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Maternal Immune-Mediated Conditions, Autism Spectrum Disorders, and Developmental Delay

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Abstract

The maternal immune system may play a role in offspring neurodevelopment. We examined whether maternal autoimmune disease, asthma, and allergy were associated with child autism spectrum disorder (ASD) and developmental delay without autism (DD) using 560 ASD cases, 391 typically developing controls, and 168 DD cases from the Childhood Autism Risk from Genetics and the Environment (CHARGE) study. Results from conditional logistic regression demonstrated few significant associations overall. Maternal autoimmune disease was significantly associated with a modest increase in odds of developmental disorders (combined ASD + DD; OR = 1.46, 95 % CI 1.01, 2.09) but not of ASD alone. Associations with certain allergens and onset periods were also suggested. These findings suggest maternal autoimmune disease may modestly influence childhood developmental disorders (ASD + DD).

Keywords

Autoimmune disease; Asthma; Allergy; Autism; Developmental delay; Maternal risk factors

There is growing evidence, both from children affected with ASD and from their unaffected family members, that the immune system may be relevant in at least a subset of ASD cases.

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A number of reports have noted increased prevalence of autoimmune conditions in family members of children affected with ASD (Money et al. 1971; Comi et al. 1999; Sweeten et al. 2003; Keil et al. 2010), but whether this association is due to common genetic factors, an effect of maternal immune dysregulation during neurodevelopment, a combination of such factors, or to some other mechanism, is not known. Further, little is known about overlap of underlying etiologic mechanisms of ASD and broader developmental delay (DD).

Maternal autoimmune conditions may be of relevance given that they often have an onset around the childbearing years (Jones 1994). Autoimmunity during pregnancy has been shown to lead to poorer fetal outcomes, including pre-term birth, intrauterine growth restriction, small for gestational age, and congenital malformation (Carvalheiras et al. 2012), many of which have also been associated with ASD and DD (Boyce et al. 1999; Gardener et al. 2011; Kerstjens et al. 2012). Consideration of other maternal immune-mediated conditions, including asthma and allergy, have been little explored, but were significantly associated with ASD in one study (Croen et al. 2005). In addition, different maternal autoimmune disorders have been associated with developmental disorders; a few prior studies have suggested possible associations with maternal systemic lupus erythmatosus (SLE) and a range of adverse developmental outcomes, such as learning disabilities (Lahita 1988; McAllister et al. 1997; Ross et al. 2003). However, whether DDs are related to a broader set of maternal immune-mediated conditions is not known.

An investigation of maternal immune-mediated conditions that includes and compares both ASD and DD without ASD, has not been conducted to our knowledge, but could be useful in identifying common or disparate risk factors. Limitations in prior work include small sample sizes (Money et al. 1971; Comi et al. 1999; Sweeten et al. 2003; Mouridsen et al. 2007), lack of case confirmation on gold-standard measures (Croen et al. 2005), and lack of medical record confirmation of conditions (Comi et al. 1999; Sweeten et al. 2003). Further, studies have suggested associations with different individual autoimmune conditions (Croen et al. 2005; Mouridsen et al. 2007), and have yielded different findings regarding whether family autoimmune versus specifically maternal conditions are related (Croen et al. 2005; Keil et al. 2010). These limitations and inconsistencies leave questions regarding whether and how maternal immune-mediated conditions impact risk for child developmental disorders.

We therefore sought to examine maternal immune-mediated conditions in association with two classes of developmental disorders: ASD and DD, in a large population-based case-control study. Given growing evidence for a link between the maternal immune response and ASD in particular, we hypothesized that maternal autoimmune conditions, asthma, and allergies would be associated with ASD, and that associations would differ for DD. As a number of research groups have identified a set of maternal autoantibodies to fetal brain proteins that consistently occur in approximately 10 % of ASD cases and in no controls (Zimmerman et al. 2007; Braunschweig et al. 2013), we therefore also explored whether these conditions were associated with the autoantibodies.

Methods

Study Population

Participants included are part of CHildhood Autism Risk from Genetics and the Environment (CHARGE), an ongoing, large, population-based case-control study drawn from several regions of California; CHARGE details have been previously described (Hertz-Picciotto et al. 2006). Briefly, we identified children with ASD and DD through the California Department of Developmental Services (DDS) and controls through state birth files. Controls were frequency-matched (i.e., in groups) on age, sex, and geographic area to AU cases. We confirmed DDS diagnoses of ASD by administering the Autism Diagnostic Observation Schedule (ADOS) and Autism Diagnostic Interview-Revised (ADI-R) (Lord et al. 1989, 1994). All clinicians conducting assessments have achieved research reliability on the instruments they administer. Children with ASD were defined as those who met criteria on the communication or social interaction domain of the ADI-R and were within 2 points of meeting criteria in the other domain, had onset before 36 months, and met the ASD cut-off for social and communication totals of the ADOS. In the children recruited with DD or as general population controls, the Social Communication Questionnaire (SCQ) (Rutter et al. 2003) was used to screen for autism spectrum symptoms, with a cut-off score of 15; if scores indicated possible ASD, the ADOS and ADI-R were conducted. For the current analysis, controls, designated 'typically developing' (TD), were defined as children recruited from the general population who scored 70 or higher on the Mullen Scales of Early Learning (MSEL) (Mullen 1995), 70 or higher on the Vineland adaptive behavior scales (VABS) (Sparrow et al. 1984), and 14 or lower on the SCQ. DD controls were defined according to a score of 69 or lower on the MSEL, a score of 69 or lower on the VABS, and a score of 14 or lower on SCQ, or according to clinician judgment (i.e. in rare instances when a score narrowly missed cut-off but expert judgment suggested the child had clear DD). For this analysis, we included only those children meeting these criteria. For all assessments, the version referenced is the version used in the CHARGE study (even if an updated version exists; this is to maintain consistency in methods over the on-going study period).

Exposure Information

Information on maternal autoimmune diseases, asthma, and allergies was collected from a detailed Environmental Exposures Questionnaire (EEQ), an Autoimmune Survey (AIS), a family medical history (FMH), and, when available, medical records (prenatal). The self-reported forms (EEQ, AIS, and FMH) were administered during study visits, when the index child was 2–5 years of age. The EEQ was a structured questionnaire with individual items that asked whether and when the mother had the specific condition (asthma, thyroid disease, and allergies) from 3 months prior to pregnancy through breastfeeding (defined as the index period), while the AIS and FMH asked about lifetime history of conditions (autoimmune disorders, asthma, allergies), including a list of specific types of conditions (individual autoimmune disorders, types of allergies). Self-reported age at onset was collected only for asthma and certain autoimmune conditions. Information extracted from medical records included diagnosis, whether medication was used, time period (before pregnancy, during pregnancy, or both), and, when available, age at onset. Individuals were defined as exposed if any of these sources indicated presence of the condition; sensitivity analyses examined

results for self-report and medical record information separately. Maternal autoimmune disease included over 40 autoimmune conditions (see Appendix for complete list).

Primary analyses examined the maternal immune-mediated conditions of interest according to (a) any lifetime occurrence (through the study assessment). In secondary analyses, we also examined: (b) index period conditions, defined as any occurrence from 3 months before pregnancy through breastfeeding, and (c) incident occurrence within 2 years before or after index birth (for comparison with Croen et al. 2005; for these analyses, those with prior or unknown onset of the immune-mediated condition were excluded). In order to examine the potential for bias stemming from differences in opportunity for exposure in index period analyses, duration of breastfeeding and gestation were compared between cases and controls; further, we also compared results to those seen for the pregnancy-only period. No individuals were missing all of the primary exposure categories (autoimmune condition, asthma, and allergy), but individuals missing information on a particular condition were excluded for that exposure-specific analysis.

Maternal autoantibodies were measured according to procedures previously described (Braunschweig et al. 2012). Briefly, plasma was separated from maternal blood samples collected as part of the CHARGE study, and Western blotting was used to determine reactivity to specific fetal brain proteins.

Statistical Analysis

All analyses were conducted in SAS version 9.2 (SAS Institute Inc.). Basic frequencies of maternal autoimmune conditions, asthma, and allergies were compared across diagnostic groups. Autoimmune conditions and allergies were each categorized into variables to indicate any condition/allergy, and common types within these factors were compared between groups as well. We also created a variable for any maternal immune-mediated condition, in which individuals were coded as exposed if they had any of autoimmune diseases, allergies, or asthma.

A series of multivariate regression models were used to obtain odds ratios and 95 % confidence intervals. Specifically, we used both conditional logistic regression, accounting for study matching factors, and, in order to adjust for potential biases from differential participation rates, weighted conditional logistic regression using Proc Survey Logistic (An 2002). Weighted regression models used inverse-probability of participation weights, based on maternal education level, age, country of birth, insurance status at child's delivery, and child race/ethnicity. Thus, the goal of the weights is to ensure sample representativeness of the source population. Separate models were used to assess risk of ASD compared to TD and risk of DD compared to TD (multinomial models were also used for comparison). Minimally-adjusted models included the study matching factors (child sex, regional group, and age of child) and weights. Multivariate adjusted analyses also assessed whether adjustment for health insurance status at child's birth, maternal race, maternal education, and maternal age affected results. Final models included only maternal age (given a priori knowledge; included as a continuous variable) and the matching factors, as other variables assessed were not associated with both exposure and outcome. Breastfeeding, preterm birth, and maternal medication use for the immune-mediated condition were also examined as

potential mediators by estimating mediation proportion using the SAS Mediate macro (Lin et al. 1997; Hertzmark et al. 2009), publically available here: <http://www.hsph.harvard.edu/faculty/spiegelman/mediate.html>.

For analysis of asthma and allergies defined according to index period (3 months before pregnancy through breastfeeding), we excluded individuals missing all timing information (approximately 3 % in all study groups were missing timing of asthma onset and occurrence information, and approximately 20 % were missing this information for allergies). Missingness of timing of onset/occurrence of asthma and allergy did not differ significantly by case status or demographic factors. For analysis of exposures according to incident onset (within 2 years before or after index birth), we excluded individuals with onset of condition earlier than 2 years before pregnancy, as well as those reporting the condition but missing timing and onset information (total excluded = ~20 % for asthma and ~30 % for allergies; further detail in Table 2).

Finally, we built upon prior work showing associations between maternal autoantibodies and ASD in this population (Braunschweig et al. 2008, 2012). We examined whether presence of the maternal autoantibody pair at 37/73 kDa, or 39/73 kDa, which have previously been associated with ASD, as well as other maternal autoantibodies to fetal brain proteins, were associated with any of the maternal immune-mediated conditions, in all children and stratified by case status. Frequencies of the conditions among those with the high-risk combinations of antibodies (Zimmerman et al. 2007; Braunschweig et al. 2008) were compared between those mothers with and without immune conditions, as was presence of other autoantibodies. Chi squared tests were used to test for significant differences.

Results

Included in these analyses were 560 ASD cases, 391 TD controls, and 168 DD cases. Basic characteristics of the study population are shown in Table 1. TD controls were slightly more likely to be Caucasian and more highly educated; these factors were accounted for by the inverse probability of participation weighting. The high prevalence of males in TD and ASD groups was due to the matching of these groups. Age distributions were similar in ASD, DD, and TD groups and across exposure (maternal immune condition) categories.

Diagnostic groups had similar distributions of the maternal immune conditions (Table 2), though presence of any autoimmune disorder (lifetime history to study date) was slightly more common among DD mothers compared to either TD or case mothers. The most common types of autoimmune diseases were thyroid diseases, psoriasis, and rheumatoid arthritis; other conditions accounted for 5 % or less of autoimmune diseases reported and were therefore too rare to assess individually. For those individual conditions with adequate numbers, frequencies were similar across groups, although thyroid disease was slightly higher among DD mothers. Dairy allergy was more common among both ASD and DD mothers compared to TD mothers (4 % in both case groups vs. 1 % in controls), while seasonal allergies were less common among the DD mothers.

In the primary multivariate adjusted analyses of lifetime history of conditions (Tables 3 and 4), maternal autoimmune disease was suggestively associated with elevated odds of each of DD (OR = 1.58, 95 % CI 0.96, 2.60) and ASD (OR = 1.43, 95 % CI 0.96, 2.14). Given the similar magnitude of these associations, we explored the effect of combining the case groups, to assess risk of these developmental disorders as a whole; in these analyses, the association with maternal autoimmune disease did reach statistical significance (OR = 1.46, 95 % CI 1.01, 2.09).

Only specific conditions and allergies with at least 5 exposed cases were assessed in adjusted analyses, and no significant associations emerged for individual autoimmune disorders. For individual types of allergies, only maternal dairy allergy demonstrated a statistically significant association with ASD, though the estimate was imprecise due to the small number of controls with this type of allergy (OR = 4.31, 95 % CI 1.13, 16.5). Dairy allergy was also positively associated with DD; however, confidence intervals were even wider in this smaller group, and the association was not statistically significant. Combining the ASD and DD case groups as described above for autoimmune disease also yielded a significant association with dairy allergy, though confidence intervals were wide. Maternal seafood allergy demonstrated a positive, but non-significant, association with ASD. None of the other conditions assessed demonstrated associations with either ASD or DD, or ASD and DD combined (Tables 3 and 4). Results were nearly identical in multinomial models.

In analyses of potential mediators, percent mediation estimates (the proportion of the association that may be accounted for by the potential mediator) ranged from <1 % (asthma medications for the association between maternal asthma and ASD) to 21 % (allergy medications for the association between maternal allergy and ASD), though these were not statistically significant. The association between maternal autoimmune disease and child developmental disorders (ASD and/or DD) was not mediated by preterm birth or breastfeeding.

Timing of Immune-Mediated Conditions

The prevalence of index period asthma and allergy, as well as incident/new onset asthma and allergy within 2 years of the index birth, was similar across study groups. In adjusted analyses of these exposures, maternal index period asthma and allergies were not significantly associated with either ASD or DD (Data Supplement Table A), nor was incident onset of asthma. Incident onset allergies were associated with a decrease in risk of ASD, and this association, though not significant, was also observed for the DD group. The incident-onset analyses, however, had ~35 % fewer individuals for allergy (as those with prior onset or missing timing information were excluded), and onset of allergies was missing in a slightly higher proportion for cases than controls (41 % in ASD, 32 % in TD, 30 % in DD).

When stratifying analyses of index and incident allergies and asthma by duration of breastfeeding (<6 months and >6 months) or preterm birth, in order to account for potential bias due to opportunity for being classified as exposed during these time periods, results were similar. In addition, results were materially unchanged, and non-significant, when considering asthma and allergies during pregnancy only rather than the broader index period

(which included 3 months before and breastfeeding as well). Due to lack of information on onset for most autoimmune conditions, autoimmune diseases were not assessed according to timing of occurrence.

Maternal Autoantibodies

303 ASD case and 188 TD control mothers had information on autoantibodies available. As only 32 DD mothers had autoantibody data, the DD group was not included in these assessments. Comparing prevalence of immune mediated conditions according to mothers with and without the antibody pairs that have been previously linked to autism, no differences were noted for the 37/73 kDa pair that has been found in a subgroup of mothers of children with autism, but case mothers with immune mediated conditions were less likely to have the 39/73 kDa pair compared to case mothers without the immune conditions (Data Supplement Table B). This difference in the 39/73 kDa band pattern was significant for maternal asthma ($p = 0.01$ in stratified analyses of ASD cases only, $p = 0.005$ in analyses including both ASD and TD children), but was not statistically significant for maternal autoimmune conditions and allergies.

Discussion

In this large population-based case-control study, there was a consistent suggestive finding that any autoimmune conditions were more common in mothers of children with ASD and DD (combined) than in mothers with TD children. Significant associations with ASD alone were not found in our study. Our findings as a whole suggest certain maternal immune aberrations may be modestly related to not just ASD, but child developmental disorders more broadly.

Our work has a number of strengths, including rigorous diagnostic confirmation of all study groups according to validated measures, and utilization of multiple detailed sources of information for exposure status. This study also provides more detailed information on types of allergies than any previous study of this topic, and has the benefit of examining both ASD and DD compared to TD children to assess both specific and shared associations. Our study utilized information from both self-report and medical record sources. Approximately 65 % of participants had medical records available (the proportion was similar across study groups); of these, the percent agreement between self-reported conditions and medical-record abstracted data was over 60 % for asthma, but was lower for allergies (approximately 55 %) and autoimmune conditions (approximately 30 %). These differences were largely due to the fact that environmental and food allergies were often not included in medical records (approximately 70 % of those with self-reported allergies but not medical records were allergies to these factors). For autoimmune diseases, it is possible that conditions were not recorded in the obstetric and delivery records if they did not occur during these time frames; we did not collect medical records from other health providers the mother may have seen either during the pregnancy or outside that time frame. We cannot rule out potential exposure misclassification, but given that case and control percent agreement between self-report and medical record sources was nearly identical (i.e., non-differential

misclassification), any resulting bias would tend towards the null (i.e., towards a finding of no association). Thus, Type II errors may have occurred.

Adjusted results for the association of maternal autoimmune conditions as a group with risk of ASD were suggestive of a modest association. While a 2005 study saw no significant association between maternal autoimmune diseases as a group within 2 years before and after the proband's birth (Croen et al. 2005), other investigations have noted increased autoimmune conditions in mothers of children with ASD (Comi et al. 1999; Sweeten et al. 2003; Atladottir et al. 2009). Differences in the set of conditions included as autoimmune disease, the time periods examined, in or the relative prevalence of conditions may contribute to discrepancies across studies. Diagnostic practice and characteristics of the case sample may also contribute to differences between studies. In particular, our findings were strikingly similar for the ASD and DD groups, with a modest positive association between autoimmune conditions and ASD and DD, particularly when combining these case groups. Prior information on DD specifically and overall maternal autoimmune disease is limited, though specific autoimmune disorders have been related to other conditions such as learning disabilities (Lahita 1988; McAllister et al. 1997; Ross et al. 2003). Our study thus provides novel information by addressing the question of whether autoimmunity more generally (i.e., the presence of any autoimmune condition) is associated with DD.

We did not have the ability to examine most autoimmune diseases *individually* due to low prevalence of many conditions. The largest study to date of autoimmune conditions and ASD included 3,325 cases in a Danish registry study (Atladottir et al. 2009). This investigation reported significant increases in risk of ASD in association with maternal history of rheumatoid arthritis as well as celiac disease; family history of type I diabetes (rather than maternal) was also associated with ASD. Another large study, with over 1,200 cases (Keil et al. 2010), examined a few individual autoimmune conditions, but was limited by imprecise estimates and very small numbers of exposed cases, highlighting the need for extremely large studies to investigate individual rare conditions. However, Croen et al. (2005) identified a significant association between maternal psoriasis and ASD. In our work, the ORs for maternal eczema and ASD, and for maternal psoriasis and DD, were elevated, but not statistically significant. Thus, we cannot rule out a potential but relatively modest effect of inflammatory factors related to these conditions possibly influencing ASD and DD. A significant association has been reported with rheumatoid arthritis (Comi et al. 1999), and also with maternal thyroid diseases (Sweeten et al. 2003), but neither finding was replicated in either the present study or the work of Croen et al. (2005). It may be that the condition of autoimmunity itself, rather than the specific condition type, is related to neurodevelopmental outcomes, with other factors modifying the influence of autoimmunity.

We saw no association between maternal asthma or allergies overall and having a child with ASD or DD, whether considering these conditions according to lifetime history or index period. We did observe an inverse association between maternal new-onset (within 2 years of pregnancy) allergy and ASD, which was also suggestive in association with DD. However, these results should be interpreted cautiously given missing onset information, which was slightly higher in ASD cases. Only one prior study has examined maternal asthma and allergies in adjusted analyses in relation to ASD, and found significant positive

associations (Croen et al. 2005). Differences in findings for asthma and allergies overall in our study and the prior one may be due to use of medical records versus self report (though it is not clear why case mothers would systematically underreport conditions so as to produce such a bias in our study); study power (though our exposed case numbers were similar); or differences in the distribution of types of allergies, and how allergies were defined and classified.

In addition to examining types of autoimmune diseases and broadening the consideration of immune conditions to include asthma and allergies as suggested by Croen and colleagues, we also assessed triggers for allergies and allergic responses/symptoms, which have not been previously examined. While we saw a significant association with maternal dairy allergy, which was consistent across different multivariate adjusted models, the confidence intervals were wide and the results should be interpreted with caution. However, given commonly noted food and dietary issues among children with ASD (Bandini et al. 2010), and the familiarity of allergy, specific maternal food allergies could be susceptibility factors for either ASD or subphenotypes within ASD in some cases. On a related note, we did not have sufficient numbers to investigate inflammatory bowel disease or Celiac disease individually here, though the latter has been associated with ASD (Atladdottir et al. 2009).

Finally, we examined these immune conditions in association with antibody data. The maternal immune-mediated conditions were not significantly associated with the 37/73 kDa pair of antibodies (Braunschweig et al. 2008); however, the 39/73 kDa pair, (Zimmerman et al. 2007; Braunschweig and Van de Water 2012), was actually less common among mothers with immune mediated conditions, especially asthma. These findings require further investigation, but suggest that maternal immune-mediated conditions such as asthma and known autoimmune disease do not predispose to having the specific sets of antibodies observed in ASD. Rather, if anything, case mothers with these conditions may have lower prevalence of these ASD-associated antibodies. It is possible that a new, as yet undefined autoimmune condition could lead to the generation of these antibodies, and that this condition may have different mechanisms at play than recognized immune-related conditions. In addition, most autoimmune diseases do not overlap in their targets, or target antigens (for example, in Rheumatoid arthritis, antibodies are generated to target antigens in the synovial joints, and in multiple sclerosis antibodies are generated to myelin basic protein among other target antigens (Song and Kang, 2010; Wootla et al. 2011)). Thus, it is biologically plausible that the maternal antibodies specifically and exclusively associated with ASD do not share a target with other autoimmune diseases.

Though strong associations were not found in our work, plausible pathways for maternal immune-mediated conditions impacting offspring neurodevelopment exist. While increased risks for neurodevelopmental conditions associated with maternal immune-mediated conditions could be due to shared genetic factors, more direct immune pathways have also been suggested. Animal studies support extensive interaction between the developing nervous and immune systems (Blalock and Smith 2007; Boksa 2010), and evidence suggests that certain cytokines, such as interleukin-6 (IL6), can cross the placenta (Zaretsky et al. 2004). Higher levels of circulating immune markers, including immunoglobulins and autoantibodies found in the immune-mediated conditions studied here, particularly during

autoimmune flare-ups, asthma attacks, or allergic reactions during pregnancy, may have an influence on fetal brain development perhaps through oxidative stress in the developing brain, or effects of cytokines on neural development (Boksa 2010).

Overall, although our results do not suggest strong associations between the maternal immune-mediated conditions investigated and ASD and DD, presence of some form of maternal autoimmune disease may be modestly associated with increased risk of child developmental disorders. Analyses of new onset allergies during pregnancy, along with the hypothesis that certain types of maternal allergens may be related to offspring ASD, warrant further investigation, as does consideration of similarities and differences between autism and other developmental disorders in association with immune-related factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix: List of Included Maternal Autoimmune Conditions

1. Addison's disease
2. Adult Still's disease
3. Alopecia areata
4. Amyotrophic lateral sclerosis (ALS)
5. Ankylosing spondylitis
6. Antiphospholipid antibody syndrome
7. Aplastic anemia
8. Autoimmune hepatitis
9. Autoimmune thyroid disease
10. Autoimmune thyroiditis
11. Behcet's syndrome
12. Celiac disease
13. CREST syndrome/Scleroderma/Progressive systemic sclerosis
14. Crohn's disease
15. Dermatitis herpetiformis
16. Diabetes-Type I

17. Discoid lupus
18. Eczema/Psoriasis
19. Giant cell arteritis
20. Grave's disease
21. Guillain–Barre syndrome
22. Hashimoto's thyroiditis
23. Hemolytic anemia
24. Inflammatory bowel disease (IBD)
25. Idiopathic thrombocytopenic purpura (ITP)
26. Kawasaki syndrome
27. Meniere's disease
28. Mixed connective tissue disease
29. Multiple sclerosis
30. Myasthenia gravis
31. Multiple sclerosis
32. Optic neuritis
33. Pemphigus/Pemphigus vulgaris
34. Pernicious anemia
35. Polymyositis/Dermatomyositis
36. Primary biliary cirrhosis
37. Primary Sjogren's syndrome
38. Psoriasis
39. Raynaud's disease/phenomenon
40. Reiter's syndrome/Reiter's arthritis
41. Rheumatic carditis/Rheumatic heart disease
42. Rheumatoid arthritis (RA)
43. Sarcoidosis
44. Sjogren's syndrome
45. Stevens-Johnson syndrome
46. Sydenham's chorea
47. Systemic lupus erythematosus (SLE)
48. Systemic sclerosis/Scleroderma

49. Thrombocytopenia
50. Thyroid disease
51. Tourette syndrome
52. Ulcerative colitis
53. Uveitis/Iritis
54. Vasculitis

Note: The most common autoimmune conditions in the study population were thyroid diseases, psoriasis, and rheumatoid arthritis; other conditions were rare and accounted for 5 % or less of autoimmune diseases reported.

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Table 1
Basic characteristics of the study population

	ASD n = 560 n (%)	TD controls n = 391	DD n = 168
Maternal education level			
High school or less	82 (16 %)	62 (15 %)	51 (30 %)
Some college	231 (41 %)	130 (33 %)	66 (39 %)
College or graduate degree	246 (44 %)	198 (51 %)	51 (30 %)
Maternal race			
Caucasian	333 (59 %)	251 (64 %)	89 (53 %)
Hispanic	139 (25 %)	83 (21 %)	54 (32 %)
Other	88 (16 %)	57 (15 %)	25 (15 %)
Insurance status at delivery			
Private insurance	449 (80 %)	330 (84 %)	115 (68 %)
Government program	111 (20 %)	60 (15 %)	53 (32 %)
Male child ^a	482 (86 %)	326 (83 %)	103 (61 %)
Firstborn child	260 (47 %)	162 (42 %)	64 (38 %)
Mean (std)			
Maternal age	31.1 (5.6)	31.1 (5.7)	30.7 (6.6)
Paternal age	33.6 (6.4)	33.6 (7.0)	33.2 (7.5)
Breastfeeding duration (months)	6.9 (7.8)	7.7 (5.9)	5.7 (5.8)
Child age at interview (months)	45.4 (10.1)	42.4 (9.4)	46.2 (9.0)

^aTD controls were matched to ASD cases on child sex, regional area, and child age

Table 2
Maternal immune-mediated conditions by study group

Maternal condition	ASD n = 560	TD control n = 391	DD n = 168
Autoimmune disease	91 (16 %)	60 (15 %)	36 (21 %)
Missing	7 (1.3 %)	6 (1.5 %)	0
Thyroid/Graves disease	36 (6 %)	29 (7 %)	18 (11 %)
Missing	10 (2 %)	5 (1 %)	4 (2 %)
Psoriasis	13 (2 %)	7 (2 %)	3 (2 %)
Rheumatoid arthritis	9 (2 %)	8 (2 %)	4 (2 %)
Type I diabetes	1 (0.2 %)	1 (0.3 %)	1 (0.6 %)
Lupus	4 (0.7 %)	1 (0.3 %)	2 (1 %)
Crohn's/Ulcerative colitis	2 (0.4 %)	4 (1 %)	3 (2 %)
Asthma (any time point)	93 (17 %)	74 (19 %)	37 (22 %)
Missing	10 (2 %)	5 (1.3 %)	4 (2 %)
Asthma timing			
Occurrence during index period ^a	46 (8 %)	48 (12 %)	23 (14 %)
Index period new/incident onset ^b	22 (4 %)	24 (6 %)	12 (7 %)
Prior onset	30 (5 %)	26 (7 %)	14 (8 %)
Missing timing information	22 (4 %)	10 (3 %)	5 (3 %)
Allergy (any time point)	311 (55 %)	232 (59 %)	83 (49 %)
Missing	34 (6 %)	13 (3 %)	7 (4 %)
Allergy timing			
Occurrence during index period	196 (35 %)	173 (44 %)	55 (33 %)
Index period new/incident onset	108 (19 %)	110 (28 %)	37 (22 %)
Prior onset	116 (21 %)	68 (17 %)	22 (13 %)
Missing timing information	77 (14 %)	46 (12 %)	20 (12 %)
Allergy types ^c			
Food	52 (9 %)	31 (8 %)	16 (10 %)
Dairy	20 (4 %)	3 (1 %)	7 (4 %)
Fruit	23 (4 %)	13 (3 %)	7 (4 %)
Nut	7 (1 %)	3 (1 %)	3 (2 %)
Shellfish/seafood	10 (2 %)	4 (1 %)	1 (1 %)
Environmental ^d	154 (29 %)	117 (31 %)	47 (28 %)
Dust	11 (2 %)	11 (3 %)	0
Pets/animals	52 (10 %)	33 (9 %)	1 (1 %)
Seasonal ^e	92 (17 %)	74 (20 %)	19 (11 %)
Medication	45 (14 %)	33 (14 %)	9 (11 %)
Eczema	41 (8 %)	32 (9 %)	10 (6 %)
Respiratory allergy	50 (10 %)	43 (11 %)	14 (8 %)
Unspecified	143 (27 %)	104 (27 %)	42 (25 %)

^a Defined as 3 months before pregnancy through breastfeeding

^b Defined as within 2 years before or after index birth

^c Not mutually exclusive

^d Environmental allergies include allergy to mold (n only = 3), dust, pets, and seasonal allergies, as well as those specifying only environmental allergy but with no further information, according to report in family medical history

^e Seasonal allergies include allergy to grass, pollen, reported hay fever or seasonal allergic rhinitis or overall seasonal allergy as specified by self-report or in medical record fields

Table 3
Association between maternal immune-mediated conditions and child autism spectrum disorder (ASD)

Condition	Matching factor adjusted ^a	Matching factor and maternal age adjusted ^b
Any autoimmune disease	1.43 (0.95, 2.14)	1.43 (0.96, 2.14)
Thyroid disease	0.99 (0.62, 1.60)	0.99 (0.61, 1.60)
Psoriasis	1.28 (0.47, 3.44)	1.27 (0.47, 3.43)
Rheumatoid arthritis	1.12 (0.42, 2.98)	1.11 (0.42, 2.97)
Asthma	1.00 (0.69, 1.44)	1.00 (0.69, 1.44)
Allergies	0.96 (0.70, 1.31)	0.97 (0.71, 1.32)
Food allergy	1.23 (0.71, 2.11)	1.23 (0.73, 2.06)
Dairy allergy	4.26 (1.12, 16.2)	4.31 (1.13, 16.5)
Fruit allergy	1.26 (0.59, 2.69)	1.27 (0.60, 2.70)
Nut allergy	1.41 (0.26, 7.61)	1.42 (0.27, 7.64)
Seafood	2.76 (0.88, 8.67)	2.73 (0.87, 8.57)
Environmental	1.14 (0.82, 1.60)	1.15 (0.82, 1.61)
Dust	0.73 (0.33, 1.60)	0.74 (0.33, 1.65)
Pets	0.50 (0.24, 1.01)	0.50 (0.25, 1.02)
Seasonal	1.09 (0.75, 1.58)	1.09 (0.75, 1.58)
Medication allergy	1.19 (0.85, 1.67)	1.20 (0.85, 1.68)
Eczema	1.44 (0.84, 2.48)	1.43 (0.84, 2.46)
Respiratory	0.89 (0.54, 1.49)	0.90 (0.54, 1.50)

Items in bold indicate statistical significance

^a All models shown are weighted to account for selection into the study; unweighted estimates were similar, as were results from multinomial models (examining odds of categorical ASD, DD, or TD, with TD as the reference)

^b Additional adjustment for breastfeeding, or for medication use for asthma and allergies did not materially alter results, nor did adjustment for maternal smoking during the index period, maternal race, education level, or insurance status at delivery (these latter demographic factors are accounted for in study weights)

Table 4
Association between maternal immune-mediated conditions and child developmental delay (DD)

Condition	Matching-factor adjusted	Matching-factor and maternal age adjusted
Any autoimmune disease	1.54 (0.94, 2.52)	1.58 (0.96, 2.60)
Thyroid disease	1.21 (0.62, 2.38)	1.22 (0.61, 2.43)
Psoriasis	1.90 (0.41, 8.82)	1.94 (0.42, 9.05)
Asthma	1.16 (0.66, 2.05)	1.28 (0.64, 2.55)
Allergies	0.64 (0.40, 1.01)	0.72 (0.41, 1.26)
Food allergy	0.79 (0.31, 2.00)	0.79 (0.31, 2.01)
Fruit	0.88 (0.27, 2.84)	0.90 (0.29, 2.84)
Environmental allergy	1.17 (0.71, 1.94)	1.19 (0.72, 1.97)
Seasonal	0.70 (0.35, 1.38)	0.70 (0.35, 1.39)
Medication allergy	0.83 (0.50, 1.36)	0.84 (0.51, 1.41)
Eczema	0.82 (0.34, 2.00)	0.81 (0.33, 1.97)
Respiratory	0.86 (0.44, 1.68)	0.88 (0.45, 1.73)

Notes

Other specific autoimmune disorders and types of allergies too few to assess in this group, and were non-significant. Adding 33 additional individuals with “atypical” delays (defined according to assessments listed in methods as for DD group, but with a score of 69 or lower on either the Mullen or Vineland, rather than on both) did not alter results