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Prediction of asthma in symptomatic preschool children using exhaled nitric oxide, Rint and specific IgE

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ABSTRACT

Rationale For clinicians it remains very difficult to predict whether preschool children with symptoms suggestive of asthma will develop asthma in later childhood.

Objective To investigate whether measurement of fraction of exhaled nitric oxide (FE_{NO}), interrupter resistance (Rint) or specific immunoglobulin E (IgE) in 4-year-old children with suggestive symptoms can predict asthma symptoms up to age 8 years.

Methods Children were recruited from the PIAMA birth cohort. All children with symptoms suggestive of asthma at age 3 or 4 years, who were invited for medical examination at age 4 (n=848), were eligible. Associations of FE_{NO} (n=308), Rint (n=482) and specific IgE (n=380) at 4 years with wheezing and asthma at the ages of 5—8 years were assessed using repeated measurement analyses. The added predictive value of these objective tests was then investigated by including parameters for clinical history in the model.

Results FE_{NO} and specific IgE measured at 4 years were associated with wheezing and asthma at 8 years. Both tests also remained significant predictors after mutual adjustment and adjustment for clinical history: OR on wheezing at 8 years for FE_{NO} (^{10}log-scale, per IQR) 1.6 (95% CI 1.1 to 2.2) and for specific IgE 2.8 (95% CI 1.9 to 4.1). Rint was significantly associated with wheezing at age 6, but not at 7 and 8 years.

Conclusions In preschool children with symptoms suggestive of asthma, both FE_{NO} and specific IgE measured at age 4, but not Rint, improved the prediction of asthma symptoms until the age of 8 years, independent of clinical history.

INTRODUCTION

In preschool children, asthma-like symptoms such as wheezing and coughing are highly prevalent.[1] Unfortunately, children with transient symptoms are not easily distinguished from those with persistent asthma on the basis of reported symptoms. Objective tests to support an asthma diagnosis include spirometry, to assess airway obstruction and reversibility; bronchoprovocation, to assess airway responsiveness; and sputum induction, to measure airway inflammation, a hallmark of asthma.[2] These tests are difficult to perform in children under the age of 6 years since active cooperation is necessary.[3] Non-invasive measurement of the fraction of exhaled nitric oxide (FE_{NO}) has received much interest due its ability to reflect eosinophilic airway inflammation.[4][5] Several studies have shown elevated FE_{NO} values in children with asthma or atopy.[6—12] Moeller et al showed that FE_{NO} could distinguish between the different phenotypes of preschool wheezers.[13] However, prospective data on the prognostic value of FE_{NO} in preschool children for later symptoms are scarce. In clinical practice, measurement of FE_{NO} would only be worthwhile if it offers an added predictive value over information that is already available, such as a standard clinical history. This has not been investigated so far. Interrupter resistance (Rint) measurement can be easily performed in young children and correlates with asthma symptoms.[14—16] Specific immunoglobulin E (IgE) to inhalant allergens in young children is associated with the risk of persistence of asthma symptoms.[17—20]

The aim of our study was to investigate prospectively whether FE_{NO}, Rint and/or specific IgE at the age of 4 years in children with respiratory symptoms could be used to predict asthma symptoms up to the age of 8. We used data from the 'Prevention and Incidence of Asthma and Mite Allergy' (PIAMA) birth cohort.[21] Children were eligible if they reported 'wheeze', 'shortness of breath' or 'nightly cough without a cold' at the age of 3 or 4 years. FE_{NO}, Rint and specific IgE were measured at the age of 4 years and children were followed until the age of 8. The added value of the tests to predict asthma symptoms until the age of 8 was calculated.

METHODS

Study population

Recruitment of the PIAMA cohort took place in 1996—1997; 7862 pregnant women were invited to participate; 4146 women (53%) agreed (1327 allergic and 2819 non-allergic, based on a validated screening questionnaire).[22] Their children were followed up for 8 years, using questionnaires for parental completion, partly based on the International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaires.[23] At 4 years, all children with an allergic mother and a random sample of children with a non-allergic mother were invited for a medical examination, including measurement of FE_{NO}, Rint and specific IgE levels (n=1808). A detailed description of the study design has been published previously.[21] The study protocol was approved by the medical ethics committees of the participating university hospitals. For the current study, we selected all children who were invited for the medical examination at 4 years and who reported at least one respiratory symptom

suggestive of asthma (wheeze, shortness of breath, or cough at night without a cold) in the questionnaire at age 3 or 4 years (n=848) (figure 1).

FE$_{NO}$, Rint and specific IgE measurement

FE$_{NO}$ at age 4 was measured offline according to European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines.[24] For every child, duplicate exhaled air samples and an ambient air sample were collected in Mylar balloons, and analysed using a chemoluminescence analyser (Sievers NOA 280B, Boulder, Colorado, USA). FE$_{NO}$ was expressed in parts per billion (ppb). Rint was measured in kPa/l with MicroRint (MicroMedical, Rochester, Kent, UK) during expiration, with occlusion of the airway at peak expiratory flow. Median values for at least five acceptable measurements were calculated. Detailed descriptions of both measurement techniques were previously published.[8 16 25] Sensitisation was defined as specific IgE of ≥0.70 IU/ml for at least one of six tested airborne allergens. To assess the added predictive value of these measurements over reported clinical history, three variables previously shown to have the highest predictive value on later symptoms were selected[26]: (1) allergic mother (yes/no); (2) doctor's diagnosis of eczema ever until age 4 (yes/no); and (3) wheezing frequency during the fourth year of life (no/1–3 times per year/≥ 4 times per year). Mothers were considered 'allergic' if they reported any of the following items: asthma, hay fever, house dust allergy, house dust mite allergy or pet allergy.

Outcomes

Based on data from the annual questionnaires at age 5–8 years the following dichotomous outcomes were defined, each pertaining to the past 12 months:
► Wheezing: at least one episode
► Inhaled steroid prescription by a medical doctor
► Doctor's diagnosis of asthma: a parental report of a doctor's diagnosis of asthma at any time AND a parental report of asthma symptoms during the past 12 months.

Statistical analysis

Univariate associations between FE$_{NO}$, Rint and specific IgE measurements and respiratory outcomes were investigated with logistic regression. FE$_{NO}$ values had a right-skewed distribution; a normal distribution was achieved after ^{10}log-transformation. Generalised estimating equations were used to take into account the correlation between repeatedly measured outcomes in the same individual. Variables for clinical history were included in the model to examine additional predictive value of the tests over clinical history. The study design was stratified for allergy of the mother, and any interaction with this variable was investigated. After a complete case analysis, missing data were imputed multiple times to check for any bias that could result from complete case analysis.[27 28] The 'Multivariate Imputation by Chained Equations' (MICE) procedure in the statistical program R version 2.6.2 was used to create 10 imputed data sets (n=848).[29 30] Results were combined using PROC MIANALYZE in SAS 9.1 (SAS Institute, Carey, North Carolina, USA). Finally,

Figure 1 Flow chart of the study population. All 848 eligible children enter each of the three arms of the flowchart. *Respiratory symptoms were defined as a positive response to at least one of the following three questions: 'Has your child had wheezing or whistling in the chest in the last 12 months?' and/or 'Has your child had tightness of the chest or shortness of breath in the last 12 months?' and/or 'Has your child had a cough during the night, when he/she did not have a cold or a chest infection, in the last 12 months?' †Out of 306 children with available FE$_{NO}$ (fraction of exhaled nitric oxide), 51 used steroids at the age of 4 years; these children were not excluded from the analysis. ‡The following six airborne allergens were tested for: house dust mite (*Dermatophagoides pteronyssinus*), cat, dog, grass pollen (*Dactylis glomerata*), birch and *Alternaria alternata*. IgE, immunoglobulin E; Rint, interrupter resistance.
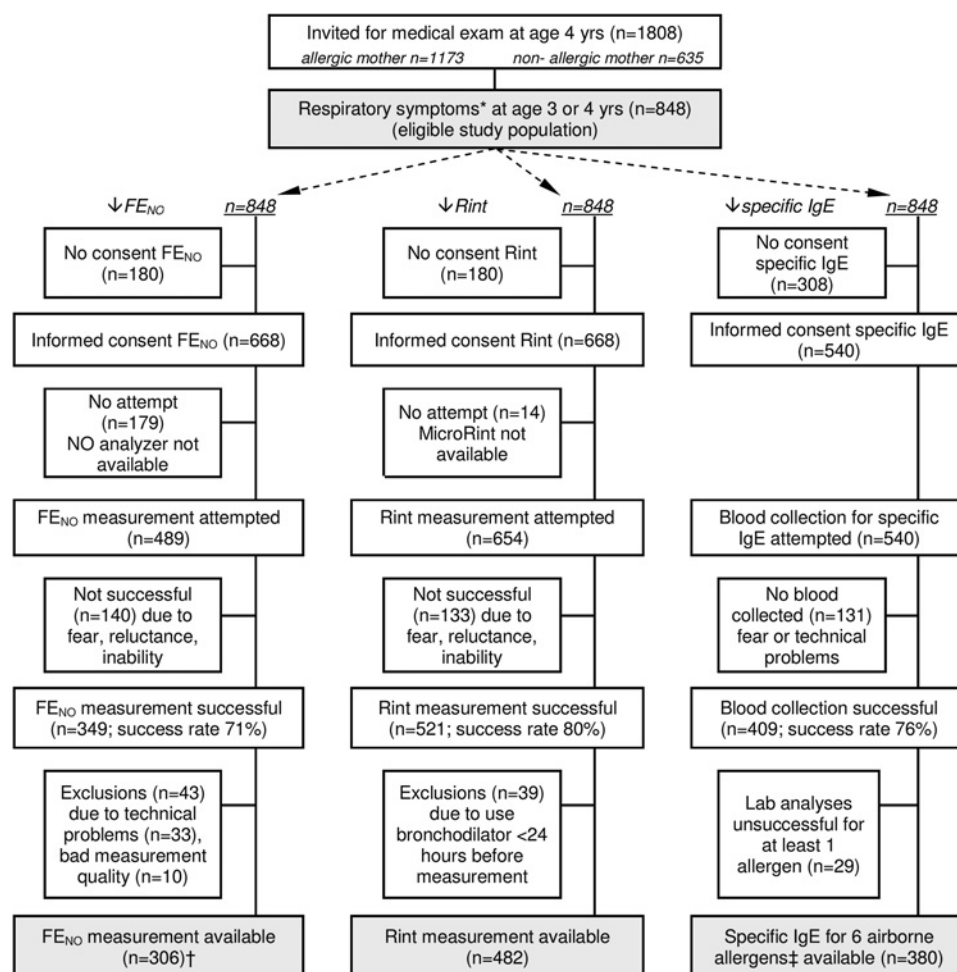
a model was built including clinical history, specific IgE and FE_{NO}, which allowed us to estimate the added predictive value of FE_{NO} over the combination of clinical history and specific IgE. The online data supplement provides a detailed description of study design, analysis and the multiple imputation procedure (table E1).

RESULTS

Study population

At the age of 4 years 1808 children were invited for medical examination, of whom 848 (46%) reported at least one of the following symptoms at 3 or 4 years: wheeze (n=379), shortness of breath (n=385) or nightly cough (n=592). The eligible study population therefore consisted of 848 children. An acceptable FE_{NO} measurement was obtained from 306, Rint from 482 and specific IgE from 380 children (figure 1). We compared children with and without available values for these measurements separately, with respect to baseline characteristics and symptoms at 8 years (table 1). Children with available FE_{NO} values (n=306) were similar to children without (n=542), the only difference being the educational level of the mother. Children with Rint values (n=482) were also more likely to have a mother with higher education than children without Rint measured (n=366), and had significantly fewer symptoms at the age of 8. Children with IgE data were more likely to be boys, to have an allergic mother, older siblings and to be exposed to cigarette smoke in utero, compared with children with missing IgE data. With respect to symptoms at baseline and at 8 years, there were no major differences. The distribution of clinical symptoms and objective tests that were used to predict later asthma symptoms is given in table 2.

Table 1 General characteristics of the eligible study population

Baseline characteristics	Eligible study population (N=848) n/N	Eligible study population (N=848) %	FE_{NO} (N=306) %	Rint (N=482) %	Specific IgE (N=380) %
Gender (female)	391/848	46	47	47	41**
Allergic mother	567/848	67	66	66	72**
Allergic father	289/846	34	35	35	35
Maternal education level					
Low	195/832	23	21	20	23
Middle	366/832	44	41	43	43
High	271/832	33	38*	36*	34
Caesarean section	86/834	10	10	11	7**
Pets in the house (at birth)	473/844	56	54	55	54
Older sibling present	422/846	50	49	52	59**
Smoking during pregnancy†	147/831	18	18	17	21*
Smoking in the house (at age 4)‡	191/798	24	26	23	24
Symptoms at baseline (age 3−4)					
Wheeze	379/848	45	47	45	48
Shortness of breath	385/848	45	48	46	47
Cough at night§	592/848	70	73	70	69
Symptoms at age 8 years					
Wheeze	104/730	14	13	13	14
Inhaled steroid use	109/722	15	15	12**	16
Doctor's diagnosis of asthma¶	55/700	8	8	6**	9

For each variable, children with and without available data were compared. Significance of differences was tested using a χ^2 test.
*p<0.05; **p<0.01.
†Positive if mother reported smoking at least 4 weeks after estimated date of conception.
‡Smoking in the child's house more than once a week.
§In period without a cold, flu or chest infection.
¶Defined as a parental report of a doctor's diagnosis of asthma ever, in combination with parental report of symptoms in the past 12 months.
FE_{NO}, fraction of exhaled nitric oxide; IgE, immunoglobulin E; Rint, interrupter resistance.

Table 2 Variables used to predict asthma symptoms

Clinical symptoms (n=848)	n/N	(%)
Allergic mother	567/848	(67)
Wheezing in fourth year of life		
Infrequent (1−3 times/year)	179/848	(21)
Frequent (>3 times/year)	64/848	(8)
Doctor's diagnosis of eczema	388/848	(46)
Objective tests	Median (range)	IQR
FE_{NO} in ppb (n=306)	9.05 (2.40−45.9)	6.30
^{10}log-transformed FE_{NO}	0.96 (0.38−1.66)	0.29
Rint in kPa/l (n=482)	0.93 (0.14−1.99)	0.32
	n/N	(%)
Positive specific IgE	102/380	(27)

FE_{NO}, fraction of exhaled nitric oxide; IgE, immunoglobulin E; Rint, interrupter resistance.

Predictive value of FE_{NO}

A higher FE_{NO} at 4 years was associated with significantly more wheezing and steroid use between the ages of 5 and 8 years. The association remained more or less stable over the 4 year follow-up period, with an OR per IQR increase in ^{10}log(FE_{NO}) on 'wheezing' at 8 years of 2.1 (95% CI 1.3 to 3.3, figure 2). A significant association with doctor's diagnosis of asthma was present only at age 7. Inclusion of three variables for clinical history in the model had very little effect on the ORs: FE_{NO} remained significantly associated with later symptoms, independent of clinical history. Multiple imputed data analyses produced similar associations (online supplement). Fifty-one children used steroids at the age of 4, which may have influenced FE_{NO} measurement. In a sensitivity analysis, exclusion of these children from the analysis led to slightly stronger associations with the outcomes 'doctor's diagnosis of asthma' and 'steroid use'. A charcoal NO scrubber was used while collecting exhaled air to eliminate an influence of ambient NO on FE_{NO} measurements, but some association between FE_{NO} and ambient air NO remained. Adjustment of our models for ambient NO did not change our results.

Predictive value of Rint

Rint values at age 4 were associated with symptoms at age 5 and 6. The association decreased after the age of 6 and was no longer significant at 8 years (figure 3). Adjustment for clinical history further decreased the association between Rint and all outcomes. The adjusted OR per IQR increase in Rint for wheezing at 8 years was 1.1 (95% CI 0.7 to 1.6). Multiple imputed analyses did not change this (online supplement).

Predictive value of specific IgE

A positive specific IgE to any airborne allergen had a strong association with later symptoms (figure 4). The association remained stable over the 4 year follow-up. At age 8 the OR for 'wheezing' was 6.6 (95% CI 3.5 to 12.7). When clinical history was taken into account the ORs decreased considerably, but the associations remained strongly significant for all outcomes (OR 4.3 (95% CI 2.1 to 9.1) for wheezing at 8 years). ORs for specific IgE decreased considerably on all outcomes in the multiple imputed analysis. Since such analyses are less likely to be influenced by selection bias, these estimates are probably more reliable. In the imputed analyses, specific IgE remained the strongest predictor of later symptoms, even when clinical history was taken into account.

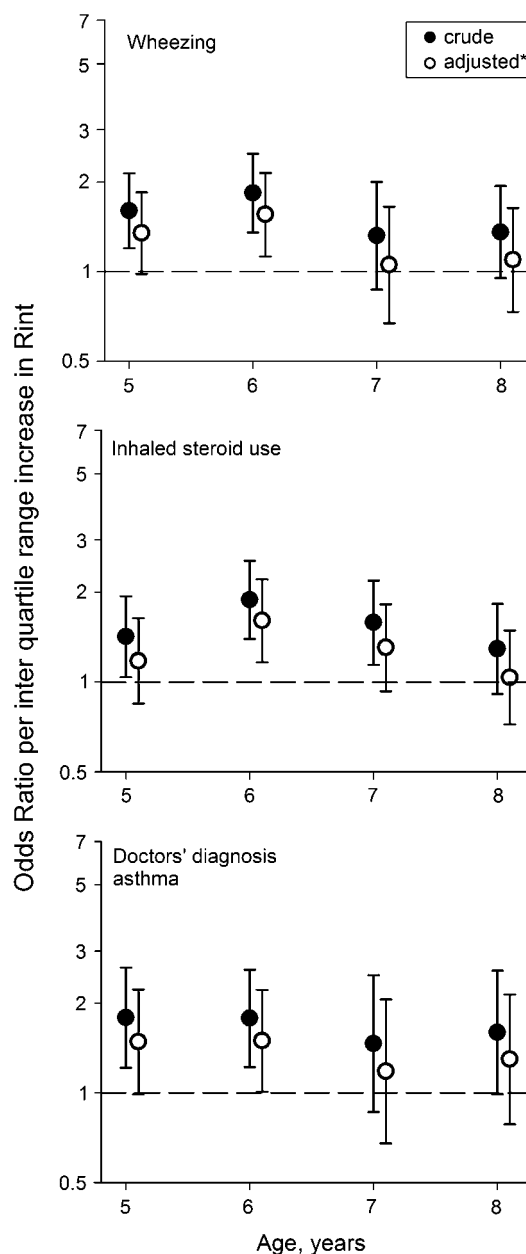### Combination of clinical history, FE_{NO} and specific IgE

These results imply that both FE_{NO} and specific IgE, independent of clinical history at 4, significantly improve the prediction of
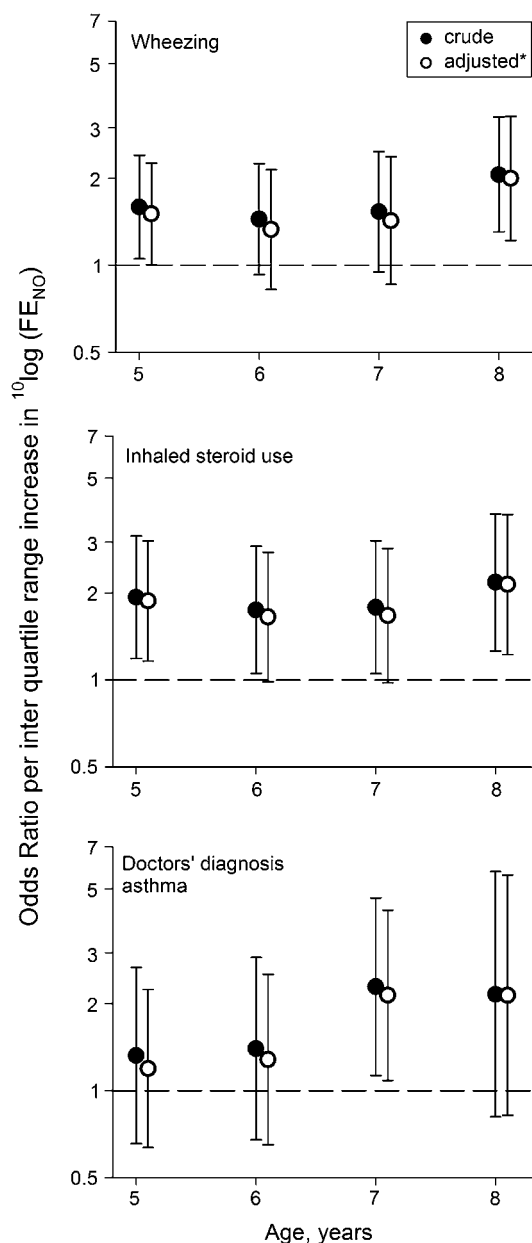
Figure 2 Predictive value of FE$_{NO}$ (fraction of exhaled nitric oxide) measured at 4 years on all outcomes at 5—8 years. Filled circles are crude ORs for FE$_{NO}$ (per IQR increase in ^{10}log(FE$_{NO}$)). *Open circles are adjusted for clinical history (allergic mother/doctor's diagnosis of eczema/wheezing at age 4).

Figure 3 Predictive value of Rint (interrupter resistance) measured at 4 years on all outcomes at 5—8 years. Filled circles are crude ORs for Rint (per IQR increase). *Open circles are adjusted for clinical history (allergic mother/doctor's diagnosis of eczema/wheezing at age 4).

asthma symptoms up to the age of 8 years. The question remains of whether FE$_{NO}$ still has an added value, when clinical history and specific IgE are already known. We investigated this in a combined model which included FE$_{NO}$, specific IgE and clinical history. Complete data on all variables were available from 185 children; the eligible population comprised 848 children. Analyses on the outcome 'wheezing' at age 8 were performed in both populations (table 3). Estimates for FE$_{NO}$ and specific IgE were constant in both analyses. The level of significance increased in the multiple imputed analysis, but even in the complete case analysis (n=185) FE$_{NO}$ remained borderline significant (table 3). Importantly, we found no interaction between FE$_{NO}$ and either 'specific IgE' or 'allergic mother'. To visualise the clinical implications of our findings, the predicted probability of wheezing is plotted against FE$_{NO}$ values measured at 4 years (figure 5).
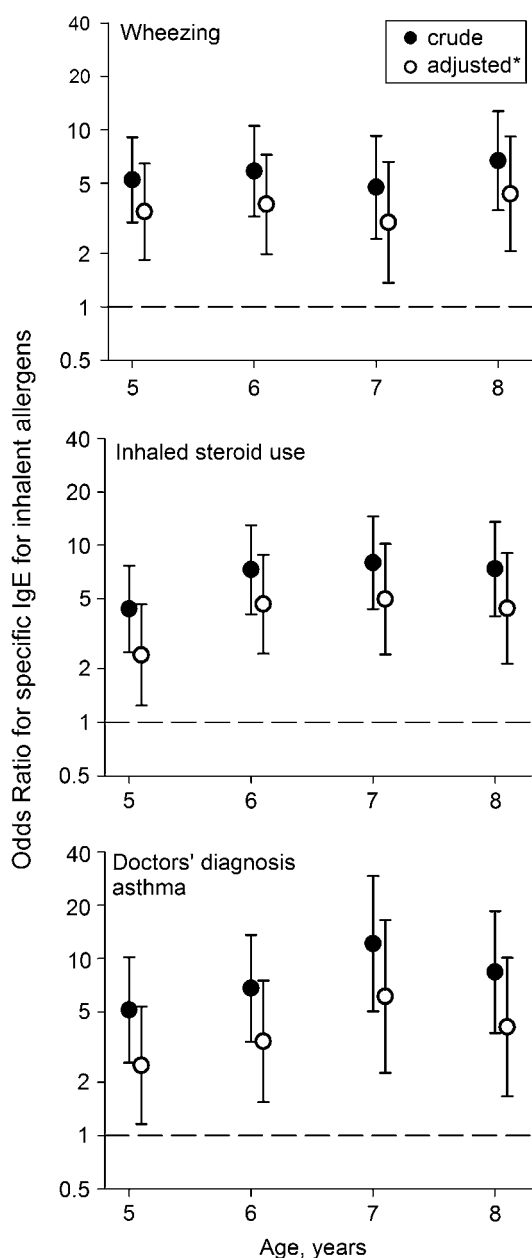
Different lines represent children with different subsets of risk factors. When all risk factors are absent, FE$_{NO}$ appears to be of limited clinical value, because the post-test probability remains low even at higher FE$_{NO}$ values. However, in children with an intermediate or high pretest probability of later wheezing, an FE$_{NO}$ test at the age of 4 could change the post-test probability to a degree that would be relevant in clinical practice. For example, in children with an allergic mother, eczema and specific IgE, but with infrequent wheezing at 4 (thick dashed line, figure 5), risk of asthma symptoms at 8 ranged from 25% to 70% depending on FE$_{NO}$ measured at 4 years.

DISCUSSION

We show that in preschool children with symptoms suggestive of asthma, measurement of FE$_{NO}$ and specific IgE could predict

Figure 4 Predictive value of specific IgE (immunoglobulin E) measured at 4 years on all outcomes at 5–8 years. Filled circles are crude ORs for specific IgE. *Open circles are adjusted for clinical history (allergic mother/doctor's diagnosis of eczema/wheezing at age 4).

Table 3 Predictive value of FE$_{NO}$ and specific IgE on 'wheezing' (with mutual adjustment and adjustment for clinical history)*

	FE$_{NO}$†	Specific IgE
n=185 FE$_{NO}$ and IgE both available	1.65 (95% CI 0.94 to 2.89) p=0.078	2.86 (95% CI 1.38 to 5.91) p=0.005
n=848 Total eligible population	1.57 (95% CI 1.10 to 2.23) p=0.016	2.78 (95% CI 1.90 to 4.07) p<0.001

ORs (95% CI) of FE$_{NO}$ and specific IgE on the outcome of 'wheezing', using complete case data (n=185) and multiple imputed data (n=848).
*ORs for FE$_{NO}$ and specific IgE were mutually adjusted for each other, and for three variables on clinical history (allergic mother/doctor's diagnosis of eczema/wheezing at age 4).
†ORs for FE$_{NO}$ are calculated per IQR increase in ^{10}log-transformed FE$_{NO}$.
FE$_{NO}$, fraction of exhaled nitric oxide; IgE, immunoglobulin E; Rint, interrupter resistance.

childhood.[33][34] In children aged 4 years, higher FE$_{NO}$ values were measured in recurrent wheezers and in children with doctor-diagnosed asthma, with considerable overlap.[8][10] Moeller et al showed that FE$_{NO}$ could be used to distinguish between different phenotypes of preschool wheezers, based on their clinical history up to the age of 4. However, FeNO will only have a clinical benefit if it offers additional information compared with clinical history.[13] Previous studies were cross-sectional, and very little is known about the predictive value of FE$_{NO}$ on later asthma in preschool children. We performed a 4 year follow-up and took the child's clinical history into account to assess the true additional predictive value of FE$_{NO}$ for later asthma. This reflects the clinical setting in which FE$_{NO}$ would be used. Our prospective analysis shows that FE$_{NO}$ measured at 4 years indeed improved prediction of asthma until the age of 8 years.

Cross-sectional studies have reported higher Rint in those with asthma compared with controls, with considerable overlap.[14][15][35] Previous analysis of our own data at age 4 showed a higher Rint in persistent wheezers, compared with
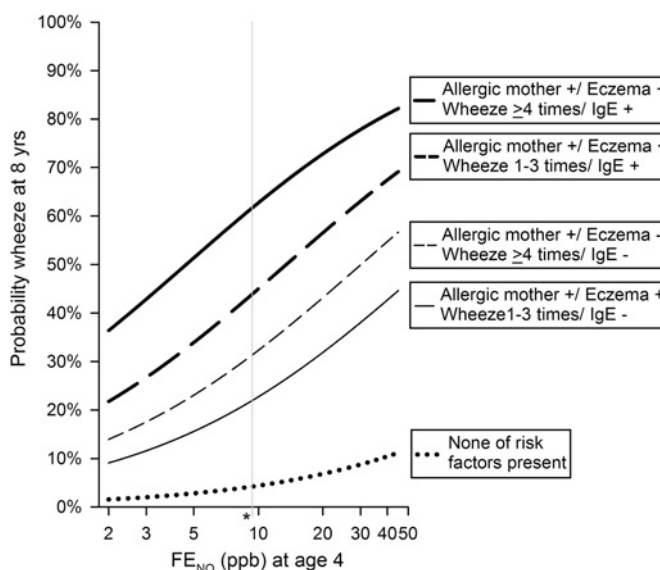
Figure 5 Predicted probability of 'asthma symptoms' depending on FE$_{NO}$ (fraction of exhaled nitric oxide) at 4 years. Predicted probability for 'wheezing' at age 8 is modelled for FE$_{NO}$ values (unit: parts per billion) measured at age 4, adjusted for specific immunoglobulin E (IgE), allergic mother, doctor's diagnosis of eczema and wheezing frequency at age 4. Different lines represent children with different subsets of risk factors. The horizontal axis is in log scale. *The vertical grey line represents the geometrical mean FE$_{NO}$ in the study population and can be used to determine the pretest probability of wheeze at 8 for individual children.

later asthma symptoms, up to the age of 8. Both tests had an added predictive value, independent of each other and of clinical history.

Several studies investigating the association between FE$_{NO}$ and airway symptoms in children reported a higher FE$_{NO}$ in children with wheezing and asthma.[6][7][9][11] Malmberg and colleagues even reported an 86% sensitivity and 92% specificity of FE$_{NO}$ to diagnose asthma, clearly superior to conventional bronchoprovocation testing and spirometry.[9] Importantly, these studies selected children already known to have asthma, and healthy controls. Such a case–control design is likely to cause selection bias, with overestimation of a test's diagnostic performance.[31] In unselected groups of schoolchildren, a much lower diagnostic performance of FE$_{NO}$ was reported.[12][32] Age is important when comparing different studies, due to heterogeneous respiratory disorders and changing FE$_{NO}$ during

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children who never or transiently wheezed.[25] The only prospective study on the predictive value of Rint measurements was performed in a cohort of 110 children diagnosed with asthma (aged 2—5 years) and found no association between Rint and asthma medication after 3 years follow-up.[36] Our study recruited children from a population-based cohort, based on reported respiratory symptoms, and results were similar: Rint at age 4 did not discriminate between children with or without symptoms at 8 years. Although Rint was associated with symptoms up to 2 years after measurement, it was not useful in the long-term management of individual children. Thirty-nine children (7%) were excluded because bronchodilators were used within 24 h prior to Rint measurement. When these children were included, the predictive power of Rint was even smaller. Nonetheless, selective exclusion of this group of high risk children may have decreased the power to detect an association of Rint with later symptoms.

Prospective studies showed that children with positive specific IgE for inhalant allergens were more likely to develop wheeze[19] and asthma[18] in childhood. Even when information from patient history is considered, specific IgE improved prediction of later asthma.[17 20] Our results show that the predictive value of specific IgE measured at 4 years remains high until the age of 8. Importantly, our data allowed us to investigate the independent added value of specific IgE and FE_{NO} measurements at 4. Several authors reported raised FE_{NO} levels in children with atopy rather than asthma.[32 37] Consequently, it has been proposed that any predictive value of FE_{NO} for asthma might be explained by its correlation with specific IgE.[38] Our combined analysis shows that even though FE_{NO} and specific IgE are correlated, they both independently contributed to the prediction of later asthma symptoms.

Major strengths of this study are its longitudinal design and large sample size. In the selection of the eligible population and the statistical analysis we aimed to mimic the clinical setting. This enabled us to estimate the true added value of the tests and hence their clinical relevance.

Selection bias could have resulted from incomplete data. However, we found that children with complete data did not differ from those with incomplete data. Furthermore, a multiple imputed analysis including all eligible children led to similar results and did not change any of our conclusions (online data supplement). Secondly, the PIAMA study is an unselected birth cohort, but due to over-representation of children with an allergic mother in the medical examination at 4, our eligible population included more children with an allergic mother. If the predictive value of FE_{NO}, Rint or specific IgE differs between children with and without an allergic mother, this would limit the generalisability of our findings. We consider this unlikely since there was no interaction between any of the tests and the variable 'allergic mother'. Hence, our findings may be generalisable to all children in the general population with asthma symptoms at 3—4 years. Although steroid use is well known to decrease FE_{NO}, we decided to include 51 (17%) children who used inhaled corticosteroids at age 4. This may have led to some underestimation of the predictive power of FE_{NO}, but we preferred this over selective exclusion of 51 high risk children. Finally, in order not to overestimate the added prognostic value of FE_{NO}, Rint and specific IgE over a clinical history we tested which variables for clinical history were the best prognostic indicators for later symptoms, and added the three variables with the strongest association in our multivariable analysis.[39] Including a variable for wheezing phenotype (multitrigger wheeze/viral induced wheeze/no wheeze) in our models did not decrease the predictive ability of any of the three investigated tests.

Do our findings have clinical relevance? In the management of wheezing preschool children a first step will always be to take a full medical history. Secondly, a specific IgE test has the highest predictive value for symptom persistence. FE_{NO} measurement as a next step can significantly improve prediction of later asthma symptoms, especially in children with an intermediate pretest risk.

In conclusion, we demonstrated that in preschool children with symptoms suggestive of asthma, both FE_{NO} and specific IgE at age 4 predicted asthma symptoms until the age of 8 years independently, and independent of clinical history. Specific IgE had the highest predictive value; the added value of FE_{NO} was limited. Nevertheless, in children with an intermediate or high risk, FE_{NO} substantially changed the risk of later wheezing and asthma to a degree that may be relevant in clinical practice.

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Lung alert

Maternal vitamin A supplementation improves lung function in offspring

Vitamin A has an important role in fetal lung development. This study tested the hypothesis that maternal vitamin A deficiency could have a long-term adverse effect on the lung function of offspring, quantified by reduced forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC).

The participants were a cohort of rural Nepali children, aged between 9 and 13 years, whose mothers had taken part in an original study aimed to determine the effects of vitamin A, β-carotene or placebo supplementation throughout pregnancy on maternal death rates.

Over a 2 year period spirometric data were collected from 1371 children (83% of those eligible for participation after the original study). Results demonstrated normally distributed FEV_1 and FVC volumes, with means of 1.54 and 1.74 litres, respectively. Compared with the placebo group, the FEV_1 was 46 ml higher in the children whose mothers had received vitamin A supplementation throughout pregnancy, and 14 ml higher in the β-carotene group than the placebo group. Even after adjustment for confounders such as age, height and sex, a similar comparison was made for FVC. Compared with the placebo group the FVC was 46 ml higher in the vitamin A group and 17 ml higher in the β-carotene group.

The study concludes that repletion of vitamin A and, to a lesser degree, β-carotene during pregnancy improves lung function, potentially providing long-term public health benefits.

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