Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: August 31, 2022

Citation: Diamond G and Jaber L, 2022. Differing Diagnostic Trends in Autism Spectrum Disorders Between Ethnic Groups Reflecting Potential Etiological Risk Factors, Medical Research Archives, [online] 10(8). https://doi.org/10.18103/mra.v10i8.2976

DOI
https://doi.org/10.18103/mra.v10i8.2976

ISSN: 2375-1924

RESEARCH ARTICLE

Differing Diagnostic Trends in Autism Spectrum Disorders Between Ethnic Groups Reflecting Potential Etiological Risk Factors

Gary Diamond[1,2] and Lutfi Jaber[2,3,4]

[1]Alyn Hospital for Children's Rehabilitation, Jerusalem 6494222, Israel
[2] Faculty of Medicine, Tel Aviv University, P.O.B 39040. Ramat Aviv, 69978, Israel
[3]The Bridge to Peace Community Pediatric Center, Taibe
[4]Department of Neurology and Child Development, Schneider Children's Medical Center of Israel, Kaplan Street 14, Petah Tikva 4920235, Israel

*dr.garydiamond@gmail.com

ABSTRACT

Introduction: Autism spectrum disorders (ASDs) are a group of developmental disabilities characterized by impairments in social interaction and communication, and by restricted, repetitive, and stereotyped patterns of behavior. Symptoms typically are apparent before age three years.

Aim: To determine the prevalence of ASD amongst children along ethno-religious lines, where differences might point to potential trigger factors in its causation in a middle to high-income country.

Methods: Diagnostic trends of ASD over the past 18 years were examined over a wide geographical area of central Israel, encompassing a database of 331,169 children, aged 3-18 years. Special importance was attached to statistics from different religious and ethno-cultural groups as potentially reflecting discrepancies in diagnosis, reporting, and possible environmentally- related factors in the presentation of a genetically determined syndrome.

Results: Overall prevalence was 0.005 (1/200 live births), well below figures from other similar studies abroad and in Israel. Prevalence figures for the ultra-orthodox Jewish community were low (0.0021), when compared with the general population and similar that among Israeli Arabs (0.0017). Time trends indicated a surge in diagnosis of ASD among Israeli Arabs between the years 2008 and 2011, in contrast with a general flattening of figures for the orthodox community.

Conclusions: Results indicated that besides discrepancies in diagnosis and reporting factors, there exists a possible relation between the actual expression of ASD, its genetic predisposition and socioeconomic/cultural status as impacting as part of the epigenetic factors in the causality of autism. Our prevalence rates are currently lower than those of ASD in Europe and the USA.

Keywords: Autism, autism spectrum disorder, Arabs, Jews, prevalence

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental syndrome characterized and diagnosed by impairments in social communication and interaction in the presence of restricted, repetitive behaviors or interests.[1] Population prevalence is estimated at ~1.5% in developed countries around the world.[2,3]

Even though the full range of etiologies underlying ASD remains largely unexplained, progress has been made in the past decade in identifying some neurobiological and genetic underpinnings of, and risk factors for, this complex condition. ASD is highly heritable, but environmental factors are also implicated in ASD.[4,5] Multiple lines of evidence suggest the etiology of ASD has prenatal origins, and thus, potential epigenetic causality.[6]

The aim of our study was to determine whether the different socioeconomic and cultural environments in which mothers give birth and children are raised, as dictated by social prohibitions and attitudes inherent in religious or ethnic cultural lifestyles, have an impact on the causality of ASD. Of interest in these cultural differences are factors potentially impacting on the quality of the mother's microenvironment during pregnancy and after the delivery: her physical and emotional health, socio-economic status, role in the home and in society and life style vis a vis her employment and education.

We examined the prevalence and diagnostic trends over time of ASD in Israel, an international location, which straddles the definition of a middle to high income country, among three strikingly different pediatric population groups, divided along ethno-religious lines: 1) Israeli Arabs, both Moslem and Christian, (IA); 2) Ultra-orthodox Jews (UOJ) and 3) the general remaining population (GRP), i.e. mostly secular, or nominally observant Jews. Israeli Arabs and Ultra-orthodox Jews tend to hail from lower socioeconomic backgrounds.

The highest recent international prevalence estimate was 2.64%, for 7–12 year- old children in South Korea in 2005–2009.[7] Within the U.S., non-white race, Hispanic ethnicity, and low socioeconomic status (SES) have been associated with lower ASD prevalence and delayed diagnosis[3,8] In contrast, in other international locations, ASD diagnosis tends to correlate with factors related to lower, rather than higher SES as in the case of the Scandinavian countries.[9]

The social and demographic characteristics of Israel present a unique opportunity to examine prevalence trends as a function of lifestyle along ethnic and religious lines. Communities tend to be homogeneous and mutually exclusive, mostly by choice, while being in close geographical proximity to each other, thereby eliminating differences in the ecological environment as possible trigger factors of ASD.

A 2009 study reported that the annual incidence rate of Israeli children with a diagnosis of ASD receiving disability benefits rose from zero between 1982 and 1984 to 190 per million in 2004 . It was not known whether these figures reflected true increases, or were related to other factors, such as changes in diagnostic measures.[10,11] Few of the epidemiological studies performed in Israel, a multiracial and multicultural society, have documented ASD prevalence along ethnic, cultural, religious and socioeconomic lines.[11,12]

In previous reviews of demographically-based prevalence trends of ASD among different ethnic, religious and immigrant groups in Israel, noticeable differences have often appeared, depending on locale and ethnic origin. In one study, the general native Israeli-born rates were compared with one distinctive ethnic group, i.e., Ethiopian Jews. The latter were in transition from immigrant status of Ethiopian-born parents, with the first generation of their children being born in Israel.[12] Rates of ASD were considerably elevated among second generation Ethiopians born in Israel, as opposed to their first generation immigrant Ethiopian-born parents.

Methods

The method used to ascertain the prevalence of ASD in two large regions of the public health system was based on estimation of the period prevalence, as of April 2014. Our prevalence population survey screened a large sample of an entire community to identify possible cases, and, where feasible, evaluated each possible case in more detail, examining the medical history and diagnostic procedures performed in each case. Within the same survey, the prevalence among UOJ, IA and the GRP was examined, with similar methodology and survey instruments applied in a standard fashion, across the three major groups under study.

It was possible to single out IA and UOJ from the GRP during the chart review process on the basis of residential data. However, such data did not permit absolute identification of an individual's ethnic or religious lifestyle, by inference.

Nevertheless, based on geographic distribution of different neighborhoods and municipal boundaries identified by the predominant religious and ethnic-cultural groups residing therein, it was possible to make a fair assumption of data on an individual basis. Israel does not by law enforce cultural or religious separation. However, in general, population groups tend to congregate homogeneously in order to assure preservation and observance of religious and lifestyle customs.

Health chart records of all children aged 0-18 years, covered by the largest provider within the public health care system (accounting for 65% of the total population in the country), within two large geographical regions in the central area of the country (DPT and SS, i.e. regions 1 and 2), at a single point in time, were systematically and universally reviewed for at least one of the ASD diagnostic designations (ASD, autism, child (hood) autism, pervasive developmental disorder [PDD], and Asperger syndrome).

Overall, we surveyed the charts of 331,169 children, of whom 1,334 were identified as having one of the ASD diagnoses, as of April 2014. The charts of the children from the two public health administrative regions were culled for additional information regarding gender, parental age at birth, and prevalence trends according to the year of diagnosis. Not all of these data were available, given that there was only partial access to some of the electronic charts, based on the vagaries of the as yet uncompleted task of combining the major components of the public health system under one reporting agency.

Statistical analysis

The data were analyzed using BMDP software.[13] Continuous variables are expressed as means ± standard deviations. Pearson's chi-square test or Fisher's exact test was used, as appropriate, for analysis of between-group differences in discrete variables. Analysis of variance (ANOVA) was used for continuous variables. A P value of $=0.05$ was considered significant.

Results

The prevalence figures for ASD of the general pediatric age group population (GRP) in the two regions were strikingly similar: 0.0053 for region 1 (DPT), (1/189 live births) and 0.0049 for region 2 (SS) (1/204 live births).

However, significant differences appeared in the prevalence figures for the two distinct low SES minority groups: 1) The IA (Israeli Arabs) who differ from the GRP (General Remaining Population) in terms of culturally ethnic and religious lifestyle and practice; and 2) the UOJ (Ultra-Orthodox Jews), who differ primarily in terms of religious lifestyle and practice. The UOJ and the GRP tend to share similar cultural and ethnic customs. Prevalence of ASD was significantly higher for children raised in either Jewish secular, or nominally religious homes.

Arab children, whether they are religious, or nominally secular, tended to have lower rates of ASD than secular or modern religious Jews (the GRP group of children), yet showed worrisome accelerated prevalence figures during the later years of the study, from 2010-2014. The distinctions between religious and nominally secular are harder to distinguish in the Arab community, as belief and practice do not always concur, nor are there geographical divisions in the Arab community, as exists between GRP versus UOJ, who tend to congregate in geographically sealed off communities,

Prevalence figures for Israeli Arabs in region 1 (DPT) were 0.002 (1/438 live births) and 0.0017 (1/594 live births) for region 2 (SS), both significantly lower than the GRP figures for both regions. The numbers analyzed were quite small: 20 out of a total IA pool of 8,779 children between the ages of 0-17 for region 1, and 125 out of a same-aged total IA pool of 74,229 for region 2.

Ultra-orthodox Jewish children had low prevalence figures for ASD. Their geographical enclaves exist only in region 1 (DPT). Prevalence was 0.0021 (1/470 live births) ($P<0.001$) compared to the GRP prevalence figures for regions 1 and 2, (0.005) and comparable with the Israeli Arab figures of 0.0017 for their same region 1 (Table1).

Table1: Prevalence of autistic spectrum disorders (ASD) according to birth data for two regions (DPT and SS) combined

	Years 1996 – 2003			**Years 2004 - 2011**				**Total Population/ Prevalence**
Israeli Arabs (IA)	DPT Reg.1	SS Reg.2	Total n	DPT Reg.1	SS Reg.2	Total n	**ASD n**	N = 83,057/ 0.0017
	7	27	**34**	13	93	**106**	**140**	
Ultra-Orthodox Jews (UOJ)	35	-	**35**	30	-	**30**	**65**	N= 30,941/ 0.0021
General Remaining Population (GRP)	177	233	**410**	314	340	**654**	**1,064**	N=214,171/ 0.005

Regarding the male: female distribution, figures were overwhelmingly similar for all ethnic and religious groups in regions 1 and 2, save for slightly more females in the Arab community in region 1 (Table 2). The average ages across regions and religious groups were 10.2 years for males and 10.7 years for females.

Table 2. Population characteristics of our child cohort

	Region 1 (DPT)		**Region 2 (SS)**	
Israeli Arabs (IA) M:F ratio	M 2.3	F 1	M 5	F 1
Average age (yrs)	10.5	9.0	7.2	6.8
Med. Age (yrs)	10.4	8.8	6.0	5.0
Paternal age at birth of child (yrs)	30.6	31.3	No data Available	
Maternal age at birth of child (yrs)	27.5	17.5		
Ultra-Orthodox Jews (UOJ) M:F ratio	5	1		
Average age (yrs)	11.1	13.1		
Med. Age (yrs)	11.8	13.5		
Paternal age at birth of child (yrs)	29.7	31.3		
Maternal age at birth of child (yrs)	28.4	28.0		
General Remaining Population (GRP) M:F ratio	5.2	1		
Average age (yrs)	10.1	10.0		
Med. Age (yrs)	9.9	9.9		
Paternal age at birth of child (yrs)	34.7	36.2		
Maternal age at birth of child (yrs)	31.6	31.2		

Discussion

The data on population trends in incidence and prevalence studies on ASD in Israel over time is of special importance, given the unstable and evolving population dynamics in the country including immigration and emigration, as well as increasingly westernized lifestyle and improved SES across the board among different sectors of the population who, from the start, differ widely in basic cultural and religious background.

Results probably reflected a combination of factors relating to compliance in diagnosis,

reporting to public health authorities, or possible real differences in rates of prevalence and phenotypical expression of genetic predisposition for a variety of environmental factors along lines associated with lifestyle and behavioral prohibitions. In discussing the physical environmental factors, there are few differences between predominantly ultra-Orthodox cities and towns, and the rest of the country, which are often in close physical proximity. Arab neighborhoods are also in close geographic proximity to Jewish neighborhoods and towns, albeit delineated separately by municipal boundaries, for purposes of fostering environments hospitable to cultural and ethnic life style and customs.

Rates among Arab and Ultra-Orthodox Jewish children tended to be about 50% less than those of the GRP.

Previous studies have noted an increased incidence of ASD in birth cohorts between 1992 and 2004. Our study confirmed a continuation of the increase in incidence for birth cohorts between 2009 and 2014, i.e., beyond the period noted in previous studies. The increase for birth cohorts pertains to the GRP and the IA, but not to the UOJ. This particular study delineates figures for the pediatric age group, and not for the general population.

In a discussion of differing incidence rates for ASD according to minority group affiliation (IA versus UOJ), previous investigators have noted that the incidence of diagnosed ASD in Israel is consistent with ASD incidence trends in other countries.[13-19]

This increase is not a part of a general increase in childhood disability benefits given by the National Insurance Institute, i.e. Social Security, as its trends are dramatically distinct from other child disabilities. Among the GRP most of the increase occurred in birth cohorts between 1992 and 2004 with little further rise thereafter. The UOJ demonstrated a less consistent time trend, and the IA population presented a dramatic increase much later in time (relative to the GRP), starting around the year 2002. This is the first report of which we are aware suggesting that the rising rates of ASD are leveling off, albeit this pertains to the GRP group only, and **not** to all the Israeli minority groups, especially among Arabs.

Of special interest in Israel, due to the ethnic, religious and social issues characteristic of that society, are the 1) Differences in the numbers of ASD in the GRP (General Remaining Population, the IA (Israeli Arabs) and within the enclaves of the UOJ (Ultra-Orthodox Jewish) communities. The UOJ's rigid lifestyle is maintained through prohibitions and semi-isolationist dictates, based on common consensus within that community. There are no similar restrictions and prohibitions on personal lifestyle which are comparable to either the larger Jewish secular and nominally religious community, or to the Arab community as a whole, despite recent trends of Islamic religiosity or fundamentalism in select locales; 2) The roles played in the environmental-genetic interface by factors unique to Israeli society, such as consanguinity within the Arab community (estimated to be 5% for first degree relatives, and upwards of 25% for second and third degree marriages),[20] and 3) Preponderance of the general population employed in the high-tech industry, almost universal exposure to the electronic communication network, and lifestyle restrictions in select locales and communities. These issues have yet to be delineated

The discussion of "advantageous" or "protective" factors from having ASD appear in the young child has bearing on interpretation of the demographic trends reported in this article as well as in others. In that sense the results here echo the findings among the Hispanic groups in the U.S, as opposed to the lower SES groups in Scandinavia, where perhaps factors more prevalent in that society, such as immigration, marginalization, family disruption and alcoholism might be at play affecting pregnant women. The accumulating evidence for such appears in the excellent discussion in the landmark epidemiological review by Lyall et al.[21]

The importance of environmental factors, including the psychological and social milieu variables, remains an integral part of the discussion of both the epigenetic as well as genetic role in the expression of inheritable "candidate risk factors for ASD" through the mechanism of DNA methylation(DNAm)".[22-26]

In Lyall et al.'s excellent review[21] emphasizes that increasing numbers of suboptimal conditions during pregnancy including immune dysregulation, inflammatory processes appear to place the particular pregnancy at increased risk of ASD and adverse developmental outcomes:

Recent studies assessing biomarker-based evidence of differential immune function during etiologically relevant (i.e., prenatal or neonatal) windows have suggested increased ASD risk associated with altered levels of c-reactive protein (CRP)[27,28] and other immune markers, including IFN-

γ, IL-4 and IL-5,[29] in maternal sera, with more conflicting results for levels of immune markers measured in newborn blood spots.[30-32] Methodological limitations in these studies suggest further work is needed to determine the importance of individual immune markers.

Other prenatal and perinatal factors such as lower gestational age/preterm birth,[33-37] as well as small- or large-size-for-gestation appear to independently increase risk of ASD,[34,35] though these factors may also be markers or mediators of other pregnancy risks. Study results "also provide general support for increased ASD risk from maternal metabolic conditions (including gestational weight gain, diabetes, and hypertension) and potentially their interplay; these conditions influence mechanisms relevant to ASD (e.g., chronic inflammation, fetal hypoxia, oxidative stress, insulin resistance).[38-41]

In discussing brain and developmental trajectories based on a variety of biological and environmental risk factors with potential benefits from targeted interventions another researcher has raised the possibility of prevention or, at least mitigation of the severity of symptoms of later ASD.[42]

Despite sharing a lower incidence of ASD between them, as well as a lower SES, the IA and the UOJ communities nevertheless differ in the rates of ASD, to the detriment of the IA community. Understanding the deterioration in the statistics for Israeli Arabs over the past 18 years could contribute to our understanding of the dynamics at work with respect to risk for ASD in general, and perhaps save the UOJ community from the same fate as the Arab, as well as the General population in general:

One of the noteworthy differences between the IA and the UOJ communities, despite commonality in attitudes towards aversion to stigmatization of the family for reasons of social standing and procreative reputation, vis a vis arranged marriages for other siblings in the family, lies in the SES gap between the two communities, to the detriment of the UOJ, despite both communities being associated with the low SES group, compared to the GRP. According to figures for 2014, the average household income for the IA was 20% higher than for the UOJ, where the average number of children was 6.0 vs 3.5 for Arab families.[11] Another possible environmental factor currently the subject of lively debate in the literature, which can differ along cultural-environmental lines, and may have a negative impact on later neurodevelopmental outcomes, specifically regarding cognitive, as well as behavioral and social communication abilities in the infant and young child as occur in autism, lies in exposure of the infant to heightened serum and transplacental cortisol levels, engendered by maternal stress during early pregnancy.[43-48]

The few studies existing on this subject indicate radically different emotional coping patterns and attitudes among Orthodox Jewish women towards their pregnancy, compared with the general population, in the sense of spiritual fulfillment and degree of acceptance of pregnancy outcomes, possibly suggesting overall lower levels of stress during the period of uncertainty of the pregnancy as embodied in an ethos of pregnancy as a proclamation of faith: Ultra-Orthodox Jewish women navigating the uncertainty of pregnancy and prenatal diagnosis.[49] The entrance of these women into the high tech work force may challenge this idyllic vision of pregnancy.

Authors of a previous study revealed that they could not provide a definite answer regarding the factors that drive ASD incidence up so sharply. However, the distinct time trends among the different Israeli sub-populations do not seem compatible with changes in a country-wide environmental factor driving this increase. As UOJ (Ultra-Orthodox) and IA (Israeli Arabs) reside with the GRP in many "mixed" Israeli urban areas, it seems unlikely that these time trends would be generated mainly by such Israel-wide environmental exposures. A contribution from environmental factors would have to relate to exposures experienced separately, and with distinct temporal patterns, by the different groups. Expanding diagnostic criteria and diagnostic substitutions could possibly contribute to some of the rise in incidence. However, the medical community serving these populations is to a large degree, although not completely, overlapping. Thus, such changes may be expected to affect all the sub-populations similarly, rather than with distinct temporal patterns as found in our study. Differences in awareness, access to the government benefit, the way the concept of ASD is perceived or accepted by the different groups, may be the most likely explanation of a major component of the rise in incidence rates.

The IA population is an ethnic minority in Israel, and the UOJ population is a cultural minority that chooses to strictly maintain the Jewish religious law and distinguish themselves from modern life. Traditionally, mental disorders in these populations

may be stigmatized and, especially in the UOJ population, may also negatively affect other family members' arranged marriage processes. The IA and UOJ populations also tend to have lower trust in state agencies, and may minimize their contact with government institutions. These factors may reduce ascertainment of ASD in those communities and their awareness of the relevant benefit. Conversely both UOJ and IA have, on average, much lower incomes, thus the disability benefit given for ASD (independently of income or other parameters) is of special importance to them. To the extent that differences in awareness or acceptance of ASD in the diverse Israeli sub-populations explain the differences in incidence time trends, would suggest health and welfare disparities, despite universal health and insurance coverage. This emphasizes the need to strengthen efforts to minimize disparities, to raise awareness and increase access to ASD diagnosis and services in the minority groups in Israel and in other countries.

The current study is unique insofar as data was based not on National Institute records, but rather medical charts available through Israel's largest medical services provider (Clalit Health Services). Furthermore, the time period examined encompasses a wider span (18 years) than previous studies, albeit lacking comprehensive incidence data for half of the subjects examined, and was based primarily on prevalence data from one defined point in time (the time of the study itself).

Limitations of the study reflect lack of data, vis a vis emigration and immigration driven factors impacting on the prevalence estimates.

Conclusions

Reported prevalence of ASD among the ultra-Orthodox pediatric population is significantly less than among secular or nominally religious Jews, and the Arab minority, exposed to similar physical environmental factors. Protective factors in ultra-orthodox life styles may be the key in understanding some of the trigger effects witnessed for ASD in other societies and communities.

Therefore, to account for the differences observed, there needs to be an examination not only of attitudes towards registering for benefits based on what is still perceived as being a mental health disability, but also culturally driven environmental factors which may positively impact on consistent reports of lower incidence and prevalence for the UOJ.

Similarly, the worrisome significant increase of reported ASD among the Arab community during recent years may also reflect accelerated negative cultural developments in that community, as IA show increasing gains in standards of living and cultural patterns similar to the GRP, this coming at the same time as increasing awareness of Muslim religious values and identity among segments of the Arab community.

It seems that the primary divide between the GRP (General) and IA (Arab) groups together, versus the UOJ (Orthodox), where epidemiological prevalence trends for ASD are low and continue to exhibit lack-luster gains, lies in the lower income level for the latter and its significance for its associated lifestyle risk factors. The lessons learned from ASD trends in three cultural sub-groups in a small country such as Israel, might contribute to future prevention efforts, as delineated in recent studies.

Declaration of Conflicting Interests: None declared.

Funding: The authors received no financial support for the research, authorship and/or publication of this article.

Ethical Approval: Not applicable, because this article does not contain any studies with human or animal subjects.

Informed Consent: Not applicable, because this article does not contain any studies with human or animal subjects

References

1. Diagnostic and Statistical Manual of Mental Disorders: DSM-V 2013, Washington, D.C.: American Psychiatric Association, 2013.
2. Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. *Psychol Med* 2015;**45**(3):601-13.
3. Christensen DL, Baio J, Van Naarden Braun K, Bilder D, Charles J, Constantino JN, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *MMWR Surveill Summ* 2016;**65**(3):1-23.
4. 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.
5. Risch N, Hoffmann TJ, Anderson M, Croen LA, Grether JK, Windham GC. Familial recurrence of autism spectrum disorder: evaluating genetic and environmental contributions. *Am J Psychiatry* 2014; **171**(11):1206-13.
6. Bauman ML, Kemper TL. Neuroanatomic observations of the brain in autism: A review and future directions. *Int J Dev Neurosci* 2005; **23**(2-3):183-7.
7. Kim YS, Leventhal BL, Koh Y, Fombonne E, Laska E, Lim EC, et al. Prevalence of autism spectrum disorders in a total population sample. *Am J Psychiatry* 2011;**168**(9):904-12.
8. King MD, Bearman PS. Socioeconomic status and the increased prevalence of autism in California. *Am Sociol Rev*, 2011;**76**(2):320-46.
9. Rai D, Lewis G, Lundberg M, Araya R, Svensson A, Dalman C, et al. Parental socioeconomic status and risk of offspring autism spectrum disorders in a Swedish population-based study. *J Am Acad Child Adolesc Psychiatry* 2012;**51**(5):467-76.e6.
10. Raz R, Roberts AL, Lyall K, Hart JE, Just AC, Laden F, et al. Autism spectrum disorder and particulate matter air pollution before, during, and after pregnancy: A nested case-control analysis within the Nurses' Health Study II Cohort. *Environ Health Perspect* 2015;**123**:264-70.
11. Raz R, Weisskopf MG, Pinto O, Levine H. Differences in autism spectrum disorders incidence by sub-populations in Israel 1992-2009: A total population study. *J Autism Dev Disord* 2014;**45**:1062-9.
12. Senecky Y, Chodick G, Diamond G, Lobel D, Drachman R, Inbar D. Time trends in reported autistic spectrum disorders in Israel, 1972–2004. *Israel Med Assoc J* 2009;**11**:30-3.
13. BMDP Statistical Software. Editor: Dixon WJ. Los Angeles, CA: University California Press, 1993.
14. Gurney JG, Fritz MS, Ness KK, Sievers P, Newschaffer CJ, Shapiro EG. Analysis of prevalence trends of autism spectrum disorder in Minnesota. *Arch Pediatr Adolesc Med* 2003;**157**:622-7.
15. Kawamura Y, Takahashi O, Ishii T, Ishii T. Reevaluating the incidence of pervasive developmental disorders: Impact of elevated rates of detection through implementation of an integrated system of screening in Toyota, Japan. *Psychiatr Clin Neurosci* 2008; **62**:152-9.
16. Keyes KM, Susser E, Cheslack-Postava K, Fountain C, Liu K, Bearman PS. Cohort effects explain the increase in autism diagnosis among children born from 1992 to 2003 in California. *Int J Epidemiol* 2012;**41**:495-503.
17. Nassar N, Dixon G, Bourke J, Bower C, Glasson E, de Klerk N, et al. Autism spectrum disorders in young children: effect of changes in diagnostic practices. *Int J Epidemiol* 2009;**38**:1245-54.
18. Saemundsen E, Magnússon P, Georgsdóttir I, Egilsson E, Rafnsson V. Prevalence of autism spectrum disorders in an Icelandic birth cohort. *BMJ Open* 2013;**3**:e002748.
19. Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. Prevalence of autism in a US metropolitan area. *JAMA* 2003;**289**:49-55.
20. Jaber L, Halpern GJ, Shohat T. Trends in the frequencies of consanguineous marriages in the Israeli Arab community. *Clin Genet* 2000;**58**:106-10.
21. Lyall K, Croen L, Daniels J, Fallin MD, Ladd-Acosta C, Brian K. et al. The changing epidemiology of autism spectrum disorders. *Annu Rev Public Health* 2017;**38**:81-102.
22. Ladd-Acosta C, Fallin MD. The role of epigenetics in genetic and environmental epidemiology. *Epigenomics* 2016;**8**(2):271-83.
23. Liu Y, Li X, Aryee MJ, Ekström TJ, Padyukov L, Klareskog L, et al. GeMes, clusters of DNA methylation under genetic control, can inform genetic and epigenetic analysis of disease. *Am J Hum Genet* 2014;**94**(4):485-95.

24. Joubert BR, Felix JF, Yousefi P, Bakulski KM, Just AC, Breton C, et al. DNA methylation in newborns and maternal smoking in pregnancy: Genome-wide Consortium Meta-analysis. *Am J Hum Genet* 2016;**98**(4):680-96.
25. Ladd-Acosta C, Shu C, Lee BK, Gidaya N, Singer A, Schieve LA, et al. Presence of an epigenetic signature of prenatal cigarette smoke exposure in childhood. *Environ Res* 2016;**144**(Pt A):139-48.
26. Argos M. Arsenic exposure and epigenetic alterations: Recent findings based on the Illumina 450K DNA methylation array. *Curr Environ Health Rep* 2015;**2**(2):137-44.
27. Brown AS, Sourander A, Hinkka-Yli-Salomäki S, McKeague IW, Sundvall J, Surcel HM, et al., Elevated maternal C-reactive protein and autism in a national birth cohort. *Mol Psychiatry* 2014;**19**(2):259-64.
28. Zerbo O, Traglia M, Yoshida C, Heuer LS, Ashwood P, Delorenze GN, et al. Maternal mid-pregnancy C-reactive protein and risk of autism spectrum disorders: the early markers for autism study. *Transl Psychiatry* 2016;**6**:e783.
29. Goines PE, Croen LA, Braunschweig D, Yoshida CK, Grether J, Hansen R, et al. Increased midgestational IFN-gamma, IL-4 and IL-5 in women bearing a child with autism: A case-control study. *Mol Autism* 2011;**2**:13.
30. Abdallah MW, Larsen N, Mortensen EL, Atladóttir HÓ, Nørgaard-Pedersen B, Bonefeld-Jørgensen EC, et al. Neonatal levels of cytokines and risk of autism spectrum disorders: an exploratory register-based historic birth cohort study utilizing the Danish Newborn Screening Biobank. *J Neuroimmunol* 2012;**252**(1-2):75-82.
31. Krakowiak P, Goines PE, Tancredi DJ, Ashwood P, Hansen RL, Hertz-Picciotto I, et al. Neonatal cytokine profiles associated with autism spectrum disorder. *Biol Psychiatry* 2017;**81**(5):442-51.
32. Zerbo O, Yoshida C, Grether JK, Van de Water J, Ashwood P, Delorenze GN, et al. Neonatal cytokines and chemokines and risk of Autism Spectrum Disorder: the Early Markers for Autism (EMA) study: a case-control study. *J Neuroinflammation* 2014;**11**:113.
33. Lampi KM, Lehtonen L, Tran PL, Suominen A, Venla Lehti P, Nina Banerjee N, et al. Risk of autism spectrum disorders in low birth weight and small for gestational age infants. *J Pediatr* 2012;**161**(5):830-6.
34. Moore GS, Kneitel AW, Walker CK, Gilbert WM, Xing G. Autism risk in small and large-for-gestational-age infants. *Am J Obstet Gynecol* 2012;**206**(4):314.e1–9.
35. Abel KM, Dalman C, Svensson AC, Susser E, Dal H, Idring S, et al. Deviance in fetal growth and risk of autism spectrum disorder. *Am J Psychiatry* 2013;**170**(4):391-8.
36. Kuzniewicz MW, Wi S, Qian Y, Walsh EM, Armstrong MA, Croen LA. Prevalence and neonatal factors associated with autism spectrum disorders in preterm infants. *J Pediatr* 2014;**164**(1):20-5.
37. Leavey A, Zwaigenbaum L, Heavner K, Burstyn I. Gestational age at birth and risk of autism spectrum disorders in Alberta, Canada. *J Pediatr* 2013;**162**(2):361-8.
38. Krakowiak P, Walker C, Bremer AA, Baker AS, ,Ozonoff S, Hansen RL. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. *Pediatrics* 2012;**129**(5):e1121-8.
39. Li M, Fallin MD, Riley A, Landa R, Walker SO, Silverstein M, et al. The association of maternal obesity and diabetes with autism and other developmental disabilities. *Pediatrics* 2016;**137**(2):1-10.
40. Li YM, OU JJ, Liu L, Zhang D, Zhao JP, Tang SY. Association between maternal obesity and autism spectrum disorder in offspring: A Meta-analysis. *J Autism Dev Disord* 2016;**46**(1):95-102.
41. Walker CK, Krakowiak P, Baker A, Hansen RL, Ozonoff S, Hertz-Picciotto I. Preeclampsia, placental insufficiency, and autism spectrum disorder or developmental delay. *JAMA Pediatr* 2015;**169**(2):154-62.
42. Elsabbagh M. State of the Art Review. Linking risk factors and outcomes in autism spectrum disorder: is there evidence for resilience? *BMJ* 2020;**368**:l6880.
43. Kinney DK, Miller AM, Crowley DJ, Huang E, Gerber E. Autism prevalence following prenatal exposure to hurricanes and tropical storms in Louisiana. *J Autism Dev Disord* 2008;**38**:481-8.
44. Li J, Vestergaard M, Obel C, Christensen J, Precht DH, Lu M, et al. A nationwide study on the risk of autism after prenatal stress exposure to maternal bereavement. *Pediatrics* 2009;**123**:1102-7.
45. Gitau R, Adams D, Fisk NM, Glover V. Fetal plasma testosterone correlates positively with

cortisol. *Arch Dis Child Fetal Neonatal Ed* 2005;**90**:F166-F169.

46. Sarkar P, Bergman K, Fisk NM, O'Connor TG, Glover V. Amniotic fluid testosterone: relationship with cortisol and gestational age. *Clin Endocrinol* 2007;**67**:743-7.
47. O'Connor TG, Heron J, Golding J, Glover V. Maternal antenatal anxiety and behavioral/ emotional problems in children: a test of a programming hypothesis. *J Child Psychol Psychiatry* 2003;**44**:1025-36.
48. Baron-Cohen S, Auyeung B, Nørgaard-Pedersen B, Hougaard DM, Abdallah MW, Melgaard L, et al. Elevated fetal steroidogenic activity in autism. *Mol Psychiatry* 2015;**20**(3):369-76.
49. Teman E, Ivry T, Bernhardt BA. Pregnancy as a proclamation of faith: Ultra-Orthodox Jewish women navigating the uncertainty of pregnancy and prenatal diagnosis. *Am J Med Genet* 2011;**155A**:69-80.