

Asthma prediction in school children; the value of combined IgE-antibodies and obstructive airways disease severity score*

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Keywords

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Abstract

Background: Allergic sensitisation increases the risk for asthma development. In this prospective birth cohort (Environment and Childhood Asthma) study, we hypothesized that combining quantitative measures of IgE antibodies (Σ -IgE) and Severity score of obstructive airways disease (OAD) at 2 years of age (Severity score) is superior to predict current asthma (CA) at 10 years than either measure alone. Secondly, we assessed if gender modified the prediction of CA.

Methods: A follow-up study at 10 years of age was performed in 371 2-year-old children with recurrent ($n = 219$) or no ($n = 152$) bronchial obstruction with available serum analysed for Σ -IgE to common food and inhalant allergens through a panel test, Phadiatop Infant[®] (Phadia, Uppsala, Sweden). Clinical variables included allergic sensitisation and exercise testing to characterise children with CA vs not CA at 10 years and the Severity score (0–12, 0 indicating no OAD) was used to assess risk modification.

Results: Severity score alone explained 24% (Nagelkerke $R^2 = 0.24$) of the variation in CA, whereas Σ -IgE explained only 6% ($R^2 = 0.06$). Combining the two increased the explanatory capacity to $R^2 = 0.30$. Gender interacted significantly with Σ -IgE; whereas Severity score predicted CA in both genders, the predictive capacity of Σ -IgE for CA at 10 years was significant in boys only.

Conclusion: Combining Σ -IgE to inhalant allergens and Severity score at 2 years was superior to predict asthma at 10 years than either alone. Severity score predicted CA in both genders, whereas Σ -IgE significantly predicted CA in boys only.

Abbreviations

BO, bronchial obstruction; rBO, recurrent/persistent BO; CA, current asthma; CI, confidence interval; ECA-study, the Environment and Childhood Asthma study in Oslo; IgE, immunoglobulin E; s-IgE, specific IgE; Σ -IgE, Quantitative levels of a mix of common food and inhalant allergens; OAD, obstructive airways disease; PAU/L, Phadia Arbitrary Units/L.

Predicting incident or persisting obstructive airways disease (OAD) is challenging. Several clinical indices have been applied to preschool children (1–4) particularly focusing on early clinical respiratory disease, all with limited predictive capacity for later or persistent childhood asthma.

Allergic sensitisation is a feature in many, but not all children with asthma (5–8), and the proportion of allergic to

nonallergic asthma varies by age (9) as well as across countries (10). Although early allergic sensitisation is recognized as part of evolving allergic disease, sometimes referred to as the 'atopic March' (11), its value as a predictor or modifier for asthma development is less clear (9, 12).

Quantification of sensitisation especially by summated specific immunoglobulin E (IgE) antibodies and also skin prick test (SPT) results has been shown to improve the prediction of asthma and rhinitis in childhood (13, 14) compared to using dichotomous results with an arbitrary cut-off for the presence or absence of allergic sensitisation. The possible causative role of the interaction between personal atopy and maternal asthma on reduced lung function in three- and five-year-old children was recently discussed (15), whereas reanalyses of their data with principal component analyses indicated a major problem with cross-sectional approaches to understanding development of disease (15).

Further, gender differences in asthma development is well-documented (16), but often not eluded to in prediction models.

We recently demonstrated that a Severity score of OAD at 2 years based only upon clinical presentation of symptoms predicted current asthma at 10 years superiorly (4) to previous prediction algorithms for similar (1) or older age groups (2).

We therefore hypothesised that combining quantitative measures of IgE antibodies and Severity score of obstructive airways disease in early preschool age is superior to predict later ongoing asthma than either measure alone.

Secondarily, we aimed to assess if gender modified the prediction of current asthma.

Methods and subjects

Study design and Subjects

The present study is part of the 10-year follow-up of the 'Environment and Childhood Asthma' (ECA) study in Oslo,

previously described in detail (17). At 2 years, a nested case control study was established to perform detailed examinations of children who at 2 years had recurrent (≥ 2 episodes or persistent (≥ 4 weeks) doctor -confirmed bronchial obstruction (BO) (rBO+ ($n = 306$)) and controls, being the child born closest in time without BO (rBO-) ($n = 306$). Recruitment strategies to identify all cases are described in detail elsewhere (17, 18). The 2-year clinical visit was attended by 516 of 612 eligible children; 265 cases and 251 controls, respectively. In 410 (246 cases) of the children stored serum from 2 years was available for analyses of IgE antibodies to a mix of the most common food and inhalant allergens at 2 years of age (Σ -IgE) performed in connection with the 10-year follow-up study.

The present study includes the 371 children of the 410 recruited from the nested case-control study who had serum stored for IgE analyses at 2 years as well as attended the 10-year follow-up study. Their demographic data are given in Table 1. The 39 nonattending children at 10 years and the included 371 children with 2-year serum analysed for Σ -IgE were similar in relation to gender (56% boys), parental atopy, age and rBO (56%) (data not shown).

The study was approved by the Regional Committee for Medical Ethics and the Norwegian data inspectorate, and reported to the National Biobank. Written informed consent was obtained from parents of all subjects.

Methods

Two year clinical visit

A parental structured interview was performed by the study doctor including details of diseases of the index child and primary family members, infections, environmental exposures, housing, socio-economic factors and any type of medical treatment. Severity of obstructive airways disease OAD was assessed by the questions: 'has the child ever had wheez-

Table 1 Demographic results of the children at 2 years who attended follow-up visit at 10 years, classified according to whether or not they had recurrent or no bronchial obstruction by 2 years

N (%)	rBO N = 219 (59)	No BO N = 152 (41)	P-value	Total N = 371
Age (months) at 2 year mean, SD	25.6, 3.4	27.8, 3.7	0.001	26.5, 3.7
Boys n (% boys)	129 (58.9)	78 (51.3)	n.s	207 (55.8)
Parental asthma (%) reported at birth	21.9	8.6	0.002	16.4
Parental rhinoconjunctivitis reported at birth	34.2	32.9	ns	33.7
Atopic eczema n (%)	83 (37.9)	40 (26.3)	< 0.001	123 (39)
Eosinophil count 2 years (mean, 95% CI)	0.26 (0.22, 0.28)	0.19 (0.16, 0.22)	0.002	0.20, 0.10–0.30
Σ -IgE above detection limit (0.1 PAU/L) n (%)	112 (51.1)	77 (50.7)	n.s	189 (50.9)
Σ -IgE* in children with > 0.1 PUA	0.18 (0.14, 0.21)	0.14 (0.12, 0.16)	0.05	0.16 (0.14, 0.18)
Total IgE 2 years*	12.9 (10.7, 15.6)	11.6 (9.4, 14.4)	n.s	12.3 (10.7, 14.2)
Cord blood IgE*	0.34 (0.30, 0.40)	0.30 (0.29, 0.35)	n.s	0.32 (0.29, 0.35)
Severity score at 2 years (mean, 95% CI)	4.6 (4.2, 5.0)	0	< 0.001	2.70 (2.37, 3.02)

Categorical data analysed by χ^2 -test, and nonnormally distributed quantitative data by nonparametrical comparisons. P-values > 0.05 are given as not significant (n.s).

rBO, Recurrent bronchial obstruction.

*(Geometric mean, 95% CI).

ing and/or shortness of breath?'; if yes, 'the number of episodes with wheezing' and/or 'the number of months with persistent wheezing' and 'was the child ever admitted to hospital because of wheezing?' and if yes, the number of hospital admissions for bronchial obstruction.

Severity score

A Severity score (0–12, maximum with most severe disease) was calculated based upon the clinical criteria present during 0–2 years of age: number of episodes of BO, number of months with persistent BO and number of hospital admissions because of BO as described previously (4).

Specific IgE analysis and Phadiatop infant®

Blood was drawn into SST vacutainer tubes between 10.00 am and 2.15 p.m and allowed to clot for 1 h in stable room temperature before centrifugation. Serum was pipetted and stored at -70°C for further analyses. One nurse only handled all blood samples according to standardized procedure.

For demographic analysis, serum was analysed for total IgE using the UniCAP fluoroenzyme immunoassay (FEIA) according to the manufacturer's instructions (Phadia AB, Uppsala, Sweden) (19). In 2004, IgE antibodies to a mix of the most common food and inhalant allergens were analysed by the Phadiatop Infant (Phadia AB, Uppsala, Sweden), Σ -IgE. The test contained a mix including 11 allergens (dermatophagoides pteronyssinus, cat, dog, egg white, cows milk, peanut, shrimp, timothy, birch, common ragweed, wall pellitory (parietaria judaica)). The lower limit of detection was 0.1 PAU/L. The determinations had a CV of less than 10%.

10-year follow-up visit

At the 10-year visit (8) study doctors conducted parental structured interviews regarding the child's symptoms of asthma and asthma management, including translated International Study of Asthma and Allergies in Children (ISAAC) questions.

Exercise test

A standardised exercise challenge test included running for six to eight minutes on a motor-driven treadmill (Woodway; Woodway® GmbH, Weil am Rhein, Germany) (inclination of 5.5%), with increasing speed during the first two minutes to reach a heart rate of 95% of estimated maximum (18). FEV₁ was measured before, and three, six, 10 and 15 min after running. The exercise challenge test was considered positive with $\geq 10\%$ fall in FEV₁ from baseline 3–20 min after running ceased. The results from the exercise test were included in the diagnosis of current asthma.

Specific IgE at ten years examination was measured using ImmunoCAP® according to the manufacturer's instruction (Phadia, Uppsala, Sweden) against the following allergens: Domestic mites (*Dermatophagoides (D.) pteromyssinus* and *D. farinae*), German cockroach, dog, cat, and rabbit dander, birch, timothy (*grass*) and mugwort pollens, moulds (*Cladosporium herbarium* and *Alternaria alternata*), egg white, milk, peanut and codfish.

Outcomes at 10 years

Asthma was defined by at least two of the following three criteria being fulfilled:

1. Dyspnoea, chest tightness and/or wheezing by years
2. Doctor's diagnosis of asthma
3. Use of asthma medication (β -2 agonist, sodium chromoglycate, corticosteroids, leukotriene antagonists and/or aminophylline) by years

Current asthma was defined as asthma (by definition above) plus asthma symptoms and/or asthma medication (see above) within the last year and/or a positive exercise test.

Wheeze ever was defined by a positive response to the questions 'Has your child experienced dyspnoea, chest tightness and/or wheezing during the age periods 0–3 years and/or 4–10 years?'

Allergic sensitisation (at 10 years) was defined by at least one specific IgE concentration of > 0.35 kU/l.

Explanatory factors

The mix of IgE antibodies determined by Phadiatop was analysed as a quantitative sum (Σ -IgE) and given as geometric mean or natural logarithmic value.

Severity score from 0 to 12, 0 being no OAD.

Statistical analysis

Continuous variables are presented as mean with SD, binary variables as counts with percentage. Two sample *t*-tests and Pearson's Chi-square test were used to assess differences for continuous and categorical variables, respectively.

The relationship between sensitisation status (Σ -IgE) and clinical status outcome measure was analysed by using ordinary logistic regression. The variables were chosen to assess their value in predicting asthma. As gender was likely to be important this was tested, found to be the case and analyses were subsequently stratified for gender.

Quantitative measures were entered into the figures as original scale for the Severity score (0–12) and in natural logarithm of the original scale for IgE. Thus, the actual scale for IgE in the figures are marked according to the relevant anti-logarithm. Odds ratios (ORs) were estimated by using the regression models, and 95% CIs were generated according to Wald. Fitted predicted probability curves were plotted using the results from the logistic regression. A *P*-value < 0.05 was considered significant.

Calculations were performed with Statistical Package for Social Sciences (SPSS) version 12.0 for Windows and Statistical Analysis System (SAS) version 9.13.

Results

At two years of age

Demographic data at 2 years are given in Table 1 according to the presence of rBO or no BO by 2 years of age in the 371 children who attended the 10-year follow-up.

Table 2 Characteristics of the children at 10 years

N (%)	Current asthma N = 91	History of asthma N = 98	Never asthma N = 182	P-value
Age (months) mean, SD	10.2, 0.7	10.4, 0.7	10.2, 0.7	n.s
Boys n (% boys)	62 (68.1)	54 (55.1)	91 (50)	n.s.
Parental asthma/rhinoconjunctivitis reported at 10 years (%)	75.8	64.3	49.5	< 0.001
Sensitised (s-IgE) to any allergen (%)	48.9	40.2	29.0	0.005
Geometric mean Total IgE (95% CI)	73.2 (50.4, 106.5)	72.1 (51.6, 100.9)	48.2 (31.2, 60.9)	0.06
FEV1% predicted (mean [95% CI])	95.7 (93.5, 97.8)	97.8 (95.7, 99.82)	99.8 (98.3, 101.3)	0.006
Bronchial hyperresponsiveness (Dose response slope)	23.25 (14.48, 32.02)	5.02 (2.87, 7.16)	4.26 (2.98, 5.55)	< 0.001
Severity score at 2 years (mean [95% CI])	5.1 (4.4, 5.8)	4.4 (3.8, 5.0)	0.6 (0.4, 0.7)	< 0.001

Children with rBO were slightly younger than those with no BO, but without significant gender differences. Compared to children without BO, the rBO children had significantly more often parents with asthma, more often atopic eczema, higher eosinophil count and borderline statistically significant higher geometric mean Σ -IgE. However, geometric means of total IgE at 2 years and in cord blood were similar in the two groups (Table 1).

Σ -IgE at 2 years of age was above the detection limit (0.1 PAU/L) in 103 (70.5%) children with allergic sensitisation at 10 years of age, as well as in 86 (38.2%) children who were not sensitised to any (detected) allergen at 10 years of age ($P < 0.001$).

At ten years of age

For the 371 children, demographic data at 10 years of age are given in Table 2 showing the presence of current asthma, history of asthma or never asthma.

Parental asthma was significantly more often reported in the children with current asthma at 10 years, as was sensitisation to any allergen and bronchial hyperresponsiveness to metacholine (BHR). The Severity score at 2 years of age was highest among children with current asthma followed by a history of asthma, both significantly higher compared to never asthma.

Σ -IgE and Severity score at 2 years and probability of having asthma at 10 years of age

Both as single predictors and used together the Severity score and Σ -IgE predicted current asthma at 10 years (Fig. 1).

The probability of having current asthma (compared to no current asthma) at 10 years of age increased with increasing levels of Σ -IgE at 10 years of age per logarithmic unit, with an OR = 1.42 (95% CI: 1.20 – 1.71). Likewise increasing Severity score was associated with current asthma (OR = 1.36 (1.25 – 1.48)). However, whereas Severity score alone explained 24% (Nagelkerke $R^2 = 0.24$) of the variation in current asthma, Σ -IgE explained only 6% (Nagelkerke $R^2 = 0.06$).

Using the Severity score and Σ -IgE together explained 30% of the variation (Nagelkerke $R^2 = 0.30$).

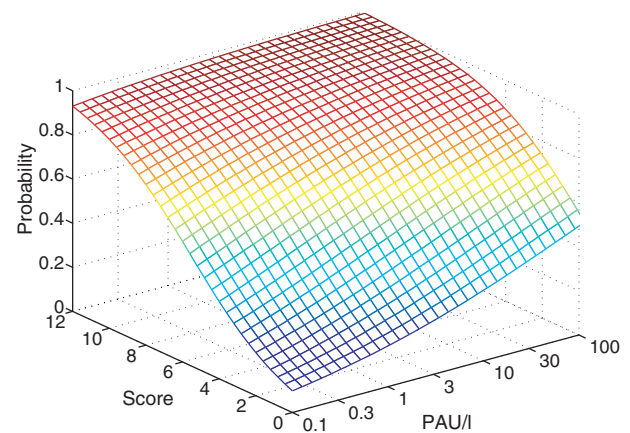


Figure 1 The predicted probability of current asthma (CA) at 10 years is demonstrated by combining the sum of specific IgE antibodies (PAU/L) and Severity score (0–12) at 2 years of age. The IgE scales are based upon the antilogarithms (natural) of IgE and the graphs of the Severity score represent the original scale.

Interactions and current asthma

No significant interaction was found between Severity score and Σ -IgE levels, whereas correcting for gender did not significantly alter the associations between Severity score and Σ -IgE for current asthma.

However, significant interaction was found for gender and Σ -IgE. Thus, whereas Severity score predicted current asthma in both genders (Figs 2 and 3), the predictive capacity of Σ -IgE for current asthma at 10 years was significant for boys only (Figs 2 and 3).

Combining Σ -IgE and Severity score correcting for and including interaction with gender, increased the explanatory capacity of current asthma at 10 years of age (Table 3 and Fig. 3) to $R^2 = 0.33$. Thus, assuming a boy and a girl both with Severity score of 6 and a Σ -IgE value of 10 PAU/L, the increased risk for current asthma in the girl is only related to the Severity score (Fig. 4) giving an OR = 6.9. For the boy, this risk is further increased because of the allergic sensitisation to an OR = 20.0.

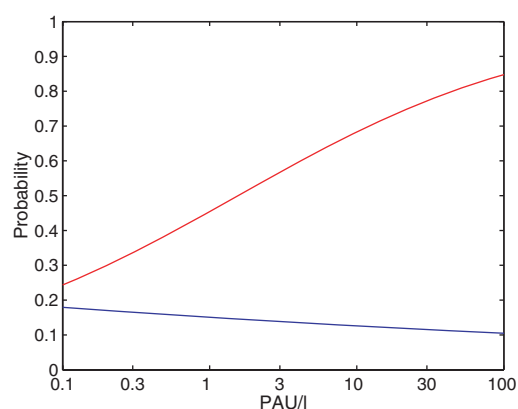
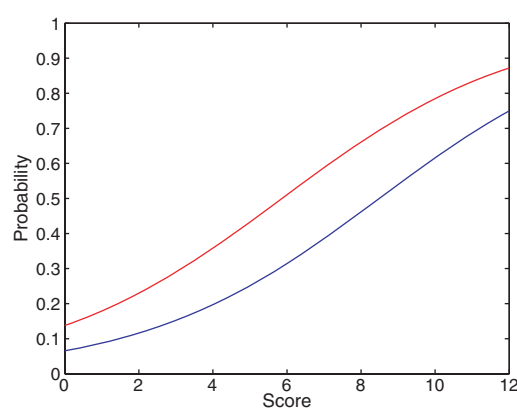


Figure 2 Predicted probability of current asthma at 10 years by the sum of specific IgE antibodies (PAU/L) (left curve) and Severity



score (right curve) at 2 years corrected for gender interaction (boys red line, girls blue line).

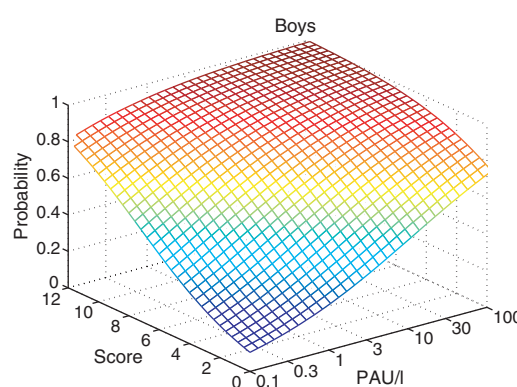
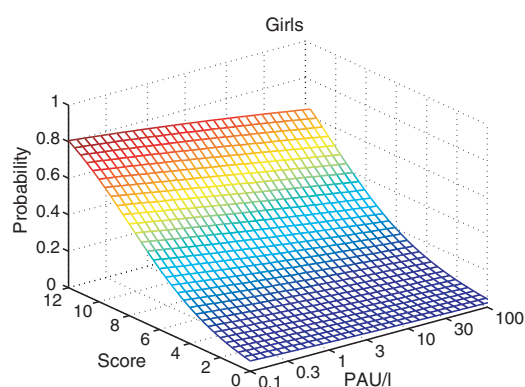


Figure 3 Predicted probability of current asthma at 10 years in girls (left curve) and boys (right curve) by the combined sum of specific IgE antibodies (PAU/L) and Severity score at 2 years corrected for and demonstrated by gender interaction. The IgE scales are based upon the antilogarithms (natural) of IgE and the graphs of the Severity score represent the original scale. As an

example of this relationship, assume a boy and a girl both with a Severity score of 6 and a Phadiatop Infant value of 10 PAU/L. The increased risk for current asthma in the girl is only related to the Severity score giving an OR = 6.9. For the boy, this risk is further increased because of the allergic sensitisation to an OR = 20.0.

Table 3 The risk of current asthma at 10 years is given for boys and girls by Severity score of obstructive airways disease and the sum of IgE (Σ -IgE) as measured by Phadiatop Infant[®] at 2 years. Nagelkerke (R^2) was 0.33, explaining 33% of the variation in current asthma at 10 years. Σ -IgE at 2 years was not significantly associated with current asthma at 10 years in girls

	Girls			Boys		
	OR	Lower	Upper	OR	Lower	Upper
At 2 years						
Severity score of obstructive airways disease (OAD)	1.38	1.27	1.50	1.38	1.27	1.50
Σ -IgE	0.88	0.52	1.50	1.58	1.26	2.00

Discussion

The present study demonstrates that although both Σ -IgE and Severity score of OAD at 2 years could predict current asthma at 10 years, combining the two and correcting for the observed gender interaction significantly increased the predictive value. Also, whereas Severity score predicted current asthma in both genders, the predictive capacity of Σ -IgE was valid in boys only.

Σ -IgE and Severity score at 2 years and probability of having asthma at 10 years of age

Our study is in line with other studies that early IgE-sensitisation increases the likelihood of later asthma (9, 20–24). Recent studies have reported the use of quantification of specific IgE antibodies in the assessment of food allergy (25–28) and recently also to address the risk of asthma (13, 14, 29–32) as well as risk of severe asthma attacks (33, 34).

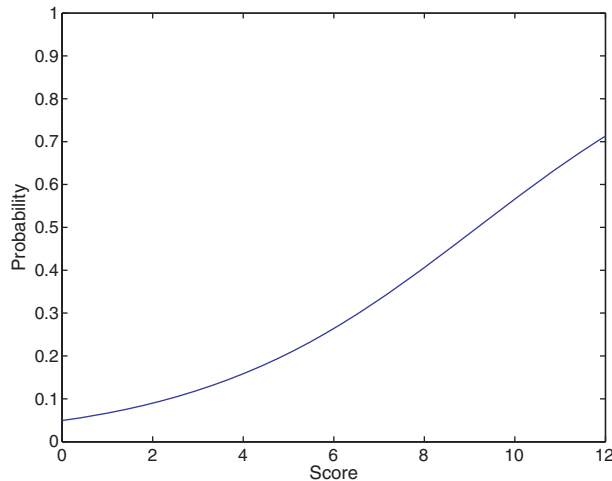


Figure 4 The single relationship between Severity score of asthma at 2 years and predicted probability of current asthma at 10 years is given for girls, as allergic sensitisation at 2 years did not influence this relationship.

In particular, one study from Manchester, United Kingdom, has suggested that the risk of wheeze and reduced lung function over time increases with increasing levels of specific IgE antibodies (13). This clearly indicates that early antibody production against specific allergens is not a dichotomous all or nothing phenomenon in the development of asthma, but is strongly dose-dependent. However, interactions with other factors like gender and early bronchial obstruction appear significant (5). The predictive capacity of the Oslo Severity score is reported elsewhere (4), whereas we are not aware of studies combining such a score with specific IgE quantification. However, several studies have observed that algorithms including various clinical, biological and family history factors increase the predictive ability compared to any factor alone. Nevertheless, the combined factors in the present paper improves the predictability of Severity score alone in boys, a score that appears more appropriate than other relevant scores ((1, 3, 35) suggesting a synergistic effect of Σ -IgE and early asthma symptoms, probably reflecting a specific subgroup of children with early manifestations of allergic airways disease (36, 37).

Σ -IgE and risk of later asthma; modifying effects of gender

A significant interaction between s-IgE and gender was found, in which early IgE-sensitisation played only a minor or no role in development of asthma in most prepubertal girls, whereas it was a significant contributor to asthma development in boys. This was particularly apparent in the combined model, in which Severity score alone was a significant predictor of asthma in girls, whereas a synergistic effect was observed in boys.

However, also children without OAD by 2 years had significantly increased risk of asthma later, in line with recent findings from Sweden where the odds ratio for asthma at age 5 years was 4.66 in 18-month-old children with allergic sensitisation and no atopic clinical manifestations (3). Our

findings extend the importance of knowing sensitisation as well as clinical manifestation of OAD for development of asthma from 2 to 10 years of age. Thus these findings further suggest early identification of children at risk to implement appropriate management at an early age (5).

Strengths and limitations of the present study

The present study is strengthened by the prospective design, including a high 8-year follow-up rate (90%) of the children of interest and careful characterisation of children during the two first years of life, as well as at 10 years. Unfortunately, serum was not available for all subjects at 2 years for s-IgE analyses, missing from more controls ($n = 87$) than children with rBO ($n = 19$). However, the 39 children who did not attend the 10-year follow-up study (27 children with rBO vs 12 controls) were similar to the attending children with respect to gender, parental atopy, age and rBO. Thus, it is unlikely that the results were significantly affected by the lack of serum available.

The main outcome (current asthma) was associated in the present study with reduced lung function, increased BHR and increased allergic sensitisation compared to children without asthma or a history of asthma, suggesting that the groups appropriately reflect ongoing disease, and all groups are accounted for in the analyses.

As the study was a follow-up of a nested case-control study, predicted probabilities must therefore be interpreted with appropriate limitations compared to analyses performed in a general population cohort.

Conclusion

The combination of quantified specific IgE antibodies to inhalant allergens and a Severity score of obstructive airways disease at 2 years were superior to predict asthma 8 years later than either alone. The IgE antibodies could, however, predict later asthma in boys only. Using these two factors may reasonable well predict individual risk of later asthma, but further studies in general populations are required to assess the predictive capacity of these measures.

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