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Review Article

Autism in Lebanon: Looking Back to Inform the Future

Dima Habanjar[1], Simone Khalife[1], Laith Haddad[1], Fatima Jaafar[1], Daniel Charouf[1], Walaa G El Sheikh[2], Hani Tamim[2,3], Rose-Mary Boustany[1,4,5*]

[1]Department of Pediatrics and Adolescent Medicine, American University of Beirut, Beirut, Lebanon

[2]Department of Internal Medicine and the Clinical Research Institute, American University of Beirut Medical Center, Beirut, Lebanon

[3]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia

[4]Department of Biochemistry and Molecular Genetics, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

[5]Department of Pediatrics, Duke University Medical Center, Durham, NC, USA

[*]**Corresponding author:** Rose-Mary Boustany, Department of Biochemistry and Molecular Genetics/ Pediatrics and Adolescent Medicine, American University of Beirut, Riad El Solh, P. O. Box 11-0236, Beirut 1107 2020, Lebanon

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Abstract

Background: Autism Spectrum Disorder (ASD) is a group of neurodevelopmental disorders with delays in communication, restricted interests and repetitive behaviors. Although the phenotype of autism is global, risk factors and underlying genetics may be regionally defined. The aim of this study is elucidation of Lebanese ASD patient characteristics and comparison to the same in different populations.

Methods: Retrospective chart review of children evaluated at the American University of Beirut Special Kids Clinic (ASKC) from January 2008-March 2022 was undertaken. Patients diagnosed from infancy to 18 years of age were included. Those with known genetic entities were excluded. Sex, age at diagnosis, presence of consanguinity, presence of prenatal/postnatal complications, a family history of autism or other psychiatric/neurological diseases, and birth order details were extracted and analyzed.

Results: A total of 1,181 children were included in the analysis with 963 (81.5%) male and 218 (18.5%) female subjects with a male to female ratio of 4.4:1 compared to a ratio of 3.8:1 from the USA. Mean age at diagnosis was 48.0 ±27.4 months. Consanguinity accounted for 159 (16.4%) of parent pairs of affected individuals. Premature birth was present in 123 (12.7%) of cases. Prenatal complications occurred in 112 (11.1%) of subjects. First order birth was documented in 419 (44.8%) of ASD cases.

Conclusion: This comprehensive study of ASD patient characteristics in Lebanon demonstrates that the ASD population is comparable with those reported from other countries with few notable exceptions.

Keywords: Autism Spectrum Disorders; Risk factors; Genetic; Consanguinity; Birth order

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder. Affected children manifest limitation in social communication and interaction. They also manifest restricted and/or repetitive behaviors [1]. It is estimated that 1/100 children are diagnosed with ASD worldwide [2]. In 2020 the Center of Disease Control and Prevention (CDC) in the USA stated that 2.76% (1 in 36) of 8-year-old children have ASD [3]. This supported a doubling of affected patients every decade from 1.13% (1 in 88) in 2008 to 2.27% (1 in 44) in 2018 [4,5]. This increase in prevalence has garnered attention worldwide. A study from Lebanon in 2018 estimated ASD prevalence in children attending nurseries between 16-48 months of age at 1.49 % (1 in 67) [6,7].

There is no one specific cause for the development of ASD. Both genetic and environmental factors increase the risk for ASD [8]. Hundreds of genes have been linked to ASD [9]. Studies from this group have uncovered a number of candidate genes for ASD in the Lebanese population [10,11] and has validated novel gene defects [12]. This suggests that the genetics and, hence, the clinical phenotype of Lebanese ASD patients differs from descriptions from other countries. Previously reported environmental risk factors linked to ASD in other studies were advanced maternal age, [13,14] maternal gestational hypertension, maternal obesity before or during pregnancy, pre-eclampsia [15], birth complications, preterm delivery [16] low birth weight and perinatal complications [13,14].

This study also describes clinical characteristics establishing a positive correlation in the Lebanese of ASD with consanguinity, birth order, high rates of prenatal/ postnatal complications, prematurity and a positive family history for psychiatric and/or other neurological disorders.

Materials and Methods

Sample selection and study design

A retrospective review of electronic health records of patients seen at the ASKC from January 2008-March 2022 was conducted. Participants meeting the following criteria were included: those diagnosed with ASD by pediatric neurologists ages 10 months -18 years of age. Patients with genetic entities with autism as an associated phenotype (e.g., Rett syndrome, Fragile X syndrome, Turner syndrome and others) were excluded.

A total of 1510 charts were reviewed. Two hundred eighty-four had incomplete data, 41 were duplicates and 4 charts lacking an examination of the patient were also excluded. Subjects remaining for analysis totaled 1181 individuals (Figure 1).

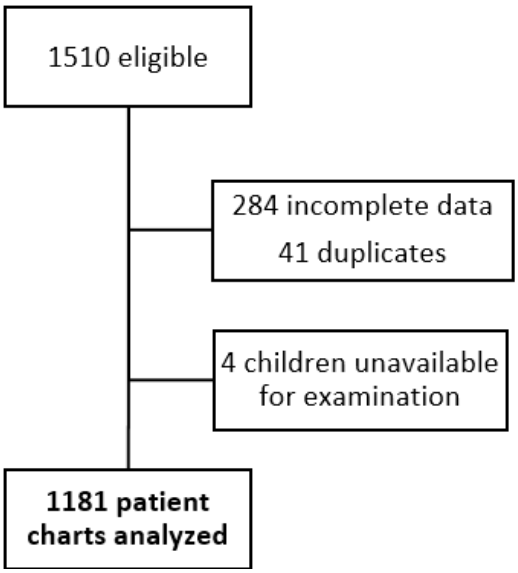

Figure 1: Sample size flow chart

Conduction of this study was approved by the Institutional Review Board (IRB) at the American University of Beirut (BIO-2020-0402). Subjects whose data was included were de-identified assuring patient confidentiality.

Data Collection

Three of the authors extracted data from 1181 medical records using a unified data collection sheet designed for this study. The latter included sex, age at diagnosis, presence or absence of parent consanguinity, birth order, history of prematurity, prenatal and/or postnatal complications, and a positive family history for neurological or psychiatric illnesses.

Statistical analysis

Data were entered into the Statistical Package for Social Sciences (SPSS, version 28), which was used for data cleaning, management and analysis. Categorical variables are presented as number and percent, whereas continuous ones are presented as mean and Standard Deviation (SD).

Results

Out of 1510 children, 1181 children diagnosed with autism at ASKC were reviewed as shown in Figure 1. Males accounted for 963 (81.5%). Mean age at diagnosis was 48.0 months ± 27.4 months. A total of 123 subjects (12.7%) were born preterm at 37 weeks of gestation or before: of those 91 (9.5%) were late preterm births (34 -35 weeks+6 days of gestation), 14 (1.5%) were moderately preterm (32 -33 weeks+6 days of gestation), and 5 (0.5%) were extreme preterm (28-31 weeks +6 days of gestation). Similarly, 112 (11.1%) of pregnancies manifested prenatal complications, the most common being preeclampsia or infection

in the mother with 16 subjects (1.6%) each accounting for one of the two categories. Prenatal bleeding occurred in 12 subjects (1.2%). Postnatal complications were seen in 60 (6.0%) of autistic patient births, with 35 subjects (3.5%) requiring admission to the neonatal intensive care unit (NICU). Another 13 subjects (1.3%) experienced respiratory distress. Consanguinity was present in 159 (16.4%) families. First order birth accounted for 44.8% of autistic children, whereas second, third and fourth order birth accounted for 30.4%, 14.3% and 4.2% of births, respectively. Additionally, 34 subjects (3.6%) had no siblings, 84 (8.9%) subjects were members of twin or triplet births and 63 (6.8%) had a sibling with autism of which 37 were twin births (table1).

Family history of psychiatric disease was present in 283 subjects (30.4%) of which 99 subjects (30.4%) had a positive family history for autism. Family history of depression and anxiety or a panic disorder accounted for 10.4% and 2.7% of subjects, respectively. To note, maternal depression was present in 35 subjects (3.8%). History of speech delay was found in 78 subjects (8.3%), 37 subjects (3.9%) had a family history of seizures and 19 subjects (2%) had a family history of global neuro-developmental delay (Table 1).

Table 1: Characteristics of Autistic Patients (n=1181).

Characteristics		Number of patients (%)
Gender, n (%)		
	Female	218 (18.5%)
	Male	963 (81.5%)
Mean age at diagnosis (months), Mean ± SD		48.0 ± 27.4
Consanguineous, n (%)		
	Yes	159 (16.4%)
	First Degree	29 (3.3%)
	Second Degree	25 (2.8%)
	Third Degree	15 (1.7%)
	No	813 (83.6%)
Prenatal complication, n (%)		
	None	895 (88.9%)
	Yes	112 (11.1%)
	Preeclampsia	16 (1.6%)
	Infection	16 (1.6%)
	Bleeding	12 (1.2%)
	Antibiotic exposure	7 (0.7%)
	Gestational diabetes	11 (1.1%)
	Urgent C-section	7 (0.7%)
	PROM	5 (0.5%)
	Oligohydramnios	6 (0.6%)
	Other	40 (4.0%)

Postnatal complication, n (%)		
	None	946 (94.0%)
	Yes	60 (6.0%)
	NICU admission	35 (3.5%)
	Respiratory distress	13 (1.3%)
	Neonatal depression	6 (0.6%)
	Meconium aspiration	4 (0.4%)
	Jaundice	10 (1.0%)
	Infection	1 (0.1%)
	Other	8 (0.8%)
Only child		34 (3.6%)
Birth order, n (%)		
	First	419 (44.8%)
	Second	285 (30.4%)
	Third	134 (14.3%)
	Fourth	39 (4.2%)
	>4	23 (2.5%)
Twins/triplets, n (%)		84 (8.9%)
Family with 2 or more children with ASD		63 (6.8%)
Twins/triplets with ASD, n (%)		37 (4.0%)
Prematurity, n (%)		
	Term	845 (87.3%)
	Preterm	123 (12.7%)
	Late 35-36.6	91 (9.5%)
	Moderate 32-33.6	14 (1.5%)
	Very 28-31.6	5 (0.5%)

Family history of psychiatric diseases, n (%)		
	No	647 (69.6%)
	Yes*	283 (30.4%)
	ASD	99 (10.6%)
	Anxiety/Panic Disorder	25 (2.7%)
	ADD/ADHD	7 (0.8%)
	Maternal depression	35 (3.8%)
	Depression	97 (10.4%)
	Schizophrenia	21 (2.3%)
	Bipolar	18 (1.9%)
	OCD	13 (1.4%)
Family history of neurological diseases, n (%)		
	Seizures	37 (3.9%)
	Speech delay	78 (8.3%)
	Global delay	19 (2.0%)
	Intellectual disabilities	12 (1.3%)
	Syndromic/genetic disorder	9 (1.0%)

The data extracted from patient's charts. SD=standard deviation. PROM: prolonged rupture of membrane *Some Patient had more than one positive family history.

Discussion

This present work represents a retrospective chart review study including more than 1000 patients with confirmed ASD diagnosis by specialists. To our knowledge, this is the largest study that analyzed characteristics of ASD patients in Lebanon and the Middle East. It investigated several factors deemed to increase the risk of autism according to available literature. The purpose was to highlight both differences and similarities between this population and those in countries reported previously.

Males and Females with ASD

In this population, males accounted for 81.5%, with a male to female ratio of 4.4:1. This is somewhat higher than in the USA according to the CDC with a male to female ratio 3.8:1 [3]. Two earlier studies conducted in Lebanon in 2016 and 2018 report a male to female ratio of 1.05 to 1 [6] and 1.13 to 1[8], respectively. These two reports were limited to toddlers aged 16-48 months. Differences may be due to the ratio in toddlers versus the ratio in those older up to 8 years of age. Also, there were methodological differences. Previous studies in Lebanon were based on a parental screening instrument, the M-CHAT. This study is based on extracted medical chart data for children from families seeking a diagnosis for their child.

A recent meta-analysis from 2017 including studies carried out in 19 countries across the globe claims that the male-to-female ratio is closer to 3:1 [17]. More than fifty-four studies relying on screening of the general population for ASD had a lower male to female ratio than studies including participants with a pre-existing diagnosis of ASD [16]. This, suggests possible diagnostic sex bias, with less diagnostic quests for females as they manifest a varied phenotype with better ability to camouflage ASD traits [18]. In addition, several studies implicate a Female Protective Effect (FPE) manifesting as a reduced incidence in females [19,20].

Mean age at diagnosis

The mean age at diagnosis in this cohort was 4.00 years ± 2.28 years. A previous study from Lebanon reports an age of onset of 2.80 ± 1.50 years [21]. The latter was based on a small cohort of 136 control versus 1181 ASD patients included in this study. In a large metanalysis that included studies from 35 countries, the mean age at diagnosis reported is 5.04 years of age with a range from 2.57-19.54 years [22]. ASD can be reliably diagnosed as early as 14-16 months of age [23].

Consanguinity

Consanguinity is a likely contributing risk factor for ASD as it may amplify the genetic impact, particularly for autosomal recessive inherited forms of autism [24]. In Lebanon rates of consanguinity may reach 35.5% [25] with percentages varying according to geographic location or religion. It is reported to be higher in rural areas and amongst Muslims.

In this cohort the consanguinity rate is 16.4%. This population may not be representative of all Lebanese communities, but has the largest number of participants. A small Lebanese case control study, with 136 cases and 178 controls determined consanguinity rates of 16.3% in ASD patients versus 7.9 % in the control group [21]. Another case control study from Lebanon, with 64 autistic cases and 67 controls states that 25% of children with autism had first-degree consanguineous parents compared to 10.4% in controls [26]. A similar study from India with 500 controls versus 500 cases establishes a consanguinity rate of 20% in patients with ASD compared to 7.2 % in the control group [27]. Some studies argue that consanguinity was not associated with ASD. In a case-control study from Qatar with participants recruited from the national ASD registry and population surveys with 891 participants, of which 361 were autistic, consanguinity accounted for 42.1% of unions in the ASD group compared to 41.3% in the control group [28].

Premature Birth

According to Lebanese Ministry of Health (MOH) surveillance data for the year 2000, 9% of total births are premature [29] versus 12.5 % in this cohort. Furthermore, MOH data determined that 5.4% of premature births occurred at 35-36 weeks +6 days of gestation and 3.6% were below 35 weeks gestation [29], compared to 9.5% and 2%, respectively for the same groups in this cohort. Hence, late preterm births in this cohort were higher than that present in the general population.

A systematic review and meta-analysis conducted in 2021 determined prevalence estimates for autism in preterm births to be up to 20%. The odds of an autism diagnosis were 3.3 times higher in individuals born preterm than in the general population [30]. Reports from Sweden, Finland and Norway conclude that the risk for ASD increases with both pre- or post-term births [31]. The rate of preterm births in this study was higher than that in the general population. In addition, most of the preterm births in this cohort were late preterm rather than very or extreme preterm. A large national cohort study from Sweden including 4,061,795 singleton births assessed premature birth occurrence and ASD and concluded that preterm and early term birth were associated with significantly increased risks of ASD, with risk being highest in those with extreme preterm birth [32]. A prospective study in the United Kingdom where parents of 2-year-olds filled the MCHAT questionnaire of whom 634 were born late to moderate preterm (32-36 weeks) and 761 were term births. The late preterm group (34-36 weeks) had the highest percentage of positive MCHAT at 14.5% compared to 9.2% in the term group [32]. Similar to this study, later preterm birth was associated with a higher risk for development of ASD.

Pre/postnatal Complications

Pre/postnatal complications were documented in 17% of ASD patients in this study compared to 5.9% in the general Lebanese population according to MOH statistics reported for the year 2000 [29]. The most common complications noted were admission to the neonatal intensive care unit, preeclampsia, presence of maternal infection and neonatal respiratory distress. This was consistent with reports from other populations [34-36].

A meta-analysis in 2011 of perinatal and neonatal difficulties including umbilical cord complications, fetal distress, birth injury or trauma, multiple birth, maternal hemorrhage, summer births, low birth weight, small for gestational age, congenital malformations, low 5-minute Apgar scores, feeding difficulties, meconium aspiration, neonatal anemia, ABO or Rh incompatibilities and hyperbilirubinemia were associated with a higher prevalence of ASD [36]. Another meta-analysis in 2017 examined additional factors associated with ASD. These included gestational hypertension or diabetes, threatened abortion, antepartum hemorrhage, delivery by Caesarian section, gestational age ≤ 36 weeks, spontaneous labor, induced labor, no labor, breech presentation, preeclampsia, fetal distress, low birth weight and postpartum hemorrhage. Maternal urinary tract infection, premature rupture of membranes and neonatal respiratory infections, umbilical cord around the neck, and 5-minute Apgar scores of <7 were not associated with an increased risk of ASD contradicting a previous study [35]. A multisite case control study from the US reports that for mothers having a febrile infection during the second trimester increased the risk for having a child with ASD two-fold [36]. A case-control study from Lebanon confirms that complications during delivery, jaundice and feeding difficulties, in addition to the presence of infections, use of antipyretics/antibiotics in the mother and presence of other complications during gestation were independently associated with higher rates of autism [21]. In conclusion, a variety of risk factors or complications are linked to autism, but none can be attributed to be solely responsible for the development of ASD.

Birth Order

In this cohort, almost half of the population were first born, (44.8%) and second, third and fourth order birth accounted for 30.4%, 14.3% and 4.2% of births, respectively.

Birth order is an extensively studied risk factor for ASD. First order birth had been associated with an increased risk of ASD in multiple reports [38-41]. A recent study from the US, however, reports that ASD prevalence is higher in later born children with an

inter-pregnancy interval of <18 or >60 months [41]. A large study from Australia, investigating the relationship between birth order and autism in 2020 reports that 34.9% of patients were first born, 29% second born, 11.2% third born, 3.5% fourth born and 21.2% had no siblings [42] The numbers are similar to what is reported in this cohort from Lebanon. A case control study from Malaysia also reports that first born children are at higher risk of ASD [43]. Other studies were contra indicatory. A previous case control study from Lebanon determined that first and second order birth were protective against ASD [21] and this is in line with a retrospective study from the US analyzing 20,206 autistic patients that states that high birth order is significantly associated with autism [44]. In this study a higher birth order correlates with a lower the association with ASD.

Family history of psychiatric and/or neurological disease

In this cohort family history of psychiatric disease was present in 30.4%, with autism being the most common disorder reported followed by depression and speech delay. A population-based study from Sweden concluded that a positive family history of mental and/or neurological disorders constitutes risk factors for ASD. It also states that having a first-degree relative with ASD was associated with a 9-fold increase risk for developing ASD [34] in line with this report from Lebanon.

A multi-site case control study conducted in the US examined impact of maternal psychiatric conditions and its relationship to ASD. ASD patients were more commonly born to mothers with psychiatric conditions versus those born to normal mothers [45]. A previous Lebanese case-control study confirmed that 21% of ASD patients had a positive family history for psychiatric disease versus 12.4 % in the control group [21]. In Lebanon, lifetime prevalence of mental disorders in the general population is 25.8% [46]. In this cohort 30.4% of ASD patients had a family history of psychiatric disorders topping numbers previously reported.

Having a sibling with ASD

In the present sample of Lebanese autistic children 63 had a sibling with ASD (6.8%) and 37(4%) had a twin with autism. A prospective longitudinal study conducted by a multi-site international network followed up on 664 infants with an older biological sibling with ASD. More than eighteen percent (18.7%) of infants with an affected older sibling developed ASD during a follow-up period of 3 years [47]. A population-based study from California, Denmark, Finland, Israel, Sweden and Western Australia, exhibits that risk of ASD increases 8.4-fold following an older sibling with ASD [48]. Another study conducted in the US compared later born siblings of ASD children versus non ASD siblings and concluded that later-born siblings of children with ASD were more likely to be diagnosed with ASD [49]. Other studies established that having an older full sibling with ASD increases the risk of developing ASD in a subsequent child 20-fold [50]. The data reported here again underscores the fact that predisposing genetic factors contribute to the risk of developing ASD.

Limitations

The retrospective nature of this study led to unavailable data for a number of subjects. The fact that this study was conducted in a single tertiary medical referral center suggests it may not be truly representative of the entire Lebanese population.

Conclusions

This is a comprehensive study of ASD patient characteristics in a large cohort from Lebanon. Risk factors for autism in this population are largely comparable to those previously reported such as consanguinity and birth order although their association with ASD reports are conflicting in the world literature. This study from Lebanon provides evidence that first birth order and consanguinity are both associated with a higher risk for developing ASD. Also, late preterm births are at heightened risk for developing ASD. Pre- and post-natal complications and a positive family history of neurological or psychiatric disease, particularly autism, increased the risk of ASD in Lebanon. This is in line with other studies.

Acknowledgement: none

Declarations of interest: none

Ethical Guidelines: Conduction of this study was approved by the Institutional Review Board (IRB) at the American University of Beirut

References

1. American Psychiatric Association IB (2022) Diagnostic and statistical manual of mental disorders, 5th Edition, Text Revision (DSM-5-TR®), 800 Maine Avenue SW, Suite 900, Washington, DC 20024-2812, American Psychiatric Publishing.
2. Zeidan J, Fombonne E, Scorah J, Ibrahim A, Durkin MS, et al. (2022) Global prevalence of autism: A systematic review update. Autism Res 15: 778-790.
3. Maenner MJ, Shaw KA, Bakian AV, Bilder DA, Durkin MS, et al. (2021) Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2018. MMWR Surveill Summ 70: 1-16.
4. Maenner MJ, warren Z, Williams AR, Amoakohene, E, Bakian AV, et al. (2023) Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2020. MMWR Surveill Summ 72: 1-14.
5. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators (2012) Prevalence of autism spectrum disorders-Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. MMWR Surveill Summ 61: 1-19.

6. Chaaya M, Saab D, Maalouf FT, Boustany RM, et al. (2016) Prevalence of Autism Spectrum Disorder in Nurseries in Lebanon: A Cross Sectional Study. J Autism Dev Disord 46: 514-22.

7. Saab D, Chaaya M, Boustany RM (2018). National Prevalence and Correlates of Autism: A Lebanese Cross-Sectional Study. Autism Open Access 8.

8. Hirota T, king BH (2023) Autism Spectrum Disorder: A Review. JAMA 329: 157-168.

9. Rylaarsdam L, Guemez-Gamboa A (2019) Genetic Causes and Modifiers of Autism Spectrum Disorder. Frontiers in Cellular Neuroscience 13.

10. kourtian S, Soueid J, Makhoul NJ, Guisso DR, Chahrour M, et al. (2017) Candidate Genes for Inherited Autism Susceptibility in the Lebanese Population. Sci Rep 7: 45336

11. Soueid J, Kourtian S, Makhoul NJ, Makoukji J, Haddad S, et al. 2016. RYR2, PTDSS1 and AREG genes are implicated in a Lebanese population-based study of copy number variation in autism. Sci Rep 6: 19088.

12. Soueid J, Hamze Z, Bedran J, Chahrour M, Boustany RM (2023) A novel autism-associated UBLCP1 mutation impacts proteasome regulation/activity. Transl Psychiatry 13: 404.

13. Song IG, Kim HS, Cho YM, Lim YN, Moon DS, et al. 2022. Association between birth weight and neurodevelopmental disorders assessed using the Korean National Health Insurance Service claims data. Scientific Reports 12: 2080.

14. Modabbernia A, Velthorst E, Reichenberg A (2017) Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. Molecular Autism 8: 13.

15. Agrawal S, Rao SC, Bulsara MK, Patole SK (2018) Prevalence of Autism Spectrum Disorder in Preterm Infants: A Meta-analysis. Pediatrics 142.

16. Kim JY, Son MJ, Son CY, Radua J, Eisenhut M, et al. (2019) Environmental risk factors and biomarkers for autism spectrum disorder: an umbrella review of the evidence. Lancet Psychiatry 6: 590-600.

17. Loomes R, Hull L, Mandy WPL (2017) What Is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis. J Am Acad Child Adolesc Psychiatry 56: 466-474.

18. Knutsen J, Crossman M, Perrin J, Shui A, Kuhlthau K (2019) Sex differences in restricted repetitive behaviors and interests in children with autism spectrum disorder: An Autism Treatment Network study. Autism 23: 858-868.

19. Wigdor EM, Weiner DJ, Grove J, FU JM, Thompson WK, et al. (2022) The female protective effect against autism spectrum disorder. Cell Genom 2: 100134.

20. Gockley J, Willsey AJ, Dong S, Dougherty JD, Constantino JN, et al. (2015) The female protective effect in autism spectrum disorder is not mediated by a single genetic locus. Mol Autism 6: 25.

21. Guisso DR, Saadeh FS, Saab D, El Deek J, Chamseddine S, et al. (2018) Association of Autism with Maternal Infections, Perinatal and Other Risk Factors: A Case-Control Study. J Autism Dev Disord 48: 2010-2021.

22. Van 'T Hof M, Tisseur C, Van Berckelear-Onnes I, Van Nieuwenhuyzen A, Daniels AM, et al. (2021) Age at autism spectrum disorder diagnosis: A systematic review and meta-analysis from 2012 to 2019. Autism 25: 862-873.

23. Pierce K, Gazestani VH, Bacon E, Barnes CC, Cha D, et al. (2019) Evaluation of the Diagnostic Stability of the Early Autism Spectrum Disorder Phenotype in the General Population Starting at 12 Months. JAMA Pediatr 173: 578-587.

24. Roy N, Ghaziuddin M, Mohiuddi S (2020) Consanguinity and Autism. Current Psychiatry Reports 22: 3.

25. Barbour B, Salameh P (2009) Consanguinity in Lebanon: prevalence, distribution and determinants. J Biosoc Sci 41: 505-517.

26. Bitar T, Gerges P, Kassab MC, Hallit S, Matar H, et al. (2020) Factors associated with Autism Spectrum Disorder: A case-control study in the Lebanese population. 20: e13218.

27. Mamidala MP, Kalikiri MK, Praveen Kumar PT, Rajesh N, Vallamkonda OR, et al. (2015) Consanguinity in India and its association with autism spectrum disorder. Autism Res 8: 224-228.

28. Alshaban FA, Aldosari M, Ghazal I, AL-Shammari H, Elhag S, et al. (2023) Consanguinity as a Risk Factor for Autism. J Autism Dev Disord

29. Ministère DE Santé Publique, CIPLD, Institut De Gestion De La Santé Et De La Protection Sociale- Université Saint-Joseph (2004) Recueil national des statistiques sanitaires au Liban, Université Saint-Joseph de Beyrouth (USJ)

30. Laverty C, Surtees A, O'sullivan R, Sutherland D, Jones C, et al. (2021) The prevalence and profile of autism in individuals born preterm: a systematic review and meta-analysis. J Neurodev Disord 13: 41.

31. Persson M, Opdahl S, Risnes K, Gross R, Kajantie E, et al. (2020) Gestational age and the risk of autism spectrum disorder in Sweden, Finland, and Norway: A cohort study. PLoS Med 17: e1003207.

32. Crump C, Sundquist J, Sundquist K (2021) Preterm or Early Term Birth and Risk of Autism. Pediatrics 148.

33. Guy A, Seaton SE, Boyle EM, Draper ES, Field DJ, et al. (2015) Infants Born Late/Moderately Preterm Are at Increased Risk for a Positive Autism Screen at 2 Years of Age. The Journal of Pediatrics 166: 269-275.e3.

34. Xie S, Karlsson H, Dalman C, Widman L, Rai D, et al. (2019) Family History of Mental and Neurological Disorders and Risk of Autism. JAMA Network Open 2: e190154-e190154.

35. Wang C, Geng H, Liu W, Zhang G (2017) Prenatal, perinatal, and postnatal factors associated with autism: A meta-analysis. Medicine (Baltimore) 96: e6696.

36. Croen LA, Qian Y, Ashwood P, Zerbo O, Schendel D, et al. (2019) Infection and Fever in Pregnancy and Autism Spectrum Disorders: Findings from the Study to Explore Early Development. Autism Res 12: 1551-1561.

37. Gardener H, Spiegelman D, Buka SL (2011) Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics 128: 344-355.

38. Schmidt K, Zimmerman A, Bauman M, Ferrone C, Venter J, et al. (2013) Brief report: Asperger's syndrome and sibling birth order. J Autism Dev Disord 43: 973-977.

39. Gardener H, Spiegelman D, Buka SL (2009) Prenatal risk factors for autism: comprehensive meta-analysis. Br J Psychiatry 195: 7-14.

40. Bilder D, Pinborough-Zimmerman J, Miller J, Mcmahon W (2009) Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. Pediatrics 123: 1293-300.

41. Schieve LA, Tian LH, Drews-Botsch C, Windham GC, Newschaffer C et al. (2018) Autism spectrum disorder and birth spacing: Findings from the Study to Explore Early Development (SEED). Autism Res 11: 81-94.

42. Alvares GA, Licari MK, Stevenson PG, Bebbington K, Cooper MN, et al. (2021) Investigating associations between birth order and autism diagnostic phenotypes. J Child Psychol Psychiatry 62: 961-970.

43. Andoy Galvan JA, Ramalingam PN, Patil SS, Bin Shobri MAS, Chinna K, et al. (2020) Mode of delivery, order of birth, parental age gap and autism spectrum disorder among Malaysian children: A case-control study. Heliyon 6: e05068.

44. Moore GS, Kneitel AW, Walker CK, Gilbert WM, Xing G (2012) Autism risk in small and large-for-gestational-age infants. Am J Obstet Gynecol 206: 314.e1-314.e9.

45. Ames JL, Ladd-Acosta C, Fallin MD, Qian Y, Schieve LA, et al. (2021) Maternal Psychiatric Conditions, Treatment With Selective Serotonin Reuptake Inhibitors, and Neurodevelopmental Disorders. Biological Psychiatry 90: 253-262.

46. Karam EG, Mneimneh ZN, Dimassi H, Fayyad JA, Karam AN, et al. (2008) Lifetime prevalence of mental disorders in Lebanon: First onset, treatment, and exposure to war. PLoS Med 5: e61.

47. Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, et al. (2011) Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study. Pediatrics 128: e488-495.

48. Hansen SN, Schendel DE, Francis RW, Windham GC, Bresnahan M, et al. (2019) Recurrence Risk of Autism in Siblings and Cousins: A Multinational, Population-Based Study. J Am Acad Child Adolesc Psychiatry 58: 866-875.

49. Miller M, Musser ED, Young GS, Olson B, Steiner RD, et al. (2019) Sibling Recurrence Risk and Cross-aggregation of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder. JAMA Pediatr 173: 147-152.

50. Risch N, Hoffmann TJ, Anderson M, Croen LA, Grether JK et al. (2014) Familial recurrence of autism spectrum disorder: Evaluating genetic and environmental contributions. Am J Psychiatry 171: 1206-1213.