The Leicester Cohorts

Non-specific chronic cough in children: a novel approach to phenotype identification

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Introduction

Non-specific chronic cough is a frequent problem in paediatric primary care. While some authors have proposed that many affected children suffer from a variant form of asthma, there still is no agreed classification of coughing disorders.

Aim

Using a novel statistical approach, we investigated whether there was evidence for the existence of several distinct clinical phenotypes within the group of children with chronic cough.

Methods

From a population-based cohort study, we included all preschool children reporting chronic cough or wheeze in at least one of two surveys (N=319). The surveys were carried out when the children were aged 1-5 and 4-8 years respectively. We employed a probabilistic clustering approach (*latent class modelling*) which allowed for the simultaneous modelling of both qualitative and quantitative data. In this approach a set of observable features (e.g. symptoms or physiological measurements) is modelled using a single unobservable categorical variable. The categories of this variable (the latent classes) can be interpreted as clinical phenotypes. After the model has been fitted each child can be assigned to the phenotype that it is most likely to belong to.

Features included

-age
-gender

symptoms reported in both surveys (repeated measures at ages 1-5 and 4-8 years):
- wheeze ever
- frequency of attacks
- shortness of breath
- triggers of wheeze (colds/other)
- seasonal variation of wheeze (winter/summer)
- diurnal variation of wheeze (day/night)
- awake at night with cough
- triggers of cough (colds/other)

physiological measurements (at age 4-8 years):
- skin-prick tests (cat, dog, house dust mite, and mixed grass pollens)
- lung function (FEV0.5)
- airway responsiveness (PC20tc-PO2).

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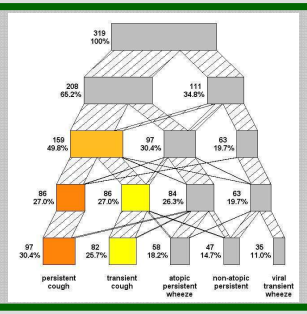
Results - Identified phenotypes

Beginning with a model with only one phenotype we proceeded stepwise by refitting the model with an additional phenotype in each step. A distinction between "coughers" (children with cough without colds but no wheeze) and "wheezers" (children with wheeze ever) began at an early stage in a model with only 3 phenotypes. Including an additional phenotype in the model led to a division of the coughers into a persistent and a transient group (4-phenotype model). These two cough phenotypes remained stable as the number of phenotypes was increased further.



The figure illustrates the formation of phenotypes as their number is increased. Dark shaded boxes in a given layer represent clusters of children belonging to the phenotypes of a single model. The size of each cluster is represented by the box widths and is also reported in numbers of children and percentage of sample beside the boxes. shaded bars connecting the layers represent the proportion of children in the phenotypes of a given model which are assigned to the phenotypes of a model including one more phenotype (next lower layer). Various statistical criteria indicated that a model with more than five phenotypes was overfitting the data. For this reason we present a 5-phenotype model.

Results - Association between phenotypes and variables included in the model

Persistent coughers were more likely to report wheeze ever than transient coughers. Compared with transient coughers (and with the asymptomatic control sample) persistent coughers had a reduced lung function and slightly increased bronchial responsiveness, though not as much as persistent atopic wheezers.

	Persistent cough (n=97)		Transient cough (n=82)		Persistent atopic wheeze (n=58)		Asymptomatics (n=169)
Survey	1990	1992-4	1990	1992-4	1990	1992-4	
Wheeze ever	0.24	0.26	0.09	0.15	0.75	0.91	
Wakened by cough at night	0.32	0.69	0.79	0.19	0.82	0.63	
Cough only with colds*	0.29	0.00	0.00	0.85	0.40	0.38	
Cough also apart from colds*	0.63	1.00	1.00	0.00	0.49	0.53	
Skin prick tests (probability of ≥1 positive)	0.19		0.16		0.70		0.11
Mean $FEV_{0.5}$ (z-scores)	-1.59		-1.18		-1.80		-1.33
Geom. mean bronchial challenge (PC_{20} g/L)	2.42		2.75		1.26		3.82

*Residual category = No cough

- Association between phenotypes and variables not included in the model

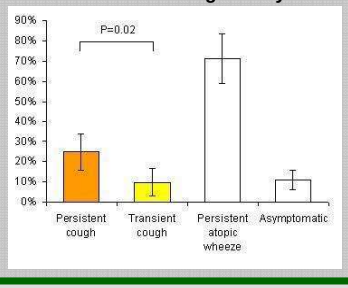
Comparing short term prognosis

At schoolage persistent coughers were much more likely to cough apart from colds than transient coughers (and aysmptomatics) and also more likely to report current wheeze.

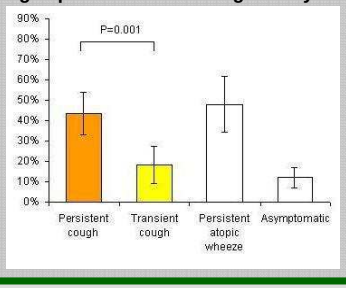
Comparing prevalence of putative risk factors

The two cougher groups differed significantly in prevalence of parental smoking at home (persistent coughers: 51%; transient coughers: 34%; P=0.03), but not in other measured factors.

Current wheeze at age 8-13 years



Cough apart from colds at age 8-13 years



Conclusions

This novel approach allowed to identify 2 distinct phenotypes* of non-specific chronic cough in preschool children:

1. A 'persistent cough' phenotype characterised by persistent chronic cough with poor prognosis into schoolage, and features are compatible with cough variant asthma. Parental smoking at home may be an important risk factor for this phenotype.
2. A 'transient cough' phenotype characterised by a transient period of cough apart from colds early in life and good prognosis into childhood.

This method is exploratory and validation is required in independent cohorts.

*Because of the statistical technique, which takes many features into account, the two phenotypes exhibit a degree of overlap in any one of their features. We have chosen their names for convenience in discussion.