

An Investigation of Physiological and Psychological Parameters in the Development of Autism Spectrum Disorder

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Abstract

Autism spectrum disorder (ASD) is characterized as heterogenic, complex neurodevelopmental disorder which is stemmed back to the Henry Maudsley, later Eugen Bleuler. It is defined as continuous decline in communication skills, incapability in social interactions, and repetitive or restricted behaviors. Early signs of ASD can be reduced response to name, poor eye contact, no gesturing, deficiency in showing and sharing, and deterioration in linguistic and social skills. Prematurity, low birth weight, impaired immune system, mitochondrial dysfunction, toxic metals, and parental effects, such as parental age, may be shown among the etiologic factors for ASD. In addition, the heavy metals, such as lead (Pb), or mercury (Hg), as environmental factors, prenatal environment also is pointed to be an etiologic factor. Chemical or protein modifications in utero, maternal diabetes, infection, fever, epilepsy, or thyroid disease have been indicated as etiologic factors. Besides physiological compounds of ASD, its psychological aspect is also more profound. Intellectual disability, attention-deficit and hyperactivity disorder (ADHD), anxiety disorders, mood disorders are also found as psychiatric comorbidity in patients with ASD. In this paper, our aim is to investigate physiological and psychological background of ASD.

Keywords: Autism spectrum disorder; physiology; psychology; history; etiology

Araştırma Makalesi

Konu: Psikoloji

Makaleye Atıf Bilgisi

Sahmurova, A.; Demir, M. B. (2026). *An Investigation of Physiological and Psychological Parameters in the Development of Autism Spectrum Disorder*. *International Journal of Social Science (IJSS Journal)*, (e-ISSN:2548-0685) Vol:10, Issue:48; s. 280- 300.

DOI: 10.52096/usbd.10.48.16

Gönderim: 12.09.2026

Kabul: 25.10.2026

 **ULUSLARARASI SOSYAL BİLİMLER DERGİSİ**
ULUSLARARASI HAKEMLİ DERGİ

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1. Introduction

Autism spectrum disorder (ASD) is characterized as heterogenic, complex neurodevelopmental disorder which affects nearly 28 million people in the world (Solmi et al., 2022). It is defined as continuous decline in communication skills, incapability in social interactions, and repetitive or restricted behaviors (Hodges et al., 2020). ASD symptoms should manifest in early development period and engender clinically significant impairments in significant areas of functioning, such as occupational, or social areas (Hodges et al., 2020). Early signs of ASD can be reduced response to name, poor eye contact, no gesturing, deficiency in showing and sharing, and deterioration in linguistic and social skills by 12 months (Hodges et al., 2020). A preponderance of children with ASD has impairments in sensory input, such as touch, sound, vision, taste, or smell, which may lead challenges in internalization/externalization, emotional/attentional regulation, and executive function (Darnal et al., 2023). Additionally, some specific behaviors were reported attributing to ASD; picky eating behavior in ASD was observed in children with ASD which leads deficiencies of vitamins, minerals, or fatty acids (Hodges et al., 2020). It is suggested that people who experience ASD or other neurodevelopmental disorders exhibit aggression; also, in comparison, while males with ASD are more tend to express external symptoms, females with ASD are likely to demonstrate less social communication (De Giacomo et al., 2016; Quetsch et al., 2023). In addition to aggression that has been associated with severity of ASD symptoms, self-injury, hyperactivity, and irritability were also reported in ASD patients (Baweja et al., 2023).

2. History of Autism

History of autism is stemmed back to Henry Maudsley (1867), who indicated that children with “very strange” behavior could be defined as having childhood psychosis. In 1911, Eugen Bleuler was the first one who spread the term “autism” as a disorder of schizophrenia defined as a limitation of personal relationships and external world. The term “autism” has spread expeditiously in European psychiatry literature. Later, in Germany, Künkel (1920) called a group of children had schizophrenic traits as “autistic”. Then, Grunja Jefimov Ssucharewa (1926), a Russian psychiatrist, used the “autistic attitude” concept to determine the observed behavior in six children with schizoid

personality disorder, which were strange thoughts (e.g., rumination, perseverance, and rationalization), social isolation, emotional dysregulation, echolalia, impulsivity, and stereotyped behavior. After that, Potter (1933) and Despert (1938) delineate children with affective relationship problems and other qualifications of autistic behaviors prioritized in the form of words over restricted interest, communicative function, and repetitive movements. In 1944, Hans Asperger defended his thesis in “Die ‘Autistischen Psychopathen’ im Kindesalter”. He reported four cases about boys who were between the ages of 7-11. He indicated that “autistic psychopathy” was a general problem, but had sparse rate in girls. The patients described by Asperger presented with lack of empathy, social problems, naivety, repetitive language, poor non-verbal communication. After all, the condition was described was named Asperger’s syndrome. After the work of Kolvin (1972) and Rutter (1972), a major development of the autism classification has emerged. The authors evidenced that autism was different from schizophrenia. In the early 1980s, autism has received a major recognition, as a different pathology from schizophrenia, and was removed from the psychosis category in DSM-III and ICD-10; and it became a part of invasive developmental disorders (TID). After all, from 1981, after the publication of Asperger’s work by Lorna Wing, the scope of the examination was on high functioning individuals. This situation permitted the construction of the concept of “spectrum” of autism, which showed useful traits for genetic researches and clinical field. In 1987, concept of autism spectrum disorder registered in DSM-III-R. After that, in 1994, autism became a member of the TID, along with invasive developmental disorder with no other specification (TID-SOE), childhood disintegrative disorder, Rett syndrome, and Asperger’s syndrome in DSM-IV.(Lebrun & Isaac da Silva, 2023; Pina-Camacho et al., 2018) Further, in DSM-V, conceptualization of autism was changed, and also made changes that have been considered contentious with the definition of autism. A crucial change from DSM-IV to DSM-V is the name used for autism; autism spectrum disorder (ASD) is the new and more inclusive name for diagnosis. In addition, besides Asperger’s syndrome was removed from DSM-V, the description of ASD was aimed more on the thought that ASD symptoms emerge on a spectrum and are discriminated how impairing they are. The three diagnostic criteria from the DSM-IV were turned into two criteria in the DSM-V, which are restricted or repetitive behaviors, and problems with social communication (Golt & Kana, 2022).

3. Etiology

At present, although the etiology of ASD is not fully understood, it is suggested that ASD is multifactorial neurodevelopmental disorder which is shaped by genetic, epigenetic, and environmental aspects (Hodges et al., 2020). To date, genetic background of ASD has been several times investigated by many researchers, which include monozygotic and dizygotic twin studies, indicating that genetic is more likely to play a crucial role in etiology of ASD; and, furthermore, more than 100 risk genes for ASD have been also reported (Huguet et al., 2016). A meta-analysis also showed, synthesizing data from over 13 studies which were published between 1977 and 2015, a concordance rate in 45% in monozygotic twins, and 16% in dizygotic twins (Huguet et al., 2016). High familial components of ASD, to understanding its nature, and etiology, has been multiple times indicated by research. Ramaswami and Geschwind (2018) found that babies who have an older sibling that has ASD 20% more likely to have ASD. Another study conducted by Constantino and colleagues (2012) suggested 70-90% concordance rate for monozygotic, 30-40% concordance rate for dizygotic, and 3-19% concordance rate for siblings. Monozygotic twins share 100% genetic similarity, and dizygotic twins share 50% genetic similarity.

Over the years, the association between heavy metals and ASD have been several times also investigated. Heavy metals are known with its neurologic impacts; lead (Pb) is linked with cognitive decline and synaptic dysfunction; mercury (Hg) can disrupt mitochondria, increase the level of oxidative stress, can enter through placenta and blood-brain barrier (BBB), and impair neurotransmission process; furthermore, cadmium (Cd) can trigger neuroinflammation and oxidative stress; and arsenic (As) may penetrate (BBB) and lead to impairment in neurodevelopment (Karri et al., 2016). It is noteworthy that, considering heavy metal toxicity, BBB is not completely functional in early brain development, that's why, developing brains can be vulnerable to heavy metal toxicity (Błażewicz & Grabrucker, 2022). Heavy metals able to disrupt enzyme functions and cell signaling progresses, generates reactive oxygen species (ROS), impair mitochondrial function, trigger autoimmune reactions, lead apoptosis, and be an etiological factor for ASD (Cheng et al., 2025; Modabbernia et al., 2017). Furthermore, heavy metals aggregate in the central nervous system of ASD children due to lack of excretory capacity leading to neurotoxic impacts (Karri et al., 2016). In addition, studies conducted with children who suffer from

ASD revealed that, they are unable to eliminate toxic metals, which may lead to toxic metal accumulation in the body (Baj et al., 2021). In addition, heavy metal toxicity during pregnancy is considered to be a risk factor for ASD (Amadi et al., 2022). Neurodevelopmentally crucial progress present during in utero, therefore, heavy metal exposure is suggested to be a contributing factor to etiology of ASD (Lyall et al., 2014). The other mechanism that is brain susceptible to high levels of oxidative stress which is suggested to be a risk factor for ASD. Due to heavy metal toxicity, actions in mitochondria may lead reactive oxygen species (ROS), reactive nitrogen species (RNS), and radicals with carbon and sulfur. Minimal ROS levels can be considered as normal, however, elevated levels of ROS which lead oxidative stress are harmful (Bjørklund et al., 2020). In a study conducted by Korean school-age children revealed that, blood Pb levels cause autistic behaviors at 7-8 years of age, and more severe symptoms at 11-12 age (Kim et al., 2016). Other studies performed with children with ASD found that high levels of blood chromium (Cr) were associated with ASD (Tinkov et al., 2019). Dickerson et al. (2015) reported that populations living close to industrial facilities emitting air pollutants and heavy metals, for example, Pb, As, and Hg, exhibit an elevated incidence of ASD. Similarly, mercury, as well as other toxic heavy metals, is known as its neurotoxic effects due to oxidative stress, neuroinflammation, and impairment in mitochondrial function (Karri et al., 2016). Several studies have linked mercury with ASD. In addition, Yoshimasu et al. (2014) found that Hg exposure was cause an increase in risk of ADH 1.7-fold. Furthermore, Ding et al. (2023) found high concentrations of As and Hg in urine test of individuals with ASD, and, therefore, they suggest that, heavy metals have an impact on emergence or progression of ASD. Aluminum (Al) has been also observed in hair and urine samples, and brain tissues of ASD donors (Mold et al., 2020; Sahmurova & Demir, 2025; Sulaiman et al., 2020; Yasuda et al., 2013).

Prenatal environment may be other etiologic factor for ASD, for instance, chemical, or protein modifications in utero may result in neurodevelopmental issues (Kubota & Mochizuki, 2016). A growing body of evidence suggests that prenatal environmental exposure can be a risk factor for ASD, such as maternal diabetes, infection, fever, thyroid disease, epilepsy, and inflammation (Andrade, 2025). In addition to maternal illness, in order to maternal infection, inordinate immune activation during pregnancy was associated with ASD (Lee et al., 2015). An analysis mentioned that after maternal

infection exposure, likelihood of ASD may incline by 32% (Tioleco et al., 2021). In a study performed on Danish population showed that viral infections, for example, influenza, gastroenteritis, and other unclassified viral infections were associated with ASD. In first trimester of pregnancy risk was found as 2.8 times increase, while second trimester risk was 1.4-fold increase (Atladóttir et al., 2010). In addition, rubella, measles, mumps, chicken pox, influenza, herpes simplex virus, pneumonia, syphilis, and varicella zoster were indicated to cause neurological damage in newborns whose mother have been infected (Yoon et al., 2020). Another study investigated maternal fever suggesting 1.3 times increase in development of ASD (Tioleco et al., 2021). Furthermore, maternal nourishment plays a significant role in ASD, in which poor diet and nutrient deficiencies are correlated with neurodevelopmental disorders; imbalances in essential fatty acids, particularly polyunsaturated fatty acids (PUFAs), have been documented in individuals with ASD and other neurodevelopmental disorders (Rodrigues et al., 2023). Furthermore, it has been posited that both shorter and longer inter-pregnancy intervals may incline ASD risk (Schieve et al., 2018). It has been reported that while prenatal folic acid supplements may decrease ASD risk, prenatal exposure to thalidomide, valproic acid, and antibiotic use may incline the risk (Bölte et al., 2019; Ornoy et al., 2015). Besides other risk factors, maternal hormone abnormalities during pregnancy are suggested to be a risk factor for ASD. Research demonstrates that progesterone modulates neurogenic responses and impairs cognitive development by downregulating estrogen receptor beta ($Er\beta$) expression; and, in addition, expressions of $Er\beta$ is considered to be suppressed in the brains of people with ASD (Li et al., 2018). Other maternal risk factors for ASD during pregnancy that are reported are polycystic ovarian disease, vitamin D and folate deficiency, acetaminophen usage, antidepressant exposure, valproate use, and cesarean section (Andrade, 2025). Birth asphyxia is also found to be risk factor for ASD: it has been proposed that birth asphyxia increases the odds of ASD by 10.63-fold (Yuan et al., 2024).

In addition, prenatal nutrition is also crucial for infants' brain development (Li et al., 2019). Imbalance in maternal nutrition intake during pregnancy is suggested to be connected with brain defects (e.g., alteration of hypothalamic and hippocampal pathways, or diminished cerebral volume), elevated risk of abnormal behavior, and neuropsychiatric disorders, such as ASD (Cortés-Albornoz et al., 2021). For example, Zhao et al. (2025)

suggested that low levels of maternal iron or ferritin are correlated with increased risk of autism in offspring. Iron is suggested to be critical for early neurodevelopment; it plays an important role in neurotransmitter production, myelination, and immune function whose dysregulation connected with the ASD (Schmidt et al., 2014). Besides iron, prenatal vitamin D deficiency was correlated with 2-fold increased risk of developing ASD (Avram et al., 2025). Vitamin D has a key role in neurodevelopment as a neurosteroid hormone. It contributes neuro cell proliferation, neurotransmission, oxidative stress, and immune function in the Central Nervous System. Accordingly, prenatal vitamin D deficiency may affect the developing brain, and cause significant neuropsychological manifestations, such as ASD (Siracusano et al., 2020). In a study conducted by Fernell et al. (2015) measured 25-hydroxyvitamin D (25(OH)D) levels in 58 Sweden-born sibling pairs in which one sibling has ASD and other sibling had not. Results revealed that, comparing to healthy sibling, ASD patients had significantly lower levels of vitamin D (Fernell et al., 2015). The other aspect that contributes the development of ASD is zinc deficiency (Sauer et al., 2022). Zinc has a crucial role in nucleic acid/protein synthesis, tissue growth and repair, and cell replication. Also, zinc serves as a basic trace element which acts as a catalytic center for more than 300 enzymes. In brain, zinc is co-localized with glutamate in presynaptic vesicles. It is fundamental for regulating excitatory neurotransmission and receptor activity on the postsynaptic membrane. Therefore, zinc deficiency is suggested to be linked with various pathological conditions which include neurodegenerative and neurodevelopmental problems (Yasuda & Tsutsui, 2013). Several studies which measure serum, nails, hair, teeth, or blood samples of ASD patients concluded that there is a negative correlation between zinc levels and ASD risk (Zhang et al., 2021). Similarly, choline is an important micronutrient for neurodevelopment and offspring brain. It can support normal brain development, improve neural and cognitive functioning, and protect from neural and metabolic insults (Derbyshire & Maes, 2023). Choline is also found at lower levels in ASD patients compared to individuals without ASD (Jennings & Basiri, 2022). It is suggested to have a crucial role in severity and incidence of core ASD symptoms (Derbyshire & Maes, 2023). Additionally, polyunsaturated fatty acids (PUFAs), particularly omega-3 fatty acids, are significant for nervous system function, and structural and functional brain development (Huang et al., 2020; Koç Gökşen et al., 2025). In a study conducted by Lyall

et al. (2013) found that there was a negative relationship between PUFA intake in pregnancy and autism risk in offspring. Other study conducted with 258 mother-child pairs by Huang et al. (2020) suggested that omega-3 intake in the 2nd half of pregnancy was linked with 40% lower risk of ASD in the offspring. Another fact that is linked with ASD is vitamin A. Serum vitamin A is suggested to be negatively associated with severity of ASD. Vitamin A deficiency in early infant development or during pregnancy may impact neurodevelopment and cause disruptions in learning, memory formation, or cognitive function (Liu et al., 2021). A study conducted by Sun et al. (2013) with 53 ASD children and 53 typically developed children between the age of 4-6 years revealed that vitamin A and calcium were significantly lower in ASD group. Another study performed in China with 154 ASD children (age=5.21 ± 1.83 years) and 73 typically-developing children (age = 4.83 ± 0.84 years) demonstrated that ASD group had highest vitamin A and iron deficiency (Liu et al., 2016). Similarly, Guo et al. (2020) performed a study which measured vitamins and minerals of 274 ASD children and 97 typically-developing children. Results showed that vitamin D, folate, calcium, magnesium, iron, and zinc levels were significantly lower in ASD group (Guo et al., 2020). A cross-sectional study conducted in China with 738 ASD children and 302 typically-developing children indicated that the serum levels of vitamin A, vitamin D, and folate had negative correlation with ASD (Zhu et al., 2020). In addition, Magnesium (Mg) is known as a crucial element for child growth, has a key role in neurodevelopment and neuronal maturation, and also it is included in multiple processes in brain development and functioning (Skalny et al., 2020). A study conducted with 45 ASD children and 50 typically-developing children revealed that magnesium was significantly lower in ASD group (Lakshmi Priya & Geetha, 2011). Other important aspect for neurodevelopment is vitamin B12; it is involved in DNA synthesis, red blood cell formation, and nervous system functioning, therefore, maternal vitamin B12 deficiency, which is also crucial for fetal neurodevelopment, may cause impaired neurodevelopmental trajectories (Zwierz et al., 2025). A meta-analysis showed that, which identified 37,932 participants, levels of vitamin B12 in ASD patients were significantly lower (Tan et al., 2023).

4. Psychological Aspects of ASD

Besides the physiology of ASD, its psychological impact is also much more profound. It has been several times indicated that individuals with autism spectrum disorder are more

tend to have psychological manifestations as comorbid disorders; elevated risks of mood disorders, anxiety disorders, schizophrenia, stress disorders, intellectual disability, and behavioral problems are common among the patients with ASD (Rim et al., 2023). It has been suggested that while approximately 70% of individuals with ASD having at least 1 psychiatric comorbidity, 40% of ASD patients have a risk of multiple comorbid disorders (Hossain et al., 2020). In addition to behavioral problems, such as irritability, aggression, or self-injurious behaviors, ADHD, obsessive-compulsive disorder, gender dysphoria, and suicidality have been also found in many patients with ASD. Lack of ability to regulate emotions may result in, or ease experiencing these symptoms exaggeratedly (Genovese & Butler, 2023). Besides the lack of emotion regulation skills in patients with ASD, age, intellectual functioning, or sex also play a role in influencing these psychiatric comorbidities (Rosen et al., 2018). Lever et al. (2016) pointed out that age and risk of having comorbid psychological disorders have a negative relationship. In a study conducted with 989 preschool age children with ASD revealed that 37.8% of them had at least 1 psychiatric comorbidity. Results also showed that 23.4% of children had Affective Problems (AP), 17.3% of them had ADHD, 16.7% of them had Anxiety Problems, and 7.9% of them had Oppositional Problems (Muratori et al., 2019). A meta-analysis also found that 26.2% of the ASD patients had attention-deficit and hyperactivity disorder (ADHD), 22.9% of them had intellectual disability, 11.1% of them had anxiety disorders, 19.7% of them had sleep disorders, 2% of them had bipolar disorders, and 2.7% of them had depression (Mutluer et al., 2022). Another study findings revealed that 28% of patients with ASD had ADHD, 20% of them had anxiety disorders, 13% of them had sleep disorders, and 11% of them had depressive disorder (Lai et al., 2019). In addition to psychological symptoms and manifestations, suicide risk also has been several times mentioned (Chen et al., 2017). In a study performed by O'Halloran et al. (2022) revealed that suicide ideation was 25.2%, suicide attempts was 8.3%, and death by suicide 0.2% in individuals with ASD.

5. Conclusion

This paper has explored the multifaceted nature of Autism Spectrum Disorder (ASD), tracing its trajectory from early historical conceptualizations to its modern standing which is known as complex neurodevelopmental condition. ASD is characterized as continuous impairment in communication skills, lack of ability in social circumstances, and repetitive

or restricted behaviors. Furthermore, its etiology is multifaceted; twin studies, in addition to epigenetic factors, indicate it familial, hereditary component. Environment also can be considered as an etiologic factor for ASD. Heavy metals, such as lead, or mercury have been posited to cause ASD. Moreover, prenatal environment is considered to be etiologic factor for ASD; maternal diabetes, infection (e.g., influenza, rubella, measles, mumps, chicken pox), fever, thyroid disease, epilepsy, and inflammation may result in ASD. In order to explain psychological aspects of ASD, mood disorders, anxiety, sleep disorders, and intellectual disability have been found in ASD patients as comorbid disorders.

6. Suggestions

Recently, the number of individuals with ASD increases. Even though exact etiology is not fully understood, several precautions should be taken due to minimize the risk of ASD:

- (1) Early biomarker screening should be applied. Given the evidence regarding heavy metal accumulation, clinical protocols should consider incorporating metabolic and toxicological screenings in early age of individuals.
- (2) Due to regulate neurotoxins, policy-makers should implement stricter regulations on industrial emissions of heavy metals.
- (3) Parental education programs should be applied. Public health campaigns should focus on educating expecting parents about the preventable etiological factors of ASD.
- (4) Since nearly 70% of individuals with ASD carry the risk of at least 1 comorbid psychiatric disorder, interventions for these individuals should be reachable.
- (5) Further researches should understand the precise “bridge” between environmental triggers and genetic expression, and clarify the possible link between ASD and given etiologic factors.

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