

The association between birth size and atopy in young North-European adults

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Summary

Background There is evidence that atopic disorders may begin in intra-uterine life; however, studies of birth characteristics and atopy show conflicting results.

Methods We wanted to investigate the association of birth weight and head circumference with serum total or specific IgE, allergic rhinitis or eczema while addressing the influence of demographic and geographical factors. In this historic prospective cohort study, data were collected from birth records for 1683 men and women born in 1947–1973, from six Nordic–Baltic populations participating in the European Community Respiratory Health Survey. Blood tests for the measurement of serum total and specific IgE were available for 1494 subjects. In multiple regression analyses, adjustments were made for birth length, gender, age, study centre, adult body mass index, level of education, parental and adult smoking.

Results There was no association of birth weight ($n = 1230$) and head circumference ($n = 285$) with serum total IgE, specific IgE antibodies, allergic rhinitis or eczema. There were neither significant interactions by gender or age, nor heterogeneity between the study centres in the analyses of birth weight and adult atopy.

Conclusion Birth size was not associated with atopy among adults in this large Nordic–Baltic population study.

Keywords atopy, birth weight, ECRHS, head circumference

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Introduction

There is substantial evidence that atopy may start before birth [1–2]. There are signs of IgE responses to environmental antigens in amniotic fluid and umbilical cord blood. The foeto-maternal environment is skewed towards lymphocyte T-helper cell type 2 (Th2) ensuring a successful pregnancy [1], while genetic, pre-natal and post-natal factors are believed to contribute to a non-allergic Th2/Th1 balance after birth. Birth size is believed to reflect intra-uterine conditions, e.g. pregnancy complications and nutritional status, which may also influence programming of the immune system and subsequently later atopic predisposition [2]. There are, however, contradictory studies of the association between birth anthropometric measures, indicating intra-uterine growth, and atopy later in life. An overview of previous studies is shown in Table 1. In studies of children, adolescents and adults in the UK [3] and New Zealand [4], birth weight and length were not associated with total serum IgE level or SPTs (SPTs) to common allergens. Neither was there an

association between birth weight and allergic rhinitis or atopic dermatitis in 9-year-old Italian children [5] nor in a cohort of adolescents from New Zealand [6]. However, large birth head circumference was associated with raised level of total serum IgE [3, 4] and more hayfever [7]. A Finnish population study of 31-year-old adults showed a U-shaped association between birth ponderal index (birth weight (g) $\times$ 100/birth length (cm)³) and at least one positive SPT [8]. A population study of 10–11-year-old Swedish children showed an association between high ponderal index and a positive SPT [9]. High birth weight and high gestational age were related to atopic dermatitis in a Danish retrospective study of children aged up to 9.5 years [10]. Birth weight was also positively related to atopic sensitization and higher total serum IgE in 5–7-year-old German children [11]. In a Norwegian historical birth cohort study, there was a weak association between birth weight above 4000 g and hayfever [12]. Finally, low birth weight was associated with more allergic rhinitis and positive SPTs in a UK study of 2-year-old children [13] and apparently with more atopic dermatitis in a Danish conscript study [14].

Thus, the literature on birth size and atopy shows highly heterogeneous findings, and we wanted to address the issue in a large multi-centre study. Our objectives were, firstly to

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Table 1. Review of previous studies on birth characteristics and atopy

Author [ref] – country	n studied	Population based?	Response (%)	Subjects' birth year (age in years)	Birth characteristics	Atopy	Results
Godfrey et al. [2] – United Kingdom	280	No*	62	1935–1943 (47–55)	Weight, length, HC	Total s-IgE	No association: birth weight, length and s-IgE Positive association HC and raised s-IgE (>80 IU/mL)
Gregory et al. [3] – United Kingdom	239	Yes†	57	1974–1991 (6–23)	Weight, length, HC	Total s-IgE ≥ one of 14 SPT	No association: birth weight, length and s-IgE, SPT - Positive association HC and raised s-IgE (>150 IU/mL)
Leadbitter et al. [4] – New Zealand	571/714	No‡	55–69	1972–1973 (11–13)	Weight, length, HC	Total s-IgE ≥ one of 14 SPT	No association: birth weight, -length and s-IgE, SPT - Positive association HC and raised s-IgE (>150 IU/mL)
Girolimoni et al. [5] – Italy	1369	Yes	71	1991 (9)	Weight§	Allergic rhinitis, atopic dermatitis	No association between birth weight and allergic rhinitis or atopic dermatitis
Fergusson et al. [6] – New Zealand	891	No	70	1977 (16)	Weight, length, HC	Allergic rhinitis, eczema	No association birth weight or HC with allergic rhinitis or eczema
Katz et al. [7] – United Kingdom	10809	Yes	35	1975–1980 (11–16)	Weight, HC	Hayfever, eczema	Association of HC and more hayfever, trend of more hayfever with increased birth weight
Xu et al. [8] – Finland	4719	Yes	56	1966 (31)	Ponderal index (g × 100/cm ³)	SPT	U-shaped association ponderal index and ≥ 1 positive of four SPT
Braback et al. [9] – Sweden	1745	Yes	68–71	1986–1987 (10–11)	Ponderal index (kg/m ³)	SPT	Ponderal index >30 kg/m ³ associated with ≥ one positive of nine SPT
Olesen et al. [10] – Denmark	7862/985	Yes	99/93	1984–1986 (5–9)	Weight for gestational age	Allergic rhinitis Atopic dermatitis	High birth weight (for date) associated with atopic dermatitis
Bohle et al. [11] – Germany	741	Yes	26	1988–1991 (5–7)	Weight, length, HC	SPT, allergic rhinitis, eczema	Positive association of birth weight and atopic sensitization, of low birth weight/HC and less positive SPT, increased total s-IgE with birth weight
Svanes et al. [12] – Norway	890	Yes	80	1947–1972 (20–23)	Weight, length	Hayfever	Weak association birth weight >4000 g and hayfever
Arshad et al. [13] – United Kingdom	1174	Yes	36	1989–1990 (2)	Weight	s-IgE, SPT, allergic rhinitis, eczema	Association of low birth weight with more allergic rhinitis and positive SPT
Steffensen et al. [14] – Denmark	4795	Yes	99 (?)	1973–1975 (18)	Weight, HC	Atopic dermatitis	Trend (NS) of more atopic dermatitis in subjects with birth weight <2501 g

*Study sample subjects living in Preston at present, selected from married mothers giving birth at a single hospital.

†Study sample community based, however limited to subjects with two or more siblings.

‡Study sample from a longitudinal birth cohort, selected from one hospital.

§Parental questionnaire-based information.

¶Second study sample (n = 985) stratified.

|| Men only.

s-IgE, serum-IgE; HC, head circumference; SPT, skin prick test; NS, not significant.

study whether birth weight or birth head circumference were related to adult levels of total serum IgE, presence of specific IgE antibodies, allergic rhinitis or eczema. Secondly, we questioned whether such associations varied by gender, age or study area.

Materials and methods

The European Community Respiratory Health Survey (ECRHS)

The data collection was a sub-study of the ECRHS I stage II [15]. Informed consent was obtained and the Regional Ethics Committees approved the study. In a structured interview, detailed questions were asked about parental tobacco smoking, the individuals' educational level and current smoking habits. Questions on atopic disorders were: 'Do you have any nasal allergies, including hay fever (allergic rhinitis)?' and 'Have you ever had eczema or any kind of skin allergy (eczema)?' Blood samples were collected for analyses of total serum IgE and specific IgE against house dust mite (HDM) (*Dermatophagoides pteronyssinus*), cat, timothy grass, mould (*Cladosporium*) and birch. The measurement range for total serum IgE was 2–2000 kU/L and a positive specific IgE test was defined as >0.35 kU/L [16].

Birth information

A Nordic–Baltic birth weight project was initiated in six centres participating in the ECRHS; Århus in Denmark, Bergen in Norway, Reykjavik in Iceland, Umeå and Uppsala in Sweden and Tartu in Estonia. The methods have been described previously [17]. In short, 4440 subjects were invited to attend ECRHS I stage II, of whom 3201 responded (72%). Information on birth weight, birth length and gestational age was collected from birth records. Birth weight was measured using mechanical 'balance weights' (grams) and crown-heel length using a measuring board with a movable foot-piece (cm) through stretching of the newborn baby. We calculated the ponderal index (birth weight (g) $\times$ 100/birth length (cm)³), taking into account that weight representing volume is three-dimensional and length is one-dimensional [18]. Information on birth head circumference (cm) was available only in Uppsala and Umeå ($n = 392$). In the birth records, prematurity was defined as birth before end of the 36th week of gestation. Subjects born after the 36th week of gestation were defined as mature. For 539 subjects from Umeå, Uppsala and Bergen information on gestational age (days) was also available. Birth data for 636 ECRHS non-responders were collected in Reykjavik, Tartu and Bergen.

Data handling and statistical analyses

Total serum IgE showed a skewed distribution and was logarithmically transformed (ln total serum IgE). Analysis of variance (ANOVA) was used for comparing birth size categories and total serum IgE. χ^2 and linear by linear association tests were used for comparing proportions. Multivariate regression analyses were used to assess the effects of birth weight and head circumference on total serum IgE and the five specific IgE antibodies, allergic rhinitis and

eczema. Adjustments were allowed for birth length and clinically relevant, possible confounders such as tobacco smoke exposure in early and adult life, age, gender, study centre, educational level as well as adult body size. We also wanted to investigate how inclusion of gestational age in the multivariate regression models influenced a possible association between birth size and adult atopy.

Since the measurement range of total serum IgE was 2–2000 kU/L, a tobit censored linear regression was used for total serum IgE, while logistic regression was used in the remaining analyses. Analyses of interactions between birth weight or head circumference by age and gender were performed both in second and third order. The analyses were repeated with stratification by study centre and meta-analyses were done. Power analyses using 10 000 simulations were performed for the associations between birth weight and total serum IgE or birch-specific IgE, based on the different values for the birth weight coefficients and model estimates for the remaining coefficients. The significance level was chosen as 0.05 for all tests. We used the statistical programs SPSS 12.0 (SPSS Inc., Chicago, IL, USA) for most analyses, R (The R Foundation for Statistical Computing, Vienna, Austria) for the meta-analyses, interaction and power analyses and STATA 7.0 (Stata Corporation, College Station, TX, USA) for the tobit regression analyses.

Results

Population characteristics

Of the 3201 ECRHS participants from the 6 centres, 1683 subjects (53%) were identified in local birth records and data registries. Altogether, 46.5% of the subjects were female. Only male subjects were included in Tartu. We found no difference between responders and non-responders with respect to smoking habits ($P = 0.34$) or gender ($P = 0.10$). Geometric mean total serum IgE ranged from 14.0 kU/L in Reykjavik to 30.4 kU/L in Bergen ($P < 0.001$). The prevalence of allergic rhinitis varied from 13% in Tartu to 31% in Uppsala ($P < 0.001$), while eczema varied from 43% in Bergen to 55% in Umeå and Århus ($P = 0.02$).

Bivariate analyses

Table 2 indicates that subjects with lower birth weight and birth length have more eczema, although not statistically significant. In subjects recorded as having been premature ($n = 34$), eczema was more prevalent ($P = 0.004$). We observed higher levels of total serum IgE ($P < 0.001$), specific IgE against HDM ($P < 0.001$) and any of the five specific IgE antibodies examined ($P = 0.049$) in males than in females. On the other hand, there was more eczema in females than in males ($P < 0.001$). In the sub-sample of participants from Uppsala and Umeå ($n = 392$), large head circumference was associated with less eczema ($P = 0.03$). Birth weight, birth length and ponderal index were not significantly associated with adult total serum IgE, specific IgE antibodies, allergic rhinitis or eczema (Table 2).

Table 2. Birth characteristics and adult atopy in a Nordic-Baltic population aged 20–47 years

	Ln total serum IgE mean (SD) <i>n</i>		Prevalence of specific IgE >0.35 kU/L (%)						Prevalence of allergic rhinitis (%) <i>n</i>		Prevalence of eczema (%)
			HDM	Cat	Timothy	Cladosporium	Birch	Any			
Gender											
Female	676	3.03 (1.39)	6.4	8.9	15.1	3.3	9.0	25.4	747	22.9	57.0
Male	795	3.32 (1.54)	13.9	9.4	17.0	2.5	10.6	30.1	864	20.4	41.5
Gestational age											
Preterm*	34	3.14 (1.31)	5.9	8.8	17.6	2.9	8.8	26.5	35	22.9	72.2
Term	1088	3.31 (1.52)	11.3	8.9	16.7	1.7	10.6	28.2	1224	20.1	47.7
Birth weight (g)											
<2500	45	3.28 (1.35)	11.1	6.7	17.8	4.4	8.9	31.1	50	20.0	58.8
2500–2999	150	3.14 (1.56)	11.3	10.6	18.5	4.0	8.6	27.8	174	24.7	51.7
3000–3499	572	3.15 (1.49)	9.8	9.4	16.3	2.1	10.8	28.9	640	20.0	48.0
3500–3999	471	3.14 (1.49)	10.2	7.0	13.8	3.4	9.1	26.1	526	21.7	47.3
>4000	256	3.23 (1.52)	11.7	11.3	17.6	2.3	9.4	27.3	282	22.0	47.0
Birth length (cm)											
<50.0	324	3.13 (1.47)	11.3	10.1	15.7	3.8	10.1	27.8	399	21.6	51.8
50.0–51.9	585	3.22 (1.52)	10.4	8.3	16.3	2.0	10.6	28.5	639	20.7	46.9
>52.0	581	3.15 (1.48)	10.0	9.0	16.0	3.1	8.8	26.9	629	21.9	47.5
Ponderal index (g × 100/cm ³) tertiles											
<2.55	498	3.19 (1.46)	9.8	7.8	17.1	3.2	8.4	27.9	550	23.3	49.9
2.55–2.75	499	3.16 (1.52)	9.6	9.8	15.6	3.0	10.8	29.3	554	20.8	47.7
≥2.75	493	3.15 (1.51)	12.0	9.3	15.4	2.2	10.1	26.0	563	20.1	47.3
Head circumference† (cm)											
<33.5	106	3.08 (1.38)	5.7	12.3	19.8	1.9	19.8	32.1	131	28.2	56.1
33.5–35	99	3.16 (1.50)	7.1	17.2	19.2	4.0	16.2	33.3	118	32.2	58.5
>35	113	3.15 (1.34)	1.8	9.7	15.9	1.8	11.5	25.7	142	31.7	43.7

*Preterm birth defined in the birth records as gestational age before completed 36th week.

†Only in Umeå and Uppsala.

HDM, house dust mite (*Dermatophagoides pteronyssinus*); SD, standard deviation.

Multivariate analysis

After adjustments for birth length, gender, age, study centre, adult body mass index, level of education, parental and adult smoking, birth weight or head circumference were not associated with adult total (Fig. 1) or specific serum IgE, allergic rhinitis or eczema (Table 3). Further inclusion of prematurity or gestational age to the main models did not alter the magnitude of the effect estimates; they however, reduced the number of subjects available for analysis. When excluding birth length from the main models, there were similar effect estimates with overlapping confidence intervals. There were no interactions of birth weight or head circumference by gender and age in the associations with adult atopy. We did not find heterogeneity between centres in the association of birth weight and adult specific IgE antibodies against birch ($P = 0.94$) or between Uppsala and Umeå in the association of head circumference and specific IgE against HDM ($P = 0.99$). Furthermore, there was no centre heterogeneity in the association between birth weight and total serum IgE (Fig. 1).

Discussion

In this Nordic-Baltic historic prospective cohort study, we observed that birth weight or birth head circumference was not associated with levels of adult total or specific serum IgE,

allergic rhinitis or eczema in adulthood. There were no significant gender differences or centre heterogeneity, indicating no geographical variation within the study area.

These negative results are in accordance with some of the previous studies [2–6] showing no association of birth weight and adult atopy. A weak U-shaped association of atopy and birth ponderal index, as reported in the large Finnish cohort [8], could possibly explain the contradictory findings in the literature. However, our analyses of ponderal index and adult atopy showed no U-shaped association. Some of the strongest associations described in the literature arise from small cohorts. This suggests publication bias with less publication of studies showing negative findings. An important feature of a multi-centre study is that all centres have to be kept in the analyses independent of the results, thus diminishing the possibility for publication or reporting bias.

Measurement errors in the birth characteristics may exist. Measurement of birth weight is considered accurate, although depending on the calibration and quality control of the different mechanical weights. Measured birth length of the newborn babies, however, depends on the extent of stretching and may therefore be less accurate. Analyses of birth length in the present study revealed a digit point preference. For example, a birth length of 50.0 cm was much more frequent than 50.2 cm in our study [17]. Ponderal index (birth weight × 100/birth length³) is used as a measure of nourishment when comparing groups of children [18]. This index of body proportion is, however, strongly influenced by measure-

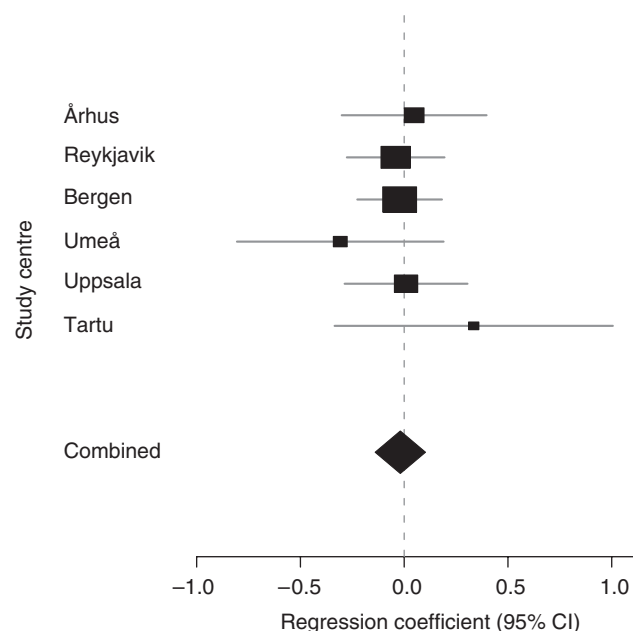


Fig. 1. Meta-analysis* of centre variation on the association of an increase of birth weight by 500 g and total serum IgE in adult responders of a Nordic-Baltic population study.

ment error in birth length. When we applied ponderal index, no associations with serum total IgE, specific IgE antibodies or symptoms of atopy were observed. In addition, analyses performed without birth length in the models with birth weight showed no relevant alteration of the effect estimates. The measurement of head circumference also depends on the positioning and tightening of the measure band. Head circumference was recorded in a smaller proportion of our subjects only, and our findings should be examined more thoroughly in larger studies, including standardization of the measurement technique. Information on prematurity was available only for a small number of subjects and was therefore not included in the main model. Analyses in this sub-sample with information on prematurity or in a smaller

sample with information on gestational age did not alter the effect estimates substantially.

A clinically relevant increase in total serum IgE was judged by the authors to be 5 U of IgE per 100 g decrease in birth weight, for a person with a birth weight of 3500 g and adult level of total serum IgE of 50 kU/L. This corresponds to a regression coefficient of -0.2 in the tobit multivariate regression analysis. When applying observations for 1216 persons in post-study power calculations, the corresponding power was 83%. Thus, our study has sufficient power to detect a clinically relevant association of birth weight and adult atopy. The confidence interval for the coefficient of birth weight and adult total serum IgE in our actual analysis (Table 3) was, however, far below the clinically relevant range.

Our findings of no association of birth size and adult atopic disorders could also be an indication of diversity in sensitization to different aero-allergens affected by geography and time. The geometric mean of total serum IgE was for our total sample 24 kU/L, and varied significantly between centres, ranging from 14 kU/L in Reykjavik to 30 kU/L in Bergen ($P < 0.001$). These findings are similar to the distribution of total serum IgE in the main study ECRHS [16], but higher than in a Norwegian population study from 1987 to 1988 of 18–73-year-old adults [19], which may be due to a higher proportion of subjects older than 47 years in that study. However, in our study we found no heterogeneity between centres in the association between birth weight and adult total serum IgE (Fig. 1). Further, there was no interaction by age in the associations between birth weight and atopic outcomes.

In conclusion, our study did not show an association of birth size and later atopic disorders. This appeared to be a valid negative finding that could not be attributed to methodological fallacies like insufficient power, selection bias or poor validity. However, this does not imply that intra-uterine environment does not influence atopic development, but only that the intra-uterine factors involved in development of atopy do not manifest strongly in size at birth. Birth weight in particular reflects growth during the last trimester.

Table 3. Adjusted effects of birth weight and head circumference on serum total IgE, specific IgE's, allergic rhinitis and eczema in adult responders of a Nordic-Baltic population study

	<i>n</i>	Birth weight (500 g)		<i>n</i>	Head circumference (cm)	
		Regression coefficient*	95% CI		Regression coefficient*	95% CI
Ln total serum IgE (kU/L)	1216	−0.036	−0.17, 0.10	285	−0.011	−0.11, 0.09
Specific IgE against		Odds ratios†	95% CI		Odds ratios†	95% CI
Dermatophagoides pteronyssinus	1231	1.20	0.90, 1.61	285	0.69	0.46, 1.02
Cat	1231	1.22	0.88, 1.67	285	1.00	0.79, 1.26
Timothy	1231	0.93	0.73, 1.18	285	0.90	0.74, 1.11
Cladosporium	1230	0.92	0.52, 1.63	285	0.74	0.34, 1.60
Birch	1231	1.37	0.99, 1.88	285	0.81	0.64, 1.03
Any positive	1230	0.98	0.80, 1.19	285	0.90	0.75, 1.06
Allergic rhinitis	1290	0.90	0.73, 1.11	316	1.08	0.93, 1.26
Eczema	1297	0.99	0.83, 1.18	317	0.94	0.82, 1.08

*Multivariate, tobit regression analyses with 95% CI, adjusted for birth length (birth weight analyses), gender, age, study centre, adult body mass index, level of education, parental and adult environmental, ex- and current smoking.

†Multivariate, logistic regression analyses with 95% CI, adjusted for birth length (birth weight analyses), gender, age, study centre, adult body mass index, level of education, parental and adult environmental, ex- and current smoking.
CI, confidence interval.

Our findings do not exclude the possibility that susceptibility to atopy may be established even earlier in intra-uterine life.

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