

Comorbidity of Atopic Disorders with Autism Spectrum Disorder and Attention Deficit/Hyperactivity Disorder

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Objective To assess the relationship between allergic manifestations in early life and the occurrence of newly diagnosed autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) throughout childhood.

Study design We collected a population-based longitudinal cohort comprising children enrolled in Taiwan's National Health Insurance Program during 2000-2010. We first identified 387 262 children who had a diagnosis of atopic dermatitis (AD) before age 2 years, with 1:1 individualized matching to children without AD. Cox regression analyses were performed to estimate the early-onset and cumulative effects of allergic manifestations on ASD and ADHD.

Results An estimated 0.5% of AD-exposed children received a diagnosis of ASD, and 3.7% were diagnosed with ADHD, significantly higher than the respective rates of 0.4% and 2.9% found in their nonexposed peers. Having AD before age 2 years was associated with an increased hazard ratio (HR) for ASD by 10% and that for ADHD by 16%; such increases were particularly prominent among those with earlier-onset or more severe AD. HRs were especially higher for children with persistent AD and emerging atopic respiratory diseases in childhood (eg, for ASD, adjusted HR, 1.75 and 2.13, respectively; $P < .001$).

Conclusion The observed increased risks of ASD and ADHD associated with AD in infancy suggest that a disordered immunologic response may exert effects on neurodevelopment and have implications for research into etiology and treatment strategies. (*J Pediatr* 2016; ■: ■-■).

Over the past decade, considerable attention has been focused on the rising prevalence of diagnosed childhood-onset neurodevelopmental disorders, especially autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD).¹⁻³ Researchers have come to the conclusion that the etiologies of ASD/ADHD are multifactorial, including environment, genetics, and environmental-genetic interactions.^{2,4-6} Notably, some studies have reported a higher prevalence of allergic manifestations among individuals with ASD or ADHD.⁷⁻¹⁰ For instance, a cross-sectional study conducted in Germany found a 5.2% prevalence of ADHD in children affected with atopic eczema, compared with 3.4% in their nonaffected counterparts, and found a similar association pattern for asthma.⁷ Another study reported that the experience of "atopic diseases" in early childhood was associated with a 3.40-fold increased risk of ASD and a 1.97-fold increased risk of ADHD.⁹

A higher incidence of allergic disorders has long been reported in individuals with neuropsychiatric disorders.^{11,12} Inflammatory processes or immune dysregulation can play a role in depression, schizophrenia, and obsessive-compulsive disorders.¹¹⁻¹⁴ Allergic disorders comprise atopic dermatitis (AD) and atopic respiratory diseases (RDs). An estimated 28% of children have suffered from at least 1 clinical allergic manifestation before age 4 years.^{15,16} AD is a chronic pruritic skin disease commonly observed in infants and children; 45% of affected children experience their first episode during the first 6 months of life, and 60% do so before their first birthday.¹⁷ As for respiratory allergy, allergic rhinitis is characterized by sneezing, rhinorrhea, and nasal pruritus, whereas asthma often causes recurrent episodes of wheezing, breathlessness, and chest tightness.¹⁶ Clinically, allergic disorders often co-occur: 20%-50% of patients with allergic rhinitis also have asthma, and more than 80% of patients with allergic asthma have concomitant symptoms of rhinitis.^{18,19}

The cumulative evidence indicates that the 3 aforementioned allergic diseases may emerge gradually in temporal succession. The cutaneous manifestation of atopy often marks the entry point of atopic march, and induces epicutaneous sensitization and the migration of sensitized T cells into airways, followed by an array of atopic

AD	Atopic dermatitis
ADHD	Attention deficit/hyperactivity disorder
aHR	Adjusted HR
ASD	Autism spectrum disorder
HR	Hazard ratio
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
NAD	Nonatopic dermatitis
NHIRD	National Health Insurance Research Database
RD	Respiratory disease

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Supported by the National Health Research Institutes (NP-103-SP02). C.-Y.C. was supported by the Ministry of Education, Aim for the Top University, and Yen Tjing Ling Medical Foundation. The authors declare no conflicts of interest.

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<http://dx.doi.org/10.1016/j.jpeds.2015.12.063>

RDs.¹⁶ Because children under age 2 years are incapable of mounting humoral responses to some environmental antigens, the infantile phase of AD reflects cutaneous manifestations that may be narrowed to the window ranging from birth to age 2 years.²⁰

Although a few studies have showed a positive connection between allergic disorders and ASD/ADHD, the temporal sequence underlying the intertwined relationships, possibly developmental stage-dependent, has remained less well explored. For example, previous studies that did not take the evolution of atopic conditions in childhood into account might have overestimated the contribution of certain allergic disorders to neurodevelopmental disorders and might even have inappropriately modeled the temporal sequence of etiologic processes. To tackle this omission in the literature, the present study aimed to investigate the connection between early-life atopic manifestations and subsequent diagnosed neurodevelopmental disorders. We compared the subsequent risks of ASD and ADHD over the period from toddlerhood into childhood in a cohort of children with AD in infancy and their AD-free peers, while simultaneously taking the gradual emergence of RDs (ie, rhinitis or asthma) into account.

Methods

We obtained data from Taiwan's National Health Insurance Research Database (NHIRD). The Taiwanese National Health Insurance Program has provided comprehensive medical care coverage to all citizens and resident foreigners since March 1, 1995. In 2014, 99.5% of Taiwan's population was enrolled (<http://www.nhi.gov.tw>). The database contains the registration files and claims data on the insured subjects. For each subject, a unique identification number is used to link all insurance information and healthcare records. Approval of this study was granted by the Institutional Review Board of the National Health Research Institutes (EC1020403-E).

The original sample comprised children born during 2000-2004 ($n = 1\,262\,810$). Children who: (1) received any diagnosis of ASD (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 299) or ADHD (ICD-9-CM code 314) before age 2 years; or (2) died during the follow-up period were excluded from the analytic sample. On the basis of a retrospective cohort study, children who received a first AD diagnosis (ICD-9-CM code 691) before age 2 years during 2000-2006 ($n = 387\,262$; 30.7%) were classified as the AD-exposed group. Based on a 1:1 ratio of exposed to nonexposed children, we used the criteria of birth year, birth season, and residential region to match individual non-AD (NAD)-affected children from the NHIRD, resulting in a total of 774 524 children. The follow-up period spanned birth until December 31, 2010, in an interval of 6-10 years. The occurrence of ASD was defined as having at least 2 outpatient visits with ASD as the primary diagnosis within 1 year; the same definition was applied to ADHD.²¹

Data were obtained not only on AD occurring before age 2 years, but also on later episodes (either first or recurring instances of AD) for children categorized AD-exposed or NAD group. Guided by the atopic march model, we further ascertained the subjects' experience with RDs, comprising allergic rhinitis (ICD-9-CM code 477) and asthma (ICD-9-CM code 493). To evaluate possible time-dependent effects of atopic disorders, the occurrence of RDs was obtained separately from 3 developmental stages (ie, infancy [0-1 years], toddlerhood/preschool [2-5 years], and childhood [6+ years]).

Data concerning all medical diagnoses were retrieved from outpatient records by unique identification number. Information on individual sociodemographic variables (ie, sex, birth year, birth season, premium category, urbanization level, and residential region) was retrieved from the beneficiary registry data files. Residential regions were categorized as northern, central, southern, and eastern. Level of urbanization was classified as level 1 (rural), level 2 (suburban), or level 3 (urban).³ The premium category, an indicator of parental income, was divided into 3 income levels: poverty and near poverty, middle income, and high income. Birth seasons were defined as spring (March, April, and May), summer (June, July, and August), autumn (September, October, and November), and winter (December, January, and February).¹⁹

Statistical Analyses

Descriptive statistics for individual sociodemographic and clinical characteristics were first summarized and tested in relation to AD exposure. The χ^2 test was used for categorical variables, and the Student t test was used for continuous variables (eg, age at diagnosis). The associations linking individual sociodemographic and clinical characteristics with ASD and ADHD were then estimated using the Cox proportional hazard model. The crude association (as indexed by hazard ratio [HR]) was obtained first, followed by multivariate regression, with simultaneous adjustment for sex, urbanization, premium category, birth year, birth season, residential region, previous history of AD diagnosis, and history of first episode of RD.

The time-dependent risks linking early AD and RD with ASD/ADHD were captured using time-dependent survival analyses. Three measures were used to assess exposure to atopic disease—diagnosis of AD before age 2 years (yes vs no), age of onset (<1 year vs 1-2 years), and number of visits (1, 2-3, or 4 or more)—to evaluate the possible critical window of exposure and clinical severity. Finally, based on age-dependent risk estimates linking atopic disorders, linear combination was used to derive the summary risk of ASD and ADHD; an episode occurring after age 2 years was added into the equations for comparison. The magnitude and strength of associations are presented in point estimates, 95% CIs, and P values. The data were prepared and the analyses performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

Selected characteristics of the study cohorts are summarized in **Table I**. A total of 387 262 “exposed” children received their first diagnosis of AD before age 2 years, with a mean age of 0.71 years. An estimated 27% ($n = 102\,433$) of AD-exposed children had at least 1 visit for AD during toddlerhood, and 7% ($n = 26\,076$) did so during childhood. By the end of 2010, in these children the cumulative incidence of ADHD was 3.7% and that of ASD was 0.5%, higher than the respective 2.9% and 0.4% in the children with NAD.

Table II presents the HRs of individual sociodemographic and clinical characteristics and early-life AD experience for ASD and ADHD. In general, children who were male, had a urban/suburban residence, and born in later years were

more likely to receive the diagnosis of ASD or ADHD. With all listed variables being adjusted simultaneously, receiving an initial diagnosis of AD before age 2 years was associated with a greater risk of ASD (adjusted HR [aHR], 1.09; 95% CI, 1.02-1.17) and ADHD (aHR, 1.15; 95% CI, 1.12-1.18). The HR of a subsequent episode of AD was 1.36 for ASD and 1.26 for ADHD. Experiencing a first episode of RD before age 2 years also was linked to an increased risk of ASD (aHR, 1.49; 95% CI, 1.35-1.64) and ADHD (aHR, 1.68; 95% CI, 1.62-1.75).

With simultaneous adjustment for sociodemographic characteristics and the time-varying experience of atopic disorders, an early-life diagnosis of AD may slightly increase the risk of being diagnosed with ASD (aHR, 1.10; 95% CI, 1.03-1.18) or ADHD (aHR, 1.16; 95% CI, 1.13-1.19) (**Table III**).

Table I. Sociodemographic and health characteristics for children with AD and NAD

Variables*	AD cohort ($n = 387\,262$)		NAD cohort ($n = 387\,262$)		P value†
	n	%	n	%	
Sex					<.001
Male	207 305	53.5	200 144	51.7	
Female	179 957	46.5	187 116	48.3	
Urbanization					<.001
Rural	36 431	9.4	36 696	9.5	
Suburban	239 437	61.8	241 878	62.5	
Urban	111 424	28.8	108 688	28.1	
Premium category					<.001
Poverty/near poverty	112 348	29.0	122 126	31.5	
Middle income	192 302	49.7	188 688	48.7	
High income	82 612	21.3	76 431	19.7	
Birth year					1.0
2000	77 619	20.0	77 619	20.0	
2001	72 342	18.7	72 342	18.7	
2002	76 547	19.8	76 547	19.8	
2003	79 594	20.6	79 594	20.6	
2004	81 160	21.0	81 160	21.0	
Birth season					1.0
Spring	88 827	22.9	88 827	22.9	
Summer	94 494	24.4	94 494	24.4	
Autumn	107 911	27.9	107 911	27.9	
Winter	96 030	24.8	96 030	24.8	
Residential region					1.0
Eastern	7575	2.0	7575	2.0	
Northern	194 646	50.3	194 646	50.3	
Central	77 676	20.1	77 676	20.1	
Southern	107 365	27.7	107 365	27.7	
Age at AD diagnosis, y, mean (SD)	0.71 (0.53)		NA		
At least 1 visit for AD at age 2-5 y‡					<.001
Yes	102 433	26.5	45 251	11.7	
At least 1 visit for AD at age ≥6 y‡					<.001
Yes	26 076	6.7	15 270	3.9	
Onset of atopic RD‡					<.001
None	95 268	24.6	141 108	36.4	
First episode before age 2 y	115 402	29.8	71 760	18.5	
First episode at ages 2-5 y	148 494	38.3	140 269	36.2	
First episode at age ≥6 y	28 098	7.3	34 125	8.8	
Onset of ASD	2048	0.5	1659	0.4	<.001
Age at ASD diagnosis, y					.520
Mean (SD)	4.63 (1.91)		4.59 (1.89)		
Onset of ADHD	14 380	3.7	11 312	2.9	<.001
Age at ADHD diagnosis, y					<.001
Mean (SD)	6.16 (1.69)		6.26 (1.67)		

NA, not applicable.

The ICD-9-CM codes are 691 for AD, 493 and 477 for atopic RD, 299 for ASD, and 314 for ADHD.

*The column may not add up to 100% due to missing data.

†The χ^2 test for categorical variables and t test for continuous variables.

‡By the end of December 31, 2010.

Table II. Estimated HRs between atopic disorders with receiving the first diagnosis of ASD and ADHD

Variables	ASD		ADHD	
	Crude HR (95% CI)	aHR (95% CI)	Crude HR (95% CI)	aHR (95% CI)
Sex				
Female	1	1	1	1
Male	5.05 (4.61-5.52)*	4.92 (4.50-5.38)*	3.39 (3.29-3.49)*	3.28 (3.19-3.38)*
Urbanization				
Rural	1	1	1	1
Suburban	1.73 (1.49-2.02)*	1.32 (1.13-1.55)*	1.50 (1.43-1.58)*	1.38 (1.30-1.45)*
Urban	2.89 (2.47-3.38)*	1.78 (1.51-2.11)*	1.97 (1.87-2.08)*	1.60 (1.51-1.70)*
Premium category				
Poverty/near poverty	1	1	1	1
Middle income	0.95 (0.88-1.03)	0.92 (0.85-0.99) [†]	0.95 (0.93-0.98)*	0.91 (0.89-0.94)*
High income	1.75 (1.61-1.90)*	1.41 (1.29-1.53)*	1.06 (1.02-1.09) [‡]	0.89 (0.86-0.92)*
Birth year				
2000	1	1	1	1
2001	1.04 (0.94-1.15)	1.04 (0.94-1.16)	1.02 (0.98-1.05)	1.02 (0.98-1.05)
2002	1.06 (0.95-1.17)	1.06 (0.96-1.18)	1.03 (0.99-1.07)	1.03 (0.99-1.07)
2003	1.05 (0.95-1.17)	1.07 (0.97-1.19)	1.05 (1.01-1.09) [†]	1.05 (1.01-1.09) [†]
2004	1.16 (1.05-1.29) [‡]	1.18 (1.07-1.32) [‡]	1.17 (1.12-1.23)*	1.18 (1.13-1.24)*
Birth season				
Spring	1	1	1	1
Summer	1.02 (0.93-1.11)	1.03 (0.94-1.13)	1.24 (1.20-1.28)*	1.25 (1.21-1.29)*
Autumn	0.88 (0.80-0.96) [‡]	0.89 (0.81-0.97) [†]	0.76 (0.73-0.79)*	0.76 (0.74-0.79)*
Winter	0.91 (0.83-1.00)	0.92 (0.84-1.01)	0.85 (0.82-0.88)*	0.85 (0.82-0.88)*
Residential region				
Eastern	1	1	1	1
Northern	2.55 (1.85-3.51)*	1.76 (1.27-2.44)*	1.48 (1.34-1.63)*	1.16 (1.05-1.28) [‡]
Central	1.18 (0.85-1.65)	1.04 (0.74-1.45)	0.76 (0.69-0.84)*	0.66 (0.60-0.74)*
Southern	1.35 (0.98-1.88)	1.20 (0.86-1.66)	1.12 (1.01-1.24) [†]	1.00 (0.91-1.11)
AD before age 2 y				
No	1	1	1	1
Yes	1.24 (1.16-1.32)*	1.09 (1.02-1.17) [†]	1.28 (1.25-1.31)*	1.15 (1.12-1.18)*
At least 1 visit for AD at age ≥2 y				
No	1	1	1	1
Yes	1.54 (1.44-1.65)*	1.36 (1.26-1.46)*	1.41 (1.37-1.45)*	1.26 (1.23-1.30)*
First episode of atopic RD				
No	1	1	1	1
Age <2 y	1.97 (1.80-2.17)*	1.49 (1.35-1.64)*	2.06 (1.99-2.14)*	1.68 (1.62-1.75)*
Age ≥2 y	1.84 (1.69-2.01)*	1.49 (1.37-1.63)*	1.86 (1.80-1.93)*	1.63 (1.58-1.69)*

ICD-9-CM codes are 299 for ASD, 314 for ADHD, 691 for AD, and 493 and 477 for atopic RD.

* $P < .001$.† $P < .05$.‡ $P < .01$.

An earlier diagnosis of AD (ie, before age 1 year) was associated with a slightly higher risk of ASD (aHR, 1.11) and ADHD (aHR, 1.17) (Table III). In terms of severity, the HR of ASD and ADHD increased with an increasing number of visits (both P values for trend analyses in the adjusted model were $<.01$). Four visits or more for AD before age 2 years was associated with the greatest risk of ASD (aHR, 1.19; 95% CI, 1.06-1.34) and ADHD (aHR, 1.21; 95% CI, 1.16-1.27).

The Figure presents the summary risks of ASD and ADHD on the basis of time-dependent experience of atopic disorders in 3 developmental stages. The risk of ASD in those children having AD in infancy and experiencing the first episode of RD during toddlerhood was elevated by 26%, significantly lower than the estimated risk for those who had AD in infancy and the first episode of RD in childhood (aHR, 1.54). For ADHD, the risk was greatest for those who had AD in infancy and the first episode of RD in toddlerhood, particularly in those with revisits for AD after age 2 years (aHR, 2.05).

Discussion

Our population-based cohort study shows that the experience of AD before age 2 years is associated with a slight increase in subsequently diagnosed ASD and ADHD. Although previous cross-sectional and longitudinal studies have reported the association between atopic disorders early in life and an increased risk of ASD and ADHD,^{7-9,22} the majority either treated multiple manifestations of allergic diseases as comorbid disorders or categorized all allergic disorders into a single broad medical condition.^{23,24} Our statistical strategies, guided by the atopic march model, allowed us to explore possible contributions of an atopic predisposition in early life (ie, critical exposure window) and the evolution/continuation of clinical features over time in a more comprehensive and systematic way.

Consistent with previous research,³ we found an increase in newly diagnosed ASD and ADHD among later birth

Table III. Estimated HR of receiving a diagnosis of ASD or ADHD, by time-dependent survival analysis

	ASD		ADHD	
	Model 1, aHR (95% CI)	Model 2, aHR (95% CI)	Model 1, aHR (95% CI)	Model 2, aHR (95% CI)
Exposure experience				
AD before age 2 y				
No	1	1	1	1
Yes	1.20 (1.12-1.28)*	1.10 (1.03-1.18) [†]	1.26 (1.23-1.29)*	1.16 (1.13-1.19)*
At least 1 visit for AD at age ≥2 y				
No		1		1
Yes		1.38 (1.29-1.49)*		1.25 (1.22-1.29)*
Onset of atopic RD [‡]				
None		1		1
Before age 2 y		0.99 (0.90-1.09)		1.01 (0.98-1.04)
Age 2-5 y		1.15 (1.04-1.26) [†]		1.40 (1.34-1.45)*
Age ≥6 y		1.40 (1.17-1.67)*		0.99 (0.95-1.05)
Age at first exposure				
AD before age 2 y				
No	1	1	1	1
Age <1 y	1.20 (1.12-1.29)*	1.11 (1.04-1.20) [†]	1.26 (1.23-1.30)*	1.17 (1.13-1.20)*
Age 1-2 y	1.17 (1.07-1.29) [†]	1.07 (0.98-1.18)	1.24 (1.20-1.29)*	1.14 (1.09-1.18)*
At least 1 visit for AD at age ≥2 y				
No		1		1
Yes		1.38 (1.29-1.49)*		1.27 (1.24-1.31)*
Onset of atopic RD [‡]				
None		1		1
Before age 2 y		0.99 (0.90-1.09)		1.01 (0.98-1.04)
Age 2-5 y		1.15 (1.04-1.26) [†]		1.40 (1.34-1.45)*
Age ≥6 y		1.40 (1.17-1.67)*		0.99 (0.95-1.05)
Exposure severity				
AD before age 2 y [§]				
No	1	1	1	1
1 visit	1.15 (1.06-1.24)*	1.09 (1.01-1.18) [¶]	1.17 (1.14-1.21)*	1.14 (1.10-1.17)*
2-3 visits	1.18 (1.07-1.29)*	1.08 (0.98-1.18) [¶]	1.22 (1.18-1.26)*	1.17 (1.13-1.21)*
4 or more visits	1.40 (1.25-1.56)*	1.19 (1.06-1.34) [†]	1.28 (1.22-1.34)*	1.21 (1.16-1.27)*
At least 1 visit for AD at age ≥2 y				
No		1		1
Yes		1.37 (1.27-1.48)*		1.26 (1.23-1.30)*
Onset of atopic RD [‡]				
None		1		1
Before age 2 y		0.99 (0.90-1.08)		1.00 (0.97-1.04)
Age 2-5 y		1.15 (1.04-1.26) [†]		1.40 (1.34-1.45)*
Age ≥6 y		1.40 (1.17-1.67)*		0.99 (0.95-1.05)

Time-varying Cox regression analysis. Model 1 adjusted for sex, urbanization, premium category, birth year, birth season, residential region, and AD before age 2 years. Model 2 adjusted for sex, urbanization, premium category, birth year, birth season, residential region, AD before age 2 years, at least 1 visit for AD at age ≥2 years, and onset of RD. ICD-9-CM codes are 299 for ASD, 314 for ADHD, 691 for AD, and 493 and 477 for atopic RD.

* $P < .001$.

[†] $P < .01$.

[‡]Time-varying factor.

[§]Trend analyses in adjusted models: $P = .003$ for ASD and $P < .001$ for ADHD.

[¶] $P < .05$.

cohorts, which may be the mixed results of increasing awareness of neurodevelopmental disorders by medical professionals/primary caregivers and increasing exposure to environmental risk factors.^{2,4} Regarding the risk linked with AD before age 2 years, our estimates were slightly lower than those reported in previous work (eg, HR for ASD, 1.10 vs 3.04; HR for ADHD, 1.16 vs 1.87²⁵). A similar pattern was seen in the risk estimates of atopic RDs for ASD and ADHD.^{9,26} The discrepancies observed may be explained in part by differences in: (1) the definitions of ASD and ADHD diagnosis (ie, at least 2 outpatient visits within 1 year); (2) population characteristics, including age (<18 years vs <2 years) and race/ethnicity; (3) adjustment and matching on different arrays of confounders; and (4) the definition of atopic disorders. Owing to a lack of objective diagnostic criteria or to logistic and ethical problems

(eg, with medication trials), available clinical guidelines generally indicate that a firm and reliable diagnosis is difficult to reach for children aged ≤5 years.²⁷ To avoid such misclassification, the present study combined asthma and allergic rhinitis as a single category of atopic RD disorder, which might have led to underestimation of the HR.²⁸ Finally, statistical adjustment of the incidence of atopic disorders over developmental stages could be another factor contributing to the discrepant findings; adding the later emergence of atopic RDs into the model might have partitioned off the association with AD exposure during infancy.⁷

Laboratory research has provided some evidence of environmental factors potentially causally involved in the manifestation of ASD and ADHD. For example, the body burden of toxic metals (eg, lead, mercury, or aluminum) has been significantly correlated with the variation in severity

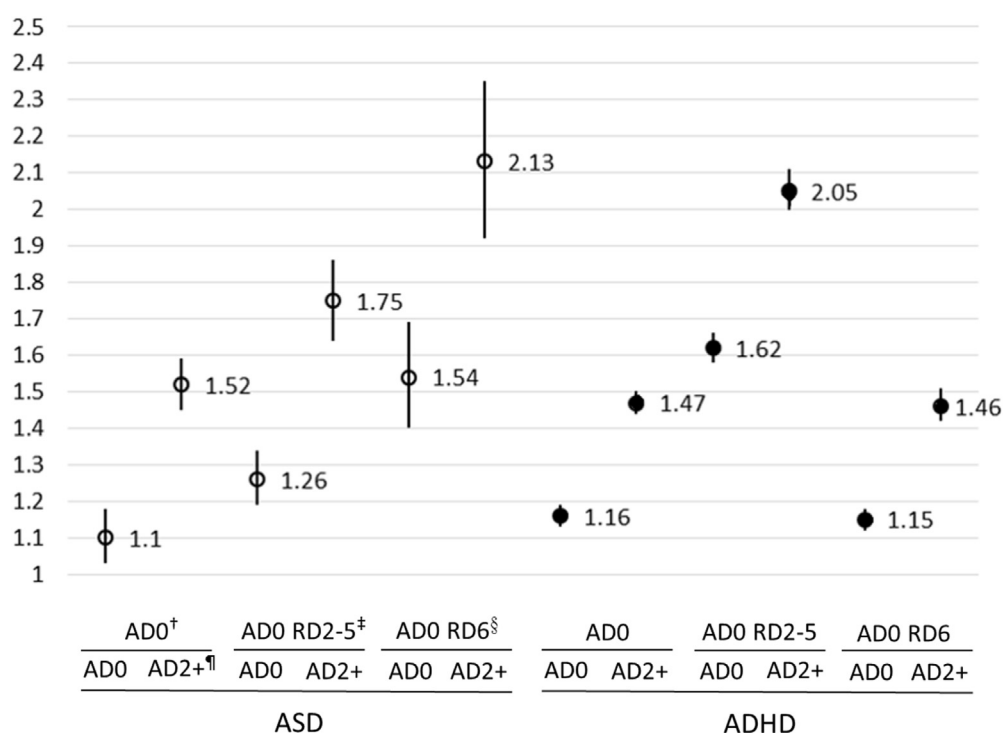


Figure. Estimated risk between atopic predisposition with ASD and ADHD. All estimates were derived from model 2 in [Table III](#). [†]AD 0: first AD diagnosis in infancy; [‡]RD 2-5: onset of atopic RD in toddlerhood; [§]RD 6: onset of atopic RD in childhood; [¶]AD 2+: episode of AD after age 2 years.

of autism.^{29,30} Certain environmental factors, including infectious pathogens, food allergens, and toxins, may exert their deleterious effects on neurodevelopment through inflammation and dysregulation of the immunologic response.³¹ In sync with the mechanisms underlying progressive atopy, our observation of a greater risk of ASD/ADHD in children whose AD initially emerged in the first year of life or who had AD in a severe or chronically persistent form, together with increased risk related with atopic RDs,¹⁶ suggest a possible contribution of an immunologic abnormality or epidermal barrier deficiency in early life to later neurodevelopmental problems.

At least 2 mechanisms have been hypothesized to account for the observed association between AD in infancy and later neurodevelopmental disorders. The first of these addressed the effects of proinflammatory cytokines on brain development,³² and the second focused on chronic sleep disturbance/deprivation subsequent to allergic disorders.³³ The present study used age 2 years as the cutpoint to reflect the maturational status of the immune system. Given that the immune system is not yet prepared to defend against environmental antigens during infancy, young children with atopic diseases may be exposed to higher levels of inflammatory cytokines released during allergic sensitization. Those cytokines may pass through the blood-brain barrier and activate neuroimmune mechanisms, leading to disruptive effects on the structure or function of the developing brain (eg,

ASD).^{34,35} Children with atopic disorders also may suffer from sleep disturbance or deprivation, which if chronic may independently elevate or modify the atopic disorder-associated risk of neurodevelopmental disorders (eg, ADHD).³⁶ Nevertheless, we cannot rule out the possibility that the observed AD-related increased risk of ASD and ADHD may be associated with other factors, such as: (1) help-seeking behaviors (seeking treatment for AD may increase the likelihood of a subsequent diagnosis of ASD/ADHD); (2) shared susceptibility (unmeasured shared etiologic/pathological processes may increase the occurrence of both AD and ASD/ADHD); and (3) confounding factors (other risk factors associated with ASD/ADHD were not taken into account in this study).²⁹⁻³¹

This study has some limitations that should be addressed. First, our analyses were based solely on the National Health Insurance datasets, lacking direct evidence regarding clinical validity of the diagnoses for ASD/ADHD.³⁷⁻³⁹ Nevertheless, to reduce the “rule out diagnosis” bias, we restricted the outcome definition to at least 2 outpatient visits with the same diagnosis. Second, the limited array of variables restricted our ability to take into account certain risk factors that may increase the predisposition for ASD or ADHD, such as family history, history of trauma, family dysfunction and family disruption, prematurity, and the age of both parents at birth.^{2,4-6} Similarly, the NHIRD did not offer information about the pattern of help-seeking behaviors, some individual-level variables (eg,

personal lifestyle, parental education level), and some other environmental factors, and so we were unable to examine or adjust for such confounding effects. Third, owing to the limited information available, we were unable to examine potential risk variation linked to the severity and clinical manifestations of neurodevelopmental disorders.

The strengths of the present study stem mainly from the nature of medical claims data. First, the large sample size from the NHIRD allowed us to examine the hypothesized links with satisfactory statistical power, and the 99.5% insurance coverage rate gives the study national representativeness. Second, the longitudinal data allowed us to explore this issue from a developmental perspective, offering the possibility of probing developmental period-dependent risk from birth through toddlerhood to childhood guided by an atopic march model.

In conclusion, this population-based study has demonstrated a significant relationship between allergic disorders early in life and subsequent diagnoses of ASD and ADHD in later life. Furthermore, our results provide empirical evidence that the risk associated with atopic diathesis for neurodevelopmental disorders may operate beyond the sensitive window of infancy. These findings suggest a possible etiologic communality between the diagnosis of allergic disorders along with comorbid ASD or ADHD. The atopic diathesis approach might influence the attention of child psychiatrists and pediatricians toward the diagnosis of ASD and ADHD. Further attention should be given to the management of allergic manifestations when treating symptoms of ASD and ADHD.⁴⁰ ■

Submitted for publication Oct 2, 2015; last revision received Dec 4, 2015; accepted Dec 22, 2015.

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