

# Autism Spectrum Disorder: Evolution of Disorder Definition, Risk Factors, and Demographic Characteristics in Israel

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**ABSTRACT:** Autism spectrum disorders (ASD) are among the most common developmental disabilities. Since its first description, autism has been redefined multiple times. In the early 20th century, autism was classified as a psychotic disorder, grouped with schizophrenia by professionals. In the latter decades of the 20th century, the diagnosis was completely revised in the third revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-3), and redefined as a pervasive developmental disorder. At the outset of the 21st century, autism was re-conceptualized as a spectrum of neurobiological developmental disorders. With the changes in the definition, there has been worldwide increase in disease incidence and prevalence. In 2013, the DSM-5 definition for ASD was changed yet again.

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One of the most difficult challenges of dealing with autism spectrum disorders (ASD) is accurate and timely diagnosis. Early diagnosis is a prerequisite for intervention and may be associated with significant improvements in outcome. In addition, comprehensive neuropsychiatric and developmental evaluation is crucial for diagnosing other conditions that may require additional management.

Community pediatricians and nurses play an important role in developmental screening, and population-based approaches are indicated. The role of community health providers is even more critical in disadvantaged populations because the awareness of ASD and the attitude toward the diagnostic

## The medical concept of autism has undergone significant changes in the past 100 years

and therapeutic process is low. Achievement of optimal developmental outcomes in ASD depends on cooperation between the various stakeholders and the development of policies to reduce gaps in diagnosing and treating autism in the population, especially for those at risk for health disparities.

### AUTISM SPECTRUM DISORDER: EVOLUTION OF DISORDER DEFINITION, RISK FACTORS, AND DEMOGRAPHIC CHARACTERISTICS IN ISRAEL

The number of people diagnosed with ASD has risen steeply in recent decades. In this article, we review the conceptual development of the disorder's definition and features over time while addressing the disparities in diagnosis in different populations within Israel.

The word autism is derived from the Greek *autos* meaning “self”. The term was first proposed by Swiss psychiatrist Eugen Bleuler in 1911. This word describes the escape from reality and poor relationships with others, as well as self-seclusion and convergence, which can be seen in schizophrenic patients [1]. In the 1940s, in a series of influential studies, Leo Kanner, a psychiatrist at Johns Hopkins University who is widely considered to be one of the most influential child psychiatrists of the 20th century, borrowed Bleuler's terminology because he also understood that these children seemed to be trying to escape reality [2].

Based on the developmental assessments of 11 children who did not fit into any known diagnostic category, Kanner found that the main characterization of these children was their inability to relate to people and to unfamiliar social situations.

Kanner differentiated patients with these findings from other types of mental disabilities through his Theory of Mind, calling the syndrome early infantile autism. The emphasis on childhood distinguishes between autism and schizophrenia. Kanner's definition, with a later description of other special characteristics of the disorder,

resulted in autism becoming a distinct diagnosis [2]. In 1944, Hans Asperger, a pediatrician from Vienna, Austria, independently described a similar series of patients [3].

However, until the 1970s, mental health professionals continued to classify autism together with schizophrenia. In 1975, autism was incorporated as a separate disease entity in the International Classification and Diagnosis of Diseases (ICD-9) of the World Health Organization (WHO). In this edition, the diagnostic criteria were not yet described, and autism was still categorized with psychoses [4].

In 1980, the first amendment to the diagnostic criteria of autism was made. The term “infantile autism” was included in DSM-III (the Diagnostic and Statistical Manual of Mental Illness of the American Psychiatric Association), and was classified as part of the pervasive developmental disorders (PDD), permanently removing autism from classification as a form of schizophrenia. The term “atypical autism” (PDD NOS) was added as a disorder belonging to the PDD group [5]. In the 1987 edition (DSM-III-R), the boundaries of the category were expanded, and the term “child-

hood autism” was replaced by the term “autistic disorder” [6]. In the fourth edition of the DSM [7], the syndrome was characterized by qualitative defects in three areas: insult to social interaction, damage to communication, and patterns of behavior-interest and/or limited repetitive stereotypes. Rett syndrome and Asperger’s syndrome were also classified as forms of PDD. In 1999, at the National Autism Conference in the United States, autism was defined as, “complex developmental disabilities resulting from a neurobiological disorder that affects brain function” [8]. DSM-IV characterized the autism syndrome by three core impairments (language, social communication, and repetitive behaviors). In the DSM-5 (2013), language delay was excluded from the diagnostic criteria. The term ASD has become an all-encompassing reference to a variety of syndromes, replacing several terms used by DSM-IV that included part of the diagnostic group under PDD (autism, Asperger’s, and PDD NOS). Rett syndrome was omitted from the classification and reclassified as a neurological diagnosis. Childhood disintegrative disorder was omitted because there was insufficient epidemiological evidence to support its existence [9].

The etiologic perception of ASD has also changed significantly from the days of Bettelheim (1967), in which the “cold mother” theory developed [10], suggesting that parenting styles had a causative role in the development of ASD.

It is now believed that the main factors are neurobiological and that ASD are not acquired disorders, although environmental factors may contribute. There is no single genetic factor related to ASD, and different genetic profiles can lead to the same phenotype. Many genetic studies of genome association and genome rearrangements have identified genes or polymorphisms that increase the risk of developing ASD [11]. Recurrence risk for

ASD when one child is diagnosed is approximately 5%–18.7% per pregnancy [12,13]. When there are two children in the same family, the per-pregnancy risk rises to 25%–35%, and the frequency is higher in identical twins. When one twin has autism, the risk for a second twin is 80%–90%. These data indicate that ASD have a significant hereditary component [12]. The ratio between boys and girls in ASD is 4:1. The excessive male predominance has suggested that there is a correlation between ASD and the X chromosome. Genetic studies have found a correlation between changes on the X chromosome and ASD, but the condition is not inherited in the classic X-linked pattern for recessive or dominant disorders [14].

Age disparity between parents, elderly parents, and teenage mothers are also risk factors for a child to be diagnosed with autism. The incidence of ASD in children born to fathers over age 50 years is 66% higher than that of a child with ASD with fathers in their 20s. Among children born to mothers in their 40s, the autism rate is 15% higher than that of children born to mothers in their 20s. An autism rate was found to be about

**The present definition of autism includes a spectrum of neurobiologic disorders with overlapping phenotypic behaviors**

18% higher among children born to teenage mothers than children born to mothers in their 20s. Cesarean sections [15],

prolonged labor [16], short inter-pregnancy intervals [17], and assisted reproductive technology induced pregnancy [18] have also been associated with a risk for ASD. These findings suggest that beyond the genetic component, environmental factors related to the pregnancy may also play a significant role.

**DIAGNOSIS**

Despite the genetic factors of autism and related physiological findings, there is no definitive laboratory or radiologic diagnostic modality for ASD, and infants who go on to develop severe ASD may have been described as completely normal during the first months of life. Clinical identification and diagnosis are possible only when difficulties in social interaction are detected and repetitive behaviors appear. However, it is clear that early and intensive developmental intervention lead to better outcomes of children with ASD [19]. According to the U.S. Centers for Disease Control and Prevention, the median age for diagnosis of ASD is 52 months [20], and more than 25% of children with ASD are not diagnosed before age 8 years [21]. The American Academy of Pediatrics recommends screening all children for signs of ASD in the second year of life [22].

There are two types of diagnostic tools: primary screening tools for identifying children with behaviors associated with an increased risk for ASD in the general population and definitive ASD diagnosis performed in specialized centers. The Modified Checklist for Autism in Toddlers (M-CHAT) is the first and most widely used ASD screening tool [23]. The questionnaire is performed between the ages of 18 and 30 months. The questionnaire has a sensitivity of 85% and a specificity of 93% [22], and

has been validated in various populations in many countries. The M-CHAT was designed to be self-administered by the parent, and some countries use internet-based questionnaires to facilitate screening. Because false-positives at the population level may result in unnecessary referral, a modified form of the M-CHAT, the M-CHAT-R/F (Revised with Follow-Up) can be performed in the community for children who test positive on the initial screen, or as initial testing for high-risk children (such as siblings of diagnosed ASD). The MCHAT-R/F is a detailed interview that asks the parent about the items that were positive in the primary M-CHAT [24].

For children identified as at-risk for ASD by the screening process, standardized tools are available for definitive diagnosis of ASD, enabling consistent measurement and definition. There are two tests that are most often applied today but which require organized training and high operator skill. The Autism Diagnostic Observation Schedule (ADOS) is considered one of the most valid and reliable tools for diagnosing the disorder [25]. ADOS is a semi-structured clinical observation that includes carefully planned activities to diagnose symptoms of ASD. This tool has four modules that are adapted in terms of their activities to the child according to age and verbal/mental level. The encoded items correlate with the DSM criteria. Severity of symptoms are reflected in a high ADOS score. A separate score can be obtained in the social, communicational, and behavioral areas with cross-sectional diagnosis of ASD compared to other difficulties on the social and behavioral communication spectrum [26]. Autism Diagnostic Interview (ADI) is a semi-structured parent interview that includes directed questions about symptoms in the areas of the disorder. A high score indicates greater severity of the disorder [27].

The evaluation process includes developmental and cognitive assessment, psychiatric evaluation, and comprehensive medical evaluation, including elaboration of related clinical conditions, genetic disorders, seizures, and audiologic and neurological assessment [28]. Unrecognized hearing loss can present with phenotypic features consistent with ASD and must be ruled out before diagnosis. Hearing loss can also result in false positives in screening. Community pediatricians and public health nurses at health maintenance organizations and maternal and child health centers identify and follow children with neurodevelopmental concerns, including ASD, cerebral palsy, mental retardation, or language disorder. To perform this task, basic but up-to-date knowledge is required in the field of child development and neurology. Long-term specialist follow-up for known or suspected conditions is usually conducted in child development institutes. In an Israeli study of pediatricians, there was high variability of knowledge of child development in general and for ASD in particular [29].

The diagnosis of ASD in Israel is achieved through a combination of medical and psychological modalities, where medical aspects are diagnosed by psychiatrists, neurologists, or child developmental specialists, and psychological diagnosis is performed by clinical, developmental, or other qualified psychologists [30]. In Israel, the use of screening and diagnostic tools is primarily for research purposes and not used systematically in clinical diagnosis because the tests are expensive and they require considerable time and training to administer. Therefore, there may be significant differences in diagnosis of ASD between centers in Israel.

#### PREVALENCE

In recent decades, the prevalence of children with ASD has increased worldwide. It is hypothesized that this increase is partly due to changes in the understanding of the disorder and diagnostic methods, and partly from an actual increase in ASD. Investigations of environmental triggers have not consistently demonstrated correlations. The prevalence of ASD has also increased in Israel [31]. In the United States, 1 out of every 59 children is diagnosed with ASD [20]. According to Israeli National Insurance Institute (NII) data for 2013, 1 out of 200 live births in Israel was diagnosed with ASD during childhood. In December

### **Despite the worldwide increase in autism prevalence, populations who experience health inequality may be underdiagnosed. In Israel, ethnic, religious, and geographic disparities lead to significant differences in diagnosis**

2013, 10,270 children with autism received monthly social security benefits for their condition, which was approximately 27% of all children receiving stipends and 0.4% of all children in Israel [32]. In a cohort study, there was a tenfold

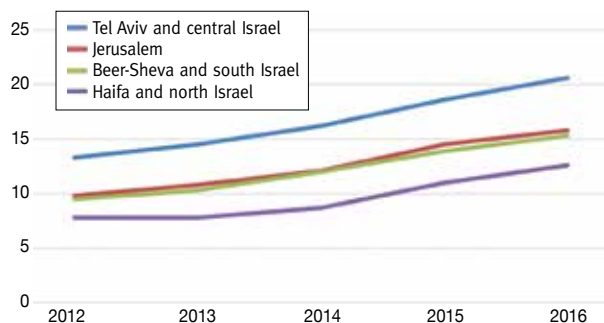
increase (from 0.049% to 0.49%) in the incidence of ASD for children born in 2003 compared to data from 1992 in children who were monitored until 2011 [33]. The change in incidence is less pronounced in the Haredi (ultra-Orthodox) Jewish and Arab populations. The overall prevalence among Arabs and Haredi Jews was significantly lower compared to the total population (1.2, 2.6, and 5.5 per 1000, respectively) [34].

#### DEMOGRAPHIC AND SOCIAL CHARACTERISTICS IN ISRAEL: PREVALENCE OF AUTISM BY DISTRICTS

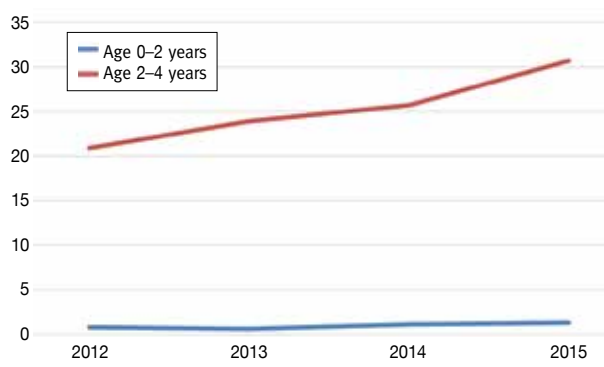
A particularly large concentration of people with autism registered with the Ministry of Social Affairs and Social Services live in the Tel Aviv and central districts. Figure 1 shows the proportion of people with autism listed in the Ministry of Social Affairs (MSA) by district (1:10,000) [35].

In 2016, the rate of people with ASD in the district that includes Tel Aviv and central Israel reached 20.6, compared to the districts of Beer Sheva and southern Israel (15.3), Jerusalem (15.8), and Haifa and northern Israel (12.6). Despite the claims of MSA that the gaps are narrowing [36], Figure 1 shows separate prevalence rates by district, with the highest rate being found in Tel Aviv and the center of the country, and the lowest rates in Haifa and northern Israel. This concentration is in

**Figure 1.** Rate of autism spectrum disorders that are registered in the Ministry of Social Affairs by district (1:10,000)



**Figure 2.** Rate of children under age 4 years with autism spectrum disorder who are registered in the Ministry of Social Affairs (1:10,000)



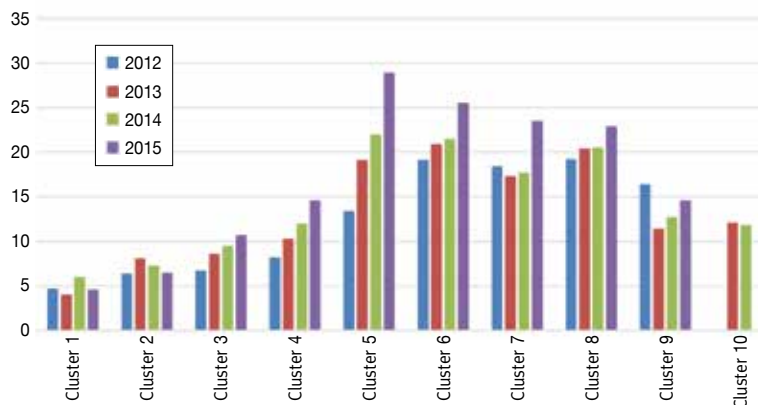
line with other findings indicating that the prevalence of ASD correlates. There was a correlation between ethnicity and ASD rates. There appears to be an association with country of origin, as the proportion of people with autism among those born in Europe and America in 2013 is 19.5 per 10,000, compared to 12 and 9 among those born in Asia and Africa, respectively. It is important to note that most of these people were born in Israel, thus it is their parents and/or grandparents with different countries of origin.

**PREVALENCE OF ASD IN EARLY CHILDHOOD**

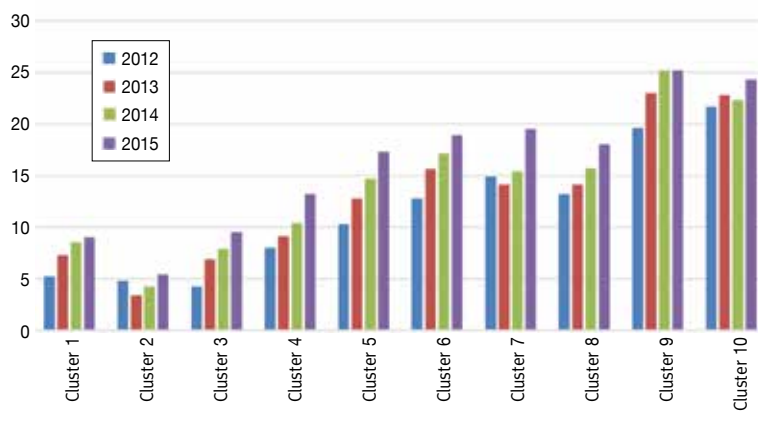
In recent years there has been an increase in the rates of young children with ASD. Figure 2 shows rates of young children with ASD enrolled in the MSA, at the age of 0–2 years, compared to 2–4 years [35].

Although recent years have shown an increase in the rate of diagnosis in early childhood, most children with ASD are diagnosed after the age 2 years. In 2015, the rate of children diagnosed up to the age of 2 years was 1.3 per 10,000 compared to 2012, when the rate for this age was only 0.8 per 10,000. From the age of 2 to 4 years, the rate of diagnosis in 2015 was 30.7 compared to 2012, when the rate was 20.9 per 10,000 [36]. The

**Figure 3.** Rate of children under age 5 years of age with autism spectrum disorder who are registered in the Ministry of Social Affairs, according to socioeconomic cluster (1:10,000)



**Figure 4.** Rate of people with autism spectrum disorder who are registered in the Ministry of Social Affairs, according to socioeconomic cluster (1:10,000)



reasons given for explaining the increase in the rate of those diagnosed are related to increased awareness, development of diagnostic tools, and changes in medical definitions.

**PREVALENCE OF ASD BY SOCIOECONOMIC CLUSTER**

People with ASD are registered in social services departments of MSA by socioeconomic cluster. Figure 3 describes the rates of people with ASD by socioeconomic cluster.

ASD is less frequently reported in low socioeconomic clusters (clusters 1,2,3) compared to high social and economic clusters (clusters 9,10). There is a high correlation between a high socioeconomic cluster and the rate of ASD. The highest rate of people with autism are in the highest clusters (clusters 9,10).

**PREVALENCE OF ASD BY SOCIOECONOMIC CLUSTER IN CHILDREN**

Children with ASD are registered in social services departments of MSA by socioeconomic cluster. Figure 4 describes the rates of people with ASD by socioeconomic cluster.

According to the data of the Department of Social Services of MSA in Israel, there are fewer diagnoses of ASD in preschoolers in the highest and lowest socioeconomic clusters. Figure 4 illustrates that in 2015 cluster 1 and cluster 10 had rates of 4.6 and 0 per 10,000, respectively, compared with 28.9 and 25.5 in clusters 5 and 6, respectively [36]. Comparison of Figure 3 and Figure 4 suggests that in low socioeconomic clusters the rates are low in early childhood and remain relatively low with increasing age, whereas in higher clusters the rates also are low in early childhood but increase with age. This phenomenon suggests disparate diagnostic rates of ASD on the basis of socioeconomic status. It is possible that the reason for low overall rates in the higher clusters is that this population does not need the services of the MSA and therefore they are not listed in the MSA database.

The number of individuals with ASD in the Arab population is lower than the national average. The 120,000 Bedouin residents of the Negev who live in unrecognized settlements are not included in the socioeconomic ranking of the State of Israel. Of the 9133 people with ASD registered with the MSA and Social Services in 2013, only 506 (5.5%) were Arabs, far below the expected number in relation to their relative population [36].

## CONCLUSIONS

ASD are a group of neurodevelopmental disorders characterized by a combination of difficulties in social communication and a tendency towards repetitive behavior. The prevalence of ASD has risen worldwide as well as in Israel [34,37]. The change in the definition of the disorder plays an important role in the increased rates of ASD in recent years, but there may be other factors as well. Over the past few decades, two critical paradigm shifts occurred in the definition of the disorder, which probably resulted in a significant increase in the rate of ASD diagnosed. The proposed hypothesis of “theory of mind” as a cardinal feature of the pathogenesis of ASD has contributed to increased diagnosis, as have changes in diagnostic criteria and the exclusion of social communication disorders from the spectrum. The increased rates of ASD have important implications for Israel’s public health policy, legislation, planning, and resource allocation.

The hereditary component of ASD has been partially elaborated, but environmental factors may also be important.

It is difficult to obtain full information on all the children diagnosed in Israel from the population of Jews and Arabs without a national registry. The data collected and presented here are from the MSA databases published each year, which represent most, but not all, of the children and people diagnosed with ASD. There is a pressing need for a national disease registry.

## Early diagnosis of autism enables effective intervention and significant improvement in function, requiring unique modalities of diagnosis and education in difficult-to-access populations

There are significant disparities in the rate of diagnosis between Jews and Arabs. These gaps most likely stem from lack of awareness, stigmatization of neurological disorders in the Arab population, and impaired access of care in the Arab population. Due to these differences, representation of under-diagnosis may not show true differences in prevalence rates. There is also a lack of service providers who understand Arab culture and

can administer diagnostic tools in culturally sensitive ways. Disparities in frequency of ASD, as measured by MSA benefits, exist in different geographical areas in Israel. ASD is less commonly diagnosed in populations at risk for health inequality and is also correlated with social and economic characteristics, raising the question of under-diagnosis. Because early diagnosis is critical for outcome, equitable and efficient health services for identifying and diagnosing children with ASD, adapted to the social, ethnic, and cultural characteristics as well as the needs and beliefs of all parts of the population, are essential. Policy makers should work with government agencies, mother and child health centers, health funds, academic institutions, and social organizations to develop policies to reduce gaps in the prevalence of ASD in populations at risk for health inequality.

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**Capsule**

**Identification of an amino acid motif in HLA-DRβ1 that distinguishes uveitis in patients with juvenile idiopathic arthritis**

Uveitis is a visually debilitating disorder that affects up to 30% of children with the most common forms of juvenile idiopathic arthritis (JIA). The disease mechanisms predisposing only a subgroup of children to uveitis are unknown. Haasnoot and colleagues aimed to identify genetic susceptibility loci for uveitis in JIA, using a genome-wide association study in 522 children with JIA. Two cohorts of JIA patients with ophthalmologic follow-up data were genotyped. Data were then imputed using a genome-wide imputation reference panel, and an HLA-specific reference panel was used for imputing amino acids and HLA types in the major histocompatibility complex (MHC). After imputation, genome-wide and MHC-specific analyses were performed and a reverse immunology approach was used to model antigen presentation at 13 common HLA-

DRβ1 alleles. Presence of the amino acid serine at position 11 (serine 11) in HLA-DRβ1 was associated with an increased risk of uveitis in JIA patients (odds ratio [OR] 2.60,  $P = 5.43 \times 10^{-10}$ ) and was specific to girls ( $P_{females} = 7.61 \times 10^{-10}$  versus  $P_{males} = 0.18$ ). Serine 11 resides in the YST motif in the peptide-binding groove of HLA-DRβ1. All 3 amino acids in this motif are in perfect linkage disequilibrium and show identical association with disease. Quantitative prediction of binding affinity revealed that HLA-DRβ1 alleles with the YST motif could be distinguished on the basis of discernible peptide-binding preferences.

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Eitan Israeli

**“I’ve learned that people will forget what you said, people will forget what you did, but people will never forget how you made them feel”**

Maya Angelou, (1928–2014), American poet, memoirist, and civil rights activist