Low social-support and trouble paying for basic needs during pregnancy are associated with increased risk of autism spectrum disorder in offspring at 3-years: A prospective cohort study

Jyssica Seebeck (jseebeck@pennstatehealth.psu.edu)
Penn State College of Medicine

Kristen K. Sznajder
Penn State College of Medicine

Kristen H. Kjerulff
Penn State College of Medicine

Research Article

Keywords: USA, autism risk factors, prenatal factors, perinatal factors, psychosocial factors

Posted Date: December 23rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2398459/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Social Psychiatry and Psychiatric Epidemiology on August 9th, 2023. See the published version at https://doi.org/10.1007/s00127-023-02538-5.

Abstract

Purpose

Few studies of risk factors for autism spectrum disorder (ASD) have been prospective in design or investigated the role of psychosocial factors measured during pregnancy. We aimed to investigate associations between prenatal psychosocial factors - including stress, social-support, depression, and trouble paying for basic needs - and risk of ASD in offspring, as part of a multicenter prospective cohort study of more than 2,000 mother-child pairs.

Methods

Nulliparous women aged 18–35 years, living in Pennsylvania, USA, were interviewed during pregnancy and multiple times postpartum over the course of a 3-year period. There were 2,388 participants who completed the Screen for Social Interaction Toddler Version (SSI-T), a measure of risk of ASD, when their child was 36 months old. We investigated the association between a variety of adverse psychosocial factors experienced during pregnancy and risk of ASD in offspring at the age of 3-years, controlling for relevant confounding variables.

Results

There were 102 children (4.3%) who scored as at risk of ASD at 3-years. Based on multivariable logistic regression, prenatal psychosocial factors that were significantly associated with risk of ASD were low social-support and trouble paying for basic needs. Other factors associated with risk of ASD were low maternal education, maternal use of antibiotics and antidepressants during pregnancy, and having a male child. None of the pregnancy or delivery complications were associated with risk of ASD.

Conclusion

These findings suggest that maternal experience of adverse psychosocial factors during pregnancy may be important intrauterine exposures related to the pathogenesis of ASD.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and repetitive behaviors that are typically detectable beginning in infancy and toddler years, and continue throughout life. Though the etiology of ASD has remained largely elusive, it is likely that the origin of ASD occurs early in life, as brain development is most rapid during fetal development through infancy [1]. Studies have documented a higher concordance of ASD in monozygotic vs. dizygotic twins [2]. While the increased concordance in siblings suggests a genetic component, the imperfect

concordance in identical twins also suggests an environmental influence to ASD [3]. Thus, while genetics can explain some of the risk associated with ASD, it can only do so partially, with environmental factors also playing an important role [1].

Very few studies have focused on psychosocial factors measured during pregnancy as potential contributing factors for ASD. Prenatal exposure to maternal stress and other adverse psychosocial factors may affect the newborn's cognitive development, affectivity, and temperament [4]. It has been hypothesized that stressful life events during pregnancy could cause an increase in cortisol and placental corticotropin-releasing hormone, which may influence fetal brain development and growth [4, 5]. Three review papers have reported an association between maternal prenatal stress and development of ASD in offspring [6–8]. However, most of the studies described in these reviews were retrospective cohort or case control studies that identified women who had experienced potentially stressful events during pregnancy, such as the death of a family member or the occurrence of a natural disaster, such as a hurricane or ice storm, and measured ASD via clinical assessment among school age children. However, none of these studies actually measured the degree to which these events were perceived as stressful for the women during pregnancy. Additionally, most of the previous studies asked parents to report the occurrence of stressful events during pregnancy, in retrospect, years after the pregnancy and after their child had been diagnosed as having ASD. This type of retrospective study design is highly vulnerable to bias because parents of children with ASD or other adverse outcomes are more likely to remember negative events that occurred in the pregnancy as a way of trying to understand why their child was different from other children [9, 10].

We found only three studies of the association between stress or other psychosocial factors during pregnancy and ASD in offspring that were prospective in design and measured one or more psychosocial factors by parental report during pregnancy [11–13]. One large scale study found maternal depressive moods and anxiety symptoms at two time points (15- and 27-weeks gestation) during pregnancy were significantly associated with ASD among 3-year-old children [12]. A prospective study of 2,900 Australian women found that prenatal maternal stress was only significantly associated with autistic traits in males at the age of 2-years, after controlling for behaviors usually associated with attention-deficit/hyperactivity disorder [13]. Amiri and colleagues [11] examined a wide range of prenatal and perinatal factors in a large population-based study of 3891 mother-child pairs in the Netherlands. They found that maternal symptoms of psychopathology measured during pregnancy were the most significant predictors of autism diagnosis in the children at the age of 6 years, including emotional problems, anxiety and difficulty concentrating.

Overall, few of the previous studies of associations between psychosocial factors and ASD have been prospective in design and measured multiple psychosocial factors during pregnancy. Fewer still, assessed risk factors for ASD exhibited among pre-school age children. This is an important limitation in light of increasing evidence of the value of early identification and treatment of children with ASD [14]. To address these limitations, we conducted a study to investigate the associations between multiple prenatal psychosocial factors measured during pregnancy and risk of ASD in offspring measured at the

age of 3-years, controlling for relevant confounding factors, such as prenatal and perinatal complications, and maternal use of antidepressants and other medications during pregnancy.

Methods

Participants and Procedure

This is a secondary analysis using data from the First Baby Study (FBS). The FBS was a prospective cohort study designed to assess the association between mode of delivery and subsequent fecundity and fertility over the course of three years after first childbirth. The sample size and power calculations, participant flow chart and sample representativeness have been described previously [15, 16]. A planned secondary analysis was to investigate the association between prenatal and perinatal factors and child development, measured at 3-years. Women were recruited from childbirth education courses, hospital tours, low-income clinics, private obstetric practices and newspaper advertisements throughout the state. Inclusion criteria were aged 18 to 35, nulliparous, singleton pregnancy, planning to deliver in Pennsylvania, and English or Spanish speaking. Exclusion criteria were: a prior pregnancy of 20 weeks gestation or longer, a prior cesarean section, a surrogate pregnancy, planning for the child to be adopted, planning to deliver at home or in a birthing center not associated with a hospital, and delivering before 34 weeks gestation. Sample representativeness found that the participants in this study were more educated, more likely to be married, white, and to have private insurance than women delivering their first child in Pennsylvania as a whole [15], and when compared to those who dropped out over the course of the study [16].

Data Collection

The study participants were interviewed by telephone by trained interviewers employed by the Penn State Center for Survey Research. Interviews were conducted during the third trimester of pregnancy (at 30 weeks gestation or later) and at 1, 6, 12, 18, 24, 30 and 36 months postpartum. The participants completed the baseline interviews and delivered their first child in 2009 to 2011. There were 3,006 women who completed the baseline and 1-month interviews and 2,423 women who remained in the study to the 36-month data collection stage, for a retention rate of 80.6%. The participants delivered at 78 hospitals. We obtained the birth certificate data, as well as the hospital discharge data for both mother and child, for these deliveries. Written informed consent was obtained from all study participants.

Assessments And Measures

Women reported demographic and background information in the baseline interview including age, education, marital status, race/ethnicity, height, pre-pregnancy weight, smoking and alcohol consumption, and use of prescription and non-prescription medications during pregnancy. Type of insurance coverage was obtained from the hospital discharge data. Women were asked about health conditions diagnosed

before becoming pregnant, including “anxiety or depression” and completed the Edinburgh Depression Scale (EDS) to measure prenatal depression level in the last trimester [17]. The EDS is a 10-item scale which askes respondents to report how they have been feeling in the previous week, with items such as “I have been so unhappy I have been crying”. We used the recommended cutoff score of 13 or higher to indicate likely depression [18]. Social-support was measured using a 5-item shortened version of the Medical Outcome Study (MOS) Social-support Scale [19]. Each item asked women to report the extent to which specific types of support was available to them, such as “Someone to confide in or talk to about your problems”. Total scores were classified into three categories of social-support: 5–19 (low), 20–23 (medium), and 24–25 (high). Women with low social-support during pregnancy were compared to those with medium or high social-support. Stress was measured using the Psychosocial Hassles Scale (PHS), which was developed to measure stress during pregnancy [20]. Respondents were asked to report the extent to which 12 specific factors, such as “Feeling generally overloaded”, had caused them to feel “no stress”, “some stress”, “moderate stress” or “severe stress”. Scores could range from 12 (no stress) to 48 (high stress). This instrument was originally developed to measure prenatal stress in an inner-city urban population. In pilot studies in our suburban and rural population we found that two of the items did not work well and exhibited low corrected item-total correlations. These items were “Sexual, emotional or physical abuse” and “Problems with alcohol or drugs”. Based on focus groups with pregnant women in our area we changed those items to more commonly reported stressors: “Fights with partner” and “Fights with other family members”. These two items worked well and exhibited good corrected item-total correlations. Women with scores of 21 or higher were classified as experiencing high stress during pregnancy. Women were also asked about financial difficulties with the question “In general do you and your family have a lot of trouble, some trouble, or no trouble at all paying for basic needs such as food, housing, gas and electric bills?” Women who reported that they had “some” or “a lot of” trouble were compared to those who reported “no trouble at all”.

The baseline interview was conducted at 30 weeks gestation or later, at a mean (standard deviation) of 35.2 (1.5) gestational weeks. In the baseline interview women were asked about health habits during pregnancy, including smoking and alcohol consumption. Women were asked if they had taken any prescription or non-prescription medications other than vitamins at least occasionally since becoming pregnant. If they answered “yes” they were asked a series of open-ended questions about each medication (including the name, dose, and frequency of use) for up to 10 medications. The medications were classified into categories including medications containing acetaminophen, antibiotics, antidepressants and antinausea medications. However, we were not able to accurately determine the dose or frequency of use of the medications because women’s reports concerning dose and frequency were often unclear, such as “one pill daily”. We used the maternal and newborn hospital discharge data and the birth certificate data to measure indications for cesarean delivery, mode of delivery, the sex of the child, gestational age, newborn birth weight, 5-minute Apgar score, assisted ventilation, neonatal intensive care unit (NICU) admission, jaundice, and fetal congenital anomalies. In the 1-month postpartum interview women were asked about gestational weight gain, which was verified by the birth certificate data. Gestational weight gain was classified as “less than recommended”, “as recommended” or “more

than recommended" based on the 2009 Institute of Medicine guidelines [21] which takes into account women's pre-pregnancy body mass index (BMI). We compared women who gained less than or as recommended to those who gained more than recommended. Women were also asked questions about childbirth, including the use of epidural, spinal, and general anesthesia. We used a series of questions to identify women who had undergone labor induction [22].

At the 36-month postpartum data collection stage women completed the Screen for Social Interaction – Toddler Version (SSI-T), in reference to their first-born child [23]. This is a 26-item inventory which was developed to screen for autism spectrum disorder in children aged 24–42 months old [24] and has been found to have predictive utility [25]. This instrument asks questions such as "When you talk with your child, does s/he look at you?", and "Can your child tell from the look on your face or the tone of your voice that you are happy?" Response options are "Almost never", "Some of the time", "Most of the time", and "Almost all of the time". Total scores can range from 0 to 78, with scores of 45 or less as indicating toddlers at risk of ASD.

Statistical Analysis

Among the 2,423 women who completed the 36-month data collection stage, there were 391 women who skipped one or more items in the SSI-T. Among the 391 women who skipped one or more of the SSI-T items, 356 missed only one item. For those missing one item, we substituted their mean score on the other 25 items for the missing item. Evidence indicates that this is a valid and accurate method for data imputation for scaled instruments [26]. Those who were missing two or more items ($n = 35$) were excluded, leaving a sample of 2,388 mother-child dyads. Scores on the SSI-T ranged from 9 to 78 and there were 102 children (4.3%) who had a score of 45 or lower on the SSI-T and were therefore classified as at risk of ASD.

Univariate analyses were conducted to describe the study population. Bivariate analyses using Pearson Chi-Square test or Fisher's Exact Test were conducted to compare the children who scored as at risk of ASD to those who did not on psychosocial, prenatal and perinatal factors. Forward conditional multivariable logistic regression was conducted which included all of the psychosocial, prenatal and perinatal factors that were significantly associated at $p < .05$ with scoring as at risk of ASD in the bivariate analyses. Because maternal and paternal education levels were collinear we did not include paternal education in the regression model. In addition, we conducted sensitivity analyses to measure associations between the individual items in our measure of stress during pregnancy and risk of ASD, in order to investigate which aspects of stress during pregnancy were associated with risk of ASD. All analyses were conducted using SPSS version 28.

Results

Table 1 shows the descriptive univariate results for the psychosocial factors under investigation, and the bivariate associations between these factors and scores on the SSI-T. The children who scored as at risk

of ASD were more than twice as likely to have a mother who reported low social-support during the pregnancy (33.3%) than the children not at risk (15.7%). Similarly, children who scored as at risk of ASD were more likely to have a mother who reported high levels of stress during pregnancy (36.3%) and some or a lot of trouble paying for basic needs during pregnancy (32.4%) than the children not at risk (25.1% and 16.5%, respectively). Neither depression during pregnancy nor a pre-pregnancy diagnosis of depression or anxiety were significantly associated with risk of ASD.

Table 1

Psychosocial factors measured during pregnancy, overall and by risk of ASD at 3-years[a]

Characteristics	**Overall** **N = 2388** **N (%)**	**Not at risk of ASD** **N = 2286** **N (%)**	**At risk of ASD** **N = 102** **N (%)**	***P* value[b]**
Low social-support[c]	392 (16.4)	358 (15.7)	34 (33.3)	< .001
High stress[d]	609 (25.5)	572 (25.1)	37 (36.3)	.011
Pre-pregnancy diagnosis of anxiety or depression	541 (22.7)	511 (22.4)	30 (29.4)	.096
Depressed during pregnancy[e]	121 (5.1)	112 (4.9)	9 (8.9)	.073
Trouble paying for basic needs	409 (17.2)	376 (16.5)	33 (32.4)	< .001

[a]Screen for Social Interaction Toddler Version (SSI-T) score of 45 or lower, (Ghuman et al. 2011)

[b]Results of Chi-square analyses

[c]Medical Outcome Study (MOS) 5-item measure of social support (McCarrier et al. 2011)

[d]Psychosocial Hassles Scale (PHS), Misra et al. 2001

[e]Edinburgh Depression Scale (EDS), Cox et al. 1996

Nearly 80.0% of the women were aged 25 or older, as were 86.6% of the fathers (Table 2). The majority of the women had college degrees or higher levels of education (63.2%) while less than half of the fathers did (49.9%). The majority of the women were married (77.9%), white non-Hispanic (88.1%) and had private health insurance (83.8%). Although more than a fifth of the women reported a previous diagnosis of anxiety or depression, only 5.1% scored as depressed during the pregnancy. Nearly a third of the women (32.0%) reported using one or more medications that included acetaminophen during the pregnancy, 11.9% reported taking antibiotics, and 4.5% reported taking an antidepressant. Common labor or delivery related complications were dystocia (21.4%), fetal distress/heart rate deceleration (21.7%), and

umbilical cord complications (27.6%). Nearly a third of the children were born by cesarean (29.5%), the majority were full term (60.8%), and had a 5-minute Apgar score of 9 or 10 (76.4%).

Table 2

Maternal and neonatal characteristics overall and by risk of ASD at 3-years[a]

Characteristics	Overall N = 2388 N (%)	Not at risk of ASD N = 2286 N (%)	At risk of ASD N = 102 N (%)	*P* value[b]
Maternal age, y				.106
18–24	523 (21.9)	492 (21.5)	31 (30.4)	
25–29	1081 (45.3)	1040 (45.5)	41 (40.2)	
30–35	784 (32.8)	754 (33.0)	30 (29.4)	
Paternal age, y				.583
16–24	318 (13.3)	301 (13.2)	17 (16.7)	
25–29	875 (36.6)	840 (36.7)	35 (34.3)	
30–57	1195 (50.0)	1145 (50.1)	50 (49.0)	
Maternal education				.001
High school or less	271 (11.3)	248 (10.8)	23 (22.5)	
Some college or technical	608 (25.5)	580 (24.5)	28 (27.5)	
College degree or higher	1509 (63.2)	1458 (63.8)	51 (50.0)	
Paternal education				.002
High school or less	595 (24.9)	559 (24.5)	36 (35.3)	
Some college or technical	602 (25.2)	570 (24.9)	32 (31.4)	

[a]Screen for Social Interaction Toddler Version (SSI-T) score of 45 or lower, (Ghuman et al. 2011)

[b]Results of chi-square analyses

[c]Based on Institute of Medicine Guidelines (IOM, 2009).

Characteristics	Overall N = 2388 N (%)	Not at risk of ASD N = 2286 N (%)	At risk of ASD N = 102 N (%)	*P* value[b]
College degree or higher	1191 (49.9)	1157 (50.6)	34 (33.3)	
Married	1861 (77.9)	1791 (78.3)	70 (68.6)	.021
Maternal race/ethnicity				.309
White non-Hispanic	2104 (88.1)	2019 (88.3)	85 (83.3)	
Black	105 (4.4)	100 (4.4)	5 (4.9)	
Hispanic	91 (3.8)	86 (3.8)	5 (4.9)	
Other	88 (3.7)	81 (3.5)	7 (6.9)	
Private insurance	2001 (83.8)	1927 (84.3)	74 (72.5)	.002
Smoked during pregnancy	188 (7.9)	175 (7.7)	13 (12.7)	.062
Alcohol consumed during pregnancy	227 (9.5)	219 (9.6)	8 (7.8)	.558
Pre-pregnancy BMI (k/m^2)				.776
< 25.0	1349 (56.5)	1294 (56.6)	55 (54.5)	
25.0-29.9	545 (22.8)	519 (22.7)	26 (25.7)	
30+	493 (20.7)	473 (20.7)	20 (19.8)	
Gestational weight-gain more than recommended[c]	1278 (53.6)	1215 (53.2)	63 (62.4)	.070
Medications mother used during pregnancy				
Acetaminophen	764 (32.0)	729 (31.9)	35 (34.3)	.608

[a]Screen for Social Interaction Toddler Version (SSI-T) score of 45 or lower, (Ghuman et al. 2011)

[b]Results of chi-square analyses

[c]Based on Institute of Medicine Guidelines (IOM, 2009).

Characteristics	Overall N = 2388 N (%)	Not at risk of ASD N = 2286 N (%)	At risk of ASD N = 102 N (%)	*P* value[b]
Antibiotics	284 (11.9)	263 (11.5)	21 (20.6)	.006
Antidepressant	108 (4.5)	97 (4.2)	11 (10.8)	.002
Antinausea	111 (4.6)	104 (4.5)	7 (6.9)	.278
Pregnancy complications				
Hypertension/preeclampsia	298 (12.5)	290 (12.7)	8 (7.8)	.148
Diabetes/abnormal glucose tolerance	165 (6.9)	154 (6.7)	11 (10.8)	.115
Thyroid disorder	127 (5.3)	119 (5.2)	8 (7.8)	.245
Fetal intrauterine growth restriction/slow fetal growth	75 (3.1)	72 (3.1)	3 (2.9)	1.000
Delivery complications				
Dystocia	510 (21.4)	485 (21.2)	25 (24.5)	.427
Breech	101 (4.2)	99 (4.3)	2 (2.0)	.320
Other malpresentation	187 (7.8)	182 (8.0)	5 (4.9)	.345
Cephalopelvic disproportion	118 (4.9)	110 (4.8)	8 (7.8)	.167
Antepartum bleeding or placenta disorders	250 (10.5)	238 (10.4)	12 (11.8)	.662
Fetal distress/heart rate	519 (21.7)	495 (21.7)	24 (23.5)	.653
Fetal intolerance of labor	297 (12.4)	281 (12.3)	16 (15.7)	.309
Umbilical cord complications	658 (27.6)	636 (27.8)	22 (21.6)	.167

[a]Screen for Social Interaction Toddler Version (SSI-T) score of 45 or lower, (Ghuman et al. 2011)

[b]Results of chi-square analyses

[c]Based on Institute of Medicine Guidelines (IOM, 2009).

Characteristics	Overall N = 2388 N (%)	Not at risk of ASD N = 2286 N (%)	At risk of ASD N = 102 N (%)	*P* value[b]
Premature or prolonged rupture of membranes	188 (7.9)	178 (7.8)	10 (9.8)	.459
Labor induced	801 (33.5)	760 (33.2)	41 (40.2)	.146
General anesthesia	78 (3.4)	71 (3.3)	7 (7.4)	.033
Epidural or spinal anesthesia	1958 (82.0)	1878 (82.2)	80 (78.4)	.339
Cesarean delivery	705 (29.5)	666 (29.1)	39 (38.2)	.049
Gestational age (weeks)				.359
Preterm (34–36)	89 (3.7)	84 (3.7)	5 (4.9)	
Early term (37–38)	457 (19.1)	432 (18.9)	25 (24.5)	
Full term (39–40)	1453 (60.8)	1399 (61.2)	54 (52.9)	
Late term/postterm (41+)	389 (16.3)	371 (16.2)	18 (17.6)	
Newborn birth weight (grams)				.667
<2500 (underweight)	67 (2.8)	65 (2.8)	2 (2.0)	
2500–4000 (normal)	2049 (85.8)	1963 (85.9)	86 (84.3)	
>4000 (macrosomic)	272 (11.4)	258 (11.3)	14 (13.7)	
Male child	1200 (50.3)	1127 (49.3)	73 (71.6)	< .001
Apgar Score 5-minutes				.246
1–7	114 (4.8)	112 (4.9)	2 (2.0)	

[a]Screen for Social Interaction Toddler Version (SSI-T) score of 45 or lower, (Ghuman et al. 2011)

[b]Results of chi-square analyses

[c]Based on Institute of Medicine Guidelines (IOM, 2009).

Characteristics	Overall N = 2388 N (%)	Not at risk of ASD N = 2286 N (%)	At risk of ASD N = 102 N (%)	*P* value[b]
8	449 (18.8)	433 (18.9)	16 (15.7)	
9–10	1825 (76.4)	1741 (76.2)	84 (82.4)	
Assisted ventilation	107 (4.5)	102 (4.5)	5 (5.0)	.804
Neonatal ICU (NICU)	119 (5.0)	111 (4.9)	8 (7.8)	.175
Jaundice	524 (21.9)	498 (21.8)	26 (25.5)	.376
[a]Screen for Social Interaction Toddler Version (SSI-T) score of 45 or lower, (Ghuman et al. 2011)				
[b]Results of chi-square analyses				
[c]Based on Institute of Medicine Guidelines (IOM, 2009).				

Table 2 shows the results of the bivariate analyses to compare those who scored as at risk of ASD (n = 102) to those who did not (n = 2,286) on each of the factors under investigation. Children who scored as at risk of ASD were more likely to have mothers and fathers in the lowest education category. Children whose mothers were married and had private insurance were at lower risk. Two of the categories of medications taken during pregnancy were associated with risk of ASD. Children who scored as at risk of ASD were more likely to have mothers who reported taking antibiotics (20.6%) and antidepressants (10.8%) during pregnancy than the children not at risk (11.5% and 4.2%, respectively). Although the children who were at risk of ASD were more likely to have been born by cesarean (38.2%) than those not at risk (29.1%), none of the pregnancy or delivery complications were associated with risk of ASD. Among the perinatal factors and newborn characteristics only general anesthesia and male sex were associated with risk of ASD. Children at risk of ASD were more likely to be male (71.6%) and have mothers who received general anesthesia at delivery (7.4%) than the children not at risk (49.3% and 3.3%, respectively). Neither labor induction nor use of epidural or spinal anesthesia were associated with risk of ASD.

Table 3 shows the adjusted ORs and 95% CIs for the factors that were significantly associated with risk of ASD in the final model resulting from stepwise forward logistic regression. The factors that were included in step 0 of the model were maternal education, marital status, insurance coverage, low social-support, high stress, trouble paying for basic needs, antibiotic use, antidepressant use, general anesthesia, mode of delivery and male sex. Six factors remained in the final step of the multivariable logistic regression model. The factors that were significantly associated with risk of screening positive for ASD at the age of 3-years were low social-support and trouble paying for basic needs during pregnancy,

lower maternal education level (high school degree or less in comparison to college degree or higher), the use of two medications during pregnancy – antibiotics and antidepressants, and male sex.

Table 3

Multivariable regression analysis of factors associated with risk of ASD at 3-years of age[a]

Factors	Adjusted OR	95% CI	*P* value
Maternal education			
High school or less	Ref		
Some college or technical	0.62	0.34–1.12	.111
College degree or higher	0.48	0.27–0.83	.009
Low social-support[b]	2.26	1.44–3.52	< .001
Trouble paying for basic needs	1.64	1.02–2.65	.042
Antibiotic use during pregnancy	1.92	1.15–3.20	.013
Antidepressant use during pregnancy	2.46	1.24–4.90	.010
Male child	2.53	1.63–3.95	< .001
[a]Screen for Social Interaction Toddler Version (SSI-T) score of 45 or lower, (Ghuman et al. 2011)			
[b]Medical Outcome Study (MOS) 5-item measure of social support (McCarrier et al. 2011)			
OR, odds ratio			
CI, confidence interval			

In order to understand why high stress during pregnancy was not significant in the final regression model, we investigated the associations between the individual stress items and scoring as at risk of ASD, via Spearman's rho correlations. As shown in Table 4, none of the stress scale items were strongly associated with ASD risk. However, two of the stress items were strongly associated with trouble paying for basic needs; these were "Worries about food, health care, and transportation" and "Money worried like paying bills". Therefore, with trouble paying for basic needs in the model, scoring high on the stress scale became non-significant.

Table 4

Correlations[a] of stress scale items with social-support, trouble paying for basic needs and risk of ASD at 3- years of age[b]

Stress scale items[c]	Low social-support[d]	Trouble paying for basic needs	Risk of ASD
Worries about food, shelter, health care, and transportation	.176	.390	.081
Money worries like paying bills	.115	.379	.051
Problems related to family	.154	.111	.025
Having to move, either recently or in the future	.164	.197	.049
Recent loss of a loved one	.026	.039	.001
The pregnancy itself	.109	.114	.024
Fights with partner	.121	.165	.036
Fights with other family members	.105	.113	.029
Work or job problems	.062	.116	.038
Problems with your friends	.087	.100	.039
Feeling generally “overloaded”	.116	.134	.024
Crime or safety in your neighborhood	.081	.110	.028

[a]Spearman’s rho correlations

[b]Screen for Social Interaction Toddler Version (SSI-T) score of 45 or lower, (Ghuman et al. 2011)

[c]Psychosocial Hassles Scale (PHS), Misra et al. 2001

[d]Medical Outcome Study (MOS) 5-item measure of social support (McCarrier et al. 2011)

Discussion

In this large-scale prospective cohort study, we investigated the associations of maternal psychosocial factors measured during pregnancy with risk of ASD in children at 3-years of age. In the multivariable logistic regression model, controlling for confounding variables, there were two prenatal psychosocial factors associated with risk of screening positive for ASD at the age of 3-years: low social-support and trouble paying for basic needs. It could be that women who are pregnant and expecting their first child may be particularly worried about who will help them after the baby arrives, and how they will make ends meet if they don’t have enough money to pay for food, rent, or other basic needs. The participants in this

study were enrolled and completed their baseline interviews in the years 2009 to 2011, shortly after the onset of The Great Recession. This could have contributed to women's fears and feelings of vulnerability when anticipating first childbirth.

Stressful life events during pregnancy could increase maternal cortisol levels which may influence fetal brain development [4, 5]. In our study, we examined depression level in the last trimester of pregnancy, social-support, prenatal stress, and financial difficulties. While prenatal stress was associated with ASD in the bivariate analyses, it was not significant in the multivariable regression model after we included the variable of trouble paying for basic needs. Based on sensitivity analyses, we found that the items in our measure of prenatal stress were not strongly associated with risk of ASD. As "stress" is an overall generic concept, it is likely that the items in our measure did not assess critical aspects of prenatal stress as specifically as our measures of low social-support and trouble paying for basic needs. These results support our contention that studies of contributing factors for ASD should measure multiple psychosocial factors during pregnancy in order to determine which prenatal psychosocial factors are most likely to adversely affect the developing child. Examining multiple psychosocial factors simultaneously allows for the investigation of the joint effects of these factors.

Maternal education level is frequently used as a marker for socioeconomic status, though this may vary between racial and ethnic groups [27]. In our study, lower maternal education level was associated with risk of developing ASD in the multivariable regression model, but type of health insurance coverage (private or public) was not. Additionally, we found no association with maternal race/ethnicity. These results are consistent with some studies [27, 28], and inconsistent with several studies which found the opposite of our findings, that higher maternal education levels were associated with risk of ASD [29, 30]. However, for the most part, previous studies have not found ASD prevalence differences between families of varying education and racial backgrounds [27].

Two classes of medications used during pregnancy were found to be associated with risk of ASD: antidepressants and antibiotics. In relation to antidepressants, several studies have found a similar association [31, 32]. However, it is possible that this association is explained by factors related to the underlying psychiatric disorder rather than the medication itself, suggesting possible confounding effects [33–39]. The severity of the disease may also be a confounding factor that leads to increased dosage and frequency of antidepressant medication use. In our study, ASD risk was not significantly associated with the mother's diagnosis of depression or anxiety prior to the pregnancy, or with depression during the third trimester of pregnancy, as indicated by scores on the EDS [17]. However, this one-time assessment of depression during pregnancy may not have adequately measured the severity level of depression over the course of the pregnancy.

There has been a focus in recent years on antibiotic use in pregnancy as a contributing factor for ASD in offspring, with mixed outcomes. Antibiotic use in pregnancy has been proposed as a contributing factor to ASD development because children who were exposed to antibiotics have been reported to have differences in microbiota composition [40]. While meta-analyses have reported an association between

antibiotic use during pregnancy and risk of ASD [41–43], one study proposed that it is maternal infection and immune system activation that leads to the increased risk of ASD and that antibiotic use may actually be protective and lower that risk [44].

Study Strengths And Limitations

Strengths of this study include the large sample size, prospective cohort study design, assessment of multiple psychosocial factors during pregnancy, and comprehensive measurement of potentially confounding variables. In addition, by limiting our study to first-born singleton children and women aged 18 to 35 at enrollment, we controlled for three known contributing factors for ASD: being first born, being a twin or higher order multiple, and born of older mothers [3, 45–47]. Our assessment of risk for ASD at 3-years of age is both a strength and a weakness. Many of the previous studies of contributing factors for ASD measured clinically diagnosed ASD among school age children, therefore potentially missing clinical signs associated with early evidence of ASD [48]. Our measure of risk of ASD in this study, the SSI-T [23, 24], is a relatively recently developed screener of ASD among pre-school children and is not as widely used as some other measures, which may make it difficult to compare the results of our study to other studies that may have used more widely known screening tools. However, studies using the SSI have reported the measure reliably discriminates children diagnosed with ASD from children with other developmental or psychiatric conditions [25, 49]. Since the SSI primarily focuses on social interaction skills, the impact on language ability is minimized, making it a valuable screening tool for capturing a wide range of symptom presentations [49].

An additional limitation of this study is that medication use was measured by maternal self-report in the baseline interview, at an average gestational age of 35 weeks, so we do not have data on maternal medication use that occurred between the baseline interview and delivery, nor on the dose and frequency of maternal use of specific medications during pregnancy. Finally, the participants in this study were all from one state in the US, were mostly white, and generally had a higher education level than the overall population, potentially limiting the generalizability of the study results.

Conclusions

Results from this large-scale, prospective birth cohort study indicate that psychosocial challenges experienced during pregnancy, specifically low social-support and financial difficulties, were associated with risk of ASD in children at three years of age. This extends our understanding of the adverse effects of stressors during pregnancy by the identification of several chronic sources of stress experienced by pregnant women that are associated with early evidence of ASD in offspring. In addition, we found that maternal use of antidepressants and antibiotics during pregnancy were associated with risk of ASD but none of the pregnancy or delivery-related complications were associated. These observed associations are potentially important to furthering our understanding of the etiology of autism, and suggest potentially fruitful areas for further study of contributing factors for ASD.

Declarations

Funding: This study was funded by grant R01-HD052990 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health.

Competing interests: The authors declare that they have no competing interests relevant to the content of this article.

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Penn State College of Medicine Institutional Review Board (IRB) as well as the IRBs of all organizations involved with participant recruitment. All participants provided signed written consent.

References

1. Lewis SJ, Relton C, Zammit S, Smith GD (2013) Approaches for strengthening causal inference regarding prenatal risk factors for childhood behavioural and psychiatric disorders. J Child Psychol Psychiatry 54:1095–108. https://doi.org/10.1111/jcpp.12127
2. Hu VW, Devlin CA, Debski JJ (2019) ASD Phenotype—Genotype Associations in Concordant and Discordant Monozygotic and Dizygotic Twins Stratified by Severity of Autistic Traits. Int J Mol Sci 20:3804. **https://doi.org/10.3390/ijms20153804**
3. Hisle-Gorman E, Susi A, Stokes T, Gorman G, Erdie-Lalena C, Nylund CM (2018) Prenatal, perinatal, and neonatal risk factors of autism spectrum disorder. Pediatr Res 84:190–8. https://doi.org/10.1038/pr.2018.23
4. Van den Bergh BRH, van den Heuvel MI, Lahti M, Braeken M, de Rooij SR, Entringer S, Hoyer D, Roseboom T, Räikkönen K, King S, Schwab M (2020) Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. Neurosci Biobehav Rev 117:26–64. https://doi.org/10.1016/j.neubiorev.2017.07.003
5. Cattane N, Richetto J, Cattaneo A (2020) Prenatal exposure to environmental insults and enhanced risk of developing schizophrenia and autism spectrum disorder: Focus on biological pathways and epigenetic mechanisms. Neurosci Biobehav Rev 117:253–78. https://doi.org/10.1016/j.neubiorev.2018.07.001
6. Kinney DK, Munir KM, Crowley DJ, Miller AM (2008) Prenatal stress and risk for autism. Neurosci Biobehav Rev 32:1519–32. https://doi.org/10.1016/j.neubiorev.2008.06.004
7. Manzari N, Matvienko-Sikar K, Baldoni F, O'Keeffe GW, Khashan AS (2019) Prenatal maternal stress and risk of neurodevelopmental disorders in the offspring: a systematic review and meta-analysis. Soc Psychiatry Psychiatr Epidemiol 54:1299–309. https://doi.org/10.1007/s00127-019-01745-3
8. Caparros-Gonzalez RA, de la Torre-Luque A, Romero-Gonzalez B, Quesada-Soto JM, Alderdice F, Peralta-Ramírez MI (2021) Stress During Pregnancy and the Development of Diseases in the

offspring: A Systematic-Review and Meta-Analysis. Midwifery 97:102939. https://doi.org/10.1016/j.midw.2021.102939

9. Kopec JA, Esdaile JM (1990) Bias in case-control studies. A review. J Epidemiol Community Health 44:179–86. https://doi.org/10.1136/jech.44.3.179
10. Prince M (2012) 9 – Epidemiology. In: Wright P, Stern J, Phelan M (eds) Core Psychiatry, Third Edition. Oxford: W.B. Saunders, pp 115–29
11. Amiri M, Lamballais S, Geenjaar E, Blanken LME, El Marroun H, Tiemeier H, White T (2020) Environment-Wide Association Study (EnWAS) of Prenatal and Perinatal Factors Associated With Autistic Traits: A Population-Based Study. Autism Res 13:1582–600. https://doi.org/10.1002/aur.2372
12. Nishigori T, Hashimoto K, Mori M, Suzuki T, Watanabe M, Imaizumi K, Murata T, Kyozuka H, Ogata Y, Sato A, Shinoki K, Yasumura S, Fujimori K, Nishigori H, Hosoya M, Japan Environment and Children's Study Group (2022) Association between maternal prenatal psychological distress and autism spectrum disorder among 3-year-old children: The Japan Environment and Children's Study. J Dev Orig Health Dis 1–7. https://doi.org/10.1017/s2040174422000411
13. Ronald A, Pennell CE, Whitehouse AJO (2011) Prenatal Maternal Stress Associated with ADHD and Autistic Traits in early Childhood. Front Psychol 1:223. https://doi.org/10.3389/fpsyg.2010.00223
14. Ashmawi NS, Hammoda MA (2022) Early Prediction and Evaluation of Risk of Autism Spectrum Disorders. Cureus 14:e23465. https://doi.org/10.7759/cureus.23465
15. Kjerulff KH, Velott DL, Zhu J, Chuang CH, Hillemeier MM, Paul IM, Repke JT (2013) Mode of first delivery and women's intentions for subsequent childbearing: findings from the First Baby Study. Paediatr Perinat Epidemiol 27:62–71. https://doi.org/10.1111/ppe.12014
16. Kjerulff KH, Paul IM, Weisman CS, Hillemeier MM, Wang M, Legro RS, Repke JT (2020) Association Between Mode of First Delivery and Subsequent Fecundity and Fertility. JAMA Netw Open 3:e203076. https://doi.org/10.1001%2Fjamanetworkopen.2020.3076
17. Cox JL, Chapman G, Murray D, Jones P (1996) Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. J Affect Disord 39:185–9. https://doi.org/10.1016/0165-0327(96)00008-0
18. Matthey S, Henshaw C, Elliott S, Barnett B (2006) Variability in use of cut-off scores and formats on the Edinburgh Postnatal Depression Scale: implications for clinical and research practice. Arch Womens Ment Health 9:309–15. https://doi.org/10.1007/s00737-006-0152-x
19. McCarrier K, Bushnell D, Martin ML, Paczkowski R, Nelson D, Buesching D (2011) PRM16 VALIDATION AND PSYCHOMETRIC EVALUATION OF A 5-ITEM MEASURE OF PERCEIVED SOCIAL SUPPORT. Value in Health 14:A148. https://doi.org/10.1016/j.jval.2011.02.824
20. Misra DP, O'Campo P, Strobino D (2001) Testing a sociomedical model for preterm delivery. Paediatr Perinat Epidemiol 15:110–22. https://doi.org/10.1046/j.1365-3016.2001.00333.x
21. Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines (2009) Weight Gain During Pregnancy: Reexamining the Guidelines.

Rasmussen KM, Yaktine AL (eds). National Academies Press, Washington DC

22. Kjerulff KH, Attanasio LB, Edmonds JK, Kozhimannil KB, Repke JT (2017) Labor induction and cesarean delivery: A prospective cohort study of first births in Pennsylvania, USA. Birth Berkeley Calif 44:252–61. https://doi.org/10.1111/birt.12286
23. Ghuman JK, Leone SL, Lecavalier L, Landa RJ (2011) The screen for social interaction (SSI): a screening measure for autism spectrum disorders in preschoolers. Res Dev Disabil 32:2519–29. https://doi.org/10.1016/j.ridd.2011.07.008
24. Mahoney EB, Breitborde NJK, Leone SL, Ghuman JK (2014) An examination of social interaction profiles based on the factors measured by the screen for social interaction. Res Dev Disabil 35:2487–94. https://doi.org/10.1016/j.ridd.2014.06.008
25. Princiotta DK, Skoch SH, Phelps R, Morris RJ, Breitborde N, Bukelis I, Grados M, Ghuman JK (2020) Predicting Autism Spectrum Disorder in Young Children: The Predictive Utility of the Ghuman-Folstein Screen for Social Interaction and Sociodemographic Factors. Psychology 11:1054–66. https://doi.org/10.4236/psych.2020.117069
26. Shrive FM, Stuart H, Quan H, Ghali WA (2006) Dealing with missing data in a multi-question depression scale: a comparison of imputation methods. BMC Med Res Methodol 6:57. https://doi.org/10.1186/1471-2288-6-57
27. Khowaja MK, Hazzard AP, Robins DL (2015) Sociodemographic Barriers to Early Detection of Autism: Screening and Evaluation Using the M-CHAT, M-CHAT-R, and Follow-Up. J Autism Dev Disord 45:1797–808. https://doi.org/10.1007%2Fs10803-014-2339-8
28. Lung FW, Chiang TL, Lin SJ, Lee MC, Shu BC (2018) Advanced Maternal Age and Maternal Education Disparity in Children with Autism Spectrum Disorder. Matern Child Health J 22:941–9. https://doi.org/10.1007/s10995-018-2470-9
29. Bhasin TK, Schendel D (2007) Sociodemographic Risk Factors for Autism in a US Metropolitan Area. J Autism Dev Disord 37:667–77. https://doi.org/10.1007/s10803-006-0194-y
30. Croen LA, Grether JK, Selvin S (2002) Descriptive Epidemiology of Autism in a California Population: Who Is at Risk? J Autism Dev Disord 32:217–24. https://doi.org/10.1023/a:1015405914950
31. Boukhris T, Sheehy O, Mottron L, Bérard A (2016) Antidepressant Use During Pregnancy and the Risk of Autism Spectrum Disorder in Children. JAMA Pediatr 170:117–24. https://doi.org/10.1001/jamapediatrics.2015.3356
32. Croen LA (2011) Antidepressant Use During Pregnancy and Childhood Autism Spectrum Disorders. Arch Gen Psychiatry 68:1104. https://doi.org/10.1001/archgenpsychiatry.2011.73
33. Dragioti E, Solmi M, Favaro A, Fusar-Poli P, Dazzan P, Thompson T, Stubbs B, Firth J, Fornaro M, Tsartsalis D, Carvalho AF, Vieta E, McGuire P, Young AH, Shin JI, Correll CU, Evangelou E (2019) Association of Antidepressant Use With Adverse Health Outcomes: A Systematic Umbrella Review. JAMA Psychiatry 76:1241. https://doi.org/10.1001/jamapsychiatry.2019.2859
34. Fitton CA, Steiner MFC, Aucott L, Pell JP, Mackay DF, Fleming M, McLay JS (2020) In utero exposure to antidepressant medication and neonatal and child outcomes: a systematic review. Acta Psychiatr

Scand 141:21–33. https://doi.org/10.1111/acps.13120

35. Kaplan YC, Keskin-Arslan E, Acar S, Sozmen K (2017) Maternal SSRI discontinuation, use, psychiatric disorder and the risk of autism in children: a meta-analysis of cohort studies. Br J Clin Pharmacol 83:2798–806. https://doi.org/10.1111/bcp.13382
36. Leshem R, Bar-Oz B, Diav-Citrin O, Gbaly S, Soliman J, Renoux C, Matok I (2021) Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) During Pregnancy and the Risk for Autism spectrum disorder (ASD) and Attention deficit hyperactivity disorder (ADHD) in the Offspring: A True Effect or a Bias? A Systematic Review & Meta-Analysis. Curr Neuropharmacol 19:896–906. https://doi.org/10.2174/1570159x19666210303121059
37. Rommel AS, Bergink V, Liu X, Munk-Olsen T, Molenaar NM (2020) Long-Term Effects of Intrauterine Exposure to Antidepressants on Physical, Neurodevelopmental, and Psychiatric Outcomes: A Systematic Review. J Clin Psychiatry 81. https://doi.org/10.4088/jcp.19r12965
38. Uguz F (2021) Neonatal and Childhood Outcomes in Offspring of Pregnant Women Using Antidepressant Medications: A Critical Review of Current Meta-Analyses. J Clin Pharmacol 61:146–58. https://doi.org/10.1002/jcph.1724
39. Viktorin A, Uher R, Reichenberg A, Levine SZ, Sandin S (2017) Autism risk following antidepressant medication during pregnancy. Psychol Med 47:2787–96. https://doi.org/10.1017/s0033291717001301
40. Hamad AF, Alessi-Severini S, Mahmud SM, Brownell M, Fan Kuo I (2019) Prenatal antibiotics exposure and the risk of autism spectrum disorders: A population-based cohort study. PLoS One 14:e0221921. https://doi.org/10.1371/journal.pone.0221921
41. Gómez-Vallejo S, Leoni M, Ronald A, Colvert E, Happé F, Bolton P (2021) Autism spectrum disorder and obstetric optimality: a twin study and meta-analysis of sibling studies. J Child Psychol Psychiatry 62:1353–62. https://doi.org/10.1111/jcpp.13526
42. Lee E, Cho J, Kim KY (2019) The Association between Autism Spectrum Disorder and Pre- and Postnatal Antibiotic Exposure in Childhood—A Systematic Review with Meta-Analysis. Int J Environ Res Public Health 16:4042. https://doi.org/10.3390%2Fijerph16204042
43. Łukasik J, Patro-Gołąb B, Horvath A, Baron R, Szajewska H, Baron R, Besseling van der Vaart I, Gieruszczak-Białek D, Horvath A, Łukasik J, Kołodziej M, Patro-Gołąb B, Pieścik-Lech M, Seidell J, Skórka A, Szajewska H, Taye M, Ujcic J, Verhoeff A, SAWANTI Working Group (2019) Early Life Exposure to Antibiotics and Autism Spectrum Disorders: A Systematic Review. J Autism Dev Disord 49:3866–76. https://doi.org/10.1007/s10803-019-04093-y
44. Holingue C, Brucato M, Ladd-Acosta C, Hong X, Volk H, Mueller NT, Wang X, Fallin MD (2020) Interaction between Maternal Immune Activation and Antibiotic Use during Pregnancy and Child Risk of Autism Spectrum Disorder. Autism Res 13:2230–41. https://doi.org/10.1002/aur.2411
45. Gardener H, Spiegelman D, Buka SL (2009) Prenatal risk factors for autism: comprehensive meta-analysis. Br J Psychiatry 195:7–14. https://doi.org/10.1192/bjp.bp.108.051672

46. Guinchat V, Thorsen P, Laurent C, Cans C, Bodeau N, Cohen D (2012) Pre-, peri- and neonatal risk factors for autism. Acta Obstet Gynecol Scand 91:287–300. https://doi.org/10.1111/j.1600-0412.2011.01325.x
47. Russell G, Steer C, Golding J (2011) Social and demographic factors that influence the diagnosis of autistic spectrum disorders. Soc Psychiatry Psychiatr Epidemiol 46:1283–93. https://doi.org/10.1007/s00127-010-0294-z
48. Sicherman N, Charite J, Eyal G, Janecka M, Loewenstein G, Law K, Lipkin PH, Marvin AR, Buxbaum JD (2021) Clinical signs associated with earlier diagnosis of children with autism Spectrum disorder. BMC Pediatr 21:96. https://doi.org/10.1186/s12887-021-02551-0
49. Munde V, Vlaskamp C, ter Haar A (2016) Social-emotional instability in individuals with Rett syndrome: parents' experiences with second stage behavior. J Intellect Disabil Res 60:43–53. https://doi.org/10.1111/jir.12233