Lung function deficits and bronchodilator reversibility at 12 years of age in children born very preterm compared with controls born at term

Ellen Tufvesson[1], Cecilia Hagman[2], Lars Bjorklund[2], Leif Bjermer[1], and Ingrid Hansen-Pupp[2]

[1]Lunds universitet Lungmedicin och Allergologi
[2]Skanes universitetssjukhus Lund

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Abstract

Introduction Very preterm birth is associated with lung function impairment later in life, but several aspects have not been studied. We aimed to comprehensively assess lung function at school age in very preterm infants and term controls, with special emphasis on bronchopulmonary dysplasia (BPD), sex and bronchodilator response. **Methods** At 12 years of age, 136 children born very preterm (85 with and 51 without BPD), and 56 children born at term performed spirometry, body plethysmography, impulse oscillometry, measurement of diffusion capacity and multiple breath washout, before and after bronchodilator inhalation. **Results** Airway symptoms and a diagnosis of asthma were more common in children born very preterm. These children had more airflow limitation, seen as lower FEV $_1$ ($p<0.001$), FEV $_1$/FVC ($p=0.011$) and FEF $_{25\text{-}75}$ ($p<0.001$), and a higher total and peripheral airway resistance compared to term born controls. There was no difference in total lung capacity, but air trapping and lung clearance index were higher in children born very preterm. Diffusion capacity was lower in children born very preterm, especially in those with a diagnosis of BPD. In most other tests, the differences between preterm-born children with or without BPD were smaller than between children born preterm versus at term. Boys born preterm had more lung function deficits than preterm born girls. In children born very preterm, airway obstruction was to a large extent reversible. **Conclusion** At 12 years of age, children born very preterm had lower lung function than children born at term in most aspects. Airway obstruction improved markedly after bronchodilator inhalation, and there was only little difference between children with or without BPD.

Introduction

Long-term pulmonary outcome in preterm infants usually involve chronic respiratory impairment such as airway obstruction[(1)]and low diffusion capacity[(2)]. Perinatal inflammation, fetal growth restriction, bronchopulmonary dysplasia (BPD) and gender are risk factors affecting the immature lung during the first years of life[(3-5)]. There is evidence that persistence of respiratory symptoms, lung function impairment and abnormalities of the lung structure may persist into adulthood[(6, 7)]. Infants with BPD have low respiratory compliance in the first month of life, but with some normalization at 2 years of age[(8)]. Up to 8 years of age, there is still a reduction of forced flows and volumes in these children[(4, 9)]. In an 11-year follow-up of extremely preterm infants, the children had reduced forced expiratory volume in 1 second (FEV_1) and forced expiratory flow between 25-75% ($FEF_{25\text{-}75}$) compared to term born classmates[(10)]. It has been suggested that the observed increase in airway obstruction could be an expression of early impaired airway development during childhood, whereas there seem to be some catch-up through early life[(7, 11)]. Furthermore, small airway abnormalities, could be a risk for future chronic lung disease and further decrease the respiratory outcome after preterm birth[(12)], since prematurity per se is also a well-known risk factor. A reduced lung function already at childhood, may lead to a lower lung function throughout life[(13)].

Since BPD is a poor predictor of prematurity-associated lung disease[11], and the respiratory outcomes after preterm birth seem to be more dependent on the prematurity per se, it is important to investigate preterm-born children also beyond BPD.[14]

The primary aim of the study was to extensively investigate lung function pattern at 12 years of age in children born very preterm, with or without BPD during infancy as compared to term born controls. The secondary aim was to study how different neonatal comorbidities and sex may affect lung function and prevalence of airway symptoms during childhood in preterm children.

Materials and methods

Study population

The study population consisted of 136 children from three prospective cohorts[9, 15, 16] of very preterm infants (gestational age <32 weeks), one also including 56 term born controls (see Table 1 and online supplement for details). Antenatal and neonatal data were collected prospectively from the patient records. There were 85 children with and 51 without a previous diagnosis of bronchopulmonary dysplasia (BPD), defined as being born at < 32 weeks gestation and still being treated with extra oxygen at 36 weeks postmenstrual age. A history of respiratory symptoms, medication and allergy was obtained from a questionnaire completed by the accompanying parent/caregiver at the 12-year visit.

Ethics

All parents/caregivers and children received oral and written information about the study, and parents/caregivers signed written informed consents. The study was approved by the Regional Ethical Review Board in Lund, Sweden.

Lung function testing

Comprehensive lung function testing was done at 12 years of age. Flow volume spirometry was performed to measure forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), mean forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}), and slow vital capacity (VC). FEV_1/FVC was calculated as a measure of expiratory flow limitation. Dysanapsis ratio, an index of discrepancy in size between the airway and the lung, was calculated as FEF_{25-75}/FVC divided by an estimate of static recoil pressure at 50% of FVC based on child age[17]. Body plethysmography was used to measure static lung volumes, i.e. total lung capacity (TLC) and residual volume (RV), and the ratio RV/TLC was calculated as a measure of air trapping. Diffusion capacity of the lung for CO (DL_{CO}) was measured with single breath technique, being the product of the rate constant for uptake of CO (K_{CO}) and alveolar volume. Impulse oscillometry (IOS) provides information about the mechanical properties of large as well as small airways. Resistance was estimated at 5 Hz (R_5, reflecting total resistance) and at 20 Hz (R_{20}, reflecting central resistance), while R_5-R_{20} reflects peripheral resistance. During small airway obstruction, reactance (elastance) of the lung (X) decreases at 5 Hz (giving a more negative value of X_5), while the resonant frequency (F_{res}) increases together with the area under the reactance curve (AX), which is a measured from X at 5 Hz to F_{res}. During multiple breath washout (MBW) of N_2, the number of lung volume turnovers required to lower the end-tidal N_2-concentration to 5% and 2.5% of the initial concentration are termed lung clearance index ($LCI_{5.0}$ and $LCI_{2.5}$ respectively) and is a measure of overall ventilation inhomogeneity. Analysis of the N_2 concentration during each breath provides more detailed information of whether the inhomogeneity arises from conductive (S_{cond}) or acinar (S_{acin}) airways. Higher values of LCI, S_{cond} and S_{acin}indicate more ventilation inhomogeneity. See supplement for detailed description.

To investigate reversibility, in most subjects, all pulmonary function measurements were performed before and 15 minutes after inhalation of 200 µg salbutamol.

Data is presented as medians with interquartile range (IQR) of absolute values or % of predicted values, proportion below lower limit of normal or above upper limit of normal, and as proportion below the 5^{th} or above the 95^{th} centile in the group of the term born controls. For more detailed information, see supplement.

Statistics

Nonparametric tests were used due to asymmetric distribution in most variables. Mann-Whitney U test was used for comparison between two groups and Chi^2-test or Fisher's exact test (when at least one cell had an expected count less than five) were used to explore relationships between categorical variables. Change in lung function variables before versus after bronchodilator were evaluated by Wilcoxon signed rank test or McNemar's test. P-values <0.05 were considered significant.

Results

Population characteristics and early respiratory morbidity

The children born preterm had a median gestational age at birth of 26 weeks+1 day, 73% were born extremely preterm, i.e. before 28 weeks, and 63% had a diagnosis of BPD (Table 1). In comparison to children born preterm without BPD, children with BPD had a lower gestational age at birth, a lower birth weight and were more often male. In the neonatal period, they were more often treated with surfactant and were more often mechanically ventilated and for longer periods (E-table 1). Smoking during early pregnancy was only reported in 13% of mothers to preterm infants.

History of airway disease

Children born very preterm had significantly more respiratory symptoms than term controls (Table 1). Caregivers reported that 59/136 (43%) children born very preterm had experienced at least one out of four symptoms related to airflow obstruction (any history of wheezing, exercise-induced wheezing, nocturnal cough without infection, sleep disturbed by wheezing) compared to 12/56 (21%) children born at term (p=0.004). Wheezing was the most common symptom, reported in 52/136 (38%) children born very preterm compared to 8/56 (14%) children born at term (p=0.001). There were no differences in symptoms within the preterm group between children with or without a diagnosis of BPD.

There were no associations between antenatal exposures and later airway symptoms except that children born preterm after maternal infection or after clinical chorioamnionitis had twice as often experienced nocturnal wheezing (34% versus 16% for maternal infection, p=0.042, and 50.0% versus 23.5% for chorioamnionitis, p=0.052) than children without these exposures. There were no associations between respiratory support (CPAP or ventilator days) in the neonatal period and airway symptoms at school age.

A diagnosis of asthma was more common in children born very preterm than in the term-born controls (36% versus 11%, p<0.001), but equally common in very preterm children with or without BPD. None of the children had any mechanical respiratory support or supplemental oxygen at the time of the lung function study.

Lung function deficits in children born very preterm versus at term

Children born very preterm had more airway obstruction, higher airway resistance, lower diffusion capacity and more ventilation inhomogeneity at 12 years of age than their term born controls. This was most evident before bronchodilator inhalation and was seen in a majority of the tests performed and both as absolute values and as percent of predicted normal values (Figure 1 and Tables 2 and 3).

Spirometry showed significantly more airway obstruction, measured as reductions in FEV_1, FEV_1/FVC and FEF_{25-75}, in children born very preterm compared to term, both as absolute values and as percent of predicted (Figure 1A-C, Table 2). FEV_1 below the lower limit of normal occurred in 23.5% of children born very preterm but only in 3.6% of children born at term (p=0.001). The corresponding proportions for FEV_1/FVC were 25.0% versus 9.1% (p=0.014) and for FEF_{25-75} 39.7% versus 10.9% (p<0.001). Dysanapsis ratio was lower in children born very preterm than in children born at term (p=0.004, Table 2).

Measurement of static lung volumes showed lower VC and higher RV as percent of predicted in very preterm infants, and also higher RV/TLC (Table 2 and 3). However, TLC and alveolar volume were not significantly different between children born preterm or at term.

Inspiratory, expiratory, and total airway resistance, as measured by body plethysmography, were higher in children born preterm (Table 3). Impulse oscillometry similarly showed a higher total resistance (R_5, Figure 1D), frequency dependence of resistance (R_5-R_{20}) and resonant frequency (F_{res}), a lower reactance at 5 Hz (more negative X_5), and an increased area under the reactance curve (AX; all $p<0.001$, Table 3), all indicating dysfunction of peripheral airways.

Diffusion capacity (DL_{CO}) and the diffusion coefficient for CO (K_{CO}) were significantly lower in preterm- than in term-born children (Table 3 and Figure 1E). However, the proportion of preterm-born children with measurements below the lower limit of normal was much smaller for DL_{CO} (5.7% for children born preterm and 0% for term born controls, E-table 2) than for expiratory flows.

During N_2 washout, children born very preterm had a significantly higher lung clearance index (both $LCI_{2.5}$and $LCI_{5.0}$) than children born at term (Table 3 and Figure 1F). This was most prominent for $LCI_{2.5}$, indicating an increased ventilation inhomogeneity most evident in the peripheral airways.

Within the whole study population, children with FEV_1/FVC or FEF_{25-75} below the lower limit of normal had significantly more often experienced wheezing, disturbed sleep or at least one of the symptoms listed in Table 1 (all $p<0.05$). A previous diagnosis of asthma was almost twice as common in children found to have FEF_{25-75} below the lower limit of normal than in those with a normal FEF_{25-75} (42.4% vs. 22.0%, p=0.004).

BPD in association to lung function at school age

At 12 years of age, children born very preterm with a former diagnosis of BPD had more airflow obstruction, higher airway resistance and a lower diffusion capacity than preterm infants without BPD (Tables 2 and 3, and Figure 1).

More airway obstruction was read as a lower FEV_1/FVC and FEF_{25-75} in children with than in children without BPD (p=0.022 and p=0.021, respectively), but there was no difference in FEV_1, FVC, or in static volumes. However, the dysanapsis ratio were lower in children with than in children without BPD (p=0.023, Table 2).

Children with a history of BPD had an increased peripheral resistance (measured as R_5-R_{20} and R_5-R_{20} % of predicted by IOS) compared to children born without BPD. The higher airway resistance in children born preterm versus term was mainly explained by specifically higher resistance among children with BPD.

Diffusion capacity was lower in children with BPD compared to children with no BPD, both as D_{LCO} and DL_{CO} % of predicted. The lower level of diffusion capacity in very preterm born children compared to term born was mainly explained by the lower values in children with BPD (Table 3).

Children with a history of BPD also had a larger ventilation inhomogeneity of the conductive airways, measured as S_{cond} than in children without BPD. In addition, preterm-born children with a diagnosis of BPD, but not children without BPD, had worse $LCI_{5.0}$, S_{cond} and S_{acin} than children born at term (Table 3).

Antenatal markers and neonatal events in association to lung function

In very preterm infants, antenatal events associated with BPD (chorioamnionitis and maternal infection) were not associated with impaired lung function at 12 years of age, neither was premature rupture of membrane.

Children that had been mechanically ventilated in the neonatal period showed increased airflow obstruction at school age; FEV_1(p=0.005) and FEF_{25-75} (p=0.027). These children also had lower diffusing capacity, DL_{CO} (p=0.005), DL_{CO} % of predicted (p=0.019), K_{CO}(p=0.16) and K_{CO} % of predicted (p=0.034). Surfactant treatment was not associated with later lung function impairment.

Effect of bronchodilator inhalation on lung function

Reversibility, here meaning an improvement in lung function after inhalation of 200 µg salbutamol, occurred both in children born at term and in children born very preterm (Figure 1), but the effect was generally

larger in the very preterm group, so that after bronchodilator the difference between the two groups was, for some parameters, no longer significant. Table 4 shows % of predicted values, E-table 3 shows absolute values, and E-table 4 proportion of children with values outside the normal range before versus after bronchodilator. E-table 5 shows reversibility in percent and E-table 6 absolute reversibility, also in relation to BPD.

Children born preterm were more reversible in FEV_1/FVC and FEF_{25-75} compared to full term controls (E-table 5 and 6), but after bronchodilator, there remained a significant difference between children born preterm versus at term for FEV_1 and FEF_{25-75}, but not for FEV_1/FVC (Tables 4 and E-table 3). After bronchodilator, the proportion of children born very preterm with FEV_1below the lower limit of normal fell from 23.5% to 7.6% (p=0.001). For FEV_1/FVC, the similar proportions were 25.0% versus 7.6%, and for FEF_{25-75} they were 39.7 % versus 16.3% (both p<0.001, Table 4).

Bronchodilator inhalation caused no significant change in lung volumes,*i.e.* FVC, TLC, RV or alveolar volume in children born very preterm (Table 4).

Children born very preterm were more reversible than children born at term in total airway resistance, as measured by body plethysmography, and frequency dependence of resistance (R_{5-20}) and airway reactance (X_5, AX and F_{res}) as measured by IOS (E-table 6). Total airway resistance (measured by body plethysmography and as R_5 by impulse oscillometry) decreased significantly after bronchodilator inhalation, so that no difference remained in comparison with children born at term. Small airway dysfunction measured by impulse oscillometry also improved after bronchodilator (all p<0.001) but remained significantly higher than in children born at term (Tables 4 and E-table 3).

In children born preterm, DL_{CO} and K_{CO}increased after bronchodilator inhalation but remained significantly lower than in term infants (Tables 4 and E-table 3). However, after bronchodilator inhalation, almost all children had values within a normal range (E-table 4).

Multiple breath wash-out in children born preterm showed a significant fall in S_{cond} and S_{acin} after bronchodilator (Table 4 and E-table 3). Notably, the proportion of children born very preterm with S_{cond} above the 95^{th} centile fell from 17.3% to 4.4% (p=0.035, E-table 4).

In a subgroup analysis of children born very preterm with or without BPD, the bronchodilator response was found to be similar with the same significance levels in both subgroups for measurements made during spirometry, body plethysmography and diffusion capacity (E-tables 5 and 6).

Sex in association to lung function at school age

Overall, the boys born preterm had in many aspects worse lung function than the boys born at term, which was not seen to the same extent in the girls born preterm compared to girls born at term. Boys born very preterm had more airflow limitation during spirometry, more air trapping, higher airway resistance, more peripheral airway dysfunction, lower diffusion capacity, and more ventilation inhomogeneity than boys born at term (Tables 5, E-tables 7 and 8). In comparison with preterm girls, preterm boys had significantly lower expiratory flows, lower dysanapsis ratio, lower diffusion capacity, and more ventilation inhomogeneity.

In girls born very preterm, expiratory flows, dysanapsis ratio, air trapping, and ventilation inhomogeneity were not significantly different from what was measured in girls born at term. However, both boys and girls born very preterm had significantly more small airway dysfunction, as measured by IOS, than their term-born counterparts (Table 5)."

Discussion

By using a broad approach of lung function measurements, we show that children born very preterm have an increased risk for impaired lung function in many aspects at 12 years of age compared to children born at term. Airway obstruction was evident, and a high proportion of children born very preterm had FEV_1/FVC or FEF_{25-75} below the lower limit of normal. They also had an increased airway resistance and IOS findings compatible with small airway dysfunction. A higher lung clearance index revealed a higher ventilation inhomogeneity in the group of preterm children, which is in line with the increased obstructive pattern

shown by spirometry. We have got a more complete picture of the lung function at 12 years of age, and all together, this reflects deficits in the lung after very preterm birth.

Airflow limitation[6, 7] and reduced diffusion capacity[2, 7, 18, 19], has also previously been reported in children born preterm and in young adults with a history of BPD. In this study, a significant reduction in diffusion capacity was seen in children born very preterm, but few children had a DL_{CO} below the lower limit of normal. Static volumes, such as alveolar volume and total lung capacity, were not significantly reduced in children born very preterm, which is in accordance with previous reports[6, 20]. However, RV/TLC, an estimate of air trapping, was higher in children born preterm than in term-born controls, supporting evidence of changes in the peripheral airways. The dysanapsis ratio has been suggested to describe the relationship between airway calibre and lung size, and has been shown in adults to be a predictor of expiratory flow limitation[17]. In addition, the lower dysanapsis ratio in preterm-born children may suggest that their airways are undersized in relation to the lungs[21].

The lower gestational age and more pulmonary morbidity in children with BPD did not translate into a markedly more severe lung function impairment at school age[3, 6, 22]. There were differences in lung function between children with versus without BPD, notably more airway obstruction and a lower DL_{CO}, but generally the difference between children within the very preterm group were smaller than the differences between the whole preterm group and their term controls. The definition of BPD has been modified to maximize the possibility to predict future respiratory morbidity up to approximately two years of age, but the later natural history of BPD, at school age and early adulthood, is less well understood[23, 24]. Previous follow-up studies have sometimes reported long-term effects of BPD in relation only to term controls, and the effects of prematurity per se may have been underestimated.

More children born very preterm had experienced wheezing or had been given a diagnosis of asthma, but there was no difference in airway symptoms in preterm born children with or without a diagnosis of BPD. Prematurity per se and not a diagnosis of BPD seems to be a more valuable factor for a variety of symptoms regarding the airways, which have also been shown in younger ages[22]. Most important is to be aware that BPD and asthma are two different entities with disparity in ongoing airway inflammation.

Lung function impairment of children born preterm is often believed to be structurally determined and unaffected by treatment, and due to lack of evidence there is no recommendation about the routine use of bronchodilators. Reversibility of lung function impairment in preterm-born children by bronchodilator inhalation has not been more widely studied than for the effect on FEV_1, and in some cases also the effect on FEV_1/FVC and FEF_{25-75}[25], and the conclusion is that bronchodilators improve the FEV_1 in short term. Our study is, to the best of our knowledge, the first to report short-term bronchodilator effect on a multitude of modalities of pulmonary function testing. We showed that a substantial proportion of preterm-born children normalized their airflows after a single dose bronchodilator inhalation. These findings indicate that some preterm-born children may be undertreated, and more studies on treatment effects are warranted.

In children born very preterm, our study shows a male disadvantage in lung function, especially for measures of airflow obstruction and total airway resistance. Harris et al.[26] identified a similar pattern of airway obstruction.

The main strengths of our study are that it included consecutively recruited inborn infants with a high acceptance rate and all born at a single regional Centre with little variation in treatment and has a long observational period. Term born controls were born in the same region as the preterm infants and collected according to a well-defined system[27]. Comprehensive pulmonary function tests were performed at a narrow age span around 12 years of age and covered different aspects of lung function. To our knowledge this is the first study covering all these different modalities of lung function parameters including reversibility.

The design of the study with an antenatal informed consent may have introduced a selection bias in the original study population, since informed consent could not be obtained for infants born after unexpected deliveries. The wide gestational age span in our cohort (23-31 weeks), with a majority of the children born extremely preterm, may confound our results, as well as different reasons for preterm birth. We are aware of

the risks of making multiple comparisons and that our findings need to be confirmed in a larger population. It would be of value to follow lung function over time during childhood, as a timeline of lung development.

In conclusion, in this study we have defined a comprehensive lung function pattern in children 12 years of age, born term or preterm, with or without BPD. We show differences in lung function and reversibility between these groups, from airway obstruction to resistance and reactance to ventilation inhomogeneity and diffusion capacity, which has not been done previously in this broad perspective. The importance of follow-up during childhood to determine lung function and establish guidelines on comprehensive monitoring strategies beyond the neonatal period seems to be vital for the future.

Figure legend:

Figure 1. Lung function at 12 years of age before and after bronchodilator inhalation in children born very preterm with or without a previous diagnosis of BPD, and children born at term. Data is presented as individual values and horizontal lines are median of % of predicted values for FEV_1 (A), FEV_1/FVC (B), FEF_{25-75} (C), R_5 (D), DL_{CO} (E) and $LCI_{2.5}$ (F). The dotted line represents the lower limit of normal in A, B, C and E, and upper limit of normal in D and F. *p<0.05, **p<0.01 and ***p<0.001.

Author contribution

All authors contributed to the conception and design of this work as well as the analysis and interpretation of data. Data acquisition was done by IH-P (neonatal data) and ET (lung function testing). All authors have had complete access to the study data. CH wrote the first draft. All authors revised the text, have approved the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interests

CH has no conflict of interest. LJB has received honoraria from Chiesi Pharma AB, Sweden, for being a member of the steering committee for the Nordic Neonatal Meetings, and from AbbVie AB for lectures and for previously being a member of the steering committee for the NEOSPEX educational project. LB has no conflict of interest. IH-P holds stock/stock options in Premalux AB and has received honoraria from Baxter International for lectures. ET has no conflict of interest.

References:

1. Doyle LW, Andersson S, Bush A, Cheong JLY, Clemm H, Evensen KAI, et al. Expiratory airflow in late adolescence and early adulthood in individuals born very preterm or with very low birthweight compared with controls born at term or with normal birthweight: a meta-analysis of individual participant data. The Lancet Respiratory medicine. 2019;7(8):677-86.

2. Hakulinen AL, Järvenpää AL, Turpeinen M, Sovijärvi A. Diffusing capacity of the lung in school-aged children born very preterm, with and without bronchopulmonary dysplasia. Pediatric pulmonology. 1996;21(6):353-60.

3. Saarenpaa HK, Tikanmaki M, Sipola-Leppanen M, Hovi P, Wehkalampi K, Siltanen M, et al. Lung Function in Very Low Birth Weight Adults. Pediatrics. 2015;136(4):642-50.

4. Ronkainen E, Dunder T, Kaukola T, Marttila R, Hallman M. Intrauterine growth restriction predicts lower lung function at school age in children born very preterm. Arch Dis Child Fetal Neonatal Ed. 2016;101(5):F412-7.

5. Morsing E, Gustafsson P, Brodszki J. Lung function in children born after foetal growth restriction and very preterm birth. Acta Paediatr. 2012;101(1):48-54.

6. Islam JY, Keller RL, Aschner JL, Hartert TV, Moore PE. Understanding the Short- and Long-Term Respiratory Outcomes of Prematurity and Bronchopulmonary Dysplasia. American journal of respiratory

and critical care medicine. 2015;192(2):134-56.

7. Simpson SJ, Logie KM, O'Dea CA, Banton GL, Murray C, Wilson AC, et al. Altered lung structure and function in mid-childhood survivors of very preterm birth. Thorax. 2017;72(8):702-11.

8. Thunqvist P, Gustafsson P, Norman M, Wickman M, Hallberg J. Lung function at 6 and 18 months after preterm birth in relation to severity of bronchopulmonary dysplasia. Pediatr Pulmonol. 2015;50(10):978-86.

9. Thunqvist P, Tufvesson E, Bjermer L, Winberg A, Fellman V, Domellof M, et al. Lung function after extremely preterm birth-A population-based cohort study (EXPRESS). Pediatric pulmonology. 2018;53(1):64-72.

10. Fawke J, Lum S, Kirkby J, Hennessy E, Marlow N, Rowell V, et al. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. American journal of respiratory and critical care medicine. 2010;182(2):237-45.

11. Kotecha SJ, Edwards MO, Watkins WJ, Henderson AJ, Paranjothy S, Dunstan FD, et al. Effect of preterm birth on later FEV1: a systematic review and meta-analysis. Thorax. 2013;68(8):760-6.

12. Bui DS, Perret JL, Walters EH, Lodge CJ, Bowatte G, Hamilton GS, et al. Association between very to moderate preterm births, lung function deficits, and COPD at age 53 years: analysis of a prospective cohort study. The Lancet Respiratory medicine. 2022;10(5):478-84.

13. Doyle LW, Adams AM, Robertson C, Ranganathan S, Davis NM, Lee KJ, et al. Increasing airway obstruction from 8 to 18 years in extremely preterm/low-birthweight survivors born in the surfactant era. Thorax. 2017;72(8):712-9.

14. Kotecha S, Doull I, Wild J, Bush A. Prematurity-associated lung disease: looking beyond bronchopulmonary dysplasia. The Lancet Respiratory medicine. 2022;10(5):e46.

15. Hansen-Pupp I, Harling S, Berg AC, Cilio C, Hellstrom-Westas L, Ley D. Circulating interferon-gamma and white matter brain damage in preterm infants. Pediatr Res. 2005;58(5):946-52.

16. Hansen-Pupp I, Hovel H, Hellstrom A, Hellstrom-Westas L, Lofqvist C, Larsson EM, et al. Postnatal decrease in circulating insulin-like growth factor-I and low brain volumes in very preterm infants. J Clin Endocrinol Metab. 2011;96(4):1129-35.

17. Turner JM, Mead J, Wohl ME. Elasticity of human lungs in relation to age. J Appl Physiol. 1968;25(6):664-71.

18. Hagman C, Bjorklund LJ, Bjermer L, Hansen-Pupp I, Tufvesson E. Perinatal inflammation relates to early respiratory morbidity and lung function at 12 years of age in children born very preterm. Acta Paediatr. 2021;110(7):2084-92.

19. Um-Bergstrom P, Hallberg J, Pourbazargan M, Berggren-Brostrom E, Ferrara G, Eriksson MJ, et al. Pulmonary outcomes in adults with a history of Bronchopulmonary Dysplasia differ from patients with asthma. Respiratory research. 2019;20(1):102.

20. Gibson AM, Reddington C, McBride L, Callanan C, Robertson C, Doyle LW. Lung function in adult survivors of very low birth weight, with and without bronchopulmonary dysplasia. Pediatric pulmonology. 2015;50(10):987-94.

21. Duke JW, Gladstone IM, Sheel AW, Lovering AT. Premature birth affects the degree of airway dysanapsis and mechanical ventilatory constraints. Exp Physiol. 2018;103(2):261-75.

22. Vrijlandt EJ, Boezen HM, Gerritsen J, Stremmelaar EF, Duiverman EJ. Respiratory health in prematurely born preschool children with and without bronchopulmonary dysplasia. J Pediatr. 2007;150(3):256-61.

23. Cazzato S, Ridolfi L, Bernardi F, Faldella G, Bertelli L. Lung function outcome at school age in very low birth weight children. Pediatr Pulmonol. 2013;48(8):830-7.

24. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-based Approach. Am J Respir Crit Care Med. 2019;200(6):751-9.

25. Kotecha SJ, Edwards MO, Watkins WJ, Lowe J, Henderson AJ, Kotecha S. Effect of bronchodilators on forced expiratory volume in 1 s in preterm-born participants aged 5 and over: a systematic review. Neonatology. 2015;107(3):231-40.

26. Harris C, Zivanovic S, Lunt A, Calvert S, Bisquera A, Marlow N, et al. Lung function and respiratory outcomes in teenage boys and girls born very prematurely. Pediatr Pulmonol. 2020;55(3):682-9.

27. Fellman V, Hellstrom-Westas L, Norman M, Westgren M, Kallen K, Lagercrantz H, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. JAMA. 2009;301(21):2225-33.

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`Table 2 spiromteri term vs prematur BPD vs non-BPD med DR 221129.docx` available at https://authorea.com/users/566537/articles/613190-lung-function-deficits-and-bronchodilator-reversibility-at-12-years-of-age-in-children-born-very-preterm-compared-with-controls-born-at-term

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`Table 3 Bodybox, IOS, DLCO N2 term vs prematur BPD vs non-BPD 221129.docx` available at https://authorea.com/users/566537/articles/613190-lung-function-deficits-and-bronchodilator-reversibility-at-12-years-of-age-in-children-born-very-preterm-compared-with-controls-born-at-term

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`Table 4 lung function before after med DR 221129.docx` available at https://authorea.com/users/566537/articles/613190-lung-function-deficits-and-bronchodilator-reversibility-at-12-years-of-age-in-children-born-very-preterm-compared-with-controls-born-at-term

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`Table 5 boys vs girls kontrollraknad utvidgad med DR 221129.docx` available at https://authorea.com/users/566537/articles/613190-lung-function-deficits-and-bronchodilator-reversibility-at-12-years-of-age-in-children-born-very-preterm-compared-with-controls-born-at-term