Prenatal, Perinatal and Postnatal Risk Factors Associated with Autism Spectrum Disorder in Palestine: A Case-Control Study

عوامل الخطر قبل الولادة وأثناء الولادة و بعد الولادة المرتبطة باضطراب طيف التوحد في فلسطين: دراسة الحالات و الشواهد

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Received: (13/2/2023), Accepted: (14/5/2023), Published: (1/3/2024)

Abstract

Background: Autism spectrum disorder (ASD) is a multifactorial neurodevelopment disorder. Several prenatal, perinatal, and postnatal factors are suggested as risk factors for ASD. This study aimed to correlate prenatal, perinatal, and postnatal factors in a limited number of ASD cases in Palestine. **Methods:** A case-control study involved 120 children (60 typically diagnosed with ASD and 60 healthy matched with the ASD group). The parents of the children in both groups were asked to fill out the questionnaire. **Results:** The study showed a higher male-to-female

ratio in the ASD group. A family history of ASD was reported in 38.3% of the ASD group and 11.7% in the healthy group. Three prenatal risk factors, including maternal passive smoking, preserving follow-up prenatal visits, and experiencing psychological stress by mothers, were significantly associated with ASD. Most of the postnatal factors were significantly associated with increased ASD risk. The studied perinatal factors were not significantly associated with ASD. The parental factors, such as paternal age greater than 30 years and lower levels of education, displayed significant risk factors associated with ASD. **Conclusion:** This study found significant associations between several prenatal, postnatal, and parental factors and ASD in a sample of Palestinian children.

Keywords: ASD, Prenatal, Perinatal, Postnatal

ملخص

المقدمة: اضطراب طيف التوحد هو اضطراب نمائي عصبي متعدد العوامل. تم تحديد العديد من العوامل قبل الولادة و أثناء الولادة وبعد الولادة كعوامل قد تكون مرتبطة بالاصابة باضطراب طيف التوحد. هدفت هذه الدراسة لفحص ارتباط عدة عوامل قبل الولادة و أثناء الولادة و بعد الولادة في عدد محدود من حالات التوحد في فلسطين. **المنهجية:** تمت الدراسة من خلال جمع معلومات من عينة ضمت 120 طفل (60 تم تشخيصهم بطيف التوحد و 60 طفل سليم و متطابقين مع مجموعة التوحد). تمت الاجابة على الاستبيان من قبل أولياء الأمور في المجموعتين. **النتائج:** أظهرت الدراسة أن نسبة الذكور الى الاناث في مجموعة طيف التوحد كانت أعلى. تم تحديد نسبة وجود تاريخ عائلي في 38.3% من مجموعة طيف التوحد و 11.7% من مجموعة الاطفال السليمين. تم تحديد ثلاثة عوامل خطورة قبل الولادة مرتبطة بشكل وثيق مع اضطراب طيف التوحد و تشمل التدخين السلبي للأم، متابعة زيارات الرعاية قبل الولادة، و التعرض للاجهاد النفسي من قبل الأمهات. معظم عوامل الخطر بعد الولادة كانت مرتبطة بشكل وثيق بزيادة خطر الاصابة بطيف التوحد. عوامل الخطر أثناء الولادة التي تمت دراستها لم ترتبط بشكل وثيق باضطراب طيف التوحد. العوامل المتعلقة بالوالدين مثل عمر الأب أكثر من 30 عام و مستويات التعليم المتدنية أظهرت ارتباطا وثيقا بالإصابة بطيف التوحد. الاستنتاج: وجدت الدراسة ارتباطات وثيقة بين عدة عوامل قبل الولادة و أثناء الولادة و بعد الولادة مع طيف التوحد في عينة من الأطفال الفلسطينيين.

الكلمات المفتاحية: اضطراب طيف التوحد، قبل الولادة، أثناء الولادة.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that affects the child's social interaction abilities (Mir, *et al*. 2021). Language and communication difficulties are the main ASD symptoms, besides deficits in interests and activities (Cogley, O'Reilly, Bramham, & Downes, 2020; Win-Shwe, Kyi-Tha-Thu, Fujitani, Tsukahara, & Hirano, 2021). ASD is mostly diagnosed at or after the age of 3 years (Liu, *et al*. 2021), and the affected children suffer from repetitive unusual behaviors that impair their communication capabilities throughout their life. Consequently, children with ASD and their families are under a tremendous amount of stress that could interfere with important child management plans (Liu, *et al*. 2021).

ASD prevalence varies around the world and it ranges from 1.9/10,000 to 116/10,000 (Chiarotti & Venerosi, 2020). The prevalence of ASD in the Eastern Mediterranean region is estimated to be 86.5 per 10,000 (Zeidan, *et al*. 2022). In Palestine, there are no comprehensive published studies on autism statistics (Shawahna, Atrash, *et al*. 2017). According to certain sources based on unpublished information found on the websites of the United Nations and the Centers for Disease Control and Prevention, there are around 5000 Palestinian children who are autistic and the prevalence of autism is 91 per 10,000 (Baker, 2021). According to many professionals, there is no connection between the prevalence of autism and regional, racial, or cultural disparities (Daley, 2002; Elsabbagh, *et al*. 2012; Feinstein, 2011). In 2015, it was estimated that 20,000 autistic children were living in the West Bank and Gaza if the prevalence rate of autism is the same in Palestine as in the UK, which is around 1% (Ashbee, 2016). There is no doubt that further research is needed in Palestine in order to examine autism statistics.

The etiology of ASD is complex and not fully understood. It is supposed to be due to the complex interaction between multiple genetic and environmental factors (Bittker & Bell, 2018; Liu, *et al*. 2021). Possible prenatal, perinatal, and postnatal risk factors including maternal diet, parents' psychology, and gestational age, etc. have been studied thoroughly at the international level and were shown to be associated with

ASD development in an increasing number of scientific studies (Cogley, *et al*. 2020; Liu, *et al*. 2021; Mir, *et al*. 2021; Wang, Geng, Liu, & Zhang, 2017). Most of these studies were performed in European and American countries. Only a few studies addressed the risk factors of ASD in Middle East children area who have different genetic backgrounds and live in different environments compared to European and American children. In the Middle Eastern countries including Palestine, very few studies have been conducted on this topic.

A good example of that is a recent Lebanese study that found significant correlations between the increased prevalence of consanguineous mirage and positive family history with ASD (Bitar, *et al*. 2020). In Palestine, research in the field of autism was scarce and focused mainly on disclosing the gaps in knowledge and awareness of the disorder among medical students and pharmacists (Basha, 2014; Shawahna, Fahed, *et al*. 2017; Shawahna, Jaber, Yahya, Jawadeh, & Rawajbeh, 2021). A recent study explored the link between low nutritional status including vitamins A, D, B1, B2, B6, B12, folic acid, niacin, iron, and zinc of Palestinian pregnant, lactating mothers and children as a modifiable risk factor of ASD (Altamimi, 2018). Besides, multivitamins intake, especially omega 3 and vitamin B, a rich cereal diet, and iron supplementation during pregnancy were protective factors against ASD among Lebanese (Gerges, *et al*. 2020). Another Palestinian study confirmed an association between autism, iron deficiency, and anemia. Furthermore, the study suggested measuring ferritin levels in children with ASD as a part of the routine investigation (Al Ali, 2013). Increased rates of having ASD children were found among Palestinian mothers who were exposed to chemicals or smoking during pregnancy and pregnant women who did not get their vaccination during pregnancy are also at increased risk for having offspring with ASD (Zamel, *et al*. 2017).

On the other hand, there is insufficient research on the risk factors associated with autism in Palestine. In the current study, we conducted for the first time a case-control study to investigate the possible association between several prenatal, perinatal, and postnatal factors in a sample of ASD children in Palestine.

Materials and methods

Study sample

A case-control questionnaire-based study was carried out on two groups of children enrolled in the study: group one consisted of 60 ASD-affected children receiving rehabilitation in Palestinian rehabilitation centers, and Group two consisted of 60 typically developing children (TD). The focus of the research was on the parents of the children in both groups who participated in the study by answering the questionnaires.

Inclusion and exclusion criteria

The inclusion criteria for the ASD group were children attending rehabilitation centers who were diagnosed by clinical staff professionals using the Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria for ASDs (DSM-5)(Joyce-Beaulieu & Sulkowski, 2016). The typically developing (TD) group served as the study's control group. It was comprised of typically developing children who were chosen from the same geographic region as the children with ASD and were matched in age with the ASD group in order to achieve nearly identical confounding parameters. Children who had any known neurogenetic conditions, mental illnesses, congenital malformations, brain injuries, visual or hearing impairments, or whose parents had not given their consent to participate were not eligible for either of the groups and comply the exclusion criteria.

Ethical consideration

The official ethical approval was received from the Institutional Review Board at An-Najah National University in Nablus, Palestine (REF: MAS. Archive number (10)). The study was conducted in accordance with the Declaration of Helsinki (DOH). Written informed consent was obtained from the participating parents. The form overviewed the study procedure, aims, and benefits. Besides, the form describes that the obtained data will be confidential and protected from any uninvolved member of the study and that it will not be used for any reason other than research purposes. The participants or their parents were fully informed

that participation in the study is voluntary, and no penalties are associated of non-participation

Study design and procedure

A case-control questionnaire-based study was conducted over 7 months from November 2019 to May 2020. The parents who had accepted to be enrolled in the study were interviewed and assisted to ensure a better understanding of the study questions. The questionnaire was designed and built following previously reported risk factors associated with ASD (Guinchat, *et al*. 2012; Langridge, *et al*., 2013; Wang, *et al*. 2017).

Study instrument

The questionnaire included the participants' basic information: gender, age, mode of birth, and family history of ASD in addition to other variables which were classified into prenatal, perinatal, postnatal, and parental factors associated with ASD. The three Likert scale responses, yes, no, and uncertain/I don't know were used to answer each question about the risk factors.

Statistical analysis

All statistical analyses were conducted using a Statistical Package for the Social Sciences version 22 (SPSS 23). Descriptive analyses were used for a sample of basic characteristics, including the frequencies for the quantitative variables, means, and standard deviations for the qualitative variables. Pearson's correlation coefficient to establish correlations between the two groups was used. A bivariate logistic regression was also conducted to generate crude odds ratios with 95% confidence intervals to determine the risk factors associated with a higher probability of having a child with ASD. A *p*-value of <0.05 was considered statistically significant.

Results

Basic characteristics of the study sample

In the ASD group, there were 60 children affected with ASD, with a predominance of males, (50 males (83.3%) and 10 females (16.7%)) and a

mean age of 8.6 years. The control group involved 60 TD children (28 males (46.7%) and 32 females (53.3%)) and a mean age of 7.9 years. The delivery method was vaginal in 63.3% of the ASD group and 80% of the TD group. The presence of a family history of autism was reported in 38.3% of the ASD group while it was 11.7% among the TD group, as shown in Table 1.

Table (1): Basic characteristics of the children in the healthy group (n=60) and autism spectrum disorder (ASD) group (n=60).

Variable		ASD sample		TD sample	
		n	%	N	%
Gender	Male	50	83.3	28	46.7
	Female	10	16.7	32	53.3
Age (years)	Mean ± SD	8.6 ±2.89		7.9 ±2.53	
Delivery method	Vaginal	38	63.3	48	80.0
	CS	22	36.7	12	20.0
Family history of autism	Yes	23	38.3	7	11.7
	No/ I do not know	37	61.7	53	88.3

Prenatal risk factors associated with ASD

The logistic regression analysis of 13 prenatal variables supposed to be associated with ASD is shown in Table 2. Taking the presence of the studied variable as the dependent variable, it was found that experiencing prenatal emotional/psychological events increased the risk of having a child with ASD by around 60-folds (p-value=0.004). Being a passive smoker mother increased the risk of having an ASD child by 18.02 times ((p-value=0.024). The probability of having a child with ASD increased by 12.85 times with more frequent follow-up doctor visits (p-value=0.032). The likelihood of having a child with ASD was not substantially increased or decreased by the other variables under study (p-value > 0.05).

Table (2): The Binary Logistic Regression Model for the prenatal risk factors associated with ASD prevalence.

Prenatal Risk factor (Ref: yes)		OR (CI 95%)	P-value
1. Being a smoker	Uncertain	0.061(0.00, 32.84)	0.38
	No	0.44 (0.023, 8.73)	0.59
2. Being passive smoker	Uncertain	11.4 (0.00)	0.99
	No	18.02 (1.45, 223.7)	**0.024**
3. Suffering severe urinary infections	Uncertain	0.44(0.003, 64.6)	0.75
	No	3.56(0.419, 30.2)	0.24
4. Threatened abortion	Uncertain	0.33(0.00, 287)	0.85
	No	0.761(0.066, 8.77)	0.827
5. Gestational diabetes	Uncertain	0.406(0.00)	0.998
	No	0.148(0.00)	0.999
6. Antepartum hemorrhage	Uncertain	0.28(0.001,100.5)	0.67
	No	0.081(0.002,4.12)	0.210
7. Preserving follow-up visits	Uncertain	54.2(0.075,0.390)	0.132
	No	12.85(1.24,133.15)	**0.032**
8. Too much medication intake	Uncertain	28.6(0.74,0.11)	0.062
	No	19.55 (0.00)	0.057
9. Experiencing emotional/ psychological events/ disorders	Uncertain	0.79(0.001, 57.2)	0.944
	No	60.28(3.57,101.5)	**0.004**
10. Exposure to multiple radiological images	Uncertain	63.1(0.00)	0.997
	No	0.323(0.00)	0.996
11. Experiencing Preeclampsia	Uncertain	0.152(0.00)	1.0
	No	0.306(0.007,12.05)	0.532
12. Parity	Uncertain	0.811(0.00)	0.998
	No	0.917(0.028,30.13)	0.961
13. Polycystic ovary syndrome	Uncertain	0.244(0.00, 0.195)	0.758
	No	0.222(0.006,8.291)	0.415

Reference category: ASD child

Perinatal risk factors associated with ASD

The logistic regression analysis of 18 perinatal variables that could be associated with ASD is shown in Table 3. Taking the presence of the studied variable as the dependent variable, it was found that none of the studied variables was significantly associated with the risk of having a child with ASD (p-value>0.05).

Table (3): The Binary Logistic Regression Model for the perinatal risk factors associated with ASD prevalence.

Perinatal Risk factor (yes)		OR (CI 95%)	P-value
1. Acute fetal distress	Uncertain	1.45(0.00)	0.974
	No	1.43(0.00)	0.982
2. Use pregnancy stabilizers	Uncertain	5.81(0.00)	0.980
	No	0.27(0.033, 2.23)	0.225
3. Prematurity	Uncertain	3.05(0.00)	0.993
	No	0.35(0.014, 8.94)	0.526
4. Exceeding the term	Uncertain	6.56(0.00)	0.990
	No	5.11(0.00)	0.969
5. Difficult labor	Uncertain	1.61(0.00)	0.964
	No	0.077(0.004,1.495)	0.090
6. Low birth weight	Uncertain	1.20(0.00)	0.966
	No	0.330(0.017,6.534)	0.466
7. Macrosomia	Uncertain	2.491(0.00)	0.973
	No	0.438(0.041,4.672)	0.494
8. Hyperemesis gravidarum	Uncertain	3.288(0.00)	0.978
	No	6.338(0.822,48.88)	0.076
9. Tocolysis therapy	Uncertain	5.22(0.00)	0.968
	No	7.51(0.00)	0.973
10. Premature rupture of membrane	Uncertain	1.22(0.00)	0.983
	No	7.44(0.00)	0.982

... continue table (3)

Perinatal Risk factor (yes)		OR (CI 95%)	P-value
11. Fetal nuchal cord	Uncertain	0.206(0.00)	0.982
	No	33.7(0.00)	0.988
12. Child delayed crying	Uncertain	0.107(0.00)	0.992
	No	2.92 (0.00)	0.996
13. Child Apnea	Uncertain	2.59(0.00)	0.990
	No	0.367(0.00)	0.986
14. Had a breech presentation	Uncertain	0.425(0.00)	0.993
	No	0.697(0.00)	0.987
15. Hair dye	Uncertain	2.13(0.00)	0.987
	No	3.16(0.00)	0.986
16. Placenta Previa	Uncertain	5.55(0.00)	0.913
	No	6.24 (0.00)	0.975
17. Placental Abruption	Uncertain	1.01(0.00)	0.978
	No	2.70(0.00)	0.994
18. Forceps delivery	Uncertain	6.70(0.00)	0.988
	No	3.67(0.00)	0.996

Reference category: ASD child

Postnatal risk factors associated with ASD

The Chi-square analysis showed a significant difference in the postnatal risk factors: respiratory infection, urinary infection, blood diseases, umbilical cord around neck, low Apgar scores of the child, Meconium Aspiration Syndrome, respiratory distress syndrome, hyperbilirubinemia, neonatal encephalopathy, band neonatal or congenital infections between the ASD group and the healthy group (p-value < 0.05). The auditory deficit was not significantly different between the two groups (p-value > 0.05), results are shown in Table 4.

Table (4): The Chi-square analysis for the postnatal risk factors associated with ASD prevalence.

Postnatal Risk factor	ASD		TD		p-value
	N	%	n	%	
1. Respiratory infection	1	0.8	7	5.8	0.000
2. Urinary infection	7	5.8	2	1.7	0.000
3. Auditory deficit	9	7.5	12	10	0.430
4. Blood diseases	4	3.3	13	10.8	0.000
5. Umbilical cord around the neck	3	2.5	8	6.7	0.000
6. low Apgar scores of the child	2	1.7	6	5	0.037
7. Meconium Aspiration Syndrome	1	0.8	11	9.2	0.000
8. Respiratory distress syndrome or assisted ventilation	6	5	8	6.7	0.000
9. Hyperbilirubinemia	17	14.2	7	5.8	0.000
10. Neonatal encephalopathy	4	3.3	1	0.8	0.000
11. Neonatal or congenital infections	3	2.5	5	4.2	0.019

Parental risk factors associated with ASD

It was observed that paternal age was a significant risk factor for ADS. Parents with an age exceeding 30 years demonstrated an increased risk of 4 times as compared with parents with lower ages. Moreover, mothers with a low level of education (primary or secondary school) had a significantly increased risk of having a child with ASD by nearly sixteen times compared with mothers with higher levels of education as shown in Table 5.

Table (5): The Binary Logistic Regression Model for the parental risk factors for ASD prevalence.

Risk factor variable	Wald	OR (CI 95%)	P-value
Paternal age (over 30 years)	3.998	4.616	0.046
Maternal educational level (primary & secondary)	3.974	16.257	0.046

Discussion

The precise causes of autism are still unknown. The growing number of researches showed heterogenous results on the possible role of genetic variants and environmental risk factors. Recent literature shows that genetic factors possibly account for only 35–40% of the causes of autism. The remaining 60–65% are likely due to environmental factors. This leads to the focus on studying these environmental factors in several international populations (Yong, *et al.* 2021).

The current study is the first in Palestine to test 42 prenatal, perinatal, and postnatal risk factors that have been linked to the etiology of autism. This study reveals that the majority of postnatal and some prenatal risk factors were significantly associated with ASD, but none of the perinatal risk factors were.

Among the 13 studied prenatal risk factors in the current study, passive smoking mothers, preserving follow-up visits, and maternal emotional stress were significantly associated with ASD, as was reported by others (Cogley, *et al*. 2020; Liu, *et al*. 2021; Mir, *et al.* 2021). Our findings suggest that stressful life experiences during pregnancy may significantly increase the likelihood of having a child with ASD, which is consistent with the findings of other studies. (Gerges, *et al*. 2020; Say, Karabekiroğlu, Babadağı, & Yüce, 2016; Varcin, Alvares, Uljarević, & Whitehouse, 2017). Stressful pregnancy events are thought to cause the hypothalamus to release the corticotropin-releasing hormone, which may set off a chain of events that allows autoantibodies and interleukins to enter and promote brain inflammation and the development of ASD.(Gerges, *et al.* 2020). This study showed that being a passive smoking mother is significantly linked to an increased risk of having an ASD child, in harmony with what has been published by others (Khalil, Kaur, Lawson, Ebert, & Nahhas, 2018; Malla, *et al*. 2017). It has been hypothesized that smoking exerts direct toxicity and impairs placental function. The most dangerous byproducts of smoking are carbon monoxide and nicotine which can damage the nicotinic acetylcholine receptors. These receptors are linked to the normal embryonic nervous system development and the normal

turnover of neurotransmitters. Also, it was found that carbon monoxide binds with fetal hemoglobin and thus impairs normal tissue oxygenation (Chatterton, *et al*., 2017; Hertz-Picciotto, *et al.* 2022). The current study also revealed that pregnant mothers who had more frequent follow-up doctor visits were at increased risk of having ASD children. Notably, it was found that frequent animal exposure to ultrasound was linked to nervous system defects (Abramowicz, 2012).

Contrary to what has been reported by several authors previously, the current study did not display any significant association between the 18 studied perinatal risk factors and ASD (Hadjkacem, *et al*., 2016; Hisle-Gorman, *et al.* 2018). This heterogeneity of results guides us to interpret any significant association between ASD and perinatal factors with caution, as this may reflect the consequences of previous prenatal complications.

The majority of the 11 postnatal risk factors that were taken into account in this study were found to have significant associations with ASD. These results are in line with research showing that the onset of ASD is correlated with illnesses including respiratory and urinary tract infections in the first six weeks (Hadjkacem, *et al*. 2016). A low Apgar score of the newborn was also found to be a risk factor for ASD in the current study, in agreement with previous findings (Modabbernia, *et al*. 2019). Furthermore, meconium aspiration, respiratory distress syndrome, asphyxia, and neonatal encephalopathy were considered risk factors for ASD. This is consistent with the previous research (Hisle-Gorman, *et al*., 2018; Modabbernia, *et al*. 2019). This finding could be explained by the effect of cytokines released due to immune system response which can affect neural development in terms of cell proliferation and differentiation (Ashwood et al., 2011; Gardener, Spiegelman, & Buka, 2011). Lozada et al. and Amin et al. came to the same conclusion that unconjugated hyperbilirubinemia may be related to ASD etiology (Cordero, *et al*. 2020; Lozada, *et al*. 2015). However, Wu *et al* have found that hyperbilirubinemia was not a risk factor for ASD (Y. W. Wu, *et al*. 2016).

Our study found that the paternal age over 30 years had an increased risk of having a child with ASD, which is consistent with earlier findings (S. Wu, *et al*. 2017). Indeed, this could be explained by the possibility of having more genetic defects in the gametes with aging (Sandin, *et al*. 2016). Notably, in line with earlier studies, a significant association between a mother's education level and ASD was discovered (Ali & Arbab). It is worth noting that a higher level of maternal education means advanced maternal age. This last factor has a higher association with the diagnosis of ASD than the mother's education level (Chiang, Lin, Lee, & Shu, 2018).

In other words, the fact that different research findings on the risk variables for ASD show such considerable heterogeneity is a clue that we should interpret them with skepticism. And more comprehensive studies in the future of different populations with different genetic backgrounds and environments are warranted before firm conclusions are drawn.

This study had some limitations, and because of the relatively small sample size, its findings cannot be extrapolated until they have been confirmed by larger studies. Palestine's lack of a formal national registry that records all cases of ASD may help to explain some of this. Additionally, many families may not have participated due to the sensitive nature of the subject. Indeed, the majority of parents had inadequate professional knowledge of autism, which negatively impacts their attitudes and increases stigma. Other published studies in the area, especially in Lebanon, were also performed on small samples (Bitar, *et al*. 2020; Hamadé, *et al*. 2013). Due to a potential recall bias, the study's retrospective design may have had an impact on the findings. The study's questionnaire was not utilized previously. None of the genetic variants known to be linked to autism were tested for in the study's affected children or their parents. Nevertheless, there were several strong points in this study. Investigating the potential association of prenatal, perinatal, and postnatal risk factors with autism was the subject of the first study of its kind in Palestine. The questions of the study's questionnaire were derived from several international studies. And before it was made available, local experts provided feedback on it. Additionally, the questionnaire was

verified by suitable statistical analysis. The study's sample was drawn from many specialist rehabilitation facilities, and it varied in terms of gender, age at which symptoms first appeared, severity, symptoms, warning indications, and potential risk factors. Therefore, in a nation that is overloaded with several health issues and priorities, this is a leading study that raises many significant concerns regarding this underserved portion of the population. This study will inspire further investigation toward revealing the potential causes of autism in Palestine.

Conclusion

ASD is a significant problem both because its prevalence is increasing and because it has detrimental effects not only on affected children but also on their families. This study succeeded in correlating several prenatal and postnatal risk factors with the etiology of ASD. However, the association of ASD with perinatal risk factors was not significant. These findings have both theoretical value for a better understanding of the etiology and mechanisms of ASD. Also, the findings of the current study have important practical value in both future prevention and reducing prevalence of ASD. We recommend improving living environment during pregnancy especially by avoiding psychological stress and smoking. In addition, effective treatment and follow up of early childhood infections especially respiratory and urinary infections, are potential effective interventions for ASD prevention.

Ethics approval and consent to participate: The official ethical approval was received from the Institutional Review Board at An-Najah National University in Nablus, Palestine (REF: MAS. Archive number (10)). The study was conducted in accordance with the Declaration of Helsinki (DOH). Written informed consent was obtained from the participating parents.

Consent for publication: The manuscript has been read and approved by all named authors who gave the permission to An-Najah University Journal for Research - B (Humanities) to publish it.

Availability of data and materials: All data and materials are included in the manuscript.

Authors' contribution: Mustafa Ghanim: project administration, validation, manuscript writing, and submission. Mariam Al-Tell: conceptualization, supervision, and data curation and analysis. Samaa Staiti: data collection and analysis and manuscript writing. Maha Rabayaa: manuscript writing, review, and editing. Johnny Amer: project administration, manuscript writing, and review. Malik Alqub: manuscript writing and editing. Sameeha Atout: manuscript writing. Nihad Al-Othman: manuscript writing, and analysis validation. Marwa Ismail: manuscript writing.

Conflicts of interest: The authors declare that they have no conflict of interest.

Funding: The study received no funding from any source.

Acknowledgments: The author(s) would like to thank An-Najah National University (www.najah.edu) for the technical support provided to publish the present manuscript.

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