

Association between allergic disease and developmental disorders in the National Health and Nutrition Examination Survey

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Clinical Implications

- We found that individuals with developmental disorders had 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 overreporting or to non-IgE-mediated mechanisms.

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 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 (DDs) and allergic disease in a nationally representative cross-sectional survey and to extend the previous study by examining the association of DDs 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 aged 1 to 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 this article’s Online Repository at www.jaci-inpractice.org. In NHANES 2005-2006, sIgE level was measured for peanut, egg, milk, shrimp, and aeroallergens, as previously described,³ and sensitization was defined as an sIgE level of greater than or equal to 0.35 kU/L. Multivariable logistic regression was used to examine the association between DDs and individual allergic outcomes, adjusting for race, age, sex, household smokers, income, insurance type, education, number of annual health care visits, and low birth weight (<5 lb).

A total of 10,185 children were included in these analyses, 799 of whom had DDs. Cohort characteristics are included in Table I. Among subjects with DDs, there were increased odds of self-reported asthma (odds ratio [OR], 1.51; 95% CI, 1.12-2.02; $P < .007$) and recent asthma exacerbations (OR, 1.61; 95% CI, 1.09-2.36; $P = .02$), and there was a trend toward increased self-reported allergic rhinitis (OR, 1.45; 95% CI, 0.95-2.21; $P = .08$). Among this population, there were increased odds of self-reported milk allergy (OR, 2.33; 95% CI, 1.21-4.49; $P =$

TABLE I. Demographic characteristics of children included in NHANES 2005-2010 analyses

Characteristic	DDs (n = 799)	Controls (n = 9386)	P value
Age (y), mean $\pm$ SE	10.2 $\pm$ 0.20	9.63 $\pm$ 0.09	.015
Sex: male (%)	67.0	49.5	<.001
Race/ethnicity (%)			<.001
White	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	<.001
Household income (%)			<.001
<1.75 $\times$ PL	45.9	36.0	
$\geq$ 1.75 $\times$ PL	54.1	64.1	
Household insurance			<.001
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	.203
Annual health care visits			<.001
0-1	26.7	35.6	
$\geq$ 2	73.3	64.4	
Low birth weight (%)	18.1	10.8	<.001

NHANES, National Health and Nutrition Examination Survey.

.01) and self-reported egg allergy (OR, 3.52; 95% CI, 1.06-11.7; $P = .04$). 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 DDs and overall sensitization to milk, egg, or aeroallergens (Table II). There were increased odds for peanut sensitization (OR, 1.83; 95% CI, 1.05-3.18; $P = .04$), but these did not persist when stratified to sIgE levels of greater than or equal to 2 kU/L, suggesting that this is low-level sensitization of unclear clinical significance (see Table E1 in this article’s Online Repository at www.jaci-inpractice.org). Conversely, children with DDs had lower odds of overall shrimp sensitization (OR, 0.44; 95% CI, 0.22-0.88; $P = .02$; Table E1).

In this study, we found that children with DDs had 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 DDs.^{2,4} We did not, however, find an increase in sIgE levels to these foods or aeroallergens. It is possible that there is a shared immunologic pathway promoting the development of both DDs and allergic disease, as there is an increasingly recognized association between DDs and dysregulation of maternal and postnatal immune pathways. However, our findings suggest that this association may instead be due to (1) overdiagnosis and/or increased perception of allergic disease in this population, or (2) a true increase in non-IgE-mediated mechanisms of allergic disease.

Evidence supporting an association between DDs and allergic disease primarily comes from cross-sectional and case-control

TABLE II. Associations between DDs and allergic disease among children in NHANES 2005-2010

Allergy Outcome	n	Crude OR (95% CI)	P value	Adjusted OR* (95% CI)	P value*
Asthma	7,335	1.65 (1.28-2.12)	<.001	1.51 (1.12-2.02)	.007
Current asthma	7,322	1.80 (1.37-2.37)	<.001	1.40 (0.98-1.99)	.06
Recent attack	6,874	2.12 (1.52-2.95)	<.001	1.61 (1.09-2.36)	.02
ED/urgent care	6,480	2.41 (1.43-4.05)	.001	1.41 (0.74-2.71)	.28
Wheezing	10,179	1.66 (1.27-2.18)	<.001	1.49 (1.11-2.01)	.01
Allergic rhinitis	10,169	1.48 (0.96-2.28)	.08	1.45 (0.95-2.21)	.08
Self-reported FA†	5,915	1.12 (0.71-1.78)	.62	1.08 (0.70-1.66)	.71
Peanut		1.72 (0.53-5.60)	.35	2.07 (0.69-6.20)	.19
Milk		1.75 (0.97-3.17)	.06	2.33 (1.21-4.49)	.01
Wheat		0.47 (0.06-3.72)	.46	0.69 (0.09-5.46)	.72
Egg		2.61 (0.87-7.85)	.09	3.52 (1.06-11.7)	.04
Soy		2.26 (0.14-36.0)	.55	3.34 (0.37-30.0)	.27
Fish		3.20 (0.83-12.3)	.09	0.53 (0.11-2.63)	.43
Shellfish		1.06 (0.83-5.87)	.11	0.79 (0.33-1.91)	.59
Corn		2.16 (0.35-13.3)	.40	1.96 (0.49-7.83)	.33
Tree nuts		2.00 (0.50-8.09)	.32	2.06 (0.45-9.47)	.34
Other		0.39 (0.24-0.65)	.001	0.34 (0.19-0.61)	.001
Sensitization (IgE)‡					
Peanut	3,309	1.92 (1.21-3.07)	.01	1.83 (1.05-3.18)	.04
Milk	3,264	0.94 (0.48-1.84)	.85	1.04 (0.57-1.90)	.89
Egg	3,299	0.70 (0.41-1.19)	.17	0.81 (0.43-1.53)	.50
Shrimp	2,382	0.51 (0.27-0.97)	.04	0.44 (0.22-0.88)	.02
Aeroallergens	3,319	0.98 (0.71-1.34)	.88	0.92 (0.64-1.33)	.64

ED, Emergency department; FA, food allergy; NHANES, National Health and Nutrition Examination Survey.

Bolded values are statistically significant ($P < .05$).

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

†NHANES 2007-2010.

‡NHANES 2005-2006.

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, have been shown to overestimate the true prevalence of this condition when compared with oral food challenges.⁶ Although it has been suggested that allergic disease may be underdiagnosed in patients with DDs because of impaired communication and lower tolerance for diagnostic tests,⁴ it is alternatively possible that patients with DDs have more frequent respiratory infections and/or other conditions that mimic allergic disease, leading to an increased perception or overdiagnosis of this condition. Future studies assessing the prevalence of allergic disease in children with DDs, using objective and reproducible measures, are clearly needed.

It is also possible that although self-reported asthma and food allergy are increased in children with DDs, 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, a milk-derived opioid receptor agonist, and its gluten homolog, gliadorphin 7. Beta-casomorphin 7 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 DDs.

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 various conditions, including speech/language impairment, developmental delay, and ASD, are eligible to receive special education or early intervention services. Thus, our definition of DDs is broad and encompasses subjects with noncognitive delays, behavioral problems, and neurologic injuries, which limits our ability to examine associations with specific causes of DDs. 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 DDs. Furthermore, food sIgE was measured only to milk, egg, peanut, and shellfish, and thus it is possible that this underestimates the true prevalence of food sensitization. Finally, sensitization data were taken in the period 2005 to 2006, but the self-reported food allergy questions were from 2007 to 2010, so these were in different subjects, which limits our ability to perform direct comparisons.

Despite these limitations, this is the first report comparing DDs with both self-reported allergy and allergic sensitization in children in a nationally representative sample. Our study showed that children with DDs 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 DDs

have a true increased risk of atopic disease, a higher rate of overdiagnosis of these conditions, or a higher prevalence of non-IgE-mediated disorders warrants further study.

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ONLINE REPOSITORY

Self-reported asthma was defined in children 6 to 17 years old as a positive answer to the question “Has a doctor or other health professional ever told you that your child has asthma?” This was followed by “Does your child still have asthma?” and further stratified by severity, as defined by “During the past 12 months, has your child had an episode of asthma or an asthma attack,” or “had a visit to an emergency room or urgent care center because of asthma?” All ages were asked, “In the past 12 months has your child had wheezing or whistling in his/her chest?” Self-reported allergic rhinitis was assessed by a positive response to the questions, “Has a doctor or other health professional ever told you that your child has hay fever?” (2005-2006) or “During the past 12 months, has your child had an episode of hay fever?” (2007-2010). Self-reported food allergy was assessed by a positive response to the question, “Does your child have any food allergies?” (2007-2010). If yes, then the subject was asked “What foods is your child allergic to?” with options including wheat, cow’s milk, eggs, fish, shellfish, corn, peanuts, other nuts, soy products, and other foods.

Allergic sensitization to foods (peanut, egg, milk, and shrimp) and aeroallergens (*Dermatophagoides Farinae*, *Dermatophagoides Pteronyssinus*, cat, dog, cockroach, mouse, rat, ragweed, rye grass, bermuda grass, oak, birch, *Aspergillus*, *Alternaria*, and thistle) was assessed by ImmunoCAP (Phadia, Upsalla, Switzerland) in the period 2005 to 2006, as has been previously described.^{E1,E2} Because of limited serum quantities, participants aged 1 to 5 years had specific IgE (sIgE) level measured to 9 allergens (peanut, milk, egg, shrimp, *Alternaria*, cat, cockroach, dog, dust mite). Participants older than 6 years had sIgE level measured to all 19 allergens. Overall sensitization was defined as sIgE level of greater than or equal to 0.35 kU/L, and for foods, *a priori* sensitization categories based on levels of sIgE were defined as previously described.^{E2} To account for oversampling, complex sampling methods, and nonresponse, cluster sampling units, pseudostrata, and sampling weights provided with the surveys were used for all analyses. All analyses were done in STATA 12.1 (StataCorp LLC, College Station, Texas).

TABLE E1. Association between DDs and levels of food sensitization among children in NHANES 2005-2006

	Crude OR (95% CI)	P value	Adjusted OR* (95% CI)	P value*
Peanut				
Overall	1.92 (1.21-3.07)	.009	1.83 (1.05-3.18)	.04
≥2 kU/L	1.06 (0.36-3.15)	.91	0.90 (0.27-2.95)	.85
≥14 kU/L	0.50 (0.16-1.54)	.21	0.22 (0.03-1.56)	.12
Milk				
Overall	0.94 (0.47-1.84)	.85	1.04 (0.57-1.90)	.89
≥2 kU/L	0.70 (0.28-1.75)	.42	0.81 (0.24-2.66)	.71
≥15 kU/L	NA		NA	
Egg				
Overall	0.70 (0.41-1.19)	.17	0.81 (0.43-1.53)	.50
≥2 kU/L	0.96 (0.26-3.58)	.94	1.83 (0.38-8.88)	.43
≥7 kU/L	0.91 (0.10-0.48)	.93	2.61 (0.34-20.3)	.33
Shrimp				
Overall	0.51 (0.27-0.97)	.04	0.44 (0.22-0.88)	.02
≥2 kU/L	1.10 (0.40-3.04)	.85	1.05 (0.35-3.15)	.93
≥5 kU/L	2.91 (0.10-8.40)	.05	2.62 (0.69-9.97)	.14

NA, Not available due to small sample size; NHANES, National Health and Nutrition Examination Survey.

Bolded values are statistically significant ($P < .05$).

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

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