

High birth weight, asthma and atopy at the age of 16 yr

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The association between high birth weight and asthma has been suggested. The Northern Finland Birth Cohort 1986, a longitudinal cohort originally including 9479 participants, has been followed up since birth until the age of 16 yr. Using the data of this study, we analyzed the association of high birth weight with asthma and atopic sensitization at the age of 16 yr. The analysis included the 5995 subjects with complete skin prick test data and the 5500 subjects with data on doctor-diagnosed asthma (written questionnaire) at the age of 16 yr. Atopy was defined as at least one positive skin prick test reaction, which definition was also used to separate atopic and non-atopic asthma. There was a significant association between high birth weight (>4510 g) and asthma among the atopic subjects (OR 2.40, 95% CI 1.33–4.32). When looking at atopy, the highest risk was observed among the subjects with highest birth weight category (>4510 g) (OR 1.44, 95% CI 1.05–1.97) and the adjacent (4200–4500 g) birth weight category (OR 1.24, 95% CI 1.01–1.53), when compared with the reference category (2500–3340 g). Our results support the notion that high birth weight is associated with an increased risk of asthma and suggest that the association is mostly explained by an increased risk of atopy. The biological mechanisms behind the associations are unknown, but they could be related to obesity.

S. T. Remes^{1,2}, S. P. Patel³, A.-L. Hartikainen⁴, M.-R. Jarvelin^{5,6} and J. Pekkanen²

¹Department of Pediatrics, Kuopio University Hospital, Kuopio, Finland, ²Unit of Environmental Epidemiology, National Public Health Institute, Kuopio, Finland, ³The University of Greenwich, London, UK, ⁴Department of Obstetrics and Gynecology, University of Oulu, Finland, ⁵Department of Epidemiology and Public Health, Imperial College School of Medicine, London, UK, ⁶Department of Public Health and General Practice, University of Oulu, Finland

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Sami T. Remes, MD, PhD, MPH, Kuopio University Hospital, PO Box 1777, 70211 Kuopio, Finland
Tel.: +358 17 173311
Fax: +358 17 172777
E-mail: sami.remes@kuh.fi

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Recent studies suggest that high birth weight (>4500 g) may be associated with an increased risk of childhood asthma, raising interesting possibility that there may be a link between obesity and asthma very early in life (1, 2). The results of these registry-based studies (1, 2), however, are limited because of the definition of asthma (cumulative incidence of asthma hospitalization by age 10–12 yr), and no information on atopic sensitization has been available. We therefore evaluated the association of birth weight with asthma and atopy at the age of 16 yr in a prospective birth cohort study.

Methods

The Northern Finland Birth Cohort 1986 (NFBC 1986), a longitudinal birth cohort orig-

inally including 9479 participants, has been followed up since birth until the age of 16 yr. We used the 16-yr follow-up data, including 5995 subjects with complete skin prick test data and 5500 subjects with data on asthma at the age of 16 yr. Asthma was defined as self-report of doctor-diagnosed asthma ever in the written questionnaire. Atopy was defined as at least one positive reaction against birch, timothy, cat or *D. pteronyssimus*. Using this definition of atopy, asthma was further divided into atopic and non-atopic forms. Skin prick test protocol, including the test extracts, was the same than in our previous study (3).

Birth weight (g), divided into six categories (see Table 1), was used as the main explanatory variable. Commonly used low birth weight definition (<2500 g) was used in this study.

Table 1. Odds ratios (95% confidence intervals) of asthma at the age of 16 yr according to birth weight, stratified by atopy

Birth weight category (g)	Risk of asthma			
	Atopic†, n/N	Subjects, OR (95% CI)	Non-atopic, n/N	Subjects, OR (95% CI)
≤ 2490	12/55	1.34 (0.67–2.65)	7/88	1.23 (0.54–2.78)
2500–3340	77/446	1.0‡	55/836	1.0‡
3350–3690	97/516	1.11 (0.80–1.54)	39/862	0.67 (0.44–1.03)
3700–4190	90/484	1.09 (0.78–1.54)	49/854	0.86 (0.58–1.29)
4200–4500	25/143	1.02 (0.62–1.67)	13/226	0.87 (0.46–1.62)
≥4510	20/60	2.40 (1.33–4.32)**	5/77	0.99 (0.38–2.54)

†At least one positive (≥3 mm) reaction against birch, timothy, cat or *D. pteronyssinus* in skin prick test at 16 yr of age.

‡Reference group.

**p < 0.01.

Selection of the highest birth weight groups (4200–4500, >4500 g) was based on the findings of Sin et al. (2) and Yuan et al. (1). The other children were categorized into three groups with approximately equal number of children in each group.

Potential confounding variables that were considered included gestational age at birth, gender, current smoking, current body mass index (BMI), maternal age at birth, maternal atopy (asthma, allergic rhinitis or eczema), diabetes, education (years), smoking during pregnancy, and the number of child's siblings at birth. The change-in-estimate criterion was used in confounder selection. Using this criterion, none of the potential confounders changed the odds ratio (OR) of birth weight and asthma or atopy more than 10%. Therefore, the unadjusted results are presented.

Results

There was a significant association between high birth weight and asthma (OR 2.54, $p < 0.001$) among the atopic subjects (Table 1). When looking at atopy, the highest risk was observed among the subjects with highest birth weight category (OR 1.44, $p < 0.05$) and the adjacent (4200–4500 g) birth weight category (OR 1.24, $p < 0.05$), when compared with the reference category (2500–3340 g) (Table 2).

In the models including birth weight, asthma or atopy, and a specified covariate (as follows), maternal atopy was strongly associated with both asthma and atopy (OR 2.03, $p < 0.001$ and OR 1.43, $p < 0.001$, respectively). Similarly, maternal education was associated with atopy (OR 1.08, $p < 0.01$) but not with asthma. Maternal age at birth or smoking during pregnancy was not associated with either asthma or

Table 2. Odds ratios (95% confidence intervals) of atopy at the age of 16 yr according to birth weight

Birth weight category (g)	Risk of atopy†	
	n/N	OR (95% CI)‡
≤ 2490	75/210	1.07 (0.79–1.45)
2500–3340	557/1632	1.0§
3350–3690	632/1720	1.12 (0.97–1.29)
3700–4190	651/1777	1.12 (0.97–1.28)
4200–4500	187/478	1.24 (1.01–1.53)*
≥4510	76/178	1.44 (1.05–1.97)*

†At least one positive (≥3 mm) reaction against birch, timothy, cat or *D. pteronyssinus* in skin prick test at 16 yr of age.

‡p for trend = 0.012.

§Reference group.

*p < 0.05.

atopy (not shown). The number of biological siblings at birth was inversely associated with atopy but unassociated with asthma (not shown). Current BMI was strongly associated with asthma, as expected (OR 1.05, $p < 0.001$). However, neither of these variables changed the association between birth weight and asthma or atopy for more than 10%.

There were six atopic mothers among the 26 mothers with diabetes and complete data on atopy ($n = 5995$) and four mothers with asthma among the 23 mothers with diabetes and complete data on asthma ($n = 5500$). Therefore, the number of diabetic mothers was very low and did not explain the associations between birth weight and asthma or atopy. Adjustment for gestational age did not have significant influence on the results, for example, for the highest birth weight category, OR for atopic asthma changed from 2.54 to 2.43 and for atopy from 1.44 to 1.41, with no influence on significance level of the respective ORs (data not shown).

Discussion

The results of our study confirm and expand the observations of Sin et al. (2) and Yuan et al. (1) that childhood asthma is associated with high birth weight. This is an important observation, as earlier studies have consistently reported an inverse association between birth weight and lung function and asthma, which has mostly been observed among the low birth weight children (4, 5). Some earlier studies may have missed the association of high birth weight and asthma, if only linear association was investigated without addressing the issue of possible non-linearity.

Both of the studies mentioned above were large and registry based, providing enough subjects also for the extreme categories of birth

weight. The definition of asthma was based on cumulative incidence of either asthma hospitalization (1) or emergency visits for asthma (2) by adolescence, and the results did not significantly change when the occurrence of these events in early life were excluded. Using a smooth interpolation method, Sin et al. (2) fitted a probability curve of asthma by birth weight. Interestingly, the probability of asthma remained stable until the birth weight of 4.5 kg, thereafter increasing rapidly in a linear manner. Similar trend was observed in the other study (1).

Two potential explanations have been suggested for the association between high birth weight and asthma (2). The first explanation relates to lung mechanics, such as disadvantage of respiratory muscle function because of obesity. Second, obesity may influence the immune development, altering the risk of developing chronic asthma (6). The latter explanation is of special interest, as obesity has been suggested to be an important factor for incident asthma at adolescence (7). On the other hand, there may be other factors associated with fetal macrosomy (such as maternal diabetes) which role on the association of asthma and high birth weight is unknown. However, it is tempting to speculate that the association of asthma and obesity may start much earlier than previously suggested, although the evidence to date supporting this hypothesis is weak. This hypothesis could be in accordance with the proposal that enhanced fetal growth may increase the risk of asthma and atopy (6, 8–10). These findings raise interesting speculation on potential explanations for the recent increase in the prevalence of childhood asthma and atopy in the western world, where obesity and over nutrition have become a serious public health concern.

In this paper, we used change-in-estimate criterion in building our logistic regression models, as it has been suggested to be superior to traditional 'full adjustment' strategy or adjustment based on statistical significance (11, 12). The change-in-estimate criterion has an advantage of focusing on variables which are most probably 'true confounders' and it decreases the number of drop-outs from the model because of missing observations. These issues decrease the risk of misinterpretation of the results (11). Therefore, we believe that the change-in-estimate criterion was most feasible model building strategy for our dataset.

We showed that the association of high birth weight and asthma was mostly explained by an increased risk of atopy. The biological mechanisms explaining this association are unknown, but they might be related to obesity. Obesity could influence the immune development, altering the risk of developing atopic asthma. The latter explanation is of a special interest, as obesity has been suggested to be an important factor for incident asthma at adolescence. It is tempting to speculate that the association of asthma and obesity may start much earlier than previously suggested, although the evidence to date supporting this hypothesis is weak.

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