TITLE

Better care of immature infants, has it influenced long-term pulmonary outcome?

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SHORT TITLE: Lung function after premature birth

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ABSTRACT

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Aims: To assess whether lung function in late childhood had improved in subjects born extremely prematurely in the early 1990's compared to the early 1980's, and whether neonatal factors in the respective periods had different impact on long-term pulmonary outcome. **Design:** Population-based, controlled cohort study. Lung function was determined in 81 of 86 (94%) eligible subjects born with gestational age ≤ 28 weeks or birthweight ≤ 1000 grams in Western Norway in 1982-85 (n=46) and 1991-92 (n=35), and in 81 matched control subjects born at term. **Results:** The incidence of bronchopulmonary dysplasia was similar in the two periods. At follow-up, airway obstruction, hyperresponsiveness and pulmonary hyperinflation were similarly increased in both preterm cohorts compared to matched controls. Furthermore, current lung function was similarly related to neonatal respiratory disease in both birth-cohorts: FEV_1 was reduced with respectively 18.6% and 18.7% of predicted in preterms dependent on supplemental oxygen at 36 weeks postmenstrual age. Lack of antenatal treatment with corticosteroids and prolonged neonatal oxygen treatment predicted similar significant airway obstruction in the two birth-cohorts. **Conclusion:** Preterms born in different eras of neonatology had similar long-term decreases in lung function. Long periods of oxygen supplementation are still required to salvage immature infants, and airway obstruction may still be a common long-term outcome.

KEY WORDS:

1. Airway Hyperresponsiveness. 2. Bronchopulmonary Dysplasia. 3. Cohort Study.

4. Extremely Preterm Infant. 5. Obstructive Lung Disease.

INTRODUCTION

To the benefit of all newborns, profound progress has occurred in perinatal and neonatal care over the past decades. Extensive refinements of therapeutic strategies and equipment at all levels have contributed (1-3). In the same period, perinatal and neonatal mortality has decreased, particularly for the most immature infants (4;5). Despite reduced mortality and improved management of acute neonatal illness, chronic respiratory morbidity remains a challenge in neonatal intensive care units (NICUs). Although the clinical presentation of bronchopulmonary dysplasia (BPD) has generally become less severe, its incidence has not changed (6;7). Increased survival rates among the most immature infants combined with unchanged or even increased rates of BPD, implies that an increasing number of preterms with chronic lung disease are being discharged from our neonatal departments (8;9). Concerns have been expressed that we may enter a period of iatrogenesis, i.e. negative overall health effects from improved neonatal intensive care and treatment schemes (8). Long-term pulmonary effects of this scenario are poorly described.

To elucidate such long-term effects, comparable regional birth cohorts from different eras of intensive care neonatology should be assessed by identical methods, preferably at the same age. However, the time span required, makes this optimal strategy demanding. Concurrent assessment at different ages facilitates identical evaluation, but precipitates a discussion regarding lung growth in adolescent preterms with obstructive lung disease. Summarising available knowledge on this issue, Eber and Zach (10) stated that hyperinflation may improve with growth whereas airway obstruction improves only slowly or not at all.

With this knowledge at hand, we aimed to study if lung function in late childhood had improved in survivors of extreme prematurity born in the early 1990's compared to those born in the early 1980's. We also aimed to assess the association between neonatal factors in the two periods and lung function outcome at follow-up, with particular emphasis on prolonged neonatal oxygen requirements.

METHODS

Subjects and study design. Two population based cohorts of young people who were born at gestational age ≤ 28 weeks or with birthweight ≤ 1000 grams in the years 1982-85 (first birth-cohort) and 1991-92 (second birth-cohort) in Western Norway were examined. This study was an extension of previously published follow-up data on the first birth-cohort (11). Medical care was provided at the only regional NICU. Preterms were considered enrolled when admitted to the neonatal department. Medical data were accessed from hospital charts, and relevant background data from a standardized questionnaire. Gestational age at birth was determined according to identical algorithms in the two inclusion periods (12), i.e. primarily by the number of completed weeks since the last menstrual period. Estimates from early ultrasound scan were used if diverging more than two weeks, while paediatric assessment was used if diverging more than three weeks from the former estimates, or if antenatal data were missing. Neonatal respiratory morbidity was classified as suggested by Jobe and Bancalari (7), i.e. as mild BPD or moderate/severe BPD (M/S BPD) according to requirement for supplemental oxygen at a postnatal age ≥ 28 days or at a post menstrual age (PMA) ≥ 36 weeks, respectively. Weaning from supplemental oxygen was based on transcutaneous measurements in the 1980's and oximetry in the 1990's. Decisions regarding discontinuation were made by a senior medical staff that was largely the same in the

two periods. In both birth-cohorts, postnatal corticosteroids was administered according to the same dosage regimen, dexamethasone 0.5 mg/(kg.day) divided in two doses for 2-4 days or until extubation, with subsequent tapering over 1-3 weeks. Between the two inclusion periods, substantial improvements had occurred in neonatal intensive care. Exogenous surfactant (Exosurf®) was available to the second birth-cohort, and was administered in essence as prescribed for selective administration in the Osiris trial (13). Most of the applied technology had been refined: Advanced Infant Star® ventilators (Infrasonics, San Diego, USA) had replaced previous generation neonatal ventilators. Pulse oximetry (3) allowed for more exact administration of ventilatory support and oxygen therapy. With modern cannulas, continuous radial arterial blood pressure surveillance had become routine in all preterms. Adequate intravenous nutrition was facilitated by peripheral central venous catheters. The importance of standardisation of complex neonatal intensive care schemes, education and quality control was advocated internationally through the Vermont Oxford Network, established in 1989 (14;15). At our department, a manual with guidelines for all aspects of intensive care was developed in the late 1980's, ensuring a systematic approach to all decisions and interventions.

For each preterm, the temporally nearest child of the same gender, born at term with a birthweight between 3-4 kilograms (Norwegian 10th-90th centiles) was recruited as control. Children were examined twice, approximately two weeks apart in 2001/2002. Methacholine provocation was performed at the second visit whereas flow-volume loops and body plethysmography were done at both. No subjects were examined within two weeks of a respiratory tract infection or an asthma event. Asthma medication was stopped prior to testing as appropriate. The Regional Ethics Committee approved the study. Informed written consent was obtained from participating subjects and parents.

Lung function measurements. Spirometry and static lung volumes were measured with Vmax 22 and Autobox 6200, respectively (*SensorMedics, Yorba Linda, USA*), applying standard quality criteria (16). Forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), forced expiratory flow at 50% and 75% of FVC (FEF_{50} and FEF_{75}), total lung capacity (TLC) and residual lung volume (RV) were recorded, and the values expressed as percentages of predicted (17;18). Mean values from the two test-days were used for statistical analysis. Providing baseline $FEV_1 \geq$ 65%, bronchial responsiveness to methacholine (PD_{20}) was determined, using an inhalation-synchronised, dosimetric nebulizer, Spira Elektra 2® (*Respiratory Care Centre, Hameenlinna, Finland*) (19). Methacholine chloride was administered in doubling doses until a 20% reduction in FEV_1 was obtained, or until a final cumulative dose of 22.3 μmol had been given. A dose-response slope (DRS) was calculated as the ratio between the maximum percentage decline in FEV_1 from baseline and the total administered dose of methacholine (in μmol) when the test was terminated (%/μmol). The DRS was $\log_{10}$ transformed (logslope) for statistical analysis (20). Atopy was defined as minimum one positive skin prick test or specific IgE (*Pharmacia, Uppsala, Sweden*) in a standard panel of local allergens (21).

Statistical methods. Non-paired group comparisons were performed with Pearson's χ^2-test or Student's t-test, as appropriate. Stepwise multiple linear regression analysis was applied to explore effects from the neonatal history on current lung function. Analysis of variance was applied to assess differences between the two preterm birth-cohorts. Asymmetrically distributed outcome variables were $\log_{10}$ transformed prior to statistical

testing. Paired relations regarding current measures of lung function between preterms and matched controls in the two birth-cohorts were tested with analysis of covariance, using the linear mixed model procedure of SPSS (22). Analyses of interaction effects were used to assess if the relations between preterms and matched controls were different in the two birth-cohorts, and if the influence from neonatal respiratory disease (M/S BPD) on current decreases in lung function differed between the two birth-cohorts (23). The level of significance was set to 0.05. The size of the study populations was defined in order to achieve a 90% power to detect a difference in FEV_1 of at least 7.5% between preterms and matched control subjects in each birth-cohort as well as between the two preterm birth-cohorts, providing a significance level (α) of 0.05 and 1 SD = 10% predicted. SPSS version 11.0 was used for the computations.

RESULTS

Subjects. Eighty-six (66%) of 130 included preterms were alive at the follow-up examination. In the first inclusion period, 39% of the admitted infants died in the neonatal department compared to 27% in the second ($p = 0.157$). For infants < 750 g, corresponding figures were 67% and 30% ($p = 0.072$). Five eligible preterms were inaccessible. Hence, 81 (94%) surviving preterms were tested, 46 born in the 1980's and 35 in the 1990's. Sixty-one (75%) of the primarily 81 invited control subjects responded positively. To complete a 1:1 matched control group, at average 1.3 subjects were approached for each preterm. One control was excluded for medical reasons. All but two participating subjects were Caucasians. Mean age at examination [standard deviation (SD)] was 17.7 (1.2) years in the first cohort and 10.6 (0.4) years in the second. Population characteristics are presented in Table 1. Two subjects with spastic tetraplegic cerebral palsy (CP) and scoliotic thorax restriction were excluded from the

statistical analyses. All subjects performed satisfactory flow volume loops. Methacholine responsiveness was not assessed in seven preterms (five due to FEV1% < 65% and two for other medical reasons) whereas two controls of the youngest cohort did not cope. Six preterms were unable to enter the plethysmograph. The coefficient of variation for repeated measurements of FEV_1 was 4.7%, and the precision of lung volume measurements was comparable to results from other studies (24).

Background variables. Maternal asthma and antenatal cigarette exposure were similarly distributed in the two birth-cohorts (p = 0.509 and 0.402, respectively). Fifteen mothers of each preterm cohort had received antenatal corticosteroids, i.e. 33% of the first cohort and 44% of the second (p = 0.328). Synthetic surfactant was administered to seventeen (49%) preterms in the second inclusion period. Postnatal corticosteroids had been administered in four (9%) infants from the first and ten (29%) from the second cohort (p = 0.022). Neonatal septicaemia was diagnosed in 18% in the first birth-cohort and 28% in the second (p = 0.251). Bronchiolitis requiring re-admittance to hospital during the first two years of life occurred in 29.5% and 31.4% of the first and second birth-cohort, respectively (p = 0.857).

Neonatal characteristics. Mean birthweight (SD) was 1014 (193) and 933 (204) grams, and mean gestational age (SD) 27.3 (1.4) and 26.7 (1.7) weeks in the first and second inclusion period, respectively (Table 2). Distribution according to weight-centiles at birth was similar in the two periods (p = 0.824), and respectively 20% and 25% were ≤ the 10^{th} centile. The five subjects not examined were comparable to those examined with respect to gestational age (29.4 weeks, SD: 3.3) and birthweight (958 grams, SD: 225). Mean birthweight (SD) of the controls was 3494 (300) grams. Distribution

according to severity of BPD did not differ between the inclusion periods (p = 0.545), but gestational age and birthweight tended to be lower within each category of BPD in the second period (p = 0.071 and 0.056, respectively) (Table 2). Supplemental oxygen was stopped at similar PMAs in both periods (p = 0.804). The duration of oxygen treatment for preterms born in the 1990's was shorter for those without BPD, but longer for those with BPD (test of interaction, p = 0.001).

Lung function. Compared to the control subjects born at term, preterms had obstructed airways, higher RV/TLC and increased methacholine reactivity, while TLC was similar (Table 3). For all the assessed lung function variables, paired differences between preterms and their matched controls were similar in the two birth-cohorts (Table 4). Except for TLC, there was a trend towards poorer lung function in preterms with the more severe neonatal respiratory disease (Table 3), and for important variables this trend was similar in both birth-cohorts. Thus, mean FEV_1% was nearly identical in the two birth-cohorts within each category of BPD (Table 4). With respect to FEF_{75}, a neonatal diagnosis of M/S BPD was significantly stronger related to long-term outcome in preterms born in the second birth-cohort compared to preterms born in the first birth-cohort (Table 4, test of interaction, p = 0.020).

The effects on current FEV_1% from perinatal and neonatal exposures were explored within both preterm populations. The background variables maternal asthma, antenatal cigarette exposure and early bronchiolitis were left out of the final analysis as they did not contribute significantly and were similarly distributed between the cohorts. Gestational age, birthweight, birthweight ≤ the 10^{th} centile, gender, number of days on ventilator, persistence of ductus arteriosus, antenatal maternal infection, neonatal

septicaemia, antenatal and postnatal systemic corticosteroids and exogenous surfactant (in the 1991-92 cohort) were included in the final analysis, in addition to variables describing neonatal oxygen exposure. The effects on subsequent FEV_1% did not differ between the birth-cohorts (two-way analyses of variance, p-values not shown). In a stepwise multiple linear regression analysis, increased number of days with neonatal oxygen supplementation ($p < 0.001$) and lack of antenatal treatment with corticosteroids ($p = 0.045$) remained the only significant predictors of reduced current FEV_1% with an adjusted R squared of 0.23. The overall regression coefficient (ß) for the variable *days with oxygen* was -0.12 (95% CI: -0.07, -0.17) for FEV_1% and similar in both birth-cohorts (test of interaction: $p = 0.962$). A scatterplot depicting current FEV_1% against neonatal *days with oxygen* revealed that oxygen supplementation was associated with long-term negative effects only if lasting more than approximately one month. For FEF_{50}, ß (95%CI) was -0.25 (-0.15, -0.34), and for FEF_{75} corresponding figures were -0.28 (-0.15, -0.40). Impact on FEF_{75} from neonatal oxygen supplementation was non-significantly *increased* in the second cohort compared to the first (test of interaction: $p = 0.091$), explaining 37% of its variability ($p < 0.001$). The effect of exogenous surfactant on current lung function was negative, as FEV_1% was reduced with nearly nine percent of predicted in those who had been treated (ß = - 8.8; $p = 0.010$). Adjusted for the variables *age in hours when treated* and *gestational age*, this negative effect disappeared (ß = - 0.08; $p = 0.986$).

DISCUSSION

A similar extent of airway obstruction, hyperinflation and hyperresponsiveness were demonstrated in two birth-cohorts born extremely prematurely in two different eras of neonatology. Current deficits in important lung function variables were similarly

associated with the severity of neonatal respiratory disease in both cohorts. Lack of antenatal maternal treatment with corticosteroids and prolonged neonatal oxygen exposure predicted similar significant decreases in FEV_1% in both birth-cohorts.

Despite the retrospective design of the study, the organisation of medical care in the region and an identical algorithm for determination of gestational age ensured that included preterms would have been the same subjects, had they been identified prospectively. Low dropout rates reduced possible bias and strengthened the population-based design of the study. To construct comparable measures of lung function in subjects of unequal gender, age and height, absolute values were transposed to percentages of predicted (17;18). Subsequently, all statistical comparisons focused on paired discrepancies between preterms and their matched term-born controls. The statistical power of the study was sufficient to detect clinically relevant differences between the two birth-cohorts with respect to the main outcome variable (FEV_1). Factors that could potentially confound comparisons, such as maternal asthma, antenatal cigarette exposures, intrauterine growth retardation, neonatal infection rates and early occurrence of bronchiolitis (25;26), were similarly distributed in the two birth-cohorts and did not influence the results. The trend towards lower birthweights and gestational ages of the NICU survivors in the second inclusion period, suggests that the second birth-cohort, at average, was more immature due to increased perinatal and neonatal survival rates of extremely premature infants. Regional epidemiological data from The Medical Birth Registry of Norway (5) from the time periods supports that notion, and this development may be explained by general improvements in neonatal care. Based on available knowledge, the comparison of airway obstruction between two cohorts of

unequal age seems legitimate, whereas some of the hyperinflation observed in the most recent cohort might still improve with growth (10).

The relationship between decreases in current lung function and prolonged neonatal exposure to supplemental oxygen is consistent with previous reports (27-29), but like Kennedy et al. (30), we found little impact from oxygen supplementation in the first month of life. Compared to matched control subjects born at term, decreases in lung function were basically similar in the two preterm birth-cohorts. Furthermore, for important variables such as FEV_1, decreases in the two cohorts were of similar magnitudes in preterms within each category of BPD. With respect to current FEF_{75}, the effect from a neonatal diagnosis of M/S BPD seemed stronger in the most recent birth-cohort (Table 4, test of interaction). This indicates that the long-term influence from neonatal BPD-status and prolonged oxygen requirements on small airway obstruction may in fact have become *more* important. Thus, important measures of lung function continued to be significantly and substantially affected in preterms with a more severe neonatal clinical course. Calculated from the present study, 100 days with oxygen treatment reduced FEV_1 with 12% predicted and FEF_{50} with approximately 25%, and these figures were similar in subjects born in the 1980's and the 1990's.

Severity of BPD increased with decreasing birthweight and gestational age, and this tendency seemed stronger in the last inclusion period with somewhat increased survival among the most immature infants (Table 2). There was, however, no difference between the two periods with respect to the PMA at which infants could be weaned from supplemental oxygen. Thus, the more immature survivors of the 1990's were exposed to longer periods of oxygen supplementation. Since the duration of oxygen

supplementation in the two periods was similarly related to subsequent decreases in lung function, increased survival of the most immature infants may have had the cost of increased pulmonary sequelae. In recent studies of immature infants, high proportions of survivors are reported to require supplemental oxygen at 36 weeks PMA (31). Combined with our data, this implies that an increasing number of immature infants are at risk of growing up with long-term pulmonary morbidity. Whether this represents a noxious effect of oxygen *per se* or if prolonged oxygen requirement is just a marker of other unresolved lung injury, remains to be established. The pathophysiology of oxidative stress and its putative role in the development of BPD, is subject to an ongoing debate (32). In adult men, persistent small airway dysfunction has been observed after exposure to prolonged hyperoxia (33). Whatever role oxygen supplementation may play in the lungs of immature infants, prolonged requirements seems to be a continued and well-suited prognostic indicator for subsequent long-term airway obstruction.

The fraction of neonates treated with exogenous surfactant was comparable to what was reported from other centres at the time (1), but its introduction did not seem to influence subsequent FEV_1%. As surfactant was prescribed as rescue therapy (13), selection bias may explain this phenomenon and the current policy of prophylactic administration of natural surfactant may change this picture. However, multiple factors are involved in the development of lung injury after premature birth, among which surfactant deficiency is only one (34). The assessments of lung function in premature children and adolescents will have to be an evaluation of the therapeutic strategies of the past. Therefore, continually long-term surveillance and follow-up studies are required to identify

positive trends as well as potentially untoward and iatrogenic consequences of neonatal intensive care medicine.

Conclusion:

There were few differences in lung function outcome between these two cohorts of preterm subjects who were born in two different eras of intensive care neonatology. Prolonged neonatal requirement for supplemental oxygen was similarly associated with subsequent decreases in FEV_1%. Survival in immature infants continues to be paralleled by long periods of oxygen requirements. It is therefore not unlikely that airway obstruction will continue to be a frequent long-term sequel in these subjects.

Reference List

(1) The Vermont-Oxford Trials Network: very low birth weight outcomes for 1990. Investigators of the Vermont-Oxford Trials Network Database Project. Pediatrics 1993; 91: 540-5.

(2) Langer VS. Minimal handling protocol for the intensive care nursery. Neonatal Netw 1990; 9: 23-7.

(3) Ramanathan R, Durand M, Larrazabal C. Pulse oximetry in very low birth weight infants with acute and chronic lung disease. Pediatrics 1987; 79: 612-7.

(4) Tin W, Wariyar U, Hey E. Changing prognosis for babies of less than 28 weeks' gestation in the north of England between 1983 and 1994. Northern Neonatal Network. BMJ 1997; 314: 107-11.

(5) Medical Birth Registry of Norway. In: Medical Birth Registry of Norway, editor. Births in Norway through 30 years: 1967-1996. Bergen 1997.

(6) Bancalari E, Claure N, Sosenko IR. Bronchopulmonary dysplasia: changes in pathogenesis, epidemiology and definition. Semin Neonatol 2003; 8: 63-71.

(7) Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001; 163: 1723-9.

(8) Hack M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990's. Early Hum Dev 1999; 53: 193-218.

(9) Parker RA, Lindstrom DP, Cotton RB. Improved survival accounts for most, but not all, of the increase in bronchopulmonary dysplasia. Pediatrics 1992; 90: 663-668.

(10) Eber E, Zach MS. Long term sequelae of bronchopulmonary dysplasia (chronic lung disease of infancy). Thorax 2001; 56: 317-23.

(11) Halvorsen T, Skadberg BT, Eide GE, Roksund OD, Carlsen KH, Bakke P. Pulmonary outcome in adolescents of extreme preterm birth: a regional cohort study. Acta Paediatr 2004; 93: 1294-300.

(12) Yudkin PL, Aboualfa M, Eyre JA, Redman CW, Wilkinson AR. New birthweight and head circumference centiles for gestational ages 24 to 42 weeks. Early Hum Dev 1987; 15: 45-52.

(13) The OSIRIS Collaborative Group. Early versus delayed neonatal administration of a synthetic surfactant--the judgment of OSIRIS (open study of infants at high risk of or with respiratory insufficiency--the role of surfactant). Lancet 1992; 340: 1363-9.

(14) Horbar JD. The Vermont Oxford Network: evidence-based quality improvement for neonatology. Pediatrics 1999; 103 Suppl E: 350-9.

(15) Horbar JD. The Vermont-Oxford Neonatal Network: integrating research and clinical practice to improve the quality of medical care. Semin Perinatol 1995; 19: 124-31.

(16) Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993; 16: 5-40.

(17) Quanjer PH, Borsboom GJ, Brunekreff B, Zach M, Forche G, Cotes JE, et al. Spirometric reference values for white European children and adolescents: Polgar revisited. Pediatr Pulmonol 1995; 19: 135-42.

(18) Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am Rev Respir Dis 1983; 127: 725-34.

(19) Nieminen MM, Lahdensuo A, Kellomaeki L, Karvonen J, Muittari A. Methacholine bronchial challenge using a dosimeter with controlled tidal breathing. Thorax 1988; 43: 896-900.

(20) O'Connor G, Sparrow D, Taylor D, Segal M, Weiss S. Analysis of dose-response curves to methacholine. An approach suitable for population studies. Am Rev Respir Dis 1987; 136: 1412-7.

(21) The European Academy of Allergology and Clinical Immunology. Position paper: Allergen standardization and skin tests. Allergy 1993; 48 Suppl 14: 48-82.

(22) Spss Inc. SPSS 11.0 Syntax Reference Guide, Volume II. 2001: 136-51.

(23) Pocock SJ, Collier TJ, Dandreo KJ, de Stavola BL, Goldman MB, Kalish LA, et al. Issues in the reporting of epidemiological studies: a survey of recent practice. BMJ 2004; 329: 883.

(24) Halvorsen T, Skadberg B, Eide G, Røksund O, Bakke P, Thorsen E. Assessment of lung volumes in children and adolescents: Comparison of two plethysmographic techniques. Clin Physiol Funct Imaging 2005; 25: 62-8.

(25) Grischkan J, Storfer-Isser A, Rosen CL, Larkin EK, Kirchner HL, South A, et al. Variation in childhood asthma among former preterm infants. J Pediatr 2004; 144: 321-6.

(26) Jaakkola JJ, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. Am J Public Health 2004; 94: 136-40.

(27) McLeod A, Ross P, Mitchell S, Tay D, Hunter L, Hall A, et al. Respiratory health in a total very low birthweight cohort and their classroom controls. Arch Dis Child 1996; 74: 188-94.

(28) Jacob SV, Coates AL, Lands LC, MacNeish CF, Riley SP, Hornby L, et al. Long-term pulmonary sequelae of severe bronchopulmonary dysplasia. J Pediatr 1998; 133: 193-200.

(29) Korhonen P, Laitinen J, Hyodynmaa E, Tammela O. Respiratory outcome in school-aged, very-low-birth-weight children in the surfactant era. Acta Paediatr 2004; 93: 316-21.

(30) Kennedy JD, Edward LJ, Bates DJ, Martin AJ, Dip SN, Haslam RR, et al. Effects of birthweight and oxygen supplementation on lung function in late childhood in children of very low birth weight. Pediatr Pulmonol 2000; 30: 32-40.

(31) Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. Pediatrics 2000; 106: 659-71.

(32) Saugstad OD. Bronchopulmonary dysplasia-oxidative stress and antioxidants. Semin Neonatol 2003; 8: 39-49.

(33) Thorsen E, Kambestad BK. Persistent small-airways dysfunction after exposure to hyperoxia. J Appl Physiol 1995; 78: 1421-4.

(34) Bancalari E, del MT. Bronchopulmonary dysplasia and surfactant. Biol Neonate 2001; 80 Suppl 1: 7-13.

Table 1

Demographic data of the premature and the term cohorts

	Birth cohort	Preterm	Control	p-values
Number of females / number in group (%)	91-92	22/35 (63%)	22/35 (63%)	-
	82-85	21/46 (46%)	21/46 (46%)	-
Height (cm)	91-92	140.1 (7.9)	144.7 (6.3)	0.008 *
	82-85	169.4 (8.1)	172.9 (7.5)	0.034 *
Weight (kg)	91-92	35.1 (12.3)	38.3 (6.4)	0.176 *
	82-85	63.4 (15.9)	67.6 (11.1)	0.179 *
Number with atopy ‡ (% of cohort)	91-92	9 (25.7%)	8 (22.9%)	0.500 †
	82-85	13 (28.3%)	20 (43.5%)	0.128 †

Except for ratios, figures are group mean (standard deviation). P-values refer to differences between preterm and control subjects in the respective two birth cohorts. * Student's t-test. † Pearson's χ^2-test. ‡ Hypersensitivity towards at least one tested allergen.

Table 2

Neonatal characteristics of the preterm cohorts

	Birth cohort	Non-BPD (n = 19)	Mild BPD (n = 38)	M/S BPD (n = 24)	p-values
Number of subjects (% of cohort)	91-92	9 (26%)	14 (40%)	12 (34%)	0.545 *
	82-85	10 (22%)	24 (52%)	12 (26%)	
Number of females (% of group)	91-92	7 (78%)	9 (64%)	5 (42%)	0.182 †
	82-85	5 (50%)	11 (46%)	5 (42%)	
Gestational age, weeks; mean (SD)	91-92	28.3 (1.4)	26.5 (1.5)	25.8 (1.5)	0.071 ‡
	82-85	28.3 (1.6)	27.0 (1.3)	27.0 (1.2)	
Birth weight, grams; mean (SD)	91-92	1053 (153)	927 (208)	851 (202)	0.056 ‡
	82-85	1171 (150)	1013 (193)	887 (126)	
Days on ventilator; median (range)	91-92	0.5 (0, 1.7)	3.0 (0, 40)	12.7 (1.7, 54.5)	0.046 ‡
	82-85	0.4 (0, 4.8)	8.6 (0.8, 35.0)	25.4 (0.7, 54.0)	
PMA when supplemental oxygen was stopped; median (range)	91-92	29.0 (28, 31)	33.5 (30, 35)	37.5 (36, 50)	0.804 ‡
	82-85	30.0 (28, 34)	33.0 (31, 35)	37.5 (36, 63)	
Days with supplemental O_2; median (range)	91-92	2.0 (2, 26)	45.5 (28, 70)	91.0 (61, 180)	0.001 $
	82-85	12.5 (1, 25)	41.0 (28, 71)	72.5 (55, 257)	

PMA = post menstrual age (weeks). M/S BPD = moderate/severe Bronchopulmonary Dysplasia. The p-values assess differences between the two birth cohorts. * Pearson's χ^2-test. † Mantel-Haenszel-test. ‡ Two-way analysis of variance, adjusted for BPD-classification. $ Two-way analysis of variance with a significant interaction effect with BPD, i.e. number of days with oxygen supplementation was significantly more related to the severity of BPD in the 1990-91 cohort (the p value refers to test of interaction).

Table 3

Lung function in percents of predicted, by birth cohort and the extent of neonatal Bronchopulmonary Dysplasia (BPD)

	Birth cohort	Controls n = 81	Non-BPD and mild BPD † n = 55	Moderate and severe BPD † n = 24	p-values ‡
FEV_1	91-92	98.2 (95.0, 101.4)	92.0 (88.0, 96.0)	80.8 (75.8, 85.9)	< 0.001
	82-85	98.9 (95.6, 102.1)	90.9 (86.8, 94.9)	81.9 (74.1, 89.7)	
FEF_{50}	91-92	102.0 (94.1, 109.9)	88.7 (79.8, 97.6)	64.2 (51.0, 77.4)	< 0.001
	82-85	103.5 (96.8, 110.2)	82.2 (76.5, 87.9)	71.8 (54.3, 89.3)	
FEF_{75}	91-92	96.5 (86.8, 106.2)	86.2 (74.8, 97.6)	51.4 (39.7, 63.1)	< 0.001
	82-85	106.5 (97.5, 115.6)	80.1 (72.1, 88.0)	78.4 (56.6, 86.8)	
FVC	91-92	97.5 (94.7, 100.3)	91.9 (87.6, 96.3)	90.7 (85.7, 95.7)	0.003
	82-85	95.2 (92.0, 98.4)	92.4 (87.7, 97.1)	86.4 (77.6, 95.3)	
TLC	91-92	93.7 (91.1, 96.3)	91.2 (87.7, 94.8)	97.0 (92.3, 101.8)	0.511
	82-85	110.9 (106.5, 115.3)	110.2 (105.6, 114.8)	108.3 (100.7, 115.8)	
RV/TLC	91-92	21.7 (20.5, 23.0)	22.5 (20.2, 24.7)	28.1 (24.6, 31.7)	0.005
	82-85	19.0 (17.5, 20.5)	20.5 (18.2, 22.7)	23.4 (20.6, 28.4)	
DRS *	91-92	2.1 (1.2, 3.4)	10.0 (4.5, 22.2)	32.5 (8.5, 124.4)	< 0.001
	82-85	1.3 (0.8, 2.1)	3.0 (1.5, 5.9)	8.0 (2.5, 25.5)	

The figures are group mean values (95% confidence interval) expressed as percent of predicted, except for the variable * DRS (dose-response slope to methacholine) where figures are geometric means. † The criteria for classification of BPD are given in the text. ‡ The p-values refer to differences between preterms and their matched term-born controls. For clarity, controls are tabulated separately as one group, although statistical analyses were performed according to the paired design of the study.

Table 4

Paired decreases in lung function, by birth cohort and the extent of neonatal Bronchopulmonary Dysplasia (BPD).

		Extent of BPD †		p- values ‡	
	Birth cohort	**None or mild (n = 55)**	**M/S (n = 24)**	**Differences between birth-cohorts**	**Influence from BPD**
FEV_1	91-92	5.5	18.7	0.901	0.762
	82-85	7.2	18.6		
FEF_{50}	91-92	13.8	36.8	0.698	0.107
	82-85	18.7	40.3		
FEF_{75}	91-92	12.1	41.6	0.566	0.020
	82-85	24.2	36.2		
FVC	91-92	4.9	8.0	0.650	0.388
	82-85	2.6	8.9		
TLC	91-92	1.7	- 1.8	0.818	0.184
	82-85	0.8	1.6		
RV/TLC	91-92	- 0.5	- 7.0	0.810	0.158
	82-85	- 0.8	- 6.4		
DRS *	91-92	-2.5	-28.9	0.134	0.996
	82-85	- 1.7	- 14.8		

The figures are group mean differences between preterms and individually matched controls in percent of predicted, except for the variable * DRS (dose-response slope to methacholine) where differences between preterms and controls are given as median values. † The criteria for classification of BPD are given in the text. ‡ The p-values test "*differences between the birth-cohorts"* with respect to lung function outcome, and if the "*influence from BPD"* on subsequent lung function outcome differed between the birth-cohorts (interaction analyses).