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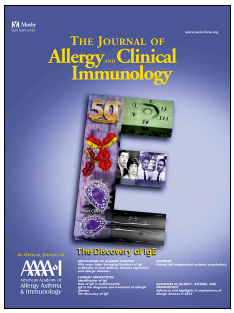

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Minna Lukkarinen, MD, Annamari Koistinen, MD, Riitta Turunen, MD, Pasi Lehtinen, MD, Tytti Vuorinen, MD, Tuomas Jartti, MD

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

Minna Lukkarinen, MD,[a] Annamari Koistinen, MD,[a] Riitta Turunen, MD,[a,b] Pasi Lehtinen, MD,[a] Tytti Vuorinen, MD,[b] and Tuomas Jartti, MD,[a]

From [a]Department of Paediatrics, University of Turku and Turku University Hospital; [b]Department of Clinical Virology, Division of Microbiology and Genetics, Turku University Hospital, Turku, Finland.

Corresponding author and reprint requests:
Dr. Minna Lukkarinen, Department of Paediatrics, Turku University Hospital,
P.O. Box 52, 20521 Turku, FINLAND, E-mail: mimapo@utu.fi, Tel: +358 40 7017876.

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Abstract

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

Objective: To identify risk factors at the first severe wheezing episode for the current asthma 7 years later, and separately for atopic and non-atopic asthma.

Methods: One hundred and twenty-seven steroid-naive children with the first severe wheezing episode (90% hospitalized/10% emergency room treated) were followed for 7 years. The primary outcome was current asthma at age 8 years, which was also analyzed separately as atopic and non-atopic asthma. Risk factors including sensitization, viral etiology 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 to atopic (n = 19) and non-atopic (n = 18) asthma. The risk factors for current atopic asthma at study entry were sensitization (adjusted odds ratio 12; *P*<.001), eczema (4.8; *P* .014, respectively) and wheezing with rhinovirus (5.0; *P* .035). The risk factors for non-atopic asthma were the first severe respiratory syncytial virus/rhinovirus-negative wheezing episode (adjusted odds ratio 8.0; *P* .001), first wheezing episode at age <12 months (7.3; *P* = .007, respectively), and parental smoking (3.8; *P* .028).

Conclusions: The data suggest diverse asthma phenotypes and mechanisms that can be predicted using simple clinical markers at the time of the first severe wheezing episode. Findings are important in designing early intervention strategies for secondary prevention of asthma.

(ClinicalTrials.gov number, NCT00494624 and NCT00731575)

Key Message:

- Sensitization, eczema and the rhinovirus etiology at the first severe wheezing episode predict atopic asthma at school-age, whereas RSV-/rhinovirus-negative etiology, age <12 months and parental smoking predict non-atopic asthma.
- The data suggest diverse asthma phenotypes and mechanisms that can be predicted 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.

Capsule summary:

The data suggest that sensitization, eczema and the rhinovirus etiology and atopic characteristics already at the first severe wheezing episode predict atopic but not non-atopic asthma at age 8 years, and therefore are worth assessing early.

Short title: Rhinovirus wheeze predicts atopic asthma

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

Abbreviations:

API	Asthma Predictive Index
B-eos	Blood eosinophil count
CI	Confidence interval
COAST	Childhood Origins of ASThma
FEV1	Forced expiratory volume in one second

ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IL	Interleukin
IQR	Interquartile range
OCS	Oral corticosteroids
OR	Odds ratio
PCR	Polymerase chain reaction
RCT	Randomized controlled trial
RSV	Respiratory syncytial virus
SD	Standard deviation

The 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 (mAPI), based mainly on atopic characteristics, has widely been used to assess risk of school-age asthma regardless of the asthma phenotype.[10 11] There are studies investigating separately risk factors for atopic *vs.* non-atopic asthma at school-age.[8, 12-14] These studies have shown that classical atopic risk factors, also those considered in the modified API, were associated with atopic but not with non-atopic asthma.[10] However, the study settings have been heterogeneous being conducted on birth cohorts, and have not focused not on the first wheezing episode. Awareness of which early risk factors predict atopic or non-atopic asthma in later childhood could also provide 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 pharmacological intervention already at the time of the first wheezing episode.[1, 4, 9, 20, 21] This is noteworthy since it has been shown that oral corticosteroid (OCS) treatment may decrease the risk of recurrent wheezing and asthma in hospitalized first-time wheezing children affected by rhinovirus and/or eczema.[1, 4, 9, 18, 20] Our study aim was to assess risk factors at the first severe wheezing episode in corticosteroid-naive children for school-age (age 8 years) atopic and non-atopic asthma, and to add the rhinovirus

114 etiology to the risk assessment. Based on the previous literature, we hypothesized that the first

115 rhinovirus-induced wheezing episode predicts later atopic asthma.[1-5, 17-19, 22, 23]

116

Methods

Subjects

This study consisted of Vinku and Vinku2 studies (*vinku* means wheeze in Finnish) using similar follow-up protocol, carried out in the Department of Pediatrics, Turku University Hospital (Turku, Finland).[1, 4, 18] The recruitment for the Vinku study was carried out in 2000-2002 [1, 4], and for the Vinku2 study 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 design of a randomized controlled trial (RCT). To the current long-term follow-up analysis, we included from both studies all the steroid-naive children aged 3-23 months with the first severe wheezing episode from both studies (Fig. 1).[1, 4, 18] The exclusion criteria were the use of inhaled or systemic corticosteroids before the study entry, chronic non-atopic 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.

Study protocol

In both studies, at study entry, venous blood was drawn and nasopharyngeal aspirate collected, and then the children were randomized to be given either oral prednisolone or a placebo.[4] Study physicians (TJ, PL, 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 using standardized questionnaires at the long-term visits (Online supplements).[1, 4, 24 18]

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 1).[4, 9, 18] In addtiton, 57% (73/127) of children attended to the 7-year follow-up visit either in Vinku study in 2007-2008, or in Vinku2 study in 2014-2015, and parents of 13% (16/127) were interviewed by phone 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 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 1-4, polyomaviruses WU and KI, rhinovirus types A, B and C, and respiratory syncytial virus (RSV). In both studies, polymerase chain reaction (PCR) was used to detect all viruses, and additional serology for human bocavirus.[18 27, 28] Vinku study used also culture, antigen detection and/or serology for adenovirus, enteroviruses, human metapneumovirus, influenza A and B virus, parainfluenza virus types 1-3, rhinovirus types A and B, and RSV.[27, 28] Laboratory studies at study entry and at age 8 years included allergen-specific serum immunoglobulin (Ig) E levels and blood eosinophil (B-Eos) counts, which were measured by the routine diagnostics of the Central Laboratory of Turku University Hospital.

The long-term follow-up visit was arranged at age 8 years (Fig. 1).[4] The flow-volume spirometry (Jaeger MasterScreen system, Jaeger GmbH, Würzburg, Germany in Vinku, and Medikro Spirometry Software, Medikro Oy, Kuopio, Finland in Vinku 2) was measured in both studies with bronchodilatation test; spirometry at baseline and 15 minutes after 400 micrograms of albuterol

(Ventoline®) administered by inhalation through a spacer (Babyhaler®, both from Glaxo Smith Kline, Brentford, UK), and in Vinku2 also with free running test designed to measure bronchial hyper-reactivity in children; spirometry at baseline and 1, 5, and 10 minutes after exercise testing.[11, 29] The registered index was the forced expiratory volume in one second (FEV1). Families were instructed to withhold the child's regular asthma medications with inhaled corticosteroids (ICS) during the preceding 4 weeks, and to withhold salbutamol for 12 hours before the spirometry. The test was re-scheduled, 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, analyzed separately for atopic and non-atopic asthma. The risk factors were assessed at the time of the severe first wheezing episode (Table 1).

Children were diagnosed to have current asthma at age 8 years if they met one or more of the subsequent criteria during the preceding 12 months: patient charts report of doctor-diagnosed asthma and need for regular use of doctor-prescribed asthma therapy with ICS for over a month, use of OCS for asthma exacerbations, acute asthma attack relieved by repeated use of bronchodilator, and/or hyper-reactivity in spirometry defined as reversible airflow obstruction with an increase of ≥12% in FEV1 in the bronchodilatation test, or a decrease of ≥15% in 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 2). Non-atopic asthma was defined as asthma without these. Children were in remission if they were without asthma symptoms and therapy within 12 months prior to the study visit and/or without hyper-reactivity in spirometry at the study visit.

192

193 Definitions

194

195 Wheezing episode was defined as sharp whistling sound in expiratory breathing together with
196 expiratory distress.[11] Severe wheezing refers to that 90% of the children were hospitalized and 10%
197 were admitted to emergency room of the tertiary hospital. Any sensitization was defined as positive
198 IgE antibodies against common allergens (cut-off level 0.35 kU/L for codfish, cow's milk, egg,
199 peanut, soybean, wheat, cat, dog, horse, birch, mugwort, timothy, *Cladosporium herbarum* and
200 *Dermatophagoides pteronyssinus*; fluoro-enzyme immunoassay, CAP FEIA, Phadiatop Combi®,
201 Phadia, Uppsala, Sweden).[4, 18] Aeroallergen sensitisation was defined as IgE antibodies to any of
202 the latter 8 allergens. Eczema was a physician-made diagnosis with typical symptoms including
203 pruritus, typical morphology and chronicity of disease.[11] In this article, viral findings were
204 combined into 3 subgroups according to the viral etiology of the first wheezing episode at study
205 entry: the rhinovirus group (rhinovirus alone or with other viruses, RSV included), the RSV group
206 (RSV alone or with other viruses, rhinovirus excluded), and the RSV-/rhinovirus-negative group
207 (other viruses or no viruses found).[1, 4 30]

208

209 Statistics

210

211 The risk for current asthma at age 8 years was assessed using the unadjusted logistic regression
212 model with baseline characteristics at study entry. Fisher's exact tests were also used when there
213 was 0 cell counts. The 3 viral subgroups were individually tested as dichotomous variables (the
214 rhinovirus group *vs.* the other two, the RSV group *vs.* the other two, and the RSV-/rhinovirus-
215 negative group *vs.* the other two). The multivariable analyses were adjusted with eczema, any
216 sensitization, parental smoking, rhinovirus-positivity, age <12 months at study entry, which all

showed significant effects. The logistic regression analyses were also done for atopic and non-atopic asthma outcomes separately. Because of the time difference of the two 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's exact tests. A two-sided *P* value <.05 was regarded as statistically significant. Analyses were made using IBM SPSS 23.0 software (SPSS Inc, Chicago, Ill, USA).

Results

Study population

Originally, 417 children were enrolled (Fig. 1). Of these, 281 children were not eligible due to age ≥2 years, previous wheezing, ICS or OCS treatment, the development of chronic disease after enrollment, or need for intensive care during the hospitalization, and 136 children were eligible for the long-term follow-up. Nine children (7%) declined the follow-up or were lost, of whom 8 (89%) were boys, 3 (33%) were sensitized, 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) first-time wheezing children completed the follow-up and were included in this analyses. Of these children, 49 (39%) were from Vinku study and 78 (61%) from 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 addititon 73 (57%) children attended to the 7-year follow-up visit, whereas the rest, 54 (43%) children were followed-up from patient charts (n = 38) and the parents were also interviewed (n = 16) (Fig. 1 and Table II).

Patient 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 1). At the end of the follow-up the median age was 7.7 years (interquartile range 7.1; 8.2 years) (Table 2). Overall, during the follow-up 67 (53%) children were diagnosed to have recurrent wheezing or asthma ever, and regular long-term asthma control therapy with 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, 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 37/127 (29%) children, specified to atopic in 19 (15%) and non-atopic asthma in 18 (14%) (Tables I and II, please see allergy testing characteristics and the Results section in this article's Online Repository).

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% confidence interval [CI] 1.2-7.8), eczema (2.7; 1.2-6.5, respectively), and the first wheezing episode at age <12 months (2.3; 1.0-5.0, respectively) (all *P*<.05, Table III). In the multivariable analyses the first wheezing episode at age <12 months (3.6; 1.4-9.5), sensitization (3.5;1.1-11), eczema (2.9; 1.1-7.3), and parental smoking (2.8; 1.2-6.9) remained significant risk (all *P*<.05, Table III).

Risk factors for current atopic asthma at school-age

Current asthma was specified to atopic and non-atopic asthma. The unadjusted risk factors for current atopic asthma were sensitization (OR 13; 95% CI 4.3-41), rhinovirus etiology of the first wheezing episode (6.4; 1.8-23, respectively) and eczema (4.8; 1.7-13) (all *P*<.05, Table III). In the multivariable analyses sensitization (12; 3.0-44), rhinovirus etiology (5.0; 1.1-22) and eczema (4.8; 1.4-17) remained significant risk (all *P*<.05, Table III).

Risk factors for current non-atopic asthma at school-age

The unadjusted risk factors for non-atopic asthma were the RSV-/rhinovirus-negative etiology (OR 5.4; 95% CI 1.9-16) and age <12 months (5.3; 1.4-19, respectively) (all $P<.05$, Table III). In the multivariable analyses the RSV-/rhinovirus-negative etiology (8.0; 2.3-28), age <12 months (7.3; 1.7-31), and parental smoking (3.8; 1.2-13) remained significant risk (all $P<.05$, Table III). When the multivariable regression analyses were also adjusted for cohorts Vinku or Vinku2, they were not significant in the multivariable models for any, atopic or non-atopic 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 (Table IV, Fig. 2). The incidence of asthma was high with both eczema and sensitization (70%) *vs.* either one (37%) *vs.* neither (21%) ($P = .003$), respectively with sensitization and rhinovirus (59%/24%/25%) ($P = .015$), with eczema and rhinovirus (55%/27%/21%) ($P = .018$), or with age <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 on the atopic risk factors at study entry (Table IV). The incidence of atopic asthma was high with eczema and sensitization (70%) *vs.* either one (23%) *vs.* neither (4%) ($P<.001$), respectively with sensitization and rhinovirus (59%/12%/4%) ($P<.001$), with eczema and rhinovirus (45%/15%/15%) ($P<.001$), with B-eos $\geq 0.4 \times 10^9$/L and rhinovirus (27%/18%/5%) ($P = .015$), or with parental asthma and rhinovirus (29%/20%/6%) ($P = .038$) (Table IV and Fig. 2).

The incidence of non-atopic asthma increased with age <12 months and RSV-/rhinovirus-negative etiology (50%) *vs.* either one (15%) *vs.* neither (2%) (*P*<.001). Respectively, the age <12 months with parental smoking increased the asthma incidence (33%) *vs.* either one (12%) *vs.* age 13-23 months and no parental smoking (3%) (*P* = .003) (Table IV).

Sensitivity analyses

The sensitivity analyses in the subset of children with allergy testing (n = 91) did trend in the same direction as the main results (Tables III and E1 in this article's Online Repository). The sensitivity analyses of children without allergy testing (n = 36) was unsuitable for statistical analyses due to several 0 cell counts and small number of outcomes (1 atopic asthma and 1 non-atopic asthma).

Discussion

This is the first study assessing risk factors at the time of the severe first wheezing episode for atopic and non-atopic asthma phenotypes at age 8 years. It is novel by adding the 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 non-atopic school-age asthma. These results are noteworthy, since currently the school-age asthma risk of children with recurrent wheezing episodes is evaluated in with the modified API that includes closely atopy-related characteristics, but yet does not differentiate between asthma phenotypes.[10, 11] The risk factors for non-atopic asthma were the first wheezing before age 12 months, parental smoking and the RSV-/rhinovirus-negative first wheezing episode.

We show that 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-age asthma in birth cohorts.[6, 7] However, the Childhood Origins of ASThma (COAST) and the Australian birth cohort studies are high-risk cohorts by having included only wheezing children with a familial predisposition to atopic asthma. Therefore, the data may reflect a different susceptibility of atopic airways to rhinovirus infections. On the contrary, the Tuscon Children's Respiratory Study is a non-selected population based birth cohort that included healthy infants. They 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 the age of 13 years[31]. In addition, there was no link between RSV infections and sensitization[31]. Previous studies on different childhood asthma phenotypes noticed that atopic risk factors from the modified API were associated with atopic, but not with non-atopic asthma.[8, 10-14, 32] However, their study settings were different from ours since they were conducted on birth cohorts, focused not 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 asthma-increasing effect from male sex.[8, 12-14] We showed that parental smoking predicted non-atopic 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, mainly hospitalized with severe wheezing (90% hospitalized and 10% treated at emergency department of tertiary hospital), and of whom one third had asthma 7 years later. Therefore, our results could be adapted to hospitalized first-time wheezing children, and may give new perspective when estimating their future asthma risk. Bønnelykke *et al*. found no specific viral or bacterial risk factor for school-age asthma, and hence suggested that the underlying susceptibility to triggers instead of the specific triggering agent was the important asthma risk factor.[33] We agree with the host-dependent susceptibility, but we 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, we did not find rhinovirus a risk factor for current overall asthma (including atopic and non-atopic), but we found it a significant risk factor for atopic asthma. Concurrently, the RSV-/rhinovirus-negative wheezing was associated with non-atopic asthma, probably because the rhinovirus-positive wheezing children developed atopic asthma. Infant wheezing may be an asthma risk marker, as 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 three, may enable

the asthma risk assessment already at the time of the first wheezing episode, since rhinovirus-sensitive viral diagnostics is widely available.[1, 2, 4, 7, 19, 21, 34]

The underlying susceptibility to atopic disorders and viral triggers might be the true asthma risk factor, and thus the interplay between sensitization and virus infections is likely to be involved.[2, 5, 35, 36 15] The COAST study group showed in a statistical model the chronological order of causality *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 the future asthma risk.[6, 9, 37, 38] The rhinovirus-associated asthma risk has been explained by increased susceptibility to lower airway rhinovirus infections in individuals with pronounced atopic characteristics (allergen specific IgE sensitization, blood eosinophilia, eczema, maternal atopic eczema and/or increased interleukin [IL] -4, IL-5, and IL-13 responses in airway secretions), damaged airway epithelium, as well as decreased interferon α/β/γ/λ and IL-10 responses in airway secretions or cells.[34] The interactions between sensitization-associated and innate antiviral pathways may lead to more severe viral illnesses in already sensitized children when a respiratory viral infection starts a sensitization-dependent cascade that augments and maintains airway inflammation.[36]

The strengths of our study include complete analysis of atopic characteristics and virus 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 in addition 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 suffering from the first severe wheezing episode.[32] They were steroid-naive *ie.* they received no ICS/OCS before or as a treatment for this first wheezing. This is worth of note since it

has been shown that OCS may affect long-term the asthma outcome.[1, 4, 9, 18, 20] To minimize the selection bias, we included children who did not attend the long-term study visit. People adhere follow-up studies that concern their interests, in our case asthmatics. To maximize the objectivity we regarded children with bronchial hyper-reactivity in spirometry as asthmatics, who yet were without proper pediatrician-set asthma diagnose. This reflects the real-life situation and completes the asthma outcome. To minimize the heterogeneity and to make our results more generalizable we included only children with a physician-confirmed wheezing (*vs.* bronchiolitis with or without wheezing in previous studies).[17] This study has also limitations. The sample size was rather small after excluding the steroid-treated patients. The 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 non-atopic asthma at school-age. On the contrary, the first wheezing before age 12 months, parental smoking and the RSV-/rhinovirus-negative first wheezing episode predict non-atopic asthma at school-age. This observation could provide a novel approach into the mechanisms underlying childhood wheezing and asthma, prognostics, and potentially different therapies of distinct asthma phenotypes.[15] It would encourage to find future therapeutic interventions to prevent asthma, but warrants further studies.[16] Virology and atopic status are worth assessing early in severely wheezing children to recognize the children in high asthma risk, and to distinguish the risk between asthma phenotypes.

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Author Contributions

Drs Lukkarinen and Jartti have participated sufficiently in the work of this manuscript to take public responsibility for the whole content. Study concept and design: Lukkarinen, Jartti. Acquisition of data: Lukkarinen, Turunen, Koistinen, Lehtinen, Vuorinen, Jartti. Conduction of the statistical analyses: Lukkarinen. Interpretation of data: Lukkarinen, Jartti. Drafting of the manuscript: Lukkarinen, Jartti. Critical revision of the manuscript for important intellectual content: Lukkarinen, Turunen, Koistinen, Lehtinen, Vuorinen, Jartti. Study supervision: Jartti.

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527

TABLE I. Baseline patient characteristics at the first wheezing episode.

		Current asthma at age 8 years		
	All	**Any**	**Atopic**	**Non-atopic**
Risk factor	127	37 (29)	19 (15)	18 (14)
Age 3-11 months	68 (54)	25 (68)	10 (53)	15 (83)
Age 12-23 months	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 months	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)

528 Values are shown as numbers (percentage within asthma subgroups) of subjects.

529 *B-eos*, Blood eosinophil count; *RSV*, Respiratory syncytial virus.

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

531

532

TABLE II. Study characteristics at 8 years.

	N = 127
Age (years)	7.7 (7.1; 8.2)
Follow-up time (years)	6.8 (6.3; 7.1)
Followed-up from patient charts	127 (100%)
Attended the 7-year 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
Non-atopic 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 or skin prick test)	16
Atopic asthma (based on specific IgE testing)	3
Non-atopic asthma (based on specific IgE testing)	1
Patient charts and parental interviews	16 (13)
Allergy testing (allergen specific IgE or skin prick test)	2
Atopic asthma (based on specific IgE testing)	2
Atopic asthma (based on charts and questionnaire)	1
Non-atopic asthma (based on charts and questionnaire)	1
Asthma ever during the follow-up	67 (53)
Asthma in remission by the end of follow-up	30 (24)
Current asthma	37 (29)
Atopic	19 (15)
Non-atopic	18 (14)

533 Values are shown as medians (interquartile range) or numbers (percentage) of subjects.

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

535

536

TABLE III. Risk factors at the first wheezing episode for current asthma at age 8 years.

	Current asthma at age 8 years								
Unadjusted analyses	**Any**			**Atopic**			**Non-atopic**		
Risk factors	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age 3-11 months	***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***	N/A	N/A	***.041***‡
Food	***3.0***	***1.2-7.8***	***.023***	***13***	***4.3-41***	***<.001***	N/A	N/A	***.041***‡
Aeroallergen	N/A	N/A	***<.001***†	N/A	N/A	***<.001***†	N/A	N/A	.59‡
B-eos ≥0.4 x 10^9/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 months	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	N/A	N/A	***.013***§	***5.4***	***1.9-16***	***.002***
Multivariable analyses									
Age 3-11 months	***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***

537 Risk assessed with the logistic regression model. In unadjusted analyses age 3-11 months *vs.* age 12-23 months, male
538 sex *vs.* female, eczema *vs.* no eczema, sensitization to any allergen, food or aeroallergen *vs.* no sensitization, B-eos ≥0.4
539 x 10^9/L *vs.* B-eos <0.4 x 10^9/L, parental asthma and smoking *vs.* no asthma or smoking, duration of breast feeding ≥4
540 months *vs.* <4months. Multivariable analyses adjusted with age 3-11 months, eczema, any sensitization, parental
541 smoking, and rhinovirus-positivity or rhinovirus-negativity (*P* near .05 in unadjusted analyses). In N/A cells *P* was
542 assessed using Fisher's exact test due to 0 cell counts.
543 *B-eos*, Blood eosinophil count; *95% CI*, 95% Confidence interval; *N/A*: Not applicable; *OR*, Odds ratio; *RSV*,
544 Respiratory syncytial virus.
545 * Defined as IgE antibodies to any of the common allergens. See the Methods section for details.
546 † N/A for all aeroallergen-sensitized children developed atopic asthma.
547 ‡ N/A for none of the sensitized children developed non-atopic asthma.
548 § N/A for none of the RSV/rhinovirus-negative children developed atopic asthma.

549 ¶Not included in the model for there was no sensitization at study entry.

550

551

TABLE IV. The effect of concomitant characteristics at study entry for incidence of current asthma at age 8 years.

	Current asthma at age 8 years					
Risk factors	**Any**	*P*	**Atopic**	*P*	**Non-atopic**	*P*
Age 3-11 months and no rhinovirus*	13/38 (34)		3/38 (8)		10/38 (26)	
Age 12-23 months OR rhinovirus	14/53 (26)	.71	7/53 (13)	.11	7/53 (13)	***.014***
Age 12-23 months 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 x 10^9/L and no rhinovirus	14/56 (25)		3/56 (5)		11/56 (20)	
B-eos ≥0.4 x 10^9/L OR rhinovirus	12/38 (32)	.65	7/38 (18)	***.015***	5/38 (13)	.20
B-eos ≥0.4 x 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 months with RSV or rhinovirus	10/47 (21)		9/47 (19)		1/47 (2)	
Age 3-11 months OR RSV-/rhinovirus-negative‡	20/66 (30)	.11	10/66 (15)	.21	10/66 (15)	***<.001***
Age 3-11 months AND RSV-/rhinovirus-negative	7/14 (50)		0/14 (0)		7/14 (50)	
Age 12-23 months and no parental smoking	7/33 (21)		6/33 (18)		1/33 (3)	
Age 3-11 months OR parental smoking	15/65 (23)	***.004***	7/65 (11)	.33	8/65 (12)	***.003***
Age 3-11 months AND parental smoking	15/27 (56)		6/27 (22)		9/27 (33)	

552 Values are shown as numbers (percentage) of subjects. *P* was assessed using $\chi 2$ or Fisher's exact tests indicating whole
553 group's comparisons.
554 *B-eos*, Blood eosinophil count.
555 * Alone or with other viruses, RSV included.
556 † Defined as IgE antibodies to any of the common allergens. See the Methods section for details.
557 ‡ With other viruses or no viruses.
558

559 **Legends to the figures**

560

561 **FIGURE 1:** Study flow chart. *ICS*, inhaled corticosteroids; *ICU*, intensive care unit.

562

563 **FIGURE 2:** The incidence of current asthma phenotypes at age 8 years in children (N = 127) with
564 sole and overlapping atopic risk factors (sensitization, eczema, rhinovirus, parental asthma) at the
565 first wheezing episode. *N/A*, not applicable for there were no cases with risk factors.

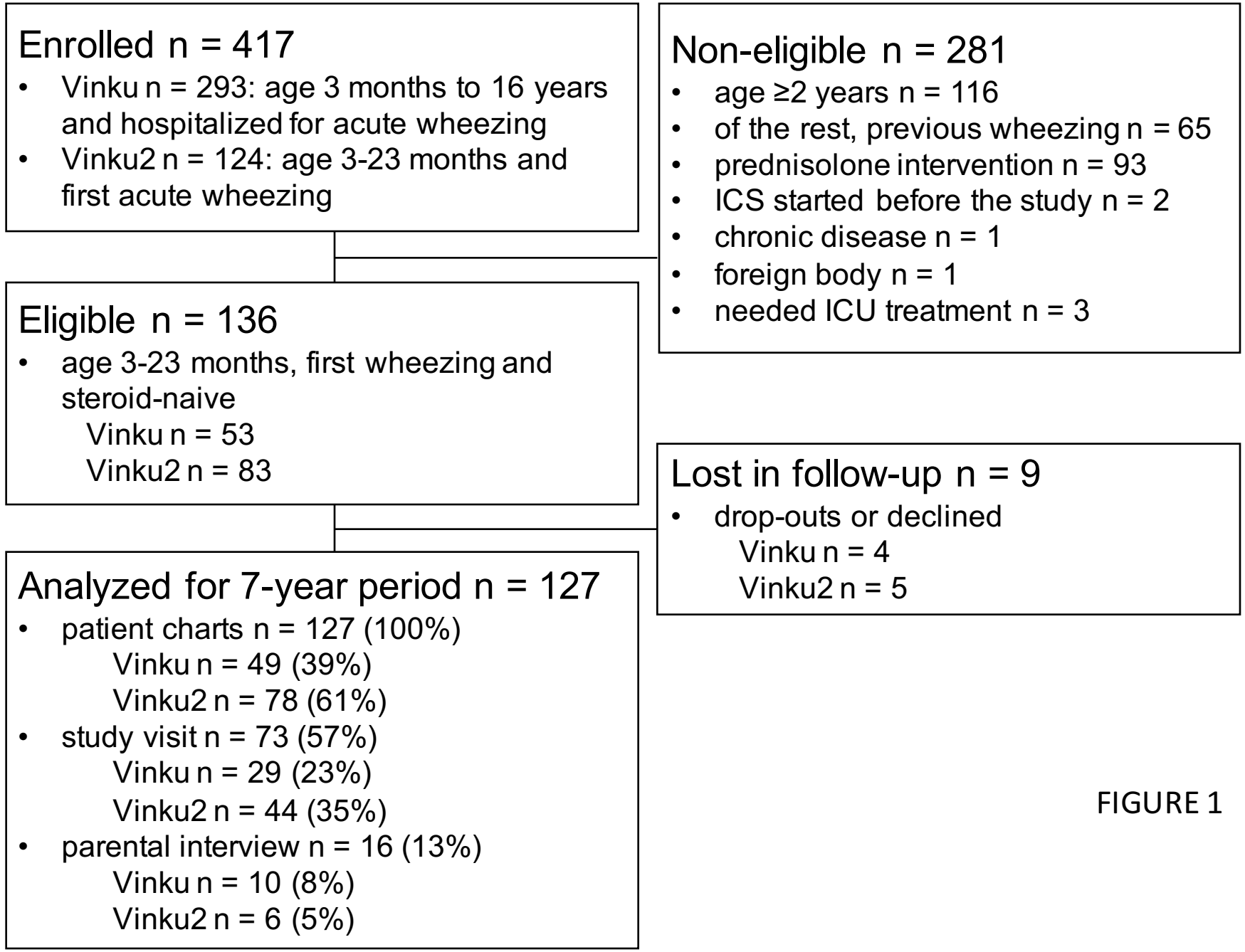
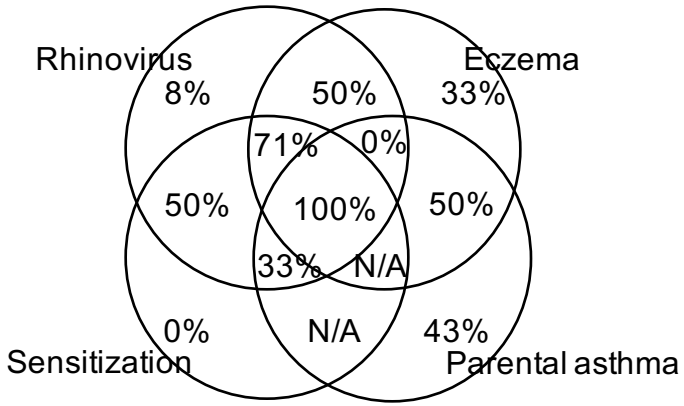
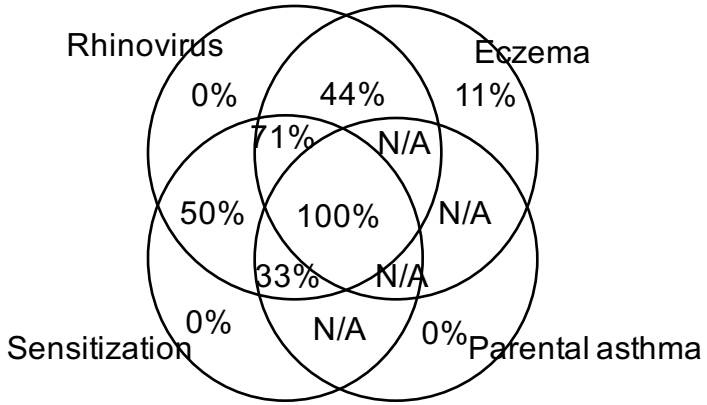

Enrolled n = 417
• Vinku n = 293: age 3 months to 16 years and hospitalized for acute wheezing
• Vinku2 n = 124: age 3-23 months and first acute wheezing
Non-eligible n = 281
• age ≥2 years n = 116
• of the rest, previous wheezing n = 65
• prednisolone intervention n = 93
• ICS started before the study n = 2
• chronic disease n = 1
• foreign body n = 1
• needed ICU treatment n = 3
Eligible n = 136
• age 3-23 months, first wheezing and steroid-naive
Vinku n = 53
Vinku2 n = 83
Lost in follow-up n = 9
• drop-outs or declined
Vinku n = 4
Vinku2 n = 5
Analyzed for 7-year period n = 127
• patient charts n = 127 (100%)
Vinku n = 49 (39%)
Vinku2 n = 78 (61%)
• study visit n = 73 (57%)
Vinku n = 29 (23%)
Vinku2 n = 44 (35%)
• parental interview n = 16 (13%)
Vinku n = 10 (8%)
Vinku2 n = 6 (5%)

FIGURE 1

Current asthma



Atopic asthma



Non-atopic asthma

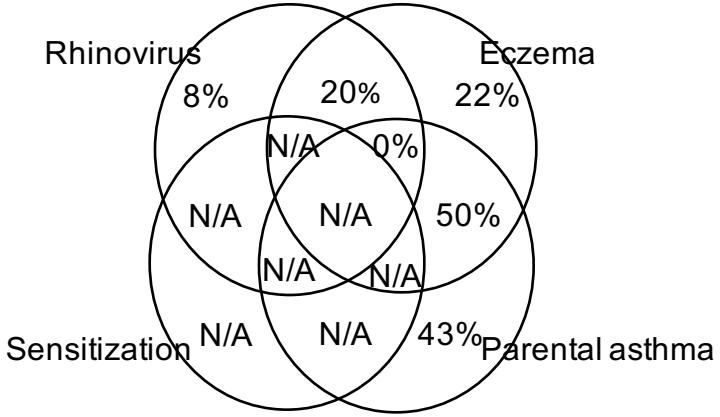


FIGURE 2

Results

Patient characteristics

Allergen specific IgE or skin prick testing was done for 91/127 (72%) children: for all 73 children at the 7-year follow-up visit and for 18/54 (33%) children who did not attend to the visit. For 42/43 (98%) of the sensitized children, sensitization was verified by laboratory testing: allergen specific IgE was analyzed at the study visit in 31/43 (72%) children, allergen specific IgE or skin prick test was verified from patient charts in 11/43 (26%) children, and of the rest, in 1/43 (2%) children, allergy diagnosis was verified from patient charts and standardized study questionnaire. This child was atopic asthmatic with clear allergy to pollen and furry animals.

TABLE E1. Risk factors at the first wheezing episode for current asthma at 8 years. Sensitivity analysis of the children with specific IgE testing at 8 years (n = 91).

	Current asthma at age 8 years								
Unadjusted analyses	**Any**			**Atopic**			**Non-atopic**		
Risk factors	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age 3-11 months	2.3	0.97-5.7	.059	0.98	0.35-2.8	.96	***4.7***	***1.2-18***	***.023***
Male sex	1.1	0.44-2.6	.89	3.3	0.88-12	.078	0.40	0.14-1.2	.095
Eczema	***2.8***	***1.1-6.9***	***.027***	***4.8***	***1.6-14***	***.005***	0.87	0.28-2.7	.81
Any sensitization*	2.7	0.93-8.1	.069	***13***	***3.7-45***	***<.001***	N/A	N/A	***.035***‡
Food	2.7	0.93-8.1	.069	***13***	***3.7-45***	***<.001***	N/A	N/A	***.035***‡
Aeroallergen	N/A	N/A	***.003***†	N/A	N/A	***<.001***†	N/A	N/A	.59‡
B-eos ≥0.4 x 10^9/L	1.2	0.49-3.0	.68	2.3	0.77-7.0	.13	0.54	0.16-1.8	.33
Parental asthma	1.8	0.64-5.1	.27	1.2	0.34-4.2	.77	2.0	0.59-6.5	.28
Parental smoking	2.0	0.84-4.7	.12	1.4	0.48-3.8	.57	2.1	0.72-6.1	.18
Breast feeding ≥4 months	1.2	0.49-2.7	.74	1.0	0.37-2.9	.95	1.2	0.42-3.5	.72
Rhinovirus alone or with other viruses, RSV included	1.4	0.59-3.3	.44	***5.4***	***1.4-20***	***.012***	0.37	0.12-1.1	.077
RSV alone or with other viruses, rhinovirus excluded	0.53	0.22-1.3	.17	***0.27***	***0.07-1.0***	***.053***	1.2	0.42-3.6	.72
RSV-/rhinovirus-negative	1.4	0.48-3.9	.56	N/A	N/A	***.019***§	***5.7***	***1.8-18***	***.003***
Multivariable analyses									
Age 3-11 months	***4.3***	***1.4-13***	***.009***	2.3	0.56-9.4	.25	***5.7***	***1.3 -25***	***.019***
Eczema	***3.3***	***1.1-9.8***	***.027***	***5.2***	***1.4-20***	***.017***	0.72	0.19-2.7	.62
Any sensitization	3.4	0.93-12	.064	***12***	***2.8-54***	***.001***	¶	¶	¶
Parental smoking	***2.9***	***1.1-7.8***	***.038***	2.3	0.57-9.2	.24	2.9	0.83-10	.097
Rhinovirus alone or with other viruses, RSV included	1.2	0.41-3.4	.78	3.9	0.78-19	.099	-	-	-
RSV-/rhinovirus-negative	-	-	-	-	-	-	***7.2***	***1.9-27***	***.003***

Risk assessed with the logistic regression model. In unadjusted analyses age 3-11 months *vs.* age 12-23 months, male sex *vs.* female, eczema *vs.* no eczema, sensitization to any allergen, food or aeroallergen *vs.* no sensitization, B-eos ≥0.4 x 10^9/L *vs.* B-eos <0.4 x 10^9/L, parental asthma and smoking *vs.* no asthma or smoking, duration of breast feeding ≥4 months *vs.* <4months. Multivariable analyses adjusted with age 3-11 months, eczema, any sensitization, and rhinovirus-positivity or rhinovirus-negativity (P<.05). In N/A cells *P* was assessed using Fisher's exact test due to 0 cell counts.

B-eos, Blood eosinophil count; *95% CI*, 95% Confidende interval; *N/A*: Not applicable; *OR*, Odds ratio; *RSV*, Respiratory syncytial virus.

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

† N/A for all aeroallergen-sensitized children developed atopic asthma.

‡ N/A for none of the sensitized children developed non-atopic asthma.

§ N/A for none of the RSV/rhinovirus-negative children developed atopic asthma.

¶ Not included in the model for there was no sensitization at study entry.

PARENTAL QUESTIONNAIRE AT THE 7-YEAR FOLLOW-UP VISIT FOR VINKU-STUDY

1. Has a doctor ever diagnosed **asthma** in your child ?

1) No 2) Yes

If yes When (month/year)?

Where? By whom?

Has the dyspnoea been relieved by *quick-relief medication* (such as Foradril, Formoterol, Oxis, Airomir, Buventol, Salbuvent, Ventoline, Serevent, Bricanyl, Seretide, Symbicort)? 1) No 2) Yes

Has the *long-term control medication* ever been started continuing for >4 weeks (such as Aerobec, Beclomet, Busonid, Pulmicort, Flixotide, Asmanex, Seretide, Symbicort)?
When?
What preparates?
How long did the regular daily long-term control therapy continue?
How long did the long-term therapy continue regularly/intermittently?

2. After the study entry has your child ever had **cough/dyspnoea with wheezing**?

1) No 2) Yes

If yes How many times to eventual asthma diagnosis?

Where were they diagnosed if some of them where doctor-confirmed?

Has the dyspnoea been relieved by *quick-relief medication* (please see the list above)?

Has the *long-term control medication* ever been started continuing for <4 weeks for wheezing (please see the list above)?
When?
What preparates?
How long did the regular daily long-term control therapy continue?
How long did the long-term therapy continue regularly/intermittently?

3. After the study entry has your child ever had **prolonged cough contiunuing >4 weeks**?

1) No 2) Yes

If yes How many times to eventual asthma diagnosis?

Where were they diagnosed if some of them where doctor-confirmed?

Has the cough been relieved by *quick-relief medication* (please see the list above)?

Has the *long-term control medication* ever been started continuing for <4 weeks for the cough (please see the list above)?
When?
What preparates?
How long did the regular daily long-term control therapy continue?
How long did the long-term therapy continue regularly/intermittently?

4. **What factors caused the wheezing or cough**?

Flu/cold?
Allergies? What allergy?
Exercise?
Cold air?
Other? What?

5. Has your child ever had **itching rash** that has been called **eczema, dermatitis, atopic dermatitis**?

1) No 2) Yes

If yes Was the rash/eczema doctor-confirmed?
On what areas it appeared?
How long did eczema continue regularly/intermittently?

6. Has your child ever had **hay fever, pollen allergy or some other allergic rhinitis** (sneezing, itching nose, rhinitis caused by pollen/animals)?

1) No 2) Yes

If yes Was it doctor-confirmed?

7. Has your child ever had **allergic conjunctivitis**?

1) No 2) Yes

If yes Was it doctor-confirmed?

8. Has your child had **wheezing or asthma attack during the preceding 12 months**?

1) No 2) Yes

If yes How many times totally?
How many times it required a doctor-admission?
How many times it required a hospitalization?
Has the *long-term control medication* ever been started continuing for >4 weeks?
When?
Who prescribed?
What preparates?
How long did the regular daily long-term control therapy continue?
How long did the long-term therapy continue regularly/intermittently?

9. Has your child had **prolonged cough continuing >4 weeks during the preceding 12 months**?

1) No 2) Yes

If yes How many coughing periods totally?
How many times it required a doctor-admission?
Has the *long-term control medication* ever been started continuing for >4 weeks?
When?
Who prescribed?
What preparates?
How long did the regular daily long-term control therapy continue?
How long did the long-term therapy continue regularly/intermittently?

10. What factors caused the wheezing or cough **during the preceding 12 months**?

Flu?
Allergies? What allergy?
Exercise?
Cold air?
Other? What?

11. Has your child neede *quick-relief medication* **during the preceding 12 months** (please see the list above)?

1) No 2) Yes

If yes Weekly?
Monthly?
More seldom?

12. Has your child needed cortisone tablets per oral or intravenously **during the preceding 12 months?**

1) No 2) Yes

If yes How many?

13. Has the mother of your child ever had **hay fever, pollen allergy or some other allergic rhinitis** (sneezing, itching nose, rhinitis caused by pollen/animals)?

1) No 2) Yes

If yes Was it doctor-confirmed?
Was it confirmed with PRICK or blood testing?
What allergens were positive?

14. Has the father of your child ever had **hay fever, pollen allergy or some other allergic rhinitis** (sneezing, itching nose, rhinitis caused by pollen/animals)?

1) No 2) Yes

If yes Was it doctor-confirmed?
Was it confirmed with PRICK orblood testing?
What allergens were positive?

15. Has the mother of your child ever had **doctor-diagnosed asthma**?

1) No 2) Yes

If yes Was it as a child, but no longer as an adult (> 16 years)?
Are there still on-going symptoms without doctor-comfirmation?
Are there stillasthma symptoms and a need for doctor-prescriped asthma therapy?

16. Has the father of your child ever had **doctor-diagnosed asthma**?

1) No 2) Yes

If yes Was it as a child, but no longer as an adult (> 16 years)?
Are there still on-going symptoms without doctor-comfirmation?
Are there stillasthma symptoms and a need for doctor-prescriped asthma therapy?

17. Have you ever had a **pet indoor**?

1) No 2) Yes

If yes What animals?
Were they before your child was born?
Totally how long?

18. Has the mother ever **smoked (**inside and/or outside)?

1) No 2) Yes

If yes Has she smoked inside?
Does she still smoke **daily (**inside and/or outside)?

Does she still smoke **occasionally (**inside and/or outside)?
How many years has she totally been smoking (daily or occasionally)?
How many cigarettes/day she smokes/smoked?

19. Has the father <u>ever</u> **smoked (**inside and/or outside)?

1) No 2) Yes

If yes Has he smoked inside?
Does he still smoke **daily (**inside and/or outside)?
Does he still smoke **occasionally (**inside and/or outside)?
How many years has he totally been smoking (daily or occasionally)?
How many cigarettes/day he smokes/smoked?

20. How many hours/day your child stays indoors where others smoke?

21. Was your child breast fed?

1) No 2) Yes

If yes How long?

22. Has there been problems with mould or humidity at the child´s home or day care?

1) No 2) Yes

If yes Only a mild problem (eg. only seldom, mild odour mainly in living rooms or in cellar)?
A significant problem (often a mild or occasionally obvious odour when coming from outdoor to indoor)?
How long your child was exposed to the mould or humidity problem?

PARENTAL QUESTIONNAIRE AT THE 7-YEAR FOLLOW-UP VISIT FOR VINKU2-STUDY

*** RISK FACTORS FOR ASTHMA**

1) Has A parent of your child <u>ever</u> had doctor-diagnosed asthma?

1) yes ☐ 2) no ☐

2) Has your child <u>ever</u> had doctor-diagnosed eczema?

1) yes ☐ 2) no ☐

b) If yes: Where and when was it diagnosed? _____

3) Has your child <u>ever</u> had wheezing without cold/flu symptoms?

1) yes ☐ 2) no ☐

4) Has your child <u>ever</u> had pet allergy?

1) yes ☐ 2) no ☐

b) If yes: Where and when was it diagnosed? _____

5) Has your child <u>ever</u> had, pollen allergy?

1) yes ☐ 2) no ☐

b) If yes: Where and when was it diagnosed? _____

6) Has your child <u>ever</u> had dust mite allergy?

1) yes ☐ 2) no ☐

b) If yes: Where and when was it diagnosed? _____

7) Has your child <u>ever</u> had doctor-diagnosed food allergy?

1) yes ☐ 2) no ☐

If yes:
b) What allergies? _____
c) Where and when was it diagnosed? _____

8) Has your child ever been tested for allergy blood tests (outside this research)?

1) yes ☐ 2) no ☐
b) If yes: Where have the tests been taken?_____

_____

*** CHILD HEALTH <u>DURING THE LAST MONTH</u>**

9) How many times did your child suffer from breathing diffidulty such as wheezing, cough or dyspnoea?

1) never ☐ 2) 1-3 times ☐ 3) once a week ☐
4) 2-3 times a week ☐ 5) 4 or more times a week ☐ 6) I don't know ☐

10) How often did your child wake up in the night due to breathing difficulty (wheezing, cough or dyspnoea)?

1) never ☐ 2) 1-3 times ☐ 3) once a week ☐
4) 2-3 times a week ☐ 5) 4 or more times a week ☐ 6) I don't know ☐

11) How much did the breathing difficulties, such as wheezing, cough or dyspnoea, restrict your child's normal life (playing, kindergarten, other)?

1) not at all ☐ 2) a little ☐ 3) to some extent ☐
4) quite lot ☐ 5) very much ☐

12) How many days a week on average your child needed inhaled bronchodilating medication (for example Airomir, Bricanyl, Buventol, Fomeda, Foradil, Formoterol, Oxis, Salbumatol, Serevent, Symbicort (as an quick-relief medicine), Ventilastin, Ventoline) **for his/hers breathing difficulty?**

1) never ☐ 2) less often than once a week ☐
3) once a week ☐ 4) twice a week ☐
5) three times a week ☐ 6) 4-6 times a week ☐
7) daily ☐ 8) many times a day ☐

*** CHILD HEALTH <u>DURING THE LAST 12 MONTHS</u>**

13) Has your child had expiratory breathimg difficulty or asthma attack?

1) yes ☐ 2) no ☐

b) If yes: How many times? _____
c) Was there expiratory wheezing?
1) yes ☐ 2) no ☐

14) Has your child had tight coughing (outside the question 13 expiratory breathimg difficulties)?

1) yes ☐ 2) no ☐

b) If yes: How many times? _____

15) Has your child benefitted from *quick-relief medication* (for example Airomir, Bricanyl, Buventol, Fomeda, Foradil, Formoterol, Oxis, Salbumatol, Serevent, Symbicort (as an quick-relief medicine), Ventilastin, Ventoline) **during the expiratory breathimg difficulties or asthma attack?**

1) yes ☐ 2) no ☐

b) If yes: During how many periods? _____
c) What product?: _____

16) Has your child benefitted from *quick-relief medication* (for example Airomir, Bricanyl, Buventol, Fomeda, Foradil, Formoterol, Oxis, Salbumatol, Serevent, Symbicort (as an quick-relief medicine), Ventilastin, Ventoline) **during the tight coughing periods (outside the question 15 expiratory breathimg difficulties)?**

1) yes ☐ 2) no ☐

b) If yes: During how many periods? _____
c) What product?: _____

17) Has your child had expiratory breathimg difficulties or asthma attacks that lasted longer than 24 hours and affected his/hers sleep?

1) yes ☐ 2) no ☐

b) If yes: During how many periods? _____

18) Has your child had periods of tight cough that lasted longer than 24 hours and affected his/hers sleep (outside the question 17 expiratory breathimg difficulties)?

1) yes ☐ 2) no ☐

b) If yes: During how many periods? _____

19) Has your child needed repeatedly (≥2 times a week) inhaled bronchodilating medication for a prolonged expiratory breathimg difficulty, tight cough or asthma attack for over a month?

1) yes ☐ 2) no ☐

20) Has your child needed systemic cortisone (intramuscular, tablets per oral or intravenously; Prednison, Prednisolon, Dexametason or Oradexon) **for an expiratory breathimg difficulty, tight cough or asthma attack?**

1) yes ☐ 2) no ☐
b) If yes: During how many periods? _____

21) Has your child needed doctor-appointments for his/hers expiratory breathimg difficulty, tight cough or asthma attack <u>during the previous 12 months</u> (excluding the times he/she was hospitalized)?

1) yes ☐ 2) no ☐

If yes:
b) How many times? _____

c) At which health centre or hospital?

_____

22) Has your child been hospitalized for his/hers expiratory breathimg difficulty, tight cough or asthma attack <u>during the previous 12 months</u>?

1) yes ☐ 2) no ☐

If yes:
b) How many times? _____
c) At which
hospital?_____

23) Has your child been described regular daily asthma controler therapy (inhaled or per oral, for example Aerobec, Astecon, Beclomet, Budesonid, Dexas, Depo-Medrol, Dexametason, Flixotide, Lomudal freoniton, Medrol, Montelukast, Novopulmon, Prednisolon, Prednison, Pulmicort, Seretide, Singulair, Solomet, Solu-medrol, Symbicort, Tilade freoniton, Xolair) **<u>during the previous 12 months</u> for his/hers repeated breathimg difficulty, prolonged cough or asthma?**

1) yes ☐ 2) no ☐

If yes:
b) What product/s? _____
c) When was it started (mo/y)? /
d) Where was it started? _____
e) How many months was the therapy in use? _____kk
f) Has the therapy been in use **<u>during the previous 4 weeks</u>**?
1) yes ☐ 2) no ☐

24) Has a doctor called the breathing difficulty "asthma" <u>during the previous 12 months</u>?

1) yes ☐ 2) no ☐

25) Has your child had itching rash (eczema, dermatitis, atopic dermatitis**) <u>during the previous 12 months</u>?**

1) yes ☐ 2) no ☐

b) If yes:
Was the rash in these locations: inside of the elbows or knees, front of the ankles, gluteals, neck, or around the ears or eyes?
1) yes ☐ 2) no ☐

26) Has your child had allergic rhinitis (sneezing, itching nose, rhinitis) **or conjunctivitis due to aeroallergens, such as pollen, room dust or animals <u>during the previous 12 months</u>?**

1) yes ☐ 2) no ☐

If yes:
b) When was it started (mo/y)? /
c) What was the possible cause? _____

_____

*** PREVIOUS HEALTH**
Has your child <u>ever, earlier than the previous 12 months</u> had

27) Acute wheezing or bronchiolitis?

1) yes ☐ 2) no ☐

b) If yes, when last time (mo/y)? /

28) Has a doctor diagnosed asthma in your child?

1) yes ☐ 2) no ☐

b) If yes, when was the diagnose set (mo/y)? /
c) Where? _____

29) Has your child been described regular daily asthma controler therapy (inhaled or per oral, for example Aerobec, Astecon, Beclomet, Budesonid, Dexas, Depo-Medrol, Dexametason, Flixotide, Lomudal freoniton, Medrol, Montelukast, Novopulmon, Prednisolon, Prednison, Pulmicort, Seretide, Singulair, Solomet, Solu-medrol, Symbicort, Tilade freoniton, Xolair) **for his/hers repeated breathimg difficulty, prolonged cough or asthma?**

1) yes ☐ 2) no ☐

If yes:
b) What product/s? _____
c) When first time (mo/y)? /
d) Where was it started(mo/y)? /
e) When was it ended (mo/y)? /

30) If your child had asthma, has the symptoms relieved?

1) yes ☐ 2) no ☐

b) If yes, when did it happen? (kk/v) /

31) Has your child any other chonic disease, what?

_____

32) Has you child any other regular medication (<u>>1 months)</u> than the above asked?

1) yes ☐ 2) no ☐

If yes:
b) What? _____
c) When started? _____
d) How long did it last (months)? _____