

Asthma, lung function and allergy in 12-year-old children with very low birth weight: A prospective study

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We assessed the relationship between very low birth weight (VLBW) (≤ 1500 g) and the development of asthma, lung function and atopy. The study groups comprised 74 of all 86 (86%) VLBW and 64 of all 86 (74%) matched term children who were prospectively followed for 12 years. A questionnaire on asthmatic and allergic symptoms was completed and skin prick tests, spirometry and hypertonic saline provocation tests were performed at 12 years of age. Cytokine secretion was analysed in stimulated blood leukocyte cultures in 28 VLBW and 23 term children. A history of asthma was more frequent among the VLBW children, as compared with the term children at age 12 (22% vs. 9%, $p = 0.046$). Among the VLBW children, very preterm birth (gestational age: week 25 to 29) (RR 2.5, 95%CI 1.1–5.8), neonatal mechanical ventilation (RR 2.8, 95%CI 1.2–6.4) and neonatal oxygen supplementation (RR 4.3, 95%CI 1.3–14.0) were significantly associated with a history of asthma by the age of 12 years in univariate analyses. In multivariate logistic regression, neonatal oxygen supplementation ≥ 9 days was the only remaining significant risk factor for a history of asthma (adjusted OR 6.7, 95%CI 1.0–44). The VLBW children who required mechanical ventilation during the neonatal period were more likely to have bronchial hyperresponsiveness than those not requiring mechanical ventilation (60% vs. 28%, $p = 0.050$). The spirometric values were similar among the VLBW and the term children at 12 years. Very low birth weight was not significantly related to allergic rhinoconjunctivitis, eczema or positive skin prick tests. Furthermore, the levels of IL-4, IL-5 and IFN- γ in stimulated cell cultures were similar in the VLBW and the term children. A history of asthma by 12 years of age was twice as common among the VLBW as the term children, and neonatal oxygen supplementation seemed to be associated with the increased risk. Furthermore, mechanical ventilation during the neonatal period was associated with bronchial hyperresponsiveness at age 12. Very low birth weight per se was not, however, related to atopy.

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Premature babies have immature lungs and immune system, and this could conceivably affect the development of asthma and allergy. In support of this hypothesis, very low birth weight (VLBW) has been reported to be related to an increased risk for asthma in children in some (1, 2), but not all studies (3). Furthermore, reduced lung function at school age has been

shown in VLBW children, in particular in those who had neonatal respiratory diseases and respiratory support (4, 5). It is unclear which would be the most important risk factor for the development of asthma in VLBW children, e.g. preterm birth by itself, intrauterine growth retardation, neonatal respiratory support, or family history of allergy (6–9). Very low birth

weight infants are more susceptible to severe neonatal respiratory diseases, e.g. bronchopulmonary dysplasia (BPD). Bronchial hyperresponsiveness to histamine at 8–14 years of age is more common in very preterm children with BPD than those without BPD (10). Furthermore, the administration of mechanical ventilation resulting from severe neonatal respiratory diseases may cause permanent impairment of alveolar development and smooth muscle hypertrophy (11, 12), which can be presumed to have a long-term impact on bronchial hyperresponsiveness.

During normal pregnancy, the feto-maternal interface is surrounded by high levels of Th2-like cytokines (13), possibly in order to divert the maternal immune response away from damaging Th1-mediated immune responses (14). Poor pregnancy outcomes, such as intrauterine growth retardation resulting in low birth weight, are associated with an up-regulation of Th1 responses and a down-regulation of Th2 responses (14). Early exposure to antigen in VLBW infants would lead to tolerance and lower risk of sensitization (15). Furthermore, the intestinal microbial flora, which is affected by the postnatal environment (16), may affect immunity (17) in VLBW infants. An inverse relationship between VLBW and atopic symptoms has been shown both in infants and in school children (15, 18).

We hypothesized that VLBW could be associated with a higher incidence of bronchial hyperresponsiveness and asthma, due to immature lung and neonatal lung damage, and lower atopy, due to neonatal immunity. The relationship between VLBW and asthma and atopic diseases cannot easily be compared among studies because of different diagnostic criteria for the disease. Therefore, our hypotheses were tested in a 12-year follow-up study of infants with VLBW, employing modules developed by the International Study of Asthma and Allergies in Childhood (ISAAC) (19).

Methods

Subjects

The very low birth weight group included all live-born infants with a birth weight ≤ 1500 g, born between 1 February 1987 and 30 April 1988 in the south-eastern region of Sweden (20, 21). All of the 86 VLBW infants who survived the first 48 h were recruited into the study. A full-term infant with a normal birth weight (≥ 2500 g) next in order to the index child with the same sex and parity was enrolled as a control at the hospital

where the VLBW infant was born or should have been born. A few mothers were not willing to allow their term babies to participate and in these cases the next term baby in line was invited. None of the infants in the control group had intrauterine infection or malformation. Seventy-four (86%) of the 86 VLBW children and 64 (74%) of the 86 term children participated in this follow-up investigation at 12 years of age. Antenatal steroids were given to eight of the mothers of the VLBW infants. Three VLBW children had BPD that was defined as oxygen dependence beyond gestational age week 36. The VLBW children were more often delivered by Caesarean section than the term children (77% vs. 5%, $p < 0.001$). Antibiotics were administered to 78% of the VLBW infants during the neonatal period and to none of the term children ($p < 0.001$). There were no significant differences in sex, number of older siblings, maternal asthma, maternal smoking during pregnancy or the first years, nor maternal age between the two groups ($p > 0.3$). At the 12-year investigation, the age of the VLBW and term children was similar (12.6 ± 0.2 vs. 12.7 ± 0.3), as well as puberty stage (by Tanner score, hair stage: 2.44 ± 0.96 of the VLBW children vs. 2.44 ± 1.13 of the term children).

Gestational age (GA) varied between 25 and 36 weeks among the VLBW children (mean $\pm$ SD: week 31 ± 2). Very preterm birth was defined as week $25 \leq \text{GA} \leq \text{week } 29$ ($n = 21$). Since children born week $30 \leq \text{GA} \leq \text{week } 32$ ($n = 35$) and week $33 \leq \text{GA} \leq \text{week } 36$ ($n = 18$) had similar risks for asthma and atopic symptoms, the two groups were merged and defined as moderate preterm birth in the subsequent analyses. Small for gestational age (SGA) was defined as birth weight $\leq -2\text{SD}$ of the mean and 37 VLBW children were SGA. Appropriate gestational age (AGA) was defined as birth weight between -2SD and $+2\text{SD}$ of the mean, and this group included 37 of the VLBW and 61 of the term children. Three term children had birth weight $> +2\text{SD}$ and they were excluded from the analyses.

History of disease, symptoms and diagnoses

The parents completed validated questionnaires developed by ISAAC regarding asthmatic and allergic diseases (19). Symptoms related to asthma, i.e. a history of wheeze, current wheeze, current exercise-induced wheeze and current night cough, were based on affirmative answers to specific questions on wheezing in the chest. A history of asthma, allergic rhinoconjunctivitis (ARC) or eczema was elicited by a combination of several

questions on symptoms. Clinical diagnoses of asthma and allergy during the past 12 months, such as current asthma, current allergic rhinoconjunctivitis and current eczema, were made by a pediatrician, according to the history of the disease, physical examination and for current asthma also based on lung function results.

Skin prick tests

Skin prick tests were performed in duplicate on the forearm adhering to methodological considerations according to the ISAAC protocol (19), and using extracts of birch and timothy pollen, dander of cat, dog and horse, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and *Alternaria* (ALK, Hørsholm, Denmark). Briefly, histamine 10 mg/ml and 50% glycerin were used as positive and negative controls. The size of a wheal was recorded as the mean of the longest diameter and the diameter perpendicular at its mid-point. A wheal with a mean diameter of 3 mm or more of the duplicate was regarded as positive. Skin prick tests were performed on 136 children by one research nurse (72 of 74 VLBW and all term children).

Spirometry measurement

Spirometry was tested using a MasterScope spirometer (Jaeger, Würzburg, Germany) which complied with the recommendation of the American Thoracic Society Statement on Standardization of Spirometry. The predicted values had been established according to sex-specific equations adjusted for height by Zapletal et al. (22). Both static spirometry measurements and flow-volume measurements were performed for VC_{in} and VC_{ex} (inspiratory and expiratory vital capacity), FEV₁ (forced expiratory volume in 1 s), FEF₇₅ (forced expiratory flow at 75% of forced vital capacity) and MMEF (maximal mid-expiratory flow). At least two spirometry tests were performed and the better of two reproducible measurements (within 5%) was recorded. One hundred and thirty-four children completed spirometric tests (72 of 74 VLBW and 62 of 64 term children).

Hypertonic saline provocation tests

Hypertonic saline provocation tests were performed according to the ISAAC protocol (19). Briefly, the higher of two reproducible measurements of FEV₁ was recorded as the baseline FEV₁. Hypertonic saline (4.5%) was nebulized via Devilbiss Ultraneb 2000 connected to a 60-cm

tubing (Devilbiss no. 8885: Devilbiss, Dahlhausen, Cologne, Germany) and a two-way valve (Laerdal valve no. 560 200/850 500: Devilbiss, Dahlhausen, Cologne, Germany). The child was encouraged to maintain tidal breathing. The exposure time was progressively increased from 30 s to 1, 2, 4 and 8 min each, and the maximal total inhalation period was 15.5 min. After each exposure, two reproducible measurements of FEV₁ were made. The exposure time was doubled if the fall in FEV₁ was less than 10%. The same dose was repeated if the fall was between 10% and 15%. The challenge test was stopped and considered to be positive when the decline in FEV₁ was more than 15%. The canister with tubing was weighed before and after the challenge test to measure the total dose of delivered saline. Response to dose ratio was used to represent the degree of bronchial hyperresponsiveness, which was defined as the fall of FEV₁ in percentage divided by the total dose of delivered saline in ml (%/ml) (23). One hundred and twenty-seven children completed hypertonic saline provocation tests (68 of 74 VLBW and 59 of 64 term children).

Cell stimulation

Cytokine analyses were performed on 28 VLBW and 23 term children due to the necessity of fresh cells. Venous blood samples were collected into heparin-treated tubes (Vacuette, Greiner Labor Technik, Kremsmünster, Austria). To 200 µl whole blood, 1.8 ml RPMI 1640 (Gibco Life Technologies, Paisley, UK) was added. The cells were stimulated with 5 µg/ml of the mitogen phytohemagglutinin A (PHA) (Sigma-Aldrich, Stockholm, Sweden) at 37°C with 5% CO₂ for 48 h in a HEPA-filtered infrared incubator (Forma Scientific Inc., OH, USA). The supernatants were collected after centrifugation at 400 g and stored at -70°C. Background responses (cultures with medium only) were subtracted from the PHA-induced responses. A whole blood count was obtained mechanically (CellDyn 4000, Abbott Laboratories, Abbott Park, IL, USA), and cytokine production was expressed as pg/ml per 10⁹ lymphocytes.

Cytokine analyses

The levels of IFN-γ, IL-4 and IL-5 were analysed in duplicate using enzyme-linked immunosorbent assay (ELISA), as described by Jenmalm et al. (24). The sensitivity limits for quantitative determinations were 3 pg/ml for IL-4 and IL-5 and 12 pg/ml for IFN-γ.

IgE antibody analyses

The presence of IgE antibodies to a panel of inhalant allergens was determined by Allergy Screen (Magic[®] Lite SQ[™] Allergy Screen, ALK, Hørsholm, Denmark), and total IgE levels by Magic[®] Lite SQ[™] Total IgE Extended Range assay (ALK). Serum samples from the same 28 VLBW and the 23 term children were analysed.

Statistical analyses

Power analyses showed that 65 children each in VLBW and term group were needed to reach 90% power at a significant level of 0.01 according to FEV₁. Because this was a cohort study, relative risks (RRs) were used to express the risk. Epi info 2000 program (Centers for Disease Control and Prevention, Epidemiology Program Office) was applied to calculate crude RRs and 95% confidence intervals (CI) for the development of asthma and atopic diseases in subgroups classified by gestational age, SGA and neonatal respiratory support. Multivariate logistic regression in STAT VIEW 5.0 for Macintosh (Abacus Concepts Inc., Berkeley, California, USA) was employed to analyse independent risk factors for a history of asthma, current asthma and a history of eczema in the VLBW children and provided odds ratios (ORs). Total IgE levels and cytokine production in VLBW and term children were compared using Mann-Whitney *U*-test in STAT VIEW due to nonparametric distribution. ANOVA unpaired *t*-test in STAT VIEW was used to compare weight, height and lung function parameters between the VLBW and the term children.

Ethical aspects

The study was approved by the Human Research Ethics Committee of the Medical Faculty at Linköping University. All parents of the participating children gave their informed consent.

Results

A history of asthma was more frequent among the VLBW children, as compared with the term children (22% vs. 9%, *p* = 0.046). Current wheeze also tended to be more common in the VLBW children (*p* = 0.07). In the subgroup of children with very preterm birth (week 25 ≤ GA ≤ week 29, *n* = 21), asthma symptoms, i.e. a history of wheeze, current wheeze, current exercise-induced wheeze and current night cough, were more common than in the term children

Table 1. Relative risks (RR) and 95% confidence intervals (CI) of preterm birth and small for gestational age for asthmatic and atopic manifestations

	Very preterm (<i>n</i> = 21) Moderate preterm (<i>n</i> = 53) vs. Term* (<i>n</i> = 64)		SGA (<i>n</i> = 37) vs. AGA* (<i>n</i> = 61)	
	<i>n</i>	RR (95% CI)	<i>n</i>	RR (95% CI)
History of wheeze	9 16 14	2.0 (1.0–4.0) 1.4 (0.7–2.6)	11 13	1.4 (0.7–2.8)
Current wheeze	4 6 3	4.1 (1.0–17.0) 2.4 (0.6–9.2)	5 3	2.8 (0.7–10.9)
Current exercise wheeze	5 3 1/63	15.0 (1.8–122.0) 3.6 (0.3–34.0)	4 1/60	6.5 (0.7–56.0)
Current night cough	6 2 4	4.6 (1.4–14.7) 0.6 (0.1–3.2)	3 4	1.2 (0.2–5.3)
History of asthma	8 8 6	4.1 (1.5–10.4) 1.6 (0.6–4.4)	7 5	2.3 (0.7–6.8)
Current asthma	6 6/52 6/63	3.0 (1.0–8.3) 1.2 (0.4–3.6)	7/36 6/60	1.9 (0.7–5.4)
History of ARC	5 6 11	1.4 (0.5–3.6) 0.7 (0.2–1.7)	4 11	0.6 (0.2–1.8)
History of eczema	9 18 24	1.1 (0.6–2.1) 0.9 (0.5–1.5)	11 24	0.8 (0.4–1.4)
Current ARC	4 8 12	1.0 (0.3–2.9) 0.8 (0.3–1.9)	6 12	0.8 (0.3–2.1)
Current eczema	3 6 8	1.1 (0.3–4.0) 0.9 (0.3–2.5)	5 8	1.0 (0.3–3.0)
Positive SPT	4 5/51 9	1.4 (0.4–4.0) 0.7 (0.2–2.0)	3/36 9	0.6 (0.1–2.0)
Positive provocation test	6/18 16/50 18/59	1.1 (0.5–2.4) 1.1 (0.6–1.9)	15/35 17/57	1.4 (0.8–2.5)

*Reference group.

Very preterm: week 25 ≤ GA ≤ week 29; Moderate preterm: week 30 ≤ GA ≤ week 36.

SGA: small for gestational age defined as birth weight ≤ −2SD of the mean among the very low birth weight children; AGA: appropriate gestational age defined as birth weight between −2SD and +2SD of the mean among the term children (three term children had birth weight >+2SD and they were excluded from the analyses); ARC: allergic rhinoconjunctivitis; SPT: skin prick test. *n* is indicated if it differs from the original number.

(Table 1). The very preterm children also had a 4-fold increased risk for a history of asthma and a 3-fold increased risk for current asthma. The cumulative incidence of asthma symptoms did not differ significantly between the SGA children

Table 2. Relative risks (RR) and 95% confidence intervals (CI) of very low birth weight (VLBW) children with neonatal mechanical ventilation or oxygen supplementation for asthmatic and atopic manifestations

	VLBW with mechanical ventilation (n = 13) no mechanical ventilation (n = 61) vs. term* (n = 64)		VLBW with O ₂ supplementation (n = 37) no O ₂ supplementation (n = 37) vs. term* (n = 64)	
	n	RR (95% CI)	n	RR (95% CI)
History of wheeze	7	2.5 (1.2–4.9)	18	2.2 (1.2–4.0)
	18	1.4 (0.7–2.5)	7	0.9 (0.3–2.0)
	14		14	
Current wheeze	3	4.9 (1.1–22.0)	8	4.6 (1.3–16.4)
	7	2.5 (0.6–9.1)	2	1.2 (0.2–6.6)
	3		3	
Current exercise wheeze	4	19.4 (2.3–160.0)	7	11.9 (1.5–94.0)
	4	4.1 (0.4–36)	1	1.7 (0.1–27)
	1/63		1/63	
Current night cough	3	3.7 (0.9–14.6)	6	2.6 (0.7–8.6)
	5	1.3 (0.3–4.7)	2	0.9 (0.1–4.5)
	4		4	
History of asthma	6	4.9 (1.8–12.9)	13	3.8 (1.5–9.1)
	10	1.8 (0.6–4.6)	3	0.9 (0.2–3.3)
	6		6	
Current asthma	4	3.2 (1.0–9.9)	10	2.8 (1.1–58.0)
	8/60	1.4 (0.5–3.8)	2/36	0.6 (0.1–2.8)
	6/63		6/63	
History of ARC	3	1.3 (0.4–4.2)	8	1.3 (0.5–2.9)
	8	0.8 (0.3–1.8)	3	0.5 (0.1–1.6)
	11		11	
History of eczema	6	1.2 (0.6–2.4)	17	1.2 (0.7–2.0)
	21	0.9 (0.5–1.5)	10	0.7 (0.3–1.4)
	24		24	
Current ARC	1	0.4 (0.0–2.9)	6	0.9 (0.3–2.2)
	11	1.0 (0.4–2.1)	6	0.9 (0.3–2.2)
	12		12	
Current eczema	2	1.2 (0.2–5.2)	6	1.3 (0.4–3.5)
	7	0.9 (0.3–2.4)	3	0.7 (0.1–2.3)
	8		8	
Positive SPT	3	1.6 (0.5–5.3)	4/35	0.8 (0.2–2.5)
	6/59	0.7 (0.2–2.0)	5	1.0 (0.3–2.7)
	9		9	
Positive provocation test	6/10	2.0 (1.0–3.8)	12/33	1.2 (0.6–2.2)
	16/58	0.9 (0.5–1.6)	10/35	0.9 (0.4–1.8)
	18/59		18/59	

*Reference group.

ARC: allergic rhinoconjunctivitis; SPT: skin prick test. n is indicated if it differs from the original number.

(n = 37) in the VLBW group and the appropriate gestational age children (n = 61) in the term group (Table 1). Thus, there seemed to be no relationship between low birth weight and asthma after adjustment of gestational age. The exclusion of three term children in the analyses did not change the significance.

Very low birth weight children who had mechanical ventilation during the neonatal period had a significantly increased risk of a history of asthma and current asthma as compared with the term children (Table 2). A significantly increased risk was also shown in the VLBW children with neonatal oxygen supplementation. Several risk factors for a history of asthma among the VLBW children were considered, including very preterm birth, birth weight ≤ 1 kg, SGA, males, maternal asthma, maternal smoking during pregnancy or the first year, young maternal age, antenatal steroids administered to the mothers, delivery by Caesarean section, number of siblings, the use of antibiotics during the neonatal period and neonatal respiratory support including mechanical ventilation and oxygen supplementation. Of these, very preterm birth (RR 2.5, 95%CI 1.1–5.8), neonatal mechanical ventilation (RR 2.8, 95%CI 1.2–6.4) and neonatal oxygen supplementation (RR 4.3, 95%CI 1.3–14.0) were significantly associated with a history of asthma by the age of 12 years in univariate analyses. When the effects of very preterm birth, birth weight ≤ 1 kg, mechanical ventilation and oxygen supplementation during the neonatal period were analysed in multivariate logistic regression, oxygen supplementation seemed to be the only risk factor for a history of asthma (adjusted OR 4.2, 95%CI 0.95–19). This was particularly obvious for oxygen supplementation ≥ 9 days (adjusted OR 6.7, 95%CI 1.0–44). Furthermore, oxygen supplementation ≥ 9 days also seemed to be associated with current asthma (adjusted OR 8.1, 95%CI 0.98–68). This did not, however, reach statistical significance.

Children in the VLBW group who needed mechanical ventilation during the neonatal period (n = 13) were more likely to have bronchial hyperresponsiveness, than the VLBW children who did not require mechanical ventilation (n = 61, 60% vs. 28%, $p = 0.050$). The increased risk of bronchial hyperresponsiveness was obvious in the VLBW infants who needed mechanical ventilation ≥ 5 days (RR 2.9, 95%CI 1.5–5.4). There was also a higher degree of bronchial hyperresponsiveness in the VLBW children requiring mechanical ventilation, as compared with those not requiring mechanical ventilation, in the positive provocation tests (median value of response to dose ratio, 6.2%/ml vs. 2.1%/ml, $p = 0.012$).

The VLBW children were shorter and lighter at 12 years of age than the term children, but both the static spirometric results and the flow-volume curves were similar in the two groups when adjusted for predicted values (Table 3).

Table 3. Weight, height and lung function parameters at 12 years of age in very low birth weight (VLBW) and term children (mean $\pm$ SD)

	Total			Boys			Girls		
	VLBW n = 74	Term n = 64	p	VLBW n = 44	Term n = 33	p	VLBW n = 30	Term n = 31	p
Weight (kg)	43.0 $\pm$ 8.2	49.2 $\pm$ 11.7	<0.001	43.3 $\pm$ 8.4	49.5 $\pm$ 13.0	0.01	42.6 $\pm$ 7.8	48.8 $\pm$ 10.2	0.01
Height (cm)	152.7 $\pm$ 6.9	156.5 $\pm$ 7.6	<0.01	152.7 $\pm$ 7.0	156.6 $\pm$ 9.4	<0.05	152.7 $\pm$ 6.9	156.4 $\pm$ 5.1	<0.05
VC _{in} /pred.	0.84 $\pm$ 0.13	0.87 $\pm$ 0.10	ns	0.82 $\pm$ 0.12	0.86 $\pm$ 0.07	0.07	0.88 $\pm$ 0.14	0.87 $\pm$ 0.13	ns
VC _{ex} /pred.	0.84 $\pm$ 0.13	0.87 $\pm$ 0.10	ns	0.81 $\pm$ 0.12	0.87 $\pm$ 0.07	0.01	0.88 $\pm$ 0.14	0.87 $\pm$ 0.13	ns
FEV ₁ /pred.	0.92 $\pm$ 0.12	0.95 $\pm$ 0.10	ns	0.88 $\pm$ 0.10	0.92 $\pm$ 0.09	0.07	0.99 $\pm$ 0.12	0.98 $\pm$ 0.10	ns
FEF ₇₅ /pred.	0.93 $\pm$ 0.27	0.93 $\pm$ 0.28	ns	0.86 $\pm$ 0.27	0.93 $\pm$ 0.30	ns	1.01 $\pm$ 0.24	0.93 $\pm$ 0.26	ns
MMEF/pred.	0.85 $\pm$ 0.22	0.88 $\pm$ 0.20	ns	0.82 $\pm$ 0.22	0.87 $\pm$ 0.22	ns	0.91 $\pm$ 0.21	0.89 $\pm$ 0.18	ns

VC_{in}: inspiratory vital capacity; VC_{ex}: expiratory vital capacity; FEV₁: forced expiratory volume after 1 s.; FEF₇₅: forced expiratory flow at 75% of forced vital capacity; MMEF: maximal midexpiratory flow; ns: nonsignificant.

The VLBW boys had significantly lower VC_{ex} as compared with the term boys, before but not after adjustment for a history of asthma. Neither preterm birth, SGA or neonatal respiratory support had any impact on the spirometric values at 12 years.

The prevalence of ARC, eczema and positive skin prick tests were similar in the VLBW and the term children, regardless of preterm birth, SGA and neonatal respiratory support (Tables 1 and 2). Furthermore, the levels of total IgE, IL-4, IL-5 and IFN- γ were similar in the two groups (Fig. 1). There was no significant difference in the prevalence of a positive allergy screen between the VLBW and the term children (61% vs. 39%, $p = 0.13$). The use of antibiotics during the neonatal period was the only independent risk factor for a history of eczema (adjusted OR 11.9, 95%CI 1.4–99) after adjusting for very preterm birth and birth weight ≤ 1 kg. However, use of antibiotics was not associated with atopy (skin prick test positivity).

Discussion

A history of asthma by the age of 12 years was twice as common among the VLBW children as among the term children. This was in line with a cross-sectional study (1) and a prospective study (2). We also revealed oxygen supplementation during the neonatal period to be the only independent risk factor for asthma. Oxygen supplementation during the neonatal period has been shown to be associated with a low FEV₁ in VLBW children at 11 years of age (8), and the mechanism behind this is not well understood. Airway inflammation is present in premature infants during their first month of life (25). It is conceivable that VLBW infants who required oxygen supplementation may have more severe respiratory problems and airway inflammation

than those not requiring oxygen supplementation. It is also conceivable that neonatal oxygen supplementation may aggravate the airway inflammation and damage the lung in VLBW infants, thus increasing the risk of asthma. Airway hyperresponsiveness and inflammation have been demonstrated in animal models with a prolonged moderate hyperoxia (26, 27). Interestingly, maternal asthma and environmental factors such as maternal smoking during pregnancy or the first year were not risk factors for asthma among the VLBW children. It differed from the term children, indicating that family history may have less influence on childhood asthma among the VLBW children (8).

The cumulative incidence of a history of asthma, as identified by ISAAC questionnaires among the term children, was similar to the findings in a previous study from the same region (28). Three experienced pediatricians performed the follow-up examinations on both the VLBW and the term children. Although the investigators were not always unaware of which group the child belonged to, the case history and examinations were performed according to a strict protocol to reduce any observer biases.

Pulmonary surfactants reduce wheezing at 8 years of age from 50% to 16% in VLBW infants with BPD, and antenatal steroid therapy may also have a protective effect against wheezing later in childhood (2). Pulmonary surfactants were not available in neonatal care at that time in Sweden and the lack of effect of antenatal steroids in our study might be false because there were too few cases. Thus, the use of surfactants would possibly reduce the risk of asthma among VLBW children.

A permanent impairment of alveolar development and hypertrophy of airway smooth muscle in VLBW infants who were subject to mechanical ventilation (11, 12) may induce airway

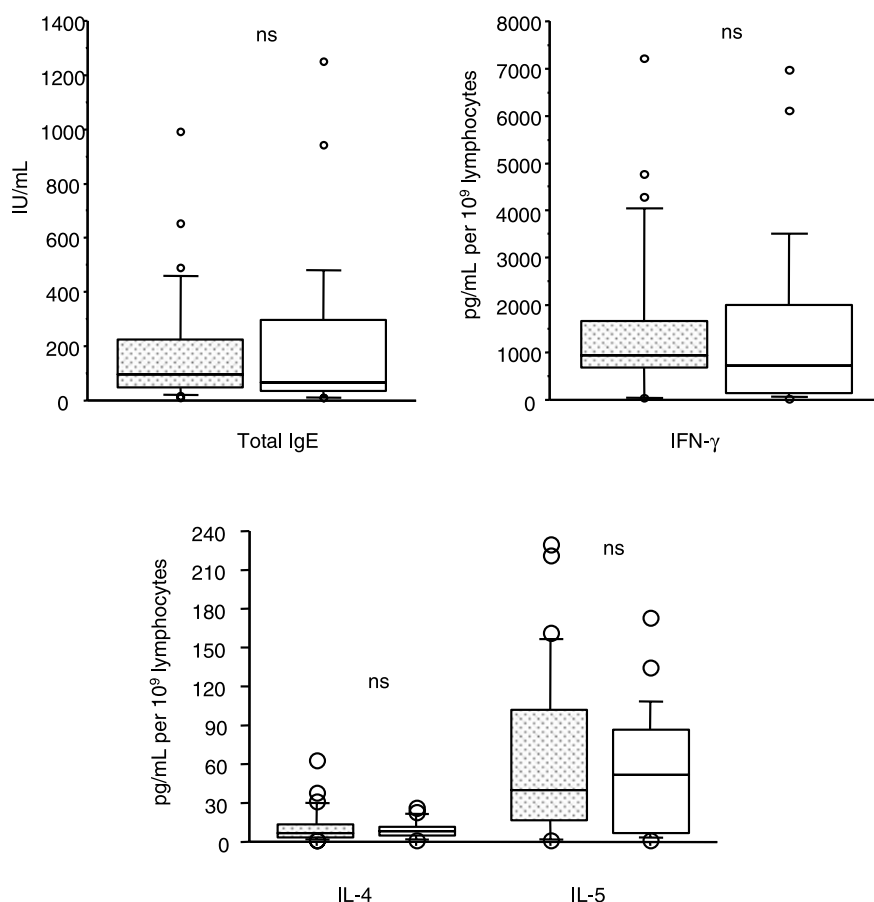


Fig. 1. The levels of total IgE, IFN- γ , IL-4 and IL-5 in the very low birth weight (shaded boxes) and term (open boxes) children. Cytokine production is expressed as pg/ml per 10⁹ lymphocytes. The 10th, 25th, 50th, 75th and 90th percentiles are indicated. The comparisons were made with Mann-Whitney U-test. ns: nonsignificant.

remodelling, which may explain the association between mechanical ventilation during the neonatal period and bronchial hyperresponsiveness at 12 years.

Lung function, as determined by spirometric tests, was similar at 12 years of age among the VLBW and the term children after adjustment for body size. This indicated that the VLBW children had a catch-up development in their lung function relative to body measures, although they did not catch up with their term peers in weight and height. Thus, small airway size relative to body size was not the case in the VLBW children, and it could not explain the increased risk of asthma among VLBW children in the present study.

Low birth weight and prematurity have been reported to be inversely related to atopic eczema (15) and positive skin prick tests (18). Furthermore, a lower prevalence of allergic rhinitis has been found in Swedish conscripts with low gestational age (29). We could not confirm any significant relationship between VLBW and atopic manifestations, since the prevalences of ARC, eczema and positive skin prick tests were similar in the VLBW and the term children. In

addition, the levels of IgE in serum and IL-4, IL-5 and IFN- γ *in vitro* did not differ significantly between the two groups. This might possibly be due to type II error, as cytokine analyses were only performed in less than half of the children. A previous study, however, also failed to show any significant relationship (30).

The use of antibiotics was the only identified risk factor for the development of eczema in the VLBW group, but it was not associated with atopy. The finding of no increase in atopy among the VLBW children, despite their markedly higher use of early antibiotics, argued against antibiotics at an early stage being an important determinant of atopy (31).

In summary, a history of asthma by 12 years of age was twice as common among the VLBW children as among the term children, and neonatal oxygen supplementation seemed to be associated with the increased risk, but the reasons have not been established. Furthermore, mechanical ventilation during the neonatal period was associated with bronchial hyperresponsiveness at age 12. Very low birth weight was not, however, significantly related to atopy. It addresses an important clinical issue in that the

determinants of childhood asthma are not necessarily the determinants of childhood atopy, since asthma is a heterogeneous disease (32). Very low birth weight may lead to nonatopic rather than atopic asthma.

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References

- BROOKS AM, BYRD RS, WEITZMAN M, AUINGER P, MCBRIDE JT. Impact of low birth weight on early childhood asthma in the United States. *Arch Pediatr Adolesc Med* 2001; 155: 401–6.
- PALTA M, SADEK-BADAWI M, SHEEHY M, et al. Respiratory symptoms at age 8 years in a cohort of very low birth weight children. *Am J Epidemiol* 2001; 154: 521–9.
- DOYLE LW, CHEUNG MM, FORD GW, OLINSKY A, DAVIS NM, CALLANAN C. Birth weight < 1501 g and respiratory health at age 14. *Arch Dis Child* 2001; 84: 40–4.
- KENNEDY JD, EDWARD LJ, BATES DJ, et al. Effects of birthweight and oxygen supplementation on lung function in late childhood in children of very low birth weight. *Pediatr Pulmonol* 2000; 30: 32–40.
- MCLEOD A, ROSS P, MITCHELL S, et al. Respiratory health in a total very low birthweight cohort and their classroom controls. *Arch Dis Child* 1996; 74: 188–94.
- KELLY YJ, BRABIN BJ, MILLIGAN P, HEAF DP, REID J, PEARSON MG. Maternal asthma, premature birth, and the risk of respiratory morbidity in schoolchildren in Merseyside. *Thorax* 1995; 50: 525–30.
- VON MUTIUS E, NICOLAI T, MARTINEZ FD. Prematurity as a risk factor for asthma in preadolescent children. *J Pediatr* 1993; 123: 223–9.
- GIFFIN F, GREENOUGH A, YUKSEL B. Does a family history of atopy influence lung function at follow-up of infants born prematurely? *Acta Paediatr* 1995; 84: 17–21.
- DARLOW BA, HORWOOD LJ, MOGRIDGE N. Very low birthweight and asthma by age seven years in a national cohort. *Pediatr Pulmonol* 2000; 30: 291–6.
- PELKONEN AS, HAKULINEN AL, TURPEINEN M. Bronchial lability and responsiveness in school children born very preterm. *Am J Respir Crit Care Med* 1997; 156: 1178–84.
- HISLOP AA, WIGGLESWORTH JS, DESAI R, ABER V. The effects of preterm delivery and mechanical ventilation on human lung growth. *Early Hum Dev* 1987; 15: 147–64.
- HISLOP AA, HAWORTH SG. Airway size and structure in the normal fetal and infant lung and the effect of premature delivery and artificial ventilation. *Am Rev Respir Dis* 1989; 140: 17–26.
- WEGMANN TG, LIN H, GUILBERT L, MOSMANN TR. Bidirectional cytokine interactions in the maternal–fetal relationship: is successful pregnancy a TH2 phenomenon? *Immunol Today* 1993; 14: 353–6.
- MARZI M, VIGANO A, TRABATTONI D, et al. Characterization of type 1 and type 2 cytokine production profile in physiologic and pathologic human pregnancy. *Clin Exp Immunol* 1996; 106: 127–33.
- BÜHRER C, GRIMMER I, NIGGEMANN B, OBLADEN M. Low 1-year prevalence of atopic eczema in very low birthweight infants. *Lancet* 1999; 353: 1674.
- GRÖNLUND MM, SALMINEN S, MYKKÄNEN H, KERO P, LEHTONEN OP. Development of intestinal bacterial enzymes in infants – relationship to mode of delivery and type of feeding. *Apmis* 1999; 107: 655–60.
- BJÖRKSTÉN B. The intrauterine and postnatal environments. *J Allergy Clin Immunol* 1999; 104: 1119–27.
- SILTANEN M, KAJOSAARI M, POHJAVUORI M, SAVILAHTI E. Prematurity at birth reduces the long-term risk of atopy. *J Allergy Clin Immunol* 2001; 107: 229–34.
- ISAAC STEERING COMMITTEE. Phase II Modules of the International Study of Asthma and Allergies in Childhood (ISAAC). Münster: Institute of Epidemiology and Social Medicine, University of Münster, 1998.
- BYLUND B, CERVIN T, FINNSTRÖM O, et al. Morbidity and neurological function of very low birth weight infants from the newborn period to 4 y of age. A prospective study from the south-east region of Sweden. *Acta Paediatr* 1998; 87: 758–63.
- BYLUND B, CERVIN T, FINNSTRÖM O, et al. Very low-birth-weight children at 9 years: school performance and behavior in relation to risk factors. *Prenat Neonat Med* 2000; 5: 124–33.
- ZAPLETAL A, SAMANEK M, PAUL T. Lung function in children and adolescents. In: HERZOG H. *Progress in Respiration Research*. Basel, Karger, 1987, Vol. 22.
- SPECTOR SL. *Provocation Testing in Clinical Practice*. New York: Marcel Dekker, 1995: pp. 455–6.
- JENMALM MC, VAN SNICK J, CORMONT F, SALMAN B. Allergen-induced Th1 and Th2 cytokine secretion in relation to specific allergen sensitisation and atopic symptoms in children. *Clin Exp Allergy* 2001; 31: 1528–35.
- SHEIKH S, NULL D, GENTILE D, et al. Urinary leukotriene E(4) excretion during the first month of life and subsequent bronchopulmonary dysplasia in premature infants. *Chest* 2001; 119: 1749–54.
- DENIS D, FAYON MJ, BERGER P, et al. Prolonged moderate hyperoxia induces hyperresponsiveness and airway inflammation in newborn rats. *Pediatr Res* 2001; 50: 515–9.
- SCHULMAN SR, CANADA AT, FRYER AD, WINSETT DW, COSTA DL. Airway hyperreactivity produced by short-term exposure to hyperoxia in neonatal guinea pigs. *Am J Physiol* 1997; 272: L1211–6.
- ANNUS T, BJÖRKSTÉN B, MAI X-M, et al. Wheezing in relation to atopy and environmental factors in Estonian and Swedish schoolchildren. *Clin Exp Allergy* 2001; 31: 1846–53.
- BRÅBACK L, HEDBERG A. Perinatal risk factors for atopic disease in conscripts. *Clin Exp Allergy* 1998; 28: 936–42.

30. STRACHAN DP, HARKINS LS, JOHNSTON ID, ANDERSON HR. Childhood antecedents of allergic sensitization in young British adults. *J Allergy Clin Immunol* 1997; 99: 6–12.
31. CELEDON JC, LITONJUA AA, RYAN L, WEISS ST, GOLD DR. Lack of association between antibiotic use in the first year of life and asthma, allergic rhinitis or eczema at age 5 years. *Am J Respir Crit Care Med* 2002; 166: 72–5.
32. PEARCE N, PEKKANEN J, BEASLEY R. How much asthma is really attributable to atopy? *Thorax* 1999; 54: 268–72.