ORIGINAL ARTICLE

Lung function and respiratory health in adolescents of very low birth weight

D Anand, C J Stevenson, C R West, P O D Pharoah

Arch Dis Child 2003;**88**:135–138

See end of article for authors' affiliations

Correspondence to: Dr D Anand, FSID Unit of Perinatal and Paediatric Epidemiology, Department of Public Health, Muspratt Building, Liverpool L69 3GB, UK; anand@liverpool.ac.uk

Accepted 5 August 2002

Aims: To determine if very low birth weight (VLBW; birth weight <1500 g) is associated with reduced lung function and respiratory health in adolescence and, if it is, whether this impairment is associated with prematurity or intrauterine growth restriction.

Methods: A geographically defined cohort of 128 VLBW infants and an age, sex, and school matched comparison group born in 1980/81 were studied. The cohort and comparison group were assessed at 15 years of age. The birth weight ratio of the index cases (observed birth weight/expected birth weight for the gestation) was determined to assess the degree of growth restriction. Respiratory support received during the neonatal period was obtained from hospital records. Smoking habits and respiratory morbidity were obtained through questionnaires. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and forced expiratory flow when 25–75% of FVC is expired ($FEF_{25–75\%}$) were measured using a portable spirometer. The values are expressed as percentage predicted for height, age, and gender using standard reference values. Adjustments were made for smoking habits of mother and children.

Results: The differences in means between index and comparison groups for $FEF_{25–75\%}$ (–12.42%; $p < 0.001$) and FEV_1/FVC (–3.53%; $p < 0.001$) ratio were statistically significant. The differences in FVC and FEV_1 were not significant. No correlation was found between the birth weight ratio and lung function among the index cohort. Chronic cough, wheezing, and asthma were more common among the index cohort than in the comparison group. Within the index group, there was no difference in lung function between those who received and those who did not receive respiratory support.

Conclusion: Adolescents who were VLBW compared with matched controls showed medium and small airways obstruction. This was associated with prematurity rather than intrauterine growth restriction or having received respiratory support during the neonatal period. The index VLBW cohort compared with their controls were also more prone to chronic cough, wheezing, and asthma.

Over the past two decades, the survival rates of Very low birth weight (VLBW; birth weight <1500 g) infants have been improving. Most of these infants are preterm and many require respiratory support during the early part of their life. Hence, they are more prone to lung injury that gives rise to concern regarding their long term respiratory health. Earlier studies showed that these children regained normal lung function by school age,[1 2] but later studies reported that airflow indices were reduced in these infants even during childhood.[3 4] These studies were predominantly in preadolescent children; only one study observed the effects of VLBW on respiratory function in adolescence and found that, although the variables measuring airflow were reduced, the overall clinical respiratory health and lung function were comparable to those of normal birth weight controls.[5]

A drawback of most of the studies previously reported was that they relate to hospital population groups of children with the inherent bias associated with such studies. The study we report here is of a population of children from a defined geographical area and does not suffer those biases.

VLBW could be a result of intrauterine growth restriction (IUGR), preterm delivery, or a combination of both. Prevention strategies will differ because the causal factors in IUGR differ from those leading to preterm delivery. Therefore it is important to assess the independent effects of intrauterine growth restriction and preterm delivery on lung function and respiratory health in later life.

The aim of this study was to determine whether there is any association between VLBW and respiratory function and health at adolescence. Furthermore, is the association attributable to intrauterine growth restriction or to preterm delivery?

METHODS

Study population

Details of the VLBW cohort and the comparison group of children have been described previously.[6] Briefly, of the 399 infants with a birth weight ⩽1500 g born in the County of Merseyside during 1980–81, 219 survived to the age of 15 years. Ten children have either refused assessment, gone abroad, or could not be traced. Thirty four children with clinical disability, predominantly cerebral palsy and severe learning disability, were excluded because the disability would have affected the lung function tests. Forty seven children from twin pregnancies were also excluded as measures of IUGR would differ from the singletons. The remaining 128 children comprised the index cohort. When the index population was followed up at 8 years of age, a comparison group individually matched for age, sex, and school was obtained. Subsequently, both the index cohort and the comparison group were assessed for lung function and respiratory health at 15 years of age.

Abbreviations: BPD, bronchopulmonary dysplasia; FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IUGR, intrauterine growth restriction; VLBW, very low birth weight

Table 1 Characteristics of cases and controls

	Index cohort n=128	Comparison group n=128
Sex (M/F)	72/56	72/56
Mean (SD) birth weight	1249 (185.2) g	3338 (507.6) g
Range	630–1500	2098–4550
Mean (SD) gestational age	30.7 (2.7) wk	Not known
Range	26–36	
Mean (SD) height	159.7 (7.9) cm	163.7 (7.8) cm*
Range	140–185	147–183
Mean (SD) weight	50.8 (10.7) kg	55.3 (10.3) kg**
Range	33–88	35.5–87
Adolescents smoking	19.5%	10.9%
Maternal smoking during pregnancy	45.3%	40.6%
Current maternal smoking	51.6%	33.6%

*Difference between means 4.0 cm (95% CI 2.1 to 5.9; p<0.001).
**Difference between means 4.4 kg (95% CI 1.8 to 7.0; p=0.001).

Table 2 Lung function indices expressed as percentage of predicted value

Lung function	Index cohort Mean (SD)	Comparison group Mean (SD)	Adjusted difference‡ between means
FVC	109.5 (14.6)	106.0 (12.2)	1.57 (–1.80 to +4.96)
FEV_1	94.9 (13.8)	96.5 (10.8)	–2.45 (–5.5 to +0.67)
$FEF_{25–75\%}$	88.1 (25.6)	100.5 (20.0)	–12.42 (–18.30 to –6.55)*
FEV_1/FVC (%)	87.0 (9.04)	90.8 (6.4)	–3.53 (–5.52 to –1.53)*

Mean expressed as percentage predicted for height, age, and gender.
‡Adjusted for smoking.
*p<0.001.

Lung function tests

The standard lung function test used to measure airway obstruction is the forced expiratory spirogram. This allows an assessment of the rate of change in volume that occurs as a function of time. The lung function tests were performed using a portable spirometer, Vitalograph-Alpha-II, with an attached printout. The output provided numerical as well as graphical data. The graphical data enabled the detection of any error in subject technique. The Vitalograph was calibrated daily before use.

All assessments were carried out by one examiner (CJS) either at school or at home. The examiner demonstrated to each subject the technique for performing the forced vital capacity (FVC). The subjects were given an opportunity to perform a few practice efforts. Later each subject was required to perform a minimum of three reproducible FVC measures (within 5% of maximal FVC). The spirogram that produced the highest sum of FVC and FEV_1 was used in the analysis.[7] Forced expiratory volume in 1 second (FEV_1), the ratio of FEV_1/FVC, and forced expiratory flow when 25–75% ($FEF_{25–75\%}$) of FVC was expired were used as markers of airway obstruction. The lung function indices are calculated using standard reference values as percentage of predicted for FVC, FEV_1, and $FEF_{25–75\%}$.[8] To avoid the potential pitfalls of correction for size, the FEV1/FVC ratio was also calculated as a method of size compensation.

Lung function was compared in those who did and did not receive respiratory support. Respiratory support was defined as any form of supplementary oxygen, continuous positive airway pressure, or intermittent positive pressure ventilation.

Physical measures and IUGR

Height was measured, using the Leicester height measure, to the nearest 0.5 cm; weight was determined to the nearest 0.5 kg with the child lightly clothed using SECA patient scales.

For the index cohort, the birth weight ratio (observed birth weight/expected birth weight for gestational age) was determined to assess the degree of IUGR. The expected birth weight for the gestation was based on Scottish national data.[9]

Questionnaires

The Medical Research Council's questionnaire on respiratory symptoms was used to obtain information on respiratory morbidity.[10] Details of respiratory management during the neonatal period were extracted from hospital neonatal notes.

Information on smoking habits was obtained by two questionnaires. One questionnaire completed by the mother provided information on her smoking during the pregnancy and on her current smoking habits. The other questionnaire, completed by the children, provided data on their current smoking habit. The children were classified as smokers if they had been smoking for six months or more.

Statistical methods

The data were analysed using the statistical package SPSS, PC version 10.07. Means were compared using the paired *t* test, and adjustment of the respiratory function tests for maternal smoking (current and during pregnancy) and teenage smoking was made by analysis of co-variance. Categorical variables were analysed by the χ^2 test with Yates's correction for small 2×2 tables (that is, any expected frequency <5).

The effects of age, sex, and school (as a proxy for social class) were excluded by the matched study design.

The study was approved by the local ethics committee, and informed written consent was obtained from the parents of the children in the study.

RESULTS

Table 1 shows the characteristics of the index cohort and the comparison group. Mean gestational age of the comparison group is not known, but from their mean birth weight it is reasonable to assume that it is near to term. Only four children had a birth weight <2400 g, the lowest being 2098 g; six weighed 2400–2499 g. The remaining 118 all weighed ⩾2500 g. Height and weight were significantly different between the index cohort and the comparison group.

Table 2 shows the lung function indices, after adjustment for the smoking habits of the mother and the teenager. FVC and FEV_1 in the index cohort and comparison group were not

Table 3 Lung function indices among the cases who did and did not receive respiratory support in the neonatal period

	Respiratory support		
	Yes (n=83) Mean (SD)	No (n=45) Mean (SD)	Difference in means (95% CI)
FVC	108.1 (14.1)	112.1 (15.0)	4.0 (–1.2 to +9.3)
FEV_1	94.1 (14.9)	96.5 (11.2)	2.4 (–2.6 to +7.4)
$FEF_{25–75\%}$	87.6 (26.9)	89.4 (22.8)	1.8 (–7.5 to +11.2)
FEV_1/FVC	87.1 (9.3)	86.6 (8.5)	–0.5 (–3.7 to +2.8)

Mean (SD) expressed as percentage predicted for height, age, and gender.

Table 4 Respiratory morbidity data

Symptom/disease	Index cohort (n=128)	Comparison group (n=128)	Odds ratio (95% CI)
Chronic cough	24 (18.8%)	9 (7%)	3.05 (1.28 to 7.44)*
Wheezing	40 (31.3%)	18 (14.1%)	2.78 (1.43 to 5.44)*
Asthma	24 (18.8%)	8 (6.3%)	3.46 (1.41 to 8.79)*
Bronchitis	16 (12.5%)	9 (7%)	1.89 (0.75 to 4.85)
Pneumonia	6 (4.7%)	2 (1.6%)	3.10 (0.55 to 22.6)

*p<0.01.

significantly different, either before or after adjusting for smoking. However, FEV_1/FVC and $FEF_{25–75\%}$ differed significantly, even after adjusting for smoking, indicating that there is a persisting medium and small airway obstruction among VLBW adolescents compared with the comparison group.

To determine whether this difference is associated with preterm delivery or IUGR, the birth weight ratio was calculated for the index cohort and plotted against the lung function parameters. The birth weight ratio ranged from 0.4 to 1.2, mean 0.8 (SD 0.2). No significant correlation was observed for any of the lung function parameters.

Among the 128 index cohort, 83 had received respiratory support. Table 3 shows no difference in lung function indices between those who received respiratory support compared with those who did not. The consequence of bronchopulmonary dysplasia (BPD) for subsequent respiratory function is of interest. However, oxygen dependency for more than 28 days as a marker of BPD occurred in only eight of our cases, which did not allow a meaningful examination of the problem.

Table 4 shows the prevalence of respiratory symptoms or diseases in the index cohort and comparison group. Cough, wheezing, and asthma were significantly more common among the index cohort compared with the comparison group. Although bronchitis and pneumonia were more prevalent among the index cohort, the difference was not significant.

DISCUSSION

The aim of the study was to determine whether being of low birth weight had an adverse effect on respiratory function measured in adolescence and, if so, whether this could be attributed to IUGR or preterm delivery. Very low birth weight was associated with medium and small rather than large airways obstruction, and this effect was mediated through preterm delivery rather than IUGR.

An advantage of this study is that it reports on respiratory function in adolescence of a cohort of VLBW infants and a matched comparison group from a geographically defined population. Furthermore it deals with respiratory function in adolescence, and not preadolescence, as in the majority of other studies. A similar study of adolescent respiratory function from a tertiary referral centre may have been biased because referral may have been because of severe respiratory problems.[5]

A significant reduction in both FEV_1/FVC ratio and $FEF_{25–75\%}$, reflecting the medium and small airway obstruction in adolescents, was observed in the VLBW index group. Smoking is potentially an important variable when making comparisons of respiratory function as it is known to impair lung growth.[11] Our data on smoking were limited as they were not obtained with the intention of assessing its effect on respiratory function. However, adjusting for smoking as a binomial variable (smoking/non-smoking) had a negligible effect on the index and comparison group differences in FEV_1/FVC and $FEF_{25–75\%}$. Similar medium and small airway obstruction was observed in a cohort of 14 years old children.[5] However contrary to our observations, a reduction in FEV_1, a marker of upper airways obstruction, was also noted. Several studies of preadolescent subjects who were born preterm, reported a reduction in expiratory flow rates.[3 4 12] Though these studies were in preadolescent subjects and are not strictly comparable to our current study, it suggests that the reduction in expiratory flow noted in VLBW infants in childhood persists into adolescence.

Whether the effect on respiratory function is attributable to IUGR or preterm delivery is clinically important. It has been proposed that intrauterine factors that impair fetal growth may increase the risk of developing chronic obstructive airways disease in adulthood.[13] These subjects were born at a time when methods for gestational assessment were imprecise, and it is uncertain whether they were growth retarded or premature. In a later cohort, among preterm infants, the birth weight for gestational age was significantly associated with FVC and FEV_1 but not with $FEF_{25–75\%}$ and $FEF_{75–85\%}$.[14] However, in the total sample of 2036, the proportion who were preterm (<37 weeks) was only 13%, of whom 79 (3.8% of the total sample) were <2500 g. In contrast, we found no correlation between birth weight ratio and any of the airflow measures, indicating that prematurity rather than IUGR is important. Another study of 300 VLBW infants compared those who were IUGR with those who were not and found no difference in airflow variables.[15] Similarly, in a study of term infants, no association was found between low birth weight (as a measure of growth restriction) and lung function.[16]

Respiratory support in the neonatal period appeared not to be of importance in influencing lung function in adolescence. In contrast, a hospital based study found significant differences between those who received ventilatory support and

those who did not.[4] A possible explanation of these contradictory observations may result from the bias that can occur when hospital populations are assessed. A regional hospital centre is likely to include infants transferred from other neonatal units because of severe respiratory problems.

The association of long term respiratory morbidity with low birth weight is less certain. In our study the reduction in airflow indices was associated with a significant increase in the prevalence of chronic cough, wheezing, and asthma among the VLBW subjects. An increased prevalence of asthma and recurrent bronchitis was also found in a cohort of children at age 8 years.[17] However, subsequent assessment of the cohort at 14 years found similar rates of asthma and pneumonia when compared with normal subjects.[5] In another study the increased prevalence of asthma persisted into adolescence.[18]

In conclusion, the reduction in adolescent lung function indices, reflecting medium and small airway obstruction, is associated with preterm delivery rather than IUGR but is not associated with respiratory support in the neonatal period. The possible confounding effect of smoking could not be discounted entirely because of the limitation in the data on smoking. Compared with normal birth weight infants, VLBW infants have an increased prevalence of chronic cough, wheezing, and asthma in adolescence.

Authors' affiliations
D Anand, C J Stevenson, C R West, P O D Pharoah, FSID Unit of Perinatal and Paediatric Epidemiology, Department of Public Health, Liverpool, UK

REFERENCES

1 **Bryan MH**, Levison H, Swyer PR. Pulmonary function in infants and children following the acute neonatal respiratory distress syndrome. *Bull Eur Physiopathol Respir* 1973;**9**:1587–600.
2 **Dinwiddie R**, Mellor DH, Donaldson SHC, *et al*. Quality of survival after artificial ventilation of the new born. *Arch Dis Child* 1974;**49**:703–10.
3 **Coats AL**, Bergsteinsson H, Desmond K, *et al*. Long-term pulmonary sequelae of premature birth with and without idiopathic respiratory distress syndrome. *J Pediatr* 1977;**90**:611–16.
4 **Chan KN**, Noble-Jamieson CM, Elliman A, *et al*. Lung function in children of low birth weight. *Arch Dis Child* 1989;**64**:1284–93.
5 **Doyle LW**, Cheung MMH, Ford GW, *et al*. Birth weight <1501g and respiratory health at age 14. *Arch Dis Child* 2001;**84**:40–4.
6 **Stevenson CJ**, West CR, Pharoah POD. Dermatoglyphic patterns, very low birth weight, and blood pressure in adolescence. *Arch Dis Child Fetal Neonatal Ed* 2001;**84**:F18–F22.
7 **American Thoracic Society**. ATS statement. Snowbird workshop on standardization of spirometry. *Am Rev Respir Dis*1979;**119**:831.
8 **European Respiratory Society**. Standardized lung function testing. *Eur Respir J Suppl* 1993;**6**(suppl 16).
9 **Scottish Health Service Common Services Agency**. *Scotland: birthweight, head circumference and length for gestational age*. Edinburgh: Scottish Health Service Common Services Agency, 1990.
10 **Medical Research Council**, Committee on Environmental and Occupational Health. *Questionnaire on respiratory symptoms*. London: MRC, 1986.
11 **Tager IB**, Munoz A, Rosner B, *et al*. Effect of cigarette smoking on the pulmonary function of children and adolescents. *Am Rev Respir Dis* 1985;**131**:752–9.
12 **Mansell AL**, Driscoll JM, James LS. Pulmonary follow-up of moderately low birth weight infants with and without respiratory distress syndrome. *J Pediatr* 1987;**110**:111–15.
13 **Barker DJP**, Godfrey KM, Fall C, *et al*. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ* 1991;**303**:671–4.
14 **Rona RJ**, Gulliford MC, Chinn S. Effects of prematurity and intrauterine growth on respiratory health and lung function in childhood. *BMJ* 1993;**306**:817–20.
15 **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.
16 **Matthes JWA**, Lewis PA, Davies DP, *et al*. Birth weight at term and lung function in adolescence: no evidence of programmed effect. *Arch Dis Child* 1995;**73**:231–4.
17 **Kitchen WH**, Olinsky A, Doyle LW, *et al*. Respiratory health and lung function in 8-year old children of very low birth weight: a cohort study. *Pediatrics* 1992;**89**:1151–8.
18 **Seidman DS**, Laor A, Gale R, *et al*. Is low birth weight a risk factor for asthma during adolescence. *Arch Dis Child* 1991;**66**:584–7.

ARCHIVIST

Lung pathology in Africa

Respiratory diseases are common in children in sub-Saharan Africa. They are usually treated empirically and there is little information about the pathology of fatal diseases. A study in Zambia (Chifumbe Chintu and colleagues. *Lancet* 2002;**360**:985–90) has illustrated the range of pathology.

At the university hospital in Lusaka between 15 September 1997 and 15 June 2000 a total of 1603 children aged between 1 month an 16 years died from respiratory illnesses. Of those parents approached for permission for a restricted (chest only) autopsy 75% refused. Two hundred and sixty-four autopsies were performed. Multiple lung pathology was common; a total of 357 main diagnoses were made in the 264 children. They included acute pyogenic pneumonia (44%), *Pneumocystis carinii* pneumonia (22%), tuberculosis (20%), cytomegalovirus infection (16%) (mostly mild but three cases of severe necrotising CMV pneumonia), interstitial pneumonitis (11%), shock lung (10%), pulmonary oedema (7%), and lymphocytic interstitial pneumonia (4%). Seven children had measles.

One hundred and eighty of the 264 children were HIV-positive. *P carinii* pneumonia, CMV, shock lung, and lymphocytic interstitial pneumonitis were more common in the HIV-positive group although acute pyogenic pneumonia was the most common finding in both groups. Of the 58 cases of *P carinii* pneumonia 52 were HIV positive and 45 of those were infants, 39 under 6 months. All six HIV-negative cases were under 6 months. Tuberculosis occurred at all ages and in both HIV-positive and HIV-negative children.

Many children die of preventable or treatable disease and better tests for pathogens are needed. WHO guidelines do not mention the management of HIV-positive children specifically and these authors call for that omission to be corrected.