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Autism in Children and Correlates in Lebanon: A Pilot Case-Control Study

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ABSTRACT

Background: Autism spectrum disorder (ASD) is a neurological disorder typically appearing before the age of three. The exact cause of autism remains uncertain, and several factors may be involved in its onset: genetic factors and possible environmental factors. The aim of this study was to assess the correlates of autism in the Lebanese population.

Methods: We investigated the association of autism with several factors in 86 autism cases from specialized schools for children with developmental disabilities and 172 control children from regular public schools in the same regions. Several risk factors for autism were investigated after comparison with a cohort control on parental age, sex, maternal unhappy feeling during pregnancy, consanguineous marriage, and province of residence. The Chi-square test was used to compare nominal variables, and Fisher exact test was used in case expected values within cells were inferior to five. For quantitative variables, we used *t*-test to compare means between two groups, after checking their distribution normality. For multivariate analysis, we used a forward stepwise likelihood ratio logistic regression.

Results: We observed male predominance (79.1%) among autistic infants. There was a significant association between autism and older parents age (OR=1.27), male sex (OR=3.38), unhappy maternal feeling during pregnancy (OR=5.77), living close to industry (OR=6.58), previous childhood infection (OR=8.85), but none concerning maternal age, paternal age and consanguinity.

Conclusions: In this pilot epidemiological study of autism in Lebanon, we found several prenatal and perinatal risk factors for autism that could be modified.

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Introduction

Autism is a neurodevelopmental disorder characterized by communication and social contact impairment and stereotypic movements. It manifests early in life, usually before the age of three. This Pervasive Developmental Disorder (PDD) belongs to the broad family of Autism Spectrum Disorders (ASD) which includes Asperger syndrome, Rett syndrome and PDD-not otherwise specified [1]. Its mean prevalence rate is 1/1000 children[1], whereas other studies showed a greater prevalence with an increase in the frequency from 4 per 10,000 in 1950 to 40 to 60 per 10,000 as of 2008 [2].

Many risk factors have been proposed to play role in the etiology of autism. Genetic predisposition was first suggested by twin and family studies [3] and genetic studies later revealed the presence of a number of susceptibility genes which interaction could account for the variable expressivity observed in this disorder[4]. Suggested environmental factors include mother's age and psychological status, toxic exposures, prenatal infections and reactions to vaccines, particularly MMR (Measles, Mumps and Rubella vaccines). However, this latter factor has been much investigated and does not seem to be involved in the occurrence of autism[5,6].

This etiologic heterogeneity is reflected in the specific features of the illness, such as delayed speech for example, that are more similar in affected relatives than in unrelated cases, and that could be phenotypic markers for various causes of the disorder [7]. Genome-wide screening, cytogenetic studies, microarray analysis and whole exome sequencing was performed on a large number of families and lead to the detection of autism susceptibility loci, structural chromosomal aberrations, copy number variations and *de novo* mutations in a number of genes [8-12]. Epidemiological studies screening one or more environmental factors and their correlation with autism in different populations were also reported[13-15].

The needs for various types of support to Lebanese autistic children were discussed in a letter to the Editor of the Lebanese Medical Journal in 2001[16]. However, the present study is the first case-control study on Lebanese autistic children, with the objective to investigate possible correlations of some variables related to the family or to the mother's or child's health to autism.

Methods

Study type and sampling

We conducted a case-control study to investigate the correlates of autism in the Lebanese population. The prenatal and perinatal conditions were assessed to identify potential risk factors for autism.Cases were taken from ten specialized schools for children with developmental disabilities in all Lebanese regions (Beirut, Bekaa, Mount Lebanon and North), except for the South where no specialized school agreed to participate. All parents of autistic children were contacted; all age groups were included. One child per family was selected. All children were diagnosed as having autistic disorder by psychiatrics based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR criteria).

Controls were randomly selected from lists provided by ten non specialized public schools administrators, age-matched and taken from the same regions as the corresponding cases. The number of controls was to be the double of cases. No exclusion criteria were applied for both cases and controls. The study was conducted between March and July 2012.

Data collection

Information concerning potential risk factors was obtained using a questionnaire that was addressed to the parents of the children, through the schools administration and after the approval of the institutions' review boards. Anonymity and confidentiality of the data were ensured through a written informed consent form.

The questionnaire consisted of three parts: sociodemographic characteristics (age of parents, parents' occupation, number of siblings, dwelling region, presence of industrial plants in the vicinity of the house), characteristics of the child (sex, age, diagnosis age if autistic, type of autism, other known diseases, specific diet, vaccination history, drugs taken, tests performed, infection history, type of school and sport performing), and finally health characteristics of parents (age of mother and father at the beginning of the pregnancy, drugs taken by mother during pregnancy, vaccination of the mother, known disease of the mother, presence of other autistic children in the family, history of previous abortion, number of abortions, sadness during pregnancy, complications during pregnancy, war exposure during pregnancy, type of delivery, alcohol consumption and smoking). These risk factors were chosen based on predisposing factors suggested in previous studies[3-6; 13-15].

Statistical analysis

Data were entered and analyzed using SPSS (Statistical Package for Social Sciences), version 20. Data entry was checked twice by lay persons. A *P*-value of less than 0.05 was considered significant. The Chi-square test was used to compare nominal variables, and Fisher exact test was used in case expected values within cells were inferior to five. For quantitative variables, we used the Student *t*-test to compare means between two groups, after checking their distribution normality.

For multivariate analysis, we used a forward stepwise likelihood ratio logistic regression, taking the variable (autistic/non autistic) as the dependent variable, and variables which resulted in a *P*-value of <0.20 in the bivariate analysis as the independent variables: sex, father occupation, dwelling region, family hereditary disease history, type of family disease, mumps-measles and rubella vaccination in mother and child, drug intake during pregnancy, sadness during pregnancy, delivery type, siblings disease and infection.

Results

Description of the sample

Table 1 presents the main characteristics of each of the two groups: cases and controls and a comparison of boys and girls in each group. In total, 86 autistic cases were evaluated; they were aged between three and 27 years, 68 (79.1%) boys and 18 (20.9%) girls. The control group was chosen from non-specialized schools in five different regions in Lebanon: a total of 172 children were assessed, including 100 boys (58.1%) and 72 girls (41.9%). Moreover, we describe in Table 1 some parental variables, such as parental consanguinity, the presence of hereditary diseases in the family, dwelling region, mother's and father's work; there were no statistically significant differences between boys and girls of both cases and controls regarding the listed characteristics.

Table 1: Comparison of the characteristics of cases (68 boys and 18 girls) and controls (100 boys and 72 girls) using *t*-test for continuous variables and Fisher's exact test for dichotomous variables

Characteristics	Cases		*P* value	Controls		*P* value
	Boys	Girls		Boys	Girls	
Mean age (± SD) (yr)						
Child	12.39 ± 5.92	10.83 ± 3.23	0.144	8.09 ± 3.38	8.45 ± 3.74	0.502
Mother's age at pregnancy	28.88 ± 5.03	28.72 ± 5.35	0.906	28.66 ± 5.57	30.40 ± 5.81	0.052
Father's age at pregnancy	35.16 ± 5.99	33.66 ± 5.86	0.347	34.78 ± 6.03	36.34 ± 6.71	0.111
Parents' consanguinity, n (%)			0.692			0.329
Yes	8 (72.7)	3 (27.3)		8 (47.1)	9 (52.9)	
No	60 (80.0)	15 (20.0)		92 (59.4)	63 (40.6)	
Disease hereditary in the family, n (%)			0.692			0.455
Yes	8 (72.7)	3 (27.3)		54 (55.7)	43 (44.3)	
No	60 (80.0)	15 (20.0)		46 (61.3)	29 (38.7)	
Dwelling region, n (%)			0.976			0.051
Beirut	16 (80.0)	4 (20.0)		19 (55.9)	15 (44.1)	
Mount Lebanon	39 (79.6)	10 (20.4)		43 (59.7)	29 (40.3)	
North	1 (100.0)	0 (0.0)		21 (80.8)	5 (19.2)	
South	3 (75.0)	1 (25.0)		12 (41.4)	17 (58.6)	
Bekaa	9 (75.0)	3 (25.0)		5 (45.5)	6 (54.5)	
Smoking mother, n (%)			0.973			0.153
Yes	21 (80.8)	5 (19.2)		29 (67.4)	14 (32.6)	
No	47 (78.3)	13 (21.7)		71 (55.0)	58 (45.0)	
Mother consumption of alcohol, n (%)			0.310			0.570
Yes	11 (68.8)	5 (31.2)		20 (54.1)	17 (45.9)	
No	57 (81.4)	13 (18.6)		80 (59.3)	55 (40.7)	
Mother's work, n (%)			0.280			0.086
Jobless	44 (78.6)	12 (21.4)		68 (57.1)	51 (42.9)	
Working /self Worked	19 (79.2)	5 (20.8)		27 (69.2)	12 (30.8)	
Health worker	5 (83.3)	1 (16.7)		5 (35.7)	9 (64.3)	
Father's work, n (%)			0.392			0.342
Jobless	2 (100.0)	0 (0.0)		1 (100.0)	0 (0.0)	
Self employed	22 (71.0)	9 (29.0)		30 (56.6)	23 (43.4)	
Employee	43 (84.3)	8 (15.7)		63 (61.2)	40 (38.8)	
Health profession	1 (50.0)	1 (50.0)		6 (40.0)	9 (60.0)	

Socio-demographic comparison between cases and controls

We analyzed the potential association of the different socio-demographic factors with autism in both cases and controls groups and their potential association with autism. There was a significant difference between cases and controls regarding dwelling region (Mount Lebanon and Bekaa included the highest percentages of cases; $P<0.001$) (Table 2).

In both case and control groups, maternal and paternal age at pregnancy were close (28.84 and 29.38 for cases and 34.84 and 35.43 for controls, respectively). The percentage of working mothers show a non-significant difference between the two groups. Other factors such as living close to an industrial plant, parental consanguinity, type of family diseases, autism in the family and in addition mother's and father's work and age were not significantly different between cases and controls (Table 2).

Mother's health related factors comparison between cases and controls

In Table 3, we present mother's health differences between cases and controls: mothers of the case group have significantly lower vaccination against rubella, measles and mumps compared with controls ($P<0.001$ for all); they also had higher drug intake during pregnancy ($P=0.007$), higher frequency of sadness during pregnancy ($P<0.001$), and preterm delivery ($P<0.001$). Other mother's health related factors such as mother chronic diseases, previous abortions, complications during pregnancy, war exposure during pregnancy, smoking and alcohol consumption during pregnancy did not show any significant association with autism.

Table 2: Comparison of socio-demographic distribution between cases (n=86) and controls (n=172) using *t*-test for continuous variables and Fisher's exact test for dichotomous variables

Risk factors	Cases	Controls	*P* value
Dwelling region, n (%)			0.001
Beirut	20 (37.0)	34 (63.0)	
Mount Lebanon	49 (40.5)	72 (59.5)	
North	1 (3.7)	26 (96.3)	
South	4 (12.1)	29 (87.9)	
Bekaa	12 (52.2)	11 (47.8)	
Lives close to an industrial plant, n (%)			0.728
Yes	16 (35.6)	29 (64.4)	
No	70 (32.9)	143 (67.1)	
Consanguinity, n (%)			0.479
Yes	11 (39.3)	17 (60.7)	
No	75 (32.6)	155 (67.4)	
Type of family disease, n (%)			0.101
Cardiovascular	9 (9.7)	84 (90.3)	
Cancer	0 (0.0)	10 (100.0)	
Anemia	0 (0.0)	1 (100.0)	
Epilepsy	2 (50.0)	2 (50.0)	
Autism in the family, n (%)			1.000
Yes	0 (0.0)	1 (100.0)	
No	86 (33.5)	171 (66.5)	
Mother's work, n (%)			0.643
Jobless	56 (32.0)	119 (68.0)	
Working	24 (38.1)	39 (61.9)	
Health professional	6 (30.0)	14 (70.0)	
Father's work, n (%)			0.113
Does not work	2 (66.7)	1 (33.3)	
Self employed	31 (36.9)	53 (63.1)	
Employee	51 (33.1)	103 (66.9)	
Health profession	2 (11.8)	15 (88.2)	
Mother's age at pregnancy, Mean ± SD	28.84 ± 5.07	29.38 ± 5.72	0.459
Father's age, Mean ± SD	34.84 ± 5.96	35.43 ± 6.35	0.476

Child's health related factors distribution between cases and controls

Concerning cases, there were more boys (*P*=0.001), more siblings with autism (*P*=0.012), more previous infection (*P*=0.005), and less vaccination against mumps (*P*=0.017) and measles (*P*=0.002) compared with controls (Table 4). However, the type of previous infection (*P*=0.692) and vaccination against rubella (*P*=0.109) showed no significant difference.

Table 3: Mother's health related factors distribution between cases and controls using either Fisher's exact test or Chi-square test

Variables	Cases	Controls	*P* value
Mother chronic disease, n (%)			0.404
Yes	3 (50.0)	3 (50.0)	
No	83 (32.9)	169 (67.1)	
Vaccination against rubella, n (%)			0.001
Yes	58 (25.9)	166 (74.1)	
No	8 (57.1)	6 (42.9)	
Unknown	20 (100.0)	0 (0.0)	
Vaccination against measles, n (%)			0.001
Yes	58 (25.9)	166 (74.1)	
No	8 (57.1)	6 (42.9)	
Unknown	20 (100.0)	0 (0.0)	
Vaccination against mumps, n (%)			0.001
Yes	58 (26.1)	164 (73.9)	
No	8 (50.0)	8 (50.0)	
Unknown	20 (100.0)	0 (0.0)	
Drug intake during pregnancy, n (%)			0.007
Yes	7 (77.8)	2 (22.2)	
No	79 (31.7)	170 (68.3)	
Had an abortion, n (%)			0.780
Yes	30 (34.9)	56 (65.1)	
No	56 (32.6)	116 (67.4)	
Sadness during pregnancy, n (%)			0.001
Yes	40 (55.6)	32 (44.4)	
No	46 (24.7)	140 (75.3)	
Complications during pregnancy, n (%)			0.603
Yes	2 (50.0)	2 (50.0)	
No	84 (33.1)	170 (66.9)	
War exposure during pregnancy, n (%)			0.249
Yes	58 (26.1)	164 (73.9)	
No	8 (50.0)	8 (50.0)	
Unknown	20 (100.0)	0 (0.0)	
Delivery type, n (%)			0.001
At term and normal	55 (31.1)	122 (68.9)	
At term and caesarian	18 (27.3)	48 (72.7)	
Preterm and normal	7 (100.0)	0 (0.0)	
Preterm and caesarian	6 (75.0)	2 (25.0)	
Smoking mother, n (%)			0.371
Yes	26 (37.7)	43 (62.3)	
No	60 (31.7)	129 (68.3)	
Mother consumption of alcohol, n (%)			0.586
Yes	16 (30.2)	37 (69.8)	
No	70 (34.1)	135 (65.9)	

Multivariate analysis

The retained model explained 76.9% of the autism variability (Nagelkerke R^2 = 0.769); Hosmer-Lemeshow test had a *P*-value of 0.26, and 89.9% of individuals were correctly classified. We found that living close to an industry (OR=6.58; *P*=0.018), older parents (OR=1.27; *P*<0.001), maleness in children (OR_a=3.38; *P*=0.024), previous childhood infection (OR=8.85; *P*=0.017) and mother's sadness during pregnancy (OR=5.77; *P*=0.001) were all associated with autism (Table 5).

Excluded variables include: dwelling region, delivery type, vaccination of mother, and child against rubella, measles and mumps, drug intake during pregnancy, and siblings' disease.

Table 4: Comparison of Children's characteristics among cases (n=86) and controls (n=172) using *t*-test for continuous variables and Chi square or Fisher's exact tests for dichotomous variables

Characteristic	Cases	Controls	*P* value
Sex of the child, n (%)			0.001
Boy	68 (40.5)	100 (59.5)	
Girl	18 (20.0)	72 (80.0)	
Siblings with autism, n (%)			0.012
Yes	4 (100.0)	0 (0.0)	
No	82 (32.3)	172 (67.7)	
Vaccination against rubella, n (%)			0.109
Yes	83 (32.7)	171 (67.3)	
No	3 (75.0)	1 (25.0)	
Vaccination agaisnt measles, n (%)			0.002
Yes	79 (31.6)	171 (68.4)	
No	7 (87.5)	1 (12.5)	
Vaccination agaisnt mumps, n (%)			0.017
Yes	81 (32.1)	171 (67.9)	
No	5 (83.3)	1 (16.7)	
Previous infection, n (%)			0.005
Yes	10 (66.7)	5 (33.3)	
No	76 (31.3)	167 (68.7)	
Type of infection, n (%)			0.692
Otitis	4 (44.4)	5 (55.6)	
Bronchitis	1 (100.0)	0 (0.0)	
Varicella	1 (100.0)	0 (0.0)	
Pseudomonas	1 (100.0)	0 (0.0)	
Urinary Tract Infection	1 (100.0)	0 (0.0)	
Viral diarrhea	1 (100.0)	0 (0.0)	

Table 5: Multivariate analysis: risk factors of autism using logistic regression (stepwise forward)

Correlates	OR [a]	CI 95%	*P* value
Living close to an industry	6.58	1.38, 31.44	0.018
Older age of the child	1.27	1.12, 1.43	0.001
Male sex of the child	3.38	1.18, 9.69	0.024
Previous childhood infection	8.85	1.47, 53.39	0.017
Mother's sadness during pregnancy	5.77	2.11, 15.80	0.001

OR_a = Odds ratio adjusted for all other variables in the table

Discussion

In this study, we were able to describe the characteristics of an autistic population, in comparison with normal children, and we found that autism was associated with several characteristics. Male predominance (79.1%) among autistic infants was observed in comparison with normal children, similar to other researchers findings; in fact, the most constant collective finding in autism spectrum conditions is gender ratios showing a greater preponderance of males over females (approximating 4:1) [17].

Several studies show that the age of both parents is associated with autism[18-20]. Advanced maternal and paternal age may increase the chance of chromosomal abnormalities in offspring, and the risk for gestational brain damage in fetus[21,22]. However, in the present study, we found no

significant relation between parental age and gender, and the prevalence of autism. It may be partly a consequence of the small sample sizes. Previous findings showed that children with autism had a higher risk of having autistic siblings[23]. In our study we found a higher frequency of siblings with autism in the cases group but no correlation was established with this potential risk factor.

Our investigation identified mother's sadness during pregnancy as a risk factor for autism (OR_a=5.77). Previous research revealed that unhappy emotional state during pregnancy, regardless of causes, was significantly associated with autism[24]. This may be because of a higher secretion of maternal hormones such as adrenalin causing placental vasoconstriction which may affect fetal hormone levels, with a negative impact on fetal development. Moreover, exposure to environmental or social stressors including family problems has been associated with increased risk for autism[25-27].

Previous studies reported that preterm delivery of children occurs more frequently in the birth of autistic children [28]. Our study found maternal delivery type suggestively associated with autism in the unadjusted analysis, with a high frequency for preterm normal and preterm cesarean deliveries for cases group. This association did not reach statistical significance. The strongest factor associated with autism was childhood infections which were frequently seen in the case group and resulting in an 8.85 fold increase in the risk of autism. The observed infections were otitis, bronchitis, varicella, pseudomonas, urinary tract infections and viral diarrhea. However, studies that explore the association between childhood infections and autism show that during the first 2 years, children with autism may be at higher risk for certain types of infections and lower risk for others [29]. Other significant associations were observed. In fact, living close to an industry is more frequently observed in the case group. It showed an almost 6.58 fold increased risk for autism. Recent studies found that women living in high-pollution areas were twice as likely to have a child with autism[30,31]

Although dwelling region was significantly different between cases and controls in bivariate analysis, this factor was not retained in the final model; apparently, the differences between cases and controls were better accounted for by other variables.

Consanguinity is high in Middle Eastern communities. In Lebanon, the overall prevalence of consanguineous marriages is 35.5%[32]. Consanguinity is an important factor which was found to increase the risk of autism. In a Saudi Arabian study, Al-Salehi and colleagues found that almost one third of a cohort of children with autism had a history of consanguinity[33]. However in our study this correlation was not evident. It may be due to the relatively small number of cases of consanguinity included in the study.

Some limitations of our study should be noted. First, information were based on self-administered questionnaires completed by parents and may have differential reporting by cases as compared with controls; although we used standardized questionnaires, recall bias is still possible and may direct the results away from the null. Missing replies were recorded, which may cause selection bias; moreover, the fact that cases and controls were selected from different types of schools may also induce selection bias. However, in Lebanon, the majority of cases of autism go to specialized schools, where they do not mingle with normal children who go to public or private non-specialized schools. It was also not possible to have information about the temporality of some factors versus that of autism diagnosis; it is possible that infections and living close to an industry occurred after autism diagnosis was established. This remains to be established in future prospective studies. Finally, residual confounding is possible due to unmeasured variables. In order to complete collected data, medical records of obstetric examinations and delivery should be consulted and discussion with parents should be performed. The sample size should also be increased.

Conclusion

Our findings support several prenatal and perinatal risk factors for autism. We found that male sex, older age, living close to an industry; previous childhood infection and mother's sadness during pregnancy were all associated with autism. Additional studies are necessary to confirm our results, and public health measures could be taken to avoid modifiable risk factors.

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

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References

1. Gillberg C, Wing L. Autism: not an extremely rare disorder. *Acta Psychiatr Scand.* 1999;99(6):399-406.

2. Jones JR, Skinner C, Friez MJ, Schwartz CE, Stevenson RE. Hypothesis: dysregulation of methylation of brain-expressed genes on the X chromosome and autism spectrum disorders. *Am J Med Gen A.* 2008;146A(17):2213-2220.

3. Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, et al. Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol Med.* 1995;25(1):63-77.

4. Muhle R, Trentacoste SV, RapinI. The genetics of autism. *Pediatrics.* 2004;113(5):e472-486.

5. Honda H, Shimizu Y, Rutter M. No effect of MMR withdrawal on the incidence of autism: a total population study. *J Child Psychol Psychiatry.* 2005;46(6):572-579.

6. Uno Y, Uchiyama T, Kurosawa M, Aleksic B, Ozaki N. The combined measles, mumps, and rubella vaccines and the total number of vaccines are not associated with development of autism spectrum disorder: the first case-control study in Asia. *Vaccine.* 2012;30(28):4292-4298.

7. Silverman JM, Smith CJ, Schmeidler J, Hollander E, Lawlor BA, Fitzgerald M, et al. Symptom domains in autism and related conditions: evidence for familiality. *Am J Med Genet.* 2002;114(1):64-73.

8. Szatmari P, Paterson AD, Zwaigenbaum L, Roberts W, Brian J, Liu XQ, et al. Mapping autism risk loci using genetic linkage and chromosomal rearrangements. *Nat Genet.* 2007;39(3):319-328.

9. Gauthier J, Siddiqui TJ, Huashan P, Yokomaku D, Hamdan FF, Champagne N, et al. Truncating mutations in NRXN2 and NRXN1 in autism spectrum disorders and schizophrenia. *Hum Genet.* 2011;130(4):563-573.

10. Glessner JT, Wang K, Cai G, Korvatska O, Kim CE, Wood S, et al. Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. *Nature.* 28 2009;459(7246):569-573.

11. Neale BM, Kou Y, Liu L, Ma'ayan A, Samocha KE, Sabo A, et al. Patterns and rates of exonic de novo mutations in autism spectrum disorders. *Nature.* 10 2012;485(7397):242-245.

12. Sanders SJ, Murtha MT, Gupta AR, Murdoch JD, Raubeson MJ, Willsey AJ, et al. De novo mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature.* 2012;485(7397):237-241.

13. Atladottir HO, Henriksen TB, Schendel DE, Parner ET. Autism after infection, febrile episodes, and antibiotic use during pregnancy: an exploratory study. *Pediatrics.* 2012;130(6):e1447-1454.

14. Suren P, Bakken IJ, Aase H, Chin R, Gunnes N, Lie KK, et al. Autism spectrum disorder, ADHD, epilepsy, and cerebral palsy in Norwegian children. *Pediatrics.* 2012;130(1):e152-158.

15. Newschaffer CJ, Croen LA, Fallin MD, Hertz-Picciotto I, Nguyen DV, Lee NL, et al. Infant siblings and the investigation of autism risk factors. *J Neurodev Disord.* 2012;4(1):7.

16. Kouba-Hreich E, Henri G, Megarbane A. [Speech pathology intervention for autistic children in Lebanon: status, needs and perspectives]. *Le Journal Medical Libanais. The Lebanese Medical Journal.* 2001;49(3):130-131.

17. Scott FJ, Baron-Cohen S, Bolton P, Brayne C. Brief report: prevalence of autism spectrum conditions in children aged 5-11 years in Cambridgeshire, UK. *Autism.* 2002;6(3):231-237.

18. Durkin MS, Maenner MJ, Newschaffer CJ, Lee LC, Cunniff CM, Daniels JL, et al. Advanced parental age and the risk of autism spectrum disorder. *Am J Epidemiol.* 2008;168(11):1268-1276.

19. Reichenberg A, Gross R, Weiser M, Bresnahan M, Silverman J, Harlap S, et al. Advancing paternal age and autism. *Arch Gen Psychiatry.* 2006;63(9):1026-1032.

20. Shelton JF, Tancredi DJ, Hertz-Picciotto I. Independent and dependent contributions of advanced maternal and paternal ages to autism risk. *Autism Res.* 2010;3(1):30-39.

21. Crow JF. The high spontaneous mutation rate: is it a health risk? *Proc Natl Acad Sci USA.* 1997;94(16):8380-8386.

22. Gillberg C. Maternal age and infantile autism. *J Autism Dev Disord.* 1980;10(3):293-297.

23. Piven J, Simon J, Chase GA, Wzorek M, Landa R, Gayle J, et al. The etiology of autism: pre-, peri- and neonatal factors. *J Am Acad Child Adolesc Psychiatry.* 1993;32(6):1256-1263.

24. Zhang X, Lv CC, Tian J, Miao RJ, Xi W, Hertz-Picciotto I, et al. Prenatal and perinatal risk factors for autism in China. *J Autism Dev Disord.* 2010;40(11):1311-1321.

25. Kinney DK, Munir KM, Crowley DJ, Miller AM. Prenatal stress and risk for autism. *Neurosci Biobehav Rev.* 2008;32(8):1519-1532.

26. O'Donnell K, O'Connor TG, Glover V. Prenatal stress and neurodevelopment of the child: focus on the HPA axis and role of the placenta. *Dev Neurosci.* 2009;31(4):285-292.

27. Ward AJ. A comparison and analysis of the presence of family problems during pregnancy of mothers of "autistic" children and mothers of normal children. *Child Psychiatry Hum Dev.* 1990;20(4):279-288.

28. Hultman CM, Sparen P, Cnattingius S. Perinatal risk factors for infantile autism. *Epidemiology.* 2002;13(4):417-423.

29. Rosen NJ, Yoshida CK, Croen LA. Infection in the first 2 years of life and autism spectrum disorders. *Pediatrics.* 2007;119(1):e61-69.

30. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-related air pollution, particulate matter, and autism. *JAMA Psychiatry.* 2013;70(1):71-77.

31. Windham GC, Zhang L, Gunier R, Croen LA, Grether JK. Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco bay area. *Environ Health Perspect.* 2006;114(9):1438-1444.

32. Barbour B, Salameh P. Consanguinity in Lebanon: prevalence, distribution and determinants. *J Biosoc Sci.* 2009;41(4):505-517.

33. Al-Salehi SM, Al-Hifthy EH, Ghaziuddin M. Autism in Saudi Arabia: presentation, clinical correlates and comorbidity. *Transcult Psychiatry.* 2009;46(2):340-347.