**Lung function evolution in children with old and new type bronchopulmonary
dysplasia: a retrospective cohort analysis.**

*Frederik Cardoen¹, François Vermeulen¹, Marijke Proesmans¹, Marleen Moens², Kris De
Boeck¹*

¹ *Department of Pediatric Pulmonology, University Hospital Leuven, University of Leuven,
3000 Leuven, Herestraat 49, Belgium.*

² *Rehabilitation center Pulderbos, Reebergenlaan 4, 2242 Zandhoven, Belgium*

*Frederik.cardoen@stlucas.be; Francois.vermeulen@uzleuven.be;
Marijke.proesmans@uzleuven.be; Marleen.moens@revapulderbos.be*

Corresponding author:

Kris De Boeck

Pediatric Pulmonology

University Hospital Leuven

Herestraat, 49

B-3000 Leuven

Belgium

christiane.deboeck@uzleuven.be

Authors contribution

FC, FV, MP, MM and KDB designed the study. FC and FV collected the data and performed the analyses. FC wrote the draft manuscript. FC, FV, MP, MM and KDB reviewed the manuscript and made significant additions. All authors take responsibility for the data and results.

Acknowledgments

Thanks to Mrs. Els Aertgeerts for secretarial assistance.

Abstract

Bronchopulmonary dysplasia (BPD) is one of the most important sequelae of premature birth. There is concern that in some patients lung injuries early in life may have lifelong consequences. In this retrospective observational cohort study lung function evolution in children with BPD was investigated from childhood to young adulthood. Data from 355 pulmonary function tests (PFT) in 24 patients were analyzed, with a median age at first PFT of 7.6 years and at last PFT 18.2 years. FEV₁ and FEV₁/FVC were below the 5th percentile in respectively 18 and 13/24 patients. Comparing first and last measurement there was significant worsening in FEV₁ from a mean of 71.3%pred(SD 18.3) to 66.7%pred(SD 21.7) (p<0.05) and in FEV₁/FVC from 85.4%pred(SD 15.2) to 79.8%pred(SD 17.3) (p=0.01). Evaluation of the individual lung function changes with linear regression showed deterioration in FEV₁, FVC and FEV₁/FVC in respectively 17, 13 and 17/24 patients. Total group analysis showed significant deterioration in FEV₁(-0.7%/year, p=0.002) and FEV₁/FVC(-0.5%/year, p=0.01). None of the 11 patients born up to 1990 improved in FEV₁ vs 7 of the 13 patients born after 1990 (p=0.006).

Conclusion: This points out to further deterioration of the lung function during childhood in this selected group of children with BPD.

Keywords

chronic lung disease, longitudinal, spirometry, outcome, preterm newborn

List of abbreviations

BD: bronchodilator

BPD: bronchopulmonary dysplasia

FEV₁: forced expiratory volume in 1 second

FVC: forced vital capacity

LLN: lower limit of normal

PFT: pulmonary function test

pp: percent of predicted

61

62 ***What is known***

- 63 • Data on longitudinal changes in lung function in children with BPD are scarce.

64 ***What is new***

- 65 • In children with BPD at the severe end of the disease spectrum, lung function does not
66 improve over time. On the contrary, in two thirds of the subjects studied FEV₁ and FEV₁/FVC
67 worsen over time.
- 68 • Lung function evolution towards adulthood was somewhat more favorable in children born
69 after 1990 compared to those born earlier, probably reflecting improvements in neonatal
70 care in subjects with new type BPD.

Introduction

Bronchopulmonary dysplasia (BPD) is one of the most important sequelae of premature birth.[1] BPD is defined as oxygen dependency beyond 28 days of life and disease severity is graded by assessing ventilatory support and the fraction of inspired oxygen needed near term.[2, 3]

During the first years of life, a trend towards clinical improvement is usually seen,[1, 4] but in infants with a particularly severe neonatal course, symptoms may persist into adolescence and adulthood.[5] The relationship between clinical symptoms and pulmonary function tests (PFT) is however not clear-cut: patients with marked airway obstruction detected by spirometry may report few if any respiratory symptoms.[1, 4]

Over the decades much has changed: the cohort of premature infants, the neonatal treatment strategies, the resulting lung damage. This led to the description of old (mainly airway obstruction) and new type BPD (arrest in lung growth).[3, 4]

In recent years, evidence accumulates that alveoli continue to be formed throughout childhood and even in adulthood.[6-8] Although this points towards the possibility of lung repair in the lung periphery, it does not necessarily imply improvement in the more central airways, assessed by routine spirometry.

Many cross-sectional studies have assessed PFT in patients with BPD. However, only a few studies have assessed PFT longitudinally and none have done so using the Global Lung Initiative (GLI) reference values[9] that offer seamless transition from childhood to adulthood. Differences in PFT evolution between old and new type BPD have also not been reported. We therefore set up this retrospective cohort evaluation.

Materials and methods

The database of the respiratory center at the University Hospital of Leuven and the Rehabilitation Center Pulderbos was searched in the period January 2001 to October 2011 using the terms “bronchopulmonary dysplasia” or “BPD” (n=116). We only included patients who were at least 12 years of age at the last pulmonary function test (PFT), who had performed at least 4 lung function tests over a time period of at least 5 years and who met the BPD consensus definition criteria (n=24).[3] A STROBE flow diagram

of the study population is included in figure 1. We defined the cohort born from 1991 on, when surfactant treatment was initiated at our hospital, as new type BPD; the earlier cohort being considered old type BPD. BPD was defined as mild or moderate/severe.[3]

All patient charts were reviewed in detail until December 2016. Recurrent wheezing, use of inhaled corticosteroids and diagnosis of hyperreactive airway disease or asthma mentioned in the chart were considered as evidence of ‘asthma like symptoms’. Surgical interventions and additional diagnoses were also retrieved.

The study was approved by the ethical committee of UZ LEUVEN (Study number S61294).

Lung function measurements

All lung function tests had been performed on a Jaeger spirometer following ATS guidelines.[10, 11] Lung function tests were reviewed and results were expressed as percent predicted (pp or %pred) according to the GLI equations.[9] Data expressed as z-scores are reported the online supplement. Data from 355 pulmonary function tests performed in 24 patients were included in the analysis. For longitudinal analysis, we present the lung function data obtained post bronchodilator (BD, 4 puffs of 100 mcg salbutamol) from 314/355 tests, because these results best reflect true lung size and airway diameter. For all parameters, the fifth percentile was considered as the lower limit of normal (LLN). To assess the reversibility of airflow obstruction, a positive bronchodilator response was defined as an increase in FEV₁ of > 12% from baseline.

Statistical analysis

Normality of data distribution was assessed with Kolmogorov-Smirnov and Shapiro-Wilk test. The lung function data at first and last measurement were compared using a paired t-test. The old and new BPD birth cohorts were compared using an unpaired t-test, Mann-Whitney, or Fisher exact test as appropriate. Linear regression analysis was applied to investigate how lung function parameters changed over time in each individual. Since the degree of tracking of lung function parameters in healthy individuals is not known, we arbitrarily defined a positive or negative slope as improvement or deterioration

A mixed linear regression model was used to calculate the mean intercept at age 6 and the slope for each lung function parameter. Mixed effects model analysis was used to assess the effect of birth cohort, birth weight, gestational age, duration of ventilation and oxygen supplementation and grading of BPD on intercept and slope for FEV₁, FVC and FEV₁/FVC.

A p value less than 0.05 was considered statistically significant.

Results

Subjects

Twenty-four children (13 females, 11 males) were included in the analysis: 11 in the early BPD cohort (old type) and 13 in the late BPD cohort (new type). Patient characteristics and number and timing of the PFT during childhood are reported in Table 1. There were no differences in patient characteristics between the early and late cohort (Table S1).

Twenty-one of 24 patients reported asthma-like symptoms during childhood. At the time of last encounter 16/24 patients were using daily inhaled corticosteroids. In this group, 9 patients reported good respiratory control over the last winter without any significant problems, 5 reported a stable situation but still had had several respiratory infections with exacerbation in the last winter, 1 patient had an acute respiratory exacerbation during the last consultation with need for systemic steroids and antibiotics and 1 patient had severe dyspnea and was classified as NYHAIII. The remaining 8 patients did not take any inhaled corticosteroids at last encounter. In this group 1 patient had stopped this therapy 3 months earlier and 1 patient was treated with azithromycin prophylaxis during the winter months. All 8 patients reported good respiratory control in the last winter but 4/8 still needed salbutamol during intensive physical activity. There was no significant difference in the use of inhaled corticosteroids or ongoing respiratory symptoms between both birth cohorts (Fisher exact, respectively p=1 and p=0.66). Hence in total 7/24 subjects reported ongoing respiratory symptoms. Hence in total 7/24 subjects reported ongoing respiratory symptoms.

Eight of 24 patients had some degree of psychomotor impairment and 10/24 patients had undergone surgery (patent ductus arteriosus clipping 3, ventricle septum closure 1, coarctectomy 1, thoracoscopic bullectomy 1, diaphragm plication 1, laparotomy for necrotizing enterocolitis 2, repair of inguinal hernia 4, correction of scoliosis 2, correction of pectus excavatum 1, multilevel orthopedic procedure 1).

Lung function

Median age at first lung function was 7.6 years (IQR 6.3;8.4) and at last lung function 18.2 years (IQR 15.5;26.3). A positive bronchodilator response was present in 10/24 patients at first PFT and in 6/24 patients at last PFT. At first PFT, mean ppFEV₁ was 71.3%, mean ppFVC 83.3% and ppFEV₁/FVC 85.4% (Table 2). FEV₁, FVC and FEV₁/FVC were below the LLN in respectively 18, 11 and 13/24 patients, indicating airflow obstruction in the majority of subjects. At last PFT, FEV₁, FVC and FEV₁/FVC were below the LLN in respectively 16, 11 and 14/24 patients. Between the first lung function and the last lung function, mean ppFEV₁ and ppFEV₁/FVC had worsened (respectively p<0.05 and p<0.01), suggesting worsening airway obstruction.

Using regression analyses, deterioration (negative slope) for ppFEV₁, ppFVC and ppFEV₁/FVC was found in respectively 17, 13 and 17/24 patients (Figure 2). Mean intercept at age 6 and slopes for lung function parameters calculated using the mixed linear model are reported in Table 2 and confirm a significant deterioration in ppFEV₁ and ppFEV₁/FVC post-BD over time, amounting to a mean decline of 0.7%/year for ppFEV₁ (p=0.002) and 0.5%/year for ppFEV₁/FVC (p=0.01). Analysis using z-scores rather than percent of predicted value led to similar findings (Figure S1 and table S2).

There were no significant differences in lung function evolution between the early and late birth cohort (Table 3). However all subjects with old type BPD deteriorated in FEV₁ in contrast with only 6/13 of new type BPD (p=0.006). Old type BPD subjects were slightly older at time of first PTF. However, the mean change in lung function did not differ for any parameter studied.

Using mixed effects model analysis, several parameters came out as significantly influencing the extrapolated PFT values at age 6 years as well as the slope of decline (Table 4). Compared to patients with mild BPD, those with moderate/severe BPD had a 22.9% lower ppFVC at age 6 years (p=0.01) but their ppFVC declined less and their ppFEV₁/FVC declined more. Birth weight had a statistically significant effect on slope of decline of ppFVC but the effect size was small; no effect from gestational

age was seen. Increasing duration of ventilation and to a lesser extent duration of oxygen supplementation worsened the mean ppFEV₁ and ppFVC at age 6 years but not the slope of decline.

Correlation between lung function and respiratory symptoms

Lung function at start and at last encounter were not significantly related with the report of ongoing respiratory symptoms during last winter season (Mann-Whitney U test, respectively p=0.053 and p=0.061). Nevertheless there might be a correlation between lung function and clinical symptoms since the 4 patients with worst lung function at start were 4 of the 7 patients who reported ongoing respiratory symptoms. All 4 belonged to the early birth cohort.

Discussion

In children with moderate to severe BPD, improvement in FEV₁, FVC and FEV₁/FVC was not seen during childhood. On the contrary, in the majority of children, lung function was already abnormal at early school age and further deteriorated throughout adolescence. This in contrast with healthy people in whom lung size increases to a maximum during early adulthood, remains stable for some years and then declines until senescence.[4] 'Respiratory healthy elderly' however still have PFT values above the threshold to cause symptoms of airway disability.[12] In patients with abnormal lung function, like survivors of BPD, there is therefore concern that the susceptibility to symptoms of airflow limitation in later life will be increased, since the adult respiratory health is shaped early in life.[2, 13, 14]

Smyth et al.[15] were among the first to report airway obstruction, airway hyperreactivity and hyperinflation in long term survivors of BPD. Filippone et al.[16] studied lung function in children with BPD at 2 time points: age 2 years and early school age. He reported an abnormal FEV₁ in 15/18 children with BPD at a mean age of 8.8 years. Mean FEV₁ % predicted was 76% and correlated (r=0.68) with maximal flow at functional residual capacity (V_{maxFRC}) at 2 years of age. Many cross-sectional evaluations comparing lung function of survivors with BPD and controls confirmed this finding.[4]

Some authors have suggested improvement of lung function over time in subjects with BPD.[17, 18] Our longitudinal data however contradict this and therefore raise concern. Differences in initial disease severity, in definition of BPD, shorter follow-up period and use of different lung function reference

values can explain these contradictory findings. Few studies indeed evaluated spirometry longitudinally in children with BPD, from childhood through to young adulthood.

Koumbourlis et al.[18] performed a prospective, longitudinal evaluation of pulmonary function in 17 subjects born preterm with radiographic evidence of chronic lung disease at 4 weeks of age. Many subjects had a short duration of ventilation and oxygen supplementation, indicating milder BPD, which could explain the normal lung function in 8/17 patients. Blayney et al.[17] showed improvement in FEV₁ in 32 children with BPD, but based on only two measurements between the age of 7 and 10 years. Doyle et al.[19] reported a cohort of 147 survivors with birth weight < 1500 g of whom 33 (22%) had developed BPD. For 29/33 patients with lung function data at age 8 and 18 years, mean FEV₁ did not change between the age of 8 and 18, while FEV₁/FVC decreased from 81.8 % at age 8 to 73.9 % at age 18. The use of only 2 time points however limits reliability of estimates of lung function evolution over time.

Vollsaeter et al.[20] found a low FEV₁ at age 10 in patients with BPD, but without further change at the age of 18 years. In their cohort, Z-score for FEV₁ at age 10 in children with mild/severe BPD (-1.4) was higher than in our study at the mean age of 8 (-2.3), likely reflecting inclusion of sicker patients in our cohort. Recently Hirata et al.[21] published a retrospective study about 89 extremely low birthweight survivors with or without a history of BPD or bubbly/cystic lung appearance in the neonatal period. Mean lung function values at ages 8 and age 12 years were lower than Japanese reference values and the obstructive pattern of lung function impairment deteriorated from 8 to 12 years of age regardless of history of neonatal respiratory disease: FEV₁ 83.0 ± 17.0% decreased to 76.6 ± 17.8% (mean difference-6.43, 95%CI -9.10 to -3.75) and FEV₁/FVC decreased from 84.0 ± 10.1% to 78.2 ± 13.4% (mean difference-5.82, 95%CI -8.56 to -3.08. Differences in initial severity between these cohorts is the most likely explanation for the differences in outcome. Indeed, our data show that grading of BPD has the largest influence on outcome.

Narayanan et al.[6] provided evidence that alveolarization continues during childhood and adolescence. In follow-up work they further substantiated this evidence.[8] These exciting findings would imply that the lungs may be able to recover from damage in early life. Assessing alveolar count is of course very different from measuring central airway patency. And in the accompanying editorial, Jobe et al. pointed towards the larger standard deviation for alveolar dimension in children with BPD and discusses the

heterogeneity of survivors of newborn lung disease.[22] He ‘predicts’ that abnormalities will be found in higher risk survivors. In our study, we mainly assessed children with moderate and severe BPD and see no evidence for improvement in lung function over a median follow-up period of 11.7 years.

Since the birth year ranged from 1984 to 2004, the patients in the current cohort received variable initial treatments. In Belgium, the first administrations of surfactant started in 1991 and the use of antenatal corticosteroids only got accepted into practice in the mid-nineties. The subjects therefore most likely represent a mixture of old type BPD with mainly structural lung damage and new type BPD first described by Jobe in 1999 with mainly arrest in lung growth. In 7 of the 13 children born in more recent years FEV₁ improved, compared to 0 of the 11 patients born before 1991 (p=0.006). Advances in neonatal care have led to a change in the pathophysiology of BPD and also to a somewhat better outcome in our later cohort.

Our study certainly has strengths: the large number of PFT per subject and the long follow-up time allowed for reliable individual longitudinal assessment; we used GLI reference values (pp as well as as z-scores),[9] most appropriate to assess lung function changes over time since they offer a seamless transition from childhood to adulthood. Like Merkus et al.[23] we chose to present postbronchodilator lung function data because these best reflect true lung size and airway diameter since enhanced bronchomotor tone and/or inflammation can be ruled out.

Our study has limitations. We studied a selected group of children at the more severe end of the BPD spectrum and this introduces bias. Indeed, more symptomatic patients are more likely to continue to attend the respiratory clinic or rehabilitation center, and thus have lung function data available over a prolonged time period. We thereby may overestimate the proportion of children with BPD and worsening of lung function over time. The numbers in the subgroup of early and late BPD are small; hence we cannot make firm statements on the trend towards improved outcome in the late versus early birth cohort. We arbitrarily defined a change in % predicted above 0% predicted/year as improvement or deterioration, since the actual closeness of lung function tracking over the years is unknown. However, changing to another cut-off (e.g. 1% predicted/year) would not significantly modify the conclusion, since a mean drop in FEV₁ of 4.7 % predicted was seen towards early adulthood. Also, poor

spirometry technique is unlikely to explain the results, since this would be more likely at a young age rather than during adolescence or early adulthood.

The findings in the current study should not be taken lightly. Few evidence based treatments are available for children with BPD. Systematic follow up of lung function in all BPD survivors (able to perform lung function) seems necessary to obtain a better understanding of lung growth in survivors with BPD. Wheeze, diagnosis of hyperreactive airway disease and asthma were a prominent feature in our cohort and have been reported by others.[4] At present many patients with BPD receive bronchodilators and inhaled corticosteroids throughout infancy and childhood[4] with especially the latter having at least the potential of hampering rather than improving lung growth. Therefore, randomized controlled trials are needed to evaluate the effect of such therapies on long term lung growth. Ideally future lung assessment in survivors of BPD should combine measurements of lung function with measurements of gas mixing efficiency as well as estimates of alveolar count and dimension.

In conclusion, we provide evidence that in children with BPD at the severe end of disease spectrum, lung function does not improve over time. On the contrary, FEV₁ and also FVC worsen over time in two thirds of the subjects studied.

Compliance with Ethical Statements

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: There is no funding source.

Ethical approval: The Ethics Committee of UZ Leuven approved the study.

- 284 1. Baraldi E, Carraro S, Filippone M: **Bronchopulmonary dysplasia: definitions and**
285 **long-term respiratory outcome.** *Early Hum Dev* 2009, **85**:S1-3.
- 286 2. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, Wrage LA,
287 Poole K: **Validation of the National Institutes of Health consensus definition of**
288 **bronchopulmonary dysplasia.** *Pediatrics* 2005, **116**:1353-1360.
- 289 3. Jobe AH, Bancalari E: **Bronchopulmonary dysplasia.** *Am J Respir Crit Care Med*
290 2001, **163**:1723-1729.
- 291 4. Baraldi E, Filippone M: **Chronic lung disease after premature birth.** *N Engl J Med*
292 2007, **357**:1946-1955.
- 293 5. Narang I, Baraldi E, Silverman M, Bush A: **Airway function measurements and the**
294 **long-term follow-up of survivors of preterm birth with and without chronic lung**
295 **disease.** *Pediatr Pulmonol* 2006, **41**:497-508.
- 296 6. Narayanan M, Owers-Bradley J, Beardsmore CS, Mada M, Ball I, Garipov R, Panesar
297 KS, Kuehni CE, Spycher BD, Williams SE, Silverman M: **Alveolarization continues**
298 **during childhood and adolescence: new evidence from helium-3 magnetic**
299 **resonance.** *Am J Respir Crit Care Med* 2012, **185**:186-191.
- 300 7. Butler JP, Loring SH, Patz S, Tsuda A, Yablonskiy DA, Mentzer SJ: **Evidence for**
301 **adult lung growth in humans.** *N Engl J Med* 2012, **367**:244-247.
- 302 8. Narayanan M, Beardsmore CS, Owers-Bradley J, Dogaru CM, Mada M, Ball I,
303 Garipov RR, Kuehni CE, Spycher BD, Silverman M: **Catch-up alveolarization in ex-**
304 **preterm children: evidence from (3)He magnetic resonance.** *Am J Respir Crit Care*
305 *Med* 2013, **187**:1104-1109.
- 306 9. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL,
307 Hankinson JL, Ip MS, Zheng J, et al: **Multi-ethnic reference values for spirometry**
308 **for the 3-95-yr age range: the global lung function 2012 equations.** *Eur Respir J*
309 2012, **40**:1324-1343.
- 310 10. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC: **Lung**
311 **volumes and forced ventilatory flows. Report Working Party Standardization of**
312 **Lung Function Tests, European Community for Steel and Coal. Official**
313 **Statement of the European Respiratory Society.** *Eur Respir J Suppl* 1993, **16**:5-40.
- 314 11. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R,
315 Enright P, van der Grinten CP, Gustafsson P, et al: **Standardisation of spirometry.**
316 *Eur Respir J* 2005, **26**:319-338.
- 317 12. Dyer C: **The interaction of ageing and lung disease.** *Chron Respir Dis* 2012, **9**:63-
318 67.
- 319 13. Northway WH, Jr., Moss RB, Carlisle KB, Parker BR, Popp RL, Pitlick PT, Eichler I,
320 Lamm RL, Brown BW, Jr.: **Late pulmonary sequelae of bronchopulmonary**
321 **dysplasia.** *N Engl J Med* 1990, **323**:1793-1799.
- 322 14. Filippone M, Baraldi E: **On early life risk factors for COPD.** *Am J Respir Crit Care*
323 *Med* 2011, **183**:415-416; author reply 416.
- 324 15. Smyth JA, Tabachnik E, Duncan WJ, Reilly BJ, Levison H: **Pulmonary function and**
325 **bronchial hyperreactivity in long-term survivors of bronchopulmonary dysplasia.**
326 *Pediatrics* 1981, **68**:336-340.
- 327 16. Filippone M, Sartor M, Zacchello F, Baraldi E: **Flow limitation in infants with**
328 **bronchopulmonary dysplasia and respiratory function at school age.** *Lancet* 2003,
329 **361**:753-754.

- 330 17. Blayney M, Kerem E, Whyte H, O'Brodovich H: **Bronchopulmonary dysplasia:**
331 **improvement in lung function between 7 and 10 years of age.** *J Pediatr* 1991,
332 **118:**201-206.
- 333 18. Koumbourlis AC, Motoyama EK, Mutich RL, Mallory GB, Walczak SA, Fernald K:
334 **Longitudinal follow-up of lung function from childhood to adolescence in**
335 **prematurely born patients with neonatal chronic lung disease.** *Pediatr Pulmonol*
336 1996, **21:**28-34.
- 337 19. Doyle LW, Faber B, Callanan C, Freezer N, Ford GW, Davis NM:
338 **Bronchopulmonary dysplasia in very low birth weight subjects and lung function**
339 **in late adolescence.** *Pediatrics* 2006, **118:**108-113.
- 340 20. Vollsaeter M, Roksund OD, Eide GE, Markestad T, Halvorsen T: **Lung function**
341 **after preterm birth: development from mid-childhood to adulthood.** *Thorax* 2013,
342 **68:**767-776.
- 343 21. Hirata K, Nishihara M, Kimura T, Shiraishi J, Hirano S, Kitajima H, Fujimura M:
344 **Longitudinal impairment of lung function in school-age children with extremely**
345 **low birth weights.** *Pediatr Pulmonol* 2017, **52:**779-786.
- 346 22. Jobe AH: **Good news for lung repair in preterm infants.** *Am J Respir Crit Care*
347 *Med* 2013, **187:**1043-1044.
- 348 23. Merkus PJ, van Pelt W, van Houwelingen JC, van Essen-Zandvliet LE, Duiverman EJ,
349 Kerrebijn KF, Quanjer PH. **Inhaled corticosteroids and growth of airway function**
350 **in asthmatic children.** *Eur Respir J* 2004, 23(6):861-8.
351

Figure 1. STROBE flow diagram of the study population. PFT: pulmonary function test. BPD: bronchopulmonary dysplasia

Figure 2. Linear regression lines for FEV₁, FVC and FEV₁/FVC in each subject (Post bronchodilator values expressed as % predicted using the Global Lung Initiative reference values.[9])

Figure S1 Linear regression lines for FEV₁, FVC and FEV₁/FVC in each subject. (Post bronchodilator values expressed as z-scores using the Global Lung Initiative reference values.[9] Horizontal lines depict the median values and the lower limit of normal).

Table 1 Patient characteristics in the neonatal period and at time of first and last lung function test; number of and age at time of pulmonary function measurements. N=24 but N=22 for number of days on supplemental oxygen and N=21 for days on assisted ventilation.

	Median (IQR) or <i>n</i>
Gestational age (<i>weeks</i>)	29.0 (26.9;31.3)
Birth weight (<i>grams</i>)	1227 (900;1647)
Supplemental oxygen (<i>days</i>)	66 (51;287)
Assisted ventilation (<i>days</i>)	31 (19;38)
Grading of BPD	
Mild	5
Moderate/Severe	19
Number of lung function measurements per patient	13 (9;20)
Age at first measurement (<i>years</i>)	7.6 (6.3;8.4)
Age at last measurement (<i>years</i>)	18.2 (15.5;26.3)
Interval between first and last measurement (<i>years</i>)	11.7 (7.6;15.9)

Table 2: Mean lung function parameters at first and last measurement. Mean lung function at age 6 years and slope in lung function evolution as derived from mixed linear models. Post bronchodilator values are used; these are expressed as % predicted using the Global Lung Initiative reference values,[9]

	<i>Descriptive</i>			<i>Mixed Linear Model</i>		
	First lung function	Last lung function	Difference		Intercept at age 6 years	Slope
	mean (SD)	mean (SD)	mean (SD)	<i>p-value</i>	Mean (95%CI)	<i>p-value</i>
Age (years)	7.79 (1.98)	19.90 (5.68)	12.10 (4.64)	<0.001		
FEV ₁ % pred	71.34 (18.27)	66.66 (21.71)	-4.68 (13.24)	<0.05	73.45 (67.01;79.89)	-0.70 (-1.14;-0.27) 0.002
FVC % pred	83.26 (17.29)	81.67 (16.34)	-1.59 (14.97)	0.54	84.37 (78.49;90.25)	-0.46 (-0.96;0.04) 0.07
FEV ₁ /FVC % pred	85.38 (15.15)	79.80 (17.32)	-5.58 (12.30)	0.01	86.58 (81.78;91.38)	-0.45 (-0.78;-0.12) 0.01

Table 3 Comparison of early and late birth cohorts.

	Birth cohort			<i>p-value for the difference</i>
	Early (1984-1990)	Late (1991-1996)		
Values at first visit				
Age (years)	Mean (SD)	9.26 (1.84)	6.55 (1.02)	< 0.001^a
Height z-score	Mean (SD)	-0.04 (1.03)	-0.79 (1.25)	0.12 ^a
ppFEV ₁ (%)	Mean (SD)	67.51 (24.86)	74.58 (9.99)	0.39 ^a
ppFVC (%)	Mean (SD)	80.98 (18.68))	85.18 (16.54)	0.57 ^a
ppFEV ₁ /FVC (%)	Mean (SD)	81.38 (17.56)	88.76 (12.49)	0.26 ^a
Change between first and last visit				
Age (years)	Mean (SD)	13.75 (5.18)	10.71 (3.79)	0.12 ^a
Height z-score	Mean (SD)	-0.13 (0.89)	0.37 (0.66)	0.14 ^a
ppFEV ₁ (%)	Mean (SD)	-9.30 (9.60)	-0.77 (14.93)	0.1 ^a
ppFVC (%)	Mean (SD)	-6.24 (10.96)	2.35 (17.12)	0.15 ^a
ppFEV ₁ /FVC (%)	Mean (SD)	-7.15 (15.13)	-4.25 (9.74)	0.59 ^a
N with improving individual slopes				
Slope ppFEV ₁	N	0/11	7/13	0.006^b
Slope ppFVC	N	3/11	8/13	0.12 ^b
Slope ppFEV ₁ /FVC	N	1/11	6/13	0.078 ^b

^a Mann-Whitney U test ^b Fisher Exact Test

Table 4: Mixed effects model analysis exploring the effect of birth cohort, initial grading of BPD, birth weight, gestational age, duration of oxygen supplementation, duration of ventilation on intercept at age 6 and slope of each lung function parameter

	FEV ₁ % predicted			FVC % predicted			FEV ₁ /FVC % predicted		
	Intercept (95%CI)	p- value	Slope (95%CI)	p- value	Intercept (95%CI)	p- value	Slope (95%CI)	p- value	p- value
Birth cohort (late vs early)	5.64 (-8.34;19.62)	0.43	0.45 (-0.47;1.38)	0.34	3.85 (-9.39;17.09)	0.57	0.74 (-0.28;1.77)	0.16	
Grading BPD (mild vs moderate/severe)	-14.97 (-31.38;1.43)	0.07	0.82 (-0.36;2.00)	0.17	-22.86 (-36.46;-9.26)	<0.01	1.61 (0.38;2.83)	0.01	
Birth weight (/100g)	0.39 (-0.90;1.69)	0.55	-0.06 (-0.15;0.03)	0.23	1.06 (-0.08;2.29)	0.07	-0.10 (-0.20;-0.00)	0.04	
Gestational age (/24 weeks)	1.77 (-0.52;4.06)	0.13	-0.10 (-0.26;0.06)	0.22	1.90 (-0.20;4.01)	0.08	-0.13 (-0.31;0.05)	0.16	
Duration of oxygen supplementation (/100 days)	-1.58 (-2.35;-0.81)	<0.01	-0.00 (-0.07;0.07)	0.96	-1.08 (-1.95;-0.20)	0.02	0.01 (-0.06;0.09)	0.71	
Duration of ventilation (10 days)	-3.65 (-6.99;-0.31)	0.03	0.11 (-0.16;0.38)	0.44	-3.60 (-6.89;-0.32)	0.03	0.14 (-0.15;0.43)	0.35	

Example: With every 100 days of oxygen supplementation, the extrapolated FEV₁ at age 6 years will drop by 1.58 pp but there is no difference in the rate of decline of FEV₁.

Table S1: Comparison of demographics between early and late birth cohorts . N=24 but N=22 for number of days on supplemental oxygen and N=21 for number of days with assisted ventilation. Data are represented as Median (IQR) or *n*.

	Birth cohort		
	Early (1984-1990)	Late (1991-1996)	<i>p</i> -value for the difference
Gestational age (<i>weeks</i>)	29 (28;30)	29 (27;32)	0.93 ^a
Birth weight (<i>grams</i>)	1320 (1080;1660)	940 (730;1570)	0.21 ^a
Supplemental oxygen (days)	186 (51;780)	61 (57;128)	0.39 ^a
Assisted ventilation (days)	36 (27;50)	28 (13;33)	0.18 ^a
Grading of BPD			0.63 ^b
Mild	3/11	2/13	
Moderate/Severe	8/11	11/13	
Daily inhaled corticosteroids	8/11	9/13	1 ^b

^a Mann-Withney U test ^b Fisher Exact Test

Table S2: Mean lung function parameters at first and last measurement. Mean lung function at age 6 years and slope in lung function evolution as derived from mixed linear models. Post bronchodilator values are used; these are expressed as z-scores using the Global Lung Initiative reference values.

	<i>Descriptive</i>			<i>Mixed Linear Model</i>		
	First lung function	Last lung function	Difference		Intercept at age 6 years	Slope
	mean (SD)	mean (SD)	mean (SD)	<i>p-value</i>	Mean (95%CI)	<i>p-value</i>
Age (years)	7.79 (1.98)	19.90 (5.68)	12.10 (4.64)	<0.001		
FEV ₁ z-score	-2.34 (1.51)	-2.73 (1.72)	-0.39 (1.04)	0.03	-2.19 (-2.71;-1.66)	-0.06 (-0.09;-0.03) 0.001
FVC z-score	-1.41 (1.45)	-1.57 (1.39)	-0.15 (1.23)	0.47	-1.35 (-1.87;-0.84)	-0.04 (-0.08;0.00) 0.06
FEV ₁ /FVC Z-score	-1.53 (1.70)	-2.02 (1.53)	-0.49 (1.27)	0.03	-1.51 (-2.07;-0.94)	-0.04 (-0.07;0.00) <0.05