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Background: Persistent childhood asthma is mainly atopy driven. However, limited data exist on the risk factors for childhood asthma phenotypes. 

Objective: We sought to identify risk factors at the first severe wheezing episode for current asthma 7 years later and separately for atopic and nonatopic asthma. 

Methods: One hundred twenty-seven steroid-naive children with the first severe wheezing episode (90% hospitalized/10% emergency department treated) were followed for 7 years. The primary outcome was current asthma at age 8 years, which was also analyzed separately as atopic and nonatopic asthma. Risk factors, including sensitization, viral cause, and other main asthma risk factors, were analyzed.

Results: At study entry, median age was 11 months (interquartile range, 6-16 months); 17% were sensitized, and 98% were virus positive. Current asthma (n = 37) at 8 years was divided into atopic (n = 19) and nonatopic (n = 18) asthma. The risk factors for current asthma at study entry were sensitization (adjusted odds ratio [OR], 12; P < .001), eczema (adjusted OR, 4.8; P = .014), and wheezing with rhinovirus (adjusted OR, 5.0; P = .035). The risk factors for nonatopic asthma were the first severe respiratory syncytial virus/rhinovirus-negative wheezing episode (adjusted OR, 8.0; P = .001), first wheezing episode at age less than 12 months (adjusted OR, 7.3; P = .007), and parental smoking (adjusted OR, 3.8; P = .028).

Conclusions: The data suggest diverse asthma phenotypes and mechanisms that can be predicted by using simple clinical markers at the time of the first severe wheezing episode. These findings are important for designing early intervention strategies for secondary prevention of asthma. (J Allergy Clin Immunol 2017;140:988-95.)

Key words: Allergy, atopy, bronchiolitis, child, eczema, rhinovirus, respiratory syncytial virus, sensitization, virus, wheeze, wheezing

Rhinovirus-induced wheezing, atopic characteristics, and severe illness are currently the most important early risk factors for childhood asthma in young hospitalized wheezing children.1-5 Persistent childhood asthma is mainly atopy driven.1,2,4-9 The modified Asthma Predictive Index (API), which is based mainly on atopic characteristics, has been used widely to assess the risk of school-age asthma, regardless of the asthma phenotype.10,11 There are studies investigating separately risk factors for atopic versus nonatopic asthma at school age.12-14 These studies have shown that classical atopic risk factors and also those considered in the modified API were associated with atopic but not nonatopic asthma.15 However, the study settings have been heterogeneous, being conducted on birth cohorts, and have not focused on the first wheezing episode. Awareness of which early risk factors predict atopic or nonatopic asthma in later childhood could also provide a novel approach into the mechanisms underlying childhood wheezing and asthma phenotypes.16 Simple clinical markers would also offer a way to find early intervention strategies to prevent asthma.17

The development of viral diagnostics has led to good recognition of rhinovirus-induced early severe wheezing as an important asthma risk factor.1,4,17-19 In addition, already at the first wheezing episode, cross-sectional studies have linked rhinovirus-induced wheezing to atopic characteristics.3,17-20 However, the asthma risk associated with rhinovirus-induced early wheezing has been included in asthma predictive indices in a limited way. These findings have led to a suggestion that asthma risk could be evaluated and potentially modified by targeted pharmacologic intervention at the time of the first wheezing episode.1,4,9,20,21

This is noteworthy because it has been shown that oral corticosteroid (OCS) treatment can decrease the risk of recurrent wheezing and asthma in hospitalized children with first-time wheezing affected by rhinovirus, eczema, or both.1,4,9,18,20

The aim of this study was to assess risk factors at the first severe wheezing episode in corticosteroid-naive children for school-age (age, 8 years) atopic and nonatopic asthma. Based on the previous literature, we hypothesized that the first rhinovirus-induced wheezing episode predicts later atopic asthma.

METHODS

Subjects

This study consisted of the Vinku and Vinku2 studies (vinku means wheeze in Finnish), which used a similar follow-up protocol carried out in the Department of Pediatrics, Turku University Hospital (Turku, Finland).1,4,18
Recruitment for the Vinku study was carried out in 2000-2002,1,4 and recruitment for the Vinku2 study was carried out in 2007-2010.18 The original aim of both studies was to evaluate the effect of a 3-day course of oral prednisolone for an acute severe wheezing episode using a randomized controlled trial design. To the current long-term follow-up analysis, we included all the steroid-naive children aged 3 to 23 months with their first severe wheezing episode from both studies (Fig 1).1,4,18 The exclusion criteria were use of inhaled corticosteroids (ICSs) or systemic corticosteroids before study entry, chronic nonatopic disease, and a need for intensive care.1,4,18 The studies were approved by the Ethics Committee of the Turku University Hospital and commenced only after obtaining written informed consent from the guardians.

Study protocol

In both studies, at study entry, venous blood was drawn, and nasopharyngeal aspirates were collected, and then the children were randomized to be given either oral prednisolone or a placebo.5 Study physicians (TJ, PL, and ML) recruited the patients to both studies and/or prospectively followed them at scheduled visits (2 weeks, 2 months, 12 months, 4 years [Vinku2 only], and 7 years). The children were examined at each visit, and parents were interviewed by using standardized questionnaires at long-term visits (see the parental questionnaire in this article’s Online Repository at www.jacionline.org).1,4,18,24 For the current analysis, all (100% [127/127]) children were followed from patient charts for asthma symptoms, medications, and laboratory tests for the full 7-year follow-up period (Fig 1 and Table I).4,9,18 In addition, 57% (73/127) of children attended the 7-year follow-up visit either in the Vinku study in 2007-2008 or in the Vinku2 study in 2014-2015, and parents of 13% (16/127) were interviewed by telephone at age 8 years (Fig 1). The study protocols were registered at ClinicalTrials.gov (Vinku: NCT00494624 and Vinku2: NCT00731575).

Virus, laboratory, and pulmonary function data

At study entry, the nasopharyngeal aspirates for viral diagnostics were drawn by using a standardized procedure.25,26 The nasopharyngeal aspirates were analyzed for adenovirus; coronaviruses (229E, OC43, NL63, and HKU1); enteroviruses; human bocavirus; human metapneumovirus; influenza A and B; parainfluenza virus types 1 to 4; polyomaviruses WU and KI; rhinovirus types A, B, and C; and respiratory syncytial virus (RSV). In both studies PCR was used to detect all viruses, and additional serology was done for human bocavirus.18,26,27 Also, the Vinku study used culture, antigen detection, PCR was used to detect all viruses, and additional serology was done for human bocavirus; human metapneumovirus; influenza A and B virus, parainfluenza virus types 1 to 3, rhinovirus types A and B, and RSV.18,26,27 Laboratory studies at study entry and age 8 years included allergen-specific serum IgE levels and blood eosinophil counts, which were measured by using routine diagnostics of the Central Laboratory of Turku University Hospital.

Long-term follow-up visit was arranged at age 8 years (Fig 1).4 Flow-volume spirometry [Jaeger MasterScreen system [Jaeger GmbH, Würzburg, Germany] in Vinku and Medikro Spirometry Software [Medikro Oy, Kuopio, Finland] in Vinku2] was measured in both studies with a bronchodilatation test, as was spirometry, at baseline and 15 minutes after 400 μg of albuterol (Ventoline) administered by means of inhalation through a spacer (Babyhaler; both from GlaxoSmithKline, Brentford, United Kingdom). In Vinku2 a free running test designed to measure bronchial hyperreactivity in children was used, as was spirometry, at baseline and 1, 5, and 10 minutes after exercise testing.11,28 The registered index was FEV1. Families were instructed to withhold the child’s regular asthma medications with ICSs during the preceding 4 weeks and to withhold salbutamol for 12 hours before spirometry. The test was rescheduled if the child was ill or taking salbutamol for asthma symptoms.

Outcome

The outcome of this study was the risk for current asthma at age 8 years, which was analyzed separately for atopic and nonatopic asthma. Risk factors were assessed at the time of the first severe wheezing episode (Table I).

Children were given a diagnosis of current asthma at age 8 years if they met 1 or more of the subsequent criteria during the preceding 12 months: reports from patient charts of doctor-diagnosed asthma and need for regular use of doctor-prescribed asthma therapy with ICSs for more than a month, use of OCSs for asthma exacerbations, acute asthma attack relieved by repeated use of bronchodilator, and/or hyperreactivity in spirometry defined as reversible airflow obstruction with an increase of 12% or greater in FEV1 in the bronchodilatation test or a decrease of 15% or greater in the exercise challenge test.11 Current atopic asthma at age 8 years was defined as asthma with laboratory-verified sensitization (95% [18/19]) or parent–chart– and parent-reported allergy symptoms (5% [1/19], Table II). Nonatopic asthma was defined as asthma without these features. Children were in remission if they were without asthma symptoms and therapy within 12 months before the study visit and/or without hyperreactivity on spirometry at the study visit.

Definitions

A wheezing episode was defined as a sharp whistling sound in expiratory breathing together with expiratory distress.1,18 Severe wheezing refers to the fact that 90% of the children were hospitalized and 10% were admitted to the emergency department of the tertiary hospital. Any sensitization was defined as positive IgE antibody results against common allergens (cutoff level of 0.35 kU/L for codfish, cow’s milk, egg, peanut, soybean, wheat, cat, dog, horse, birch, mugwort, timothy, Cledasporeum herbarum, and Dermatophagoides pteronyssinus; fluoroenzyme immunoassay, CAP FEIA; Phadatop Combi [Phadia, Uppsala, Sweden]).1,18,19 Aeroallergen sensitization was defined as IgE antibodies to any of the latter 8 allergens. Eczema was defined as a physician-made diagnosis with typical symptoms, including pruritus; typical morphology; and chronicity of disease.1,2 In this article viral findings were combined into 3 subgroups according to the viral etiology of the first wheezing episode at study entry: the rhinovirus group (rhinovirus alone or with other viruses, with RSV included), the RSV/adenovirus-negative group (other viruses or no viruses found),1,4,29

Abbreviations used

API: Asthma Predictive Index
ICS: Inhaled corticosteroid
OCS: Oral corticosteroid
OR: Odds ratio
RSV: Respiratory syncytial virus

FIG 1. Study flow chart. ICU, Intensive care unit.
Statistics
The risk for current asthma at age 8 years was assessed by using the unadjusted logistic regression model with baseline characteristics at study entry. Fisher exact tests were also used when there was 0 cell counts. The 3 viral subgroups were individually tested as dichotomous variables (the rhinovirus group vs the other 2 groups, the RSV group vs the other 2 groups, and the RSV/rhinovirus-negative group vs the other 2 groups). Multivariable analyses were adjusted with eczema, any sensitization, parental smoking, rhinovirus positivity, and age less than 12 months at study entry, all of which showed significant effects. Logistic regression analyses were also done for atopic and nonatopic asthma outcomes separately. Because of the time difference of the 2 cohorts (recruited either in 2000-2002 or 2007-2010), we also adjusted for cohort in the multivariable regression analyses to study whether a cohort was significant in the models or modified the magnitude of the other factors in the models. The effect of overlapping risk factors on the incidence of asthma at age 8 years was tested with $\chi^2$ or Fisher exact tests. A 2-sided $P$ value of less than .05 was regarded as statistically significant. Analyses were made with IBM SPSS 23.0 software (SPSS, Chicago, Ill).

RESULTS
Study population
Originally, 417 children were enrolled (Fig 1). Of these, 281 children were not eligible because of age of 2 years or greater, previous wheezing, ICS or OCS treatment, development of chronic

| TABLE I. Baseline patients’ characteristics at the first wheezing episode |
|-----------------------------|-----------------------------|-----------------------------|
| Risk factor | Current asthma at age 8 y | | |
| | All | Any | Atopic | Nonatopic |
|-----------------------------|-----------------------------|-----------------------------|
| Risk factor | 127 | 37 (29) | 19 (15) | 18 (14) |
| Age 3-11 mo | 68 (54) | 25 (68) | 10 (53) | 15 (83) |
| Age 12-23 mo | 59 (46) | 12 (32) | 9 (57) | 3 (17) |
| Male sex | 81 (64) | 24 (65) | 15 (79) | 9 (50) |
| Female sex | 46 (36) | 13 (35) | 4 (21) | 9 (50) |
| Eczema | 35 (28) | 16 (43) | 11 (58) | 5 (28) |
| Food | 22 (17) | 11 (31) | 11 (61) | 0 |
| Aerollergen | 6 (5) | 6 (17) | 6 (33) | 0 |
| B-eos $\geq 0.4 \times 10^3$/L | 41 (32) | 13 (37) | 9 (53) | 4 (22) |
| Parental asthma | 23 (18) | 10 (27) | 4 (21) | 6 (33) |
| Parental smoking | 51 (40) | 20 (54) | 9 (47) | 11 (61) |
| Breast-feeding $\geq 4$ mo | 55 (43) | 20 (54) | 10 (53) | 10 (56) |
| Rhinovirus alone or with other viruses, RSV included | 65 (51) | 22 (60) | 16 (84) | 6 (33) |
| RSV alone or with other viruses, rhinovirus excluded | 35 (28) | 5 (14) | 2 (11) | 3 (17) |
| RSV/rhinovirus-negative (other viruses or no viruses) | 26 (21) | 9 (24) | 0 | 9 (50) |

Values are shown as numbers (percentage within asthma subgroups) of subjects.
B-eos, Blood eosinophil count.
*Defined as IgE antibodies to any of the common allergens. See the Methods section for details.

| TABLE II. Study characteristics at age 8 years (n = 127) |
|-----------------------------|-----------------------------|
| Age (y) | 7.7 (7.1-8.2) |
| Follow-up time (y) | 6.8 (6.3-7.1) |
| Followed up from patient charts | 127 (100%) |
| Attended the 7-y follow-up visit and followed up from patient charts | 73 (57) |
| Any sensitization* | 31/73 (42) |
| Food | 19 (26) |
| Aerollergen | 23 (32) |
| Atopic asthma (based on specific IgE testing) | 13 |
| Nonatopic asthma (based on specific IgE testing) | 16 |
| Followed up from patient charts and parental interviews | 54 (43) |
| Only patient charts | 38 (30) |
| Allergy testing (allergen-specific IgE measurement or skin prick test) | 16 |
| Atopic asthma (based on specific IgE testing) | 3 |
| Nonatopic asthma (based on specific IgE testing) | 1 |
| Patient charts and parental interviews | 16 (13) |
| Allergy testing (allergen-specific IgE measurement or skin prick test) | 2 |
| Atopic asthma (based on specific IgE testing) | 2 |
| Nonatopic asthma (based on charts and questionnaires) | 1 |
| Asthma ever during follow-up | 67 (53) |
| Asthma in remission by end of follow-up | 30 (24) |
| Current asthma | 37 (29) |
| Atopic | 19 (15) |
| Nonatopic | 18 (14) |

Values are shown as medians (interquartile ranges) or numbers (percentages) of subjects.
*Defined as IgE antibodies to any of the common allergens. See the Methods section for details.
TABLE III. Risk factors at the first wheezing episode for current asthma at age 8 years

| Unadjusted analyses | Current asthma at age 8 y |
|---------------------|--------------------------|
|                      | Any                      | Atopic                  | Nonatopic               |
|                      | OR  | 95% CI | P value | OR  | 95% CI | P value | OR  | 95% CI | P value |
| Age 3-11 mo          | 2.3 | 1.0-5.0 | .045    | 0.96 | 0.36-2.5 | .93    | 5.3 | 1.4-19 | .012    |
| Male sex             | 1.1 | 0.48-2.4 | .87    | 2.4 | 0.74-7.7 | .15    | 0.51 | 0.19-1.4 | .19    |
| Eczema               | 2.7 | 1.2-6.5 | .013    | 4.8 | 1.7-13  | .002   | 1.0 | 0.33-1.0 | .98    |
| Any sensitization*   | 3.0 | 1.2-7.8 | .023    | 13  | 4.3-41  | <.001  | NA  | NA    | .041    |
| Food                 | 3.0 | 1.2-7.8 | .023    | 13  | 4.3-41  | <.001  | NA  | NA    | .041    |
| Parental smoking     | NA  | NA     | <.001‡  | NA  | NA     | <.001† | NA  | NA    | .59‡    |
| Aeroallergen         | NA  | NA     | <.001‡  | NA  | NA     | <.001† | NA  | NA    | .59‡    |
| B-eos 20.4 × 109/L   | 1.3 | 0.57-2.9 | .55    | 2.6 | 0.93-7.4 | .067   | 0.53 | 0.16-1.7 | .30    |
| Parental asthma      | 2.1 | 0.83-5.4 | .12    | 1.2 | 0.36-4.0 | .76    | 2.6 | 0.86-7.9 | .089   |
| Parental smoking     | 2.2 | 0.99-4.7 | .053  | 1.4 | 0.51-3.7 | .53    | 2.6 | 0.94-7.3 | .065   |
| Breast-feeding ≥ 4 mo| 1.8 | 0.85-4.0 | .12    | 1.6 | 0.59-4.1 | .38    | 1.8 | 0.65-4.9 | .26    |
| Rhinovirus alone or with other viruses, RSV included | 1.6 | 0.74-3.5 | .23    | 6.4 | 1.8-23  | .005   | 0.42 | 0.15-1.2 | .11    |
| RSV alone or with other viruses, rhinovirus excluded | 0.31 | 0.11-0.88 | .028  | 0.27 | 0.06-1.2 | .089   | 0.48 | 0.13-1.7 | .27    |
| RSV/rhinovirus negative | 1.4 | 0.55-3.5 | .49    | NA  | NA     | .013§  | 5.4 | 1.9-16 | .002    |

Risk was assessed by using the logistic regression model. Unadjusted analyses were performed for age 3 to 11 months versus age 12 to 23 months; male versus female sex; eczema versus no eczema; sensitization to any allergen, food, or aeroallergen versus no sensitization; B-eos count of 0.4 × 109/L or greater versus B-eos count of less than 0.4 × 109/L; parental asthma and smoking versus no asthma or smoking; and duration of breast-feeding of 4 months or greater versus less than 4 months. Multivariable analyses were adjusted with age 3 to 11 months, eczema, any sensitization, parental smoking, and rhinovirus positivity or negativity (P = .05 in unadjusted analyses). In NA cells P values were assessed by using the Fisher exact test because of 0 cell counts. Boldface and italic font indicate statistical significance.

B-eos, Blood eosinophil count; NA, not applicable.

*Defined as IgE antibodies to any of the common allergens. See the Methods section for details.

†NA for all aeroallergen-sensitized children who had atopic asthma.

‡NA for none of the sensitized children who had nonatopic asthma.

§NA for none of the RSV/rhinovirus-negative children who had atopic asthma.

Current asthma was specified to be atopic or nonatopic asthma.

Patients’ characteristics

At study entry, the median age was 11 months (interquartile range, 6-16 months), 64% of the children were boys, 17% were sensitized, 28% had eczema, and 98% were virus positive (Table I). At the end of the follow-up period, median age was 7.7 years (interquartile range, 7.1-8.2 years; Table II). Overall, during follow-up, 67 (53%) children were given a diagnosis of recurrent wheezing or asthma ever, and regular long-term asthma control therapy with an ICS was started. Thirty (24%) children with asthmatic symptoms were in remission by the end of follow-up, of whom 23 (77%) were boys, 12 (24%) were sensitized at study entry, and 35 (69%) were rhinovirus positive, and the mean age was 12.6 months (range, 3.5-23 months [SD, 5.8 months]). Current asthma was diagnosed in 37 (29%) of 127 children and specified to be atopic asthma in 19 (15%) and nonatopic asthma in 18 (14%; Tables I and II and see allergy testing characteristics and the Results section in this article’s Online Repository at www.jacionline.org).

Risk factors for current asthma at school age

At study entry, the unadjusted risk factors (listed in the Table I) for current asthma were sensitization (odds ratio [OR], 3.0; 95% CI, 1.2-7.8), eczema (OR, 2.7; 95% CI, 1.2-6.5), and the first wheezing episode at age less than 12 months (OR, 2.3; 95% CI, 1.0-5.0; all P < .05; Table III). In the multivariable analyses the first wheezing episode at age less than 12 months (OR, 3.6; 95% CI, 1.4-9.5), sensitization (OR, 3.5; 95% CI, 1.1-11), eczema (OR, 2.9; 95% CI, 1.1-7.3), and parental smoking (OR, 2.8; 95% CI, 1.2-6.9) remained a significant risk (all P < .05, Table III).

Risk factors for current atopic asthma at school age

Current asthma was specified to be atopic or nonatopic asthma. The unadjusted risk factors for current atopic asthma were...
Overlapping characteristics

The incidence of current asthma increased cumulatively if the child had concomitant risk characteristics at study entry (Fig 2 and Table IV). The incidence of asthma was high with both eczema and sensitization (70%) versus only one (37%) or versus neither (21%, P = .003), respectively, with sensitization and rhinovirus (59%/24%/25%, P = .015), eczema and rhinovirus (55%/27%/21%, P = .018), or age less than 12 months and parental smoking (56%/23%/21% with age 13-23 months and no parental smoking, P = .004).

The incidence of atopic asthma increased cumulatively when the concomitant rhinovirus etiology was added to the atopic risk factors at study entry (Table IV). The incidence of atopic asthma was high with eczema and sensitization (70%) versus only one (23%) or versus neither (4%; P < .001), with sensitization and rhinovirus (59%/12%/4%, P < .001), eczema and rhinovirus (45%/15%/15%, P < .001), blood eosinophil counts of 0.4 × 10^9/L or greater and rhinovirus (27%/18%/5%, P = .015), or parental asthma and rhinovirus (29%/20%/6%, P = .038; Fig 2 and Table IV).

The incidence of nonatopic asthma increased with age less than 12 months and RSV/rhinovirus-negative etiology (50%) versus only one (15%) or versus neither (2%, P < .001). Respectively, age less than 12 months and parental smoking increased the asthma incidence (33%) versus only one (12%) versus age of 13 to 23 months and no parental smoking (3%, P = .003; Table IV).

Risk factors for current nonatopic asthma at school age

The unadjusted risk factors for nonatopic asthma were the RSV/rhinovirus-negative etiology (OR, 5.4; 95% CI, 2.3-128), age less than 12 months (OR, 7.3; 95% CI, 1.7-31), and parental smoking (OR, 3.8; 95% CI, 1.2-13) remained significant risk (all P < .05, Table III). In multivariable analyses sensitization (OR, 12; 95% CI, 3.0-44), rhinovirus etiology (OR, 5.0; 95% CI, 1.1-22), and eczema (OR, 4.8; 95% CI, 1.4-17) remained a significant risk (all P < .05, Table III).

Sensitivity analyses

Sensitivity analyses in the subset of children with allergy testing (n = 91) did trend in the same direction as the main results (Table III and see Table E1 in this article’s Online Repository at www.jaconline.org). Sensitivity analyses of children without allergy testing (n = 36) were unsuitable for statistical analyses because of several 0 cell counts and the small number of outcomes (1 atopic asthma and 1 nonatopic asthma).

DISCUSSION

This is the first study assessing risk factors at the time of the first severe wheezing episode for atopic and nonatopic asthma phenotypes at age 8 years. Its novelty is in the addition of rhinovirus etiology to the phenotype-based risk assessment and showing that the first rhinovirus-induced wheezing alone or together with sensitization and/or eczema predicts atopic but not nonatopic school-aged asthma. These results are noteworthy because currently the school-age asthma risk of children with recurrent wheezing episodes is evaluated by using the modified API, which includes closely atopy-related characteristics but does not differentiate between asthma phenotypes.10,11 The risk factors for nonatopic asthma were first wheezing before age 12 months, parental smoking, and the RSV/rhinovirus-negative first wheezing episode.

We show that the rhinovirus-induced first severe wheezing episode predicts atopic asthma at school age in this population-based study. Previously, early-life rhinovirus-induced wheezing has been linked to school-aged asthma in birth cohorts.6,7 However, the Childhood Origins of Asthma and the Australian birth cohort studies are high-risk cohorts because of including only wheezing children with a familial predisposition to atopic asthma. Therefore the data might reflect a different susceptibility of atopic airways to rhinovirus infections. On the contrary, the Tucson Children’s Respiratory Study is a nonselected population-based birth cohort that included healthy infants. These investigators observed that children with early-life RSV-induced lower respiratory tract infections had frequent wheeze by school age, but the risk of wheezing decreased, being insignificant by age 13 years.30 In addition, there was no link between RSV infections and sensitization.30 Previous studies on different childhood asthma phenotypes noticed that atopic risk factors from the modified API were
TABLE IV. Effect of concomitant characteristics at study entry for incidence of current asthma at age 8 years

| Risk factors                                      | Current asthma at age 8 y |
|--------------------------------------------------|---------------------------|
|                                                  | Any | Atopic | Nonatopic |
| Age 3-11 mo and no rhinovirus*                    | 13/38 (34) | 3/38 (8) | 10/38 (26) |
| Age 12-23 mo or rhinovirus                        | 14/53 (26) | 7/53 (13) | 7/53 (13) | .014 |
| Age 12-23 mo and rhinovirus                       | 10/36 (28) | 9/36 (25) | 1/36 (3) |
| No eczema and no sensitization†                   | 16/77 (21) | 3/77 (4) | 13/77 (17) |
| Eczema or any sensitization                       | 13/35 (37) | 8/35 (23) | <.001 |
| Eczema and any sensitization                      | 7/10 (70) | 7/10 (70) | 0/10 (0) |
| Eczema and rhinovirus                             | 10/47 (21) | 1/47 (2) | 9/47 (19) |
| Eczema or rhinovirus                              | 16/60 (27) | 9/60 (15) | <.001 |
| Eczema and rhinovirus                             | 11/20 (55) | 9/20 (45) | 2/20 (10) |
| No parental asthma and no rhinovirus              | 14/56 (25) | 2/56 (4) | 12/56 (21) |
| Any sensitization or rhinovirus                   | 12/56 (24) | 6/50 (12) | <.001 |
| Any sensitization and rhinovirus                  | 10/17 (59) | 10/17 (59) | 0/17 (0) |
| B-eos <0.4 × 10^9/L and no rhinovirus             | 14/56 (25) | 3/56 (5) | 11/56 (20) |
| B-eos ≥0.4 × 10^9/L or rhinovirus                 | 12/38 (32) | .65 | 7/38 (18) | .015 |
| B-eos >0.4 × 10^9/L and rhinovirus                | 11/33 (33) | 9/33 (27) | 2/33 (6) |
| No parental asthma and no rhinovirus              | 11/51 (22) | 3/51 (6) | 8/51 (16) |
| Parental asthma or rhinovirus                     | 20/59 (34) | .20 | 12/59 (20) | .038 |
| Parental asthma and rhinovirus                    | 6/14 (43) | 4/14 (29) | 2/14 (14) |
| Age 12-23 mo with RSV or rhinovirus               | 10/47 (21) | 9/47 (19) | 1/47 (2) |
| Age 3-11 mo or RSV/rhinovirus negative†           | 20/66 (30) | .11 | 10/66 (15) | .21 |
| Age 3-11 mo and RSV/rhinovirus-negative           | 7/14 (50) | 0/14 (0) | 7/14 (50) |
| Age 12-23 mo and no parental smoking              | 7/33 (21) | 6/33 (18) | 1/33 (3) |
| Age 3-11 mo or parental smoking                   | 15/65 (23) | .004 | 7/65 (11) | .33 |
| Age 3-11 mo and parental smoking                  | 15/27 (56) | 6/27 (22) | 9/27 (33) | .003 |

Values are shown as numbers (percentages) of subjects. *P values were assessed by using χ² or Fisher exact tests, indicating whole-group comparisons. Boldface and italic font indicate statistical significance.

B-eos, Blood eosinophil count.

* Alone or with other viruses, RSV included.
† Defined as IgE antibodies to any of the common allergens. See the Methods section for details.
‡ With other viruses or no viruses.

associated with atopic but not nonatopic asthma. However, their study settings were different from ours because they were conducted on birth cohorts, not focused on the first wheezing episode, included older children, or included no virus etiology of the wheezing. Unlike these studies, we found no clear asthma-reducing effect from breast-feeding or, conversely, an asthma-increasing effect from male sex. We showed that parental smoking predicted nonatopic asthma.8,12,13 On the contrary, parental asthma was insignificant in the univariable analysis, sensitization, and eczema status, and especially the combination of these 3, might enable the asthma risk assessment already at the time of the first wheezing episode because rhinovirus-sensitive viral diagnostics are widely available.2,3

The underlying susceptibility to atopic disorders and viral triggers might be the true asthma risk factor, and thus interplay between sensitization and viral infections is likely to be involved. The Childhood Origins of Asthma study group showed the chronological order of causality in a statistical model (ie, early-life aeroallergen sensitization precedes rhinovirus illnesses and asthma). However, the slow development of aeroallergen sensitization decreases its value in asthma risk indices during early life, whereas food sensitization is likely to develop earlier, predicting aeroallergen sensitization and future asthma risk.38 The rhinovirus-associated asthma risk has been explained by an increased susceptibility to lower airway rhinovirus infections in patients with pronounced atopic characteristics (allergen-specific IgE sensitization, blood eosinophilia, eczema, maternal atopic eczema, and/or increased IL-4, IL-5, and IL-13 responses in airway secretions), damaged airway epithelium, and decreased IFN-α/β/γ/λ and IL-10 responses in airway
shown that OCSs can affect long-term asthma outcomes. They were steroid naïve; that is, they received no ICS/OCS before or as a treatment for this first wheezing. This is of note because it has been shown that OCSs can affect long-term asthma outcomes.

The strengths of our study include complete analysis of atopic characteristics and viral etiology and a careful long-term follow-up. The inclusion rate was high (93%), 100% of the children were followed up from patient charts, and 57% of the children attended the study visit at age 8 years. This study set-up is different from birth cohort studies by being population-based, with all children experiencing their first severe wheezing episode. They were steroid naïve; that is, they received no ICS/OCS before or as a treatment for this first wheezing. This is of note because it has been shown that OCSs can affect long-term asthma outcomes.

To minimize selection bias, we included children who did not attend the long-term study visit. People adhere to follow-up studies that concern their interests, in our case asthmatic patients. To maximize the objectivity, we regarded children with bronchial hyperreactivity in spirometry as asthmatic patients who were without a proper pediatrician-set asthma diagnosis. This reflects the real-life situation and completes the asthma outcome. To minimize the heterogeneity and make our results more generalizable, we included only children with physician-confirmed wheezing (vs bronchiolitis with or without wheezing in previous studies).

In addition, this study has limitations. The sample size was rather small after excluding the steroid-treated patients, and rhinovirus typing was not done.

In conclusion, we show that sensitization, eczema, and/or rhinovirus etiology at the first severe wheezing episode predict atopic but not nonatopic asthma at school age. On the contrary, first wheezing episode before age 12 months, parental smoking, and RSV/rhinovirus-negative first wheezing episode predict nonatopic asthma at school age. This observation could provide a novel approach to the mechanisms underlying childhood wheezing and asthma, prognostics, and potentially different therapies of distinct asthma phenotypes. It would be encouraging to find future therapeutic interventions to prevent asthma, but this warrants further study.

Virology and atopic status are worth assessing early in children with severe wheezing to recognize those at high asthma risk and to distinguish the risk between asthma phenotypes.

We thank Mrs Tiina Peromaa for her valuable help in conducting the exercise tests and Tero Vahlberg, MSc, for his contribution to statistical analyses.

Key messages
- Sensitization, eczema, and rhinovirus etiology at the first severe wheezing episode predict atopic asthma at school age, whereas RSV/rhinovirus-negative etiology, age less than 12 months, and parental smoking predict nonatopic asthma.
- The data suggest diverse asthma phenotypes and mechanisms that can be predicted by using simple clinical markers at the time of the first severe wheezing episode. Findings are important in designing phenotype-based therapies and early intervention strategies for asthma secondary prevention.

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