Effect of Bronchodilators on Forced Expiratory Volume in 1 s in Preterm-Born Participants Aged 5 and Over: A Systematic Review

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Key Words

Lung spirometry · Chronic lung disease of prematurity · Bronchopulmonary dysplasia · Bronchodilator · Inhaled corticosteroids

Abstract

Background and Objectives: Preterm-born participants are at risk of long-term deficits in percentage predicted forced expiratory volume in 1 s (%FEV₁). Since it is unclear if these deficits respond to bronchodilators, we systematically reviewed the evidence for reversibility of deficits in %FEV₁ by bronchodilators in preterm-born participants. **Design:** Studies reporting a change in %FEV₁ in response to bronchodilator treatment in preterm-born participants at ≥5 years of age, with or without a term-born control group, were identified. The quality of studies was assessed by adapted tools. Due to considerable heterogeneity between studies, formal meta-analysis was not possible. **Results:** From 8,839 titles, 22 studies were identified after an updated search in May 2013. Twenty-one studies assessed the response to a single inhaled dose of a bronchodilator, and 1 study assessed longer-term effects. Most studies observed decreased %FEV₁ in preterm-born participants compared with controls. Most studies observed improved %FEV₁ after a single dose of

bronchodilator, with the largest improvements noted in those with bronchopulmonary dysplasia, who had greater deficits of %FEV₁ when compared with preterm and term controls. One long-term study investigated a 2-week terbutaline administration, but the initial FEV₁ after a single dose did not show a change in %FEV₁ of ≥15%, but 5/29 (17%) children had an increased %FEV₁ of ≥10%. **Conclusions:** In this systematic review, disparate studies were identified. Although single doses of bronchodilators appear to improve the FEV₁ in the short term, further studies are required to assess their longer-term benefits not only on airway obstruction, but also their effect on respiratory symptoms.

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Introduction

Prematurity is associated with decreased lung function in later life [1], with a potential to develop obstructive pulmonary disease in the future [2]. Late preterm-born children (33–34 weeks' gestation) had significantly lower lung function values at 8–9 years, although most of these differ-

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ences were reduced by 14–17 years [3]. In our previous systematic review and meta-analysis, we reported that preterm-born participants with and without bronchopulmonary dysplasia (BPD) have deficits in percentage predicted forced expiratory volume in 1 s (%FEV₁) [1]. The mean differences for %FEV₁ compared with term-born controls were –7.2% (95% CI –8.7 to –5.6%) for the preterm-born group without BPD and –18.9% (–21.1 to –16.7%) for the preterm-born group with BPD. These children may also have increased respiratory symptoms [4].

The EpiCure study of 11-year-old children born at ≤25 weeks' gestation observed that 56% of survivors had an abnormal spirometry and 27% had positive bronchodilator responses, but <50% had received any bronchodilator therapy over the previous year [5]. We reported significant reversible exercise-induced bronchoconstriction in 8- to 12-year-old children who had had BPD in infancy, but only 10% of the preterm-born children with BPD and 12% of the preterm-born without BPD were receiving bronchodilator treatment [6]. It is clear that we need to establish whether preterm-born children and adults need long-term monitoring and treatment, e.g. with bronchodilator treatment, and whether earlier treatment with bronchodilators improves the respiratory symptoms and long-term outcomes of preterm-born children. Currently it is unclear how to optimally manage preterm-born children with respiratory symptoms and airway obstruction.

To the best of our knowledge, there has not been a systematic review of studies that examined whether the deficits for %FEV₁ in preterm-born participants with and without BPD are reversible with bronchodilator treatment. We therefore systematically reviewed the evidence in preterm-born children and adults.

Materials and Methods

We adapted the search strategy used in our previous systematic review on %FEV₁ and preterm birth [1] to include additional key words relating to bronchodilator drug responsiveness (more information on additional key words is given in the online suppl. data; for all online suppl. material, see www.karger.com/doi/10.1159/000371539). The original search strategy is given in appendix 1 (online suppl. data), and the original data collection form is also given in appendix 2 (online suppl. data). Eight databases and 3 charity websites were searched (see online suppl. data) in May 2013. Ethical approval was not required.

Eligibility Criteria

Studies on bronchodilator responsiveness in preterm-born children or adults with or without BPD were included. 'Preterm' was defined as being born at <37 weeks' gestation, and 'term' was birth at ≥37 weeks' gestation. BPD was defined as either the depen-

dence on supplementary oxygen at 28 days of life or dependence on supplementary oxygen at 36 weeks postmenstrual age. Papers not mentioning the response to bronchodilators were excluded. Only studies reporting a change in %FEV₁ in response to bronchodilators were included, hence they were limited to participants ≥5 years of age. Studies in all languages from all countries were considered.

Study Selection

The initial search [1] from May 2010 to October 2011 was adapted in May 2013 to include the additional key words relating to bronchodilator drug responsiveness (more information on additional key words is given in the online suppl. data). The original search strategy is given in appendix 1 (online suppl. data), and the original data collection form is given in appendix 2 (online suppl. data). All additional included studies were reviewed by 2 reviewers (M.O.E. and S.J.K.).

Data Collection Process

Data extraction of all studies was performed by 2 reviewers (S.J.K. and M.O.E.). Multiple articles from the same cohort were reviewed, and the article reporting the most complete data was included in the analysis.

Assessing the Quality of the Study and Risk of Bias

A pro forma analysis modified from the Newcastle Ottawa criteria and the Cochrane risk of bias tool assessed the quality of the studies included (more information is given in the online suppl. data, and the data collection form is given in the online suppl. appendix 2). The minimum score was 6 and the maximum 20.

Outcome Measures

We measured the change in %FEV₁ in response to bronchodilator treatment in preterm-born participants.

Analysis of Results

A formal meta-analysis for a change in %FEV₁ after using a bronchodilator was not possible due to the considerable heterogeneity of the disparate studies, hence the results are descriptive.

Results

Studies Selected and Their Characteristics

The initial searches identified 8,839 titles and abstracts, of which 20 studies met the inclusion criteria; when the searches were adapted, we identified a further 2 studies. Twenty-two studies were included [5–26]. Demographic details are shown in tables 1 and 2, and further details are given in the online supplementary tables E1 and E2. Twenty-one papers reported a change in %FEV₁ after a single bronchodilator dose, including 3 that administered a single dose of a bronchodilator after exercise [6, 13, 24]. Only 1 study assessed the effect of longer-term (2 weeks) administration of an inhaled β₂-agonist [7].

The mean ages of participants in the 22 studies ranged from 5.7 to 20.2 years, including 2 studies of young adults

Table 1. Demographics of all included articles

Study, country	Study group	Gestation, weeks	Years of birth
Fawke et al. [5], UK and Ireland	182 extremely preterm (≤ 25 weeks' gestation) children, 53 no BPD, 129 BPD Postbronchodilator data obtained in 162 children, 45 extremely preterm, no BPD, 117 extremely preterm, BPD	Extremely preterm: mean 25.0, SD 0.7 No BPD: mean 25.1, SD 0.6 BPD: mean 24.9, SD 0.8 Control: no details given, excluded if preterm	1995
Joshi et al. [6], UK	29 preterm children with chronic lung disease 33 preterm children (≤ 32 weeks' gestation) Only data from 24 children with chronic lung disease, 26 in the preterm and 26 in the term group who had spirometry at baseline, after exercise and after albuterol	Chronic lung disease group: mean 27.3, SD 2.1 Preterm group: mean 30.0, SD 2.0 Term group: mean 39.8, SD 1.5	No details given
Pelkonen et al. [7], Finland	29 preterm children (12 BPD, 17 no BPD)	BPD group: median 27, range 24–30 No-BPD group: median 28, range 25–35 Control group: term	1980–1985
Broström et al. [8], Sweden	60 very-low-birth-weight children, 28 no BPD, 28 mild-to-moderate BPD, 4 severe BPD	No-BPD group: median 30, range 28–31 Mild-BPD group: median 27, range 24–30 Moderate-BPD group: median 27.5, range 25–30 Severe-BPD group: median 28, range 25–29	1992–1997
Mieskonen et al. [9], Finland	40 children with a gestational age of ≤ 30 weeks or a birth weight of $< 1,500$ g; 18 no BPD, 9 BPD	Preterm group: median 27.9, range 24.1–30.9 No-BPD group: median 27.6, range 25.3–30.9 BPD group: median 26.9, range 24.1–30.7 Control group: term	1989–1991
De Kleine et al. [10], The Netherlands	40 preterm children ventilated for hyaline membrane disease (29 no BPD, 27 with lung function results, 11 BPD) and 38 preterm non-ventilated children with hyaline membrane disease	No-BPD group: mean 32.2, SD 1.8 BPD group: mean 30.6, SD 2.0 Non-ventilated group: mean 31.8, SD 1.9 Controls: no details given	1967–1977
Korhonen et al. [11], Finland	Very-low-birth-weight cohort ($< 1,500$ g): 34 no BPD, 28 of whom had bronchodilator response results; 34 BPD, 25 of whom had bronchodilator response results, and 14 severe BPD, 7 of whom had acceptable spirometry	No-BPD group: mean 29, SD 2, range 25–35 BPD group: mean 27, SD 2, range 23–30 Severe-BPD group: mean 28, SD 2, range 23–30 Control group: term	1990–1994
Sadeghi et al. [12], USA	11 children, BPD	BPD group: < 35 Asthma group: ≥ 37	No details given
Nixon et al. [13], USA	68 very-low-birth-weight ($< 1,501$ g) children: 38 received dexamethasone, 35 of whom performed reliable pulmonary function tests; 30 received placebo, 28 of whom performed reliable pulmonary function tests	Dexamethasone group: median (5th, 95th percentiles) 25.0, range 23.0–28.1 Placebo group: median (5th, 95th percentiles) 26.0, range 23.6–29.9	1992–1995
Kulasekaran et al. [14], Australia	45 preterm children (44 with lung function results) 47 children, BPD	Preterm group: mean 28.3, SD 1.0 BPD group: mean 28.5, SD 1.5	1989–1990
Andreasson et al. [15], Sweden	40 children who had ventilation during the neonatal period, 11 BPD, 29 no BPD 16/20 children who were in the BPD group or who had abnormal spirometry, or both, were tested with a bronchodilator	No-BPD group: median 29, range 26–36 BPD group: median 28, range 25–30 Group tested with bronchodilator: median 28, range 25–33	No details given
Baraldi et al. [16], Italy	31 preterm children, no BPD: 30/31 took part in a bronchodilator test 31 preterm children, BPD, < 31 weeks, birth weight $< 2,000$ g, 29/31 took part in a bronchodilator test	No-BPD group: mean 28.9, SEM 0.4 BPD group: mean 28.6, SEM 0.3 Control group: term	1990–1994
Telford et al. [17], UK	133 preterm children split into 2 groups: 123 children with bronchodilator results 69 children in a continuous negative extrathoracic pressure group, 64 standard respiratory care	Preterm group: median 31, interquartile range 29–33	No details given
Doyle et al. [18], Australia	44 extremely-low-birth-weight survivors, 14 (32%) were active smokers; 11/15 participants with a FEV ₁ /FVC ratio $< 75\%$ were given a bronchodilator, 3/29 with an FEV ₁ /FVC ratio $\geq 75\%$ were given a bronchodilator	Mean 27.4, SD 2.0	1977–1980

Table 1. (continued)

Study, country	Study group	Gestation, weeks	Years of birth
Koumbourlis et al. [19], USA	17 BPD, preterm birth ≤ 32 weeks, birth weight $\leq 1,500$ g	BPD group: mean 29.1, SD 1.7, median 29, range 26–32	No details given
Halvorsen et al. [20], Norway	46 preterm children, gestational age ≤ 28 weeks or birth weight $\leq 1,000$ g, 3 of whom did not perform a reversibility test Of the 46 preterm children, 10 had no BPD, 24 mild BPD, 12 moderate-to-severe BPD	Preterm group: mean 27.3, SD 1.4 No-BPD group: mean 28.3, SD 1.6 Mild-BPD group: mean 27.0, SD 1.3 Moderate-to-severe-BPD group: mean 27.0, SD 1.2 Control group: term	1982–1985
Northway et al. [21], USA	26 children, BPD	BPD group: mean 33.2, SD 3.8 Control group: term	1964–1973
Jacob et al. [22], Canada	30 preterm children: 15 no BPD, 15 BPD (1 subject in each group had trouble performing spirometry after bronchodilator)	No-BPD group: mean 28.5, SD 2.6 BPD group: mean 28.7, SD 2.1	1981–1987
Pianosi and Fisk [23], Canada	15 children, no BPD 17 children, BPD Term controls did not take part in the bronchodilator trial	Conventional mechanical ventilation, no BPD: median 29, interquartile range 28–30 High-frequency ventilation, no BPD: median 29.5, interquartile range 27.5–31 Conventional mechanical ventilation, BPD: median 27, interquartile range 26.8–29 High-frequency ventilation, BPD: median 28, interquartile range 26–28.8 Control: term	1986–1987
Gross et al. [24], USA	125 preterm children born at 24–31 weeks' gestation, of whom 96 had spirometry results: 53 no BPD 43 with BPD 108 term controls	No-BPD group: mean 29, SD 2 BPD group: mean 27, SD 2 Control group: mean 40.1, SD 1.1	1985–1986
Kaplan et al. [25], Israel	53 preterm participants (28 BPD, 25 no BPD)	BPD group: mean 26.2, SD 1.4 No-BPD group: mean 27.2, SD 1 Term group: mean 39.8, SD 1.38	1997–2001
Jones [26], UK and Ireland	111 children with chronic lung disease had spirometry data after bronchodilator 50 children were in the dexamethasone group, 61 in the placebo group	No details given	1984 and 1989

at a mean of 18.3 and 20.2 years, respectively [18, 21]. Participants included were born between 1964 and 2001 and between 24 and 36 weeks' gestation with birth weights ranging from 570 to 2,480 g. The majority of studies included participants born at <32 weeks' gestation or very-low-birth-weight infants. Rates of ventilation and surfactant administration varied widely. Bronchodilator administration was often part of studies investigating lung function.

Of the 21 studies assessing response to a single dose of bronchodilator:

- 16 (76.2%) administered salbutamol (also known as albuterol)
- 2 (9.5%) administered isoproterenol

- 1 (4.8%) administered terbutaline
- 2 (9.5%) did not report the type of bronchodilator administered

The majority of studies (14; 66.7%) included preterm-born participants with and without BPD, 4 (19.0%) studies included only preterm-born participants with BPD, and 3 (14.3%) included only preterm-born participants without BPD. Some studies included term-born controls.

Risk of Bias across Studies

Overall, the studies were of moderate quality, with scores ranging from 8 to 19 and a mean score of 13.5 (online suppl. table E1). Across studies, there was a moderate risk of selection bias.

Table 2. Bronchodilator drug administration method and results of bronchodilator drug treatment

Study, country	Bronchodilator drug administration method	Results of bronchodilator drug treatment
Fawke et al. [5], UK and Ireland	After baseline spirometry, spirometry was repeated 20 min after administering a bronchodilator (2 puffs of salbutamol, 100 µg via a spacer)	<i>Percent change in FEV₁</i> Extremely preterm no-BPD group: mean 5.5%, SD 7.3% Extremely preterm BPD group: mean 10.7%, SD 10.0% All extremely preterm children: mean 9.3%, SD 9.6% Controls: mean 4.0%, SD 5.0% <i>Change in FEV₁ >12%</i> Extremely preterm no-BPD group: mean 16%, 7/45 cases Extremely preterm BPD group: mean 32%, 37/117 cases All extremely preterm children: mean 27%, 44/162 cases Controls: mean 8%, 12/149 cases
Joshi et al. [6], UK	After baseline spirometry, albuterol was administered 45–60 min after exercise via an Aerochamber with a face mask. 4 × 100 µg doses were administered, and spirometry was repeated after 15 min	Chronic lung disease group baseline FEV ₁ : mean 81.9% (95% CI 76.6–87.0), after albuterol FEV ₁ : mean 86.8% (95% CI 81.7–92.0) Preterm group baseline FEV ₁ : mean 92.0% (95% CI 87.2–96.8), after albuterol FEV ₁ : mean 92.1% (95% CI 87.3–96.9) Term group baseline FEV ₁ : mean 97.5% (95% CI 92.5–102.6), after albuterol FEV ₁ : mean 97.1% (95% CI 92.0–102.3)
Pelkonen et al. [7], Finland	After baseline spirometry, spirometry was repeated 15 min after inhalation of 0.5 mg terbutaline from a dry powder inhaler at the first visit. Then the effect of the β ₂ -agonist was measured by performing spirometry every morning and evening before and after terbutaline inhalation. Lung function was monitored twice daily at home for 4 weeks. For the first 2 weeks, the child inhaled 0.25 mg terbutaline twice daily and performed spirometry before and 15 min after terbutaline inhalation. At the 2nd visit, spirometry and a histamine test were performed	At the first-visit bronchodilator test, none of the children had a significant response to the bronchodilator (change in %FEV ₁ ≥15%). Five children had a response of ≥10%, 1 no BPD, 4 BPD. There was no significant difference between the BPD and no-BPD group. The median change in FEV ₁ was 5.8% (5.1–14.3%) in the BPD group and 1.4% (range 2.1–12.2%) in the no-BPD group During the 2 weeks of home recording, PEF increments of ≥15% after terbutaline were observed at least 3 times in 31% of patients. Six children had a diurnal variation of ≥20% at least 4 times during home monitoring. Significant responses in the bronchodilator test and/or abnormal diurnal PEF variations were observed in 11/29 children tested and in 8/14 children with obstruction
Broström et al. [8], Sweden	After baseline spirometry, spirometry was repeated 15 min after inhalation of 5 mg salbutamol via a nebulizer	<i>Change in FEV₁ of >10%</i> Severe BPD 50%, mild-to-moderate BPD 29%, no BPD 21%
Mieskonen et al. [9], Finland	After baseline spirometry, spirometry was repeated 15 min after inhalation of 0.3 mg salbutamol via a spacer	<i>Percent change in FEV₁</i> All preterm children (n = 39): mean 9.5%, SD 6.4% BPD group: mean 11.8%, SD 6.2% No-BPD group: mean 7.8%, SD 5.4% Controls: mean 1.8%, SD 4.2%
De Kleine et al. [10], The Netherlands	After baseline spirometry, spirometry was repeated 20 min after a 0.75-min inhalation with salbutamol (5 mg/ml) from a nebulizer	<i>Percent change in FEV₁</i> No-BPD group (n = 24): mean 12%, SD 17% BPD group (n = 11): mean 13%, SD 10% Non-ventilated group (n = 37): mean 6%, SD 10% Controls: no details given
Korhonen et al. [11], Finland	After baseline spirometry, spirometry was repeated 10 min after inhalation of 0.2 mg salbutamol via a spacer	<i>Bronchodilator response FEV₁ in percentages</i> BPD group: median 34, range 14–63 No-BPD group: median 34, range –1 to 62 Term group: median 29, range –1 to 90 <i>Change in FEV₁ >15%</i> BPD group: 96%, i.e. 24/25 cases No-BPD group: 89%, i.e. 25/28 cases Term group: 79%, i.e. 23/29 cases
Sadeghi et al. [12], USA	Spirometry was carried out before and 15 min after administration of 2.5 mg albuterol sulphate in 2.5 ml of normal saline using a small-volume hand-held nebulizer	<i>Percent change in FEV₁</i> BPD group: median 9.2, interquartile range –0.5 to 18 Asthma group: median 9.4, interquartile range 5.1–14.6
Nixon et al. [13], USA	A subsample of children (n = 53) underwent maximal progressive exercise testing on a cycle ergometer. Spirometry was carried out immediately and 5 min after exercise as well as 20 min after 3 puffs of albuterol delivered via a spacer	<i>Change in FEV₁ after bronchodilator dexamethasone</i> BPD group: median (5th, 95th percentiles) 3%, range –20 to 39 Placebo group: median (5th, 95th percentiles) 7%, range –35 to 40 A positive bronchodilator response of ≥12% increase in FEV ₁ was seen in 20% of the dexamethasone group and in 23% of the placebo group

Table 2. (continued)

Study, country	Bronchodilator drug administration method	Results of bronchodilator drug treatment
Kulasekaran et al. [14], Australia	No details given	<p><i>Baseline FEV₁</i> BPD group: mean 82.3%, SD 13.9% Preterm group: mean 87.3%, SD 12.0%</p> <p><i>Spirometry after bronchodilator</i> BPD group: mean FEV₁ 89.8%, SD 13.0% Preterm group: mean 93.1%, SD 10.6%</p> <p>The bronchodilator response was defined as an improvement in FEV₁ of ≥12% or in FVC of ≥12% or in FEF_{25–75} of ≥25% after bronchodilator therapy. A bronchodilator response was found in 61.7% of the BPD group and in 47.7% of the preterm group</p>
Andreasson et al. [15], Sweden	4 × 0.5 mg doses of terbutaline were inhaled through a spacer at 1-min intervals. Spirometry was carried out before and 10 min after inhalation	<p><i>Percent change in FEV₁</i> In all 16 children tested: median 13%, range –6 to 33% In 5 children in the BPD group and in 4 in the no-BPD group the increase was over 10%</p>
Baraldi et al. [16], Italy	After baseline spirometry, spirometry was repeated after administering 300 µg of inhaled salbutamol by metered-dose inhaler via a spacer	<p>Reversibility to agonist was defined as a >12% increase in FEV₁ after salbutamol inhalation</p> <p>The airflow limitation of the BPD group was not reversible by ≤12% in 21/29 (72%) cases (mean increase in FEV₁: 5.8±0.9%) In 8/29 cases, the mean increase in FEV₁ was 18.8±2.7%. In the whole BPD group, the mean increase was 9.4±1.5% In the no-BPD group FEV₁ increased by ≥12% in 5/30 (17%) of cases tested</p>
Telford et al. [17], UK	After baseline spirometry, spirometry was repeated 15 min after 500 µg of salbutamol were given via a spacer	<p>FEV percent change of the continuous negative extrathoracic pressure group: mean 6%, SD 8% Standard group: mean 8%, SD 9%</p>
Doyle et al. [18], Australia	Participants with an FEV ₁ /FVC ratio of <75% were given a bronchodilator treatment, and FEV ₁ /FVC was repeated	<p>In 7 smokers, the FEV₁/FVC ratio improved significantly after bronchodilator administration: mean change 6.5% (95% CI 1.5–11.2). In 7 non-smokers, the mean improvement in the FEV₁/FVC ratio after bronchodilator administration was 3.4% (95% CI –1.5 to 7.8)</p>
Koumbourlis et al. [19], USA	After baseline spirometry, 3 puffs of isoproterenol were given from a metered-dose inhaler (131 µg/puff) during deep inspiration, and maximal expiratory flow volume curves were measured 15 min later	<p>A positive response to bronchodilator administration was defined as a significant increase from baseline values of at least 2 indices</p> <p>12/17 children responded to the bronchodilator, 8/9 with a lower airway obstruction and 4/8 with normal airway function</p>
Halvorsen et al. [20], Norway	After baseline spirometry, spirometry was repeated 10 min after the administration of salbutamol (Ventolin-metered dose inhaler via a Volumatic spacer, 100 µg/10 kg body weight)	<p><i>FEV₁ after administering salbutamol in percent of baseline</i> Controls: mean 102.4, SD 4.3 No-BPD group: mean 104.6, SD 2.7 Mild-BPD group: mean 103.9, SD 5.7 Moderate-to-severe-BPD group: mean 107.9, SD 9.6 Only 1 control subject and 3 participants with BPD had a ≥12% response to salbutamol (non-significant)</p>
Northway et al. [21], USA	Study participants who had an FEV ₁ of <80% were given 3.75 mg of aerosolized isoproterenol at a dilution of 1:400, and flow-volume curves were determined again. The diagnosis of reactive airway disease was based on an increase of >10% in FEV ₁ after inhalation of isoproterenol	<p>4 children with BPD had an increase of 10–15% in FEV₁ after isoproterenol, 3 had increases of 15–20% and 4 had increases of >20%</p>
Jacob et al. [22], Canada	After baseline spirometry, spirometry was repeated 15 min after albuterol (nebulized dose of albuterol 2.5 mg in 2.5 ml)	<p>8/14 children in each group showed a significant response to the bronchodilator with an increase in FEV₁ of ≥12% or an increase in FEF_{25–75} of ≥25%</p>
Pianosi and Fisk [23], Canada	Preterm group only: after baseline spirometry, spirometry was repeated after inhalation of 200 µg of albuterol from a metered-dose inhaler with a spacer in order to determine bronchodilator responsiveness defined as a >10% increase in FEV ₁ or a 25% increase in FEF _{25–75}	<p>7 children (3 with high-frequency ventilation) had significant improvement in spirometry following bronchodilator administration</p>

Table 2. (continued)

Study, country	Bronchodilator drug administration method	Results of bronchodilator drug treatment
Gross et al. [24], USA	Spirometry was carried out in children with an FEF_{25-75} of <80% of the predicted value after exercise albuterol had been administered by a metered-dose inhaler (180 µg, Aerochamber), and spirometry was repeated after 10 min. For this study, asthma was defined as bronchodilator responsiveness with an increase in FVC $\geq 15\%$, $FEV_1 \geq 15\%$ or $FEF_{25-75} \geq 20\%$ after albuterol	Asthma (bronchodilator responsiveness) was observed twice as often among the preterm children with previous BPD (20/43 cases, 47%) than among the children without BPD (13/53, 25%) or the term group (23/108, 21%)
Kaplan et al. [25], Israel	After baseline spirometry, spirometry was repeated following the administration of 400 µg salbutamol. Both tests were completed via a valved spacer device	<i>FEV₁ percent change after using a bronchodilator</i> BPD group: mean 5.2, SD 6.5% No-BPD group: mean 4.2, SD 5.7% Term controls: mean 1.8, SD 4.6%
Jones [26], UK and Ireland	After baseline spirometry, spirometry was repeated 15 min after the inhalation of 400 µg salbutamol administered with a spacer	<i>FEV₁ percent change after salbutamol</i> Dexamethasone group: mean 4.7%, SD 4.0% Placebo group: mean 6.6%, SD 4.8%

Study Outcomes

The data are presented in tables 1 and 2 and in the on-line supplementary tables E1 and E2. Due to the heterogeneity of the studies, we were unable to conduct a formal meta-analysis. The heterogeneity was due to:

- Range of bronchodilators used
- Variable dosage method, timing and frequency of administration
- Different criteria used to assess drug response

In addition, some of the papers commented on the proportion of preterm-born participants with a percentage change in %FEV₁ above varying nominal threshold values that varied. The numerical values were presented in some studies as means and in others as medians, which leads to further difficulty in comparing the studies directly.

Twenty-one papers reported spirometry after a single dose of a bronchodilator [5, 6, 8–26]. Sixteen studies administered salbutamol, with doses ranging from 100 µg by meter-dosed inhalers to 5 mg by nebulization [5, 6, 8–13, 16, 17, 20, 22–26]:

- 3/16 studies administered salbutamol after exercise; doses were 180 µg [24], 4 × 100 µg [7], and 1 study gave 3 puffs without stating the dosage [13]. Of the studies administering bronchodilators after exercise, 2 reported improvement in %FEV₁ after salbutamol [6, 13], and in the third study, bronchodilator responsiveness was defined as an increase in forced vital capacity (FVC) of $\geq 15\%$, FEV₁ of $\geq 15\%$ or in mid-expiratory flow at 75–25% of forced vital capacity (FEF_{25-75}) of $\geq 20\%$ and was observed in 47% of the preterm-born participants with BPD and 25% without BPD [24]

- 7/16 studies reported the mean change in %FEV₁ after salbutamol in preterm-born participants; results ranged from 4.2 to 13% [5, 9, 10, 16, 17, 25, 26]
- 2/16 studies [11, 12] reported a median change of 9.2 and 34% in %FEV₁ after salbutamol
- 1/16 study reported response to salbutamol as a change in FEV₁ of >10%, where 50% of preterm-born in the severe BPD group, 29% in the mild-to-moderate BPD group and 21% in the group without BPD had this response [8]
- 1/16 study reported that 7/32 preterm-born participants studied had a significant improvement in spirometry following bronchodilator administration [23]
- 1/16 study reported that 8/14 preterm-born participants with BPD and 8/14 preterm-born participants without BPD showed a significant response to bronchodilator administration with an increase in FEV₁ of $\geq 12\%$ or an increase in FEF_{25-75} of $\geq 25\%$ [22]
- 1/16 study reported a change in %FEV₁ after administering salbutamol as a percentage of the baseline value, resulting in postbronchodilator values of 107.9% for preterm-born participants with moderate to severe BPD, 103.9% in the mild-to-moderate BPD group and 104.6% without BPD [20]

Two studies administered isoproterenol: 393 µg by metered aerosol [19] and 3.75 mg by nebulization [21]. In the former case, 12/17 preterm-born participants with BPD had a positive response defined as a significant increase from baseline of at least 2 indices defined as a change of >10% for the FVC of >20% for the FEV₁ and of >25% for the peak expiratory flow (PEF) rate, FEF_{25-75} ,

FEF₅₀ and FEF₇₅, respectively [19]. In the latter case, 4/26 preterm-born participants with BPD had increases of 10–15% in %FEV₁ after nebulized isoproterenol, 3/26 cases had increases of 15–20%, and 4/26 cases had increases of >20% [21].

One study administered 4 doses of terbutaline at 1-min intervals and reported the median change in %FEV₁ as 13% [15]. Two studies did not report the bronchodilator used [14, 18]. One noted an improvement in %FEV₁, and, interestingly, in the other study of young adults [18], the mean change in FEV₁/FVC after a bronchodilator administration was 6.5% in 7 smokers but only 3.4% in 7 non-smokers.

Only 1 study assessed the impact of longer-term bronchodilator administration. In that study, the initial response to 0.5 mg of terbutaline did not show a change in %FEV₁ of $\geq 15\%$, but 5/29 cases (17%) had an increased %FEV₁ of $\geq 10\%$. Thereafter, data are reported for the PEF during 2 weeks of treatment with terbutaline (0.25 mg twice daily) [7] with twice daily monitoring of PEF at home for 4 weeks to assess diurnal variation. Postbronchodilator PEF increments of $\geq 15\%$ were observed at least 3 times in 31% of patients. Six children had a diurnal variation of $\geq 20\%$ at least 4 times during the 4 weeks of home monitoring.

In summary, the majority of studies reported a deficit in %FEV₁ in preterm-born participants with or without BPD compared with term controls or historical control (reference value) data. The majority of papers reported an improvement in %FEV₁ after bronchodilators. The largest improvements in %FEV₁ were seen in the preterm-born participants with BPD, who had the greatest deficits in %FEV₁ when compared to the preterm-born participants without BPD or the term controls, if studied.

Discussion

We systematically reviewed articles that reported the short- and longer-term effect of bronchodilator administration on %FEV₁ in preterm-born children and adults. The majority reported short-term effects of a single-dose administration with an improvement in %FEV₁ after bronchodilator treatment. We only identified 1 study which investigated longer-term administration (2 weeks) of a β_2 -agonist, although it appears that %FEV₁ results were only reported after the initial dose of terbutaline [7]. The study noted that regardless of BPD, increased bronchial responsiveness was common in preterm-born participants.

Study Limitations

This systematic review has a number of limitations. We were unable to conduct a formal meta-analysis as the publications were disparate. We were limited by the quality and quantity of information presented in the included articles. Overall, the studies were of only moderate methodological quality, and there was a moderate risk of selection bias. The studies are likely to have had recruitment bias, often selecting the worst cases, and were often focussing on areas other than specifically drug intervention. Furthermore, the studies were conducted over a number of years during which much progress in neonatal medicine occurred. We were also limited by the duration of the treatment and the type of bronchodilator used.

With improvements in the medical management of extremely preterm-born infants, more of them are surviving. As we reported previously, these children are at risk of long-term deficits in %FEV₁ even if they do not have BPD in the early neonatal period [1]. In our previous systematic review and meta-analysis, we reported that preterm-born participants with and without BPD have deficits in %FEV₁ compared with term-born participants [1]. There are also growing numbers of late-preterm-born participants who are at risk of deficits in lung function. We reported that these children have deficits in lung function at 8–9 years of age which is similar to the deficits seen in the very preterm children, although these deficits appeared to improve when spirometry was repeated at 14–17 years of age [3]. Although we identified deficits in FEV₁, it is unclear if these deficits are reversible.

It is possible that deficits in lung function of this magnitude lead to respiratory symptoms. Preterm-born children with and without BPD may experience increased respiratory symptoms, often reported as asthma, which is usually non-atopic; they have increased reported inhaled drug use and increased health utilization, including hospitalization, especially in early childhood [27]. Preterm-born participants with BPD may also have increased exercise-induced bronchoconstriction and, importantly, may have reversible bronchoconstriction, as recently reported when they were studied at 8–12 years of age [6].

There is a paucity of data on the impact of longer-term administration of bronchodilators on the lung function of preterm children and therefore a lack of data upon which to make informed decisions and to guide treatment for the survivors of prematurity. It may be that a better understanding of the underlying mechanisms may aid

better targeted therapy especially for those with significant airway obstruction. The underlying mechanisms of airway obstruction are likely to be either inflammatory, as suggested by a single study reporting neutrophilic airway inflammation [28] and increased oxidant stress assessed by measuring 8-isoprostane concentration in exhaled breath condensate [29], or due to smooth muscle hypertrophy, as suggested by pathological studies of preterm infants dying from respiratory failure. There is a clear need to understand the underlying mechanisms before progressing to trials to assess the role of bronchodilators or anti-inflammatory treatments in this group of vulnerable children. Although bronchodilator treatment appears, in the majority of single dose studies, to improve deficits in %FEV₁, there are many reports of preterm-born children being undertreated with bronchodilators. There may be a tendency to regard respiratory symptoms in preterm-born children as an inevitable consequence of airway injury and remodelling. There is a need to increase awareness of the potential for reversible airway obstruction and to understand the effects of treatment on symptoms and long-term respiratory outcomes in this patient population.

In conclusion, in this systematic review we have identified a number of small disparate studies that suggest a short-term benefit of bronchodilator treatment on FEV₁ in preterm-born participants. However, there is a paucity of data on the effect of longer-term administration of bronchodilators on the lung function of preterm-born children. We would suggest that, on the current low level of evidence of the short-term benefits of bronchodilator treatment on FEV₁, it would be reasonable to treat deficits in FEV₁ in symptomatic preterm-born participants with bronchodilators with a view to assessing clinical and/or physiological improvements. However, there is an urgent need to not only understand the underlying mechanisms, but also for an adequately powered study to determine whether the use of regular bronchodilators improves existing deficits in lung function and/or respiratory symptoms in preterm-born survivors.

Disclosure Statement

There are no competing interests.

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