-glutamyl transpeptidase (γ-GT), glutathione reductase and glutamate cysteine ligase that contribute to the synthesis of the major cellular redox buffer glutathione (GSH), is regulated by vitamin D. Vitamin D also increases the activity of Glucose-6-Phosphate Dehydrogenase (G6PD) to increase the formation of GSH.

It down regulates the NADPH oxidase that generates ROS while upregulating the superoxide dismutase that rapidly converts $O_2^{-\bullet}$ to H_2O_2. Vitamin D also up regulates expression of the glutathione peroxidase that leads to the conversion of H_2O_2 to water [76]. It turns out that vitamin D working together with Nrf2 and Klotho plays an essential role in maintaining the phenotypic stability of many of these cell signaling pathways and particularly the Ca_2^- and redox signaling systems [77-82].

Conclusion

The vitamin D/Klotho/Nrf2 trio are the major custodians of such phenotypic stability and this may explain why a deficiency in vitamin D seems to affect so many of the processes that occur during development and could explain the problem of infertility and the onset of the neurodevelopmental diseases such as ADHD, autism, and schizophrenia. There is now considerable evidence to show that the epigenetic landscape is of critical importance during neural development and function. For example, a deficiency in the epigenetic factor euchromatin histone methyltransferase1 results in an alteration in brain wiring during development. The ability of vitamin D to modulate the epigenetic landscape may thus maintain the development processes via its ability to control phenotypic stability so that the right genes are activated to control each phase of development.

References

1. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marci'n C, et al. Global prevalence of autism and other pervasive developmental disorders. Autism Res. 2012;2(5):160-79.
2. Fombonne E, Quirke S, Hagen A. Epidemiology of pervasive developmental disorders. In Amaral DG, Dawson G, Geschwind DH, editors. Autism spectrum disorders. New York. NY: Oxford University Press. 2011.
3. Whiteley P. Food and the gut: Relevance to some of the autisms. Proc Nutr Soc. 2017;76(4):478-83.
4. DeFilippis M. The Use of Complementary Alternative Medicine in Children and Adolescents with Autism Spectrum Disorder. Psychopharmacol Bull. 2018;48(1):40-63.
5. Hamadneh S, Alazzam M, Kassab M, Barahmeh S. Evaluation of Intervention Programs for Children with Autism. Int J Pediatr. 2019;7(4): 9341-47.
6. Holingue C, Newill C, Lee L, Pasricha P, Fallin D. Gastrointestinal symptoms in autism spectrum disorder: A review of the literature on ascertainment and prevalence. Autism Res. 2017;11(1):24-36.
7. Gurney JG, McPheeters ML, Davis MM. Parental report of health conditions and health care use among children with and without autism: National Survey of Children's Health. Arch Pediatr Adolesc Med. 2006;160(8):825-30.
8. Stewart PA, Hyman SL, Schmidt BL, Macklin EA, Reynolds A, Johnson CR, et al. Dietary Supplementation in Children with Autism Spectrum Disorders: Common, Insufficient, and Excessive. J Acad Nutr Diet. 2015;115(8):1237-48.
9. Lai WW, Goh TJ, Oei TP, Sung M. Coping and Well-Being in Parents of Children with Autism Spectrum Disorders (ASD). J Autism Dev Disord. 2015;45(8):2582-93.
10. Rudra A, Belmonte MK, Soni PK, Banerjee S, Mukerji S, Chakrabarti B. Prevalence of autism spectrum disorder and autistic symptoms in a school-based cohort of children in Kolkata. Autism Res. 2017;10(10):1597-605.
11. Carter CJ, Blizard RA. Autism genes are selectively targeted by environmental pollutants including pesticides, heavy metals, bisphenol A, phthalates and many others in food, cosmetics or household products. Neurochem Int. 2016.
12. Ozzola G. Pollution, the thyroid and neurodevelopment. Clin Ter. 2016;167(6):191-7.
13. Ornoy A, Weinstein-Fudim L, Ergaz Z. "Genetic syndromes, maternal diseases and antenatal factors associated with Autism Spectrum Disorders (ASD)". Front Neurosci. 2016;10:316.
14. Lucarelli J, Pappas D, Welchons L, Augustyn M. "Autism spectrum disorder and avoidant/restrictive food intake disorder". J Dev Behav Pediatr. 2017;38(1):79-80.
15. Yang S, Dong X, Guo X, Han Y, Song H, Gao L, et al. "Serum oxytocin levels and an oxytocin receptor gene polymorphism (rs2254298) indicate social deficits in children and adolescents with autism spectrum disorders". Front Neurosci. 2017;11:221.
16. Valstad M, Alvares GA, Egknud M, Matziorinis AM, Andreassen OA, Westlye LT, et al. "The correlation between central and peripheral oxytocin concentrations: A systematic review and meta-analysis". Neurosci Biobehav Rev. 2017;117-20.
17. Constantino JN, Todd RD. Autistic traits in the general population: A twin study. Arch Gen Psychiatry. 2003;60(5):524-30.
18. Vorstman JAS, Parr JR, Moreno-De-Luca D, Anney RJL, Nurnberger JI Jr, Hallmayer JF. Autism genetics: Opportunities and challenges for clinical translation. Nat Rev Genet. 2017;18(6):362-76.
19. Tammimies K, Falck-Ytter T, Bolte S. Quo Vadis clinical genomics of ASD? Autism. 2016;20(3):259-61.
20. 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(3):255-74.
21. Tick B, Bolton P, Happe F, Rutter M, Rijsdijk F. Heritability of autism spectrum disorders: A meta-analysis of twin studies. J Child Psychol Psychiatry. 2016;57(5):585-95.
22. Frans EM, Sandin S, Reichenberg A, Langstrom N, Lichtenstein P, McGrath JJ, et al. Autism risk across generations: A population-based study of advancing grand paternal and paternal age. JAMA Psychiatry. 2013;70(5):516-21.
23. 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(11):1095-102.
24. Turkheimer E, Waldron M. Nonshared environment: A theoretical, methodological, and quantitative review. Psychol Bull. 2000;126(1):78-108.
25. Willfors C, Carlsson T, Anderlid BM, Nordgren A, Kostrzewa E, Berggren S, et al. Medical history of discordant twins and environmental etiologies of autism. Transl Psychiatry. 2017;7(1):1014.
26. Plomin R, DeFries JC, McClearn GE, McGuffin P. Behavioral Genetics, 5th ed. Worth Publisher. New York. 2008.
27. Bolte S, Sonya G, Marschik PB. The contribution of environmental exposure to the etiology of autism spectrum disorder. Cell Mol Life Sci. 2019;76(7):1275-97.
28. Grafodatskaya D, Chung B, Szatmari P, Weksberg R. Autism spectrum disorders and epigenetics. J Am Acad Child Psychiatry. 2010;49(8):794-809.
29. Wong CC, Meaburn EL, Ronald A, Price TS, Jeffries AR, Schalkwyk LC, et al. Methylomic analysis of monozygotic twins discordant for autism spectrum disorder and related behavioural traits. Mol Psychiatry. 2014;19(4):495-503.
30. Schuch V, Utsumi DA, Costa TV, Kulikowski LD, Muszkat M. Attention deficit hyperactivity disorder in the light of the epigenetic paradigm. Front

Psychiatry. 2015;6:126.

31. Daskalakis NP, Bagot RC, Parker KJ, Vinkers CH, de Kloet ER. The three-hit concept of vulnerability and resilience: toward understanding adaptation to early-life adversity outcome. Psychoneuroendocrino. 2013;38(9):1858-73.

32. Mottron L, Belleville S, Rouleau GA, Collignon O. Linking neocortical, cognitive, and genetic variability in autism with alterations of brain plasticity: the trigger-threshold-target model. Neurosci Biobehav Rev. 2014;47:735-52.

33. Merikangas AK, Calkins ME, Bilker WB, Moore TM, Gur RC, Gur RE. Parental age and offspring psychopathology in the philadelphia neurodevelopmental cohort. J Am Acad Child Adolesc Psychiatry. 2017;56(5):391-400.

34. Janecka M, Mill J, Basson MA, Goriely A, Spiers H, Reichenberg A, et al. Advanced paternal age effects in neurodevelopmental disorders-review of potential underlying mechanisms. Transl Psychiatry. 2017;7(1):1019.

35. Goldmann JM, Wong WS, Pinelli M, Farrah T, Bodian D, Stittrich AB, et al. Parent-of-origin-specific signatures of *de novo* mutations. Nat Genet. 2016;48(8):935-9.

36. Jonsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, et al. Parental influence on human germline *de novo* mutations in 1,548 trios from Iceland. Nature. 2017;549(7673):519-22.

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(7412):471-5.

38. Atsem S, Reichenbach J, Potabattula R, Dittrich M, Nava C, Depienne C, et al. Paternal age effects on sperm FOXK1 and KCNA7 methylation and transmission into the next generation. Hum Mol Genet. 2016;25(22):4996-5005.

39. Kojima M, Yassin W, Owada K, Aoki Y, Kuwabara H, Natsubori T, et al. Neuro anatomical correlates of advanced paternal and maternal age at birth in autism spectrum disorder. Cereb Cortex. Cereb Cortex. 2019;29(6):2524-32.

40. 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(12):1203-12.

41. Chang Z, Lichtenstein P, D'Onofrio BM, Almqvist C, Kuja-Halkola R, Sjölander A, et al. Maternal age at childbirth and risk for ADHD in offspring: A population-based cohort study. Int J Epidemiol. 2014;43(6):1815-24.

42. Bolte S, Poustka L, Geurts H. Comorbidity: Autism Spectrum Disorder. In: Banaschewski T, Coghill D, Zuddas A, editors. Oxford textbook of attention deficit hyperactivity disorder. University Press. Oxford. 2018.

43. Sandin S, Schendel D, Magnusson P, Hultman C, Suren P, Susser E, et al. Autism risk associated with parental age and with increasing difference in age between the parents. Mol Psychiatry. 2016;21(5):693-700.

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(5):477-86.

45. Kosidou K, Dalman C, Widman L, Arver S, Lee BK, Magnusson C, et al. Maternal polycystic ovary syndrome and risk for attention-deficit/hyperactivity disorder in the offspring. Biol Psychiatry. 2017;82(9):651-9.

46. Ferri SL, Abel T, Brodkin ES. Sex differences in autism spectrum disorder: A Review. Curr Psychiatry Rep. 2018;20(2):9.

47. Baron-Cohen S, Lombardo MV, Auyeung B, Contu L, Hawkes CA. A review of the impact of maternal obesity on the cognitive function and mental health of the offspring. Int J Mol Sci. 2017;18(5):1093.

48. Rivera HM, Christiansen KJ, Sullivan EL. The role of maternal obesity in the risk of neuropsychiatric disorders. Front Neurosci. 2015;9:194.

49. Edlow AG. Maternal obesity and neurodevelopmental and psychiatric disorders in offspring. Prenat Diagn. 2017;37(1):95-110.

50. Godfrey KM, Reynolds RM, Prescott SL, Nyirenda M, Jaddoe VW, Eriksson JG, et al. Influence of maternal obesity on the long-term health of offspring. Lancet Diabetes Endocrinol. 2017;5(1):53-64.

51. 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(4):125-34.

52. Armaly Z, Jadaon JE, Jabbour A, Abassi ZA. Preeclampsia: Novel mechanisms and potential therapeutic approaches. Front Physiol. 2018;9:973.

53. Smith SE, Li J, Garbett K, Mirnics K, Patterson PH. Maternal immune activation alters fetal brain development through interleukin-6. J Neurosci. 2007;27(40):10695-702.

54. Macova L, Bicikova M, Ostatnikova D, Hill M, Starka L. Vitamin D, neurosteroids and autism. Physiol Res. 2017;66(3):333-40.

55. Cannell JJ, Grant WB. What is the role of vitamin D in autism? Dermatoendocrinol. 2013;5(1):199-204.

56. Bhan I, Powe CE, Berg AH, Ankers E, Wenger JB, Karumanchi SA, et al. Bioavailable vitamin D is more tightly linked to mineral metabolism than total vitamin D in incident hemodialysis patients. Kidney Int. 2012;82(1):84-9.

57. Mazahery H, Conlon C, Beck KL, Kruger MC, Stonehouse W, Camargo CA Jr, et al. Vitamin D and omega-3 fatty acid supplements in children with autism spectrum disorder: A study protocol for a factorial randomised, double-blind, placebo-controlled trial. Trials. 2016;17(1):295.

58. Tabrizi R, Moosazadeh M, Akbari M, Dabbaghmanesh MH, Mohamadkhani M, Asemi Z, et al. High prevalence of vitamin D deficiency among Iranian population: A systematic review and meta-analysis. Iran J Med Sci. 2018;43(2):125-39.

59. Kocovska E, Gaughran F, Krivoy A, Meier UC. Vitamin-D deficiency as a potential environmental risk factor in multiple sclerosis, schizophrenia, and autism. Front Psychiatry. 2017;8:47.

60. Stubbs G, Henley K, Green J. Autism: Will vitamin D supplementation during pregnancy and early childhood reduce the recurrence rate of autism in newborn siblings? Med Hypotheses. 2016;88:74-8.

61. Mostafa GA, Al-Ayadhi LY. Reduced serum concentrations of 25-hydroxy vitamin D in children with autism: relation to autoimmunity. J Neuroinflammation. 2012;17;9:201.

62. Cannell JJ. Autism and vitamin D. Med Hypotheses. 2008;70(4):750-9.

63. Kocovska E, Andorsdottir G, Weihe P, Halling J, Fernell E, Stora T, et al. Vitamin D in the general population of young adults with autism in the Faroe Islands. J Autism Dev Disord. 2014;44(12):2996-3005.

64. Fernell E, Bejerot S, Westerlund J, Miniscalco C, Simila H, Eyles D, et al. Autism spectrum disorder and low vitamin D at birth: A sibling control study. Mol Autism. 2015;6:3.

65. Schmidt RJ, Hansen RL, Hartiala J, Allayee H, Sconberg JL, Schmidt LC, et al. Selected vitamin D metabolic gene variants and risk for autism spectrum disorder in the Charge Study. Early Hum Dev. 205;91(8):483-9.

66. Ghanizadeh A, Akhondzadeh S, Hormozi M, Makarem A, Abotorabi-Zarchi M, Firoozabadi A. Glutathione-related factors and oxidative stress in autism, a review. Curr Med Chem. 2012;19(23):4000-5.

67. Halicka HD, Zhao H, Li J, Traganos F, Studzinski GP, Darzynkiewicz Z. Attenuation of constitutive DNA damage signaling by 1,25-dihydroxyvitamin D3. Aging (Albany NY). 2012;4(4):270-8.

68. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol. 2005;57(1):67-81.

69. Goines P, Van de Water J. The immune system's role in the biology of autism. Curr Opin Neurol. 2010;23(2):111-7.

70. Cantorna MT, Mahon BD. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. Exp Biol Med (Maywood). 2004;229(11):1136-42.

71. Fernell E, Bejerot S, Westerlund J, Miniscalco C, Simila H, Eyles D, et al. Autism spectrum disorder and low vitamin D at birth: A sibling control study. Mol Autism. 2015:6:3.

72. Nakai K, Fujii H, Kono K, Goto S, Kitazawa R, Kitazawa S, et al. Vitamin D activates the Nrf2-Keap1 antioxidant pathway and ameliorates nephropathy in diabetic rats. Am J Hypertens. 2014;27(4):586-95.

73. Forster RE, Jurutka PW, Hsieh J-C, Haussler CA, Lowmiller CL, Kaneko I, et al. Vitamin D receptor controls expression of the anti-aging klotho gene in mouse and human renal cells. Biochem Biophys Res Commun. 2011;414(3):557-62.

74. Pike JW, Zella LA, Meyer MB, Fretz JA, Kim S. Molecular actions of 1,25-dihydroxyvitamin D3 on genes involved in calcium homeostasis. J Bone Miner Res. 2007;22(2):V16-9.

75. Brewer LD, Porter NM, Kerr DS, Landfield PW, Thibault O. Chronic 1alpha,25-(OH)2 vitamin D3 treatment reduces $Ca2^{+}$-mediated hippocampal biomarkers of aging. Cell Calcium. 2006;40(3):277-86.

76. Michael JB. Vitamin D deficiency: Infertility and neurodevelopmental diseases (attention deficit hyperactivity disorder, autism, and schizophrenia). Am J Physiol Cell Physiol. 2018;314(2):135-51.

77. Berridge MJ. Vitamin D: A custodian of cell signalling stability in health and disease. Biochem Soc Trans. 2015;43(3):349-58.

78. Chason RJ, Csokmay J, Segars JH, DeCherney AH, Armant DR. Environmental and epigenetic effects upon pre implantation embryo metabolism and development. Trends Endocrinol Metab. 2011;22(10):412-20.

79. Nelson ED, Monteggia LM. Epigenetics in the mature mammalian brain: Effects on behavior and synaptic transmission. Neurobiol Learn Mem. 2011;96(1):53-60.

80. Martens MB, Frega M, Classen J, Epping L, Bijvank E, Benevento M, et al. Euchromatin histone methyltransferase 1 regulates cortical neuronal network development. Sci Rep. 2016;6:35756.

81. Raio L, Bolla D, Baumann M. Hypertension in pregnancy. Curr Opin Cardiol. 2015;30(4):411-5.

82. Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. The familial risk of autism. JAMA. 2014;311(17):1770-7.