

Elevated cord serum IgE increases the risk of aeroallergen sensitization without increasing respiratory allergic symptoms in early childhood

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Summary

Background Increasing prevalence of allergic disorders has focused attention on primary prevention. There is a need to improve the accuracy of early-life predictors of atopy so that the at-risk population can be accurately defined and preventive measures instituted.

Objective The predictive capacity of elevated cord IgE, with or without family history of atopy, to allergic symptoms and skin prick test (SPT) sensitization is evaluated in a birth cohort followed up prospectively for 4 years.

Methods A birth cohort of 1456 consecutively born children was recruited in 1989. Data were collected on family history of atopy and cord serum total IgE (cord IgE) was measured. Of these, 1218 children were seen in the clinic at 4 years to determine the development of symptoms and signs of allergic disease and 981 were skin tested to a range of common food and aeroallergens.

Results Of 1218 children reviewed at age 4 years, 218 (17.8%) had symptoms of respiratory allergy and, of those skin tested ($n=981$), 192 (19.6%) reacted positively. Twice as many children with elevated cord IgE (≥ 0.5 kU/L) at birth became sensitized to aeroallergens by age 4 years (34.8% vs 17.3%, $P<0.001$). Positive predictive value (PPV) of elevated cord IgE for the development of aeroallergen sensitization was better than that of family history of atopy (34.8 vs 22.6%). Combining paternal atopy with elevated cord IgE substantially increased the predictive capacity (PPV 77.8%). Cord IgE levels did not correlate with clinical asthma or rhinitis at age 4 years and PPV for allergic respiratory symptoms remained poor at all cutoffs.

Conclusion Cord IgE is better than family history for predicting atopy as defined by allergen sensitization and this predictive value can be further increased by combining cord IgE with paternal atopy.

Keywords: asthma, atopy, cohort study, cord IgE, prediction, prevention, skin prick test

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Introduction

There is increasing evidence that early-life exposure to allergens and adjuvants determines the development of atopy in an at-risk population. Increase in the prevalence of allergic disorders in the developed countries has led to a degree of urgency to devise safe and effective measures for

primary prevention of atopy. Any such measures would be most suitable for children who can reliably be identified at birth as carrying a high risk. At present family history remains the most reliable predictor for atopy [1,2]. There is a need to define the at-risk population accurately so that preventive measures can be instituted with greater confidence.

During the last two decades there has been a considerable interest in the possible predictive value of an elevated cord IgE level at birth. Apart from family history of atopy, the

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new-born's ethnic origin, and maternal tobacco smoking or ingestion of progesterone during pregnancy may influence cord serum IgE [3–5]. The association of high cord IgE with the development of allergic disease during childhood has been a matter of debate. The period of follow-up in several published reports claiming a link between cord IgE and allergy is short when the aetiology of respiratory symptoms could not be determined with certainty [3,4,6]. Furthermore, a majority of the studies relied solely on historical data for the diagnosis of allergic disorders without seeking confirmation of allergen sensitization by SPT or radioallergo-sorbent test [4,7]. For clinical disorders, cord IgE seems to have poor sensitivity [2], however, its relationship to the development of atopy as defined by SPT sensitization has not been elucidated in a large unselected population.

There is a lack of consensus regarding the optimum cut-off level for cord IgE which could best define the infant population at risk. Levels from 0.5 to 1.3 kU/L have been quoted [2,4,7–9]. This renders comparison of the results difficult. Nevertheless, a number of researchers argue that cord IgE is more reliable than family history for the prediction of allergic disorders [9].

In 1989, a whole population birth cohort was recruited on the Isle of Wight to study the development of and risk factors for atopy through childhood. Cord serum IgE was measured at birth in a majority of infants. This report assesses the predictive capacity of elevated cord IgE at birth for the development of aeroallergen sensitization and respiratory allergic disease by the age of 4 years.

Materials and methods

Study population

Of 1536 consecutive births on the Isle of Wight between January 1989 and February 1990, 1456 were available for follow-up. Information on the history of atopic disorders among first degree relatives was obtained from the mothers (and fathers if available) in an interview soon after the birth of their child. A diagnosis of asthma, eczema, allergic rhinitis and food allergy was accepted when it had been made by a doctor. Details of environmental factors such as parental smoking, exposure to pets and housing conditions were recorded at birth and updated at each follow-up. The study was fully explained and informed consent obtained. The findings at ages 1, 2 and 4 years have been reported [2,10–12].

Cord serum IgE measurement

The method of cord IgE estimation has been described in a previous report [2]. Briefly, duplicate measurements of cord IgE were made on serum from umbilical vein blood samples

using ULTRA EIA[®] kit (Pharmacia Diagnostics AB, Uppsala, Sweden) which is designed to measure IgE between 0.2 and 50 kU/L on 0.1 mL of serum or plasma. It is a solid phase enzyme immunoassay, using monoclonal antihuman IgE, with a high degree of correlation ($r = 0.99$) with the Phadebas IgE PRIST[®] method [2]. Cord IgA was measured on samples where IgE was higher than 0.3 kU/L. Any samples with IgA > 10 mg/L were deemed contaminated by maternal blood and excluded. Data on cord IgE measured at birth was available in 1064 (87.4%) of 1218 children reviewed at 4 years of age.

Diagnostic criteria for respiratory allergic disease

Criteria for the diagnosis of respiratory allergic disorders have been described [10]. A diagnosis of asthma required three or more separate episodes of wheeze and/or cough each lasting ≥ 3 days. For rhinitis, at least two of three nasal symptoms of discharge, blockage and recurrent sneezing accompanied by eye symptoms were considered.

Skin prick tests

At the age of 4 years 981 (85.4%) children were given SPT with a standard battery of aeroallergens (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%) in phosphate-buffered saline, and physiological saline were used, respectively, as positive and negative controls. All extracts were from Biodiagnostics, Hamburg, Germany. The tests were read after 15 min and mean weal diameter (the sum of the longest diameter and the diameter diagonal to it divided by two) at least 3 mm > negative control was taken as positive.

Statistical analysis

Data was entered into a computer file (SPSS PC⁺ V4, Chicago, IL, USA). Chi square with Yate's correction was used to analyse differences between proportions. For contingency tables with < 10 cases in any cell the Fisher's Exact test was used. Sensitivity, specificity and predictive value were calculated using the method described by Galen and Gambino [13].

Results

Of 1218 children reviewed at age 4 years 218 (17.8%) had symptoms of respiratory allergic disease (asthma 180, rhinitis 65, both 28). One hundred and ninety-two of 981 (19.6%) children given SPT reacted positively, with almost all ($n = 190$) reacting to one or more aeroallergens. Of the

children with respiratory allergic symptoms at 4 years of age, 195 were skin prick tested, of which 86 (44.1%) had become sensitized to aeroallergens ($P < 0.01$). Cord serum IgE was below the range of detection (< 0.2 kU/L) in 615 (57.8%) babies, and only 139 (13.1%) babies had levels ≥ 0.5 kU/L. Infants born to atopic families were more likely to have an elevated (≥ 0.5 kU/L) cord IgE (94 of 526 [15.2%]) as compared with those from families with no history of atopic disease (45 of 444 [10.1%]; $P < 0.03$).

Cord serum IgE and respiratory allergic disease

Using a cut-off level of ≥ 0.5 kU/L, cord serum IgE did not predict the development of respiratory allergic disease (Table 1). Twenty-one of 195 (10.8%) children with respiratory allergic symptoms at age 4 years had cord IgE ≥ 0.5 kU/L as compared with 118 of 869 (13.6%) of those without respiratory symptoms (not significant). Cord

Table 1. The relationship of elevated cord serum IgE (≥ 0.5 kU/L) at birth with respiratory allergic disorders (cumulative and at age 4 years) and aeroallergen sensitization (at 4 years)

	Cord IgE (≥ 0.5 kU/L)		
	Number (%)	kU/L	P-value
<i>Asthma at 4 years</i>			
Yes ($n = 160$)	11	6.9	NS†
No ($n = 904$)	120	13.3	
<i>Asthma to 4 years</i>			
Yes ($n = 239$)	29	12.1	NS†
No ($n = 825$)	110	13.3	
<i>Rhinitis at 4 years</i>			
Yes ($n = 59$)	4	6.8	NS‡
No ($n = 1005$)	135	13.4	
<i>Rhinitis to 4 years</i>			
Yes ($n = 106$)	8	7.5	NS‡
No ($n = 958$)	131	13.7	
¶ <i>Respiratory disorders at 4 years</i>			
Yes ($n = 195$)	21	10.8	NS†
No ($n = 869$)	118	13.6	
<i>Respiratory disorders to 4 years</i>			
Yes ($n = 291$)	32	11.0	NS†
No ($n = 773$)	107	13.8	
<i>Aeroallergen sensitization at 4 years</i>			
Yes ($n = 165$)	39	23.6	<0.001†
No ($n = 695$)	73	10.5	

†Chi square with Yate's correction. ‡Fisher's Exact test.

¶Respiratory disorders = asthma and rhinitis combined.

Table 2. Sensitivity, specificity and positive predicted value of elevated cord IgE (≥ 0.5 kU/L) at birth for respiratory allergic disease and aeroallergen sensitization at 4 years of age

	n	Sensitivity	Specificity	Positive predictive value
<i>Respiratory allergic disease</i>				
Asthma	218	10.8	86.4	15.1
Rhinitis	180	11.9	86.7	13.7
Aeroallergen sensitization	190	23.6	89.5	34.8

All figures for sensitivity, specificity and positive predictive value in percentage.

IgE did not correlate with asthma or rhinitis at age 4 years or with cumulative prevalence of respiratory allergic disorders up to the age of 4 years (Table 1). The sensitivity, specificity and PPV of cord IgE for respiratory allergic disease at 4 years of age are given in Table 2.

A history of atopy among first degree relatives predicted the development of respiratory allergic disease in early childhood with sensitivity, specificity and PPV of 67.7, 43.2 and 20.6%, respectively. One hundred and forty-seven of 713 (20.6%) with a history of atopy among first degree relatives had respiratory allergy as compared with 71 of 505 (14.1%) with no family history of atopy ($P < 0.005$). Adding cord IgE data to a positive family history did not improve the overall predictive capacity for respiratory allergic disease (Fig. 1).

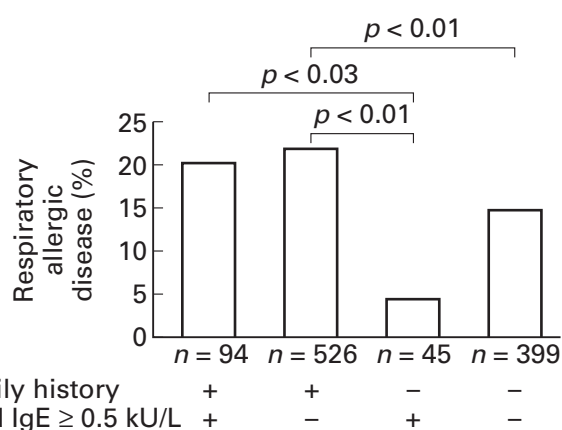


Fig. 1. Effect of family history of atopy and cord IgE on development of respiratory allergic disease ($n = 1064$). All significant comparisons shown, all others non-significant.

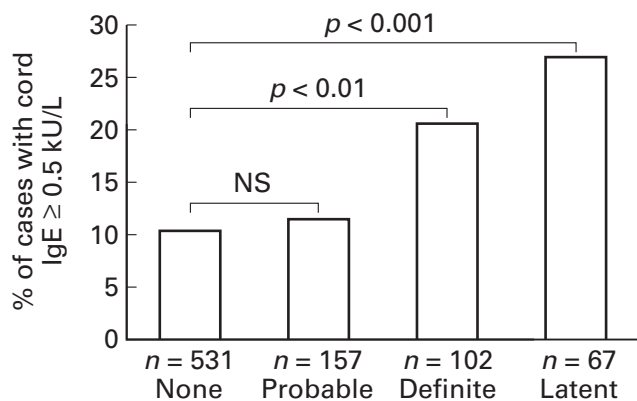
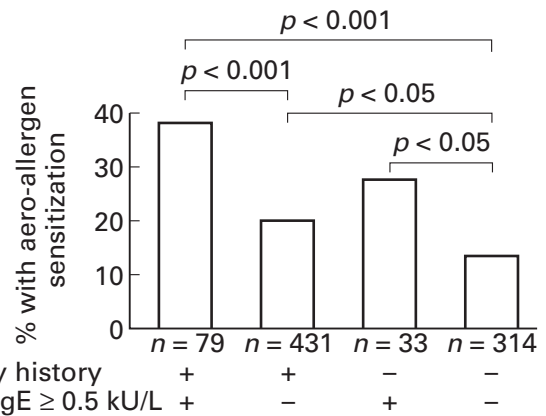
Table 3. The relationship of elevated cord serum IgE (≥ 0.5 kU/L) at birth with sensitization to common aeroallergens at 4 years of age

Allergen	Reaction	n	Cord IgE (≥ 0.5 kU/L)		P-value
			Number	%	
House dust mite	+	101	19	18.8	NS†
	-	705	93	13.2	
Grass pollen	+	69	17	24.6	<0.01†
	-	789	95	12.0	
Cat	+	52	16	30.8	<0.001†
	-	806	96	11.9	
Dog	+	22	6	27.3	NS‡
	-	835	106	12.7	
Alternaria	+	41	14	34.1	<0.001†
	-	816	98	12.0	
Cladosporium	+	20	4	20.0	NS‡
	-	837	108	12.9	

†Chi-square with Yate's correction. ‡Fisher's Exact test.

Cord serum IgE and aeroallergen sensitization

Twice as many children born with elevated cord IgE became sensitized to aeroallergens as compared with those with low levels of cord IgE (39 of 112 [34.8%] vs 129 of 746 [17.3%], $P < 0.001$). The sensitivity, specificity and PPV of cord IgE were better for aeroallergen sensitization than for respiratory allergic disease (Table 2). Furthermore, an elevated cord IgE at birth was associated with an increased sensitization at 4 years to most of the aeroallergens tested (Table 3).

**Fig. 2.** Atopic status in relation to cord IgE ≥ 0.5 kU/L ($n = 857$). None = negative SPT and no symptoms of allergic disease; probable = negative SPT with symptoms of allergic disease; definite = positive SPT with symptoms of allergic disease; latent = positive SPT without allergic disease.**Fig. 3.** Effect of family history of atopy and cord serum IgE on aeroallergen sensitization ($n = 857$).

Using *no atopy* (negative SPT and no symptoms of allergic disease) as control, elevated cord serum IgE had a statistically significant association with *definite* (positive SPT with symptoms of allergic disease) and *latent atopy* (positive SPT but no allergic disease) but not with *probable atopy* (negative SPT with symptoms of allergic disease) (Fig. 2).

Figure 3 shows the relationship between cord serum IgE at birth and family history of atopy on the development of sensitization to aeroallergens. The PPV of high cord IgE was better than that of family history of atopy (34.8 vs 22.6%) though sensitivity remained relatively poor (23.6%).

A summary of the 4-year follow-up results has recently been published and shows that male sex (odds ratio: 1.7, confidence interval: 1.1–2.8, $P < 0.05$), a paternal history of atopy (1.8, 1.1–3.0, $P < 0.05$) and cord serum IgE at birth ≥ 0.5 kU/L (2.3, 1.2–4.4, $P < 0.01$) are independent risk factors for aeroallergen sensitization [12]. The predictive value of elevated cord IgE at birth together with paternal

Table 4. Sensitivity, specificity and positive predictive value of various cut-offs of cord serum IgE for respiratory allergic disease and aeroallergen sensitization

Cord IgE (kU/L)	Sensitivity		Specificity		PPV	
	R	A	R	A	R	A
≥ 0.2	41.0	51.5	57.5	60.1	17.8	23.5
≥ 0.5	10.8	23.6	86.4	89.5	15.1	34.8
≥ 1.0	4.6	10.3	94.9	96.5	17.0	41.5

All figures for sensitivity, specificity and positive predictive value in percentage. PPV = positive predictive value. R = respiratory allergic disease, A = aeroallergen sensitization.

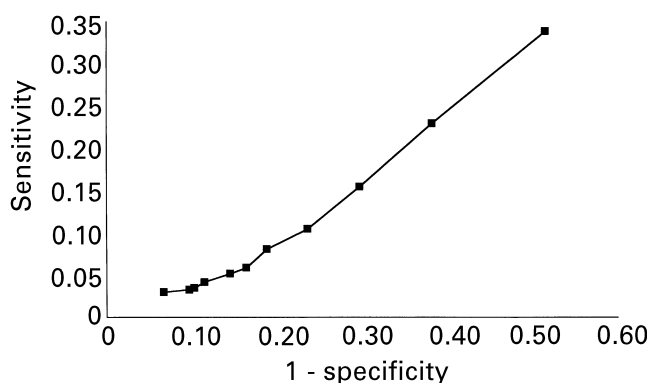


Fig. 4. ROC curve for cord serum IgE as a predictor for aeroallergen sensitization by 4 years of age. The solid squares represent a range of cut-off levels (0.2, 0.3, ... 1.2 kU/L).

atopy was therefore assessed. Combining these two variables substantially increased the predictive capacity for aeroallergen sensitization (sensitivity 15.9%, specificity 96.4% and PPV 77.8%) but not for respiratory allergic disease (5.4%, 94.6% and 17.9%, respectively).

The sensitivity, specificity and PPV of various cut-off levels of cord serum IgE for respiratory allergic disease and aeroallergen sensitization at 4 years are shown in Table 4. For respiratory allergic disease the predictive value remained poor at all cut-offs whereas for aeroallergen sensitization, there was a marginal improvement in the predictive capacity of cord IgE at a cut-off level of ≥ 1.0 kU/L.

As elevated cord serum IgE was related significantly with the development of aeroallergen sensitization at 4 years, a receiver operating characteristics curve (ROC) was plotted to assess its discriminating ability (Fig. 4). The ROC curve provides a measure of the relationship between the true positive rate (sensitivity) and the false positive rate (1 — specificity) and has been used to assess the overall performance of a test [14]. For cord serum IgE as a predictor of aeroallergen sensitization, the ROC curve more or less follows the diagonal and does not yield useful information (Fig. 4).

Discussion

The observation that, in children, an elevated serum IgE may precede allergic manifestations, led Orgel *et al.* to propose that measurements of IgE *at birth* could predict the subsequent development of allergic diseases [15]. A number of studies followed suggesting that elevated cord IgE reliably predicts atopy. Most of these studies were on a small number of subjects followed over a short period [3,4,6] and many lacked objective data on allergen sensitization [4,7,15].

It is well recognized that infantile eczema and early-life food (cow's milk protein, egg albumin) allergies give way to aeroallergen sensitization and respiratory allergic disorders as the child progresses through early childhood [12,16]. The study of an association of cord IgE levels measured at birth with the development of respiratory allergic disease and aeroallergen sensitization is therefore of clinical relevance. Studies following children only through the first 1 or 2 years of life are likely to have encountered a heterogeneous group of early-life wheezers and those with infantile eczema or perhaps even seborrhoeic dermatitis. It is possible that the significant PPV of high cord IgE for atopy in some short-term studies is largely due to its strong association with the development of eczema [7]. Other studies were unable to confirm a useful predictive capacity of cord IgE for the development of allergic disorders including the report on a previous follow-up of this birth cohort [2]. It is well known that a substantial number of wheezy infants are not necessarily atopic and they lose their wheeze as they grow older. One would expect, however, that by the age of 4 years the picture becomes clearer, as respiratory allergic disease and aeroallergen sensitization manifest among children genetically predisposed to atopy [12].

Varying cut-off values for cord serum IgE have been used in previous studies [4,7–9]. As IgE in cord blood is very low (below the range of detection) in the majority of new-borns and its distribution is markedly skewed towards low values, it is difficult to ascertain its optimal cut-off for the prediction of atopy. The German Multicentre Allergy Study (MAS) found that elevated cord IgE (>0.9 kU/L) was significantly associated with eczema and allergen sensitization at age 1 year [17]. However, its PPV at all cut-off levels was poor (maximum PPV for allergen sensitization at one year was 42% using a cut-off level of 3.0 kU/L). Furthermore, there was no association between cord IgE and recurrent wheezing up to age 5 years. Our results showing a PPV of cord IgE for aeroallergen sensitization at age 4 years are similar (41.5% at a cut-off level of 1.0 kU/L). As in the MAS study, the ROC curve does not provide useful information as to the optimum cut-off level of cord IgE. Nevertheless, using the simplistic method of obtaining the level yielding the highest sum of sensitivity and specificity, the optimal cut-off level of cord IgE for aeroallergen sensitization in this study was ≥ 0.5 kU/L. In a report on a large cohort followed from birth to 7 years a higher cut-off level of 1.3 kU/L was found to be a reliable predictor for the development of multiple ($\geq$ three) allergic disorders [16]. In our study, increasing the cut-off level of cord IgE to 1.0 kU/L increased the specificity at the expense of sensitivity with only a marginal improvement in the predictive capacity (Table 4).

Previous studies have shown that maternal smoking during pregnancy tends to increase the level of cord serum

IgE measured at birth [4,5]. In our study maternal smoking during pregnancy neither influenced the mean cord IgE (0.29 ± 0.66 vs 0.32 ± 0.97 kU/L), nor increased allergen sensitization at age 4 years.

A few earlier studies suggested that high cord IgE may predispose to allergen sensitization [3,6,8]. They, however, reported findings after relatively short periods of follow-up, and concentrated primarily on sensitization to food allergens. Unfortunately, the largest comparable study following 1701 children did not include confirmation of allergen sensitization either by skin prick tests or by serological tests for specific IgE [16]. Our study clearly shows a dichotomy with high cord IgE at birth related to aeroallergen sensitization but not to symptomatic respiratory allergic disease. The reasons for this dichotomy are unclear. The development of sensitization to allergens could carry genetic determinants which are distinct from those predisposing to symptomatic respiratory allergy. The findings that paternal atopy is an independent risk factor for reactivity to skin prick tests and that combining cord IgE and paternal atopy increases the predictive capacity for aeroallergen sensitization lend support to this proposition. It is possible therefore, that progression from asymptomatic aeroallergen sensitization to the development of respiratory allergic disease requires certain specific genetic influences which probably act at the epithelial level within the respiratory tract priming it to mount an allergic response. It is also possible that sensitization to aeroallergens detected at the age of 4 years is merely a marker for the subsequent onset of asthma or rhinitis as a large minority ($n = 78$) of those with positive skin prick tests at 4 years were asymptomatic (latent atopy) and showed the strongest association with elevated cord IgE at birth (Fig. 2). Follow-up studies have shown that the expression of atopy increases throughout childhood [16,18]. Furthermore, high cord IgE at birth may predispose to subsequent higher levels of total IgE, whereas an elevated total serum IgE may precede the development of allergic symptoms [5,15,19]. Ongoing follow-up of this cohort therefore may provide invaluable information as to the outcome of the so-called latent atopics and further clarify the relationship between cord IgE, allergen sensitization and respiratory symptoms.

In contrast with the cord IgE studies, one study reported that high serum IgG antibodies with intrinsic anti-IgE activity (> 350 AU/L) at birth were associated with reduced allergic disease during the first 18 months of life [20].

It is possible that more mothers than the fathers were interviewed after the birth of the child. This may have caused under-reporting of paternal allergic disease with only the more severe disease symptoms among the fathers being reported consistently. However, when maternal and paternal atopy was studied separately, it was maternal atopy which was related to asthma (odds ratio: 1.9, confidence

interval 1.1–3.1, $P < 0.05$) and rhinitis (2.9, 1.3–6.1, $P < 0.01$), and paternal atopy to a positive skin prick test (1.8, 1.1–3.0, $P < 0.05$) [12]. Unfortunately, the question whether the pattern of allergen sensitization among the children mirrors that of their fathers, cannot be answered as confirmation of paternal allergies was not undertaken.

Regarding aeroallergen sensitization among the children, the PPV of elevated cord IgE together with paternal atopy was, in fact, higher than the sum of the individual PPVs of these variables (77.8 vs 62.8%) suggesting that they carry a synergistic effect for the development of atopy.

Based on the cut-off yielding the highest sum of sensitivity and specificity, the level of ≥ 0.5 kU/L was found to be optimal for the development of aeroallergen sensitization. The addition of paternal atopy did not alter the optimal cord IgE level for the prediction of sensitivity to aeroallergens (data not shown).

An unexplained but interesting observation was that elevated cord IgE with a negative family history was associated with the least risk for the development of respiratory allergic disease (Fig. 1). This is unlikely to be a spurious result due to a small number of children in this subgroup, as the observations at a previous follow-up at age 1 year were similar [2].

In conclusion, elevated cord IgE measured at birth increases sensitization to aeroallergens by the age of 4 years without leading to a concomitant increase in respiratory allergic disorders. This lends support to the view that there are separate (though possibly overlapping) genetic determinants for IgE sensitization and organ-specific diseases. Although elevated cord IgE proved to be better than family history of atopy in predicting allergen sensitization, the low sensitivity and lack of any relationship to clinical disorders makes it a less useful test for selecting infants suitable for preventive measures.

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