

The significance of early recurrent wheeze for asthma outcomes in late childhood

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ONLINE SUPPLEMENTARY

METHODS:

Skin prick tests:

Skin prick tests to common inhalant and food allergens were performed in 548. Sensitisation was considered positive if wheal diameter was ≥ 3 mm larger than the negative control (NaCl) (1). The following allergens were used:

Alyostal® (Stallergenes, France): dermatophagoides farinae, cockroach, mugwort.

ALK prick SQ® (ALK Scherax, Germany): grass, alternaria alternata, cat and dog dander

Allergopharma® (Denmark): birch, cladosporium herbarum, aspergillus fumigatus, hazel and alder.

Cow's milk (diluted 1:10 with 0,9% saline).

Metacholine challenge:

A methacholine challenge test with controlled tidal breathing was used to assess BHR according to ATS' guidelines. A baseline lung function measurement, post saline inhalation, was followed by inhalation of doubling methacholine doses via a SPIRA® dosimeter (Spira Respiratory Care Center Ltd, Hemeelinna, Finland). The children inhaled with a flow of 0.5 l/s, the aerosolisation started after 100ml air was inhaled from functional respiratory capacity and the aerosol delivery time was set to 0.5 seconds. The first dose was 0.05 μ mol and the test continued until a fall ≥ 20 % compared to post-saline (baseline) FEV₁ or the maximum dose of 22.4 μ mol methacholine was reached. PD₂₀ was calculated as the estimated cumulative methacholine dose required to reduce FEV₁ by 20% compared to baseline. Based upon

previously used cut-off values, we defined mild, moderate and severe BHR as $PD_{20} \leq 8 \mu\text{mol}$ (2).

Results:

Prognosis by reported wheeze

The prognosis of rBO as regards reported wheeze from 2-10 and 10–16 years of age, is given in figure 4. Wheeze was reported in 47 % of the rBO-subjects from 10-16 years of age, as opposed to 34 % fulfilling asthma criteria in the same period. Also, only 53% were in "rBO wheeze-remission" 10-16 years compared to 66% in remission in the same time-period as classified by a diagnosis of asthma (Supplementary figure 1).

Reference List

- (1) Position paper: Allergen standardization and skin tests. The European Academy of Allergology and Clinical Immunology. *Allergy* 1993;48(14 Suppl):48-82.
- (2) Hewitt DJ. Interpretation of the "positive" methacholine challenge. *Am J Ind Med* 2008 October;51(10):769-81.

Supplementary table 1:

Demography at 10 years of the 540 children participating at the 16-year follow up compared to the non-attending at 16 (n=479).

Demography at 10 years	Included 16 (n=540)	Nonincluded 16 (n=479)	p-value vs non- included
Gender boys (%(n))	52,3 (282)	55,6 (257)	0,3
Age at 10 years (mean (SD))	10,7 (0,8)	10,9 (0,8)	<0,001
Weight (mean (SD))	37,8 (7,6)	39,6 (8,5)	<0,001
Height cm (mean (SD))	145,3 (7,6)	146,6 (8,0)	0,007
Asthma ever (%(n))	30,7 (165)	28,9 (138)	0,5
Active asthma (%(n))	11,9 (64)	12,6 (60)	0,8
Family history of asthma (%(n))	23,2 (125)	26,0 (125)	0,3
Maternal smoking at birth (%(n))	14,8 (80)	19,8 (95)	0,04
Smoking at home (%(n))	13,2 (71)	16,5 (79)	0,1
Atopic dermatitis (%(n))	37,2 (200)	34,2 (163)	0,3
FEV1% (mean (SD))	97,4 (9,2)	97,3 (10,0)	0,9
FEF50% (mean (SD))	97,65 (20,00)	99,10 (22,37)	0,5
FVC%	98,1 (9,5)	97,7 (9,8)	0,5
FEV1/FVC	0,98 (0,06)	0,98 (0,07)	0,5
FeNO ppb (mean (SD))	8,5 (8,7)	8,9 (7,1)	0,5
At least 1 specific IgE <0,35 (%(n))	31,5 (165)	39,3 (179)	0,01
SPT any pos (%(n))	26,0 (140)	32,7 (154)	0,02

Asthma ever: fulfilling asthma criteria. Active asthma: fulfilling asthma criteria and reporting symptoms and/or use of asthma medication within last 12 months. FeNO: exhaled nitric oxide.
ppb: particles per billion

Supplementary table 2:

Questions from the ECA-questionnaires used in the present study.

Period	Question
6 months	<p>Has the child had periods/episodes with heavy or laboured breathing?</p> <p>If so, how many episodes/periods?</p> <p>Has the child had periods/episodes with unusually rapid breathing?</p> <p>Has the child had periods/episodes for more than one week with</p> <p>troublesome cough?</p> <p>Has the child been coughing at night/in the morning/when</p> <p>crying/upset etc without having a cold?</p> <p>Has the child been examined by a physician due to airway</p>
12, 18 and 24 months	<p>symptoms?</p> <p>Has the child had period(s) with heavy or laboured breathing with</p> <p>wheezing/rattling/whistling sounds form the chest when having a</p> <p>cold/bronchitis etc?</p> <p>Has the child had period(s) with heavy or laboured breathing with</p> <p>wheezing/rattling/whistling sounds form the chest without having a</p> <p>cold/bronchitis etc?</p> <p>Description of type and duration of symptoms and doctor's diagnosis</p> <p>for each episode</p> <p>Has the child had period(s) with prolonged (more than 14 days)</p> <p>troublesome cough at night / in the morning without having a</p> <p>cold/bronchitis etc?</p> <p>Does the child cough severely or have wheezy breathing (asthmatic</p> <p>breathing) when it is cold, humid, foggy etc?</p>

10 years

Has the child had heavy breathing, chest tightness or wheezing from the chest? (From 0-3 years and from 4-10 years respectively)

Has the child had dry cough at night without having a cold or other lower airways infections?

Has the child ever been diagnosed with asthma?

Has the child ever used medication for the lower airways (excluding antitussive syrups)?

Has the child used (as home treatment): Short acting β_2 -agonist, long acting β_2 -agonist, sodium chromoglycate, inhalation corticosteroid, leukotrieneantagonists, ipratropiumbromide, epinephrine, aminophylline, hyposensitisation, systemical corticosteroids, omalizumab

(With information notification of use after 4 years, last 12 months or last 14 days)

16 years

As at 10 years with the exception that the questions were formulated;

”Have you after 10 years of age...”

Supplementary table 3

Assessments of influence by maternal and parental smoking and lung function for the effect of rBO on asthma from 10 to 16 years. Although maternal smoking and t_{PTEF}/t_E were not significant predictors, reduced lung function at birth significantly reduced the influence of rBO on asthma from 10 to 16 years.

Birth	Explanatory variable	OR(95CI)	p-value	2 years	Explanatory variable	OR(95CI)	p-value
Univariate	rBO	2.98(1.91,4.64)	<0.001	Univariate	rBO	2.98(1.91,4.64)	<0.001
Multivariate 1	rBO	2.96(1.90,4.62)	<0.001	Multivariate 1	rBO	2.85(1.79,4.55)	<0.001
	Maternal smoking	1.12(0.68,1.83)	0.66		Parental indoor smoking	0.88(0.51,1.51)	0.64
Multivariate 2	rBO	2.13(0.92,4.91)	0.08	Multivariate 2	rBO	2.58(1.12,5.96)	0.03
	Maternal smoking	1.06(0.53,2.11)	0.87		Parental indoor smoking	0.83(0.32,2.16)	0.70
	t_{PTEF}/t_E -birth	0.17(0.011,2.53)	0.29		t_{PTEF}/t_E -2yrs	3.30(0.09,117.40)	0.51

Figure Legend:

Supplementary figure 1: Flow chart describing the incidence, remission and relapse-rates for rBO and non-rBO/never asthma- subjects with regards to reported wheeze through the periods 2-10 and 10-16 years. Percentages describe the rate either changing or maintaining status concerning asthma between the given periods.

Supplementary figure 1

