

Gestational age and occurrence of atopy at age 31— a prospective birth cohort study in Finland

J. PEKKANEN, B. XU and M.-R. JÄRVELIN*

Unit of Environmental Epidemiology, National Public Health Institute, Kuopio, Finland and

**Department of Public Health and General Practice, University of Oulu and Department of Epidemiology and Public Health, Imperial College School of Medicine, London, UK*

Summary

Background It has been suggested that main risk factors for development of allergic diseases operate already during pregnancy and in early childhood.

Objective To study the association between gestational age, birth weight, parity and parental farming with the risk of atopy and asthma in young adults.

Methods In a prospective birth cohort study, 5192 subjects born in Northern Finland in 1966 were followed up at the age of 31. Skin prick tests were done to three of the most common allergens in Finland and to house dust mite. Data on doctor-diagnosed asthma was obtained from questionnaires. Perinatal data had already been collected during pregnancy.

Results The risk of atopy increased linearly with increasing length of pregnancy among babies born in the 35th week of gestation or later. Gestational age equal to, or over 40 weeks compared with less than 36 weeks was associated with an increased risk of atopy (multivariate odds ratio 1.65, 95% CI 1.16, 2.34). The association was stronger among farmers' children (*P* for interaction 0.01). High parity and being a farmer's child (multivariate odds ratio 0.50, 95% CI 0.42–0.60) was associated with decreased risk of atopy. In contrast, no associations were observed for doctor-diagnosed asthma.

Conclusions The results underline the importance of pregnancy and very early childhood in the development of atopy, and suggest that timing of the environmental exposure is of importance for the immune system. No association was observed for asthma, which may be due to the multifactorial origins of asthma.

Keywords: atopy, skin prick test, asthma, birth cohort, follow-up, gestational age, birth weight, farming

Clinical and Experimental Allergy, Vol. 31, pp. 95–102. Submitted 18 November 1999; revised 22 February 2000; accepted 4 April 2000.

Introduction

There is currently very little information on the risk factors, other than genetic factors, which determine whether a person develops asthma or not [1]. This is in contrast to the extensive literature on factors associated with exacerbation of asthma. Atopy is often seen as the major determinant and precursor of asthma. However, asthma has several phenotypes [2] and overall, the importance of atopy may have been exaggerated [3].

It has been suggested that the main risk factors for

development of allergic diseases already operate during pregnancy and in early childhood [4]. The immunological development of the fetus has already started before the second trimester. It has been suggested that allergen exposure and the cytokine profile of the mother may have an influence on the developing fetus, which may lead to intrauterine priming [5]. The effect on the immune system can also be more general, and can be reflected in the fetus as intrauterine growth retardation [6].

These suggestions parallel the theory on intrauterine programming. Several studies have shown an increased risk of cardiovascular diseases and diabetes in adulthood among babies with low birth weight or with intrauterine growth

Correspondence: J. Pekkanen, Unit of Environmental Epidemiology, National Public Health Institute, P.O. Box 95, 70701, Kuopio, Finland.

retardation [7]. These perinatal factors also appear to have an influence on atopy and allergic diseases [8–12].

On the other hand, it has been suggested that the environment during the first few months of life is of primary importance. Several studies have shown higher risk of atopy among children with few siblings [13,14], possibly indicating a lower risk of infections. Recent studies [15] have also indicated a lower risk of atopy among farmers' children.

The association of pre- and perinatal characteristics and their interactions on the risk of atopy and asthma in adulthood was therefore investigated in a prospective birth cohort study of 5192 subjects born in Northern Finland in 1966, and examined at the age of 31 years.

Subjects and methods

The original cohort consisted of 12 058 live births from the two northernmost provinces of Finland, Oulu and Lapland, and covered 96% of the children born in that region between January 1 and December 31, 1966 [16]. The data collection started during pregnancy and follow-up data on the health status of the children were collected at various ages [17,18]. In 1997, 8463 survivors who were still living in Northern Finland or in the capital area were sent postal questionnaires and invited to clinical examinations; 6025 (71.2%) attended the examinations [12].

The sensitivity to three of the most common allergens in Finland, i.e. cat, birch and timothy, and sensitivity to the

Table 1 Prevalence of atopy and asthma at age 31 by gestational age, weight at birth, parity, paternal occupation and parental allergy

	Men No.	Atopy (%)	Asthma (%)	Women No.	Atopy (%)	Asthma (%)	All No.	Atopy (%)	Asthma (%)
Gestational age (weeks)									
≤ 35	119	26.9	8.4	128	21.1	9.4	247	23.9	8.9
36–38	743	30.1	7.5	633	25.4	8.5	1376	28.0	8.0
39–40	1239	33.8	6.9	1325	28.9	8.4	2564	31.3	7.6
≥41	491	37.5	8.4	514	31.7	9.1	1005	34.5	8.8
<i>P</i> for global test		0.023	0.713		0.029	0.945		0.001	0.684
<i>P</i> for trend		0.002	0.902		0.003	0.907		0.000	0.830
Weight at birth (g)									
1, ≤3090	518	30.1	7.1	498	28.7	8.4	1016	29.4	7.8
2, 3100–3390	515	36.3	8.9	544	26.8	8.5	1059	31.4	8.7
3, 3400–3620	509	35.6	7.1	512	27.1	9.2	1021	31.3	8.1
4, 3630–3900	521	29.9	6.9	526	27.9	8.4	1047	28.9	7.6
5, ≥ 3910	529	33.8	7.0	520	30.6	8.7	1049	32.2	7.8
<i>P</i> for global test		0.801	0.699		0.679	0.991		0.418	0.910
<i>P</i> for trend		0.866	0.524		0.427	0.930		0.503	0.709
Parity									
0	819	38.5	7.1	798	31.3	8.6	1617	34.9	7.9
1	612	36.8	6.7	615	30.7	8.6	1227	33.7	7.7
2–3	674	30.7	8.3	680	27.1	8.7	1354	28.9	8.5
≥4	484	23.1	7.6	504	21.8	8.5	988	22.5	8.1
<i>P</i> for global test		0.000	0.703		0.001	1.000		0.000	0.875
<i>P</i> for trend		0.000	0.457		0.000	0.961		0.000	0.625
Paternal occupation									
Non-farmers	2059	36.0	7.7	2055	31.3	9.1	4114	33.7	8.4
Farmers	533	22.1	6.4	545	16.5	7.0	1078	19.3	6.7
<i>P</i> for global test		0.000	0.309		0.000	0.124		0.000	0.070
Parental history of allergy									
No	1721	31.1	5.8	1478	25.4	6.7	3199	28.5	6.2
Yes	721	39.3	11.8	1007	32.9	11.0	1728	35.5	11.3
<i>P</i> for global test		0.000	0.000		0.000	0.000		0.000	0.000

house dust mite (*Dermatophagoides pteronyssinus*), was assessed by skin prick tests during clinical examinations. Histamine dihydrochloride (10 mg/mL) and diluent of the allergen extracts were used as positive and negative controls, respectively. Skin reactions to each allergen tested were recorded after 10 min as the average of the maximum weal diameter and the diameter perpendicular to the maximum. People with a weal reaction ≥ 3 mm to one or more of the four allergens tested were considered to be atopic. Twelve subjects with a positive reaction to the negative control were excluded. All subjects had a positive reaction to histamine. The analyses were limited to 5192 people with data on the length of gestation, birth weight, atopy and asthma.

Data on whether a person had ever been diagnosed by a doctor as having asthma, and data on parental history of allergies were obtained using a postal questionnaire at the age of 31. All perinatal data were collected during, or immediately after pregnancy. The number of completed weeks of gestation was calculated based on the first day of the last menstrual period and the day of delivery. Birth weight and length were divided into quintiles. Parental allergy was defined as being present if either of the parents had asthma, allergic rhinitis or atopic eczema.

The confounders in multivariate models were as follows: sex, maternal age in 5-year categories, maternal smoking in pregnancy defined as yes if mothers smoked at least one cigarette a day from the second month of pregnancy and otherwise no, current BMI as quintiles, and current vocational training in five categories. All these variables were significantly associated with either atopy or asthma, except for maternal smoking which was only weakly associated with asthma (9.3% vs 7.8%, $P = 0.15$). All multivariate models presented, including tests for interaction, are adjusted for these variables and for parental allergy, gestational age, birth weight, parity and paternal occupation.

Differences in the prevalence of atopy and asthma were examined by the Chi-square test. Logistic regression models were used to adjust for potential confounders. In the tests of interactions between gestational age and other factors, gestational age was analysed as a continuous variable with four categories.

Results

The overall prevalence of atopy and of a person ever having been diagnosed by a doctor as having asthma were 30.7% and 8.0%, respectively. The prevalence of atopy, but not asthma, increased with increasing length of gestation and decreasing parity among both men and women (Table 1). The children whose fathers were farmers had a lower prevalence of atopy. No associations were observed

Table 2 Adjusted odds ratios of atopy and asthma at age 31 for gestational age, weight at birth, parity, paternal occupation and parental allergy

	No.	Atopy OR* (95% CI)	Asthma OR* (95% CI)
Gestational age (weeks)			
≤ 35	229	1.00	1.00
36–38	1303	1.22 (0.87, 1.70)	0.90 (0.54, 1.49)
39–40	2435	1.42 (1.02, 1.98)	0.81 (0.49, 1.33)
≥ 41	952	1.65 (1.16, 2.34)	0.94 (0.55, 1.61)
Weight at birth (g)			
1, ≤ 3090	951	1.00	1.00
2, 3100–3390	1006	1.02 (0.84, 1.25)	1.14 (0.81, 1.60)
3, 3400–3620	974	0.99 (0.81, 1.22)	1.12 (0.79, 1.59)
4, 3630–3900	996	0.87 (0.70, 1.07)	1.02 (0.71, 1.46)
5, ≥ 3910	992	1.05 (0.85, 1.31)	1.07 (0.74, 1.55)
Parity			
0	1563	1.83 (1.42, 2.35)	0.93 (0.61, 1.41)
1	1170	1.65 (1.30, 2.09)	0.85 (0.57, 1.26)
2–3	1290	1.28 (1.03, 1.59)	0.98 (0.69, 1.38)
≥ 4	921	1.00	1.00
Paternal occupation			
Non-farmers	3899	1.00	1.00
Farmers	1020	0.50 (0.42, 0.60)	0.71 (0.53, 0.95)
Parental history of allergy			
No	3192	1.00	1.00
Yes	1727	1.49 (1.31, 1.69)	1.90 (1.54, 2.45)

OR = odds ratio; CI = confidence interval; *Adjusted for maternal age, sex, parental allergy, maternal smoking during pregnancy, current BMI and vocational training and other variables listed in the table.

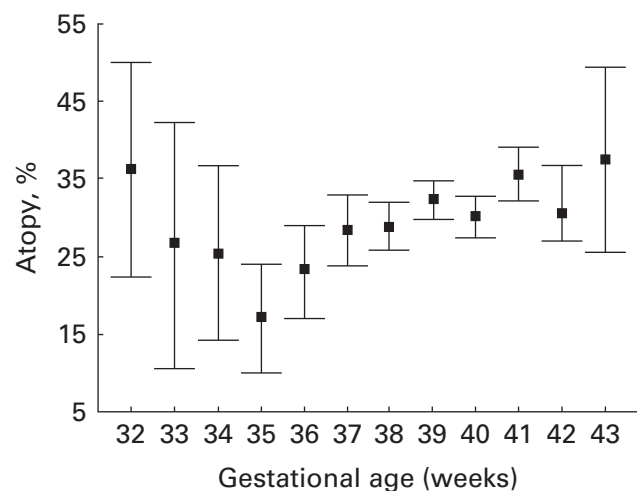


Fig. 1. Atopy (prevalence $\pm$ 95% confidence interval) at the age of 31 years.

with birth weight. However, the prevalence of asthma was 11.5% and 7.9% ($P = 0.100$) for those children with a birth weight below 2500 g ($n = 156$) and above, respectively. This association was independent of gestational age.

The observed associations were similar among men and women (Table 1) and therefore, both sexes were analysed in combination. Adjusting for other main risk factors had little effect on the associations (Table 2) except that in adjusted analyses, farmers' children also had a significantly lower prevalence of asthma. Parental allergy was associated with increased risk of both atopy and asthma.

There were no significant associations between birth length and atopy or asthma. The prevalences of atopy in quintiles of birth length, from the lowest quintile to the highest, were 30.7%, 28.7%, 29.4%, 32.4% and 32.7% (P for global tests = 0.21). The respective prevalences for asthma were 8.5%, 7.6%, 9.2%, 7.2% and 7.4%

($P = 0.40$). Further adjustment for birth length did not change the odds ratios in Table 2. Birth weight and birth length are also highly correlated ($r = 0.74$). Therefore, birth length was not included in the final models.

Gestational age tended to be positively associated with all allergens tested. The prevalence of positive skin test reactions among babies born before the 36th week compared with those born after the 40th week of gestation were as follows: cat 10.9% and 19.0% ($P = 0.00$), timothy 12.1% and 18.3% ($P = 0.02$), birch 13.0% and 16.4% ($P = 0.14$), and house dust mite 7.7% and 8.0% ($P = 0.16$).

The lowest risk of atopy tended to be among children born in the 35th week of gestation, after which the risk increased linearly with longer gestation (Fig. 1). There were only 136 babies born before the 35th week, i.e., 2.6% of the population. The risk of atopy tended to be higher

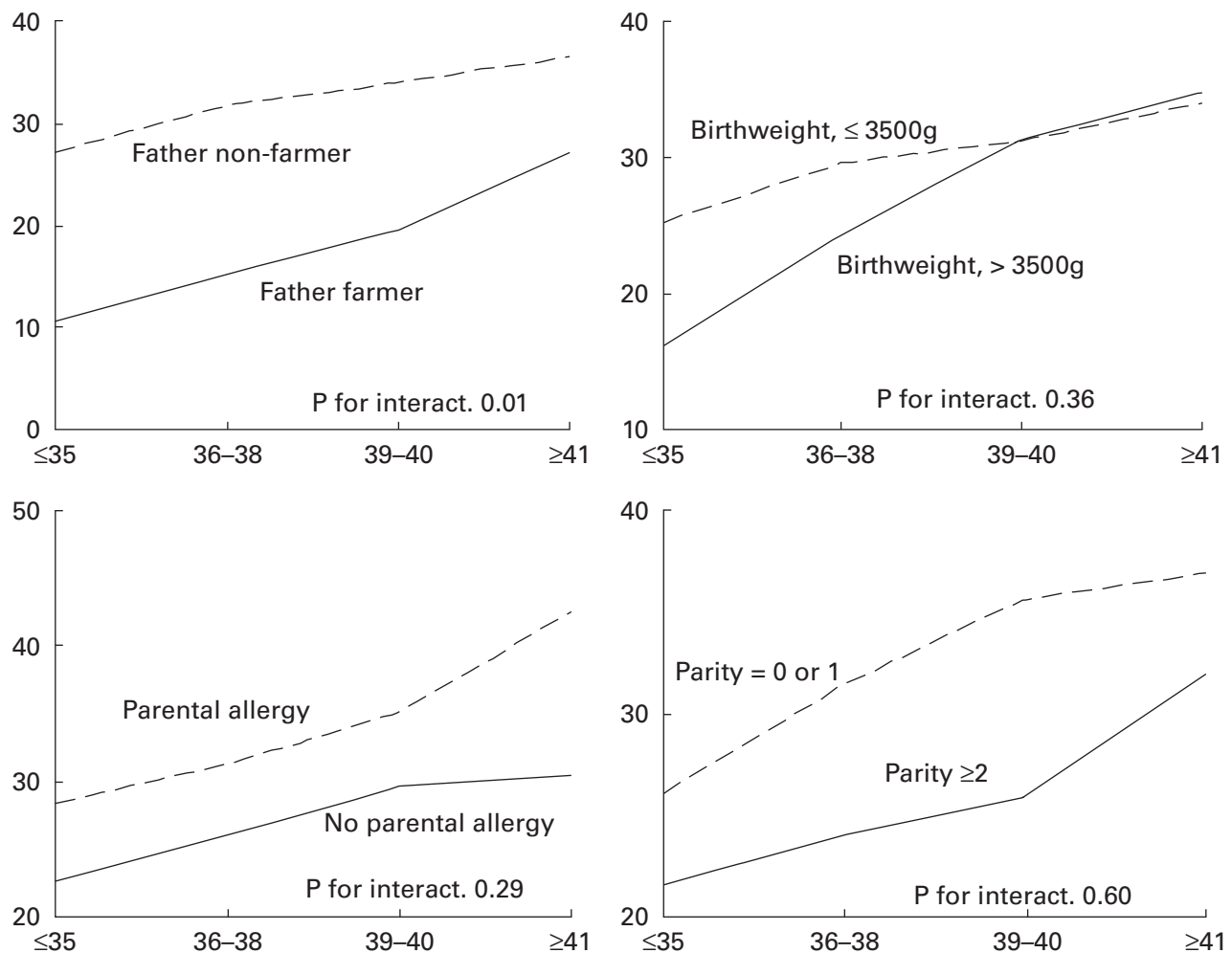


Fig. 2. Prevalence (%) of atopy at the age of 31 years (y-axis) by gestational age in weeks (x-axis), stratified by the father being a farmer or non-farmer, parental allergy, birth weight and parity.

Table 3 Cross-tabulations of gestational age, birth weight, parity, parental allergy and paternal occupation with combination of asthma and atopy at age 31

	No.	Asthma with atopy %	Asthma without atopy %	Atopy without asthma %	Neither %
Gestational age, week					
≤35	247	5.3	3.6	18.6	72.5
36–38	1376	4.7	3.3	23.3	68.7
39–40	2564	4.9	2.7	26.4	66.0
≥41	1005	6.1	2.7	28.5	62.8
<i>P</i> for trend		0.230	0.223	0.000	0.004
Weight at birth (g)					
1, ≤ 3090	1016	5.0	2.8	24.4	67.8
2, 3100–3390	1059	5.4	3.3	26.1	65.3
3, 3400–3620	1021	5.5	2.6	25.9	66.0
4, 3630–3900	1047	4.1	3.5	24.8	67.5
5, ≥3910	1049	5.4	2.4	26.8	65.4
<i>P</i> for trend		0.832	0.745	0.416	0.591
Parity					
0	1617	5.3	2.5	29.6	62.5
1	1227	5.2	2.4	28.5	63.8
2–3	1354	5.3	3.2	23.6	67.9
≥4	988	4.3	3.8	18.2	73.7
<i>P</i> for trend		0.326	0.039	0.000	0.000
Paternal occupation					
Non-farmers	4114	5.5	2.8	28.1	63.5
Farmers	1078	3.3	3.3	16.0	77.4
<i>P</i> for Chi-Square		0.003	0.367	0.000	0.000
Parental history of allergy					
No	3199	3.8	2.4	24.7	69.1
Yes	1728	7.7	3.6	27.8	60.8
<i>P</i> for Chi-Square		0.000	0.013	0.016	0.000

among these very premature babies, but the standard errors were large.

Being a farmer's child modified the association between gestational age and atopy (Fig. 2). When, among the farmers' children, the risk of atopy almost tripled from 11% to 28% with increasing length of gestation, among non-farmers' children it increased only by about one third from 27% to 36%. It should be noted that the evaluation of the statistical significance of the interaction was done on a relative scale using logistic regression, whereas Fig. 2 is drawn on a linear scale. A less pronounced and non-significant effect modification was observed for parental allergy, birth weight and parity. However, gestational age appears to be more important among babies born large.

When analysing separately those asthmatic subjects with and without atopy, and atopics without asthma, the strongest associations were observed for atopy alone (Table 3). Asthma with atopy tended to show associations

similar to atopy alone, but it reached statistical significance only for farming and parental allergy. All associations for asthma without atopy were non-significant but if anything, the associations were opposite to those observed for asthma with atopy.

Discussion

In a 31-year follow-up, a long length of gestation was associated with an increased risk of atopy, as measured with skin prick tests. The association tended to be stronger among children born to farmers. High parity and being a farmer's child was also associated with a decreased risk of atopy. In contrast, little association was observed for asthma. These associations were consistent among both sexes and independent of the main confounders.

The risk of atopy increased linearly with increasing length of pregnancy among babies born in the 35th week of

gestation or later. Babies born very prematurely, 2.6% of all babies, tended to have a higher risk of atopy. This parallels the findings from a small sample of men and women aged 50, among whom the prevalence of high total IgE levels was lowest in those born at the 37th and 38th week of gestation [8], and from a small sample of British children, among whom the prevalence of skin prick positivity, but not IgE levels, increased non-significantly with higher gestational age [11]. Other studies on atopy have mostly analysed prematurity and have not separately examined babies with high gestational age, which makes comparison with the present results difficult. Girls, but not boys, born prematurely and given ventilatory support had less skin prick test positivity at the age of 9–11 years than girls born full-term [19]. In contrast, gestational age below 38 weeks was positively associated with skin prick test positivity in a large population-based sample of children aged 6–8 years [20].

Consistent with the present findings on atopy, a very large study of military recruits showed a positive association of gestational age with hay fever [10], and a Danish study found a positive association with atopic dermatitis at the age of 7 [9]. Similar associations, although non-significant for atopic dermatitis, were also observed in the present study population (data not shown). On the other hand, several [19,21–23] but not all [24–26] studies have shown prematurity to be associated with the risk of respiratory symptoms and asthma in childhood. However, consistent with the present results, none of the studies on adults have shown an association between gestational age and asthma [10,27,28].

Taken together with the results from the present study, high gestational age appears to be associated with increased risk of atopy, and possibly also of allergic rhinitis and eczema, with the possible exception of very premature babies. In contrast, the association with asthma appears more complicated, possibly due to the several phenotypes of asthma [2]. On the one hand, prematurity predisposes to respiratory problems in early childhood, possibly unrelated to atopy, which increases the risk of asthma or at least the risk of being labelled as an asthmatic. On the other hand, high gestational age may be associated with atopic asthma, leading to little overall association between gestational age and asthma.

Gestational age is probably not causally related to an increased risk of atopy but rather, it is an indicator of the duration or the timing of the effect of other exposures. In a younger Finnish birth cohort study, gestational age modified the effect of infections during pregnancy on the risk of childhood allergic disorders [29,30]. There is some evidence suggesting intrauterine priming of a fetal immune response to specific allergens to which the mother is exposed during pregnancy [5]. Previous studies have not

examined the association between gestational age and specific allergens, but the results from the present study suggest a more general effect, not specific to allergens.

Based mostly on murine models, it has been suggested that during pregnancy, a mother's immune system is biased towards humoral Th2 type, rather than cell-mediated Th1 type immunity. The rationale would be to protect the fetus from Th1 cytokines, which are generally harmful to the maintenance of pregnancy [6]. As the humoral Th2 type immunity is associated with atopy, a longer exposure to the Th2 cytokines during pregnancy could modify the development of the immune system of the fetus towards the Th2 type, and increase the risk of atopy. First results from human pregnancies do not, however, support the idea of Th2 dominance during pregnancy, but underline the importance of a balanced immune response [31,32].

On the other hand, gestational age may indicate the timing of the first environmental exposures after birth. Babies born earlier with a less developed immune system may react differently to the first direct exposure to allergens, or to microbes and microbial antigens, compared with babies born later. It has been suggested that exposure to microbial antigens early in life directs the development of the immune system towards Th1 type responses [4,33]. This could also explain the observed interaction between gestational age and being a farmer's child on the occurrence of atopy.

The finding of a lower prevalence of atopy among farmers' children agrees with recent studies [15]. The farming environment may facilitate the development of tolerance through very high exposure to antigens, or alternatively it may enhance the Th1 type immune response through contact with microbial antigens such as LPS [33]. Some studies have suggested that atopy is less prevalent among lower socioeconomic groups, so the present association may be partly confounded by the low socioeconomic status of most farmers. There were no available data on farm sizes but data did exist on maternal education, adjusting for which did not change the association with farming. The analyses are also adjusted for current vocational training.

The observed associations with parity, possibly reflecting infection pressure in early childhood, are also in agreement with previous studies. However, other studies have mostly analysed the number of older siblings, which may in some families be different from parity. The inverse association with skin prick positivity has been reported repeatedly [13,14,34–36], whereas associations with asthma has been shown in some [35,37–40], but not all studies [41–44].

The major strengths of the present study are its prospective nature, size, representativeness, and the objective assessment of long-term risk of atopy. Self-report of

doctor-diagnosed asthma has been shown to be highly sensitive and specific for asthma in Finland [45]. The analyses were also repeated to include only asthmatics with symptoms in the past year, and the same associations were found with perinatal factors (data not shown). The observed prevalence of asthma was also close to that expected based on other Finnish studies [45,46]. Although gestational age was mostly determined based on the last menstrual period, this would probably only bias the observed associations towards the null.

The main weakness of the present study was the lack of data on head circumference, which has been positively associated with total IgE levels [8,11] but not skin prick test positivity [11]. However, according to previous studies, the associations of head circumference and gestational age are independent of each other [8]. Also, in the present study the effect of gestational age was independent of other perinatal factors. Data on IgE or cytokine profiles, and several postnatal risk factors such as infant feeding practices, which might be associated with atopy and prematurity, were also lacking.

In conclusion, high gestational age increased the risk of atopy at the age of 31 in a prospective birth cohort study of 5192 subjects. The association tended to be stronger among children born to farmers. The results underline the importance of pregnancy and very early childhood in the development of atopy, and suggest important interactions between timing of environmental exposures and the immune system. No association was observed for asthma, which may be due to the multifactorial origin of asthma.

Acknowledgements

The study was supported by the Academy of Finland, National Public Health Institute and University of Oulu.

References

- 1 Sear MR. Epidemiology of childhood asthma. *Lancet* 1997; 350:1015–20.
- 2 Kauffmann F, Dizier M-H, Pin I *et al.* Epidemiological study of the genetics and environment of asthma, bronchial hyperresponsiveness and atopy. *Am J Respir Crit Care Med* 1997; 156:S123–S129.
- 3 Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999; 54:268–72.
- 4 Björkstén B. Allergy priming early in life. *Lancet* 1999; 353:167–8.
- 5 Warner JA, Jones AC, Miles EA, Warner JO. Prenatal sensitization. *Pediatr Allergy Immunol* 1996; 7 (Suppl. 9): 98–101.
- 6 Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? *Immunol Today* 1993; 14:353–6.
- 7 Barker DJP. *Fetal and Infant Origins of Adult Disease*. London: BMJ Publishing Group, 1992.
- 8 Godfrey KM, Barker DJP, Osmond C. Disproportionate fetal growth and raised IgE concentration in adult life. *Clin Exp Allergy* 1994; 24:641–8.
- 9 Olesen AB, Ellingsen AR, Olesen H, Juul S, Thestrup-Pedersen K. Atopic dermatitis and birth factors: historical follow up by record linkage. *BMJ* 1999; 314:1003–8.
- 10 Brabäck L, Hedberg A. Perinatal risk factors for atopic disease in conscripts. *Clin Exp Allergy* 1998; 28:936–42.
- 11 Gregory A, Doull I, Pearce N *et al.* The relationship between anthropometric measurements at birth: asthma and atopy in childhood. *Clin Exp Allergy* 1999; 29:330–3.
- 12 Xu B, Järvelin M-R, Pekkanen J. Body build and atopy. *J Allergy Clin Immunol* 2000; 105:393–4.
- 13 von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Reitmeir P, Thiemann H. Skin test reactivity and number of siblings. *BMJ* 1994; 308:692–5.
- 14 Strachan D. Allergy and siblings: a riddle worth solving. *Clin Exp Allergy* 1997; 27:235–6.
- 15 Braun-Fahrlander C, Gassner M, Grize L *et al.* Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. *Clin Exp Allergy* 1999; 29:28–34.
- 16 Rantakallio P. Groups at risk in low birth weight children and perinatal mortality. *Acta Paediatr Scand* 1969; 193 (Suppl.): 1–71.
- 17 Rantakallio P. A follow-up study up to the age of 14 of children whose mothers smoked during pregnancy. *Acta Paediatr Scand* 1983; 72:747–53.
- 18 Rantakallio P, von Wendt L. A prospective comparative study of the etiology of cerebral palsy and epilepsy in a one-year birth cohort from Northern Finland. *Acta Paediatr Scand* 1986; 75:586–92.
- 19 von Mutius E, Nicolai T, Martinez FD. Prematurity as a risk factor for asthma in preadolescent children. *J Pediatr* 1993; 123:223–9.
- 20 Kuehr J, Frischer T, Karmaus W *et al.* Early childhood risk factors for sensitization at school age. *J Allergy Clin Immunol* 1992; 90:358–63.
- 21 Schwartz J, Gold D, Dockery DW, Weiss ST, Speizer FE. Predictors of asthma and persistent wheeze in a national sample of children in the United States. Association with social class, perinatal events, and race. *Am Rev Respir Dis* 1990; 142:555–62.
- 22 Frischer T, Kuehr J, Meinert R, Barth R, Hermann-Kunz E, Urbanek R. Relationship between low birth weight and respiratory symptoms in a cohort of primary school children. *Acta Paediatr* 1992; 81:1040–1.
- 23 Schaubel D, Math B, Johansen H *et al.* Neonatal characteristics as risk factors for preschool asthma. *J Asthma* 1996; 33:255–64.
- 24 Chan N, Elliman A, Bryan E, Silverman M. Respiratory symptoms in children of low birth weight. *Arch Dis Child* 1989; 64:1294–304.

- 25 Sears AR, Holdaway D, Flannery EM, Herbison G, Silva PA. Parental and neonatal risk factors for atopy, airway hyper-responsiveness, and asthma. *Arch Dis Child* 1996; 75:392–8.
- 26 Lewis SA, Britton JR. Consistent effects of high socioeconomic status and low birth order, and the modifying effect of maternal smoking on the risk of allergic disease during childhood. *Respir Med* 1998; 92:1237–44.
- 27 Fergusson DM, Crane J, Beasley R, Horwood LJ. Perinatal factors and atopic disease in childhood. *Clin Exp Allergy* 1997; 27:1394–401.
- 28 Kaplan BA, Mascie-Taylor CGN. Smoking and asthma among 23-year-olds. *J Asthma* 1997; 34:219–26.
- 29 Xu B, Järvelin M-R, Pekkanen J. Prenatal factors and occurrence of rhinitis and eczema among offspring. *Allergy* 1999; 54:829–36.
- 30 Xu B, Pekkanen J, Järvelin M-R, Olsen P, Hartikainen A-L. Maternal infections in pregnancy and the development of asthma among offspring. *Int J Epidemiol* 1999; 28:723–7.
- 31 Jones AC, Finlay-Jones JJ, Hart PH. Type-1 and type-2 cytokines in human late-gestation decidual tissue. *Biol Reprod* 1997; 57:303–11.
- 32 Brown MA, Chun A, Lohman IC *et al.* Human decidual cells produce both TH1-like and TH2-like cytokines in vitro. *Am J Res Crit Care Med* 1998; 157:A395.
- 33 Martinez FD. Maturation of immune responses at the beginning of asthma. *J Allergy Clin Immunol* 1999; 103 (3 Part 1):355–61.
- 34 Brabäck L, Breborowicz A, Julge K *et al.* Risk factors for respiratory symptoms and atopic sensitisation in the Baltic area. *Arch Dis Child* 1995; 72:487–93.
- 35 Jarvis D, Chinn S, Luczynska C, Burney P. The association of family size with atopy and atopic disease. *Clin Exp Allergy* 1997; 27:240–5.
- 36 Forastiere F, Agabiti N, Corbo G *et al.* Socioeconomic status, number of siblings, and respiratory infections in early life as determinants of atopy in children. *Epidemiology* 1997; 8: 566–70.
- 37 Bodner C, Godden D, Seaton A. Family size, childhood infections and atopic diseases. *Thorax* 1998; 53:28–32.
- 38 Stoddard JJ, Miller T. Impact of parental smoking on the prevalence of wheezing respiratory illness in children. *Am J Epidemiol* 1995; 141:96–102.
- 39 Rona RJ, Duran-Tauleria E, Chinn S. Family size, atopic disorders in parents, asthma in children, and ethnicity. *J Allergy Clin Immunol* 1997; 99:454–60.
- 40 Sunyer J, Anto JM, Kogevinas M *et al.* Risk factors for asthma in young adults. *Eur Resp J* 1997; 10:2490–4.
- 41 Horwood L, Fergusson D, Shannon F. Social and familial factors in the development of early childhood asthma. *Pediatrics* 1985; 75:859–68.
- 42 Lewis S, Butland B, Strachan D *et al.* Study of the aetiology of wheezing illness at age 16 in two national British birth cohorts. *Thorax* 1996; 51:670–6.
- 43 Räsänen M, Laitinen T, Kaprio J, Koskenvuo M, Laitinen L. Hay fever, asthma and number of older siblings – a twin study. *Clin Exp Allergy* 1997; 27:515–8.
- 44 Pekkanen J, Remes S, Kajosaari M, Husman T, Soininen L. Infections in early childhood and risk of atopic disease. *Acta Paediatr* 1999; 88:710–4.
- 45 Remes ST, Korppi M, Pekkanen J. Prevalence of asthma at school age: a clinical population-based study in eastern Finland. *Acta Paediatr* 1996; 85:59–63.
- 46 Timonen KL, Pekkanen J, Korppi M, Vahteriston M, Salonen RO. Prevalence and characteristics of children with chronic respiratory symptoms in eastern Finland. *Eur Respir J* 1995; 8:1155–60.