



How does autism spectrum disorder affect the risk and severity of childhood asthma?

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ABSTRACT

Background: Autism spectrum disorder (ASD) and asthma are among the most common chronic disorders in childhood. Both are associated with altered immune regulation and share several risk factors. The effects of ASD on risk for later asthma and asthma severity remain unclear.

Objective: To determine whether ASD in children increases the risk of incident asthma and worsens asthma severity.

Methods: We performed 2 distinct analytic designs (case-control and retrospective longitudinal cohort) using a multistate electronic health records database to assess the odds of new asthma and asthma severity among children with ASD. In both designs, children with ASD were matched with children without ASD according to sex, age, race, ethnicity, location, and insurance status. Pulmonary function, controller medication prescriptions, asthma exacerbations, and asthma-related hospitalizations were collected. The effects of ASD on asthma risk and severity were assessed using multivariable linear and logistic regression.

Results: Among children with asthma, ASD was associated with reduced exacerbations (odds ratio [OR], 0.71; 95% confidence interval [CI], 0.54–0.92), better forced expiratory volume in 1 second/forced vital capacity ratio (0.876 vs 0.841, $P < .001$), and lower odds of airflow obstruction (OR, 0.53; 95% CI, 0.31–0.90) but had higher odds of asthma controller prescription (OR, 2.18; 95% CI, 1.62–2.93). In a longitudinal analysis of children without asthma, ASD was found to be protective for new asthma (OR, 0.44; 95% CI, 0.26–0.74).

Conclusion: Among children with asthma, concomitant ASD is associated with better asthma-related outcomes but a higher controller treatment burden. In addition, our data did not support ASD as a risk factor for incident asthma.

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Introduction

Autism spectrum disorder (ASD) and asthma are among the most common chronic diseases in childhood.¹ Both conditions involve altered immune regulation^{2–11} and typically present during early childhood,^{12,13} most often in young boys. Recent decades have seen an increase in asthma and ASD prevalence that has not yet been conclusively explained.^{14,15} Both conditions also share similar risk factors, including prematurity, low birth weight, urban environment, phthalate exposure, and firstborn birth order.^{16–24} A shared inflammatory origin could explain an association between the 2 conditions. In addition, a direct association from ASD to asthma might partially explain the recent increased prevalence in childhood asthma. The gene *CD38* has been implicated in both

asthma and ASD,^{25,26} whereas several of the genes that have been linked to ASD encode proteins involved in the respiratory cilia of the airway barrier system.²⁷ Branching anomalies of the subsegmental airways, possibly leading to obstruction, have been described among children with ASD.²⁸ Three cross-sectional, population-based studies using parents' report found higher asthma prevalence among individuals with ASD (odds ratios [ORs], 1.35–1.74),^{29–31} which would be consistent with but not conclusive of ASD increasing the risk of incident asthma. However, other studies have found no association between ASD and asthma risk.^{32–34} Three case-control and 1 cross-sectional population-based study did not find a significant difference in asthma prevalence between those with and without ASD, using maternal reports or physician diagnoses. Another retrospective study using clinical diagnoses from outpatient records determined asthma to be significantly less common among children with ASD compared with those without ASD.³⁵ A recent meta-analysis found a significant association between ASD and asthma among cross-sectional studies, whereas among case-control studies no association was

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found.³⁶ Longitudinal cohort studies are needed to better measure the risk of incident disease. Thus, the association between ASD and subsequent asthma risk remains very much unclear. Considering the high morbidity related to childhood asthma and the recent increased prevalence of ASD, it is important to understand the association between ASD and the risk of incident asthma.

Another related question is whether ASD among patients with asthma is related to more severe asthma outcomes. Coexistence of 2 or more chronic conditions can interact and lead to greater combined disease severity.³⁷ Children with ASD have impaired communication skills.³⁸ Their reduced ability to recognize and verbalize symptoms can make early disease diagnosis and disease management more difficult. Discomfort related to other disease comorbidities (including asthma) can result in worsening and exacerbations of ASD symptoms.^{39,40} The association between ASD and asthma severity is not known, but considering the population prevalence of each condition, many children worldwide would be expected to have both conditions. Few studies have examined the effect of ASD on severity of asthma in children affected by both conditions. Therefore, to address these 2 important epidemiologic and clinical questions, we sought to conduct 2 separate studies using a large multistate electronic health database: (1) to determine whether ASD serves as a risk factor for incident asthma and (2) to compare the severity of asthma among children with and without ASD.

Methods

This study uses real-world clinical data obtained from the Nemours Children's Health System electronic health records (Epic, Verona, Wisconsin) using 2 separate designs: a case-control design (asthma severity) and a retrospective longitudinal cohort design (asthma risk). Patient data originated from more than 11 clinical sites that involved primary and subspecialty care from 3 main sites in Florida (Jacksonville, Orlando, and Pensacola) and throughout the Delaware Valley (Delaware, New Jersey, Maryland, and Eastern Pennsylvania). The Nemours data warehouse includes clinical care data which reflects pragmatic care patterns. The Nemours data network has taken advantage of advances in data collection methods adhering to the PEDSNet common data model^{41,42} to increase data validity, database size and diversity, and data linkage (connecting clinical diagnoses to laboratory data to pulmonary function tests to medication use to health care use) and has been able to uncover accurate and hidden value from longitudinal analyses. In developing the common data elements across the network, we have considered the entire life cycle of the clinical data, the source of the data, the challenges arising from missing data, and possible inaccuracies in the data itself.^{43,44} Our methodologic approach addresses the traditional limitations that have challenged database research in the past, including adequate and compatible computer systems, inconsistent data standards across sites, lack of quality-control checks during data collection, and entry and large-scale data cleaning. The study was approved by the Nemours Institutional Review Board.

Participant Selection

To assess *asthma severity* among children with asthma and ASD, we conducted a cross-sectional case-control analytic study that involved children 2 to 17 years of age with asthma with and without ASD. Cases were children with confirmed asthma and ASD seen from January 1, 2008, through March 30, 2016. Children were considered to have confirmed asthma if they had 2 or more clinical diagnoses of asthma and at least 1 antiasthma drug prescription in the previous 12 months. ASD and asthma diagnoses were collected using the *International Classification of Diseases, Ninth Revision* (ICD-9) codes 299.x and the *International Classification of Diseases,*

10th Revision (ICD-10) codes F84.0-5 and F84.8-9 and ICD-9 codes 493.x and ICD-10 codes J45.x, respectively. Each patient with ASD and asthma was matched with one comparator (control) patient with confirmed asthma but without ASD diagnosis. Comparators were matched for sex, race (white, black, Asian, other), ethnicity (Hispanic/Latino), insurance status (private, Medicaid, none), and current age (within 12 months). Patients with cystic fibrosis were excluded.

To assess *risk of asthma* attributed to ASD diagnosis, we conducted a separate retrospective cohort study of children with and without ASDs. Both groups were without asthma at baseline. The ASD risk group included all children seen at Nemours from January 1, 2008, through April 30, 2016, with at least 2 visits with an ASD diagnosis before the age of 6 years and without asthma at or before the time of the first ASD diagnosis. Children in the ASD cohort must have had at least 4 total Nemours visits, 2 or more of which must have been after the age of 5 years, and with a total observation period of at least 5 years. The total observation period was defined as the time between the first ASD diagnosis and last Nemours visit. Each patient with ASD was matched with 2 similar comparator patients with no ASD diagnosis at or before their initial visit, defined as the visit that corresponds to within 12 months of matched ASD patient's initial diagnosis visit. Comparators were matched for age (date of birth $\pm$ 12 months), date of initial visit ($\pm$ 12 months), sex, race (black, white, or other), ethnicity (Hispanic/Latino or other), insurance status (private, Medicaid, or none), and Nemours location (Delaware, Jacksonville, Orlando, or Pensacola). Patients with cystic fibrosis were excluded.

Clinical Data

Asthma severity was measured using forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), forced expiratory ratio (FER), the number of asthma exacerbations, the number of asthma-related hospitalizations, and prescriptions for asthma controller medications. Controller medications included any inhaled corticosteroid (ICSs) with a long-acting β -agonist (ICS-LABA) or a leukotriene receptor antagonist (LTRA). Spirometry results were used to create the binary variables airflow obstruction and bronchodilator responsiveness, defined as an FER less than 0.85 and FEV₁ or FVC percent change of 12% or greater after bronchodilator, respectively. When multiple spirometry results were available for a single patient, the best set that included both pre and postbronchodilator results were used.

To assess asthma risk and compare rates of incident asthma, patients and comparators had all subsequent Nemours visits assessed for incident asthma diagnosis, defined by ICD-9 or ICD-10 codes. Absolute and relative risks of asthma were calculated for each risk group. Other variables collected included number of prescriptions for controller medications, number of visits with an asthma diagnosis, age at first asthma diagnosis, length of observation period, number of prescriptions for the most common medications prescribed to patients with ASDs (sleep, antipsychotic, and attention-deficit/hyperactivity disorder medications), any cause visits (primary care, emergency department, hospitalization, and specialty visits), gestational age at birth, number of diagnoses of known comorbidities of asthma (eczema, gastroesophageal reflux disease, allergic rhinitis, and obstructive sleep apnea), and spirometry results when available. We collected individual race, ethnicity, sex, location, observation period, and insurance status on all participants.

Statistical Analysis

The χ^2 test was used for comparing percentages, whereas the *t* or Wilcoxon tests were used comparing continuous variables, as appropriate. For analysis of asthma severity, we performed simple

Table 1
Characteristics in Children With Asthma With and Without ASD^a

Characteristic	No. of children	Children with ASD (n = 783)	Children without ASD (n = 785)	P value ^b
Age, mean (SD), y	1,568	9.8 (4.0)	9.8 (4.0)	.98
Male	1,568	644 (82.3)	646 (82.3)	.98
Race	1,568			>.99
White		400 (51.1)	401 (51.1)	
Black		221 (28.2)	221 (28.2)	
Asian		15 (1.9)	15 (1.9)	
Native American		3 (0.4)	3 (0.4)	
Missing		7 (0.9)	7 (0.9)	
Other		137 (17.5)	138 (17.6)	
Hispanic/Latino	1,560	138 (17.7)	138 (17.7)	.981
Observation period, mean (SD), d	1,568	719.0 (783.0)	707.7 (811.9)	.779
Age at asthma diagnosis, mean (SD), y	1,568	5.6 (4.0)	5.1 (4.1)	.016
Gestational age at birth, mean (SD), wk	1,151	37.04 (4.25)	37.95 (3.04)	<.0001
Insurance status	1,568			.166
Medicaid		458 (58.5)	458 (58.3)	
Private		290 (37.1)	290 (37.0)	
None		35 (4.5)	37 (4.7)	
Clinical site	1,568			<.001
Jacksonville		84 (10.7)	135 (17.2)	
Orlando		166 (21.2)	65 (8.3)	
Pensacola		37 (4.7)	37 (4.7)	
Delaware		496 (63.4)	548 (69.9)	

Abbreviation: ASD, autism spectrum disorder.

^aData are presented as number (percentage) of children unless otherwise indicated.^bP values are from the *t* test or χ^2 test as appropriate.

linear or logistic regression to assess the univariate effect of ASD status on outcome measures of asthma severity. Adjusted analyses were performed using multivariable linear or logistic regression which took into account influential covariables that differed at baseline between groups. For analysis of asthma risk, we calculated the risk and odds of a new asthma diagnosis in both groups and an odds and risk ratio comparing the 2 risk groups. We performed similar analyses on confirmed asthma diagnoses. We performed multivariable logistic regression to adjust for the influential covariables and to determine adjusted odds of incident asthma. The level of significance was taken as $P < .05$. Statistical analyses were performed using SAS statistical software (SAS Institute Inc, Cary, North Carolina).

Results

Asthma Severity Study

Baseline characteristics of 783 participants with asthma and ASD and 785 matched comparators with asthma without an ASD are given in Table 1. The ASD group had a significantly lower

gestational age at birth and a significantly higher age at asthma diagnosis. There was also a significant difference in location between the 2 groups. Fitting with the matching design, age, sex, race, ethnicity, observation period, and insurance status were similar between groups.

Asthma controller burden and health care use

Asthma controller burden among children with asthma with and without ASDs is reported in Table 2. The percentage of participants with at least one prescription for a controller medication (ICS only, ICS-LABA, or LTRA) was significantly higher in children with ASD, following univariable and multivariable analyses adjusting for gestational age and clinic location. The adjusted odds for any controller prescription among children with ASDs was significantly greater in children with ASD compared with children without (Fig 1). In addition, the percentage of participants with at least one prescription for ICS-LABA and for LTRA was significantly higher in the ASD group. Asthma-related health care use is reported in Table 2. The percentage of participants with one or more exacerbations was significantly lower in children with ASD in crude

Table 2
Asthma Controller Burden and Health Care Use^a

Variable	No. of children	Children with ASD (n = 783)	Children without ASD (n = 786)	P value ^b	Adjusted P value ^{a,b,c}
Any controller prescription	1,569	640 (81.7)	537 (68.3)	<.001	<.001
Any ICS only prescription	1,569	581 (74.2)	473 (60.2)	<.001	<.001
Any ICS-LABA prescription	1,569	113 (14.4)	86 (10.9)	.04	.20
Any LTRA prescription	1,569	354 (45.2)	245 (31.2)	<.001	<.001
Any nasal ICS prescription	1,569	303 (38.7)	288 (36.6)	.40	.59
Asthma exacerbation ever	1,569	225 (28.7)	280 (35.6)	.004	.01
Total exacerbations, mean (SD)	1,568	0.63 (1.45)	0.80 (1.63)	.03	.12
Total exacerbations, mean (SD) ^d	505	2.20 (2.0)	2.24 (2.10)	.81	.83
Asthma hospitalization ever	1,569	43 (5.5)	32 (4.1)	.19	.38
Total asthma hospitalizations, mean (SD)	1,568	0.1 (0.5)	0.1 (0.5)	.60	.85
Total asthma hospitalizations, mean (SD) ^d	75	1.6 (1.6)	1.8 (1.4)	.52	.13

Abbreviations: ASD, autism spectrum disorder; ICS, inhaled corticosteroid; LABA, long-acting β -agonist; LTRA, leukotriene receptor antagonist.^aData are presented as number (percentage) of patients unless otherwise indicated.^bP values are from the *t* test or χ^2 test as appropriate.^cP values adjusting for gestational age and clinical site.^dIncluding patients with 1 or more event.

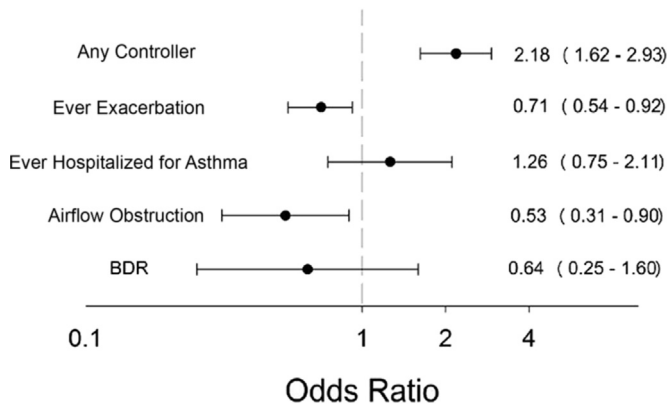


Figure 1. Odds of asthma outcomes among children with autism spectrum disorder (ASD) compared with controls. Airflow obstruction was defined as forced expiratory volume in 1 second/forced vital capacity ratio less than 0.85. Error bars indicate 95% confidence intervals. BDR indicates bronchodilator reversibility ($\geq 12\%$ improvement after albuterol in forced expiratory volume in 1 second or forced vital capacity).

analyses and multivariable analyses after adjusting for gestational age and clinical site. The odds for ever-exacerbation was significantly reduced among children with ASDs compared with children without (Fig 1). Hospitalizations did not differ significantly by ASD status in crude and multivariable analyses.

Spirometry

FVC and FEV₁ percent predicted values were similar between children with asthma without and without ASD (Table 3). However, children with ASDs had a significantly higher FER and forced expiratory flow between 25% and 75% (FEF_{25%–75%}) percent predicted compared with similar children without ASD. This difference remained significant after adjustment for gestational age and clinical site. The percentage of children with airflow obstruction was significantly higher among children without ASDs after adjustment. The adjusted odds for airflow obstruction among children with ASDs compared to children without ASDs was significantly lower (Fig 1). The percentage of children with bronchodilator responsiveness was not significantly different between the 2 groups; however, a greater percent change in FEV₁ and FEF_{25%–75%} after bronchodilator use was seen among children without ASDs, which was statistically significant after adjustment. A greater percent change in FVC was also observed among children without ASDs before adjusting for gestational age and clinical site,

although this significance did not remain after adjustment. The results in Table 3 did not change on further adjustment for insurance status and observation period.

Asthma Risk Study

Characteristics of 464 participants with ASDs at study entry and 912 matched comparators without ASDs at study entry are listed in Table 4. Because of the matching design, age at entry, age at completion, sex, race, ethnicity, gestational age at birth, and insurance status were similar between groups. There was a difference between the 2 groups in clinic location and observation period. Asthma risk by ASD status is given in Table 5. The risk and odds of incident asthma diagnosis were significantly lower among children with ASD in crude and multivariable analyses. Even after adjusting for length of observation period and clinical site, the odds of incident asthma among children with ASD were still reduced (56% reduced odds compared with children without ASD).

Discussion

Our study found that among children with asthma, children who also have ASD are more often prescribed asthma controller medications, have fewer exacerbations, and have better lung function. These results are important because they provide some contrast with the few previous studies that involve children with asthma and ASD.

Asthma medication prescriptions among individuals with ASDs have not been specifically studied before. Our finding of higher asthma prescription rates among children with ASDs are consistent with a recent cross-sectional study of ambulatory prescription fills among children with ASDs. House and colleagues⁴⁵ found that prescription use is significantly higher among children with ASDs, even for nonpsychotropic drug categories, such as antacids and antibiotics. In contrast, Koehler et al⁴⁶ performed a cross-sectional study and found no difference in parentally reported preventative asthma medication use between 70 children with various developmental disabilities, including ASDs, and 460 controls. Our study compared asthma prescriptions abstracted from medical records and did not rely on parental recall. In addition, our medication data reflect medication prescribed, and we were not able to measure adherence. The number of controller prescriptions from our study reflects a clinician's estimation of the child's recent asthma impairment and risk for worsening, which is a measure of asthma severity.⁴⁷ LTRAs can also be prescribed for allergic rhinitis. Requiring at least 2 asthma diagnoses to be included in the study

Table 3
Pulmonary Function Test Results^a

Variable	No. of children	Children with ASD	Children without ASD	P value ^b	Adjusted P value ^c
FVC, % predicted	360	98.7 (17.5)	100.7 (18.7)	.29	.34
FEV ₁ , % predicted	360	96.5 (18.9)	94.3 (17.0)	.24	.35
FER	360	.876 (.106)	.841 (.098)	.001	<.001
FEF _{25%–75%} , % predicted	360	92.4 (92.4)	84.0 (30.4)	.02	.03
Airflow obstruction, ^d No. (%)	360	59 (38.3)	100 (48.5)	.053	.02
FVC, % change	181	1.8 (1.8)	4.7 (9.9)	.02	.10
FEV ₁ , % change	181	7.1 (7.1)	9.7 (13.3)	.20	.02
FER, % change	181	5.8 (5.8)	4.9 (8.4)	.53	.29
FEF _{25%–75%} , % change	181	24.2 (34.9)	32.5 (45.1)	.19	.02
Bronchodilator responsiveness, ^e No. (%)	181	16 (27.6)	42 (34.1)	.38	.22

Abbreviations: ASD, autism spectrum disorder; FEF_{25%–75%}, forced expiratory flow between 25% and 75%; FER, forced expiratory ratio; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

^aData are presented as mean (SD) unless otherwise indicated.

^bP values are from the *t* test or χ^2 test as appropriate.

^cAdjusting for gestational age and clinical site.

^dAirflow obstruction defined as FER less than 0.85.

^eBronchodilator responsiveness defined as 12% improvement in FVC or FEV₁ after bronchodilator use.

Table 4
Baseline Characteristics of Longitudinal Cohorts With and Without ASD^a

Characteristic	No. of children	Children with ASD at entry (n = 464)	Children without ASD at entry (n = 912)	P value ^b
Age at entry, mean (SD), y	1,376	3.4 (1.1)	3.4 (1.1)	.93
Age at completion, mean (SD), y	1,376	10.2 (1.6)	10.2 (1.5)	.62
Male	1,376	365 (78.7)	710 (77.9)	.73
Race	1,376			>.99
White		320 (69.0)	633 (69.4)	
Black		75 (16.2)	144 (15.8)	
Asian		15 (3.2)	28 (3.1)	
Other		54 (11.6)	107 (11.7)	
Hispanic/Latino	1,376	43 (9.3)	83 (9.1)	.92
Observation period, mean (SD), d	1,376	1,790 (728)	2,270 (338)	<.001
Gestational age at birth, mean (SD), wk	832	38.5 (2.7)	38.3 (2.8)	.29
Insurance status	1,376			.89
Medicaid		156 (33.6)	310 (34.0)	
Private		18 (63.2)	28 (62.8)	
None		15 (3.2)	30 (3.3)	
Clinical site	1,376			<.001
Jacksonville		65 (14.0)	313 (34.3)	
Orlando		39 (8.4)	45 (4.9)	
Pensacola		7 (1.5)	43 (4.7)	
Delaware		353 (76.1)	511 (56.0)	

Abbreviations: ASD, autism spectrum disorder.

^aData are presented as number (percentage) of patients unless otherwise indicated.^bP values are from the *t* test or χ^2 test as appropriate.

population limits the amount of LTRA prescriptions that were issued for indications other than asthma.

The only other study²⁹ that examined exacerbations among children with ASDs found a 70% higher odds of parental report of asthma attack in the preceding 12 months among children with ASD. Our study did not rely on parental recall but rather measured exacerbations via documented systemic steroid prescriptions. Our database could have missed exacerbations occurring outside the Nemours health system, although differential measurement bias between groups seems unlikely.

Our finding of better lung function among children with ASDs compared with children without ASDs is an interesting and novel finding. It contrasts with one prior report of double-branching anomalies in the subsegmental airways in children with ASDs,²⁸ which might be expected to result in smaller airway caliber and worse lung function. Stewart and Klar²⁸ found that all 49 children with ASDs and none of the 410 children without ASDs undergoing bronchoscopy had smaller-caliber doublets or double-branching airways. Our spirometric findings clearly indicate that ASD among children with asthma is not associated with reduced lung volumes or airflow obstruction. These findings are consistent with children with asthma and ASD being responsive to asthma controllers, leading to good lung function.

As with all case-control studies, this study assessing asthma severity had limitations. The data stemmed from a retrospective assessment of medical records and is therefore dependent on the quality of medical documentation. We were limited to the data that were recorded at the time of visit, which was not necessarily complete. In addition, ASD and asthma are conditions whose

diagnoses are made on clinical grounds and are not made uniformly by all health care professionals. Because of the study's cross-sectional design, we cannot infer causality. Another limitation includes possible ascertainment bias stemming from the possibility of different health literacy, health-related behaviors, and underlying treatment burdens between families affected by ASD and those who are not. These factors could affect exposure to health care and likelihood of asthma diagnosis. However, our study had a fairly large study population with 783 children with ASDs and asthma. Use of medical records instead of parental report for measures of asthma severity limits recall bias, and external validity of this report is robust because it represents a diverse group of children from several states across the eastern United States seen in inpatient and outpatient clinical settings.

Our results of children having better lung function, reduced exacerbations, and greater controller treatment burden can be interpreted in a variety of ways. Although the number of asthma controller prescriptions was meant as a surrogate measure of asthma severity, the number of prescriptions can also reflect physician prescribing practices. One barrier that pediatricians face when prescribing asthma medications includes parental attitudes toward risk and benefit and concerns about corticosteroids.⁴⁸ It is possible that parents of children with ASD have a more pragmatic view of risk and benefit, and concerns about ICSs are less of a barrier for families affected by ASDs, leading to greater controller prescriptions. We speculate that parents of children with ASD may be more motivated to do everything possible to avoid other medical symptoms that might exacerbate ASD symptoms.

Table 5
Asthma Risk^a

Variable	No. of Children	Children With ASD at Entry (n = 464)	Children Without ASD at Entry (n = 912)	RR	OR	aOR ^b (95% CI)	aOR P Value ^c
Asthma ever	1,376	35 (7.5)	132 (14.5)	0.52	0.48	0.44 (0.282–0.689)	<.001
Asthma confirmed	1,376	25 (5.4)	100 (11.0)	0.49	0.46	0.4 (0.263–0.731)	.002

Abbreviations: aOR, adjusted odds ratio; ASD, autism spectrum disorder; CI, confidence interval; OR, odds ratio; RR, risk ratio.

^aData are presented as number (percentage) of patients.^bAdjusting for observation period and clinical site.^cP values are from the *t* test or χ^2 test as appropriate.

The lower odds of having had an exacerbation and airflow obstruction are consistent with higher ICS prescribing and better medication adherence, leading to better asthma control. Another possibility is that more children with ASDs with mild intermittent disease are diagnosed with persistent disease to foster preventive treatment and avoid exacerbating ASD symptoms. Lastly, it is possible that some of the genes associated with ASD may also associate with better lung function or response to ICSs.

The other retrospective cohort study was designed to investigate whether ASD is a risk factor for the development of new asthma in children. A recent meta-analysis that evaluated the epidemiologic link between asthma and ASD found and analyzed only cross-sectional and case-control studies. The investigators found a significant association between ASD and asthma among cross-sectional studies, whereas no association was found among case-control studies.³⁶ They concluded, using current data, that a clear link could not be established. They also stated that prospective and longitudinal studies are needed to better measure risk of incident disease. To our knowledge, this is the first longitudinal cohort study designed specifically to answer this question. Our results clearly indicate that among this longitudinal sample of more than 1,300 patients, ASD was not a risk factor for new asthma. We found that children with ASD had a 56% reduced odds of being diagnosed with asthma.

The few studies that have attempted to assess ASD as a potential risk factor for asthma found conflicting results.^{29–34,36,49–51} Only one previous study has studied asthma that occurs after the date of first ASD diagnosis.³⁵ Our results are consistent with their findings of significantly lower odds of asthma among children with ASDs, with an OR of 0.63 compared with our 0.44. These results are not consistent with the other studies on the association between asthma and ASDs, which all found an equal or higher prevalence of asthma among individuals with ASDs compared with individuals without. However, these studies did not take into consideration when the asthma diagnosis was made in relation to the first ASD diagnosis. Our results are again inconsistent with double branching in the airways of children with ASD, which would be expected to result in narrower airways and a higher prevalence of asthma.²⁸

Our study relied on medical records rather than parental report, thus limiting recall bias. The definition of confirmed asthma cases used in our study should limit erroneous diagnoses, although we cannot be certain that all those with asthma truly had asthma. Conversely, without periodic, systematic evaluation of all study participants, we cannot be certain that those without asthma, truly did not have asthma. Our study was limited by the retrospective nature of data collection, although we were able to limit the effect of certain confounders through matching cases with controls and adjusting for measured differences between the 2 groups. However, there is the possibility of unknown confounders influencing our findings. The external validity of this report is robust because it represents children from several states across the eastern United States with diverse backgrounds.

Our results are consistent with ASD status reducing the risk of future asthma diagnosis. It is possible that there is an underlying biological explanation for this, but the literature is sparse regarding a biological link between ASDs and the lungs or asthma.

It is also possible that other factors explain our results. We speculate that children in early life who will develop ASD may more commonly experience environments that are protective for asthma (eg, agricultural or farm exposure) or more rarely experienced environments that incite asthma pathogenesis (eg, viral infections or tobacco smoke). Children with ASD can have intellectual and motor delays, social and communicative impairments, and certain fears, anxieties, and sensory issues, which may result in less exposure to contagions.

Lastly, it is possible that children with ASD are less likely to be brought to a physician for treatment of asthma symptoms. They may be less aware of their symptoms or less able to communicate them. Their parents may also be reluctant to add to their already numerous medical visits. Although our results are consistent with asthma being less common in children with ASD, they may be the result of underdiagnosis of asthma in this population.

Although the potential for ascertainment bias is a clear limitation to our study, it is not clear whether parents of children with ASD would be more or less likely to bring their children to a physician for mild asthma symptoms. On one hand, they are more likely to be connected to health care, but on the other hand they might be more hesitant to seek care specifically for mild respiratory symptoms, thus adding to their child's hospital visits. Although a prospective cohort study with periodic asthma assessment would be ideal to answer the study questions, it is a costly and time-consuming approach. Despite its limitations, this study is clinically relevant for clinicians caring for children with ASD. The reduced risk of asthma diagnosis, better lung function, and reduced exacerbations among those with asthma are reassuring. We speculate that better asthma outcomes in ASD stem from greater medication adherence (corroborated by the greater controller treatment burden for children with ASD). Children with ASD do not need the added burden of unnecessary asthma diagnosis, and we hope this study will help avoid the burden of excess visits for chronic disease. However, it is likely that, when necessary, treatment is generally effective.

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