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FAMILY HISTORY OF PSYCHOLOGICAL DISORDERS MODERATES THE ASSOCIATION BETWEEN PRENATAL MATERNAL STRESS AND RISK OF AUTISM

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Abstract

The increase in number of cases with autism spectrum disorder (ASD) requires further investigation to the etiology of it, which is not fully understood. It is suggested that children who are vulnerable to psychological disorders more likely to develop ASD when experience prenatally stress than children who do not. The researcher sought to conduct a natural experiment by collecting data from a sample derived from population lived in a region that experienced number of the worst civil wars in Libya. The sample consisted of 38 parents of children with ASD and 40 parents of typical children living in south Tripoli. These children were in utero during the civil wars that happened in 2011, 2014, and 2019. A case-control study was carried out comparing the two groups in terms of family history of psychological disorders. The child's sex, parents' age, and birth complications were controlled. Conditional logistic regression models were utilized to examine whether family history of psychological disorders predicted ASD. Findings from this study indicated that: children with ASD were more likely to have relatives with psychological disorders than those without ASD; the proportion of relatives with psychological disorders was significantly higher among children with ASD than those without ASD; there was significant associations between ASD and parents', grandparents', uncles', aunts' psychological disorders, having a first-degree relative suffers from a psychological disorder was associated with increase in odds of ASD. ,having second-degree relatives with a psychological disorder was significantly associated with increase odds of ASD, psychological disorders in first degree relatives and second degree relatives had comparable effect on the risk of ASD, when first degree relatives and second degree relatives affected the risk of ASD did not increase compared to the presence of a psychological disorder in either relatives.

Key words: Autism Spectrum Disorder, Libya, Etiology, Risk factor, Natural Experiment.

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Introduction

The term autism comes from the Greek word"autós", which means self. Eugene Bleuler is the first to use this term while defining the symptoms of schizophrenia (Bleuler, 1950 [1911]). Leo Kanner and Hans Asperger used the term autism in the early forties to introduce a syndrome in children characterized by difficulties related to their relationships with others and their high sensitivity to changes in the environment around them (Kanner, 1943; Asperger, 1944). Currently and according to the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V), the term autism spectrum disorders (ASD) fall under the umbrella of neurodevelopmental disorders. DSM-V set some key features to diagnose ASD. These include impairments in social interaction, and verbal and nonverbal communication and restricted, repetitive patterns of behavior, interest, or activities. These behaviors difficulty range from mild to severe and must be manifest in the early age of development (American Psychiatric Association-APA,2013). ASD may be associated with a combination of psychological and physiological impairments such as intellectual disability, attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, and epilepsy (Croen, 2015; Matson &Cervantes, 2014).

In 2020, the overall prevalence of ASD per 1,000 children aged 8 years is estimated to be 27.6, (one in every 36 children) though there were differences between the 11 Autism and Developmental Disabilities Monitoring (ADDM) Network sites. The prevalence ratio between boys to girls was 3.8, with the estimated overall prevalence of ASD in boys 43.0 and 11.4 in girls. Here should be notice that the estimated overall prevalence was sharply increased comparing to previous estimates done by the ADDM Network (CDC, 2023). This increase in the proportion of indivduals diagnosed with ASD along with their need most of them for life-long care and support, results in increase in associated cost for caring them. For example, The estimated cost of ASD in the United States exceeds $2.4 million per individual (Olusanya et al., 2018); and by 2025 it is predicted that the cost of ASD will increase to over $450 billion (Leigh & Du, 2015). In the United Kingdom the annual estimated cost associated with ASD was £32 billion (Lemmi, Knapp, & Ragan, 2017).

This rise in prevalence of ASD and related increase in financial cost requires further investigation to the etiology of it, which is not fully understood. Present consensus suggests an interaction between environmental and genetic factors that contribute to incidence of ASD (Jeste, & Geschwind, 2014, Tick B, et al, 2016, Lyall, 2017). Prenatal stressful events may be the most important environmental factor that have been identified as a risk factor for developing ASD. Family history of psychological disorders also have been found to be important risk factor in developing ASD.

A growing line of research indicates that prenatal stress can have negative effects on embryo/fetus development. Prenatal stress could be natural disaster, wars, or daily life problems. In a study conducted by Beversdorf et al. (2005) compared surveys completed by 188 mothers of children with ASD, 202 mothers of typical children, and 92 mothers of children with Down syndrome regarding the incidence of presence of stressful events during their

pregnancies. Findings of this study showed that mothers of children with ASD reported significantly more stressful events during their pregnancies than did mothers of children with Down syndrome and mothers of typical children. This results have been confirmed by a Swedish registry study conducted by Class et al (2014), showing a significant association between prenatal stress exposure and incidence of ASD. A prospective study support the association between prenatal stress and ASD. The sample consisted of 89 children who were in utero during the 1998 Quebec Ice Storm. Their mothers filled in questionnaires related to stress straightforward after the storm, and ASD screen tool for their children when they are at 6.6 years. The findings showed significant association between objective and subjective stress and ASD traits and ASD prevalence (Walder, et al,2014). The relation between prenatal stress and incidence of ASD has been also reported by Abdi, et al (2016). In this control-study, mothers of children with ASD, and typically developing children were compared regarding the frequency of prenatal stressful life events measured by the Social Readjustment Rating Scale. A higher frequency of stressful life events was found among the mothers of children with ASD than the mothers of neurotypical children. A retrospective study conformed the associations between exposure to prenatal stressful life events experienced during pregnancy and onset of ASD. Varcin et al (2017) examined relations between the severity of ASD-associated symptoms and prenatal stressful life events. Findings showed that experiencing stressful events during pregnancy significantly predicted ASD-related symptom severity and communication abilities. Follow-up analyses revealed that multiple prenatal stressful life events significantly increase ASD symptoms severity. Similar findings have been reported by independent group, showing significant association between the moderate severity of prenatal stressful life events and the severity of ASD compared to no stress (Alamoudi et al,2023). Furthermore, results from A prospective cohort study over a 3- year period showed that prenatal adverse psychosocial factors were significantly correlated with risk of ASD (Seebeck, Sznajder, & Kjerulff, 2023). On the other hand, two population-based studies did not find an association between incidence of ASD and prenatal stressful events (Rai et al., 2012) or maternal bereavement (Li et al., 2009). These conflict findings may be explained by another factor mediates the relation between prenatal stress exposure and incidence of ASD. Prenatal stressors may not result in incidence of ASD in all children, instead prenatal stressors may cause ASD in some cases. Family history of psychological disorders of interest.

There has been accumulating body of research found significant association between family history of psychological disorders and the risk for developing ASD. Bolton et al (1998) compared family history of psychological disorders in 99 children with ASD, and 36 children with Down syndrome probands. They found family history of motor tics, OCD and affective disorders more common among children with ASD comparing to children with Down syndrome. The researchers concluded that family history of OCD may be the risk factor for incidence of ASD. Piven, & Palmer (1999) compared some axis I psychiatric disorders in families who have at least 2 children with ASD to matched families who have children with Down syndrome. They found higher ratio among parents and relatives of children with ASD

probands than parents and relatives of children with Down syndrome probands. Larson et al (2005) in a prospective cohort study compered 698 children with ASD with individually matched 25 controls in terms of sex, birth year, and age. Findings revealed significant association between risk of ASD and parental history of schizophrenia-like psychosis and affective disorder. In population- cohort study conducted by Jokiranta, et al (2013) found significant association between parental histories of schizophrenia, affective psychological disorders, and non- affective disorders, and risk of ASD. The association between family history of psychological disorders and risk of ASD was also supported by Xie, et al (2019) and Grifa (2020).

In all of the studies linking maternal prenatal stress and family history of psychological disorders and developing ASD there were children typically developed. Furthermore, the mechanism underling the relationship whether between prenatal maternal stress or family history of psychological disorders and incidence of ASD has not been fully explained. This study is the first (to my knowledge) to investigate more than one risk factor linked to developing ASD. Taken together, it is hypothesized that family history of psychological disorders may moderate the association between prenatal maternal stress and risk of ASD.

Existing research focused on examining the association between prenatal stress and risk of ASD or history of psychological disorders and risk of ASD. This study is the first to examine whether children who have history of psychological disorders and experienced prenatal maternal stress are more likely to develop ASD than children exposed to prenatal maternal stress but do not have history of psychological disorders. In addition, most studies followed retrospective procedure that make it difficult to determine whether the effects of stressful events because of the objective hardship experienced due to the event or to the mother's tendency to distress. Also, in retrospective studies reports that provided by mother may be biased because she may seek for causes of her child condition or because of postnatal stressful events. The researcher sought to conduct natural experiment by collecting data from a sample derived from population lived in a region that experienced number of the worst civil wars in Libya occurred on 2011, 2014, and 2019, when some people lost their relatives, and the majority of them lost their properties, and became displaced for a year or more without any psychosocial support.

Material and Methods

Study design

The sample consisted of 38 parents of children with ASD and 40 parents of typical children living in south Tripoli (Libya). These children were in utero during the civil wars that happened in 2011, 2014 and 2019. A case-control study was carried out comparing the two groups in terms of family history of psychological disorders. The child's sex and parents' age, and birth complications were controlled. Inclusion criteria included children living in south Tripoli, there were in utero during one of the civil wars, diagnosed with ASD or typically

developed, and living with parents. Exclusion criteria included children not living in south Tripoli, were not in utero during one of the civil wars and been with another neurodevelopmental disorders. Parents' cases were recruited through electronic advertisements posted on social media platforms. All ASD cases already had their official diagnosis that usually done by a child neurology, child or adolescent psychiatry or pediatrics. While the typical children were elected from schools and kindergarten that located in south Tripoli . The study carried out between 21 March 2021and 13 August 2023.

Ethical considerations:

Subjects in the study voluntary participated and written informed consent was obtained from all the participants who were assured that their information would be treated in the strictest confidence and would be safeguarded. The consent form further stressed that the obtained data will be used for scientific purpose only.

Research tool

A questionnaire was developed to assess children and parents demographic data, general information, and family socioeconomic status (SES).

Data Collection Procedure

Initially, participants were given the consent form to read and sign. Then, children and parents demographic data was collected. This data included children' sex, parents' and children' age, and whether there were birth complications. Data collection was conducted through semi-structured interviews utilizing an interview guide with open-ended questions that was developed to collect data regarding family history of psychological disorders. Parents were asked to determine whether there were relatives had been diagnosed or suffered from any psychological disorders for maternal and paternal histories. Relatives may include the child aunts, uncles, cousins and grandparents. The interviews lasted between 30 and 45 min in average.

Statistical Analysis

Parental age and birth complications were examined by using chi-square and t test. Differences were considered significant at $p<0.05$ (two-tailed). Conditional logistic regression analysis was performed to examine the association between diagnosing relatives with any psychological disorders and the likelihood of the ASD. Odds ratios (ORs) with 95 % confidence intervals (CIs) were utilized as a measure of association. It was referred to x2-test to calculate P-values a significance threshold of $p < 0.05$. The model was adjusted for maternal and paternal age and birth complications. The statistical analyses were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

Results

Participants' demographic characteristics

In ASD group, females (n=8) represented 21% of the sample, while males (n=30) represented 78.9%. In control group females (n=10) represented (25%), and males (n=30) were 75%. Both conditions were aged 4-11 years. The mean age of children with ASD was 7.3 years (standard deviation 3.5 years), while the mean age of children without ASD was 8.1 years (standard deviation 4 years). There was no significant difference between maternal age at (t=1.522, df = 76, p=0.32), paternal age (t= 1.157,df= 76, p=.167), birth complications (x2= 3.35,df=1, p=0.22), among cases and controls.

The logistic regression model was statistically significant, x2 = 27.402 df= 2, p < .0005. The model explained 40.0% (Nagelkerke R2) of the variance in ASD and correctly classified 71.0% of cases.

Psychiatric Disorder in Relatives

Because many parents could not determine the exact diagnosis for psychological disorders that their children's relatives suffer from, statistical analysis included psychological disorders as a hole. As shown in Table 1, Children with ASD were more likely to have relatives with psychological disorders than those without ASD (P values from x2 test for equality of proportions range from < 0.05 to <.001). In addition, the proportion of relatives with psychological disorders was significantly higher among children with ASD than those without ASD. In that, children with ASD (64.21%) had higher proportion of relatives suffer from psychological disorders than those in the control group (15%). Prevalence of Psychological disorders among first degree relatives and second degree relatives for children with ASD (23%, 26.9% respectively) was higher than that in the controls (33.33%). Additionally, there was a highly significant association between the risk of ASD and family history of psychological disorders (p=0.000). Moreover, proportions of psychological disorders in parents (31.58%), grandparents (10.5%), and uncles (2.6%) of children with ASD were higher than that in children without ASD (5%, 2.5%, 7.5% respectively). Table 1 shows these findings.

Table 1: Frequencies and percentages for psychological disorders among first and second degree relatives

Psychological disorders	ASD cases n (%)	Control n (%)
in any relatives	26 (64.21%)	6(15%)
in first degree relatives	12 (23%)	2(33.33%)
Parents	12 (23%)	2(33.33%)
Full siblings	-	-
in second degree relatives	14 (26.9%)	4(66.66%)
Grandparents	4 (10.5%	1(2.5. %)
Uncles or aunts	10 (15.3)	3(50%)

Additionally, first and second degree relatives were strongly associated with ASD. Findings showed that ASD was more common between first degree relatives of a child with ASD compering to first degree relatives of a child without ASD ($p<0.01$). In addition, ASD was more common among second degree relatives of a child with ASD than second degree relatives of a child without ASD ($p<0.01$). Table 2 demonstrates these results.

Table 2: OR's with 95 % CI's for first and second degree relatives' psychological disorders

relatives	ASD cases OR	95%CI
First degree	2.5	1.9,3.2***
Second degree	1.7	1.4,2.0***

*** $p<0.001$

Findings from this study also showed significant associations between ASD and parents', grandparents', uncles', aunts' psychological disorders. Having a first-degree relative suffers from a psychological disorder was associated with increase in odds of ASD compared with those with unaffected first-degree relatives. Furthermore, results indicated that having second-degree relatives with a psychological disorder was significantly associated with increase odds of ASD. An additional analysis was carried out to examine the risk of ASD when psychological disorders in relative separately reported as only first degree relatives, only second degree relatives, either relatives degree, and both relatives degree. It has been found that psychological disorders in first degree relatives and second degree relatives had comparable effect on the risk of ASD. Furthermore, when first degree relatives and second degree relatives affected the risk of ASD (1.3 [0.8,2.2[) did not increase significantly compared to the presence of a psychological disorder in either relatives. Table 3 illustrates these findings.

Table3: Frequencies, percentages and OR's with 95 % CI's for first degree relatives, second degree relatives, either relatives degree, both relatives degree

Psychological disorders	ASD cases n (%)	Control n(%)	OR (95%CI)
only in the first degree relatives	9 (7.6 %)	2(4.1%)	1.8(1.6,2.2)*
only in the second degree relatives	12(9.8%)	3(5%)	1.6(1.5,1.8)*
in either relatives	20 (17.2%)	5(6.7%)	1.7(1.6,1.9)*
in both relatives	4(1%)	1(.4%)	1.9(1.8,2.4)*

*p < 0

Discussion

The present study aimed at examining the association between family history of psychological disorders and the incidence of ASD among children who exposed to prenatal stress. Main findings from this study are: (1) Children with ASD were more likely to have relatives with psychological disorders than those without ASD; (2) the proportion of relatives with psychological disorders was significantly higher among children with ASD than those without ASD; (3) there were significant associations between odds of ASD and parents', grandparents', uncles', aunts' psychological disorders; (4) having a first degree relative suffers from psychological disorders was associated with increase in odds of ASD compared with those with unaffected first-degree relatives; (5) having second degree relatives with psychological disorders was significantly associated with increase odds of ASD; psychological disorders in first degree relatives and second degree relatives had comparable effect on the risk of ASD., when first degree relatives and second degree relatives affected the risk of ASD did not increase significantly compared to the presence of a psychological disorder in either relatives.

To my knowledge, this is the first study in examining the most important two factors linked to incidence of ASD. Participants of the study experienced prenatal stress; ASD cases were compered to controls in terms of family history of psychological disorders. Findings of this study in line with previous studies found linkage between prenatal stress and odds of ASD (Ward,1990; Beversdorf et al, 2005; Varcin, et al, 2017; Alamoudi, et al, 2023; Seebeck, Sznajder, & Kjerulff, 2023) .These studies had several limitations include: (1) depending on retrospective recall that may lead to biased information, (2) mothers of children with ASD may frequently experience stressful life events even they are not pregnant, (3) as a result they may expose to stressor in all pregnancies regardless their children have ASD, (4) there were several confounding factors that did not controlled such as problems related to postnatal environments (Kinney, et al, 2008). Present study considered these limitations by using design overcame these difficulties. This study utilized natural experiment (real stressor), so maternal

provided data did not rely on retrospective recall. Findings from this study consistent with previous findings used natural disaster (Kinney, et al, 2008; Walder, 2014). However, this finding does not agree with Raj et al (2012), and Liet et al, (2009). This conflict result may be because of another factor mediate the relation between prenatal stress and risk of ASD. Findings from this study consistent with previous findings linking odds of ASD and psychological disorders on parents (Jokiranta, et al, 2013), first-degree relatives (Sullivan, et al, 2012), and second degree relatives (Xie, et al, 2019).Also findings of this study agree with prior findings revealing associations between ASD and affective disorders in relatives (Bolton et al., 1998; Piven and Palmer, 1999; DeLong et al., 2002; Cederlund and Gillberg, 2004; Ghaziuddin, 2005; Larsson et al., 2005; Daniels et al., 2008; Morgan et al., 2012).

Following is the suggested model that may explain the underling mechanism of the interaction of prenatal maternal stress and family history of psychological disorders and incidence of ASD.

It is suggested that children who are vulnerable to psychological disorders more likely to develop ASD when experience prenatally stress than children who do not. In other words, embryo /fetus who is in a high risk to develop psychological disorders may experience cortisol reactive when he/she exposed to prenatal maternal stress. It has been found that individuals at ultra risk for psychological disorders manifest cortisol reactivity than healthy people after applying different kinds of stressors ((Mittal and Walker, 2011, Walker et al., 2013, Karanikas and Garyfallos, 2014; Lee, Park, & Kim, 2023). Also patients surfing from psychosis at any stage showed cortisol reactivity than healthy people (Corcoran et al, 2012; Mizrahi, et al, 2012; Pruessner, et al, 2013; Walker, et al, 2013; Day, et al;2014).

Cortisol hormone is regulated by the hypothalamic-pituitary-adrenal (HPA) axis (Makris, et al, 2023). Reactivation of cortisol reflects the HPA axis dysfunction (Herman, et al, 2016). Importantly, dysfunction of the (HPA) axis can alter structure and function in many regions in the brain (McEwen and Morrison, 2013; Kim et al., 2015; Ressler, 2010; Buss, et al, 2013; Pagliaccio, 2014; McEwen,. Nasca,,& Gray, 2016). This may be lead to substantial neurological and developmental deficits in early embryonic brain development, which may explain ASD-related features (Mennes et al. 2006). Consequently, reactivation of cortisol that resulted from (HPA) axis dysfunction suggest that an atypical development of brain may be involved in the etiological pathway of ASD. These errors may be the consequences of prenatal stressful events that experienced from embryo/fetus who is predisposed to develop psychological disorders. It has been found that HPA axis dysfunction that resulted from stress was significantly associated to mood disorders (Stephens, M.A.C.; Wand, 2012).

Limitations:

The present study is the first to examine the association between family history of psychological disorders and incidence of ASD among children experienced prenatal maternal stress. One limitation of this study is that there were not official record for familial aggregation

for psychological disorders this may make it difficult to ascertain for existing any psychological disorders that may not reported because of social stigma. A study is urgently needed to confirm findings of this study and to investigate psychological disorders beyond first and second degrees. Such research can be done in countries where recorded data systems exist for mental health.

Conclusions

This study provides evidence that family history of psychological disorders may mediate the association between prenatal stress exposure and incidence of ASD. This suggests an interaction between environmental and genetic factors that contribute to ASD incidence. Consequently, this finding highlights the important role of environmental risk factor which is crucial in early intervention or for developing strategies that may prevent incidence of ASD in the cases that genetically vulnerable.

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