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Pulmonary outcome in adolescents of extreme preterm birth: a regional cohort study

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Aims: The pulmonary outcome of extreme prematurity remains to be established in adults. We determined respiratory health and lung function status in a population-based, complete cohort of young preterms approaching adulthood. *Methods.* Forty-six preterms with gestational age $\leq$28 wk or birthweight $\leq$1000 g, born between 1982 and 1985, were compared to the temporally nearest term-born subject of equal gender. Spirometry, plethysmography, reversibility test to salbutamol and methacholine bronchial provocation test were performed. Neonatal data were obtained from hospital records and current symptoms from validated questionnaires. *Results:* When entering the study at a mean age of 17.7 (SD: 1.2) y, a doctor's diagnosis of asthma and use of asthma inhalers were significantly more prevalent among preterms than controls (one asthmatic control compared to nine preterms, all but one using asthma inhalers). Peak expiratory flow (PEF) and forced expiratory volume in 1 s (FEV_1) were decreased and the discrepancies relative to controls increased parallel to increased severity of neonatal lung disease. Parameters of increased neonatal oxygen exposure significantly predicted FEV_1. Adjusted for height, gender and age, FEV_1 was reduced by a mean of 580 ml/s in subjects with a history of bronchopulmonary dysplasia. Fifty-six percent of preterms had a positive methacholine provocation test compared to 26% of controls.

Conclusion: A substantially decreased FEV_1, increased bronchial hyperresponsiveness and a number of established risk factors for steeper age-related decline in lung function were observed in preterms. A potential for early onset chronic obstructive pulmonary disease is present in subsets of this group.

Key words: *Infant, premature, bronchopulmonary dysplasia, lung diseases, obstructive, cohort studies*

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Since the 1970s, improved neonatal care and new treatment modalities have brought into life an increasing number of immature infants (1). There are several areas of concern regarding future health and quality of life in this population. As adequate gas exchange is a critical challenge for intensive care neonatology, the prospect of lung injury and subsequent abnormal lung development is present. Solid evidence for increased childhood respiratory morbidity (2–5) was recently reviewed (6). In toddlers, symptoms manifest as recurrent episodes of wheeze and high re-hospitalization rates (7), whereas airway obstruction (2, 3) and bronchial hyperresponsiveness (8) have been reported in schoolchildren. Regarding older subjects, evidence-based knowledge is fragmented, although improvement in symptoms and persistence of lung function abnormalities have been reported in selected populations (9).

To provide unbiased estimates of lifetime respiratory outcome, complete cohorts of consecutive premature births, preferably representing entire geographic regions, should be followed into adulthood. Such optimal long-term follow-up studies are, however, demanding and challenging to carry out. Consequently, the majority of published literature focuses on younger children (3, 4), studies tend to be hospital-based (2, 9) rather than population-based or they concentrate on particular subsets of preterms with prolonged oxygen dependency (9, 10) or requirement for assisted ventilation (11). Birthweight as the sole criterion for inclusion (4, 12) is practical, but assumptions regarding effects of prematurity *per se* might be confused by small-for-date infants.

No published studies have so far provided solid, population-based information on pulmonary outcome

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into adulthood in survivors of extreme prematurity from the early era of neonatal intensive care. These pioneer subjects are entitled to adequate and evidence-based health care, for which purpose relevant knowledge is required. Furthermore, data from this era are important as baseline when evaluating long-term respiratory health after contemporary neonatal intensive care. The aims of the present study were to provide descriptive data and determine early predictive factors for respiratory health and lung function in a complete regional cohort of survivors of extreme prematurity approaching adulthood.

Methods

Study design and subjects

A population-based cohort of preterm subjects with gestational age $\leq$28 wk or birthweight $\leq$1000 g, born within a health region in western Norway between 1982 and 1985, was compared to individually matched controls. For each preterm, the temporally nearest term-born subject of the same gender was selected as control, providing a birthweight between 3–4 kg, i.e. approximately within the 10th and 90th percentile for Norwegian babies born at term (13). Admission protocols at the only regional neonatal intensive care unit at Haukeland University Hospital served to define preterms. Controls were identified through birth protocols. Both cohorts were established in 2000. Clinical data were accessed through hospital charts. Gestational age was reassessed and determined according to department policy at the time of delivery (14). Mild and moderate/severe bronchopulmonary dysplasia (BPD) were defined according to requirement for supplemental oxygen $\geq$28 postnatal days and $\geq$36 wk postmenstrual age (PMA), respectively (15). Subjects with moderate and severe BPD were assessed together as oxygen at 36 wk PMA was supplied by low flow nasal catheters without exact knowledge of FiO_2. Subjects were examined twice within 2 wk in 2001. Spirometry and whole body plethysmography were performed at both visits. Questionnaires were filled in and the salbutamol reversibility test was performed at first visit and methacholine provocation, skin prick tests and blood sampling at the second. No subjects were examined within 2 wk of a respiratory tract infection. The Regional Ethics Committee approved the study. Informed written consent was obtained from participating subjects and parents.

Lung function measurements and questionnaires

Asthma medication was stopped prior to testing as appropriate. Standing height was substituted by arm span in two subjects with tetraplegic cerebral palsy (CP). Spirometry and static lung volumes were measured with a Vmax 22 spirometer and Autobox 6200 whole body plethysmography, respectively (SensorMedics Inc., Anaheim, USA). Standard criteria for quality performance were applied (16). Forced vital capacity (FVC), peak expiratory flow (PEF), forced expiratory volume in 1 s (FEV_1), forced expiratory flow at 50% and 75% of FVC (FEF_{50} and FEF_{75}), total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV) and airway resistance (Raw) were recorded. Measurements were compared to values predicted with standard reference equations (17, 18) and expressed as percentages of predicted. Mean values from the two test-days were used for statistical analysis. Bronchodilator responsiveness was assessed by measuring FEV_1 before and 10 min after administration of salbutamol (Ventoline® metered dose inhaler in Volumatic® spacer, 100 μg per 10 kg bodyweight). Bronchial responsiveness to methacholine (PD_{20}) (19) was determined, providing baseline $FEV_1 \geq 65\%$ predicted, using an inhalation-synchronized, dosimetric nebulizer, Spira Elektra 2® (Respiratory Care Centre, Hameenlinna, Finland) (20). Criterion for positive test was a decline in $FEV_1 \geq 20\%$ from baseline at a cumulative dose of $\leq$6.6 μmol methacholine (21). A dose response slope was calculated (22). Atopy was defined as minimum one positive skin prick test (23) or specific IgE assay (CAP-FEIA, Pharmacia, Uppsala, Sweden) in a panel of relevant allergens. The questionnaire from the International Study of Asthma and Allergy in Childhood (ISAAC) (24) and a standardized interview served to obtain the medical history. Current asthma was defined as wheeze in the last 12 mo plus methacholine hyperresponsiveness (BHR) (25).

Statistical methods

Paired group comparisons were performed with McNemar's χ^2 test, paired *t*-test or analysis of covariance (ANCOVA) (26) and non-paired comparisons with Pearson's χ^2 test, linear regression or the Kruskal-Wallis test, as appropriate. The level of significance was 0.05. SPSS version 11.0 was used for computations.

Results

Subjects

Eighty-four preterm infants were enrolled. Fifty-two (62%) survived the neonatal period and one died after hospital discharge. Two eligible preterms were inaccessible, two refused to participate and one was excluded due to severe Eisenmenger syndrome. Hence, 46 (90%) surviving adolescents were tested. Thirty-five (76%) of the primarily 46 invited control subjects responded positively. To recruit a full control cohort, an average of 1.4 term-born subjects had to be invited for each included preterm. Control subjects who refused to participate were average adolescents, reluctant to spend two afternoons participating in a clinical study. One control was excluded for medical reasons. All participating subjects were caucasians and native Norwegians. Mean age at examination was 17.7 (SD: 1.2) y. There

Table 1. Neonatal characteristics of the preterm cohort.

	Non-BPD $n = 10$	Mild BPD $n = 24$[a]	Mod/severe BPD $n = 12$	*p*-value
Number of females (% of group)	5 (50.0%)	11 (45.8%)	5 (41.7%)	0.926[b]
Gestational age; wk, mean (SD)	28.3 (1.6)	27.0 (1.3)	27.0 (1.2)	0.038[c]
Birthweight; g, mean (SD)	1171 (150)	1013 (193)	887 (126)	<0.001[c]
Duration of ventilator treatment; d, median (range)	0.4 (0–4.8)	8.6 (0.8–35.0)	25.4 (0.7–54.0)	<0.001[d]
Postnatal age when supplemental O_2 was stopped; d, median (range)	12.5 (1–25)	41.0 (28–71)	72.5 (55–257)	<0.001[d]
Post-conceptional age when supplemental O_2 was stopped; wk, median (range)	30.0 (28–34)	33.0 (31–35)	37.5 (36–63)	<0.001[d]

[a] For the variable "duration of ventilator treatment", $n = 23$ due to one set of missing data.
Statistical group comparisons performed with: [b] Pearson's χ^2 test; [c] linear regression; or [d] the Kruskal-Wallis test.

was no significant difference in age or gender between the subgroups of the study.

Neonatal characteristics and background variables

Mean gestational age of the preterm cohort was 27.3 (SD: 1.4) wk and mean birthweight 1014 (SD: 195) g. The five preterms not examined were comparable to those examined with respect to gestational age (29.4 wk, SD: 3.3) and birthweight (958 g, SD: 225). Three (7%) of the examined preterms were included due to a birthweight $\leq$1000 g, despite gestational age $>$28 wk. Eight preterms (17%) were small for gestational age, defined by a birthweight $\leq$10th percentile (14). Mean birthweight of the control cohort was 3441 (SD: 311) g. Ten preterms were classified as non-BPD, 24 as mild BPD and 12 as moderate/severe BPD. Birthweight decreased and neonatal requirements for ventilatory support increased parallel to increased severity of BPD (Table 1). Significantly more preterms (49%) than controls (22%) were exposed to antenatal maternal cigarette smoking (Table 2). No significant differences were seen for other background variables of potential relevance for lung function. The prevalence of antenatal or postnatal passive cigarette exposure or self-reported smoking did not increase with increasing severity of BPD (data not shown). Two preterms had spastic tetraplegic CP with accompanying scoliosis (one male and one female), another two had disabling diplegic CP and, altogether, three were dependent on a wheelchair.

Respiratory symptoms and diagnoses

One parent refused to complete the questionnaires. Previous pneumonia and hospitalization for airway respiratory problems as well as a current doctor's diagnosis of asthma and use of asthma inhalers were significantly more prevalent among preterms compared to the controls (Table 3). More preterms than control subjects tended to report current respiratory symptoms and recurrent wheeze in the preceding 12 mo; however, the difference was of only borderline significance (OR: 4.5, 95% CI: 0.9–42.8, $p = 0.065$). The other ISAAC core questions did not separate preterms from their term controls (data not shown). Comparison of the current prevalence of asthma was possible in 41 preterm/control pairs, as methacholine provocation test could not be performed in five preterms. Nine (22%) preterms and five (12%) controls were defined as current asthmatics ($p = 0.388$).

Lung function measurements

All subjects produced satisfactory and reproducible

Table 2. Demographic data for preterm and control subjects ($n = 46$, both groups[a]).

	Preterm	Control	*p*-value
Number of females	21 (45.6%)	21 (45.6%)	–
Height, cm (SD)	169.4 (8.1)	172.9 (7.5)	0.015
Weight, kg (SD)	63.4 (15.9)	67.6 (11.1)	0.220
BMI (SD)	22.2 (4.6)	22.6 (3.5)	0.757
Antenatal exposure to maternal cigarette smoking	22 (48.9%)	10 (22.2%)	0.008
Postnatal exposure to regular household smoking	23 (51.1%)	20 (44.4%)	0.664
Self-reported smoking	15 (32.6%)	14 (30.4%)	1.000
Atopic symptoms reported in at least one first-grade relative[b]	32 (71.1%)	36 (80.0%)	0.481
Atopic study subjects[c]	13 (28.3%)	20 (43.5%)	0.115

Figures in brackets reflect percent of group, unless stated otherwise. Statistical paired group comparisons were performed with McNemar's χ^2 test and the paired *t*-test, as appropriate.
[a] For the variables "antenatal" and "postnatal cigarette exposure" and "atopic symptoms in first grade relatives", 45 pairs were compared due to one set of missing data.
[b] Hay fever, atopic eczema or asthma.
[c] Hypersensitivity towards at least one tested allergen.

Table 3. Respiratory diagnoses, symptoms and treatment for preterm and control subjects ($n = 46$, both groups[a]).

	Preterm	Control	OR[b]	95% CI[b] for OR	*p*-value
Has your child ever had pneumonia?	26 (57.8)	12 (26.7)	3.8	1.4–13.0	0.007
Has your child ever been hospitalized for airway respiratory problems?	20 (44.4)	7 (15.6)	3.6	1.3–12.4	0.011
Has your child ever had asthma?	16 (35.6)	3 (6.7)	14.0	2.1–592.0	0.001
Doctors diagnose of asthma when entering the study	9 (19.6)	1 (2.2)	9.0	1.2–394.5	0.021
Wheeze or whistling in the chest during the last 12 mo	16 (34.8)	12 (26.1)	1.5	0.6–4.2	0.503
More than three attacks of wheeze during the last 12 mo	10 (22.2)	3 (6.7)	4.5	0.9–42.8	0.065
Use of inhaled β2-agonists at inclusion	8 (17.4)	1 (2.2)	8.0	1.1–355.0	0.039
Use of inhaled corticosteroids at inclusion	5 (10.9)	0 (0)	–	–	–
Current asthma[c]	9 (22.0)	5 (12.2)	2.0	0.5–9.1	0.388

Values express number of subjects with positive answer (% of group). Statistical paired group comparisons were performed with McNemar's χ^2 test.
[a] For questions requiring parental response, 45 pairs were compared due to one set of missing data.
[b] OR: odds ratio; CI: confidence interval.
[c] Bronchial hyperresponsiveness (positive methacholin provocation test) plus wheeze in the last 12 mo.

flow volume loops. Six preterms were unable to perform whole body plethysmography, five could not perform methacholine provocation test whereas three preterms and one control subject did not perform reversibility test. For preterms, mean values for PEF percent of predicted (PEF%) and FEV_1% were significantly reduced compared to term controls, and the discrepancies increased significantly with increasing severity of BPD (Table 4, interaction analysis). Mean FEF_{50}% and FEF_{75}% was significantly reduced and Raw significantly increased in preterms (Table 4 preterm versus control), but no trend for increased discrepancies with increasing severity of BPD could be verified. For FVC%, FRC%, TLC% and RV%, no significant differences between preterms and controls were demonstrated, nor was there any particular trend with increasing severity of BPD. Mean FEV_1% for preterm subjects with BPD was 93.2, a reduction relative to their respective control subjects of 14.4% of predicted ($p < 0.001$) (Fig. 1). Adjusted for height, gender and age, this difference constituted 480 ml/s ($p < 0.001$). If the two preterms with scoliosis were included, mean FEV_1% decreased to 89.6, a deficit relative to controls of 18.1% of predicted ($p < 0.001$) or 580 ml/s, adjusted for height, gender and age ($p < 0.001$). Within-subject FEV_1 day-by-day variability was not increased in preterms nor was there any significant trend for increased variability with increasing severity of BPD (data not shown). In control subjects with recurrent wheeze, mean FEV_1 % was reduced by 27.6% of predicted compared to asymptomatic controls ($p < 0.001$). In preterms, this reduction was 1.2% of predicted ($p = 0.850$). In a stepwise multiple linear regression model within the preterm population, FEV_1% was regressed on the BPD classification employed in this study, as well as the variables gestational age, birthweight, antenatal maternal infection, neonatal septicaemia, persistence of ductus arteriosus and number of days on ventilator. The BPD classification remained the only significant predictor of FEV_1% in the model ($p = 0.016$).

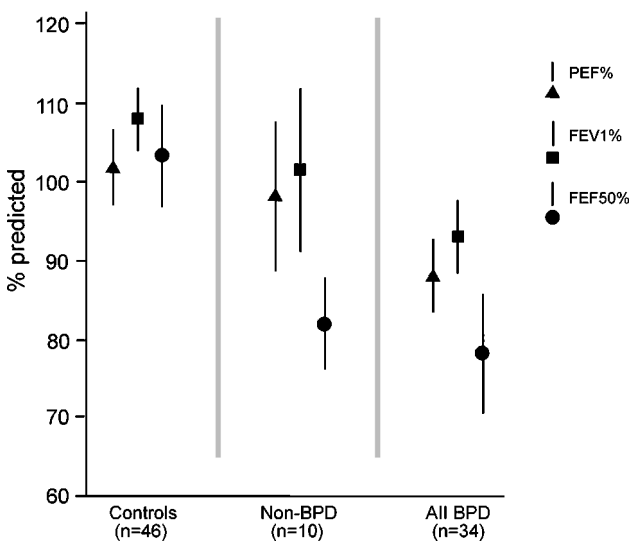

Fig. 1. Mean with 95% confidence interval for PEF, FEV_1 and FEF_{50} for control subjects, for preterms without bronchopulmonary dysplasia (non-BPD) and for all preterms with a diagnosis of BPD (all BPD). Two subjects with tetraplegic cerebral palsy with scolioses were not included.

Bronchial hyperreactivity and reversibility to salbutamol

The prevalence of bronchial hyperresponsiveness to methacholine was higher among preterms than term controls. Twelve of 46 control subjects (26%) tested positive compared to 4 (40%), 12 (60%) and 7 (64%) subjects with non-BPD, mild BPD and moderate/severe BPD, respectively. Assuming a lognormal distribution, the PD_{20} dose response slope was significantly increased in preterms relative to term controls (Table 4, case versus control), but no significant increase in slope with increasing severity of BPD was demonstrated (Table 4, interaction). The response to salbutamol was

Table 4. Lung function of the preterm subgroups compared to their respective control subjects.

	Controls $n = 46$	Non-BPD $n = 10$	Mild BPD $n = 24$	Moderate/severe BPD $n = 12$	p interaction[d]	p preterm versus control[d]
PEF%[a]	102.0 (16.2)	98.5 (13.3)	89.7 (13.2)	85.7 (14.7)	0.017	–
FEV_1%[a]	108.1 (13.8)	101.8 (14.6)	96.1 (12.1)	87.8 (13.8)	0.020	–
FEF_{50}%[a]	103.5 (22.6)	82.3 (8.4)	82.2 (18.5)	71.8 (27.5)	n.s.	<0.001
FEF_{75}%[a]	106.5 (30.5)	75.9 (15.4)	82.0 (24.6)	78.4 (34.3)	n.s.	<0.001
FVC%[a]	111.1 (14.9)	116.1 (19.7)	103.3 (16.4)	101.0 (17.1)	n.s.	0.100
TLC%[a]	110.9 (14.8)	112.0 (12.5)	109.8 (12.3)	108.3 (11.3)	n.s.	0.753
RV%[a]	102.6 (33.7)	105.7 (36.8)	112.1 (38.3)	123.5 (45.9)	n.s.	0.200
FRC%[a]	125.0 (23.8)	121.2 (25.6)	129.3 (21.2)	131.6 (20.1)	n.s.	0.532
Raw (kPa/l/sec)	0.175 (0.038)	0.216 (0.043)	0.225 (0.050)	0.244 (0.059)	n.s.	<0.001
DRS[b]	1.21 (0.2–6.4)	2.57 (0.5–13.8)	3.28 (0.5–22.0)	8.04 (1.4–44.7)	n.s.	0.006
$Beta_2$-response[c]	102.4 (4.3)	104.6 (2.7)	103.9 (5.7)	107.9 (9.6)	n.s.	0.072

Values express mean (SD) unless stated otherwise. Control subjects are presented as one group.
[a] Percent of predicted.
[b] Dose response slope to methacholine (22) presented as geometric mean (interval corresponding to ±1 SD on log10 scale).
[c] FEV_1 after administering salbutamol in percent of baseline (SD).
[d] Analysis of covariance (ANCOVA) using the linear mixed model procedure MIXED of SPSS (26), assuming a first order autoregressive structure between preterm and term-matched pairs. *P*-values for interaction refer to divergent trends for preterm and control subjects, i.e. increased discrepancies with increasing severity of BPD. In the case of non-significant interaction, analysis for any difference between preterms and control subjects was performed (preterm versus control).

non-significantly increased in preterms, and no trend for increased response with increasing severity of BPD was observed (Table 4). Only one control subject and three subjects with BPD (9.1%) had a 12% or greater response to salbutamol, a non-significant difference.

Discussion

To our knowledge, this is the first population-based study on respiratory outcome of extremely preterm subjects approaching adulthood. Compared to term-born controls, premature birth was associated with increased occurrence of asthma, pneumonia and hospitalizations for airway respiratory problems during childhood. At follow-up, the prevalence of doctor's diagnosed asthma, use of asthma inhalers and current wheeze was increased in preterms. Prematurity was associated with increased methacholine bronchial hyperresponsiveness and also with substantially increased airway obstruction that increased with increasing severity of neonatal BPD.

Technically, the study was a retrospective paired controlled cohort study. Due to regional medical logistics, no eligible preterm could escape inclusion and the algorithm used to reassess gestational age was identical to that in use at the time of delivery. Therefore, the preterm cohort would have consisted of the same subjects, had it been defined prospectively. As only five eligible preterms did not participate and their neonatal characteristics were comparable to those examined, bias due to loss of follow-up was small. Differences in perinatal and neonatal mortality rates could influence any quality of the surviving preterm population and thereby introduce the possibility for bias. There was no indication of increased perinatal or neonatal death rates in Norway or in the study region during the inclusion period (27). To ensure assessment of all infants considered to be extreme at the time of delivery, all subjects with birthweight $\leq$1000 g were included, despite gestational age $>$28 wk. Only three such subjects were examined and, overall, the cohort was of reasonably appropriate weight for gestational age. As only 1.4 potential control subjects were approached for each preterm, systematic bias in the control population is improbable. Two subjects with tetraplegic CP and scoliosis produced technically highly satisfactory and reproducible flow volume loops. Their exclusion from the analyses would imply exclusion of extrapulmonary thorax restriction as a possible cause of reduced lung function in preterms. As CP is a well-described consequence of preterm delivery, this would bias outcome. Hence, data were analysed with these subjects included as well as excluded. Polgar and Promadhat's (17) prediction equations for lung function measurements have been widely used in children. In the present study as well as in a number of European spirometric data sets (28), mean FEV_1 in unselected control subjects was higher than the value predicted. This observation underscores the importance of including appropriate controls when assessing lung function in subsets of a population.

The classification of BPD used in the present study was based on a workshop summary by Jobe and Bancalari (15). At the age of 28 postnatal days, 78% of the study population required supplemental oxygen compared to 26% at a PMA of 36 wk, figures that are in line with reports from larger populations (29). A significant trend for reduced FEV_1% and PEF% paralleled increased severity of BPD (Table 4, interaction). In a stepwise regression model, including birthweight, gestational age and perinatal variables of possible

relevance for outcome, the BPD classification significantly predicted FEV_1%. Thus, the present long-term study suggests that in extremely preterm infants this classification of BPD (15) offers an important predictive measure for respiratory function into adulthood. Due to co-linearity between the variables and a relatively narrow range for gestational age and birthweight, this result should, however, be interpreted with some caution.

Several studies have addressed childhood pulmonary sequela of preterm birth. Gross et al. (3) studied lung function at the age of seven in a large population based cohort with a gestational age of 24–31 wk and found a deficit of 14% of predicted for FEV_1% in subjects with a history of BPD. Doyle et al. (2) made a similar observation at the age of 14 in a hospital-based cohort of children with birthweight less than 1500 g and BPD. In a population-based cohort of adolescents (mean age 15 y) with birthweight less than 1500 g, Anand et al. (12) found evidence for medium and small airway obstruction but no difference in FEV_1. Compared to our cohort, their study group was of higher gestational age and birthweight, and only eight of 128 subjects were diagnosed with BPD. Northway et al. (9) described airway obstruction, bronchial hyperresponsiveness and hyperinflation in a highly selected group of young adults with a history of severe BPD born at Stanford, USA. The results of the present study thus represent an important extension of knowledge established in various paediatric populations: airway obstruction observed in comparable but younger populations of preterm birth does not seem to resolve towards adulthood.

The majority of young people have large ventilatory reserves and a good tolerance for deficits in airflow capacities. However, FEV_1 follows a well-described track throughout a lifespan. Subsequent to childhood growth, a stable plateau phase is followed by a decline throughout adulthood (30). The maximum level of FEV_1 obtained, as well as the timing of onset and subsequent rate of decline in adulthood determine when and if lung function impairment will occur. Thus, the deficit in FEV_1 observed for BPD subjects in this study represents more than a decade of normal age-related decline. Furthermore, the rate of decline in lung function in adulthood differs between population subgroups (30). Cigarette smoking, childhood pneumonias (31), asthma (32) and bronchial hyperreactivity (BHR) (33) may accelerate the normal aging process of the lung. Our preterm population smoked cigarettes at the same rate as their controls, had experienced more childhood pneumonias, used more asthma inhalers and had a distinctly increased prevalence of BHR. A prospect of an accelerated decline in lung function in adulthood is therefore possible.

It has been proposed that chronic obstructive pulmonary disease (COPD) may start in early childhood (34). Extreme preterm delivery and BPD may well represent risk factors for future COPD. The observed absence of association between reduced FEV_1 and wheeze and a limited response to $beta_2$-receptor agonists as well as to inhaled corticosteroids (35) indeed suggest a chronic pattern. Appreciating this scenario, an obligation for proper follow-up, treatment and guidance falls upon the health profession that made survival in these young people possible.

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