EUROPEAN RESPIRATORY SOCIETY
ANNUAL CONGRESS 2009
VIENNA, AUSTRIA, SEPTEMBER 12–16

E-communication : E4254

Childhood wheeze: one or several diseases?

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BACKGROUND & AIMS:

For several decades it has disputed whether childhood wheeze represents a single disease with a continuous spectrum of variability such as a severity gradient (here referred to as ' gradient model' - possibly more than one gradients exist, for instance degree of atopy and frequency of episodes), or whether it consists of discrete disease subgroups, here referred to as phenotypes ('phenotype model').
Using a statistical approach suited to analyse this type of question, we assessed which of these models better explained cross-sectional data on symptoms in children 1-8 years of age.

METHODS

Population

We used data from repeated questionnaire surveys (1998, 2001, 2003) of a population based (N=4400) childhood cohort in Leicestershire, UK [1]. Including only children with current wheeze (past 12 months), we separately analysed data on symptoms at ages 1-2 years (N=451), 3-4 years (N=426), and 5-8 years (N=423).

Symptoms included

We included the following respiratory symptoms:

- Wheezing: frequency of attacks; shortness of breath (SOB); triggers (colds; exercise; eating and drinking; animals; dust; grass or hay); sleep disturbance; interference with activities
- Coughing: cough usually with colds, cough also without colds; dry cough at night
- Ears, nose and throat: frequency of colds; sneezing, runny or blocked nose; other throat infections.

Statistical analysis

We fitted different latent variable models each designed to model a different type of underlying variability [2, 3]:
A gradient model: only one phenotype, one or more gradients (factor analysis),
B phenotype model: more than one phenotypes and no gradients (latent class analysis),
C combination model: more than one phenotypes and a gradient within each group (factor mixture modelling).
We compared the performance of these models using the Bayesian Information Criterion (BIC). Low BIC values indicate good performance.

RESULTS

1. In all age groups, gradient models performed better (lower BIC) than phenotype or combined models (**Table**).
2. In the youngest age group a single gradient model was preferred while in the older age groups two gradients were preferred.
3. The first of these gradients (observed in all three age groups) was mainly determined by indicators of severity of wheeze: frequency of attacks, SOB, sleep and activity disturbance. A second gradient (observed in the two older age groups, particularly in 5-8 year olds) related to the following triggers of wheeze: animals, dust, grass or hay.

DISCUSSION

These results, which are based on cross-sectional data on reported symptoms, suggest that the occurrence of respiratory symptoms varies between children with wheeze along few continuous disease dimensions (severity gradients) and the data provide no evidence that children cluster together into discrete groups or phenotypes. The results show that frequency of wheeze, and airway reactivity to aero-allergens capture two important dimensions of variability. Such dimensions likely reflect the intensity of different underlying disease mechanisms. These findings need not conflict with existing classifications of childhood wheeze into discrete phenotypes (e.g. early 'transient wheeze', 'persistent wheeze'; or 'exclusive viral wheeze' or 'multiple trigger wheeze') as such categories may represent different ends of a continuous dimension. However continuous dimensions, such as the factors obtained in the present factor analyses, may better reflect the true variability between individuals and be more informative of underlying disease processes.
The data used in this study were parent reported and cross-sectional. Possibly, children do naturally cluster into groups with respect to objective measurements (lung function, bronchial responsiveness, atopy, bronchial inflammation) and/or time course of disease. Therefore future studies on this issue should also include physiological measurements and longitudinal data.

REFERENCES

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Table: Statistical performance of gradient vs phenotype models
Minimum BIC across a row (shading) indicates preferred model for that age group

Type of model	A Gradient model		B Phenotype model			C Combination model
No of phenotypes	1	1	2	3	4	2
No of gradients	1	2	0	0	0	1
1-2 yrs (n=451)	10302	10304	10491	10539	10623	10450
3-4 yrs (n=426)	10230	10187	10437	10464	10541	10306
5-8 yrs (n=423)	9345	9334	9508	9540	9608	9428