

ORIGINAL ARTICLE: ASTHMA

Effects of age, sex, race/ethnicity, and allergy status in obesity-related pediatric asthma

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Funding information

Patient-Centered Outcomes Research Institute, Grant/Award Number: CDRN-1306-01556

Abstract

Rationale: Obesity in children increases the risk for new asthma. How age, sex, race/ethnicity, and allergy status affect the relationship between obesity and asthma is unclear. This study describes the relationship between high body mass index (BMI) and incident asthma.

Methods: We conducted a retrospective cohort study to compare asthma incidence among normal weight, overweight, and obese 2 to 6, 7 to 11, and 12 to 17 year olds to define the effects of sex, race/ethnicity, and allergy status. Weight status was determined at baseline and asthma incidence was defined as ≥ 2 asthma encounters and ≥ 1 asthma prescriptions. We used multivariable Poisson regression to estimate adjusted incident asthma rates and risk ratios.

Results: Data from 192 843 2 to 6 year olds, 157 284 7 to 11 year olds, and 157 369 12 to 17 year olds were included. The relative risks (95% confidence interval [CI]) of new asthma among obese children in 2 to 6 year olds, 7 to 11 year olds, and 12 to 17 year olds were 1.25 (1.15, 1.37), 1.49 (1.32, 1.69) and 1.40 (1.21, 1.63), respectively. Among children with underlying allergic rhinitis, obesity did not increase the risk of new asthma. In children without allergic rhinitis, the risk for obesity-related asthma was highest in 7 to 11 year olds (risk ratio = 1.50 95% CI, 1.33, 1.60). Before age 12, females had a higher risk for obesity-related asthma; but after age 12, obese males had a higher asthma risk (interaction P -value $< .05$).

Conclusion: Obesity is a major preventable risk factor for pediatric asthma that appears to vary along the pediatric age continuum and depends on sex, race/ethnicity and atopy status.

KEYWORDS

asthma and early wheeze, child, epidemiology, overweight, pulmonary function testing (PFT)

1 | INTRODUCTION

Obesity is one of few modifiable risk factors for asthma, the most common chronic disease in children. Childhood asthma causes frequent hospitalizations and impaired quality of life,¹⁻³ and obesity is a key risk factor for poor asthma control and excess asthma-related health care utilization. The latest evidence suggests that obesity continues to be highly prevalent in US children and has recently increased in prevalence in young children.⁴ Using the *Key determinants on the path from Obesity to Asthma in Children* (KOACH) PEDSnet longitudinal study, we recently showed that 23%-27% of new asthma cases in the setting of pediatric obesity can be attributed specifically to obesity; furthermore, roughly 10% of all US cases of pediatric asthma would be prevented in the absence of obesity.

Epidemiologic studies of pediatric asthma demonstrate that the risk of new asthma is not uniform across the pediatric population. Several common disease modifying factors including age, sex, race and ethnicity, and the development of atopic conditions significantly affect the inception and phenotypic characteristics of asthma. The majority of new pediatric asthma cases present before the onset of puberty when there is a clear male predominance⁵ and high co-incidence of allergy.^{6,7} After puberty, the risk for females increases and new asthma is less commonly related to allergic conditions. African American and Puerto Rican children, compared to non-Hispanic Whites, experience significantly higher incidence rates⁸ and asthma severity. Presence of allergic disease, particularly in early-onset asthma, is a predictor for greater symptom severity, risk of airway hyperresponsiveness⁹ and a natural history that persists throughout childhood.¹⁰ How overweight and obesity change these pediatric asthma incidence patterns is unknown, but is important to understand considering the increasing rates of overweight and obesity.

We used the PEDSnet clinical research network (<https://pedsnet.org/>) to describe the relationship between pediatric overweight and obesity on asthma incidence over the pediatric age continuum and interactions with sex, race/ethnicity, and allergy status.

2 | METHODS

We previously described the parent KOACH study¹¹ published using PEDSnet assembled electronic health data. The current analyses were predefined and involved only deidentified data. The Duke Institutional Review Board [Pro00077780] determined this project to be exempt research with human subjects. Under 45 CFR 46.116, the requirement for informed consent was waived at all PEDSnet institutions.

2.1 | Study design

Data from January 2009 to December 2015 was assembled into a retrospective cohort study design. Patients with overweight or obesity were matched 1:1 with a healthy weight comparator. All data were derived from routine care documented in electronic health

records from six large pediatric institutions. Data from each participant included all of their inpatient, outpatient, and Emergency Department setting encounters. We assigned participants to one of three body weight groups from their initial visit: *overweight*—a body mass index (BMI) 85 to 94th percentile adjusted for sex and age, *obese*—BMI $\geq$ 95th percentile adjusted for sex and age; and a *healthy weight* group of matched comparators whose BMI percentile ranged between 25 and 64th percentile adjusted for sex and age. No participant had a prior diagnosis of asthma before their study-defined initial visit. We determined and compared rates of incident asthma between BMI groups, primarily obese vs normal and then stratified by targeted determinants.

2.2 | PEDSnet

PEDSnet (pedsnet.org) uses the Observational Health Data Sciences and Informatics (OHDSI) common data model¹² to standardize electronic health record data across sites. PEDSnet includes eight US pediatric institutions, six of which participated in this study: Nemours Children's Health System, Children's Hospital of Philadelphia, Colorado Children's Hospital, St. Louis Children's Hospital, and Nationwide Children's Hospital, and Seattle Children's Hospital. The catchment area for PEDSnet institutions includes more than 20 US states in addition to an international referral base. Each contributing PEDSnet site, utilized research data from all clinical settings including ambulatory/primary care, ambulatory/subspecialty care, hospital admissions, emergency department care, and all laboratory and imaging results.

2.3 | Participant selection

Eligible patients were children aged 2 to 17 years seen within a PEDSnet institution from January 1, 2009 to December 31, 2015 and with: (a) an age- and sex-adjusted BMI $\geq$ 85th percentile, (b) no health record diagnosis of asthma (ICD-9-CM code 493.x) or wheezing (786.07) at, or before, the baseline visit, and (c) at least 2 subsequent (total of 3) clinic visits spanning at least 12 months. Requiring subsequent visits for eligibility avoided the inclusion of patients who could not develop the endpoint of interest (asthma diagnosis). The baseline visit was the first healthcare visit following January 1, 2009. We excluded patients with any documented diagnosis of cystic fibrosis, ciliary dyskinesia, childhood cancer, inflammatory bowel disease, or bronchopulmonary dysplasia. For each overweight/obese subject, we randomly selected one normal weight comparator identically matched for age at initial visit (± 12 months), sex, race (White, Black, Asian, Other), ethnicity (Hispanic/Latino vs non), insurance status (Medicaid, Private, other), and PEDSnet site.

2.4 | Baseline data and outcome measures

Baseline data for each subject were taken from the study-defined initial visit encounter or from encounters before the initial visit and included demographics, insurance status (Medicaid, private, other), BMI-percentile, BMI z-score, past and current co-morbid health

conditions and medications. Age groupings were evenly dispersed between 2 and 17 years and adhering generally to NAEPP age groupings (2-6, 7-11, and 12-17 years of age). Race and ethnicity classifications were determined by self-identification. We defined each participant's observation period as the time from initial visit to the patient's last recorded encounter, and provided observation period duration, encounter diagnoses, encounter medications, and spirometry values. Spirometry values included forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1), measured in liters and as a percentage of the age- and sex-adjusted predicted value. Percent predicted values were calculated centrally for all patients using a combination of reference values depending on age group and race/ethnicity.¹³⁻¹⁶

2.5 | Diagnosis of asthma

The primary outcome was incidence of asthma, defined as ≥ 2 different encounters with a diagnosis of asthma and ≥ 1 antiasthma medication prescription during the observation period: January 1, 2009 to December 31, 2015. Secondary outcomes included stricter criteria for asthma diagnosis, which included ≥ 2 encounter with asthma diagnosis with additional confirmation by spirometry. Spirometry confirmation required either FEV1 percent predicted $< 80\%$, FEV1/FVC < 0.85 or post-bronchodilator improvement $\geq 10\%$ in either FEV1 or FVC.^{17,18}

2.6 | Analysis

Crude and adjusted incident asthma rates (per person-time) and rate (risk) ratios were determined for each group (normal weight, overweight and obese) using univariable and multivariable Poisson regressions. Asthma incidence for each risk group was adjusted for each group's observation period duration and was expressed as an incidence rate (per person-time). In addition to the rates and rate ratios, we estimated: attributable risk (AR) ($[Incidence_{exposed}] - [Incidence_{unexposed}]$), AR percent ($AR/Incidence_{exposed}$), population AR (PAR) ($[Incidence_{population}] - [Incidence_{unexposed}]$), and PAR percent ($PAR/Incidence_{population}$) for overweight and obese participants using standard formulas.¹¹ Variables in the multivariable model included sex, race, ethnicity (as appropriate), insurance status, observation period, and institution. The model was checked for over- and under-dispersion of response variables. All tests were two-sided and P values < 0.05 were considered statistically significant. The statistical packages SAS version 9.4 (SAS Institute Inc, Cary, NC) was used for data analysis.

3 | RESULTS

3.1 | Baseline characteristics

The baseline demographic characteristics of all eligible patients meeting criteria are shown by BMI groupings in 2 to 6 year olds (Table 1a), 7 to 11 year olds (Table 1b) and 12 to 17 year olds (Table 1c). Due to the matching design, the number of participants

were evenly split between normal BMI and overweight/obese BMI groups. Baseline characteristics differed statistically by body habitus groups for age, sex, race, ethnicity, and health insurance status. BMI grouping was associated with healthcare utilization including total observation period, total encounters, outpatient and inpatient encounters and emergency department visits. Prevalence of allergic rhinitis, food allergy, and urticaria were reduced among obese children in all age groups.

3.2 | Incidence of asthma by BMI category across age groups

Among children with a normal BMI, the incidence of asthma was highest and roughly double in the 2 to 6 year olds (3.6 per 1000 patient-years) compared to 1.8 per 1000 patient-years and 1.6 per 1000 patient-years among the 7 to 11 and 12 to 17 year olds, respectively (Table 2). In the youngest patients with obesity, the adjusted relative risk for incident asthma was increased 24% (95% confidence interval [CI], 14%-36%) compared to children with normal BMI. The risk for asthma among overweight 2 to 6 years olds was increased 14% (95% CI, 5%-24%) over normal weights.

Among 7 to 11 year olds, the adjusted risks for incident asthma among obese children and overweight children were increased 45% (95% CI, 29%-64%) and 22% (95% CI, 7%-39%), respectively, compared to similar aged children with healthy weights. Among 12 to 17 year olds, the adjusted risk for incident asthma among obese children was increased 35% (95% CI, 16%-56%), while among similar overweight children the adjusted risk was nonsignificantly increased by 12% (95% CI, -5%-32%), compared to healthy weights.

3.3 | Spirometry-confirmed asthma

In the analysis involving children with spirometry where asthma diagnosis required spirometric confirmation of asthma, the crude relative risks for new asthma among obese participants remained significantly increased for 7 to 11 year olds ($RR = 1.39$, 95% CI, 1.18-1.65) and 12 to 17 year olds ($RR = 1.29$, 95% CI, 1.01-1.65). Overweight 2 to 6 and 12 to 17 year old children did not display significant increases in spirometry-confirmed asthma.

3.4 | Attributable risk estimates by age group

The proportion of incident asthma in children with obesity that was attributable to obesity was highest among 7 to 11 year olds at 33.1% (95% CI, 32.5-33.7) (Figure 1A). Attributable risk percent for 2 to 6 and 12 to 17 year olds were 20.1% (95% CI, 19.0-21.5) and 28.6% (95% CI, 27.5-29.7), respectively. When considering asthma confirmed by spirometry, the proportions attributable to obesity were generally similar (Table 3). The proportions of incident asthma in the whole population specifically attributable to obesity in 2 to 6, 7 to 11, and 12 to 17 year olds were 7.0 (95% CI, 6.2-8.1), 14.5 (95% CI, 13.0-16.6), and 12.0% (95% CI, 10.3-14.4), respectively (Figure 1B). The proportion of incident asthma in children with overweight that was

TABLE 1a Participant characteristics among 2-6 y olds by BMI at baseline

Variables	Total participants	BMI-percentile groupings			P value
		Normal (5-84)	Overweight (85-94)	Obese (≥ 95)	
N (%)	192 843	96 451 (50.0)	54 326 (28.2)	42 066 (21.8)	
Age in years	192 843	3.968 (1.541)	3.858 (1.534)	4.109 (1.536)	<.0001
Male, n (%)	103 943	51 981 (53.89)	29 034 (53.44)	22 928 (54.5)	.0047
Race, n (%)	192 843				<.0001
White	101 893	50 952 (52.83)	29 723 (54.71)	21 218 (50.44)	
Black	43 083	21 555 (22.35)	12 092 (22.26)	9436(22.43)	
Asian	5341	2987 (3.10)	1368 (2.52)	986 (2.34)	
Native American	393	179 (0.19)	114 (0.21)	100 (0.24)	
Hawaiian/Pacific Islander	517	229 (0.24)	144 (0.27)	144 (0.34)	
Multiple races	6524	3107 (3.22)	1848 (3.40)	1569 (3.73)	
Other/refused	35 092	17 442 (18.08)	9037 (16.63)	8631 (20.47)	
Hispanic/Latino, n (%)	33 992	17 008 (17.63)	8391 (15.45)	8593 (20.43)	<.0001
Health Insurance status, n (%)					<.0001
Medicaid/sCHIP	86 424	43 232 (44.82)	23 048 (42.43)	20 144 (47.89)	
Other Public	1014	517 (0.54)	292 (0.54)	205 (0.49)	
Private/Commercial	60 013	30 010 (31.11)	18 231 (33.56)	11 772 (27.98)	
Self-pay	19 470	9829 (10.19)	5980 (11.01)	3661 (8.70)	
Observation period in years		4.217 (1.900)	4.109 (1.889)	4.149 (1.898)	<.0001
Total encounters	192 843	34.72 (51.725)	34.649 (52.175)	38.989 (60.533)	<.0001
Outpatient	192 843	33.478 (0.163)	33.595 (0.227)	37.553 (0.287)	<.0001
Inpatient	192 843	0.377 (0.005)	0.370 (0.006)	0.473 (0.010)	<.0001
Emergency Department	192 843	0.851 (0.006)	0.841 (0.008)	0.948 (0.011)	<.0001
Comorbidities at baseline, n (%)					
Esophageal reflux	6380	3293 (3.41)	1673 (3.08)	1414 (3.36)	.0018
Eczema/atopic dermatitis	4990	2459 (2.55)	1511 (2.78)	1020 (2.42)	.0014
Hives/urticaria	3862	1929 (2.00)	1123 (2.07)	810 (1.93)	.2968
Food allergy	2847	1490 (1.54)	846 (1.56)	511 (1.21)	<.0001
Allergic rhinitis	23 300	11 818 (12.25)	6694 (12.32)	4788 (11.38)	<.0001

attributable to overweight was negative among 2 to 6 and 12 to 17 year olds, suggesting possibly some protective effect.

3.5 | Effects of sex, race and atopy status

Overall, sex did not significantly affect the relationship between obesity and asthma incidence across age groups (sex*obesity-status interaction P value > .05; Figure 2A). In males, older age group was associated with a higher RR for obesity-related incident asthma. In females, the risk of obesity-related incident asthma peaked between 7 and 11 years of age. In 7 to 11 year olds, there was a weak trend for interaction between sex and obesity status on asthma risk (sex*obesity interaction P value = .181).

The effect estimates of obesity on asthma incidence also varied by race/ethnicity and atopy status. In Blacks, the increased risk of asthma in obesity was generally consistent across age groups; while in Whites, the effects of obesity increased asthma risk after age six. Compared to children 6 and under, obesity-related asthma was significantly increased among 7 to 11 year olds (P < .001) and 12 to 17 year olds (P < .001). Among Hispanic/Latino children, only children aged 7 to 11 years displayed an obesity-related increased risk of

asthma (Figure 2B). Finally, we found that obesity significantly increased asthma risk in all age groups among children without allergic rhinitis; while among children with allergic rhinitis, obesity did not increase risk of new asthma. Risk of obesity-related asthma was significantly higher among children without allergic rhinitis compared to children with allergic rhinitis (P = .05; Figure 2C).

4 | DISCUSSION

Because asthma is so prevalent in childhood and frequently leads to missed school, impaired quality of life and hospitalization,^{1,2,19} its epidemiology is a subject of intense research. The cause of asthma remains poorly defined but is thought to stem in part from interactions between genetics and environmental factors including early microbial and pollutant exposures. Since obesity is one of very few modifiable risk factors for new asthma, the epidemiology of 'obese-asthma' during childhood is of pressing importance. This more in-depth analysis focused on three age groups generally corresponding to preschoolers (age 2-6 years), school age children (7-11 years), and adolescents (12-17 years). Incidence rates and risk ratios were

TABLE 1b Participant characteristics among 7-11 y olds by BMI at baseline

Variables	Total participants	BMI-percentile groupings			P value
		Normal (5-84)	Overweight (85-94)	Obese (≥ 95)	
N (%)	157 284	78 614 (50.0)	37 143 (23.6)	41 527 (26.4)	
Age in years	157 284	9.575 (1.441)	9.562 (1.451)	9.595 (1.430)	.0050
Male, n (%)	80 705	40 322 (51.29)	18 753 (50.49)	21 630 (52.09)	<.0001
Race, n (%)	157284				<.0001
White	88 490	44 237 (56.27)	22 230 (59.85)	22 023 (53.03)	
Black	36 332	18 170 (23.11)	7825 (21.07)	10 337 (24.89)	
Asian	3750	2097 (2.67)	908 (2.44)	745 (1.79)	
Native American	325	143 (0.18)	70 (0.19)	112 (0.27)	
Hawaiian/Pacific Islander	489	213 (0.27)	118 (0.32)	158 (0.38)	
Multiple races	3879	1889 (2.40)	826 (2.22)	1164 (2.80)	
Other/refused	24 019	11 865 (15.09)	5166 (13.91)	6988 (16.83)	
Hispanic/Latino, n (%)	20 799	10 371 (13.19)	4065 (10.94)	6363 (15.32)	<.0001
Health Insurance status, n (%)					<.0001
Medicaid/sCHIP	54 488	27 209 (34.61)	11 548 (31.09)	15 731 (37.88)	
Private/Commercial	58 897	29 448 (37.46)	14 917 (40.16)	14 532 (34.99)	
Self-pay	18 913	9525 (12.12)	5150 (13.87)	4238 (10.21)	
Observation period in years		4.347 (1.911)	4.351 (1.909)	4.309 (1.896)	.0014
Total encounters	157 284	34.649 (52.175)	33.743 (50.457)	36.48 (50.163)	<.0001
Outpatient	157 284	33.588 (0.181)	32.691 (0.255)	35.310 (0.240)	<.0001
Inpatient	157 284	0.384 (0.007)	0.366 (0.009)	0.403 (0.008)	.0126
Emergency Department	157 284	0.663 (0.007)	0.673 (0.010)	0.752 (0.010)	<.0001
Comorbidities at baseline, n (%)					
Esophageal reflux	5791	3001 (3.82)	1266 (3.41)	1524 (3.67)	.0026
Eczema/atopic dermatitis	2205	1060 (1.35)	575 (1.55)	570 (1.37)	.0220
Hives/urticaria	1817	895 (1.14)	491 (1.32)	431 (1.04)	.0008
Food allergy	1722	933 (1.19)	419 (1.13)	370 (0.89)	<.0001
Allergic rhinitis	17 288	8606 (10.95)	4384 (11.80)	4298 (10.35)	<.0001

determined for each age group independently and took into account individual observation periods and adjusted for sex, race and ethnicity. As expected, the highest incidence rates were noted in the youngest group. Though asthma incidence overall was lower in the school-age and adolescent children compared to preschool children, the effect of obesity became greater in terms of magnitude after age six.

This study extends our previous epidemiologic findings and demonstrates that the effects of obesity on incident asthma are not uniform in all children, and depends on age at which obesity occurs (before asthma), allergy status, ethnicity and race. Our findings show that obesity increases asthma incidence in all age groups across the pediatric age continuum and involves notable interactive effects that add to the epidemiologic understanding of obesity-related asthma. Prepubertal school-age children (age 7-11) displayed the highest risk for obesity-related asthma compared to both preschoolers and adolescents. We estimated that among the 7 to 11 year olds, roughly one-third of obese children with asthma (33.1%), had asthma attributable to their obese body weight. The contributions of obesity to new asthma among preschoolers and adolescents, albeit less than among 7 to 11 year olds, were still considerable. Before age 12, an age generally corresponding to the onset of puberty, females had a

higher risk for obesity-related asthma while after age 12 the risk of obesity-related asthma was higher in males. Finally, among obese children, allergic rhinitis appeared to be partially protective against the development of asthma.

Obese children without underlying allergic rhinitis had an increased risk for incident asthma (compared to leans), while similar obese children with allergic rhinitis did not. Past pediatric studies have demonstrated the presence of several common disease modifying factors that can affect the inception and phenotypic characteristics of asthma. Age, sex and the development of allergies are key factors. The majority of new pediatric asthma cases present before the onset of puberty when there is a clear male predominance⁵ and high prevalence of various allergic conditions such as allergic rhinitis, eczema and food allergy.^{6,7} After puberty, the risk for new asthma slowly shifts to females. It is important to note that predictors of various wheezing phenotypes can differ by sex.²⁰ Race and ethnicity also alter asthma risk in children, with African American and Puerto Rican children experiencing significantly higher prevalence rates compared to non-Hispanic white children.⁸ Presence of allergic disease among children is also an important asthma disease modifier, increasing symptom severity, risk for airway hyperresponsiveness⁹ and disease that persists throughout childhood.¹⁰ Several

TABLE 1c Participant characteristics among 12-17 y olds by BMI at baseline

Variables	Total participants	BMI-percentile groupings			P value
		Normal (5-84)	Overweight (85-94)	Obese (≥ 95)	
N (%)	157 369	78 683 (0.50)	37 786 (0.24)	40 900 (0.26)	
Age in years	157 369	14.529 (1.580)	14.534 (1.579)	14.519 (1.586)	.3701
Male, n (%)	72 790	36 416 (46.28)	16 423 (43.46)	19 951 (48.78)	<.0001
Race, n (%)	157 369				<.0001
White	91 011	45 508 (57.84)	22 990 (60.84)	22 513 (55.04)	
Black	37 749	18 857 (23.97)	8147 (21.56)	10 745 (26.27)	
Asian	3017	1757 (2.23)	684 (1.81)	576 (1.41)	
Native American	465	208 (0.26)	94 (0.25)	163 (0.40)	
Hawaiian/Pacific Islander	451	220 (0.28)	107 (0.28)	124 (0.30)	
Multiple races	3216	1511 (1.92)	755 (2.00)	950 (2.32)	
Other/refused	21 460	10 622 (13.50)	5009 (13.26)	5829 (14.25)	
Hispanic/Latino, n (%)	16 699	8366 (10.63)	3440 (9.10)	3399 (8.31)	<.0001
Health Insurance status, n (%)					<.0001
Medicaid/sCHIP	50 706	25 367 (32.24)	10 788 (28.55)	14 551 (35.58)	
Other public	1048	527 (0.67)	283 (0.75)	238 (0.58)	
Private/Commercial	61 162	30 578 (38.6)	15 820 (41.87)	14 764 (36.10)	
Self-pay	19 641	9915 (12.60)	5357 (14.18)	4369 (10.68)	
Observation period in years		3.373 (1.658)	3.380 (1.653)	3.328 (1.640)	<.0001
Total encounters	157 369	30.29 (46.12)	29.788 (43.94)	32.739 (47.568)	<.0001
Outpatient	157 369	29.264 (0.159)	28.772 (0.219)	31.609 (0.228)	<.0001
Inpatient	157 369	0.394 (0.008)	0.381 (0.010)	0.426 (0.010)	.0068
Emergency Department	157 369	0.616 (0.006)	0.619 (0.009)	0.689 (0.009)	<.0001
Comorbidities at baseline, n (%)					
Esophageal reflux	6376	3150 (4.00)	1528 (4.04)	1698 (4.15)	.4658
Eczema/atopic dermatitis	1246	596 (0.76)	340 (0.9)	310 (0.76)	.0249
Hives/urticaria	1334	728 (0.93)	322 (0.85)	284 (0.69)	.0002
Food allergy	1368	712 (0.90)	343 (0.91)	313 (0.77)	.0311
Allergic rhinitis	11 521	5742 (7.30)	2870 (7.60)	2909 (7.11)	.0321

Note: Numbers are means (SD) unless noted.

Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; CHIP, children's health improvement program; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist.

groups have demonstrated a greater obesity effect on wheezing/asthma among non-atopic children. Taveras et al. evaluated 1 to 3 year olds in a Boston area cohort, finding that high adiposity increased the odds of recurrent wheezing at age 3 by 46%.²¹ However, obesity did not increase risk for the atopic form of recurrent wheezing. Gilliland et al. studied 7 to 21 year olds in Southern California finding that high BMI was associated with an adjusted RR = 2.87 among nonallergic males only.²² We speculate that the genetic and environmental interactions that underlie the development of allergic inflammation and asthma remain the predominant risk factors for early onset asthma. Asthma stemming from obesity is not routed in allergic inflammation but rather likely from a combination of dysanaptic airflow limitation²³ and heightened ventilator demands. Common asthma triggers such as viral respiratory infections and exercise in the setting of these obesity-related mechanisms would be expected to lead to more cases of clinical asthma.

Our findings suggest that both the duration and degree of excess weight play important roles in obesity-related asthma in children. The

years just before the onset of puberty may constitute a high-risk period for obesity-related asthma as seen among the 7 to 11 years olds in our study. This pattern is in line with findings of Chinn and Rona who studied 5 to 10 year olds in England and Scotland and found that both boys and girls who were obese at 5 to 6 years of age displayed and OR > 4 for new asthma compared to normal weight children.²⁴ Black et al. found in a large study of 6 to 19 year olds (n = 623 358) in a Southern California healthcare organization that the greatest effect of obesity was seen among girls aged 6 to 10 years of age.²⁵

The effects of overweight (BMI 85-94th percentile) on incident asthma were not as clear. Some evidence exists in our data for a 'dose-response' relationship with asthma incidence increasing with increasing BMI-percentile. For example, this was shown in the increasing adjusted RR in normal weight, overweight and obese 7 to 11 year old children. However, in several groups, overweight status was not significantly associated with asthma risk compared to normal weights, and in some instances overweight may be protective. Among 2 to 6 year olds, the RR point estimate for spirometry-confirmed

TABLE 2 Incidence rates and risk ratios for new asthma by body mass index percentile

Age 2-6 y	Normal (25%-64%)	Overweight (85%-94%)	P values	Obese (≥95%)	P values
Two asthma diagnoses and antiasthma medication					
Incidence rate ^a (95% CI)	3.6 (3.4, 3.7)	4.1 (3.8, 4.3)	.0020	4.5 (4.1, 4.8)	<.0001
Crude RR (95% CI)	1.00	1.14 (1.05, 1.24)	.0020	1.25 (1.15, 1.37)	<.0001
Adjusted IR (95% CI)	2.5 (2.2, 2.9)	2.9 (2.5, 3.3)	.0015	3.1 (2.7, 3.6)	<.0001
Adjusted RR (95% CI)	1.00	1.14 (1.05, 1.24)	.0015	1.24 (1.14, 1.36)	<.0001
Two asthma diagnoses plus confirmation with spirometry					
Incidence rate ^a (95% CI)	1.2 (1.1, 1.3)	1.2 (1.1, 1.4)	.8089	1.8 (1.6, 2.0)	<.0001
Crude RR (95% CI)	1.0	0.98 (0.85, 1.14)	.8089	1.46 (1.26, 1.68)	<.0001
Age 7-11 y					
Two asthma diagnoses and antiasthma medication					
Incidence rate ^a (95% CI)	1.8 (1.6, 1.9)	2.1 (1.8, 2.3)	.0148	2.6 (2.4, 2.9)	<.0001
Crude RR (95% CI)	1.00	1.18 (1.03, 1.35)	.0148	1.49 (1.32, 1.69)	<.0001
Adjusted incidence rate ^a (95% CI)	1.1 (0.9, 1.3)	1.3 (1.0, 1.6)	.0039	1.6 (1.2, 1.9)	<.0001
Adjusted RR (95% CI)	1.00	1.22 (1.07, 1.39)	.0039	1.45 (1.29, 1.64)	<.0001
Two asthma diagnoses plus confirmation with spirometry					
Incidence rate ^a (95% CI)	0.9 (0.8, 1.0)	1.1 (1.0, 1.3)	.0344	1.30 (1.1, 1.5)	.0001
Crude RR (95% CI)	1.00	1.22 (1.01, 1.46)	.0344	1.39 (1.18, 1.65)	.0001
Age 12-17 y					
Two asthma diagnoses and antiasthma medication					
Incidence rate ^a (95% CI)	1.6 (1.4, 1.7)	1.7 (1.5, 1.9)	.3952	2.2 (1.9, 2.4)	<.0001
Crude RR (95% CI)	1.0	1.07 (0.91, 1.27)	.3952	1.4 (1.21, 1.63)	<.0001
Adjusted incidence rate ^a (95% CI)	0.8 (0.6, 1.0)	0.9 (0.6, 1.2)	.1809	1.1 (0.8, 1.4)	<.0001
Adjusted RR (95% CI)	1.0	1.12 (0.95, 1.32)	.1809	1.35 (1.16, 1.56)	<.0001
Two asthma diagnoses plus confirmation with spirometry					
Incidence rate ^a (95% CI)	0.6 (0.5, 0.7)	0.6 (0.4, 0.7)	.8832	0.8 (0.6, 0.9)	.0431
Crude RR (95% CI)	1.0	0.98 (0.74, 1.29)	.8832	1.29 (1.01, 1.65)	.0431

Note: P values describe comparisons with the normal BMI group. Multivariable model 1 adjusts for race, ethnicity, sex.

Abbreviations: CI, confidence interval; IR, incidence rate; RR, risk ratio.

^aPer 1000 patient-years.

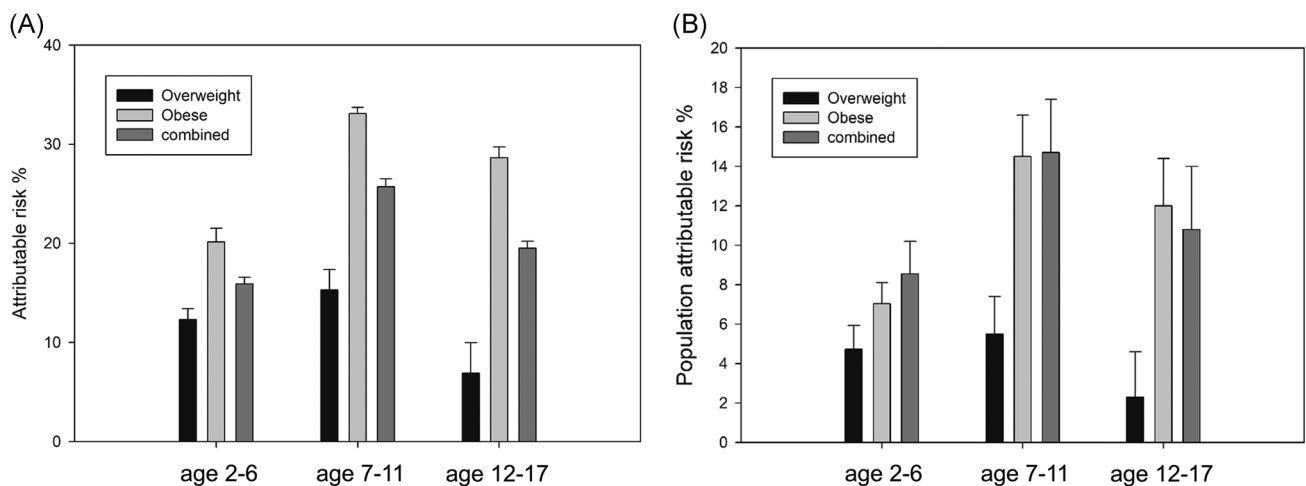


FIGURE 1 A, Attributable risk (AR) percents for overweight (85-94th BMI%), obese (≥95th BMI%) and combined (≥85th BMI%) by age groups. AR percent = $[(\text{Incidence}_{\text{exposed}}) - (\text{Incidence}_{\text{unexposed}})] / \text{Incidence}_{\text{exposed}} \times 100$. B, Population attributable risk (PAR) percents for overweight (85-94th BMI%), obese (≥95th BMI%) and combined (≥85th BMI%) by age groups. PAR percent = $[(\text{Incidence}_{\text{population}}) - (\text{Incidence}_{\text{unexposed}})] / \text{Incidence}_{\text{population}} \times 100$. BMI, body mass index

TABLE 3 Attributable risk of overweight and obesity in asthma incidence by age group

Age 2-6 y	Overweight (85%-94%)	Obese (≥95%)	Overweight + Obesity (≥85%)
Two asthma diagnoses and asthma medication			
Attributable risk incidence ^a	0.5 (0.42, 0.58)	0.9 (0.77, 1.03)	0.67 (0.66, 0.69)
Attributable risk % ^b	12.27 (0.11, 13.38)	20.14 (0.19, 21.53)	15.9 (0.16, 15.57)
Population attributable risk incidence ^c	0.18 (0.15, 0.21)	0.27 (0.25, 0.30)	0.33 (0.29, 0.38)
Population attributable risk % ^d	4.72 (3.76, 5.93)	7.04 (6.2, 8.1)	8.55 (7.13, 10.2)
Two asthma diagnoses plus confirmation with spirometry			
Attributable risk incidence ^a	Negative ^e	0.56 (0.47, 0.65)	0.23 (0.22, 0.25)
Attributable risk % ^b	Negative ^e	31.3 (0.3, 32.71)	16.0 (0.17, 15.5)
Population attributable risk incidence ^c	Negative ^e	0.17 (0.16, 0.18)	0.12 (0.09, 0.15)
Population attributable risk % ^d	Negative ^e	12.0 (10.7, 14.0)	8.6 (6.3, 11.5)
Age 7-11 y			
Two asthma diagnoses and asthma medication			
Attributable risk incidence ^a	0.32 (0.24, 0.40)	0.87 (0.77, 0.96)	0.61 (0.58, 0.63)
Attributable risk % ^b	15.3 (0.13, 17.36)	33.1 (0.32, 33.7)	25.7 (0.27, 24.9)
Population attributable risk incidence ^c	0.1 (0.08, 0.13)	0.3 (0.28, 0.32)	0.3 (0.27, 0.34)
Population attributable risk % ^d	5.5 (4.2, 7.4)	14.5 (13.0, 16.6)	14.7 (12.5, 17.4)
Two asthma diagnoses plus confirmation with spirometry			
Attributable risk incidence ^a	0.2 (0.14, 0.26)	0.37 (0.30, 0.43)	0.29 (0.27, 0.30)
Attributable risk % ^b	17.76 (0.14, 20.34)	28.22 (0.27, 29.43)	23.63 (0.25, 22.72)
Population attributable risk incidence ^c	0.06 (0.05, 0.08)	0.13 (0.12, 0.14)	0.14 (0.12, 0.17)
Population attributable risk % ^d	6.47 (4.92, 9.08)	11.9 (10.1, 14.7)	13.3 (10.6, 17.0)
Age 12-17 y			
Two asthma diagnoses and asthma medication			
Attributable risk incidence ^a	0.12 (0.04, 0.19)	0.63 (0.53, 0.73)	0.38 (0.36, 0.40)
Attributable risk % ^b	6.9 (0.03, 9.98)	28.63 (0.27, 29.72)	19.5 (0.2, 18.79)
Population attributable risk incidence ^c	0.04 (0.02, 0.07)	0.21 (0.2, 0.24)	0.19 (0.16, 0.23)
Population attributable risk % ^d	2.3 (1.0, 4.6)	12.0 (10.3, 14.4)	10.8 (8.3, 14.0)
Two asthma diagnoses plus confirmation with spirometry			
Attributable risk incidence ^a	Negative ^e	0.17 (0.12, 0.23)	0.08 (0.08, 0.09)
Attributable risk % ^b	Negative ^e	22.5 (0.19, 24.9)	12.3 (0.13, 11.7)
Population attributable risk incidence ^c	Negative ^e	0.06 (0.05, 0.08)	0.04 (0.02, 0.07)
Population attributable risk % ^d	Negative ^e	8.9 (6.8, 13.2)	6.5 (2.9, 12.1)

^aAttributable risk (AR) expressed as an incidence rate (I) per 1000 patient-years.

^bAttributable risk % = percent of the incidence due to the exposure; and the proportion of the incidence of a disease in the exposed population that would be eliminated if exposure were absent.

^cIncidence of disease in the whole population due to the exposure; PAR = $I(\text{population}) - I(\text{unexposed})$ expressed per 1000 patient-years.

^dPopulation attributable risk % is the percent of disease incidence for the whole population due to the exposure. Percent of disease incidence avoided if the study population were unexposed; PAR/I (population).

^eEstimate is negative or protective for developing asthma.

incident asthma was <1. Similarly, AR and PAR point estimates among overweight 2 to 6 and 12 to 17 year olds were negative suggesting a possible protective effect.

Strengths of our study include its large number of total cases coming from a wide geographic distribution across the United States. This allowed us to provide risk estimates for a number of important sub-groups. In addition, few studies have provided attributable risk estimates. Attributable risk from obesity (risk of asthma attributable to obesity) is simply the incidence of asthma among obese children minus the incidence of asthma among normal weight children; while population attributable risk is the incidence of asthma in the whole population minus the incidence of asthma in the normal weight children. A limitation of this study is its retrospective nature and its use of EHR data not collected specifically for purposes of research.

Therefore, our findings would be affected by any diagnostic or measurement errors occurring during routine clinical care. These include errors in diagnosis documented using ICD coding which also had abnormal lung function testing results (eg bronchomalacia, hypersensitivity pneumonitis). Our dataset was limited by the lack of family history or environmental history data. Factors such as parental smoking could be a confounding variable not included in analysis.

In conclusion, obesity in children significantly increases the risk for new physician-diagnosed asthma and asthma confirmed by pulmonary function testing. Pediatric obesity accounts for a substantial component of new asthma among children in the United States, particularly children who are nonallergic. New cases of obesity-related asthma appear to favor a nonallergic phenotype. There are practical implications of these findings for both future

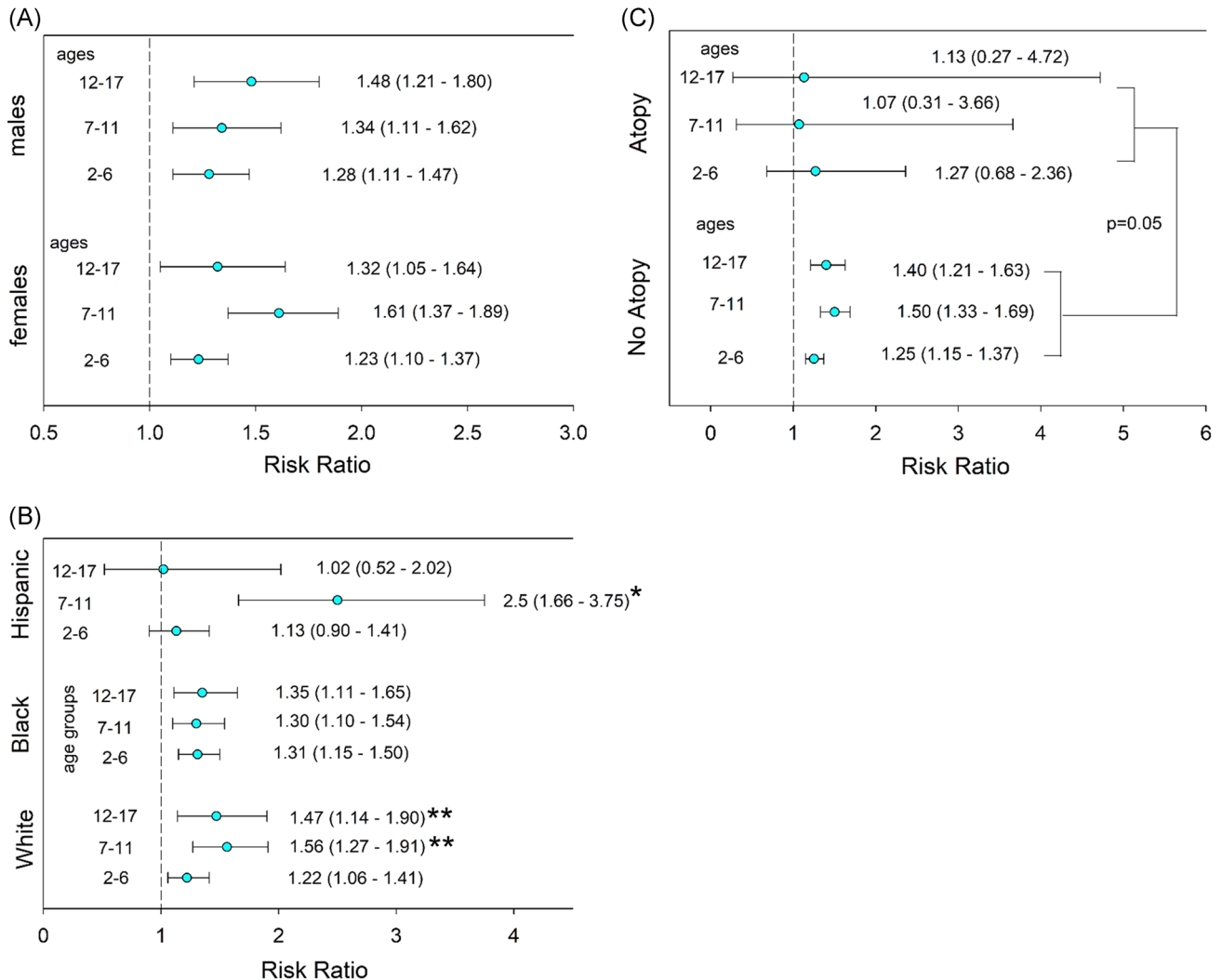


FIGURE 2 Risk ratios of obese participants (compared to normal weight participants) by (A) sex, (B) race/ethnicity and (C) atopy status, by age groups. * $P < .01$ comparing asthma incidence among obese vs normal weight children; ** $P < .001$ comparing risk of obesity-related asthma by age-group vs age 2 to 6 years [Color figure can be viewed at wileyonlinelibrary.com]

clinical management and research priorities. Control of asthma in patients without allergy or eosinophilic airway inflammation are frequently poorly responsive to inhaled corticosteroids and thus require novel treatments. Children who are obese and have developed asthma symptoms without atopic stigmata may require alternative approaches beside inhaled steroid monotherapy. Future trials which compare asthma controllers in this population are warranted to optimize asthma care and reduce drug side-effects. In addition, successful interventions that reduce pediatric obesity and address obesity-related asthma must be a major public health priority to improve the quality of life of children and to reduce its contribution to pediatric asthma.

ACKNOWLEDGMENTS

The research reported in this publication was conducted using PEDSnet, A Pediatric Learning Health System, and includes data from the following PEDSnet institutions: Children's

Hospital Colorado, Children's Hospital of Philadelphia, Nemours Children's Health System, Nationwide Children's Hospital, Seattle Children's Hospital, and St. Louis Children's Hospital. PEDSnet is a Partner Network Clinical Data Research Network in PCORnet®, the National Patient-Centered Clinical Research Network, an initiative funded by the Patient-Centered Outcomes Research Institute (PCORI). PEDSnet's participation in the development of PCORnet® was partially funded through PCORI Award 1306-01556 and institutional development funds from the Nemours Children's Hospital/Nemours Children's Health System.

CONFLICT OF INTERESTS

Amanda Dempsey serves on advisory boards for Merck, Sanofi Pasteur, and Pfizer, and as a consultant for Pfizer. She does not receive any research funding from these entities. The remaining authors declare that there is no conflict of interests.

AUTHOR CONTRIBUTIONS

JEL, JH, HTB, and TW conceptualized and designed the study, assisted in data collection, contributed to data analysis, drafted the initial manuscript, and revised the manuscript. LB, AD, LA, and MRT assisted in data collection, reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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How to cite this article: Lang JE, Bunnell HT, Lima JJ, et al. Effects of age, sex, race/ethnicity, and allergy status in obesity-related pediatric asthma. *Pediatric Pulmonology*. 2019;1-10. <https://doi.org/10.1002/ppul.24470>