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Rhinovirus-induced first wheezing episode predicts atopic but not nonatopic asthma at school age

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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 atopic 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.[8,12-14] 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.[10] 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.[15] Simple clinical markers would also offer a way to find early intervention strategies to prevent asthma.[16]

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.[2,3,17-20] 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.[1-5,17-19,22,23]

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]

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

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.[1,18] The studies were approved by the Ethics Committee of the Turku University Hospital and commenced only after obtaining written informed consent from the guardians.

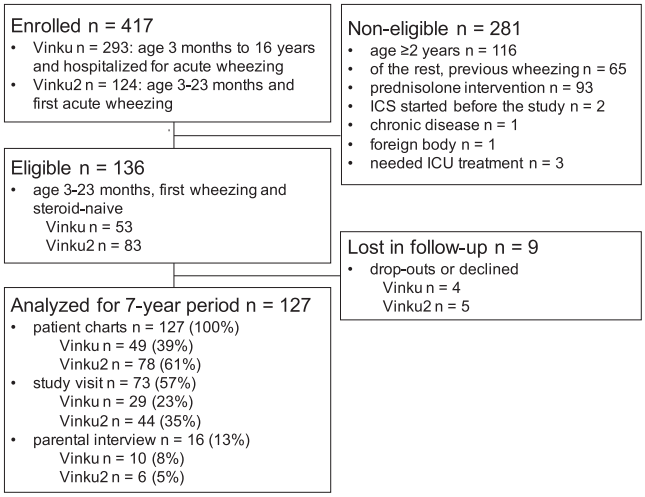

FIG 1. Study flow chart. *ICU*, Intensive care unit.

Study protocol

In both studies, at study entry, venous blood was drawn, and nasopharyngeal aspirate was collected, and then the children were randomized to be given either oral prednisolone or a placebo.[4] 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, and/or serology for adenovirus, enteroviruses, human metapneumovirus, influenza A and B virus, parainfluenza virus types 1 to 3, rhinovirus types A and B, and RSV.[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 FEV_1. 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 FEV_1 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 patient 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.[11] 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, *Cladosporium herbarum*, and *Dermatophagoides pteronyssinus*; fluoroenzyme immunoassay, CAP FEIA, Phadiatop Combi [Phadia, Uppsala, Sweden]).[4,18] 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.[11] 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 group (RSV alone or with other viruses, with rhinovirus excluded), and the RSV/rhinovirus-negative group (other viruses or no viruses found).[1,4,29]

TABLE I. Baseline patients' characteristics at the first wheezing episode

	All	Current asthma at age 8 y		
		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)
Any sensitization*	22 (17)	11 (31)	11 (61)	0
Food	22 (17)	11 (31)	11 (61)	0
Aeroallergen	6 (5)	6 (17)	6 (33)	0
B-eos $\geq 0.4 \times 10^9$/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 ≥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)
Aeroallergen	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
Atopic asthma (based on charts and questionnaires)	1
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.

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 χ^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 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		
Risk factors	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***‡
Aeroallergen	NA	NA	***<.001***†	NA	NA	***<.001***†	NA	NA	.59‡
B-eos ≥0.4 × 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***
Multivariable analyses									
Age 3-11 mo	***3.6***	***1.4-9.5***	***.009***	1.8	0.49-6.4	.38	***7.3***	***1.7-31***	***.007***
Eczema	***2.9***	***1.1-7.3***	***.028***	***4.8***	***1.4-17***	***.014***	0.66	0.18-2.4	.53
Any sensitization	***3.5***	***1.1-11***	***.030***	***12***	***3.0-44***	***<.001***	‖	‖	‖
Parental smoking	***2.8***	***1.2-6.9***	***.021***	2.3	0.63-8.5	.21	***3.8***	***1.2-13***	***.028***
Rhinovirus alone or with other viruses, RSV included	1.5	0.61-3.7	.38	***5.0***	***1.1-22***	***.035***	—	—	—
RSV/rhinovirus negative	—	—	—	—	—	—	***8.0***	***2.3-28***	***.001***

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 × 10^9/L or greater versus B-eos count of less than 0.4 × 10^9/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.

‖Not included in the model because there was no sensitization at study entry.

disease after enrollment, or need for intensive care during hospitalization, and 136 children were eligible for long-term follow-up. Nine (7%) children declined the follow-up or were lost, of whom 8 (89%) were boys, 3 (33%) were sensitized, and 3 (33%) were rhinovirus positive, and their mean age was 15.2 months (SD, 8.4 months) at study entry. Finally, 127 (93% of eligible) children with first-time wheeze completed the follow-up and were included in this analysis. Of these children, 49 (39%) were from the Vinku study, and 78 (61%) were from the Vinku2 study.

All children were followed from patient charts for asthma symptoms, medications, and laboratory tests for the full 7-year follow-up period. In addition, 73 (57%) children attended the 7-year follow-up visit, whereas of the rest, 54 (43%) were followed up from patient charts (n = 38); the parents were also interviewed (n = 16, Fig 1 and Table II).

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

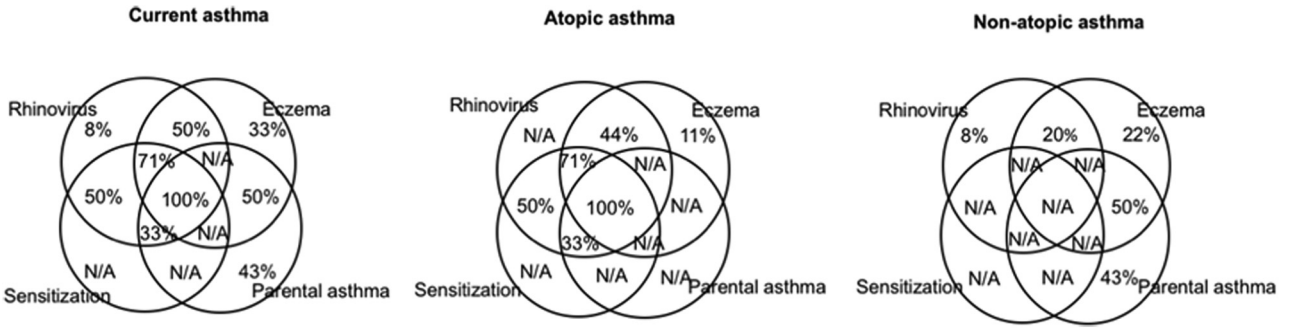

FIG 2. Incidence of current asthma phenotypes at age 8 years in children (n = 127) with sole and overlapping atopic risk factors (sensitization, eczema, rhinovirus, and parental asthma) at the first wheezing episode. *N/A*, Not applicable because there were no cases with risk factors.

sensitization (OR, 13; 95% CI, 4.3-41), rhinovirus etiology of the first wheezing episode (OR, 6.4; 95% CI, 1.8-23), and eczema (OR, 4.8; 95% CI, 1.7-13; 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).

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, 1.9-16) and age less than 12 months (OR, 5.3; 95% CI, 1.4-19; all $P < .05$, Table III). In multivariable analyses RSV/rhinovirus-negative etiology (OR, 8.0; 95% CI, 2.3-28), 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). When the multivariable regression analyses were also adjusted for the Vinku or Vinku2 cohorts, they were not significant in the multivariable models for any atopic or nonatopic asthma and did not modify the magnitude of the other risk factors.

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).

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.jacionline.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

	Current asthma at age 8 y					
Risk factors	**Any**	***P* value**	**Atopic**	***P* value**	**Nonatopic**	***P* value**
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)	.71	7/53 (13)	.11	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)	***.003***	8/35 (23)	***<.001***	5/35 (14)	.37
Eczema and any sensitization	7/10 (70)		7/10 (70)		0/10 (0)	
No eczema and no rhinovirus	10/47 (21)		1/47 (2)		9/47 (19)	
Eczema or rhinovirus	16/60 (27)	***.018***	9/60 (15)	***<.001***	7/60 (12)	.46
Eczema and rhinovirus	11/20 (55)		9/20 (45)		2/20 (10)	
No sensitization and no rhinovirus	14/56 (25)		2/56 (4)		12/56 (21)	
Any sensitization or rhinovirus	12/56 (24)	***.015***	6/50 (12)	***<.001***	6/50 (12)	.072
Any sensitization and rhinovirus	10/17 (59)		10/17 (59)		0/17 (0)	
B-eos $<0.4 \times 10^9$/L and no rhinovirus	14/56 (25)		3/56 (5)		11/56 (20)	
B-eos $\geq 0.4 \times 10^9$/L or rhinovirus	12/38 (32)	.65	7/38 (18)	***.015***	5/38 (13)	.20
B-eos $\geq 0.4 \times 10^9$/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***	8/59 (14)	.95
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	10/66 (15)	***<.001***
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	8/65 (12)	***.003***
Age 3-11 mo and parental smoking	15/27 (56)		6/27 (22)		9/27 (33)	

Values are shown as numbers (percentages) of subjects. *P* values were assessed by using χ^2 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.[8,10-14,31] However, their study settings were different from ours because they were conducted on birth cohorts, not focused on the first wheezing episode,[8,12-14] included older children,[12] or included no virus etiology of the wheezing.[8,12-14] Unlike these studies, we found no clear asthma-reducing effect from breast-feeding or, conversely, an asthma-increasing effect from male sex.[8,12-14] We showed that parental smoking predicted nonatopic asthma.[8,12,13] On the contrary, parental asthma was insignificant in the univariable model and thus was not included in the multivariable model. However, it was associated with atopic asthma with concomitant rhinovirus and/or atopic risk factors.

This population-based study consisted only of steroid-naive, first-time wheezing children who were mainly hospitalized with severe wheezing (90% hospitalized and 10% treated at the emergency department of a tertiary hospital), one third of whom had asthma 7 years later. Therefore our results could be adapted to hospitalized first-time wheezing children and might provide new perspective when estimating their future asthma risk. Bønnelykke et al[32] found no specific viral or bacterial risk factors for school-aged asthma and hence suggested that the underlying susceptibility to triggers instead of the specific triggering agent was the important asthma risk factor. We agree with the host-dependent susceptibility but suggest a trigger dependence so that rhinovirus itself would act as an important early marker uncovering the underlying susceptibility to asthma in atopic asthma-prone children by manifesting expiratory wheezing.[1,4,9,21] Like Bønnelykke et al,[32] we did not find rhinovirus to be a risk factor for current overall asthma (including atopic and nonatopic), but we did find it to be a significant risk factor for atopic asthma. Concurrently, RSV/rhinovirus-negative wheezing was associated with nonatopic asthma, probably because the children with rhinovirus-positive wheezing had atopic asthma. Infant wheezing might be an asthma risk marker because it often is rhinovirus induced, particularly in older children.[6,19] However, the rhinovirus-induced wheezing has been included in asthma-predictive indices in a limited way. We suggest that the investigation of virus etiology, 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.[1,2,4,7,19,21,33]

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.[2,5,15,34,35] 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).[2] 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.[6,9,36,37] The rhinovirus-associated asthma risk has been explained by 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

secretions or cells.[33] Interactions between sensitization-associated and innate antiviral pathways might lead to more severe viral illnesses in already sensitized children when a viral respiratory tract infection starts a sensitization-dependent cascade that augments and maintains airway inflammation.[35]

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.[31] They were steroid naive; 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.[1,4,9,18,20] 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).[17]

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.[15] It would be encouraging to find future therapeutic interventions to prevent asthma, but this warrants further study.[16] 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.

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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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