

Predictability of early atopy by cord blood-IgE and parental history

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Summary

Background Atopic family history and cord blood IgE have been used as predictors of atopic disease in newborns for about 20 years, but at least for cord blood IgE the sensitivity has been shown to be very low. The objective of this paper was to evaluate whether parental history and cord blood-IgE were more accurate predictors for the appropriate atopic phenotypes in the infants rather than for any atopy.

Methods A total of 1314 newborn infants was recruited in six German obstetric departments in 1990 and followed-up for 2 years. Four hundred and ninety-nine (38%) were at high risk for atopy with at least two first degree atopic family members and/or elevated cord-blood IgE concentrations.

Results The cumulative incidence of atopic dermatitis over the first 2 years of life (AD24) amounted to 20.1%, and there was a significant association with AD history of the mother (OR 2.5, 95%CI 1.46–4.26) and of the father (OR 3.53, 95%CI 1.90–6.54). The cumulative incidence of recurrent wheezing in the first 2 years of life (RW24) amounted to 16.1%, and was positively associated with asthma history (OR 2.11, 95%CI 1.33–3.60) and sensitization history (OR 1.64, 95%CI 1.34–2.36) of the mother, but with neither for the father. RW24 was less prevalent in girls than in boys (OR 0.64, 95%CI 0.47–0.89). Thirty-one per cent of infants were sensitized (CAP test value > 0.35 kU/L) against at least one of nine food or inhalative allergens (S24) and this was significantly associated with cord blood-IgE value (OR 2.43, 95%CI 1.69–3.49), and sensitization history of the mother (OR 1.64, 95%CI 1.18–2.41). Using multiple logistic regression analysis, the prediction of AD24 by AD of parents, of RW24 by asthma of parents, and of sensitization by cord blood IgE was of low accuracy.

Conclusion The predictive capacity of parental history and cord blood IgE is not high enough to recommend them as screening instruments for primary prevention. The majority of atopic manifestations and of sensitization occur in infants with no demonstrable risk at birth.

Keywords: cord blood-IgE, family history, risk factors, atopy infant, prediction

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Introduction

Selective primary prevention of atopic diseases requires

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early identification of healthy individuals at risk. But effective screening remains a challenge. Family history and cord blood-IgE have been proposed as easily accessible and valuable markers to screen newborns for atopy risk [1]. Cord blood-IgE has sometimes been considered an even better predictor than family history [2–9]. In the last 8 years,

however, the predictive capacity of cord blood IgE has been questioned [10–12], while family history of atopy has consistently been regarded as a useful predictor for atopic disease of the infant and child [5,13–15].

A prospective multicentre cohort study was started in Germany to observe the natural course of atopic diseases in children with different atopy risks. The objective of this paper was to evaluate the association between family history and cord blood IgE with appropriate atopic phenotypes of the infant and to calculate their predictive capacity for these phenotypes rather than for any atopy.

Methods

Subjects

Catchment population At six obstetric departments in five German cities (Berlin, Düsseldorf, Freiburg, Mainz, Munich) cord blood-IgE values were obtained from 6401 (84%) out of the total of 7609 infants born between January 1 and December 31, 1990. The detection limit of the method was set at 0.35 kU/L. Samples with an IgA value higher than 32 µg/mL (mean + 3 SD [16]) were considered to be contaminated with maternal blood and excluded (for further details see [17]). Both parents of 6019 (79%) newborns each filled in a questionnaire comprising diagnoses and relevant symptoms of atopic diseases and of allergy tests, except for 22% of the questionnaires which were answered by the mothers on behalf of the fathers. Two years later, mothers and fathers of the study cohort repeated the questionnaire. Because mothers obviously underrated the occurrence of the fathers' diseases [10] the fathers' self-reported history from the second questionnaire was used in the analysis. From the questionnaire items, 11 validated screening parameters [17] were chosen to indicate the atopic status of each parent and sibling. A parent was considered sensitized by history when he reported of having had a positive allergy test against pollen, animals, house dust, moulds, milk, egg, nuts, fish. The history had been validated by a Phadiatop test results (CAP Pharmacia) in a subsample of parents [17].

Cohort infants Infants were recruited for the cohort study within 2 weeks of their birthdate. Out of all newborns those with at least two atopic family members and/or a cord blood IgE value above the classical threshold of 0.9 kU/L [5] were assigned to a high risk group, i.e. 920 infants. A control group of 1619 infants was simultaneously drawn by a dynamic randomization procedure from the remaining newborns. After excluding prematures, newborns with major health problems, twins, or newborns from families who could not speak German, 1985 infants remained eligible and were invited to take part in the prospective study. Of these, 1314 (66%) participated and constituted the

basis of the cohort: 499 infants (38%) belonged to the high risk group, 815 infants (62%) to the control group with no or lower atopy risk.

Follow-up The 1314 infants were seen at the ages 1, 3, 6, 12, 18, 24 months (and still continue to come) with a parent at follow-up visits at the six paediatric clinics. From the first two visits through the age of 2 years, the number of infants participating regularly decreased by 17%. More families without any atopy risk than those with atopic members did not return. At follow-up visits parents (predominantly mothers) filled in a questionnaire and gave a structured interview. Physical examinations, with special emphasis on skin signs, were conducted by physicians in a standardized manner in each of the paediatric clinics, and recorded basically, e.g. in AD the single symptoms, their location, type, severity, and spreading were recorded.

Blood samples were taken at 12 and at 24 months of age for total IgE and specific IgE against four common food allergens (cow's milk f2, egg f, soy f14, wheat f4), and five inhalant allergens (mite d1, cat e1, dog e2, grass g6, birch t3) by the Pharmacia CAP essay.

Definition of atopic diseases in cohort infants Clinical manifestations of atopic diseases and atopic sensitization were treated separately. The diagnosis obvious or possible atopic manifestation was generated from one of four sources: the reported diagnosis by the family physician, the diagnosis given by the examining doctor from physical signs, the examining doctors opinion on reported relevant symptoms, and a computer algorithm for the diagnosis from relevant symptoms and signs. The last three sources needed definitions of atopic diseases: obvious atopic dermatitis was defined as a combination of 'dry skin' and at least three out of nine typical signs (itching, erythema, red papules, vesicles, rhagades, excoriation, squamulae, lichenification, perifollicular accentuation) at three or more of 26 typical anatomical sites (e.g. cheeks, retroauricular, extensor and flexural areas in a centrifugal distribution). Obvious recurrent wheezy bronchitis required at least two wheezing episodes (expiratory stridor) with shortness of breath. Possible recurrent wheezy bronchitis did not require shortness of breath. From symptoms and signs only a probable diagnosis was given for atopic rhinitis or atopic conjunctivitis, an obvious disease was accepted when these diagnoses were made by a physician. Repeated vomiting, diarrhoea and colic, not caused by an infectious diseases, after consumption of milk, eggs, fish or nuts, were regarded as symptoms and signs of probable food intolerance; the diagnosis of a physician was needed for an obvious food intolerance.

Not all parents agreed to blood tests for their infants: 738 infants had blood tests at 12 months and 661 at 24 months of age. An infant was considered sensitized if the IgE

concentration against at least one of the nine tested allergens was equal or higher than 0.35 kU/L ($\geq$ CAP class 1).

Statistical evaluation Associations in two dimensional contingency tables were assessed by Pearson's chi-square tests with SPSS. Odds ratios and approximative Cornfield's 95% confidence intervals were computed with EPI-Info 6. Multiple logistic regression analysis were computed with the software program BMDP.

Only infants who came to follow-up visits at least twice in the first year and three times in the first 2 years were included in the analysis. Three components of atopy rather than the total entity were used as outcome variables to evaluate the influence of risk factors at birth and in early infancy: 1. the cumulative incidence (C.I.) of an obvious atopic dermatitis (AD) in the first 24 months of life (AD24), 2. the C.I. of obvious recurrent wheezing (RW) in the first 24 months of life (RW24), 3. infants with a CAP-test value $\geq$ 0.35 kU/L against at least one of nine allergens either at 12 or/and at 24 months, i.e. the sensitization rate in the first 24 months (S24).

The remaining infants, i.e. with no or probable atopic phenotypes, were pooled to provide a baseline value for the respective atopic manifestation. Infants with negative CAP-tests at 12 and at 24 months gave a baseline for sensitization.

Cord blood-IgE values were grouped into values below detection level, i.e. <0.35 kU/L (64%) and detectable values, i.e. ≥ 0.35 kU/L (36%).

Results

Occurrence of atopic manifestations, and sensitization

The cumulative incidence (C.I.) of atopic individuals in this cohort, i.e. the percentage of infants who were considered to have had any obvious atopic manifestation for the first two years of life, was 36%. The most prevalent manifestation was atopic dermatitis (AD), followed by recurrent wheezy bronchitis (RW), (Table 1). These were used as outcome variables for further analysis.

Sixteen per cent of infants in this cohort were sensitized against at least one of nine allergens at age 12 months, 25.3% at age 24 months, and 31.2% at either 12 or 24 months. 20.0% of infants had any atopic manifestation in the first 2 years and were sensitized.

Risk factors at birth for atopic dermatitis in the first 24 months

The cumulative incidence of obvious atopic dermatitis in the first 2 years (AD24) was shown to be associated with AD history of the mother ($P < 0.001$) and of the father ($P < 0.001$). No association was found between AD24 and

Table 1. Cumulative incidence of obvious and possible atopic manifestations in the first 2 years of life

Manifestation	% Cases	
	Obvious	Possible
Atopic dermatitis	20.1	43.1
Recurrent wheezing	16.1	8.1
Atopic rhinitis	3.4	11.1
Atopic conjunctivitis	2.5	9.6
Food intolerance	4.8	19.5

other atopic diseases of the parents, their sensitization status, cord blood-IgE value or gender of the infant. In a multiple logistic regression analysis, considering all these potential risk factors simultaneously, and also controlling for study centre, the main risks for AD24, i.e. AD of the mother or the father, became even more pronounced (Table 2).

Risk factors at birth for recurrent wheezing in the first 24 months

The cumulative incidence of obvious recurrent wheezing in the first 2 years (RW24) was significantly associated with asthma history of the mother ($P < 0.005$) and with sensitization of the mother ($P < 0.01$), but not with asthma or sensitization history of the father. RW24 was higher in boys than in girls ($P < 0.01$). RW24 was not associated with other atopic diseases of the parents, nor with cord blood-IgE value. When all these factors were considered simultaneously in a multiple logistic regression analysis, and confounding by study centre was also controlled for, only gender was found to be a significant risk factor for RW24 (Table 3).

Risk factors for sensitization at 12 and/or at 24 months

Sensitization of the infant at 12 or 24 months of age (S24) was significantly associated with cord blood IgE value ($P < 0.0001$) and with sensitization history of the mother ($P < 0.02$) but not with atopic manifestations of the parents, the father's sensitization or with gender of the infant. Only cord blood IgE remained a significant risk factor in a multiple logistic regression analysis, when confounding by study centres was also controlled for (Table 4).

Prediction of AD24, RW24, S24

The preceding analyses suggested, that AD24, RW24 and S24 each have their own specific set of relevant risk factors.

Table 2. Cumulative incidence of atopic dermatitis in the first 2 years of life (AD24) according to parental history and cord blood IgE; unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (95CI) for AD24 according to these risk factors. Adjusted odds ratios were calculated by logistic regression analysis taking into account all other risk factors of this table and controlling for study centre

		Unadjusted		Adjusted	
	AD24 (%)	OR	(95CI)	OR	(95CI)
AD history mother					
No atopy	18.1	1.00		1.00	
Other atopic manifestations	21.0	1.20	(0.86–1.60)	1.35	(0.83–2.20)
Atopic dermatitis	35.5	2.50	(1.46–4.26)	3.24	(1.61–6.52)
AD history father					
No atopy	19.6	1.00		1.00	
Other atopic manifestations	20.9	1.09	(0.76–1.56)	1.47	(0.90–2.39)
Atopic dermatitis	46.2	3.53	(1.90–6.54)	4.92	(2.34–10.3)
Sensitization history mother					
Never sensitized	19.7	1.00		1.00	
Ever sensitized	23.5	1.25	(0.89–1.76)	1.08	(0.65–1.80)
Sensitization history father					
Never sensitized	21.4	1.00		1.00	
Ever sensitized	20.6	0.95	(0.65–1.40)	0.60	(0.35–1.03)
<i>Gender</i>					
Male	21.4	1.00		1.00	
Female	18.7	0.84	(0.63–1.13)	0.79	(0.55–1.13)
Cord blood IgE					
< 0.35 kU/L	19.9	1.00		1.00	
≥0.35 kU/L	20.1	1.02	(0.75–1.38)	0.90	(0.65–1.80)

Therefore, the most accurate prediction was expected when the specific neonatal risk factors were used for each outcome variable. Of the risk factors at birth, parental history of AD or asthma, and cord blood IgE were evaluated as predictors of AD24, RW24 or S24, respectively.

According to a logistic regression analysis (Fig. 1), the predicted AD24 increases from 16% if neither parent ever had AD, to 41% if at least one parent had AD ($P < 0.00001$). The predicted RW24 rises only slightly from 12% with no parental atopy, to 21% if at least one parent had asthma ($P < 0.0157$). The predicted S24 rises from 33% with a cord blood-IgE value below 0.35 kU/L to 55% with values above 0.9 kU/L ($P < 0.0001$).

Even in this cohort with many individuals at higher risk for atopy, a high proportion of infants with obvious atopic diseases had parents without atopy or with other atopic phenotypes, i.e. the sensitivity (fraction of atopic infants whose risk was recognized at birth) of the chosen predictors is not very high (Table 5). The specificities for these predictors, i.e. the fractions of healthy infants with a negative history or low IgE were better. The positive predictive value, i.e. the proportion of correctly predicted

atopic states is also low for all potential predictors, even within this cohort. In comparison, the risk of having any atopic disease in combination with any sensitization is also used as an outcome. Preventive measures are usually recommended when either two parents (or close family members) have an atopic disease or one parent is atopic and cord blood IgE is elevated. But in this cohort only 21% of infants with the first and 38% with the second risk constellation developed an atopic disease with sensitization. The positive predictive value in the total population would be even lower than this due to the expected lower prevalence of risks.

Discussion

Cord blood IgE as a risk factor and its use as a predictor of allergic diseases in the infant was first observed and promoted by Hamburger *et al.* (1974) [18]. Kjellman [19] and Kjellman and Johansson [20] found that elevated cord blood IgE values predicted atopic manifestations in infancy. Although this has been confirmed by several studies [21], the predictive capacity of cord blood-IgE has been

Table 3. Cumulative incidence of wheezy bronchitis in the first 2 years of life (RW24), according to parental history and cord blood IgE; unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (95CI) for RW24 according to these risk factors. Adjusted odds ratios were calculated by logistic regression analysis taking into account all other risk factors of this table and controlling for study centre

	RW24 (%)	Unadjusted		Adjusted	
		OR	(95CI)	OR	(95CI)
Asthma history mother					
No atopy	13.8	1.00		1.00	
Other atopic manifestations	18.6	1.42	(0.98–2.06)	0.99	(0.56–1.74)
Asthma	25.3	2.11	(1.33–3.60)	1.87	(0.83–4.23)
Asthma history father					
No atopy	14.9	1.00		1.00	
Other atopic manifestations	18.1	12.6	(0.84–1.89)	1.24	(0.70–2.19)
Asthma	16.4	1.12	(0.55–2.24)	1.34	(0.55–3.26)
Sensitization history mother					
Never sensitized	14.0	1.00		1.00	
Ever sensitized	21.1	1.64	(1.34–2.36)	1.61	(0.87–2.97)
Sensitization history father					
Never sensitized	15.7	1.00		1.00	
Ever sensitized	18.1	1.19	(0.79–1.80)	1.06	(0.56–2.00)
Gender					
Male	18.8	1.00		1.00	
Female	13.0	0.64	(0.47–0.89)	0.62	(0.41–0.94)
Cord blood IgE					
< 0.35 kU/L	15.0	1.00		1.00	
≥0.35 kU/L	16.8	1.14	(0.82–1.60)	1.17	(0.77–1.78)

questioned in the last years [9,10,11,14,17,22,23,24]. The discrepancy between earlier findings and more recent studies may be explained largely by methodological differences. The reliable determination of low cord blood-IgE concentrations requires a high accuracy of laboratory methods, and avoidance or subsequent control for contamination by maternal blood [8]. The earlier studies (before 1990) may also have had analytical problems.

The cut-off point for cord blood-IgE-values in the present study was still rather high, placing 75% of the screening values below detection level [25]. Contamination was avoided and also controlled for by concomitant IgA determination [25]. The extent to which cord blood IgE may be masked by maternal IgG anti-IgE [26] or the severity of atopic diseases in infants blunted by IgG anti-IgE [27] is not known.

Reporting bias and misclassification can be expected from questionnaire data recalling atopic diseases in children and adults [5,10]. In some earlier studies, selection bias might have caused underrating of atopic disorders in infants with low cord blood-IgE, since data came from questionnaires, while infants with high cord blood IgE were scheduled and seen by a physician.

Some earlier research relied on clinical manifestations confirmed by high total IgE and sensitization results. The present study analyses immunological markers and two major manifestations separately, to determine their specific risk profile. But even with this clear focus, we were somehow left with only a suspected diagnosis when relying on history and physical examination. According to Hanifin *et al.*, as well as Sampson, several main criteria are required for the clinical diagnosis of AD in infancy and childhood [28–30] including family history and personal history. One of the objectives of this study was to evaluate the usefulness of parental history as a predictor. Therefore it could not be included in the diagnosis of AD. Personal history of atopy did not exist in the newborn infant and consequently we had to rely on the morphological phenomena and their location. These differ from the phenomena found in adults, e.g. regarding the distribution and the presence of itching.

The atopic phenotype may also include different diseases with a similar clinical phenomenology, as in recurrent wheezing in early childhood, which reflects a diminished airway function in the majority of infants, and a predisposition to asthma in only a minority [31]. To cope with the uncertainty in the definition distinction is usually

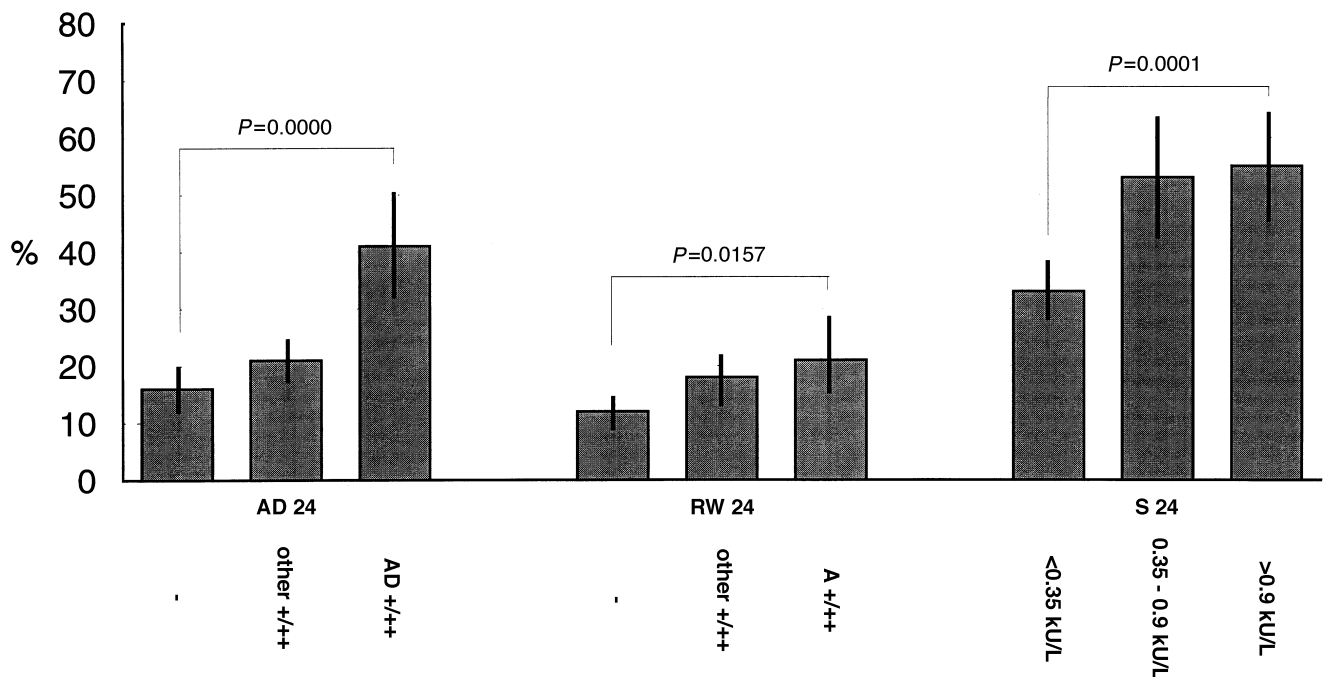


Fig. 1 a–b: Predicted risk of AD24, RW24, and S24 for infants with different risk constellations: – no atopic parent, AD +/+ one or both parents have atopic dermatitis, A +/+ one or both parents have asthma, <0.35 kU/L, 0.35–0.9 kU/L (0.9 kU/L refers to ranges of cord blood-IgE values). The *P*-value above each phenotype refers to the statistical comparison between the two extreme subgroups of each phenotype.

Table 4. Sensitization at 12 or/and at 24 months of age against at least $\geq$ one of nine allergens (S24), according to parental history and cord blood-IgE; unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (95CI) for S24 according to these risk factors. Adjusted odds ratios were calculated by logistic regression analysis taking into account all other risk factors of this table and controlling for study centre

	S24 (%)	Unadjusted		Adjusted	
		OR	(95CI)	OR	(95CI)
Atopy history mother					
Never	38.4	1.00		1.00	
Ever	43.9	1.26	(0.89–1.78)	0.99	(0.57–1.72)
Atopy history father					
Never	37.1	1.00		1.00	
Ever	45.3	1.40	(0.97–2.04)	1.47	(0.83–2.61)
Sensitization history mother					
Never	33.7	1.00		1.00	
Ever	45.5	1.64	(1.18–2.41)	1.38	(0.75–2.54)
Sensitization history father					
Never	38.1	1.00		1.00	
Ever	48.8	1.43	(0.93–2.20)	1.14	(0.60–2.17)
Gender					
Male	39.4	1.00		1.00	
Female	32.8	0.75	(0.54–1.03)	0.78	(0.52–1.17)
Cord blood IgE					
< 0.35 kU/L	32.6	1.00		1.00	
$\geq$ 0.35 kU/L	54.0	2.43	(1.69–3.49)	1.69	(1.10–2.60)

Table 5. Sensitivity, specificity, positive and negative predictive value, and efficiency of 1. AD of father or mother for the prediction of AD24, 2. asthma of father or mother for the prediction of RW24, 3. cord-blood IgE for the prediction of S24, and 4. atopic disease of both parents or of one parent and cord blood IgE ≥ 0.35 kU/L

Outcome	Risk	Sensitivity (%)	Specificity (%)	Predictive value (%)		Efficiency (%)
				positive	negative	
1. AD24						
	AD at least one parent	22	91	41	81	77
2. RW24						
	Asthma at least one parent	17	86	25	80	71
3. S24						
	Cord blood IgE, ≥ 0.35 kU/L	47	71	48	71	63
4. Any atopy + sensitization						
	Both parents atopic	21	88	30	82	75
	One parent atopic + cord blood IgE, ≥ 0.35 kU/L	38	74	25	84	67

made in obvious or definite and possible or probable atopic manifestation [5,14,15,20,32,33].

Under these conditions, it could be shown by univariate and multivariate analysis that atopic dermatitis (AD24) has a strong association with parental history of AD, but not with cord blood IgE, which is in accordance with the Isle of Wight study [13,34] but in contrast to Halonen *et al.* [35] who found eczema in 9-month-old infants of the Tuscon study to be related to cord blood IgE. Lower cord blood values than in our study could be measured by their method, and eczema was diagnosed by a questionnaire at a mean age of 1.6 years, indicating whether the child had physician-confirmed eczema during the first year (including sensitization?). This approach is prone to overlook other forms or less severe eczema.

In a follow-up study, Guillet and Guillet [36] observed for infants and children with AD that those who were sensitized against food allergens had a more severe and longer lasting disease than those without sensitization. In the present study, 44% of infants with obvious AD in the first two years were sensitized against food allergens at 12 months of age and 41% sensitized against inhalant allergens at 24 months of age, while of the remaining infants only 17% and 18%, respectively, were sensitized.

RW24 in the present study was associated with asthma history and sensitization history of the mother only, with gender, and not with cord blood IgE. Martinez *et al.* [31], following children up to 6 years of age, found persistent wheezing to be associated with cord blood-IgE and maternal asthma, while wheezing in the first 3 years only was not associated with cord blood IgE. In the present study both types of recurrent wheezers are still indistinguishable in symptoms and signs.

Sensitization of the infants was predicted by cord blood IgE. The tracking of total serum IgE in children was first described by Kjellman [20], further by Halonen *et al.* for infants from birth to 9 months of age [37], and by Hansen *et al.* from birth to 18 months of age [37]. As specific IgE antibodies and total IgE values were highly correlated at 18 months of age [38], the significant association between cord blood-IgE and S24 we observed is in line with these findings. For the prediction of sensitization in the infant from family traits, indicators for elevated specific IgE values in the parents were used, i.e. the reported test results on sensitization (validated by Phadiatop® test, [17]). S24 was shown to be significantly associated with sensitization history of the mother and with cord blood IgE.

Although specific predictors for each of the outcome variables were applied, the overall precision of the predictions was not very high. The positive predictive value is especially important for the recommendation of preventive measures. According to our evaluation, these measures would be justified in less than 30% of the newborns selected for prevention, but would have been needed in over 15% of those not considered. In absolute terms, this might be a much higher number of infants from the entire population than the number selected for prevention. The positive predictive value would even be lower if it had been calculated for the total population instead of this risk enriched cohort [39].

Our findings suggest that the majority of atopic manifestations and of sensitization occur in infants with no demonstrable risk at birth. This may justify the search for measures applicable to the population at large, independent of individual risk assessment, to reduce the occurrence of atopic diseases in the general population [40].

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