

ORIGINAL PAPER

Association between first-degree familial predisposition of asthma and atopy (total IgE) in newborns

S. Kuiper*, J. W. M. Muris*, E. Dompeling†, C. P. van Schayck*, H. J. A. M. Schönberger†, G. Wesseling‡ and J. André Knottnerus*

Departments of *General Practice, †Paediatrics, and ‡Pulmonology, University Hospital Maastricht, Maastricht, The Netherlands

Clinical and Experimental Allergy

Summary

Background It is generally thought that infants with a first-degree familial predisposition of asthma are at higher risk of developing asthma than infants without predisposition.

Objective To investigate whether there is an association between being at high risk for developing asthma and increased level of total IgE in newborns and whether total IgE is influenced by gender, family size, birth season, maternal smoking, birth weight, gestational age, and maternal diet.

Methods Two hundred and twenty-one high risk and 308 low-risk infants were prenatally selected in a 5-year-period. Three to 5 days after birth, the total IgE was measured in capillary heel blood.

Results Data on total IgE and first-degree familial predisposition were available for 170 high-risk and 300 low-risk infants. There was a statistically significant relationship between being at high-risk (maternal asthma) and increased levels of total IgE in newborns (total IgE cut-off levels: 0.6–0.9 IU/mL (odds ratio (OR) = 2.1, 95% confidence interval (CI): 1.2–3.7 to 3.0, 95% CI: 1.5–5.9)), between being born in autumn and increased levels of total IgE in newborns [total IgE cut-off levels: 0.5–0.6 IU/mL (OR = 2.5, 95% CI: 1.2–5.1 to 2.5, 95% CI: 1.2–5.4)] and between maternal vitamin supplements intake and decreased levels of total IgE in newborns (total IgE cut-off level: 0.9 IU/mL (OR = 0.5, 95% CI: 0.3–1.0)). There was no interaction between the effects of maternal asthma and birth season on total IgE, as well as between the effects of maternal asthma and maternal vitamin supplements intake. Gender, family size, maternal smoking, birth weight, and gestational age did not influence the associations.

Conclusion Being at high-risk of asthma (maternal asthma) and birth season are positively associated with the presence of increased levels of total IgE at birth, whereas maternal vitamin supplements intake is negatively associated with the presence of total IgE at birth.

Keywords asthma, infants, maternal, newborn, total IgE

Submitted 11 May 2005; revised 14 November 2005; accepted 13 January 2006

Correspondence:

Sandra Kuiper, MSc, Department of General Practice, Care and Public Health Research Institute, University of Maastricht, PO Box 616, 6200 MD, Maastricht, The Netherlands.
E-mail: Sandra.Kuiper@HAG.unimaas.nl

Introduction

Asthma is a common chronic disease in childhood and is predominantly newly diagnosed in infants and small children. The prevalence of asthma is high [1, 2] although there are large variations throughout the world [3].

The development of asthma is partly determined by genetic factors, which suggests that familial predisposition of asthma is a possible risk factor for future asthma. Another factor that is at least partly determined by genetic factors is IgE. The foetus synthesizes IgE already from the 11th week of gestation [4]. Moreover, IgE production has been shown to differ between men and women [5–9] as

well as between different races [10]. In the present study, we investigate whether infants with a first-degree familial predisposition of asthma are more often born with increased levels of IgE than infants without such a predisposition.

Several studies have been performed in this field. However, in most studies family history was determined after the study group was selected or after the baby was born using questionnaires that were completed by the parents [10–15] instead of a physician, which does not exclude possible recall bias. Also in most cases the effect of a first-degree family history of atopy instead of a first-degree family history of asthma was studied [10–12, 14].

Some of the studies showed an association between a first-degree family history of atopy and newborn IgE [10–14]. One study failed to do so [13]. Johnson et al. [15] and Kaan et al. [16] showed in their studies an association between newborn IgE and maternal asthma. However, in the study of Johnson no multivariable adjustment was made for potential confounders, whereas in the study of Kaan et al. a control group (of infants without a first-degree familial predisposition of asthma) was lacking.

Furthermore, the presence of newborn IgE seems to be influenced by other factors like gender [9, 12, 13, 15–19], birth season [12, 16–18, 20, 21], ethnicity [10, 14, 16, 18], prenatal parental smoking [12, 16, 18, 22–24], gestational age [12, 13, 15, 17, 20], birth weight [12, 15, 17], and possibly maternal diet during pregnancy [25–27] that are not taken completely into account in most studies.

In the present study, the general practitioner (GP) determined family history of asthma as, in the Netherlands in most cases, all family members share the same physician and the GP registers prospectively whether a family member has asthma. Therefore, it was expected that the GP had a comprehensive overview of asthma in a family. In addition to other studies in this field, in this study the effect of first-degree familial predisposition of asthma on newborn total IgE (from capillary heel blood) will be assessed by comparing a high-risk group with a low risk-group.

Methods

Recruitment of subjects

A detailed description of recruitment of participants is given elsewhere [28]. Briefly, in a period of 5 years (1997–2002), 793 infants, from 3 to 7 months pregnant women, were prenatally included in a Dutch primary care setting, for a randomized clinical prevention trial (RCPT) and a natural history study. Recruitment took place in primary care (RCPT and natural history study) and by advertisements (RCPT). From the 793 infants, 27 were excluded because of intra-uterine neonatal death, major language problems in the family, serious birth defects, or moving abroad. Fifteen infants were lost to follow-up. Four hundred and forty-three infants had a first-degree familial predisposition of asthma (high-risk group) and participated in the RCPT. Two hundred and twenty-two infants from the RCPT were allocated to an intervention group (not discussed in this paper) [28] whereas the other 221 of the control group, as well as 308 infants without a familial predisposition of asthma, received usual care according to the Guideline of the Dutch College of General Practitioners [29]. According to these guidelines, children with a symptom-based diagnosis received an initial treatment with short-acting bronchodilators and, when no adequate asthma control was achieved, a step-up approach with inhaled

corticosteroids in increasing dosage. Fifty-five infants dropped out because mothers refused newborns' blood sampling ($n = 11$) or the baby's blood sample was too small for analysis ($n = 44$). Four infants dropped out because it was not clear which first-degree family member(s) had asthma. For the analysis complete data on total IgE and first-degree familial predisposition were available for 170 high-risk and 300 low-risk infants. From the 470 infants that were left for the analyses, information on prenatal maternal smoking was lacking in 12 infants (seven high-risk infants and five low-risk infants) and information concerning maternal intake of vitamin supplements during pregnancy was lacking in five infants (five high-risk infants). From six infants information concerning prenatal maternal smoking as well as maternal intake of vitamin supplements during pregnancy (three high-risk infants and three low-risk infants) was missing. These infants were included in the bivariate analyses, but excluded from the multiple logistic regression analyses.

'High risk' (first-degree familial predisposition of asthma) was defined in our study as 'at least one first-degree family member (i.e. the pregnant woman, the biological father of the unborn child or an older sibling) suffering from GP registered asthma', whereas 'low-risk' was defined as absence of GP registered asthma in family members [28]. The group of infants who had a positive family history of maternal asthma only or maternal asthma as well as asthma in one or more other first-degree family members, were labelled as the maternal asthma group. The group of infants who had a positive family history of 'asthma in first-degree family members', in which the mother was not included were labelled as the paternal and/or sibling asthma group.

Asthma was defined according to the International Classification of Primary Care [30] as recurrent episodes of reversible acute bronchial obstruction with wheeze and/or dry cough.

Total immunoglobulin E measurements

Between 3 and 5 days postpartum, blood samples were collected on a filter paper by using a heel prick to measure the concentration of total IgE. The analysis of total IgE was performed according to the method described by Stapel et al. [31]. In brief, total IgE was determined with an immunoradiometric assay. Absorbed material was cut and eluted by incubation with PBS-T (PBS/Tween-20 (0.1% v/v)) for 16 h under constant rotation. Eluates were separated from filter paper by centrifugation. Determination of total IgE in eluted blood spots was performed using Sepharose-immobilized reagents and ^{125}I -labelled anti-IgE, raised in sheep ('in house'-developed tests). Test results were expressed in IU/mL (1 IU representing approximately 2.4 ng of total IgE).

The detection limit of the assay was (depending on the size of the blood spot) 0.2 IU/mL and the cut-off levels chosen for elevated total IgE were 0.5, 0.6, 0.7, 0.8, and 0.9 IU/mL.

Potential confounders and effect modifiers

Number of siblings was documented at inclusion. Gender, birth season, birth weight, and gestational age were registered at the moment the infant was born. Prenatal smoking by the mother was registered by use of a questionnaire after the infant was born.

Information concerning maternal intake of vitamin supplements during pregnancy was collected by use of a questionnaire, which was completed by the mother when the infant was 6 months of age. With this questionnaire information was obtained concerning the intake of several dietary products like milk, eggs, fish, fruit, and vitamin supplements during pregnancy. The questionnaire contained 16 items. Mothers were asked, whether they had consumed more, equal, or less of the questioned products during their pregnancy than before their pregnancy.

Statistical methods

To get an impression of the distribution of total IgE, a scatter plot was generated for the high- and low-risk group. To be able to generate a scatter plot, all values that were below the detection limit were set at 0.01 IU/mL. Mann–Whitney's *U*-test was performed to compare the median total IgE values in the high- and low-risk groups.

As the total IgE levels were not normally distributed, even after logarithmic transformation, the remaining analyses were carried out with the total IgE level dichotomized at different cut-off levels. The χ^2 -test and Student's *t*-test were used to examine the bivariate relationships of (the presence or absence of) first-degree familial predisposition of asthma with the potential confounders and/or effect modifiers. These tests were also used to examine the bivariate relationships between the dependent variable total IgE and the independent variable first-degree familial predisposition of asthma as well as the potential confounders and/or effect modifiers gender, family size, birth season, prenatal smoking by the mother, birth weight, pregnancy duration, and maternal diet during pregnancy. In a backward multiple logistic regression analysis the simultaneous contributions of the independent variables to the presence of total IgE 3–5 days postpartum were evaluated as follows. Firstly, all variables that could potentially act as confounder were entered in the model. Then linearity was checked for birth weight and pregnancy duration (as these variables were continuous). Finally, stepwise backward regression analyses were performed, in which the least significant variable was dropped one by one. As the variables family size, birth

season, and maternal intake of vitamin supplements during pregnancy differed for the high- and low-risk group, these variables were kept in the models. First order interactions between first-degree familial predisposition of asthma with birth season, family size and maternal intake of vitamin supplements during pregnancy were checked. *P*-values less than 0.05 were considered to be statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 11.0.

Ethical approval

Ethical approval for this study was obtained from the ethics committees of the participating institutes. All participants gave written, informed consent.

Results

In Table 1, the asthma status of first-degree family members in high-risk infants is shown. The demographic characteristics of the study population are shown in Table 2. For the infants for whom complete data were not available, the demographic characteristics were comparable with those of the analysed group. Five infants from the high-risk group and 14 infants from the low-risk group were premature at birth (< 37 weeks). A statistically significant difference between the high- and low-risk groups was detected for family size (infants from the high-risk group had more siblings), birth season (in the low-risk group most births were in spring and summer) and maternal intake of vitamin supplements during pregnancy (more low-risk than high-risk mother consumed vitamin supplements). Total IgE levels ranged from < 0.2 to 23.2 IU/mL (median < 0.2 IU/mL) in the high-risk group versus < 0.2 to 7.97 IU/mL (median < 0.2 IU/mL) in the low-risk group. Seventy-one per cent of the high-risk infants and 70% of the low-risk infants had undetectable total IgE levels (median (total IgE) < 0.2 IU/mL, geometric mean < 0.2 IU/mL). Using the Mann–Whitney's test, there was no statistically significant difference in total IgE between high- and low-risk infants (*P* = 0.47) (Fig. 1).

Table 1. Asthma status in first-degree family members of high-risk infants

	<i>N</i> (%)
Mother with asthma, <i>n</i> (%)	50 (29.4)
Father with asthma, <i>n</i> (%)	32 (18.8)
Sibling with asthma, <i>n</i> (%)	31 (18.2)
Mother and father with asthma, <i>n</i> (%)	15 (8.8)
Mother and sibling with asthma, <i>n</i> (%)	21 (12.4)
Father and sibling with asthma, <i>n</i> (%)	16 (9.4)
Mother and father and sibling with asthma, <i>n</i> (%)	5 (2.9)

Table 2. Demographic characteristics of the study population

	High-risk group	Low-risk group	P-value
N	170	300	
Mother's age (years) ($\pm$ SD)	31 ($\pm$ 3)	31 ($\pm$ 4)	0.73
Father's age (years) ($\pm$ SD)	33 ($\pm$ 4)	34 ($\pm$ 4)	0.31
Gender, n (%)			
Male	85 (50.0)	157 (52.3)	0.63
Female	85 (50.0)	143 (47.7)	
Birth weight in grams ($\pm$ SD)	3494 ($\pm$ 488)	3457 ($\pm$ 580)	0.48
Gestational age in weeks ($\pm$ SD)	39.9 ($\pm$ 1.5)	39.8 ($\pm$ 1.7)	0.62
Birth season, n (%)			
Spring	39 (22.9)	90 (30.0)	0.002
Summer	42 (24.7)	101 (33.7)	
Autumn	34 (20.0)	55 (18.3)	
Winter	55 (32.4)	54 (18.0)	
Siblings, n (%)			
0	64 (37.6)	136 (45.3)	0.04
1	66 (38.8)	124 (41.3)	
2	31 (18.2)	32 (10.7)	
≥ 3	9 (5.3)	8 (2.7)	
Prenatal maternal smoking, n (%)	19 (11.9)	32 (10.7)	0.77
Maternal intake of vitamin supplements during pregnancy, n (%)	81 (50.0)	188 (63.0)	0.06

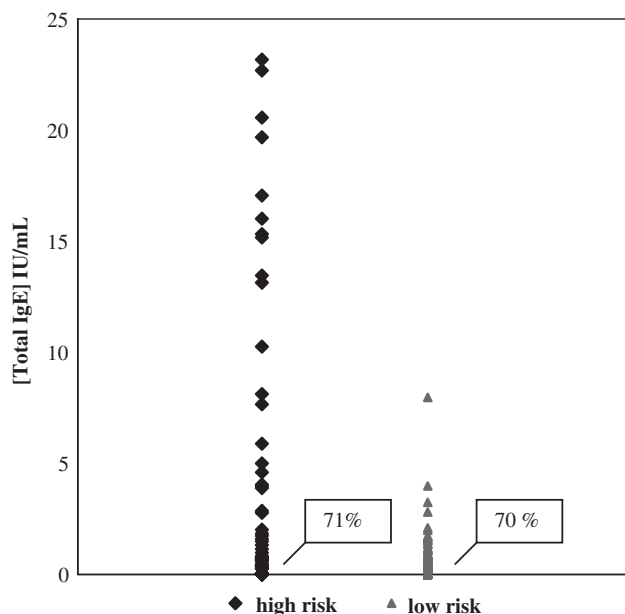


Fig. 1. Total newborn IgE levels in high-risk (HR) infants and low-risk (LR) infants. Seventy-one per cent of the HR infants as well as 70% of the LR infants had undetectable IgE levels. In the HR as well as in the LR group the median total IgE level was < 0.2 IU/mL.

Using bivariate analysis, a statistically significant higher proportion of infants with increased levels of total IgE was found in the group with maternal asthma at a total IgE

cut-off level of 0.6, 0.7, 0.8, and 0.9 IU/mL (Table 3). In comparison with other birth seasons there was the tendency that infants born in autumn had more often increased levels of total IgE at all total IgE cut-off levels except 0.9 IU/mL. There also was a tendency that infants with three or more siblings had more often detectable total IgE levels than infants with two or less siblings. However, this did not reach statistical significance. Maternal intake of vitamin supplements during pregnancy resulted statistically significantly more often in decreased total IgE levels in infants at a total IgE cut-off level of 0.9 and 0.8 IU/mL compared with when no vitamin supplements were consumed by pregnant women (Table 3). No effect was seen from all other food components studied. Boys had more often detectable total IgE at all total IgE cut-off levels than girls, however, this was not statistically significant. Moreover, the same association was seen in the group of infants with maternal asthma. In this group there was again a tendency of increased total IgE in boys compared with girls, which was not statistically significant (data not shown). No differences were found between total IgE at birth and prenatal smoking by the mother, birth weight, and gestational age at any total IgE cut-off level studied (Table 3).

In Table 4 the results of the multiple logistic regression analysis are shown. In this table only the variables for which the high- and low-risk group differed are reported. Maternal asthma (vs. no asthma in first-degree family members) remained statistically significantly associated with increased total IgE at a cut-off level of 0.6, 0.7, 0.8, and 0.9 IU/mL (Table 4). Paternal asthma as well as asthma in siblings had no statistically significant contribution to the level of total IgE. Number of siblings was retained in the presented models for comparison, given the interest paid to this variable in literature. At a cut-off level of 0.5 to be born in autumn and winter (vs. to be born in spring) were statistically significantly associated with increased total IgE, whereas at a cut-off level of 0.6 IU/mL to be born in summer and autumn (vs. to be born in spring) were statistically significantly associated with increased total IgE (Table 4). Maternal intake of vitamin supplements during pregnancy remained statistically significant at a total IgE cut-off level of 0.9 IU/mL, but not at a cut-off level of 0.8 IU/mL (Table 4).

Discussion

Elevated total IgE levels were more often found in high-risk newborns than in low-risk newborns. The high- and low-risk group differed in family size, birth season, and maternal consumption of vitamin supplements during pregnancy, which made those variables potential confounders in this study. After controlling for these and other potential confounders, multiple logistic regression analysis revealed that maternal asthma and born in

Table 3. Bivariate relationship between total newborns IgE and independent variables

	N	IgE < 0.5 IU/ mL, n (%) [†]	IgE ≥ 0.5 IU/ mL, n (%) [†]	IgE < 0.6 IU/ mL, n (%) [†]	IgE ≥ 0.6 IU/ mL, n (%) [†]	IgE < 0.7 IU/ mL, n (%) [†]	IgE ≥ 0.7 IU/ mL, n (%) [†]	IgE < 0.8 IU/ mL, n (%) [†]	IgE ≥ 0.8 IU/ mL, n (%) [†]	IgE < 0.9 IU/ mL, n (%) [†]	IgE ≥ 0.9 IU/ mL, n (%) [†]
No asthma	300	246 (82)	54 (18)	254 (85)	46 (15)	258 (86)	42 (14)	268 (89)	32 (11)	277 (92)	23 (8)
Maternal asthma	91	65 (71)	26 (29)	65 (71)	26 (29)*	68 (75%)	23 (25)*	70 (77)	21 (23)*	71 (78)	20 (22)**
Paternal and/or sibling asthma	79	65 (82)	14 (18)	65 (82)	14 (18)	67 (85%)	12 (15)	69 (87)	10 (13)	70 (89)	9 (11)
Gender											
Boys	242	193 (80)	49 (20)	196 (81)	46 (19)	201 (83)	41 (17)	209 (86)	33 (14)	212 (87)	31 (13)
Girls	228	183 (80)	45 (20)	188 (83)	40 (17)	192 (84)	36 (16)	198 (87)	30 (13)	206 (90)	22 (10)
Sibling's											
0	200	154 (77)	46 (23)	158 (79)	42 (21)	164 (82)	36 (18)	171 (85)	29 (15)	174 (87)	26 (13)
1	190	157 (83)	33 (17)	160 (84)	30 (16)	163 (86)	27 (14)	168 (88)	22 (12)	173 (91)	17 (9)
2	63	53 (84)	10 (16)	54 (86)	9 (14)	54 (86)	9 (14)	56 (89)	7 (11)	58 (92)	5 (8)
≥ 3	17	12 (71)	5 (29)	12 (71)	5 (29)	12 (71)	5 (29)	12 (71)	5 (29)	13 (77)	4 (24)
Birth season											
Spring	129	113 (88)	16 (12)	115 (89)	14 (11)	115 (89)	14 (11)	117 (91)	12 (9)	118 (91)	11 (9)
Summer	143	113 (79)	30 (21)	115 (80)	28 (20)	119 (83)	24 (17)	125 (87)	18 (13)	128 (90)	15 (10)
Autumn	89	65 (73)	24 (27)	67 (75)	22 (25)	70 (79)	19 (21)	73 (82)	16 (18)	77 (87)	12 (13)
Winter	109	85 (78)	24 (22)	87 (80)	22 (20)	89 (82)	20 (18)	92 (84)	17 (16)	95 (87)	14 (13)
Maternal prenatal smoking											
Yes	50	41 (80)	10 (20)	42 (82)	9 (18)	42 (82)	9 (18)	43 (84)	8 (16)	46 (90)	5 (10)
No	402	319 (80)	82 (20)	326 (81)	75 (19)	335 (83)	66 (17)	350 (87)	54 (13)	356 (89)	45 (11)
Mean birth weight in grams (± SD)	470	N = 364	N = 94	N = 372	N = 86	N = 381	N = 77	N = 395	N = 63	N = 406	N = 52
Mean gestational age in weeks (± SD)	470	3457 (561)	3524 (489)	3454 (557)	3544 (500)	3451 (555)	3568 (501)	3461 (561)	3531 (453)	3463 (555)	3537 (484)
		N = 376	N = 94	N = 384	N = 86	N = 393	N = 77	N = 407	N = 63	N = 418	N = 52
Maternal vitamin supplements intake during pregnancy											
Yes	269	222 (83)	47 (17)	226 (84)	43 (16)	231 (86)	38 (14)	240 (89)	29 (11)*	247 (92)	22 (8)*
No	190	144 (76)	46 (24)	148 (78)	42 (22)	152 (80)	38 (20)	157 (83)	33 (17)	161 (85)	29 (15)

 * $P < 0.05$, ** $P < 0.01$.

[†]% = row percentage.

Table 4. Summary of backward multiple logistic regression analyses

	Adjusted OR (95% CI), 0.5 IU/mL	Adjusted OR (95% CI), 0.6 IU/mL	Adjusted OR (95% CI), 0.7 IU/mL	Adjusted OR (95% CI), 0.8 IU/mL	Adjusted OR (95% CI), 0.9 IU/mL
No asthma	1.00	1.00	1.00	1.00	1.00
Maternal asthma	1.67 (0.94–2.95)	2.06 (1.15–3.68)*	1.89 (1.03–3.45)*	2.22 (1.17–4.22)*	2.99 (1.50–5.93)**
Paternal asthma and/or sibling asthma	0.97 (0.49–1.91)	1.19 (0.60–2.39)	1.05 (0.50–2.17)	1.12 (0.51–2.48)	1.53 (0.65–3.60)
Siblings					
0	1.00	1.00	1.00	1.00	1.00
1	0.72 (0.43–1.21)	0.72 (0.42–1.24)	0.77 (0.44–1.36)	0.79 (0.42–1.47)	0.65 (0.33–1.29)
2	0.68 (0.31–1.49)	0.66 (0.29–1.49)	0.81 (0.35–1.84)	0.77 (0.31–1.92)	0.54 (0.19–1.53)
≥3	1.59 (0.51–4.94)	1.76 (0.56–5.50)	2.12 (0.67–6.63)	2.72 (0.85–8.72)	2.11 (0.60–7.36)
Birth season					
Spring	1.00	1.00	1.00	1.00	1.00
Summer	1.96 (1.00–3.83)	2.12 (1.05–4.29)*	1.77 (0.86–3.64)	1.54 (0.70–3.40)	1.35 (0.58–3.16)
Autumn	2.46 (1.19–5.08)*	2.53 (1.18–5.42)*	2.13 (0.97–4.64)	2.02 (0.87–4.70)	1.42 (0.57–3.58)
Winter	2.07 (1.02–4.21)*	2.07 (0.98–4.38)	1.88 (0.88–4.01)	1.80 (0.80–4.07)	1.47 (0.62–3.52)
Maternal intake of vitamin supplements during pregnancy	0.68 (0.43–1.09)	0.70 (0.43–1.15)	0.69 (0.41–1.14)	0.60 (0.35–1.05)	0.53 (0.29–0.97)*

* $P < 0.05$, ** $P < 0.01$.

All variables that were studied in the bi-variate analyses were entered in the multiple logistic regression models. With a stepwise backward regression procedure all variables that had no statistically significant effect on IgE were dropped one by one. With each step it was checked whether the omitted variable was a confounder. As the number of siblings, birth season, and maternal intake of vitamin supplements during pregnancy differed between the high- and low-risk group they were kept in the models.

autumn remained associated with elevated total IgE, whereas maternal intake of vitamin supplements during pregnancy remained associated with decreased total IgE. We found that the odds ratio for detectable total IgE in high-risk newborns with maternal asthma compared with low-risk newborns increased with increasing total IgE cut-off levels, indicating that the higher the total IgE cut-off level, the better high-risk newborns could be distinguished from low-risk newborns. Paternal asthma as well as asthma in siblings had no contribution to the level of total IgE in newborns.

Our study is the first that used a GP registered population. Accordingly, we had the advantage that an impression could be obtained of the newborn total IgE pattern in a primary care population. We expected that a GP had a comprehensive overview of asthma in a family, as in the Netherlands, in almost all cases, all family members share the same physician and the GP registers prospectively whether a family member has asthma.

A disadvantage of this selection procedure may be that in some cases a sibling below 6 years could not have been given a definite asthma diagnosis. Another important point is the chance of underestimation of the asthma risk because of the selection procedure used. When asthma in siblings is involved in defining 'high risk', an underestimation of the risk in smaller families compared with larger families will exist. However, when the definition of high risk is exclusively based on asthma in the parents, the underestimation might be even more pronounced. To

account for the mentioned possible underestimation of the risk in our design, we controlled for family size in the multiple logistic regression analysis.

It has been suggested that cord-blood may be contaminated with maternal blood and that high levels of cord-blood total IgE could be due to this contamination [12, 15, 32]. Lilja *et al* [32] showed that in 50% of infants with cord-blood total IgE ≥ 0.9 kU/L the total IgE concentrations decreased below this value on days 4–5 and that there was a correlation between maternal total IgE and cord-blood total IgE concentrations. In order to prevent for maternal contamination we collected capillary heel blood for total IgE detection at days 3–5 after birth.

We found that maternal asthma was associated with elevated total IgE at all total IgE cut-off levels studied except 0.5 IU/mL. An association between maternal asthma and total IgE in newborns was also found by two other study groups [15, 16]. In other studies, an association was found between maternal atopy and total IgE in newborns [11, 12, 14]; however, one study failed to do so [13]. In most studies the total IgE cut-off level that was chosen differed, which makes comparison difficult. We examined our data at various total IgE cut-off levels. A total IgE cut-off level of 0.9 IU/mL was chosen because this cut-off level represents the clinical cut-off level, a cut-off level of 0.5 IU/mL was chosen to be able to better compare our findings with those of others, as this cut-off level was used in most studies. We chose the cut-off levels 0.6–0.8 IU/mL to investigate a possible dose–response relationship.

Birth season was also associated with detectable newborns total IgE, which agrees with others [16–18, 20]. There is however no agreement on the season that most affects newborns total IgE. We found the highest percentage of elevated total IgE in the autumn in high risk as well as in low-risk infants. In the high-risk group, a more or less cyclic pattern of birth season and newborn total IgE was observed. Halonen et al. [18] and Kimpen et al. [20] found in an unselected population a cyclic sinusoidal pattern of month of birth with total IgE with the highest values in spring [18, 20] as well as in winter [21] and the lowest values in autumn. Hansen et al. [17] found the lowest values in october, but no cyclic total IgE pattern throughout the year. Kaan et al. [16] and Bjerke et al. [21] found the highest proportion of newborns with detectable total IgE in winter and late autumn, respectively. These seasonal differences between the study groups are probably partly because of the climate differences throughout the world.

We asked mothers whether they consumed several food components during their pregnancy and tested whether these were associated with newborn total IgE. None of the components showed a relationship with newborn total IgE, except the consumption of vitamin supplements. Unfortunately, information concerning the frequency and duration of vitamin supplements intake as well as the composition of the vitamin supplements was not collected. The consumption of vitamin supplements remained significant in the multiple logistic regression analysis. However, at this moment we are not able to give a satisfactory explanation for this finding, therefore further research is necessary to confirm this observation.

Although more male than female newborns had detectable total IgE, there was no significant effect of gender on total newborn IgE in the group as a whole as well as in the group with maternal asthma, which is in accordance with some other studies [15, 16]. However, in other studies an association of gender and total newborn IgE was found [12, 13, 17–19]. A difference of these studies with our study and the studies of Kaan et al. [16] and Johnson et al. [15] was that the size of the study populations in the former studies was larger, which might be responsible for the differences found. We saw no effect of prenatal maternal smoking and gestational age. However, only 10% of the mothers smoked during pregnancy and 19 infants were pre-term. Therefore, we were not able to assess the effects of these phenomena on total newborn IgE.

There are several studies in which maternal atopy or asthma and birth season have been shown to affect total IgE in newborns. With this primary-care study we tried to add another piece of the puzzle. We confirm at different total IgE cut-off levels, in a GP registered population where we compared infants with a first-degree familial predisposition of asthma to infants without this predisposition, the results of former studies. We found an association of total IgE in newborns with birth season

and maternal asthma but not with paternal or sibling asthma, which confirms the idea that besides a genetic pathway an environmental pathway plays a role.

Acknowledgements

This study was a joint project of the Departments of General Practice of the University of Maastricht and the Radboud University Nijmegen. We would like to thank the GPs, the practice assistants and the research assistants allied to these departments and the participating midwives for recruiting eligible families. We are grateful to all families for their participation in the study. We also thank the datamanager Jacqueline Pisters; the statisticians Jildou Sijbrandij and Arnold Kesters as well as Steven Stapel and Janny de Vrieze from the Department of Allergy at the information center diagnostics, Amsterdam, the Netherlands, for the analysis of the blood samples. We finally thank all other people who were (scientifically) involved in the study.

References

- 1 The International Study of Asthma and allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998; 351:225–32.
- 2 Eldeirawi K, Persky VW. History of ear infections and prevalence of asthma in a national sample of children aged 2 to 11 years. *Chest* 2004; 125:1685–92.
- 3 Beasley R, Crane J, Lai CKW, Pearce NI. Epidemiology and genetics of asthma. Prevalence and etiology of asthma. *J Allergy Clin Immunol* 2000; 105:S466–72.
- 4 Miller DL, Hirvonen T, Gitlin D. Synthesis of IgE by the human conceptus. *J Allergy Clin Immunol* 1973; 52:182–8.
- 5 Klink M, Cline MG, Halonen M, Burrows B. Problems in defining normal limits for serum IgE. *J Allergy Clin Immunol* 1990; 85:440–4.
- 6 Barbee RA, Halonen M, Lebowitz M, Burrows B. Distribution of IgE in a community population sample: correlations with age, sex and allergen skin test reactivity. *J Allergy Clin Immunol* 1981; 68:106–11.
- 7 Grassi J, Didierlaurent A, Stadler BM. Quantitative determination of total and specific human IgE with the use of monoclonal antibodies. *J Allergy Clin Immunol* 1986; 77:808–22.
- 8 Kjellman NI. Atopic allergy and serum IgE concentrations in randomly selected children followed up from 8 to 12 years of age. *Allergy* 1984; 39:443–50.
- 9 Vankrunkelsven P. Verband van leeftijd en geslacht met astma, rhinitis, specifieke allergiën en serum-IgE. Omgevingsfactoren en allergie: aan de hand van een patiëntenbestand met 20.000 dossiers. Leuven, 1999, p.18–34.
- 10 Haus M, Heese HD, Weinberg EG, Potter PC, Hall JM, Malherbe D. The influence of ethnicity, an atopic family history, and maternal ascariasis on cord blood serum IgE concentrations. *J Allergy Clin Immunol* 1988; 82:179–89.

- 11 Michel FB, Bousquet J, Greillier P, Robinet-Levy M, Coulomb Y. Comparison of cord blood immunoglobulin E concentrations and maternal allergy for the prediction of atopic diseases in infancy. *J Allergy Clin Immunol* 1980; 65 :422–30.
- 12 Bergmann RL, Schulz J, Günther S *et al*. Determinants of cord-blood IgE concentrations in 6401 German neonates. *Allergy* 1995; 50:65–71.
- 13 Croner S, Kjellman N-IM, Erkişon B, Roth A. IgE screening in 1701 newborn infants and the development of atopic disease during infancy. *Arch Dis Child* 1982; 57:364–8.
- 14 Magnusson CGM. Cord serum IgE in relation to family history and as predictor of atopic disease in early infancy. *Allergy* 1988; 43:241–51.
- 15 Johnson CC, Ownby DR, Peterson EL. Parental history of atopic disease and concentration of cord blood IgE. *Clin Exp allergy* 1996; 26:624–9.
- 16 Kaan A, Dimich-Ward H, Manfreda J *et al*. Cord blood IgE: its determinants and prediction of development of asthma and other allergic disorders at 12 months. *Ann Allergy Asthma Immunol* 2000; 84:37–42.
- 17 Hansen LG, Host A, Halken S *et al*. Cord blood IgE. I. IgE screening in 2814 newborn children. *Allergy* 1992; 47:391–6.
- 18 Halonen M, Stern D, Lyle S, Wright A, Taussig L, Martinez FD. Relationship of total serum IgE levels in cord and 9-month sera of infants. *Clin Exp Allergy* 1991; 21:235–41.
- 19 Kimpen J, Callaert H, Embrechts P, Bosmans E. Influence of sex and gestational age on cord blood IgE. *Acta Paediatr Scand* 1989; 78:233–8.
- 20 Kimpen J, Callaert H, Embrechts P, Bosmans E. Cord blood IgE and month of birth. *Arch Dis Child* 1987; 62:478–82.
- 21 Bjerke T, Hedegaard M, Henriksen TB, Nielsen BW, Schiøtz PO. Several genetic and environmental factors influence cord blood IgE concentrations. *Pediatr Allergy Immunol* 1994; 5:88–94.
- 22 Magnusson CGM. Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. *J Allergy Clin Immunol* 1986; 78:898–904.
- 23 Ownby DR, Johnson CC, Peterson EL. Maternal smoking does not influence cord serum IgE or IgD concentrations. *J Allergy Clin Immunol* 1991; 88:555–60.
- 24 Oryszczyn M-P, Godin J, Annesi I, Hellier G, Kauffmann F. In utero exposure to parental smoking, cotinine measurements, and cord blood IgE. *J Allergy Clin Immunol* 1991; 87: 1169–74.
- 25 Mithrshahi S, Peat JK, Webb K, Oddy W, Marks GB, Mellis CM. Effect of omega-3 fatty acid concentrations in plasma on symptoms of asthma at 18 months of age. *Pediatr Allergy Immunol* 2004; 15:517–22.
- 26 Diez U, Schlink U, Reuter W *et al*. Fatty acids in colostrum from mothers of children at high risk of atopy in relation to clinical and laboratory signs of allergy in the first year of life. *Allergy* 2004; 59:394–400.
- 27 Dunstan JA, Mori TA, Barden A *et al*. Maternal fish oil supplementation in pregnancy reduces interleukin-13 levels in cord blood of infants at high risk of atopy. *Clin Exp Allergy* 2003; 33:442–8.
- 28 Kuiper S, Maas T, van Schayck CP *et al*. The primary prevention of asthma in children (PREVASC) study: design of a multifaceted prevention program. *Pediatr Allergy Immunol* 2005; 16:321–31.
- 29 Dirksen WJ, Geijer RMM, de Haan M *et al*. Astma bij kinderen. NHG-Standaard. *Huisarts en Wet* 1998; 41:130–43.
- 30 The WONCA classification committee. *ICPC-2. International Classification of Primary Care*. Oxford University Press, Oxford, 1998.
- 31 Stapel SO, Eysink PED, de Vrieze J, Aalberse RC. IgE testing in capillary blood. *Pediatr Allergy Immunol* 2004; 15: 230–3.
- 32 Lilja G, Johansson SGO, Kusoffsky E, Öman H. IgE levels in cord blood and at 4–5 days of age: relation to clinical symptoms of atopic disease up to 18 months of age. *Allergy* 1990; 45:436–44.