

## Does the Sibling Effect Have Its Origin In Utero? Investigating Birth Order, Cord Blood Immunoglobulin E Concentration, and Allergic Sensitization at Age 4 Years

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There is a great body of evidence that siblings have a protective effect against atopic manifestations such as hay fever, atopic eczema, allergic sensitization, or asthma. Factors that may explain this association remain largely unknown. One hypothesis is that siblings promote early infections in childhood, and repeated infections protect against atopic disorders. Another hypothesis, the potential in utero programming, has been neglected. The authors investigated if cord blood immunoglobulin E (IgE) is dependent upon birth order and if both are associated with an increased incidence of allergic sensitization (skin prick test) at the age of 4 years in a cohort of 981 newborns recruited between January 1989 and February 1990 on the Isle of Wight, England. The authors found that IgE is reduced with increasing birth order (first child: odds ratio (OR) = 1; second child: OR = 0.78, 95% confidence interval (CI): 0.57, 1.05; third child: OR = 0.59, 95% CI: 0.41, 0.83). Cord IgE, but not birth order, is a significant predictor of skin prick test positivity at age 4 (IgE below detection limit: OR = 1; IgE of 0.2–<0.5 kilounits/liter: OR = 1.11, 95% CI: 0.73, 1.68; IgE of  $\geq 0.5$  kilounits/liter: OR = 2.63, 95% CI: 1.62, 4.29). The findings suggest that cord IgE is reduced in pregnancies with higher order, indicating that the sibling effect may have its origin in utero. *Am J Epidemiol* 2001;154:909–15.

allergy and immunology; birth order; child; fetal blood; IgE; immunoglobulins; prospective studies; skin tests

It has been suggested that children with a higher number of siblings have a reduced risk of developing allergic sensitization (1–6) and clinical manifestations of atopy such as hay fever (7–11), atopic eczema (7, 10), asthma or its symptoms (10, 12, 13), reduced pulmonary function (14), or atopy in general (15, 16). There is some ambiguity as to what the sibling effect represents. It can be defined as the birth order, the number of siblings, or the family size (17), the number of older siblings (2, 4, 7, 8, 16, 18), or even the number of brothers (19, 20).

The consistency in these reports supports a true relation of the protective effect of sibship size. However, the underlying cause remains uncertain. Atopy is characterized by an exaggerated T-helper-2 (Th2) cell response to common allergens with secretion of cytokines that promote immunoglobulin E

(IgE) production and eosinophil activation (interleukin-4, interleukin-5, interleukin-13). An early pre- or postnatal programming of Th2 cells is seen as a risk factor for atopic disorders (21). In this explanatory approach, the birth order of the child is seen as a surrogate variable for frequency of infections, which increases with the growth in sibship size (7). Infections, in turn, could increase the proliferation of T-helper-1 (Th1) cells with the secretion of cytokines such as interleukin-12 and interferon gamma, which inhibit the proliferation of Th2 cells and production of Th2-type cytokines. However, there are conflicting findings of whether exposure to infections in early childhood varies with atopic manifestations (22–24). There is also conflicting evidence regarding a protective effect of specific infections and vectors of exposure (e.g., tuberculosis, measles, fecal contamination) (10, 25–32).

A high cord IgE level predisposes to the development of atopic disorders and allergen sensitization during childhood (33–37). Whether the sibling effect has its origin in fetal life or whether it is a consequence of early childhood priming of the immune response due to infections is not known. A fetal effect could manifest itself in a reduced level of cord blood IgE with increasing birth order. To investigate this, we (W. K., J. M.) were looking for studies that also ascertained fetal factors. In the Isle of Wight study, in addition to the number of siblings, their birth order and cord blood IgE levels were determined (38, 39). The cohort was followed up to the age of 4 years with an objective measure of allergic sensitization, that is, the skin prick test, to common allergens.

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Abbreviations: CI, confidence interval; IgE, immunoglobulin E; OR, odds ratio.

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Previous reports on results of the 4-year follow-up show that male sex, paternal history of atopy, and cord IgE at birth of  $\geq 0.5$  kilounits/liter (odds ratio (OR) = 2.3, 95 percent confidence interval (CI): 1.2, 4.4) were independent risk factors for allergen sensitization (38–42).

Given that cord blood IgE is a risk factor for allergic sensitization, we will test two additional hypotheses:

1. The concentration of IgE in cord blood decreases with the birth order of the child.
2. Controlling for cord blood IgE, a higher birth order of the child independently reduces the relative risk of allergen sensitization at age 4 years.

## MATERIALS AND METHODS

### Study population

Of the 1,456 newborns recruited between January 1989 and February 1990 on the Isle of Wight, England, available for follow-up, 1,218 children were reviewed at age 4 years. Cord serum IgE levels were available in 1,064 children. After the study was approved by the Local Research Ethics Committee, informed written parental consent was taken.

### Questionnaire

In the first survey at the child's birth, parents were asked about their age, maternal smoking during pregnancy, profession of the father, and history of asthma, hay fever, and atopic eczema in parents and sibling(s) of the index child. Information on parental smoking and method of feeding of the index child was obtained and updated at 1 and 2 years of age. Information on dampness of the house, heating, time living in the house, number of children in the family, and birth order of the index child was gathered in the survey at age 4 years.

### Immunoglobulin E determination

The method of cord IgE estimation has been described in a previous report (43). Briefly, duplicate measurements of cord IgE were made on serum from umbilical vein blood samples using an ULTRA EIA kit (Pharmacia Diagnostics AB, Uppsala, Sweden), which is designed to measure IgE between 0.2 and 50 kilounits/liter on 0.1 ml of serum or plasma (38, 43).

### Skin prick tests

Every child was offered a skin prick test with a standard battery of aero- (house dust mite (*Dermatophagoides pteronyssinus*), grass pollen mix, cat and dog epithelia, *Alternaria alternata*, *Cladosporium herbarum*) and food (milk, egg, soya, cod, wheat, peanut) allergens. Histamine (0.1 percent) in phosphate-buffered saline and physiologic saline were used, respectively, as positive and negative controls. The tests were read after 15 minutes, and a mean wheal diameter of at least 3 mm greater than the negative control was taken as positive.

## Statistical analysis

We restricted the analyses to a group of toddlers with skin prick tests ( $n = 981$ ) for whom we had initial information on cord blood IgE ( $n = 1,064$ ) and on questionnaire data. The group comprised 857 children.

The cord blood IgE concentration was grouped in three categories ( $<0.2$ ,  $\geq 0.2$ – $<0.5$ ,  $\geq 0.5$  kilounits/liter), following the previous investigation of this cohort. A child was defined as having an allergic sensitization (skin prick test positivity) if at least one reaction to the tested allergens was positive.

Regarding the birth order of the child, three groups were considered: first, second, third and higher position. Birth order equals the number of older siblings plus one. Birth months of the index child were categorized into three indicator variables for seasons (spring: March, April, May; summer: June, July, August; fall: September, October, November).

Potential confounders included housing conditions such as reported dampness, central heating, and the source of energy. For the latter two, we compared central heating/electric heaters versus single room heating with coal, gas, solid fuel, oil, or wood. Information on the parental socioeconomic conditions was available only for 506 of the 857 families, based on the father's profession. We categorized the ranked order of the professions into three groups: low (unskilled workers); medium (skilled workers); high (professionals, farmers, managers, teachers, engineers, and so on). Information on breastfeeding was dichotomized: ever versus never.

The importance of the predictors was estimated with logistic regression for dichotomous (skin prick test positivity) and ordinal (cord blood IgE) variables (44). The proportional odds assumption was checked for the three IgE categories. Odds ratios estimating the relative risks and their 95 percent confidence intervals are provided. We modeled three steps. The first model includes gender and birth order as predictors. We then added maternal and paternal atopy. For the outcome skin prick test, we also included the two indicator variables for the IgE categories ( $\geq 0.2$ – $<0.5$  and  $\geq 0.5$  kilounits/liter). As potential confounders, we included in the IgE models the season of birth, heating of the house, dampness and maternal smoking during pregnancy, and additional breastfeeding in the skin prick test models.

## RESULTS

A total of 1,218 children (83.6 percent of the original cohort) were seen after their fourth birthday, 981 of whom (80.5 percent) were given skin prick tests. Comparing the initial sample ( $n = 1,218$ ) and the sample used in this analysis, no selection biases were obvious (table 1). The prevalence of maternal history of atopy did not change with the birth cohort of the mother (born 1960 or earlier: 38.3 percent,  $n = 227$ ; born 1961–1965: 31.6 percent,  $n = 247$ ; born 1966 or later: 32.2 percent,  $n = 379$ ). About 97 percent of the families lived more than 4 years in their house when the child was reexamined at age 4 years.

Of the sample used, 169 of 857 children (19.6 percent) had a positive reaction to allergens (table 1). Of these, 65 children showed a reaction to house dust mite allergens

**TABLE 1. Composition of the original sample and the sample with cord blood immunoglobulin E used in the analysis, Isle of Wight, England, 1989–1990 and 1993–1994**

|                                                                | Initial follow-up sample<br>( <i>n</i> = 1,218)<br>(%) | Sample used in analyses<br>( <i>n</i> = 857)<br>(%) |
|----------------------------------------------------------------|--------------------------------------------------------|-----------------------------------------------------|
| Proportion of boys                                             | 51.2                                                   | 50.1                                                |
| Maternal history of asthma, hay fever, or atopic eczema        | 33.7                                                   | 33.5                                                |
| Missing                                                        | 0.4                                                    | 0.5                                                 |
| Paternal history of asthma, hay fever, or atopic eczema        | 25.5                                                   | 26.4                                                |
| Missing                                                        | 0.5                                                    | 0.5                                                 |
| Skin prick test missing                                        | 19.5                                                   |                                                     |
| Positive reaction in nonmissing                                | 13.2                                                   | 19.6                                                |
| Season of birth                                                |                                                        |                                                     |
| Spring (March/April/May)                                       | 24.2                                                   | 23.7                                                |
| Summer (June/July/August)                                      | 22.9                                                   | 21.1                                                |
| Fall (September/October/November)                              | 21.6                                                   | 23.6                                                |
| Room heating with fossil fuels                                 | 16.8                                                   | 17.2                                                |
| Missing                                                        | 1.1                                                    | 0.6                                                 |
| Reported dampness of the house                                 | 84.5                                                   | 83.9                                                |
| Missing                                                        | 0.5                                                    | 0.1                                                 |
| Maternal smoking during pregnancy                              | 20.5                                                   | 20.0                                                |
| Missing                                                        | 0.3                                                    | 0.4                                                 |
| Breastfeeding (yes)                                            | 74.2                                                   | 75.5                                                |
| Missing                                                        | 7.6                                                    | 4.8                                                 |
|                                                                | Initial follow-up sample<br>( <i>n</i> = 1,064)<br>(%) | Sample used in analyses<br>( <i>n</i> = 857)<br>(%) |
| Cord blood immunoglobulin E (kilounits/liter)                  |                                                        |                                                     |
| <0.2                                                           | 57.8                                                   | 57.8                                                |
| ≥0.2–<0.5                                                      | 29.1                                                   | 29.2                                                |
| ≥0.5                                                           | 13.1                                                   | 13.1                                                |
|                                                                | Initial follow-up sample<br>( <i>n</i> = 723)<br>(%)   | Sample used in analyses<br>( <i>n</i> = 506)<br>(%) |
| Socioeconomic status of the father according to his profession |                                                        |                                                     |
| Low (unskilled workers)                                        | 10.1                                                   | 11.2                                                |
| Medium (skilled workers)                                       | 73.9                                                   | 72.3                                                |

combined with other positive skin prick tests, and 36 children showed a reaction to dust allergens only. The second largest group is children with reaction to grass pollens, with *n* = 51 in combination with other allergens and *n* = 18 as monosensitization.

The concentration of cord blood IgE decreases with the birth order (table 2). In firstborn children, 16.5 percent had an IgE concentration of 0.5 kilounits/liter or higher; in children with a birth order of three or higher, only 8 percent did. The odds ratio for increased IgE diminished in a dose-response pattern (table 3). In children with a birth order of three or higher, cord blood IgE was significantly reduced (OR = 0.60, 95 percent CI: 0.42, 0.85). Maternal atopy showed an increased relative risk (OR = 1.50, 95 percent CI: 1.13, 1.99) for the offspring having a higher cord blood IgE, but paternal atopy did not. The inclusion of the parental histories of atopy in the model did not affect the birth order associations with IgE (table 3). We controlled for season of childbirth, dampness of the house, single room heating with fossil fuels, and maternal smoking during pregnancy; however, the estimations in table 3 did not change. Second, when we added two indicator variables of the socioeconomic status of the father (low, medium) to the model, which was available for only 506 children, the odds ratio for birth order became more accentuated (second child: OR = 0.8–0.69; third child: OR = 0.6–0.46). With the exception of birth in September, October, or November (OR = 2.36, 95 percent CI: 1.29, 4.3), none of the confounders gained statistical significance.

The stratification of cord blood IgE and birth order for the prevalence of skin prick test positivity revealed an increase in allergic sensitization with increasing cord blood IgE (first

**TABLE 2. Association of cord blood immunoglobulin E (grouped) and birth order of the child (*n* = 857), Isle of Wight, England, 1989–1990**

| Grouped cord blood immunoglobulin E (kilounits/liter) | Birth order of the child (%) |                        |                                  |
|-------------------------------------------------------|------------------------------|------------------------|----------------------------------|
|                                                       | 1<br>( <i>n</i> = 340)       | 2<br>( <i>n</i> = 305) | 3 or higher<br>( <i>n</i> = 212) |
| <0.2 ( <i>n</i> = 495)                                | 52.7                         | 58.7                   | 64.6                             |
| 0.2–<0.5 ( <i>n</i> = 250)                            | 30.9                         | 28.5                   | 27.4                             |
| ≥0.5 ( <i>n</i> = 112)                                | 16.5                         | 12.8                   | 8.0                              |

**TABLE 3. Odds ratio for gender, birth order, and parental atopy explaining three levels of cord blood immunoglobulin E (<0.2, 0.2–<0.5, ≥0.5 kilounits/liter) estimated in ordinal regression, Isle of Wight, England, 1989–1990**

|                | Model without parental atopy<br>( <i>n</i> = 849)* |            | Model with parental atopy<br>( <i>n</i> = 848)* |            |
|----------------|----------------------------------------------------|------------|-------------------------------------------------|------------|
|                | OR†                                                | 95% CI†    | OR                                              | 95% CI     |
| Gender, boy    | 1.26                                               | 0.97, 1.65 | 1.28                                            | 0.98, 1.67 |
| First child    | 1                                                  |            | 1                                               |            |
| Second child   | 0.78                                               | 0.57, 1.05 | 0.80                                            | 0.59, 1.09 |
| Third child +  | 0.59                                               | 0.41, 0.83 | 0.60                                            | 0.42, 0.85 |
| Maternal atopy |                                                    |            | 1.50                                            | 1.13, 1.99 |
| Paternal atopy |                                                    |            | 1.1                                             | 0.81, 1.48 |

\* Adjusted for season of birth, heating of the house, dampness, and maternal smoking during pregnancy.

† OR, odds ratio; CI, confidence interval.

child: 16.2, 20.0, 37.5 percent; figure 1). There was no clear, protective effect of birth order. The probability of an allergic sensitization was lowest in the third-born child with lowest cord blood IgE. The combined effect, however, was not significant on an additive scale of interaction ( $p = 0.29$ ).

Birth order showed a weak, insignificant dose-dependent association with allergic sensitization at 48 months (table 4). Inclusion of maternal and paternal history of atopy in the model reduced the effect of birth order and so did the inclusion of the two cord blood IgE indicator variables. In the case of the skin prick test, paternal, but not maternal, history of atopic manifestation was a risk factor. The odds ratio of allergic sensitization increased with increasing cord blood IgE concentrations and gained statistical significance for IgE levels of 0.5 kilounits/liter and higher (table 4). Of the potential confounders, breastfeeding showed a reduction in the relative risk of a positive skin prick test (OR = 0.72, 95 percent CI:

0.48, 1.1). When we additionally controlled for the socioeconomic status of the father (low, medium vs. high), the odds ratio for cord blood IgE of  $\geq 0.5$  kilounits/liter gained in importance (OR = 3.1 compared with 2.63; table 4). The sibling effect, however, did not change. As information was available on only 506 fathers (table 1), we did not include the socioeconomic status of the father as a confounder.

## DISCUSSION

In support of our first hypothesis, we were able to show that cord IgE decreases with the birth order. The weak association of birth order with allergic sensitization (hypothesis 2) was further reduced after stepwise inclusion of maternal and paternal atopy and of cord blood IgE, which suggested that at least some part of the association of birth order was mediated through cord blood IgE.

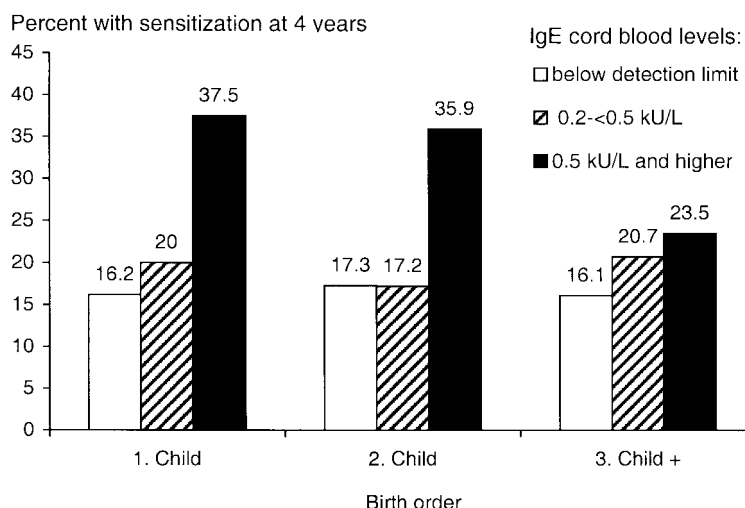


**FIGURE 1.** Combined effect of cord blood immunoglobulin E (IgE) and birth order on the prevalence of allergic sensitization at 48 months, Isle of Wight, England, 1989–1990 and 1993–1994. kU/L, kilounits/liter.

**TABLE 4.** Odds ratio for gender, birth order, parental atopy, and immunoglobulin E groups explaining allergic sensitization at 48 months of age, Isle of Wight, England, 1989–1990 and 1993–1994

|                                   | Model without parental atopy and without cord blood IgE*<br>(n = 811) |            | Model with parental atopy<br>(n = 810)† |            | Model with parental atopy and cord blood IgE<br>(n = 810)† |            |
|-----------------------------------|-----------------------------------------------------------------------|------------|-----------------------------------------|------------|------------------------------------------------------------|------------|
|                                   | OR*                                                                   | 95% CI*    | OR                                      | 95% CI     | OR                                                         | 95% CI     |
| Gender, boy                       | 1.50                                                                  | 1.06, 2.13 | 1.46                                    | 1.02, 2.08 | 1.47                                                       | 1.04, 2.11 |
| First child                       | 1                                                                     |            | 1                                       |            | 1                                                          |            |
| Second child                      | 0.94                                                                  | 0.63, 1.39 | 0.99                                    | 0.66, 1.48 | 1.03                                                       | 0.68, 1.55 |
| Third child +                     | 0.82                                                                  | 0.52, 1.30 | 0.88                                    | 0.56, 1.41 | 0.97                                                       | 0.6, 1.55  |
| Maternal atopy                    |                                                                       |            | 1.15                                    | 0.79, 1.67 | 1.11                                                       | 0.76, 1.62 |
| Paternal atopy                    |                                                                       |            | 2.06                                    | 1.42, 3.00 | 2.02                                                       | 1.39, 2.95 |
| IgE (<0.2 kilounits/liter)        |                                                                       |            |                                         |            | 1                                                          |            |
| IgE (0.2–0.5 kilounits/liter)     |                                                                       |            |                                         |            | 1.11                                                       | 0.73, 1.68 |
| IgE ( $\geq 0.5$ kilounits/liter) |                                                                       |            |                                         |            | 2.63                                                       | 1.62, 4.29 |

\* IgE, immunoglobulin E; OR, odds ratio; CI, confidence interval.

† Adjusted for season of birth, heating of the house, dampness, maternal smoking during pregnancy, and breastfeeding.

In our analysis, we included 837 children but did not see any selection bias compared with the initial follow-up sample of the newborns (table 1). Ambiguities over the definition of asthma, especially during infancy and early childhood, make the estimates of prevalence less reliable. Skin prick tests are an objective measure of sensitization (45) and, therefore, a less information-biased indicator of allergic status. A limitation of the study is the follow-up period of 4 years. As elevated cord blood IgE may predispose to subsequent higher levels of serum IgE, which, in turn, may precede the development of allergic symptoms, one might speculate that the expression of atopic manifestation increases throughout childhood (46). The relation of the skin prick test with asthma-like symptoms, eczema, and rhinitis in childhood seems not to be fully established in childhood. Additionally, variable and unspecific respiratory signs not related to atopy are frequent in children and complicate clinical diagnoses (47).

An effect of parental atopy on cord IgE has been reported previously (34, 48, 49). In previous reports, maternal atopy showed a stronger association with elevated cord blood IgE than did paternal atopy (33, 48–50). We found that a maternal, but not paternal, history of atopic manifestations increased the relative risk of a higher level of cord IgE (OR = 1.50, 95 percent CI: 1.13, 1.99; table 3). In addition, the association of parental atopy and allergic sensitization in children has been described in other investigations (51, 52). In this study, maternal atopy had no influence, but paternal atopy had a marked influence on the development of allergic sensitization (table 4). It is likely that maternal atopy acted via an increase of cord IgE, a pathway that was not open for paternal atopy. However, the association of maternal atopy with skin prick test positivity is weak and did not change if cord IgE was controlled for (table 4). The latter would be expected if cord blood IgE acts as an intervening variable.

To our knowledge, there is only one other study that investigated the effect of birth order on cord IgE. Bergmann et al. (49) found that IgE levels decreased with increasing parity. Our results are in accordance with this finding and showed that birth order may affect the risk for later atopy even before the child is born. When controlling for the socioeconomic status of the father, the association of birth order and cord blood IgE was strengthened. However, as this confounder increased the hypothesized relation and was only available for 59 percent of the sample, we chose not to present the birth order effect on IgE adjusted for socioeconomic status. Controlling for socioeconomic status could have possibly introduced an unidentified selection bias (e.g., exclusion of single mothers).

There is as yet no cutoff for cord IgE that is universally accepted. We grouped the cord IgE following the previous investigations of this cohort (39). Having three groups, we could investigate a dose-response relation. The odds ratio for allergic sensitization at 48 months increases over these three groups (below detection limit: OR = 1; 0.2–<0.5 kilounits/liter: OR = 1.11;  $\geq 0.5$  kilounits/liter: OR = 2.63; table 4).

Cord IgE is thought to be genetically determined (53). The dependence of cord IgE levels on birth order in our

data, however, suggests that the in utero environment may also have some influence. The fetus starts to synthesize IgE as early as the 11th week of gestation. A variation of the in utero environment might result from the lifestyle of the mother (54) or the family environment (55). Some studies have shown that maternal smoking during pregnancy is associated with increased cord blood IgE (56, 57); others could not confirm this finding (48, 49). In our study, the relative risk of smoking during pregnancy for higher levels of IgE was not different from 1 (OR = 0.92, 95 percent CI: 0.66, 1.29).

As the birth order effect is further reduced after controlling for cord IgE, it suggested that at least some part of the association of birth order is mediated by cord blood IgE. This fact and the association of maternal atopy with cord blood IgE support the notion that programming of the immune system starts in utero and is influenced by maternal factors. The concept of fetal-maternal interaction suggests that, for example, in the maternal part of the placenta, the decidua, cytokines produced by Th2 cells predominate over those produced by Th1 cells, resulting in the maintenance of pregnancy (58). These cytokines induce human chorionic gonadotropin release and stimulate progesterone production. The latter, in turn, seems to support the fetal Th2 response (59). Within this atopy-supporting environment, maternal exposure might contribute to an increase in cord blood IgE (60–62). The underlying mechanisms by which birth order might decrease both the levels of fetal IgE production and possibly the risk of allergic sensitization have yet to be elucidated.

We assume that the in utero environment changes with parity, which could lead to a decreasing risk of increased cord blood IgE levels with increasing birth order. Two candidate explanatory factors are infections during pregnancy and endocrine changes. Endocrine disruptors such as organochlorine may alter the hormone pattern (progesterone, testosterone, and estrogens) (59) during pregnancy; additionally the organochlorine burden seems to decrease with birth order (63, 64). Recently, placental organochlorine concentrations were related to cord blood IgE concentrations (65). Recent studies also indicated that infection during pregnancy might increase the relative risk of asthma in childhood (66–68). However, whether increased IgE levels result from infection during pregnancy is in dispute (34, 69–71). Our data do not include information on infections during pregnancy, which might have affected the cord blood IgE concentration.

We speculate that both the pattern of Th2 and Th1 response and the pattern of infection versus atopy in early childhood could result from this fetal-maternal interaction. Following this thought, the Th2-Th1 pattern, with increased cord blood IgE being a marker, is already programmed at birth (61, 72). This pattern, then, would influence the number of infections and the risk of atopy. Thus, the negative association of infections and atopic manifestation is not causal but more likely to be spurious.

In conclusion, in this follow-up study the level of cord IgE was reduced with increasing birth order. Elevated cord IgE, measured at birth, increased the prevalence of allergic

sensitization by the age of 4 years. The level of IgE at birth was reduced in pregnancies with a higher order. It seems that the level of cord IgE is determined by the outcome of a fetal-maternal interaction during the prenatal period. Thus, the sibling effect may have its origin in utero. This programmed susceptibility might then influence both the risk of early infections and the risk of atopic manifestations.

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