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Bronchial hyper-responsiveness in preterm-born subjects: A systematic review and meta-analysis.

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Abstract

Background: Preterm-born survivors have increased respiratory symptoms and decreased lung function, but the nature of bronchial hyper-responsiveness (BHR) is unclear. We conducted a systematic review and meta-analysis for BHR in preterm-born survivors including those with and without chronic lung disease in infancy (CLD) comparing results to term-born subjects.

Methods: We searched eight databases up to December 2016. Included articles compared BHR in preterm-born and term-born subjects. Studies reporting BHR as decreases in forced expiratory volume in 1 second (FEV₁) after provocation stimuli were included. Analysis used Review Manager V5.3.

Results: From 10,638 titles, 265 full articles were screened, and 28 included in a descriptive analysis. Eighteen articles were included in a meta-analysis as they reported the proportion of subjects who had BHR. Pooled Odds Ratio (OR) estimates (95% Confidence Interval) for BHR comparing the preterm and term-born groups was 1.88 (1.32, 2.66). The majority of the studies reported BHR after a methacholine challenge or an exercise test. Odds Ratio were 1.89 (1.12, 3.19) after methacholine challenge and 2.59 (1.50, 4.50) after exercise test. Nine of fifteen articles reporting BHR in CLD subjects were included in a meta-analysis. Differences for BHR including for methacholine (OR 4.35;

2.36, 8.03) and exercise (OR 5.13; 1.82, 14.47) were greater in the CLD group compared to the term group.

Conclusions: Preterm-born subjects especially those who had CLD had increased rates of BHR to direct (methacholine) and indirect (exercise) stimuli compared to term-born subjects suggesting subgroups might benefit from anti-inflammatory or bronchodilator therapies.

Keywords:

Asthma, bronchial hyper-responsiveness, bronchopulmonary dysplasia, chronic lung disease of prematurity, exercise, methacholine, prematurity

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Introduction

Preterm-birth is associated with increased respiratory symptoms (1, 2) and decreased lung function. (3) However, whilst it is often stated that these adverse events result from birth at an early stage of lung development (4) and interventions such as mechanical ventilation, the underlying mechanisms for the respiratory deficits continuing into childhood and beyond remain uncertain. These deficits may be due to long standing structural consequences of preterm birth, as evidenced by smooth muscle extension into the smaller airways well beyond that observed in term-born infants, especially where the infant has been diagnosed with chronic lung disease of prematurity (CLD, also called bronchopulmonary dysplasia, BPD). (5, 6) Alternatively, there is limited data suggesting that an active pro-inflammatory neutrophilic status (7) and oxidant process may be continuing. (8)

The nature of the airway narrowing observed in preterm-born children can be tested using pharmacological stimuli e.g. directly acting on smooth muscle cells' receptors, or indirectly via release of mediators by pro-inflammatory airway cells. (9) This process of assessment of bronchial hyper-responsiveness (BHR) has been extensively used in asthma, although it is not as discriminatory as expected as many asymptomatic subjects may have increased BHR and those with the disease may not. (10) Nevertheless, BHR by both direct (e.g. histamine, methacholine) and indirect (e.g. exercise, mannitol) means have been used in preterm-born survivors to try to elucidate the potential mechanisms underlying the airway obstruction observed. The current data do not conclusively confirm that BHR is increased in preterm survivors; furthermore, it is even less clear if direct agents have greater or similar effects to indirect agents. Thus, we conducted a systematic review and meta-analysis to identify if:-

- (a) BHR was increased after preterm birth when compared to term-born controls.
- (b) BHR was increased in preterm-born subjects who had CLD compared to term-born subject
- (c) Any increase in BHR was due to responses to (i) direct or (ii) indirect stimuli.

Methods

We used methodologies and data from our 3 previous systematic reviews. (3, 11, 12) Since data for BHR is often not reported in titles or abstracts, we combined several approaches. We (a) re-ran the initial searches for articles reporting FEV₁ in preterm-born subjects(3); (b) adapted the initial search strategies to include additional keywords relating to BHR and ran them in eight databases; and (c) searched references in the included articles to identify additional papers reporting BHR in preterm-born subjects compared to term-born subjects (see online supplement for protocol, search strategy, and data collection form). Eight databases were searched: Embase, Health Management Information Consortium (HMIC), Medline, Medline in Process, Scopus, OpenSIGLE, CINAHL, and Web of Science. Ethical approval was not required.

Eligibility criteria

Studies on BHR in preterm-born subjects of any age, (adults and children), with or without CLD, and of any gender were included. Randomised and non-randomised intervention studies, prospective and retrospective case control studies, and prospective and retrospective cohort studies were included. Preterm defined as birth <37 weeks' gestation and term as birth ≥37 weeks' gestation. Studies which recruited on the basis of birth-weight were included if they reported gestational age and all subjects in the study group were preterm and the control group were term-born, or the birth-weight cut off for the preterm group was <1,501g. Authors' definitions of CLD and what constituted BHR, and all methods of assessing BHR were accepted. However, only studies reporting change in FEV₁ after a challenge were included. Studies in all languages from all countries were considered.

Study Selection

Searches were conducted in December 2016 and January 2017. Two reviewers (SJK, and HC) independently screened each reference title and available abstracts, using the inclusion criteria. Complete manuscripts were obtained for those that met the inclusion criteria as judged by either reviewer. The two reviewers then screened the full manuscripts against the inclusion criteria. Where there was disagreement, a third reviewer (SK) made the final decision.

Data collection process

SJK data extracted included articles. Authors of articles were contacted, where possible, for further details if the information was not in a format which enabled data extraction for inclusion in the systematic review. Multiple articles from the same cohort were reviewed by SK and SJK, and the article reporting the most complete data was included.

Assessment of study quality and risk of bias

Study quality was assessed based on criteria from the Newcastle Ottawa criteria and the Cochrane risk of bias tool. The quality assessment sheet is shown in the online supplement. Each study was scored for representativeness of the cohort, appropriate selection of the non-exposed group, exposure ascertainment and demonstration that the outcome of interest was not present at the start of the study, outcome assessment and adequacy of follow-up by SJK. Minimum score was 6 and maximum score was 20.

Outcome measures

Number of subjects with BHR (given by a defined change in FEV₁ after BHR challenge) in the premature group and in the premature CLD subgroup, compared with a term control group.

Analysis of results

A formal meta-analysis was conducted for the studies which reported the number of subjects in the (a) preterm (with and without CLD) and control group, and (b) preterm group with CLD and a term control group who had a positive BHR result as defined by the authors of each manuscript. Both meta-analyses were further analysed by dividing the subjects into the different methods of testing for BHR to separate out the effects of direct and indirect challenges. The results of all studies including those not in the meta-analyses are also presented descriptively. A sensitivity analysis was performed to investigate the effect of year of birth of the preterm-born subjects on BHR by dividing the preterm-born subjects into two groups (1) born on or after 1990, and (2) born before 1990. Where the subjects were born over a range of years a mid-point was used.

Statistical analysis

Statistical analyses were performed using Review Manager (RevMan) Version 5.3 (13). After initial exploration of the data we used random effects meta-analyses to allow for heterogeneity. Heterogeneity was assessed using the I^2 statistic produced by RevMan. The following were used as a rough guide I^2 “0% to 40% might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity” (14). There was large heterogeneity between the articles, due to a range of methods

to assess BHR, variable outcomes measures, and range of ages and gestations studied over a number of years.

Results

Studies selected and their characteristics

10,638 article titles were identified of which 265 full articles were screened for inclusion. Twenty-eight (15-42) met the inclusion criteria (Figure 1). For the two studies that overlapped (24) (26), the one reporting BHR as a proportion of responders (26) was included in the meta-analyses. Detailed demographics of included articles are shown in Table E1 (online supplement), and a summary of the demographics for the direct and indirect methods of assessing BHR are shown in Tables 1a and 1b respectively.

Of the 28 articles reporting BHR:

- 14 performed a methacholine challenge
- 12 performed an exercise test
- 1 performed a cold air challenge
- 1 performed testing with hypertonic saline

Many of the articles studied preterm-born subjects where prematurity was defined as being born at a gestation of <37 weeks, (15, 18-21, 23, 29, 34, 37, 39, 40, 42) but there was heterogeneity in the groups as articles also sometimes only included extremely (<28 weeks' gestation) or very (≤32 weeks' gestation) (17, 24-28, 31-33, 35, 36, 41) or late (33 -36 weeks' gestation) preterm-born subjects (38). Although the majority of studies studied randomly selected preterm subjects or studied cohorts, one study included preterm infants with congenital diaphragmatic hernia (CDH), but the

authors provided data to us to only include the preterm and term control infants excluding CDH.(22)

Sensitivity analyses removing that study from all analyses marginally increased the odds ratios in favour of the preterm groups. In most of the included studies, BHR was tested as part of wider ranges of lung function assessments.

Risk of bias across studies

The quality scores ranged from 9 to 18 (median 14). The studies not included in the meta-analyses had similar quality scores to those included in the meta-analyses. Included studies range 11 to 16 (median 14), not included studies range 9 to 18 (median 14.5).

Study Outcomes

a) BHR in Preterm group compared to term control group

18 of the 28 included articles were included in a meta-analysis.

The results of the meta-analysis of the 18 articles are shown in Figure 2a; demographics are described in the online supplement (Table E1). The pooled estimates of OR (95% CI) for BHR in the preterm group was 1.88 (1.32, 2.66) $p=0.01$.

The results for subjects who had a methacholine (direct) challenge or who had an exercise test (indirect challenge) are reported in Figures 2b and 2c respectively; and demographics are shown in Table E1 (online supplement). The pooled estimates of OR (95% CI) for BHR in the preterm group was 1.89 (1.12, 3.19) $p=0.009$ for the 8 articles reporting results after a methacholine challenge and 2.59 (1.50, 4.50) $p=0.0007$ for the 8 articles reporting results after an exercise test.

OR were greater for studies where the preterm-born subjects were born on or after 1990 than studies where the preterm-born subjects were born before 1990.

BHR in Preterm group who had CLD in infancy compared to term control group

Fifteen of the 18 articles also compared BHR in preterm-born subjects who had CLD with term controls. (17, 18, 21, 24-27, 29, 31, 33-37, 41) See online supplement for demographics (Table E1).

We performed a meta-analysis for 9 of the 15 articles although the total number studied were small (Figure 3a). The definitions of CLD used by the authors' of the 9 articles are reported in Table E2 (online supplement). The pooled estimates of OR (95% CI) for BHR in the preterm group who had CLD was 4.54 (2.68, 7.69), $p < 0.00001$. The results for the subjects who had a methacholine challenge or who had an exercise test are reported in Figures 3b and 3c respectively. The pooled estimates of OR (95% CI) for BHR in the preterm group who had CLD was 4.35 (2.36, 8.03), $p < 0.00001$ for the 4 articles reporting results after a methacholine challenge and 5.13 (1.82, 14.47), $p = 0.002$ for the 5 articles reporting results after an exercise test. It should be noted that one study used different definitions for the preterm ($PC_{20} < 4$ mg/ml) and CLD ($PC_{20} < 1$ mg/ml) groups to define a positive BHR response. (27)

b) Description of studies not included in the meta-analyses

Ten articles were not included in the meta-analysis. (17, 19, 23-26, 29, 33, 36, 39, 40) Six articles reported BHR after a methacholine challenge (17, 19, 23-26, 39) and four articles reported after an exercise test. (29, 33, 36, 40) The studies are described in detail in the online supplement (Table E1). In general, all studies for both methacholine and exercise reported increases in BHR but the results were not always significantly different from included term-born controls. However, comparisons between articles were difficult due to heterogeneity.

Discussion

The results of our systematic review and meta-analyses suggest preterm-born subjects have greater BHR compared to term-born subjects and differences are greatest for subjects who had CLD.

Furthermore, the commonest used direct agent, methacholine, and indirect method, exercise testing, both resulted in greater BHR in preterm-born survivors with and without CLD and preterm born subjects with CLD compared to term controls. Of note was the variety of different stimuli and outcome measures used, making comparisons difficult between studies.

Respiratory symptoms in school-age preterm-born children are often inappropriately labelled as asthma; however, the underlying mechanisms are likely to be different to those in asthma. Previous studies (43) have suggested that studying BHR by both direct and indirect means may help elucidate the underlying mechanisms and aid targeted therapy e.g. anti-inflammatory or smooth muscle relaxants. However, despite the various methods used in the meta-analyses and descriptive analyses, the collated results strongly suggest that BHR is more prevalent in preterm-born group compared to term-born subjects, especially in those who had CLD – a finding similar to those with asthma.

Since different mechanisms may potentially be identified by using direct, (assessing smooth muscle phenotypes and responses), and indirect methods, (pathways of inflammatory mediators), to assess BHR, (9) we classified the studies using direct and indirect means to assess BHR. This is an important distinction to make as there is a suggestion that BHR responses may be different in asthma and in lung disease of preterm-born children: Kim et al. reported children with asthma responded to both methacholine and to adenosine 5'-monophosphate but children with CLD only responded to the methacholine suggesting that continuing inflammation may not be a factor in preterm-born subjects. (43) Methacholine is a direct method of assessing BHR by assessing bronchial smooth muscle response and adenosine 5'-monophosphate is an indirect method of assessing BHR by pathways of inflammatory mediator release from airway mast cells. Therefore, as children with CLD only

responded to the direct method not indirect methods it is possible inflammation may not be a factor in BHR of the CLD subjects in the study by Kim et al. This is clearly contradictory to two studies which reported increased neutrophilic inflammation in induced sputum and increased oxidant activity in exhaled breath condensate from children with CLD. (7, 8) The results however, are in agreement with reports of low exhaled nitric oxide in children with CLD. (44)

Interestingly, separating the data on whether a direct or indirect method was used showed that both methods resulted in increased BHR in preterm-born subjects including the CLD group despite smaller numbers available for inclusion. Historically, it has been shown at autopsy that airway smooth muscle is both thicker and extends further down the airways in preterm subjects especially those dying from CLD when compared to matched term controls. (5, 6) However, what happens in the current cohorts of survivors can only be speculative. Our data suggest that preterm born subjects have increased responses to direct stimuli suggesting that treatment with bronchodilators may be successful. Our previous systematic review confirmed responses to single doses of bronchodilators but longer-term studies of bronchodilators in this group are lacking. (11) Currently, treatment is variable with individual clinicians forming their own opinions based on limited data. The situation is further complicated as the smooth muscle phenotype may initially respond to bronchodilators but there is speculation that these cells may develop a more fixed unresponsive myofibroblast phenotype which may not respond to bronchodilator treatment. (45)

Our data also showed that exercise also resulted in convincing differences between the preterm groups when compared to term controls. Two small studies show that (neutrophilic) airway inflammation and oxidant injury may be continuing in childhood in preterm airway disease but replication of these studies in larger numbers is required. (7, 8) The evidence for the efficacy of inhaled corticosteroids in lung disease of preterm-born survivors is also limited, although, taken together with our data, there is a suggestion that subgroups of preterm-born subjects may benefit from inhaled corticosteroids, although they may not be effective if neutrophilic inflammation is

confirmed. Role of targeting the leukotriene pathway is also poorly studied in preterm-born children with lung disease. Appropriate studies to evaluate the efficacy of both bronchodilators and inhaled corticosteroids are urgently required.

The preterm group with and without CLD have increased BHR to both direct and indirect but we were not able to assess if both were present in the same individuals. Besides the study by Kim et al. (43) (who assessed BHR by auscultation and oximetry), the study by Nikolajev and colleagues of moderately preterm-born children (mean gestation of 35 weeks) reported overlap between exercise, methacholine and cold air challenges as well as with responses to bronchodilators. (46) It is likely that preterm-born subjects have either structural abnormalities or airway inflammation or both, but the relevant studies to confirm or refute either are currently lacking.

Limitations

As with all systematic reviews, we were limited by the data in included articles. The majority of articles examined BHR as part of a wider range of lung function tests and there was disparity in the articles. Interpreting the results was complex as the articles reported a range of methods used to test BHR. Variable inclusion criteria and agents – both pharmacological and physiological – were used to assess and report BHR outcomes which included induction of wheeze, changes in spirometry, and changes in oxygen saturation. Even when a change in FEV₁ was used, the definitions of a positive response varied. A number of articles were excluded as they not only defined BHR after testing with a provocative agent/test, but they also included data on subjects with a low FEV₁ who had responded to an inhaled bronchodilator. In addition, articles reporting BHR in preterm-born subjects without a term-born control group, and articles with preterm and term-born subjects combined in the results were excluded. Variable criteria were used to define CLD in articles included in the meta-analyses. We ideally would have liked to further analysis the CLD group by dividing the

group into two; (1) CLD defined as a requirement for supplemental oxygen at ≥ 28 postnatal days, and (2) CLD defined as a requirement for supplemental oxygen at ≥ 36 weeks post menstrual age. However, the small number of subjects in the articles with the later definition meant this was not possible. Additionally, the subjects were born at a wide range of gestational ages over a number of decades when medical management has progressed – whether BHR is affected by survival of the extremely preterm babies is unclear.

Conclusions

This is the first comprehensive systematic review and meta-analysis which collated and reported the effect of preterm birth on later BHR. Suggesting an increased rate of BHR in preterm-born subjects compared to term-born subjects; differences were greatest for subjects who had CLD. Both direct (methacholine challenge) and indirect (exercise) challenges resulted in increased BHR suggesting that subgroups of preterm born subjects could potentially benefit from anti-inflammatory and/or bronchodilator therapies.

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Contributorship statement

SJK, SK, HC and TH substantially contributed to the conception, and design of the work, the acquisition, analysis and interpretation of data. SJK and SK wrote the first draft of the manuscript which all the authors revised critically for important intellectual content. All authors approved the final version 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 Interest

TH, HHC and SJK report no conflict of interest. SK reports grants from the NIHR (16/111/106), Welsh Government, EU FP7, and MRC (MR/M022552/1) outside of the submitted work.

References

- 1 Edwards MO, Kotecha SJ, Lowe J, Richards L, Watkins WJ, Kotecha S. Management of Prematurity-Associated Wheeze and Its Association with Atopy. *Plos One*. 2016; **11**.
- 2 Been JV, Lugtenberg MJ, Smets E, *et al*. Preterm Birth and Childhood Wheezing Disorders: A Systematic Review and Meta-Analysis. *Plos Medicine*. 2014; **11**.
- 3 Kotecha SJ, Edwards MO, Watkins WJ, *et al*. Effect of preterm birth on later FEV1: a systematic review and meta-analysis. *Thorax*. 2013; **68**: 760-6.
- 4 Joshi S, Kotecha S. Lung growth and development. *Early Hum Dev*. 2007; **83**: 789-94.
- 5 Tiddens HA, Hofhuis W, Casotti V, Hop WC, Hulsmann AR, de Jongste JC. Airway dimensions in bronchopulmonary dysplasia: implications for airflow obstruction. *Pediatr Pulmonol*. 2008; **43**: 1206-13.
- 6 Bush A, Busst CM, Knight WB, Hislop AA, Haworth SG, Shinebourne EA. Changes in pulmonary circulation in severe bronchopulmonary dysplasia. *Arch Dis Child*. 1990; **65**: 739-45.
- 7 Teig N, Allali M, Rieger C, Hamelmann E. Inflammatory markers in induced sputum of school children born before 32 completed weeks of gestation. *Journal of Pediatrics*. 2012; **161**: 1085-90.
- 8 Filippone M, Bonetto G, Corradi M, Frigo AC, Baraldi E. Evidence of unexpected oxidative stress in airways of adolescents born very pre-term. *European Respiratory Journal*. 2012; **40**: 1253-59.
- 9 Clemm HH, Engeseth M, Vollaeter M, Kotecha S, Halvorsen T. Bronchial hyper-responsiveness after preterm birth. *Paediatr Respir Rev*. 2017.
- 10 Liem JJ, Kozyrskyj AL, Cockroft DW, Becker AB. Diagnosing asthma in children: what is the role for methacholine bronchoprovocation testing? *Pediatr Pulmonol*. 2008; **43**: 481-9.
- 11 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**: 231-40.

- 12 Edwards MO, Kotecha SJ, Lowe J, Watkins WJ, Henderson AJ, Kotecha S. Effect of preterm birth on exercise capacity: A systematic review and meta-analysis. *Pediatric Pulmonology*. 2015; **50**: 293-301.
- 13 Zysman-Colman Z, Tremblay GM, Bandea S, Landry JS. Bronchopulmonary dysplasia - trends over three decades. *Paediatrics & child health*. 2013; **18**: 86-90.
- 14 Bolton CE, Bush A, Hurst JR, *et al*. Are early life factors considered when managing respiratory disease? A British Thoracic Society survey of current practice. *Thorax*. 2012; **67**: 1110.
- 15 von Mutius E, Nicolai T, Martinez FD. Prematurity as a risk factor for asthma in preadolescent children. *Journal of Pediatrics*. 1993; **123**: 223-9.
- 16 Schraeder BD, Czajka C, Kalman DD, McGeedy SJ. Respiratory health, lung function, and airway responsiveness in school-age survivors of very-low-birth-weight. *Clinical Pediatrics*. 1998; **37**: 237-45.
- 17 Lum S, Kirkby J, Welsh L, Marlow N, Hennessy E, Stocks J. Nature and severity of lung function abnormalities in extremely pre-term children at 11 years of age. *European Respiratory Journal*. 2011; **37**: 1199-207.
- 18 Korhonen P, Laitinen J, Hyodynmaa E, Tammela O. Respiratory outcome in school-aged, very-low-birth-weight children in the surfactant era. *Acta Paediatrica, International Journal of Paediatrics*. 2004; **93**: 316-21.
- 19 Galdes-Sebaldo M, Sheller JR, Grogard J, Stahlman M. Prematurity is associated with abnormal airway function in childhood. *Pediatric Pulmonology*. 1989; **7**: 259-64.
- 20 Kotecha SJ, John Watkins W, Paranjothy S, Dunstan FD, John Henderson A, Kotecha S. Effect of late preterm birth on longitudinal lung spirometry in school age children and adolescents. *Thorax*. 2011; **27**.
- 21 Landry JS, Tremblay GM, Li PZ, Wong C, Benedetti A, Taivassalo T. Lung Function and Bronchial Hyperresponsiveness in Adults Born Prematurely. A Cohort Study. *Annals of the American Thoracic Society*. 2016; **13**: 17-24.
- 22 Ijsselstijn H, Tibboel D, Hop WJC, Molenaar JC, deJongste JC. Long-term pulmonary sequelae in children with congenital diaphragmatic hernia. *American Journal of Respiratory and Critical Care Medicine*. 1997; **155**: 174-80.
- 23 Pike KC, Davis SA, Collins SA, *et al*. Prenatal development is linked to bronchial reactivity: epidemiological and animal model evidence. *Scientific Reports*. 2014; **4**.
- 24 Halvorsen T, Skadberg BT, Eide GE, Roksund O, Aksnes L, Oymar K. Characteristics of asthma and airway hyper-responsiveness after premature birth. *Pediatric Allergy & Immunology*. 2005; **16**: 487-94.
- 25 Vollsaeter M, Skromme K, Satrell E, *et al*. Children Born Preterm at the Turn of the Millennium Had Better Lung Function Than Children Born Similarly Preterm in the Early 1990s. *PLoS ONE [Electronic Resource]*. 2015; **10**: e0144243.
- 26 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 Paediatrica*. 2004; **93**: 1294-300.
- 27 Kaplan E, Bar-Yishay E, Prais D, *et al*. Encouraging pulmonary outcome for surviving, neurologically intact, extremely premature infants in the postsurfactant era. *Chest*. 2012; **142**: 725-33.
- 28 Ronkainen E, Dunder T, Peltoniemi O, Kaukola T, Marttila R, Hallman M. New BPD predicts lung function at school age: Follow-up study and meta-analysis. *Pediatric Pulmonology*. 2015; **50**: 1090-8.
- 29 Mitchell SH, Teague WG. Reduced gas transfer at rest and during exercise in school-age survivors of bronchopulmonary dysplasia. *American Journal of Respiratory & Critical Care Medicine*. 1998; **157**: 1406-12.
- 30 McLeod A, Ross P, Mitchell S, *et al*. Respiratory health in a total very low birthweight cohort and their classroom controls. *Archives of Disease in Childhood*. 1996; **74**: 188-94.

- 31 Kriemler S, Keller H, Saigal S, Bar-Or O. Aerobic and lung performance in premature children with and without chronic lung disease of prematurity. *Clinical Journal of Sport Medicine*. 2005; **15**: 349-55.
- 32 Hamon I, Varechova S, Vieux R, *et al*. Exercise-induced bronchoconstriction in school-age children born extremely preterm. *Pediatric Research*. 2013; **73**: 464-8.
- 33 Gross SJ, Iannuzzi D, Kveselis DA, Anbar RD. Effect of preterm birth on pulmonary function at school age: A prospective controlled study. *Journal of Pediatrics*. 1998; **133**: 188-92.
- 34 Barker M, Merz U, Hertl MS, Heimann G. School-age lung function and exercise capacity in former very low birth weight infants. *Pediatric Exercise Science*. 2003; **15**: 44-55.
- 35 Bader D, Ramos AD, Lew CD. Childhood sequelae of infant lung disease: Exercise and pulmonary function abnormalities after bronchopulmonary dysplasia. *Journal of Pediatrics*. 1987; **110**: 693-99.
- 36 Joshi S, Wilson DG, Kotecha S, Pickerd N, Fraser AG, Kotecha S. Cardiovascular function in children who had chronic lung disease of prematurity. *Archives of Disease in Childhood Fetal & Neonatal Edition*. 2014; **99**: F373-9.
- 37 Abreu L, Costa-Rangel R, Gastaldi A, Guimarães R, Cravo S, Sologuren M. Cardio-respiratory capacity assessment in children with bronchopulmonary dysplasia. *Rev bras fisioter* 2007; **11**: 95-100.
- 38 Todisco T, de Benedictis FM, Iannacci L, *et al*. Mild prematurity and respiratory functions. *European Journal of Pediatrics*. 1993; **152**: 55-8.
- 39 Rona RJ, Smeeton NC, Bustos P, Amigo H, Diaz PV. The early origins hypothesis with an emphasis on growth rate in the first year of life and asthma: a prospective study in Chile. *Thorax*. 2005; **60**: 549-54.
- 40 Siltanen M, Savilahti E, Pohjavuori M, Kajosaari M. Respiratory Symptoms and Lung Function in Relation to Atopy in Children Born Preterm. *Pediatric Pulmonology*. 2004; **37**: 43-49.
- 41 Santuz P, Baraldi E, Zaramella P, Filippone M, Zacchello F. Factors limiting exercise performance in long-term survivors of bronchopulmonary dysplasia. *American Journal of Respiratory & Critical Care Medicine*. 1995; **152**: 1284-9.
- 42 Mai XM, Gaddlin PO, Nilsson L, *et al*. Asthma, lung function and allergy in 12-year-old children with very low birth weight: a prospective study. *Pediatric Allergy & Immunology*. 2003; **14**: 184-92.
- 43 Kim DK, Choi SH, Yu J, Yoo Y, Kim B, Koh YY. Bronchial responsiveness to methacholine and adenosine 5'-monophosphate in preschool children with bronchopulmonary dysplasia. *Pediatr Pulmonol*. 2006; **41**: 538-43.
- 44 Baraldi E, Bonetto G, Zacchello F, Filippone M. Low exhaled nitric oxide in school-age children with bronchopulmonary dysplasia and airflow limitation. *Am J Respir Crit Care Med*. 2005; **171**: 68-72.
- 45 Pandya HC, Kotecha S. Chronic lung disease of prematurity: clinical and pathophysiological correlates. *Monaldi Arch Chest Dis*. 2001; **56**: 270-5.
- 46 Nikolajev K, Korppi M, Koskela H, *et al*. Methacholine, cold air and exercise challenge tests in the diagnosis of bronchial responsiveness at school age: A follow-up study from birth to school age. *Allergology International*. 2002; **51**: 131-38.

Table 1a: Characteristics of the studies using direct bronchial provocation tests

STUDY	YEAR OF PUBLICATION	TYPE OF STUDY	PREMATURITY	AGE RANGE	SAMPLE SIZE	METHOD USED	EFFECT OF INTERVENTION	QUALITY SCORE
Todisco(38)	1993	Unselected population Retrospective	34-36 weeks'	8-15 years	34 preterms 34 terms	Methacholine	BHR preterms 4/34 BHR terms 2/34	14
Schraeder(16)	1998	Prospective longitudinal study of development	Birth-weight ≤ 1500g	10-11 years	28 VLBW 42 NBW	Methacholine	BHR VLBW 17/28 BHR NBW 23/42	15
Rona(39)	2005	Non-concurrent prospective study	Not stated <37 weeks'	Not stated	1232 subjects in total approx. 10% <37 weeks	Methacholine	Increased OR of a positive BHR response with a gestation of <37 weeks', not statistically significantly	15
Lum(17)	2011	Population based study Prospective	≤ 25 weeks +6	11 years	49 preterms 52 terms	Methacholine	Airway hyperresponsiveness abnormalities were most marked in EP with BPD	17
Korhonen (18)	2004	Cohort Prospective	23-35 weeks'	7-8 years	54 preterms 30 terms	Methacholine	BHR preterms 43/54 BHR terms 14/30	16
Galdes-Sebaladt(19)	1989	Cross sectional Retrospective	26-32 weeks' Mixed group <39weeks'	10-13 years	41 preterms 22 terms	Methacholine	VLBW preterm subjects had significantly higher rates of BHR than terms	12
Kotecha(20)	2011	Population based cohort Prospective	25-36 weeks'	8-9 years	238 preterms 4123 terms	Methacholine	BHR preterms 40/238 BHR terms 646/4123	15
Landry(21)	2016	Cross-sectional study Retrospective	<37 weeks'	21-22 years	76 preterms 33 terms	Methacholine	BHR preterms 51/76 BHR terms 15/33	13
Ijsselstijn(22)	1997	Matched study Retrospective	29-36 weeks'	7-18 years	18 preterms 38 terms	Methacholine	BHR preterms 5/18 BHR terms 17/38	13
Pike(23)	2014	Human mother-child cohort Prospective	<37 weeks'	6-7 years	246 children in total	Methacholine	Term-born children with lower abdominal growth had a significantly higher rate of BHR but preterm-born children did not.	14
Halvorsen(24)	2005	Population based cohort Prospective	≤28 weeks or birthweight	First cohort mean 17.7 SD	74 preterms 79 terms	Methacholine	Airway hyperresponsiveness was	15

			≤1000g	1.2 years Second cohort mean 10.6 SD 0.4 years			substantially increased in the preterms compared to the terms.	
Vollsaeter(25)	2015	Population based cohort Prospective	<28 weeks or birthweight <1000g	Preterms mean 11.4 SD 0.6	57 preterms 54 terms	Methacholine	Preterms had more BHR than terms	15
Halvorsen(26)	2004	Population based cohort Prospective	≤28 weeks or birthweight ≤1000g	Mean 17.7 years SD 1.2	41 preterms 46 preterms	Methacholine	BHR preterms 23/41 BHR terms 12/46	15
Kaplan(27)	2012	Cohort Retrospective	≤28 weeks'	Mean age 9- 10 years	43 preterms 23 terms	Methacholine	BHR preterms 21/43 BHR terms 5/23	14

Table 1b: Characteristics of the studies using indirect bronchial provocation tests

STUDY	YEAR OF PUBLICATION	TYPE OF STUDY	PREMATURITY	AGE RANGE	SAMPLE SIZE	METHOD USED	EFFECT OF INTERVENTION	QUALITY SCORE
Ronkainen(28)	2015	Prospective birth cohort	<32 weeks	6-14 years	87 preterms 88 terms	Exercise	BHR preterms 2/87 BHR terms 3/88	15
Mitchell(29)	1998	Cross sectional Retrospective	BPD mean 30 SD 5 Non BPD mean 31 SD 3	6-9 years	20 preterms 10 terms	Exercise	Exercise induced bronchospasm though statistically significant was mild for preterms.	11
McLeod (30)	1996	Population based cohort Prospective	VLBW <1500g	8-9 years	300 VLBW 590 terms	Exercise	BHR VLBW 30/300 BHR terms 31/590	15
Kriemler(31)	2005	Cohort Prospective	24-30 weeks'	5-7 years	28 preterms 23 terms	Exercise	BHR preterms 14/28 BHR terms 5/23	13
Hamon(32)	2013	Cohort Prospective	<32 weeks'	7 years	42 preterms 27 terms	Exercise	BHR preterms 10/42 BHR terms 0/27	15
Gross(33)	1998	Cohort Prospective	<32 weeks'	7 years	96 preterms 108 terms	Exercise	After exercise FEV ₁ was abnormal more often in the preterms compared to terms.	18
Barker(34)	2003	Cross sectional cohort Retrospective	28-36 weeks'	8-14 years	26 preterms 13 terms	Exercise	BHR preterms 4/26 BHR terms 0/13	16
Bader(35)	1987	Cohort Retrospective	26-32 weeks'	7-12 years	10 preterms 8 terms	Exercise	BHR preterms 5/10 BHR terms 0/8	12
Joshi(36)	2014	Cross sectional Retrospective	≤32 weeks'	8-12 years	49 preterms 26 terms	Exercise	CLD group had significant EIB	9
Abreu(37)	2007	Cohort Retrospective	28-36 weeks'	7-10 years	23 preterms 17 terms	Exercise	BHR preterms 3/23 BHR terms 0/17	14
Siltanen(40)	2004	Cohort Retrospective	23-33 weeks'	9-10 years	72 preterms 65 terms	Exercise	Changes in lung function after exercise were not significantly different.	13

Santuz(41)	1995	Control study Retrospective	27-32 weeks'	6-12 years	12 preterms 16 terms	Exercise	BHR preterms 2/12 BHR terms 0/16	11
Mai(42)	2003	Cohort Prospective	25-36 weeks'	12 years	68 preterms 59 terms	Hypertonic saline provocation test	BHR preterms 22/68 BHR terms 18/59	13
Von Mutius(15)	1993	Population study Retrospective	Not stated < 37 weeks'	9-11 years	118 preterms 2113 terms	Cold air challenge	BHR preterms 7/118 BHR terms 133/2113	12

FIGURE LEGENDS

Figure 1: Study Selection Results

Figure 2a: Number of subjects with BHR in the premature group compared with term control group.

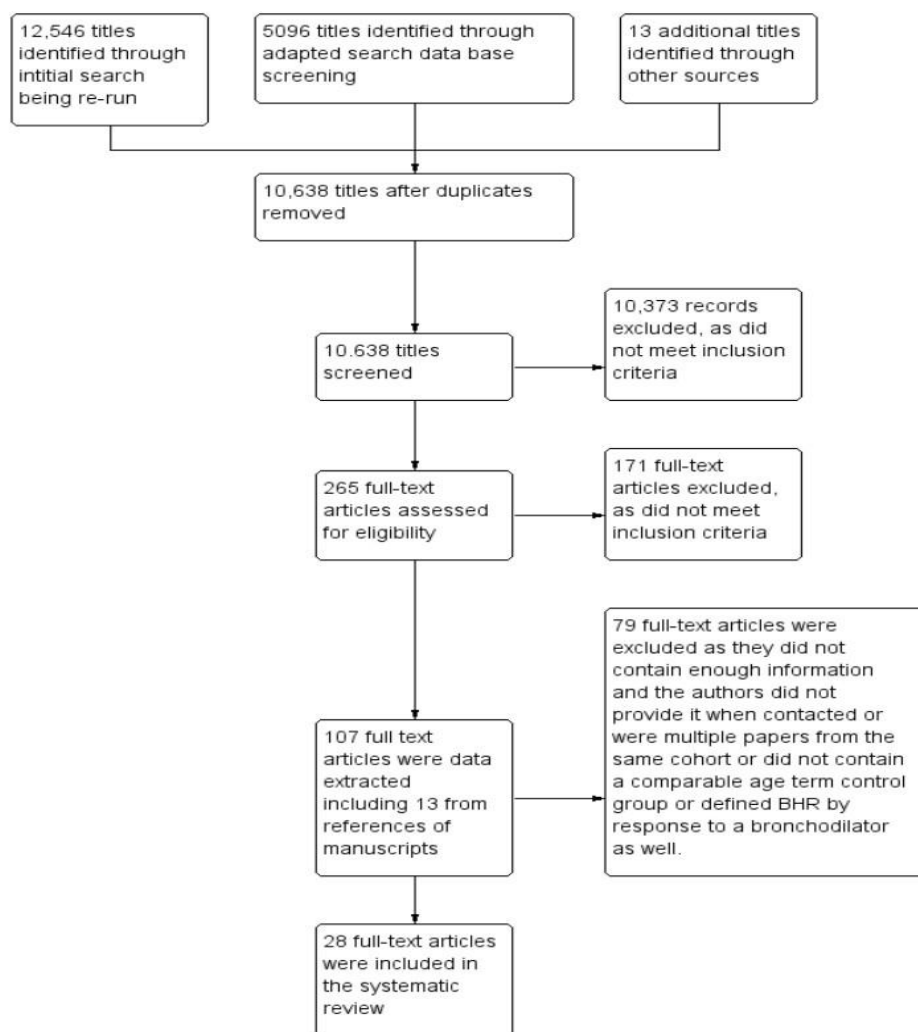
Figure 2b: Number of subjects with BHR after a methacholine challenge in the premature group compared with term control group.

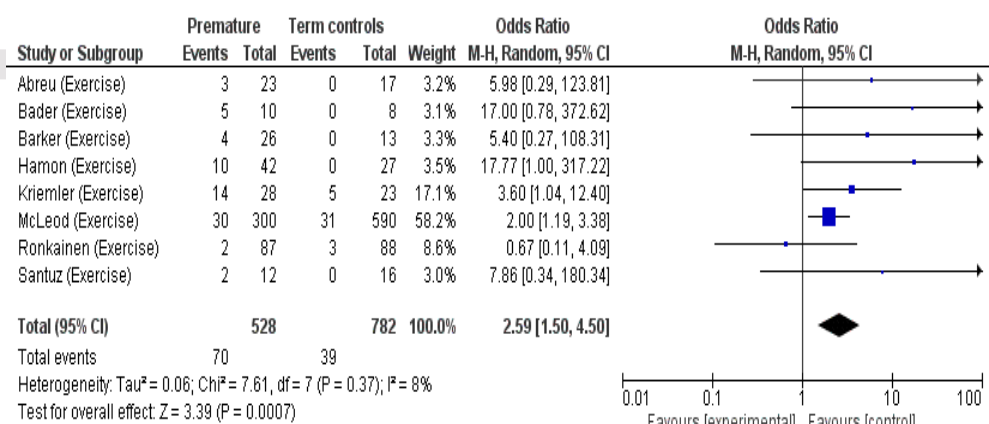
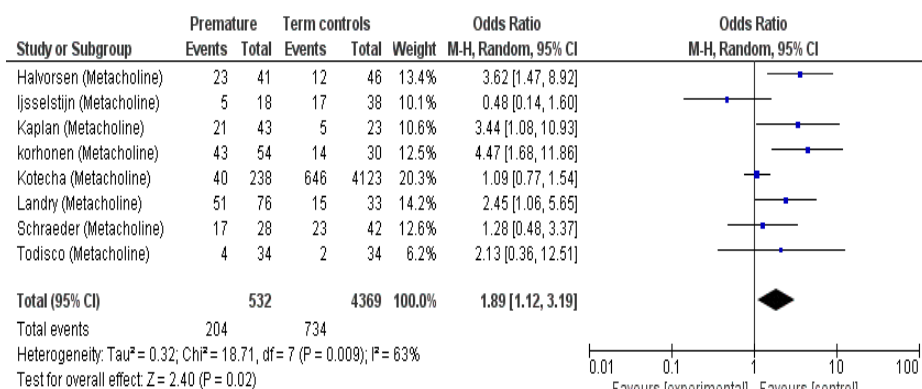
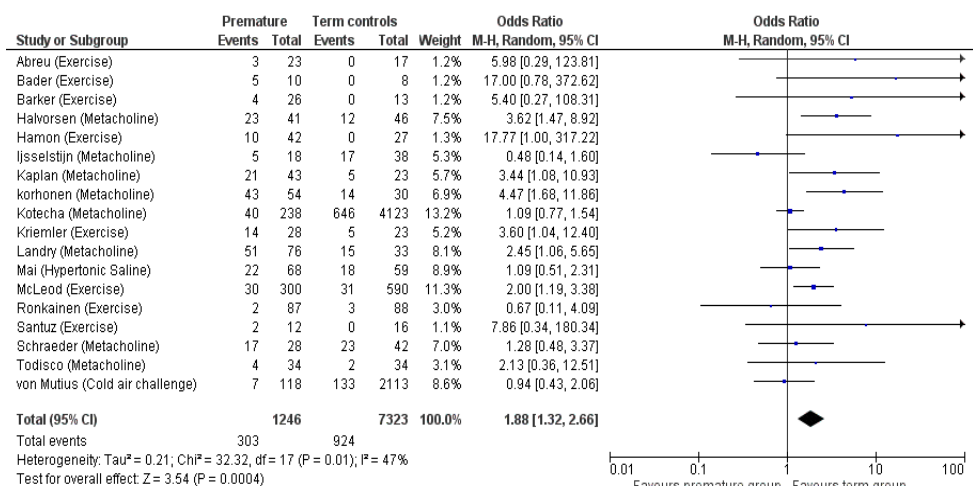
Figure 2c: Number of subjects with BHR after an exercise test in the premature group compared with term control group.

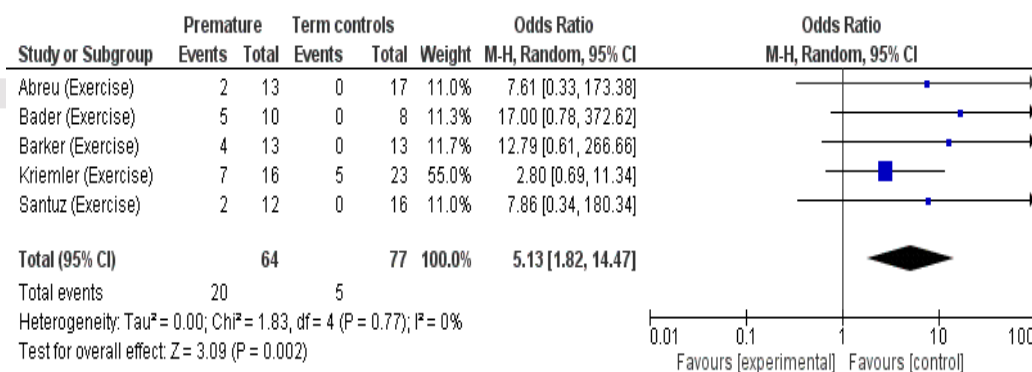
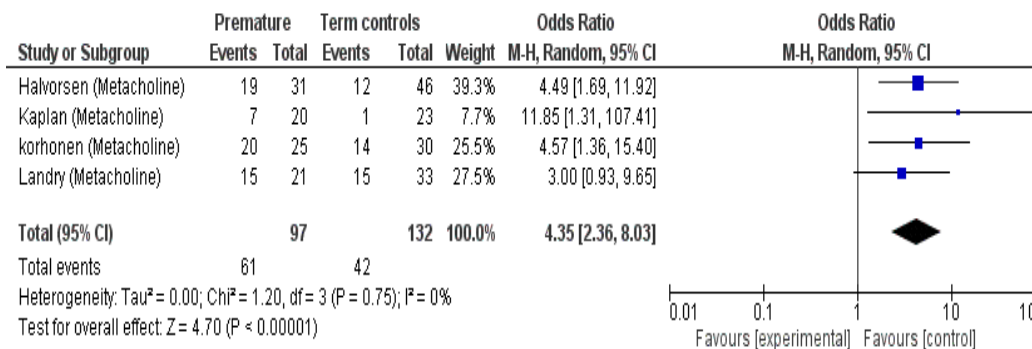
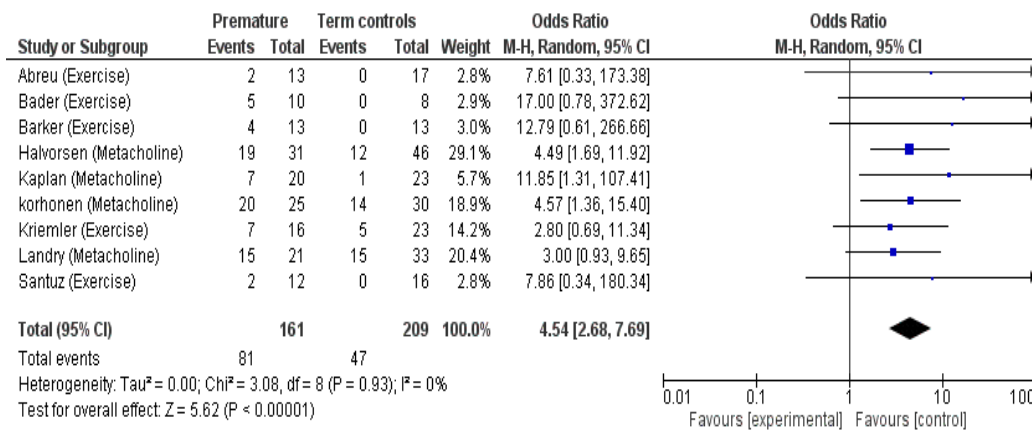
Figure 3a: Number of subjects with BHR in the premature group who had CLD in infancy compared with term control group.

Figure 3b: Number of subjects with BHR after a methacholine challenge in the premature group who had CLD in infancy compared with term control group.

Figure 3c: Number of subjects with BHR after an exercise test in the premature group who had CLD in infancy compared with term control group.







Online Supplement

Bronchial hyper-responsiveness in preterm-born subjects: A systematic review and meta-analysis.

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Protocol

BHR in preterm-born subjects compared to term born subjects - a systematic review of the literature.

Review Question

Is there increased BHR in preterm-born subjects compared to subjects born at term?

Outcome of interest

BHR results measured by a change in FEV₁

Study population

Studies that include people of any age living in any country. Studies published from any year.

Search strategy

A search strategy was developed for electronic databases using the keywords and MeSH headings below. The search strategy was tested for citations on the OVID Medline database 1950-2010. The Observational Studies search filter used by SIGN (Scottish Intercollegiate Guidelines Network) <http://www.sign.ac.uk/methodology/filters.html#obs> was adapted to retrieve types of study designs included in the review.

The search strategy will be modified to search rest of the bibliographic databases. In addition, a range of 'snowballing' techniques will be used to increase the sensitivity of the search, including reference list follow up, contact with subject experts and relevant websites/organisations, and table of content scanning for the top three most frequently cited journals.

Inclusion and exclusion process of identified citations

The agreed search strategy will be applied to the agreed databases and information sources.

A single Reference Manager file will be produced of all references identified through the search process. Duplicates will be removed. Each reference will be given a unique identifier code number.

Two electronic copies of references in this file will be produced, and one set given to each reviewer. Two people will review the papers.

Both reviewers will independently screen each reference title and abstract (if available) from their copies of the file, using the agreed inclusion and exclusion criteria. Reviewers will receive an electronic spreadsheet to indicate yes for probable or possible inclusion for each citation, or no for exclusion. At this stage abstracts only will be translated if the citation is not written in English.

The independent screening assessments will be merged.

Where both reviewers have indicated no for a citation then that citation will be excluded at this stage, and the full article will not be obtained.

Where both reviewers have indicated yes for a citation then the full article will be obtained. They will go into the second round of inclusion/exclusion assessment of articles.

Where one reviewer has indicated yes and the other no then the full article will be obtained and go into the second round as above.

The second round will involve each reviewer assessing the full article based on the agreed inclusion/exclusion criteria. Each will decide yes or no for exclusion for each citation reaching the second round.

The second round assessments will be merged.

Where both indicate yes in the second stage the citation will go forward for subsequent data extraction and critical appraisal. Where both indicate no the citations will be excluded. Where there is disagreement then a third reviewer will apply the inclusion/exclusion criteria and their yes or no will be final.

Inclusion criteria

Studies clearly or potentially primarily about

- Subjects born prematurely compared to subjects born at term and containing BHR data should be included.

Other criteria

- The study population can be of any age and sex.
- The study population can be from any country.
- The studies must be randomised or non randomised intervention studies; prospective or retrospective cohort studies; or prospective or retrospective case control studies.
- Studies written in any language.

Exclusion Criteria

- Case reports, case series, letters, editorials or expert opinions only.
- Studies primarily about the clinical management of broncho pulmonary dysplasia or other lung conditions or management of the lung when the premature infant is born.

Languages included

All languages will be considered.

Study data extraction and critical quality appraisal

Data extraction form.

Study designs included

1. Randomised and non-randomised intervention studies.
2. Prospective and retrospective case control studies.
3. Prospective and retrospective cohort studies

Study characteristics to be collected

1. Relevance or appropriateness of studies gathered for assessing hypothesis to be tested.
2. Rationale for the selection and coding of data.
3. Documentation of how data were classified and coded.
4. Assessment of confounding.
5. Assessment of study quality.
6. Assessment of heterogeneity.
7. Statistical methods.

Results

Descriptive information

Descriptive information for each included study. Details of study design, participants, interventions, definitions of outcomes, will be included in the table of characteristics of

included studies. Between study heterogeneity will be assessed and explained. The reasons for excluding any studies will be clearly reported.

Search strategy

Ovid MEDLINE – Search Strategy

1. exp Infant, Low Birth Weight/
2. exp Infant, Very Low Birth Weight/
3. exp Infant, Extremely Low Birth Weight/
4. exp Infant, Premature/
5. Obstetric Labor, Premature/
6. exp Premature Birth/
7. Fetal Growth Retardation/
8. Birth Weight/
9. Low Birth Weight.mp.
10. ((Preterm* or Premature*) adj2 (labo#r* or birth* or born or infant or baby or babies or child or children or girl*1 or boy*1)).mp.
11. Prematurity.mp.
12. IUGR.mp.
13. intrauterine growth restriction.mp.
14. or/1-13
15. Epidemiologic Studies/
16. exp case control studies/
17. exp cohort studies/
18. Case control.tw.

19. (cohort adj (study or studies)).tw.
20. Cohort analy*.tw.
21. (Follow up adj (study or studies)).tw.
22. (observational adj (study or studies)).tw.
23. Longitudinal.tw.
24. Retrospective.tw.
25. Cross sectional.tw.
26. Cross-sectional studies/
27. case-control studies/ or longitudinal/ or follow-up studies/ or prospective studies/
28. or/15-27
29. bronchial hyperreactivity/
30. bronchial hyperreactivity.mp.
31. exp Bronchial Hyperreactivity/
32. bronch* hyperreactivit*.mp.
33. (airway hyperresponsiveness or bronchial hyperresponsiveness or bronchial responsiveness or airway responsiveness).mp.
34. metacholine.mp.
35. methacholine.mp.
36. exp Methacholine Chloride/
37. metacholine/
38. methacholine/
39. exp Exercise Test/
40. Exercise testing.mp.
41. exp Saline Solution, Hypertonic/
42. Hypertonic Saline.mp.
43. exp Histamine/

44. Histamine/ or histamine.mp.
45. cold air challenge.mp.
46. exp Bronchial Provocation Tests/
47. exp Exercise Test/ or exp Exercise/ or exp Asthma, Exercise-Induced/ or exercise.mp.
48. exp Mannitol/
49. mannitol.mp.
50. exp Adenosine/
51. adenosine.mp.
- eucapnic voluntary hyperpnoea.mp. [mp=title, abstract, original title, name of substance word,
52. subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
53. EVH.mp.
54. isocapnic hyperventilation.mp.
55. exp Carbachol/
- carbachol.mp. [mp=title, abstract, original title, name of substance word, subject heading word,
56. keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
- 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or
57. 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
58. 14 and 57
59. 28 and 58

The following table is an explanation of the symbols used in the search strategy above.

- | | |
|-------|--|
| / | after an index term (MeSH heading) indicates that all subheadings were selected. |
| * | before an index term indicates that that term was focused - i.e. limited to records where the term was a major MeSH/Emtree term. |
| "exp" | before an index term indicates that the term was exploded. |
| .tw. | indicates a search for a term in title/abstract |
| .mp. | indicates a free text search for a term |

- # retrieves records that contain the search term with substituted character(s) in the specified location.
- * at the end of a term indicates that this term has been truncated.
- *n The limited truncation symbol, \$n, Retrieves records that contain the search term and all possible suffix variations of a root word with the maximum number of characters that may follow the root word or phrase, specified by n.
- ? in the middle of a term indicates the use of a wildcard.
- adj indicates a search for two terms where they appear adjacent to one another

Databases and information sources

Bibliographic databases
CINAHL 1982-
Embase 1980-
HMIC Health Management Information Consortium 1979
Medline 1950-
Medline in Process
Scopus
OpenSIGLE
Web of Knowledge
Science Citation Index Expanded 1981-
Social Science Citation Index 1981-
ISI Proceedings 1990-

Data Collection Form

STUDY AND COUNTRY		OBJECTIVE		STUDY DESIGN	STUDY GROUP	CONTROL GROUP		OUTCOME MEASURES		SUBJECTS (GENDER)
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR		RESULTS	NOTES	

Assessment of study quality

Quality	Scores awarded	
Selection		
1) Representativeness of the exposed cohort		
a) truly representative of the average in the community	4	
b) Somewhat representative of the average in the community	3	
c) Selected group of users eg nurses, volunteers	2	
d) no description of the derivation of the cohort	1	
2) Selection of the non exposed cohort		
a) Drawn from the same community	3	
b) Drawn from a different source	2	
c) no description of the derivation of the non exposed cohort	1	
3) Ascertainment of exposure (weeks gestation)		
a) secure record (scan +/- LMP)	3	
b) Written self report (medical assessment)	2	
c) no description	1	
4) Demonstration that outcome of interest was not present at start of study		
a) yes	2	
b) no	1	
Outcome		
1) Assessment of outcome		
a) independent blind assessment	4	
b) record linkage	3	
c) self report	2	
d) no description	1	
2) Adequacy of follow up of cohorts		
a) complete follow up all subject accounted for	4	
b) subjects lost to follow up unlikely to introduce bias	3	
c) follow up rate low and no description of those lost	2	
d) no statement	1	

Results

Description of the 18 studies included in the meta-analysis of BHR in Preterm group compared to term control group

The age of the included preterm-born subjects range from 5.8 to 22 years, birth-weight from 605g to 2800g and gestational age from 23 to 36 weeks. The year of birth ranged from 1973 to 2001. The rates of mechanical ventilation and surfactant administration varied greatly between studies. The term-born groups in general were of a similar age to the preterm-born subjects. BHR was defined as follows in the included studies: a drop in $FEV_1 \geq 9\%$, the 95th percentile of the reference population after cold air challenge; or a fall in FEV_1 of 20% or greater from baseline after methacholine challenge, or methacholine produced a $\geq 20\%$ drop in FEV_1 when compared with saline control; or a decrease in FEV_1 and/or FEF_{25-75} of 15% or more after exercise; or FEV_1 decreased by 7% or 10% or 15% or more after exercise; or drop in $FEV_1 > 8\%$ and/or $MEF_{50} > 20\%$ after exercise; or a significant fall in maximal expiratory flow rates after exercise; or the decline in FEV_1 was more than 15% after a hypertonic saline challenge.

Description of studies not included in the meta-analyses

Ten articles were not included in the meta-analysis.¹⁻¹¹ Six articles reported BHR after a methacholine challenge.¹⁻⁷

- Galdes-Sebaladt et al. Reported VLBW preterm subjects with and without hyaline membrane disease had significantly higher rates of BHR than a term group when BHR was defined as

the dose required to cause a 20% fall in FEV, and a 35% fall in specific airway conductance.

The subjects were born between 1973 to 1977 and tested between 10-13 years of age.¹ The article reported on 4 groups of subjects, groups I and II contained preterm subjects only, group III contained preterm subjects and two term subjects, and group IV contained term subjects; therefore the article was excluded as we could not include all the term and preterm subjects separately in the meta-analyses.

- Rona et al. studied the associations between variables and later BHR, there was an increased odd ratio of a positive BHR response with a gestation of <37 weeks' but it was not statistically significantly. BHR was defined as decrease in FEV₁ of 20% compared with baseline in a subjects born in 1974-1978.² The article was excluded from the meta-analyses as it reported the association of variables and later BHR, but did not report the number of subjects in the preterm group with BHR and the number of subjects with BHR in the term group.
- Lum et al. studied extremely preterm-born children (<26 weeks' gestation with a mean birthweight of 747g born in 1995 studied at 11 years of age) and reported BHR was higher in preterm-born children with BPD; but the difference between the preterm group and the term group was not significant.³ The article was excluded from the meta-analyses as it reported the PC₂₀ for preterm subjects and term subjects, but did not reported the number of children in the preterm subjects with BHR and the number of subjects in the term group with BHR.
- The authors of an article by Pike et al. supplied data to enable the article to be included in the systematic review. The data reported the relationship between foetal abdominal circumference growth and BHR, term-born children with lower abdominal growth had a significantly higher rate of BHR but this was not observed in preterm-born children, but the power is very low. The children were born between 2006-2010 and tested at 6-7 years of age.⁴ The article was excluded from the meta-analyses as we did not have the number of

subjects in the preterm group with BHR and the number of subjects in the term group with BHR.

- Three cohorts, one of which is included in the systematic review, from Norway reported significantly increased BHR in preterm-born subjects compared to term-born-subjects these subjects were extremely preterm (≤ 28 weeks' gestation or had a birth-weight ≤ 1000 g) were born between 1982-1985, 1991–1992 and 1999-2000 and tested at a mean age of 17.7, 10.6 and 11.4 years.⁵⁻⁷ We included in the meta-analyses the one article which reported the number of preterm subjects with BHR and the number of term subjects with BHR. The two excluded articles reported the dose response to methacholine, but did not reported the number of subjects in the preterm group with BHR and the number of subjects in the term group with BHR.
- Four articles reported BHR after an exercise test.⁸⁻¹¹
- Mitchell et al. reported exercise induced bronchospasm by measuring spirometry before, during and after exercise and though it was significant it was mild for preterm-born children with and without BPD. The children were studied at 6-9 years of age and had a mean gestation and birthweight of 30 weeks' and 1359g in the BPD group, 31 weeks' and 1421g in the non-BPD preterm group.⁹ We excluded the article from the meta-analyses as it reported spirometry before, during and after exercise, but did not reported the number of subjects in the preterm group with BHR and the number of subjects in the term group with BHR.
-
- Gross et al. also studied spirometry in preterm-born children < 32 weeks' gestation, mean birthweight 1173g with and without BPD compared to term-born children and reported that after exercise FEV_1 was abnormal more often in the preterm groups compared to the term groups. The children were studied at 7 years of age and were born in 1985-1985.⁸ We excluded the article from the meta-analyses as it did not report the number of subjects in

the preterm group who had BHR and the number of subjects in the term group who had BHR. The article reported spirometry.

- Joshi et al. studied preterm-born children with and without CLD and a term-born group reported that preterm-born children with CLD had significant exercise induced bronchoconstriction. The children were born at ≤ 32 weeks' gestation, with mean birthweight of 1100g in the CLD group and 1500g in the preterm group and where tested at 8-12 years of age.¹⁰ We excluded the article from the meta-analyses as it did not report the number of subjects in the preterm group who had BHR and the number of subjects in the term group who had BHR. The article reported spirometry.
- Siltanen et al. studied preterm-born children with a birth-weight $<1,501$ g born at 23-33 weeks' gestation compared to a term-born group and the changes in lung function after exercise were not significantly different. The children were born between 1987-1988 and tested at 10 years of age.¹¹ We excluded the article from the meta-analyses as it did not report the number of subjects in the preterm group who had BHR and the number of subjects in the term group who had BHR. The article reported spirometry.

Table E1
COLD AIR CHALLENGE

STUDY AND COUNTRY	OBJECTIVE		STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Von Mutius ¹² Germany	To investigate the significance of gestational age, birth weight, mechanical ventilation after birth and a family history of asthma for the development of childhood asthma in an unselected population of 9-11 year old schoolchildren		Unselected population study	Parents were asked if child was born premature had to have a birth weight ≤ 2500 g as well to be classified premature. 5030 children in total considered 253 reported being born prematurely with a birth weight ≤ 2500 g.		"Changes in FEV ₁ (in percentages) after cold air inhalation were calculated as (FEV ₁ after inhalation – FEV ₁ before inhalation) x 100 divided by FEV ₁ before inhalation. Bronchial hyperresponsiveness was defined as a drop in FEV ₁ $\geq$ -9%, the 95 th percentile of the reference population."	Premature, ventilatory support M (n = 27) F (n = 42) Premature, no ventilatory support M (n = 63) F (n = 87) Term M (n = 2241) F (n = 2333)
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
Not stated parents asked if premature had to have a birth weight ≤ 2500 g as well to be classified premature	Premature, ventilatory support % (N) M <1500 gm 33.3, 9 1500-1999 gm 22.2, 6 2000-2500 gm 44.5, 12 F <1500 gm 26.2, 11 1500-1999 gm 30.9, 13 2000-2500 gm 42.9, 18 Premature, no ventilatory support M <1500 gm 7.9, 5 1500-1999 gm 9.5, 6 2000-2500 gm 82.5, 52 F <1500 gm 8.0, 7 1500-1999 gm 12.6, 11 2000-2500 gm 79.4, 69 Term not stated	253 children were reported as preterm and 69 were ventilated (27.3%)	9-11 years Premature, ventilatory support mean SEM M 10.2 +/-0.1 F 10.1 +/-0.1 Premature, no ventilatory support mean SEM M 10.2 +/-0.1 F 10.1 +/-0.1 Term mean SEM M 10.1 +/-0.10 F 10.0 +/-0.0	Not stated	Not stated	"Cold air challenge was performed by using the RHES cold air hyperventilation provocation device (Jager). The test consisted of 4 minutes of isocapnic (5% carbon dioxide) hyperventilation (i.e., 22 X FEV ₁ /min) of dry, cold air (-15 °C, measured at the mouthpiece). Ventilatory effort was guided by a target balloon. The balloon was constantly filled with air at the predetermined rate and had to be held in a constant filling state throughout the child's respiratory effort. Lung function tests were repeated about 2 to 4 minutes after completion of the cold air provocation. Children with baseline FEV ₁ values equal to or less than 70% of the predicted value were excluded from the cold air challenge."	NS for boys between groups data not shown. For girls NS difference for BHR Premature, ventilatory support (n = 40) 10% abnormal (calculated as 4 girls) Premature, no ventilatory support (n = 78) 3.8% abnormal (calculated as 3 girls) Term (n = 2113) 6.3% abnormal (calculated as 133)

METHACHOLINE

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Todisco ¹³ Not stated but authors in Italy		To study a group of mild prematures without RDS using term born siblings as controls.	Randomly selected preterms and siblings	34 randomly selected preterms	34 siblings of preterm group	"A fall or in FEV ₁ of 20% or greater from baseline was observed in which case the child was a responder. A dose response curve was obtained and the concentration provoking a 20% fall in FEV ₁ was calculated by interpolation."	Preterms 21 males, 13 females Terms 22 males, 12 females
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
Preterms mean gestational age 34.9 weeks SD 1.1, 34-36 weeks. Terms mean gestational age 39.5 weeks SD 0.9, 38-41 weeks.	Preterms mean birthweight 1980g SD 450, 1520-2500g. Terms mean birthweight 3030g SD 475, 2540-3710g.	None had been ventilated	Preterms mean age 11.6 years SD 2.5, 8-15 years. Terms mean age 12.5 years SD 2.0, 9-15 years	Not stated	Not stated	"MCH solutions in doubling concentrations from 0.075 to 25mg/ml were used. 5 respiratory capacity breaths of each MCH concentrations were taken from a DeVilbiss 646 nebulizer attached to a dosimeter which was connected to a compressed air source at a pressure of 20PSI. 3 minutes later 2 forced expiratory manoeuvres were performed. This continued until all concentrations had been used or a fall or in FEV ₁ of 20% or greater from baseline was observed in which case the child was a responder. A dose response curve was obtained and the concentration provoking a 20% fall in FEV ₁ was calculated by interpolation, A control inhalant solution was performed."	No significant difference was observed for BHR to MCH between the groups. 4, 11.8% of preterms and 2, 5.9% of terms were hyper responsive. PC ₂₀ in preterms who responded were 1.54, 3.86, 4.5, 8.37 mg/ml. in the terms 4.51, 7.5 mg/ml.

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Schraeder ¹⁴ Not stated authors based in USA		"To determine the respiratory symptoms, pulmonary function and airway reactivity in school age survivors of very low-birth-weight and to describe the influence on BW and perinatal illness on their pulmonary function."	"Prospective longitudinal study of development"	30 VLBW <=1500g From the 30 1 Child had low FEV ₁ so was excluded and 1 could not cooperate	30 NBW peers and 15 NBW siblings of VLBW group From the 30 NBW 1 Child had low FEV ₁ so was excluded and 2 could not cooperate	"Children were rated positive if they had an FEV ₁ <=70% of predicted and responded immediately with a ≥ 15% increase in baseline after receiving albuterol, or ≥10% drop in FEV ₁ following saline control inhalation compared with the baseline recording and MCH produced a ≥ 20% drop in FEV ₁ when compared with saline control." The highest FEV ₁ was recorded total MCH tolerated were quantified as PC20 and PD20.	VLBW 13M, 17F NBW 12M, 18F Siblings 7M, 8F
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
Not stated	30 VLBW <=1500g, mean 1,193 g range 780-1,500g Both control groups >2495g	Mean days of mechanical ventilation 11.76 range 0-125	10-11 years VLBW 128m NBW 128m Siblings 134m	August 1982 and May 1983.	Not stated	"Metacholine challenge testing proceeded if the child met the following criteria: the child had a baseline FEV ₁ of at least 70% predicted, was not symptomatic for respiratory illnesses and had not takeb bronchodilators or cromolyn within the previous 24hours. The inhalation of metacholine was preceded by five inhalations with to assess the presence of a non specific airway response. MCH was delivered by a Rosenthal dosimeter system delivering compressed oxygen at 20 psi to a #646 DeVilbiss nebuliser for 0.06s. First 5 slow inhalations from FRC to TLC without breath holding. The highest FEV ₁ following saline inhalation was considered the control value. 3 mins after saline and each MCH inhalation the patient performed 3 spirometry manoeuvres. The highest FEV ₁ was recorded. Total MCH doses tolerated were quantified as PC20 and PD20. Challenge was discontinued when there was a 20% or greater drop in FEV ₁ as compared with saline control or all ten steps had been completed."	VLBW (means,SD) PC20 mg/ml 11,9.8 PD20 BUs 82,80.6 Total Dose BUs 141,92.2 % change in FEV ₁ 21,13.3 NBW PC20 BUs mg/ml 14, 10.4 PD20 BUs 105, 90.4 Total Dose 173, 81.9 % change in FEV ₁ 17,13.3 Siblings PC20 mg/ml 16, 9.5 PD20 BUs 143, 77.6 Total Dose BUs 181, 80.1 % change in FEV ₁ 19,10.5 NS Responders 62% VLBW 54% NBW peers 53% Siblings

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Rona ² Chile		“There is uncertainty about the impact of the programming hypothesis in terms of nutritional status at birth, rate of growth in the first in the first year of life, length of gestation, breast feeding and episodes of illness on asthma. An analysis was therefore carried out to test this hypothesis.”	“Non-concurrent prospective study”	1232 subjects in total, approximately 10% had a gestation of <37 weeks		“A decrease in 20% compared with baseline FEV ₁ at any concentration up to 16mg/ml (PC ₂₀) was considered a positive BHR.”	In total cohort 556M 676F.
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
Not stated	In whole cohort with measurement Males mean (SD) 3226g (491) Women 3160g (503)	Not stated	Study carried out in 2001 to 2003.	1974-1978	Not stated	BHR challenge to MCH was assessed using the tidal breathing methodology. Increasing concentrations of 0.5, 1.0, 4, 8 and 16mg/ml were used with a Hudson nebuliser at a flow rate of 0.13 l/min over a period of 2 mins. FEV ₁ was measured. A decrease in 20% compared with baseline FEV ₁ at any concentration up to 16mg/ml (PC ₂₀) was considered a positive BHR.” Excluded FEV ₁ below 70%, heart conditions, epilepsy, current pregnancy or BF.	Association between variables at birth, socioeconomic factors, and smoking and BHR and atopy by polytomous regression analysis (n=1213) length of pregnancy <37 weeks positive BHR OR (95%CI), p value 1.24 (0.61,2.51) 0.551. length not known 0.93 (0.56,1.53)0.764 NS

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Lum ³ UK and republic of Ireland		“To ascertain whether ongoing respiratory morbidity in EP children born in 1990s primarily reflects alterations in the lung periphery.”	“Population based study”	49 extremely preterm EP with BPD n=34 EP without BPD n=15	52 control term born classmates	PC20	EP with BPD n=34 35% M EP without BPD n=15 40% M All EP n=49 37%M Control n=52 37% M
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
EP ≤ 25 weeks +6 days EP with BPD mean (SD) 24.8±0.8 EP without BPD 25.0±0.6 All EP 24.9±0.7 Control 40.1±1.6	EP with BPD mean (SD) 0.740±0.101 EP without BPD 0.762±0.093 All EP n=49 0.747±0.098 Control 3.361±0.450	Not stated	11 years Adjusted for prematurity EP 10.9 vs controls 11.0. EP with BPD mean 11.2 SD 0.4 EP without BPD 11.2 (0.5) All EP n=49 11.2 (0.4) Control 11.0 (0.5)	March-December 1995	Not stated	Methacholine challenge all LFTs were performed according to ATS/ERS standards.	“Airway hyperresponsiveness abnormalities were most marked in EP with BPD.” PC20 mgmL-1 mean (SD) EP BPD mean 0.41 (SD2.9) EP no BPD 0.39 (2.64) EP 0.41 (2.75) Control 1.72 (5.31) 95% CI of difference (EP–control)0.12-0.46 not sign

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Korhonen ¹⁵ Finland		"To assess respiratory outcomes and its predictors during the surfactant era in very-low-birthweight <1500g school children with and without BPD."	Cohort study	34 VLBW <1500g with BPD 25 completed MCH 34 VLBW <1500g without BPD 29 completed MCH	34 term children 30 completed MCH	"FEV ₁ was used to determine the response. MCh was terminated when FEV ₁ fell by at least 20% of the post-saline value. The fall in FEV ₁ was plotted against the dose of metacholine on a log scale and the dose provoking a 20% fall in FEV ₁ (PD ₂₀) calculated. Children who did not reach a 20% fall in FEV ₁ after the highest cumulative dose of metacholine were coded with a PD ₂₀ value of 7500 ug. Bronchial hyper-reactivity was analysed using two cut-off points: 2610 ug (BHR) and 810ug (BHR ₈₁₀)."	BPD n = 34 male n(%)21 (62%) sBPD subgroup n = 14 10 (71%) No-BPD n =34 21 (62%)
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
BPD n = 34 mean 27 (SD2) [range23–30] sBPD subgroup n = 14 28 (2) [23–30] No-BPD n =34 29 (2) [25–35] Term controls n=34 40 (1)	BPD n = 34 mean 951 SD (207) range [570–1300] sBPD subgroup n = 14 893 (225) [570–1300] No-BPD n =34 1132 (235) [605–1490] Term controls n=34 3597 (498)	BPD n = 34 male n(%) 32 (94%) median 27 days range 0-89 sBPD subgroup n = 14 13 (93%) median 45 (0-89) No-BPD n =34 23 (68%) median 3 (0-44)	7-8 years The BPD, no-BPD and term children were examined at median (range) ages of 7.1 (6.7–7.8), 7.1 (6.9–8.1) and 7.2 (6.9–8.3) y, respectively	1990-1994	BPD n = 34 male n(%)14 (41%) sBPD subgroup n = 14 4 (29%) No-BPD n =34 8 (24%)	"MCh was performed using a dosimeter technique with controlled tidal breathing. An automatic, inhalation synchronized dosimetric jet nebulizer (Spira Electro 2, Respiratory Care Center,Finland) was adjusted to nebulize for 0.5 s from the beginning of each inhalation. After nebulization of saline solution, metacholine was delivered in five cumulative doses of 18, 72, 270, 810 and 2610 ug at intervals of about 5 minutes. FEV ₁ was used to determine the response. MCh was terminated when FEV ₁ fell by at least 20% of the post-saline value. The fall in FEV ₁ was plotted against the dose of metacholine on a log scale and the dose provoking a 20% fall in FEV ₁ (PD ₂₀) calculated. Children who did not reach a 20% fall in FEV ₁ after the highest cumulative dose of metacholine were coded with a PD ₂₀ value of 7500 ug. Bronchial hyper-reactivity was analysed using two cut-off points: 2610 ug (BHR) and 810 ug (BHR ₈₁₀).	Higher rate of BHR was detected in both groups of VLBW children compared to term controls. PD ₂₀ (ug) Median (range) BPD 270 [33–7500] NO BPD 357 [16–7500] controls 953 [46–7500] p=0.006 </=2610 BPD n=24 (96%) no BPD n= 26 (90%) controls n=21 (70%) p=0.020 </=810 BPD n=20 (80%) no BPD n= 23 (79%) controls n= 14 (47%) p=0.008

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN	STUDY GROUP		CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Galdes-Sebaldt ¹ USA		“To evaluate the long term effect of prematurity and/or HMD on pulmonary function and airway reactivity.”	Cross sectional	49 PT Group 1 19 <1500g no HMD Group 2 11 <1500g HMD Group 3 19>1500g HMD 41 had MCH		27 age matched controls born at term 22 controls had MCH	The dose required to cause a 20% fall in FEV ₁ (PC ₂₀ FEV ₁) and a 35% fall in specific airway conductance (SGaw)(PC ₃₅ ,SGaw) was calculated by interpolation from the loglinear dose response curve	Group 1 11M 8F Group 2 3M 8F Group 3 11M 8F Term 14M 13 F
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS	
Group 1 mean 29.3 SEM 0.4 Range (26-32) Group 2 29.5 0.6 (26-32) Group 3 34.7 0.4 (32-38) 1was born at 37 weeks and 1 was born at 38 weeks Term 39.9 0.2 (38-42)	Group 1 mean 1,044 SEM 30 Range (900-1,290) Group 2 1,217 34 (964-1,361) Group 3 2,446 111 (1,644-3,487) Term 3,429 64 (2,707-4,111)	Positive pressure ventilation was required in 13, 9 and 3 children in groups 1,2 and 3 respectively.	10-13 years Group 1 mean 11.1 SEM 0.2 Group 2 11.2 0.2 Group 3 11.7 0.1 Term 11.6 0.2	Jan 1973- Dec 1977	Not stated	“A baseline FEV ₁ of at least 70% of predicted normal values was required. Triplicate measurements of airway conductance were made in a constant volume body plethysmograph (Warren E. Collins, Inc., Braintree, MA), and duplicate forced vital capacity maneuvers were successively performed after completion of each MCh inhalation. Inhalations of doubling concentrations of MCh solutions (from 0.3 to 40 mg/mL) were used at 5 minute intervals, each dose taken in five successive breaths inhaled from FRC to TLC. A nebulizer (model 646, De-Vilbiss) was connected to a dosimeter (Rosenthal-French Nebulization dosimeter, model 2A, Laboratory for Applied Immunology, Inc., Baltimore, MD) which nebulized MCh solution for 0.5 seconds. The MCh challenge was stopped when the maximum concentration was reached or when a 20% decrease in FEV ₁ was obtained. The dose required to cause a 20% fall in FEV ₁ (PC ₂₀ FEV ₁) and a 35% fall in specific airway conductance(SGaw)(PC ₃₅ SGaw) was calculated by interpolation from the loglinear dose response curve.	“Airway reactivity was significantly increased in Groups I and II. A 20% drop in FEV ₁ after MCh challenge was found in 88%, 62%, 53%, and 36% of children in Groups I, II, and III and controls, and a 35% drop in SG, occurred in 87%, 88%, 53%, and 59%.” “Figures illustrate the response of each subject to MCh inhalation. There was a significant difference between the PC ₂₀ FEV ₁ of Groups 1 and IV. When responsiveness was assessed by the PC ₃₅ ,SGaw, both Groups I and 2 were statistically significantly more reactive than the control group. One subject each in Groups I and 2 had an FEV ₁ that precluded methacholine challenge; neither of these children responded to bronchodilators.”	

STUDY AND COUNTRY		OBJECTIVE		STUDY DESIGN		STUDY GROUP		CONTROL GROUP	OUTCOME MEASURES		SUBJECTS (GENDER)
Kotecha ¹⁶ UK		“To compare lung function at 8-9 and 14-17 years in children born late preterm (33-34 and 35-36 weeks gestation) with children of a similar age born at term.”		Population based cohort		Number of children who had spirometry at 8-9 or 14 -17 years 78 25-32 weeks 33 had Mch 88 33-34 weeks 47 had Mch 269 35-36 weeks 158 had Mch		Number of children who had spirometry at 8-9 or 14 -17 years 6979 terms 4123 had Mch	“The challenge ended when the maximum dose was reached (non-responders to the challenge), or when FEV ₁ fell by 20% or more from the baseline reading (responders to the challenge).”		25-32 weeks 48M (62%), 33-34 weeks 54M (61%), 35-36 weeks 144M (54%), Term 3446M (49%)
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)		AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR		RESULTS		
25-32 weeks Mean 29.7 SD 2.0 33-34 weeks Mean 33.6 SD 0.5 35-36 weeks mean 35.7 SD 0.5 Terms mean 39.7 SD 1.3	25-32 weeks Mean 1437g SD 439.5 33-34 weeks Mean 2449g SD 416.8 35-36 weeks mean 2634 SD 424.7 Terms mean 3478g SD 476.6	25-32 weeks 59/78 76% 33-34 weeks 15/88 17% 35-36 weeks 2/269 1% Terms 12/6979 0.2% For those ventilated 25-32 weeks 245 hours range 1-1416 33-34 weeks Mean 77 days range 9-168 35-36 weeks mean 15 days range 8-22 Terms mean 107 hours range 1-576		8-9 years 25-32 weeks Mean 8.7 SD 0.4 33-34 weeks Mean 8.6 SD 0.3 35-36 weeks mean 8.7 SD 0.3 Terms mean 8.6 SD 0.3	1990S	25-32 weeks 35/78 44.9% 33-34 weeks 6/88 6.8% 35-36 weeks 0 Terms 1/6979 0.01%	“A bronchial challenge test with metacholine using the method of Yan et al. Children unselected for asthma status or wheezing had a bronchial challenge test with methacholine using the method of Yan and others. No selection criteria were applied other than not performed on those with a FEV ₁ as percentage for height <70%, cold in past 3 weeks, or refusal to do it/technical failure of test. During the methacholine challenge the children inhaled methacholine solutions from hand-operated nebulisers that were individually calibrated for each tester (De Vilbiss Co. Pennsylvania, USA). Initially each child inhaled normal saline and the FEV ₁ measurement taken one minute later was used as the baseline for the challenge. The children then inhaled eight doses of methacholine, from 0.048 to 6.1µmol, at 60 second intervals. The doses doubled each minute and FEV ₁ was measured a minute after each dose, just before the next dose was given. The challenge ended when the maximum dose was reached (non responders to the challenge), or when FEV ₁ fell by 20% or more from the baseline reading (responders to the challenge).”		“No significant differences were found between the different gestation groups for the geometric mean provocative dose of metacholine causing a fall in FEV ₁ of 20% or more (PD ₂₀) in either responders or the whole study population.” Number (%) who responded to methacholine challenge 25-32 weeks 9 (27.3%) 33-34 weeks 9 (19.1%) 35-36 weeks 22 (13.9%) term 646 (15.7%) Geometric mean PD ₂₀ in responders (µmol) 25-32 weeks 1.20 (0.43, 3.35) 33-34 weeks 2.25 (1.08, 4.70) 35-36 weeks 2.27 (1.50, 3.42) term 1.71 (1.57, 1.87) Geometric mean PD ₂₀ for the whole population who underwent the challenge (µmol) 25-32 weeks 6.46 (4.15, 10.04) 33-34 weeks 8.86 (7.08, 11.09) 35-36 weeks 9.62 (8.65, 10.69) term 8.96 (8.73, 9.19)		

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN		STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Landry ¹⁷ Canada		"To describe quality of life, pulmonary lung function, BHR, body composition, and trends in physical activity of adults born prematurely with or without respiratory complications."	Cohort study		26 PT subjects with no neonatal respiratory complications 26 had Mch, 31 PT subjects with neonatal RDS but without BPD 29 had Mch, 31 preterm subjects with BPD 21 had Mch	35 term 33 had Mch	"the PC ₂₀ (provocative concentration of methacholine causing a 20% fall in FEV ₁) was calculated using a logarithmic interpolation equation"	BPD 11M 35% RDS 18M 58% PT 6M 23% Term 11M 31%
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS	
BPD mean 192d SD 18 RDS mean 224d SD 25 PT mean 230d SD 23 Term mean 277d SD 10	BPD mean 1.06KG SD 0.37 RDS mean 1.96KG SD 0.78 PT mean 2.17KG SD 0.8 Term mean 3.45KG SD 0.42	Not stated	21-22 years of age BPD mean 22 years SD 2 RDS mean 21 SD 2 PT mean 22 years SD 2 Term mean 22 years SD 2	1987-1993	Not stated	"Metacholine challenge tests were performed by a qualified technician using the 2-minute tidal breathing dosing protocol (according to ATS guidelines)). Spirometry was performed with an Easy on-PC spirometry sensor (nidd Medical, Zurich, Switzerland). A diluent step (normal saline) was done before the first dose of methacholine was administered. Postdiluent FEV ₁ was used as the reference for the challenge. When participants had no history of asthma and/or symptoms and had a normal FEV ₁ , the first dose of methacholine administered was 0.25 mg/ml. To ensure safety, the test was not performed if FEV ₁ at baseline or postdiluent was lower than 60% predicted and was supervised by a doctor if it was between 60 and 70%. The test was stopped when a 20% fall in FEV ₁ was observed or after the highest concentration. Salbutamol (200 mg) was administered if there was a fall of 10% or more in FEV ₁ or if the participant had any symptoms. When applicable (fall of 20% or greater in FEV ₁) and as recommended by the ATS, the PC ₂₀ (provocative concentration of methacholine causing a 20% fall in FEV ₁) was calculated using a logarithmic interpolation equation."	"All PT groups had a high prevalence of BHR compared term subjects. BPD 71% had evidence of BHR. This was not significantly different from results for the RDS group and the PT group with 62 and 69% respectively although 25% of the subjects with BPD couldn't undergo the challenge because of an FEV₁ that was less than 60%." PC₂₀, mean (mg/ml) (SD) BPD 2.68 (2.72) RDS 2.54 (2.85) PT 3.65 (3.15) Term 4.11 (3.76) p value 0.369 PC₂₀<8 mg/ml, n (%) BPD 15 (71) RDS 18 (62) PT 18 (69) Term 15 (45) p value 0.169	

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Ijsselstijn ¹⁸ The Netherlands		To evaluate the long term pulmonary sequelae in CDH.	Matched study	40 CDH. From data sent we have 20 prems mean gestation 35 weeks range 29-36 weeks.	65 age matched controls without CDH. From data sent have 68 controls mean gestation 39.8 weeks range 37-43	"FEV ₁ was measured in triplicate after each dose-step until the best value had fallen from baseline by at least 20%. The provocative dose that resulted in a 20% fall in FEV ₁ (PO ₂₀) was calculated by interpolation of the dose-response curve on a loglinear scale."	CDH 21/38 M Control 44/65 M
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
20 prems mean gestation 35 weeks range 29-36 weeks. 68 controls mean gestation 39.8 weeks range 37-43	CDH median 3275g range 1-4.3kg Control 2950g (range 1.25-4.2kg)	CDH median 4d range 0-49 Control 4.3 (range 0-25)	7 to 18 years CDH median 11.7 range 7.4-17.8 Control 12.1 (range 7.7-18.2)	1975-1986	Not stated	"Inhalation provocation was carried out with aerosolized methacholine bromide and sodium metabisulfite (Na ₂ S ₂ O ₅ , buffered to pH 7.4 by adding phosphate buffer). MCH was given in doubling concentrations of 0.15 to 39.2 mg/ml, MBS in doubling concentrations of 2 to 256 mg/ml. The aerosols were generated by a calibrated De Vilbiss 66 Nebulizer (De Vilbiss Co., Somerset, PA), with closed vent, attached to a French-Rosenthal dosimeter (Laboratory for Applied Immunology, Baltimore, MO) driven by air at 138kPa. The children were instructed to inspire slowly and as deeply as possible. During inspiration the dosimeter was triggered for 0.6 s. After full inspiration, breath was held for 5 s. A total of 20ul of aerosol was delivered to the mouth in 4 consecutive breaths. Mouth doses were 3 to 784 ug for MCH, and 40 to 5,120 ug for MBS. Provocations with MCH and MBS were preceded by inhalation of normal saline. The interval between consecutive doses was 3 min. FEV ₁ was measured in triplicate after each dose-step until the best value had fallen from baseline by at least 20%. The provocative dose that resulted in a 20% fall in FEV ₁ (PD ₂₀) was calculated by interpolation of the dose-response curve on a loglinear scale."	Results obtained from authors. From data sent 6/20 (30%) of preterms responded to MCH the mean PD ₂₀ of responders is 157.33. 34/68 of controls responded (50%) mean PD ₂₀ of responders is 173.0294 From the children without CDH 5/18 of preterms responded to MCH 17/38 of controls responded to MCH

STUDY AND COUNTRY		OBJECTIVE			STUDY DESIGN		STUDY GROUP CONTROL GROUP		OUTCOME MEASURES		SUBJECTS (GENDER)	
Pike ⁴ UK		“The influence of developmental programming on bronchial hyperreactivity is investigated in an animal model and evidence for comparable associations is sought in humans. In a human mother-child cohort ultrasound measurements of fetal growth were related to bronchial hyperreactivity, measured at age six years using methacholine.”			Human mother-child cohort		Excluded children <35 weeks gestation. 246 children had methacholine challenge. Information supplied by authors.		“Challenges were terminated following a 20% fall in the FEV ₁ or, if this did not occur, following the 16 mg/ml dose. BHR was expressed as the inverse of the slope of the regression line through FEV ₁ drop and logged methacholine concentration such that lower inverse log slope values indicate increased BHR”		Not available	
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR			RESULTS			
Excluded children <35 weeks gestation	Not stated	Not stated	6-7 years	Not stated tested between 2006 and 2010	Not stated	“Bronchial hyperreactivity was measured by bronchial provocation challenge, according to ATS/ERS guidelines. Incremental methacholine concentrations (0.06 mg/ml to 16 mg/ml) were delivered using a dosimeter (Koko; PDS Instrumentation; Louisville, USA) and a compressed air driven nebulizer (SidestreamH; Respironics, UK). Challenges were terminated following a 20% fall in the FEV ₁ or, if this did not occur, following the 16 mg/ml dose. BHR was expressed as the inverse of the slope of the regression line through FEV ₁ drop and logged methacholine concentration such that lower inverse log slope values indicate increased BHR.2			“Children with lesser abdominal circumference growth during 11–19 weeks’ gestation had greater bronchial hyperreactivity than those with more rapid abdominal growth.” From authors:- “I have replicated the significant association reported in our paper between lower abdominal growth and greater BHR. This is significant in those greater than or equal to 37 weeks (our reported result was for greater than or equal to 35 weeks). It is not found less than 37 weeks but the power is very low.”			

STUDY AND COUNTRY	OBJECTIVE		STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Halvorsen ⁵ Norway	"Asthma-like symptoms and airway hyper-responsiveness are frequently reported in children subsequent to premature birth and BPD. There is limited knowledge on the mechanisms underlying these respiratory manifestations. Generally, childhood asthma and AHR is described within a context of inheritance, allergy and eosinophilic airway inflammation, and often in relation to cigarette exposures. We investigated these factors in relation to current asthma and AHR."		Population based cohort	81 gestational age ≤ 28 weeks or birthweight ≤ 1000g PT BPD Non (n = 19) Mild (n = 38) Moderate-severe (n = 24) 7 PT did not have challenge.	Matched term population of same gender with birthweight between 3 and 4kg. 2 controls did not have challenge.	"A dose-response slope (DRS) was calculated as the ratio between the maximum percentage decline in FEV₁ from baseline and the total administered dose of methacholine (in umol) when the test was terminated (%/umol)). The DRS was log₁₀ transformed (logslope) for statistical analysis."	Number of females (% of group) Controls 42 (52) PT BPD Non 12 (63) Mild 20 (53) Moderate-severe 10 (42)
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
PT 27.1 (SD 1.6) weeks PT BPD Non 28.3 (1.5) Mild 26.8 (1.4) Moderate-severe 26.4 (1.4)	PT 979 (SD 200) g Terms 3494 (300)g PT BPD Non 1115.1 (158.5) Mild 981.0 (200.2) Moderate-severe 868.8 (166.0)	Days with ventilator treatment (range) PT BPD Non 0.5 (0–4.8) Mild 7.2 (0–40.0) Moderate-severe 13.8 (0.7–54.5)	First birth cohort mean 17.7 (SD 1.2) years Second birth cohort mean 10.6 (SD 0.4) years	1982–1985 (first birth-cohort) and 1991–1992 (second birth-cohort).	Not stated	"Methacholine provocation test (PD₂₀) was performed with an inhalation-synchronised, dosimetric nebulizer, Spira Elektra 2 (Respiratory Care Centre, Hameenlinna, Finland), providing baseline FEV₁ $\geq 65\%$ predicted. Methacholine chloride was administered in doubling doses until a 20% reduction in FEV₁ was obtained, or until a final cumulative dose of 22.3 umol had been given. A dose-response slope (DRS) was calculated as the ratio between the maximum percentage decline in FEV₁ from baseline and the total administered dose of methacholine (in umol) when the test was terminated (%/umol)). The DRS was log₁₀ transformed (logslope) for statistical analysis."	Airway hyperresponsiveness was substantially increased in the preterm population compared to the term population. DRS to methacholine (95% CI) expressed as geometric means (95% CI). Controls 1.6 (1.1, 2.3) PT BPD Non 3.9 (1.7, 9.2) Mild 5.9 (3.0, 11.8) Moderate-severe 15.6 (6.6, 36.9) PT 7.0 (4.5,11). Between PT and terms p<0.001. "Within the pre-term population, there was a significant trend for increased methacholine responsiveness parallel to more severe neonatal BPD. FEV₁ decreased 20% from baseline at a cumulative dose of <1.0 umol methacholine in 67% of pre-terms with moderate/severe BPD, in 32% of pre-terms with mild BPD, in 26% of pre-terms without BPD and in 8% of control subjects."

STUDY AND COUNTRY	OBJECTIVE		STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Vollsaeter ⁶ Norway	“Compare respiratory health in children born extremely preterm (EP) or with extremely low birthweight (ELBW) nearly one decade apart, hypothesizing that better perinatal management has led to better outcome.”		Population based controlled longitudinal studies	57 children <28 weeks gestation or <1000g Non BPD 26 BPD 31	54 Matched term controls >37 weeks birthweight >3000g	The test continued until a fall of 20% or more compared to baseline FEV ₁ , or until the maximum dose of 11.5 µmol methacholine. Dose-response slope (DRS) was calculated as the ratio of maximum percentage decline in FEV ₁ from baseline to cumulative administered dose of methacholine (%/µmol).”	Control 25 F PT 28 F Non BPD 16 F BPD 12 F
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
Control >=37 weeks PT 26.8 SD 1.6 Non 27.3 (1.6) BPD 26.3 (1.4)	Control mean 3701 SD (434) PT 850 (175) Non 873 (200) BPD 831 (151)	PT Median 5.0 RANGE (0-24) Non 2.5 (0-21) BPD 8.0 (0-24)	Control mean 11.7 SD (0.7) PT 11.4 (0.6) Non 11.4 (0.6) BPD 11.5 (0.6)	1999-2000	PT 49/56 Non 20/25 BPD 29	“Methacholine provocation was performed with an inhalation-synchronised dosimetric nebulizer (Spira Electra, Finland), providing baseline FEV ₁ ≥ 65% predicted.. The test continued until a fall of 20% or more compared to baseline FEV ₁ , or until the maximum dose of 11.5 µmol methacholine. Dose-response slope (DRS) was calculated as the ratio of maximum percentage decline in FEV ₁ from baseline to cumulative administered dose of methacholine (%/µmol).”	EP1999–2000 had more bronchial hyperresponsiveness to methacholine (dose-response-slope 13.2 vs. 3.5; p<0.001). higher DRS from the methacholine challenge than terms. Controls DRS Geometric Mean 3.47 (2.19, 5.50) All EP 13.18 (8.16,21.37) EP non BPD 11.48 (5.75, 23.44) EP BPD 14.79 (7.24,29.51)

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Halvorsen ⁷ Norway		To determine respiratory health and lung function status in a population-based, complete cohort of young preterms approaching adulthood	Population based cohort	46 preterms with gestational age ≤ 28 weeks or birthweight ≤ 1000 g 5 could not perform challenge	46 Term born with a birthweight between 3-4kg	"Criterion for positive test was a decline in FEV1 $\geq 20\%$ from baseline at a cumulative dose of ≤ 6.6 umol methacholine. A dose response slope was calculated."	Preterm 21/46 Terms 21/46
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
Preterm mean 27.3 SD 1.4	Preterm mean 1014g SD 195g Terms 3-4kg Mean 3441g SD 311g	Duration of ventilator treatment; d, median (range) Non BPD 0.4 (0–4.8) Mild BPD 8.6 (0.8–35.0) Mod/Severe BPD 25.4 (0.7–54.0)	Mean age 17.7 SD 1.2 years	1982-1985	Not stated	"Bronchial responsiveness to methacholine (PD ₂₀) was determined, providing baseline FEV ₁ $\geq 65\%$ predicted, using an inhalation-synchronized, dosimetric nebulizer, Spira Elektra 2 (Respiratory Care Centre, Hameenlinna, Finland). Criterion for positive test was a decline in FEV1 $\geq 20\%$ from baseline at a cumulative dose of ≤ 6.6 umol methacholine. A dose response slope was calculated."	"Fifty-six percent of preterms had a positive methacholine provocation test compared to 26% of controls." 12/46 controls 23/41 preterms

STUDY AND COUNTRY	OBJECTIVE		STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Kaplan ¹⁹ Israel	“To determine the long-term pulmonary outcome of extreme prematurity at a single tertiary care centre”		cohort	28 BPD 25 without BPD	23 Terms	“Provocative concentration of methacholine required to decrease FEV ₁ by 20%.”	All PT 26M 49.1% BPD 53M 53.6%, No BPD 11M 44% Controls 13M 56.5%
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
All PT born ≤28 weeks mean (SD) 26.7 weeks +/- 1.3 BPD 26.2 +/- 1.4 weeks; No BPD 27.2 +/- 1 weeks 23 term control subjects ≥37 week 39.8 +/- 1.38.	All PT mean (SD) 930 +/- 205 BPD 821 +/- 164 g No BPD, 1,050 +/- 181 g Term were all ≥ 2500g 3230 +/- 413	PT median 4 range 0-48 BPD 13 (0-48) non BPD 2 (0-9)	ALL PT mean (SD) 10 +/- 1.5 years All PT 10 +/- 1.5 BPD 9.7 +/- 1.7, No BPD 10.3 +/- 1.4 Control s 9.9 +/- 1.2	1997-2001	44/53 83% PT received postnatal surfactant. BPD 24/28 85.7%, non BPD 20/25 80%	“Methacholine challenge tests were done using a KoKo spirometer with dosimeter (Pds Instrumentation Inc) and triple doses of fresh methacholine solutions in saline by ATS recommendations, ending when FEV ₁ dropped to ≥ 20% or when a methacholine conc of 13.9 mg/ML was reached. Airway hyperreactivity (AHR) was defined as provocative concentration of methacholine required to decrease FEV ₁ by 20% PC ₂₀ <4 mg/mL, and severe AHR was defined as PC ₂₀ < 1 mg/mL. MCT was not performed if baseline FEV ₁ was ≤ 70%.”	“For preterm and control Subjects, respectively (mean +/- SD), and PC ₂₀ was 6.5 +/- 5.8 mg/mL and 11.7 +/- 5.5 mg/mL (P < 0..001). BPD 5.9 +/- 6.1 Non BPD 6.9 +/- 5.6 “PC ₂₀ was < 4 mg/mL in 49% of preterm subjects despite normal exhaled nitric oxide. For the MCT (n =66), AHR (PC ₂₀ < 4 mg/mL) was found in 21 of 43 preterm subjects (49%) and in only five of 23 control subjects (22%) (P= .04). A PC ₂₀ < 1 mg/mL, which defined a more severe reaction, was found in nine of 43 preterm subjects (21%), as follows: seven of 20 (35%) in the BPD group (three of four [75%] with moderate BPD), two of 23 (9%) in the non-BPD group, and only one of 23 control subjects (4%). This finding highlights the prevalence of noteworthy AHR in the children with BPD (P < .02).”

EXERCISE

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Ronkainen ²⁰ Finland		Aim was to investigate whether preterm birth BPD and severity of BPD predict lung function in school children born in the surfactant era.	Prospective birth cohort	88 children <32 weeks gestation 1 child failed EIB test	88 term ≥ 37 weeks gestation children matched for age and sex	"EIB was diagnosed if f FEV ₁ declined by at least 15%".	Preterms male 47 (53%) terms male 47 (53%)
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
Preterms mean (SD) 28.8 weeks +/-2.1 Terms 39.9 +/- 1.2	Preterms mean (SD) 1133g +/- 409 Terms 3574g +/- 514	Preterms duration of respirator therapy mean (SD) 9 +/- 13.2	6-14 years Preterms mean (SD) 10.9 +/- 1.4 Terms 11.6 +/- 1.7	November 1997 to October 2003	Preterm 56 given surfactant	"Exercise test according to ERS Task force guidelines in a standardized setting by a free run test. EIB was diagnosed if FEV ₁ declined by at least 15%."	EIB diagnosed in (2) 2% of preterms and (3) 3% of terms NS. Change in FEV ₁ after ET Preterms mean (SD) -2.8 (8.3) Terms -0.3 (5.1) NS

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN		STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Mitchell ⁹ USA		To test if “school-age children who survive BPD may have a permanent reduction in alveolar surface area that could limit gas transfer both at rest and during exercise.”	Cross sectional		10 BPD 10 preterm non BPD	10 healthy children	FEV ₁ before during and after exercise	BPD 7M 3F preterm non BPD 6M 4F healthy children 4M 6F
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS	
BPD mean 30 SD 5 preterm non BPD mean 31 SD 3 healthy children mean 40 SD 1	BPD mean 1359 SD 1041 preterm non BPD mean 1421 SD 411 healthy children mean 3157 SD 606	Not stated	6-9 years BPD mean 7 SD 1 preterm non BPD mean 7 SD 1 healthy children mean 7 SD 1	Discharged from NNU 1985, 1986, 1987	Not stated	“Measured pulmonary function, heart rate, SaO ₂ , and intra-breath gas transfer at 3-min intervals with the subjects at rest, during moderate exercise on a treadmill, and during recovery from exercise. In this way, each subject attempted the intrabreath maneuver once before exercise, twice during exercise at 1 to 3 min (acute) and at 6 to 12 min (steady state), and three times (at 3, 9, and 12 to 15 min) during recovery from exercise. Subjects exercised in an air-conditioned in-door laboratory with a mean ambient temperature of 20+/- 2 (SD) ⁰ C and barometric pressure of 737+/- 9 mm Hg. The subjects walked or ran on a treadmill via the modified Bruce protocol in which the treadmill speed and incline were increased in four 3-min intervals, progressing to a 16-degree incline at 4.2 miles per hour in the final interval. We discontinued the exercise phase of the protocol if the subjects reached a 12-min endurance limit or sooner if they complained of exhaustion and were unable to continue the protocol despite verbal coaching. The endurance time was the elapsed time from the start to the stop of the exercise phase. During recovery from exercise, we continued pulmonary function measurements for up to 20 min before ending the study. “	“Exercise induced bronchospasm though statistically significant was mild with a mean decrease in FEV ₁ from pre exercise of 9 +/-7% (p=0.003) for BPD, 8 +/- 7% (p=0.006) for preterms.” FEV1(% pred) mean SD BPD Pre-exercise 78+/- 21 Exercise 80 +/- 8 Recovery 69+/- 18- Premature Pre-exercise 85+/- 15 Exercise 90 +/- 19 Recovery 77+/- 18 Term Pre-exercise 91 +/- 14 Exercise 84 +/- 23 Recovery 86 +/- 17	

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
McLeod ²¹ Scotland		"To compare the respiratory health and function at 8-9 years of age of a total population based cohort of 300 VLBW children with controls matched for age and sex."	Population based cohort	300 VLBW children <1500g	590 classroom controls matched for age and sex 2 per index child	"The prevalence of exercise induced airways narrowing (EIAN) was assessed by the number of children experiencing a 10% or more fall in FEV ₁ after five minutes of free range running. The risk of EIAN in the VLBW population compared with the controls was estimated by the odds ratio (OR) with approximate CI and adjusted for confounding variables using logistic regression."	VLBW girls 153 (51%) Controls girls 298 (51%)
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
Not stated	<1500g VLBW	Artificial ventilation (days) None 134 1-6 66 7-27 57 28+ 34	8-9 years Mean age for both groups 8.8 years SD 0.3	1984	Not stated	"FVC and FEV ₁ were measured on 3 occasions; at baseline, and again at 5 and 10 minutes after 5 minutes of running exercise according to the protocol of Strachan. The period of exercise took place in most settings within a school corridor or gymnasium, but on a few occasions had to be done outside because of pressure of space. Each measurement recorded was the best of three attempts (based on the greatest sum of FVC and FEV ₁) achieved by the child, wearing a nose clip. The mean (SD) ambient temperature recorded at the time of lung function measurement was 21.0 (2.2)°C (minimum 15.0)."	"Exercise induced narrowing was increased in VLBW children. A total of 30 (10%) VLBW and 31 (5%) control children experienced a 10% or more decrease in FEV ₁ after the exercise period, a significantly increased prevalence of EIAN in the VLBW population (OR=2.0; 95% CI 1.2 to 3.4). To correct for these factors, logistic regression was carried out adjusting for whether or not the child was currently using an inhaler and whether or not the child's mother smoked. Adjusting for inhaler use, which was significantly associated with EIAN, the odds ratio for the VLBW population became 1.9 (95% CI 1.1 to 3.3). Adjusting for any smoking or heavy (>20/day) smoking resulted in a negligible increase in the odds ratio for the VLBW population."

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN		STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Kriemler ²² Canada		"This study intended to identify pulmonary and exercise-related effects of CLD versus prematurity without CLD in 5-7 year old children who were born at 24-30 weeks gestation with a birthweight of 500-1500g"	cohort		17 CLD 1 child excluded from analysis of EIB 14 prematurity without CLD 2 children excluded from analysis of EIB	24 term controls >2500g. 1 child excluded from analysis of EIB	"EIB was defined as a decrease in FEV ₁ and/or FEF ₂₅₋₇₅ of 15% or more at any time up to 10 minutes post exercise."	CLD 7M 10F Premature 8M 6F Control 15M 9F
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS	
CLD mean 27.1 SD 1.9 Premature mean 28.3 SD 1.7 Control term	CLD mean 970g SD 285 Premature mean 1108 SD 202 Control mean 3455 SD 595	CLD had longer ventilation and O ₂ supplementation of 40% or more (30.3 +/- 19.4 vs 9.2+/-8)	5-7 year old CLD 5.8-7.0 Premature 6.1-7.8 Control 5.5-7.4	1988-1990	Not stated but some participants were in a trial of synthetic surfactant.	Spirometry at rest and at 1,5 and 10 minutes post exercise. "Each child performed a graded exercise test on a cycle ergometer to determine maximal aerobic power. A modified McMaster continuous cycling test was applied with the initial load and increment based on child's height. Load increased every 2 minutes until the child could no longer pedal at the prescribed cadence of 50rpm. The test duration was 6-10 minutes. The child was breathing through a mouthpiece from which expired gas concentrations were continuously monitored. Maximal effort was defined as the inability of the child to keep pedaling at the required speed despite continuous encouragement,"	"EIB was more prevalent among the 2 premature groups (P<0.05). Mean exercise induced changes in FEV₁ were not significant among the groups (CLD -6.9 (2.3), PT -9.8 (3.8), controls -6.4 (1.8)). FEF₂₅₋₇₅ (CLD -19.6 (6.0), PT -24.9 (6.5), controls -11.2 (3.6)). This represents a sign higher degree of EIB in the prem gps compared to controls CLD vs CON p<0.005, PT vs CON p=0.01. EIB defined as a decrease in FEV₁ and FEF₂₅₋₇₅ of 15% or more at any time up to 10 minutes post exercise. CLD 5/16, Preterm 6/12 Controls 3/23 EIB defined as a decrease in FEV₁ or FEF₂₅₋₇₅ of 15% or more at any time up to 10 minutes post exercise. CLD 7/16, Preterm 7/12 Controls 5/23""	

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Hamon ²³ France		"Aim was to describe the characteristics of and potential determinants to the airway response to exercise in children born extremely preterm."	cohort	42 non asthmatic, non atopic children <32 weeks	27 healthy non asthmatic non atopic healthy term children	spirometry	PT 17M 25 F Term 9M 18F
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
PT mean 28.9 SD 1.8 Control 39.7 (1.2)	PT mean 1.16 SD 0.32 Control 3.26 0.42	PT group 41/42 ventilated median duration 28d range 1-102	7 years PT mean 7.1 SD 0.4 Control 7.0 (0.6)	July 1999-Feb 2001	No stated	Lung function measurements were obtained at baseline measured at baseline and repeated 5 min and 15 min after a 6 min run on a treadmill exercise. The response to exercise was computed using the largest of 2 post exercise responses and expressed as percentage change from baseline."	"PT group showed significant bronchoconstriction induced by exercise. Overall FVC and FEV ₁ responses were significantly larger in patients than controls p<0.003 and p<0.001. Figure shows the distribution of responses to exercise. There is a clear leftward shift in patients as compared with controls, in whom no FEV ₁ decrease below 5% is found, which contrasts with 24% of the patients in whom an FEV ₁ decrease of 7% or more was found ($P < 0.005$). Within the former premature group, the FEV ₁ response to exercise was not different between those with and those without chronic lung disease in the neonatal period." Peak lung response to exercise FVC(%) PT mean -3.5 SD 7 control 0.7 (3) FEV ₁ (%) PT -4.4(6) CONTROL -0.2(3) FEV ₁ No difference was seen between CLD and no CLD in PT group. CLD n=12 FVC -1.6(6) no CLD n=30 -4.3(7) FEV1 CLD -3.1(6) no CLD -4.9(6)

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN	STUDY GROUP		CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Gross ⁸ USA		"To assess long term pulmonary outcome of a regional cohort of children born at <32 weeks' gestation compared with a matched term control group."	cohort	96 PT born at 24-31 weeks gestation BPD n =43 No BPD n = 53		108 Matched term control group 38-42 weeks gestation	Spirometry	BPD 23 M (53%) No BPD 27M (51%) Term 62M (57%)
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS	
125 PT born at 25-31 weeks gestation mean 28.2 (2.1) BPD 27 (2) No BPD 29 (2) Matched term control group 38-42 weeks gestation mean 40.1 SD 1.1	Term mean 3565g SD 427 PT mean 1173 g SD 345g BPD 1053g SD 356 No BPD 1270g SD 306	BPD 95% median 34 days ventilated No BPD 55% median 6 days ventilated	7 years	July 1985 –June 1986	No surfactant given	"Spirometry was measured at rest and after graded treadmill exercise performed to exhaustion on a treadmill (Marquette Electronics T 2000, St Louis, Mo) with continuous electrocardiographic monitoring (Marquette Electronics Max-1 Stress System). Metabolic measurements were made with a Sensor Medics 2900 Metabolic Measurement Cart and included inspired/expired gas concentrations and expired flow rate with calculation of minute ventilation, oxygen consumption, carbon dioxide production, and respiratory quotient. These values were assessed at baseline and throughout exercise with an appropriately sized low dead space, minimal resistance face mask (Hans Rudolph, Inc, Kansas City, Mo)".	After exercise children with previous BPD continued to have significantly reduced FVC ($P < .001$), FEV_1 ($P < .001$), and $FEF_{25\%-75\%}$ ($P < .001$). After exercise FEV_1 was abnormal in most of the BPD group (23 of 43, 54%), but in only 16 (30%) of 43 of the no BPD group and 18 (17%) of 108 of the term group ($P < .001$). After exercise 8 (19%) of 43 children with previous BPD, 5 (9%) of 53 children without BPD, and 2 (2%) of 108 term children had $FEV_1 < 60\%$ of predicted. No significant differences were found in any pulmonary function measurements between preterm children without BPD and the term control group Baseline FVC (% predicted) mean (SD) BPD 93 ± 16 No BPD 104 ± 15 Term 103 ± 11 FEV1 (% predicted) BPD 83 ± 17 No BPD 98 ± 18 Control 97 ± 12 FEF25%-75% (% predicted) BPD 66 ± 24 No BPD 84 ± 27 Term 88 ± 21 After exercise FVC (% predicted) BPD 89 ± 17 No BPD 100 ± 15 Term 100 ± 11 FEV1 (% predicted) BPD 76 ± 19 No BPD 91 ± 20 Term 92 ± 13 FEF25%-75% (% predicted) BPD 55 ± 25 No BPD 77 ± 31 Term 82 ± 25	

STUDY AND COUNTRY		OBJECTIVE	STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Barker ²⁴ Germany		Pulmonary function and exercise performance were evaluated in a cohort of prematurely born VLBW children	Cross sectional	26 prematurely born <37 weeks VLBW <1.5kg children 13 BPD 13 No BPD	13 healthy term ≤37 weeks controls	spirometry	BPD 6F No BPD 8F Contrtol 5F
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
BPD mean 30.3 range 28-33 No BPD mean 33.5 range 30-36 CON term	BPD mean 1139 range 710-1480 No BPD mean 1264 range 900-1490	BPD mean 30.3d range 7-81 No BPD mean 2.1 range 0-13	8-14 years BPD mean 9.8 range 8-14 No BPD mean 10.4 range 8-14 CON Mean 10.5 range 8-12	1983-1989	Not stated	“Subjects exercised on a cycle ergometer (jaeger ER900, Germany) at a constant rate of 60rpm for approx. 25 minutes. The applied protocol combined submaximal testing below the anaerobic threshold with a maximal step test. It consisted of 4 consecutive phases: a 4 min warm up at 20 W; two 5 mins cycle of a pseudo-random binary sequence with work rate switches between 20 W and 40% of predicted WRmax; a second steady-state for 4 minutes at upper PRBS level and finally a progressive ramp with increments of 10W(height <140cm) or 15W per min (height ++140cm). Tests were terminated at voluntary exhaustion despite maximal effort. The latter was indicated by a HR above 175/min, a respiratory exchange ratio (RER) >1, a rapidly declining pedal speed and the clinical impression of the examiner. Spirometry was repeated after 5 minutes of recovery and additionally 10 minutes after inhalation of 200ug salbutamol in the case of a ++8% decrease in FEV ₁ or ++20% in maximal expiratory flow at 50% of FVC.”	“After exercise FEV ₁ fell by a mean of -2.3-5.1% in the BPD group and -2.6-2.6% in the no BPD group. A more pronounced reaction with a drop in FEV ₁ >8% and/or MEF ₅₀ >20% was seen only in 4 BPD subjects. 2 of these patients stated that they had stopped exercise because of dsypnea, all 4 had a complete recovery after bronchodilator application.”

STUDY AND COUNTRY		OBJECTIVE		STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Bader ²⁵ USA		"To determine the long-term pulmonary sequelae and effect on exercise tolerance of BPD."		cohort	10 children with BPD	8 age matched children born at term	"The change in maximal expiratory flow, FEV ₁ , FEF ₂₅₋₇₅ , specific airway conductance and residual volume that occurred after exercise was considered normal if it was within the mean +/- 2SD of the change observed in the control group."	BPD 6M, 4F Control 4M, 4F
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACT ANT GIVEN	METHOD OF MEASURING BHR	RESULTS	
BPD Mean 29 weeks SEM 0.7 range 26-32 Control mean 40 SEM 0.3 Range 39-41	BPD Mean 1173g SEM 120 range 765-2000 Control mean 3248g SEM 166 Range 2500-3960	IPPB BPD mean 44 days SEM 6 range 7-65 Control mean 0 SEM 0	BPD Mean age of 10.4 years SEM 0.6 range 7.3-12.2 Control mean 10.1 SEM 0.9 Range 7.5-14	1973-1979	Not stated	"Graded exercise test on a treadmill during which speed and slope were increased in stepwise progression. Data were obtained for 2 minutes at rest, treadmill speed and slope were then increased every 2 minutes until the child could not exercise further. The protocol for increase in work load was designed to assure that exercise would last between 8 and 12 minutes and maximal oxygen consumption would be attained. Lung volumes, expiratory flow rates and airway resistance was measured 10 minutes after exercise."	Exercise induced bronchospasm occurred in 50% of the BPD group but not in the control group. "10 minutes after exercise 5 (50%) children in the BPD group had a significant fall in maximal expiratory flow rates, indicating the presence of exercise induced bronchospasm. However when the mean values for the BPD group were measured expiratory flow rates were not significantly different before and after exercise." FEV₁ (%) BPD group mean +/- SEM -2.8 +/- 3.3 control group -1.0 +/- 1.2 Children with abnormal FEV₁ BPD group 4 control group 0 FEF_{25%-75%} (%) BPD group -7.6 +/- 5.9 control group -6.2 +/- 5.1 Children with abnormal FEF_{25%-75%} BPD group 0 control group 0 FEFmax (%) BPD group -6.5 +/- 4.8 control group -6.4 +/- 2.3 Children with abnormal FEFmax BPD group 2 control group 0 Children with exercise-induced bronchospasm BPD group 5 control group 0	

STUDY AND COUNTRY		OBJECTIVE		STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Joshi ¹⁰ UK		"To assess for exercise induced bronchoconstriction in 8-12 year old children who had CLD and to evaluate the response of bronchoconstriction to bronchodilation with albuteral in comparison with preterm and term controls."		Cross sectional	29 with CLD 33 born preterm at ≤ 32 weeks gestation "Only data from 75 children who had data after baseline, after exercise and after BD (26 in CLD group, 23 in PT group, and 26 in term group were included in these analyses.)"	30 born at term ≥37 weeks gestation. "Only data from 75 children who had data after baseline, after exercise and after BD (26 in CLD group, 23 in PT group, and 26 in term group were included in these analyses.)"	"Spirometry was performed at 5, 10, 15, 30, and 40 minutes after the exercise and the lowest FEV ₁ was recorded for each child. At each stage at least 3 spirometry maeuvers with at least 2 reproducible recordings were recorded. Albuterol was administered 45-60 minutes after exercise via a paediatric aerochamber (GSK, UK) with an appropriate sized face mask. 4 100ug doses (total dose 400ug) were administered with the child instructed to take 10 normal breaths after each dose. Spirometry was repeated after 15 minutes"	CLD 17M 59% PT 15M 46% Term 15M 50%
GA (WEEK S)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR		RESULTS
CLD mean 27.3 SD 2.1 PT mean 30.0 SD 2 Term mean 39.8 SD 1.5	CLD mean 1.1 SD 0.4 PT mean 1.5 SD 0.4 Term mean 3.4 SD 0.5	Assisted ventilation, days, median, range CLD 28 (5-80) PT 3 (0-50) Term none	8-12 year old CLD mean 10.2 SD 1.4 PT mean 10.3 SD 1.1 Term mean 10.5 SD 1.5	Not stated	CLD 29/29 100% PT 15/33 45% Term none	"Maximal exercise capacity was measured using an incremental symptom limited electrically braked cycle ergometer (Jaeger). Pedalling was started on an unloaded cycle and then every 3 minutes thereafter the load was increased in 30W increments until volitional exhaustion or until the HR reached 80-90% of the predicted maximum (220-age in years). Pedalling cadence was held at approximately 60rpm. Each child was given the same vigorous verbal encouragement to cycle as long as possible. The test continued until at least 2 of the following criteria were met 1. Maximum HR was ≥80% of predicted maximum. 2. Respiratory exchange ratio was >1.3. Peak VO ₂ was achieved or 4 volitional exhaustion was present as assessed by the Borg scale of perceived exhaustion. Spirometry was performed at 5, 10, 15, 30, and 40 minutes after the exercise and the lowest FEV ₁ was recorded for each child. At each stage at least 3 spirometry maeuvers with at least 2 reproducible recordings were recorded. Albuterol was administered 45-60 minutes after exercise via a paediatric aerochamber (GSK, UK) with an appropriate sized face mask. 4 100ug doses (total dose 400ug) were administered with the child instructed to take 10 normal breaths after each dose. Spirometry was repeated after 15 minutes. "		"After maximal exercise predicted FEV ₁ decreased from a mean baseline of 81.9% (95%CI 76.6-87.0%) to 70.8% (65.5-76.1%) after exercise in the CLD group, from 92.0% (87.2-96.8%) to 84.3%(79.1-89.4) in the PT, and from 97.5%(92.5-102.6%) to 90.3% (85.1-95.5%) in the term group. After albuterol administration FEV ₁ increased to 86.8% (81.7-92.0%) in the CLD group, 92.1%(87.3-96.9%) in the PT group, and 97.1% (92.0-102.3% in the term group. The decreases in predicted FEV ₁ after exercise and increase in predicted FEV ₁ after BD use were greatest in the CLD group (-11% 95% CI -18.4 to -3.6%) and 16.0% 8.6-23.4% respectively p<0.005 for both with differences of <8% in the 2 control groups."

STUDY AND COUNTRY	OBJECTIVE			STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Abreu ²⁶ Brazil	"To assess cardiorespiratory capacity and investigate the presence of exercise induced bronchospasm among children with BPD."			Cohort	13 PT BPD 13 PT no BPD All BPD children had the effort test considered maximal, 3 on PT, and 3 on the control did not.	20 Term controls. All BPD children had the effort test considered maximal, 3 on PT, and 3 on the control did not	Spirometry. "After 10 minutes of the assessment conclusion, it was performed a new pulmonary function test to verify the BIE presence."	BPD 9M 4F PT 8M 5F Term 9M 11F
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR		RESULTS
BPD mean 32 SD 1.5 range 30-34 PT mean 35 SD 2.3 range 28-36	BPD mean 1037 SD 229 range 830-1670 PT mean 1765 SD 621 range 850-2800	BPD mean 11 days SD 6.6 range 3-26 PT mean 1 SD 2 range 0-6	7-10 years BPD mean 8.5 SD 0.97 PT mean 8.3 SD 1.11 Term 8.2 SD 1.14	PT children were born between 1993 and 1996	Not stated	"During the test, a maximum effort protocol was used, with progressive load individualized for every child, based on the protocol proposed by Karila et al. Individualization of maximum power in watts (W) was based on maximal VO₂ (VO₂max) predicted for each child. Basal VO₂ was calculated according to the equation: (height in cms x 2) – 100. The predicted VO₂max was calculated according to the scores proposed by Cooper et al. From these scores, it was calculated the maximum power, through the equation: Wmax = (predicted VO₂max – basal VO₂ / 10.3. The oxygen equivalent for each power (watts) was 10.3 ml O₂/min/W. The protocol was divided into: a) 3 minutes of rest; b) 3 minutes of warming-up, with an average power of 45% of the predicted maximum; c) approx 8 min of exercise with a 10% increase of the predicted maximum power for each min until exhaustion and d) 2-3 mins of cooling down period with the same power used during warm-up. The exercise time of this protocol lasted for 10-12 mins (stages "b" and "c"). Power was manually increased on the cyclergometer. The children's parents were allowed to be present during the assessment session, so that the children would feel safer and the parents could encourage them during the test. The assessment was interrupted when the participant reached exhaustion or when he/she could not keep the right rotation at the cyclergometer (45 RPM), even without having accomplished the proposed protocol. After 10 mins of the assessment conclusion, it was performed a new pulmonary function test to verify the BIE presence. For the exercise to be considered maximal, three of the following criteria should be reached: a) participant's exhaustion or incapacity to maintain a rotation higher than 45 RPM, despite verbal encouragement; b) participants reaching the VO₂ plateau (when the final increase of the VO₂ did not exceed 2 mL/kg/min for a 10% load increase) or when the volunteer has reached a score equal or higher than 85% of the predicted VO₂max; c) reaching predicted HRmax or score equal or higher than 90% of the predicted; d) maximal R (Rmax) higher than 1."		"The FEV ₁ values before and after exercise were 99 +/- 12% and 94 +/- 14, 100 +/- 14% and 100 +/- 15% and 102 +/- 15% and 101 +/- 15% for the BPD, PT, and control group respectively. Comparison of FEV ₁ before and after exercise did not show any differences and exercise induced bronchospasm was not characterised in any of the groups. However, an individualized analysis demonstrated that one child of the Pre-term group and two children of the BPD group presented > 10% VEF ₁ reduction characterizing BIE, representing 6.5% of all children that participated of the research."

STUDY AND COUNTRY		OBJECTIVE		STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Siltanen ¹¹ Finland		"To compare the background of respiratory problems of children born preterm with that of children born full term with special reference to atopy."		cohort	72 born preterm <1501g	65 born full term >2500g	Spirometry	PT 46M 26 F Term 34M 31F
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS	
PT Mean gestational age, weeks (SD, range) 28.5 (2.4, 23.4–33.7)	Mean birth weight, g (SD, range) PT 1,075 (271, 550–1,500) Term 3,593 (470, 2,540–5,200)	Not stated	10 years old mean in both groups 10.1 Mean age, year (SD, range) PT 10.1 (0.3, 9.6–10.8) Term 10.1 (0.4, 9.4–10.9)	1987–1988	PT Human surfactant treatment, n (%) 2 19 (26)	EXERCISE SPIROMETRY "Flow-volume spirometry testing with the Vitalograph Compact Spirometer (Vitalograph Ltd., UK) was performed on the children at rest and 10 min after an exercise challenge. At testing, the children were sitting and wearing nose clips. The criteria for acceptance of the recording were based on the guidelines of the American Thoracic Society. During the exercise, performed by jumping on a trampoline for 6–8 min, the arterial pulse was monitored by a pulse meter (Polar Accurex, Finland), and arterial oxygen saturation by a pulse oxymeter (Nellcor N-20). The aim of the exercise was to produce breathlessness and a pulse level of over 170 beats per minute for a 6-min period. The following spirometry values were analyzed: forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV ₁), FEV ₁ /FVC ratio, forced expiratory flow after 50% of vital capacity has been exhaled (FEF ₅₀), and forced expiratory flow during middle half of FVC (FEF _{25–75}). The results were expressed and analyzed as percentages of predicted values adjusted for the age, sex, and height of the child."	"During the exercise challenge, 2 children, both from the preterm group, developed manifest wheezing, and the other child also had major changes in lung function values measured after exercise. However, the overall changes in FEV₁, FEF₅₀, and FEF_{25–75} post exercise did not differ significantly between groups. Neither did mean arterial pulse nor arterial oxygen saturation differ between groups during exercise." FEV₁ change, % after exercise_SD PT -1.5+/-10.2 Term -0.8+/-3.1 FEF₅₀ change, % after exercise_SD PT -4.3+/-15.1 Term -1.6+/-10.1 FEF_{25–75} change, % after exercise_SD PT -1.3+/-16.3 Term -3.4+/-11.5	

STUDY AND COUNTRY		OBJECTIVE			STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)
Santuz ²⁷ Italy		“Undertook this study in children following BPD with the purpose (1) to evaluate the lung function of BPD children at school age and (2) to assess the level of exercise tolerance of BPD survivors by comparing ventilation and gas exchange during exercise of BPD and healthy children.”			Control study	12 PT BPD children	“16 age, sex and physically activity matched healthy children born at term.”	Spirometry before and after exercise	PT BPD 9M 3F Controls 11M 5F
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION (DAYS)	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR		RESULTS	
PT BPD mean 30 weeks SD 2 weeks range 27-32 Control mean 39 SD 1 range 37-40	PT BPD mean 1400g SD 335g range 890-1900. Control mean 3335g SD 418 range 2800-4100	All had received ventilation for at least 7 days. Mean 20 d SD 15, median 17, range 7-60	6 to 12 years. BPD mean 8.1 SD 1.8 Range 6-12 Control mean 8.1 SD 1.5 range 6-12	1981-1987	Not stated	“Pulmonary function at rest was measured in all children before exercise testing. Spirometry was performed according to standardized criteria by means of a 10 L bell spirometer connected to a computerized system (Baires; Biornedin, Padova, Italy). Exercise was performed on a previously calibrated treadmill (P. K. Morgan, Gillingham, England) using a stepwise protocol by which the speed of the belt was set at 6.5 km/h and the inclination was increased by 2% every minute. The exercise test was performed under stable environmental conditions, that is, a temperature of 20 to 25° C and a relative humidity of 60 to 80%. All the participants exercised to the point of exhaustion. The test was considered to represent a maximal cardiorespiratory effort when the observation of at least two of the following criteria was met: (1) reaching a heart rate close to the theoretical maximal HR; (2) stability of oxygen consumption (<i>Voz</i>) despite the increase in workload; and (3) inability of the subject to maintain the treadmill speed despite vigorous encouragement. The children were connected, via a fitting mask and a corrugated tube, to a spirometer and a gas analyzer, as detailed previously. In short, they inhaled and exhaled through a low-resistance three-way valve at the mouth, with a 40 ml dead space, and a second emptying valve at a 10 L bell spirometer suitable for fast emptying. Respiratory variables were measured by an open-circuit method.”		“Baseline mean spirometric values (% of predicted) were in the normal range for both groups but were lower in BPD children with respect to control children (p <0.05). The postexercise FEV ₁ fall, with respect to the baseline, was 8 ± 6% in BPD and 2 ± 1% in control children (p < 0.01).” Baseline FEV ₁ PT mean 83 SD 13, control 100 (8). 2 children had a fall in FEV ₁ >15% matching the diagnosis of exercise induced asthma. None of the control children had evidence of EIB.	

HYPERTONIC SALINE PROVOCATION TEST

STUDY AND COUNTRY	OBJECTIVE	STUDY DESIGN	STUDY GROUP	CONTROL GROUP	OUTCOME MEASURES	SUBJECTS (GENDER)	
Mai ²⁸ Sweden	To assess the relationship between VLBW ≤1500g and the development of asthma, lung function and atopy.	VLBW cohort	74 VLBW ≤1500G 68 of 74 VLBW completed hypertonic saline provocation tests.	64 matched term children ≥2500g 59 of 64 term children completed hypertonic saline provocation tests.	“The challenge test was stopped and considered to be positive when the decline in FEV ₁ was more than 15%. Response to dose ratio was used to represent the degree of bronchial hyperresponsiveness, which was defined as the fall of FEV ₁ in percentage divided by the total dose of delivered saline in ml (%/ml).”	VLBW M 44 F 30 Control M 33 F 31	
GA (WEEKS)	BW (GRAMS)	DURATION ON MECHANICAL VENTILATION	AGE TESTED (YEARS)	YEAR OF BIRTH	SURFACTANT GIVEN	METHOD OF MEASURING BHR	RESULTS
VLBW 25-36 weeks mean 31 (2) 25-29 N=21 30-32 N=35 33-36 N=18	VLBW ≤1500G term children ≥2500g	13 in total ventilated	12 Years VLBW 12.6 (0.2) Control 12.7 (0.3)	Feb 1987 to April 1988	Not available	“Hypertonic saline provocation tests were performed according to the ISAAC protocol. the higher of 2 reproducible measurements of FEV ₁ was recorded as the baseline FEV ₁ . Hypertonic saline (4.5%) was nebulized via Devilbiss Ultraneb 2000 connected to a 60-cm tubing (Devilbiss no. 8885: Devilbiss, Dahlhausen, Cologne, Germany) and a two-way valve (Laerdal valve no. 560 200/850 500: Devilbiss, Dahlhausen, Cologne, Germany). The child was encouraged to maintain tidal breathing. The exposure time was progressively increased from 30 s to 1, 2, 4 and 8 min each, and the maximal total inhalation period was 15.5 min. After each exposure, two reproducible measurements of FEV ₁ were made. The exposure time was doubled if the fall in FEV ₁ was less than 10%. The same dose was repeated if the fall was between 10% and 15%. The canister with tubing was weighed before and after the challenge test to measure the total dose of delivered saline. “	“VLBW children who required mechanical ventilation during the neonatal period were more likely to have BHR than those not requiring it (60% vs28% p=0.050)” Positive provocation test Very preterm n=21 RR (95%CI) N= 6/18 1.1 (0.5–2.4) Moderate preterm (n = 53) N=16/50 1.1 (0.6–1.9) vs. term* (n = 64) n=18/59 The increased risk of bronchial hyperresponsiveness was obvious in the VLBW infants who needed mechanical ventilation ≥5 days (RR 2.9, 95%CI 1.5–5.4). There was also a higher degree of bronchial hyperresponsiveness in the VLBW children requiring mechanical ventilation, as compared with those not requiring mechanical ventilation, in the positive provocation tests (median value of response to dose ratio, 6.2%/ml vs. 2.1%/ml, p = 0.012).

TABLE E2: Definition of BPD/CLD for the studies included in the meta-analysis.

STUDY	DEFINITION OF BPD OR CLD
Bader ²⁵	"Chest radiographs at the end of the first month of life showed radiologic findings (hyperinflation or multiple cystic areas or fibrotic "strands") compatible with the diagnosis of BPD, as described by Northway et al."
Barker ²⁴	"Neonatal chest x-rays were reviewed by an experienced pediatric radiologist for characteristic features of BPD. Regardless of their length of oxygen requirement, all subjects with a history of mechanical ventilation were assigned to groups BPD+ or BPD- according to radiologic criteria at one month of age. Non-ventilated preterm children were included in BPD-."
Santuz ²⁷	"The diagnosis of BPD was made according to the criteria of Bancalari and coworkers. Chest radiographs at the end of the first month of life showed the featuring criteria of BPD (hyperinflation, multiple cystic areas, and fibrotic strands) as described by Northway and colleagues." "The diagnosis of BPD was made in cases that fulfilled the following criteria: (1) Required intermittent positive pressure ventilation during the first week of life and for a minimum of three days. (2) Developed clinical signs of chronic respiratory disease characterized by tachypnea, intercostal and subcostal retraction, and tales on auscultation, all persisting for longer than 28 days. (3) Required supplemental oxygen for more than 28 days to maintain a Pa% over 50 mm Hg. (4) Chest radiograph showed persistent strands of densities in both lungs, alternating with areas of normal or increased lucency. In some infants, these areas became coalescent into larger structures resembling bullae."²⁹
Abreu ²⁶	"Inclusion criteria for the BPD group (born with gestating clinical age lesser than 37 weeks) were proposed by Bancalari et al. 1) positive pressure ventilation during the first week of life for at least three days; 2) clinical signs of chronic respiratory disease – tachypnea, respiratory discomfort 3) oxygen supplement necessity for over 28 days in order to keep an oxygen arterial pressure over 50 mmHg or pulse oxymetry over 90%; and 4) trunk radiographies abnormalities, showing persistent grooves in both lungs, alternating with radio-luminescence areas; these formations may coalesce, giving it a bubble aspect."
Kaplan ¹⁹	"National Institutes of Health consensus definition and severity grading (lung disease requiring oxygen supplementation at 28 days, severity graded by oxygen requirement at a corrected gestational age of 36 weeks [mild, none; moderate, F io 2 5 0.22-0.30; severe, F io 2 . 0.30], or CPAP or mechanical ventilation)"

Korhonen ¹⁵	“Criteria for BPD diagnosis at 28 d postnatal age (BPD) and 36 wk corrected gestational age (sBPD) were the requirement of supplemental oxygen (O ₂) and chest X-ray findings typical of BPD, interpreted by a paediatric radiologist.”
Kriemler ²²	“Briefly, diagnosis was based on oxygen dependency and persistent respiratory distress at 28 days after delivery in prematurely born infants who had undergone mechanical ventilation for at least 1 week, and a radiologic picture including rounded radiolucent areas in the lung beside thin strands of radiodensity.”
Landry ¹⁷	“The hospital discharge diagnosis data at birth were obtained for a majority of subjects from the Régie de l’Assurance Maladie du Québec (RAMQ), using the International Classification of Diseases, 9 th revision (ICD-9) diagnostic codes for preterm birth (765.**), RDS (769.*), and BPD (770.7).”
Halvorsen ⁷	“mild and moderate/severe bronchopulmonary dysplasia (BPD) were defined according to requirement for supplemental oxygen ≥28 postnatal days and ≥36 wk postnatal (PMA) respectively)”

References

1. Galdes-Sebaladt M, Sheller JR, Groggaard J, Stahlman M. Prematurity is associated with abnormal airway function in childhood. *Pediatric Pulmonology* 1989; **7**: 259-64.
2. Rona RJ, Smeeton NC, Bustos P, Amigo H, Diaz PV. The early origins hypothesis with an emphasis on growth rate in the first year of life and asthma: a prospective study in Chile. *Thorax* 2005; **60**: 549-54.
3. Lum S, Kirkby J, Welsh L, Marlow N, Hennessy E, Stocks J. Nature and severity of lung function abnormalities in extremely pre-term children at 11 years of age. *European Respiratory Journal* 2011; **37**: 1199-207.
4. Pike KC, Davis SA, Collins SA, et al. Prenatal development is linked to bronchial reactivity: epidemiological and animal model evidence. *Scientific Reports* 2014; **4**.
5. Halvorsen T, Skadberg BT, Eide GE, Roksund O, Aksnes L, Oymar K. Characteristics of asthma and airway hyper-responsiveness after premature birth. *Pediatric Allergy & Immunology* 2005; **16**: 487-94.
6. Vollsaeter M, Skromme K, Satrell E, et al. Children Born Preterm at the Turn of the Millennium Had Better Lung Function Than Children Born Similarly Preterm in the Early 1990s. *PLoS ONE [Electronic Resource]* 2015; **10**: e0144243.
7. 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 Paediatrica* 2004; **93**: 1294-300.
8. Gross SJ, Iannuzzi D, Kveselis DA, Anbar RD. Effect of preterm birth on pulmonary function at school age: A prospective controlled study. *Journal of Pediatrics* 1998; **133**: 188-92.
9. Mitchell SH, Teague WG. Reduced gas transfer at rest and during exercise in school-age survivors of bronchopulmonary dysplasia. *American Journal of Respiratory & Critical Care Medicine* 1998; **157**: 1406-12.
10. Joshi S, Wilson DG, Kotecha S, Pickerd N, Fraser AG, Kotecha S. Cardiovascular function in children who had chronic lung disease of prematurity. *Archives of Disease in Childhood Fetal & Neonatal Edition* 2014; **99**: F373-9.
11. Siltanen M, Savilahti E, Pohjavuori M, Kajosaari M. Respiratory Symptoms and Lung Function in Relation to Atopy in Children Born Preterm. *Pediatric Pulmonology* 2004; **37**: 43-9.
12. von Mutius E, Nicolai T, Martinez FD. Prematurity as a risk factor for asthma in preadolescent children. *Journal of Pediatrics* 1993; **123**: 223-9.
13. Todisco T, de Benedictis FM, Iannacci L, et al. Mild prematurity and respiratory functions. *European Journal of Pediatrics* 1993; **152**: 55-8.
14. Schraeder BD, Czajka C, Kalman DD, McGeady SJ. Respiratory health, lung function, and airway responsiveness in school-age survivors of very-low-birth-weight. *Clinical Pediatrics* 1998; **37**: 237-45.
15. Korhonen P, Laitinen J, Hyodynmaa E, Tammela O. Respiratory outcome in school-aged, very-low-birth-weight children in the surfactant era. *Acta Paediatrica, International Journal of Paediatrics* 2004; **93**: 316-21.

16. Kotecha SJ, John Watkins W, Paranjothy S, Dunstan FD, John Henderson A, Kotecha S. Effect of late preterm birth on longitudinal lung spirometry in school age children and adolescents. *Thorax* 2011; **27**.
17. Landry JS, Tremblay GM, Li PZ, Wong C, Benedetti A, Taivassalo T. Lung Function and Bronchial Hyperresponsiveness in Adults Born Prematurely. A Cohort Study. *Annals of the American Thoracic Society* 2016; **13**: 17-24.
18. Ijsselstijn H, Tibboel D, Hop WJC, Molenaar JC, deJongste JC. Long-term pulmonary sequelae in children with congenital diaphragmatic hernia. *American Journal of Respiratory and Critical Care Medicine* 1997; **155**: 174-80.
19. Kaplan E, Bar-Yishay E, Prais D, et al. Encouraging pulmonary outcome for surviving, neurologically intact, extremely premature infants in the postsurfactant era. *Chest* 2012; **142**: 725-33.
20. Ronkainen E, Dunder T, Peltoniemi O, Kaukola T, Marttila R, Hallman M. New BPD predicts lung function at school age: Follow-up study and meta-analysis. *Pediatric Pulmonology* 2015; **50**: 1090-8.
21. McLeod A, Ross P, Mitchell S, et al. Respiratory health in a total very low birthweight cohort and their classroom controls. *Archives of Disease in Childhood* 1996; **74**: 188-94.
22. Kriemler S, Keller H, Saigal S, Bar-Or O. Aerobic and lung performance in premature children with and without chronic lung disease of prematurity. *Clinical Journal of Sport Medicine* 2005; **15**: 349-55.
23. Hamon I, Varechova S, Vieux R, et al. Exercise-induced bronchoconstriction in school-age children born extremely preterm. *Pediatric Research* 2013; **73**: 464-8.
24. Barker M, Merz U, Hertl MS, Heimann G. School-age lung function and exercise capacity in former very low birth weight infants. *Pediatric Exercise Science* 2003; **15**: 44-55.
25. Bader D, Ramos AD, Lew CD. Childhood sequelae of infant lung disease: Exercise and pulmonary function abnormalities after bronchopulmonary dysplasia. *Journal of Pediatrics* 1987; **110**: 693-9.
26. Abreu L, Costa-Rangel R, Gastaldi A, Guimarães R, Cravo S, Sologuren M. Cardio-respiratory capacity assessment in children with bronchopulmonary dysplasia. *Rev bras fisioter* 2007; **11**: 95-100.
27. Santuz P, Baraldi E, Zaramella P, Filippone M, Zacchello F. Factors limiting exercise performance in long-term survivors of bronchopulmonary dysplasia. *American Journal of Respiratory & Critical Care Medicine* 1995; **152**: 1284-9.
28. Mai XM, Gaddlin PO, Nilsson L, et al. Asthma, lung function and allergy in 12-year-old children with very low birth weight: a prospective study. *Pediatric Allergy & Immunology* 2003; **14**: 184-92.
29. Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. *J Pediatr* 1979; **95**: 819-23.