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Association Between Allergic Disease and Developmental Disorders in the National Health and Nutrition Examination Survey (NHANES)

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To the Editor:

Allergic conditions, including food allergy, asthma, and allergic rhinitis, are common in children, affecting up to 20% of the pediatric population.[1] A recent cross-sectional study of the National Health Interview Survey demonstrated that children with autism spectrum disorder (ASD), which is hypothesized to be driven by immune system dysregulation, had an increased odds of self-reported food, respiratory, and skin allergies.[2] However, this previous report was limited by a broad question regarding food allergy, the potential for residual confounding, and a lack of data on correlative immunologic biomarkers. In this study, we sought to further explore the association between developmental disorders (DD) and allergic disease in a nationally-representative cross-sectional survey and to extend the previous study by examining the association of DD with specific food and environmental allergies and allergen-specific IgE (sIgE), a biomarker of allergic disease.

In this study, data from the National Health and Nutrition Examination Surveys (NHANES) 2005–2010 were analyzed for children ages 1–17 years. DD was defined as a positive answer to the question “Does your child receive Special Education or Early Intervention Services?” Self-reported asthma, allergic rhinitis, and food allergy were defined as described in the Online Supplement. In NHANES 2005–2006, sIgE was measured for peanut, egg, milk, shrimp, and aeroallergens, as previously described[3], and sensitization was defined as sIgE ≥0.35 kU/L. Multivariable logistic regression was used to examine the association

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between DD and individual allergic outcomes, adjusting for race, age, sex, household smokers, income, insurance type, education, number of annual healthcare visits, and low birth weight (<5 lbs).

A total of 10,185 children were included in these analyses, 799 of whom had DD. Cohort characteristics are included in Table 1. Among subjects with DD, there was an increased odds of self-reported asthma (OR1.51; 95% CI 1.12–2.02; p<0.007) and recent asthma exacerbations (OR 1.61; 95% CI 1.09–2.36; p=0.06), and there was a trend towards increased self-reported allergic rhinitis (OR 1.45; 95% CI 0.95–2.21; p=0.08). Among this population, there was also an increased odds of self-reported milk allergy (OR 2.33; 95% CI 1.21–4.49; p=0.01) and self-reported egg allergy (OR 3.52; 95% CI 1.06–11.7; p=0.04). There was a decreased odds of self-reported allergy to "other," which represents foods not otherwise categorized.

However, when examining allergic sensitization, there was no association between DD and overall sensitization to milk, egg, or aeroallergens (Table 2). There was an increased odds for peanut sensitization (OR 1.83, 95% CI 1.05–3.18; p=0.04), but this did not persist when stratified to sIgE ≥2 kU/L, suggesting that this is low-level sensitization of unclear clinical significance (Supplemental Table E1). Conversely, children with DD had a lower odds of overall shrimp sensitization (OR 0.44; 95% CI 0.22–0.88; p=0.02, Supplemental Table E1).

In this study, we found that children with DD had an increased odds of self-reported asthma, milk, and egg allergy. These findings are similar to those of previous studies demonstrating an increased risk of self-reported allergic disease in patients with ASD and other DD.[2, 4] We did not, however, find an increase in sIgE to these foods or aeroallergens. It is possible that there is a shared immunologic pathway promoting the development of both DD and allergic disease, as there is an increasingly recognized association between DD and dysregulation of maternal and post-natal immune pathways. However, our findings suggest that this association may instead be due to a) over-diagnosis and/or increased perception of allergic disease in this population, or b) a true increase in non-IgE mediated mechanisms of allergic disease.

Evidence supporting an association between DD and allergic disease primarily comes from cross-sectional and case-control studies,[2, 5] and, to our knowledge, has not included the measurement of biomarkers of allergic disease. These studies, including the current study, have relied on either self-reported allergic disease or insurance claims which, for food allergy, has been shown to overestimate the true prevalence of this condition when compared to oral food challenges.[6] Although it has been suggested that allergic disease may be underdiagnosed in patients with DD because of impaired communication and lower tolerance for diagnostic tests,[4] it is alternatively possible that patients with DD have more frequent respiratory infections and/or other conditions that mimic allergic disease, leading to an increased perception or over-diagnosis of this condition. Future studies assessing the prevalence of allergic disease in children with DD, using objective and reproducible measures, are clearly needed.

It is also possible that while self-reported asthma and food allergy are increased in children with DD, this does not represent IgE-mediated conditions. Previous studies have shown that diagnoses of food intolerances, food aversions, and eosinophilic esophagitis are more common in children with ASD.[7] Elimination diets have garnered research attention in ASD, and one study showed promising improvement in some of the symptoms of this disease, namely communication, attention and hyperactivity, with a gluten and casein-free diet.[8] Possible mediators of these food-mediated symptoms include beta-casomorphin 7 (BCM7), a milk-derived opioid receptor agonist, and its gluten homologue, gliadorphin 7. BCM7 has been shown to slow gastrointestinal transit, has been linked to gastrointestinal symptoms, and in one study was associated with slower cognitive response times.[9] Additional research is needed to further elucidate the underlying mechanisms of these possible non-IgE mediated food intolerances in individuals with ASD and DD.

This analysis is limited by the available questionnaire data, in that recall bias is a systematic issue in surveys. Furthermore, in the United States, children with a variety of conditions, including speech/language impairment, developmental delay, and ASD, are eligible to receive special education or early intervention services. Thus, our definition of DD is broad and encompasses subjects with non-cognitive delays, behavioral problems, and neurologic injuries, which limits our ability examine associations with specific causes of DD. In our analysis, we adjusted for potential confounders but there remains the possibility that the association seen could be due to unmeasured variables, such as prematurity, for which we used a proxy of low birth weight, or underlying respiratory disorders associated with DD. Furthermore, food sIgE was only measured to milk, egg, peanut, and shellfish, and thus it is possible that this underestimates the true prevalence of food sensitization. Lastly, sensitization data was taken in 2005–2006 but the self-reported food allergy questions were from 2007–2010, so these were in different subjects, which limits our ability to perform direct comparisons.

Despite these limitations, this is the first report comparing DD with both self-reported allergy and allergic sensitization in children in a nationally representative sample. Our study showed that children with DD are more likely to have self-reported asthma, milk allergy, and egg allergy, but not sensitization to either these foods or aeroallergens. Whether patients with DD have a true increased risk of atopic disease, a higher rate of over-diagnosis of these conditions, or a higher prevalence of non-IgE mediated disorders warrants further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Implications

We found that individuals with developmental disorders had a higher odds of self-reported allergic disease but not of allergic sensitization to foods or environmental allergens, suggesting that the elevated risk may be due to over-reporting or to non-IgE mediated mechanisms.

Table 1:

Demographic Characteristics of Children Included in NHANES 2005–2010 Analyses

	Developmental Disorders (n = 799)	Controls (n=9,386)	p value
Age (years) *	10.2 ± 0.20	9.63 ± 0.09	0.015
Male (%)	67.0	49.5	<0.001
Race/ethnicity (%)			<0.001
Caucasian	59.7	58.1	
Black	18.7	14.0	
Hispanic	13.9	20.5	
Other	7.7	7.4	
Household smokers	24.0	14.8	<0.001
Household income (%)			<0.001
< 1.75 × PL	45.9	36.0	
≥ 1.75 × PL	54.1	64.1	
Household insurance			<0.0010
None	7.1	10.6	
Private	43.4	58.2	
Government	45.4	29.3	
Other	4.1	1.8	
College education	53.3	56.2	0.203
Annual healthcare visits			<0.001
0–1	26.7	35.6	
≥2	73.3	64.4	
Low birth weight (%)	18.1	10.8	<0.001

* Mean +/− SE

Table 2:

Associations between Developmental Disorders and Allergic Disease among Children in NHANES 2005–2010

	n	Crude OR (95% CI)	p value	Adjusted OR* (95% CI)	p value*
Asthma	7335	**1.65 (1.28 – 2.12)**	**<0.001**	**1.51 (1.12 – 2.02)**	**0.007**
Current asthma	7322	**1.80 (1.37 – 2.37)**	**<0.001**	1.40 (0.98 – 1.99)	0.06
Recent attack	6874	**2.12 (1.52 – 2.95)**	**<0.001**	**1.61 (1.09 – 2.36)**	**0.02**
ED/urgent care	6480	**2.41 (1.43 – 4.05)**	**0.001**	1.41 (0.74 – 2.71)	0.28
Wheezing	10179	**1.66 (1.27 – 2.18)**	**<0.001**	**1.49 (1.11 – 2.01)**	**0.01**
Allergic rhinitis	10169	1.48 (0.96 – 2.28)	0.08	1.45 (0.95 – 2.21)	0.08
Self-reported FA§	5915	1.12 (0.71 – 1.78)	0.62	1.08 (0.70 – 1.66)	0.71
Peanut		1.72 (0.53 – 5.60)	0.35	2.07 (0.69 – 6.20)	0.19
Milk		1.75 (0.97 – 3.17)	0.06	**2.33 (1.21 – 4.49)**	**0.01**
Wheat		0.47 (0.06 – 3.72)	0.46	0.69 (0.09 – 5.46)	0.72
Egg		2.61 (0.87 – 7.85)	0.09	**3.52 (1.06 – 11.7)**	**0.04**
Soy		2.26 (0.14 – 36.0)	0.55	3.34 (0.37 – 30.0)	0.27
Fish		3.20 (0.83 – 12.3)	0.09	0.53 (0.11 – 2.63)	0.43
Shellfish		1.06 (0.83 – 5.87)	0.11	0.79 (0.33 – 1.91)	0.59
Corn		2.16 (0.35 – 13.3)	0.40	1.96 (0.49 – 7.83)	0.33
Tree nuts		2.00 (0.50 – 8.09)	0.32	2.06 (0.45 – 9.47)	0.34
Other		**0.39 (0.24 – 0.65)**	**0.001**	**0.34 (0.19 – 0.61)**	**0.001**
Sensitization (IgE)†					
Peanut	3309	**1.92 (1.21 – 3.07)**	**0.01**	**1.83 (1.05 – 3.18)**	**0.04**
Milk	3264	0.94 (0.48 – 1.84)	0.85	1.04 (0.57 – 1.90)	0.89
Egg	3299	0.70 (0.41 – 1.19)	0.17	0.81 (0.43 – 1.53)	0.50
Shrimp	2382	**0.51 (0.27 – 0.97)**	**0.04**	**0.44 (0.22 – 0.88)**	**0.02**
Aeroallergens	3319	0.98 (0.71 – 1.34)	0.88	0.92 (0.64 – 1.33)	0.64

*Models adjusted for sex, age, race/ethnicity, household income, and low birth weight

§NHANES 2007–2010; FA, food allergy

†NHANES 2005–2006