The role of IgG and IgE in the development of allergy and asthma
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Chapter 9

Methodological Issues
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In this final chapter, some methodological issues of the findings and implications for daily practice are raised. The findings, particularly those of our study on IgE antibodies as to the prediction of asthma, invite further discussion, which will focus on the definition of asthma, diagnostic studies, and generalizability.

We developed a clinical prediction rule to assess the predictive accuracy of IgE tests in the diagnosis of asthma. Given the diagnostic information from the clinical history, IgE tests provided additional information on the probability of asthma. The results of our study in coughing children agree with the results from earlier studies [1-3]. In these studies in wheezing children, the value of IgE tests was examined in isolation, without reference to diagnostic information that is available in a diagnostic work-up in practice.

One study [4] also developed a clinical index or prediction rule, but did not evaluate the added value of the tests. Their stringent and loose index included frequent wheeze under the age of three, parental history of asthma or eczema, eosinophilia, wheezing without colds, and allergic rhinitis. However, this study was performed in an open population and it is therefore questionable whether it is applicable in a general practice setting. In addition, the definition of asthma was left to the individual physicians or was based on more than three episodes of wheezing during the previous year.

Definition of asthma /'gold standard'

In many diagnostic studies it is important to have a technique that measures the presence of the target disease in an objective and independent way, which is 100% valid. Such a technique is called a reference standard or 'gold standard' [5]. However, for asthma in young children no such technique exists [6,7]. In our studies we used both a doctor's diagnosis of asthma (in chapter 6) and asthma based on a lung function test and symptoms (chapters 7 and 8). Since the medical record's study (chapter 6) was performed when the children were younger than six years of age, we had to
depart from a doctor’s diagnosis of asthma. In the study presented in chapters 7 and 8, we were able to define asthma consistently, basing it on symptoms and/or medication and lung function test result. In addition, the GPs were asked whether the children had been given an asthma diagnosis. There were 108 children with both asthma according to the study criteria and on their GP’s judgement. These two diagnoses of asthma did not match very well, with $\kappa=0.51$. We calculated a 18.5% disagreement between physician-based diagnosis of asthma and asthma according to the study criteria; if asthma based on symptoms and lung function is considered to be the gold standard, GPs both underdiagnose (17%) and overdiagnose (26%) asthma. We decided not to use the physician-based classification in the final analysis of this study. In our study, lung function was tested by one pulmonary nurse according to a standard protocol [8], whereas a physician-based diagnosis of asthma was given by forty-seven GPs who had not been instructed how to diagnose asthma according to a common algorithm. Since, in theory, each GP may have used his own “algorithm”, the diagnostic indicators whose predictive impact we might want to calculate are not interpretable. Although GPs usually diagnose asthma according to the Dutch guidelines for General Practitioners [9], these guidelines leave much room for interpretation, e.g. most airway symptoms are not quantified. In conclusion, the results of a predictive function cannot be interpreted without a protocol for diagnosing asthma.

**Diagnostic study**

Diagnostic practice is a process that starts with a patient with symptoms and signs. To get more diagnostic certainty in the discrimination of presence or absence of the disease, the results of added laboratory tests can be used. The aim in diagnostic studies is to find those determinants or tests that together discriminate best between absence and presence of target disease. First, optimal prediction pursued using information that become available early in the diagnostic work-up and often virtually for free (clinical history, physical
examination). Next, the diagnostic impact of added information that does not come for free (lab tests, imaging) is estimated conditional on the information already available.

The prediction rules we constructed should be tested in another primary care population as these prediction rules usually perform better in a population in which the rule is constructed than in an independent data set [10]. Therefore, a resampling technique called bootstrapping was used to adjust regression coefficients and counteract over-optimism [10]. However, research shows that even after resampling techniques, external validation of a prediction model is still necessary before implementation in practice [11].

**Generalizability: general practice**

For theoretical and empirical reasons, the idea that there is one sensitivity or specificity associated with a particular kind of test irrespective of other clinical circumstances should generally be given up. It is unlikely that, for example, the association between wheezing and asthma is identical in a group of children in the open population, a general practice population, and a population seen by a pulmonologist. Whereas in our study wheezing proved to be strongly associated with (the development of) asthma, a pulmonologist may find weaker associations, since it may be expected that wheezing will be present in almost all children s/he suspects of having asthma. Learning that a child wheezes, does not give the pulmonologist additional diagnostic information.

The implication for the model that we developed is that its applicability is limited to a general practice population. In theory, the predictive function in e.g. chapter 7 would be valid in the open population if the parents' decision to visit the GP was completely unrelated to the probability of asthma being present at the age of six. We think that the latter is too extreme an assumption. However, from the outset the aim of the study has been to produce a predictive instrument for GPs, and the selection step introduced by the parents should not be seen as a bias.
In diagnostic studies, patients should be selected on the basis of the presenting problem that triggers a particular set of differential diagnostic possibilities. In our study, the presenting complaint was coughing for at least five consecutive days, presented in general practice. The criterion of five days of coughing is an arbitrary criterion. This criterion was chosen after consultation with the participating GPs. They said that, in general practice, children with "simple" respiratory infections would have been excluded after five days. Indeed, in our population of pre-school children presenting with coughing for at least five days, 13% of these children were sensitized (>0.5 U/ml) to mites and animal dander. This indicates that this rather simple criterion is of great value for general practice. Coughing for five days or more seems to be a relevant first selection criterion to identify sensitization among these children.

**Treatment paradox**

Our predictive model did not involve treatment. Some children in the study may have received some form(s) of (intermittent) treatment, which - if effective- may have influenced the health status at the age of six. Under such circumstances, a model's predictive power is reduced unless treatment is explicitly incorporated in the model. It is currently controversial to which extent asthma treatment may cure or prevent asthma, thus causing misclassification on health status in our model. The picture becomes slightly more complicated when one realizes that a lung function test does not have a dichotomous result inherently, but is interpreted as positive or negative based on a cut-off value. This implies that even treatment that partly improves some aspects of airway functioning may cause some misclassification on health status. Assuming that the prevalence of effective treatment in our study population is typical of that in a general practice setting, the overall predictive power of our model might still hold. However, for particular individual children the estimated probabilities may be wrong dependent on their treatment.
In some cases, the knowledge of the child’s allergy-status shortly after the first blood sample was taken, could have altered the management over the follow-up period. Furthermore, it can have improved the symptoms of the children or altered symptom-perception by the parents. As the definition of asthma was based on both symptoms and/or medication and lung function, this might have influenced the development (or diagnosis of) asthma. In that case, our study would have underestimated the association between IgE and asthma. The above-mentioned mechanisms appear to have been small or non-operative as judged by the fact that analyses with asthma based on lung function only showed similar results for the estimated probabilities and ROC curve.

Implications for future research and daily practice

Although many researchers have studied asthma and allergy, this study is one of the few constructing a clinical prediction rule and evaluating the added value of allergy tests for the diagnosis of asthma in young children in general practice.

IgE testing in children under four is not in line with the Dutch guidelines for General Practitioners [9]. In these guidelines, allergy testing in these children is not recommended because it is argued that a negative test does not rule out that a child will become positive in the future. In our study, 12.3% of the children younger than four years of age were sensitized. If GPs adhered to the NHG-guidelines, these children would not have been tested in daily life. Not knowing whether a child is sensitized or not can have implications for adequate treatment and management as well as for future asthma.

Recurrent cough is a very common childhood symptom. For GPs, especially the young pre-school coughing children who will or will not develop asthma are difficult to recognize. We provided practical information on probabilities of sensitization and asthma for different patient profiles that
might support the GP in decision making in persistently coughing children. Allergy tests may guide the physician to tailor asthma therapy. Further research is necessary to evaluate their true value to physicians and to show whether they lead to better therapeutic interventions and prognosis. The role of allergy tests needs to be explored further in both coughing and wheezing children.

We only evaluated the added value of allergy tests in the prediction of asthma. Other tests, that are easily performed or less troublesome for patients in general practice, might provide even better information on the prediction of asthma and allergy in general practice. Consequently, if practice changes, the prediction rule should be re-examined.

References


