

Determinants of cord-blood IgE concentrations in 6401 German neonates

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For screening atopy risk in 6401 (84%) of all infants born during the year 1990 in six obstetric departments of five German cities, cord-blood IgE values were determined with CAP-RAST-FEIA. After cases with elevated IgA values had been excluded, 25% of the values were above the detection limit of 0.35 kU/l, and 8.5% were above 0.9 kU/l. Boys had significantly higher values than girls ($P < 0.001$). The distribution of values was significantly different for different nationalities of mothers ($P < 0.001$). The percentage of elevated values (> 0.9 kU/l) increased significantly with the number of close family members with atopic history ($P < 0.001$).

Regarding the atopic history of the father, siblings, and mother separately, only the mother's history had a significant association with the cord-blood IgE class ($P < 0.001$). The IgE values of 81 twin pairs correlated significantly with a coefficient of $r = 0.4909$ ($P < 0.001$). The smoking history of the parents during pregnancy showed an association with cord-blood IgE values ($P < 0.02$). No significant association could be shown between cord-blood IgE distribution and other variables, i.e., gestational age, birth size, birth modus, Apgar score, cord-blood pH value, neonatal problems, parity, age of the mother, medication during pregnancy, educational level of mother or father, time of year, or obstetric department. It is hypothesized that, in addition to some postpartum contamination or placental transfer of maternal IgE, cord-blood IgE values are also determined by the fetal immunologic reaction to intrauterine exposure to allergens and trigger factors, and by genetic influences.

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Cord-blood IgE has been considered to be an effective immunologic predictor which can be used to screen neonates for the risk of atopic diseases (6, 8, 25), although the predictive value of cord-blood IgE has been questioned in recent years (4, 14, 20, 24, 28, 31). The fetus can probably synthesize IgE (9) starting in week 11 of gestation (26), and maternal IgE is believed by many authors not to cross the placenta (2, 7, 17, 29, 30). But IgE values in cord blood are very low, and contamination with even minute amounts of maternal blood could therefore be of great significance (20).

Cord-blood IgE values have been shown to be higher in boys than in girls (1, 8, 11, 12, 16, 19); to be lowest in autumn (1, 11, 12, 15); to be related to parental atopy (1, 23, 25, 29), parental smoking (22, 27), and ethnic background (11); and to be higher when the mother receives progesterone during pregnancy (27).

The German Multicenter Atopy Study (MAS-90) was initiated to assess the predictive value of cord-blood IgE, among other risk factors, for atopic diseases in early childhood. In this study, the neonate populations in six hospitals in 1 calendar year were screened. The distribution of these cord-blood IgE values and their association with other variables will be presented in this paper.

Material and methods

Population and sampling

A total of 6401 cord-blood IgE values was obtained from 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 cord-blood IgE determinations. It was requested that cord blood be drawn by puncturing a cord vein after

the cord had been clamped. Blood samples were immediately stored in the refrigerator for up to 4 days.

IgE assay

Serum was separated by a centrifuge at 3500 U/min for 13 min, and serum samples were stored at -20°C for less than 1 week before they were shipped in dry ice to the laboratory, where IgE was determined by CAP-RAST-FEIA (Pharmacia Germany). The standard calibration curve had an upper limit of 100 kU/l, and the detection limit was set at 0.35 kU/l. The intra-assay variation was less than 5% (10). After 2 years, a random subsample of 252 cord sera which had been stored at -20°C was reanalyzed. A good correlation of $r = 0.8383$ with the original values was found, although slightly more values were above 0.9 kU/l in the first determination and below this threshold in the second one than vice versa.

IgA assay

IgA was determined by a highly sensitive radioimmunoassay in cord-blood samples of all neonates whose IgE values were above 0.5 kU/l, i.e., 1012 samples. There was no significant correlation between the IgE and IgA values of these samples, of which 62 had an IgA value higher than 32 µg/ml (mean plus 3 SD, according to Kimpen et al. (15). These were therefore considered to be contaminated with maternal blood and excluded. For further assessment of the extent of contamination with maternal blood, antibodies against inhalative antigens and food antigens were measured in a random subsample of cord serums by two RAST multiantigen screening tests, i.e., the Phadiatop and the Pediatric Phadiatop (Pharmacia). All of the 252 samples had negative results in both tests.

Family history

A questionnaire on atopic diseases of the parents and siblings, relevant symptoms, and allergy tests, as well as sociodemographic variables, was distributed in the delivery wards to the parents of the neonates. A total of 6019 parents filled in the questionnaire, each parent separately, except for 22% of the questionnaires for the fathers which were answered by the mothers. Of the questionnaire items, 11 validating screening conditions (5) were chosen to indicate the atopic status of each close family member of the neonate.

Information on the course of pregnancy and events of delivery and the length and weight of the neonate was collected from the birth records of all infants born in 1990 in the study centers.

Cohort parents

A cohort was recruited from high-risk infants and controls. One month after delivery, cohort mothers had a structured interview which included questions on medication and events during pregnancy. Cohort parents were requested to have a blood sample taken for a RAST multiantigen screening test (Phadiatop, Pharmacia, Germany).

Statistics

For statistical analysis, IgE values were divided either into three classes according to the CAP classification, i.e., <0.35 kU/l (CAP 0), 0.35–0.70 kU/l (CAP I), >0.70 kU/l (≥CAP II), or into two classes according to the classical cutoff value (8), i.e., <0.9 and >0.9 kU/l. Statistical analysis was done with SPSS/PC. For calculation of the geometric mean, all values below the detection level were assigned a value of 0.01 kU/l.

Results

Distribution of cord-blood IgE values

Of 6142 cord-blood IgE values in single-born infants, 74.5% were below the detection limit of 0.35 kU/l; 522 cord-blood samples (8.5%) had a value above the traditional threshold of 0.9 kU/l. The highest value was 136 kU/l. The geometric mean had the value of 0.106 kU/l; the median, the value of 0.198 kU/l. The distribution of the untransformed IgE values according to CAP classes in Table 1, or according to percentiles in Fig. 1, shows only a steady decline.

Factors associated with cord-blood IgE values: bivariate analysis

Sex. Boys had IgE values in the higher class more often than girls ($P < 0.001$): 10.9% of the boys, but only 6.0% of the girls, had a value greater than 0.9 kU/l. Values below 0.35 kU/l were found in 77.8% of the girls, but in only 71.4% of the boys (Fig. 2).

Gestational age, birth size. Cord-blood IgE values and data on gestational age (GA) were available for 5964 neonates. Although there was a tendency to increasing IgE values with increasing gestational age,

Table 1. Percentage distribution of cord-blood IgE values according to CAP classes

CAP 0 (<0.35 kU/l)	CAP 1 (0.35–0.7 kU/l)	CAP 2 (0.7–3.5 kU/l)	CAP 3 (3.5–17.5 kU/l)	CAP 4 (> 17 kU/l)
74.5%	14.1%	9.9%	1.4%	0.2%

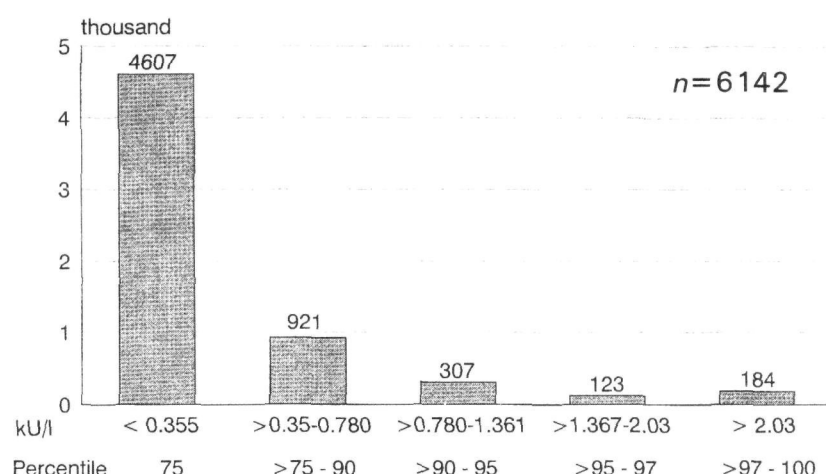


Fig. 1. Cord-blood IgE distribution according to percentile classes.

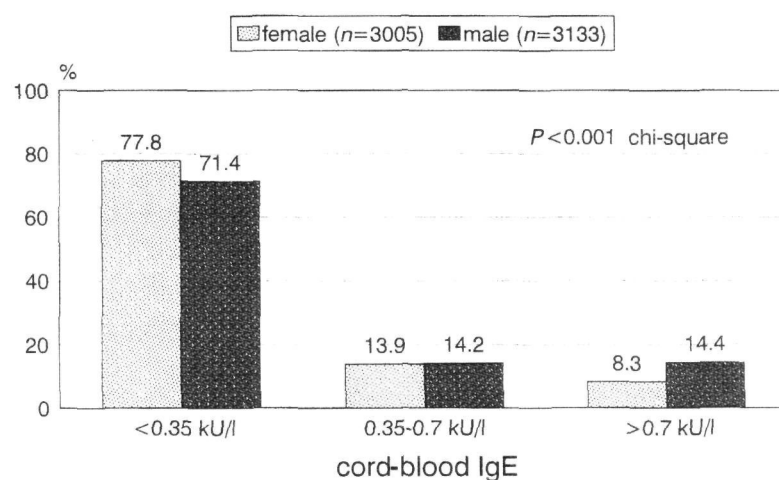


Fig. 2. Distribution of cord-blood IgE CAP classes according to sex of neonate.

e.g., 21% of the prematures (GA <37 weeks) had measurable IgE values, while in mature neonates 26% of values and in neonates >43 weeks GA, 39% of values were measurable, no significant difference in the distribution of IgE classes was found between these gestational age groups, nor between weight or length groups.

Birth stress, medication during pregnancy. No significant differences were found in cord-blood IgE classes between pH values above or below 7.2 nor among Apgar scores. There was also no significant difference in cord-blood IgE distribution among infants born spontaneously, by cesarean section, by vacuum extraction, or by other obstetric interventions. Neonates with minor problems or those who had been transferred to an intensive care unit were

not significantly different from normal neonates in cord-blood IgE values.

According to the questionnaire data of 1100 *cohort* mothers, 142 had suffered from maternal hypertension, 47 had taken corticosteroids during pregnancy, and 152 had taken labor-suppressing medication. Cord-blood IgE values were not significantly different in these subgroups from the rest, although slightly more neonates of mothers who had taken corticosteroids had IgE values in the higher classes.

Parity, age of mother. Although IgE values decreased with increasing parity, this association did not have statistical significance. Cord-blood IgE values in neonates with mothers younger than 20 years were slightly higher and values of neonates with mothers older than 40 years slightly lower than in those neonates whose mothers were between 20 and 40 years old, but this difference was also not statistically significant.

Nationality. Mothers were classified into seven nationality classes according to their citizenship: there was a significant difference in the distribution of cord-blood IgE values according to nationality ($P < 0.001$) (Table 2). Neonates whose mothers came from Far Eastern countries had the highest values.

Region. Although the proportion of non-German citizens varied among the study centers, there was no significant difference in the distribution of cord-blood IgE classes.

Sociodemography. No significant differences were found in the distribution of IgE values among six *educational* levels of the fathers or of the mothers, although there was a slight, though not significant, tendency to higher IgE values with increasing educational level of the mother. Moreover, no significant differences in the cord-blood IgE distribution could be seen among the seven *occupational* classes of the fathers or of the mothers.

Atopic family history. Complete atopic family history and cord-blood IgE values were available for 4851 neonates. Of those with at least two close atopic family members, 11.1% had a cord-blood IgE above 0.9 kU/l; of those without an atopic family history,

Table 2. Percentage of cord-blood IgE values above 0.7 kU/l according to nationality of mother

State	German	Central and northern Europe	Mediterranean	Eastern Europe	Near East	Far East	Others
n	4550	142	325	216	458	86	71
>0.7 kU/l	10.5%	8.5%	12.6%	12.0%	17.0%	25.6%	11.3%

$P < 0.001$.

7.7% were above this threshold. But there was only a small overlap between both risk factors (Fig. 3). The percentage of elevated IgE values (above 0.7 kU/l or above 0.9 kU/l) increased significantly with the number of atopic family members ($P < 0.001$) (Fig. 4).

The atopic history of the father or a sibling had only a slight, nonsignificant association with cord-blood IgE. But cord-blood IgE classes differed significantly in neonates of atopic mothers from those of nonatopic mothers ($P < 0.001$).

Smoking history of parents. The family smoking history was divided into four classes: 1) no smokers, 2) only the father smoked, 3) only the mother smoked, and 4) both parents smoked. The percentage of elevated IgE values rose from class 1 to class 3 and dropped in class 4. Thus, the difference in the distribution of IgE values among these four family smoking classes did not reach statistical significance. But when the parents were asked whether they had smoked in the last 9 months, the distribution of IgE values among the four smoking classes was significantly different ($P < 0.02$) (Table 3).

Time of year. Taking all centers together, the percentage of undetectable cord-blood IgE values was highest in January and lowest in August, but not significantly so. In each study center, the highest and lowest values were found in different months of the year. When cord-blood IgE values were corrected for the monthly return rate of IgE determinations in cord blood within each center, the differences in IgE distribution over the year leveled off.

Twins. There were 151 twin pairs in the neonate population in the study centers, of whom both twins had an IgE determination in 81 pairs. The correla-

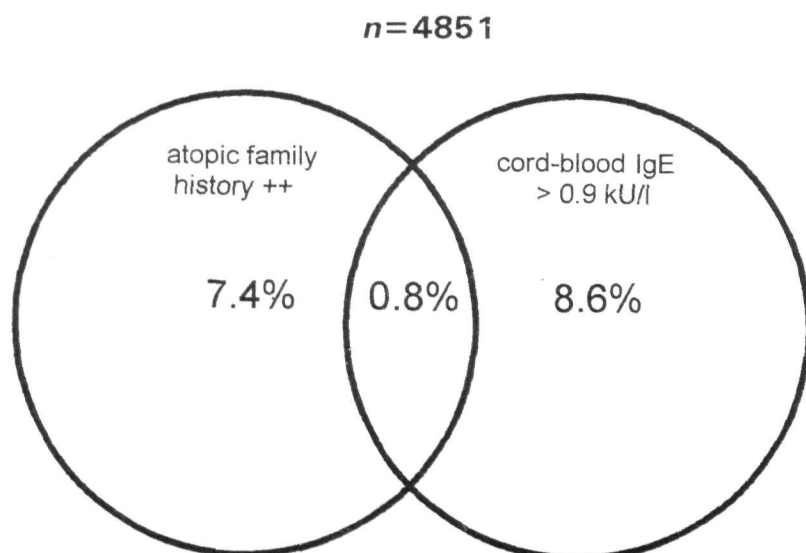


Fig. 3. Model for small overlap between risk factors at birth: prevalence of elevated cord-blood IgE values (> 0.9 kU/l) and of at least two close atopic relatives (+ +) in neonate population.

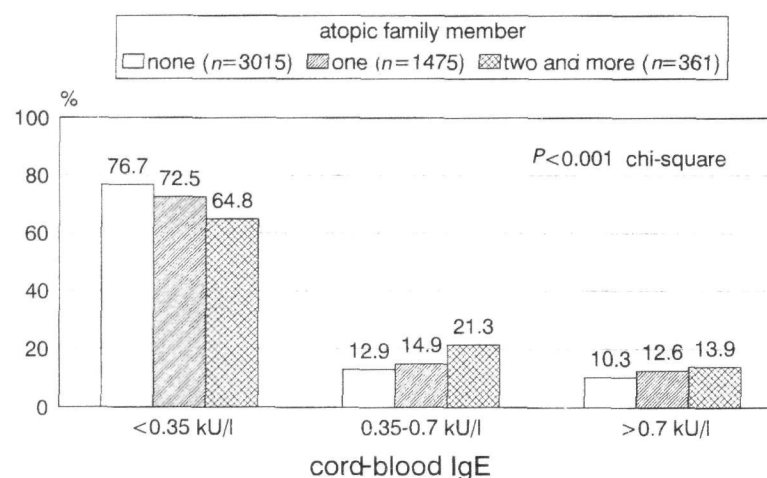


Fig. 4. Distribution of cord-blood IgE (CAP) classes according to atopic history of close relatives.

tion between the IgE values of the twin pairs was significant, the linear correlation coefficient being $r = 0.4909$ ($P < 0.001$).

RAST multiantigen screening test (Phadiatop) in parents. A total of 847 mothers had a Phadiatop screening. The percentage of elevated cord-blood IgE values was not significantly different between those neonates whose mothers had a positive test result and those whose mothers had negative test results. Similarly, no association could be found between test results in 479 fathers and the cord-blood IgE of their infants.

Multifactorial analysis

Multinomial logit models were used to analyze simultaneously the contribution of the risk factors which had been shown to have a significant influence on cord-blood IgE in the bivariate analysis. After ruling out insignificant variables in the models, only three factors were found to be necessary to predict the risk of an elevated cord-blood IgE value sufficiently well. These were 1) mother's atopic history, 2) male sex, and 3) non-German citizenship. The predicted prevalences of elevated cord-blood values for several risk constellations are summarized in Fig. 5.

Discussion

The 7609 neonates of 1 calendar year, screened at birth for the MAS-90 study, were representative of the catchment area of six German delivery wards. The distribution of cord-blood IgE values is similar to that in many population-based studies. Irrespective of the test used, most of the samples were very low or even below detection limits (1, 11, 12, 16, 19). Proportions of elevated values (differently defined) ranged from 3% above 1.0 kU/l (15) to 13% above 0.5 kU/l (12); 8.5% of values above 0.9 kU/l in the

Table 3. Percentage of cord-blood IgE values above 0.7 kU/l according to smoking history through pregnancy

Smoking history	Nonsmoking parents	Only father smoked	Only mother smoked	Both smoked
<i>n</i>	2228	1267	282	1016
> 0.7 kU/l	10.9%	12.9%	15.2%	9.3%

P < 0.02.

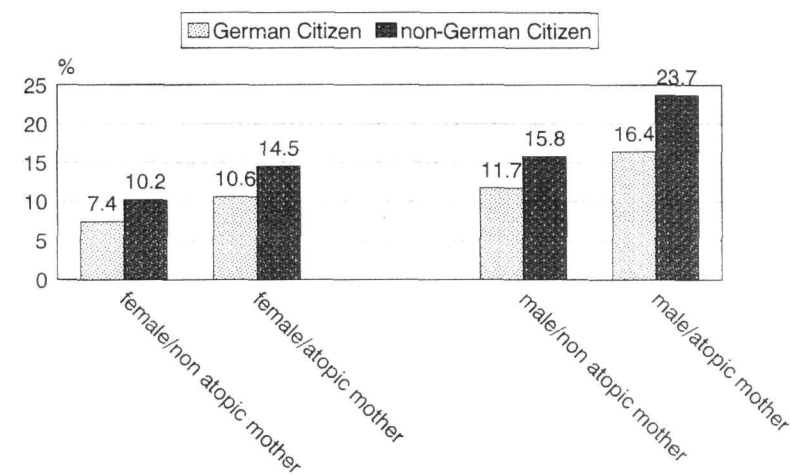


Fig. 5. Percentage of elevated cord-blood IgE values (> 0.7 kU/l) according to several risk constellations. Left side represents female, right side male neonates. For both sexes, additional influence of atopic history and citizenship of mother was calculated with multinomial logit analysis.

MAS-90 study is within this range of observations and nearly equal to the prevalence of 9.0% in a previous German study (19). The geometric mean of 0.106 kU/l is on the order of that in other studies, e.g., 0.09 (11), 0.11 kU/l (27), and 0.17 kU/l (14).

Because one of the objectives of this multicenter study was to detect neonates at risk by using high cord-blood IgE values, the lower cutoff value of the assay was set at 0.35; therefore, only 25% of the values were regarded as detectable. Therefore, an analysis of the true distribution is difficult. The log normal distribution of serum IgE values in the general population (18) has been verified for cord-blood (serum) IgE by Halonen et al. (11), who transformed the data of Kimpen et al. (15), which had a lower test threshold of 0.01 kU/l.

Although sampling had to be done by vein puncture in this study, and 62 samples were excluded because of suspected contamination by maternal blood (according to elevated cord-blood IgE and IgA values), samples with low maternal IgA and samples with only slight contaminations still could have been included. Moreover, a maternofetal transfer during delivery (33) could have occurred in some of the samples. These events cannot be ruled out by a negative Phadiatop test in cord blood. The higher threshold gives some protection against maternal transfer or contamination, but leaves us, with only 25% of the original sample, to study the “tip of the iceberg”, whereas interesting influences could perhaps have been seen in the low-value range.

With these restrictions in mind, we have confirmed the finding that IgE values in boys tend to be higher than in girls, suggesting that the risk threshold for boys should perhaps be set at a higher level (Fig. 3).

The finding of fewer elevated values in premature than term infants, although not to a significant extent, is in line with the findings of Kimpen et al. (16) and could indicate that the production of IgE in the fetus increases with proceeding maturation.

No influence of the birth modus or gestational or neonatal problems on cord-blood IgE values was found. But, confirming the results of other studies (22, 27), we found rising IgE values with a history of parental smoking through pregnancy, progressing from no smokers, to father smoking, to mother smoking, and a lower value in families with two smoking parents. This could be due to an unspecific stimulation of IgE production by the fetus with lower passive smoke exposure and suppression with higher exposure.

A recent German study found positive Phadiatop test results more often in young adults than those over 40 years old (3). Although the influence of maternal age was not significant in our study, the trend of cord-blood IgE values is in the same direction, suggesting that some maternofetal transfer could indeed have occurred.

In an earlier study, we did not find a significant difference between cord-blood IgE values in neonates of German and Turkish mothers in Berlin (19). The present and much larger sample shows significant differences between nationality classes with the highest values for foreigners from Far Eastern countries. This is comparable to the study of Halonen et al. (11), who found higher cord-blood values in Hispanic neonates than Anglo. From the findings of Weil et al. (32), it is tempting to speculate that this might be due to some maternofetal transfer either of antibodies or antigens because of a higher prevalence of infestation with parasites in mothers from these countries (21, 32) or to genetic differences in total IgE values of the mothers and their infants.

It would also fit this hypothesis to find seasonal influences on cord-blood IgE values, as described in other studies (11, 12, 16). This influence could not be verified in our study for the total sample, but only for some of the centers at different times of year. But when we controlled for the return rate of cord-blood samples in each month, this fluctuation leveled off.

The association between the number of close atopic family members and cord-blood IgE values points to an influence of genetic factors on cord-blood IgE values. On the other hand, the small overlap of cord-blood IgE values and atopic family history suggests that both risk factors may, to some degree, be independent determinants of atopy risk. Regarding the influence of the family members separately, the significant association of cord-blood IgE values in the neonate with the atopic history of the mother, and not of the father or siblings, could again be the result of a contamination or prenatal transfer. Another explanation for the greater influence of the mother's history could be a recall bias: 22% of the fathers had their questionnaire answered by the mother, who probably underrated the lifetime prevalence of their atopic diseases (4). The concordance of IgE values in twins, on the other hand, can hardly be explained by contamination with maternal blood and points to the influence of genetic factors or of a shared environment.

The higher significance of maternal than paternal atopic history for the prevalence of atopy in the offspring, together with a higher incidence of boys having the atopic signs and symptoms, has been considered to be evidence for the Carter effect in the heredity of atopic disorders (13). It is tempting to speculate that this pathogenetic mechanism could already be operating in cord-blood IgE values.

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