

Several genetic and environmental factors influence cord blood IgE concentration

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Cord blood samples were collected from a birth cohort of 2631 infants to elucidate the association between genetic and environmental factors and fetal production of IgE. The cord blood IgE values were treated both as a continuous and as a dichotomous variable in the statistical analyses. Multivariate analysis was used to control for confounding factors. Infants with single and biparental atopic heritage had higher IgE concentrations in cord plasma than children of parents without atopy. Multiple logistic regression analysis revealed a significant association to maternal allergic eczema or perennial rhinitis. The cord blood IgE concentration varied with month of birth with peaks in late autumn. This seasonal variation was not related to parental atopic disease. Boys had significantly higher levels of IgE and more often elevated IgE values (≥ 0.5 kU/l) than girls. Alcohol and caffeine consumption by the mothers during pregnancy were both significantly associated with elevated IgE concentration. There was also a relation between mothers prepregnant weight and elevated CB-IgE levels. No significant association was observed between maternal smoking and cord plasma IgE levels. The fact that many factors presumably not related to child allergy seem to influence the regulation of fetal IgE production, could explain the questionable value of cord blood IgE in predicting allergy in childhood.

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Increasing incidence of atopic diseases constitutes a major pediatric problem. Therefore, considerable efforts have been made to find a reliable predictor of allergy in early childhood. Several studies have been performed in order to assess the value of cord blood IgE (CB-IgE) (1–6). However, conflicting results from these studies makes it difficult to assess the validity of CB-IgE in predicting the development of allergy.

Several factors including sex (7, 8), month of birth (8, 9), racial differences (10) and smoking during pregnancy (11) have been reported to be associated with increased levels of CB-IgE. Conflicting results have also been reported (12, 13). The present study focuses on the association between atopic disposition, month of birth, sex of the infant and CB-IgE. Furthermore, we investigated the possible association between smoking and intake of alcohol and caffeine during pregnancy and CB-IgE.

Material and methods

This investigation is part of a prospective study evaluating basophil histamine release and plasma IgE levels during the first year of life in normal infants and in infants with a known risk of developing allergy.

Study population

CB was collected from infants born in the Department of Obstetrics, Aarhus University Hospital during the period February 1, 1990 to May 16, 1991. Women living in a well-defined geographical area of about 250,000 inhabitants are referred to the department, which has the only maternity ward in the city. The number of CB-samples taken were 2638, corresponding to 47% of the total number of infants born during this period. Pregnant women, who planned to give birth in this ward, were recruited by their midwives during routine antenatal visits. During these visits, a detailed description of the project was given

Table 1. Contents of the three questionnaires*: Q_{basic}, Q₁₆ and Q₃₀.

Questions	Q _{basic}	Q ₁₆	Q ₃₀
Medical history	x		
Obstetrical history	x		
Mothers age and prepregnant weight	x		
Smoking habits	x		x
Alcohol consumption	x		x
Level of theoretical and practical education (mother and father)		x	
Occupational status (mother and father)		x	
Marital status		x	
Consumption of caffeine		x	
Detailed information about atopic diseases (mother and father)			x

* The percentages of total answers on Q_{basic}, Q₁₆ and Q₃₀ were 91%, 78% and 68%, respectively.

to the women who wanted to participate. Before enrolment, in the 16th week of gestation, the women were asked to answer a basic questionnaire (Q_{basic}) about their medical and obstetrical history, smoking habits and alcohol consumption, and a second questionnaire (Q₁₆) about their educational and occupational and marital status. The questionnaires were completed at home. A reminder was mailed to non-responders twice. In the 28th week of gestation, the women received a third questionnaire (Q₃₀) which was returned to their midwives in the 30th week of gestation. This questionnaire was largely identical to Q₁₆, but contained detailed questions about atopic diseases of the pregnant woman and the father. A reminder was mailed once to non-responders. More details of the different questionnaires and the percentage of answers are outlined in Table 1.

Immediately after delivery, the attending midwife secured a CB sample and filled in a special registration-form about the baby (gestational age, weight, length, Apgar score, CB-pH).

Total plasma IgE and IgA measurements

CB was collected by direct needle aspiration of the cord vein. The samples were anticoagulated with 10 mM EDTA and the plasma was separated and stored at -20°C pending analysis.

The content of IgE in the plasma was quantitated with an enzyme-linked immunoassay (ELISA) with a detection limit of 0.2 kU/l. IgE below 0.2 kU/l was assumed to be 0.1 kU/l in the statistical analyses. The value of 0.1 kU/l was arbitrarily chosen, and could therefore possibly induce bias in the statistical analyses. In order to clarify this question, all the analyses were carried out with 0.0 kU/l and 0.2 kU/l in cases with IgE below the detection limit. The

choice of value did not have a perceptible influence on the results. CB-IgE ≥ 0.5 kU/l was primarily used as cut-off value defining high IgE levels. However, IgE ≥ 0.3 kU/l and IgE ≥ 0.9 kU/l were also selected as CB-IgE cut-off values in some of the statistical analyses.

In order to evaluate possible admixture of the cord blood samples with maternal blood, total plasma IgA was determined in samples with CB-IgE ≥ 0.5 kU/l. The IgA was assayed in an ELISA with a detection limit of 60 mg/l, and values exceeding this value were considered potentially contaminated. These cases were excluded from further analysis.

Statistical methods

As previously suggested by Ownby et al. (13), the variable for IgE was treated in two ways: 1) as a continuous variable and 2) as a dichotomous variable, using the cut-off levels for CB-IgE as described above. The continuous IgE variable was chosen in order to evaluate a possible dose-response relationship between independent variables and CB-IgE concentration. However, an association between the independent variables and the dichotomous CB-IgE value can easily be expected, without this association being seen in the continuous value. The dichotomisation of the data could imply a loss of information. As a consequence, we also conducted additional analysis (multiple linear regression) within our data, in order to validate our findings. The main results were consistent, even when using this alternative strategy (data not shown). The IgE values were analysed as log transformed, as this transformation made the proximity to the normal distribution more appropriate. However, the IgE values reported in the text are geometric means of the IgE distribution, i.e. they are exponential mean values of log-transformed data.

Bivariate analyses of categorical data were based on Chi²-test and Chi²-test for trend. Analyses of categorical exposures in relation to continuous effects were based on one-way analysis of variance, including test for linearity when appropriate (14). Mean values with one standard deviation are presented as (mean $\pm$ SD). Multivariate analyses of dichotomous effects were carried out by multiple logistic regression (15). Statistical significance was defined as ($P < 0.05$), relative risk (odds ratio) is presented with 95% confidence intervals (CI).

In the present study, the following variables were included as independent variables with a possible association with CB-IgE: sex of the infant, month of birth, atopic family history, mother's smoking habits and consumption of alcohol during pregnancy, mother's weight, and birth weight and length of the infant.

Table 2. Geometric mean and relative risk (odds ratio) of elevated level of CB-IgE (≥ 0.50 kU/ml) in cord blood by sex and atopic heritage. Multiple logistic regression.

Variable	IgE	P*	Odds ratio	95% CI
Gender N = 2631				
Male	0.21	0.001	1.00	(Reference)
Female	0.19		0.53**	(0.40–0.71)
Atopic heritage N = 1544				
Mother – No	0.19	0.001	1.00	(Reference)
– Yes	0.22		1.64**	(1.22–2.20)
Father – No	0.20	0.19	1.00	(Reference)
– Yes	0.21		1.04	(0.76–1.44)
No parental allergy			1.00	(Reference)
Only mother			1.98**	(1.40–2.80)
Only father			1.47	(0.97–2.21)
Biparental			1.65**	(1.05–2.59)

* Oneway-analysis-of-variance.

The multiple logistic regression results presented as odds ratios above are controlled for confounding by month of birth and the mother's smoking habits, weight, use of alcohol, and educational background. Model fitted using dummy-variables.

** $p < 0.005$

Ethical considerations

The Committee for Scientific Ethics in the county of Aarhus has approved this study and recognized it as being fully compatible with the Helsinki Declaration II.

Results

Of the 2638 cord blood samples taken, the IgE level was ≥ 0.50 kU/l in 389 blood samples. Admixture with maternal blood was suspected in 7 samples

Table 3. Relative risk (odds ratio) of elevated level of CB-IgE (≥ 0.50 kU/ml) in cord blood by parental atopic heritage. Multiple logistic regression N = 1544.

Atopic heritage	Odds ratio	95% CI	P
Mother:			
Rhinitis (perennial)	1.88	(1.17–3.00)	0.009
Rhinitis (seasonal)	0.85	(0.42–1.73)	0.65
Allergic/Atopic dermatitis	1.60	(1.06–2.41)	0.03
Urticaria	0.82	(0.43–1.56)	0.54
Bronchial asthma	0.78	(0.32–1.94)	0.60
Father:			
Rhinitis (perennial)	1.27	(0.77–2.08)	0.33
Rhinitis (seasonal)	1.41	(0.69–2.79)	0.34
Allergic/Atopic dermatitis	0.58	(0.93–2.69)	0.09
Urticaria	0.76	(0.21–2.78)	0.68
Bronchial asthma	0.68	(0.27–1.70)	0.41

Controlled for the confounding by month of birth, mother's smoking habits, weight, use of alcohol, and mothers educational background. Model fitted using dummy-variables.

(CB-IgA ≥ 60 mg/l) and these samples were excluded from further processing, yielding a total sample size of 2631 and 382 with IgE ≥ 0.5 kU/l. The geometric mean of the IgE values (the exponential mean value of log-transformed data) was 0.20 kU/l (range 0.10 to 18.9 kU/l). The 10-, 50-, 90- and 95-percentiles were 0.10, 0.20, 0.60 and 1.0 kU/l, respectively. The use of 0.30 kU/l and 0.50 kU/l as the mean cut off value resulted in 35.1% and 14.5% "high IgE values", respectively.

Our study group did not differ significantly from the total population of mothers delivered at our hospital during this period (N = 5658) with respect to the maternal age, mean gestational age at birth, birth weight and length.

CB-IgE was not significantly associated with paternal age, parental education, marital status, gestational age, birth weight and length, and parity, either when CB-IgE was evaluated as a dichotomous, or as a continuous variable.

Atopic disposition and IgE concentration

A total of 1694 women (64%) answered the questions about parental atopic disease. No atopic disposition was reported in the parents of 883 infants (52%) (geometric mean IgE: 0.18 kU/l), single disposition was present in 608 infants (36%) (geometric mean IgE: 0.21 kU/l), and 203 infants (12%) had biparental atopic disposition (geometric mean IgE: 0.22 kU/l). There was a significant difference in CB-IgE between the groups (F-test, $p = 0.006$). Children with maternal atopic disposition had a RR of 1.98 for elevated IgE (≥ 0.5 kU/l, $p < 0.001$, 95% CI 1.40–2.80) but paternal atopic disease was not associated with significant increase in the CB-IgE concentration (Table 2).

A significant association was found between CB-IgE ≥ 0.5 kU/l and maternal seasonal rhinitis and allergic eczema ($p < 0.001$). Maternal perennial rhinitis, but not eczema and CB-IgE, remained significantly associated when using 0.3 kU/l as the cut-off level. Continuous CB-IgE was significantly elevated in the two groups of infants with these two maternal atopic diseases ($p < 0.001$ and $p < 0.03$, respectively). Children of mothers who suffered from perennial rhinitis and allergic eczema accounted for 24% and 22% of the elevated CB-IgE values (≥ 0.5 kU/l), respectively.

When the associations were controlled for confounders, only maternal perennial rhinitis and allergic/atopic eczema remained significantly associated with elevated CB-IgE (≥ 0.5 kU/l) and relative risks of 1.88 ($p = 0.009$, 95% CI: 1.17–3.0) and 1.60 ($p = 0.03$, 95% CI: 1.06–2.41), respectively (Table 3).

Fig. 1. Fluctuations of elevated CB-IgE levels (>0.5 kU/ml) throughout the year $P < 0.001$.

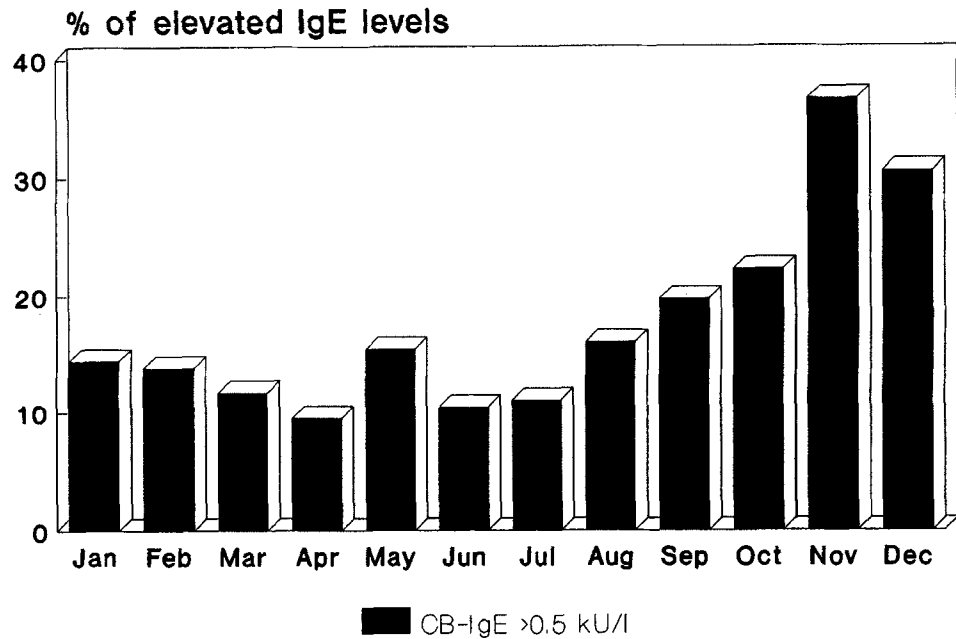


Table 4. Incidence of elevated cord blood IgE and IgE concentration by smoking, alcohol consumption, caffeine consumption, and prepregnant weight. The cut-off value for IgE concentration is 0.5 kU/ml.

Variable	IgE < 0.50 N	IgE ≥ 0.50 N (%)	P*	Geometric mean	P**
Smoking (cigarettes/day)					
					0.12/0.15
0	1421	260 (15)	0.20/0.03	0.20	
1-4	117	21 (15)		0.21	
5-9	198	27 (12)		0.18	
10+	377	49 (12)		0.20	
Alcohol (12-mg doses/week)					
					0.07/0.04
0	1206	196 (14)	0.001/0.02	0.20	
1-2	594	79 (12)		0.20	
3-4	197	48 (20)		0.21	
5-14	64	20 (24)		0.24	
Caffeine (mg/day)					
					0.08/0.007
0	77	15 (16)	0.18/0.04	0.21	
<200	362	78 (18)		0.21	
200-400	626	101 (14)		0.20	
400-800	588	99 (14)		0.19	
800+	147	17 (10)		0.18	
Prepregnant weight (kg)					
					0.23/0.08
<50	122	16 (12)	0.23/0.04	0.18	
50-59	892	136 (13)		0.20	
60-69	738	137 (16)		0.20	
70-79	217	47 (18)		0.22	
80+	103	19 (16)		0.20	

* Test for difference between extreme groups under comparison: Chi²-test/Chi²-test for trend.

** Oneway-analysis-of-variance/test for linearity.

Table 5. Relative risk (odds ratio) of elevated level of IgE (≥ 0.50 kU/ml) in cord blood by different environmental factors. Multiple logistic regression $N=2470$.

Variable	Odds ratio	95% CI	P
Mothers smoking (cigarettes/day)			
Non-smoker	1.00	(Reference)	
1-4	0.97	(0.51-1.81)	0.28
5-9	0.79	(0.71-2.25)	0.49
10-14	0.82	(0.47-1.42)	0.48
15+	0.58	(0.28-1.23)	0.49
Intake of alcohol (12 mg-doses/week)			
0	1.00	(Reference)	
1-2	0.75	(0.53-1.08)	0.11
3-4	1.58	(1.01-2.49)	0.04
5+	2.53	(1.35-4.75)	0.004
Intake of caffeine (mg/day)			
<200	1.00	(Reference)	
200-400	0.63	(0.44-0.92)	0.01
400-800	0.68	(0.33-1.40)	0.04
800+	0.63	(0.34-1.18)	0.16
Pregestational weight (kg)			
<50	1.00	(Reference)	
50-59	1.06	(0.51-2.19)	0.87
60-69	1.47	(0.71-3.02)	0.29
70+	1.65	(0.79-3.65)	0.17

Controlled for the confounding by atopic heritage, sex of child, mothers weight, mothers educational background. Model fitted with use of dummy-variables.

Month of birth and CB-IgE

Fig. 1 shows the fluctuations of elevated IgE levels (≥ 0.5 kU/l) with peaks in May and during the winter. To test if the seasonal variation was mainly seen in babies with parental atopic disease, the seasonal variation was investigated by stratification of the atopic variables. To increase the statistical power, the year was divided into 4 seasons; spring: April-May, summer: June-August, autumn: September-October, winter: November-March. The results showed that the CB-IgE pattern during the year was not modified by parental atopic disease (data not shown).

Sex of the infant and CB-IgE concentration

Information about the sex of the infant was available in 2503 cases (95% of our study population). There were 1267 male and 1236 female births (ratio 1:1). The geometric mean IgE concentrations for boys and girls were 0.21 kU/l and 0.19 kU/l, respectively ($p < 0.001$). Boys had significantly more often CB-IgE values ≥ 0.5 kU/l than girls ($p < 0.001$). This association was also seen when 0.3 kU/l ($p < 0.01$) and 0.9 kU/l ($p < 0.005$) was used as cut-off levels for IgE. After controlling for possible confounders

by multiple logistic regression analysis the odds ratio comparing boys with girls remained significant ($p < 0.001$) (Table 2).

Environmental factors and CB-IgE

In all, 2473 mothers (94%) answered the questions about cigarette smoking during pregnancy. To test the validity of the answers, birth weight was assessed on the basis of the reported smoking status (we had the information about birth weight from 97% of our infants). The mean birth weight of babies of non-smokers was 3.58 ± 0.51 kg ($N = 1619$), and in babies of mothers who smoked between 1 and 10 or more than 10 cigarettes daily, 3.48 ± 0.54 kg ($N = 356$) and 3.26 ± 0.51 kg ($N = 414$), respectively ($p < 0.001$). Thirty-three percent of the mothers were smokers (smoked more than one cigarette per day), and 67% were non-smokers. Table 4 shows that the number of infants that had CB-IgE ≥ 0.5 kU/l decreased with increasing number of cigarettes smoked by the mothers (Chi²-test for trend: $p = 0.03$). Thirteen percent of the infants of mothers who smoked more than 10 cigarettes per day had CB-IgE ≥ 0.5 kU/l as compared with 18% for infants of non-smoking mothers (Table 4). Maternal smoking was not associated with CB-IgE in the linear regression model adjusting for the possible confounding variables ($p = 0.49$, Table 5).

Fifty-eight percent of the pregnant women consumed more than one dose of alcohol (12 mg pure alcohol) per week (Table 4). The frequency of high CB-IgE (≥ 0.5 kU/l) was significantly related to maternal intake of alcohol ($p < 0.001$). The mean IgE concentration in cord blood increased from 0.30 kU/l in mothers with no alcohol consumption to 0.41 kU/l in mothers consuming more than 4 doses per week (test for linearity: $p = 0.04$) (Table 4). Using multiple logistic regression analysis, a highly significant association was seen between the intake of alcohol and the frequency of elevated IgE values (≥ 0.5 kU/l) ($p = 0.001$). Likewise, a significant dose-related increase in RR was observed (Table 5).

To test another widely used stimulant, the daily intake of caffeine (total intake of coffee, cocoa, cola and tea) by the pregnant women was evaluated, the results are outlined in Tables 4 and 5.

An association between pre-pregnant weight and the frequency of elevated CB-IgE values was seen when using multiple logistic regression (cut-off values: ≥ 0.3 kU/ml; $p = 0.03$, ≥ 0.5 kU/ml; $p = 0.01$, ≥ 0.9 kU/ml; $p = 0.05$). In contrast, no significant difference was seen when testing the continuous IgE data by analyses of variance, but there was a significant linear trend in the frequency of elevated cord blood IgE ($p = 0.04$) (Table 4).

Discussion

The influence of several factors on CB-IgE has been investigated by several groups with somewhat conflicting results. The results in the present study are based upon data from 2631 newborn infants who were prospectively studied. We found a significant increase in both the mean IgE level and the percentage of elevated IgE values in newborn infants with single or biparental atopic disposition compared with those without atopic heritage. However, there was no statistical difference between single and biparental atopic disposition in terms of CB-IgE concentration. In our study group, 12% of the infants had biparental atopic heritage whereas other studies report 4–5% (16). The reason for the relatively high percentage of single and biparental atopic heritage in this study could be due to a positive selection, as parents suffering from atopy will be extra motivated to participate in a study dealing with allergy. Maternal atopic heritage was significantly more often associated with elevated CB-IgE concentration than paternal disposition. Information about parental atopic diseases was gathered from questionnaires given to the mothers during pregnancy. Croner & Kjellman concluded in a recent study that a detailed questionnaire for establishing the prevalence of atopic disease gives adequate information about both parents and can be used in epidemiological investigations (17).

In the present study, we found significant fluctuations of the CB-IgE concentration according to month of birth with peaks in the late autumn and early winter. This time dependence in occurrence of abnormal IgE values has also been shown by other groups (8,9). In contrast to these studies, however, our results indicate higher overall absolute CB-IgE concentrations in the early winter, and not in the spring. The reason for the fluctuations in IgE values throughout the year is not clear. A possible explanation for the findings could be intrauterine sensitization, e.g., during the house-dust-mite season. To further explore this hypothesis, we correlated the information about parental atopic disposition gathered from the questionnaires and the month of birth to the CB-IgE concentration, but did not find any association between CB-IgE levels during the four seasons and parental atopic disease.

There is controversy concerning the influence of sex on CB-IgE concentration. Several prior studies show higher levels in males (7,8,18), whereas others do not find any relation to the sex of the child (13,16). In agreement with previous studies, we found a significantly higher proportion of elevated IgE using three cut-off values and to a significantly higher mean IgE concentration in boys. This was also true when multivariate statistical analysis was

applied. The influence of sex on CB-IgE can hypothetically be due to genetic impairment of the gene encoding for atopy in males, predisposing for secondary higher IgE values, and maybe higher incidence of atopy. In agreement with this hypothesis, Croner et al. found a significantly increased number of boys with obvious atopic disease as compared with girls (19).

In 1986 a positive correlation between maternal smoking and CB-IgE was reported (11). No other group has, however, been able to reproduce these results (12,13). The smoking histories in Magnusson's study were based on retrospectively collected information. In our study, the parents answered three different questionnaires during the pregnancy. The questions concerning cigarette smoking were asked twice which allowed us to investigate the validity of the answers. The smoking histories were further supported by the findings of a significant association between maternal smoking and low birth weight, which is a well-known association (11,13). In contrast to the previous studies, we recorded the numbers of cigarettes smoked per day which enabled us to describe a possible dose response on the CB-IgE concentration. There was a not statistically significant trend towards a negative correlation between maternal smoking during pregnancy and CB-IgE concentration. This trend was obvious in all the statistical analyses. Although the reduction in both the binary and the continuous IgE variable was not significant, it suggests that there is not a positive correlation between smoking and CB-IgE concentration present.

Surprisingly, we found a significantly positive correlation between the intake of alcohol and CB-IgE. The results revealed both a threshold effect (≥ 0.5 kU/l), and a positive, dose-response effect on the continuous IgE variable. Furthermore, the multiple regression analysis that controlled for several confounders also indicated a significant correlation. The relative risk of elevated IgE (≥ 0.5 kU/ml) was estimated to be as high as 2.53 for infants of mothers who consumed more than 60 mg of alcohol weekly. When using 0.3 kU/ml and 0.9 kU/ml as cut-off values for IgE, however, the significance on the binary IgE variable disappeared. These results indicate that discrepancies in results from different studies can also be due to the use of different cut-off levels for CB-IgE when testing for threshold effects of factors influencing CB-IgE. The biological mechanisms related to the alcohol induced increase in IgE synthesis are unknown.

We hypothesize that only a limited number of factors affecting CB-IgE are known at the present time. This could explain the rather low predictive value of IgE which has recently been reported by different groups (2–4,6).

The main conclusions of the present study are: 1) both single and biparental atopic heritage is associated with an increased level of CB-IgE and maternal atopic disease seems to play a more important role than paternal heritage; 2) parental rhinitis and allergic/atopic dermatitis are the main atopic diseases which are associated with an elevated CB-IgE level; 3) there is a significant fluctuation of CB-IgE concentration according to month of birth; 4) boys have higher CB-IgE than girls; 5) maternal intake of alcohol during pregnancy, but not smoking is statistically related to elevated CB-IgE concentration; 6) multivariate statistical methods should be used in further studies to evaluate the associations as many of factors seem to influence CB-IgE.

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