



# Association of Autism with Maternal Infections, Perinatal and Other Risk Factors: A Case-Control Study

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Published online: 13 January 2018  
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## Abstract

This case-control study explores the association between pregnancy/birth complications and other factors with Autism Spectrum Disorder (ASD) in Lebanese subjects aged 2–18 years. Researchers interviewed 136 ASD cases from the American University of Beirut Medical Center Special Kids Clinic, and 178 controls selected by systematic digit dialing in the Greater-Beirut area. Male gender (Adjusted Odds Ratio [95% CI]: 3.9 [2.2–7.0]); postpartum feeding difficulties (2.5 [1.2–5.4]); maternal infections/complications during pregnancy (2.9 [1.5–5.5], 2.1 [1.1–3.9]); consanguinity (2.5 [1.0–6.0]); family history of psychiatric disorders (2.2 [1.1–4.4]) were risk factors for ASD. Being born first/second (0.52 [0.28–0.95]) and maternal psychological support during pregnancy (0.49 [0.27–0.89]) were negatively associated with ASD. Identifying ASD correlates is crucial for instigating timely screening and subsequent early intervention.

**Keywords** Autism · Risk factors · Maternal infections · Perinatal factors · Consanguinity

## Introduction

Autism spectrum disorder (ASD) is a constellation of developmental disorders characterized by diminished social interactions, restrictive behaviors and stereotypies, reduced eye contact and delayed acquisition of speech (Christensen et al. 2016). The prevalence of this disorder has risen with numbers reaching 1 in 68 children in 2010 in the United States (Christensen et al. 2016). In 2014, ASD was associated with

\$3020 higher health care costs and \$14,061 higher aggregate non-health care costs than those for typically developing children in the United States (Lavelle et al. 2014).

The etiology of ASD is diverse and there is a wide variety of genetic and environmental factors associated with this disorder (Chaste and Leboyer 2012). Newschaffer, Fallin and Lee (2002) segregated risk factors into genetic predisposition of the mother and the child and environmental factors affecting the mother and the child. Moreover, the number of research looking at gene versus environment interactions has risen (Kim and Leventhal 2015; Tordjman et al. 2014). Focusing on finding environmental factors associated with autism and exploring interactions between the genetic and environmental components for the development of autism are, therefore, needed (Chaste and Leboyer 2012).

Many major environmental risk factors are implicated as associated with the development of ASD, including prenatal and perinatal factors, socio-economic status and drugs and toxic exposure (Chaste and Leboyer 2012). Among prenatal and perinatal factors, ASD may be associated with maternal infections (Mazina et al. 2015) with one study reporting a 30% increased risk of ASD with inpatient diagnosis of maternal infection (Lee et al. 2015). A study from Denmark identified a more specific correlation between first trimester viral infections and second trimester bacterial infections

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**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s10803-017-3449-x>) contains supplementary material, which is available to authorized users.

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with the occurrence of ASD according to Atladottir and colleagues (2010). Two studies by Limperopoulos and colleagues (2008) and Moore and colleagues (2012) reported an increased risk of ASD in children of mothers with chorioamnionitis during pregnancy. With ~64% of women reporting infection during pregnancy, this factor may increase the risk of mortality and morbidity of mother and fetus, as well as cause premature delivery (Collier et al. 2009). In addition, maternal complications of gestational diabetes and hypertension were found to increase the risk of ASD (Deykin and MacMahon 1979; Limperopoulos et al. 2008; Moore et al. 2012). Another factor associated with ASD was premature birth (Goldin and Matson 2016; Hultman et al. 2002; Kuzniewicz et al. 2014; Lampi et al. 2012; Larsson et al. 2005) perhaps linked to potential fetal brain abnormalities (Kerstjens et al. 2012; Volpe 2009). Though evidence remains inconclusive, different studies suggested that there might be an association between fetal hypoxia and hypoxia related obstetric complications and ASD (Burstyn et al. 2011; Gardener et al. 2009; Kolevzon et al. 2007; McGinnis et al. 2013). Additionally, independent studies have supported the association between advanced parental age and autism (Gardener et al. 2009; Kogan et al. 2009; Kolevzon et al. 2007). Furthermore, a comprehensive meta-analysis exploring prenatal risk factors for autism found that maternal prenatal medication use increased the risk of autism (Gardener et al. 2009). Other studies that looked at psychiatric disorders determined that poor mental health of the mother (Guy et al. 2015), as well as mothers with a history of psychiatric care before delivery (Lee et al. 2015), were risk factors for autism.

Moreover, male gender has been extensively studied as an important risk factor for the development of autism. In fact, the Center for Disease Control and Prevention (CDC) reported that ASD is about 4.5 times more common among boys (Christensen et al. 2016).

In Lebanon, the burden of ASD is high, with an estimated prevalence of 153 per 10,000 in toddlers 16–48 months of age, according to a recent study conducted in preschool childcare centers or nurseries in Greater Beirut and Mount Lebanon governorates (Chaaya et al. 2016). An increased burden of ASD is faced in Lebanon due to lack of coverage for vital speech and applied behavior analysis by insurance companies and the National Social Security Fund (NSSF). National policies regarding ASD are either incomplete and/or not adequately implemented. Genetic studies in certain countries of the Middle East and North Africa (MENA) region, including Lebanon, reported some shared and distinctive genetic elements compared to other populations (El-Fishawy and State 2010; Hussein et al. 2011; Salhia et al. 2014). More precisely, very recent studies reported that Lebanese patients with ASD share unique genetic alterations. Soueid and colleagues (2016) found that a duplication

at 1q43 classified as likely pathogenic encompasses RYR2 as a potential ASD candidate gene. This previously identified CNV has been classified as both pathogenic, and, of uncertain significance. The novel potential autism susceptibility genes PTSS1 and AREG were also uncovered. All warrant further genetic and functional analyses (Soueid et al. 2016).

The exclusivity of these changes in the Lebanese endorses the importance of conducting regionally and nationally relevant studies in this population looking into environmental risk factors or gene-environment interactions. In Lebanon, to date, only one published pilot study explored environmental risk factors for autism (Hamade et al. 2013). This study found previous childhood infections, male gender, living close to an industry and maternal unhappiness during pregnancy to be associated with autism (Hamade et al. 2013).

The current study was conducted, in response to the gap in knowledge on environmental risk factors for autism in Lebanon and the inconsistencies in the global evidence for some of the factors. Its goal was to assess the impact of maternal infections and complications and other perinatal and socio-demographic factors on the occurrence of autism in the Lebanese population.

## Methods

### Study Design and Sample

A case-control study was conducted on 314 Lebanese children aged 2–18 years old. Cases were 136 Lebanese children from the American University of Beirut Medical Center Special Kids Clinic (ASKC) diagnosed with ASD. Diagnosis of cases at ASKC was performed by an experienced American Board of Neurology and Psychiatry licensed pediatric neurologist using the Diagnostic and Statistical Manual of Mental Disorders DSM-IV (American Psychiatric Association 1993) or DSM-V (American Psychiatric Association 2013), depending on the year of diagnosis. Patients diagnosed with Pervasive Developmental Disorder-Not Otherwise Specified and Asperger syndrome were excluded from the study. Controls included 178 typically developing Lebanese individuals without ASD of the same age group selected by randomized systematic digit dialing in the Greater Beirut area. The biggest catchment area of ASKC, the Greater Beirut area, was chosen so that cases and controls were selected from the same at risk population. For both cases and controls, mothers were the source of information. Mothers who did not speak Arabic or English, non-Lebanese mothers, deceased mothers and mothers of adopted children were excluded. For controls, mothers of children with ASD or other neurodevelopmental disorders were excluded. Ascertainment of controls was achieved by asking mothers if their children were diagnosed or suspected to have autism or any other

psychiatric illness. Main signs and symptoms of ASD were listed for the mothers of potential controls to ensure that that controls were typically developing. These were mostly related to social challenges, communication difficulties and repetitive or unusual behaviors, interests and activities and were provided to mothers in lay terms with examples to make sure they were clearly understood. Genetic disorders were not accounted for in the ascertainment of controls. Data were collected by telephone interviews using an Institutional Review Board (IRB) approved structured questionnaire in Arabic or English. Parents, especially mothers, of cases from the ASKC were contacted by a member of the treating team to check if they would allow sharing their phone number with the research team. If they agreed, second year medical students called the mothers to first obtain oral consent prior to conducting the interview. This process avoided undue coercion. Interviewers were trained on interviewing and probing techniques by experienced investigators on the research team. Furthermore, the first few phone calls were conducted in the presence of the experienced investigators for feedback and improvement. The study was approved by the IRB at the American University of Beirut (IRB ID: BIOCh.RB.13).

## Measures and Assessments

The questionnaire consisted of three parts. The first included general information about the child such as gender, age, birth order, birth weight, nutrition, and presence or absence of delivery and/or post-natal complications. A specific section for the cases covered questions about diagnosis, treatment and education. The second part comprised questions about the gestational period, maternal weight, infection during pregnancy, medication during pregnancy, travel history, complications during pregnancy and/or delivery, smoking and alcohol ingestion, nutrition, maternal diabetes/hypertension and their psychological status. Finally, the questionnaire surveyed parental demographic, socioeconomic, educational and occupational information in conjunction with parental age at delivery of the child and maternal blood type.

Complications during delivery included meconium aspiration, maternal hemorrhage, forceps aided delivery, malpositioning of fetus, umbilical cord complications, respirator aid, jaundice, and others. Complications during pregnancy encompassed gestational diabetes, gestational hypertension and other health complications present before pregnancy or due to it. Infections during pregnancy included rubella, measles, mumps, cytomegalovirus infection, influenza, genital herpes, Lyme disease infection, pyelonephritis and other infections not included in the aforementioned list. This study reported the presence or absence of infections, and no analysis was done on infection types due to the low sample size for each. Moral support encompassed any help

provided to the pregnant mother consisting of psychological or emotional support from family, friends or mental health professionals.

Some variables were recoded after univariate analysis due to small numbers within those categories. Birth order was recoded into two categories: children born first and second amongst siblings and those with a third or later birth order. Folic acid intake start date was also recoded to divide mothers who began supplementation at or before pregnancy compared to ones who started after pregnancy. Maternal and paternal highest levels of education achieved were also recoded to three categories: elementary school or less, secondary or professional diploma, and university degree or higher. Blood type was likewise recoded into three categories: A, O, and others. The most common blood types in Lebanon are A and O (Blake et al. 1973).

## Statistical Analysis

Descriptive univariate analysis was conducted for description of the study population and for bracketing and recoding of variables. Variables that exhibited little variability with a category of the variable containing 95% or more of the observations were not carried forward in the analysis. Some variables had few missing observations; hence, no imputation of data to replace missing observations was done. Bivariate analysis using Pearson Chi square test for categorical variables and T-test for independent samples for comparison of means were conducted to compare cases and controls with respect to individual risk factors. A bivariate logistic regression was also conducted to generate crude odds ratios (ORs) with their 95% confidence intervals (CIs). A multivariable logistic regression was conducted for significant variables ( $p < .05$ ) and borderline significant variables and adjusted ORs with their 95% CIs were generated. A stepwise logistic regression was then used to generate a final model. Adjusted ORs and their confidence intervals were reported. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22.0.

## Results

### Description of the Study Population

The final sample consisted of 314 children aged 2–18 years with a mean age of 8.3 years ( $\pm 4.8$  years). While cases had a mean age of 6.1 years ( $\pm 3.1$  years), controls had a higher mean age of 10.1 years ( $\pm 5.1$  years). More than half of the study population were males (64%). The majority of children were singletons (95%) and 17 were the product of twin births (5.4%). The mean birth weight was  $3,158 \pm 611.59$  g (Table 1). Only a quarter of the study population was born

**Table 1** Comparison between cases and controls with respect to perinatal variables (N = 314)

Perinatal variables <sup>a</sup>	Cases n (%) <sup>b</sup> mean (±SD)	Controls n (%) <sup>b</sup> mean (±SD)	OR [95% CI]	Test of significance <i>p</i> value <sup>b</sup> T-test
Gender				
Male	109 (54.0)	93 (46.0)	3.7 [2.2–6.2]	<0.001*
Female	27 (24.1)	85 (75.9)	1	
Age (years)	6.1 ± 3.1 <sup>b</sup>	10.1 ± 5.1 <sup>b</sup>	1.2 [1.2–1.3]	<0.001 <sup>b*</sup>
Birth order				
First and second	104 (46.6)	119 (53.4)	0.61 [0.37–1.0]	0.057
Third or later	31 (34.8)	58 (65.2)	1	
Blood type				
A	40 (38.8)	63 (61.2)	1.3 [0.68–2.4]	0.738
O	38 (39.6)	58 (60.4)	1.2 [0.65–2.3]	
AB or B	29 (44.6)	36 (55.4)	1	
Gestational period				
≤ 37 weeks	25 (34.2)	48 (65.8)	0.62 [0.36–1.1]	0.081
≥ 38 weeks	109 (45.8)	129 (54.2)	1	
Type of delivery				
Vaginal	72 (38.1)	117 (61.9)	0.59 [0.37–0.93]	0.022*
Caesarian	64 (51.2)	61 (48.8)	1	
Birth weight (grams)	3140.0 ± 574.0 <sup>b</sup>	3173.0 ± 640.0 <sup>b</sup>	1.0 [1.0–1.0]	0.634 <sup>b</sup>
Complications during delivery				
Yes	30 (55.6)	24 (44.4)	1.8 [1.0–3.3]	0.046*
No	106 (40.8)	154 (59.2)	1	
Jaundice				
Yes	15 (50.0)	15 (50.0)	1.3 [0.63–2.9]	0.437
No	121 (42.6)	163 (57.4)	1	
If yes, jaundice treated				
Yes	10 (66.7)	5 (33.3)	4.6 [1.5–14]	0.006*
No	35 (30.4)	80 (69.6)	1	
Breastfeeding				
Yes	106 (41.7)	148 (58.3)	0.74 [0.42–1.3]	0.300
No	29 (49.2)	30 (50.8)	1	
Breastfeeding duration (weeks)	32.8 ± 33.5	32.1 ± 34.5	0.99 [0.99–1.0]	0.885
Feeding difficulty				
Yes	38 (69.1)	17 (30.9)	3.9 [2.1–7.2]	<0.001*
No	93 (36.8)	160 (63.2)	1	

\*Significant at 0.05

<sup>a</sup>Some totals do not add up to 314 because of missing values<sup>b</sup>Means and standard deviations and *p* value for T-test for continuous variables

premature (< 37 weeks of gestation). Around 85% of mothers and 80% of fathers had completed a secondary level of education. Moreover, ~40% of mothers and ~97% of fathers were employed.

### Description of the Cases

For the 136 cases with ASD, the mean age at diagnosis was 2.8 years (± 1.5 years). The majority of children

with ASD (94%) had received some form of treatment. Among those, 108 (84%) were still receiving therapies at the time of the study. The average age at which they started treatment was 2.8 years (± 1.3). The most common interventions were speech (34%), psychomotor (31%) and applied behavior analysis therapies (21%). More than half the cases (69.1%) were enrolled in a regular school or nursery as compared to 32 (31%) who were not.

## Comparison Between Cases and Controls with Respect to Risk Variables

Table 1 examines the association of specific perinatal variables with autism. Male gender (OR 3.7, 95% CI [2.2, 6.2]), age (OR 1.2, 95% CI [1.2, 1.3]), complications during delivery (OR 1.8, 95% CI [1.0, 3.3]), perinatal treatment for jaundice (OR 4.6, 95% CI [1.5, 14]) and feeding difficulties (OR 3.9, 95% CI [2.1, 7.2]) were independently associated with autism. Vaginal delivery was negatively associated with ASD (OR .59, 95% CI [0.37, 0.93]).

Table 2 lists gestational variables and compares cases and controls with respect to each variable. The odds of occurrence of maternal infection (OR 3.3, 95% CI [1.8, 5.9]), influenza (OR 2.9, 95% CI [1.2, 7.0]), fever (OR 2.5, 95% CI [1.2, 5.2]), pregnancy complications (OR 2.2, 95% CI [1.2, 3.8]) and intake of medication (OR 4.7, 95% CI [2.8, 8.2]) and folic acid (OR 2.5, 95% CI [1.4, 4.6]) during pregnancy were higher among cases as compared to controls. The odds of having received psychological support (OR .45, 95% CI [.27, .80]) and being exposed to smoking at work (OR .58, 95% CI [.35, .96]) during pregnancy were lower for cases than controls. Presence of other infections (OR 3.2, 95% CI [1.5, 6.6]), use of antipyretics (OR 5.2, 95% CI [2.1, 13]) or antibiotics (OR 2.7, 95% CI [1.3, 5.5]) and presence of other complications during gestation (OR 3.4, 95% CI [1.7, 6.8]) were also independent risk factors for autism.

Cases and controls were compared relative to socioeconomic variables. Mothers who had completed a university education (OR .77, 95% CI [.38, 1.6]) and those who went to secondary school or received a technical diploma (OR .31, 95% CI [.15, .63]) were less likely to have children with ASD than mothers who had an elementary or lower level of education. The same applied to paternal education, with fathers who had completed university education (OR .40, 95% CI [.21, .75]) and those with a secondary education or a technical diploma (OR .83, 95% CI [.43, 1.6]) having lower odds of having children with ASD than fathers with elementary or lower level of education. Having extended family members living in the household (OR 3.6, 95% CI [1.7, 7.3]) and having a family history of psychiatric disease (OR 2.9, 95% CI [1.6, 5.1]) were associated with higher odds of having ASD. Parental consanguinity was a risk factor for ASD (OR 2.1, 95% CI [.98, 4.3]) (Table 3).

Table 4 lists crude and adjusted ORs for factors associated with autism with a  $p < .05$  by bivariate analysis. The perinatal variables that were considered were gender, age, type of delivery, delivery complications, and feeding difficulty. Gestation variables comprised infection during pregnancy, influenza, other infections, fever, ingestion of medication, antipyretics, or antibiotics, pregnancy complications, other pregnancy complication, folic acid intake, psychological support, and exposure to smoking at work. Maternal

education, paternal education, extended family living in the household, and family history of psychiatric disease were the socioeconomic variables examined. Birth order ( $p = .057$ ) and consanguinity ( $p < .054$ ) were also included in Table 4 because they were borderline significant. Treatment for jaundice was excluded due to the very small number of respondents to whom this question was applicable ( $n = 30$ ). In the multivariable analysis that included all the above-mentioned variables, delivery complications (OR .66, 95% CI [.25, 1.8]), infections during pregnancy (OR .57, 95% CI [.010, 32]), use of antipyretics (OR .63, 95% CI [.77, 5.1]), antibiotics (OR .61, 95% CI [.064, 5.8]), pregnancy complications (OR .55, 95% CI [.10, 3.0]) and folic acid intake (OR .75, 95% CI [.26, 2.1]) became negatively associated with ASD. Smoking at work was negatively associated with ASD at the bivariate level of analysis (OR .58, 95% CI [.35, .96]) but became a risk factor in the multivariable analysis (OR 1.8, 95% CI [.74, 4.1]). However, variables that changed direction of association with ASD from crude to adjusted analysis also lost their significance with a 95% CI that included 1.

The final model is also presented in Table 4. It included 7 variables, all significantly associated with autism. Male gender (OR 3.9, 95% CI [2.2, 7.0]), presence of infection (OR 2.9, 95% CI [1.5, 5.5]), complications during pregnancy (OR 2.1, 95% CI [1.1, 3.9]), consanguinity (OR 2.5, 95% CI [1.0, 6.0]) and a family history of psychiatric illness (OR 2.2, 95% CI [1.1, 4.4]) were risk factors for autism. First or second order birth (OR .52, 95% CI [.28, .95]) and moral support for the mother during pregnancy (OR .49, 95% CI [.27, .89]) were negatively associated with ASD. The odds of being born first or second among brothers and sisters for cases were 2 times less than the odds of being first or second born among controls. Cases were 2.1 times less likely to have a mother who received moral support during pregnancy compared to controls. Based on the statistical test for goodness of fit, the multivariable analysis model fit the data adequately (Hosmer and Lemeshow goodness of fit test ( $8$ ) = 2.643,  $p = .955$ ).

## Discussion

This study was able to support the association between maternal infections and complications during pregnancy with ASD. Other factors were also found to be associated with ASD such as male gender, feeding difficulties after birth, consanguinity, family history of psychiatric disorders, being born third or later among siblings and absence of maternal support during pregnancy.

Similarly to results from the CDC (Christensen et al. 2016), gender was found to be associated with ASD with an OR of 3.93, providing evidence that the correlation may apply to the Lebanese population as well. Findings from

**Table 2** Comparison between cases and controls with respect to gestational variables (N = 314)

Gestation variables <sup>a</sup>	Cases n (%) <sup>b</sup> mean (±SD)	Controls n (%) <sup>b</sup> mean (±SD)	OR [95% CI]	Test of significance <i>p</i> value <sup>b</sup> T-test
<b>Infection during pregnancy</b>				
Yes	41 (66.1)	21 (33.9)	3.3 [1.8–5.9]	<0.001*
No	94 (37.5)	157 (62.5)	1	
<b>Influenza</b>				
Yes	16 (66.7)	8 (33.3)	2.9 [1.2–7.0]	0.014*
No	117 (40.8)	170 (59.2)	1	
Influenza duration (days)	7.3 ± 7.8 <sup>b</sup>	4.3 ± 2.2 <sup>b</sup>	0.86 [0.58–1.3]	0.238 <sup>b</sup>
<b>Other infections</b>				
Yes	25 (67.6)	12 (32.4)	3.2 [1.5–6.6]	0.001*
No	108 (39.4)	166 (60.6)	1	
<b>Infection onset</b>				
First trimester	7 (50.0)	7 (50.0)	2.5 [0.61–10]	0.437
Second trimester	11 (61.1)	7 (38.9)	1.6 [0.41–6.1]	
Third trimester	15 (71.4)	6 (28.6)	1	
<b>Fever</b>				
Yes	22 (62.9)	13 (37.1)	2.5 [1.2–5.2]	0.012*
No	112 (40.4)	165 (59.6)	1	
Fever duration (days)	4.6 ± 7.1 <sup>b</sup>	2.3 ± 1.1 <sup>b</sup>	0.78[0.46–1.3]	0.274 <sup>b</sup>
<b>Medication</b>				
Yes	58 (69.0)	26 (31.0)	4.7 [2.8–8.2]	<0.001*
No	71 (32.0)	151 (68.0)	1	
<b>Antipyretics</b>				
Yes	21 (75.0)	7 (25.0)	5.2 [2.1–13]	<0.001*
No	87 (35.1)	161 (64.9)	1	
<b>Antibiotics</b>				
Yes	22 (61.1)	14 (38.9)	2.7 [1.3–5.5]	0.004*
No	86 (35.7)	155 (64.3)	1	
<b>Travel</b>				
Yes	29 (51.8)	27 (48.2)	1.5 [0.86–2.7]	0.149
No	106 (41.2)	151 (58.8)	1	
<b>Complication during pregnancy</b>				
Yes	37 (57.8)	27 (42.2)	2.2 [1.2–3.8]	0.006*
No	94 (38.8)	148 (61.2)	1	
<b>Other pregnancy complications</b>				
Yes	31 (70.5)	13 (29.5)	3.4 [1.7–6.8]	<0.001*
No	100 (38.9)	157 (61.1)	1	
<b>Folic acid intake</b>				
Yes	110 (47.2)	123 (52.8)	2.5[1.4–4.6]	0.002*
No	18 (26.1)	51 (73.9)	1	
<b>Folic acid start</b>				
Before pregnancy	69 (48.6)	73 (51.4)	1.2 [0.68–2.0]	0.561
After pregnancy	37 (44.6)	46 (55.4)	1	
Folic acid duration of intake (months)	5.7 ± 3.2 <sup>b</sup>	6.5 ± 3.4 <sup>b</sup>	1.1[0.98–1.2]	0.108 <sup>b</sup>
<b>Multivitamin intake</b>				
Yes	115 (43.1)	152 (56.9)	0.99 [0.52–1.9]	0.989
No	19 (43.2)	25 (56.8)	1	
<b>Psychological support</b>				
Yes	26 (29.5)	62 (70.5)	0.45 [0.27–0.80]	0.003*

**Table 2** (continued)

Gestation variables <sup>a</sup>	Cases n (%) <sup>b</sup> mean ( $\pm$ SD)	Controls n (%) <sup>b</sup> mean ( $\pm$ SD)	OR [95% CI]	Test of significance <i>p</i> value <sup>b</sup> T-test
No	108 (48.2)	116 (51.8)	1	
Alcohol before pregnancy				
Yes	19 (45.2)	23 (54.8)	1.1 [0.57–2.1]	0.787
No	117 (43)	155 (57)	1	
Smoking before pregnancy				
Yes	46 (47.4)	51 (52.6)	1.3 [0.79–2.1]	0.326
No	90 (41.5)	127 (58.5)	1	
Smoking during pregnancy				
Yes	14 (38.9)	22 (61.1)	0.81 [0.40–1.7]	0.569
No	122 (43.9)	156 (56.1)	1	
Smoking at home				
Yes	62 (44.3)	78 (55.7)	1.1 [0.69–1.7]	0.755
No	74 (42.5)	100 (57.5)	1	
Smoking at work				
Yes	31 (34.1)	60 (65.9)	0.58 [0.35–0.96]	0.035*
No	105 (47.1)	118 (52.9)	1	
Maternal weight at delivery (kg)	72.0 $\pm$ 11.0 <sup>b</sup>	73.0 $\pm$ 12.0 <sup>b</sup>	1.0 [0.98–1.0]	0.431 <sup>b</sup>
Maternal age at delivery (years)	31.0 $\pm$ 5.0 <sup>b</sup>	30.0 $\pm$ 6.0 <sup>b</sup>	0.97 [0.93–1.0]	0.164 <sup>b</sup>
Paternal age at delivery (years)	36.8 $\pm$ 6.7 <sup>b</sup>	36.3 $\pm$ 6.7 <sup>b</sup>	0.99 [0.96–1.0]	0.544 <sup>b</sup>
Maternal blood type				
A	44 (37.9)	72 (62.1)	1.6 [0.89–2.9]	0.293
O	50 (43.5)	65 (56.5)	1.3 [0.71–2.3]	
AB or B	37 (49.3)	38 (50.7)	1	

\*Significant at 0.05

<sup>a</sup>Some totals do not add up to 314 because of missing values

<sup>b</sup>Means and standard deviations and *p* value for T-test for continuous variables

this study related to male gender were also supported by a pilot case-control study from Lebanon that found a significant association between autism and male gender (OR 3.38; Hamade et al. 2013).

Results from population studies indicated a much less dramatic association between male gender and ASD. In fact, a prevalence study conducted by Chaaya and colleagues (2016) found a male to female ratio of 1.05:1 when estimated in the general population and 2.5:1 according to diagnosis by a physician. This was also observed in a South Korean study that found a male to female ratio of 5.1:1 in high probability children and 2.5:1 in the general population (Kim et al. 2011). Having a higher male to female ratio in clinical settings as compared to population studies could be explained by the diagnostic criteria being more likely to capture male than female traits of the disorder. In a recent study, restricted behaviors were more noticeable in boys than in girls (Frazier et al. 2014). According to the growing body of scientific evidence, clinicians are less likely to identify ASD in girls than in boys due to the gender difference in

presentation of the disorder (Hiller et al. 2014). Moreover, a new unpublished study in the United States showed that pediatricians are twice more likely to miss girls as boys on autism screening (Furfaro 2017). It is hard to determine if male gender is a true risk factor for autism or an artifact of diagnostic criteria.

While the present study did not specify the type of infection, it established a similar correlation to European studies (Lee et al. 2015; Atladottir et al. 2010), suggesting maternal infections are strong potential indicators for ASD in Europeans and the Lebanese. Such infections may cause fetal distress in utero and/or affect the immunity of the fetus, and hence predispose to autism.

Furthermore, complications during pregnancy comprising diabetes, hypertension, and anemia were associated with an increased risk for ASD. This is in line with previous studies that have determined significant correlations between the development of ASD in the child and chronic hypertension in his/her mother (Moore et al. 2012) and maternal bleeding during pregnancy (Deykin and MacMahon 1979).

**Table 3** Comparison between cases and controls with respect to socioeconomic variables (N = 314)

Socioeconomic variables <sup>a</sup>	Cases n (%) ^ mean (± SD)	Controls n (%) ^ mean (± SD)	OR [95% CI]	Test of significance <i>p</i> value ^T-test
<b>Maternal education</b>				
Elementary or less	14 (29.2)	34 (70.8)	1	<0.001*
Secondary or technical diploma	47 (34.8)	88 (65.2)	0.77 [0.38–1.6]	
University education	74 (57.4)	55 (42.6)	0.31 [0.15–0.63]	
<b>Maternal work</b>				
Employed	59 (46.1)	69 (53.9)	1.2 [0.78–1.9]	0.370
Unemployed	75 (41.0)	108 (59.0)	1	
<b>Paternal education</b>				
Elementary or less	20 (32.8)	41 (67.2)	1	0.003*
Secondary or technical diploma	46 (37.1)	78 (62.9)	0.83 [0.43–1.6]	
University education	68 (55.3)	55 (44.7)	0.40 [0.21–0.75]	
Number of children in household	2.4 ± 0.8 <sup>b</sup>	2.6 ± 1.0 <sup>b</sup>	1.3 [0.99–1.6]	0.060
<b>Family living in household</b>				
Yes	28 (70.0)	12 (30.0)	3.6 [1.7–7.3]	0.001*
No	107 (39.6)	163 (60.4)	1	
<b>Consanguinity</b>				
Yes	19 (59.4)	13 (40.6)	2.1 [0.98–4.3]	0.054
No	116 (41.6)	163 (58.4)	1	
<b>Family history of psychiatric disease</b>				
Yes	39 (63.9)	22 (36.1)	2.9 [1.6–5.1]	<0.001*
No	96 (38.2)	155 (61.8)	1	

\*Significant at 0.05

<sup>a</sup>Some totals do not add up to 314 because of missing values<sup>b</sup>Means and standard deviations and *p* value for T-test for continuous variables

Nevertheless, given the retrospective nature of the study, mothers of cases might have better recalled infections and complications during pregnancy than mothers of controls. The mother of a child with ASD might have been more likely to remember any abnormalities during her pregnancy while trying to find explanations for her child having ASD.

Consanguinity and family history of psychiatric disorders being risk factors for ASD further supports the genetic component in ASD. Though few studies have addressed consanguinity as a direct risk factor for ASD, it was important to identify its role in the current study, knowing that the prevalence of consanguinity in Lebanon is as high as 35.5% (Barbour and Salameh 2009). A study conducted in Lebanon in 2016 identified specific copy number variations and ASD susceptibility genes in certain families (Soueid et al. 2016). This provides further proof for the genetic predisposition and impact of consanguinity on the pathophysiology of the disorder. Results of the current study suggesting a link between mental disorders and ASD in Lebanon echoed findings from international studies (Guy et al. 2015; Lee et al. 2015).

Our study found that first and second order birth were negatively associated with ASD compared to third or higher

birth order. On the one hand, these results are in line with a previous study that determined third or higher birth order as a risk factor for ASD (Moore et al. 2012). On the other hand, a study published in 2015 concluded the opposite: being first-born was a risk factor for ASD (Lee et al. 2015). A possible explanation for first and second birth order being negatively associated with ASD is that mothers tend to take better care of themselves with their first pregnancy in terms of nutrition and overall health and wellbeing. The inconsistency in different studies highlights the importance of regional studies when assessing ASD risk factors.

Presence of moral support for the mother during pregnancy was also negatively associated with ASD. This included moral support from family members, psychiatrists, psychologists and others. A previous pilot study on autism in Lebanon echoed this finding and found a correlation between sadness in the mother during pregnancy and autism (OR 8.85) (Hamade et al. 2013). It is worth noting that moral support was assessed in a subjective manner. Given the retrospective nature of the study, the memory of the feeling might not have been faithful to the actual moral support during pregnancy and might have been affected by the status of the child (with or without ASD).

**Table 4** Factors associated with ASD according to bivariate and multivariable logistic regression analysis

Variable	Bivariate analysis	Multivariable analysis	Multivariable analysis-final model
	Crude OR[95% CI]	Adjusted OR[95% CI]	Adjusted OR[95% CI]
<b>I. Perinatal variables</b>			
<b>Gender</b>			
Male	3.7 [2.2–6.2]	5.0 [2.3–11]	3.9 [2.2–7.0]
Female	1	1	1
<b>Age</b>			
	1.2 [1.2–1.3]	1.2 [1.1–1.4]	
<b>Birth order</b>			
First and second	0.61 [0.37–1.0]	0.97 [0.40–2.3]	0.52 [0.28–0.95]
Third or later	1	1	1
<b>Type of delivery</b>			
Vaginal	0.59 [0.37–0.93]	0.78 [0.37–1.6]	
Caesarian	1	1	
<b>Complications during delivery</b>			
Yes	1.8 [1.0–3.3]	0.66 [0.25–1.8]	
No	1	1	
<b>Feeding difficulty</b>			
Yes	3.9 [2.1–7.2]	2.3 [0.88–6.2]	
No	1	1	
<b>II. Gestation variables</b>			
<b>Infection pregnancy</b>			
Yes	3.3 [1.8–5.9]	0.57 [0.010–32]	2.9 [1.5–5.5]
No	1	1	1
<b>Influenza</b>			
Yes	2.9 [1.2–7.0]	4 [0.091–175]	
No	1	1	
<b>Other infections</b>			
Yes	3.2 [1.5–6.6]	3.3 [0.073–150]	
No	1	1	
<b>Fever</b>			
Yes	2.5 [1.2–5.2]	1.4 [0.30–6.3]	
No	1	1	
<b>Medication</b>			
<b>Antipyretics</b>			
Yes	4.7 [2.8–8.2]	3.5 [0.30–40]	
No	1	1	
<b>Antipyretics</b>			
Yes	5.2 [2.1–13]	0.63 [0.77–5.1]	
No	1	1	
<b>Antibiotics</b>			
Yes	2.7 [1.3–5.5]	0.61 [0.064–5.8]	
No	1	1	
<b>Complication during pregnancy</b>			
Yes	2.2 [1.2–3.8]	0.55 [0.10–3.0]	2.1 [1.1–3.9]
No	1	1	1
<b>Other pregnancy complications</b>			
Yes	3.4 [1.7–6.8]	2.2 [0.27–18]	
No	1	1	
<b>Folic acid intake</b>			
Yes	2.5 [1.4–4.6]	0.75 [0.26–2.1]	

**Table 4** (continued)

Variable	Bivariate analysis	Multivariable analysis	Multivariable analysis-final model
	Crude OR[95% CI]	Adjusted OR[95% CI]	Adjusted OR[95% CI]
No	1	1	
Psychological support			
Yes	0.45 [0.27–0.80]	0.59 [0.23–1.5]	0.49 [0.27–0.89]
No	1	1	1
Smoking at work			
Yes	0.58 [0.35–0.96]	1.8 [0.74–4.1]	
No	1	1	
III. Socioeconomic variables			
Maternal education			
Elementary Or Less	1	1	
Secondary or technical diploma	0.77 [0.38–1.6]	0.51 [0.15–1.7]	
University education	0.31 [0.15–0.63]	0.31 [0.080–1.3]	
Paternal education			
Elementary or less	1	1	
Secondary or technical diploma	0.83 [0.43–1.6]	1.0 [0.35–3.0]	
University education	0.40 [0.21–0.75]	0.68 [0.19–2.4]	
Family living in household			
Yes	3.6 [1.7–7.3]	5.6 [1.9–17]	
No	1	1	
Consanguinity			
Yes	2.1 [0.98–4.3]	1.6 [0.44–5.5]	2.5 [1.0–6.0]
No	1	1	1
Family history of psychiatric disease			
Yes	2.9 [1.6–5.1]	2.8 [1.0–7.5]	2.2 [1.1–4.4]
No	1	1	1

Some findings from other studies could not be supported by the current study. Though many studies found an association between prematurity and autism (Goldin and Matson 2016; Guy et al. 2015; Hultman et al. 2002; Kuzniewicz et al. 2014; Lampi et al. 2012; Larsson et al. 2005), we could not elicit this association in the current study. This might be because the sample size was not large enough to capture this association. Factors including smoking or alcohol intake during pregnancy and other indicators of prematurity like low birth weight were not associated with ASD in this study. It is noteworthy to mention that the rate of prematurity found in this study is 23.5% and is higher than the 6.7% estimate using data from the National Collaborative Perinatal Neonatal Network (NCPNN) (El Rafei et al. 2016). This might be due to a different definition of preterm births. In the current study preterm births were defined as those born during or before the 37th week of gestation whereas in the El Rafei et al. (2016) study, only those born before the 37th week were considered preterm. On the other hand, the 23.5% prematurity rate in this study is comparable to the 29% rate found in a study that examined all newborns in the year

2009 in Mount-Lebanon hospital (Rizk et al. 2014). Further larger scale studies should explore the association between prematurity and ASD. Studies of a prospective nature might be able to better determine the absence or existence of such an association.

The main strength of the current study is that it is the first to explore environmental and proxy of genetic factors associated with ASD in Lebanon. Another strength is that cases were selected from one of the biggest referral centers in Lebanon and all had a confirmed diagnosis by a highly experienced pediatric neurologist.

Nonetheless, it is worthy to acknowledge the limitations of this study. First, since interviews were conducted over the telephone, parents who did not have telephone lines might have been missed. However, this research was based on the observation that a big majority of people in the Greater Beirut area have telephones. Second, ascertainment of the absence of ASD in controls could not be achieved due to the nature of the telephone interviewing. We attempted to remedy this by explaining to parents the main signs and symptoms of ASD. Third,

due to the retrospective nature of the study, results might be subject to an element of recall bias, as the questionnaire was detailed and required mothers to remember and report information as far as 18 years back. Though questions were kept clear and concise, recall bias might have affected the accuracy of the results. It was noted that mothers tend to clearly remember details of the pregnancy and delivery periods. Not all risk factors, however, required the reliance on a good memory. Factors such as parental consanguinity, socio-economic factors and parental age were not subject to an element of recall bias. Fourth, the sample of cases might have not been representative of children with ASD in the Lebanese population. Cases at the ASKC might be of a higher socio-economic status than the general Lebanese population, though over a third of patients seen there receive medical assistance from a university affiliated Non-Governmental Organization (NGO) called OpenMinds for special needs children. The American University of Beirut Medical Center is one of the biggest referral centers in Lebanon. Given the study type (case-control), validity is more important than generalizability when it comes to the confirmation of diagnosis. To account for the potential confounding effect, educational level of parents and mother's employment were included in the regression analysis.

With ASD prevalence figures being relatively high and the burden of treatment lying mostly on parents paying out-of-pocket in Lebanon, understanding underlying factors is of utmost importance. Identifying ASD correlates is important in raising awareness of parents, practitioners and the government facilitating timely screening and implementation of early intervention. It is also needed to inform policy makers and influence evidence-based policy change needed to alleviate the emotional and financial burden inflicted on parents and families. Additional research exploring genetic and environmental factors and the link between the two is essential to build on current findings and help in the contextual understanding of the disorder and the factors associated with it.

**Acknowledgments** The authors would like to acknowledge the efforts of Mr. Chris Kaspar for his assistance in data collection. This study was funded by OpenMinds (private foundation/NGO).

**Author Contributions** DRG conceived of the study, participated in its design, data collection and interpretation, performed statistical analysis and drafted the manuscript; FSS conceived of the study, participated in its design, data collection and interpretation and drafted the manuscript; DS conceived of the study, participated in its design and coordination, performed statistical analysis and data interpretation and drafted the manuscript; JED, SC, HAEH and GM conceived of the study, participated in its design, data collection and interpretation, and assisted in drafting the manuscript; RMB conceived of the study, participated in its design and coordination, interpreted the data and drafted the manuscript. All authors read and approved the final manuscript.

## Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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