Being Overweight or Obese and the Development of Asthma

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abstract

OBJECTIVES: Adult obesity is linked to asthma cases and is estimated to lead to 250 000 new cases yearly. Similar incidence and attributable risk (AR) estimates have not been developed for children. We sought to describe the relationship between overweight and obesity and incident asthma in childhood and quantify AR statistics in the United States for overweight and obesity on pediatric asthma.

METHODS: The PEDSnet clinical data research network was used to conduct a retrospective cohort study (January 2009–December 2015) to compare asthma incidence among overweight and/or obese versus healthy weight 2- to 17-year-old children. Asthma incidence was defined as ≥2 encounters with a diagnosis of asthma and ≥1 asthma controller prescription. Stricter diagnostic criteria involved confirmation by spirometry. We used multivariable Poisson regression analyses to estimate incident asthma rates and risk ratios and accepted formulas for ARs.

RESULTS: Data from 507 496 children and 19 581 972 encounters were included. The mean participant observation period was 4 years. The adjusted risk for incident asthma was increased among children who were overweight (relative risk [RR]: 1.17; 95% confidence interval [CI]: 1.10–1.25) and obese (RR: 1.26; 95% CI: 1.18–1.34). The adjusted risk for spirometry-confirmed asthma was increased among children with obesity (RR: 1.29; 95% CI: 1.16–1.42). An estimated 23% to 27% of new asthma cases in children with obesity is directly attributable to obesity. In the absence of overweight and obesity, 10% of all cases of asthma would be avoided.

CONCLUSIONS: Obesity is a major preventable risk factor for pediatric asthma.

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WHAT'S KNOWN ON THIS SUBJECT: Obesity has been linked to new asthma cases in adults, but the nature of asthma risk in children is less clear. In previous research, attributable risk has not been measured across a large diverse population of US children.

WHAT THIS STUDY ADDS: An estimated 23% to 27% of new asthma cases in children with obesity is directly attributable to obesity. In the absence of overweight and obesity, 10% of all US cases of pediatric asthma could be avoided.

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Obesity and asthma both cause enormous suffering and cost for children in the United States and around the world.[1–3] Despite reports of progress in slowing pediatric obesity, the latest evidence suggests an increase in obesity, particularly in 2- to 5-year-old children.[4] Adult obesity is linked to adult-onset asthma[5,6] and is estimated to cause 250 000 new adult asthma cases each year.[7] Similar incidence and attributable risk (AR) estimates have not been developed for children.

Roughly, 18% of US children are obese, which impairs quality of life and increases the risk for chronic disease.[4,8,9] The link between obesity and new asthma cases in children has been debated and remains incompletely defined. Authors of more than a dozen longitudinal studies report on the risk of obesity and incident asthma.[10–27] Authors of several studies report that obesity increases incident asthma in a subset of the patients,[17–19,21,22,25,26] whereas other studies revealed no effect.[10–16,23,24,27] Among positive studies, the findings were remarkably inconsistent regarding the effects of race, sex, atopic status, and timing of obesity, although most studies were underpowered to assess the effects of these covariables. Previous authors have argued that strong effect differences across subgroups undermine the likelihood that obesity directly causes asthma because causality would be expected to work across demographic groups.[18]

Most cases of asthma are diagnosed clinically without confirmation by pulmonary function testing.[28,29] Numerous studies have demonstrated the imprecise nature of physician diagnosis of asthma,[30–35] and expert guidelines recommend the use of spirometry to assess for airflow obstruction defects or airway reversibility in the confirmation of asthma.[36–38] Thus, reliance solely on physician-diagnosed asthma in measuring the incidence rates and causative determinants of asthma is problematic. To date, authors of longitudinal pediatric studies in which overweight and obesity and asthma risk are assessed have not used pulmonary function testing.

The nature and degree of a possible association between obesity and asthma in children may benefit from novel approaches with improved power and feasibility.[39] Large prospective epidemiological studies are costly and time consuming and have been criticized for developing evidence too slowly.[40] Newly distributed data networks have been used to take advantage of advances in electronic health records (EHRs) and clinical informatics, such as common data models, allowing for consistent data standards across sites and improved quality control checks during data collection and entry as well as allowing for extracting, transforming, and loading EHRs into common data models to increase the validity, linkage, size, and diversity of pooled EHR data. The recent development of PEDSnet, a national pediatric network that is used to pool and standardize EHR data, offers a novel opportunity to define the obesity-asthma relationship in children.[41,42] PEDSnet includes data recorded during real-world clinical care across all clinical settings among 8 large pediatric health systems across the United States in a single common data model.[41,42]
Our purpose for this study was to leverage data obtained by PEDSnet to conduct a longitudinal study in which we compare the risk of asthma among children with normal weight and obesity, taking into account important covariates and assessing the AR of excess body weight in pediatric asthma.

METHODS

This study, which involved only deidentified data, was evaluated by the Duke University Health System Institutional Review Board (No. Pro00077780) and determined to be exempt research. The requirement for informed consent was waived under 45 CFR 46.116 at all participating institutions.

Study Design

We used a retrospective cohort study design that included data from January 2009 to December 2015. We matched each individual case of overweight or obesity with children with a healthy weight using a 1:1 ratio. Routine clinical data were obtained from 6 PEDSnet institutions. The 3 groups were defined as follows: overweight, those with a BMI in the 85th to 94th percentile adjusted for sex and age; obesity, those with a BMI in the ≥95th percentile adjusted for sex and age; and a group of matched comparators whose BMI percentile ranged between the 25th to 64th percentile adjusted for sex and age (to reduce weight status misclassification). None of the participants had previous documentation of asthma at baseline. Rates of incident, study-defined asthma were compared over time for each group.

PEDSnet

PEDSnet (pedsnet.org) standardize EHR data to the observational health data sciences and informatics common data model.[42] PEDSnet currently comprises 8 US pediatric academic medical centers, 6 of which participated in this study: Nemours Children's Health System, Children's Hospital of Philadelphia, Seattle Children's Hospital, Children's Hospital Colorado, St Louis Children's Hospital, and Nationwide Children's Hospital. The primary market for PEDSnet institutions crosses 22 states; each institution also serves as a national and international referral base. All clinical settings are included in the data network, inclusive of primary, hospital, emergency, ambulatory, and subspecialty care

as well as laboratory and imaging settings.

Participant Selection

Patients aged 2 to 17 years seen within a PEDSnet site from January 1, 2009, to December 31, 2015, were eligible for inclusion if they had (1) an age- and sex-adjusted BMI value in the ≥85th percentile, (2) no health record diagnosis of asthma (all 493 codes) or wheezing (786.07) at or before the study-defined initial visit, and (3) at least 2 subsequent (total of 3) clinic visits spanning at least 12 months. The initial visit was defined as the first health care visit after January 1, 2009. Patients with any documented diagnosis of cystic fibrosis, ciliary dyskinesia, childhood cancer, inflammatory bowel disease, or bronchopulmonary dysplasia were excluded. For each subject who fit the criteria for the overweight or obesity risk groups, we randomly selected 1 control patient with normal weight who was identically matched for age at initial visit (±12 months), sex, race (white, African American, Asian American, or other), ethnicity (Hispanic versus non-Hispanic), insurance status (Medicaid, private, or other), and PEDSnet site. Subjects in the comparator group with a normal BMI adhered to the same comorbidity exclusions and requirements for follow-up visits. Matching occurred within each site to reduce confounding due to geographic factors and site-specific differences in care. To reduce the erroneous inclusion of children with occult (undiagnosed) asthma at baseline who had been prescribed an asthma controller, a more select cohort was created, which excluded patients who did not have asthma at baseline but were prescribed an asthma controller medication and patients who were diagnosed with asthma within 18 months of their initial visit.

Baseline Data and Outcome Measures

Baseline data for each subject were taken from the initial visit encounter or from encounters before the study-defined initial visit and included demographics, year and month of birth, age, race, sex, ethnicity, insurance status (Medicaid, private, or other), gestational age, BMI percentile, BMI *z*-score, past and current comorbid health conditions, and medications. Each participant had their own observation period, which was defined as the time from the initial visit to the patient's last recorded encounter and provided the following data: observation period duration, number and setting of encounters, encounter diagnoses, encounter medications, and spirometry values. Spirometry values included forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1), measured in liters and as a percentage of the age- and sex-adjusted predicted value.

Diagnosis of Asthma

The primary outcome was the incidence of asthma during the observation period, defined as ≥2 encounters with a diagnosis of asthma and ≥1 asthma medication prescription. Secondary outcomes included looser and stricter criteria for an asthma diagnosis, including ≥1 encounter with an asthma diagnosis, ≥2 encounters with an asthma diagnosis (without the requirement of an asthma drug prescription), and ≥2 encounters with an asthma diagnosis with an additional confirmation by spirometry. A spirometry confirmation required either a predicted percentage of forced expiratory volume in 1 minute of <80%, an FEV_1/FVC ratio of <0.85, or postbronchodilator improvement of ≥10% in either the FEV_1 or FVC.[43,44]

Analysis

Crude and adjusted incident asthma rates (per person time) and rate (risk) ratios were determined for each group (normal weight and overweight and obese) by using univariable and multivariable Poisson regressions. Because each participant had a different observation period duration, the asthma incidence in each risk group was adjusted for each group's observation period duration and expressed as an incidence rate (per person time). In addition to the rates and rate ratios, we estimated the following indices for participants who were overweight and obese using standard formulas: AR ($[\text{incidence}_{exposed}] - [\text{incidence}_{unexposed}]$), AR percent ($\text{AR}/\text{incidence}_{exposed}$), population attributable risk (PAR) ($[\text{incidence}_{population}] - [\text{incidence}_{unexposed}]$), and PAR percent ($\text{PAR}/\text{incidence}_{population}$) (see Supplemental Tables 6 and 7). Variables in the multivariable model included age at initial visit, sex, race, ethnicity, insurance status, observation period, and institution. A second model included adjustments for baseline allergic rhinitis, baseline food allergy, and baseline proton pump inhibitor medication use. The model was checked for over- and underdispersion of response variables. All tests were 2-sided, and *P* values <.05 were considered statistically significant. The statistical package SAS version 9.3 (SAS Institute, Inc, Cary, NC) was used for data analysis.

RESULTS

Baseline Characteristics

The baseline characteristics of 507 496 patients meeting criteria for inclusion are shown by BMI and body habitus category in Table 1. By the matching design, participants were evenly split between normal BMI (50%) and

overweight or obese BMI (50%). Baseline characteristics differed statistically by body habitus groups for age, sex, race, ethnicity, health insurance status, and institution. Health care use, including total observation period, total encounters, outpatient and inpatient encounters, and emergency department visits, were associated statistically with body habitus. Several comorbidities were associated with body habitus, including esophageal reflux, eczema, urticaria, anaphylaxis, food allergy, and allergic rhinitis. Prevalence of allergic rhinitis, food allergy, anaphylaxis, urticaria, and eczema was reduced among children with obesity. Nearly all medications collected at baseline were more common in the obesity group.

Risk Factors for Study-Defined Incident Asthma

Among the 507 496 total children meeting inclusion criteria for study entry, 41 330 (8.14%) and 27 461 (5.41%) were diagnosed with asthma by a pediatric health care provider at least 1 and 2 encounters, respectively. The overall incidence rate for new asthma cases in the population was 2.7 per 1000 patient years, ranging from 2.4 per 1000 patient years among children with normal weight to 3.2 per 1000 patient years among children with obesity. In univariate analyses, both overweight and obesity were associated with an increased risk for new asthma diagnosis (Table 2). Male sex, African-American race, multiple race, Medicaid insurance, no insurance or self-pay, and younger age grouping were associated with a higher asthma incidence. Baseline presence of allergic rhinitis, food allergy, anaphylaxis, and past use of various medications (any proton pump inhibitor or histamine-2 blocker) was significantly associated with a higher risk for incident asthma (Table 3).

Baseline Body Habitus and Risk for Incident Asthma

Multivariable models used to assess the independent risk of overweight and obesity on incident asthma are shown in Table 4. Obesity was significantly associated with a greater risk of incident asthma by using the primary definition and all other definitions, including confirmation by spirometry. The crude effect size range for obesity-related risk for new asthma was generally consistent and ranged from 1.30 to 1.38. For children who were overweight, the risk for incident asthma was significant for the primary incidence end point and looser definitions. The overweight-related crude risk ratio (normal weight referent) was modest, ranging from 1.08 to 1.17. However, when children were evaluated with spirometry testing, overweight was not associated with a significant increase in asthma incidence.

The risk of asthma confirmed by a repeat diagnosis and either asthma medication or spirometry was only modestly increased among children who were overweight. However, an increased risk of confirmed asthma in children with obesity ranged from 26% to 38% in crude and both multivariable models. In the selected cohort in which patients taking baseline asthma controllers and patients with an asthma diagnosis early in the observation period were excluded, the rate ratio for asthma among children who were overweight and obese was 1.14 (95% confidence interval [CI]: 1.10–1.18) and 1.28 (95% CI: 1.23–1.32), respectively.

ARs of Overweight and Obesity in Childhood Asthma

ARs and PARs of incident asthma related to overweight status and obesity status are shown in Table 5. The proportion of clinically diagnosed asthma incidence in children with obesity that is attributed specifically to obesity was 23% to 25%. When considering asthma confirmed by spirometry, the proportion of asthma attributable to obesity in children with obesity was 28%. The percentage of clinically diagnosed asthma among all children in the population attributable to obesity was 10%, whereas the percentage of incident asthma confirmed by spirometry among all children in the population attributable to obesity was 13%.

DISCUSSION

This study demonstrates that obesity in children increases the risk of new asthma diagnosis even when the asthma diagnosis is confirmed by rigorous diagnostic means (eg, by repeated asthma encounters, medication prescription, and spirometry evidence of airway obstruction, bronchodilator reversibility, or both). These results do not support evidence of an overdiagnosis of asthma in children who are overweight and obese. The effect of overweight status was only a modest risk factor and was not associated with a greater risk of spirometry-confirmed asthma. However, obesity status was a significant risk factor for confirmed asthma by all definitions and was a significant contributor to incident asthma. Roughly one-quarter of the incidences of new asthma were directly attributable to obesity. Currently, there are few known preventable risk factors that can be used to reduce childhood asthma. With these data, it is suggested that reducing the onset of obesity in childhood would significantly reduce the public health burden of asthma in children.

Because of the lack of a simple objective definition for asthma, attempts at measuring asthma prevalence and incidence have been challenging and have been called into question.[33] Prevalence data for

TABLE 1 Participant Characteristics by Body Habitus at Baseline

Variables	Total Participants	BMI Percentile Groupings			*P*
		Normal Weight (5th–84th)	Overweight (85th–94th)	Obesity (≥95th)	
N (%)	507 496	253 748 (50.0)	129 255 (25.5)	124 493 (24.5)	—
Age, y, mean (SD)	507 496	8.98 (4.64)	8.62 (4.73)	9.36 (4.52)	<.0001
Male sex, *n* (%)	257 438 (50.73)	128 719 (50.73)	64 210 (49.68)	64 509 (51.82)	<.0001
Race, *n* (%)	507 496				<.0001
White	281 394	140 697 (55.45)	74 943 (57.98)	65 754 (52.82)	—
African American	117 164	58 582 (23.09)	28 064 (21.71)	30 518 (24.51)	—
Asian American	12 108	6841 (2.7)	2960 (2.29)	2307 (1.85)	—
American Indian	1183	530 (0.21)	278 (0.22)	375 (0.3)	—
Hawaiian or Pacific Islander	1457	662 (0.26)	369 (0.29)	426 (0.34)	—
Multiple races	13 619	6507 (2.56)	3429 (2.65)	3683 (2.96)	—
Other or refused	80 571	39 929 (15.74)	19 212 (14.86)	21 430 (17.21)	—
Ethnicity, *n* (%)					
Hispanic	71 490	35 745 (14.09)	16 100 (12.46)	19 645 (15.78)	<.0001
Health insurance status, *n* (%)					<.0001
Medicaid or SCHIP	191 618	95 808 (37.76)	45 384 (35.11)	50 426 (40.51)	—
Medicare	58	30 (0.01)	17 (0.01)	11 (0.01)	—
Other public	2870	1486 (0.59)	768 (0.59)	616 (0.49)	—
Private or commercial	180 072	90 036 (35.48)	48 968 (37.88)	41 068 (32.99)	—
Self-pay	58 024	29 269 (11.53)	16 487 (12.76)	12 268 (9.85)	—
Undetermined	74 854	37 119 (14.63)	17 631 (13.64)	20 104 (16.15)	—
Clinical centers, *n* (%)					<.0001
Site 1	47 298	23 649 (9.32)	12 270 (9.49)	11 379 (9.14)	—
Site 2	103 476	51 738 (20.39)	24 490 (18.95)	27 248 (21.89)	—
Site 3	140 456	70 228 (27.68)	34 057 (26.35)	36 171 (29.05)	—
Site 4	44 334	22 167 (8.74)	11 274 (8.72)	10 893 (8.75)	—
Site 5	16 732	8366 (3.3)	3991 (3.09)	4375 (3.51)	—
Site 6	155 200	77 600 (30.58)	43 173 (33.4)	34 427 (27.65)	—
Observation period, y, mean (SD)	507 496	4.00 (1.88)	3.97 (1.87)	3.93 (1.87)	<.0001
Total encounters, mean (SD)	19 581 972	24.52 (33.46)	24.54 (33.18)	25.92 (34.24)	<.0001
Outpatient, mean (SD)	16 637 436	32.21 (0.097)	31.93 (0.1364)	34.85 (0.1465)	<.0001
Outpatient other, mean (SD)	2 338 964	4.55 (0.0285)	4.96 (0.0416)	4.37 (0.0411)	<.0001
Inpatient, mean (SD)	199 720	0.38 (0.0038)	0.37 (0.0047)	0.43 (0.0055)	<.0001
Emergency department, mean (SD)	376 049	0.72 (0.0037)	0.73 (0.0051)	0.8 (0.0058)	<.0001
Emergency to hospital, mean (SD)	7093	0.01 (0.0005)	0.01 (0.0006)	0.01 (0.0008)	.1647
Comorbidities at baseline, *n* (%)					
Esophageal reflux	18 547	9444 (3.72)	4467 (3.46)	4636 (3.72)	<.0001
Eczema or atopic dermatitis	8441	4115 (1.62)	2426 (1.88)	1900 (1.53)	<.0001
Hives or urticaria	7013	3552 (1.4)	1936 (1.5)	1525 (1.22)	<.0001
Anaphylaxis	633	353 (0.14)	166 (0.13)	114 (0.09)	.0005
Food allergy	5937	3135 (1.24)	1608 (1.24)	1194 (0.96)	<.0001
Allergic rhinitis	52 109	26 166 (10.31)	13 948 (10.79)	11 995 (9.64)	<.0001
Medications at baseline, *n* (%)					
Proton pump inhibitors	33 012	16 216 (6.39)	8088 (6.26)	8708 (6.99)	<.0001
Histamine-2 receptor blockers	32 542	15 820 (6.23)	8219 (6.36)	8503 (6.83)	<.0001
Albuterol	69 949	32 650 (12.87)	18 959 (14.67)	18 340 (14.73)	<.0001
Inhaled corticosteroids	33 601	15 457 (6.09)	9035 (6.99)	9109 (7.32)	<.0001
ICS/LABA	3495	1541 (0.61)	910 (0.7)	1044 (0.84)	<.0001
Prednisone or prednisolone	55 631	26 095 (10.28)	15 428 (11.94)	14 108 (11.33)	<.0001
Dexamethasone	25 772	12 200 (4.81)	6651 (5.15)	69 201 (5.56)	<.0001
Progesterone	32 916	15 845 (6.24)	9425 (7.29)	7646 (6.14)	<.0001
Metformin	5842	338 (0.13)	746 (0.58)	4758 (3.82)	<.0001
Sulfonylurea	80	21 (0.01)	12 (0.01)	47 (0.04)	<.0001
Leukotriene modifiers	18 508	8392 (3.31)	5037 (3.9)	5079 (4.08)	<.0001
ACE inhibitors	5805	2158 (0.85)	1257 (0.97)	2390 (1.92)	<.0001

ACE, angiotensin-converting enzyme; ICS, inhaled corticosteroid; LABA, long-acting β-2 agonist; SCHIP, State Children's Health Insurance Program; —, not applicable.

asthma typically have come from self-report and have been widely published.[1,45,46] Asthma is thought to affect roughly 8.4% of children in the United States, with the highest prevalence (10.2%) occurring among 15- to 19-year-old children.[1] Overall prevalence of a single asthma diagnosis in the current study was 8.1%, remarkably close to current US prevalence rates. Incidence rates are more difficult to determine and

TABLE 2 Crude Demographic Determinants of Incident Asthma

	Incidence Rate[a] (SE)	Rate Ratio	95% CI	*P*
Body habitus				
Lean (referent)	2.4 (0.05)	1.00	1.00–1.00	—
Overweight	2.8 (0.07)	1.17	1.10–1.25	<.0001
Obese	3.2 (0.08)	1.30	1.22–1.38	<.0001
Sex				
Female (referent)	2.3 (0.05)	1.00	1.00–1.00	—
Male	3.1 (0.06)	1.30	1.24–1.38	<.0001
Ethnicity				
Non-Hispanic (referent)	2.9 (0.04)	1.00	1.00–1.00	—
Hispanic	2.3 (0.09)	0.79	0.72–0.86	<.0001
Other or missing	1.2 (0.12)	0.41	0.34–0.51	<.0001
Race				
White (referent)	1.8 (0.04)	1.00	1.00–1.00	—
African American	5.1 (0.10)	2.74	2.58–2.90	<.0001
Asian American	1.4 (0.18)	0.76	0.59–0.97	.0303
American Indian or Alaskan native	0.9 (0.42)	0.51	0.21–1.22	.1290
Hawaiian or Pacific Islander	3.4 (0.89)	1.87	1.12–3.10	.0161
Multiple race	4.6 (0.29)	2.48	2.17–2.83	<.0001
Refused	1.9 (0.08)	1.01	0.92–1.11	.8768
Age groupings, y				
0–4 (referent)	4.4 (0.01)	1.00	1.00–1.00	—
5–11	2.2 (0.05)	0.50	0.47–0.53	<.0001
12–17	1.8 (0.06)	0.40	0.37–0.43	<.0001
Payer				
Private (referent)	1.3 (0.04)	1.00	1.00–1.00	—
Medicaid	2.5 (0.06)	1.95	1.80–2.11	<.0001
Medicare	0.0 (0.00)	0.00	0.00–0.00	.9979
Self-pay	1.6 (0.08)	1.21	1.08–1.37	.0014
Other public	0.8 (0.29)	0.59	0.28–1.24	.1644

Asthma was defined as ≥2 encounters with a diagnosis and prescription of ≥1 asthma drug. —, not applicable.
[a] Rate per 1000 patient years.

TABLE 3 Baseline Comorbidities and Medications and Incident Asthma

	Incidence Rate[a] (SE)	Rate Ratio	95% CI	*P*
Comorbidities present at baseline				
Allergic rhinitis	3.45 (0.12)	1.32	1.23–1.42	<.0001
Food allergy	3.91 (0.39)	1.45	1.20–1.77	.0002
Anaphylaxis	5.88 (2.22)	2.17	1.03–4.55	.0405
Atopic dermatitis	2.38 (0.25)	0.88	0.71–1.08	.2173
Urticaria	2.61 (0.31)	0.96	0.76–1.22	.7417
GERD	1.10 (0.10)	1.11	0.89–1.38	.3582
Medications present at baseline				
PPI	5.39 (0.19)	2.15	2.00–2.32	<.0001
Histamine-2 blockers	5.99 (0.20)	2.45	2.28–2.63	<.0001
ACE inhibitors	3.30 (0.35)	1.22	0.99–1.50	.0616
Metformin	2.35 (0.31)	0.87	0.67–1.12	.2769

The reference group for each row analysis are children without the specified baseline comorbidity or medication. Asthma was defined as ≥2 encounters with a diagnosis and prescription of ≥1 asthma drug. ACE, angiotensin-converting enzyme; PPI, proton pump inhibitor.
[a] Rate per 1000 patient years.

are less frequently reported. Using National Health Interview Survey self-reports, Rudd and Moorman[47] calculated an asthma incidence of 6.0 per 1000 patient years over 1980–1996. Similarly, Behavioral Risk Factor Surveillance System self-report data (asthma call-back survey) were used to estimate an overall pediatric asthma incidence of 12.5 per 1000 patient years from 2006 to 2008.[48] Incidence rates in the current study were influenced by how asthma was defined. When asthma required a single encounter with a physician diagnosis, the incidence ranged from 18.41 per 1000 patient years in children with normal weight to 24.53 per 1000 patient years in children with obesity. When an asthma diagnosis was defined as 2 encounters with a physician diagnosis and medication prescription, the incidence ranged from 2.4 (normal weight) to 3.2 (obesity) per 1000 patient years.

Previous studies have not had sufficient power to detect differences between racial and/or ethnic groups and other important modifiers. Significant risk determinants in our data included male sex, age <5 years, African-American race, and public or Medicaid insurance. Hispanic ethnicity was associated with a reduced incidence, likely reflecting the heterogeneity of the Hispanic population in the United States and the so-called "Hispanic Paradox."[49] The comorbidities allergic rhinitis, food allergy, and anaphylaxis were significantly associated with asthma risk. The role of gastroesophageal reflux disease (GERD) in promoting asthma has been debated, but we found no association between GERD-related conditions (heartburn, esophagitis, and esophageal reflux) and incident asthma. Interestingly, proton pump inhibitors and histamine-2 blockers, commonly used to treat GERD, were significantly associated with asthma risk and warrant further study.

Regardless of the diagnostic definition we used, the risk of incident asthma diagnosis among children with obesity was increased by 26% to 38% compared with that of children with a normal-range BMI percentile in our study. The risk of asthma among children who were overweight was modestly increased by 8% to 17%. Importantly, when an asthma diagnosis required a second asthma encounter and confirmation by spirometry, the association between obesity and asthma risk remained. After adjustments for site and demographic variables (and

TABLE 4 Incidence Rates and RRs for New Asthma by BMI Percentile at Baseline

	Normal Weight (5th–84th)	Overweight (85th–94th)	*P*	Obesity (≥95th)	*P*
Any asthma diagnosis					
N (%)	18 661 (7.35)	10 660 (8.5)	—	12 009 (9.65)	—
Incidence rate[a]	18.41	20.80	—	24.53	—
Crude RR (95% CI)	1.0 (reference)	1.13 (1.10–1.16)	<.0001	1.33 (1.30–1.36)	<.0001
Model 1 (95% CI)	1.0 (reference)	1.14 (1.11–1.17)	<.0001	1.32 (1.29–1.35)	<.0001
Model 2 (95% CI)	1.0 (reference)	1.14 (1.11–1.17)	<.0001	1.31 (1.28–1.34)	<.0001
2 asthma diagnoses and asthma medication					
N (%)	2462 (0.97)	1455 (1.13)	—	1545 (1.24)	—
Incidence rate[a]	2.43	2.84	—	3.16	—
Crude RR (95% CI)	1.0 (reference)	1.17 (1.10–1.25)	<.0001	1.30 (1.22–1.38)	<.0001
Model 1 (95% CI)	1.0 (reference)	1.17 (1.09–1.25)	.002	1.28 (1.20–1.36)	<.0001
Model 2 (95% CI)	1.0 (reference)	1.17 (1.09–1.24)	<.0001	1.26 (1.18–1.34)	<.0001
2 asthma diagnoses plus confirmation with spirometry					
N (%)	976 (0.38)	527 (0.41)	—	649 (0.52)	—
Incidence rate[a]	0.96	1.03	—	1.33	—
Crude RR (95% CI)	1.0 (reference)	1.08 (0.96–1.20)	.2231	1.38 (1.25–1.52)	<.0001
Model 1 (95% CI)	1.0 (reference)	1.08 (0.97–1.20)	.1411	1.31 (1.18–1.44)	<.0001
Model 2 (95% CI)	1.0 (reference)	1.09 (0.98–1.21)	.1255	1.29 (1.16–1.42)	<.0001

Multivariable model 1 was adjusted for age, race, ethnicity, sex, site, and insurance status. Multivariable model 2 was adjusted for age, race, ethnicity, sex, site, insurance status, baseline allergic rhinitis, baseline food allergy, and baseline proton pump inhibitor use. RR, risk ratio; —, not applicable.

[a] Per 1000 patient years.

TABLE 5 AR of Overweight and Obesity in Asthma Incidence

	BMI Percentile at Baseline		
	Overweight (85th–94th)	Obesity (≥95th)	Overweight and Obesity (≥85th)
Any asthma diagnosis			
AR incidence[a]	2.39 (2.26, 2.52)	6.12 (5.95, 6.29)	4.21 (4.18, 4.24)
AR%[b]	11.49 (11.08, 11.89)	24.95 (24.68, 25.21)	18.61 (18.50, 18.73)
PAR incidence[c]	0.80 (0.75, 0.85)	1.99 (1.95, 2.03)	2.09 (2.02, 2.16)
PAR%[d]	4.16 (3.88, 4.45)	9.75 (9.47, 10.05)	10.20 (9.78, 10.63)
2 asthma diagnoses and asthma medication			
AR incidence[a]	0.41 (0.36, 0.46)	0.73 (0.67, 0.79)	0.57 (0.55, 0.58)
AR%[b]	14.48 (13.44, 15.42)	23.07 (22.25, 23.81)	18.90 (18.63, 19.20)
PAR incidence[c]	0.14 (0.12, 0.15)	0.24 (0.23, 0.25)	0.28 (0.26, 0.31)
PAR%[d]	5.38 (4.67, 6.23)	8.90 (8.18, 9.75)	10.38 (9.27, 11.61)
2 asthma diagnoses plus confirmation with spirometry			
AR incidence[a]	0.07 (0.04, 0.09)	0.36 (0.32, 0.40)	0.21 (0.20, 0.22)
AR%[b]	6.32 (4.00, 8.28)	27.38 (26.29, 28.30)	17.90 (17.41, 18.45)
PAR incidence[c]	0.02 (0.01, 0.03)	0.12 (0.11, 0.13)	0.10 (0.09, 0.12)
PAR%[d]	2.20 (1.15, 3.62)	10.90 (9.78, 12.37)	9.78 (8.06, 11.83)

AR%, attributable risk percent; PAR%, population attributable risk percent.

[a] AR is expressed as an incidence rate per 1000 patient years.

[b] AR% is the 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.

[c] The incidence of disease in the whole population due to the exposure; PAR = $\text{incidence}_{population} - \text{incidence}_{unexposed}$, expressed per 1000 patient years.

[d] PAR% is the percent of disease incidence for the whole population due to the exposure or the percent of disease incidence avoided if the study population were unexposed; $\text{PAR}/\text{incidence}_{population}$.

including the addition of influential atopic conditions and proton pump inhibitor use), obesity remained a strong risk factor for spirometry-confirmed asthma.

With our study, we provide a novel understanding for the extent to which childhood obesity worsens the pediatric asthma epidemic in the United States. On account of childhood obesity alone, the rate of new asthma diagnosis increases by >6 cases per 1000 patient years. By avoiding obesity, children would reduce their risk for new asthma by 26% to 38% compared with children with a normal BMI percentile. The World Health Organization and the 2014 Global Asthma Report show that as many as 334 million persons worldwide suffer from asthma, with a sizable portion being children. Assuming that current estimates of the US pediatric asthma prevalence (6–8 million cases) are correct, it is suggested in our data that up to 12.7% (or up to 1 million) of cases of childhood asthma are directly attributable to overweight and obesity. Currently, there are few known preventable factors that can be used to reduce childhood asthma. With these data, it is suggested that reducing the onset of obesity in childhood may significantly reduce the public health burden of asthma. Our data reveal that the effect of obesity makes a common high-morbidity condition significantly more common. In addition, because we and others have shown that obesity among children with asthma

appears to increase disease severity,[50–52] the findings of the current report are particularly compelling.

There are several limitations of this study, including retrospective electronic health data. Our study results depended on the accuracy of record-keeping that was collected for clinical care, not research. The documentation of asthma diagnosis and ordering of spirometry was made at the discretion of the treating clinician. Given the retrospective nature of the study, we are unable to draw absolute conclusions regarding the causal nature of the association between obesity and asthma. Selection bias and the inability to affect exposures are also limitations for retrospective studies. Our study reflects a fairly broad geographic distribution of the United States that involves local urban and suburban patient populations and likely many surrounding rural patients sent to these generally urban centers; the relative representativeness of urban versus rural populations is not known. Rural children may be relatively underrepresented. Considering that current rates of childhood overweight and obesity are greater in rural areas versus suburban and urban areas,[53] the finding that 10% to 13% of all US cases are directly due to overweight or obesity should be considered a conservative estimate.

Strengths of this study are its large sample size and matching design used to adjust for region, demographic effects, and variable observation periods. Additionally, this longitudinal data set spans over 7 years and includes multidimensional data (involving all clinical settings) from 6 large pediatric hospital systems across the United States, with locations in the Northeast, mid-Atlantic, Southeast, West, and Pacific Northwest. The health care data came from diverse settings, including primary, subspecialty, urgent, and hospital care, from urban and rural settings and has been curated for quality assurance.[41,42,54] Lastly, in this study, we reduced the potential for differential misdiagnostic bias between children with normal weight and obesity by excluding children with the highest likelihood for occult asthma at baseline and using both clinical features and spirometry (airflow obstruction or bronchodilator responsiveness) to confirm asthma.

CONCLUSIONS

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 cases among children in the United States. Successful interventions which reduce pediatric obesity must be a major public health priority to improve the quality of life of children and reduce obesity's contribution to pediatric asthma.

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ABBREVIATIONS

AR: attributable risk
CI: confidence interval
EHR: electronic health record
FEV_1: forced expiratory volume in 1 second
FVC: forced vital capacity
GERD: gastroesophageal reflux disease
PAR: population attributable risk

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