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Infection and Fever in Pregnancy and Autism Spectrum Disorders: Findings from the Study to Explore Early Development

Lisa A. Croen, **Yinge Qian**, **Paul Ashwood**, **Ousseny Zerbo**, **Diana Schendel**, **Jennifer Pinto-Martin**, **M. Daniele Fallin**, **Susan Levy**, **Laura A. Schieve**, **Marshalyn Yeargin-Allsopp**, **Katherine R. Sabourin**, **Jennifer L. Ames**

Division of Research, Kaiser Permanente, Oakland, California (L.A.C., Y.Q., O.Z., J.L.A.); Department of Medical Microbiology and Immunology, University of California, Davis, California (P.A.); Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH; National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark (D.S.); Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark (D.S.); Department of Biobehavioral Health Sciences, Philadelphia, Pennsylvania, USA (J.P.-M.); Department of Mental Health, Baltimore, Maryland, USA (M.D.F.); Department of Developmental and Behavioral Pediatrics, Philadelphia, Pennsylvania, USA (S.L.); National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia (L.A.S., M.Y.-A.); Department of Epidemiology, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, Colorado (K.R.S.)

Abstract

Maternal infection and fever during pregnancy have been implicated in the etiology of autism spectrum disorder (ASD); however, studies have not been able to separate the effects of fever itself from the impact of a specific infectious organism on the developing brain. We utilized data from the Study to Explore Early Development (SEED), a case-control study among 2- to 5-year-old children born between 2003 and 2006 in the United States, to explore a possible association between maternal infection and fever during pregnancy and risk of ASD and other developmental disorders (DDs). Three groups of children were included: children with ASD (N = 606) and children with DDs (N = 856), ascertained from clinical and educational sources, and children from the general population (N = 796), randomly sampled from state birth records. Information about infection and fever during pregnancy was obtained from a telephone interview with the mother shortly after study enrollment and maternal prenatal and labor/delivery medical records. ASD and DD status was determined by an in-person standardized developmental assessment of the child at 3–5 years of age. After adjustment for covariates, maternal infection anytime during pregnancy was not associated with ASD or DDs. However, second trimester infection accompanied by fever elevated risk for ASD approximately twofold (aOR = 2.19, 95% confidence interval 1.14–4.23).

Address for correspondence and reprints: Lisa A. Croen, Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94612. lisa.a.croen@kp.org.

Conflict of Interests

The authors report no competing interests.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

These findings of an association between maternal infection with fever in the second trimester and increased risk of ASD in the offspring suggest that the inflammatory response to the infectious agent may be etiologically relevant.

Lay Summary:

Using data from a large multisite study in the United States—the Study to Explore Early Development—we found that women who had an infection during the second trimester of pregnancy accompanied by a fever are more likely to have children with ASD. These findings suggest the possibility that only more severe infections accompanied by a robust inflammatory response increase the risk of ASD.

Keywords

prenatal; autism; neurodevelopment; immune function; developmental disorder; infection

Introduction

Autism spectrum disorder (ASD) is a prevalent neurodevelopmental disorder characterized by impairments in social interaction and communication and restricted and repetitive patterns of behavior [American Psychiatric Association, 2013].

Maternal infection was one of the earliest suggested non-genetic risk factors for ASD. Following the rubella epidemic of 1964, children with congenital rubella syndrome were found to have an increased rate of ASD [Chess, 1971; Deykin & MacMahon, 1979]. Since then, additional studies have reported elevated rates of ASD among children gestationally exposed to viral infection. Studies examining maternal influenza infections during pregnancy provide inconsistent results [Atladottir, Henriksen, Schendel, & Parner, 2012; Brucato et al., 2017; Fang, Wang, Huang, Yeh, & Chen, 2015; Mahic et al., 2017; Zerbo et al., 2012; Zerbo et al., 2016; Zerbo et al., 2013]. Among women who were hospitalized for infection, increased risk of ASD was reported for any infection in each trimester [Lee et al., 2015], viral infection in the first trimester and bacterial infections in the second trimester [Atladottir et al., 2010], or bacterial infection in the third trimester [Zerbo et al., 2015]. Bacterial and genitourinary (GU) infections during the third trimester were also associated with ASD risk [Fang et al., 2015].

Fever also has been implicated in ASD etiology in a few studies, such as prolonged fevers during pregnancy [Atladottir et al., 2012], untreated fevers in the first and second trimester [Zerbo et al., 2013], and fever in the second trimester [Hornig et al., 2017] or third trimester [Brucato et al., 2017]. However, these studies could not separate the effects of fever itself from those of a specific infectious organism on the developing brain [Croen et al., 2018].

The inconsistencies summarized above are likely the result of methodologic differences across investigations, including study design, ascertainment source for maternal infection and child outcome, type and severity of infection examined, timing of exposure, and covariates included in analyses. Given that up to 60% of women report infection during

pregnancy [Collier, Rasmussen, Feldkamp, & Honein, 2009], and the need for further clarification of infection's relationship with ASD, we attempted to address several limitations of prior work on this topic by conducting a comprehensive analysis using detailed diagnostic and covariate data from a large case-control study. Specifically, we investigated how different types of infection by their timing during pregnancy, treatment, and presentation with fever relate to ASD and other developmental disorders (DD) in the child.

Methods

Study Population

The study population was drawn from the Study to Explore Early Development (SEED), a multisite case-control study of ASD and other developmental disabilities conducted in six sites across the United States: California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania [Schendel et al., 2012]. Children born between 2003 and 2006 who lived in a site catchment area both at birth and at study enrollment (2007–2011) were eligible to participate. Eligible children were also required to live with an English- (six sites) or Spanish-speaking (two sites) caregiver from at least 6 months of age. Three groups of children were enrolled at ages 2–5 years: children with ASD (cases), children with any one of a range of other neurodevelopmental disorders (DD controls—details summarized in Schendel et al., 2012), and children from the general population (POP controls). Children with ASD and DD were ascertained from multiple clinical and educational sources providing services for children with DD. POP controls were randomly sampled from state birth records in each site. The institutional review boards for each site approved the study and we obtained written informed consent for all enrolled participants.

Outcome Definition and Assessment

Final study group classification (ASD, DD, or POP) was determined by an in-person standardized developmental assessment [Wiggins et al., 2015]. During the study enrollment telephone call, the primary caregiver completed for the child the Social Communication Questionnaire (SCQ) [Rutter, Bailey, & Lord, 2003], a brief screener for ASD. Children who scored ≥11 on the SCQ, and children with a prior ASD diagnosis, were subsequently evaluated with the full assessment battery, which included the Autism Diagnostic Observation Schedule (ADOS) [Gotham, Risi, Pickles, & Lord, 2007; Lord et al., 2000; Lord, Rutter, DiLavore, & Risi, 1999], the Autism Diagnostic Interview Revised (ADI-R) [Lord, Rutter, & Le Couteur, 1994; Rutter, Le Couteur, & Lord, 2003], the Mullen Scales of Early Learning (MSEL) [Mullen, 1995], and the Vineland Adaptive Behavior Scales-Second Edition (VABS-II) [Sparrow, Cichetti, & Balla, 2005]. Children who scored <11 on the SCQ and who had no prior ASD diagnosis were evaluated with the MSEL followed by the VABS-II if the MSEL standard score was <78. If the assessor then suspected ASD, the full assessment battery was administered.

Children with a final classification of ASD ($N = 707$) were those who met the study ASD case classification criteria on both the ADOS and ADI-R [Wiggins et al., 2015]. We further classified ASD cases according to presence or absence of intellectual disability (ID), defined

as a composite standard score ≤70 on the MSEL. Children with a final classification of DD (N = 1270) were those who were ascertained from clinical or education sources with an indication of a neurodevelopmental disorder and who either scored <11 on the SCQ or who scored ≥11 but did not meet study ASD criteria after the full developmental assessment. Children with a final classification of POP (N = 1223) were those ascertained from random sampling of birth certificate files who either scored <11 on the SCQ or scored ≥11 but did not meet study ASD criteria. Only one child per family was included.

Ascertainment of Maternal Infection and Fever

Information on maternal infection and fever during pregnancy was obtained from the SEED caregiver interview (CGI) and the prenatal and labor/delivery medical record. The CGI, conducted over the telephone shortly after study enrollment when the study child was between 2 and 5 years old [Schendel et al., 2012], asked about infections in the period from 3 months before conception through the delivery of the study child. For each specific infection reported, the mother was asked to specify the timing during pregnancy, the types of medications taken, and whether any fever was present. Medical records were abstracted blinded to participant status and provided information on the timing of infections, any medications taken for infections, and the timing and severity of any fever related or unrelated to infection during the pregnancy through 24 hr postpartum.

The primary exposure of interest was maternal infection during the pregnancy with the study child, as reported on either the CGI and/or the maternal medical record. Infection was further classified by the researchers according to microorganism (virus, bacteria, fungus, parasite, unknown) and organ system affected (cardiovascular, eye, skin, gastrointestinal [GI], lower respiratory, other respiratory, GU, and unknown). To evaluate the independent effects of infection and fever, we also examined associations with maternal infections accompanied by fever, and infections for which fever was absent.

Covariates

We examined several factors previously found to be associated with ASD [Lyall et al., 2017] or maternal infection during pregnancy as potential confounders [Jiang et al., 2016]. Maternal age and child sex were ascertained during study enrollment. Maternal education, race-ethnicity, hypertension during pregnancy, and household income were collected during the caregiver interview. Maternal history of psychiatric diseases was ascertained from both the CGI and a self-administered maternal medical history form.

Statistical Analysis

Children whose mothers completed the CGI and provided a prenatal medical record comprised the analytic sample. Initial analyses compared the distributions of each potential confounder by outcome group and separately by exposure status using chi-square tests to assess statistical significance.

For each exposure definition, we ran separate unadjusted and adjusted logistic regression models to estimate the association with ASD (vs. POP controls, vs. DD) and DD (vs. POP controls) by trimester of exposure (T0 = 3 months preconception; T1 = first trimester; T2 =

second trimester; T3 = third trimester; and pregnancy [any trimester]). Adjusted logistic regression models included the following covariates: maternal self-reported race/ethnicity, maternal education, household income during pregnancy, maternal age at birth, maternal psychiatric condition history, maternal hypertension, child's sex, and study site. To evaluate the association with maternal infection or fever independent of potential effects of medication used to treat the condition, we also ran models that additionally adjusted for treatment with any medication. Because all analyses were conducted as part of a single hypothesis of whether ASD is associated with maternal infection, we did not control for multiple comparisons.

Results

The proportion of males was significantly higher in the ASD group compared to the DD and POP groups (Table 1). Mothers of children with ASD or DD were significantly more likely to be non-White, and to have a lower educational attainment at time of the index child's birth and lower household income during pregnancy compared with mothers of POP controls. ASD case mothers were also more likely to have a lifetime history of psychiatric conditions and hypertension during pregnancy than POP mothers. The majority of ASD cases had ID (59.2%).

Approximately 60% of mothers in each study group experienced an infection during pregnancy (Table 2). GU infections were the most frequently reported maternal infections in all three study groups, and were significantly more common among the mothers of children with ASD compared with the mothers of POP controls (31.5% vs. 26.4%, $P = 0.04$). Respiratory tract infections occurred in approximately 25% of mothers of ASD, DD, and POP children. Cardiovascular, skin, eye, ear, and GI infections each occurred in 3% or less of mothers of children in all outcome groups. According to microorganism, bacterial infections occurred in roughly a third of the population, and significantly more often in mothers of children with ASD than mothers of POP controls (36.3% vs. 31.3%, $P = 0.05$). The most commonly reported bacterial infections in all study groups were Group B Streptococcus (16.8% ASD, 10.5% DD, and 13.3% POP) and urinary tract infections (17% ASD, 13.8% DD, and 11.8% POP). Viral infections occurred in ~13% of the study population, with influenza (5.6% ASD, 5.6% DD, 5.4% POP) and human papillomavirus (2% ASD, 2.6% DD, 2.1% POP) being the most frequently reported in each study group. Fungal infections (11%–13%), all of which were yeast infections, and parasitic infections (~1%–2%) were the least common infections reported during pregnancy; there were no differences in prevalence across study groups (Table 2). Among women with any infection during pregnancy, there was laboratory confirmation of infection (positive cultures) for mothers of 155 (42.2%) ASD, 197 (31.1%) DD, and 197 (41.9%) POP children. The frequency of all laboratory-identified microorganisms is listed in Supporting Information Table S1. Only conditions with at least 10 affected women in each study group in each time period were analyzed further.

Crude and adjusted odds ratios (ORs) and 95% confidence interval (CI) for ASD and DD in association with timing of maternal infection during pregnancy are shown by organ system and by microorganism (Table 3). There was no association between any infection anytime

during pregnancy (T1–T3) and risk of ASD in crude and adjusted analyses (Table 3), and odds were similar for ASD with ID (aOR = 0.89, 95% CI 0.67–1.2) and ASD without ID (aOR = 1.31, 95% CI 0.67–2.56; Supporting Information Table S2). However, maternal infection in the 3 months prior to conception (T0) was significantly associated with higher risk of ASD after adjustment for covariates (Model 1), including adjustment for treatment with medication (Model 2; Table 3). This risk was only observed for ASD with ID (aOR = 2.06, 95% CI 1.31–3.24; Supporting Information Table S2). Any maternal infection in T3 was significantly associated with reduced risk for DD after adjustment for covariates (Model 1), but this association was no longer statistically significant after additional adjustment for treatment (Table 3). In all adjusted analyses, no significant associations with ASD or DD were observed for infections with specific organ systems or specific microorganisms (Table 3).

Among women who had an infection during pregnancy, fever was present for 23% of ASD cases, and 21% of both DD and POP controls. Infection accompanied by fever in T2 was associated with a doubling in odds of ASD versus POP in crude and adjusted analyses (Table 4). Infection with fever in T2 was also associated with higher odds of ASD compared to DD but the point estimate was smaller and not significant (Supplementary Table 3). Over 85% of infections with fever in T2 were respiratory infections (14% bacterial, 45% viral, 50% unknown organism). Additional adjustment for treatment with any medication (88% ASD, 52% POP), including antibiotics and antipyretics, did not alter the point estimate, but the association was no longer statistically significant (Table 4). Only two mothers (both of ASD cases) who did not report an infection reported a fever in T2. When fever from infection was combined with fever unrelated to infection, we observed a twofold increased risk for ASD associated with fever in T2, after adjusting for all covariates and treatment with any medication (aOR = 2.11, 95% CI 1.04–4.25) or treatment with acetaminophen (15% ASD, 14% POP, aOR = 2.23, 95% CI 1.15–4.35; Table 5). Risk was significantly elevated only for the ASD without ID subgroup (aOR = 3.17, 95% CI 1.51–6.67; Supporting Information Table S2). Infection without fever in T0 was associated with a marginally significant 70% increase in risk of ASD, after adjustment for all covariates including treatment with any medication (Table 4), and was driven by the ASD with ID subgroup (aOR = 1.92, 95% CI 1.26–2.92). The majority (52%) of these T0 infections without fever were GU (39% bacterial, 29% viral, 24% fungal, and 21% unknown organism). Infection without fever in T3 was associated with lower odds of DD (aOR = 0.71, 95% CI 0.55–0.90; Table 4).

Discussion

In this large and diverse U.S. study population, maternal infection during pregnancy occurred in approximately 60% of women. ASD was associated with maternal infection accompanied by fever during the second trimester and maternal infection without fever during the 3 months before conception, after controlling for several covariates including treatment with medication. By contrast, DD was not adversely associated with maternal infection with or without fever preconceptionally or in any trimester of pregnancy.

The prevalence of infection reported in the SEED study is comparable to that reported in another US study that defined infection based on diagnoses prospectively documented in electronic medical records [Zerbo et al., 2013]. That study also found no association between maternal infection overall and ASD. Unlike previous studies showing associations with maternal viral infection [Atladottir et al., 2012; Atladottir et al., 2010; Chess, 1971; Deykin & MacMahon, 1979; Libbey, Sweeten, McMahon, & Fujinami, 2005; Lintas, Altieri, Lombardi, Sacco, & Persico, 2010], bacterial infections [Atladottir et al., 2010; Fang et al., 2015; Zerbo et al., 2015], or GU tract infections [Fang et al., 2015], we did not identify any particular type of infection associated with ASD.

Our finding of an increased odds of ASD associated with maternal infection accompanied by fever in the second trimester is consistent with the results of three large cohort studies [Atladottir et al., 2012; Brucato et al., 2017; Hornig et al., 2017] and one case-control study [Zerbo et al., 2012]. Maternal fever in the second trimester was associated with elevated risk of ASD in a large Norwegian pregnancy cohort [Hornig et al., 2017], with prevalence of maternally reported fever (~16%) similar to that in our study. Second trimester fever of any length and fever lasting ≥7 days in the first and second trimester were also associated with increased risk of ASD in a large Danish cohort [Atladottir et al., 2012]. An increased risk for ASD was associated with maternal fever at any time during pregnancy and during the third trimester in a prospective birth cohort in Boston [Brucato et al., 2017]. Finally, second trimester fever doubled risk of ASD in CHARGE, a case-control study in California [Zerbo et al., 2012]. Unlike the CHARGE study, where use of any antipyretic treatment attenuated ASD risk, adjustment for acetaminophen use in our study and the Hornig study did not alter findings. Neither study was able to examine the impact of treatment with ibuprofen, an antipyretic with anti-inflammatory properties, since no ASD case mothers reported this exposure during pregnancy. Larger studies with information on fever and specific fever-related medications would help elucidate whether use of an anti-inflammatory to reduce fever results in lower risk of ASD compared to use of other antipyretics that do not have anti-inflammatory properties (i.e., acetaminophen).

Our finding that risk of ASD was elevated only in the presence of fever during pregnancy suggests that more severe infections accompanied by a robust inflammatory response may be etiologically relevant. Previous studies reporting increased ASD risk in association with severe, hospitalized infections [Atladottir et al., 2010; Lee et al., 2015; Zerbo et al., 2015] during pregnancy support this hypothesis. Furthermore, evidence from animal models demonstrate associations between maternal immune activation during pregnancy in the absence of infection, and behavioral and brain abnormalities in the offspring [Bauman et al., 2014; Shi, Fatemi, Sidwell, & Patterson, 2003; Shi et al., 2009], suggesting that the immune response rather than the infectious agent itself may have a direct impact on neurodevelopment. For example, rodent studies have shown that cytokines released during infection such as interleukin (IL)-6 or IL-17, can directly alter neurodevelopment [Choi et al., 2016; Shi et al., 2003]. In nonhuman primates, immune activation during pregnancy led to offspring with altered behaviors and immune responses [Rose et al., 2017]. Human studies also provide evidence that disrupted levels of immune molecules in the prenatal or neonatal periods is associated with ASD [Brown et al., 2014; Goines et al., 2011; Grether et al., 2016; Jones et al., 2016; Zerbo et al., 2016; Zerbo et al., 2014]. It is also possible that the

increase in maternal body temperature alone could adversely impact fetal brain development [Duong et al., 2011].

The association specific to second trimester fever was observed for ASD but not DD, and only among the subgroup of children with ASD without ID. We also observed that infections without fever were associated with lowered risk of DD in T3. The biological bases for these findings are not clear but this specificity of fever in the second trimester to an increased risk of ASD without ID was also observed in the Norwegian study [Hornig et al., 2017].

Strengths

In this large study population drawn from several geographic areas across the United States, child development status (ASD or DD) was validated by a comprehensive in-person developmental assessment using gold-standard diagnostic instruments. Our case-control design, including a DD group, allowed us to look at the specificity of our findings to ASD and its specific phenotypes. The comprehensive data collection battery, aggregating data from self-report and medical records, allowed us to conduct analyses by time period during pregnancy for types of infections and also examine treatment and fever effects. The prevalence of maternal infection and fever during pregnancy in our study was similar to reports in previous studies with prospective data collection [Hornig et al., 2017] indicating that ascertainment of exposure was likely accurate. Finally, we carefully controlled for several potential confounders.

Limitations

The prevalence of specific types of infections was low, precluding analyses of specific infections that were associated with ASD risk in previous studies. We did not have data on number, duration, and intensity of fevers, nor the severity of infection. Maternal self-reporting of infection and fever may have introduced some exposure misclassification; however, final exposure status included information recorded in maternal medical records, diminishing the possibility of biased results due to faulty recall. Given the small counts for some analyses, our findings could be due to chance or residual confounding by unmeasured confounders. We also lacked data to explore phenotypic subtypes by behavioral or psychiatric comorbidities such as ADHD. Finally, several families of potentially eligible children did not respond to the SEED invitation letter, and the sociodemographic profile of the enrolled study population was somewhat different than expected, with a higher proportion of non-White, lower educational attainment, and lower income mothers among the ASD and DD cases than POP controls [DiGuiseppi et al., 2016]. We hypothesize that the developmental assessment offered to participants in the SEED study was more of an incentive for mothers of potential ASD and DD cases than POP controls, especially those who had lower education and income, and thus less access to clinical evaluations for autism or DDs. Despite differential response between cases and controls on select sociodemographic characteristics, findings from the SEED study appear robust for other nondemographic factors [Schieve, Harris, Maenner, Alexander, & Dowling, 2018]. Furthermore, our analyses were adjusted for maternal age, education, and race-ethnicity, the only variables associated with nonresponse.

Conclusion

Our findings suggest that maternal infection with fever in the second trimester may be associated with increased risk of ASD in offspring. Future studies with adequate sample size, detailed information on type and timing of maternal exposure to infection and fever, and specific developmental outcomes in the child are needed to further understand the specificity of the associations and elucidate potential biologic mechanisms underlying them.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of the Study Population, Study to Explore Early Development (SEED), 2003–2006 Births

	ASD (*N* = 606)	DD (*N* = 856)	POP (*N* = 796)	ASD vs. POP	DD vs. POP	ASD vs. DD
Variable name	***N* (%)**	***N* (%)**	***N* (%)**	***P*-value**	***P*-value**	***P*-value**
Child sex (Male)	496 (81.85)	569 (66.47)	417 (52.39)	<0.0001	<0.0001	<0.0001
Intellectual disability	359 (59.24)	180 (21.03)	16 (2.01)	<0.0001	<0.0001	<0.0001
Maternal age at birth (years)				0.0499	0.0131	0.3524
<20	17 (2.81)	30 (3.50)	26 (3.27)			
21–25	75 (12.38)	113 (13.20)	65 (8.17)			
26–30	176 (29.04)	212 (24.77)	211 (26.51)			
31–35	206 (33.99)	290 (33.88)	305 (38.32)			
≥36	132 (21.78)	211 (24.65)	189 (23.74)			
Maternal race/ethnicity				<0.0001	<0.0001	0.0429
White	397 (65.51)	581 (67.87)	621 (78.02)			
Black	109 (17.99)	146 (17.06)	82 (10.30)			
Asian	45 (7.43)	32 (3.74)	31 (3.89)			
Hispanic	25 (4.13)	46 (5.37)	23 (2.89)			
Other	26 (4.29)	45 (5.26)	34 (4.27)			
Unknown	4 (0.66)	6 (0.70)	5 (0.63)			
Maternal education				<0.0001	<0.0001	0.1078
High school or less	92 (15.18)	155 (18.11)	66 (8.29)			
College or some college	378 (62.38)	491 (57.36)	485 (60.93)			
Graduate school	133 (21.95)	209 (24.42)	244 (30.65)			
Unknown	3 (0.50)	1 (0.12)	1 (0.13)			
Family income during pregnancy				<0.0001	<0.0001	0.3011
<30 K	148 (24.42)	185 (21.61)	101 (12.69)			
30–70 K	183 (30.20)	256 (29.91)	233 (29.27)			
70–110 K	156 (25.74)	227 (26.52)	264 (33.17)			
>110 K	102 (16.83)	147 (17.17)	180 (22.61)			
Unknown	17 (2.81)	41 (4.79)	18 (2.26)			
Maternal psychiatric condition history				<0.0001	0.0005	0.5475

Variable name	ASD (*N* = 606) *N* (%)	DD (*N* = 856) *N* (%)	POP (*N* = 796) *N* (%)	ASD vs. POP *P*-value	DD vs. POP *P*-value	ASD vs. DD *P*-value
Yes	256 (42.24)	344 (40.19)	247 (31.03)			
No	331 (54.62)	490 (57.24)	526 (66.08)			
Unknown	19 (3.14)	22 (2.57)	23 (2.89)			
Hypertension during pregnancy				0.0006	<0.0001	<0.0001
Yes	115 (18.98)	132 (15.42)	93 (11.68)			
No	472 (77.89)	558 (65.19)	680 (85.43)			
Unknown	19 (3.14)	166 (19.39)	23 (2.89)			
Site				0.7983	0.049	0.0035
2	75 (12.38)	108 (12.62)	100 (12.56)			
3	134 (22.11)	165 (19.28)	179 (22.49)			
4	111 (18.32)	180 (21.03)	142 (17.84)			
5	102 (16.83)	102 (11.92)	115 (14.45)			
6	101 (16.67)	200 (23.36)	151 (18.97)			
7	83 (13.70)	101 (11.80)	109 (13.69)			

Abbreviations: ASD, autism spectrum disorder; DD, developmental disorder; POP, population controls.

Table 2.

Maternal Infection During Pregnancy[a], by Organ System and Organism, Study to Explore Early Development, 2003–2006 Births

Maternal infection	ASD (*N* = 606) *N* (%)	DD (*N* = 856) *N* (%)	POP (*N* = 796) *N* (%)	ASD vs. POP *P*-value	DD vs. POP *P*-value	ASD vs. DD *P*-value
Any infection	367 (60.56)	504 (58.88)	470 (59.05)	0.58	0.96	0.52
Organ system						
Cardiovascular	1 (0.17)	0 (0.00)	1 (0.13)	1.00		0.41
Eye	5 (0.83)	4 (0.47)	6 (0.75)	1.00	0.54	0.50
Gastrointestinal	17 (2.81)	32 (3.74)	24 (3.02)	0.87	0.50	0.33
Genitourinary	191 (31.52)	244 (28.50)	210 (26.38)	**0.04**	0.35	0.21
Lower respiratory	6 (0.99)	11 (1.29)	6 (0.75)	0.77	0.34	0.60
Other respiratory[b]	144 (23.76)	217 (25.35)	201 (25.25)	0.53	1.00	0.49
Skin	11 (1.82)	15 (1.57)	6 (0.75)	0.09	0.08	0.93
Other organ	25 (4.13)	38 (4.44)	29 (3.64)	0.68	0.87	0.77
Unknown organ	189 (31.19)	206 (20.07)	198 (24.87)	**0.01**	0.73	**0.002**
Organism						
Bacteria	220 (36.30)	264 (30.84)	249 (31.28)	**0.05**	0.87	**0.02**
Virus	82 (13.53)	114 (13.32)	104 (13.07)	0.81	0.88	0.91
Fungus	82 (13.53)	101 (11.80)	90 (11.31)	0.22	0.76	0.32
Parasite	9 (1.49)	20 (2.34)	11 (1.38)	1.00	0.20	0.25
Unknown	188 (31.22)	269 (31.43)	244 (30.65)	0.91	0.75	0.77

Abbreviations: ASD, autism spectrum disorder; DD, developmental disorder; POP, population controls.

[a]Infection data obtained from both CGI and medical records.

[b]Other respiratory includes all respiratory infections not medically identified as lower respiratory. These include upper respiratory, throat, or other infections of the respiratory system.

The bold indicates that the *P*-value is <0.05.

Table 3.

Maternal Infection[c] by Organ System, Organism, and Timing During Pregnancy and Risk of Autism Spectrum Disorder and Developmental Disorder, Study to Explore Early Development, 2003–2006 Births

Infection by trimester	ASD (*N* = 606) *N* (%)	DD (*N* = 856) *N* (%)	POP (*N* = 796) *N* (%)	ASD vs. POP Crude OR (95% CI)	ASD vs. POP ORadjl (95% CI)	ASD vs. POP ORadj2 (95% CI)	DD vs. POP Crude OR (95% CI)	DD vs. POP ORadjl (95% CI)	DD vs. POP ORadj2 (95% CI)
Any infection									
T0	76 (12.5)	73 (8.5)	62 (7.8)	**1.70 (1.2–2.4)**	**1.58 (1.05–2.37)**	**1.73 (1.03–2.93)**	1.10 (0.08–1.57)	0.98 (0.65–1.46)	0.91 (0.53–1.57)
T1	174 (28.71)	227 (26.52)	203 (25.50)	1.18 (0.93–1.49)	1.19 (0.90–1.56)	1.09 (0.79–1.50)	1.05 (0.85–1.31)	0.99 (0.77–1.28)	0.93 (0.69–1.25)
T2	187 (30.86)	260 (30.37)	221 (27.76)	1.16 (0.92–1.46)	1.02 (0.78–1.33)	0.87 (0.65–1.17)	1.14 (0.92–1.40)	0.88 (0.69–1.13)	0.81 (0.62–1.06)
T3	252 (41.58)	308 (35.98)	311 (39.07)	1.11 (0.90–1.38)	1.04 (0.81–1.33)	1.11 (0.84–1.45)	0.88 (0.72–1.07)	**0.74 (0.59–0.93)**	0.83 (0.65–1.06)
Pregnancy	367 (60.6)	504 (58.9)	470 (59.0)	1.07 (0.86–1.3)	1.02 (0.79–1.31)	0.94 (0.68–1.31)	0.99 (0.81–1.2)	0.84 (0.67–1.05)	0.80 (0.59–1.08)
Organ system									
Respiratory[a]									
T0	17 (2.81)	12 (1.40)	14 (1.76)	1.61 (0.79–3.30)	1.35 (0.59–3.10)	1.73 (0.46–6.49)	0.79 (0.37–1.73)	1.00 (0.43–2.30)	0.79 (0.20–3.10)
T1	48 (7.92)	70 (8.18)	59 (7.41)	1.07 (0.72–1.60)	1.32 (0.84–2.08)	1.24 (0.77–1.99)	1.11 (0.78–1.60)	1.13 (0.74–1.70)	1.10 (0.72–1.68)
T2	64 (10.56)	106 (12.38)	87 (10.93)	0.96 (0.68–1.35)	1.05 (0.70–1.56)	0.97 (0.64–1.45)	1.15 (0.85–1.56)	1.01 (0.71–1.45)	0.98 (0.68–1.41)
T3	69 (11.39)	99 (11.57)	103 (12.94)	0.86 (0.62–1.20)	0.81 (0.56–1.19)	0.84 (0.57–1.25)	0.88 (0.66–1.18)	0.76 (0.53–1.08)	0.78 (0.55–1.12)
Pregnancy	145 (23.93)	219 (25.58)	205 (25.75)	0.91 (0.71–1.16)	0.97 (0.73–1.30)	0.79 (0.51–1.23)	0.99 (0.79–1.24)	0.88 (0.68–1.15)	0.86 (0.58–1.26)
Genitourinary									
T0	38 (6.27)	39 (4.56)	28 (3.52)	**1.84 (1.11–3.03)**	1.67 (0.94–2.98)	1.52 (0.76–3.04)	1.31 (0.80–2.15)	1.20 (0.67–2.13)	0.93 (0.46–1.86)
T1	87 (14.36)	99 (11.57)	98 (12.31)	1.19 (0.88–1.63)	1.16 (0.81–1.66)	1.01 (0.66–1.55)	0.93 (0.69–1.25)	0.80 (0.57–1.14)	0.66 (0.44–1.00)
T2	87 (14.36)	123 (14.37)	87 (10.93)	1.37 (0.99–1.88)	1.02 (0.70–1.47)	0.80 (0.53–1.20)	**1.37 (1.02–1.83)**	0.99 (0.70–1.39)	0.91 (0.62–1.32)
T3	107 (17.66)	128 (14.95)	120 (15.08)	1.21 (0.91–1.61)	1.09 (0.79–1.51)	1.17 (0.82–1.67)	0.99 (0.76–1.30)	0.80 (0.58–1.10)	0.86 (0.61–1.21)
Pregnancy	191 (31.52)	244 (28.50)	212 (26.63)	1.27 (1.00–1.60)	1.12 (0.86–1.48)	1.08 (0.74–1.57)	1.10 (0.88–1.36)	0.86 (0.67–1.12)	0.83 (0.57–1.19)
Other/unknown[b]									
T0	27 (4.46)	32 (3.74)	25 (3.14)	1.44 (0.83–2.50)	1.51 (0.81–2.83)	1.48 (0.64–3.41)	1.20 (0.70–2.04)	0.78 (0.41–1.50)	0.59 (0.20–1.71)
T1	83 (13.70)	105 (12.27)	85 (10.68)	1.33 (0.96–1.83)	1.23 (0.85–1.79)	1.21 (0.78–1.86)	1.17 (0.86–1.58)	1.07 (0.76–1.52)	1.01 (0.67–1.51)
T2	74 (12.21)	94 (10.98)	82 (10.30)	1.21 (0.87–1.69)	0.99 (0.68–1.45)	0.86 (0.56–1.32)	1.07 (0.79–1.47)	0.79 (0.54–1.14)	0.78 (0.53–1.16)
T3	148 (24.42)	155 (18.11)	156 (19.60)	**1.33 (1.03–1.71)**	1.28 (0.95–1.71)	1.33 (0.95–1.87)	0.91 (0.71–1.16)	0.84 (0.64–1.11)	0.89 (0.64–1.22)
Pregnancy	213 (35.15)	263 (30.72)	237 (29.77)	**1.28 (1.02–1.60)**	1.18 (0.91–1.53)	1.25 (0.87–1.79)	1.05 (0.85–1.29)	0.95 (0.75–1.21)	1.02 (0.73–1.42)

Infection by trimester	ASD (*N* = 606) *N* (%)	DD (*N* = 856) *N* (%)	POP (*N* = 796) *N* (%)	ASD vs. POP			DD vs. POP		
				Crude OR (95% CI)	ORadjl (95% CI)	ORadj2 (95% CI)	Crude OR (95% CI)	ORadjl (95% CI)	ORadj2 (95% CI)
Organism									
Bacteria									
T0	31 (5.12)	31 (3.62)	19 (2.39)	**2.20 (1.23–3.94)**	1.77 (0.90–3.50)	1.61 (0.66–3.90)	1.54 (0.86–2.74)	1.06 (0.52–2.15)	0.75 (0.23–2.51)
T1	74 (12.21)	79 (9.23)	80 (10.05)	1.24 (0.89–1.74)	1.22 (0.82–1.79)	1.07 (0.65–1.77)	0.91 (0.66–1.26)	0.81 (0.55–1.19)	0.74 (0.45–1.21)
T2	79 (13.04)	87 (10.16)	68 (8.54)	**1.60 (1.14–2.26)**	1.15 (0.78–1.71)	0.80 (0.50–1.28)	1.21 (0.87–1.69)	0.82 (0.55–1.22)	0.72 (0.46–1.13)
T3	152 (25.08)	167 (19.51)	171 (21.48)	1.22 (0.95–1.57)	1.14 (0.86–1.52)	1.07 (0.77–1.49)	0.89 (0.70–1.13)	0.78 (0.59–1.03)	0.87 (0.64–1.19)
Pregnancy	221 (36.47)	264 (30.84)	249 (31.28)	**1.26 (1.01–1.58)**	1.14 (0.88–1.48)	0.96 (0.67–1.36)	0.98 (0.80–1.21)	0.85 (0.67–1.08)	0.90 (0.65–1.24)
Virus									
T0	21 (3.47)	20 (2.34)	21 (2.64)	1.32 (0.72–2.45)	1.44 (0.72–2.88)	1.65 (0.78–3.47)	0.88 (0.47–1.64)	1.01 (0.51–2.01)	1.04 (0.51–2.13)
T1	40 (6.60)	44 (5.14)	38 (4.77)	1.41 (0.89–2.23)	1.48 (0.88–2.47)	1.48 (0.83–2.64)	1.08 (0.69–1.69)	0.89 (0.54–1.49)	0.81 (0.46–1.42)
T2	38 (6.27)	57 (6.66)	55 (6.91)	0.90 (0.59–1.38)	0.86 (0.53–1.39)	0.81 (0.48–1.37)	0.96 (0.65–1.41)	0.90 (0.59–1.39)	0.78 (0.49–1.25)
T3	44 (7.26)	59 (6.89)	56 (7.04)	1.03 (0.69–1.56)	0.98 (0.62–1.55)	0.91 (0.54–1.53)	0.98 (0.67–1.43)	0.91 (0.59–1.39)	0.90 (0.56–1.44)
Pregnancy	82 (13.53)	114 (13.32)	104 (13.07)	1.04 (0.76–1.42)	0.99 (0.69–1.40)	0.83 (0.54–1.30)	1.02 (0.77–1.36)	0.87 (0.63–1.21)	0.75 (0.49–1.14)
Fungus									
T0	14 (2.31)	19 (2.22)	14 (1.76)	1.32 (0.62–2.79)	1.65 (0.70–3.86)	3.22 (0.45–22.99)	1.27 (0.63–2.55)	0.90 (0.39–2.06)	
T1	38 (6.27)	51 (5.96)	37 (4.65)	1.37 (0.86–2.19)	1.11 (0.66–1.88)	0.92 (0.43–1.93)	1.30 (0.84–2.01)	1.16 (0.71–1.90)	0.89 (0.43–1.82)
T2	39 (6.44)	44 (5.14)	37 (4.65)	1.41 (0.89–2.24)	1.17 (0.69–1.97)	1.55 (0.75–3.23)	1.11 (0.71–1.74)	0.77 (0.45–1.30)	0.82 (0.40–1.66)
T3	36 (5.94)	39 (4.56)	37 (4.65)	1.30 (0.81–2.08)	1.08 (0.63–1.84)	1.51 (0.70–3.27)	0.98 (0.62–1.55)	0.81 (0.48–1.36)	1.05 (0.53–2.09)
Pregnancy	82 (13.53)	101 (11.80)	90 (11.31)	1.23 (0.89–1.69)	1.05 (0.72–1.51)	1.64 (0.83–3.25)	1.05 (0.78–1.42)	0.87 (0.62–1.23)	1.09 (0.55–2.17)
Unknown									
T0	18 (2.97)	14 (1.64)	15 (1.88)	1.59 (0.80–3.19)	1.38 (0.62–3.10)	1.51 (0.52–4.38)	0.87 (0.42–1.81)	0.99 (0.44–2.23)	1.07 (0.35–3.20)
Tl	79 (13.04)	96 (11.21)	87 (10.93)	1.22 (0.88–1.69)	1.38 (0.95–2.01)	1.38 (0.92–2.07)	1.03 (0.76–1.40)	1.05 (0.74–1.49)	1.05 (0.72–1.54)
T2	77 (12.71)	127 (14.84)	97 (12.19)	1.05 (0.76–1.44)	0.98 (0.68–1.42)	0.85 (0.57–1.25)	1.26 (0.95–1.67)	1.02 (0.73–1.43)	0.98 (0.70–1.39)
T3	103 (17.00)	124 (14.49)	128 (16.08)	1.07 (0.80–1.42)	1.10 (0.79–1.53)	1.22 (0.87–1.73)	0.88 (0.68–1.16)	0.78 (0.57–1.07)	0.82 (0.59–1.14)
Pregnancy	186 (30.69)	269 (31.43)	243 (30.53)	1.01 (0.80–1.27)	1.02 (0.79–1.34)	0.90 (0.61–1.32)	1.04 (0.85–1.28)	0.93 (0.73–1.18	0.82 (0.58–1.16)

Abbreviations: ASD, autism spectrum disorder; DD, developmental disorder; POP, population controls; OR, odds ratio; ORadj, adjusted odds ratio; T0, 3 months before conception; T1, trimester one; T2, trimester two; T3, trimester three.

Note. ORadj1 = adjusted for child sex, maternal age, maternal race, maternal education, income during pregnancy, maternal psychiatric disease history, hypertension, site. ORadj2 = adjusted by all variables in model 1 plus any medication for infection.

[a]Respiratory = lower respiratory, other respiratory.

[b] Other/Unknown = cardiovascular, skin, eye, GI, other, unknown.

[c] Infection data obtained from both CGI and medical records.

The bold entries indicate that the confidence interval does not include 1.0, indicating statistical significance.

Table 4.

Maternal Infection[a] With and Without Fever by Timing During Pregnancy and Risk of Autism Spectrum Disorder, Study to Explore Early Development, 2003–2006 Births

				ASD vs. POP			DD vs. POP		
Infection by trimester	**ASD *N* (%)**	**DD *N* (%)**	**POP *N* (%)**	**Crude OR (95% CI)**	**ORadjl (95% CI)**	**ORadj2 (95% CI)**	**Crude OR (95% CI)**	**ORadjl (95% CI)**	**ORadj2 (95% CI)**
Any infection with fever									
T0	11 (2.03)	4 (0.51)	7 (0.94)	2.18 (0.84–5.65)	2.11 (0.68–6.58)	-	0.54 (0.16–1.84)	0.26 (0.05–1.48)	-
T1	20 (4.42)	16 (2.48)	25 (4.05)	1.10 (0.60–2.00)	0.91 (0.46–1.79)	0.87 (0.32–2.40)	0.60 (0.32–1.14)	0.55 (0.27–1.15)	0.61 (0.25–1.49)
T2	31 (6.89)	38 (5.99)	21 (3.52)	**2.03 (1.15–3.58)**	**2.19 (1.14–4.23)**	2.05 (0.95–4.45)	**1.75 (1.01–3.01)**	1.65 (0.87–3.11)	1.46 (0.74–2.87)
T3	30 (7.81)	48 (8.05)	44 (8.32)	0.93 (0.58–1.52)	0.80 (0.45–1.40)	1.04 (0.56–1.93)	0.97 (0.63–1.48)	0.88 (0.54–1.44)	1.05 (0.60–1.81)
Pregnancy	73 (23.40)	92 (20.72)	86 (20.87)	1.16 (0.81–1.65)	1.08 (0.71–1.62)	0.95 (0.45–1.98)	0.99 (0.71–1.38)	0.86 (0.59–1.26)	0.63 (0.32–1.27)
Any infection without fever									
T0	65 (10.92)	69 (8.10)	55 (6.97)	**1.64 (1.12–2.33)**	1.51 (0.98–2.31)	**1.72 (1.01–2.94)**	1.18 (0.81–1.70)	1.05 (0.69–1.59)	0.96 (0.55–1.66)
T1	154 (26.28)	211 (25.12)	178 (23.09)	1.19 (0.93–1.52)	1.23 (0.92–1.64)	1.16 (0.84–1.62)	1.12 (0.89–1.40)	1.06 (0.81–1.39)	0.94 (0.69–1.28)
T2	156 (27.13)	222 (27.14)	200 (25.81)	1.07 (0.84–1.37)	0.92 (0.69–1.22)	0.83 (0.61–1.12)	1.07 (0.86–1.34)	0.82 (0.63–1.06)	0.77 (0.58–1.01)
T3	222 (38.45)	260 (32.18)	267 (35.51)	1.14 (0.91–1.43)	1.07 (0.83–1.38)	1.13 (0.85–1.49)	0.86 (0.70–1.06)	**0.71 (0.55–0.90)**	0.80 (0.62–1.04)
Pregnancy	294 (55.16)	412 (53.93)	384 (54.08)	1.04 (0.83–1.31)	1.01 (0.78–1.31)	0.96 (0.68–1.36)	0.99 (0.81–1.22)	0.82 (0.65–1.04)	0.83 (0.60–1.13)

Abbreviations: ASD, autism spectrum disorder; DD, developmental disorder; POP, population controls; OR, odds ratio; ORadj, adjusted odds ratio; T0, 3 months before conception; T1, trimester one; T2, trimester two; T3, trimester three.

Note. ORadj1 = adjusted by child sex, maternal age, maternal race, maternal education, income during pregnancy, maternal psychiatric disease history, hypertension, site. ORadj2 = adjusted by all variables in model 1 plus any medication for infection.

[a]Infection data obtained from both CGI and medical records.

The bold entries indicate that the confidence interval does not include 1.0, indicating statistical significance.

Table 5.

Maternal Fever (Infection and Noninfection Related)[a] by Timing During Pregnancy and Risk of Autism Spectrum Disorder, Study to Explore Early Development, 2003–2006 Births

Fever by trimester	ASD (N = 606) *N* (%)	DD (*N* = 856) *N* (%)	POP (*N* = 796) *N* (%)	ASD vs. POP			
				Crude OR	ORadj1	ORadj2	ORadj3
Any fever							
T0	11 (1.82)	4 (0.47)	7 (0.88)	2.08 (0.80–5.41)	2.00 (0.64–6.23)	2.68 (0.62–11.60)	2.27 (0.71–7.24)
T1	22 (3.63)	16 (1.87)	26 (3.27)	1.12 (0.63–1.99)	1.01 (0.53–1.91)	0.84 (0.40–1.75)	0.84 (0.41–1.72)
T2	33 (5.45)	40 (4.67)	21 (2.64)	**2.13 (1.22–3.17)**	**2.31 (1.21–4.39)**	**2.11 (1.04–4.25)**	**2.23 (1.15–4.35)**
T3	64 (10.56)	99 (11.57)	86 (10.80)	0.97 (0.69–1.37)	0.88 (0.60–1.30)	0.89 (0.60–1.31)	0.84 (0.56–1.25)
Pregnancy	105 (17.33)	138 (16.12)	124 (15.58)	1.14 (0.85–1.51)	1.06 (0.77–1.47)	1.05 (0.75–1.47)	0.99 (0.71–1.38)

Abbreviations: ASD, autism spectrum disorder; DD, developmental disorder; POP, population controls; OR, odds ratio; ORadj, adjusted odds ratio; T0, 3 months before conception; T1, trimester one; T2, trimester two; T3, trimester three.

Note. ORadj1 = adjusted by child sex, maternal age, maternal race, maternal education, income during pregnancy, maternal psychiatric disease history, hypertension, site. ORadj2 = adjusted by all variables in model 1 plus any medication for infection. ORadj3 = adjusted by all variables in model 1 plus acetaminophen use.

[a]Infection data obtained from both CGI and medical records.

The bold entries indicate that the confidence interval does not include 1.0, indicating statistical significance.