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ORIGINAL ARTICLE

Prenatal, perinatal, postnatal risk factors, and excess screen time in autism spectrum disorder

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Abstract

Background: The aim of this study was to investigate pre-, peri-, and postnatal factors, screen time in a group of patients with autism spectrum disorder (ASD) and age and sex-matched clinical controls to evaluate risk factors specific to ASD.

Methods: The study included 211 ASD patients (177 boys, 34 girls; mean age 44.3 ± 13.0 months) and 241 (190 boys, 51 girls; mean age 44.6 ± 14.1 months) age and sex group matched clinical controls. Non-ASD diagnoses were expressive language disorder (n = 135, 56.0%), intellectual disability (n = 15, 6.2%), attention deficit-hyperactivity disorder (n = 6, 2.4%), oppositional disorder (n = 6, 2.4%), and other behavioral or emotional problems (no diagnosis; n = 79, 32.8%). A sociodemographic data form was used to collect data regarding pre-, peri-, and postnatal factors and total daily screen exposure.

Results: According to our findings, maternal severe psychological stress and depression during pregnancy, and maternal postpartum depression were more frequent in the ASD group (p = 0.005, p = 0.035, and p = 0.001 respectively). There was a statistically significant difference between groups with regards to maternal any medication use during pregnancy (p = 0.004). The mean duration of daily screen exposure was higher in the ASD group (9.90 ± 5.10 h) compared to non-ASD children (4.46 ± 3.40 h; p < 0.001). A ROC curve showed that 8.5 h and above total daily screen exposure (AUC = 0.808 [95% CI: 0.769–0.848], p < 0.001; 55% sensitivity, 90.5% specificity) is likely to be associated with increased risk for ASD.

Conclusion: Our study suggests that prenatal maternal psychological stress, prenatal and postpartum depression, and excess exposure to screen might be related to an increased risk for ASD.

KEYWORDS
autism, perinatal, postnatal, prenatal, screen exposure

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and interactions, stereotypic behaviors, and restricted interests beginning in early childhood.[1] ASD is the leading cause of disability in children under 5 years of age and accounted for 7.7 million disability adjusted life years in 2010.[2] The global prevalence estimate of ASD has increased from 0.6% to 1%–2% since 2012, despite being highly variable across different sites of the world.[3–6]

Although no clear pathogenesis has so far been identified, a substantial body of evidence has revealed that both genetic and environmental factors interact in the etiology of ASD. A metanalysis of twin studies suggests a heritability estimate of 64%–91%.[7] Genetic factors include copy number variations, point mutations, and translocations involved in neurodevelopment, neural communication, and social interaction. DNA methylation, histone modification, and noncoding RNA are among the epigenetic factors suggested to have an important role in the pathogenesis of ASD.[8]

To date, a few meta-analyses on pre-, peri- and postnatal environmental risk factors associated with ASD have been conducted using both different and overlapping data.[9–13] Kolevzon et al.[10] included seven studies in their meta-analysis, of those four were prospective, population-based cohort studies, and the others were retrospective. The authors suggested that advanced parental age, maternal birthplace outside of North America and Europe, low birthweight, preterm delivery, and intrapartum hypoxia were potential risk factors for autism. Gardener et al. conducted a meta-analysis of studies through March 2007 performing less strict inclusion criteria. Results have been published in two different articles.[12,13] Associated prenatal risk factors were advanced parental age at birth, maternal prenatal medication use, bleeding, gestational diabetes, being first born versus third or later, and having a mother born abroad.[12] Peri- and neonatal risk factors associated with increased risk of autism were cesarean delivery, abnormal presentation, umbilical-cord complications, fetal distress, birth injury or trauma, multiple birth, maternal hemorrhage, summer birth, low birthweight, small for gestational age, congenital malformation, low 5-min Apgar score, feeding difficulties, meconium aspiration, neonatal anemia, ABO or Rh incompatibility, and hyperbilirubinemia.[13] Guinchat et al.[11] performed a meta-analysis of 85 case–control and population-based studies. The authors incorporated the results with regard to pregnancy risk factors provided by Gardener et al.[12] into their review with the addition of data from articles later published. Bleeding and maternal medication use but not gestational diabetes were confirmed as ASD related risk factors after the inclusion of recent data.[11] Peri- and postnatal risk factors which emerged in the meta-analysis by Guinchat et al.[11] were generally consistent with the review by Gardener et al.[13] The most recent of these meta-analyses published by Wang et al.[9] pooled data from 12 case control and five cohort studies and favored advanced parental age, parental race: White and Asian, gestational hypertension, gestational diabetes, maternal and paternal education college graduate+, threatened abortion, antepartum hemorrhage, prenatal infections, maternal autoimmune disease as prenatal risk factors; preterm birth, cesarean delivery, gestation age ≤36 weeks, spontaneous labor, induced labor, no labor, breech presentation, preeclampsia, fetal distress as perinatal risk factors; low birthweight, postpartum hemorrhage, male gender, and brain anomaly as postnatal risk factors related to ASD. When a subgroup analysis based on inclusion criteria was performed, low Apgar score was identified as a risk factor in the studies using DSM − 4/5. Mother's country of birth outside Europe or North America was not confirmed as a risk factor for ASD by Wang et al.[9]

The Center for Disease Control and Prevention reported 2.5 times increase in the prevalence estimate of ASD from 2000 to 2014 in USA.[5] It has not yet been clarified whether this could be attributable to changes in diagnostic criteria, better diagnostic tools, better identification and screening methods, younger age at diagnosis, inclusion of milder cases, and increased public and clinician's awareness or there is a true increase in the risk of ASD.[14–16] Albeit controversial, the increase in the prevalence of ASD redirects researchers' attention to environmental factors. Among those, excess screen time is a growing concern amongst clinicians since it is known to have negative effects on early learning and development. A number of studies have shown that children and adolescents with ASD are exposed to more screen time than their typically developing peers or other clinical groups and that the exposure starts at a younger age.[17] Therefore, in this study we aimed to investigate pre-, peri-, and postnatal factors, and screen time in a group of patients with ASD and age and sex matched clinical controls to evaluate the risk factors specific to ASD.

METHODS

Participants

This study involved 211 ASD patients with ages ranging from 2 to 6 years old and 241 age and sex group matched clinical controls admitted to Bakirkoy Research and Training Hospital for Mental Health and Neurological Disorders, Istanbul, Turkey, Child and Adolescent Psychiatry Department between April and December 2018. An ASD diagnosis was made using DSM-5 criteria[1] and confirmed by child psychiatrists with at least 5 years of experience. The assessment was based on clinical interview with the parents, direct examination of the child and the evaluation of global development of the child by standardized instruments for the age group. To eliminate possible recalling problems study included only patients who were diagnosed within the last 6 months and aged between 2 and 6. Children under the age of 2 were not included to avoid misdiagnosis. Exclusion criteria for the study and the control group were having a visual or hearing impairment, and any genetic or neurological disorder (children with epileptic disorders were included).

Materials

Sociodemographic data form

A sociodemographic data form was created by the authors to collect data. The data form was comprised of questions with regard to parental factors including maternal and paternal age, maternal and paternal education, maternal and paternal lifetime psychiatric diagnosis; prenatal factors such as risk of miscarriage, birth order (first vs. later born), maternal hypertension, gestational diabetes, maternal thyroid dysfunction, maternal depression, severe psychological stress, maternal medication use, and cigarette smoking during pregnancy, peri- and postnatal factors such as any problem in the delivery, gestational age, birthweight, incubator need or intensive care unit treatment, neonatal jaundice, phototherapy need for neonatal jaundice, epileptic seizure of the child, maternal postpartum depression, frequent change in the caretaker (more than 3 caretakers in the first 2 years), and daily total screen time (ST). ST refers to time spent on visual screen-based technologies including televisions, computers/tablets, smart phones, and gaming devices. Both active and passive screen exposure (e.g., background TV watching) were calculated by asking parents how many hours a day their child was exposed to screen.

The data form was completed by the researchers via directing question to the parents during the clinical interviews.

Ethics

The study protocol has been approved by the Medical Ethics Committee of the Bakirkoy Training and Research Hospital for Psychiatric and Neurological Disorders. The procedures followed in this study were in accordance with the ethical standards of the medical ethics committee and with the Helsinki Declaration of 1964, as revised in 2000.[18] An informed consent was obtained from the parents prior to participation in the study.

Statistical analysis

Descriptive statistics were calculated using the Statistical Package for the Social Sciences for Windows (SPSS) program, version 17. Demographic data are reported as mean ± standard deviation, median (range), number, and percentage. Univariate analysis was performed for demographic and clinical characteristics of the patients to predict our groups using student-*T* test, Chi-square test, or Fisher's exact test as appropriate for individual variables. $p < 0.05$ was considered statistically significant. Analysis of the discriminatory ability of two groups were performed using the C statistic comparison with receiver operating characteristic (ROC) curves. The best cutoff value for the daily screen time was derived, having maximum accuracy and minimal weighted error.

RESULTS

In total, 452 children aged 2 to 6 were included in the study. A total of 211 children (177 boys, 34 girls; mean age 44.3 ± 13.0 months) were diagnosed with ASD and 241 (190 boys, 51 girls; mean age 44.6 ± 14.1 months) were non-ASD children. Non-ASD diagnoses were expressive language disorder (n = 135, 56.0%), intellectual disability (n = 15, 6.2%), attention deficit-hyperactivity disorder (n = 6, 2.4%), oppositional disorder (n = 6, 2.4%), and other behavioral or emotional problems (no diagnosis; n = 79, 32.8%). There was no significant difference between ASD and non-ASD group with regards to age ($p = 0.587$) and sex ($p = 0.186$).

Comparison of parental characteristics between ASD and non-ASD groups is shown in Table 1. Comparisons of ASD and Non-ASD groups regarding prenatal factors and peri- postnatal factors are shown in Tables 2 and 3, respectively. Maternal severe psychological stress and depression during pregnancy, and maternal postpartum depression were more frequent in the ASD group ($p = 0.005$, $p = 0.035$, and $p = 0.001$, respectively). There was a statistically significant difference between groups with regards to maternal any medication use during pregnancy ($p = 0.004$).

A statistically significant difference was found between ASD and Non-ASD groups concerning total daily screen time. The mean duration of daily screen exposure (9.90 ± 5.10 h) was higher in the ASD group compared to non-ASD children, of those mean total daily screen exposure was 4.46 ± 3.40 h ($p < 0.001$). Receiver operating curve (ROC) showed that 8.5 h and above total daily screen exposure (AUC = 0.808 [95% CI: 0.769–0.848],

TABLE 1 Comparison of parental characteristics

	ASD (n=211)	Non-ASD (n=241)	*p*-value
Mother's age at birth (year ± SD)	28.60 ± 5.74	28.45 ± 5.56	0.780
Father's age at birth (year ± SD)	32.65 ± 5.85	32.27 ± 5.88	0.492
Mother's education level (year ± SD)	8.23 ± 4.14	8.65 ± 3.84	0.264
Father's education level (year ± SD)	8.90 ± 3.71	9.45 ± 3.60	0.106
Lifetime psychiatric disorder diagnosis of mother (n, [%])	37 (17.5%)	30 (12.4%)	0.145
Lifetime psychiatric disorder diagnosis of father (n, [%])	7 (3.3%)	7 (2.9%)	0.794

Abbreviation: ASD, autism spectrum disorders.

TABLE 2 Comparison of prenatal factors

	ASD (n=211)	Non-ASD (n=241)	*p*-value
Risk of miscarriage (*n*, [%])	24 (11.4%)	17 (7.1%)	0.139
First born child (*n*, [%])	96 (45.5%)	112 (46.5%)	0.850
Maternal hypertension during pregnancy (*n*, [%])	7 (3.3%)	16 (6.6%)	0.134
Maternal gestational diabetes (*n*, [%])	15 (7.1%)	15 (6.2%)	0.710
Thyroid dysfunction of the mother during pregnancy (*n*, [%])	8 (3.8%)	5 (2.1%)	0.399
Severe psychological stress of the mother during pregnancy (*n*, [%])	12 (5.7%)	2 (0.8%)	**0.005***
Depression of the mother during pregnancy (*n*, [%])	11 (5.2%)	4 (1.7%)	**0.035***
Smoking of the mother during pregnancy (*n*, [%])	28 (13.3%)	33 (13.7%)	1.000
Any medication use by the mother during pregnancy (*n*, [%])	44 (20.9%)	26 (10.8%)	**0.004***

Abbreviation: ASD, autism spectrum disorders.

*$p < 0.05$.

Statsitically significant p ($p < 0.05$) values are in bold.

TABLE 3 Comparison of peri- and postnatal factors

	ASD (n=211)	Non-ASD (n=241)	*p*-value
Any problem during delivery (*n*, [%])	33 (15.6%)	23 (9.5%)	0.062
Preterm birth (gestation week < 38) (*n*, [%])	23 (10.9%)	35 (14.5%)	0.324
Low birthweight (2500 < g) (*n*, [%])	14 (6.7%)	25 (10.5%)	0.180
Incubator need or intensive care unit stay (*n*, [%])	48 (22.7%)	45 (18.7%)	0.296
Neonatal jaundice (*n*, [%])	76 (36.4%)	81 (33.6%)	0.553
Phototherapy need for neonatal jaundice (*n*, [%])	26 (12.4%)	29 (12%)	1.000
Epileptic seizure of the child (*n*, [%])	11 (5.2%)	10 (4.1%)	0.658
Maternal postpartum depression (*n*, [%])	77 (36.5%)	53 (22%)	**0.001***
Frequent change in the caretaker (*n*, [%])	3 (1.4%)	11 (4.6%)	0.054
Total daily screen time (h ± SD)	9.90 ± 5.10	4.46 ± 3.40	**<0.001***

Abbreviation: ASD, autism spectrum disorders.

*$p < 0.05$.

Statsitically significant p ($p < 0.05$) values are in bold.

$p < 0.001$; 55% sensitivity, 90.5% specificity) was likely to be associated with increased risk for ASD in the child (Figure 1).

DISCUSSION

In this study we aimed to identify pre-, peri-, and postnatal environmental factors, and screen time in a group of children with ASD and age matched clinical controls. According to our findings, maternal prenatal depression, severe psychological stress, and maternal medication use during pregnancy, maternal postpartum depression, and excess screen time were risk factors associated with ASD. According to the meta-analyses on pre-, peri-, and postnatal factors associated with ASD, factors consistently found to be related with ASD are advanced parental age, maternal prenatal medication use, gestational hypertension, gestational diabetes, preterm delivery, abnormal presentation, fetal distress, low birthweight, and low Apgar score.[9–13]

Evidence from animal and human studies suggest that prenatal stress interacts with genetics to increase the risk for neurodevelopmental disorders[19,20] Accordingly, the results of our study show that maternal exposure to significant psychological stress during pregnancy, prenatal and postpartum depression are associated with offspring ASD. In line with our findings, previous studies employing natural disasters as a model for maternal stress exposure during pregnancy support the possibility of a link between prenatal stress and autism.[21–23] Moreover, maternal history of childhood abuse,[24] and fear of partner or sexual, emotional, or physical abuse in the 2 years before the birth year are reported to contribute to the risk for ASD.[25] In a Danish nationwide population based cohort study, parental psychiatric history for affective disorders before or after birth was associated with an independent risk of autism with a RR of 2.91 (95% CI: 1.65, 5.14).[26] Another large epidemiological study in Denmark refuted an association between maternal bereavement and autism; however, an association was found before accounting for cofounders including

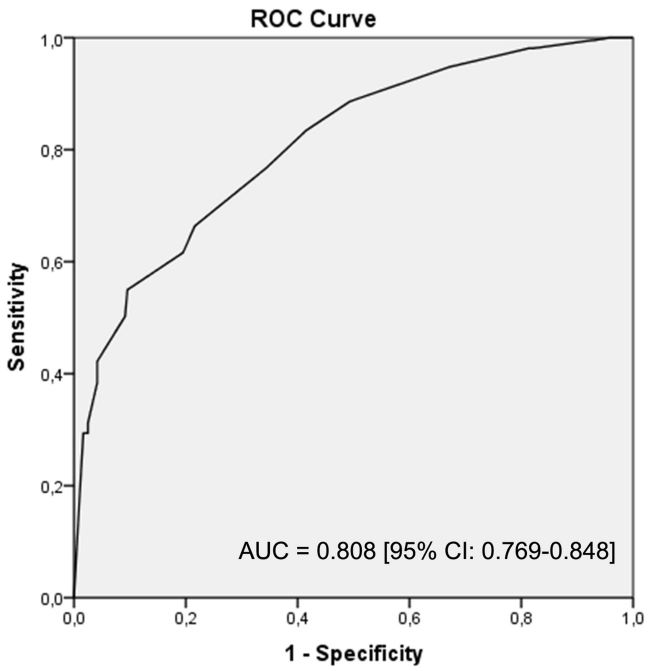

FIGURE 1 Receiver operating characteristic (ROC) curve analysis of daily total screen time

maternal psychiatric conditions.[27] A large Swedish register study reported that maternal bereavement stress in the third trimester of pregnancy, and during the second postnatal year increased the risk for ASD in offspring.[28] Prenatal maternal stress exposure is also shown to be a significant predictor of ASD-related symptom severity and communication abilities in children with ASD.[29]

Studies examining the relationship between offspring autism and prenatal medication use primarily focus on anticonvulsive and psychotropic medications.[11,12,30] A large systematic review and network meta-analysis examined the effect of antiepileptic drugs on neurodevelopment of children exposed in utero or during breast feeding. This network meta-analysis on autism including five cohort studies, 2551 children, 12 treatments evidenced that oxcarbazepine (OR 13.51, CrI 1.28 to 221.40), valproate (OR 17.29, 95% CrI 2.40 to 217.60), lamotrigine (OR 8.88, CrI 1.28 to 112.00) and lamotrigine + valproate (OR 132.70, CrI 7.41 to 3851.00) were associated with a significantly greater risk of autism.[31] Studies investigating the links between prenatal antidepressant exposure and autism present inconsistent results. A recent meta-analysis on six case–control studies (117 737 patients), however, demonstrated a positive association between preconception and prenatal antidepressant exposure and ASDs (odds ratio [OR], 1.81; 95% CI: 1.49–2.20). The association weakened when controlled for past maternal mental illness (OR, 1.52; 95% CI: 1.09–2.12) yet being significant.[32] Results from a large observational prospective cohort study from Sweden supported the association between prenatal antidepressant exposure and autism, particularly without intellectual disability; and suggested that the emerged link between prenatal antidepressant use and autism might not be a byproduct of confounding factors. The authors also mentioned that the absolute risk of autism was lower.[33] Nevertheless, a recent epidemiological study from Canada proved against in utero serotonergic antidepressant exposure and ASDs.[34] In the current study, any medication use during pregnancy was recorded without specifying subcategories, therefore we abstain from drawing any conclusions. However, our results might implicate a benefit in widening the focus of future research on the association between prenatal medication exposure and ASD risk.

Technological developments impose a great change in our daily lives. In connection with this, concerns about the impact of screen-based technologies are increasing. There is a growing body of research suggesting a link between excessive exposure to screen and psychological outcomes particularly in children and adolescents.[35] For young children under 5 years of age, ST is associated with poorer cognitive and language development, and impaired communication abilities.[35–39] Adverse connections between behavior problems, total difficulties, self-regulation, and prosocial behavior have also been shown.[35] A review and metanalysis of 16 studies on relations between ST and autism reports that children and adolescents with ASD are exposed to more ST than their typically developing peers or other clinical groups and the exposure starts at a younger age.[17] Accordingly, in this study, young children with ASD were reported being exposed to more ST compared to clinical controls including children with developmental delay in language and cognition, and behavioral problems. Moreover, a ROC curve analysis showed that screen exposure over 8.5 h at a younger age is related to an increased risk of ASD. ST is hypothesized to associate ASD through displacement of activities that promote learning, such as imaginative play, with stimulus of no significant developmental value, by limiting social interactions with friends and family members which are vital for developing language, communication, and socioemotional skills, and by its impact on processing social and psychological situations that require adequate time and reflection due to rapid and parallel processing of information on electronic media.[17] Despite all the abovementioned cumulating evidence regarding the link between screen exposure and ASD, the direction of the relationship remains questionable, or a bidirectional link should be considered since recent research points that excessive media exposure is more likely in infants and toddlers with a difficult temperament, or self-regulation problems or toddlers with social emotional delays possibly as a parent coping strategy.[40–43] Additionally, children with ASD may prefer screen media use over social and physical activities.[17]

In this study we failed to prove associations between advanced parental age, gestational diabetes, gestational

hypertension, preterm birth, low birthweight and ASD despite substantial evidence provided in recent research.[9–13] We assume that the small sample size of this study accounts for the lack of related evidence. Moreover, the study sample was recruited from a tertiary mental health care center serving children and adolescents with parents from lower socioeconomic background and lower educational levels which might have resulted in relatively lower mean maternal and paternal age at birth, and therefore, a lack of findings supporting the association between advanced parental age and ASD. Larger epidemiological studies from Turkey might prove similar associations.

CONCLUSION

There are two intriguing results of the current study. First, prenatal maternal psychological stress, prenatal and postpartum depression, and second, excess exposure to screen were more frequent in children with ASD compared to clinical controls including children with cognitive and language delay, and behavioral problems. However, there are certain limitations to the present study that should be taken into account. First, the study has a retrospective design relied on maternal report of pre-, peri-, and postnatal events. It is plausible to assume that mothers of children with ASD might be more likely to recall pre-, peri-, postnatal events compared to mothers of children presenting with other problems. In addition, the data might have been different if medical records of the children and the mothers could have been obtained. Almost all above mentioned studies are based on parental reports or surveys that are inclined to reporter bias. Prospectively designed future research should collect data via clinical observations and verifiable medical records. Moreover, despite many studies on the potential role of pre- and perinatal complications in the emergence of ASD, the casual direction of the relationship is to be argued.[10] Additionally, in this study, ST has been defined as the children's time spent on TV, computer, tablet, and smart phones; background TV exposure and screen exposure through parental use of electronic devices have been included. There is a growing body of research implicating deleterious effects of ST in children and adolescents[44] and the potential associations between children's growing exposure to screens and the increase of ASD prevalence is an important topic to discuss. Future studies should compare passive ST (background screen exposure etc.) versus active ST, ST with versus without parent interaction, and different contents to better evaluate these associations. Further research may raise clinician, policymaker, and public awareness regarding the link between excess screen exposure and the increased risk for developmental disorders in young children and protective strategies (ST limitation, etc.) can be established.

AUTHOR CONTRIBUTIONS

Study concept and design: HG, CT, HD, SY, DY, FÖ, SB, GO. Data collection: HG, CT, HD, SY, DY, FÖ, SB, GO. Statistical analysis: HG, CT. Analysis and interpretation of data: HG, CT, HD, SY, DY, FÖ, SB, GO. Manuscript writing process: HG, CT. Revising the manuscript: HG, CT, HD, SY, DY, FÖ, SB, GO. Final approval of the version to be published. HG, CT, HD, SY, DY, FÖ, SB, GO.

CONFLICT OF INTEREST

On behalf of all authors, we declare that no financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The study protocol has been approved by Medical Ethics Committee of the Bakirkoy Training and Research Hospital for Psychiatric and Neurological Disorders.

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