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Sensitization at the first wheezing episode increases risk for long-term asthma therapy

Minna Lukkarinen¹, Tytti Vuorinen², Pasi Lehtinen¹, Olli Ruuskanen¹, and Tuomas Jartti¹

¹Department of Pediatrics, Turku University Hospital; Turku, Finland

²Department of Clinical Virology, Division of Microbiology and Genetics, Turku University Hospital, Turku, Finland

Corresponding author:

Dr Minna Lukkarinen, Department of Pediatrics, Turku University Hospital,

P.O. Box 52, 20521 Turku, FINLAND,

E-mail: mimapo@utu.fi,

Telephone: +358 40 7017 876,

Fax : +358 2 3131460

Supporting Information: Parental questionnaires at study entry and 7 years and Study Flow Chart.

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Keywords:

Asthma; bronchiolitis; child; corticosteroid; rhinovirus; sensitization; therapy; wheeze; wheezing; virus.

Abbreviations:

B-Eos: blood eosinophil count; CI: confidence interval; HR: hazard ratio; ICS: inhaled corticosteroids; IgE: immunoglobulin E; IQR: interquartile range; OCS: oral corticosteroids; OR: odds ratio; RSV: respiratory syncytial virus.

To the Editor,

Childhood asthma risk assessment has relied on clinical risk factors such as atopic characteristics, wheezing frequency and severity (1). The recent development of viral diagnostics has lead to a suggestion that asthma risk could be assessed already at the time of the first wheezing episode (2-5). Still, only three studies have focused on the first wheezing episode/bronchiolitis and have analyzed complete virology and children's sensitization status (2, 3, 5). These three studies used wheezing as inclusion criterion, while other bronchiolitis studies have also included crackles, and missed blood samples (6, 7). At the first wheezing episode, sensitization and rhinovirus have been linked to recurrent wheezing/asthma, and rhinovirus has been linked to atopic characteristics, whereas respiratory syncytial virus (RSV)-induced bronchiolitis has mainly not (2, 3, 5, 8). Still, there is scarcely information on long-term outcome after the first wheezing episode. Only three studies have investigated risk factors for the need of long-term asthma control therapy in children (9-11).

The first choice maintenance therapy for childhood asthma is the regular control therapy with inhaled corticosteroids (ICS) (1). We suggest that the need for long-term ICS therapy indicates best the symptom activity and asthma persistence (1, 11). Many children with asthma symptoms improve, especially those with non-atopic asthma (1, 8, 11). Therefore, more data is required about the risk factors for long-term therapy already at the first episode of wheezing. We aimed to identify the risk factors for persistent asthma defined by the need of regular long-term asthma control therapy with ICS in hospitalized, first-time wheezing children.

The Vinku study was carried out in the Department of Pediatrics, Turku University Hospital, Turku, Finland 2000-2002 (3). The aim of the initial study, from which data in this manuscript was retrieved, was to evaluate the effect of a 3-day course of oral corticosteroids (OCS) with prednisolone (first dose 2 mg/kg, then 2 mg/kg/day in 3 divided doses, maximum dose 60 mg/day, Prednisolon® 5 mg tablets, Leiras Takeda, Helsinki, Finland) in a randomized double-blind placebo-controlled paralleled trial (3). Inclusion criteria for long-term follow-ups were the first wheezing episode and age <3 years (3). The study was approved by the Ethics Committee of the Turku University Hospital and was commenced after obtaining written informed consent from guardians. Study physicians recruited patients and the long-term follow-up visit was at 12 months. Parents were interviewed at study entry, 12 months and 7 years (Supporting Information) and patient charts were reviewed of the full 7-year follow-up period for the first wheezing episode, asthma symptoms, medications, and adherence to therapy (3). At study entry samples of venous blood and nasopharyngeal aspirates for virus analyses of 21 viruses were assessed (3).

The long-term ICS therapy was mainly started after the third physician-confirmed wheezing episode and used with doses that held children symptom-free (1, 3). Only the ICS therapy, but not leukotriene antagonists, was considered (1). The children were followed-up by a paediatrician every 3-6 months until the regular therapy was discontinued, and they had been symptom-free at least 6 months. The regular therapy was re-introduced if asthma symptoms emerged during therapy pauses which were held despite season. Therefore, the periodic therapy was considered comparable to regular therapy. The asthma therapy duration was determined by assessing the first and the last date of the regular or periodic therapy. The term 'regular' refers to daily and continuous and 'long-term' to permanent, long-lasting therapy use.

The primary outcome was to find risk factors at the time of the first wheezing episode for the need of regular ICS therapy in different ages during the 7-year follow-up. The secondary outcome was the time to the end of regular asthma control therapy. Wheezing episode refers to a whistling sound in expiratory breathing together with expiratory distress (1).

Sensitization was defined as allergen-specific immunoglobulin E (IgE) antibodies against any allergen with a cut-off level >0.35 kU/l (fluoro-enzyme immunoassay, CAP FEIA, Phadiatop Combi[®], Phadia, Uppsala, Sweden), and increased blood eosinophil count (B-Eos) was defined as $\geq 0.40 \times 10^9/l$ all measured by the standard diagnostics of the Central Laboratory of Turku University Hospital (3). Eczema was a physician-made diagnosis with characteristic features (1).

The proportions were analyzed with χ^2 and differences in therapy durations with Mann-Whitney U tests. The risk for the need of regular asthma therapy in different ages was assessed with the univariable logistic regression with risk factors listed in the Table. The

multivariable analyses were performed with clinically relevant risk factors such as age <1 year, B-Eos $\geq 0.40 \times 10^9/l$, eczema, sex, parental asthma, prednisolone intervention, rhinovirus, and sensitization at study entry. Then, the modifying effect of all risk factors on treatment effect was studied *post hoc* with interactions between the risk factors (Table) and treatment grouping (prednisolone vs. placebo) overall, and also after adjustment to sensitization. Odds ratio (OR) indicated the risk of therapy use at different ages. The Cox model was used for the risk assessment of the time to the end of regular asthma control therapy. The univariable, multivariable and interaction analyses were repeated with identical factors as in the logistic regression (3). Cox hazard ratio (HR) indicated the risk of regular asthma therapy need throughout the follow-up. Each study subject was censored from the analyses after finishing the long-term therapy. Analyses were made using IBM SPSS 21.0 software (SPSS Inc, Chicago, Ill, USA).

The long-term follow-up criteria were fulfilled by 131 children. Nine children were lost and 11 children were excluded because they were treated with ICS for prolonged cough. Of the 20 excluded children, 14 (70%) were boys, 5 (20%) were sensitized, 6 (12%) were rhinovirus-positive, 10 (50%) received prednisolone as the study intervention, and their median age was 18 months. Finally, 111 (85%) children were included. Their median age was 12 months (interquartile range [IQR] 7, 18 months) at study entry, and 8.0 years (7.3, 8.7 years, respectively) at the end of follow-up. The mean follow-up time was 6.3 years. The placebo (n = 56) and prednisolone (n = 55) recipients were evenly distributed (Table). Therapy was started in 51 (46%) children, of whom 43 (84%) children used regular and 8 (16%) used periodic therapy. Median age at therapy start was 19 months (IQR 12, 26 months).

The logistic regression model showed an increased risk for a need of asthma therapy in sensitized children (univariable $p = 0.039$, multivariable $p = 0.029$) (Fig. 1a). Age <1 year increased the risk until the age 2 years (univariable OR 4.0, 95% CI 1.6-10, $p = 0.004$, multivariable 5.0, 1.7-15, 0.003, respectively) (Fig. 1a). Prednisolone did not reduce the overall risk or shorten the therapy duration ($p > 0.1$). However, in the interaction analyses between the intervention and rhinovirus status, prednisolone showed a trend for risk reduction only on the rhinovirus-group during ages 3 to 5 years, effect remaining after adjustment to sensitization ($p \leq 0.051$) (Fig. 1a and b).

The Cox model with no significant interactions showed that sensitization was the only risk factor for a need of regular asthma therapy throughout the follow-up period (univariable HR 2.9, 95% CI 1.3-7.4, $p = 0.03$, multivariable 4.5, 1.4-15, 0.01, respectively) (Fig. 2). The median duration of therapy was 3.1 years (IQR 1.2, 5.4), whereas in sensitized children it was 5.4 years (3.3, 6.5, respectively) vs. in non-sensitized 2.4 years (1.2, 5.1), ($p = 0.02$).

We found an increased risk for regular long-term asthma control therapy and longer duration of therapy (5.4 vs. 2.4 years) if the child was sensitized mainly to food allergens at the time of the first acute wheezing episode necessitating hospitalization. Half of the study children needed long-term asthma therapy during the follow-up, which makes it a high-risk population, and thereby also giving new perspective when estimating the future asthma risk. Interestingly, the early OCS showed a trend for risk reduction if the first wheezing episode was associated with rhinovirus, but not with other viruses.

We suggest that the need for long-term asthma therapy would discover asthmatic children with persistent symptoms. Therefore, we found important to study risk factors for the need of

long-term ICS therapy. The majority of asthmatic children has tendency to improve, especially those with non-atopic asthma (1, 11). Our current finding is in line with a study that showed in 78 asthmatic children that sensitized asthmatics (n = 50) needed regular asthma therapy longer (11). A Dutch birth cohort investigated prospectively asthma therapy use until school age in 777 children by means of annual questionnaires, but lacked information of cohort's early virological and sensitization status (9, 10). They showed that asthma symptoms at early age and the asthma severity were associated with longer duration of therapy.

Aeroallergen sensitization is a specific childhood asthma risk factor (1, 3, 8). However, its value in early asthma prognostics is limited, since it develops seldom before age 3 years (12). IgE antibodies to aeroallergens increase towards adolescence, whereas antibodies to food persist throughout childhood (12). To support this, the early appearance of both food and aeroallergen sensitizations is high in asthma-prone children (1, 8, 11). The frequency of sensitization in generally at ages 1.5 and 5 years is 6-12% and 23%, whereas in children with early wheezing/asthma as high as 20% and 50% (12). We showed the frequency of sensitization 16%, but in asthmatics even 71%. Therefore, the early-onset food sensitization, starting before age 2 years, would appear to be feasible clinical tool when predicting persistent asthma in young wheezing children (1, 8, 12).

The viral diagnostics has improved (5), while studies on first-time wheezing children support the role of rhinovirus aetiology and sensitization as early risk markers for recurrent wheezing (2, 3, 8, 12). This suggests that the future asthma risk could be assessed already at the time of the first wheezing episode. However, only few studies have particularly focused on the first wheezing episode (3, 5), while most bronchiolitis studies have also included crackles with or

without wheezing (2, 6, 7). Bronchiolitis is classically an RSV-induced illness in infants, whereas wheezing typically occurs in older children and is more closely linked to rhinovirus (2, 5). Thus, infant wheezing may be an important risk marker for asthma, and studies on bronchiolitis should clearly define wheezing status of the subjects.

Previously, we showed that early OCS halved the risk of recurrent wheezing in children with the first rhinovirus-induced wheezing and/or eczema (3). Likewise, our new results show that early OCS might reduce the risk for needing long-term asthma therapy only in children with the first rhinovirus-induced wheezing. However, this possible risk-reducing effect of prednisolone for an acute rhinovirus-induced wheezing could not be confirmed as clearly in another study by our group (4) compared with current study, presumably due to differences in sensitivities of polymerase chain reaction (PCR) techniques (real-time PCR, which more efficiently detects rhinoviruses also in lower loads *vs.* the conventional PCR without quantitative properties) and the delay in the initiation of intervention (45 *vs.* 0 hours) due to completion of rhinovirus PCR (4).

The strengths of our study include complete analysis of atopic characteristics and virus aetiology, 7-year follow-up, and initially controlled and randomized study design without delay in study drug initiation. Our novel ideas to childhood asthma risk assessment were the development of a new, illustrative outcome, and to focus on the hospitalized, first-time wheezing children considering them a high-risk population. Therefore, the results may not be generalised for outpatient care unlike studies on birth cohorts. Therapy duration was confirmed from health care records and parental interviews, which endorses high adherence to the therapy. The long-term ICS asthma therapy was generally started after 3 physician-confirmed wheezing episodes within a year, mainly adapted from the National Asthma

Education and Prevention Program (NAEPP) (1, 3). There are also limitations. Subgroups were analysed *post hoc* and subgroup sizes were small. The PCR detection covered rhinovirus A, B and C species, but they were not sequenced.

In conclusion, we consider clinically newsworthy that this study on high asthma risk children shows an association between early food allergen sensitization and increased risk for persistent asthma until school-age.

Minna Lukkarinen¹, Tytti Vuorinen², Pasi Lehtinen¹, Olli Ruuskanen¹ & Tuomas Jartti¹

¹Department of Pediatrics, Turku University Hospital; ²Department of Clinical Virology, Division of Microbiology and Genetics, Turku University Hospital, both in Turku, Finland

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Table. Distribution of risk factors at study entry

Risk factor	Entire cohort	7-year follow-up					
		Children with asthma therapy			Children without asthma therapy		
		All	Prednisolone	Placebo	All	Prednisolone	Placebo
	111	51/111 (46)	24/51 (47)	27/51 (53)	60/111 (54)	31/60 (52)	29/60 (48)
Age							
3-11 months	51 (46)	27/51 (53)	12/27 (44)	15/27 (56)	24/60 (47)	13/24 (54)	11/24 (46)
12-35 months	60 (54)	24/60 (40)	12/24 (50)	12/24 (50)	36/60 (60)	18/36 (50)	18/36 (50)
Sex							
Male	75 (68)	37/75 (49)	18/37 (49)	19/37 (51)	38/75 (51)	16/38 (42)	22/38 (58)
Female	36 (32)	14/36 (39)	6/14 (43)	8/14 (57)	22/36 (61)	15/22 (68)	7/22 (32)
Eczema							
Yes	36 (32)	20/36 (56)	7/20 (35)	13/20 (65)	16/36 (44)	8/16 (50)	8/16 (50)
No	75 (68)	31/75 (41)	17/31 (55)	14/31 (45)	44/75 (59)	23/44 (52)	21/44 (48)
Sensitization*							
Any allergen	17/109 (16)	12/17 (71)	7/12 (58)	5/12 (42)	5/17 (29)	2/5 (40)	3/5 (60)
None	94 (85)	39/94 (41)	17/39 (44)	22/39 (56)	55/94 (59)	29/55 (53)	26/55 (47)
Food allergens	16 (14)	11/16 (69)	7/11 (64)	4/11 (36)	5/16 (31)	2/5 (40)	3/5 (60)
Aeroallergens	3 (3)	3/3 (100)	1/3 (33)	2/3 (67)	0 (0)	0 (0)	0 (0)
Seasonal allergens	3 (3)	3/3 (100)	1/3 (33)	2/3 (67)	0 (0)	0 (0)	0 (0)
Perennial allergens	2 (2)	2/2 (100)	1/2 (50)	1/2 (50)	0 (0)	0 (0)	0 (0)
Blood eosinophil count							
<0.4 x 10 ⁹ /l	81 (73)	39/81 (48)	19/39 (49)	20/39 (51)	42/81 (52)	23/42 (55)	19/42 (45)
≥0.4 x 10 ⁹ /l	30 (27)	12/30 (40)	5/12 (42)	7/12 (58)	18/30 (60)	8/18 (44)	10/18 (56)
Parental asthma	18 (16)	8/18 (44)	5/8 (63)	3/8 (37)	10/18 (56)	5/10 (50)	5/10 (50)
Parental smoking	48 (43)	23/48 (48)	10/23 (43)	13/23 (57)	25/48 (52)	11/25 (44)	14/25 (56)
Day care							
Home	78 (70)	35/78 (45)	16/35 (46)	19/35 (54)	43/78 (55)	25/43 (58)	18/43 (42)
Family day	17 (15)	6/17 (35)	4/6 (67)	2/6 (33)	11/17 (65)	4/11 (36)	7/11 (64)
care							
Viral aetiology							
RSV	44 (40)	12/44 (27)	7/12 (58)	5/12 (42)	32/44 (73)	18/32 (56)	14/32 (44)
rhinovirus	34 (30)	19/34 (56)	7/19 (37)	12/19 (63)	15/34 (44)	10/15 (67)	5/15 (33)
rhinovirus-/RSV-negative	33 (30)	20/33 (61)	10/20 (50)	10/20 (50)	13/33 (39)	3/13 (23)	10/13 (77)

Data presented as n/N (%). RSV: respiratory syncytial virus.

* Sensitization was specified as IgE antibodies against any general allergen (cut-off level 0.35 kU/l for codfish, cow's milk, egg, peanut, soybean, wheat, cat, dog, horse, birch, mugwort, timothy, *Cladosporium herbarum* and *Dermatophagoides pteronyssinus*; fluoro-enzyme immunoassay, CAP FEIA, Phadiatop Combi[®], Phadia, Uppsala, Sweden). Aeroallergen sensitization was specified as allergen specific IgE antibodies against common allergens.

Legends to the figures

FIGURE 1: The yearly proportion of asthma therapy use and risk (OR) for asthma control therapy with inhaled corticosteroids in different ages during the 7-year follow-up a) in univariable model and b) by treatment effect between intervention (prednisolone vs. placebo) and rhinovirus status.

The p values indicate risk testing for asthma control therapy at 0 to 7 years of age.

Risk assessed with the logistic regression (n = 111).

CI: confidence interval, NA: Not applicable, OR: Odds ratio.

FIGURE 2: Time to the end of regular asthma control therapy during the 7-year follow-up.

Risk assessed with the Cox model (n = 111).

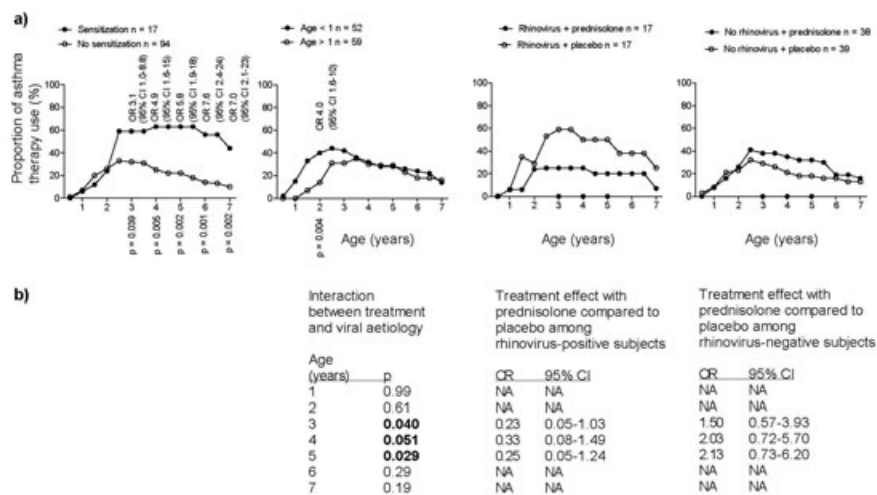


FIGURE 1

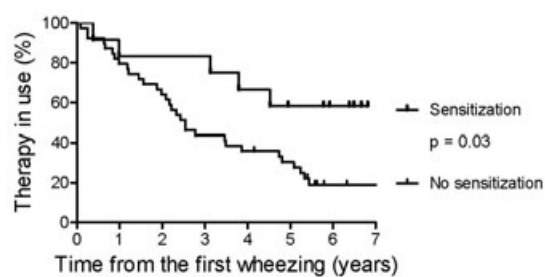


FIGURE 2

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 need *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 or blood 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-confirmation?
Are there still asthma symptoms and a need for doctor-prescribed 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-confirmation?
Are there still asthma symptoms and a need for doctor-prescribed 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 ever **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 ON ADMISSION FOR VINKU-STUDY

1. Does your child have an out-patient family paediatrician?

1) No	2) Yes, Dr _____ practicing in _____
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2. Day care?

Home	Family day care	Day care center
Other, what? _____		

3. Home

House	Apartment building	Row house
Farm	Other, what? _____	

4. Number of children in the family _____

5. Parents' smoking?

	1) No 2) Yes, if they smoke, do they smoke
inside the home	1) No 2) Yes
in the car	1) No 2) Yes

6. Is there at home

dog	1) No 2) Yes
cat	1) No 2) Yes
other animals	1) No 2) Yes, what? _____
feather pillows/blankets	1) No 2) Yes
fitted carpet	1) No 2) Yes

7. Are there at day care?

pets/animals	1) No 2) Yes, what? _____
smoking	1) No 2) Yes

8. Does the child visit weekly places where there are

animals	1) No 2) Yes
smoking	1) No 2) Yes

9. Are there other family members with allergic symptoms?

eczema	1) No	2) Yes, mother/ father/ sisters
rhinitis	1) No	2) Yes, mother/ father/ sisters
asthma	1) No	2) Yes, mother/ father/ sisters

10. Does your child (the one in this study) have allergic symptoms? Please, mark the suspected source on the reverse side.

eczema	1) No	2) Yes
rhinitis	1) No	2) Yes
asthmatic	1) No	2) Yes

11. Does your child have an “allergy diet”?

1) No	2) Yes. Please, specify the diet to study nurse.
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12. Have the skin prick tests been done to your child?

1) No	2) Yes, when ___/___(mo/yr), where _____
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13. Information about **allergies** (please circle the suspected sources):

Dietary; chocolate, cocoa, citrus, egg, fish, tomato, strawberry, pea, apple, carrot, nuts, pear, peach, cow's milk, breast milk substitute, rye, barley, oats, wheat

other _____

Animals; dog, cat, horse, cow, guinea pig, feather

other _____

Pollen; birch, alder, conifer, hay, mugwort

other _____

Other causes; room dust, fungal spore

other _____

14. Information about the child's respiratory infections:

During the **last 12 months:**

"common cold"	_____ times
antibiotic prescription	_____ times
pneumonias	_____ times
bronchitis	_____ times
otitis	_____ times
parasentesis	_____ times
other, what?	_____

Adenoidectomy 1) No 2) Yes, when ___/___ (mo/yr), where _____

Parasentesis 1) No 2) Yes, when ___/___ (mo/yr), where _____

15. Information about breathing difficulty symptoms:

Were there "common cold" symptoms during the **current** difficulty in breathing?

1) No 2) Yes 3) I can not say

If you suspect other causes, please name them;

How long was the difficulty in breathing before admission to hospital acute care? _____ hours.

Have other family members had "common cold" symptoms?

1) No 2) Yes

16. How many difficulties in breathing has your child had during the life (including the current one) _____

The first difficulty was ___/___ (mo/yr)

During the **last 12 months:**

How many times has your child had difficulties in breathing? _____ times

How many times has the child been to hospital because of breathing difficulties?

at the hospital acute care _____ times

on the hospital ward _____ times

Breathing difficulties have previously appeared only with the “common cold”?

1) No 2) Yes

If you suspect other causes, please name them;

_____, _____, _____

Does your child have a booked appointment to a pediatrician for his/hers breathing difficulty?

Date __/__/__, where _____

17. Does your child have the daily/ regular asthma medication?

1) No 2) Yes, what?

medicine	dose/day	divice (f ex Spira, Babyhaler)	Started (mo/yr)	Where
_____	_____	_____	__/____	_____
_____	_____	_____	__/____	_____
_____	_____	_____	__/____	_____

18. Information about the **prolonged cough/ asthma**:

How old was your child when the symptoms started? _____ years.

The child has had prolonged (=over 4 weeks)

cough or coughing attacks	1) No	2) Yes
wheezy breathing	1) No	2) Yes
difficulty in breathing	1) No	2) Yes
nocturnal cough	1) No	2) Yes

The child has symptoms

during the “common cold”	1) No	2) Yes
in contact with animals/pollen	1) No	2) Yes
in contact smoking	1) No	2) Yes
in exercise	1) No	2) Yes
when laughing/crying	1) No	2) Yes
when cold outside	1) No	2) Yes

How many times has your child had symptoms during the last 12 months?

1-4 times	1) No	2) Yes
4-6 times	1) No	2) Yes
monthly	1) No	2) Yes
weekly	1) No	2) Yes
daily	1) No	2) Yes
often nightly	1) No	2) Yes

19. Information about rash/eczema:

Eczema started at (age) _____.

Eczema appeared first time in

face 1) No 2) Yes

bends 1) No 2) Yes

other location, where? _____

Eczema is currently situated in

bends 1) No 2) Yes

other location, where? _____

Eczema appears year-round? 1) No 2) Yes

Eczema gets worse in certain time-of-year? 1) No 2) Yes

Eczema disappears periodically? 1) No 2) Yes

Eczema gets worse with

swetting 1) No 2) Yes

food 1) No 2) Yes

colourants in clothing 1) No 2) Yes

sauna 1) No 2) Yes

other, what? _____

Eczema is itching at nighttime? 1) No 2) Yes

What kind of creams have been used for the eczema? _____

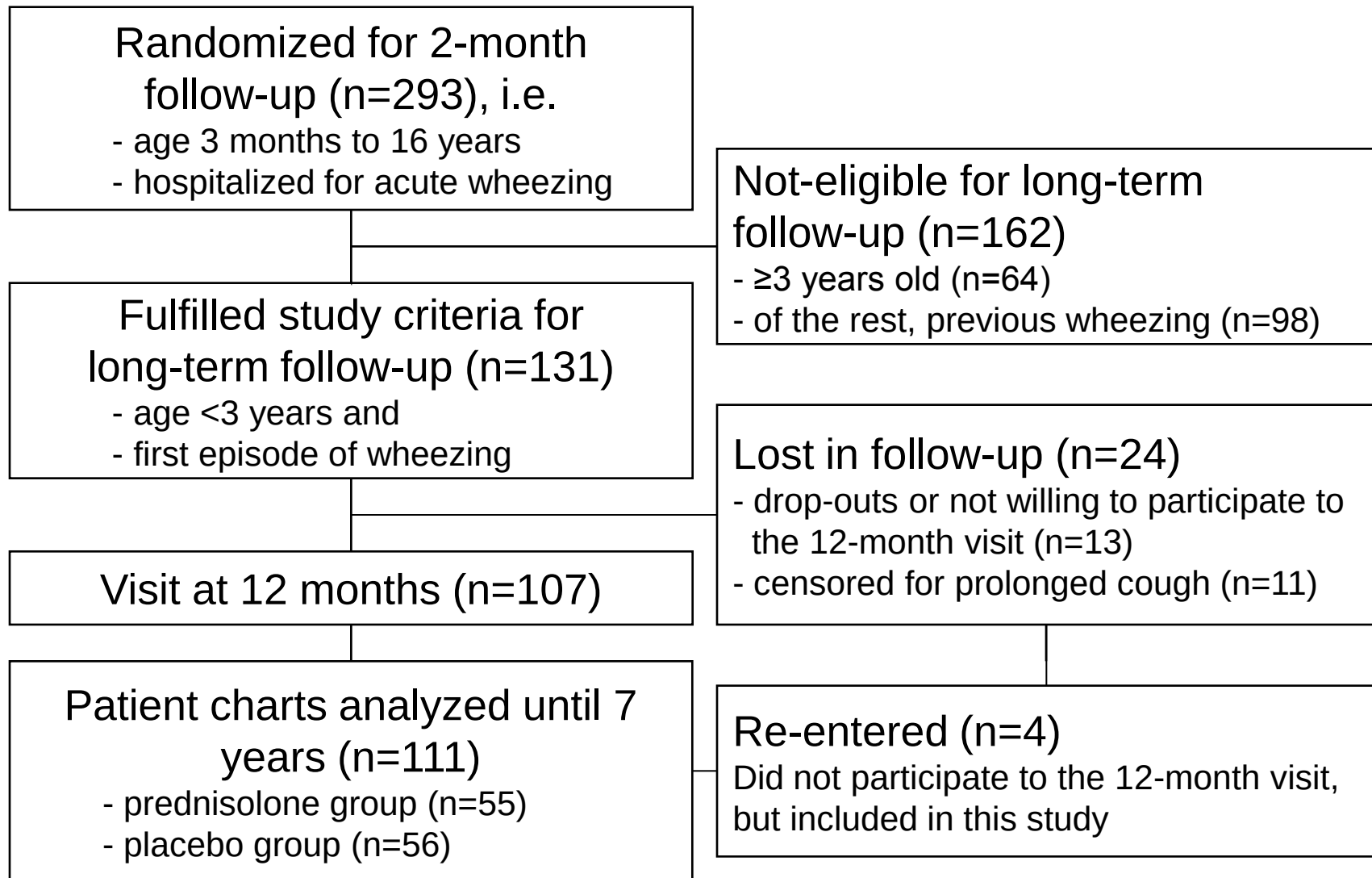


FIGURE 1