

Cord blood-IgE as risk factor and predictor for atopic diseases

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Summary

Background Cord blood-IgE as risk factor or predictor for atopic diseases in infants has been discussed in a large number of papers with contradictory results. Our aim was to evaluate cord blood-IgE as risk factor and predictor for atopic dermatitis, recurrent wheezing and sensitization with emphasis on a clear-cut distinction between risk factor and predictor.

Methods A cohort of 1314 newborns was recruited in six German obstetric departments and followed-up for 5 years. Four hundred and ninety-nine infants (38%) were considered to be at high risk with at least two atopic family members and/or a cord blood-IgE value above the threshold of 0.9 kU/L. At follow-up visits, parents filled in a questionnaire, the infants were clinically examined, and blood samples were taken.

Results With regard to early onset atopic dermatitis up to 12 months we found that the odds ratios at the cord blood-IgE cut-off points of 0.70 kU/L and 1.25 kU/L with values of 0.53 and 0.32, respectively, were smaller than one (i.e. protective factors) and highly statistically significant. No significant association was found between elevated cord blood-IgE and recurrent wheezing. There was a strong positive association between elevated cord blood-IgE levels and sensitization at 12 months, but even in this case the predictive performance was rather poor: a maximum positive predictive value of 42% was attained with a cut-off point of 3.0 kU/L, but the sensitivity was only 10%.

Conclusion We conclude that even when elevated cord blood-IgE levels are identified as a strong risk factor for sensitization, their poor predictive performance may make them useless as a basis for preventive measures.

Keywords: cord blood-IgE, atopic dermatitis, recurrent wheezing, sensitization, ROC curve

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Introduction

Elevated serum IgE is known to be a hallmark of atopic diseases. Especially with regard to preventive measures, a frequently given recommendation is to determine IgE levels as soon as possible in infants, i.e. to analyse cord blood-IgE (CB-IgE).

The role of CB-IgE as a risk factor or predictor for

atopic disease has been widely discussed. Early empirical evidence was uniformly in favour of the usefulness of CB-IgE [1–10].

However, most papers published since 1988 have reported empirical evidence in the opposite direction [11–17]. An exception is, e.g. Halonen *et al.* [18], who reported a positive association between early atopic dermatitis and elevated CB-IgE levels. An interesting contribution was made by Hansen *et al.*, who found CB-IgE useful not for the prediction of atopic disease [19] but for the prediction of allergic disease, which they defined as atopic disease combined with elevated total IgE levels [20].

The German Multicentre Allergy Study (MAS) was

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initiated to evaluate determinants for the natural course of atopic diseases in children. The aim of this paper is to evaluate CB-IgE as a risk factor and predictor for atopic dermatitis, recurrent wheezing and sensitization, with emphasis on a clear-cut distinction between risk factor and predictor.

Materials and methods

Catchment population

A total of 6401 CB-IgE values was obtained from the 7609 infants born between 1 January and 31 December 1990 at six obstetric departments in five German cities (Berlin, Düsseldorf, Freiburg, Mainz and Munich), i.e. 84% of all neonates had IgE determinations of cord blood drawn by puncturing a cord vein after the cord had been clamped. A total of 6019 (79%) parents filled in a questionnaire on atopic diseases, relevant symptoms and allergy tests. From the questionnaire items, 11 validated screening parameters [21] were chosen to define the atopic status of first degree family members, i.e. parents and siblings.

IgE assay

Serum was separated by a centrifuge at 3500 U/min and then stored at -20°C for less than 1 week before being shipped on dry ice to the laboratory, where IgE was determined by Pharmacia CAP RAST FEIA. The standard calibration curve had an upper limit of 100 kU/L and a detection limit of 0.35 kU/L.

IgA assay

In order to control for maternal blood contamination, IgA was determined by a highly sensitive radio-immunoassay in cord blood samples of all neonates whose IgE values were above 0.5 kU/L, i.e. 1012 samples. Sixty-two cord blood samples with an IgA value higher than $32\text{ }\mu\text{g/mL}$ were classed as contaminated [22] and excluded from further analysis.

Cohort infants

A cohort of 1314 newborns was recruited from the catchment population for the prospective study: 499 infants (38%) were selected as being at 'high risk' with at least two atopic first degree family members and/or a CB-IgE value above the classic threshold of 0.9 kU/L [4]; a control group of 815 infants (62%) was chosen at random from the remaining newborns (one or no atopic first degree family member and cord blood value less than 0.9 kU/L). Of the cohort, 1261 (96%) infants had valid CB-IgE

measurements. Prematures, newborns with major health problems, twins, or newborns from families who could not speak German were not included. The study was approved by the local Ethics Committee. All parents gave informed consent before joining the study.

Follow-up

The infants were seen at the ages 1, 2, 3, 6, 12, 18, 24, 36, 48 and 60 months with at least one parent at follow-up visits at the six paediatric clinics. By the age of 5 years the number of participating children had decreased to 1004 (76.4%). At follow-up visits parents filled in a questionnaire and gave a structured interview. Physical examinations were conducted by physicians in a standardized manner, special attention was paid to skin signs.

Blood samples were taken at 12, 24, 36, 48 and at 60 months of age. Total IgE and specific IgE against four common food allergens (cow's milk f 2, egg f 1, soy f 14, wheat f 4) and 5 inhalant allergens (mite d 1, cat e 1, dog e 2, grass b 6, birch t 3) were determined using the Pharmacia CAP assay.

Definition of atopic diseases

Clinical manifestations of atopic diseases and atopic sensitization were treated separately. A negative, probable or obvious diagnosis of atopic diseases (atopic dermatitis, recurrent wheezing, atopic conjunctivitis, rhinitis and food intolerance) was based on clinical manifestations. For the analysis here only atopic dermatitis and recurrent wheezing are considered, cases with probable diagnosis are treated as negative cases.

The diagnosis was based on a combination from four different sources of information:

- 1 the reported diagnosis by the family physician,
- 2 the examining doctor's opinion on reported relevant symptoms,
- 3 the diagnosis made by the examining doctor and,
- 4 a computer algorithm which was used to construct a diagnosis from elemental atopic symptoms and signs: obvious atopic dermatitis was diagnosed from a combination of 'dry skin' and at least three out of nine typical signs (itching, erythema, red papules, vesicles, rhagades, excoriation, squamae, lichenification, perifollicular accentuation) on at least three out of 26 typical anatomical sites (e.g. cheeks, retroauricular, extensor and flexural areas). At least two wheezing episodes with shortness of breath were required for obvious recurrent wheezing.

The consistency of diagnoses from the different sources of information was reviewed by one physician (RLB) and a few cases were reclassified.

An infant was considered sensitized when the IgE

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

Outcome variables

In spite of the fact that atopic diseases have a common IgE mediated aetiology they are different with regard to age of onset, age of maximum prevalence and also potential misclassification error. Because of this, only single components of atopy rather than a total entity will be considered as outcome variables.

- 1 The cumulative incidence of atopic dermatitis in the first 12 months of life and in the first 60 months of life.
- 2 The cumulative incidence of recurrent wheezing in the first 12 months of life and in the first 60 months of life.
- 3 The prevalence of sensitization at 12 months and at 60 months.

Statistical methods

CB-IgE is evaluated as risk factor for atopic diseases by computing odds ratios (ORs) as a measure of association between the outcome variables and the dichotomized CB-IgE at different cut-off points (0.35, 0.50, 0.70, 1.25, 3.00 kU/L). Approximate Cornfield's 95% confidence intervals (95% CI) for the odds ratios were computed, *P*-values were derived from the exact Fisher-Test of the two-by-two contingency table.

For the evaluation of CB-IgE as predictor of atopic diseases, the dichotomized CB-IgE is regarded as a diagnostic screening test for the outcome variables:

Test +	Test –
Disease +	a b
Disease –	c d
	a + c b + d

The performance of a screening test is usually described with the following characteristics. Specificity, $SP = d/(c + d)$, the proportion of healthy patients who are correctly classified as negative. Sensitivity, $SE = a/(a + b)$, the proportion of patients with disease who are correctly classified as positive. Positive predictive value, $PV+ = a/(a + c)$, the proportion of true test-positive patients among all test-positive results. Negative predictive value, $PV- = d/(b + d)$, the proportion of true test-negative patients among all test-negative results.

There is a trade off between specificity and sensitivity – as one increases the other decreases. This can be visualized by receiver operator characteristic (ROC) curves [23]: an ROC curve is constructed by plotting the true positive rate (sensitivity) against the false positive rate ($1 - SP$) for several cut-off values of the diagnostic criterion. The point in the upper left corner where the false positive rate is 0%

and sensitivity is 100% represents a perfect diagnostic test. A diagnostic test that conveys no information has a ROC curve that is identical to the main diagonal running from the lower left to the upper right. ROC curves that are useful trace out a concave curve above the main diagonal. Unfortunately, there is no general cost or utility function with which to determine an optimal solution to the trade off problem. The positive and negative predictive value of a screening test are of greater concern for clinical decision-making than specificity and sensitivity, e.g. the positive predictive value informs the physician about the probability that a patient with a positive test result really develops the disease. Positive and negative predictive value are dependent on the prevalence of the disease in the target population. Even a screening test with high sensitivity and specificity can give poor results in terms of the positive predictive value if the disease is rare in the target population [24].

For statistical computations we used SPSS for Windows, Version 6.1.

Results

Distribution of CB-IgE

Some 64.2% of the infants had CB-IgE values below the detection limit of the assay, i.e. 0.35 kU/L. The 95th percentile was 2.4 kU/L, the 99th percentile was 10.75 kU/L. Two values (117.10 and 135.75 kU/L) were beyond the upper limit of the calibration curve. Figure 1 shows the number of infants falling below and above the chosen cut-off points of the dichotomized CB-IgE.

Occurrence of atopic manifestations and sensitization

The cumulative incidence of obvious atopic dermatitis up to 12 months was 12.9%; up to 60 months it was 30.3%. For obvious recurrent wheezing the cumulative incidences up to 12 and 60 months were 10.4% and 26.8%, respectively.

Blood samples were not taken at all examinations, therefore for sensitization the prevalences are preferred as outcome variables. The number of valid blood samples at age 12 months and at age 60 months were 802 and 654, respectively. At age 12 months 16.4% of the infants with valid blood samples were sensitized against at least one of nine allergens and at the age 60 months 34.9% were sensitized.

CB-IgE as a risk factor

Atopic dermatitis

Early onset atopic dermatitis: for all the selected cut-off points the resulting odds ratios indicated a negative association between CB-IgE and atopic dermatitis up to

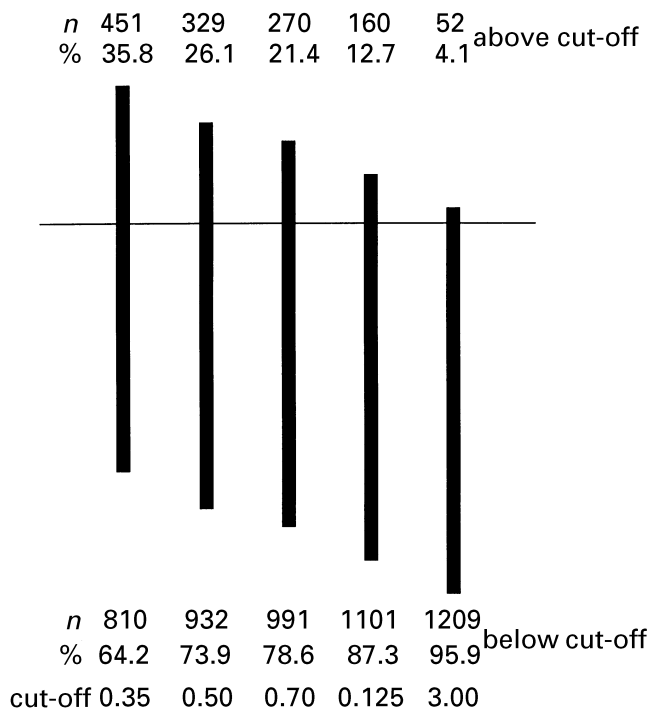


Fig. 1. Number of infants falling above and below each CB-IgE cut-off point.

12 months (Fig. 2a). The negative association was highly significant (P -value < 0.01) for the cut-off values at 0.70 and 1.25 kU/L with odds ratios [95% CI] equal to 0.52 [0.31,0.85] and 0.32 [0.15,0.70], respectively. For the cut-off value at 3.00 kU/L the odds ratio [95% CI] equals 0.15 [0.02,1.09], the approximate 95% confidence interval includes 1.00 but the P -value based on the Fisher exact test is significant (P -value < 0.05). The strong negative association between CB-IgE and atopic dermatitis up to 12 months is substantially weakened in the longer run (Fig. 2b). For the cumulative incidence of atopic dermatitis up to 60 months only the cut-off point at 1.25 kU/L provides a significant negative association (OR = 0.58, 95% CI [0.37,0.91]).

Recurrent wheezing

Neither a significant positive nor a significant negative association exists between CB-IgE and the cumulative incidence of recurrent wheezing up to 12 months, (Fig. 3a). The odds ratios obtained by analysing the association between CB-IgE and the cumulative incidence of recurrent wheezing up to 60 months are greater than one for all five cut-off points (Fig. 3b). But only the odds ratio resulting from the cut-off point at 0.35 kU/L can be regarded as borderline significant (OR = 1.32, 95% CI [1.00,1.75]).

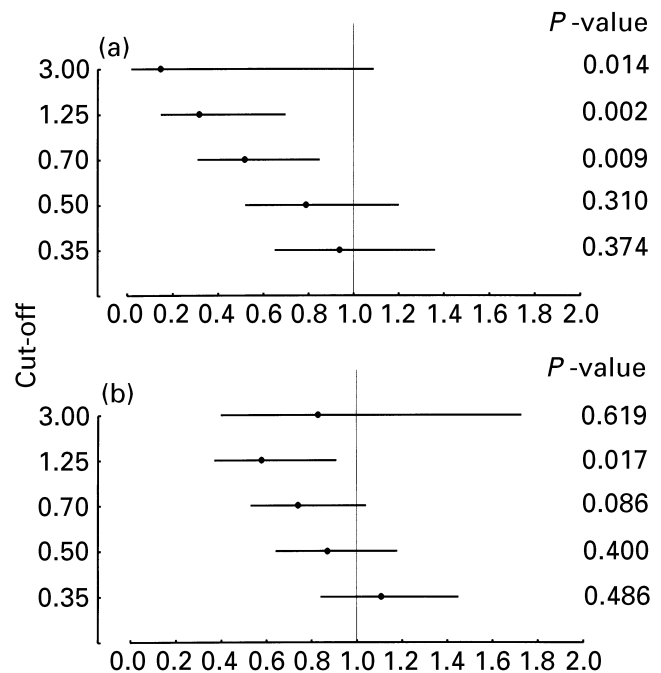


Fig. 2. Association between elevated CB-IgE levels and the cumulative incidence of atopic dermatitis, odds ratios and 95% confidence intervals, (a) CB-IgE and atopic dermatitis up to 12 months, (b) CB-IgE and atopic dermatitis up to 60 months.

Sensitization

A strong positive association exists between CB-IgE and early sensitization at age 12 months, (Fig. 4a). All odds ratios exceed 2.50 and are highly significant (P -values < 0.001). A maximum odds ratio is reached at a cut-off point of 3.00 kU/L (OR = 4.21, 95% CI [1.88,9.43]). At age 60 months the positive association between CB-IgE and sensitization is far less pronounced (Fig. 4b). Only the two smallest cut-off points provide highly significant odds ratios which are close to 2.00 (P -value < 0.01), the three upper cut-off points result in odds ratios which are not significant.

CB-IgE as predictor

No empirical evidence could be found that elevated CB-IgE levels are a risk factor for atopic dermatitis or recurrent wheezing (cumulated incidences up to 12 and 60 months). Therefore an evaluation of the predictive capability of CB-IgE with regard to these atopic diseases can be omitted.

There was a strong positive association between elevated CB-IgE levels and early sensitization at 12 months, a weaker positive association was found with regard to sensitization at 60 months.

Figure 5 gives the ROC curves for the prediction of sensitization at 12 and 60 months by CB-IgE, cut-off points are 0.35, 0.50, 0.60, 0.70, 0.90, 1.25, 1.50 and

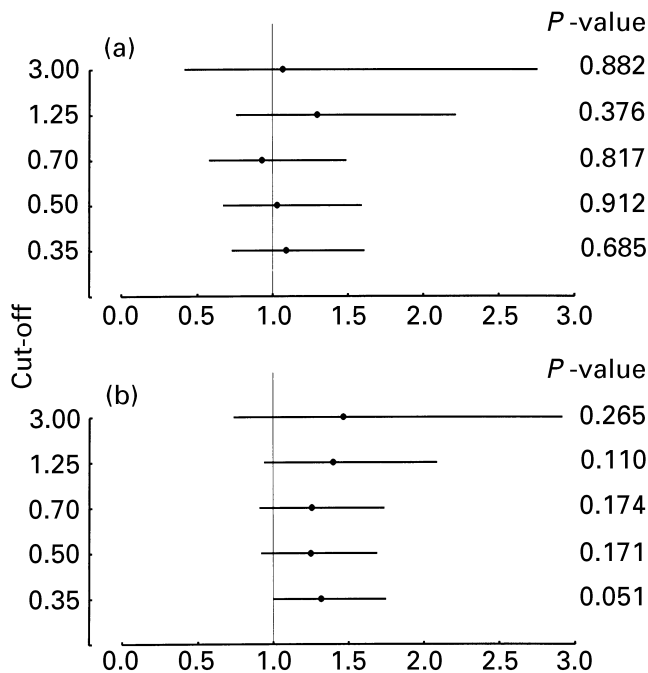


Fig. 3. Association between elevated CB-IgE levels and the cumulative incidence of recurrent wheezing, odds ratios and 95% confidence intervals, (a) CB-IgE and recurrent wheezing up to 12 months, (b) CB-IgE and recurrent wheezing up to 60 months.

3.00 kU/L. It is easily seen that both ROC curves, even that for sensitization at 12 month, are far away from being a useful ROC curve. The detection limit of the IgE assay restricts the ROC curves to the lower left quadrant. The curves exhibit no concavity but run more or less in parallel to the main diagonal. The visual impression of the poor predictive performance of CB-IgE for sensitization at 12 months is confirmed by looking at the positive predictive value which is given along with specificity, sensitivity and the negative predictive value in Table 1. The maximum positive predictive value of 42.3% is achieved with the cut-off point set to 3.0 kU/L, where sensitivity reaches its minimum value of 9.8%, i.e. 90.2% of sensitized children would not be identified using this cut-off point. The corresponding results for sensitization at 60 months are even worse (not included).

Discussion

Our analysis demonstrates that the predictive performance of elevated CB-IgE is poor not only with regard to atopic dermatitis or recurrent wheezing but also with regard to sensitization, although a strong association exists between elevated CB-IgE levels and sensitization.

An unexpected result is the strong negative association between elevated CB-IgE levels and early onset atopic dermatitis up to 12 months.

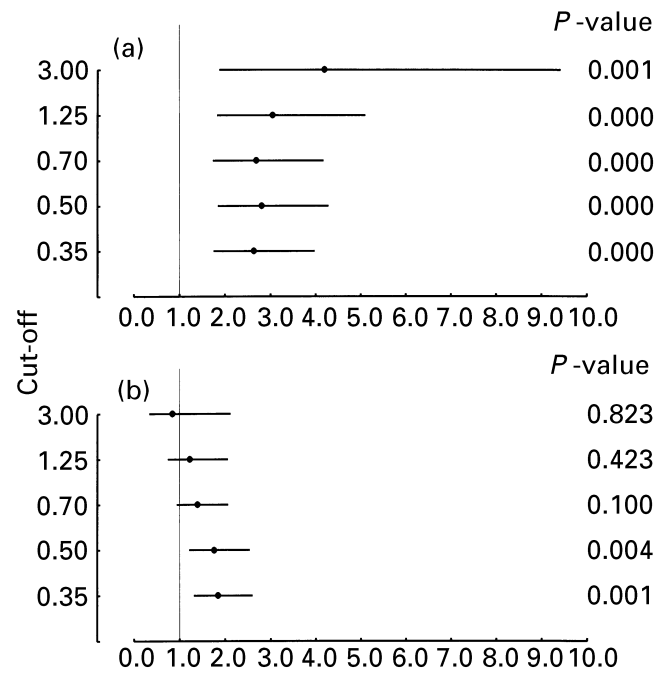


Fig. 4. Association between elevated CB-IgE levels and the prevalence of sensitization, odds ratios and 95% confidence intervals, (a) CB-IgE and sensitization at 12 months, (b) CB-IgE and sensitization at 60 months.

IgE synthesis and the pathogenic mechanisms that can cause atopic symptoms are complex processes which are only partly understood. This makes observational studies on atopic disorders in infants a real challenge. Meaningful comparisons between different studies are almost impossible. Differences concern not only selection of subjects, follow-up times, laboratory and survey methods but also the precise definitions of atopic outcomes, which vary considerably between the studies.

It can be argued that a substantial improvement in laboratory methods and blood sampling techniques explains the transition from a positive evaluation of CB-IgE as predictor of atopic diseases in the early paper of Hamburger *et al.* 1974 [1] and subsequently [2–10] to a negative point of view, starting with a paper by Merret *et al.* 1988 [11], followed by many others [12–17]. An unsolved question is the IgA control for maternal blood contamination. Lilja *et al.* [13] find no correlation between elevated IgA levels and positive RAST results against inhalant allergens in cord blood, so the determination of IgA in cord blood may not be a reliable method for excluding maternal contamination. Their conclusion is supported by an independent study of Hansen *et al.* [25], who find no correlation between the concentrations of CB-IgE and CB-IgA. In our group, we have not only found a strong positive association between elevated CB-IgE levels and sensitization at 12 months but

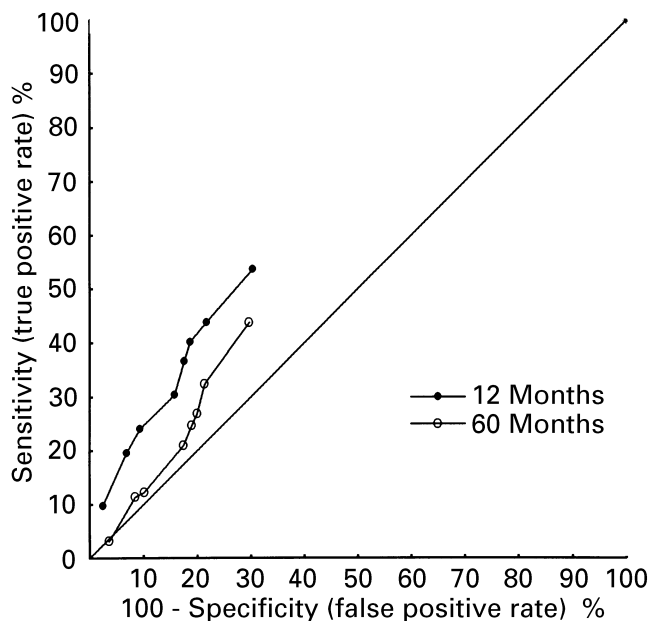


Fig. 5. ROC curves for the prediction of sensitization (prevalence at 12 and 60 months) by elevated CB-IgE levels. The curves are evaluated at the cut-off points 0.35, 0.50, 0.60, 0.70, 0.90, 1.25, 1.50 and 3.00 kU/L. Both curves run more or less in parallel to the main diagonal, i.e. elevated CB-IgE levels convey no useful predictive information for sensitization.

also between elevated CB-IgE levels and elevated total IgE levels in the infants at 12, 24, 36, 48 and 60 months (Bergmann *et al.* 1998, to be published). This tracking of the future immunological status gives us confidence that our CB-IgE measurements represent the infants' immunological status at birth. Of course, some misclassifications cannot be totally excluded.

A more important point is the great variation in the definition of atopic outcomes between the different studies: Rivas *et al.* [17] '... looked for any probable atopic diseases (recurrent wheezing, immediate food reactions and eczema)' as atopic outcome. Hide *et al.* [14] diagnosed a definite atopy, when there is a positive skin-prick test result in addition to typical atopic symptoms. Hansen *et al.* introduced the distinction between atopic diseases [19] and allergic diseases [20], the latter requiring elevated levels of total IgE in addition to atopic symptoms. Most studies include urticaria as an atopic symptom [2,5,15,19,20] others disregard it [26], as we have done in our study. At first glance, the approach of Hide *et al.* [14] or Hansen *et al.* [20], who define definite atopy/allergy as a combination of atopic symptoms with immunological markers, looks appealing. It might be expected that these approaches will result in a more precise definition of atopy as an IgE-mediated response and that the comparability of

Table 1. Sensitization, prevalence at 12 months, characteristics of prediction by CB-IgE for various cut-off values

Cut-off	SP*	SE†	PV+‡	PV-§
0.35 kU/L	69.6	53.6	24.9	88.8
0.50 kU/L	78.3	43.8	27.5	88.1
0.60 kU/L	81.3	40.2	28.8	87.8
0.70 kU/L	82.4	36.6	28.1	87.3
0.90 kU/L	84.2	30.4	26.6	86.5
1.25 kU/L	90.6	24.1	32.5	86.4
1.50 kU/L	93.1	19.6	34.9	86.0
3.00 kU/L	97.5	9.8	42.3	86.0

*SP, specificity; †SE, sensitivity; ‡PV+, positive predictive value; §PV-, negative predictive value.

findings from different studies would be enhanced. But this need not be the case. The evaluation of skin-prick tests is itself the subject of intensive discussions [27]. Some researchers use allergen weal diameters adjusted for the histamine weal diameter, others prefer to use the allergen mean weal diameters alone. Skin-prick testing is prone to interobserver variation in the way the test is performed and in measurement of the weal. The usefulness of elevated total IgE levels in infants to confirm the diagnosis of an atopic disease is even more questionable. There is no doubt that elevated total IgE levels are positively associated with atopic diseases, but total IgE is also influenced by other factors. A comparative study among preschool children in East and West Germany [28] found a tendency to higher total IgE serum levels in cities with higher air pollution. Other factors that influenced total IgE serum levels in East German children were a history of parasitic infection, number of persons per dwelling, gender, and passive smoking. In West German children other influencing factors were gender and passive smoking. As high air pollution and parasitic infections were much more common in East Germany than in West Germany, higher total IgE levels were observed in East Germany. It is interesting that von Mutius *et al.* [29] found the proportion of children with a positive skin-prick test against aeroallergens higher in West Germany than in East Germany. These results show that elevated total IgE levels and positive skin-prick tests may represent different aspects of the immunological status of children. We suggest that our approach of analysing immunological markers and well defined atopic manifestations separately should be preferred in epidemiological studies, until the complex genesis of the atopic phenotype is better understood.

In accordance with the majority of papers published since 1988, our results show that elevated CB-IgE levels are not a risk factor for atopic dermatitis or recurrent wheezing. An

explanation for the missing association between elevated CB-IgE levels and recurrent wheezing is that wheezing episodes are not necessarily related to a predisposition to atopic asthma [30] but may be only transient conditions associated with diminished airway functions. Using stronger definitions for this outcome in combination with different immunological markers is likely to produce other results. We are currently working on a forthcoming paper that will analyse the problem of varying results in dependence of different outcome definitions in detail.

The strong negative association between elevated CB-IgE levels and early onset atopic dermatitis up to 12 months raises a lot of questions and contradicts results of Halonen *et al.* [18], who describe a positive relationship between increasing CB-IgE levels and the proportion of infants with atopic eczema. There are three major differences between their study and ours. First, they used a more sensitive IgE assay, measuring CB-IgE levels as low as 0.10 kU/L. Second, the presence or absence of eczema was determined by a questionnaire completed by the parents in the infant's second year of life (mean age 1.6 years), indicating whether the child had had physician-confirmed eczema during the first year (which could include allergy tests for confirmation). It can be assumed that this kind of diagnosis overlooks less severe forms of eczema. Third, their analysis was based on an unselected cohort from a healthy population. This must be contrasted with our 'high risks cohort, as described already above.

It would be interesting to attach a biologically significant meaning to the negative association between elevated CB-IgE levels and atopic dermatitis, but we can only speculate about this. Vassella *et al.* [31] discuss the role of elevated IgG anti-IgE levels in cord blood, which are assumed to protect children of increased allergy risk from early development of atopic disease. Especially, they point out that children with a dual heredity of allergy who remained healthy had significantly higher IgG anti-IgE at birth than children with a similar predisposition, who became allergic. We do not have cord blood IgG anti-IgE measurements available from the infants in our study, but we can make the purely conjectural proposition that the observed protective effect on early onset atopic dermatitis in our 'high-risk' cohort is not directly related to CB-IgE but to IgG anti-IgE. Another speculative hypothesis that would also attach a biological meaning to the negative association of elevated CB-IgE with early atopic dermatitis is that there is some kind of antenatal infection that has the same effect as a helminth infection: despite up-regulation of the helper T lymphocytes 2 (TH₂) response and elevation of IgE levels, there may be at least a transient protective effect against atopic diseases. As we do not have data available that allow for empirical evidence for any of the mentioned hypotheses, we are left with a conservative meta-analytical point of

view, i.e. to merge positive and negative results and finally conclude that there is no association at all.

It is interesting that, Halonen *et al.* [18] use the term 'predictive relationship' when they evaluate CB-IgE as a risk factor in our terms, with an odds ratio of 2.88 (95% CI [1.42, 5.75]) in their highest IgE group, i.e. CB-IgE levels greater than 1.0 kU/L. But interpreting their data with regard to predictive performance, it can be shown, e.g. that the positive predictive value for eczema in their highest IgE group is as low as 19.2%. This points to the importance of making a clear-cut distinction between risk factor and prediction.

That a significant risk factor is not sufficient as predictor was demonstrated in this paper when we looked at the relationship between elevated CB-IgE levels and sensitization at 12 and 60 months. Especially the use of ROC curves showed how far elevated CB-IgE levels are from any reasonable prediction, despite the fact that there is a highly significant positive association measured by odds ratios.

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