

Role of environmental factors in autism spectrum disorders in Saudi children aged 3-10 years in the Northern and Eastern regions of Saudi Arabia

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ABSTRACT

الأهداف: دراسة العوامل البيئية التي يمكن أن تسهم في تطوير اضطرابات طيف التوحد في الأطفال السعوديين الذين تتراوح أعمارهم بين 3-10 سنوات في المنطقة الشمالية (عرعر) والمنطقة الشرقية (الدمام) في المملكة العربية السعودية.

الطريقة: أجريت دراسة الحالة وتم جمع البيانات من سبتمبر 2017 إلى ديسمبر 2017 من خلال إجراء مقابلات مع أولياء أمور 100 طفل مصاب بالتوحد السعودي و 100 طفل عادي من سن 3-10 سنوات من عرعر والدمام، المملكة العربية السعودية. تم استخدام استبيان مصمم خصيصاً لجمع البيانات التي تشمل الخصائص الاجتماعية والديموغرافية للوالدين وتاريخ ما قبل الولادة للأم والتاريخ التطوري والتاريخ الاجتماعي والعادات الغذائية للطفل. لمعرفة العلاقة بين العوامل البيئية وتطور التوحد لدى الأطفال، واستخدم الانحدار اللوجستي مع نسبة الأرجحية.

النتائج: كان هناك ارتباط كبير بين زواج الأقارب والتوحد. تم العثور على ارتباط كبير أيضاً بين الأدوية التي استخدمتها الأم أثناء الحمل والتوحد. لوحظ انخفاض كبير في نسبة الأرجحية للأطفال التوحد في العائلات ذات الدخل الكافي والأطفال الذين يستهلكون غذاء غني بفيتامين (د). لوحظ زيادة في عمر الأم عند الأطفال المصابين بالتوحد بالمقارنة مع الأطفال العاديين.

الخاتمة: إن العوامل البيئية التي يمكن أن تسهم في تطور التوحد هي زواج الأقارب، وعدم كفاية دخل الأسرة، والأدوية التي تستخدمها الأم أثناء الحمل، والنظام الغذائي الناقص من فيتامين (د) للطفل وعمر الأم خلال فترة الحمل.

Objectives: To study the environmental factors which can contribute to the development of autism spectrum disorders in Saudi children aged 3-10 years in Northern region (Arar) and Eastern region (Dammam) in the Kingdom of Saudi Arabia.

Methods: A case control study was conducted and the data was collected from September 2017 to December 2017 by interviewing the parents of 100 Saudi autistic children and 100 normal children aged

3-10 years from Arar and Dammam. A specially designed questionnaire was used to collect the data which includes socio-demographic characteristics of the parents and ante-natal history of the mother and developmental history, social history and dietary habits of the child. To find out the association between environmental factors and development of autism in children, logistic regression with odds ratio used.

Results: There was a significant association between consanguineous marriages and autism. A significant association was also found between medications taken by the mother during pregnancy and autism. Significantly lowered ORs for Autism were observed for children in families of perceived adequate income and children consuming a Vitamin-D rich diet. Increased maternal age was observed in autistic children when compared to normal children.

Conclusion: The environmental factors which could contribute to the development of autism are consanguineous marriage, inadequate family income, medications taken by the mother during pregnancy, vitamin D deficient diet of the child and maternal age during pregnancy.

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Autism spectrum syndrome (ASD) consists of a group of developmental disorders that are difficult to detect without trained personnel. It is characterized by qualitative impairments in social interaction, qualitative impairments in communication, and restricted repetitive, stereotyped patterns of behavior, interests, and activities.¹ The number of children diagnosed with autism spectrum disorder is rising.^{2,3} It is not clear whether it is due to better detection and reporting or a real increase in the number of cases.^{4,5} Many factors can contribute to increase in prevalence estimates including changes in diagnostic criteria and specialized diagnostic tools.

The causes of autism remain unclear even though genetic and environmental factors may play a role in increasing the risk of autism. Researchers claim that toxic food contaminants like mercury can affect metabolism and alter neuronal plasticity and cause autism in children.⁶ Studies have shown that supplementation with Vitamin D and Tryptophan is an affordable solution to prevent autism.⁷ According to one study, high iron intake decreases autism.⁸ Other risk factors that increase the chance of having a child with autism are consanguinity, advanced parental age, and maternal lifestyle.⁹⁻¹¹ Vaccinations are sometimes cited as a cause of autism, but there is no definite evidence to prove it.¹²

According to World health organization (WHO) fact sheet published in April 2017, one in 160 children have autism spectrum disorder. Despite its increasing rate, currently autism remains untreatable.¹³ Most of the research in the field of autism has been conducted in Western countries. In the Arab world, the research conducted in the field of autism is relatively less. Autism was not the subject of interest in the region until the late 1990s. Lack of awareness and culture as well as lack of resources contribute to the unmet needs of autism patients in the region.¹⁴ The males diagnosed with autism are 4 times more when compared to females.

Although various studies have been conducted in ASD's etiology across the world, only few scientific researches have been conducted in Middle East especially in Kingdom of Saudi Arabia (KSA).¹⁵ Also, dietary habits should be looked into as they could help in identifying high risk foods that could affect their children.¹⁶ The present study was therefore undertaken

to explore the various environmental factors including dietary factors which can contribute to the development of autism.

Methods. Subjects. A case control study was conducted in 200 Saudi children from Northern region (less developed region) and Eastern region (more developed region) of Saudi Arabia. Ethical approval was given by Local Committee of Bioethics of Northern Border University and Ministry of Health, Arar, Kingdom of Saudi Arabia. The subjects were selected by convenient sampling. Informed consent of the parents of autistic children and normal children were taken after explaining the purpose of the study. The study was conducted according to the principles of Helsinki declaration.

Inclusion criteria. Saudi autistic children aged 3-10 years of both sexes whose diagnosis were confirmed by DSM-5 criteria.¹⁷

Exclusion criteria. Autistic children who had deafness, congenital malformations and metabolic disorders were excluded from the study.

The data was collected from September 2017 to December 2017 by parent interviews of autistic children who were attending the child psychiatry clinic of Al Amal Mental health complex, Arar, Kingdom of Saudi Arabia, Shumua Al Amal Center for Special Education & Rehabilitation, Dammam, Kingdom of Saudi Arabia, Shamah Autism Center, Dammam, Kingdom of Saudi Arabia and Prince Naif Pediatric Physical Therapy Center, Dammam, Kingdom of Saudi Arabia.

It was compared with the data obtained by parent interviews of 100 normal Saudi children, who attended the Department of Pediatrics, Arar Maternity and Child Health Center, Arar, Kingdom of Saudi Arabia and Baraam Al Sharqiyah School, Dammam, Kingdom of Saudi Arabia. For both the autistic children and normal children, a specially designed questionnaire (containing 25 items) was used to collect the socio-demographic data, family history, antenatal history of the mother, previous medical history, developmental history, social history and dietary habits of the child.

Statistical analysis. The data was analyzed using Stata 15 Statistical Software (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as means \pm standard deviations, whereas categorical variables were presented as counts and percentages. The 4 questions, regarding regularity of meals, milk intake, egg, fish and meat consumption, fruit and vegetables consumption of children were combined into one variable namely, Vitamin-D rich diet of children and was included into the regression analyses.

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The odd ratios of environmental factors and development of autism in children were estimated via a univariate logistic regression between the outcome and each of the independent variables and only variables that were significant at the 0.1 level, where subsequently considered for entry in the multivariate ordinary logistic regression. The backward elimination method was used for covariate selection where variables that are not significant nor are confounders were taken out from the model. The final retained covariates after the adjustment of age and gender were consanguineous marriage, family income, medications during pregnancy, Vitamin D rich diet and age of the mother when the child was born. A similar method was used to investigate any differences between the 2 regions of Saudi Arabia in terms of environmental factors and development of autism, amongst autistic children in which the outcome variable was the region. Since the sample size was small (n=100), only very few variables were considered for the model.

Model fit diagnostics including residual analyses were performed to ensure that the final model was indeed the best model. A p -value<0.05 was taken to be evidence for a statistically significant association.

Results. Data collected from the parents of 200 children is compiled in (Table 1). Among the 100 autistic children (cases), 76% were males and 24% were females. In the normal children (controls), males comprised 53% and females 47%. In both cases and controls, majority of the children were above 5 years (87% and 64%).

A higher percentage of consanguineous marriages were observed in cases (52%) as compared to controls (37%) (Table 2). There was a significantly positive association between consanguineous marriages and autism (OR=3.32, 95% CI=1.15-4.68, p -value=0.02) after adjusting age and gender. A similar association was found with the use of medications by the mother during pregnancy (OR=3.00, 95% CI=1.08-8.34, p -value=0.03). Significantly lowered odds ratio (ORs) for Autism were observed for children in families of perceived adequate income (OR=0.37, 95% CI=0.41-0.94, p -value=0.04) and children consuming a Vitamin-D rich diet (OR=0.23, 95% CI=0.11-0.46, p -value<0.001) (Figure 1). However, the analysis showed that increased maternal age may be a factor contributing to autism (OR=1.13, 95% CI=1.05-1.20, p -value<0.001) (Table 2).

The number of siblings were divided into 3 categories (0-3, 4-6, 7 and >7). There was a significant association between number of siblings and autism in

Table 1 - Child and family characteristics in cases and controls. N=200

Child and family characteristics	Cases		Controls	
	n=100	(%)	n=100	(%)
<i>Mother's occupation</i>				
Housewife	75	(75)	46	(46)
Working	25	(25)	54	(54)
<i>Father's occupation</i>				
High income job	09	(9)	18	(18)
Middle income job	77	(77)	77	(77)
Low income job	14	(14)	5	(5)
<i>Antenatal visits of mother</i>				
No	7	(7)	1	(1)
Yes	93	(93)	99	(99)
<i>Viral infections during pregnancy</i>				
No	90	(90)	94	(94)
Yes	10	(10)	6	(6)
<i>Diet during pregnancy</i>				
No	19	(19)	7	(7)
Yes	81	(81)	93	(93)
Yes	03	(3)	1	(1)
<i>Complications during pregnancy</i>				
No	86	(86)	90	(90)
Yes	14	(14)	14	(14)
<i>Complications during birth</i>				
No	80	(80)	88	(88)
Yes	20	(20)	12	(12)
<i>Type of delivery</i>				
Normal	80	(80)	76	(76)
C-Section	20	(20)	33	(33)
<i>Time of delivery</i>				
Term	89	(89)	80	(80)
Pre-term	08	(8)	17	(17)
Post-term	03	(3)	3	(3)
<i>Birth weight of child</i>				
Normal	90	(90)	92	(92)
Low weight	8	(8)	7	(7)
Overweight	2	(2)	1	(1)
<i>Regular vaccinations</i>				
No	0	(0)	3	(3)
Yes	100	(100)	97	(97)
<i>Childhood infections</i>				
No	91	(91)	93	(93)
Yes	9	(9)	7	(7)

the univariate analysis (p -value=0.001) only in the 4-6 sibling category, however after accounting for all other variables it became non-significant (p -value=0.07) and was subsequently removed. Regarding the spacing between children, the means±standard deviations in autistic children was 2.61±1.296 while in normal children it was 2.506±1.497. Factors like type of delivery, birth complications and vaccinations were not

Table 2 - Descriptive statistics and Odds ratios for prenatal and natal characteristics retained in the model between cases and controls.

Child and family characteristics	Case		Controls		Odds ratio	95%	p-value
	n=100	(%)	n=100	(%)			
<i>Consanguineous marriage</i>							
No	48	(48)	63	(63)	1		
Yes	52	(52)	37	(37)	3.32	1.15-4.68	0.02
<i>Family income</i>							
Not adequate	30	(30)	13	(13)	1		
Adequate	70	(70)	87	(87)	0.37	0.41-0.94	0.04
<i>Medications during pregnancy</i>							
No	78	(78)	88	(88)	1		
Yes	22	(22)	12	(12)	3.00	1.08-8.34	0.03
<i>Vitamin-D rich diet of children</i>							
No	65	(65)	34	(34)	1		
Yes	35	(35)	66	(66)	0.23	0.11-0.46	< 0.001
Maternal age during pregnancy	29.57	(5.76)	26.68	(4.95)	1.13	1.05-1.20	< 0.001

significant in the univariate regression, therefore, they were not considered for the multivariable model.

While comparing the role of environmental factors in autistic children between Arar (Northern region) and Dammam (Eastern region), the final retained covariates after the adjustment of age and sex were the mother's education, father's education and mother's medication during pregnancy. Our results showed that mothers in Dammam were more likely to have college and postgraduate education, even though not statistically significant (OR=0.58, 95% CI=0.20-1.64, p -value=0.31) and fathers in Arar were more likely to have a college and postgraduate education in our sample (OR=2.77, 95% CI=1.01-7.64, p -value<0.001) (Table 3). The wide confidence Intervals reflect the small sample size for this model (n=100) and may mean that a degree of sampling error may have been introduced. The use of medication by mothers during pregnancy was significantly less in Arar when compared to Dammam (OR=0.03, 95% CI=0.003-0.25, p -value=0.001).

Discussion. In our study, although we included 25 different items, the most significant environmental factors were consanguineous marriage, family income, medications taken by the mother during pregnancy, vitamin D rich diet consumption of the child and maternal age during pregnancy.

Consanguineous marriage. A group of researchers who compared the DNA of family members, found missing regions of genes that could play a role in autism.¹⁸ A group of researchers from Kingdom of Saudi Arabia recommended that association of consanguinity

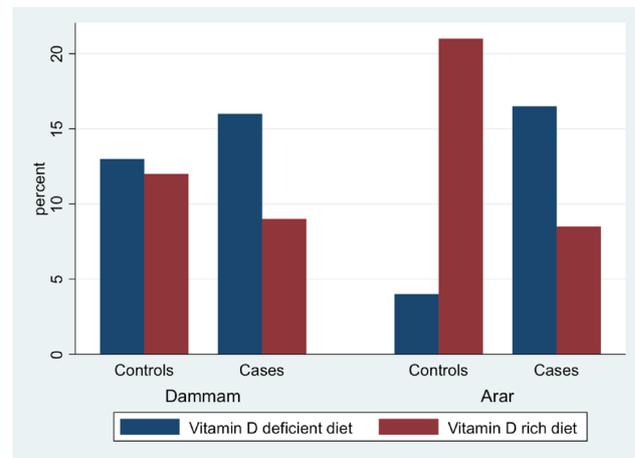


Figure 1 - Percentage of Vitamin-D rich food consumption among cases and controls in Dammam and Arar, Kingdom of Saudi Arabia.

and autism should be studied.¹⁹ Our findings correlated with the opinion of researchers that children with ASD were more frequent in family relatives among the Arab patients.²⁰

Family income. Recent European studies suggested that, unlike reports from the United States, low socioeconomic status is associated with an increased risk of ASD.²¹ In our study, there was a significantly lowered odd ratios for children from families of perceived adequate income

Medications taken during pregnancy. Maternal prenatal medication use can be associated with a 46% increased risk of fetus autism.²² In our study, there was a

Table 3 - Descriptive statistics and Odds ratios for family characteristics retained in the model between Dammam and Arar.

Child and family characteristics	Dammam		Arar		Odds ratio	95% confidence interval	p-value
	n=100	(%)	n=100	(%)			
<i>Mother's education</i>							
School education	29	(58)	32	(64)			
College and postgraduate	21	(42)	18	(36)	0.58	0.20-1.64	0.31
<i>Father's education</i>							
School education	34	(68)	22	(44)	1		
College and postgraduate	16		28	(56)	2.77	1.01—7.64	<0.001
<i>Medications during pregnancy</i>							
No	29	(58)	49	(98)	1		
Yes	21	(42)	01	(02)	0.03	0.003-0.25	0.001

significant association between autism and medications taken during pregnancy for hypertension, diabetes, asthma, ante partum hemorrhage, depression and infections.

Vitamin D rich diet. Researchers have reported Vitamin D deficiency in Saudi children.²³ A group of researchers found that Vitamin D deficiency was higher in autistic children when compared to healthy children.^{24,25} Our results showed that Vitamin D rich diet may protect the children from developing autism.

Maternal age during pregnancy. In many studies, maternal and paternal age older than or equal to 34 years were found to be associated with increased risk of autism in their offspring. Researchers who studied the risk of autism with older reproductive age concluded that maternal age is an important factor in the development of autism, which matched with our results.²⁶

Limitations of the study. Since only 100 autistic children were included in our study, due to the small sample size, a degree of sampling error may have been introduced.

Recommendations. The role of Vitamin D rich diet in the prevention of development of autism has to be emphasized.

In conclusion, in our study, the significant environmental factors which could contribute to the development of autism were consanguineous marriage, inadequate family income, medications taken by the mother during pregnancy, vitamin D deficient diet of the child and increased maternal age during pregnancy. The association of number of siblings with autism in the univariate analysis was highly significant (0.001) for the 4 to 6 siblings, category.

More in depth studies with larger sample size are needed to assess the role of environmental factors like artificial food additives, chemical poisons in toys, use of

i-pads by children, television watching, parental conflict and emotional state of the mother in the development of autism.

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