RESEARCH ARTICLE

Family History of Immune Conditions and Autism Spectrum and Developmental Disorders: Findings from the Study to Explore Early Development

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Numerous studies have reported immune system disturbances in individuals with autism and their family members; however, there is considerable variability in findings with respect to the specific immune conditions involved, their timing, and the family members affected and little understanding of variation by autism subphenotype. Using data from the Study to Explore Early Development (SEED), a multi-site case-control study of children born 2003–2006 in the United States, we examined the role of family history of autoimmune diseases, asthma, and allergies in autism spectrum disorder (ASD) as well as other developmental disorders (DD). We investigated maternal immune conditions during the pregnancy period, as well as lifetime history of these conditions in several family members (mother, father, siblings, and study child). Logistic regression analyses included 663 children with ASD, 984 children with DD, and 915 controls ascertained from the general population (POP). Maternal history of eczema/psoriasis and asthma was associated with a 20%–40% increased odds of both ASD and DD. Risk estimates varied by specific ASD subphenotypes in association with these exposures. In addition, children with ASD were more likely to have a history of psoriasis/eczema or allergies than POP controls. No association was observed for paternal history or family history of these immune conditions for either ASD or DD. These data support a link between maternal and child immune conditions and adverse neurodevelopmental outcomes, and further suggest that associations may differ by ASD phenotype of the child. ***Autism Res*** *2018, 0: 000–000.* © 2018 International Society for Autism Research, Wiley Periodicals, Inc.

Lay Summary: Using data from a large multi-site study in the US—the Study to Explore Early Development—we found that women with a history of eczema/psoriasis and asthma are more likely to have children with ASD or DD. In addition, children with ASD are more likely to have a history of psoriasis/eczema or allergies than typically developing children. These data support a link between maternal and child immune conditions and adverse neurodevelopmental outcomes.

Keywords: autism; autoimmune; pregnancy; asthma; allergy; prenatal

Introduction

Autism spectrum disorder (ASD) is defined by impairments in social interaction and communication and restricted and repetitive patterns of behavior [American Psychiatric Association, 2013]. Typically, symptoms manifest by early childhood and persist throughout an individual's lifetime [Volkmar, Chawarska, & Klin, 2005]. While the genetic contribution to ASD etiology is well documented in a subset of individuals [Sandin et al., 2014; Gaugler et al., 2014] a growing body of evidence is revealing that nongenetic factors also play a critical role, especially during gestation and the early postnatal period [Hallmayer et al., 2011; Lyall et al., 2017].

There is strong evidence from animal and human studies that activation of the immune system, influenced by both genetic and nongenetic components, is involved in ASD etiology [Meltzer & Van de Water, 2017; Onore, Careaga, & Ashwood, 2012]. Numerous studies have found immune system dysregulation in individuals with ASD and among their family members,

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including disruptions in levels of immune system molecules and increased rates of clinical immune-mediated conditions. Several studies have provided evidence that disruption of normal levels of immune molecules (e.g., cytokines, chemokines, immunoglobulins, C-reactive protein) during gestation [Goines et al., 2011; Jones et al., 2017; Grether et al., 2016; Zerbo et al., 2016; Brown et al., 2014; Koks et al., 2016; Mahic et al., 2017], at birth [Zerbo et al., 2014; Grether et al., 2016; Grether, Croen, Anderson, Nelson, & Yolken, 2010; Abdallah et al., 2013] or in early childhood [Ashwood et al., 2011b, 2011c; Careaga et al., 2017; Ashwood et al., 2011a] is associated with ASD. Furthermore, associations between maternal and child autoantibodies to fetal brain proteins and risk of ASD has been reported across multiple study populations [Edmiston, Ashwood, & Van de Water, 2017].

Frequently, studies have found that children with ASD have a higher prevalence of allergies, atopic dermatitis, asthma, and autoimmune diseases including psoriasis [Mostafa, Hamza, & El-Shahawi, 2008; Magalhaes et al., 2009; Chaidez, Hansen, & Hertz-Picciotto, 2014; Zerbo et al., 2015; Jyonouchi, Geng, Cushing-Ruby, & Quraishi, 2008] than typically developing children, but the specific conditions and magnitude of the effect have varied across studies. Moreover, many studies have reported associations between increased ASD risk and immune-mediated conditions in the mother [Brown et al., 2015; Andersen, Laurberg, Wu, & Olsen, 2014; Atladottir et al., 2009; Lyall, Ashwood, Van de Water, & Hertz-Picciotto, 2014; Lyall, Pauls, Spiegelman, Ascherio, & Santangelo, 2012; Keil et al., 2010; Croen, Grether, Yoshida, Odouli, & Van de Water, 2005; Comi, Zimmerman, Frye, Law, & Peeden, 1999; Mouridsen, Rich, Isager, & Nedergaard, 2007; Sweeten, Bowyer, Posey, Halberstadt, & McDougle, 2003]. There is, however, considerable variability in the specific conditions found to be associated with ASD risk, and only a handful of studies had information on presence of these conditions during the pregnancy period [Chen et al. 2016]. Finally, some studies have investigated ASD risk in association with history of autoimmune conditions in fathers [Andersen et al., 2014; Atladottir et al., 2009; Keil et al., 2010; Mouridsen et al., 2007] or any family member [Atladottir et al., 2009; Comi et al., 1999; Mostafa & Shehab, 2010; Valicenti-McDermott et al., 2006] again with varying results [Wu et al., 2015].

The goal of this paper was to further examine the role of family history of autoimmune diseases, asthma, and allergies in ASD as well as other developmental disorders (DD) in a large, geographically and demographically diverse US population. Using data from the Study to Explore Early Development (SEED) multi-site case-control study, we investigated maternal immune conditions during the pregnancy period, as well as lifetime history of these conditions in several family members (mother, father, siblings, and study child). The comprehensive and robust data collection in SEED allowed for more refined exposure assignments based on both diagnoses and treatment for condition, and more in-depth analysis of ASD phenotypes, features that were lacking in previous studies. Findings will contribute to a better understanding of the etiology of ASD and may also aid earlier identification, intervention and subsequent prevention of these conditions.

Methods and Materials

Study Population

The study population was drawn from the Study to Explore Early Development (SEED), a multi-site case-control study conducted in six sites across the USA: California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania [Schendel et al., 2012]. SEED was designed to investigate a broad range of potential risk factors for ASD, as well as to characterize ASD phenotypes and co-morbidities in a large geographically, racially and ethnically diverse population. Children born between 2003 and 2006 who lived in a study site catchment area both at birth and at study enrollment were eligible to participate. Eligible children were also required to live with an English- (all 6 sites) or Spanish-speaking (California and Colorado only) caregiver from at least 6 months of age. At each study site, three groups of children were enrolled at 2–5 years of age: children with ASD, children with any one of a range of other neurodevelopmental disorders (DD), and children from the general population (POP). Children with ASD and DD were ascertained from multiple clinical and educational sources providing services for children with developmental disorders. Children from the POP control group were randomly sampled from State birth records in each site. The study was approved by the institutional review boards for each site, and written informed consent was obtained for all enrolled participants.

Outcome Assessment

For each enrolled child, final study group classification (ASD, DD, or POP) was determined by an in-person standardized developmental assessment, described in detail elsewhere [Wiggins et al., 2015] and summarized here. During the study enrollment telephone call, the primary caregiver completed the Social Communication Questionnaire (SCQ) [Rutter, Bailey, & Lord, 2003a], a brief screener for ASD. Children who scored >=11 on the SCQ, and children with a prior ASD diagnosis regardless of their SCQ score, were subsequently evaluated with the full assessment battery which included the Autism

Diagnostic Observation Schedule (ADOS) [Lord, Rutter, DiLavore, & Risi, 1999; Lord et al., 2000; Gotham, Risi, Pickles, & Lord, 2007], the Autism Diagnostic Interview Revised (ADI-R) [Lord, Rutter, & Le Couteur, 1994; Rutter, Le Couteur, & Lord, 2003b], 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, and VABS-II if the MSEL standard score was less than 78. All assessors were fully trained on each assessment. If, during the evaluation, the assessor suspected ASD, the full assessment battery was administered.

Children with a final classification of ASD ($N = 707$) were those who met ASD criteria based on the ADOS and ADI-R. Children with a final classification of DD ($N = 1270$) or POP ($N = 1223$) were those who were originally ascertained as DD or POP, respectively, and who scored below 11 on the SCQ or who scored at or above 11 but did not meet ASD criteria after the full developmental assessment [Wiggins et al., 2015].

We further defined subgroups of ASD based on severity (mild/moderate, severe), having sibling(s) with ASD (simplex (none), multiplex (one or more)), and on presence/absence of intellectual disability (ID) and developmental regression. Severity was defined according to the ADOS calibrated severity score [Gotham, Pickles, & Lord, 2009], which measures severity of social communication deficits and restricted interests and repetitive behaviors separate from co-occurring conditions such as intellectual disability and language delay. Presence of ASD among siblings was determined by the caregiver interview. ID was defined by a MSEL Composite Standard Score <70. Regression was based on parent report of language or social regression on the ADI-R. While only one child per family (index child) was recruited into SEED, some families enrolled a sibling as well. Only index children were included in these analyses.

Family History of Immune Conditions

Three categories of immune conditions were examined—autoimmune diseases, asthma, and allergies. The information on these conditions was collected during a computer-assisted telephone interview with the primary caregiver, on various paper forms/questionnaires (autoimmune disease survey, maternal and paternal medical history forms) completed by the primary caregiver or parent, and abstracted by research staff from prenatal medical records [Schendel et al., 2012]. We collected information on the presence and age at first diagnosis of 32 distinct autoimmune conditions and asthma for the birth mother, birth father, siblings of the index child, and the index child; history and age of onset of allergies for the birth mother, birth father, and index child; and medications taken for these conditions by the birth mother from 3 months prior to conception through the date of delivery of the index child, and by the index child. Information about siblings was collected only on the autoimmune disease survey which asked about autoimmune diseases and asthma but not allergies. Among the children who completed the clinic visit and had a final classification, the autoimmune disease survey was completed by the primary caregiver for 672 (95%) children with ASD, 997 (79%) children with DD, and 925 (76%) POP controls, of whom 99% completed the maternal medical history form, 97% completed the caregiver interview, and 85% had an abstracted prenatal medical record.

The primary exposures of interest were maternal autoimmune diseases, asthma, and allergies during the pregnancy of the study child. A mother was categorized as having these conditions if (a) she reported them on the autoimmune disease survey or maternal medical history form with age of first diagnosis or onset prior to the child's delivery date, (b) she reported during the caregiver interview the use of medication to treat these conditions during pregnancy, or (c) the prenatal medical record indicated treatments for these conditions during pregnancy.

Secondary exposures of interest included family history of these immune conditions (maternal, paternal, index child, or family (mother, father, or siblings)). History was defined as presence of these conditions at any point in life up to the date of data collection (i.e., including conditions diagnosed before or after the delivery of the index child).

Covariates

We examined several factors previously found to be associated with ASD [Lyall et al., 2017] or maternal immune conditions during pregnancy as potential confounders, including maternal age and education at date of delivery of index child, maternal race-ethnicity, household income at time of caregiver interview, and child sex. Maternal age and child sex were ascertained during study enrollment. Maternal education, race-ethnicity, and household income were collected during the caregiver interview.

Statistical Analysis

Children with a completed autoimmune disease survey and maternal medical history form comprised the final analytic sample ($N = 2562$; 663 ASD, 984 DD, and 915 POP). 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.

Table 1. Characteristics of the Study Population, Study to Explore Early Development (SEED), 2003–2006 Births

Demographic	ASD ($N = 663$) N (%)	DD ($N = 984$) N (%)	POP ($N = 915$) N (%)	ASD vs POP P value	DD vs POP P value
Child Sex					
Female	117 (17.6)	331 (33.6)	419 (45.8)	<.0001	<.0001
Male	546 (82.3)	653 (66.4)	496 (54.2)		
Maternal Age (in years)					
<= 20	14 (2.1)	31 (3.1)	29 (3.2)	0.064	0.1917
21–25	73 (11.0)	106 (10.8)	69 (7.5)		
26–30	163 (24.6)	220 (22.4)	205 (22.4)		
31–35	224 (33.8)	347 (35.3)	339 (37.0)		
36+	189 (28.5)	280 (28.5)	273 (29.8)		
Maternal Race/Ethnicity					
White	405 (61.1)	649 (66.0)	682 (74.5)	<.0001	<.0001
Black	132 (19.9)	175 (17.8)	112 (12.2)		
Asian	57 (8.6)	37 (3.8)	42 (4.6)		
Hispanic	27 (4.1)	53 (5.4)	23 (2.5)		
Other/ Unknown	42 (6.3)	70 (7.1)	56 (6.1)		
Material Education					
High School or less	105 (15.8)	191 (19.4)	87 (9.5)	<.0001	<.0001
College & Some College	409 (61.7)	546 (55.5)	544 (59.4)		
Graduate Degree	141 (21.3)	233 (23.7)	272 (29.7)		
Unknown	8 (1.2)	14 (1.4)	12 (1.3)		
Current Household Income					
< 30K	159 (24.0)	209 (21.2)	121 (13.2)	<.0001	<.0001
30–70K	170 (25.6)	253 (25.7)	200 (21.9)		
70–110K	157 (23.7)	239 (24.3)	238 (26.0)		
>110K	154 (23.2)	219 (22.3)	315 (34.4)		
Unknown	23 (3.5)	64 (6.5)	41 (4.5)		

Table 2. Phenotypic Characteristics of ASD Cases, Study to Explore Early Development (SEED), 2003–2006 Births

Phenotypes	ASD ($N = 663$) N (%)
ASD Severity	
Mild/moderate	397 (59.9%)
Severe	264 (39.8%)
Sibling(s) with ASD	
No (Simplex)	606 (91.40)
Yes (Multiplex)	57 (8.60)
ID Status	
No	249 (37.56)
Yes	414 (62.44)
Regression	
No	475 (71.64)
Yes	188 (28.36)
Language Regression	111 (16.74)
Social Regression	141 (21.27)

For both primary and secondary exposure definitions, we ran separate unadjusted and adjusted logistic regression models to estimate the association between each immune condition and ASD versus POP controls, and DD versus POP controls. Adjusted logistic regression models included maternal race-ethnicity (white, black, Asian, Hispanic-race not specified, other/unknown), maternal education (high school or below, some college/bachelor's degree, advanced degree, unknown), current household income at time of caregiver interview (<$30,000, $30,000–$70,000, $70,000–$110,000, $110,000+, unknown), maternal age at birth (continuous), and child's sex. Only conditions with at least 10 affected women in each study group were analyzed as individual conditions.

We also investigated whether associations with the maternal immune conditions differed by treatment status of the mother during pregnancy. Treatment might indicate active status or severity of the disease. To investigate whether associations varied by child sex or ASD phenotype, we also ran separate models for males and females, ASD+ID and ASD-ID, ASD+ regression and ASD-regression, ASD simplex and ASD multiplex, and ASD mild/moderate and ASD severe.

Results

The distribution of demographic covariates is shown for each study group in Table 1. As expected, the proportion of males was significantly higher in the ASD group compared to the DD and POP groups. Mothers of ASD cases were significantly more likely to be non-White, and to have a lower educational attainment at time of birth of index child and lower current household income compared with mothers of POP controls. Most ASD cases were classified as mild/moderate, simplex, having ID, and not experiencing developmental regression (Table 2).

Table 3. Frequency of Maternal Immune Conditions Diagnosed by the Birth of the Study Child, Study to Explore Early Development, 2003–2006 Births

	ASD ($N = 663$)	DD ($N = 984$)	POP ($N = 915$)	ASD vs POP	DD vs POP
Maternal Condition	N (%)	N (%)	N (%)	p-value	p-value
Allergy	336 (50.68)	468 (47.56)	463 (50.60)	0.97	0.18
Asthma	198 (29.86)	280 (28.46)	233 (25.46)	0.05	0.14
Any Autoimmune	131 (19.76)	204 (20.73)	155 (16.94)	0.15	0.03
Addison's Disease	–	–	–	–	–
Autoimmune Hepatitis	2 (0.30)	2 (0.20)	2 (0.22)		
Ankylosing Spondylitis	2 (0.30)	0 (0.00)	0 (0.00)		
Aplastic Anemia	6 (0.90)	6 (0.61)	6 (0.66)		
Celiac Disease	1 (0.15)	1 (0.10)	3 (0.33)		
Crohn's Disease	1 (0.15)	0 (0.00)	5 (0.55)		
Dermatitis herpetiformis	6 (0.90)	3 (0.30)	3 (0.33)		
Eczema/Psoriasis	89 (13.42)	122 (12.40)	95 (10.38)	0.07	0.17
Giant Cell Arteritis	–	–	–		
Grave's Disease	2 (0.30)	9 (0.91)	7 (0.77)		
Guillain-Barre Syndrome	0 (0.00)	1 (0.10)	0 (0.00)		
Hashimoto Thyroiditis	9 (1.36)	15 (1.52)	11 (1.20)		
Hemolytic Anemia	1 (0.15)	3 (0.30)	2 (0.22)		
Scleroderma	1 (0.15)	0 (0.00)	0 (0.00)		
Mixed Connective Tissue Disease	2 (0.30)	0 (0.00)	0 (0.00)		
Irritable Bowel Syndrome	–	–	–		
Multiple Sclerosis	4 (0.60)	2 (0.20)	4 (0.44)		
Myasthenia Gravis	–	–	–		
Narcolepsy	1 (0.15)	3 (0.30)	0 (0.00)		
Optic Neuritis	3 (0.45)	2 (0.20)	2 (0.22)		
Pemphigus	–	–	–		
Rheumatoid Arthritis	9 (1.36)	7 (0.71)	6 (0.66)		
Reiter's Syndrome	–	–	–		
Systemic lupus erythematosus	1 (0.15)	4 (0.41)	3 (0.33)		
Sjogren's Syndrome	3 (0.45)	4 (0.41)	2 (0.22)		
Stevens-Johnson Syndrome	1 (0.15)	1 (0.10)	1 (0.11)		
Sydenham's Chorea	–	–	–		
Thrombocytopenia	4 (0.60)	8 (0.81)	5 (0.55)		
Type 1 Diabetes Mellitus	5 (0.75)	18 (1.83)	4 (0.44)		
Ulcerative Colitis	3 (0.45)	10 (1.02)	6 (0.66)		
Tourette's Syndrome	–	–	–		
Other Autoimmune Condition*	7 (1.06)	11 (1.12)	11 (1.20)		

p-value from Fisher's Exact test.

Maternal Immune Conditions Present during Pregnancy

The frequency of maternal immune conditions present in the mother by the delivery of the study child is shown in Table 3. Maternal allergy was the most frequently reported immune condition (47%–51%) with no significant differences in occurrence across the three study groups. Maternal asthma occurred in 25%–30% of women and was reported significantly more often among mothers with children with ASD than mothers of POP children ($P = 0.05$). Maternal autoimmune diseases were present during pregnancy in 17%–21% of women, and significantly more common among children with DD than POP controls ($P = 0.03$). The most common maternal autoimmune condition reported across the study groups was eczema/psoriasis (10%–13%). All other conditions were rare, occurring in less than 2% of the study population.

After adjustment for covariates, the odds of ASD were between 20% and 30% higher among women with any autoimmune condition, eczema/psoriasis, or asthma when compared to POP controls; however, no increase in odds was observed among women with allergies (Table 4). A minority of women with eczema/psoriasis (overall 6%; 6% ASD, 6% DD, 6% POP) or allergies (overall 22%; 23% ASD, 22% DD, 20% POP) were treated with medication during pregnancy. In contrast, most women with asthma received treatment during pregnancy (overall 76%; 77% ($N = 152$) ASD, 80% ($N = 225$) DD, 71% ($N = 165$) POP), and odds of ASD were significantly elevated among the treated group (Table 4). The type of asthma medication taken by mothers during pregnancy was available for only a subset of ASD cases ($N = 55$, 36%) and POP controls ($N = 51$, 31%). There were no ASD versus POP differences in types of asthma

Table 4. Risk of ASD or DD Associated with Maternal Immune Conditions Diagnosed by Delivery of the Study Child, Study to Explore Early Development, 2003–2006 Births

Maternal Conditions Diagnosed by Delivery of Study Child	ASD vs POP Crude OR (95% CI)	ASD vs POP Adj OR* (95% CI)	DD vs POP Crude OR (95% CI)	DD vs POP Adj OR* (95% CI)
Any Autoimmune	1.21 (0.93–1.56)	1.29 (0.97–1.70)	1.28 (1.02–1.62)	1.37 (1.08–1.74)
Eczema/Psoriasis	1.34 (0.98–1.82)	1.39 (1.00–1.95)	1.22 (0.92–1.62)	1.32 (0.98–1.77)*
Asthma	1.25 (1.00–1.56)	1.26 (0.99–1.60)	1.16 (0.95–1.43)	1.21 (0.98–1.50)
Asthma Treated During Pregnancy	1.35 (1.05–1.73)	1.41 (1.07–1.85)	1.32 (1.05–1.66)	1.40 (1.11–1.78)
Allergy	1.00 (0.82–1.23)	1.13 (0.91–1.41)	0.89 (0.74–1.06)	0.98 (0.81–1.18)

*Adjusted child sex, current household income, maternal age, race, and education.

medications taken (beta-2 adrenergic receptor agonists (B2AR): 87% vs. 92%, $P = 0.41$; steroids: 38% vs. 41%, $P = 0.75$). Patterns similar to the ASD results across all three immune conditions were observed for risk of DD compared to POP controls (Table 4).

The adjusted association between each maternal immune condition and ASD is displayed separately for males and females and several ASD phenotypes (Table 5). For each immune condition, odds ratios were similar for male and female children. However, the association with maternal autoimmune conditions, and specifically eczema/psoriasis, was significantly elevated among children with ASD without ID (ORadj = 2.17, 95% CI 1.45–3.25), children from multiplex families (Oradj = 3.37, 95% CI 1.70–6.68), and children with mild/moderate severity (ORadj = 1.59, 95% CI 1.09–2.32). In contrast, a significant association with maternal asthma was observed among children with ASD with ID (ORadj = 1.41, 95% CI 1.07–1.87) and children who experienced developmental regression (ORadj = 1.56, 95% CI 1.09–2.22). Maternal allergies were not associated with ASD for any phenotypic subgroup analyzed.

Family History of Immune Conditions

Like the pregnancy period, lifetime maternal history of eczema/psoriasis and asthma but not allergy were associated with a 20%–36% elevation in odds of ASD and DD (Table 6). History of eczema/psoriasis and allergy diagnosed in the index child was significantly associated with ASD (37%–48% higher odds) but not DD. Paternal history and family history of any of the immune conditions, however, were not associated with increased risk of ASD or DD (Table 6).

Discussion

In this large and diverse study population with robust exposure and outcome assessment, the maternal immune conditions assessed during pregnancy were relatively common, occurring in 17%–50% of all women. Pregnancy and lifetime maternal eczema/psoriasis and asthma were associated with a 20%–40% increased odds of both ASD and DD. There was some indication that risk estimates varied by specific ASD phenotypes in association with these exposures. In addition, children with ASD were more likely to have a history of eczema/psoriasis or allergies than POP controls.

In this study we found an association with maternal autoimmune conditions and ASD risk which is in line with previous literature [Andersen et al., 2014; Atladottir et al., 2009; Brown et al., 2015; Lyall et al., 2014; Lyall et al., 2012; Keil et al., 2010; Croen et al., 2005; Comi et al., 1999; Mouridsen et al., 2007; Sweeten et al., 2003]. Several specific autoimmune diseases have been reported to be associated with elevated risk of ASD in past studies (e.g., rheumatoid arthritis, thyroid disease, inflammatory bowel disease, systemic lupus erythematosus); however, these conditions occurred very infrequently in our study population, precluding further analyses. Women with eczema/psoriasis diagnosed by delivery, the most commonly reported autoimmune disease during pregnancy in this study, were significantly more likely to have children with ASD, consistent with some [Croen et al., 2005] but not other [Mouridsen et al., 2007; Keil et al., 2010] previous studies. Although not yet defined as a specific autoimmune condition, several studies have reported associations between ASD and the presence of maternal autoantibodies, where an as yet unknown auto-inflammatory process in the mother led to the increased presence of antibodies reactive to fetal brain proteins.

Asthma is one of the most common chronic diseases among pregnant women, [Meakin, Saif, Jones, Aviles, & Clifton, 2017] with up to 45% of pregnant women seeking medical help and at least 6% being hospitalized [Murphy 2015]. Our finding of an association between maternal asthma during pregnancy and ASD and DD is consistent with previous studies showing links between maternal asthma and risk for neurodevelopmental disorders including ASD, intellectual disability and attention-deficit/hyperactivity disorder (ADHD) [Croen et al., 2005; Lyall et al., 2014; Theoharides, Tsilioni, Patel, & Doyle, 2016; May-Benson, Koomar, & Teasdale, 2009; Langridge et al. 2013; Leonard, de Klerk, Bourke, & Bower, 2006]. Furthermore, a recent mouse model

Table 5. Risk of ASD Associated with Maternal Immune Conditions Present by Date of Delivery of Index Child, Stratified by Child Sex and ASD Subtypes, Study to Explore Early Development, 2003–2006 Births

Maternal exposure	ASD vs POP Adj OR* (95% CI)	ASD (*n/N*)	POP (*n/N*)
Autoimmune (all)	1.29 (0.97–1.70)	131/663	155/915
Male	1.32 (0.95–1.83)	107/546	80/496
Female	1.20 (0.70–1.86)	24/117	75/419
With ID^	0.95 (0.67–1.35)	62/414	155/915
Without ID^	1.93 (1.36–2.74)	69/249	155/915
Simplex	1.21 (0.91–1.62)	114/606	155/915
Multiplex	2.27 (1.20–4.28)	17/57	155/915
Regression	1.25 (0.82–1.92)	37/188	155/915
No Regression	1.31 (0.96–1.78)	94/475	155/915
Mild/Moderate ASD	1.46 (1.06–2.01)	86/397	155/915
Severe ASD	1.03 (0.70–1.53)	44/264	155/915
Eczema/Psoriasis	1.39 (1.00–1.95)	89/663	95/915
Male	1.50 (1.01–2.22)	75/546	50/496
Female	1.06 (0.53–2.09)	14/117	45/419
With ID^	0.97 (0.63–1.49)	39/414	95/915
Without ID^	2.17 (1.45–3.25)	50/249	95/915
Simplex^	1.24 (0.87–1.75)	74/606	95/915
Multiplex^	3.37 (1.70–6.68)	15/57	95/915
Regression	1.41 (0.85–2.32)	26/188	95/915
No Regression	1.40 (0.97–2.02)	63/475	95/915
Mild/Moderate ASD	1.59 (1.09–2.32)	60/397	95/915
Severe ASD	1.04 (0.65–1.68)	28/264	95/915
Asthma	1.26 (0.99–1.60)	198/663	233/915
Male	1.30 (0.98–1.72)	165/546	123/496
Female	1.15 (0.71–1.86)	33/117	110/419
With ID	1.41 (1.07–1.87)	129/414	233/915
Without ID	1.08 (0.77–1.50)	69/249	233/915
Simplex	1.23 (0.96–1.57)	178/606	233/915
Multiplex	1.62 (0.89–2.94)	20/57	233/915
Regression	1.56 (1.09–2.22)	67/188	233/915
No Regression	1.16 (0.88–1.52)	131/475	233/915
Mild/Moderate ASD	1.40 (1.06–1.85)	128/397	233/915
Severe ASD	1.09 (0.78–1.53)	70/264	233/915
Allergy	1.13 (0.91–1.41)	336/663	463/915
Male	1.16 (0.89–1.50)	282/546	260/496
Female	1.02 (0.65–1.58)	54/117	203/419
With ID	1.09 (0.84–1.41)	196/414	463/915
Without ID	1.19 (0.88–1.61)	140/249	463/915
Simplex	1.11 (0.88–1.39)	304/606	463/915
Multiplex	1.53 (0.86–2.73)	32/57	463/915
Regression	1.19 (0.85–1.68)	98/188	463/915
No Regression	1.12 (0.88–1.43)	238/475	463/915
Mild/Moderate ASD	1.28 (0.99–1.66)	212/397	463/915
Severe ASD	0.95 (0.71–1.29)	122/264	463/915

*Adjusted for child sex, family current income, maternal age, race, and education.

^Test for heterogeneity $P < 0.005$.

showed that induction of maternal asthma during pregnancy led to offspring with ASD-like behaviors including deficits in social interactions and repetitive behaviors as well as significantly longer body length and higher body weight than controls throughout neonatal development [Schwartzer et al. 2017; Schwartzer, Careaga, Chang, Onore, & Ashwood, 2015].

The significant association we observed with asthma among women treated for asthma could indicate that more severe asthma increases ASD risk or that asthma must be active during the pregnancy period to impact neurodevelopment. During mid-gestation, cytokines associated with allergic responses (e.g., interleukin-4) have been shown to be elevated in maternal blood of mothers whose child was diagnosed with ASD [Goines et al., 2011; Jones et al., 2017], suggesting that an active asthma process in pregnancy may be responsible. Interestingly, elevated levels of IL-4 in amniotic fluid and newborn blood spots have also been associated with ASD risk [Krakowiak et al., 2017], again suggesting that a prolonged or sustained immune response is associated with ASD risk. Although treatment for asthma in the mothers during pregnancy could reflect severity of or persistent maternal asthma, it is possible that the treatment per se negatively impacted neurodevelopment. Recent studies of B2AR agonists, medications commonly used to treat asthma, have identified increased risk of ASD with exposure during pregnancy [Croen et al., 2011; Gidaya et al., 2016]. Where we had medication history we saw no difference in the frequency of reported B2AR use among mothers of ASD and POP children. Further studies are necessary to disentangle the effects of treatment and immunological effects of asthma and risk for ASD.

The observation of no association between ASD and maternal allergy during pregnancy contrasts with an earlier study conducted in northern California that found a significantly elevated risk of ASD among women with an allergy diagnosis recorded in prenatal medical records [Croen et al., 2005]. In that study, the prevalence of maternal allergy was 25%, roughly half the rate reported in the present study. The high prevalence of allergy reported in this study suggests that a more heterogeneous group of allergic conditions was included than in the previous report, with potentially different mechanisms of action (e.g., IgE mediated and non-IgE mediated allergies). Therefore, the null findings should be interpreted with caution, and future studies that delineate the specific types of allergies are warranted.

Our results suggest that different maternal immune conditions during pregnancy may be associated with different ASD phenotypes. We found that maternal eczema/psoriasis was associated with increased risk of ASD among children without ID, children from multiplex families, and children with mild/moderate ASD severity. In contrast, maternal asthma was associated with increased risk of ASD among children with ID and children who experienced regression. While ours is the first study to examine ASD phenotypes in relation to these maternal conditions, a strong inflammatory profile marked by increased levels of cytokines associated with asthma has been previously reported for mothers

Table 6. Risk of ASD or DD Associated with Lifetime Family History of Immune Conditions, Compared to General Population Controls, Study to Explore Early Development, 2003–2006 Births

Family History	ASD ($N = 663$)	DD ($N = 984$)	POP ($N = 915$)	ASD vs POP Adj OR* (95% CI)	DD vs POP Adj OR* (95% CI)
Autoimmune					
Maternal Hx	151 (22.78)	232 (23.58)	192 (20.98)	1.20 (0.92–1.55)	1.23 (0.99–1.54)
Paternal Hx	71 (11.75)	72 (8.11)	90 (10.60)	1.13 (0.79–1.62)	0.79 (0.57–1.10)
Index Child Hx	211 (32.12)	261 (26.93)	212 (23.56)	1.44 (1.13–1.84)	1.24 (1.00–1.54)
Family Hx**	284 (42.84)	388 (39.43)	382 (41.75)	1.05 (0.85–1.31)	0.97 (0.81–1.18)
Eczema/Psoriasis					
Maternal Hx	98 (14.78)	137 (13.92)	110 (12.02)	1.36 (0.99–1.86)	1.25 (0.95–1.65)
Paternal Hx	47 (7.78)	46 (5.18)	56 (6.60)	1.22 (0.79–1.88)	0.80 (0.53–1.20)
Index Child Hx	207 (31.51)	248 (25.59)	203 (22.56)	1.48 (1.15–1.89)	1.23 (0.99–1.53)
Family Hx	227 (34.24)	294 (29.88)	301 (32.90)	1.05 (0.84–1.33)	0.91 (0.74–1.11)
Asthma					
Maternal Hx	203 (30.62)	295 (29.98)	235 (25.68)	1.29 (1.01–1.64)	1.29 (1.05–1.59)
Paternal Hx	59 (9.77)	72 (8.11)	64 (7.54)	1.37 (0.92–2.04)	1.12 (0.78–1.60)
Index Child Hx	86 (13.09)	141 (14.55)	93 (10.33)	0.98 (0.70–1.39)	1.26 (0.94–1.68)
Family Hx	282 (42.53)	409 (41.57)	350 (38.25)	1.18 (0.95–1.48)	1.15 (0.95–1.39)
Allergy					
Maternal Hx	339 (51.13)	487 (49.49)	475 (51.91)	1.08 (0.87–1.35)	1.01 (0.84–1.22)
Paternal Hx	217 (35.93)	266 (29.92)	291 (34.28)	1.17 (0.92–1.49)	0.89 (0.72–1.09)
Index Child Hx	216 (32.88)	277 (28.59)	227 (25.22)	1.37 (1.08–1.74)	1.15 (0.93–1.43)
Family Hx				No data on siblings so can't compute this	No data on siblings so can't compute this

*Adjusted for child sex, current household income, maternal age, race, and education.
**Family history includes mother, father, and/or siblings, but excludes index child.

of children with ASD+ID [Jones et al., 2017], consistent with our results. The exact role of specific cytokines or immune mediators in the development of specific behavioral or comorbid phenotypes in unclear. Future studies with sufficient sample size could further explore phenotypic variability in relation to these exposures and to specific immune responses elicited.

Our finding that children with ASD were more likely to have a history of autoimmune diseases or allergies than POP controls is consistent with findings from previous studies [Gurney, McPheeters, & Davis, 2006; Magalhaes et al., 2009; Bakkaloglu et al. 2008; Jyonouchi 2010; Angelidou et al. 2011; Zerbo et al., 2015; Chang et al. 2013; Tsai, Chang, Mou, Sung, & Lue, 2013; Yaghmaie, Koudelka, & Simpson, 2013; Chen et al. 2014; Billeci et al. 2015; Mostafa et al., 2008]. ASD-relevant behaviors have also been observed in models of early life exposure to food allergies [de Theije et al. 2014]. Immune activation in cells taken from children with ASD also exhibit an activated immune profile, one which was associated with worse behavioral symptoms [Careaga et al., 2017; Onore et al., 2012]. Immune conditions may be considered co-morbid features of ASD and may reflect potential treatment targets that could alleviate or reduce behavioral impairments. Interestingly, no significant associations were shown with immune conditions in children and DD status. This is in line with previous studies that suggest immune profiles in ASD are unique when compared to DD [Onore et al., 2012; Ashwood et al. 2008]. We also did not observe any association between paternal history of autoimmune diseases, asthma, or allergies and ASD or DD, contrary to findings from a recent meta-analysis of four studies that reported a significant 27% increase in risk of ASD associated with paternal history of autoimmune disease [Wu et al., 2015]. The inconsistency in findings across studies could be due to differences in how paternal history of these conditions were ascertained and age of the fathers.

Since different maternal immune conditions were associated with risk of ASD and DD, these data suggest a potential biological framework whereby increased immune activation during gestation rather than a specific disease process drives neurodevelopmental changes. This notion is supported by evidence from animal models that demonstrate associations between increased maternal immune activation during pregnancy and behavioral and brain abnormalities in the offspring [Bauman et al. 2014; Shi, Fatemi, Sidwell, & Patterson, 2003; Shi, 2009; Giulivi, Napoli, Schwartzer, Careaga, & Ashwood, 2013; Onore, Schwartzer, Careaga, Berman, & Ashwood, 2014; Rose et al. 2017; Schwartzer, Careaga, Onore, Rushakoff, & Berman, 2013].

Several studies have shown genetic links within the major histocompatibility complex (MHC) region and neuropsychiatric disorders such as schizophrenia, autism and bipolar disorder [Torres et al. 2016; Mokhtari & Lachman, 2016] The MHC region encodes both

immune molecules such as human leukocyte antigen (HLA), complement proteins and cytokines, as well as many non-immune molecules. In addition, studies have linked various HLA molecules with autoimmune diseases and asthma [Kontakioti, Domvri, Papakosta, & Daniilidis, 2014; Prinz 2017]. It is possible that a genetic association with asthma and autoimmune diseases may also explain some of the risk for autism. An investigation studying the connections between HLA genetic risk factors in the MHC region with autoimmunity/asthma and autism in the same subjects would be warranted. As all immune responses are governed by genetic mechanisms the role of immune genes in neurodevelopmental risk in the context of maternal immune activation needs further investigation.

Pregnancy is a time when epigenetic changes help the genome adapt to the maternal environment. Activation of the maternal immune system may alter the regulation of gene expression in the developing fetal brain or immune system. For example, perinatal exposure to maternal asthma has been shown to alter DNA methylation of immune-related genes in human infants, suggesting that maternal asthma has long-lasting effects on the offspring's immune function that may make them more susceptible to developing further allergies [Gunawardhana et al. 2014]. In nonhuman primates, immune activation during pregnancy led to offspring with altered behaviors and immune responses [Rose et al., 2017]. In this study, immune conditions in the mother were linked to increased risk of ASD in the child. Moreover, we observed increased risk of immune conditions in children with ASD. The exact epigenetic changes as a consequence of early life immune activation requires further analysis.

In this large and diverse study population drawn from several geographic areas across the United States, all ASD and DD status was validated by a comprehensive in-person developmental assessment protocol 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. The comprehensive data collection battery allowed us to conduct analyses by specific ASD subgroups. The immune conditions were ascertained from several different sources, including maternal interview, self-reported questionnaires, and medical records, likely resulting in more complete ascertainment than previous studies that relied on only one source. Finally, we controlled for several potential confounders.

Despite these strengths, several study limitations deserve mention. While this is a large study population, the prevalence of most autoimmune diseases is quite low among individuals of reproductive age, resulting in very small numbers of children exposed to specific conditions. Thus, we were not able to conduct adjusted or stratified analyses of several autoimmune conditions that have been reported to increase risk of ASD in previous studies. We had no information on the status (active, flaring-up, or dormant) of the autoimmune conditions and asthma during the pregnancy period, and no indication of severity, other than whether women were being treated with medication for the disorder during pregnancy. Information on specific type of medications taken to treat asthma was not available for the majority of our study sample, and we were thus unable to fully disentangle treatment and disease indication effects. Observed associations were modest and given the multiple analyses that were performed, significant findings could be due to chance. Finally, while several families of potentially-eligible children did not respond to the SEED invitation letter, analyses of data from one SEED site with the most complete data available to assess nonresponse indicated that maternal age, education, and race-ethnicity were associated with nonresponse but other pregnancy variables were not (unpublished analysis). All multivariable analyses were thus adjusted for all three aforementioned demographic factors.

In conclusion, these data support a link between maternal and child immune conditions and ASD, and further suggest that associations may be influenced by disease severity in the mother and ASD phenotype of the child.

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Conflict of interest

The authors report no conflict of interest to declare.

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