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Development and Initial Testing of Asthma Predictive Index for a Retrospective Study: An Exploratory Study

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Abstract

Objective—Asthma Predictive Index (API) has been used for predicting asthma in prospective or cross-sectional studies, not for a retrospective study. We aim to develop and validate API for a retrospective study.

Methods—This is a cross-sectional study based on a convenience sample of children who participated in a previous retrospective cohort study. API was operationalized by 2 or more wheezing episodes in a year during the first 3 years of life PLUS one of the major or two of the minor criteria of the original API. We assessed validity of retrospective API against Predetermined Asthma Criteria (PAC) which has been extensively used in clinical studies for asthma. We assessed criterion validity by measuring kappa and agreement rate between API and PAC and construct validity by determining associations of API with known risk factors for asthma.

Results—Of the eligible 105 children, 55 (52.4%) were male, 90 (85.7%) Caucasians, and the mean age (±SD) was 5.8 years (±1.5). API criteria was met by 15 (14.3%), compared to 33 (31.4%) by PAC, respectively. The agreement rate and kappa between API and definite asthma of PAC were 89.5% and 0.66 ($p<0.01$). Atopic conditions, lower parental education, no history of breastfeeding, and family history of asthma were significantly associated with risk of asthma by API.

Conclusions—Application of API to a retrospective study for ascertaining asthma status is suitable. Our study findings need to be replicated by future studies with a larger sample size.

Keywords

Asthma ascertainment; Asthma Predictive Index (API); Predetermined Asthma Criteria; Retrospective study; Wheezing

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Introduction

Asthma Predictive Index (API) was developed in the year of 2000 to predict asthma at school age using factors that were found during the first 3 years of life,(1) which was based on the study findings that early wheezing episodes were probably related to a predisposition to asthma.(2) Given the lack of gold standard to ascertain or diagnose asthma, National Asthma Education and Prevention Program (NAEPP) guidelines suggest API in predicting childhood asthma.(3) Since it was designed to predict the future risk of childhood asthma, it has been used in multiple prospective or cross-sectional studies concerning development of asthma.(4–6) Also, it has been applied for ascertainment of asthma for clinical trials or other studies.(7, 8) However, despite application of API for prediction or ascertainment of asthma status in prospective or cross-sectional studies, it has not been used for a retrospective study.

As API was based on parental self-reports on the major and minor criteria, this information is likely to be available in medical records and medical record-based ascertainment of asthma status by API can be suitable if patients' (and their parents') medical records are complete in a way capturing all medical events and available for comprehensive reviews. In this respect, Olmsted County, Minnesota is an ideal study setting to apply API to a retrospective study because health care environment is self-contained and all medical records (inpatient and outpatient records) are retrievable from all health care providers by using uniquely assigned identification number to each Olmsted County resident. Given the increasing trends of utilizing medical records or administrative data derived from medical records for asthma research and the potential suitability of API to a retrospective study, developing and validating API for a retrospective study might be worthwhile. The main aim of this exploratory study was to assess validity of API for a retrospective study.

Methods

Study setting

Rochester, Minnesota is centrally located in Olmsted County. During the study period, characteristics of the City of Rochester and Olmsted County populations were similar to those of the U.S. Caucasian population, with the exception of a higher proportion of the working population employed in the health care industry.(9–11) Olmsted County, Minnesota is virtually self-contained within the community, and when patients register in any health care providers in the community at first time, they are asked whether they authorize using their medical records for research. If one grants the authorization (95%) for using medical record for research, each patient is assigned a unique identifier under the auspices of the Rochester Epidemiology Project (REP),(12–15) which has been continuously funded by the NIH since 1960. All clinical diagnoses and information from every episode of care are contained within detailed patient-based medical records. This unique longitudinal population-based resource has been the source of over 2000 publications on the epidemiology of disease.(16) Using REP resources, we previously demonstrated that incidence rates of asthma for this community are similar to other communities.(17)

Study design and subjects

This is a cross-sectional study based on a convenience sample of children who participated in a previous retrospective cohort study. Details of study subjects were previously described.(18, 19) Briefly, the study subjects were children who were enrolled in the Mayo Clinic sick child care program and their parents to agree to participate in a previous study assessing factors associated with parents' care-seeking behavior for mild acute illness of young children. Parents (i.e. Mayo Clinic employees) who took their children to the sick child care program were allowed to request on-site medical evaluations for their children with mild acute illness. Thus, children with or without medical evaluations at the sick child care program were eligible for the original study. This sampling approach had an advantage over clinic-based sampling, which is limited to subjects seeking medical evaluations. We enrolled all children of the original study in this present study and reviewed their medical records to determine asthma status as of the end of 2007, because it allowed the study subjects to become at least 3 years or older which is requirement for API. In addition to the exclusion criteria of the original study which included; children who were turned away or excluded by the sick child care program due to lack of availability for care, and those being seen for follow-up care/post-surgery/trauma care, we also excluded for this study children whose parents had declined research authorization status since the original study, and those who were not eligible for ascertaining asthma status by API (e.g., adopted children or first registration in clinic after 3 years). This study was approved by the Institutional Review Board at the Mayo Clinic and Olmsted Medical Center.

Ascertainment of Asthma status by Asthma Predictive Index (API)

We operationalized the original API criteria for this present study. Specifics of the operationalized API are summarized in Table 1. Briefly, we defined the term of "frequent wheezing" which was defined by a value of ≥3 in a scale of 1 ("very rarely") to 5 ("on most days") in the original API study, as recurrent (2 or more) wheezing episodes in a year during the first 3 years of life. Since the original API study did not report the mean number of wheezing episodes per year based on their scale to measure the frequency of wheezing episodes, we defined the mean number of wheezing episodes per year for our own study which was 2 (95%CI: 1–3) among children with physician-diagnosed asthma during the first 3 years of life. A physician diagnosis of atopic dermatitis (or eczema) and allergic rhinitis (or hay fever) of patients were obtained from their medical records instead of administrating a questionnaire to parents. As for the item of 'wheezing apart from cold', 'cold' was defined by upper respiratory infection (URI) or cold documented, OR fever (≥100.4°F) plus runny or stuffy nose documented in medical records. Eosinophilia was considered to be present if eosinophils were ≥4% of the total white blood cells in the test performed before the age 1 year because blood specimens of the original study were obtained at the age 1 year (10.9±0.6mo). For parental history of asthma, we obtained it from parents' medical records and patients' family history as of the last follow-up date (not limited to during the first 3 years of child's life) in the original study, because onset of parental asthma is a function of follow-up duration and independent of child's atopic conditions. The asthma index date was defined as the earliest date patients fulfilled the API criteria, which is useful for assessing temporality between exposure and outcome in retrospective studies allowing causal inference.(20–23)

Ascertainment of Asthma status by Predetermined Asthma Criteria (PAC)

We applied Predetermined Asthma Criteria (PAC) delineated in Table 2 to ascertain asthma status to assess criterion validity of the retrospective API criteria. PAC was originally developed by two renown asthma researchers, Drs. John Yunginger and Charles Reed.(11) Since its development, it has been extensively used in asthma research and has shown excellent construct validity and reliability (0.72–92) of the criteria.(11, 24–28) As most subjects with probable asthma (85%) became definite asthma over time we combined both probable and definite asthma.(11) The onset date of asthma (asthma index date) by PAC, was defined as the earliest constellation of symptoms found in the medical record that met the PAC for asthma regardless of physician diagnosis of asthma.

Other variables

To determine the association of these asthma criteria with known risk factors (construct validity), we collected known risk factors for asthma. Family history of asthma was identified as the presence of asthma among first-degree relatives from medical records. The patients' atopic history included allergic rhinitis, atopic dermatitis, and food allergy, ascertained by a physician diagnosis documented in medical records. Some variables such as smoking exposure, parental education level, or breast-feeding history were collected by a validated questionnaire during the original study.(18)

Data analysis

We summarized the prevalence of asthma by API and PAC alone. To assess criterion validity of API, we calculated overall agreement and Cohen's unweighted kappa index between retrospective API and PAC. To further determine the correlation between API and PAC, we calculated the specific proportionate agreement for positive (2a / (2a+b+c); a (positive for both criteria), b (positive for API only), c (positive for PAC only), d (negative for both criteria)) and the specific proportionate agreement for negative (2d / (2d+b+c)).(29) To determine the construct validity of each asthma ascertainment method, we assessed the associations of known risk factors for asthma with each asthma criteria by using logistic regression models. The associations were summarized by calculating odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). All analyses were performed using JMP statistical software package (Ver 9.0.1; SAS Institute, Inc, Cary, NC).

Results

Study cohort

Of the original 115 children, 10 subjects were excluded in our study due to the change of research authorization status (n=2) or unavailability of medical records during the first 3 years of life (n=8). Since each item of the original API was based on during the first 3 years of life, children who were registered after 3 years of life or adopted were excluded. Of the remaining 105 children, 55 (52.4%) were male, 90 (85.7%) Caucasians, and the mean age (±SD) at the time of the original study was 5.8 years (±1.4). Thirty two children (30.5%) had a family history of asthma, and 23 (21.9%) had other atopic conditions such as atopic dermatitis, allergic rhinitis, or food allergy (Table 3).

Prevalence and agreement of asthma by API and PAC

API criteria was met by 15 (14.3%), compared to 24 (22.9%) and 33 (31.4%) by definite and by both probable and definite asthma of PAC, respectively (Table 3). The agreement rate and kappa index between API and definite asthma of PAC or both asthma of PAC were 89.5% and 0.66 ($p<0.01$) or 82.9% and 0.53 ($p<0.01$), respectively (Table 4). There were groups of 15 children (14.3%) who met both criteria and 18 children (17.1%) who met only PAC but not API. There was no child who met only API criteria but not PAC.

Association of known risk factors with asthma status by different criteria (PAC vs. API)

The results of univariate analysis for the association between risk factors and asthma status by API vs. PAC are summarized in Table 5. Known risk factors for asthma such as atopic conditions, family history of asthma, lower parental education, and no history of breastfeeding were significantly associated with risk of asthma by retrospective API and PAC. On the other hand, other risk factors such as smoking exposure, ethnicity, and gender (male) were not associated with either criterion.

Comparison of asthma index date between API and PAC

We also compared the index date of asthma by API with that by PAC. Two thirds of children with asthma had the identical index date of asthma by both criteria. Among the number of subjects with discrepant index dates by the two criteria (n=5), 3 (60%) were observed within 1 year and 2 (40%) were 4.7 and 5.9 years. The primary reason for the discrepancy was due to children whose parents were diagnosed with asthma by a physician later.

Discussion

Main findings

To our knowledge, this is the first study, which attempted to apply API to a retrospective study for ascertaining asthma status. We found that API showed high overall agreement with PAC (89.5% with definite asthma of PAC, and 82.9% with both asthma of PAC, respectively). Although our findings need to be replicated by future studies with a larger sample size, our study results suggest that determination of asthma status by API is suitable for a retrospective study in study settings like ours.

Specifically, specific proportionate agreement for positivity (for asthma) was 63–72% and specific proportionate agreement for negativity (for asthma) was 89–94% suggesting a higher concordance for negativity for asthma than positivity for asthma. Despite this small discrepancy in specific proportionate agreement, the patterns of the association of known risk factors with each asthma criteria were almost same reassuring similar construct validity. For example, known risk factors for asthma such as atopic conditions, family history of asthma, lower parental education, and no history of breastfeeding were all significantly associated with the asthma status ascertained by API and PAC. These findings suggest that the retrospective API criteria has reasonable construct validity in which it differentiates groups of children with and without known risk factors for asthma. Smoking rate among the participants in our study was pretty low (10.5%) compared to national level (21.6% in

2003),(30) possibly resulting in mitigating the association of secondhand smoke during the pregnancy with risk of asthma in early life.

Interpretation of findings in relation to previously published work

Given the unavailability of gold standard on the diagnosis of asthma, some previous retrospective studies for asthma determined asthma status based on ICD-9 codes or medication use or a hospitalization history for asthma.(31, 32) Our previous study found that ICD code-based asthma ascertainment under-identified children with asthma compared to criteria-based medical record review (PAC).(20) This concern was observed in other study settings by a recent study which showed 41% high school students from rural counties in Georgia did not have a diagnosis of asthma despite having typical and recurrent asthma symptoms.(33) This result supports that solely relying asthma ascertainment on a physician diagnosis leads to significant underestimate of asthma prevalence. These data also provides a basis for the need of predetermined criteria for asthma independent of a physician diagnosis of asthma alone in asthma research. The numbers of children with asthma identified by API and PAC in our study also showed a substantial difference (14.3% vs. 31.4%), suggesting a potential discrepancy in identifying children with asthma. There might be two sources of heterogeneity of asthma resulting in this discrepancy: true heterogeneity of asthma (vs. methodological heterogeneity in defining asthma), which might reflect the feature of asthma as a disease with heterogeneous phenotypes as recently demonstrated.(34–38)

Alternatively, different features of API (vs. PAC) might be another source for this discrepancy. For example, API criteria 1) did not consider a physician's diagnosis of asthma, nor the response to bronchodilator treatment nor lung function test results, and 2) put a weight on the first three years of life. As a result, the retrospective API criteria might omit children with a physician diagnosis of asthma, especially late-onset asthma, those with abnormal lung function tests, and those whose parents develop asthma beyond the first three years of life of children. Specifically, bronchodilator reversibility of airway obstruction (i.e. 12% change of FEV1 following inhalation of a short-acting β2-agonist) might not be considered by API,(3) while favorable clinical response to bronchodilator which is one of the items in PAC (item 3 of PAC, see Table 2) is important to clinicians in ascertaining asthma, especially young children who could not undergo a formal lung function test. For example, of the 18 children who met only PAC, but not API in our study, physicians documented 16 children (89%) showed favorable clinical response to bronchodilator treatment, and diagnosed 10 (56%) with asthma subsequently.

Therefore, given the purpose of developing API (predicting the future risk of asthma in early childhood when a physician's diagnosis of asthma rarely occurs), the discrepancy was somehow expected. However, to use API in a retrospective study including a physician diagnosis of asthma, longer follow up period beyond the first 3 years of life, and taking into account bronchodilator responsiveness may increase a likelihood of identifying children with asthma.

While PAC allowed us to determine asthma index date which has been extensively used for epidemiologic investigations, asthma index date was not part of the original API study.

However, it may be useful, if not critical, for epidemiologic studies, which helps to determine temporality between exposure and outcome event discerning causal inference. We attempted to define asthma index date as the date when one met the criteria for the retrospective API. For example, for a patient who had 2 or more wheezing episodes and met one of major criteria, the later date, whichever comes later between the first diagnosis date of the met major criteria and the date of 2nd wheezing episode was considered the patient's asthma index date. The same rule was applied to patients who met two of the minor criteria instead of major criteria. We compared the index date of asthma by API with the one by PAC, and found that 2/3 of subjects had the exact same index date and all index dates were concordant within 1 year, except for 2 cases in which index dates were 4 year apart. This was primarily due to a delay diagnosis of parental asthma beyond the first 3 years of life. Overall, despite the retrospective nature, the index date of asthma was surprisingly consistent between the two retrospective asthma criteria (PAC and API) suggesting reasonable precision of the criteria in determining the onset of asthma.

Strengths and limitations of this study

The main strength of the study is epidemiologic advantages of our study setting in which all medical records for study subjects are available under the Rochester Epidemiology Project. Also, this study was based on predetermined criteria for asthma (instead of self-report or ICD-9 codes), which were extensively used for previous epidemiologic investigations.

There are inherent limitations in our study as a retrospective study. The main limitation was no comparison between API according to the original study (i.e., cross-sectional or prospective collection of pertinent data from parents) and the retrospective API. Given the purpose which addresses a proof of concept for the future validation study, this exploratory study provides an important basis for applying API to a retrospective study. Another limitation is unavailability of all data for API such as lab data (eosinophil count). Lab testing for eosinophil count is not routinely performed in clinical practice (93% of subjects were not tested for eosinophil count) and the original API study reported only 10% of subjects had eosinophilia. We postulate that the missing data of eosinophilia might primarily occur among patients with mild asthma who might not have eosinophilia.(39, 40) Unavailability of eosinophil counts among the majority of subject did not affect asthma prevalence as discussed below and is likely to be a non-differential misclassification bias. Thus, we believe it minimally influences ascertainment of asthma status by API.

Along these lines, insufficient retrospective data might miss people with asthma by either API or PAC. The unique epidemiological advantages of our study setting discussed above enables us to capture most relevant clinical episodes to clinical diagnosis or ascertainment of asthma, as asthma is still a clinical diagnosis. In addition, if both criteria miss significant number of patients with asthma (i.e., false negativity or type 2 error), such misclassification bias is likely to result in the lower prevalence rates of asthma and poor construct validity (no association between asthma and its known risk factors). However, based on the presented results, we found that asthma prevalence by API (14.3%) is similar to that at the national level (4–17%)(41–46) and asthma prevalence by PAC (22.9%–31.4%) was close to that reported by Bisgaard and Szefler et al (32%).(47)

Since the subjects in our cohort were enrolled in the Mayo Clinic sick child care program, their asthma status might tend to be easily detected compared to those who were not enrolled.(18) Recognizing this limitation, this sampling approach had an advantage over clinic-based sampling, which is limited to only subjects seeking medical evaluation. Finally, our study subjects are predominantly Caucasians (86%) and generalizability of our study findings to other study settings might be limited.

Implications for future research, policy and practice

Asthma might not be a single disease, but a disease with heterogeneous phenotypes,(34–38) and therefore a potential discrepancy in asthma identified by API and PAC might reflect clinical heterogeneity of asthma and/or methodological heterogeneity in defining asthma. In this respect, combination of the two criteria which generates groups of children with asthma by different criteria might be a practical way to help clinicians identify children at risk for asthma early on and researchers identify a specific group of children with asthma suitable for their research purpose. Also, given the rising trend of using large-scale medical-record based datasets and natural language processing approaches for clinical research, making predetermined criteria for asthma such as PAC and retrospective API criteria examined in this paper available to retrospective studies will be scientifically meritorious and innovative since they enable a large-scale retrospective asthma research based on predetermined criteria for asthma, not self-reported asthma or ICD-9 code.

Conclusions

In conclusion, application of API to retrospective study for ascertaining asthma status is suitable. Our study findings need to be replicated and further validated by future studies with a larger sample size and the original API.

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Table 1

Operationalization of the original Asthma Predictive Index (API)

	Original Asthma Predictive Index	Operationalized Asthma Predictive Index
Early frequent wheezer	Parental report • a value ≥3 in the scale (scale: 1 to 5, from "very rarely" to "on most days")	≥2 wheezing in a year at any given time on history or examination during the first 3 years of life
Parental asthma [a]	Parental report (diagnosed by a physician)	**1** A history of parental asthma documented in parental medical record (OR) **2** patient(children)'s family history
Eczema	Parental report (diagnosed by a physician)	Physician-diagnosed atopic dermatitis or eczema documented
Allergic rhinitis	Parental report (diagnosed by a physician) • Hay fever or any other condition that made a child's nose stuffy, itchy, or runny apart from colds during the first 3 years of life and whether a doctor had said that these symptoms were due to allergies.	Physician-diagnosed allergic rhinitis or hay fever documented
Wheezing apart from cold	Parental report	Wheezing on examination without any symptom of cold [b]
Eosinophilia (≥4%)	Blood specimens obtained around at 1 year of age (10.9±0.6 month)	Blood specimen obtained prior to the original enrollment date (≤1 year of age)
Asthma Index date	N/A	The date when operationalized API was all met.

[a] Parental history of asthma was reviewed up to the last follow-up date.

[b] "Cold" was defined by URI or Cold documented, OR fever (≥100.4 F) plus runny/stuffy nose.

Table 2

Predetermined Asthma Criteria (PAC)

Patients were considered to have *definite* asthma if a physician had made a diagnosis of asthma and/or if each of the following three conditions were present, and they were considered to have *probable* asthma if only the first two conditions were present:

1 History of cough with wheezing, and/or dyspnea, OR history of cough and/or dyspnea plus wheezing on examination,

2 Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent, and

3 Two or more of the following:

- Sleep disturbance by nocturnal cough and wheeze
- Nonsmoker (14 years or older)
- Nasal polyps
- Blood eosinophilia higher than 300/uL
- Positive wheal and flare skin tests OR elevated serum IgE
- History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to an antigen
- Pulmonary function tests showing one FEV_1 or FVC less than 70% predicted and another with at least 20% improvement to an FEV_1 of higher than70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV_1
- Favorable clinical response to bronchodilator

Patients were excluded from the study if any of these conditions were present:

- Pulmonary function tests that showed FEV_1 to be consistently below 50% predicted or diminished diffusion capacity
- Tracheobronchial foreign body at or about the incidence date
- Hypogammaglobulinemia (IgG less than 2.0 mg/mL) or other immunodeficiency disorder
- Wheezing occurring only in response to anesthesia or medications

The following diseases excluded the patient from study if they occurred before the incidence date:

- Bullous emphysema or pulmonary fibrosis on chest radiograph
- PiZZ $alpha_1$-antitrypsin
- Cystic fibrosis
- Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis FVC forced vital capacity; FEV1, forced expiratory volume in 1 sec.

Table 3

Characteristics of study subjects (n=105)

	Child	Parents
Age (years, mean±SD)	5.75 (±1.47)	32.82 (±5.18)
Gender, n (%)		
Male	55 (52.4%)	8 (7.8)
Female	50 (47.6%)	95 (92.2)
Race/Ethnicity, n (%)		
White	90 (85.7%)	95 (90.5)
Non-whites	15 (14.3%)	10 (9,5)
Parents' educational status [a], n (%)		
High school diploma / GED	-	1 (1.0%)
Vocational school or some college	-	25 (23.8%)
College degree	-	39 (37.1%)
Professional or graduate degree	-	40 (38.1%)
Family history of asthma, n (%)	32 (30.5%)	-
Smoking exposure, n (%)	11 (10.5%)	-
History of atopic conditions, n (%)	23 (21.9%)	-
History of breast-feeding, n (%)	89 (84.8%)	-
Asthma prevalence, n (% and 95%CI)		
Asthma Predictive Index	15 (14.3, 95%CI: 8.9–22.2)	-
Definite by Predetermined Asthma Criteria	24 (22.9, 95%CI: 15.9–31.8)	-
Both by Predetermined Asthma Criteria [b]	33 (31.4, 95%CI: 23.3–40.8)	-
ICD-9 code	15 (14.3, 95%CI: 8.9–22.2)	-

[a] Higher one between parental education statuses

[b] Including both probable and definite asthma by PAC

Table 4

Agreement table between Asthma Predictive Index (API) and Predetermined Asthma Criteria (PAC)

		API (+)	API (−)	Total	Proportion of all agreement	kappa	SPAP[a]	SPAN[b]
Definite by PAC	(+)	14	10	24	89.5%	0.66 (p<0.01)	71.8%	93.6%
	(−)	1	80	81				
Both by PAC[c]	(+)	15	18	33	82.9%	0.53 (p<0.01)	62.5%	88.9%
	(−)	0	72	72				
Total		15	90	105				

[a] SPAP: Specific proportionate agreement for positive (2a / (2a+b+c); a (positive for both criteria), b (positive for API only), c (positive for PAC only), d (negative for both criteria));

[b] SPAN: Specific proportionate agreement for negative (2d / (2d+b+c));

[c] Either definite or probable asthma by PAC

Table 5

Association between known risk factors and asthma status by Asthma Predictive Index (API) and Predetermined Asthma Criteria (PAC)

		API		Definite by PAC		Both by PAC [a]	
		N (%)	**OR (95%CI)**	**N (%)**	**OR (95%CI)**	**N (%)**	**OR (95%CI)**
Gender	Male	9/55(16)	(reference)	15/55(27)	(reference)	19/55(36)	(reference)
	Female	6/50(12)	0.70 (0.23–2.12)	9/50(18)	0.59 (0.23–1.49)	14/50(28)	0.74 (0.32–1.69)
Race	White	13/90(14)	(reference)	21/90(23)	(reference)	29/90(32)	(reference)
	Non_white	2/15(13)	0.91 (0.18–4.52)	3/15(20)	0.82 (0.21–3.19)	4/15(27)	0.76 (0.22–2.61)
Smoking exposure	No	14/94(15)	(reference)	22/94(23)	(reference)	29/94(31)	(reference)
	Yes	1/11(9)	0.57 (0.07–4.82)	2/11(18)	0.73 (0.15–3.6)	4/11(36)	1.28 (0.35–4.72)
Atopic condition	No	8/82(10)	(reference)	14/82(17)	(reference)	21/82(26)	(reference)
	Yes	7/23(30)	**4.05 (1.28–12.8)**	10/23(43)	**3.74 (1.37–10.2)**	12/23(52)	**3.17 (1.22–8.25)**
Family history of asthma	No	4/73(5)	(reference)	11/73(15)	(reference)	18/73(25)	(reference)
	Yes	11/32(34)	**9.03 (2.60–31.4)**	13/32(41)	**3.86 (1.49–10.0)**	15/32(47)	**2.70 (1.12–6.47)**
Parental education	Lower	9/26(35)	(reference)	13/26(50)	(reference)	13/26(50)	(reference)
	Higher b	6/79(8)	**0.16 (0.05–0.50)**	11/79(14)	**0.16 (0.06–0.44)**	20/79(25)	**0.34 (0.13–0.85)**
Breast-feeding	No	5/16(31)	(reference)	8/16(50)	(reference)	10/16(63)	(reference)
	Yes	10/89(11)	**0.28 (0.08–0.97)**	16/89(18)	**0.22 (0.07–0.67)**	2389(26)	**0.21 (0.07–0.64)**

[a] Either definite or probable asthma by PAC;

[b] college degree or more; statistically significant in **bold**