

Pulmonary function in children with initial low birth weight

Wjst M, Popescu M, Trepka MJ, Heinrich J, Wichmann H-E. Pulmonary function in children with initial low birth weight.
Pediatr Allergy Immunol 1998; 9: 80–90. © Munksgaard 1998.

The objective of this analysis was to examine the effect of low birth weight and prematurity on bronchial air-flow, bronchial reactivity, airway symptoms and asthma diagnosis at school age. A cross-sectional epidemiological study was performed in three small towns in the eastern part of Germany on 2470 school children aged 5–14 (89.1% of eligible children). A 78 item questionnaire to determine risk factors at birth and in early childhood was employed. 7.8% of the children were born before completing 38 gestational weeks; 6.6% had a birth weight less than 2500 g. Pulmonary function analysis were done by a mobile plethysmography at the school. There were only weak restrictions in lung volume in term low birth weight (LBW) children (100 ml lower TLC, $p=0.107$), and flow (257 ml lower PEF, $p=0.108$), were low. However, bronchial hyper-responsiveness indicated by 292 ml lower FEV_{1.0} after cold air bronchial provocation, was significantly increased compared to term normal birth weight children ($p<0.001$). The effect of LBW was less in older children, only slightly stronger in girls and increased in children mechanically ventilated during the postnatal period. Correspondingly, there was a higher prevalence of diagnosed asthma in term LBW children (OR 1.6, 95%-confidence interval 1.0–2.6), however these were without an increased risk for any allergic sensitization. LBW, therefore, seems to be a risk factor for smaller lungs and hyperreactive airways primarily in term born children, whereas in pre-term children the immature bronchial system seems to be recover by school age.

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Key words: asthma; bronchial hyperreactivity; respiratory function test; premature infant; low birth weight infant

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Accepted 25 March 1998

The recent advances in neonatal intensive care have substantially improved the survival of low birth weight (LBW) infants (1). Respiratory problems following neonatal respiratory distress, however, have been frequently observed (2). The majority of the clinical studies dealing with this problem report follow-up of infants ventilated in the early 1970s for bronchopulmonary dysplasia (3–5), which was first described in 1967 by Northway (6). Many of the available studies are flawed by their design, low numbers of participants, and from today's point of view, technical limitations. Less is known currently about the long-term respiratory outcome of LBW in general. Only a few studies have investigated pulmonary function and bronchial hyperreactivity of formerly LBW children.

The aim of the current analysis is to examine the effect of low birth weight and prematurity on lung volume, flow and bronchial hyperresponsiveness (BHR) together with the clinical manifestation of airway symptoms and asthma diagnosis at school

age. Birth weight has been used as a measure of fetal growth but it is strongly dependent on gestational age (7). Because prematurity itself may influence later pulmonary development, the effects of prematurity and birth weight will be assessed separately as much as possible.

Subjects and methods

Subjects and Setting

The study was conducted in the eastern part of Germany. The presented results are from the first survey in 1992/1993 of an ongoing cohort study of the effects of genetic and environmental factors on respiratory health. Three age groups of school children formed the study population: school entrants (5–7 years old), third graders (8–10 years old), and sixth graders (11–14 years old). All participants were Caucasians. All school children in these age groups in the small towns of Zerbst and Hettstedt and of a

randomly selected subgroup of schools in Bitterfeld school were invited to participate. Approval of the study design and examinations was granted by the University of Rostock Ethics Committee.

Informed and written consent was obtained from all parents.

Questionnaire

Letters explaining the study as well as the questionnaires were distributed to the children's parents by the class teacher and collected one week later. The parents of 89.1% of the children filled out the questionnaires. The questionnaire had 78 items and was developed using questions previously tested in several national (see (8) repeatability data) and international studies (9) adapted to address East German living conditions. In detail, the questions addressed socioeconomic factors, housing characteristics, nutrition, indoor environmental exposures such as environmental tobacco smoke, and outdoor environmental exposures such as proximity of home to an industrial complex. For birth weight (question 5) the parents were asked, "How much did your child weigh at birth? Please look at the child's birth record" with a four digit space for answer. For prematurity (question 6) they were asked, "Was your child premature, e.g. 3 weeks before calculated date?" with the answer categories yes/no/do not know. During the physical examination, the recorded birth weight was validated by the original birth certificate. The wording of the other question was: "Did a physician ever notice one of following diseases?" (answer categories: asthma, asthma-like bronchitis, obstructive bronchitis, bronchitis, none of these) "If your child suffered from asthma, did he or she have asthma attacks during the last year?" "Does your child cough frequently in the morning or during the day without having a cold?" "Did your child ever experience wheezing during breathing?" (answer categories: never, one time, several times, do not know). For a diagnosis of asthma, the first two answer categories were combined.

Pulmonary Function Tests

Technicians were trained at the beginning of the study. The children were examined throughout the whole year, except from July through August to September because of school vacations. Each child was asked about present respiratory illness. Height and weight were measured with clothes but without shoes. Then pulmonary function tests were performed from 8 a.m. to 2 p.m. using in random order either an electronic spirometer or a bodyplethysmograph (both from Jaeger, Wuerzburg, Germany) mounted on a bus. Subjects did forced expiration in a

sitting position using a nose-clip. The forced vital capacity (FVC), forced expiratory volume in one second (FEV_{1.0}), forced expiratory peak flow (PEFR) and forced expiratory flows at 25% FVC expired (MEF75VC), at 50% FVC expired (MEF50VC), and at 75% FVC expired (MEF25VC) were recorded, followed by a whole bodyplethysmography with total lung capacity (TLC), residual volume (RV) and airway resistance (RTOT). Units of measurements are shown in Table 1. Forced flow volume tests were performed until three reproducible loops were achieved. Of these, the test with the maximum sum of FVC and FEV_{1.0} was used for the analysis. All spirometers were calibrated daily. Cold air challenge with -15°C air was carried out using a respiratory heat exchange system (Jaeger, D-Wuerzburg, Germany) as described earlier (10). The children hyperventilated cold air supplemented with 5% carbon dioxide for four minutes at 75% of their maximum rate of ventilation per minute. Pulmonary function testing was repeated within the following five minutes.

Skin prick tests and RAST determination

Skin prick tests (SPT) were done on the same occasion as the pulmonary function tests. A SPT result was defined as positive if the diameter of the elevated skin reaction on the right forearm was at least 3 mm 15 minutes after puncturing the skin with lancets manufactured by ALK (Horsholm, Denmark). Tested and analyzed allergens were mixed grass, birch (*Betula verrucosa*), hazel (*Corylus avellana*), ribwort (*Plantago lanceolata*), mugwort (*Artemisia vulgaris*), mites (*D. pteronyssinus*, *D. farinae*), animal epithelia (cat), fungi (*Aspergillus fumigatus*), and food antigens (milk, egg). All allergens in this survey were obtained by Allergopharma (Reinbeck, Germany). A positive control (histamine chloride) and a negative control (dilution of sodium chloride) were also examined, but not included in the analysis. At least one positive SPT of the above allergens was necessary for the definition of a positive SPT.

Serum samples were drawn from more than 80% of the children, all of whom consented, and were immediately frozen and stored at -80°C until they could be analyzed together at the end of the second survey. Specific serum IgE was determined in the Pharmacia laboratory (Freiburg) with the RAST technique (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). The following antigens were tested: *Ascaris* p 1, grass g 6, *Dermatophagoides pteronyssinus* d 1, cat e 1 and birch t 3. Levels greater than or equal to 0.35 IU/ml (level 1 on the RAST scale) were considered as positive antibody concentration. At least one positive reaction to grass or *D. pteronyssinus* was necessary for a positive RAST sensitization.

Table 1. Respiratory symptoms and diseases in 2470 children of the Bitterfeld study 1992/1993 by gestational age and birth weight. Preterm birth was defined as pregnancy with less than 38 gestational weeks and low birth weight (LBW) as less than or equal 2500g in contrast to normal birth weight (NBW).

	prevalence number (% of group)				Odds ratio with 95% confidence limits compared with term NBW children, adjusted for age and sex					
	preterm birth		term birth		preterm birth		term birth			
	LBW	NBW	LBW	NBW	LBW vs. term NBW		NBW vs. term NBW		LBW vs. term NBW	
number of children	N=98	N=89	N=58	N=2,092	OR	CI	OR	CI	OR	CI
former or current asthma	1 (1.0)	1 (1.1)	2 (3.5)	19 (0.9)	0.79	0.19–3.28	1.14	0.63–2.06	1.42	1.00–2.02
current asthma	2 (2.0)	3 (3.4)	4 (6.9)	54 (2.6)	1.13	0.15–8.51	1.09	0.40–3.01	1.61	0.98–2.64
cough without cold	11 (12.1)	4 (4.7)	7 (12.7)	124 (6.2)	2.09	1.08–4.04	0.86	0.52–1.44	1.29	0.98–1.69
recurrent wheezing	14 (14.3)	11 (12.4)	6 (10.3)	248 (11.9)	1.24	0.69–2.22	1.01	0.73–1.40	0.96	0.72–1.27
allergic rhinitis	4 (4.1)	1 (1.1)	2 (3.5)	93 (4.4)	0.93	0.33–2.59	0.49	0.10–1.32	0.95	0.59–1.52
any SPT positive	14 (16.5)	16 (20.8)	9 (16.9)	359 (19.2)	0.84	0.47–1.51	1.04	0.78–1.38	0.98	0.77–1.25
any RAST positive	23 (29.5)	21 (31.8)	11 (25.6)	493 (30.2)	0.95	0.58–1.58	1.03	0.79–1.35	0.96	0.76–1.21

Analysis

Pulmonary function data were stored after the examination on personal computers and transferred later to a mainframe computer. The questionnaire data were entered twice and checked before merging with the pulmonary function data. All subsequent statistical analyses were performed using SAS (Statistical Analysis Software 6.08, Cary, NC, PROC FREQ, GLM, LOGISTIC) (11). Preterm birth was defined as birth after a pregnancy with less than 38 gestational weeks. LBW was defined as weight less or equal than 2500 g. The first quartile of the actual height of the children ranged from 104 cm to 122 cm, the second to 137 cm, the third to 152 cm and the fourth to a maximum of 178 cm as used in Fig. 3.

Pulmonary function values were converted to logarithms before any further calculation. Of 2470 available data sets, 388 had to be excluded from the pulmonary function analysis because of missing or incomplete data (Fig. 1). The analysis of pulmonary function relied on a multiple regression model. Each pulmonary function variable was analyzed in a separate model including the birth weight group of interest and the term normal birth weight children as controls. The natural logarithm (ln) of the pulmonary function value was then modelled with height, sex and age (Table 1). Other possible confounders as assessed in the questionnaire could be excluded in a preliminary analysis. A multiple logistic regression was used to estimate the effect of LBW on respiratory symptoms, while controlling for the effects of age and sex.

An expected 5% asthma prevalence in 2500 children compared with an expected 1.5 fold increase in prevalence in 225 LBW children would be detected

under the assumption of one-tailed $\alpha=0.05$ at a power of 0.46.

Results

Data on 2470 children could be analyzed (Fig. 1). In each age group more than 750 children participated; 49.5% of the children were female. The prevalence of preterm birth was 7.8% and of LBW 6.6%. Combined prematurity and LBW was reported in 98 (4.2%) children, prematurity alone in 89 (3.8%) and LBW alone in 58 (2.5%) children. The distribution of birth weight in the full term children shows a smaller first peak at 2,500 g and a second larger one at 3500 g (Fig. 2). The preterm children had generally lower birth weights with slight peak around 2500 g. There was no difference in the sex ratio between preterm and full-term children or between low- and normal birth weight children.

The odds ratios for either LBW or premature children (adjusted for age and sex) compared with term NBW are 1.5 (95% confidence limit 0.7–3.0) for asthma ever, 1.8 (0.6–5.4) for actual asthma, 1.6 (1.0–2.6) for cough without cold and 1.1 (0.7–1.6) for wheezing. Table 1 shows the occurrence of respiratory symptoms and asthma by the separate groups. The risk of physician-diagnosed current or former asthma is increased with an odds ratio (OR) of 1.6 (CI 1.0–2.6) and of 1.4 (CI 1.0–2.0), respectively, in full-term LBW. Cough without cold is significantly increased only in preterm LBW children. No significant differences could be found between boys and girls. There was no difference in allergic sensitization, whether by SPT or RAST between the different groups in children. In summary, asthma was seen more frequently in LBW full term children without any increase in allergic sensitization. In the

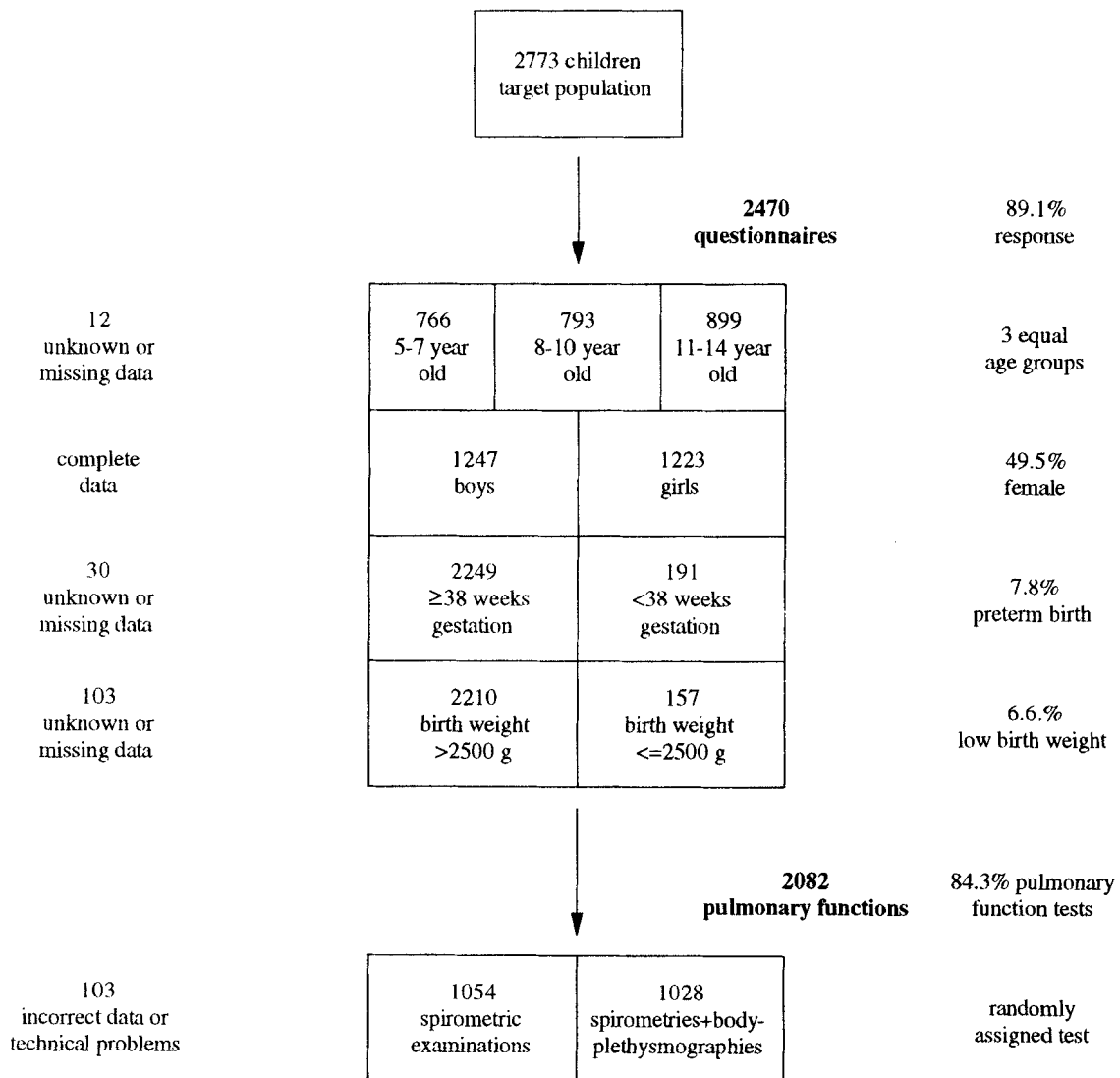


Fig. 1. Selection of the study population.

other groups, respiratory symptoms are not consistently increased, with no clear symptom pattern for the upper or lower respiratory tract.

The results of the pulmonary function test are shown in Table 2. Compared with children at full term birth and normal weight, the RV is predominantly reduced in preterm LBW children, resulting in a significantly reduced RV/TLC ratio ($p=0.034$). RV is also reduced in full term LBW children but due to the reduced TLC, the RV/TLC ratio is normal. The reduced TLC is also correlated with reduced FVC and $FEV_{1.0}$ in the same group, but has a large variation, not reaching a nominal significance level ($p=0.107$). The static lung volume seems

therefore restricted primarily in LBW children. In the LBW children with preterm birth, the residual volume is diminished ($p=0.063$). In contrast, the bronchial resistance is not increased in LBW. All bronchial flow parameters are normal in preterm LBW children, but slightly reduced in the large airways of full term LBW children ($p=0.307$). The results of the airway challenge procedure are in the same direction, e.g. that full term LBW children have a statistically significant lower $FEV_{1.0}$ level after cold air challenge ($p=0.001$). The relative decrease of the baseline $FEV_{1.0}$, however, is not exaggerated by low initial $FEV_{1.0}$ level. In summary, there are only weak abnormalities in the RV of pre-

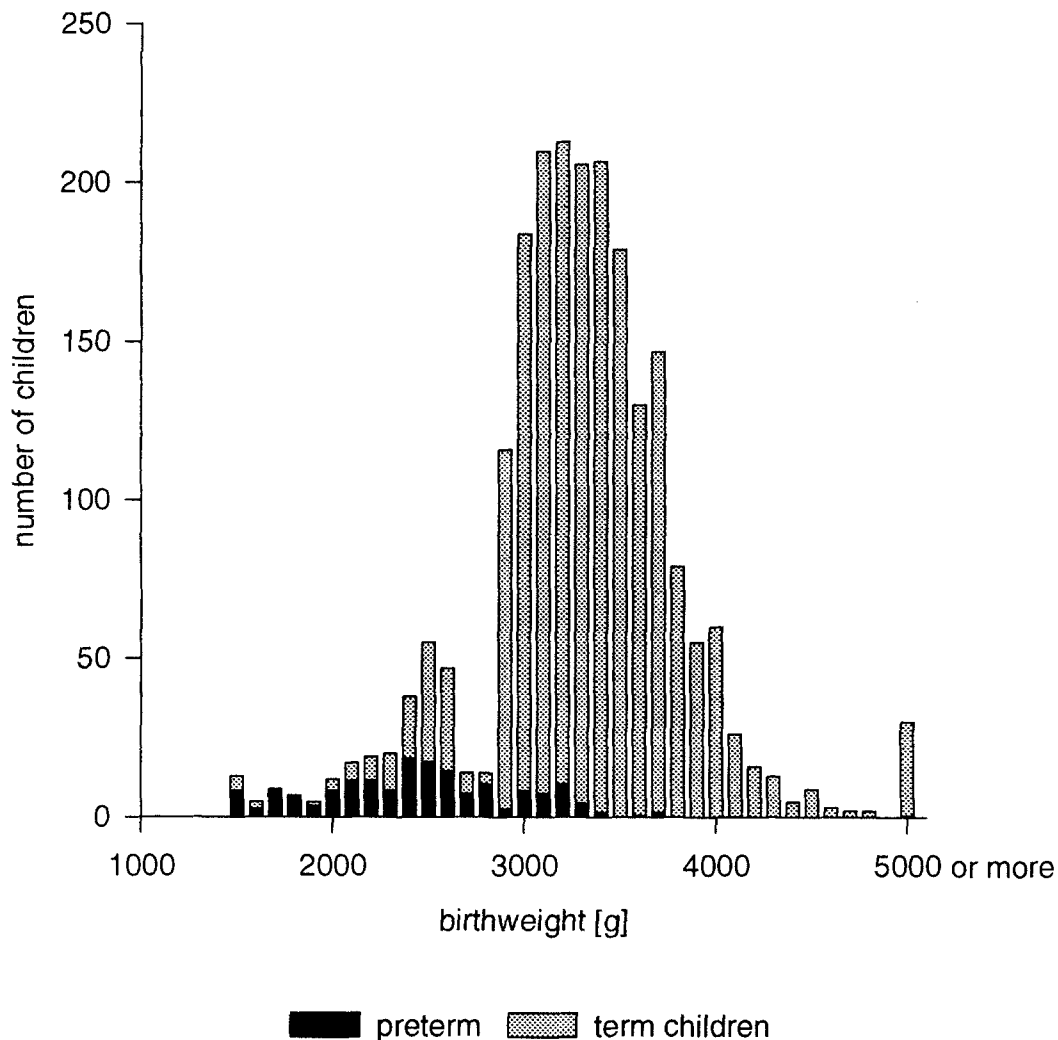


Fig. 2. Distribution of birth weight in the study population stratified by gestational date of birth.

term LBW children, but measurable restrictions in lung size, bronchial flow and bronchial reactivity to cold air in full term LBW children.

Because birthweight was shown as a major factor for reduced pulmonary function, FEV_{1.0} baseline values are examined in the same subgroups (Fig. 3). As expected, FEV_{1.0} increases with age. FEV_{1.0} values in term LBW children could be seen in all subgroup analyses with stronger effects of boys than girls and with increasing height. Among the children requiring ventilatory support during the neonatal period FEV_{1.0} is reduced primarily in LBW term children compared to term NBW children ($p=0.009$).

Discussion

We have shown smaller lung sizes of full term LBW children (100 ml lower TLC compared to full term NBW, $p=0.107$), bronchial airflow (257 ml lower PEFR, $p=0.108$) and increased bronchial hyperreactivity (292 ml lower FEV_{1.0} after bronchial challenge, $p<0.001$). The effect of LBW decreased with increasing age, was slightly greater in girls and was increased in children requiring mechanical ventilation during the prenatal period. This is in accordance with a higher prevalence of asthma diagnoses among LBW term children (OR 1.6, 95%-CI 1.0–

Table 2. Pulmonary function parameters in 2,082 children (TLC, RV and RTOT tested only in 1028 children) of the Bitterfeld Study 1992/1993 by gestational age and birth weight. Preterm birth was defined as pregnancy of less than 38 gestational weeks and low birth weight (LBW) as less than 2500g, in contrast to normal birth weight (NBW). All pulmonary function values were logarithmized before and antilogged after the calculations. For abbreviations see the Methods section.

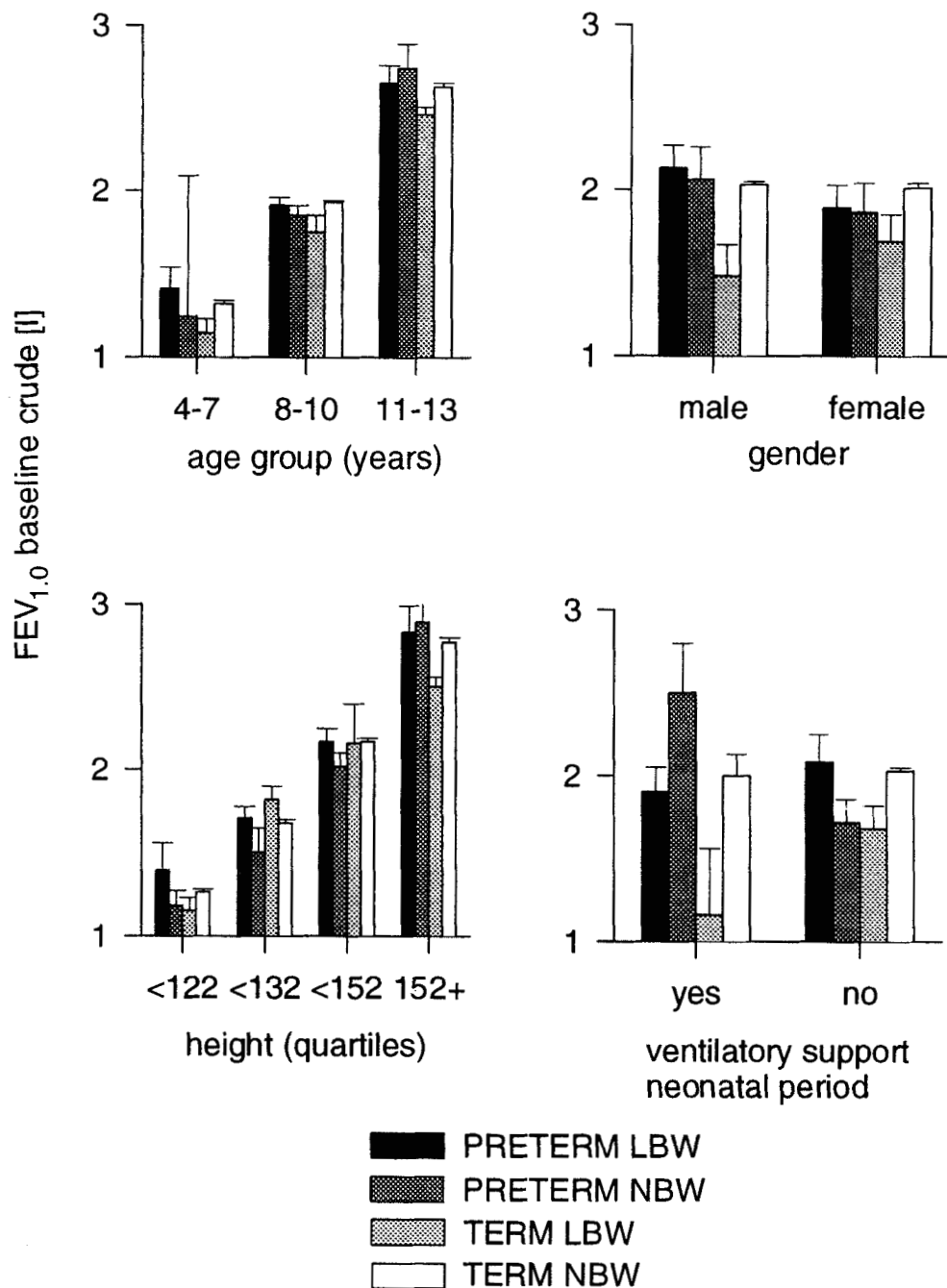
	mean value				differences in the mean value compared to term NBW, adjusted for height, sex and age					
	preterm birth		term birth		preterm birth		NBW		term birth	
	LBW	NBW	LBW	NBW	LBW				LBW	
pulmonary function parameter baseline	mean±S.D	mean±S.D	mean±S.D	mean±S.D	Δ [ml]	P Δ [ml]		P Δ [ml]		P
TLC [l]	2.01±1.48	1.91±1.54	1.61±1.43	2.07±1.43	-4	0.935	-61	0.218	-105	0.107
RV [l]	0.62±2.20	0.74±1.53	0.67±1.61	0.77±1.66	-137	0.063	-1	0.991	12	0.869
RV/TLC [%]	24.0±1.7	29.6±1.4	30.2±1.6	28.7±1.5	-4.7	0.034	0.4	0.831	0.0	0.985
RTOT [kPa*s/l]	0.52±1.58	0.49±1.60	0.57±1.44	0.49±1.54	0.0	0.476	0.0	0.442	-6.8	0.831
FVC [l]	2.01±1.48	1.91±1.54	1.61±1.43	2.07±1.43	-4	0.935	-61	0.218	-93	0.107
FEV _{1.0} [l]	1.90±1.41	1.78±1.49	1.52±1.43	1.92±1.39	21	0.629	-66	0.171	-86	0.182
PEF [l/s]	3.51±1.55	3.37±1.59	2.80±1.66	3.60±1.45	-22	0.849	-64	0.626	-257	0.108
MEF75 [l/s]	3.27±1.53	3.08±1.59	2.67±1.66	3.36±1.45	-17	0.873	-125	0.307	-176	0.276
MEF50 [l/s]	2.51±1.41	2.34±1.51	2.09±1.50	2.57±1.39	-8	0.923	-132	0.161	-154	0.218
MEF25 [l/s]	1.38±1.39	1.24±1.47	1.16±1.35	1.38±1.41	31	0.607	-90	0.163	-63	0.467
pulmonary function parameter after cold air										
FEV _{1.0} [l]	1.91±1.41	1.76±1.33	1.41±1.62	1.96±1.37	26	0.546	-35	0.477	-292	0.001
Δ FEV _{1.0} [%]	0.88±2.19	2.10±1.40	1.53±1.58	1.20±1.91	-0.3	0.091	0.6	0.167	0.1	0.764

2.6). Pulmonary and bronchial symptoms, however, were not consistently increased in the other groups of preterm children.

The study has the strength of a carefully standardized and extensive respiratory function measurements. While cross-sectional studies by the nature of their design cannot establish causal relationships, a more than occasional association may be assumed for several reasons: First, a recall bias for birth weight was ruled out in most cases by validating the parents' recordings with the original birth certificate. About 75% of all reported birth weights were accurate to within 100 g and a similar proportion of reported gestational age was correct within one month in another study (12). We can therefore assume that the reported gestational age is also correct in our study. The interval time from the last menstruation before the pregnancy may be less accurate than determining the gestational age of the newborn directly by physical examination, but the latter is not done routinely. Second, selection bias is unlikely to have occurred since the response rate of the participants was nearly 90%. There may be, however, a masked selection by survival, with the consequence that the results are valid only for surviving newborns. The number of children with neonatal respiratory distress syndrome (RDS) is not known exactly but was estimated to 20% among premature infants with hyaline membrane disease (HMD) (13). Because HMD occurs at a rate of approximately 10 per 1000 live births, the overall incidence of RDS is estimated to approximately 2 per 1000 live births,

leading to an estimate of 3 children in our population which is too small to cause any significant effect. However, a "healthy child" effect might have influenced the results particularly in the youngest age group. Sick children who did not attend school were not reached by the survey. Third, exposure and outcome were assessed blindly by objective methods and the analysis strategy designed before calculations were made. Fourth, the association was clinically important. The objective lung function measurements and subjective symptom and diagnosis reporting show a consistent pattern. Fifth, an adjustment for the most important factors like age, sex and height was done. Residual confounding, however, is possible. A "dose-response relationship" of birth weight and pulmonary function which would strongly support a causal relationship could not be shown, due to either a missing association or the small sample size. As shown in the Methods section, the power of the study was rather low. Further studies should use a larger sample size, e.g. at least 200 children per group. The present study gains from being whole population based but does not have the ability to discriminate effects that might only occur in those with more extreme prematurity or extreme degrees of low birth weight.

Lastly, the findings are consistent with those from earlier case-control and cohort studies. More than 100 studies were identified that examined date of birth and later outcome on the respiratory tract. Summarized in Table 3 are studies of children older than one year at the last examination, with a sample



* with questionnaire data for asthma

Fig. 3. FEV_{1.0} values in different subgroups. Age (upper left), gender (upper right), actual height (lower left) and ventilatory support (lower right) stratified by birth weight group LBW=low birth weight, NBW=normal birth weight.
* with questionnaire data for asthma.

size of more than 50 children, and with the selection of a control group. Furthermore, studies which were specifically designed for therapeutic interventions such as mechanical ventilation, surfactant or steroid

therapy were excluded. This reduced the number to 18 studies, five cross-sectional (1, 7, 14–16), five case-control (2, 17–20) and eight cohort studies (21–27). Eleven studies included at least one pulmo-

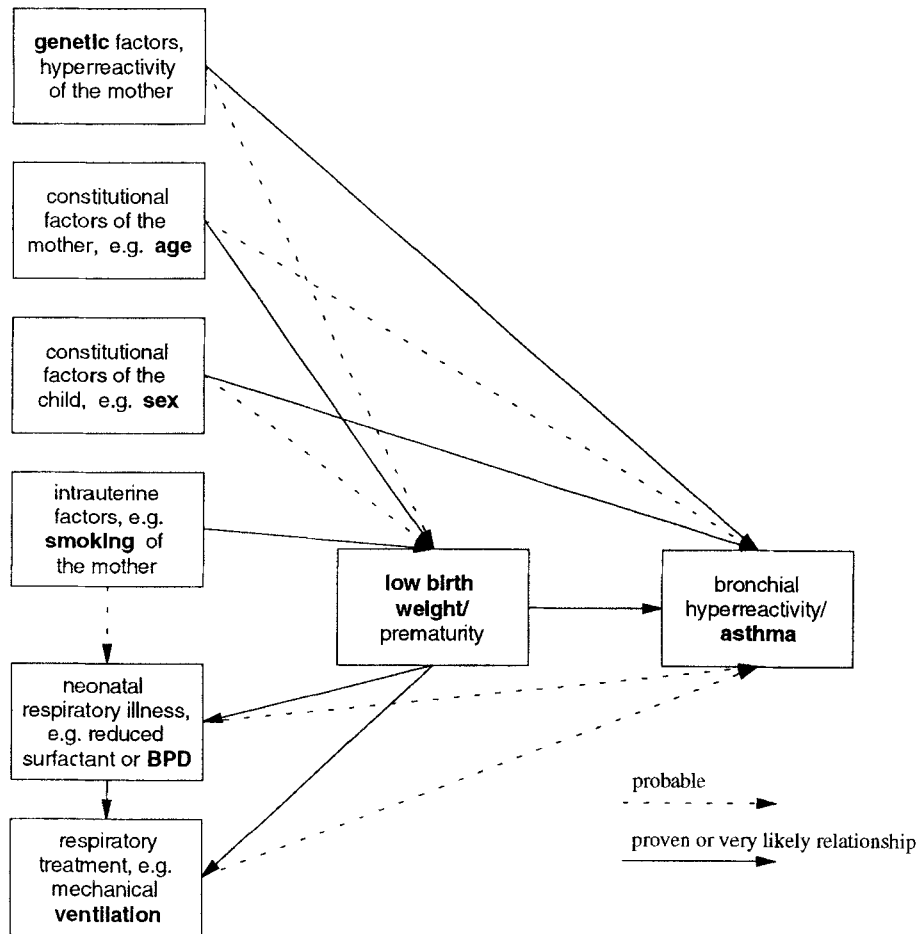


Fig. 4. Relationship of various factors with birth weight and asthma. Early neonatal exposure to pollutants, allergens and respiratory infection seems also to be related with later asthma but is not related to birth weight.

nary function test and seven included a bronchial provocation procedure (methacholine, cold air challenge, exercise test).

Airway symptoms were recorded in 14 of these studies. The results were consistent with our study, all showing an association with birth weight. The relationship with physician-diagnosed asthma was examined in 11 studies with only five showing a positive association. These inconsistencies might be explained primarily by different diagnostic thresholds and different definitions of asthma. In conjunction with the results of the respiratory function tests and the symptom reporting, an effect of LBW on asthma prevalence is likely, while the effect size remains to be determined. An effect of LBW on the airway only in girls as suggested previously (16) is unlikely from our results and seems to be due to the case definition and selective reporting of results (29).

The results on pulmonary function in previous studies show a considerable heterogeneity, due mainly to different test protocols and pulmonary function equipment. Elevated RVs were found in all

other studies identified in Table 3 (18–20, 22, 24) and a reduced FVC was shown also by the majority of the previous studies (7, 23, 24, 26). While the effect of LBW on baseline bronchial flow parameters is also unclear, all studies except two (20, 27) find an association with bronchial hyperreactivity.

It may first seem surprising that birth weight is a more important factor than prematurity for later respiratory disease, particularly because it was assumed in early studies of bronchopulmonary dysplasia (BPD) that prematurity would be the major factor. However, the predominant effect of birth weight was also shown in two other studies (14, 25), unclear in one (7), and not seen in another (17). In accord with this a recent study of the gestational ages of 17796 children showed also a significantly increased risk of "small for gestational age" for respiratory failure (30). Our findings are also consistent with a pathological study of preterm infants (31), which found that preterm birth alone had little adverse effect on lung development. While there is less information on the growth of airways *in utero*, it

Table 3. Review of recent studies on birth weight or prematurity and pulmonary outcome by publication year. If the study was reported in several publications, only the latest report was taken. Abbreviations: + positive effect ($p < 0.05$), – no effect, () weak effect, ND not determined or not shown in the paper, qst questionnaire, RV residual volume, FVC forced vital capacity, RAW airway resistance, BHR bronchial hyperreactivity, MC methacholine, BPD bronchopulmonary dysplasia, VLBW very low birth weight, COLD, chronic obstructive lung disease, &personal communication.

study characteristics				exposure and analysis					outcome pulmonary function				diseases/symptoms			
author	year	type of the study	no. of exam	age at last exam (y)	number of children	covariates included	birth weight	gestational age	RV	FVC	Flow	RAW	BHR	asthma	airway symptoms	remarks
Sauve	1985	cohort	10	8	207	ND	recorded at birth	ND	ND	ND	ND	ND	ND	ND	+	BPD cohort matched with controls by birth weight category
Chan	1988	case-control	1	7	250	height, sex, race	clinical records	ND	ND	–	+	ND	ND	–	+	“small for date” not associated with poor outcome
Schwartz	1990	cross-sectional	1	1–11	5,672	ND	interview	interview	ND	ND	ND	ND	ND	+	+	low birth weight but not prematurity significant risk for asthma
Galdès-Sebald	1989	case-control	1	13	76	ND	clinical records	ND	+	–	+	–	+(MC)	ND	ND	“hyaline membrane disease” not associated with BHR
Greenough	1990	case-control	1	2	151	ND	hospital records	ND	ND	ND	ND	ND	ND	ND	+	only VLBW examined
Hakulinen	1990	cohort	2	6–9	72	ND	clinical records	ND	+	–	–	+	ND	–	+	neonatal lung disease more important for later COLD than prematurity
Barker	1991	cohort	3	60–80	5,718	height, age	midwife reports	ND	ND	+	+	ND	ND	ND	+	only men examined, death rate by COLD was associated with diminished birth weight
Tammela	1991	case-control	1	8–10	100	no	retrospective chart review	ND	(+)	–	+	ND	(+)(MC)	–	+	
Seidman	1991	cross-sectional	1	17	20,312	ND	link to birth registry	ND	ND	ND	ND	ND	ND	+	ND	men of military service
Frischer	1992	cross-sectional	1	8	1,812	ND	qst	ND	ND	ND	–	ND	(+)(free running)	+	+	50% of LBW children had retrospectively confirmed history of mechanical ventilation
Kitchen	1992	cohort	3	8	455	sex, BPD, social status,	recorded at birth	ND	+	+	–	ND	ND	–	+	primary effect on wheezing during the first 2 years of life
von Mutius	1993	cross-sectional	1	9–11	6,537	age, sex, height, weight	parent qst, parent 5 categories	parent qst	ND	ND	ND	ND	(cold air, girls+)	+	+	birth weight examined only in combination with gestational age. Effects shown only in girls.
Todisco	1993	case-control	1	8–15	68	ND	medical records	ND	+	ND	ND	ND	–(MC)	ND	ND	no clinical differences between index child and sibling as control. Smoking risk factor for prematurity
Rona	1993	cross-sectional	1	5–11	5,573	height, age	parent qst continuous	ND	ND	+	+	ND	ND	–	+	effect on pulmonary function mainly by birth weight
Lewis	1995	cohort	3	16	15,712	ND	interview by midwives	interview by midwives	ND	ND	ND	ND	ND	ND	+	effect only by birth weight but not gestational age
McLeod	1996	cohort	4	8–9	866	height, sex, weight, social status	recorded at birth / parent qst	recorded at birth / parent qst	ND	+	(+)	ND	+(free running)	+(inhaler use)	+	FVC reduced in VLBW associated with pneumothorax and prolonged artificial ventilation
Sears	1996	cohort	7	18	1,037	ND	recorded at birth	ND	ND	–	–	ND	–	–	–	slight trend of LBW for lower FEV1/ FVC ratio
Stein	1997	cohort	1	38–59	286	age, sex, height	recorded at birth	ND	ND	+	+	ND	ND	ND	ND	small head circumference associated with lower FEV1
own study	1998	cross-sectional	1	5–14	2,470	age, sex, height	parent qst validated by birth certif.	parent qst	(+)	–	–	+	(cold air)	+	+	“small for date” babies are at highest risk for non allergic asthma

has been pointed out that the only major changes in airways from birth to adulthood are their size, while parenchymal lung growth is different (32). Children are born with around 20 million alveoli at birth and alveolar multiplication is rapid during the first four years of life (33). This could explain why (mild) prematurity alone may not be a risk factor for later

pulmonary impairment. The “physiological” low weight and maturity is being recovered until school age by a “catch up” improvement in their bronchial growth (Fig. 3A). This could be shown also in children with BPD when examining them at ages 7 and 10 (34), whose symptoms gradually improved. On the other hand, “unphysiological” low weight at

birth seems to be an indicator of a damaging factor like passive smoking during pregnancy which does not improve during infancy. In a recent study, birth weight adjusted for exact gestational age remained an important risk factor for later pulmonary function, indicating that environment *in utero* is an important factor. Whether there is a direct effect on pulmonary development or an indirect action, e.g. by altering the immune system or making the bronchi more susceptible for viral infections, remains to be established.

Fig. 4 shows the complex relationship of factors linking birth weight and asthma. The exact contribution of each risk factor remains unclear because of the complex relationship of confounding and intermediate factors. While genetic factors are most likely to act directly on bronchial hyperreactivity and inflammation, there could also be a parallel effect on LBW. Similar relationships seem to exist for constitutional factors of the mother (like age) and the child (like sex). The overall attributable risk from smoking was estimated to be 12.7 cases of low weight births per 1000 total births (35). An analysis of our own data is limited by the retrospective nature of the study. It should be stressed once more that parental smoking should be discouraged during pregnancy. While there is no doubt about the association of maternal smoking on LBW there could also be a direct effect on bronchial hyperreactivity of the baby. Finally, LBW may influence neonatal respiratory illness, requiring mechanical ventilation which may itself act on bronchial development.

Maternal asthma was more likely to cause preterm birth in one study (36) but not found in an earlier study, in which no difference could be found between the babies of asthmatic and control mothers with regard to length of gestation, birth weight, low Apgar scores and neonatal respiratory difficulties (37). Risk factors for "small for date" babies are also not well established. Discussed are multiparity, race, and age lower than 19 or higher than 34 years (38), third-trimester bleeding, twin gestation and chorionamnitis, uterine anomalies and uterine tract infection (39). The baby's weight in the latter study was also influenced by maternal cigarette smoking and drug or alcohol use. Further risk factors include height of the mother, hypertension, weight gain during pregnancy and previous LBW children (40). In more than the half of the cases, two or more possible risk factors can be identified.

Elucidating which of these factors are responsible for term LBW and the intrauterine growth retardation should be the aim of future research efforts. By using biomarkers of fetal lung maturity, the relationship between the bronchial system and potential risk factors could be further examined.

Abbreviations

(in alphabetical order)

CI confidence interval

FEV_{1.0} volume exhaled in 1 second

FVC forced vital capacity

HMS hyaline membrane syndrome

MEF75 forced flow at 25% FVC exhaled

MEF50 forced flow at 50% FVC exhaled

MEF25 forced flow at 75% FVC exhaled

NBW normal birth weight

OR odds ratio

PEF peak flow

RDS respiratory distress syndrome

RTOT airway resistance

RV residual volume

TLC total lung capacity

Acknowledgments

We wish to thank DR. S. Dold, Dr. I. Goldstein and Dr. A. Peters for helpful comments on the manuscript; Dr. G. Wassmer for statistical assistance; Mr. H. Schneller and Ms. K. Honig-Blum for data handling; Dr. H. Adam and Dr. H. Bach for examining the children; Mr. G. Burmester, R. J. Rudzinski and Ms. B. Holstein for gathering regional information and local assistance; all teachers in Hettstedt, Zerbst and Bitterfeld together with the local school authorities and health care centers for their support; all parents and children for their participation.

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