

The Prevalence and Relationship between Maternal Medical Conditions and Autism Spectrum Disorder

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Abstract: ***Objectives:** to identify the prevalence of certain maternal medical conditions among the mothers of children with autism spectrum disorder. **Methods:** An observational cross sectional analytic study included all mothers of children diagnosed with ASD according to the DSM-5 criteria who visited the pediatric clinics at Al-Amal Hospital. The sample of study consists of 66 participants. The study was conducted using face-to-face semi-structured interviews. The interview consisted of questions regarding socio demographic data, chronic diseases of the mothers, pregnancy of the autistic child and delivery events, and psychological history of the mother and other family members. **Results:** The Majority of autistic children following with the clinics aged from 5 to 10 years. About 19.7 % of the families of autistic children had other autistic children. Only 18.2 % of mothers suffered from chronic diseases. The most common chronic diseases among those mothers was diabetes, followed by hypertension, obesity, and asthma. Only 15.2% of mothers were more than 35 years old when they got pregnant with an autistic child. About half of mothers were exposed to tobacco. Approximately 28.8% of mothers were exposed to family problems during the pregnancy of their autistic children. **Conclusion:** There was no significant prevalence of chronic diseases among mothers of autism children during their pregnancy. Also there was no effect of conditions and diseases of motherhood during pregnancy on developing an autism spectrum disorder in the offspring.*

Keywords: autism, prevalence, relationship, risk, mother, Saudi Arabia

1. Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopment disorder characterized by impairments in social interaction, verbal and nonverbal communication, and a restricted repertoire of activities and interests. ASD is diagnosed according to guidelines listed in the Diagnostic and Statistical Manual of Mental Disorders, fifth Edition⁽¹⁾. The parents will feel and complain that their child is different from other normal children as autistic child cannot develop peer relationships because of marked impairment in the ability to initiate or sustain a conversation with others, and has impairment in non-verbal behaviors such as eye-to-eye gaze and facial expressions. In addition to these, autistic patients have inflexible adherence to specific, non-functional routines or rituals and some of them show stereotyped and repetitive motor mannerisms such as hand flapping or twisting⁽²⁾.

This disorder typically begins at birth, but the parents of autistic children will not note it until their children start to grow and develop. Noticeable symptoms gradually begin to appear after the age of six months, and become established in varying patterns by the first two or three years of life. It is more prevalent in males more than females with a ratio of (4:1).⁽³⁾ Estimates of the prevalence of autism vary widely depending on diagnostic criteria, age of children screened, and geographical location.

A 2012 study of the global prevalence of ASD found a median of 62 cases per 10,000 people.⁽³⁾ There was a lack of evidence from low- and middle-income countries⁽³⁾. The prevalence of autism in the united states is about 1 out of every 68 children, or 14.7 per 1,000, have some form of ASD⁽⁴⁾. In Canada, an epidemiological study conducted at Montreal Children's Hospital in the 2003-2004 school year found a prevalence rate of 0.68%⁽⁵⁾. Prevalence studies were conducted in UAE, Saudi Arabia, Oman, 20 and Bahrain. The prevalence of ASD was 1.4 per 10,000 in Oman, and 29 per

10,000 for PDD in UAE, and 4.3 per 10,000 in Bahrain in 2014⁽⁶⁾. A cross-sectional study was conducted in Al-Taif-KSA, 2013. The overall prevalence of autism in the primary school of Al-Taif district whose age ranged from 7 to 12 years was 0.035% from a sample population of 22950 student, in which the prevalence of autism in male (0.031%) was greater than female (0.004%)⁽⁷⁾. The prevalence is known in some cities of Saudi Arabia but still vague in Al-Madinah⁽⁸⁾.

There are many causes that have been linked with autism spectrum disorder (ASD), mainly genetic factors, environmental causes, prenatal and perinatal causes. Some epidemiological studies have shown that certain maternal medical conditions could cause autism spectrum disorder (ASD). A cohort study conducted in northern California, 1995/1999, has shown that the risk of ASD increased significantly with each 10 year increase in maternal and paternal age⁽⁹⁾. Other Case control study showed that the risk of ASD increased significantly with antidepressant use during pregnancy⁽¹⁰⁾.

In 2011, other Case control study shows that metabolic diseases were more prevalent among case mothers compared with controls. These conditions were associated with a higher likelihood of ASD relative to controls (odds ratio: 1.61)⁽¹¹⁾. The studied metabolic diseases includes: Diabetes during pregnancy, insulin resistance, systemic arterial hypertension and obesity.

The impact of this problem on the families is really bad, parents of children with autism spectrum disorders (ASD) experience higher levels of stress in comparison to parents of neurotypical children and consequently are more susceptible to negative health and social outcomes⁽¹²⁾. Specifically, parents of children with ASD are more likely to experience depression, anxiety, somatic complaints, isolation, and burnout⁽¹³⁾.

Based on these previous studies, it is observed that some maternal conditions and diseases could influence autism spectrum disorder (ASD) risk. So we target this subject in our study in Al-Madinah Al-Munawara, which is defective in this type of researches.

Our aim is to identify the prevalence of certain maternal medical conditions among the mothers of autistic children's. The goal of this paper is to identify the possible conditions that may correlate with getting an autistic child and try to manage them and to educate the residences about the risk factors that Saudi people have that may lead to have a baby with autism, through publishing the results of this research.

The hypothesis is:

- Maternal conditions and diseases could influence autism spectrum disorder (ASD) risk.
- Maternal conditions and diseases could not influence autism spectrum disorder (ASD) risk.

2. Methods

This observational cross sectional analytic study was conducted in Al-amal and psychiatry hospital in Almadinah in November-December 2016.

A total number of (66) participants were included in this study.

Mothers of children diagnosed with ASD according to the DSM-5 criteria who visited the pediatric clinics at Al-amal Hospital were recruited based on inclusion and exclusion criteria.

The including criterion was that the child must be diagnosed with autism spectrum disorder according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (**DSM-5**) criteria. The exclusion criterion included: suspected cases of autism spectrum disorders that have not yet been fully evaluated by a psychiatrist during the time of data collection.

Participants were approached by their attending clinician during their clinic appointments. The nature of the study was explained and informed consent was taken. The study was conducted using face-to-face semi-structured interviews.

The interview was developed based on the literature and was consisted of sociodemographic data, chronic diseases of the mothers, the pregnancy of the autistic child and delivery events and psychological history of the mother and other family members. Sociodemographic data included age of mother and child, nationality, residency, consanguinity and educational level. The studied chronic diseases of the mothers included DM, HTN, obesity, asthma and other allergic diseases. The interview was conducted in a private room in the clinics and took 5-10 minutes in average. The interviewers were at least 2 members of the research team with the supervision of a pediatric psychologist.

The questions of semi-structured interview was pretested before the conduction of the study and was proven valid and easily understood.

Data were entered and analyzed using the Statistical Package for Social Sciences (SPSS). Descriptive analysis was done to summarize information by calculating the number and percent for categorical variables, whereas the mean and standard deviation (SD) were calculated for continuous variables. Chi-squared test was used to measure difference in the prevalence of smoking between different groups of students. P values less than 0.05 was considered an indicator for statistically significant differences.

3. Population & Sample of the Study

The study population includes all mothers of children diagnosed with ASD according to the DSM-5 criteria who visited the pediatric clinics at Al-amal Hospital, a sample of (66) mothers were randomly chosen.

The next table shows their properties according to their personal information:

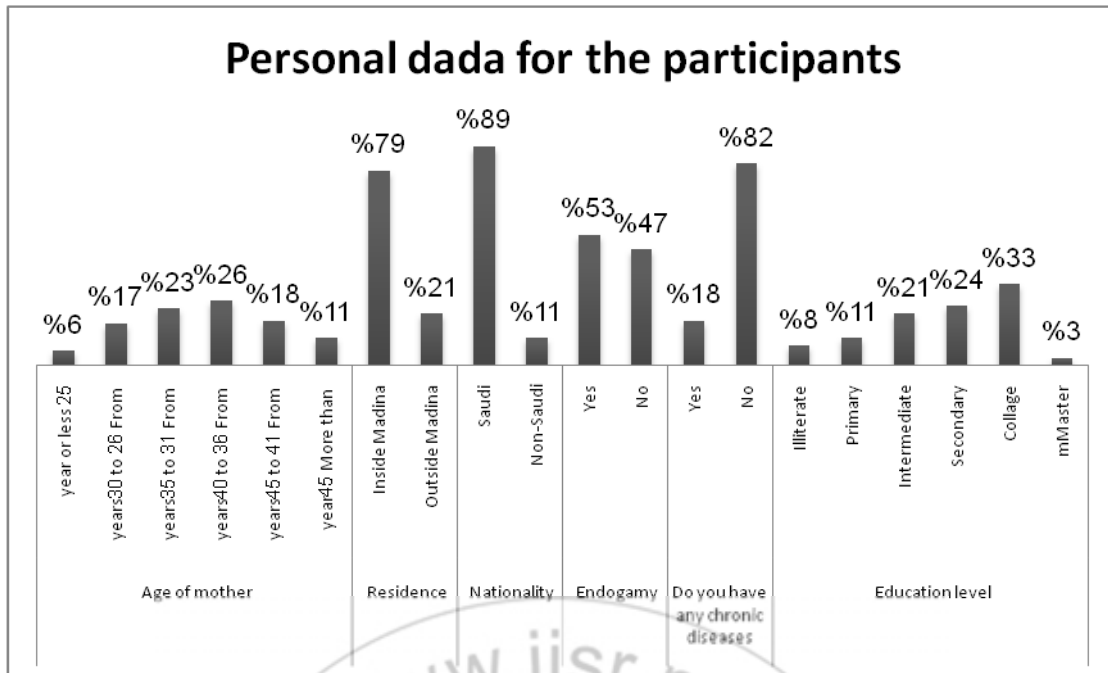
Table 1: Shows the mothers' distribution according to their personal information (N =66)

		Frequency	Percent	P-value
Age of Mother	25 year or less	4	6%	0.057
	From 26 to 30	11	17%	
	From 31 to 35	15	23%	
	From 36 to 40	17	26%	
	From 41 to 45	12	18%	
	More than 45 year	7	11%	
Residence	Inside Madina	52	79%	0.000*
	Outside Madina	14	21%	
Nationality	Saudi	59	89%	0.000*
	Non-Saudi	7	11%	
Consanguinity	Yes	35	53%	0.622
	No	31	47%	
Education level	Illiterate	5	8%	0.000*
	Primary	7	11%	
	Intermediate	14	21%	
	Secondary	16	24%	
	Collage	22	33%	
	Master	2	3%	

*Chi Square test - Significant at the 0.05 level.

The previous table shows that 26% of the autistic children mothers' ages were between (36- 40) years old, while 23% of them were between (31- 35) years old, 18% of them were between (41- 45) years old, and 17% of them were between (26-30) years old. Their distribution according to their residence was that 79% of them lived in Al-Madina, while the remaining participants lived in other cities. The majority of autistic children's mothers were Saudi with percent of 89% of them, while the other were non-Saudi. We noticed also that 53% of them were married to one of their cousins, while 47% of them were not. Finally, their distribution according to their educational level; 33% of them had university degrees, 24% of them had secondary school certificates, and 21% of them had a preparatory school levels.

The next diagram shows that:



4. Results

The next table (2) shows the distribution of autism children by age, who were following-up in the psychiatric clinics, where we note that 80% of them were located with the ages of 5-10 years.

Table 2: The distribution of autism children by age

	Frequency	Percent
Less than 5 years	9	13.6
From 5 to 10 years	53	80.3
More than 10- years	4	6.1
Total	66	100.0

Table number (3) makes it clear whether any of autistic children's family members suffered from the same disease, where we note that 80% of the families of autistic children did not have any other autistic children. On the other hand, only 19.7% of the families of autistic children had another family member with the same condition.

Table 3: The family history of ASD among autism children's family

ASD child among family members	Frequency	Percent
Yes	13	19.7
No	53	80.3
Total	66	100.0

The data shown in the table (4) determined the participants' distribution according to whether they were suffering from chronic diseases, in which we noted that 82% of them did not suffer from any chronic diseases, while the rest suffered from chronic diseases.

Table 4: Shows the participants' distribution according to whether they were suffering from chronic diseases

Chronic diseases	Frequency	Percent
Yes	12	18.2
No	54	81.8
Total	66	100.0

Table (5) shows more detailed information about the participants' distribution according to the chronic disease type, we note that 75% of them were diabetics, while 58% of them had hypertension, 50% of them were obese, 33% were suffering from asthma and 8% have allergic dermatitis.

Table 5: Chronic diseases prevalence among the participants

Type of disease	Yes		No		P-value
	#	%	#	%	
Diabetes	9	75.0	3	25.0	0.083
Hypertension	7	58.3	5	41.7	0.564
Obesity	6	50.0	6	50.0	1.000
Asthma	4	33.3	8	66.7	0.248
Eczema	1	8.3	11	91.7	0.004

*Chi Square test - Significant at the 0.05 level.

By looking at table (6), we note that 39% of their ages were between (26- 30) years old, 23% of their ages were between (31- 35) years old, 18% of their ages were between (21- 25) years old, and to validate the extent of existing differences in the mothers' distribution according to their ages when they got pregnant with an autistic child, the p-value for the Chi Square test was less than the level of significance 5%, which indicates that there is a relation between the pregnancy age and autism disease.

Table 6: The participants' distribution according to their ages when they got pregnant with an autistic child

	Frequency	Percent	P-value
20 or less	3	4.5	0.000*
From 21 to 25	12	18.2	
From 26 to 30	26	39.4	
From 31 to 35	15	22.7	
From 36 to 40	6	9.1	
More than 40	4	6.1	
Total	66	100.0	

*Chi Square test - Significant at the 0.05 level.

As shown in the table (7), 59% of them were the first, second or third children in their families, while 27% of them

were the fourth, fifth or sixth, and 9% of them were seventh, eighth or ninth.

Table 7: Children distribution according to their order in their families

<i>children distribution according to their order in their families</i>	<i>Frequency</i>	<i>Percent</i>
1-2-3	39	59.1
4-5-6	18	27.3
7-8-9	6	9.1
10-11-12	3	4.6
Total	66	100.0

The next table shows the autistic children distribution according to the gestational age(GA), 86% of them born with a GA of (37- 42) weeks, while 11% of them born with age less than (37) weeks, and 3% with more than (42) weeks.

Table 8: The autistic children distribution according duration of pregnancy (in weeks)

<i>Duration of pregnancy (in weeks)</i>	<i>Frequency</i>	<i>Percent</i>
less than 37 weeks	7	10.6
37-42 weeks	57	86.4
More than 42 weeks	2	3.0
Total	66	100.0

As shown in table (9) , we find that most of them weren't smokers and have never smoked while being pregnant, while 32% of them were exposed to smoking/ Passive smoking during pregnancy.

Table 9: The participants' distribution according to being exposed to smoking/ Passive smoking

	<i>Yes</i>		<i>No</i>		<i>P-value</i>
	<i>#</i>	<i>%</i>	<i>#</i>	<i>%</i>	
Smoker	4	6.1	62	93.9	0.000*
Have been smoking during pregnancy	4	6.1	62	93.9	0.000*
exposed to smoking during pregnancy (Passive smoking)	21	31.8	45	68.2	0.003*

*Chi Square test - Significant at the 0.05 level.

The next table shows the participant's distribution according to being exposed to any family problems during pregnancy; 29% of them were faced family problems during their pregnancy with autistic child.

Table 10: The participant's distribution according to being exposed to any family problems during pregnancy

<i>Family problems</i>	<i>Frequency</i>	<i>Percent</i>
Yes	19	28.8
No	47	71.2
Total	66	100.0

The next table data shows that 61% of the autistic children were born normally, while 24% of them were admitted to intensive care after birth.

Also we notice that 21% of the autistic children's mothers used stimulating drugs during labor, 27% of them used analgesics during labor, and 77% of them were using folic acid during pregnancy.

We also notice that most of the autistic children mothers did not suffer any gynecological diseases, and 96% of them were following-up during their pregnancy.

Table 11: The participant's distribution according to conditions and diseases of motherhood

	<i>Yes</i>		<i>No</i>		<i>P-value</i>
	<i>#</i>	<i>%</i>	<i>#</i>	<i>%</i>	
Normal delivery	41	62.1	25	37.9	0.000*
use stimulating drugs during labor	14	21.2	52	78.8	0.000*
use analgesics during labor	18	27.3	48	72.7	0.000*
child admission to intensive care after birth	16	24.2	50	75.8	0.000*
suffer from any gynecological diseases	5	7.6	61	92.4	0.000*
using Folic acid during pregnancy	51	77.3	15	22.7	0.000*
Following-up during pregnancy	63	95.5	3	4.5	0.000*

*Chi Square test - Significant at the 0.05 level.

5. Discussion

The global prevalence of autism spectrum disorders has been reported to be increased, however it is not so clear if it is due to a real increase in incidence rate of ASD or better diagnostic methods.⁽¹⁴⁾ Over the past decade, research into the risk factors for autism has grown greatly, bringing evidence that a group of non-genetic factors including maternal medical conditions during pregnancy might affect neurodevelopment.⁽¹⁵⁾ Therefore this study aimed to identify the prevalence of certain maternal medical conditions among the mothers of autistic children.

This study included 66 mothers of children diagnosed with ASD. The demographic data showed that the majority of mothers at this study were Saudi from Madina. About half of the mothers were married to one of their relatives, and most of them did not have a high level of education.

Several studies stated that ASD is four times more common in boys than girls.⁽²²⁻²⁴⁾ Mandell et al., reported that the average age for diagnosis of ASD was 3.1 years.⁽²⁵⁾ On the other hand, the majority of autistic children (80.3%) following-up in the psychiatric clinics at our study aged from 5 to 10 years. This may reflect the poor knowledge and recognition of ASD by the families in our society, which may lead to the late presentation, and subsequently a delay in the intervention and treatment.

There is strong evidence that genetic factors play a critical role in vulnerability to ASD,⁽²⁶⁾ The prevalence of ASD without associated medical conditions in siblings of children with ASD has been estimated to range from 3 to 10 percent.⁽²⁷⁾ But according to our study 19.7 % of the families of autistic children had other autistic children. Our results are consistent with the results of studies published since 2010 suggested that it may be as high as 20 percent.⁽²⁸⁻²⁹⁾ This recent rise in the incidence of autism among the siblings is may be due to an actual increase in incidence of autism among the siblings or better detection methods and more awareness of family members of autistic child about Autism .Also another recent study in KSA reported that 2.2% other autistic children in the family with autistic

child.⁽²⁷⁾The difference between our finding and this study could be due to the difference in the targeted area and sample size.

In the present study only 18.2 % of mothers suffered from chronic diseases in which the most common disease among them was diabetes. A positive association between maternal diabetes and ASD risk in the offspring was recently reported in a case-control study⁽³⁰⁾, and two subsequent cohort studies.⁽³¹⁻³²⁾ Maternal diabetes can increase ASD risk through multiple and varied mechanisms, such as fetal hypoxia, free-radical production and antioxidant system impairment.^(33,34)

Hypertension was the second most common chronic diseases at our study. Conversely, one study found that no relation between ASD and hypertensive disorders in general.⁽³⁵⁾The third most common disease at our study was obesity. A new meta-analysis study found that children born to obese mothers have a 36% higher risk of developing ASD. It has also been reported that for every 5 kg/m² increase in BMI of mothers, the risk of having an autistic child increases by 16%.⁽³⁶⁾Asthma represented the fourth most common chronic diseases at our study.

Croen et al., found significant positive associations between ASD and maternal asthma and allergies.⁽³⁷⁾While Lyall et al., found no association between maternal asthma or allergies overall and having a child with ASD.⁽³⁸⁾Differences in findings for asthma and allergies overall in these two studies may be due to use of medical records versus self-report.

Multiple previous studies reported that the risk of ASD is increasing with increased parental age, above 35 and 40 for maternal and paternal age, respectively.⁽²⁷⁾ In our study 15.2% of mothers were more than 35 years old when they got pregnant with an autistic child. However, although some studies have reported a positive association between maternal age and ASD,⁽³⁹⁻⁴¹⁾ other studies report that there is no association between maternal age and ASD.⁽⁴²⁻⁴⁴⁾

The majority of autistic children at this study were born with normal gestational age. Only 10.6% of the pregnancies were less than 37 weeks in duration. Children born prematurely and with low birth weight were found to have a higher risk of the disorder.⁽⁴⁵⁾

Maternal smoking could influence neurodevelopment and risk for ASD through mechanisms such as placental insufficiency, reduced blood flow and oxygen deprivation in the brain,⁽⁴⁶⁾changes in fetal brain gene expression,⁽⁴⁷⁾altered nicotinic receptors,⁽⁴⁸⁾persistent changes in neurotransmitter activity and turnover,⁽⁴⁹⁾ and increased intrauterine testosterone.⁽⁵⁰⁾ In addition, smoking among pregnant mothers might reflect that they had psychosocial problems during pregnancy, which in turn could influence the risk of ASD in the fetus.⁽⁵¹⁾

Kalkbrenner et al. reported a positive association between maternal smoking and higher functioning autism syndrome disorder (ASD).⁽⁵²⁾Evidence suggests that the risk factor reported by Kalkbrenner et al., that maternal smoking may increase maternal testosterone levels. Baron-Cohen proposed

that one cause of autism is exposure to high levels of intrauterine testosterone.⁽⁵³⁾ 6.1% of mothers smoked during pregnancy, while 31.8% were exposed to passive smoking. This means that about half of the mothers at our study were exposed to tobacco during their pregnancy, and this is a large proportion. Kaur and Bhupinder, found that that second hand tobacco smoking is not significantly associated with ASDs.⁽⁵⁴⁾In the end, we can say that the population-based studies examining associations between smoking during pregnancy and autism spectrum disorders (ASD) are contradictory.⁽⁵⁵⁾

One third of mothers at our study exposed to family problems during pregnancy of their autistic children. Extreme levels of stress experienced by a mother during pregnancy can have an impact on her child, resulting in eventual cognitive, behavioral, and emotional problems. It is believed this is because the stress hormone, cortisol, can cross the placenta and disturb developmental processes.⁽⁵⁶⁻⁵⁷⁾ A study looking at more than a million children born in Denmark from 1978 to 2003 explored whether stress during pregnancy was linked to ASD by comparing mothers who had lost a close relative during pregnancy, or up to one year before pregnancy, with those who had not. The study conclude that their data do not support any strong association between prenatal stress after maternal bereavement and the risk of autism.⁽⁵⁸⁾

According to our results there was no effect of conditions and diseases of motherhood such as stimulating drugs and analgesics during labor, gynecological diseases, and using folic acid during pregnancy on developing an ASD in the offspring of our participants.

6. Conclusion

There was a low prevalence of chronic diseases among mothers during their pregnancy at autism children, knowing that the studies conflict about the proof of the relationship between chronic diseases during pregnancy and ASD. The most common chronic diseases among those mothers was diabetes, followed by Hypertension, after that obesity, and then asthma. 15.2% of mothers were more than 35 years old when they got pregnant with an autistic child. It has been reported that increased maternal age (above 35) is known to increase the risk of ASD. The majority of autistic children at this study spend the normal period of pregnancy at their mothers' uterus. About half of mothers at this study were exposed to tobacco during their pregnancy with autistic child. While one third of mothers at our study exposed to family problems during pregnancy of their autistic children. Also there was no effect of conditions and diseases of motherhood such as stimulating drugs and analgesics during labor, uterus diseases, and using folic acid during pregnancy on developing an autism spectrum disorder in the offspring.

7. Recommendation

- Conduct further studies to confirm or deny the relationship between chronic disease among mothers in pregnancy and the occurrence of ASD at their children.
- Awareness campaigns about ASD, and the early signs of the disease.

- Awareness campaigns among mothers to show risk factors that lead to the occurrence of autism ASD.
- The need to avoid direct and passive smoking of mothers during pregnancy.
- Mothers need to maintain a healthy and balanced diet during pregnancy.
- The mothers need to avoid psychological stress during pregnancy.
- On the state to provide adequate number of specialized centers for autism children, and these centers should be symbolic prices.

References

- [1] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric, Arlington, Va, USA, 5th edition, 2013.
- [2] http://www.autism.net.au/Autism_Definition.htm
- [3] Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcin C, et al. Global prevalence of autism and other pervasive developmental disorders. *Autism Res* 2012; 5: 160-179.
- [4] Centers for Disease Control and Prevention.
- [5] Childhood Autism in Canada: Some issues relating to behavioural intervention by Sonya Norris, Science and Technology Division; Jean-RodrigueParé, Political and Social Affairs Division; Sheena Starky, Economics Division, 2006
- [6] Systemic review of the epidemiology of autism in Arab Gulf countries . Huda O. Sahlia, BSPS, MPH, Lubna A. Al-Nasser, BDS, MPH, Lama S. Taher, BSc, MSc, Ali M. Al-Khathaami, MD, MPH, Ashraf A. El-Metwally, MD, PhD.
- [7] Prevalence and clinical characteristics of autism spectrum disorders in school-age children in Taif- KSA . Ali H.S Al-Zahrani.
- [8] Al-Salehi SM, Al-Hifthy EH, Ghaziuddin M. Autism in Saudi Arabia: presentation, clinical correlates and comorbidity. *Transcult Psychiatry*. 2009;46(2):340–7. doi:10.1177/1363461509105823. PMID 19541755.
- [9] Maternal and paternal age and risk of autism spectrum disorders. Croen LA1, Najjar DV, Fireman B, Grether .
- [10] Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. Rai D1, Lee BK, Dalman C, Golding J, Lewis G, Magnusson C.
- [11] Maternal Metabolic Conditions and Risk for Autism and Other Neurodevelopmental Disorders ; Paula Krakowiak, MS, Cheryl K. Walker, MD, Andrew A. Bremer, MD, PhD, Alice S. Baker, BA, Sally Ozonoff, PhD, Robin L. Hansen, MD, b, f and Irva Hertz- Picciotto, PhD, a, b
- [12] M. E. Dunn, T. Burbine, C. A. Bowers, and S. Tantleff-Dunn, "Moderators of stress in parents of children with autism," *Community Mental Health Journal*, vol. 37, no. 1, pp. 39–52, 2001.
- [13] M. J. Weiss, "Hardiness and social support as predictors of stress in mothers of typical children, children with autism, and children with mental retardation," *Autism*, vol. 6, no. 1, pp. 115–130, 2002.
- [14] Ganaie, S. A., and A. Bashir. "Global Autism: Autism, Autism Etiology, Perceptions, Epistemology, Prevalence and Action." *Int J ClinTherDiagn* 2.2 (2014): 39-47.
- [15] Lyall, Kristen, Rebecca J. Schmidt, and Irva Hertz-Picciotto. "Maternal lifestyle and environmental risk factors for autism spectrum disorders." *International journal of epidemiology* 43.2 (2014): 443-464.
- [16] Fombonne, Eric. "Epidemiology of autistic disorder and other pervasive developmental disorders." *Journal of Clinical Psychiatry* 66 (2005): 3.
- [17] Leonard, Helen, et al. "Autism and intellectual disability are differentially related to sociodemographic background at birth." *PloS one* 6.3 (2011): e17875.
- [18] Nassar, Natasha, et al. "Autism spectrum disorders in young children: effect of changes in diagnostic practices." *International journal of epidemiology* 38.5 (2009): 1245-1254.
- [19] Bertrand, Jacquelyn, et al. "Prevalence of autism in a United States population: the Brick Township, New Jersey, investigation." *Pediatrics* 108.5 (2001): 1155-1161.
- [20] Baird, Gillian, et al. "Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP)." *The lancet* 368.9531 (2006): 210-215.
- [21] Ganaie, S. A., and A. Bashir. "Global Autism: Autism, Autism Etiology, Perceptions, Epistemology, Prevalence and Action." *Int J ClinTherDiagn* 2.2 (2014): 39-47.
- [22] Fombonne, Eric. "Epidemiology of pervasive developmental disorders." *Pediatric research* 65.6 (2009): 591-598.
- [23] Centers for Disease Control and Prevention (CDC). "Mental health in the United States: parental report of diagnosed autism in children aged 4-17 years--United States, 2003-2004." *MMWR. Morbidity and mortality weekly report* 55.17 (2006): 481.
- [24] Taylor, Julie Lounds, et al. "A systematic review of vocational interventions for young adults with autism spectrum disorders." *Pediatrics* (2012): peds-2012.
- [25] Mandell, David S., Maytali M. Novak, and Cynthia D. Zubritsky. "Factors associated with age of diagnosis among children with autism spectrum disorders." *Pediatrics* 116.6 (2005): 1480-1486.
- [26] Losh, Molly, et al. "Current developments in the genetics of autism: from phenotype to genome." *Journal of Neuropathology & Experimental Neurology* 67.9 (2008): 829-837.
- [27] AL-ZAALAH, MOUSA A., et al. "Characteristics of Autism Spectrum Disorder among Saudi Children and its Impact on their Families." *Neurologist* 31: 13-6.
- [28] Ozonoff, Sally, et al. "Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study." *Pediatrics* 128.3 (2011): e488-e495.
- [29] Constantino, John N., et al. "Sibling recurrence and the genetic epidemiology of autism." *American Journal of Psychiatry* (2010).
- [30] Leonard, Helen, et al. "Maternal health in pregnancy and intellectual disability in the offspring: a population-based study." *Annals of epidemiology* 16.6 (2006): 448-454.
- [31] Burstyn, I., F. Sithole, and L. Zwaigenbaum. "Autism spectrum disorders, maternal characteristics and obstetric complications among singletons born in Alberta, Canada." *Chronic Diseases and Injuries in Canada* 30.4 (2010).

- [32] Lyall, Kristen, et al. "Pregnancy complications and obstetric suboptimality in association with autism spectrum disorders in children of the Nurses' Health Study II." *Autism Research* 5.1 (2012): 21-30.
- [33] Biri, A., et al. "Oxidant status in maternal and cord plasma and placental tissue in gestational diabetes." *Placenta* 27.2 (2006): 327-332.
- [34] Chen, Xinhua, and Theresa O. Scholl. "Oxidative stress: changes in pregnancy and with gestational diabetes mellitus." *Current diabetes reports* 5.4 (2005): 282-288.
- [35] Hultman, Christina M., PärSparén, and Sven Cnattingius. "Perinatal risk factors for infantile autism." *Epidemiology* 13.4 (2002): 417-423.
- [36] Wang, Ying, et al. "Maternal Body Mass Index and Risk of Autism Spectrum Disorders in Offspring: A Meta-analysis." *Scientific Reports* 6 (2016).
- [37] Croen, Lisa A., et al. "Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study." *Archives of pediatrics & adolescent medicine* 159.2 (2005): 151-157.
- [38] Lyall, Kristen, et al. "Maternal immune-mediated conditions, autism spectrum disorders, and developmental delay." *Journal of autism and developmental disorders* 44.7 (2014): 1546-1555.
- [39] Croen, Lisa A., Judith K. Grether, and Steve Selvin. "Descriptive epidemiology of autism in a California population: who is at risk?." *Journal of autism and developmental disorders* 32.3 (2002): 217-224.
- [40] Finegan, Jo-Anne, and Bruce Quarrington. "PRE-, PERI-, AND NEONATAL FACTORS AND INFANTILE AUTISM." *Journal of Child Psychology and Psychiatry* 20.2 (1979): 119-128.
- [41] Croen, Lisa A., et al. "Maternal and paternal age and risk of autism spectrum disorders." *Archives of pediatrics & adolescent medicine* 161.4 (2007): 334-340.
- [42] Cryan, Elizabeth, et al. "Brief report: a case-control study of obstetric complications and later autistic disorder." *Journal of Autism and Developmental Disorders* 26.4 (1996): 453-460.
- [43] Mason-Brothers, Anne, et al. "The UCLA-University of Utah epidemiologic survey of autism: prenatal, perinatal, and postnatal factors." *Pediatrics* 86.4 (1990): 514-519.
- [44] Lord, Catherine, et al. "Pre-and perinatal factors in high-functioning females and males with autism." *Journal of Autism and Developmental Disorders* 21.2 (1991): 197-209.
- [45] Kaur, Bhupinder. "The Association between Autism Spectrum Disorders and Secondhand Tobacco Exposure." (2014).
- [46] Albuquerque, Cheryl A., et al. "Influence of maternal tobacco smoking during pregnancy on uterine, umbilical and fetal cerebral artery blood flows." *Early human development* 80.1 (2004): 31-42.
- [47] Luck, W., et al. "Extent of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers." *Developmental pharmacology and therapeutics* 8.6 (1984): 384-395.
- [48] Williams, Gail M., et al. "Maternal cigarette smoking and child psychiatric morbidity: a longitudinal study." *Pediatrics* 102.1 (1998): e11-e11.
- [49] Muneoka, Katsumasa, et al. "Nicotine exposure during pregnancy is a factor which influences serotonin transporter density in the rat brain." *European journal of pharmacology* 411.3 (2001): 279-282.
- [50] James, William H. "Potential explanation of the reported association between maternal smoking and autism." *Environmental health perspectives* 121.2 (2013): a42.
- [51] Fergusson, David M., Lianne J. Woodward, and L. John Horwood. "Maternal smoking during pregnancy and psychiatric adjustment in late adolescence." *Archives of general psychiatry* 55.8 (1998): 721-727.
- [52] Kalkbrenner, Amy E., et al. "Maternal smoking during pregnancy and the prevalence of autism spectrum disorders, using data from the autism and developmental disabilities monitoring network." *Environmental health perspectives* 120.7 (2012): 1042.
- [53] Baron-Cohen, Simon. "The extreme male brain theory of autism." *Trends in cognitive sciences* 6.6 (2002): 248-254..
- [54] Kaur, Bhupinder. "The Association between Autism Spectrum Disorders and Secondhand Tobacco Exposure." (2014).
- [55] Tran, Phuong Lien, et al. "Smoking during pregnancy and risk of autism spectrum disorder in a Finnish National Birth Cohort." *Paediatric and perinatal epidemiology* 27.3 (2013): 266-274.
- [56] Van den Bergh, Bea RH, et al. "Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review." *Neuroscience & Biobehavioral Reviews* 29.2 (2005): 237-258.
- [57] Mulder, Eduard JH, et al. "Prenatal maternal stress: effects on pregnancy and the (unborn) child." *Early human development* 70.1 (2002): 3-14.
- [58] Li, Jiong, et al. "A nationwide study on the risk of autism after prenatal stress exposure to maternal bereavement." *Pediatrics* 123.4 (2009): 1102-1107.