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Reduced exhaled breath condensate pH and severity of allergic sensitization predict school age asthma.

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PII: S2213-2198(20)31214-9

DOI: <https://doi.org/10.1016/j.jaip.2020.10.058>

Reference: JAIP 3237

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 3 March 2020

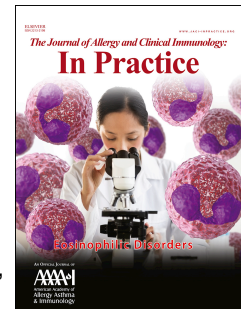
Revised Date: 21 October 2020

Accepted Date: 27 October 2020

Please cite this article as: Kreißl S, Hendler S, Akmatov MK, von Meien M, Range U, Pessler F, Vogelberg C, Reduced exhaled breath condensate pH and severity of allergic sensitization predict school age asthma., *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: <https://doi.org/10.1016/j.jaip.2020.10.058>.

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Title: Reduced exhaled breath condensate pH and severity of allergic sensitization predict school age asthma.

Short title: dEBC pH and CAP class predict school age asthma.

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29 **Sources of funding:** iMed – the Helmholtz Association's Cross Programme Initiative on Personalised
30 Medicine, and internal funds of the University Children's Hospital of the Medical Faculty "Carl Gustav
31 Carus", Technical University of Dresden, Germany.

32 **Disclosure of potential conflict of interest:** The authors have declared that they have no conflict of
33 interest.

34

ABSTRACT

Background: We previously reported that deaerated breath condensate pH (dEBC pH) can identify preschool children with recurrent wheezing at high asthma risk.

Objective: To assess the ability of preschool dEBC pH to predict asthma risk at school age.

Methods: Children of the baseline cohort were re-contacted for follow-up. Asthma diagnosis at school age was evaluated according to GINA recommendations in 135 children who at baseline had been classified into the following groups: (asymptomatic) atopic wheezers (n=30), (asymptomatic) non-atopic wheezers (n=57), allergic rhinitis only (n=14), healthy controls (n=34).

Results: All children (100%) of former atopic wheezers, 12 (21%) of non-atopic wheezers, 2 (14%) of allergic rhinitis group, and 1 (3%) of healthy controls had developed asthma at follow-up. Among all children with baseline wheezing, baseline dEBC pH predicted asthma at follow-up with an area under the ROC curve (AUC) of 0.72 (sensitivity, 0.67; specificity, 0.76; at pH 7.83). Combining pH and Capacity class (CAP) led to substantial gain in sensitivity (0.96) and negative predictive value (NPV, 0.94). Additional clinical information (Asthma Predictive Index, Family Atopy, Family Asthma, Inhaled Corticosteroids) further increased the potential to predict asthma (AUC, 0.94) and raised sensitivity (0.98) and NPV (0.97) to nearly perfect values.

Conclusion: Our findings suggest (1) that dEBC pH combined with CAP class may serve as highly sensitive, non-invasive marker for the early detection of young asymptomatic preschool children with increased asthma risk, and (2) the need for additional biomarkers with high specificity to optimize early risk stratification in this clinically challenging scenario.

Words: 250

Highlights:

1. What is already known about this topic? Early risk stratification in young children with a history of wheezing is of great clinical importance. Our baseline study identified dEBC pH as a potential predictive marker to detect asymptomatic preschoolers at high asthma risk.

2. What does this article add to our knowledge? The present follow-up suggests that dEBC pH combined with CAP class and clinical information constitutes a sensitive, non-invasive marker with high negative prediction value for early detection of asymptomatic preschool children with increased asthma risk.

3. How does this study impact current management guidelines? Diagnosing asthma at preschool age with a low rate of false negative cases will enable early guideline-based therapy, thus reducing undertreatment and risk of future exacerbations, improving symptom control, and possibly preserving

- 77 **KEY WORDS:** asthma, asthma predictive index (API), atopic sensitization, biomarkers, children,
78 deaerated exhaled breath condensate pH (dEBC pH), diagnosis, prediction, prospective study, wheezing.

79 **ABBREVIATIONS USED**

80	API	Asthma Predictive Index
81	AR	Allergic rhinitis
82	AUC	Area under the curve
83	CAP	Capacity class
84	dEBC pH	Deaerated exhaled breath condensate pH
85	EBC pH	Exhaled breath condensate pH
86	FA	Family asthma score
87	FAT	Family atopy score
88	FeNO	Fractional exhaled nitric oxide
89	FEV ₁	Forced expiratory volume in one second
90	GINA	Global Initiative for Asthma
91	ICS	Inhaled corticosteroids
92	IQR	Interquartile range
93	INS	Intranasal treatment
94	MEF ₂₅	Maximal expiratory flow at 25% of forced vital capacity values
95	ROC	Receiver operating characteristic
96	RWB	Recurrent wheezy bronchitis
97	SPT	Skin prick test
98		

99 1 INTRODUCTION

100 The diagnosis of asthma in early childhood is challenging due to an overlap of symptoms between
101 asthma and wheezy bronchitis (reactive airway disease). For this reason, alternative approaches to
102 diagnosing asthma in young children are needed. In recent years, measuring the pH of deaerated
103 exhaled breath condensate (dEBC) has been shown to be an especially promising method that is non-
104 invasive and can be applied at any age [1, 2]. We previously showed that dEBC pH might be a
105 potential predictive marker to identify young asymptomatic children at high risk of asthma [3]. In
106 2007/08 a cohort of 191 preschool children were divided into 5 groups according to individual risk of
107 developing asthma, and dEBC pH was measured during an asymptomatic (wheeze-free) interval. The
108 acute wheezy bronchitis group formed an exception in that dEBC pH was measured during a
109 symptomatic episode requiring hospitalization. In this baseline study, we found that dEBC pH was
110 significantly lower in the group at highest risk of asthma (atopic children with recurrent wheezy
111 bronchitis [RWB]), than in the lower-risk group (non-atopic children with RWB).

112 The present follow-up study enabled us to reclassify the children at school age according to Global
113 Initiative for Asthma (GINA) recommendations for the diagnosis of asthma [4], thus allowing to
114 evaluate the ability of dEBC pH at baseline to predict the risk of developing asthma at school age.

2 MATERIAL & METHODS

2.1 Study design

In the baseline study (*conducted in 2007/08*), 191 preschoolers had been classified into the following 5 groups on the basis of medical history as well as clinical and laboratory findings (details have been published previously [3]): recurrent wheezers with atopy, recurrent wheezers without atopy, acute (but not recurrent) wheezy bronchitis, allergic rhinitis only, and healthy controls (Table I). More than two-thirds (68%) of the atopic recurrent wheezers had a history of rhinitis [3]. The group was, however, not subdivided further for additional analyses because of its rather small size.

All children ($n = 173$) except those of the acute wheezy bronchitis group were re-contacted at school age for the follow-up study in 2011/12 to be investigated according to the baseline classification. The initial intention to investigate children with an acute wheezy bronchitis at baseline (9.4% of the population) was to measure dEBC pH during an acute episode of a viral bronchitis and compare it with a group that might have subclinical inflammation measured during an asymptomatic interval. Since measuring dEBC during an acute respiratory infection was not part of the follow-up questions this group of former acute bronchitis children was not retested.

Exclusion criteria for the study population were (1) a diagnosis of gastroesophageal reflux disease; (2) a specific respiratory disease, such as cystic fibrosis, primary ciliary dyskinesia, interstitial lung disease, pneumonia, or tuberculosis; and (3) recurrent fever of unknown origin, or (4) inability to assess atopy status. In case of an acute infection, clinical tests were delayed and performed during an infection-free interval of at least 2 weeks. All included children were non-smokers.

Exhaled breath condensate (EBC) was collected and pH values were measured in deaerated EBC according to American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations [5], identically to the baseline study [3], during an asymptomatic (wheeze-free) interval. Forced expiratory volume in one second (FEV_{10}) and maximal expiratory flow at 25% (MEF_{25}) of forced vital capacity values were measured and parameters were expressed as percentage of predicted values. Fractional exhaled nitric oxide (FeNO) was analyzed according to ATS/ERS standards [6]. Asthma status was determined conforming to the GINA recommendations [4]. Asthma was considered present if ≥ 2 of the following criteria were met [6]: typical asthma history with symptoms such as dyspnea, wheezing, cough, lung function test with positive exercise-induced bronchial provocation result or

pathological lung function test (bronchial obstruction) with positive bronchodilator response; positive skin prick test/blood test (atopic sensitization).

Allergic sensitization was defined as CAP class ≥ 2 and/or positive skin prick test (SPT) result. SPT (Allergopharma, Reinbek, Germany) were performed in a subgroup with mugwort, ribwort, dog and cat scurf, rye, timothy, hazelnut, birch, alder, *Dermatophagoides farina*, *Dermatophagoides pteronyssinus*, *Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Mucor racemosus* and *Alternaria alternans* allergen solution. However, these tests could be performed on only 12 participants and were therefore excluded from logistic regression analysis. Serological allergy diagnostics were performed by means of fluorescence immunoassay; the concentration of specific IgE and total IgE was determined from peripheral blood testing for the same allergens as with SPT. Measured values were classified according to the Capacity Class (CAP) - System. In addition, eosinophilic cationic protein (ECP), and peripheral blood eosinophils were quantified. Inhaled corticosteroid treatment (ICS) was documented.

A comprehensive standardized and adapted International Study of Asthma and Allergies in Childhood (ISAAC) Phase II questionnaire, to be completed by the parents, was sent to those children and parents who could not come to the hospital [7].

2.2 Statistical analysis

Descriptive data were presented as either absolute or relative frequencies or as medians and interquartile ranges (IQR). dEBC pH values were not normally distributed. We thus used the Kruskal-Wallis test to assess differences across the study groups. Between-group comparisons were made with the Mann-Whitney U test. The chi-squared test was used to assess between-group differences in categorical variables. Pearson correlation was used to test correlations between dEBC pH values and continuous data.

Receiver operating characteristic (ROC) analysis and multiple logistic regression analysis were used to quantify the ability of dEBC pH at baseline to correctly classify patients with asthma at follow-up [8, 9]. Accuracy in binary ROC analysis was defined as (sensitivity+specificity) / 2 at the trade-off value. To examine the concordance between diagnosis of asthma at baseline and at school age, percent agreement and kappa were calculated [10]. Statistical significance was defined as a P value $\leq$

0.05. Odds ratios were calculated to illustrate the strength of the association between asthma and the examined factors. All statistical analyses were carried out with SPSS for Windows, Version 22.0.

The study was approved by the Ethics Committee of the Technical University Dresden, Germany.

Written informed consent was obtained from all parents, and assent from all children.

3. RESULTS

3.1 Cohort characteristics

Thirty-eight (22%) of the 173 baseline participants could either not be re-contacted or they, or their parents, refused to participate in the follow-up study (main reasons: no interest, no time, distance to the hospital). There were no significant differences between participants and non-participants at follow-up with respect to basic demographic variables (gender and age) and baseline dEBC pH. About 70% of the remaining 135 children (median age, 7.6 years; IQR, 6.2-8.6 years) successfully completed pulmonary function tests with results adequate for further analyses. Follow-up dEBC pH values could be measured in 84% (n=114) of the participants. The median follow-up dEBC pH values of all groups ranged between 7.87 (allergic rhinitis group [IQR, 7.66-7.96]) and 8.12 (control group [IQR, 7.91-8.27]), but differences across groups did not reach statistical significance (Kruskal-Wallis test, $P=0.08$). There was a significant difference ($p=0.008$) of dEBC pH values between baseline and follow-up in the atopic wheezers group only (Figure 1). Demographic, clinical, and atopic characteristics are shown in Table II.

3.2 Asthma diagnosis at follow-up

At follow-up, 40 children (30%) of the available study population were diagnosed with allergic asthma (Table III). Notably, this diagnosis was made in 100% (n=30) of the members of the baseline group of atopic wheezers, and this proportion was substantially higher in this group than in the others ($P<0.001$). In the former non-atopic wheezers group, more than three fourth (79%) of the children did not have any type of asthma, 12% (n=7) were diagnosed with allergic asthma, and 8.8% (n=5) with non-allergic asthma. Among the children of the previous allergic rhinitis group none developed non-allergic asthma, but two (14%) were diagnosed with allergic asthma. Only one child (2.9%) of the control group developed allergic asthma (Table III).

Across all groups, the percentage agreement between predicted diagnosis at preschool age (baseline) and determined diagnosis at school age (follow-up) was 89% (kappa, 0.73); it accounted for 86% (kappa, 0.72) when only considering the two groups of children with recurrent wheezing at baseline.

3.3 Association between dEBC pH at baseline and diagnosis of asthma at follow-up

Asthma risk at school age as a function of preschool dEBC pH was analysed by comparing tertiles of baseline dEBC pH in logistic regression. Children with values in the lowest tertile ($\text{pH} \leq 7.8$) compared to the highest ($\text{pH} > 8.0$) were at increased risk of asthma at school age (unadjusted OR [uOR], 4.56; 95% CI, 1.44–14.48, $P < 0.0001$).

Another strong association was discovered between the diagnosis of asthma at follow-up and a positive baseline API [11] (uOR, 8.24; 95% CI, 3.00–22.63; $P < 0.001$). However, the frequency of having at least one family member with any kind of atopic disease (family atopy score, FAT [12], assessed at baseline) did not differ between children with or without allergic asthma at follow-up (uOR, 1.02; 95% CI, 0.99–1.04; $P = 0.147$).

3.4 Predictive ability of dEBC pH and atopic sensitization (CAP) at baseline

Binary ROC curve analysis was then used to assess the ability of preschool dEBC pH and other markers to predict asthma at school age (Table IV). The area under the curve (AUC) of dEBC pH for the distinction between asthma (both allergic and non-allergic) and no asthma in the baseline atopic and non-atopic wheezers was 0.72. At the trade-off value of pH 7.83 (i.e. the pH value with the highest sum of sensitivity+specificity), sensitivity was 0.67 and specificity was 0.76 (accuracy, 0.71; positive predictive value (PPV), 0.72; negative predictive value (NPV), 0.71).

Baseline atopic sensitization $\text{CAP} \geq 2$ identified children with asthma at school age with an area under the ROC curve (AUC) of 0.76 (sensitivity, 0.74; specificity, 0.79; PPV, 0.78; NPV 0.76) which was similar to the group of non-invasive baseline markers (API, FAT, FA and ICS) that determined asthma at follow-up with an AUC of 0.77 (sensitivity, 0.76; specificity, 0.76; PPV, 0.77; NPV 0.74). Integrating all CAP classes [CAP (all)] into the model an AUC of 0.85 (sensitivity, 0.69; specificity, 0.96; PPV, 0.94; NPV 0.77) was reached. Compared with CAP (all) alone, the AUC (0.85) did not increase when CAP (all) was combined with all non-invasive markers. However, sensitivity (0.98) and NPV (0.97) distinctly rose while specificity (0.71) and PPV (0.79) declined.

Similarly, combining dEBC pH and CAP (all) only marginally enlarged the area under the curve (AUC, 0.86) but markedly increased sensitivity (0.96) and NPV (0.94), at the same time losing specificity (0.74) and PPV (0.80). Incorporating all additional clinical information (i.e. API, FAT, FA, ICS) into the model led to a further increase in sensitivity (0.98) and NPV (0.97) and the AUC (0.94), and also some regain in specificity (0.79) and PPV (0.83).

3.5 Further statistically relevant associations

There was a statistically significant difference ($P < 0.001$) between the four former groups regarding the proportion of children with ICS treatment (binary value: yes/no; unadjusted): atopic wheezers: 63% [$n=19$]; non-atopic wheezers, 26% [$n=15$]; allergic rhinitis group, 43% [$n=6$]; controls, 6% [$n=2$]; (Table II). Comparing ICS treatment at baseline and at follow-up, we found a marked increase in atopic wheezers and in the allergic rhinitis group as well as a marked decrease in the previous non-atopic wheezers. Significant dEBC pH differences between ICS treated and untreated children were, however, only found in the baseline atopic wheezers group. Intranasal treatment (INS) was only seen in 2 children of the control group probably because INS was usually given according to seasonal demand. Further, a positive correlation was found between dEBC pH value and MEF_{25} ($R=.199$, 95% CI: 0.01 to 0.37, $P=0.039$, $n=108$). FeNO was determined in 42% of the study population. A negative correlation was found between FeNO and dEBC pH in girls ($R=-0.652$, 95% CI: -0.858 to -0.265, $P=0.003$, $n=18$) but not in boys ($R=0.106$, 95% CI: -0.252 to 0.438, $P=0.564$, $n=32$).

4. DISCUSSION

We present a follow-up study that evaluated the potential of dEBC pH in asymptomatic preschool children with recurrent wheezing to predict the likelihood of progression to asthma at school age. Our findings suggest that dEBC pH combined with information about atopic sensitization and additional clinical parameters may serve as a highly sensitive prognostic, non-invasive composite marker for the early detection of young asymptomatic preschool children with increased risk of developing asthma. Since asthma in childhood is predominantly allergic asthma, we included the criteria of allergic sensitization in the definition of asthma, although it is not specific. However, it might additionally help to exclude other chronic diseases with lung function alterations or bronchial hyperresponsiveness.

At follow-up, about one third of the available study population was diagnosed with allergic asthma (Table III); a diagnosis that was shared by every single participant of the previous (at baseline) atopic wheezers but by only about one out of eight members of the former non-atopic wheezers. Non-allergic asthma was only developed by about 9% of former non-atopic wheezers, which is consistent with previous reports that the risk of developing asthma is higher in atopic than non-atopic wheezers [13, 14].

Our ROC analysis at baseline had demonstrated that dEBC pH alone could “excellently” (AUC, 0.80) [9] classify wheezing preschool children into those at high (atopic) and those at low (non-atopic) risk of asthma [3]. At follow-up, baseline dEBC pH values had a lower (“acceptable” [9]) potential to predict asthma as evidenced by lower AUC (0.72), sensitivity (0.67) and specificity (0.76), but the association between decreased (lowest tertile) dEBC pH and asthma risk (uOR, 4.56, CI 1.44-14.5) was nonetheless substantial. Taken together, these data, however, suggested that dEBC pH alone could not be used as a general screening test, in particular because of its low sensitivity. We therefore combined the baseline values pH and CAP class in a logistic regression analysis. This combination led to quite substantial gain in sensitivity (0.96) and NPV (0.94). This finding illustrates that although pH alone does not represent an efficient tool to predict asthma, its combination with CAP class (all) constitutes a promising, easy-to-handle non- or minimally invasive test to identify preschool children with a history of wheezing who are at highest risk of asthma at school age.

Adding additional clinical information which is easily obtained by non-invasive means (i.e. API, FAT, FA, ICS) not only further increased the potential to predict asthma (AUC, 0.94) but also raised

sensitivity (0.98) and NPV (0.97) to nearly perfect values. This indicates that a combination of dEBC pH and CAP class complemented by additional clinical information could be used as a nearly perfect screening tool. Indeed, other studies have shown similar synergistic effects [15, 16]. However, specificity and PPV, even though they also improved, were still clearly below 0.9. Thus, in order to minimize overtreatment, it is now important to reduce the still considerable fraction of false positive cases ($n=24$ in our analysis) by incorporating additional clinical or molecular parameters [15]. Likely candidates would be for example eosinophil-derived neurotoxin (EDN) [17, 18], volatile organic compounds (VOCs) in exhaled breath [19-21], genetic markers [22], or biomarkers still to be identified [23, 24].

There was, however, a second combination - CAP (all) and elements of patient history - that led to very similar results [AUC (0.85), sensitivity (0.98) and NPV (0.97)] as the combination of dEBC pH and CAP (all). This raised the question in what type of clinical scenario measuring dEBC pH and CAP (all) might prove most useful. Considering that both are easy-to-measure objective laboratory parameters, we propose that they may find important applications in settings where obtaining the reliable patient history is either cumbersome (e.g., due to language barriers) or not feasible (e.g. unaccompanied patients, disrupted families). In any case, the present study confirmed the importance of acidic pH in exhalate in the pathophysiology of preschool asthma within the robust setting of a prospective study design.

The present study showed no statistically significant difference between dEBC pH values across the four groups at follow-up. (Deaerated) EBC pH has shown high reproducibility both in children and adults [25-27]. These relatively normal pH values were not unexpected and can easily be explained by clinically stable disease after several years of treatment. The proportion of children with ICS treatment differed between the groups ($P<0.001$) with the highest proportion of about 63% found in the former atopic wheezers (previous non-atopic wheezers: 26%, former rhinitis group: 43%). Moreover, dEBC pH differences between ICS treated and untreated children were only seen in the former atopic wheezers group. This also seems to be an effect of the much higher treatment rate in this group compared to the others. Reasons for not taking steroid therapy at follow-up were, for example, seasonal therapy, defective inhalation device, attempts to omit, parental misperception of disease, and false statements of the parent.

Our study has several potential limitations. First of all, there was a statistically significant age difference between the four study groups at baseline. It has, however, been pointed out previously that small age differences do not affect dEBC pH appreciably [28]. As reported by other authors, we noticed that not only age but also prior experience influences the correct implementation of lung function tests. However, independent of their technical experience and higher age, lung function values of allergic wheezers differed significantly from those of the other groups. Thus, we believe that our results can be regarded as representative. In addition, we could not adjust for exposure to pollutants or to tobacco smoke since the follow-up study followed the design of the baseline study. Of note, there are studies that indicate associations between dEBC and tobacco smoke [5, 29, 30] and pollutants [31-33]. We also could not assess any influence of ethnicity due to the ethnic (Caucasian) homogeneity of the cohort; this is important to note because other studies have shown that dEBC pH may vary among ethnicities [34].

In summary, the present study suggests that dEBC pH combined with CAP class and additional clinical information may serve as a highly sensitive, non-invasive prognostic marker for the early detection of young asymptomatic preschool children with increased risk of developing asthma. Future studies should test for associations between dEBC pH at baseline and clinical outcomes in subgroups of specific interest, and assess effects of potentially confounding diseases, medications, and disease severity on dEBC pH.

Words: 3.029

ACKNOWLEDGEMENTS

This work was supported by internal funds from the University Children's Hospital of the Medical Faculty "Carl Gustav Carus", Technical University Dresden, and by iMed - the Helmholtz Association's Cross-Programme Initiative on Personalised Medicine.

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FIGURES

Title:

FIGURE I. Changes in dEBC pH between baseline and follow-up[†] by group[‡].

Legend:

[†] Wilcoxon-Test.[‡] Groups as classified in the baseline assessment performed in 2007/8 [3].

TABLES

TABLE I. Definition of group classification at baseline.

Group	Definition
Atopic wheezers	Asymptomatic children with recurrent wheezy bronchitis (RWB) [†] and atopic sensitization [‡] /atopic disease [§]
non-atopic wheezers	asymptomatic children with RWB [†] without atopic sensitization [‡] /atopic disease [§]
allergic rhinitis	children with allergic rhinitis (AR) [#] and without a history of RWB [†]
healthy control subjects	children without parentally or clinically reported wheeze or asthma, symptoms of airway inflammation in the last 8 weeks, allergy, AR [#] , or atopic eczema

[†] RWB (recurrent wheezy bronchitis) was defined as ≥ 3 episodes of wheeze within the preceding 12 months (acute bronchitis was defined as cough, normal or slightly increased body temperature ($<38^{\circ}\text{C}$), and wheezy lung sounds on auscultation lasting less than 3 weeks).

[‡] Allergic sensitization was defined as positive skin prick test /blood test (CAP class ≥ 2).

[§] Atopic disease was defined as positive SPT response to ≥ 1 common airborne allergen.

[#] AR (allergic rhinitis) was diagnosed according to the Allergic Rhinitis and Its Impact on Asthma criteria [29].

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447 **TABLE II.** Demographic and clinical characteristics of the study population[†].

Characteristics	atopic [‡]		non-atopic [‡]		allergic rhinitis [‡]		controls [‡]		P value [§]	
	2007/ 2008	2011/ 2012	2007/ 2008	2011/ 2012	2007/ 2008	2011/ 2012	2007/ 2008	2011/ 2012	2007/ 2008	2011/ 2012
No (%) [*]	34 (18)	30 (22)	64 (34)	57 (42)	15(8)	14 (10)	60 (31)	34 (25)		
Male Sex; no (%)	130 (68)	95 (70)	118 (62)	82 (61)	101 (53)	77 (57)	99 (52)	72 (53)	.561 [~]	.588 [~]
Age in years (IQR)	5.4 (1.3)	8.5 (1.5)	3.5 (2.3)	6.7 (2.4)	5.7 (1.6)	8.8 (1.5)	4.4 (2.2)	7.3 (2.2)	<.001	<.001
API score, positive; %	97	ND	22	ND	ND	ND	ND	ND	<.001	ND
Total IgE (kU/L); no	289.0 (534.0)	627 (1570.0); 27	25.0 (42.7)	42 (105.0); 46	282.0 (331.0)	374 (450.0); 11	ND	56.4 (168.0); 23	<.001	<.001
FEV ₁ (% predicted); no	105.3 (22.0); 22	99.4 (22.9); 29	101.6 (14.3); 23	103.7 (15.0); 46	112.6 (24.3); 8	104.7 (18.8); 12	ND	104.3 (18.0); 22	.122	.403
MEF ₂₅ (% predicted); no	92.3 (42); 22	68.5 (52.5); 29	89.3 (15.6); 23	79.8 (39.6); 51	110.3 (33.4); 8	84.8 (38.5); 12	ND	109.8 (33.8); 25	.011	.006
FeNO (ppb); no	13.4 (15.6); 21	13.0 (42.0); 20	5.4 (4.0); 18	6.1 (5.1); 20	12.4 (11.3); 7	9.9 (12.3); 11	ND	5.1 (10.1); 5	.001	.004
ICS treatment; no (%)	16 (47)	19 (63)	28 (44)	15 (26)	3 (20)	6 (43)	0 (0)	2 (6)	.75 [~]	<.001
dEBC pH; no	7.49 (0.94); 34	8.07 (0.29); 26	7.93 (0.23); 64	7.98 (0.43); 52	8.02 (0.17); 15	7.85 (0.30); 10	7.96 (0.25); 6 0	8.12 (0.34); 26	<.001	.152
Positive atopic sensitisation [#] ; no (%)	34 (100)	30 (100)	0 (0)	14 (24.6)	15 (100)	14 (100)	0 (0)	8 (23.5)		<.001

448 [†] Results are expressed as medians (interquartile ranges) unless stated otherwise.

449 ND not determined.

450 [‡] Group assignments made at baseline in 2007/8 [3].

451 [§] Kruskal-Wallis analysis unless stated otherwise.

452 [~] χ^2 Test.

453 [#] CAP ≥ 2 and/or positive SPT.

454 ^{*} Total study populations (baseline values include acute wheezy bronchitis group).

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Table III. Frequency of development of asthma by group[†].

Group assignment at baseline	Diagnosis at follow-up			
	No asthma [‡]	Any	Asthma [‡]	Non-allergic
Atopic wheezers (n=30), (%)	0 (0)	30 (100)	30 (100)	0 (0)
Non-atopic wheezers (n=57), (%)	45 (79)	12 (21)	7 (12)	5 (8.8)
Allergic rhinitis (n=14), (%)	12 (86)	2 (14)	2 (14)	0 (0)
Healthy controls (n=34), (%)	33 (97)	1 (2.9)	1 (2.9)	0 (0)
Total (% [§])	90 (67)	45 (33)	40 (30)	5 (4)

[†] Groups as classified in the baseline assessment performed in 2007/8 [3].[‡] Values refer to n/total n in group (% of total n in group).[§] Percentage of study population.

457 **Table IV.** Binary ROC analysis of values obtained at baseline for the prediction of asthma at follow-up.

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Baseline values	AUC (95% CI)	p value	Sensitivity	Specificity	Accuracy	PPV	NPV
dEBC pH	0.72 (0.62-0.83)	<0.0001	0.67	0.76	0.71	0.72	0.71
CAP ≥ 2	0.76 (0.66-0.87)	<0.0001	0.74	0.79	0.76	0.78	0.76
CAP ≥ 3	0.82 (0.74-0.92)	<0.0001	0.64	1.0	0.82	1.0	0.75
CAP ≥ 2 or positive prick test	0.81 (0.71-0.90)	<0.0001	0.83	0.78	0.81	0.78	0.83
CAP ≥ 3 or positive prick test	0.86 (0.77-0.94)	<0.0001	0.71	1.0	0.86	1.0	0.79
CAP class (all)	0.85 (0.77-0.94)	<0.0001	0.69	0.96	0.82	0.94	0.77
API score	0.73 (0.62-0.84)	<0.0001	0.83	0.62	0.73	0.67	0.80
FAT	0.69 (0.50-0.74)	0.06	0.86	0.47	0.66	0.60	0.78
FA	0.64 (0.53-0.76)	0.02	0.90	0.38	0.64	0.58	0.80
ICS	0.52 (0.40-0.65)	0.70	0.38	0.67	0.52	0.51	0.54
API + FAT + FA + ICS	0.77 (0.67-0.87)	<0.0001	0.76	0.76	0.76	0.77	0.74
CAP class (all) + API	0.86 (0.78-0.94)	<0.0001	1.0	0.64	0.82	0.75	1.0
CAP class (all) + API + FAT	0.88 (0.81-0.96)	<0.0001	0.96	0.74	0.85	0.80	0.94
CAP class (all) + API + FAT + FA	0.86 (0.77-0.95)	<0.0001	0.98	0.74	0.86	0.80	0.97
CAP class (all) + API + FAT + FA + ICS	0.85 (0.77-0.94)	<0.0001	0.98	0.71	0.85	0.79	0.97
CAP ≥ 2 + dEBC pH	0.81 (0.72-0.91)	<0.0001	0.77	0.79	0.78	0.79	0.77
CAP ≥ 2 + dEBC pH + API	0.83 (0.74-0.92)	<0.0001	0.86	0.76	0.81	0.79	0.84
CAP ≥ 2 + dEBC pH + API + FAT	0.86 (0.78-0.93)	<0.0001	0.79	0.79	0.79	0.79	0.79
CAP ≥ 2 + dEBC pH + API + FAT + FA	0.85 (0.77-0.93)	<0.0001	0.79	0.78	0.79	0.79	0.78
CAP ≥ 2 + dEBC pH + API + FAT + FA + Eos	0.88 (0.80-0.96)	<0.0001	0.85	0.78	0.81	0.81	0.82
CAP ≥ 2 + dEBC pH + API + FAT + FA + Eos + ICS	0.88 (0.81-0.96)	<0.0001	0.88	0.75	0.81	0.80	0.84
CAP class (all) + dEBC pH	0.86 (0.78-0.95)	<0.0001	0.96	0.74	0.85	0.80	0.94
CAP class (all) + dEBC pH + API score	0.88 (0.80-0.96)	<0.0001	0.91	0.74	0.82	0.79	0.89
CAP class (all) + dEBC pH + API score + FAT	0.90 (0.87-0.98)	<0.0001	0.96	0.79	0.87	0.83	0.94
CAP class (all) + dEBC pH + API score + FAT + FA	0.93 (0.87-0.99)	<0.0001	0.91	0.86	0.88	0.87	0.90
CAP class (all) + dEBC pH + API score + FAT + FA + ICS	0.94 (0.89-0.99)	<0.0001	0.98	0.79	0.88	0.83	0.97

Abbreviations: API, Asthma Predictive Index; FAT, family atopy; FA, family asthma; ICS, inhaled corticosteroid.

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