A comparison of childhood asthma case definitions based on parent-reported data

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Abstract

Purpose: To compare research definitions of childhood asthma based on parent-reported data.

Methods: We conducted a multicenter, prospective cohort study of 921 infants hospitalized for bronchiolitis. Follow-up was conducted via biannual parent interviews. Asthma definitions were developed using parent-reported data: clinician diagnosis by age 5 years ("broad definition"); clinician diagnosis by age 5 years with either asthma medication use or asthma symptoms during age 4–4.9 years ("epidemiologic definition"); clinician diagnosis by age 5 years with either long-term inhaled corticosteroid use or asthma symptoms during age 4–4.9 years ("strict definition"); and a "flexible definition" met by any 2 of the 3 criteria in the epidemiologic definition. Asthma outcome definitions were evaluated using unadjusted associations with known major asthma risk factors, and validated against the medical record in a subset (n=116).

Results: Asthma prevalence for the broad definition was 294/875 (34%); epidemiologic definition, 235/859 (27%); strict definition, 229/859 (27%); and flexible definition, 364/826 (44%). Risk factors had similarly strong associations with definitions that required clinician diagnosis, and weaker associations with the flexible definition. The epidemiologic and strict definitions had the highest specificity (96%) and PPV (92%).

Conclusions: Parent report of clinician-diagnosed asthma correlates well with known asthma risk factors.

Keywords

asthma; bronchiolitis; epidemiology; prospective studies; pediatrics

INTRODUCTION

Asthma is the most common chronic illness in children [1]. Case definitions for childhood asthma vary across epidemiologic studies, leading to discrepancies in prevalence estimates and interpretation [2, 3]. While an ideal case definition would incorporate physician diagnosis and measurement of airway inflammation and bronchial reactivity [2], lung function data often are unavailable in large observational studies. Furthermore, guidelines for childhood asthma diagnosis in clinical practice vary and there is no gold standard [4]. Due to the reliance of many large studies on parent-reported data, better understanding of the performance of childhood asthma definitions based on parent-reported data is needed. Our objective was to compare four definitions of childhood asthma based on parent-reported data, by evaluating their associations with known major asthma risk factors.

METHODS

Study Design and Participants

The 35th Multicenter Airway Research Collaboration (MARC-35) is a prospective cohort study of infants hospitalized for bronchiolitis (Appendix). The study design, participants, and data collection have been reported previously [5]. Briefly, researchers at 17 U.S. sites consecutively enrolled infants (age <1 year) hospitalized for bronchiolitis during the 2011–2014 winter seasons, using the American Academy of Pediatrics definition of bronchiolitis [6]. Exclusion criteria included known heart-lung disease and gestational age <32 weeks. All sites obtained approval from their local institutional review board.

Data Collection

Data collected during the index hospitalization by parent interview included maternal asthma history, paternal asthma history, maternal eczema history, paternal eczema history, infant eczema history, sex, race/ethnicity, and insurance type. Parent-reported home ZIP codes at enrollment were linked to median household income estimates from Esri Business Analyst Desktop (Esri, Redlands, CA) to estimate median household income by ZIP code. Trained research staff at the Emergency Medicine Network (EMNet) Coordinating Center at Massachusetts General Hospital conducted longitudinal follow-up through age 5 years via biannual parent telephone interviews. Starting at age 30 months, parents were asked whether the child had ever been diagnosed with asthma by a physician or other health professional, and the child's age at diagnosis. We used the parent-reported age at diagnosis from the earliest interview at which asthma diagnosis was reported. Details about parent-reported data on asthma medication use and asthma symptoms are provided in the Supplemental Methods.

Asthma Definitions

Using the parent-reported data collected through age 5 years, we evaluated 4 asthma definitions: (1) "broad definition" – clinician diagnosis by age 5 years; (2) "epidemiologic definition" – clinician diagnosis by age 5 years with either asthma medication use or asthma symptoms during age 4–4.9 years, as described previously [7]; (3) "strict definition" – clinician diagnosis by age 5 years with either long-term inhaled corticosteroid use or asthma symptoms during age 4–4.9 years; and (4) "flexible definition" – fulfillment of any 2 of the 3 following criteria: clinician diagnosis by age 5 years, asthma medication use during age 4–4.9 years, and asthma symptoms during age 4–4.9 years, as described previously by Lødrup Carlsen *et al.* [8]. Asthma medication use was defined as any use of inhaled or systemic corticosteroids, montelukast, or inhaled bronchodilator during age 4–4.9 years. Asthma symptoms were defined as the child having any breathing problem episodes during age 4–4.9 years, or being bothered by breathing problems or woken up at night due to breathing problems once or more in the past month at the 4.5-year or 5-year interview. Long-term inhaled corticosteroid use was defined as 8 weeks of inhaled corticosteroid use during age 4–4.9 years, or inhaled corticosteroids prescribed for daily long-term or daily seasonal use taken before, during, or after a breathing problem.

Statistical Analyses

We calculated the prevalence of each asthma definition and examined the distribution of age at asthma diagnosis, overall and across asthma definitions. We identified male sex, maternal asthma, paternal asthma, maternal eczema, paternal eczema, and infant eczema *a priori* as well-established risk factors for asthma development [9–11]. We compared the prevalence of asthma risk factors across asthma definitions.

We examined the associations of asthma risk factors with asthma definitions using logistic regression models to calculate odds ratios (OR) and 95% confidence intervals (CI). Regression models used a clustered sandwich estimator to account for potential patient clustering by site. We conducted a structured medical record review to ascertain physician-diagnosed asthma and asthma medication use in a subset (n=116; see Supplemental Methods for details), and calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating characteristic curve (AUC) and corresponding 95%CI of asthma definitions based on parent report. Analyses were conducted using Stata version 14.0 (College Station, TX). A two-sided P-value of 0.05 was considered statistically significant.

RESULTS

Overall, 921 infants participated in the longitudinal cohort. The cohort was 60% male and had a median age of 3 (interquartile range [IQR] 2–6) months at enrollment (Table S1). Asthma outcome data by age 5 years were available for 875/921 participants (95%), who comprised the analytic cohort. Overall, the analytic cohort was similar to the non-analytic cohort on the major asthma risk factors.

The prevalence of asthma by age 5 years using the broad definition was 294/875 (34%); epidemiologic definition, 235/859 (27%); strict definition, 229/859 (27%); and flexible definition, 364/826 (44%) (Figure S1). Most (83%) asthma diagnoses occurred before age 3 years (median 18 [IQR 12–28] months) (Table 1). The distribution of age at asthma diagnosis was similar across definitions.

Unadjusted associations of asthma risk factors with the broad, epidemiologic, and strict definitions were similar, while associations of asthma risk factors with the flexible definition were generally weaker (Table 2). For example, the unadjusted association of maternal asthma history with childhood asthma for the broad definition was OR 3.83 (95%CI 2.69–5.45); epidemiologic definition, OR 3.94 (95%CI 2.70–5.74); strict definition, OR 3.90 (95%CI 2.70–5.63); and flexible definition, OR 2.81 (95%CI 1.96–4.02), with all P<0.001.

Validation study participants were more likely to be female and non-Hispanic white, to live in a ZIP code with median household income $80,000, and to have private insurance (Table S2). However, most of the asthma risk factors and asthma definition components did not differ by inclusion in the validation study. Infant eczema and long-term inhaled corticosteroid use during age 4–4.9 years were more prevalent in validation study participants. The prevalence of asthma did not differ by inclusion in the validation study. The epidemiologic and strict definitions overlapped completely in the validation study participants.

The prevalence of confirmed asthma in the medical record was 45/116 (39%). The flexible definition had the highest sensitivity (0.88), lowest specificity (0.86), and lowest PPV (0.79), while the epidemiologic and strict definition had the lowest sensitivity (0.77), highest specificity (0.96), and highest PPV (0.92) (Table 3). Similar AUCs (0.86–0.87) were observed across asthma definitions (Figure S2).

DISCUSSION

In a prospective cohort study of infants hospitalized for bronchiolitis, we created 4 asthma definitions based on parent-reported data collected through age 5 years and compared the associations of these definitions with known asthma risk factors. The prevalence of asthma by age 5 years ranged from 27% (epidemiologic and strict definitions) to 44% (flexible definition). These results align with previous reports of asthma prevalence of 30–40% among children with a history of severe bronchiolitis [12–14]. The 3 definitions that required parent report of clinician-diagnosed asthma had similar associations with the asthma risk factors. In contrast, the flexible definition had a weaker association with the asthma risk factors, and the lowest specificity and PPV when validated against the medical record. Our results support the use of childhood asthma definitions that require parent report of clinician-diagnosed asthma, in the context of observational research limited to parent-reported data.

Previous studies have validated parent-reported asthma against clinical assessment [15, 16] and medical record data [17]. These studies reported high sensitivity (89–96%) and specificity (87–96%) [15–17]. Additionally, studies have validated parent report of child's

asthma medication prescriptions against national prescription databases, and observed high sensitivity (72–92%) and specificity (85–97%) [18–20]. We validated parent report of clinician-diagnosed asthma by age 5 years against the medical record in a subset, and observed high sensitivity (80%) and specificity (92%). The additional criteria of asthma medication use or asthma symptoms during ages 4–4.9 years (epidemiologic definition) resulted in slightly lower sensitivity (77%) and higher specificity (96%). Pekkanen and Pearce [21] recommend prioritizing high specificity and PPV for asthma definitions in etiologic studies, because the bias in the relative risk depends on the PPV of the outcome [21, 22]. While all asthma definitions that we tested had similar AUCs (0.86–0.87), the epidemiologic definition and the strict definition had the highest specificity and PPV, and thus may be considered preferable for etiologic research.

There is considerable heterogeneity among asthma definitions in epidemiologic research. Sá-Sousa *et al.* reviewed 117 cross-sectional studies of asthma prevalence conducted in the general population and observed 8, 12, and 29 different definitions of lifetime asthma, diagnosed asthma, and current asthma, respectively [23]. In a recent systematic review of asthma case definitions in 67 birth cohort studies, Dubovyi *et al.* identified consistent definitions of "asthma ever", most frequently defined as parent report of physician-diagnosed asthma [3]. Definitions of "current asthma" were inconsistent; however, the most common definition was "asthma ever" with either asthma symptoms or asthma medication use in the past 12 months [3], similar to our epidemiologic definition. To align with existing research, our results support continued use of the epidemiologic definition.

Other studies have compared childhood asthma definitions using additional diagnostic criteria including physician evaluation, bronchial reactivity, and airway inflammation. de Jong *et al.* analyzed data from children referred for evaluation of suspected asthma in Switzerland [24]. Assessments included parent questionnaire, skin-prick tests, exhaled nitric oxide, spirometry, bronchodilator reversibility test, and bronchial provocation tests (BPT), all of which informed physician diagnosis (the reference standard). The criteria with the highest diagnostic accuracy were frequent wheeze, awakening due to wheeze, wheeze triggered by pollen or pets, exhaled nitric oxide measurement, BPT by methacholine, and BPT by exercise. Similar to previous reports [25–27], parent-reported wheeze was sensitive (80%) but not specific (48%), whereas frequent wheeze and awakening due to wheeze were specific (90%) but not sensitive (44% and 41%, respectively) [24]. Silva *et al.* conducted a cross-sectional study of children attending the 3rd and 4th grades in Porto [2]. The authors observed poor agreement between objective (airway reversibility and exhaled nitric oxide) and parent-reported measures (doctor diagnosis, symptoms, medication use), while parent report of physician-diagnosed asthma was correlated with parent-reported asthma symptoms. The authors recommended incorporating questionnaire data and airway reversibility in childhood asthma definitions for research. However, measures of airway reversibility are usually not feasible in large population-based studies, underscoring the need to compare definitions based solely on parent-reported data.

While clinical guidelines note the difficulty of asthma diagnosis in children under 5 years of age [4], most of the parent-reported asthma diagnoses in our cohort were before age 3 years. These early diagnoses may be accurate in our severe bronchiolitis population. Alternatively,

the early parent-reported clinician diagnoses may reflect "pre-asthma" labels that are predictive of later asthma diagnosis. In lower-risk populations (e.g., the general population), asthma prevalence would be lower and early asthma diagnoses may be less accurate. Therefore, in lower-risk populations, the epidemiologic definition would likely out-perform the broad definition by a greater margin in terms of specificity and PPV. Likewise, while the strict definition yielded similar results to the epidemiologic definition in our study, the strict definition might have insufficient sensitivity in lower-risk populations.

The main limitation of our study is the lack of a "criterion standard". Indeed, there is no such standard for the diagnosis of childhood asthma at age 5 years, in either the clinical or research setting [2, 4]. We validated asthma outcomes against the medical record in a subset, but a standardized clinical evaluation would have been a more optimal reference standard. Another limitation is that exposure misclassification may be differential, i.e., parents with asthma may be more likely to recall their child's asthma diagnosis. Indeed, the asthma diagnosis may be more readily applied to children with known asthma risk factors, so our observed associations may reflect circular logic. Future research could address this issue by assessing correlations of asthma definitions with asthma phenotype data, including measurement of airway inflammation, bronchial reactivity, eosinophilia, and aeroallergen sensitization, as well as medical record review. Finally, results from our severe bronchiolitis cohort may not be generalizable to the general population. However, infants with severe bronchiolitis are an important high-risk population for asthma research and prevention [14], and over one-third of childhood asthma in the US is attributable to RSV infection [28]. Strengths of our study include relevance to current epidemiologic research and analysis of a large, racially/ethnically and geographically diverse US cohort with high retention.

CONCLUSIONS

In our severe bronchiolitis cohort, parent report of clinician-diagnosed asthma by age 5 years correlated well with known asthma risk factors and demonstrated validity compared to medical record review. Our results align with previous assessment of definitions of childhood asthma in epidemiologic research [3] and support the use of the epidemiologic definition [7] (clinician diagnosis by age 5 years with either asthma medication use or asthma symptoms during age 4–4.9 years) to define current asthma in observational research using parent-reported data. We encourage future work that compares parent-reported asthma diagnosis against clinical evaluation, incorporating measurements of airway inflammation and bronchial reactivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations:

AUC	area under the receiver operating characteristic curve
BPT	bronchial provocation test
CI	confidence interval
EMNet	Emergency Medicine Network
IQR	interquartile range
MARC	Multicenter Airway Research Collaboration
NPV	negative predictive value
OR	odds ratio
PPV	positive predictive value

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Table 1.

Descriptive cohort characteristics, overall and by asthma definition, based on parent-reported data for up to age 5 years

	Overall (n=875)	Broad[a] (n=294)	Epidemiologic[b] (n=235)	Strict[c] (n=229)	Flexible[d] (n=364)
	n (%)	n (%)	n (%)	n (%)	n (%)
Child demographics					
Age at enrollment (median [IQR]), mo.	3 (2–6)	4 (2–6)	4 (2–6)	4 (2–6)	3 (2–6)
Sex					
Male	523 (60)	187 (64)	150 (64)	145 (63)	220 (60)
Female	352 (40)	107 (36)	85 (36)	84 (37)	144 (40)
Race/ethnicity					
Non-Hispanic white	385 (44)	101 (34)	85 (36)	84 (37)	148 (41)
Non-Hispanic black	199 (23)	93 (32)	74 (31)	72 (31)	94 (26)
Hispanic	258 (29)	92 (31)	68 (29)	65 (28)	108 (30)
Other	33 (4)	8 (3)	8 (3)	8 (3)	14 (4)
Median household income by ZIP code					
<$40,000	301 (34)	112 (38)	82 (35)	79 (35)	127 (35)
$40,000–$79,999	471 (54)	148 (50)	123 (52)	121 (53)	190 (52)
$80,000	103 (12)	34 (12)	30 (13)	29 (13)	47 (13)
Insurance type					
Public or none	506 (59)	193 (67)	150 (65)	147 (65)	217 (61)
Private	356 (41)	95 (33)	80 (35)	78 (35)	140 (39)
Parent and child history					
Maternal asthma history					
Yes	183 (21)	107 (37)	91 (39)	89 (39)	112 (31)
No	684 (79)	184 (63)	143 (61)	139 (61)	250 (69)
Paternal asthma history					
Yes	142 (16)	61 (21)	51 (22)	51 (22)	73 (20)
No	687 (79)	215 (73)	169 (72)	164 (72)	273 (75)

	Overall (n=875)	Asthma definition			
		Broad[a] (n=294)	Epidemiologic[b] (n=235)	Strict[c] (n=229)	Flexible[d] (n=364)
	n (%)	n (%)	n (%)	n (%)	n (%)
Missing	46 (5)	18 (6)	15 (6)	14 (6)	18 (5)
Maternal eczema history					
Yes	114 (13)	56 (19)	49 (21)	49 (21)	60 (17)
No	753 (87)	235 (81)	185 (79)	179 (79)	302 (83)
Paternal eczema history					
Yes	69 (8)	40 (14)	32 (14)	32 (14)	37 (10)
No	760 (87)	236 (80)	188 (80)	183 (80)	309 (85)
Missing	46 (5)	18 (6)	15 (6)	14 (6)	18 (5)
Infant eczema history					
Yes	126 (14)	62 (21)	51 (22)	49 (21)	67 (18)
No	748 (86)	231 (79)	184 (78)	180 (79)	297 (82)
Asthma definition components					
Age at diagnosis (median [IQR]), mo., among children with parent-reported clinician diagnosis of asthma	18 (12–28)	18 (12–28)	18 (12–30)	18 (12–30)	18 (12–30)
Number of breathing problem episodes, age 4–4.9 years (median [IQR])	0 (0–2)	1 (0–3)	2 (1–3)	2 (1–3)	1.5 (1–3)
Asthma symptoms, age 4–4.9 years					
Yes	501 (57)	228 (78)	228 (97)	228 (100)	357 (98)
No	326 (37)	50 (17)	7 (3)	1 (0)	7 (2)
Missing	48 (5)	16 (5)	0	0	0
Asthma medication use, age 4–4.9 years					
Yes	339 (39)	205 (70)	205 (87)	199 (87)	334 (92)
No	487 (56)	73 (25)	30 (13)	30 (13)	30 (8)
Missing	49 (6)	16 (5)	0	0	0
Long-term inhaled corticosteroid use, age 4–4.9 years					
Yes	84 (10)	77 (26)	77 (33)	77 (34)	84 (23)
No	736 (84)	199 (68)	156 (66)	150 (66)	277 (76)
Missing	55 (6)	18 (6)	2 (1)	2 (1)	3 (1)

Abbreviations: IQR, interquartile range

[a] Parent report of clinician diagnosis of asthma by age 5 years.

[b] Parent report of clinician diagnosis of asthma by age 5 years with either asthma medication use or asthma symptoms during age 4–4.9 years.

[c] Parent report of clinician diagnosis of asthma by age 5 years with either long-term inhaled corticosteroid use or asthma symptoms during age 4–4.9 years.

[d] Two of the 3 parent-reported criteria: clinician diagnosis by age 5 years, asthma medication use during age 4–4.9 years, and asthma symptoms during age 4–4.9 years.

Table 2.

Unadjusted associations between major asthma risk factors and 4 definitions of childhood asthma

	Asthma definition							
	Broad[a]		Epidemiologic[b]		Strict[c]		Flexible[d]	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Child demographics								
Sex								
Male	1.27 (0.94–1.73)	0.12	1.27 (0.96–1.67)	0.09	1.23 (0.91–1.66)	0.18	1.15 (0.95–1.38)	0.16
Female	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
Parent and child history								
Maternal asthma history	3.83 (2.69–5.45)	<0.001	3.94 (2.70–5.74)	<0.001	3.90 (2.70–5.63)	<0.001	2.81 (1.96–4.02)	<0.001
Paternal asthma history[e]	1.65 (1.17–2.34)	0.005	1.74 (1.19–2.54)	0.004	1.81 (1.25–2.63)	0.002	1.57 (1.02–2.40)	0.04
Maternal eczema history	2.13 (1.48–3.06)	<0.001	2.42 (1.78–3.28)	<0.001	2.53 (1.85–3.44)	<0.001	1.62 (1.07–2.45)	0.02
Paternal eczema history[e]	3.06 (1.99–4.72)	<0.001	2.81 (1.77–4.45)	<0.001	2.91 (1.83–4.64)	<0.001	1.76 (1.06–2.91)	0.03
Infant eczema history	2.17 (1.35–3.48)	0.001	2.13 (1.28–3.52)	0.003	2.05 (1.24–3.38)	0.005	1.86 (1.31–2.64)	0.001

Abbreviations: 95%CI, 95% confidence interval; OR, odds ratio

[a] Parent report of clinician diagnosis of asthma by age 5 years.

[b] Parent report of clinician diagnosis of asthma by age 5 years with either asthma medication use or asthma symptoms during age 4–4.9 years.

[c] Parent report of clinician diagnosis of asthma by age 5 years with either long-term inhaled corticosteroid use or asthma symptoms during age 4–4.9 years.

[d] Two of the 3 parent-reported criteria: clinician diagnosis by age 5 years, asthma medication use during age 4–4.9 years, and asthma symptoms during age 4–4.9 years.

[e] Results for the missing data category are not shown.

Table 3.

Test characteristics of 4 asthma definitions based on parent report compared to physician ascertainment of asthma from medical record review

Definition	Sensitivity	Specificity	PPV	NPV	AUC (95%CI)
Broad[a]	0.80	0.92	0.86	0.88	0.858 (0.790–0.925)
Epidemiologic[b]	0.77	0.96	0.92	0.87	0.863 (0.795–0.931)
Strict[c]	0.77	0.96	0.92	0.87	0.863 (0.795–0.931)
Flexible[d]	0.88	0.86	0.79	0.92	0.869 (0.805–0.933)

The epidemiologic and strict definitions overlapped completely in the validation study participants. The reference standard, physician ascertainment of asthma from medical record review, was defined as documentation of clinician-diagnosed asthma in the age 3.0–5.0 year medical record and documentation of at least two asthma medication events in the age 3.0–5.0 year medical record.

[a] Parent report of clinician diagnosis of asthma by age 5 years.

[b] Parent report of clinician diagnosis of asthma by age 5 years with either asthma medication use or asthma symptoms during age 4–4.9 years.

[c] Parent report of clinician diagnosis of asthma by age 5 years with either long-term inhaled corticosteroid use or asthma symptoms during age 4–4.9 years.

[d] Two of the 3 parent-reported criteria: clinician diagnosis by age 5 years, asthma medication use during age 4–4.9 years, and asthma symptoms during age 4–4.9 years.