Birth weight <1501 g and respiratory health at age 14

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Abstract

***Aims*—To determine the respiratory health in adolescence of children of birth weight <1501 g, and to compare the results with normal birthweight controls.**

***Methods*—Prospective cohort study of children born in the Royal Women's Hospital, Melbourne. Two cohorts of preterm children (86 consecutive survivors 500–999 g birth weight, and 124 consecutive survivors 1000–1500 g birth weight) and a control group of 60 randomly selected children >2499 g birth weight were studied. Children were assessed at 14 years of age. A paediatrician determined the clinical respiratory status. Lung function was measured according to standard guidelines.**

***Results*—Of 180 preterm children seen at age 14, 42 (23%) had bronchopulmonary dysplasia (BPD) in the newborn period. Readmission to hospital for respiratory ill health was infrequent in all groups and the rates of asthma were similar (15% in the 500–999 g birth weight group, 21% in the 1000–1500 g birth weight group, 21% in controls; 19% BPD, 18% no BPD). Overall, lung function was mostly within the normal range for all cohorts; few children had lung function abnormalities in clinically significant ranges. However, the preterm children had significantly lower values for variables reflecting flow. Lung function in children of 500–999 g birth weight was similar to children of 1000–1500 g birth weight. Preterm children with BPD had significantly lower values for variables reflecting flow than children without BPD.**

***Conclusions*—The respiratory health of children of birth weight <1501 g at 14 years of age is comparable to that of term controls.**

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Developments in neonatal intensive care have meant that more preterm children, particularly those of less than 1501 g birth weight, are surviving into childhood. These children often require prolonged periods of assisted ventilation and oxygen therapy, with the potential for long term lung injury, including the development of bronchopulmonary dysplasia (BPD).[1 2] Of the sequelae of intensive care of preterm children, one area of concern is their respiratory health, including lung function, in later life.

Recurrent wheezing episodes and hospital admissions in early childhood caused by respiratory tract illnesses are more frequent in preterm children, but it is not clear whether this early increase in respiratory morbidity persists.[3] Reviews of lung function studies published up to 1986 indicated that some children had evidence of airway obstruction, air trapping, bronchial hyper-reactivity, and oxygen desaturation with increased work, but these studies involved small groups of children.[4] A detailed study of preterm children with bronchopulmonary dysplasia (BPD) in the first three years of life using serial lung function tests also confirmed these findings, but by 36 months of age the forced vital capacity (FVC) had returned to the normal range, although other variables reflecting airflow were still reduced.[5]

To provide further information about respiratory health later in childhood, preterm children have been followed prospectively to a corrected age of 14 years. The aims of this study were to determine the respiratory health of two cohorts of preterm children, one of 500–999 g birth weight and the other of 1000–1500 g birth weight, and to compare the results with a control group of randomly selected normal birth weight (>2499 g) children. An additional aim was to compare the respiratory health of preterm children with and without BPD.

Methods

All children were born at the Royal Women's Hospital, the largest of the three level III perinatal units in Melbourne, Australia. There were two cohorts of preterm children. The first comprised 86 consecutive survivors of 500–999 g birth weight born during the 63 months from 1 January 1977, and the second comprised 124 consecutive survivors of 1000–1500 g birth weight born during the 18 months from 1 October 1980. The control group comprised 60 randomly selected term children of >2499 g birth weight born within the Royal Women's Hospital during the last six months of the recruitment phase. The respiratory health at 8 years of age of these cohorts has been reported previously.[6]

Details of nursery care, including the duration of assisted ventilation and oxygen therapy, were recorded. Z scores (SD scores) for birth weight and height at 14 years of age were computed relative to the British Growth Reference.[7] BPD was defined as clinical signs of respiratory distress with an abnormal chest *x* ray consistent with Northway[8] stage 3 or 4, and an

oxygen requirement after 28 days of age. No infants received surfactant, high frequency ventilation, or steroids postnatally to treat BPD.

Social circumstances at home were noted, including an estimate of the number of cigarettes smoked per day by household members. The children were also asked, in the absence of their guardians, about active smoking. Social class was dichotomised into higher or lower (unskilled or unemployed) on the basis of the occupation of the main income earner in the family. Some mothers had been born in countries where English was not the chief language. Maternal education was dichotomised at more than 10 years of schooling.

The state of their current respiratory health was assessed by asking about respiratory symptoms such as cough and wheeze, the use of bronchodilators or other asthma therapy, and the frequency of hospital admissions for respiratory illnesses. Asthma was defined as recurrent wheezing episodes requiring treatment with bronchodilators within the previous 12 months. The subjects were not asked to maintain diaries to verify the accuracy of their recall of medical events.

All available children were evaluated as close as possible to their 14th birthday, corrected for prematurity where appropriate, using a predetermined protocol designed to assess the growth and health of the study children. All assessors were unaware of the perinatal history, including birth weight, of the children.

Lung function was measured as follows. Spirometry and lung volumes were measured using a Jaeger Bodyscreen II–Bodybox (Jaeger, Germany), with Masterlab (ML3) software. Maximum expiratory flow–volume curves were recorded while the subject sat in the body plethysmograph with the door open. Flow was measured with a pneumotachograph and volume was obtained by integration of flow. Vital capacity (VC), forced vital capacity (FVC), and forced expired volume in one second (FEV_1) were measured, as were flow rates at 75% ($V'_{EMAX75\%}$), 50% ($V'_{EMAX50\%}$), and 25% ($V'_{EMAX25\%}$) of VC , and forced mid expiratory flow ($FEF_{25-75\%}$). Total lung capacity (TLC) and residual volume (RV) were measured in the body plethysmograph. The best of three satisfactory tests was recorded. Results at body temperature and pressure saturated with water vapour were expressed as a percentage predicted for height, gender, and age of Australian children.[9] Children were not subjected to bronchial provocation tests, or to tests of chest wall stiffness or muscle power.

Data were edited and analysed using SPSS for Windows programs.[10] Differences in dichotomous variables were contrasted by χ^2 analysis, with correction for continuity where appropriate, and differences in continuous variables were compared by *t* test. To contrast lung function variables between the three subgroups without using multiple comparisons, data were analysed by multiple linear regression with dummy variables, firstly to compare all <1501 g birth weight children with controls, and secondly to compare those of 500–999 g birth weight with those of 1000–1500 g birth weight. Statistical significance was set at $p < 0.05$. Data were also analysed by multiple linear regression to adjust for potentially confounding variables, such as birth weight SD score, smoke exposure, asthma, and gender. The power of the study varied with the sample size of the comparison groups. For example, power was 80% to detect differences between 169 preterm children and 39 controls as small as 0.6 SD for normally distributed continuous variables, with a type I error of 5%.

Results

The follow up rate to 14 years of age was higher in the preterm children than in the controls (table 1). As expected, in those assessed at 14 years of age, children in the preterm groups were more immature and lighter at birth than the controls, and had significantly lower birthweight SD scores. There were no significant differences between the groups with respect to gender. In the preterm groups, there were no differences in the rate of exposure to steroids

Table 1 Demographic characteristics of birthweight groups

	Birthweight group		
	500–999 g	*1000–1500 g*	*>2499 g*
No. survived	86	124	60
No. lost (% survivors)	3 (3%)	5 (4%)	4 (7%)
No. refused (% survivors)	4 (5%)	13 (10%)	12 (20%)
No. inaccessible (% survivors)	1 (1%)	4 (3%)	2 (3%)
No. seen at age 14 (% survivors)	78 (91%)	102 (82%)	42 (70%)
Gestational age (wk); mean (SD)	27.5 (2.3)	29.6 (1.5)	39.9 (1.0)*
Birth weight (g); mean (SD)	859 (100)	1259 (145)	3420 (427)*
Birthweight SD score; mean (SD)	−1.04 (1.24)	−0.48 (0.84)	−0.14 (0.79)*
No. with birth weight ⩽2 SD (% seen)	14 (18%)	7 (7%)	0 (0%)*
No. received antenatal steroids (% seen)	39 (50%)	52 (51%)	0 (0%)
No. males (% seen)	35 (45%)	55 (54%)	26 (62%)
No. with BPD (% seen)	33 (42%)	9 (9%)	0 (0%)
Age seen (y); mean (SD)	14.1 (0.2)	14.2 (0.3)	14.2 (0.1)
Height at 14 years of age (cm); mean (SD)	158.2 (8.4)	160.7 (7.8)	164.3 (8.2)*
Height at 14 years of age—Z score; mean (SD)	−0.43 (1.09)	−0.11 (1.05)	0.26 (1.07)*
No. exposed to smoking (% seen)	38 (49%)	55 (54%)	16 (38%)
No. active smokers (% seen)	2 (2%)	8 (8%)	3 (7%)
No. with asthma at 14 (% seen)	12 (15%)	21 (21%)	9 (21%)
No. with mother born in English speaking country (% seen)	59 (76%)	82 (80%)	27 (64%)
No. of lower social class (% seen)	38 (49%)	28 (27%)	13 (31%)*
No. with maternal schooling >10 years (% seen)	29 (37%)	39 (38%)	21 (50%)

*Statistically significant difference between groups.

Table 2 Demographic characteristics in children not seen and those seen at age 14

	Birthweight group					
	500–999 g		*1000–1500 g*		*>2499 g*	
	Not seen (n = 8)	*Seen (n = 78)*	*Not seen (n = 22)*	*Seen (n = 102)*	*Not seen (n = 18)*	*Seen (n = 42)*
Gestational age (wk); mean (SD)	27.8 (2.9)	27.5 (2.3)	29.9 (1.5)	29.6 (1.5)	39.8 (1.2)	39.9 (1.0)
Birth weight (g); mean (SD)	891 (77)	859 (100)	1305 (153)	1259 (145)	3691 (735)	3420 (427)
No. males (%)	4 (50%)	35 (45%)	12 (45%)	55 (54%)	7 (39%)	26 (62%)

before birth, but more children of 500–999 g birth weight had BPD in the newborn period than did the children of birth weight 1000–1500 g. Smoke exposure after birth was similar in the three groups. The only significant difference between the groups with respect to other sociodemographic variables, was that more children of 500–999 g birth weight were from lower social classes.

Within the respective birthweight subgroups, there were no statistically significant differences between those assessed and those not assessed at 14 years of age in perinatal variables such as gestational age, birth weight, or gender (table 2).

At 14 years of age clinical respiratory health of preterm children was similar to that of controls. Readmission to hospital for pneumonia or asthma in the year prior to assessment at 14 years of age was uncommon in all birthweight groups (500–999 g, 1% (n = 1) with pneumonia; 1000–1500 g, 1% (n = 1) with asthma; controls 0% (n = 0)). The rates of asthma were similar in all birthweight groups (table 1). For preterm children who had BPD, the rate of readmission to hospital for pneumonia or asthma was 5% (2/42), compared with 0% (0/138) in preterm children with no BPD; the rates of asthma were similar in the two groups (BPD 19% (8/42), no BPD 18% (25/138)).

Several children in each group (n = 6, birth weight 500–999 g; n = 5, birth weight 1000–1500 g; n = 3, controls) were unable to complete lung function tests either because of sensorineural disability, or because of unavailability of lung function testing equipment on the day of assessment. Of the original preterm survivors, within birthweight subgroups there were no significant differences in perinatal variables between children with and without lung function data at 14 years of age (data not shown).

Overall lung function at 14 years of age was mostly normal in the three groups (table 3). Children of <1501 g birth weight had significantly lower values for all variables reflecting air flow, although the minority were in the clinically important range (table 3). Of the 169 children of <1501 g birth weight, 29 (17%) had a clinically important reduction in their FEV_1 (<82% both genders[9]), a significantly higher proportion than the 1/39 (3%) controls (χ^2 = 4.4, p < 0.05), whereas 38 (22%) of children < 1501 g birth weight had an FEV_1/FVC in the clinically important range (<76% for boys, <80% for girls[9]), compared with three (8%) controls, a difference that was not statistically significant (χ^2 = 3.5, NS). Variables reflecting lung volume and air trapping showed no significant differences between any birthweight groups (table 3); only 13 (8%) children of <1501 g birth weight and two (5%) controls had a clinically important elevation of the RV/TLC ratio (>36% for boys, >38% for girls[9]). Within the preterm children, there were no statistically significant differences in any lung function variables between those of 500–999 g birth weight and those of 1000–1500 g birth weight (table 3).

Within the preterm children, most of those who had BPD in the newborn period had lung function values in the normal range, but there were some statistically significant reductions in variables reflecting flow compared with preterm children with no BPD (table 4). Of the 39 preterm children with BPD, 12 (31%) had a clinically important reduction in their FEV_1, a significantly higher proportion than the 17 of 130 (13%) preterm children without BPD (χ^2 = 5.4, p < 0.02). Similarly, 17 (44%) pre-

Table 3 Lung function variables in birthweight groups

	Birthweight group			*All <1501 g v >2499 g birth weight*		*500–999 g v 1000–1500 g birth weight*	
Lung function variable	*500–999 g (n = 72)*	*1000–1500 g (n = 97)*	*>2499 g (n = 39)*	*δ**	*95% CI†*	*δ‡*	*95% CI†*
FVC	100.6 (13.3)	100.6 (12.1)	104.8 (12.0)	−4.2	−8.5 to 0.2	0.0	−3.8 to 3.8
FEV_1	93.1 (14.9)	96.1 (14.0)	104.6 (13.2)	−10.1	−15.0 to −5.1	−3.0	−7.3 to 1.3
FEV_1/FVC (%)	81.9 (10.6)	83.8 (8.9)	87.0 (7.0)	−4.1	−7.4 to −0.9	−1.9	−4.8 to 0.9
$V'_{EMAX75\%}$	93.1 (24.0)	94.7 (21.6)	110.7 (22.1)	−16.8	−24.7 to −8.9	−1.5	−8.6 to 5.5
$V'_{EMAX50\%}$	89.9 (30.5)	95.2 (27.1)	113.0 (25.7)	−20.5	−30.3 to −10.7	−5.4	−14.1 to 3.4
$V'_{EMAX25\%}$	87.5 (37.1)	93.0 (35.5)	110.7 (35.1)	−20.4	−33.0 to −7.8	−5.5	−16.6 to 5.6
$FEF_{25–75\%}$	77.0 (26.8)	83.3 (25.3)	99.1 (23.4)	−19.0	−27.9 to −10.1	−6.3	−14.7 to 1.5
RV	112.1 (43.3)	114.5 (40.2)	117.4 (30.8)	−4.1	−18.1 to 10.0	−2.4	−14.7 to 10.0
TLC	98.9 (16.0)	99.4 (13.1)	102.5 (13.9)	−3.3	−8.3 to 1.7	−0.5	−4.9 to 3.9
RV/TLC (%)	27.5 (9.2)	27.5 (7.5)	26.8 (6.3)	0.7	−2.1 to 3.5	0.1	−2.4 to 2.5

Data expressed as mean (SD), and are % predicted for height, age, and gender, unless otherwise specified.
*Difference between all <1501 g and controls.
†95% confidence interval for difference between groups.
‡Difference between 500–999 g and 1000–1500 g groups.

Table 4 Lung function variables in preterm children with and without BPD

Lung function variable	*BPD (n = 39)*	*No BPD (n = 130)*	*δ**	*95% CI†*
FVC	98.2 (14.4)	101.4 (12.0)	−3.2	−7.7 to 1.3
FEV_1	88.5 (18.2)	96.7 (12.6)	−8.2	−13.2 to −3.1
FEV_1/FVC (%)	78.6 (11.1)	84.2 (8.8)	−5.5	−8.9 to −2.1
$V'_{EMAX75\%}$	85.6 (24.9)	96.4 (21.4)	−10.7	−19.1 to −2.4
$V'_{EMAX50\%}$	83.6 (36.0)	95.7 (25.6)	−12.0	−22.6 to−1.5
$V'_{EMAX25\%}$	77.1 (36.1)	94.8 (35.3)	−17.7	−30.7 to −4.7
$FEF_{25–75\%}$	71.3 (30.9)	83.5 (23.8)	−12.2	−21.4 to −3.0
RV	115.8 (53.0)	112.8 (37.6)	3.0	−12.2 to 18.3
TLC	98.9(14.7)	99.3 (14.2)	−0.4	−5.7 to 4.9
RV/TLC (%)	27.4 (10.3)	27.5 (7.6)	−0.1	−3.2 to 2.9

Data expressed as mean (SD), and are % predicted for height, age, and gender, unless otherwise specified.
*Difference between groups.
†95% confidence interval for difference between groups.

term children with BPD had an FEV_1/FVC in the clinically important range compared with 21 (16%) preterm children without BPD ($\chi^2 = 11.4$, $p < 0.001$). Only three (8%) of 37 preterm children with BPD and 10 (8%) of 128 preterm children without BPD had a clinically important elevation of the RV/TLC ratio, a non-significant difference.

Of potentially confounding variables, asthma at 14 was associated with reductions in some variables reflecting flow (FEV_1, FEV_1/FVC, $FEF_{25–75\%}$, $V'_{EMAX75\%}$, $V'_{EMAX50\%}$, $V'_{EMAX25\%}$), as was smoke exposure ($V'_{EMAX75\%}$ only). Girls had a significantly higher FEV_1/FVC than boys. Birthweight SD score was not significantly related to any respiratory function variable. Adjustment for confounding variables did not alter any statistical conclusions regarding comparisons between birthweight subgroups or between preterm children with and without BPD, with the exception that the $FEF_{25–75\%}$ between those of 500–999 birth weight and those of 1000–1500 g birth weight became statistically significant.

Discussion

Lung function tests in our study were compared with data from a large cohort of Australian children who had been followed prospectively and who were free of lung disease, particularly asthma, at the time of testing, as reported by Hibbert *et al*.[9] The software that accompanies the lung function testing equipment computes predicted values relative to the data of Zapletal and colleagues[11] from American children. The percentage predicted values for our cohorts computed from either source of data were similar, except that flow rates at 75%, 50%, and 25% of vital capacity were lower than predicted from Zapletal *et al* compared with Hibbert *et al*. We chose to compute predicted values relative to the data of Hibbert *et al* for several reasons. Firstly, the data of Hibbert *et al* were more recent, dating from the 1980s, compared with the 1960s for Zapletal *et al*. Secondly, some flow rates were significantly different between boys and girls when computed relative to Zapletal *et al*, whereas there were no significant gender differences relative to Hibbert *et al*, which is expected as percentage predicted values were derived for boys and girls separately. The only exception was a significantly higher value for FEV_1/FVC (%) in girls, which is not adjusted for gender. As the choice of a standard group to compute percentage predicted values affects both preterm and control children equally, the statistical conclusions comparing preterm and control children in our study were not altered, regardless of which standard was used to compute percentage predicted values for lung function.

Other researchers have reported on lung function in cohorts of preterm children born during the early to mid 1980s, from the presurfactant era. Chan *et al* measured lung function of 130 preterm children with birth weights <2000 g and a reference population of 120 local schoolchildren at 7 years of age.[12] The preterm cohort showed similar values for FVC but had lower indices for expiratory flow relative to the reference population. Their preterm cohort were all less than 2000 g but the majority were relatively large and mature, with a median birth weight of 1700 g and median gestational age of 33 weeks. In a study of preterm infants with birth weights <1750 g in Scotland reported by McLeod *et al*,[13] children underwent lung function tests at 8–9 years of age. Their results were compared with a control group of classroom peers of the same sex, who were nearest in date of birth to the index child. They found that the preterm group had significantly reduced FVC. When the data for FEV_1/FVC were analysed it was found that the preterm group had significantly more cases with values less than 70% than the classroom peers. Gross *et al* studied 125 children who were less than 32 weeks' gestational age at 7 years of age.[14] They reported reductions in variables reflecting flow, but only in children who had BPD in the newborn period.

The cohort we have been following were, on average, smaller at birth or more preterm than the children in the studies of Chan, McLeod, or Gross. If lung function abnormalities in later life are going to be related to the degree of prematurity or the reduction in birth weight, then they are more likely to be observed in our study than in any of those above. Moreover, we have determined respiratory health in children at an older age than in any of these studies. We are unaware of any other studies of respiratory function of cohorts of very low birthweight children in adolescence from this era.

There are reports of respiratory function from older subjects, but they have been more highly selected than the subjects in our study. For example, Northway *et al* reported respiratory function data at an average age of 18 years in 25 subjects born between 1964 and 1973 who had BPD.[15] Results were compared with an equal number of preterm controls matched for birth weight and gender, and non-preterm controls. Those with BPD had considerable airway obstruction compared with the other groups. However, it is important to note that neither control group was randomly selected, that the preterm controls had to be not ventilated in the newborn period, and that the non-preterm controls were selected to have no lung disease and were non-smokers. These selection filters reduce the generalisability of the results of such a study. In contrast, our study is more widely applicable to children

born from that era when survival rates from our hospital were comparable with most similar centres. We recognise, of course, that there have been many changes in perinatal care since our cohort was born, and our results cannot easily be extrapolated to babies in the late 1990s. However, they do provide the best guide to what respiratory health might be like in adolescence for today's tiny babies. A recent report[16] reviews the results of lung function from other studies where the subjects were more highly selected than in our study.

Lung function in preterm children in our cohorts mostly improved between 8 and 14 years of age.[17] Those of 500–999 g birth weight improved more than those of 1000–1500 g birth weight, which explains why those of 500–999 g birth weight had more abnormalities in lung function at 8 years of age but not at 14 years of age compared with those of 1000–1500 g birth weight. The rate of change in lung function between 8 and 14 years in children with BPD was the same as for those without BPD.[17] We have previously reported that variables reflecting flow were significantly reduced in preterm children with BPD compared with those without BPD at 8[6] and 11[18] years of age; coupled with the observation of no difference in the rate of change between 8 and 14 years of age, it is not surprising that variables reflecting flow are still somewhat lower in preterm children who had BPD. What is perhaps surprising is that children with BPD have lung function mostly within the normal range at 14 years of age. On the other hand, the observation that proportionally more children with BPD have values for some variables reflecting flow in clinically important ranges is of concern. Even though they have no more respiratory symptoms at age 14, they may deteriorate in lung function at a faster rate as they attain adulthood.[17]

Reductions in variables reflecting flow with asthma were expected, as we had observed at 8 years of age.[6] Moreover, some effect of smoke exposure was expected as we had previously reported abnormalities in lung function in preterm children with passive smoking at 11 years of age.[19]

In conclusion, the clinical respiratory health and lung function of preterm children <1501 g birth weight at 14 years of age were mostly normal, and were comparable with the normal birthweight controls. Although there were significant reductions in variables measuring expiratory flow, these were uncommonly in ranges deemed clinically significant. Preterm children with BPD had similar respiratory health compared with preterm children without BPD, and although they had some reductions in variables reflecting flow, their lung function was mostly in the normal range. However, preterm children, particularly those with BPD, had reductions in airflow that may herald the earlier onset of obstructive airways disease in adult life. It will be interesting to compare these results with those of more recent cohorts, particularly those born after surfactant was introduced, and also with increasing use of corticosteroids after birth to treat chronic lung disease.

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