

## The relation of markers of fetal growth with asthma, allergies and serum immunoglobulin E levels in children at age 5–7 years

G. Bolte\*, M. Schmidt†, W. Maziak‡§, U. Keil‡, P. Nasca†, E. von Mutius¶ and S. K. Weiland\*

\*Department of Epidemiology, University of Ulm, Ulm, Germany, †Department of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA, USA, ‡Institute of Epidemiology and Social Medicine, University of Muenster, Muenster, Germany, §Syrian Center for Tobacco Studies, Aleppo, Syria and ¶University Children's Hospital Munich, Munich, Germany

### Summary

**Background** It has been suggested that fetal growth and maturation have an impact on the development of allergic diseases later in life.

**Objective** To examine the association between measures of fetal growth and allergic disease in children at age 5–7 years.

**Methods** As part of the German International Study of Asthma and Allergies in Childhood phase II surveys, a random sample of school beginners ( $n = 1138$ ) was examined in 1995. Data on anthropometric measures at birth and gestational age were obtained from maternal copies of birth records. Data on symptoms and doctor-diagnosed asthma, atopic dermatitis and hayfever were gathered by parental questionnaires. Atopic sensitization was assessed by serum IgE and skin prick tests to common aeroallergens. Children (741) had complete data for the explanatory variables of interest and were thus eligible for this analysis. Confounder-adjusted prevalence odds ratios (PORs) and means ratios with 95% confidence intervals (CI) were calculated using multiple logistic and linear regression.

**Results** Birth weight and gestational age were positively associated with atopic sensitization ( $P_{\text{trend}} = 0.025$  and  $0.035$ , respectively). Children with a low birth weight relative to head circumference had a decreased risk of sensitization (POR 0.44, 95% CI 0.21–0.91;  $P_{\text{trend}} = 0.020$ ). Moreover, total serum IgE increased with increasing birth weight ( $P_{\text{trend}} = 0.042$ ). No consistent relationship was observed between markers of fetal growth and wheezing, doctor-diagnosed asthma, atopic dermatitis and hayfever.

**Conclusion** These data suggest that fetal growth and maturity are associated with atopic sensitization and total serum IgE levels in childhood.

**Keywords** allergy, asthma, atopy, cross-sectional study, IgE

Submitted 25 June 2003; revised 30 September 2003; accepted 3 November 2003

### Introduction

There is increasing interest in the pre-natal origin of health and disease suggested initially by Barker [1]. According to this hypothesis, fetal growth and maturation characteristics (programming) may influence the likelihood of several diseases later in life. The implication of this new line of thinking for the study of allergic disease became immediately apparent, as preliminary evidence was already pointing towards an active involvement of the pre-natal environment in the development of allergic states among children [2]. Because anthropometric parameters at birth reflect fetal growth and to some extent intrauterine and nutritional status, several studies have examined the relationship between these measures and atopic disease. Larger head circumference at birth, for example, has been found to be associated with an increased risk of raised

serum IgE levels in children and adults [3, 4] and asthma in adolescence [5]. In addition, an increased risk of atopic dermatitis was found among children with increased gestational age and birth weight [6]. Most recently, data from Karmaus et al. [7] on cord blood IgE levels suggest that the protective effect of sibship size on allergy in children, which is one of the most consistent observations of the last decade, may have its origin in the differential intrauterine programming of Th1–Th2 responses.

Several biologic mechanisms have been proposed to explain the relationship between perinatal measures and allergic disease. Godfrey et al. [4] suggested that larger head circumference could be a marker for fetal undernutrition in late gestation, which might adversely affect thymic maturation and program the immune system towards the allergic, Th2 dominated, phenotype. This theory of a negative association, however, was not supported by Benn et al. [8], who observed a positive association between head circumference and thymus size. In addition, thymus size was not related to allergic disease at age 5 years in their study.

Correspondence: Dr Gabriele Bolte, Department of Epidemiology, University of Ulm, Helmholtzstr. 22, 89081 Ulm, Germany.  
E-mail: gabriele.bolte@medizin.uni-ulm.de

Others have interpreted larger head circumference, increased gestational age and birth weight to be markers for enhanced fetal growth, which may be due to factors also affecting the programming of the developing respiratory and immune system towards allergic responses [3, 9]. This interpretation would partially explain the increasing prevalence of atopic diseases in recent decades and the higher rates observed in 'westernized' countries, which have occurred concurrently with improvements in fetal and maternal health and nutrition [9].

Previous research on this topic has been limited primarily to adults and adolescents. If processes occurring *in utero* are able to promote immune system development towards allergic phenotype, we should be able to detect such changes early in life. Therefore, the aim of this study was to examine the association between measures of fetal growth and allergic disease in children age 5–7 years living in the city of Munich, Germany.

## Materials and methods

### Study population and study design

Data for this study were collected during the German International Study of Asthma and Allergies in Childhood (ISAAC) phase II cross-sectional survey conducted from August 1995 to December 1996 in Munich, a city with approximately 1.3 million residents in the south of Germany [10]. Community-wide random samples of children were selected using schools as sampling units. Eligible children for this analysis were school beginners aged 5–7 years. Participation rates in that survey were 78.6% ( $n = 2890$ ) for the questionnaire and 60.7% ( $n = 1138$ ) of a random subsample of 1875 children who were invited to participate in the examination and to bring the child's record medical book held by the mother, which contains data of preventive medical checkups and of anthropometric measures of the child at regular points in time in a nationally standardized format. For this analysis, the study population was restricted to those children with questionnaire information, data from the physical examination and complete information on the anthropometric birth measures of interest ( $n = 748$ ). Seven children had implausible values ( $> 5$  standard deviations from mean) for at least one perinatal characteristic and were thus excluded from this analysis, resulting in a final sample of 741 children.

### Data collection

**Parental questionnaire and birth records** The self-administered parental questionnaire included the ISAAC core questions on symptoms of asthma, allergic rhinitis and atopic dermatitis, which have been described elsewhere [10, 11]. Information concerning demographic characteristics, family history of allergic disease, family living conditions and the child's exposure history to a wide variety of potential risk factors was also gathered. Parental copies of birth records were used to obtain information on each child's weight, length and head circumference at birth, along with an estimate of gestational age.

**Skin prick tests (SPTs)** Sensitivity to six common aeroallergens (*Dermatophagoides pteronyssinus*, *D. farinae*, cat dander, tree pollen, mixed grass pollen, and *Alternaria tenuis*) was assessed

using standardized allergen extracts and control solutions provided by ALK (Hørsholm, Denmark). Allergens were applied on the volar side of the left forearm according to the manufacturer's recommendations. Positive (histamine 10 mg/mL) and negative (diluent) controls were applied as well, and a weal diameter  $\geq 3$  mm after subtraction of the negative control was defined as a positive skin reaction. The participation rate for the SPTs was 58.9% in the survey [10]. Among those 741 children eligible for this analysis, testing was completed on 723 children.

**Blood sampling and laboratory analysis** The children provided blood samples following parental approval with a participation rate of 44.2% in the whole study [10]. All samples were analysed in one laboratory (Free University of Berlin, Germany) for specific serum IgE antibodies (Sx1 CAP; Pharmacia, Lund, Sweden) to the following aeroallergens: *D. pteronyssinus*, birch pollen, mixed grass pollen, mugwort pollen, cat dander, dog dander, and *Cladosporium herbarum*. Total serum IgE was measured using the Insulite System (DPC Biemann, Bad Nauheim, Germany). Data on specific IgE and total IgE were available for 546 and 545 children, respectively, out of the 741 children defined as the study population for this analysis.

### Outcome variables

**Asthma** Determination of asthmatic status was based on parental response to the question 'Did a doctor ever diagnose any of the following diseases in your child: (a) asthma, (b) asthmatic, spastic or obstructive bronchitis, (c) bronchitis?'. Parents could choose one of the following responses: (a) never, (b) once or (c) more than once. Children were defined as having 'diagnosed asthma' if a parent reported that a doctor had diagnosed 'asthma' in the child at least once or 'asthmatic, spastic, or obstructive bronchitis' more often than once [10]. Children were classified as having 'current wheeze' when a parent reported at least one episode of wheezing in the past 12 months. Finally, those children with reported current wheeze and diagnosed asthma were classified as having 'current asthma'.

**Atopic sensitization** *Positive SPT.* A child was considered to be sensitized if the skin reaction was positive for at least one of the six aeroallergens used.

*Allergen-specific IgE.* A specific serum IgE level  $\geq 0.7$  kU/L for at least one allergen was considered to indicate atopic sensitization.

### Explanatory variables

The primary explanatory variables of interest included standard measures of fetal growth along with a ratio measure intended to reflect disproportionate growth. Gestational age, birth weight, birth length and head circumference measures were obtained using maternal copies of birth records. The ratio of head circumference to birth weight was used as marker of disproportionate growth. For the description in the tables, the ratio was multiplied by 100.

### Confounding variables

Based on previous research findings, the following variables were considered as potential confounders: gender, nationality, socio-economic status, maternal smoking during pregnancy, maternal and paternal history of asthma, hayfever or atopic

dermatitis, breastfeeding history, maternal age, number of older and younger siblings, and the presence of cats/dogs in the home. Variables related to both an explanatory and an outcome variable at the  $P < 0.20$  level of significance were further assessed for independent confounding effects using multi-variate regression analysis.

### Statistical analyses

Total serum IgE concentrations were log-transformed to approach normal distribution. Mean concentrations were expressed as geometric means (GMs) with 95% confidence intervals (CI). Associations between categorical variables were assessed using the  $\chi^2$ -test of independence. Linear trends of proportions were assessed using the Mantel-Haenszel  $\chi^2$ -statistic. Linear trends of total IgE concentrations were analysed with the Jonckheere-Terpstra test for trend.

Multiple logistic regression analysis was conducted to calculate confounder-adjusted prevalence odds ratios (PORs) with 95% CI for the association between allergic disease and various birth characteristics. Multiple linear regression was applied for total serum IgE as the outcome variable. Association between total IgE levels and explanatory variables were expressed as means ratios (MRs) with 95% CI. The MR is the ratio of the GM in the respective category vs. the reference category. The MRs were calculated from the co-efficients  $\beta$  of the linear regression models as  $\exp(\beta)$ . For analysing trends in multi-variate regression models, quartiles or quintiles of the independent variables were included as an ordinal variable into the models.

The statistical significance of interaction terms between explanatory variables and maternal asthma/atopy, gender and nationality, respectively, was assessed in regression models. Effect estimates (POR, MR) were adjusted in the final models for gender, socio-economic status, nationality and maternal smoking. In addition, regression models of asthma risk included maternal and paternal history of asthma as confounder while maternal and paternal history of atopy (asthma, hayfever or atopic dermatitis) was included in models with atopic sensitization or total serum IgE as the outcome variable of interest. Due to the strong association between gestational age and anthropometric measures at birth, models are presented with and without the inclusion of gestational age.

All analyses were conducted using the SAS software package version 8.2 (SAS Institute Inc., Cary, NC, USA).

## Results

Characteristics of the study subjects are given in Table 1. Nine percent of children had a diagnosis of asthma and 8.3% had current wheezing. The prevalence of atopic sensitization was higher, with 9.7% of the children having at least one positive SPT and 19.8% having elevated levels of specific IgE. There was a considerable degree of overlap among the various outcomes. Table 2 summarizes the prevalence of wheeze, asthma and other allergic parameters and the serum levels of total IgE across categories of several perinatal measures.

**Table 1.** Demographic and health characteristics of the study subjects

| Characteristics                                 | <i>n</i>           | %           |
|-------------------------------------------------|--------------------|-------------|
| <i>Parental questionnaire (n = 741)</i>         |                    |             |
| Male gender                                     | 384                | 51.8        |
| Age                                             |                    |             |
| 5 years                                         | 90                 | 12.2        |
| 6 years                                         | 631                | 85.2        |
| 7 years                                         | 20                 | 2.7         |
| High socioeconomic status                       | 334                | 47.2        |
| German nationality                              | 599                | 81.0        |
| History of asthma                               |                    |             |
| Mother                                          | 41                 | 5.8         |
| Father                                          | 34                 | 4.9         |
| History of atopy*                               |                    |             |
| Mother                                          | 207                | 29.0        |
| Father                                          | 153                | 21.6        |
| History of breastfeeding                        | 580                | 83.3        |
| Diagnosed asthma                                | 64                 | 9.0         |
| Current wheezing                                | 60                 | 8.3         |
| Current asthma†                                 | 24                 | 3.3         |
| Diagnosed atopic dermatitis                     | 93                 | 13.1        |
| Diagnosed hayfever                              | 34                 | 4.7         |
| <i>Laboratory measures</i>                      |                    |             |
| Positive skin prick test (n = 723)              | 70                 | 9.7         |
| Allergen-specific IgE $\geq 0.7$ kU/L (n = 546) | 108                | 19.8        |
|                                                 | Geometric mean     | 95% CI      |
| Serum total IgE (kU/L) (n = 545)                | 45.50              | 40.74–50.82 |
| Birth record data (n = 741)                     | Mean $\pm$ SD      | Range       |
| Birth weight (g)                                | 3336.6 $\pm$ 536.7 | 660–5500    |
| Gestational age (weeks)                         | 39.5 $\pm$ 1.9     | 25–46       |
| Head circumference (cm)                         | 34.7 $\pm$ 2.0     | 22–52       |
| Birth length (cm)                               | 51.1 $\pm$ 2.9     | 30–59       |
| Mother's age                                    | 28.3 $\pm$ 5.3     | 16–42       |
| Mother's height (cm)                            | 165.7 $\pm$ 6.5    | 150–185     |
| Parity of mother                                | 1.2 $\pm$ 0.9      | 0–5         |

Percentage values were calculated without missing data.

\*Ever asthma, hayfever or atopic dermatitis. †Diagnosed asthma and current wheezing.

### Asthma

Gestational age was inversely associated with diagnosed asthma, but not with asthma symptoms during the past 12 months (Table 2). Conversely, current wheezing but not diagnosed asthma was positively associated with the ratio of head circumference to birth weight. After adjustment for potential confounders, no consistent statistically significant relationship was observed between the measures of fetal growth and diagnosed asthma or current wheezing (Table 3). Across the categories of birth weight, birth length and the ratio of head circumference to birth weight there was a U-shaped relationship with the prevalence of diagnosed asthma, although the effect estimates did not achieve statistical significance. An inverse U-shaped relationship was observed for birth weight and birth length and the prevalence of current wheezing, also not reaching statistical significance.

Infants born before the 37th week had a twofold higher adjusted POR for diagnosed asthma compared with the reference group. Among children with diagnosed asthma, 18

**Table 2.** Asthma, atopic dermatitis, hayfever, atopic sensitization and total IgE in 5–7-year-old children by perinatal characteristics

|                              | Current wheezing<br>( <i>n</i> = 720) |          | Diagnosed asthma<br>( <i>n</i> = 715) |          | Current asthma<br>( <i>n</i> = 734) |          | Diagnosed atopic dermatitis<br>( <i>n</i> = 710) |          | Diagnosed hayfever<br>( <i>n</i> = 719) |          | Positive skin prick test<br>( <i>n</i> = 723) |          | Allergen-specific<br>IgE ≥ 0.7 kU/L<br>( <i>n</i> = 546) |          | Serum total IgE (kU/L)<br>( <i>n</i> = 545) |             |
|------------------------------|---------------------------------------|----------|---------------------------------------|----------|-------------------------------------|----------|--------------------------------------------------|----------|-----------------------------------------|----------|-----------------------------------------------|----------|----------------------------------------------------------|----------|---------------------------------------------|-------------|
|                              | %                                     | <i>n</i> | %                                     | <i>n</i> | %                                   | <i>n</i> | %                                                | <i>n</i> | %                                       | <i>n</i> | %                                             | <i>n</i> | %                                                        | <i>n</i> | GM†                                         | 95% CI      |
| Birth weight (g)             |                                       |          |                                       |          |                                     |          |                                                  |          |                                         |          |                                               |          |                                                          |          |                                             |             |
| <2500                        | 7.3                                   | 3        | 9.8                                   | 4        | 2.4                                 | 1        | 10.3                                             | 4        | 5.3                                     | 2        | 7.3                                           | 3        | 7.4                                                      | 2        | 36.90                                       | 24.38–55.84 |
| 2500–2999                    | 9.3                                   | 11       | 15.0                                  | 18       | 4.9                                 | 6        | 12.9                                             | 15       | 5.8                                     | 7        | 5.8                                           | 7        | 16.9                                                     | 15       | 44.96                                       | 34.93–57.86 |
| 3000–3499                    | 10.0                                  | 29       | 7.0                                   | 20       | 3.7                                 | 11       | 12.9                                             | 37       | 4.8                                     | 14       | 9.7                                           | 28       | 18.1                                                     | 41       | 39.47                                       | 33.12–47.04 |
| 3500–3999                    | 6.4                                   | 13       | 7.9                                   | 16       | 1.9                                 | 4        | 13.8                                             | 28       | 4.4                                     | 9        | 12.0                                          | 25       | 22.4                                                     | 34       | 57.61                                       | 46.83–70.86 |
| ≥4000                        | 6.1                                   | 4        | 9.2                                   | 6        | 3.0                                 | 2        | 13.6                                             | 9        | 3.0                                     | 2        | 10.9                                          | 7        | 30.8                                                     | 16       | 48.08                                       | 32.45–71.23 |
| χ <sup>2</sup> -linear trend | <i>P</i> = 0.325                      |          | <i>P</i> = 0.210                      |          | <i>P</i> = 0.350                    |          | <i>P</i> = 0.615                                 |          | <i>P</i> = 0.411                        |          | <i>P</i> = 0.099                              |          | <i>P</i> = 0.007                                         |          | <i>P</i> = 0.113‡                           |             |
| Gestational age (weeks)      |                                       |          |                                       |          |                                     |          |                                                  |          |                                         |          |                                               |          |                                                          |          |                                             |             |
| <37                          | 14.6                                  | 6        | 16.7                                  | 7        | 9.5                                 | 4        | 7.3                                              | 3        | 2.6                                     | 1        | 2.4                                           | 1        | 9.1                                                      | 3        | 39.56                                       | 27.29–57.36 |
| 37, 38                       | 5.8                                   | 5        | 13.3                                  | 11       | 3.5                                 | 3        | 12.4                                             | 10       | 4.7                                     | 4        | 4.7                                           | 4        | 14.9                                                     | 10       | 43.40                                       | 31.29–60.20 |
| 39, 40                       | 8.9                                   | 38       | 8.0                                   | 34       | 3.0                                 | 13       | 12.9                                             | 54       | 6.1                                     | 26       | 10.7                                          | 46       | 20.6                                                     | 67       | 48.80                                       | 42.40–56.17 |
| ≥41                          | 6.6                                   | 11       | 7.2                                   | 12       | 2.3                                 | 4        | 15.5                                             | 26       | 1.8                                     | 3        | 11.3                                          | 19       | 23.1                                                     | 28       | 40.19                                       | 31.25–51.69 |
| χ <sup>2</sup> -linear trend | <i>P</i> = 0.295                      |          | <i>P</i> = 0.027                      |          | <i>P</i> = 0.055                    |          | <i>P</i> = 0.173                                 |          | <i>P</i> = 0.439                        |          | <i>P</i> = 0.033                              |          | <i>P</i> = 0.044                                         |          | <i>P</i> = 0.371‡                           |             |
| Head circumference (cm)      |                                       |          |                                       |          |                                     |          |                                                  |          |                                         |          |                                               |          |                                                          |          |                                             |             |
| <33                          | 7.0                                   | 4        | 17.2                                  | 10       | 1.7                                 | 1        | 16.4                                             | 9        | 9.1                                     | 5        | 8.8                                           | 5        | 11.1                                                     | 5        | 48.01                                       | 33.71–68.38 |
| 33, 34                       | 9.0                                   | 24       | 9.1                                   | 24       | 3.3                                 | 9        | 14.1                                             | 37       | 3.0                                     | 8        | 9.0                                           | 24       | 19.9                                                     | 39       | 45.89                                       | 38.07–55.31 |
| 35, 36                       | 7.3                                   | 23       | 7.6                                   | 24       | 3.4                                 | 11       | 12.8                                             | 40       | 4.4                                     | 14       | 10.2                                          | 33       | 19.9                                                     | 49       | 42.77                                       | 36.51–50.10 |
| ≥37                          | 11.3                                  | 9        | 7.6                                   | 6        | 3.7                                 | 3        | 8.9                                              | 7        | 8.9                                     | 7        | 10.8                                          | 8        | 25.4                                                     | 15       | 54.99                                       | 37.08–81.56 |
| χ <sup>2</sup> -linear trend | <i>P</i> = 0.733                      |          | <i>P</i> = 0.068                      |          | <i>P</i> = 0.592                    |          | <i>P</i> = 0.180                                 |          | <i>P</i> = 0.500                        |          | <i>P</i> = 0.538                              |          | <i>P</i> = 0.139                                         |          | <i>P</i> = 0.960‡                           |             |
| Birth length (cm)            |                                       |          |                                       |          |                                     |          |                                                  |          |                                         |          |                                               |          |                                                          |          |                                             |             |
| <47                          | 3.3                                   | 1        | 13.3                                  | 4        | 3.3                                 | 1        | 17.2                                             | 5        | 3.6                                     | 1        | 6.7                                           | 2        | 13.6                                                     | 3        | 53.15                                       | 30.02–94.10 |
| 47–49                        | 10.4                                  | 14       | 12.7                                  | 17       | 5.1                                 | 7        | 10.0                                             | 13       | 6.0                                     | 8        | 6.9                                           | 9        | 16.8                                                     | 17       | 46.26                                       | 36.28–58.98 |
| 50–52                        | 9.3                                   | 32       | 7.3                                   | 25       | 2.5                                 | 9        | 13.1                                             | 45       | 4.6                                     | 16       | 8.8                                           | 31       | 18.6                                                     | 50       | 43.35                                       | 37.07–50.70 |
| 53–55                        | 6.6                                   | 12       | 7.8                                   | 14       | 3.3                                 | 6        | 13.5                                             | 24       | 4.4                                     | 8        | 12.6                                          | 23       | 22.1                                                     | 29       | 49.56                                       | 39.30–62.49 |
| ≥56                          | 3.5                                   | 1        | 13.3                                  | 4        | 3.3                                 | 1        | 20.7                                             | 6        | 3.5                                     | 1        | 17.9                                          | 5        | 39.1                                                     | 9        | 39.53                                       | 21.39–73.07 |
| χ <sup>2</sup> -linear trend | <i>P</i> = 0.382                      |          | <i>P</i> = 0.294                      |          | <i>P</i> = 0.551                    |          | <i>P</i> = 0.391                                 |          | <i>P</i> = 0.632                        |          | <i>P</i> = 0.026                              |          | <i>P</i> = 0.029                                         |          | <i>P</i> = 0.829‡                           |             |
| Head circ./birth wt. ratio   |                                       |          |                                       |          |                                     |          |                                                  |          |                                         |          |                                               |          |                                                          |          |                                             |             |
| *1st quartile (<0.96)        | 6.3                                   | 11       | 9.8                                   | 17       | 2.8                                 | 5        | 14.0                                             | 25       | 2.8                                     | 5        | 14.0                                          | 25       | 25.0                                                     | 33       | 50.07                                       | 39.96–62.75 |
| 2nd quartile (0.96–1.03)     | 7.1                                   | 13       | 5.5                                   | 10       | 2.7                                 | 5        | 12.9                                             | 23       | 4.4                                     | 8        | 10.2                                          | 19       | 21.8                                                     | 31       | 50.05                                       | 39.77–62.99 |
| 3rd quartile (1.04–1.13)     | 6.7                                   | 12       | 7.3                                   | 13       | 1.6                                 | 3        | 14.8                                             | 26       | 5.6                                     | 10       | 7.9                                           | 14       | 18.0                                                     | 25       | 43.18                                       | 34.72–53.70 |
| 4th quartile (>1.13)         | 13.1                                  | 24       | 13.2                                  | 24       | 6.0                                 | 11       | 10.8                                             | 19       | 6.2                                     | 11       | 6.7                                           | 12       | 14.3                                                     | 19       | 39.44                                       | 32.03–48.55 |
| χ <sup>2</sup> -linear trend | <i>P</i> = 0.028                      |          | <i>P</i> = 0.198                      |          | <i>P</i> = 0.147                    |          | <i>P</i> = 0.504                                 |          | <i>P</i> = 0.112                        |          | <i>P</i> = 0.014                              |          | <i>P</i> = 0.020                                         |          | <i>P</i> = 0.202‡                           |             |

\*Low ratio values represent children with high birth weight relative to head circumference. †Geometric mean. ‡Jonckheere–Terpstra test for trend.



had evidence of atopy (positive SPT or elevated specific IgE) while 44 did not. When analysed separately, the prevalence of non-atopic asthma was found to increase with decreasing gestational age ( $P_{\text{trend}} = 0.032$ ) with a threefold higher adjusted POR for children born <37 weeks (POR 3.20, 95% CI 1.08–9.49). The small number of children with both diagnosed asthma and atopic sensitization precluded a meaningful analysis of the relation between atopic asthma and perinatal measures.

### *Atopic dermatitis and hayfever*

Life-time prevalences of diagnosed atopic dermatitis and hayfever were not associated with any of the standard measures of fetal growth used in this study (Table 2).

### *Atopic sensitization and total IgE*

Birth weight, birth length and gestational age were positively associated with atopic sensitization in terms of positive SPT and elevated allergen-specific IgE (Table 2). The ratio of head circumference to birth weight was inversely associated with atopic sensitization, meaning that children with a high birth weight relative to head circumference were more often sensitized. After adjusting for potential confounders, the prevalence of atopic sensitization (specific IgE  $\geq 0.7$  kU/L) continued to be associated with birth weight, gestational age and ratio of head circumference to birth weight (Table 4). For example, children in the highest birth weight category ( $\geq 4000$  g) were at twice the risk for atopic sensitization compared with children in the middle birth weight category (3000–3499 g). The same relationship was observed for prevalence of positive SPT and gestational age ( $P_{\text{trend}} = 0.018$ ) and ratio of head circumference to birth weight ( $P_{\text{trend}} = 0.089$ ; data not shown).

GM concentrations of total serum IgE were higher in those children with a birth weight  $\geq 3500$  g and with a low ratio of head circumference to birth weight (reflecting a high birth weight relative to head circumference, Table 2). The association between birth weight and total IgE levels persisted following adjustment for confounding variables and gestational age (Table 4). However, a statistically significant interaction was observed for nationality and the ratio of head circumference to birth weight. Therefore, the data for the association with total IgE levels are given in Table 4 stratified by nationality. Those children with German nationality and a low birth weight in relation to head circumference had 0.6 times lower total IgE GM levels compared with the children with high birth weight relative to head circumference. In contrast, children with other than German nationality and a low birth weight in relation to head circumference had 2.5 times higher total IgE levels. GM concentrations of total IgE did not differ by nationality (German children: GM 46.0 kU/L, 95% CI 40.6–52.2; children with other nationality: GM 43.6, 95% CI 34.7–54.6).

Similar statistically significant linear trends for birth weight, the ratio of head circumference to birth weight and elevated total IgE were observed when total serum IgE was categorized with the cut-point of 80 kU/L and analysed using multiple logistic regression (data not shown).

## **Discussion**

The data show that some measures of fetal growth and development are associated with atopic sensitization in early childhood. Increased rates of elevated specific serum IgE levels and positive SPTs were consistently observed with increases in both birth weight and gestational age. In addition, the ratio of head circumference to birth weight was found to be associated with atopic sensitization. Lower ratio values, which reflect heavier birth weight for a given head circumference and were thought to be a marker of relative overnutrition *in utero*, were associated with higher rates of atopic sensitization. In contrast, children with the highest ratios, which potentially indicate relative undernutrition *in utero*, had the highest prevalence of current wheezing. The odds of diagnosed asthma, atopic dermatitis and hayfever, however, were not related to any of the measures of fetal growth.

Several previous studies have reported an association between anthropometrics measures and markers of atopy. In a sample of adults in the United Kingdom, Godfrey et al. [4] observed a positive association between increasing head circumference at birth with elevated levels of total serum IgE using 80 IU/mL as cut-point. Among children aged 11–13 years in New Zealand, Leadbitter et al. [3] observed a positive association between large head circumference and high serum total IgE ( $> 150$  IU/mL) and birth length and asthma in past 2 years. In contrast, low birth weight was associated with atopic sensitization assessed by SPT in 2-year-old infants [12]. Data of a Finnish birth cohort revealed a U-shaped association of the Ponderal index at birth and atopy in terms of a positive SPT at age 31 years [13].

Thus, our results add to the body of evidence suggesting that increases in parameters of fetal growth are associated with increases in atopy. Identifying the reasons for these observed associations is complicated by the strong inter-relationship between various birth measures, and by the difficulty in separating maternal factors from environmental influences during pregnancy. The association between gestational age and atopic sensitization among children may not only be due to fetal growth but also to the maturation of different fetal organs and systems. Pekannen et al. [14] have shown a linear trend for the association between gestational age and atopy in adults, too.

In accordance with our data on specific IgE, total serum IgE levels also significantly increased with higher birth weight. However, the association between a low birth weight relative to head circumference and mean IgE levels varied markedly between children of German nationality and children of other nationalities. While the mechanisms underlying these differences are yet to be elucidated, environmental and life-style factors may play a role [15].

While atopic sensitization in our study was positively associated with birth weight and gestational age, the prevalence of diagnosed asthma showed an inverse trend for gestational age and a U-shaped trend for birth weight. This apparent inconsistency may be a result of combining several asthmatic syndromes under one definition of asthma.

In particular, the life-time prevalence of diagnosed asthma used in our study is likely to have included two major groups of asthmatics: 'early transient wheezers' and 'persistent wheezers'. These groups have been shown to have distinct risk factors with persistent wheeze being associated with

**Table 4.** Crude and adjusted odds ratios (specific IgE) and means ratios (total IgE) for the association of perinatal characteristics and allergen-specific IgE  $\geq 0.7$  kU/L and serum total IgE in 5–7-year-old children

|                                                             | Allergen-specific IgE $\geq 0.7$ kU/L |             |                  |             |                        |             |              |                 |
|-------------------------------------------------------------|---------------------------------------|-------------|------------------|-------------|------------------------|-------------|--------------|-----------------|
|                                                             | Crude                                 |             |                  |             | Serum total IgE (kU/L) |             |              |                 |
|                                                             | POR*                                  | 95% CI      | Adjusted†<br>POR | 95% CI      | Adjusted‡<br>POR       | 95% CI      | Crude<br>MRS | Adjusted§<br>MR |
| <b>Birth weight (g)</b>                                     |                                       |             |                  |             |                        |             |              |                 |
| <500                                                        | 0.48                                  | (0.11–2.18) | 0.46             | (0.10–2.12) | 0.83                   | (0.15–4.62) | 1.02         | (0.56–1.85)     |
| 2500–2999                                                   | 0.83                                  | (0.38–1.81) | 0.90             | (0.41–1.99) | 1.00                   | (0.45–2.24) | 1.12         | (0.77–1.64)     |
| 3000–3499                                                   | 1.00                                  |             | 1.00             |             | 1.00                   |             | 1.00         |                 |
| 3500–3999                                                   | 1.46                                  | (0.83–2.59) | 1.50             | (0.83–2.70) | 1.45                   | (0.80–2.61) | 1.65         | (1.21–2.24)     |
| $\geq 4000$                                                 | 1.77                                  | (0.80–3.92) | 1.80             | (0.79–4.10) | 1.67                   | (0.73–3.83) | 1.33         | (0.84–2.09)     |
| $\chi^2$ -linear trend                                      | $P = 0.021$                           |             | $P = 0.025$      |             | $P = 0.144$            |             | $P = 0.037$  | $P = 0.025$     |
| <b>Gestational age (weeks)</b>                              |                                       |             |                  |             |                        |             |              |                 |
| <37                                                         | 0.46                                  | (0.13–1.60) | 0.45             | (0.13–1.57) |                        |             | 0.76         | (0.45–1.28)     |
| 37, 38                                                      | 0.56                                  | (0.22–1.38) | 0.55             | (0.22–1.39) |                        |             | 0.78         | (0.51–1.18)     |
| 39, 40                                                      | 1.00                                  |             | 1.00             |             |                        |             | 1.00         |                 |
| $\geq 41$                                                   | 1.25                                  | (0.72–2.17) | 1.28             | (0.73–2.26) |                        |             | 0.81         | (0.59–1.10)     |
| $\chi^2$ -linear trend                                      | $P = 0.042$                           |             | $P = 0.035$      |             |                        |             | $P = 0.818$  | $P = 0.773$     |
| <b>Head circumference (cm)</b>                              |                                       |             |                  |             |                        |             |              |                 |
| <33                                                         | 0.50                                  | (0.17–1.54) | 0.47             | (0.15–1.49) | 0.71                   | (0.21–2.35) | 1.11         | (0.68–1.84)     |
| 33, 34                                                      | 1.00                                  |             | 1.00             |             | 1.00                   |             | 1.00         |                 |
| 35, 36                                                      | 0.86                                  | (0.50–1.47) | 0.75             | (0.43–1.31) | 0.67                   | (0.38–1.19) | 0.95         | (0.71–1.26)     |
| $\geq 37$                                                   | 1.25                                  | (0.58–2.68) | 0.97             | (0.43–2.16) | 0.86                   | (0.38–1.94) | 1.29         | (0.83–1.98)     |
| $\chi^2$ -linear trend                                      | $P = 0.382$                           |             | $P = 0.779$      |             | $P = 0.601$            |             | $P = 0.745$  | $P = 0.504$     |
| <b>Birth length (cm)</b>                                    |                                       |             |                  |             |                        |             |              |                 |
| <47                                                         | 0.81                                  | (0.22–2.94) | 0.75             | (0.20–2.80) | 1.86                   | (0.40–8.52) | 1.05         | (0.56–1.98)     |
| 47–49                                                       | 1.00                                  | (0.50–1.97) | 1.02             | (0.51–2.04) | 1.26                   | (0.61–2.61) | 1.02         | (0.71–1.45)     |
| 50–52                                                       | 1.00                                  |             | 1.00             |             | 1.00                   |             | 1.00         |                 |
| 53–55                                                       | 1.04                                  | (0.57–1.88) | 1.04             | (0.56–1.91) | 0.98                   | (0.53–1.82) | 1.06         | (0.77–1.44)     |
| $\geq 56$                                                   | 2.58                                  | (0.94–7.08) | 2.43             | (0.86–6.85) | 2.46                   | (0.87–6.96) | 0.63         | (0.33–1.18)     |
| $\chi^2$ -linear trend                                      | $P = 0.244$                           |             | $P = 0.260$      |             | $P = 0.821$            |             | $P = 0.540$  | $P = 0.385$     |
| <b>Head circ./birth wt. ratio</b>                           |                                       |             |                  |             |                        |             |              |                 |
| #1st quartile (<0.96)                                       | 1.00                                  |             | 1.00             |             | 1.00                   |             | 1.00         |                 |
| 2nd quartile (0.96–1.03)                                    | 0.71                                  | (0.37–1.33) | 0.78             | (0.40–1.51) | 0.79                   | (0.41–1.53) | 0.90         | (0.60–1.33)     |
| 3rd quartile (1.04–1.13)                                    | 0.65                                  | (0.34–1.26) | 0.60             | (0.31–1.19) | 0.63                   | (0.32–1.25) | 0.70         | (0.47–1.03)     |
| 4th quartile (>1.13)                                        | 0.46                                  | (0.22–0.93) | 0.44             | (0.21–0.91) | 0.55                   | (0.25–1.20) | 0.61         | (0.41–0.90)     |
| $\chi^2$ -linear trend                                      | $P = 0.033$                           |             | $P = 0.020$      |             | $P = 0.095$            |             | $P = 0.006$  | $P = 0.004$     |
| <b>Children with German nationality (N = 346)</b>           |                                       |             |                  |             |                        |             |              |                 |
| #1st quartile (<0.96)                                       | 1.00                                  |             | 1.00             |             | 1.00                   |             | 1.00         |                 |
| 2nd quartile (0.96–1.03)                                    | 0.71                                  | (0.37–1.33) | 0.78             | (0.40–1.51) | 0.79                   | (0.41–1.53) | 0.90         | (0.60–1.33)     |
| 3rd quartile (1.04–1.13)                                    | 0.65                                  | (0.34–1.26) | 0.60             | (0.31–1.19) | 0.63                   | (0.32–1.25) | 0.70         | (0.47–1.03)     |
| 4th quartile (>1.13)                                        | 0.46                                  | (0.22–0.93) | 0.44             | (0.21–0.91) | 0.55                   | (0.25–1.20) | 0.61         | (0.41–0.90)     |
| $\chi^2$ -linear trend                                      | $P = 0.033$                           |             | $P = 0.020$      |             | $P = 0.095$            |             | $P = 0.006$  | $P = 0.004$     |
| <b>Children with other than German nationality (N = 60)</b> |                                       |             |                  |             |                        |             |              |                 |
| #1st quartile (<0.96)                                       | 1.00                                  |             | 1.00             |             | 1.00                   |             | 1.00         |                 |
| 2nd quartile (0.96–1.03)                                    | 0.71                                  | (0.37–1.33) | 0.78             | (0.40–1.51) | 0.79                   | (0.41–1.53) | 0.90         | (0.60–1.33)     |
| 3rd quartile (1.04–1.13)                                    | 0.65                                  | (0.34–1.26) | 0.60             | (0.31–1.19) | 0.63                   | (0.32–1.25) | 0.70         | (0.47–1.03)     |
| 4th quartile (>1.13)                                        | 0.46                                  | (0.22–0.93) | 0.44             | (0.21–0.91) | 0.55                   | (0.25–1.20) | 0.61         | (0.41–0.90)     |
| $\chi^2$ -linear trend                                      | $P = 0.033$                           |             | $P = 0.020$      |             | $P = 0.095$            |             | $P = 0.006$  | $P = 0.004$     |
| <b>Children with other than German nationality (N = 60)</b> |                                       |             |                  |             |                        |             |              |                 |
| #1st quartile (<0.96)                                       | 1.00                                  |             | 1.00             |             | 1.00                   |             | 1.00         |                 |
| 2nd quartile (0.96–1.03)                                    | 0.71                                  | (0.37–1.33) | 0.78             | (0.40–1.51) | 0.79                   | (0.41–1.53) | 0.90         | (0.60–1.33)     |
| 3rd quartile (1.04–1.13)                                    | 0.65                                  | (0.34–1.26) | 0.60             | (0.31–1.19) | 0.63                   | (0.32–1.25) | 0.70         | (0.47–1.03)     |
| 4th quartile (>1.13)                                        | 0.46                                  | (0.22–0.93) | 0.44             | (0.21–0.91) | 0.55                   | (0.25–1.20) | 0.61         | (0.41–0.90)     |
| $\chi^2$ -linear trend                                      | $P = 0.033$                           |             | $P = 0.020$      |             | $P = 0.095$            |             | $P = 0.006$  | $P = 0.004$     |
| <b>Children with other than German nationality (N = 60)</b> |                                       |             |                  |             |                        |             |              |                 |
| #1st quartile (<0.96)                                       | 1.00                                  |             | 1.00             |             | 1.00                   |             | 1.00         |                 |
| 2nd quartile (0.96–1.03)                                    | 0.71                                  | (0.37–1.33) | 0.78             | (0.40–1.51) | 0.79                   | (0.41–1.53) | 0.90         | (0.60–1.33)     |
| 3rd quartile (1.04–1.13)                                    | 0.65                                  | (0.34–1.26) | 0.60             | (0.31–1.19) | 0.63                   | (0.32–1.25) | 0.70         | (0.47–1.03)     |
| 4th quartile (>1.13)                                        | 0.46                                  | (0.22–0.93) | 0.44             | (0.21–0.91) | 0.55                   | (0.25–1.20) | 0.61         | (0.41–0.90)     |
| $\chi^2$ -linear trend                                      | $P = 0.033$                           |             | $P = 0.020$      |             | $P = 0.095$            |             | $P = 0.006$  | $P = 0.004$     |

\*Prevalence odds ratio. †Adjusted for maternal and paternal history of atopy, maternal smoking during pregnancy, German nationality, socioeconomic status and gender. ‡Adjusted for maternal and paternal history of atopy, maternal smoking during pregnancy, German nationality, socioeconomic status, gender and gestational age. §Means ratio. #Low ratio values represent children with high birth weight relative to head circumference.

atopy and maternal history of asthma while transient wheeze appears to be related to diminished airway function at birth mainly as a result of pre-maturity [16]. Our finding of an increased risk of asthma in children born before 37 weeks, especially in children not being atopic, are in accordance with studies showing an increased prevalence of asthma or symptoms of asthma with both pre-maturity [17–19] and low birth weight [12, 18, 20]. Most of these studies, however, did not attempt to classify children into separate asthma categories based on atopic status. Thus, the observed U-shaped relationship of birth weight, birth length and ratio of head circumference to birth weight with life-time prevalence of diagnosed asthma might be due to different types of asthmatics.

The strength of our study lies in the prospective design of analysing the relation of anthropometric measures recorded at birth with various measures of atopic sensitization and allergic disease in a large community-based sample of young children. Also, the inclusion of gestational age in the analyses allowed us to differentiate between intrauterine growth retardation and pre-term delivery.

We could identify several limitations in our current study, which should also be considered in the interpretation of our results. First, we have to consider that a substantial number of eligible subjects either declined to participate in the study or had incomplete information. A comparison of participating and non-participating children revealed that participants were more likely to be of German nationality (81.0 % vs. 65.2 %,  $P = 0.001$ ) and to have been born to older mothers (28.3 vs. 27.5 years,  $P = 0.003$ ). However, participation bias is unlikely as the prevalence of atopic diseases in the children and parents and the distribution of several confounding factors (socio-economic status, gender, maternal smoking, family size) was similar between participants and non-participants. Another potential source of error was the parental report of current wheeze. We assume that parental misclassification would have been independent of the children's birth characteristics, thus resulting in bias of the effect measure towards the null value. Finally, the precision of the effect estimates was limited by the small number of children especially in the extreme categories of the explanatory variables. In view of multiple statistical tests that have been performed, the results of our analyses should be interpreted with caution.

In summary, our results suggest that atopic sensitization is associated with several markers of fetal growth and maturity. These results provide further support for the hypothesis of 'fetal programming' mechanisms, which influence the likelihood of future development of diseases.

## Acknowledgements

The study was funded by the German Ministry of Education and Health. The authors thank the children and their parents for participating in the study. The authors also wish to thank the many fieldworkers for their enthusiasm and dedication. In addition, the authors are grateful to the Gesundheitsamt der Stadt Muenchen for its help and support and to Bernhard Schwertner Feldorganisation, Augsburg, for the excellent collaboration.

## References

- 1 Barker DJ. The fetal origins of diseases of old age. *Eur J Clin Nutr* 1992; 46 (Suppl. 3):S3–9.
- 2 Warner JA, Jones CA, Jones AC, Warner JO. Prenatal origins of allergic disease. *J Allergy Clin Immunol* 2000; 105:S493–6.
- 3 Leadbitter P, Pearce N, Cheng S et al. Relationship between fetal growth and the development of asthma and atopy in childhood. *Thorax* 1999; 54:905–10.
- 4 Godfrey KM, Barker DJP, Osmond C. Disproportionate fetal growth and raised IgE concentration in adult life. *Clin Exp Allergy* 1994; 24:641–8.
- 5 Fergusson DM, Crane J, Beasley R, Horwood LJ. Perinatal factors and atopic disease in childhood. *Clin Exp Allergy* 1997; 27:1394–401.
- 6 Olesen AB, Ellingsen AR, Olesen H, Juul S, Thestrup-Pedersen K. Atopic dermatitis and birth factors: historical follow up by record linkage. *BMJ* 1997; 314:1003–8.
- 7 Karmaus W, Arshad H, Mattes J. Does the sibling effect have its origin *in utero*? Investigating birth order, cord blood immunoglobulin E concentration, and allergic sensitization at age 4 years. *Am J Epidemiol* 2001; 154:909–15.
- 8 Benn CS, Jeppesen DL, Hasselbalch H et al. Thymus size and head circumference at birth and the development of allergic diseases. *Clin Exp Allergy* 2001; 31:1862–6.
- 9 Beasley R, Leadbitter P, Pearce N, Crane J. Is enhanced fetal growth a risk factor for the development of atopy or asthma? *Int Arch Allergy Immunol* 1999; 118:408–10.
- 10 Weiland SK, von Mutius E, Hirsch T et al. Prevalence of respiratory and atopic disorders among children in the East and West of Germany five years after unification. *Eur Respir J* 1999; 14:862–70.
- 11 Asher MI, Keil U, Anderson HR et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8:483–91.
- 12 Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clin Exp Allergy* 1993; 23:504–11.
- 13 Xu B, Pekkanen J, Laitinen J, Järvelin MR. Body build from birth to adulthood and risk of asthma. *Eur J Public Health* 2002; 12:166–70.
- 14 Pekkanen J, Xu B, Järvelin MR. Gestational age and occurrence of atopy at age 31 – a prospective birth cohort study in Finland. *Clin Exp Allergy* 2001; 31:95–102.
- 15 Burney P, Malmberg E, Chinn S, Jarvis D, Luczynska C, Lai E. On behalf of The European Community Respiratory Health Survey. The distribution of total and specific serum IgE in the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1997; 99:314–22.
- 16 Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995; 332:133–8.
- 17 Von Mutius E, Nicolai T, Martinez FD. Prematurity as a risk factor for asthma in preadolescent children. *J Pediatr* 1993; 123:223–9.
- 18 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.
- 19 Olivetti JF, Kercsmar CM, Redline S. Pre- and perinatal risk factors for asthma in inner city African-American children. *Am J Epidemiol* 1996; 143:570–7.
- 20 Seidman DS, Laor A, Gale R, Stevenson DK, Danon YL. Is low birth weight a risk factor for asthma during adolescence? *Arch Dis Child* 1991; 66:584–7.