ENVIRONMENTAL EITIOLOGY OF AUTISM AND SUBSEQUENT INTERVENTIONAL MANAGEMENT

Sherien A. Nasser [(1)]; Moustafa H. Ragab [(2)]; Neveen H. Nashaat [(1)]; Radwaa I. A. Hassan [(3)] and Nagwa A. Meguid [(1)]

1) Children with Special Needs Research Department, NRC .2) Department of Environmental Medical Sciences, Faculty of Graduate Studies and Environmental Research، Ain Shams University 3) Department of Public Health and Community Medicine, Cairo University

ABSTRACT

Background: Autism spectrum disorder (ASD) is a complicated disorder. Up to 50% of its variance could be related to environmental factors.

Aim: Environmental risk factors for ASD were studied among cases and controls. Additionally, the effects of some targeted interventional approaches on the severity of ASD and language abilities were compared.

Methodology: This study was conducted on 61 autistic children (3-12 years) who visited the outpatient clinic for "Children with ASD" from September 2021 to February 2022. They were subjected to the Childhood Autism Rating Scale, and the Arabic Preschool Language Scale. The control subjects (N=62) were selected from volunteers. A questionnaire was designed for studying the environmental risk factors. Children with ASD were then divided into two groups: Group a (N=30) received phoniatric therapy; Group b (N=31) received phoniatric therapy and dietary supplementation. After 3 months, both groups were reassessed.

Results: Risk factors such as maternal exposure to disinfectants and cleaners (78.7%), moderate maternal (39.3 %) and paternal (47.5 %) educational level, pregnancy in Summer (19.6%), delivery in Spring (19.6%) and prematurity (91.8%), showed significant statistical difference between cases and control subjects (P=0.01,0.00,0.04,0.00 respectively). Following intervention, the

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severity of ASD decreased (*P*=0.00) and there was a significant difference regarding receptive, expressive, and total language ages (*P*=0.00,0.01,0.00 respectively) between the two groups.
Conclusions: There were a variety of environmental risk factors associated with ASD. Merging phoniatric therapy and dietary supplements was an effective management option for children with ASD.
Keywords: Autism, Environment, Risk factors ،Intervention.

INTRODUCTION

Autism spectrum disorder (ASD) is considered a heterogeneous neurodevelopmental disorder which is characterized by impairment in social interactions and communication as well as repetitive and restrictive patterns of interests or behaviour **(Campbell *et al.*, 2021)**. Most recently, an increase in the prevalence of autism spectrum disorder (ASD) was observed by the US Centres for Disease Control and Prevention. It affects 1 in 59 children according to their reports **(Baio *et al.*, 2018)**.

While the exact aetiology of ASD is still unknown in the majority of cases, the environmental factors can account for up to 50% of the variation in ASD liability. Recent research on monozygotic twins revealed that ASD development is influenced by both genes and the environment **(Modabbernia *et al.*, 2017)**. Early in life, risk factors interact to alter brain development, which leads to a reorganisation of the neural networks which control cognition and/or behaviour. Alterations in the development of neural systems could change sensitivity to and learning from the environmental inputs **(Campbell *et al*., 2021).**

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ASD strongly interferes with the nutritional behaviour of the affected children due to their limited, self-restricted diets and gastrointestinal manifestations that could hinder the absorption of important nutrients. Some research suggested that the comorbidities and symptoms of ASD could be reduced by increasing nutrient consumption to alleviate nutritional and metabolic issues. Phoniatric rehabilitation including strengthening verbal, non-verbal communication and cognitive abilities, behavioural intervention and medications are among the management options. However, the results and effectiveness of these management options varied among studies **(Bjørklund *et al*., 2019).**

Determining the contribution of the environmental risk factors to ASD may improve detection, earlier intervention measures, and better prevention of the disorder by identifying high risk individuals before symptoms appear.

AIM OF THE STUDY

I. To explore the possible environmental risk factors associated with the occurrence of ASD, including indoor environmental risk factors (chemical, physical), outdoor environmental risk factors, prenatal, natal, postnatal, nutritional, and psychosocial factors, and to compare these factors with those in control group.

II. To implement some targeted interventional approaches for autistic children according to the frequency of the detected risk factors and comparing the

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impact of intervention on the severity of ASD and the language abilities of the children.

METHODOLOGY

This study was conducted on 61 autistic children who were recruited from the "Children with ASD" Outpatient Clinic at the Medical Research Centre of Excellence, which is affiliated to the National Research Centre, Cairo, Egypt. They visited the clinic over a period of six months (September 2021-February 2022). Their chronological age range was 3 to 12 years. Their diagnosis was achieved by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (**American Psychiatric Association "APA", 2022)** and by the Autism Diagnostic Interview-Revised (ADIR) **(Lord *et al.*, 1994).** The inclusion criteria for the children with autism were meeting the diagnostic criteria of ASD and an age range of 3 to 12 years. Children with signs which were suggestive of syndromic involvement, developmental motor delay, and neuropsychiatric disorders were excluded.

The control group (62 children) was recruited from volunteers and was matched for age with the cases. The inclusion criteria for controls were normal clinical examination, normal current communication abilities and motor development. The exclusion criteria were the existence of a history of developmental delay, neuropsychiatric disorders, chronic illness and previous phoniatric intervention. Two types of studies were performed: case control study and Interventional study.

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- **Patient and parents interviewing** included complaint and analysis of symptoms, obtaining data of personal history such as age, order of birth, details of the pedigree, parental consanguinity, similar or other conditions in the proband's family, prenatal, natal, and postnatal events, early childhood medical history, and timing of the developmental milestones. General examination including some anthropometric measures (head circumference, height, and weight), vocal tract, ear, nose, and neurological examination were performed.
- **The Childhood Autism Rating Scale (CARS)** was used for assessment of the ASD severity **(Schopler *et al.*, 1988).**
- **Arabic Preschool Language Scale:** All cases were subjected to the Arabic Preschool Language Scale to for obtaining the language age; the raw scores of receptive and expressive languages and the scaled scores for receptive and expressive language together with total language age and normal cut-off values to verify the presence of developmental language delay **(El-Sady *et al*., 2011).**
- **The questionnaire designed for studying the environmental risk factors for ASD:** The parents of cases and controls were asked to complete the designed questionnaire which addressed some child, parental and demographic characteristics. Attention was paid to thorough analysis of the pre-existing medical records to ensure reliability and minimize recall bias. The questionnaire for the parents included the following axes:

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- General data: they included data such as parental age, consanguinity, family history of ASD, or mental retardation, psychiatric diseases, language disorders and genetic diseases.
- Data related to socioeconomic status: they included data such as parental educational level, electric bill value, house area, number of rooms at home, number of children in the family and maternal migration.
- Antenatal and perinatal risk factors: they included data such as the maternal and the paternal ages at the time of pregnancy, mode of conception, maternal disease, maternal vaccination, maternal drugs, dental amalgam, vitamins during pregnancy, gestational age, birth order and spacing, birth weight(underweight <2.5 Kg, average 2.5 -3.5 kg, overweight >3.5 kg) , seasons of pregnancy and delivery, type of delivery, position of the baby, weight of the baby, twins, cyanosis, artificial ventilation in neonatal intensive care unit , neonatal jaundice, and incubation.
- Indoor environmental risk factors during pregnancy: they included chemical and physical environmental hazards. Chemical environmental hazards included data such as maternal exposure to insecticides, cleaners, disinfectants, maternal exposure to smoking, using different materials of cooking utensils, type of floor material. Physical environmental hazards included data such as maternal exposure to ionizing radiation and electromagnetic radiation during pregnancy.

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- Outdoor environmental risk factors: they included data such as distance from health care facilities, nearby gasoline stations and nearby mobile stations (nearby means beside or opposite or behind the building of proband).
- Nutritional risk factors: they included data such as breast feeding, infant feeding, and the presence of food allergies in children.

- **Interventional Approaches:**

After possible risk factors were determined in the autistic children who were included in the study, the children with ASD were divided into two groups according to the frequency of risk factors:

- The first group: Group a (N=30) who had less risk factors received phoniatric therapy sessions twice weekly for three months, to improve language, social communication, cognitive and adaptive skills.
- The second group: Group b (N=31) who had more risk factors than group a and received phoniatric therapy sessions and dietary supplementation. It was an oral supplementation of some vitamins and micronutrients which included vitamin B complex (B12, B6, B5, B3, B1), folic acid, meclofenoxate (centrophenoxine) and omega 3. This oral supplementation was given as one tablet twice daily in the form of chewable chocolate pills for three months.
- After the preliminary assessment, parents of both groups received health education sessions for environmental stimulation at home and phoniatric

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counselling sessions to enhance their cognitive, communication and behavioural performance. Then, the autistic cases were reassessed with CARS and the Arabic Preschool Language Scale after 3 months to compare the communication and behavioural manifestations in these children before and after the chosen intervention.

•Data analysis and statistical methods:

o The collected data was revised, and then coded, tabulated, and introduced. Statistical package of social science software program (SPSS), version 23 was used.

o According to the type of data obtained for each parameter, data was presented, and statistical analysis was done. The parametric quantitative data were presented as mean and standard deviation (±SD). Number and percentage were used for qualitative variables. The student's t-test was used to assess possible statistical significance for the means difference between two studied independent groups. The chi-square test was used to investigate the relationship between two qualitative variables. Furthermore, Fisher's exact test was used to examine the relationship between qualitative variables when the expected count is less than 5 in more than 20% of the cells. Paired t- test was used for pre and post interventions comparison.

o P value equal or less than 0.05 was considered to be statistically significant.

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RESULTS

The autistic participants were 61 children, 50 boys (81.9%), and 11 girls (0.18%). The control subjects were 62 healthy participants, 34 boys (54.8%), and 28 girls (45.2 %). There were substantial gender disparities among these groups (P = 0.00).

Environmental Risk Factors:

1- Indoor Environmental Risk Factors:

A-Chemical environmental hazards during pregnancy

Comparison between cases and controls revealed significant statistical difference regarding exposure to cleaners, disinfectants, and vinyl floor *(P*=0.01, 0.02 respectively), while regarding maternal exposure to insecticides, using aluminium food utensils, for both direct and indirect maternal smoking exposure, the results were non-significant(table1).

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Table 1: Comparison of maternal exposure to chemical environmental hazards during pregnancy between cases and controls

Variables	Cases		Controls		P value
	Number	%	Number	%	
Cleaners and disinfectant	48	78.7%	36	58.1%	0.01*
Yes	13	21.3%	26	41.9%	
No					
Floortypes	7	12.1%	2	3.2%	0.02*
Vinyl	1	1.7%	6	9.7%	
Wood	53	86 .2	54	87.1%	
Others					

Chi-Square, P≤ 0.05 significant relation (*)

b- Physical environmental hazards during pregnancy

Maternal exposure to ionizing radiation and electromagnetic radiation as a result of using routers, electronics, and mobile phones had non-significant outcomes between cases and controls (P=0.1,0.47,0.22 respectively).

2- Outdoor Environmental Risk Factor

The results in the present study did not show any significant difference between cases and controls as regards distance from health care facilities, nearby gasoline stations, or nearby mobile stations (P=0.96, 0.61, 0.21 respectively).

3- Antenatal and Perinatal Risk Factors

Assisted reproductive technology as IVF (In-vitro fertilization), assisted labour, weight of the baby at birth and artificial ventilation in neonatal intensive care units were reported in cases more than controls with

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statistically significant difference (*P*=0.02, 0.00, 0.00, 0.05 respectively). Most of mothers in autistic group were more likely to become pregnant in summer. The highest percentage of cases births were in spring. About 91.8% of mother of cases had premature labour. Premature labour and season of pregnancy and delivery were statistically significant among cases and controls (*P* =0.00, 0.04, 0.04 respectively) (table 2). Maternal vaccination, dental amalgam, maternal drugs, vitamins during pregnancy, maternal disease, birth order, position of the baby, twins, cyanosis, neonatal jaundice, and incubation showed non-significant statistical difference between the groups. Additionally, there were non-significant statistical differences between cases and controls in terms of positive consanguinity, family history of ASD, or mental retardation, psychiatric diseases, language disorders and genetic diseases.

A substantial statistical difference (*P* = 0.03) was found for maternal age alone, with higher percentage of mothers of autistic children (19.7% compared to 16.1 % in controls) was for age equal to or older than 35 years. The mean maternal age at the time of pregnancy among mothers of cases was (28.2±6.24) years and among control was (28.2±5.96) years while the mean paternal age at time of pregnancy among cases was (34.06±7.88) years and among control was (32.09±5.89) years. The mean of pregnancy interval was (2.6±3.2) years among cases and was (1.8. ± 2.1) years among control with a non-significant difference among cases and controls.

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Table 2: Comparison of antenatal and perinatal data between cases and controls

Variables		Cases		Controls		P value
		Number	%	Number	%	
Conception	Normal induction	56	91.8%	62	100.0%	0.02*
	IVF	5	8.2%	0	0.0%	
Delivery	CS	26	42.6%	49	79.0%	0.00*
	Assisted labor	4	6.6%	0	0.0%	
	Normal	31	50.8%	13	21.0%	
Weight of baby at birth	Overweight (>3.5kg)	4	6.6%	6	9.7%	0.00*
	Underweight (<2.5 kg)	10	16.4%	0	0.0%	
	Average (2.5-3.5kg)	47	77.0%	56	90.3%	
Artificial Ventilation (in neonatal intensive care units)	Yes	4	6.6%	0	0.0%	0.05*
	No	57	93.4%	62	100.0%	
Duration of pregnancy	<36 week	56	91.8%	8	12.9%	0.00*
	36-40	4	6.6%	51	82.3%	
	>40 weeks	1	1.6%	3	4.8%	
Season of Pregnancy	Winter	5	8.1 %	2	3.2%	0.04*
	Autumn	26	42.6%	33	53.2%	
	Spring	18	29.5%	25	40.3%	
	Summer	12	19.6 %	2	3.2%	
Season of Delivery	Winter	19	31.1%	25	40.3%	0.04*
	Autumn	4	6.5%	2	3.2%	
	Spring	12	19.6%	2	3.2%	
	Summer	26	42.6%	33	53.2%	

Chi-Square and Fisher's Exact Test, P≤ 0.05 significant (*)
IVF In-vitro fertilization, CS caesarean section

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4-Nutritional Risk Factors

As regards infant feeding during the first two years, artificial milk feeding was more in cases (16.4 %) than controls (1.6%) with significant statistical difference (*P*=0.01). The percentage of food allergies among the studied groups did not show statistically significant difference.

5- Psychosocial Risk Factors

Some proxies for different socioeconomic status in the family, namely maternal, paternal education, and the value of the electric bill, were studied among cases and controls. A higher percentage of cases had mothers (39. .3% compared to 19.4% in controls) and fathers (47.5 % compared to 19.4% in controls) with moderate education with significant differences, (*P*=0.00) for both. The difference between the cases and controls was non-significant regarding the electric bill value (*P* =0.31). The mothers in a higher percentage of cases more than controls migrate to another city or country with statistically significant difference (*P*= 0.01) (tables 3). There were non-significant statistical difference concerning the house area, number of family members at home, numbers of room at home, number of children at home (*P*= 0.14, 0.75, 0.34 respectively).

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Table 3: Comparison of maternal migration during pregnancy between cases and controls

Variables		Cases		Controls		P value
		Number	**%**	**Number**	**%**	
Migration	to another city	6	9.8%	3	4.8%	0.01*
	to another country	9	14.8%	1	1.6%	
	No migration	46	75.4%	58	93.5%	

Chi-Square, P≤ 0.05 significant (*)

Interventional Approaches

After determining the risk factors among the autistic participants, the participants with ASD were divided into 2 groups. Group a which included autistic children having less frequently reported risk factor and was subjected to language therapy sessions only (twice weekly for three months), without dietary supplementation. Group b, which included autistic children having more frequently reported risk factors, received an oral dietary supplement (twice daily for three months) together with the language therapy sessions. Then, the results before and after such intervention were compared as regards the severity of ASD and language age among both groups

1-Results of the Childhood Autism Rating Scale (CARS)

Before the intervention, there was non-significant difference in the severity of autism between the two studied groups (P = 0.51). Following intervention in both groups, the severity of ASD decreased, and the CARS

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scores mean was reduced from (35.9 ± 2.7) to (34.5±3.2) with significant difference (*P*=0.00).

2- Results of the Arabic Preschool Language Scale (PLS4)

The preliminary assessment of the language age in the autistic children revealed that all of them had delayed language development. Their language ages were less than what is expected from the children with the same chronological ages. Before the intervention. there was a statistically significant difference in the receptive, expressive, total language ages among the two ASD groups of intervention being higher in Group b (tables 4,5 ,6). After three months of intervention, group b's receptive and expressive, together with total language ages significantly improved compared to group a. Receptive language age and expressive language age, as well as total language age, all improved after the intervention in the two groups (table 7).

Table 4: Comparison regarding receptive language age change pre and post intervention for the two ASD groups

Receptive language age change				**Group a**	**Group b**	**P value**
Yes	Cases		Count	7	19	
			%	23.3%	61.3%	0 .00*
No	Cases		Count	23	12	
			%	76.7%	38.7%	
Total	Cases		Count	30	31	
			%	100.0%	100.0%	

Chi-Square, P≤ 0.05 significant (*)

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Table 5: Comparison regarding expressive language age change pre and post intervention for the two ASD group

Expressive language age change among the intervention groups				**Group a**	**Group b**	**P value**
Yes		Cases	Count	11	21	
			%	36.7%	67.7%	0.01*
No		Cases	Count	19	10	
			%	63.3%	32.3%	
Total		Cases	Count	30	31	
			%	100.0%	100.0%	

Chi-Square, P≤ 0.05 significant (*)

Table 6: Comparison regarding total language age change pre and post intervention for the two ASD groups

Total language age change				**Group a**	**Group b**	**P value**
Yes		Cases	Count	10	24	
			%	33.3%	77.4%	0.00*
No		Cases	Count	20	7	
			%	66.7%	22.6%	
Total		Cases	Count	30	31	
			%	100.0%	100.0%	

Chi-Square, P≤ 0.05 significant (*)

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Table 7: Comparison regarding the language test results pre and post intervention for the two ASD groups

Language parameters	Pre intervention		Post intervention		P value
	Mean	SD	Mean	SD	
Receptive language age					
Group a	1.9	0.7	2.1	0.8	0.12
Group b	2.8	1.3	3.1	1.4	0.02*
Expressive language age					
Group a	1.8	0.6	1.9	0.7	0.12
Group b	2.5	1.1	2.8	1.5	0.01*
Total language age					
Group a	1.9	0.6	2.0	0.7	0.13
Group b	2.6	1.1	3.0	1.5	0.00*

Paired t-test, P≤ 0.05 significant (*)

DISCUSSION

ASD is considered to be one of the most common serious neurodevelopmental conditions. It mainly affects brain development and behaviour **(Vellingiri *et al.*, 2022)**. Well-known metabolic imbalances such as oxidative stress, and mitochondrial dysfunction are frequently reported in the individuals with ASD **(Ye *et al.*, 2017).** The majority of the research on the causes of autism over the past 25 years has underscored the genetic factors. Nevertheless, there is a growing awareness of the possible significance of environmental factors in the causes of ASD. The results of some recent familial and twin studies suggested that environmental influences may have a more significant influence than previously believed **(Bölte *et al.*,**

2019). The increased prevalence of ASD would recommend directing more attention to the alteration of environmental factors instead of continuing to focus on genetic factors which are associated with ASD **(El-Baz *et al.* , 2011).** An improved understanding of the underlying environmental risk factors can forge ahead the area of early interventions even before the appearance of overt symptoms in order to minimize the effect of risk on further development **(Elsabbagh, 2020).** The current study tried to tackle most of the environmental risk factors involved in ASD across different domains.

The results of the present study pointed to the presence of a higher risk of ASD in males than females. These findings were consistent with that reported by **(Itzchak *et al.*, 2010**) who detected that 81% of the participants were male autistic patients. Boys were found to have autism more than twice as likely as girls **(El-Baz *et al.*, 2011).** This may be due to an increase in the androgen biosynthesis as well as high levels of postnatal salivary and serum testosterone in young boys with ASD which affect gene transcription and expression **(Bölte *et al.*, 2019).**

Regarding maternal exposure to some chemicals during pregnancy, the current study found significant relation between ASD and exposure to cleaners and disinfectants. Vinyl floor was used more by cases in this study compared to controls. Similarly, the US National Research Council found that 3% of neurodevelopmental disorders are caused directly by environmental

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toxicants **(Amadi *et al.*, 2022).** Results of the present study are also consistent with **(Cheng *et al.*, 2019)** who found that phthalates that were found in cleaning products, disinfectants, vinyl floor can interfere with hormones important for brain development such as reproductive hormones and thyroid hormones. Antenatal exposure to phthalates was linked to social, linguistic, as well as cognitive problems as well as ASD. Additionally, because environmental toxins are hazardous and endocrine disruptors, the growing brain of the foetus is highly vulnerable to them. Antenatal exposure therefore has the greatest effect on the brain, ranging from subclinical impairment at low exposure levels to overt toxicity, resulting in a range of neurodevelopmental problems. This is especially true during the first trimester of pregnancy. It's interesting to note that some poisonous compounds easily pass the placental barrier and enter the developing brain, where they may cause negative effects **(Amadi *et al.*, 2022).** This could happen by means of processes that start outside the central nervous system. For example, immunological dysregulation, mitochondrial dysfunction, altered lipid metabolism, and oxidative stress. These events occur as a result of disrupted neuronal network synchronisation and epigenetic change **(Modabbernia *et al.*, 2017).**

Concerning the antenatal and perinatal risk factors in this study, a higher percentage of mothers had premature labour with statistically significant difference. In agreement with these results, evidence stated by **El-Baz *et al.***

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(2011) indicated that autistic cases had a considerably greater history of births at gestational ages less than 35 weeks compared to controls, this was explained by the effect of the stress of prematurity on a developing baby's brain, which may work together with a "biological vulnerability" to increase ASD in those children **(Crump *et al.*, 2021).** IVF was reported in cases included in this study more than controls. In agreement with this study, some studies reported associations between assisted reproductive technology (ART) and risk of ASD. On the other hand, other studies showed no association between ART and an increased risk of ASD. The possible influence of ART can be explained by its association with epigenetic alterations. However, its significance in relation to ASD remains unknown **(Modabbernia *et al.* ,2017).** In this study, some of the perinatal factors were associated with ASD, such as weight of the baby at birth and artificial ventilation in neonatal intensive care units. Children with ASD were found to be more prone to experience perinatal complications that stress the foetus. This is due to hypoxic-ischemic injury, which causes inflammation, disruption of signalling pathways, and ultimately damages neurons **(Elsabbagh, 2020).**

Similar to this, other studies found a higher risk for kids born in March. In contrast, it was shown that the risk of ASD was the highest for births in fall (i.e., those who conceived in winter) and lowest for births in spring (i.e., those who conceived in summer). Some investigations revealed absolutely no seasonal trends. Such differences among studies could stem from the

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variations in the environment that could be found in different countries. This highlights the importance of studying the risk factors of different populations with autism in different countries where climate and pollution percentages differ. Seasonal relations to ASD may be explained by the fact that the changing of seasons could be associated with multiple environmental factors relevant to foetal development which include nutrition, chemical exposure, and infections (**Lee *et al*., 2019).**

Older maternal age in this study may be a possible risk factor for ASD. This is consistent with previous research that found a higher incidence of ASD with older parental ages. However, some studies indicated that there was no connection with maternal age **(Lyall *et al.*, 2020).** The significant relationship between ageing and DNA methylation can be used to explain the maternal age contribution to ASD. As the mother's age rises, she is exposed to a wider range of environmental chemicals that cause DNA damage, hypermethylation, and germline mutations, which may have contributed to the development of ASD in offspring **(Vellingiri *et al.*, 2022).**

In this study, a higher percentage of cases had mothers and fathers with moderate educational levels, with statistically significant differences when compared to control subjects. Conversely, **El-Baz *et al*. (2011)** stated that most parents of autistic patients were professionals (doctors and engineers). Parental educational level has an important role in parent-child interaction and communication; awareness; coping; understanding of ASD; efficacy;

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confidence; early seeking medical advice; early intervention; parental quality of life.

In this study, the mothers of a higher percentage of cases migrated to another city or country compared to controls, with a statistically significant difference. In agreement with these results, researchers found a link between maternal immigration and the development of ASD **(Elsabbagh, 2020)**. The connection might be explained by maternal stress (caused by immigration), which has been connected to epigenetic changes. However, it is unclear how significant this link is with regard to ASD **(Modabbernia *et al.*, 2017)**.

Artificial milk feeding was used more frequently in this study's cases than in controls, with a statistically significant difference. **Ravi *et al.* (2016)** reported similarly that breast-feeding exclusively during the first 6 months of life reduces the risk of ASD. ASD was also linked to a lack of or a late start to breastfeeding **(Bölte *et al.*, 2019).** This relationship was explained by the deprivation of artificially fed children of oxytocin in breast milk, which has a vital role in promoting baby social neurodevelopment, social interaction, maternal connection, and social recognition **(Ravi *et al.*, 2016**). Moreover, feeding cow's milk formula can increase extracellular osmolality, which could lead to injury of the developing brain cells of infants **(Hahr, 2013).**

The results of the present study did not show any association between ASD and pregnancy interval, prenatal vitamins, maternal exposure to pesticides and smoking, aluminium cooking utensils, ionising radiation,

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electromagnetic radiation, distance from health care facilities, nearby gasoline stations, nearby mobile station, parental consanguinity and positive family history of ASD, mental retardation, psychiatric diseases, language disorders and genetic diseases, birth spacing, value of electric bill, house area, number of family members at home, numbers of room at home, number of children at home. However, these risk factors were linked to ASD in previous studies such as **Amadi *et al*. 2022, Bölte *et al.* 2019, El-Baz *et al.* 2011, Larsson *et al.* 2009, Lyall *et al*. 201, Modabbernia *et al*. 2017,** and **Ng *et al.* 2017.**

After determining the risk factors among the autistic participants, the participants with ASD were divided into 2 groups: Group a which included autistic children having less frequently reported risk factors and Group b which included autistic children having more frequently reported risk factors. There was non- significant statistical difference regarding the severity of autism between the two groups. Furthermore, the preliminary assessment of the language age in the autistic children revealed that all of them had delayed language development. Their language ages were less than what is expected from the children with the same chronological ages. There was statistically significant difference regarding receptive, expressive, as well as total language ages between the two ASD groups being higher in Group b yet, both groups manifested a language delay. These results agreed with previous evidence which indicated that language impairments are very common among individuals with ASD. Moreover, receptive, and expressive language

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development in ASD children differed from neurotypical children and those with developmental delay **(Hansen, *et al.*, 2014).** Group a was subjected to language therapy sessions only (twice weekly for three months), without dietary supplements and Group b received oral dietary supplements (one tablet twice daily for three months) together with language therapy in the same frequency as the other group.

After three months of intervention, the CARS scores were reduced significantly in both groups indicating a decreased severity of ASD. Despite the improvement of language in both groups, Group b's receptive and expressive language skills, in addition to total language age, significantly improved compared to Group a. The receptive language age, expressive language age, and total language age all differed significantly between the two groups. The phoniatric therapy targeted language, social and cognitive abilities which elevated their communication and other adaptive abilities. This could have led to reducing the frustrations they could face due to the inability to communicate with others. Furthermore, increasing the cognitive abilities could have led to raising their executive functions which enabled them to overcome the difficulties in different daily life situations they are exposed to. All these factors could have contributed to better adaptive skills of children with ASD which have led to lower CARS scores and higher language scores. These results were in accordance with **Eigsti and his colleagues (2011)** who documented that ASD children are able to develop

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language only with intensive therapy. Based on **Meguid *et al.* (2017)** findings**,** the serum folic acid and vitamin B12 were lower in ASD children compared to healthy controls with a significant statistical difference, and this may cause mitochondrial dysfunction, poor neural development, and the development of the symptoms of ASD **(Mahruba *et al.*, 2019).** Furthermore, folate, vitamins B6, and vitamin B12 improved ASD children's performance in hyperactivity, overall behaviour, tantrums, and receptive language. Furthermore, substantial food selectivity, feeding difficulties, improper diet, and/or gastrointestinal problems in children with ASD could be alleviated via the supplementation of essential nutrients such as folate, vitamins B6, and vitamin B12. These nutrients were recommended by some studies to reduce ASD symptoms **(Altun *et al*., 2018).** In agreement with these results, **Robea *et al*. (2020)** reported better response in overall rated ASD symptoms after administration of vitamin B12 injection for 8 weeks. Moreover, meclofenoxate was reported to have a role in neuronal protection, memory enhancement and anxiety reduction **(Malík and Tlustoš, 2022)**. Consequently, combined intensive therapy for ASD individuals in Group b could have helped in better improvement of autistic children due to the beneficial effect of phoniatric therapy and vitamins, nutrients in the dietary supplement on the rise of antioxidants, the methylation process, and on normalizing level of glutathione and some neurotransmitters.

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Finally, a direct causal link between the risks and the outcomes is challenging to demonstrate in disorders with complex underlying causes, such as ASD. Development over time is shaped by a person's biological, environmental, and social features, and as a result, consequences vary from person to person. To account for this complexity, two people with the same characteristics may respond differently, leading to alternate trajectories toward different outcomes **(Elsabbagh, 2020).**

CONCLUSIONS AND RECOMMENDATIONS

There were associations between a variety of environmental risk factors and ASD, indicating the contribution of environmental risks factors in ASD. Merging phoniatric therapy and dietary supplements for ASD children was found to be an effective management option despite the high frequency of risk factors among ASD participants. More in-depth research with larger sample size is recommended to further emphasize the link between environmental factors and ASD.

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ETHICAL CONSENT

Ethical approval was obtained from the Ethical Committee of the Faculty of Graduate Studies and Environmental Research. This study was also approved and carried out following the code of Ethics of the Medical Research Ethics Committee, National Research Centre, Egypt (registration number 20131). Patients were given a comprehensive explanation of the study and written informed consent was obtained from parents of all children involved in the present study.

CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

REFRENCES

Altun H., Kurutaş E., Şahin N., Güngör O., and Fındıklı E. (2018): The Levels of Vitamin D, Vitamin D Receptor, Homocysteine and Complex B Vitamin in Children with Autism Spectrum Disorders. Clin Psychopharmacol Neurosci. 30;16(4):383-390.

Amadi C., Orish C., Frazzoli C., and Orisakwe O. (2022): Association of autism with toxic metals: A systematic review of case-control studies. Pharmacology Biochemistry and Behavior.; 212:173313.

American Psychiatric Association. (2022): Diagnostic and statistical manual of mental disorders: DSM-5-TR (Fifth edition, text revision). American Psychiatric Association Publishing.

Baio J., Wiggins L., Christensen D., Maenner M., and Daniels J., and Warren Z. (2018): Prevalence of autism spectrum disorder among children aged 8 years – autism and developmental disabilities monitoring network. MMWR Surveill Summ ;67(6):1–23.

Bjørklund G., Waly M., Al-Farsi Y., Saad K., Dadar M., Rahman M., Elhoufey A., Chirumbolo S., Jóźwik-Pruska J. and Kałużna-Czaplińska J. (2019): The Role of Vitamins in Autism Spectrum Disorder: What Do We Know? Journal of Molecular Neuroscience ;67(3):373-387.

Bölte S., Girdler S., and Marschik P. (2019): The contribution of environmental exposure to the etiology of autism spectrum disorder. Cell Mol Life Sci.;76(7):1275-1297.

Campbell K., Hickman R., Fallin M., and Bakulski K. (2021): Prenatal exposure to metals and autism spectrum disorder: Current status and future directions. Current Opinion in Toxicology; 26: 39-48.

Cheng J., Eskenazi B., Widjaja F., Cordero J., and Hendren R. (2019): Improving autism perinatal risk factors: A systematic review. Medical hypotheses; 127 :26-33.

Crump C., Sundquist J., and Sundquist K. (2021): Preterm or Early Term Birth and Risk of Autism. Pediatrics.;148(3): e2020032300.

Eigsti, I., de Marchena A., Schuh J., and Kelley E. (2011). Language acquisition in autism spectrum disorders: A developmental review. Research in Autism Spectrum Disorders; 5: 681-691.

El-Baz. F., Ismael N., and Nour El-Din S. (2011): Risk factors for autism: An Egyptian study. The Egyptian Journal of Medical Human Genetics; 12: 31–38.

Elsabbagh M. (2020): Linking risk factors and outcomes in autism spectrum disorder: is there evidence for resilience? BMJ.; 368- l6880.

El-Sady S., El-Shoubary A., Hafez N., Abd El-Halim I., Ewis A., and Abu-Hassebab A. (2011): A Standardization, translation, and modification of the preschool language scale-4. Doctoral Thesis of Phoniatrics presented by A.Abu-Haseeba, faculty of medicine, Ain Shams University, Egypt.

Hahr J. (2013): Iatrogenic autism. Med Hypotheses; (2):251-2. PMID: 23706997.

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Nordahl-Hansen A., Kaale A., and Ulvund S. (2014): Language assessment in children with autism spectrum disorder: Concurrent validity between report-based assessments and direct tests. Research in Autism Spectrum Disorders; 8(9): 1100–1106

Itzchak E., Zachor D., and Assaf Harofeh A. (2010): Male:female ratio is related to autism spectrum disorder in the family and to maternal age. Harofeh Medical Center, Zerifin, Israe. Franklin Hall B Level 4 (Philadelphia Marriott Downtown l).

Larsson M., Weiss B., Janson S., Sundell J., and Bornehag C. (2009): Associations between indoor environmental factors and parental-reported autistic spectrum disorders in children 6-8 years of age. Neurotoxicology;30 (5): 822-831.

Lee B., Gross R., Francis R., Karlsson H., Schendel D., Sourander A., Reichenberg A., Parner E., Hornig M., Yaniv A., Leonard H., and Sandin S. (2019): Birth seasonality and risk of autism spectrum disorder. Eur J Epidemiol.;34(8):785-792.

Lord C., Rutter M., and Le Couteur A. (1994): Autism Diagnostic Interview-Revised: A revised Version of a Diagnostic Interview for Caregivers of Individuals with Possible Pervasive Developmental Disorders. Journal of Autism and Developmental Disorders; 24: 659-685.

Lyall K., Croen L., Daniels J., Fallin, M., Ladd-Acosta C., Lee B., Park B., Snyder N., Schendel D., Volk H., Windham G., and Newschaffer C. (2017): The Changing Epidemiology of Autism Spectrum Disorders. Annual review of public health; 38: 81–102.

Lyall K., Song L., Botteron K., Croen L., Dager S., Fallin M., Hazlett H., Kauffman E., Landa R., Ladd-Acosta C., Messinger D., Ozonoff S., Pandey J., Piven J., Schmidt R., Schultz R., Stone W., Newschaffer C., and Volk H. (2020): Parental age and autism in high-risk familie. Autism Research ;13: 998–1010.

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ISSN 1110-0826
ONLINE ISSN 2636 - 3178

Mahruba S., Begum S., Shahjadi S., Afroz S., Siddiqi U., and Parvin J. (2019): Serum vitamin B12 and folic acid status in autism spectrum disorder children. Journal of Bangladesh Society of Physiologist; 14(2): 43-47.

Malík M. and Tlustoš P. (2022): Nootropics as cognitive enhancers: types, dosage and side effects of smart drugs. Nutrients; 14(16):3367.

Meguid N., Anwar M., Bjørklund G., Hashish A., Chirumbolo S., Hemimi M., and Sultan E. (2017): Dietary adequacy of Egyptian children with autism spectrum disorder compared to healthy developing children. Metab brain dis; 32(2): 607-15.

Modabbernia A., Velthorst E., and Reichenberg A. (2017): Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. Molecular autism, 8, 13.

Ng M., de Montigny J., Ofner M., and Do M. (2017): Environmental factors associated with autism spectrum disorder: a scoping review for the years 2003-2013. Health Promot Chronic Dis Prev Can.;37(1):1-23.

Ravi S., Chandrasekaran V., Kattimani S., and Subramanian M. (2016): Maternal and birth risk factors for children screening positive for autism spectrum disorders on M-CHAT-R. Asian journal of psychiatry; 22 :17–21.

Robea M., Luca A., and Ciobica A. (2020): Relationship between vitamin deficiencies and co-occurring symptoms in autism spectrum disorder. Medicina; 56(5): 245.

Schopler E., Reichler R., & Rochen Renner B. (1988): The childhood autism rating scale.Western Psychological Services.

Vellingiri B., Mahalaxmi I., Ra N., Narayanasamy A., and Gopalakrishnan A. (2022): New insights into Epigenetics as an Influencer: An associative study between maternal prenatal factors in autism spectrum disorder (ASD). Neurology Perspectives.

Ye B., Leung A. and Wong M. (2017): The association of environmental toxicants and autism spectrum disorders in children. Environmental pollution ;1 (227):234-42.

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المسببات البيئية للتوحد وما يترتب عليها من تدخلات علاجية

شيرين عبد الحميد ناصر[١]– مصطفى حسن رجب[٢]– نيفين حسن نشأت[١]
رضوى إبراهيم علي حسن[٣]– نجوى عبد المجيد محمد[١]

١) قسم بحوث الأطفال ذوي الاحتياجات الخاصة، المركز القومي للبحوث ٢) قسم العلوم الطبية البيئية، كلية الدراسات العليا والبحوث البيئة، جامعة عين شمس ٣) قسم الصحة العامة وطب المجتمع، كلية الطب، القصر العيني

المستخلص

الخلفية : يساهم التفاعل بين العوامل الجينية والبيئية ونمط الحياة في حدوث التوحد. تصل نسبة مساهمة العوامل البيئية في حدوثه إلى ٥٠٪.

الهدف :تم استقصاء عوامل الخطر البيئية المحتملة المرتبطة بالتوحد ومقارنتها مع المجموعة الضابطة ،تم تطبيق بعض التدخلات العلاجية على المصابين بالتوحد ومقارنة تأثيرهاعلى شدة التوحد و قدراتهم اللغوية.

طريقة البحث: شملت الدراسة ٦١ طفلًا مصابًا بالتوحد قاموا بزيارة عيادة اضطراب طيف التوحد في الفترة بين سبتمبر ٢٠٢١ وحتى فبراير٢٠٢٢.،أعمارهم بين ٣ و ١٢ عاما. خضع الاطفال لمقياس تقييم التوحد في مرحلة الطفولة ومقياس اللغة العربية لمرحلة ما قبل المدرسة. تم اختيار المجموعة الضابطة (٦٢ طفلاً) من المتطوعين. خضع آباء الاطفال المصابين والمجموعة الضابطةلاستبيان لدراسة عوامل الخطر البيئية. تم تقسيم الأطفال المصابين بالتوحد إلى مجموعتين ، المجموعة الأولى (٣٠ طفلا) تلقت التأهيل التخاطبي فقط، أما المجموعة الثانية (٣١ طفلا) تلقت مكملات غذائية مع التأهيل التخاطبي لمدة ثلاثة أشهر.تم إعادة تقييم حالات التوحد باستخدام مقياس تقييم التوحد في مرحلة الطفولة ومقياس اللغة العربية لمرحلة ما قبل المدرسة في كلتا المجموعتين.

النتائج:أظهرت بعض عوامل الخطرالبيئية مثل تعرض الحوامل للمطهرات والمنظفات (٧٨,٧%)، المستوى التعليمي المتوسط للأم (39.3 %) والأب (47.5 %)،الحمل في الصيف (١٩,٦%)، الولادة في الربيع (١٩,٦%)، والولادة المبكرة (٩١,٨ %)،فروقا ذات دلالة إحصائية بين حالات التوحد والمجموعة الضابطة. بعد التدخل ،انخفضت شدة التوحد وكان هناك فرق معتد به إحصائيًا في عمراللغة الاستقبالي والتعبيري والكلي بين المجموعتين.

الخلاصة: هناك مجموعة متنوعة من عوامل الخطر البيئية المرتبطة بالتوحد. يُعد الجمع بين التأهيل التخاطبي والمكملات الغذائية تدخلاعلاجيا فعالا للأطفال المصابين بالتوحد.

الكلمات الرئيسية :التوحد ، البيئة ،عوامل الخطر،التدخل العلاجي.

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