Increasing airway obstruction through life following bronchopulmonary dysplasia: a meta-analysis

James T.D. Gibbons [1,2,3], Christopher W. Course [4], Emily E. Evans[5], Sailesh Kotecha [4], Sarah J. Kotecha[4] and Shannon J. Simpson [1,3]

[1]Children's Lung Health, Wal-yan Respiratory Research Centre, Telethon Kids Institute, Perth, Australia. [2]Department of Respiratory Medicine, Perth Children's Hospital, Perth, Australia. [3]Curtin School of Allied Health, Curtin University, Perth, Australia. [4]Department of Child Health, Cardiff University School of Medicine, Cardiff, UK. [5]Department of Paediatrics, Cardiff and Vale University Health Board, Cardiff, UK.

Corresponding author: Shannon J. Simpson (shannon.simpson@telethonkids.org.au)

Shareable abstract (@ERSpublications)
This meta-analysis describes increased airway obstruction in survivors of preterm birth, with those diagnosed with bronchopulmonary dysplasia as infants having worse obstruction that also increases with age https://bit.ly/40Z9BKp

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Abstract

Background Few studies exist investigating lung function trajectories of those born preterm; however growing evidence suggests some individuals experience increasing airway obstruction throughout life. Here we use the studies identified in a recent systematic review to provide the first meta-analysis investigating the impact of preterm birth on airway obstruction measured by the forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio.

Methods Cohorts were included for analysis if they reported FEV_1/FVC in survivors of preterm birth (<37 weeks' gestation) and control populations born at term. Meta-analysis was performed using a random effect model, expressed as standardised mean difference (SMD). Meta-regression was conducted using age and birth year as moderators.

Results 55 cohorts were eligible, 35 of which defined groups with bronchopulmonary dysplasia (BPD). Compared to control populations born at term, lower values of FEV_1/FVC were seen in all individuals born preterm (SMD −0.56), with greater differences seen in those with BPD (SMD −0.87) than those without BPD (SMD −0.45). Meta-regression identified age as a significant predictor of FEV_1/FVC in those with BPD with the FEV_1/FVC ratio moving −0.04 SDS away from the term control population for every year of increased age.

Conclusions Survivors of preterm birth have significantly increased airway obstruction compared to those born at term with larger differences in those with BPD. Increased age is associated with a decline in FEV_1/FVC values suggesting increased airway obstruction over the life course.

Introduction

Lung disease remains a significant complication of preterm birth despite temporal changes in the underlying pathology of bronchopulmonary dysplasia (BPD) [1]. Advances in neonatal care during the 1990s, particularly the routine use of antenatal corticosteroids and exogenous surfactant [2], have increased survival of infants born very and extremely preterm (<32 weeks' gestation), and resulted in the emergence of "new" BPD. As such, there are more survivors of preterm birth than ever before, and those born in the contemporary era with new-BPD are born at an earlier stage of lung development with large and simplified alveoli [2] compared to the thick-walled alveoli initially described by Northway *et al.* [3]. Despite this, our understanding of the long-term implications of preterm lung disease remains limited.

We recently published an updated and extended systematic review and meta-analysis demonstrating that survivors of preterm birth have persistent deficits in spirometry measured forced expiratory volume in 1 s

(FEV_1) [4]. The greatest deficits were seen in those with BPD having a percentage predicted FEV_1 16% lower than those born at term. It has also been recognised, however, that increased airway obstruction as measured by the FEV_1/forced vital capacity (FVC) ratio is also reported in survivors of preterm birth [5]. Furthermore a progressive decline in FEV_1/FVC values suggestive of increased airway obstruction has been noted throughout childhood and adolescence in longitudinal studies by Simpson *et al.* [6] and Doyle *et al.* [7] in preterm survivors of the post-surfactant era, and extending into the sixth decade of life in those born in the pre-surfactant era [8]. As such, there is a growing recognition that very preterm birth may represent a significant risk factor for early-onset COPD [9, 10], with COPD characterised by progressive airway obstruction and commonly defined as post-bronchodilator FEV_1/FVC <0.70 [11].

To test the hypothesis that survivors of preterm birth have increased airway obstruction compared to those born at term, and that preterm birth and BPD are risk factors for developing COPD, here we will perform a *post hoc* analysis to expand on the findings from our recent systematic review on FEV_1 to provide what is to the best of our knowledge the first meta-analysis on FEV_1/FVC in all survivors of preterm birth born <37 weeks' gestation.

Methods

Research questions

This *post hoc* meta-analysis was designed to answer the following questions:

1) Do those born preterm (with and without a diagnosis of BPD) have increased airway obstruction, as measured by FEV_1/FVC, compared to individuals born at term?
2) Does airway obstruction, as measured by FEV_1/FVC, increase with age in those born preterm (with and without BPD) compared with those born at term?

The forced mid-expiratory flow ($FEF_{25–75}$) has previously been used as a marker of small airway obstruction; however due to concerns about highly variable and poorly reproducible measurements cited in the latest European Respiratory Society and American Thoracic Society technical standard [12], it has not been used as an outcome in this review. $FEF_{25–75}$ values have, however, been provided for reference from extracted studies.

Study identification and selection

Studies were identified using the systematic review methods described previously by Kotecha *et al.* [4, 13] which followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [14]. Briefly, 86 studies in total met inclusion criteria for analysis of FEV_1. Although this systematic review was designed to capture studies to answer questions specifically related to FEV_1, the search criteria were subsequently deemed acceptable to capture appropriately other spirometry measures including FVC, FEV_1/FVC ratio and $FEF_{25–75}$. Studies were included for this analysis if they fulfilled the following criteria: 1) FEV_1/FVC reported in survivors of preterm birth (with or without BPD) and those born healthy at term; or if 2) FEV_1/FVC were reported separately in survivors of preterm birth with and without BPD.

Publication bias and study quality

The effects of publication bias were measured subjectively using funnel plots and objectively using Egger's test. Study quality was assessed using a modified version of the Newcastle–Ottawa scale as previously described [4].

Data collection

Data were extracted from published manuscripts into the electronic data capture database REDCap (Research Electronic Data Capture) [15]. If data were not presented in an appropriate format, the manuscript's authors were contacted to see if they could provide the additional required data. Where available, data were collected as mean±SD. Where variances were presented as standard error, 95% confidence intervals (95% CI), interquartile range (IQR) or range (minimum and maximum values), values were converted to standard deviations using the methods outlined in *The Cochrane Handbook* [16]. Where data were presented as medians, it was first checked for skewness using the methods outlined by Shi *et al.* [17] and if found to be significantly skewed, not included in the analysis. For included data, the mean was estimated using the methods of Luo *et al.* [18], and IQR and range were estimated using the methods of Wan *et al.* [19]. Spirometry values were preferably collected as standard (Z) scores and percentage predicted, respectively, to adjust for variations in height and sex of individuals over raw ratios. Each group extracted from a study was assigned one of the following statuses: 1) preterm with BPD; 2) preterm without BPD; 3) preterm with mix of participants (both with and without BPD) or BPD status not specified; or 4) term. BPD diagnostic criteria were recorded, and it was considered acceptable to have BPD status classified on diagnostic criteria appropriate for the time of study publication. Groups were also

banded by gestational age (extremely preterm: <28 weeks' gestation, very preterm: 28–32 weeks' gestation and moderate–late preterm: >32 weeks' gestation) to allow for subgroup analysis.

Data analysis

Statistical analysis was performed in R (version 4.1.2) using the meta (version 5.1-1), metafor (version 3.0-2) and dmetar. (version 0.0.9) packages using previously documented techniques [20]. Data were extracted directly from REDCap to minimise the possibility for transcription errors during analysis. If necessary, study groups were pooled using the methods described in *The Cochrane Handbook* [16] into Preterm (All), Preterm (BPD), Preterm (no BPD) or Term groups for analysis. If a summary group of all preterm participants was not reported by the study, all individual preterm groups were combined to provide the value for Preterm (All).

As studies presented results using varying continuous measures (Z-scores, % predicted, or raw values), standardised mean difference (SMD) was calculated between groups in each study to allow for cross-study comparison as per Cochrane recommendations [16]. Heterogeneity was calculated using the restricted-maximum likelihood method, appropriate for continuous outcomes, with Knapp–Hartung adjustments used to control for uncertainty in between-study heterogeneity. Use of fixed *versus* random effects models for meta-analysis was determined by between-study heterogeneity (I^2). The Hedges' g method was used in calculating the SMD to correct for overestimation with small sample sizes.

Meta-regression analysis was conducted to investigate the effect of age and birth year on the SMD calculated for each group comparison. While age was the primary variable of interest, birth year was investigated to account for changes in lung function which may have occurred due to changes in medical care over time. A variance inflation factor (VIF) was calculated using the vif.rma function of the metafor package to measure any effects of collinearity between age and birth year. Mean participant age was rounded to the nearest whole number for each study due to studies presenting varying degrees of detail for the age of each group. F-tests were used to calculate the significance of age and birth year as moderators in reducing heterogeneity and thus having a significant effect on regression models against SMD.

Results

Study selection and study quality

Of the 86 preterm cohorts identified with spirometry data from the systematic review, 55 were identified with FEV_1/FVC data meeting inclusion criteria with 35 defined groups born preterm diagnosed with BPD and 31 defined groups born preterm without BPD [5, 8, 21–115]. Mean quality score for studies with FEV_1/FVC data was 14.4 of a total score of 20, ranging from 7 to 19 (supplementary table S1). Summarised lung function data extracted and converted to pooled mean±SD values are available in supplementary table S2.

Publication bias

Publication bias was observed when comparing Preterm (All) with Term groups subjectively with an asymmetrical distribution noted on funnel plots, and objectively with Egger's test reaching significance ($p<0.01$). When preterm groups were separated into those with and without BPD, however, a symmetrical distribution was noted on all funnel plots and Egger's test did not reach significance (supplementary figure S1). This could imply that asymmetry seen in the combined preterm group may be due to the heterogeneity of having two different disease populations defined by the presence or absence of BPD.

Meta-analysis

All spirometry outcomes were reduced in those born preterm compared with term controls (table 1). Moderate to high levels of heterogeneity were noted in all groups necessitating the use of random effects meta-analysis. However, heterogeneity was reduced when BPD status was considered.

Those born preterm had an FEV_1/FVC ratio 0.56 SDS lower than term-born controls (95% CI −0.68 to −0.45). BPD status had a significant impact on airflow obstruction (figure 1), such that those with BPD had reductions in FEV_1/FVC ratio of −0.87 SDS (−1.02 to −0.71) below term, while survivors of preterm birth without BPD had less severe but still significant airflow obstruction at −0.45 SDS (−0.62 to −0.27) below term.

Lower gestational age was associated with a greater lung function deficit. Subgroup analysis conducted by mean gestational age identified that those born at <28 weeks' gestation had the most substantial airflow obstruction with FEV_1/FVC values 0.72 SDS (−0.86 to −0.59) below term controls, with less obstruction seen in those born at 28 to 32 weeks' (−0.58 SDS, −0.79 to −0.37) and moderate-to-late preterm at >32 weeks' gestation (−0.21 SDS, −0.35 to −0.07).

TABLE 1 Meta-analysis of all spirometry variables

	n_{Cohort}	n_1	n_2	SMD (95% CI)	I^2 % (95% CI)	95% prediction interval
FEV_1						
Preterm (All) *versus* Term	90	7235	17 436	−0.67 (−0.75 to −0.58)***	80 (76–84) ***	(−1.33 to −0.00)
Preterm (BPD) *versus* Term	55	1745	2856	−1.24 (−1.38 to −1.10)***	66 (54–74)***	(−1.97 to −0.51)
Preterm (No BPD) *versus* Term	50	2342	2742	−0.46 (−0.55 to −0.38)***	46 (25–61)***	(−0.85 to −0.07)
Preterm (BPD) *versus* Preterm (No BPD)	57	1963	2743	−0.67 (−0.78 to −0.57)***	51 (34–64)***	(−1.21 to −0.14)
FVC						
Preterm (All) *versus* Term	77	6635	15 401	−0.36 (−0.43 to −0.29)***	65 (56–73)***	(−0.81 to 0.08)
Preterm (BPD) *versus* Term	50	1683	2769	−0.69 (−0.80 to −0.58)***	54 (37–67)***	(−1.23 to −0.14)
Preterm (No BPD) *versus* Term	46	2219	2663	−0.21 (−0.29 to −0.13)***	35 (7–55)*	(−0.53 to 0.12)
Preterm (BPD) *versus* Preterm (No BPD)	52	1907	2605	−0.42 (−0.51 to −0.33)***	35 (8–54)**	(−0.79 to −0.05)
FEV_1/FVC						
Preterm (All) *versus* Term	55	5501	12 648	−0.56 (−0.68 to −0.45)***	83 (78–86)***	(−1.29 to 0.16)
Preterm (BPD) *versus* Term	35	1326	1851	−0.87 (−1.02 to −0.71)***	72 (61–80)***	(−1.64 to −0.09)
Preterm (No BPD) *versus* Term	31	1606	1727	−0.45 (−0.62 to −0.27)***	79 (70–85)***	(−1.28 to 0.39)
Preterm (BPD) *versus* Preterm (No BPD)	36	1359	1902	−0.38 (−0.50 to −0.25)***	52 (29–67)***	(−0.87 to 0.12)
$FEF_{25–75}$						
Preterm (All) *versus* Term	50	4625	9540	−0.82 (−0.96 to −0.68)***	85 (80–88)***	(−1.65 to 0.00)
Preterm (BPD) *versus* Term	35	1224	1758	−1.33 (−1.50 to −1.15)***	61 (44–73)***	(−1.94 to −0.71)
Preterm (No BPD) *versus* Term	30	1458	1610	−0.60 (−0.72 to −0.47)***	47 (20–66)**	(−0.97 to −0.23)
Preterm (BPD) *versus* Preterm (No BPD)	38	1394	1972	−0.66 (−0.81 to −0.51)***	60 (43–72)***	(−1.28 to −0.04)

n_{cohort}: number of cohorts; n_1: number of individuals in group 1; n_2: number of individuals in group 2; SMD: standardised mean difference as measured by Hedges' g; I^2: heterogeneity; FEV_1: forced expiratory volume in 1 s; BPD: bronchopulmonary dysplasia; FVC: forced vital capacity; $FEF_{25–75}$: forced mid-expiratory flow. *: p<0.05; **: p<0.01; ***: p<0.001.

Identification and removal of outliers to data was not found to have a significant effect on the overall outcomes of the meta-analysis.

Meta-regression

Meta-regression analyses comparing spirometry values in preterm children to term controls, accounting separately for age and birth year, are presented in table 2. In those with BPD increased airflow obstruction was associated with increasing age, with the FEV_1/FVC ratio moving −0.04 SDs away from the term control population for every year of increased age (R^2=48.8, p<0.001) (figure 2). Over a 25-year period this amounts to the FEV_1/FVC ratio being 1 SD below those born healthy at term. The FEV_1/FVC ratio was also noted to increase by 0.02 SDs for every annual increase in birth year (R^2=11.7, p=0.04) relative to the term control group.

Cohorts with lung function data collected at older ages were noted to have come from those born in earlier birth years, and a significant correlation was noted between age and birth year (p<0.001); however in regression models accounting for both age and birth year the VIF for age was low (1.42). Additionally, ANOVA of two mixed effects models, one accounting for age alone and the other accounting for both age and birth year, was performed with results showing that after accounting for age, birth year did not significantly improve the model (p=0.91) where conversely after accounting for birth year, age was found to remain a significant predictor (p=0.001). This suggests despite the noted collinearity, age primarily accounted for the changes seen in FEV_1/FVC ratios.

No significant associations were noted in meta-regression analysis between FEV_1/FVC and age or birth year in the combined preterm group or in those born preterm without BPD. The FEV_1/FVC ratio in those with BPD was however also noted to decline by −0.03 SDs annually with age relative to those born preterm without BPD (R^2=62.6, p=0.01). The relationship between FEV_1 and birth year has been discussed in our prior manuscript.

Discussion

This meta-analysis consolidates the current literature on airway obstruction in individuals born preterm. We show that survivors of preterm birth, both with and without a diagnosis of BPD, have increased airway obstruction (FEV_1/FVC) compared with those born healthy at term. Additionally, those diagnosed with BPD have more profound airway obstruction. Meta-regression analysis show that airway obstruction

increases more rapidly with ageing in those with BPD. Therefore, a diagnosis of BPD during infancy represents a significant risk factor for lifelong preterm lung disease.

To our knowledge no previous meta-analysis has been published investigating FEV_1/FVC in those born preterm across all gestational ages <37 weeks' gestation. A recent systematic review and meta-analysis by Du Berry *et al.* [116] investigated people born at moderate–late gestational ages (32 to <37 weeks' gestation) reporting modest but significant overall decreases in FEV_1/FVC in this group compared to those born at term. Our analysis extends these findings, to show that individuals born very (28–32 weeks' gestation) and extremely (<28 weeks' gestation) preterm have progressively more profound degrees of airway obstruction reported later in life, with those diagnosed with BPD as infants at the highest risk.

Results of the meta-regression analysis reported here correlate with longitudinal data demonstrating an accelerated decline in FEV_1/FVC suggestive of increased airway obstruction following preterm birth previously reported in pre-surfactant era cohorts reported by Bårdsen *et al.* [117], and post-surfactant era cohorts by Simpson *et al.* [6] and Doyle *et al.* [7]. Additionally, a recently published study by Bui *et al.* [8] on a pre-surfactant era cohort of middle-aged survivors of preterm birth reported declining FEV_1/FVC trajectories across middle age in those born at 28 to <32 weeks' gestation compared to those born late preterm or at term, and a significant association with COPD diagnosis. Preterm birth and BPD have been

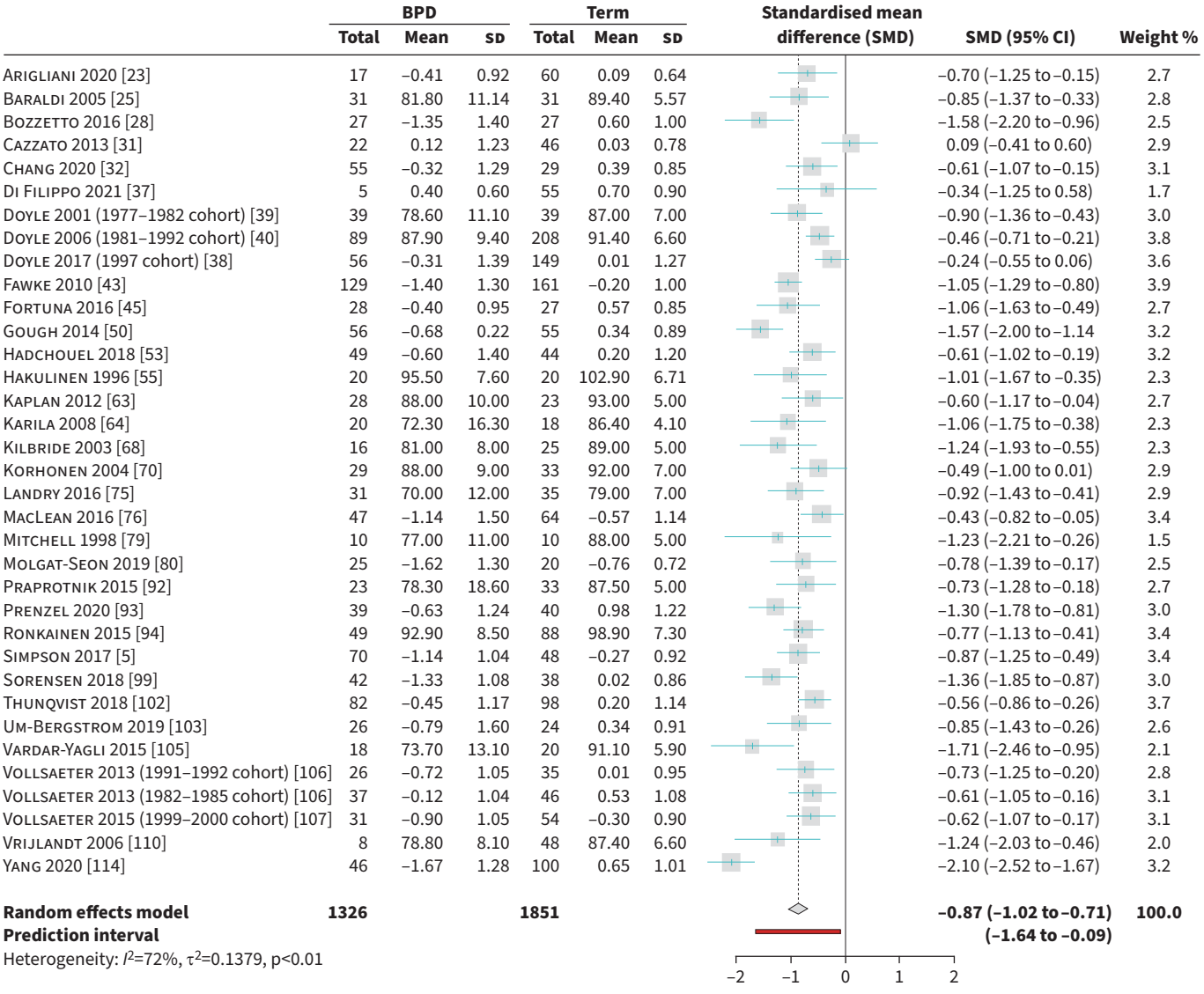

FIGURE 1 Forest plot of forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC): bronchopulmonary dysplasia (BPD) *versus* Term.

TABLE 2 Meta-regression analysis moderating for age and birth year

	Age			Birth year		
	R^2 (I^2)	β (95% CI)	p-value	R^2 (I^2)	β (95% CI)	p-value
FEV_1						
Preterm (All) *versus* Term	1.6 (78.5)	0.01 (−0.01 to 0.02)	0.39	0.0 (79.3)	0.00 (0.00 to 0.01)	0.39
Preterm (BPD) *versus* Term	0.0 (66.0)	−0.01 (−0.04 to 0.02)	0.50	20.3 (60.7)	0.02 (0.00 to 0.03)	**0.02**
Preterm (No BPD) *versus* Term	0.0 (43.4)	0.00 (−0.01 to 0.02)	0.61	0.0 (44.2)	0.00 (0.00 to 0.01)	0.27
Preterm (BPD) *versus* Preterm (No BPD)	7.4 (50.7)	−0.01 (−0.04 to 0.01)	0.18	22.9 (49.3)	0.02 (0.00 to 0.03)	**0.01**
FVC						
Preterm (All) *versus* Term	2.2 (63.5)	0.01 (−0.01 to 0.02)	0.32	0.0 (64.3)	0.00 (−0.01 to 0.01)	0.83
Preterm (BPD) *versus* Term	0.0 (56.6)	0.00 (−0.02 to 0.02)	0.99	0.0 (52.9)	0.00 (−0.01 to 0.02)	0.57
Preterm (No BPD) *versus* Term	0.0 (35.8)	0.00 (−0.01 to 0.02)	0.67	0.0 (36.9)	0.00 (−0.00 to 0.01)	0.34
Preterm (BPD) *versus* Preterm (No BPD)	0.0 (36.6)	−0.00 (−0.02 to 0.01)	0.58	0.0 (39.5)	0.00 (−0.01 to 0.02)	0.37
FEV_1/FVC						
Preterm (All) *versus* Term	1.6 (82.7)	−0.01 (−0.03 to 0.01)	0.36	0.0 (83.0)	0.00 (−0.01 to 0.01)	0.99
Preterm (BPD) *versus* Term	48.8 (56.6)	−0.04 (−0.07 to −0.02)	**0.001**	11.7 (67.7)	0.02 (0.00 to 0.04)	**0.04**
Preterm (No BPD) *versus* Term	2.1 (77.0)	−0.01 (−0.04 to 0.02)	0.41	0.0 (78.2)	0.01 (−0.01 to 0.03)	0.57
Preterm (BPD) *versus* Preterm (No BPD)	62.6 (27.8)	−0.03 (−0.05 to −0.01)	**0.01**	9.0 (48.5)	0.01 (−0.01 to 0.03)	0.19
$FEF_{25–75}$						
Preterm (All) *versus* Term	0.0 (84.8)	0.01 (−0.02 to 0.03)	0.61	1.2 (83.5)	0.01 (−0.01 to 0.02)	0.22
Preterm (BPD) *versus* Term	0.0 (59.2)	0.00 (−0.03 to 0.04)	0.79	5.2 (44.8)	0.01 (−0.01 to 0.03)	0.29
Preterm (No BPD) *versus* Term	0.0 (37.8)	0.01 (−0.01 to 0.03)	0.49	0.0 (45.2)	−0.00 (−0.02 to 0.01)	0.96
Preterm (BPD) *versus* Preterm (No BPD)	0.0 (62.3)	−0.00 (−0.03 to 0.02)	0.75	17.7 (58.1)	0.02 (0.00 to 0.04)	**0.03**

p-values in bold are statistically significant. R^2: heterogeneity accounted for by moderator (as percentage); I^2: residual heterogeneity remaining after accounting for moderator; β: regression coefficient; p-value: p-value for influence of moderator on effect size of study, calculated using F-test; FEV_1: forced expiratory volume in 1 s; BPD: bronchopulmonary dysplasia; FVC: forced vital capacity; $FEF_{25–75}$: forced mid-expiratory flow.

gaining growing recognition as risk factors for later developing a COPD-like phenotype, identified in both the recent *Lancet* commission on COPD [118] and Global Initiative for Chronic Obstructive Lung Disease (GOLD) report [119]. With findings of increasing airway obstruction associated with age, the results of this study support the suggestion that those diagnosed with BPD as infants are at significant risk of lifelong preterm lung disease and are more likely to follow a trajectory to an early-onset COPD-like disease later in life.

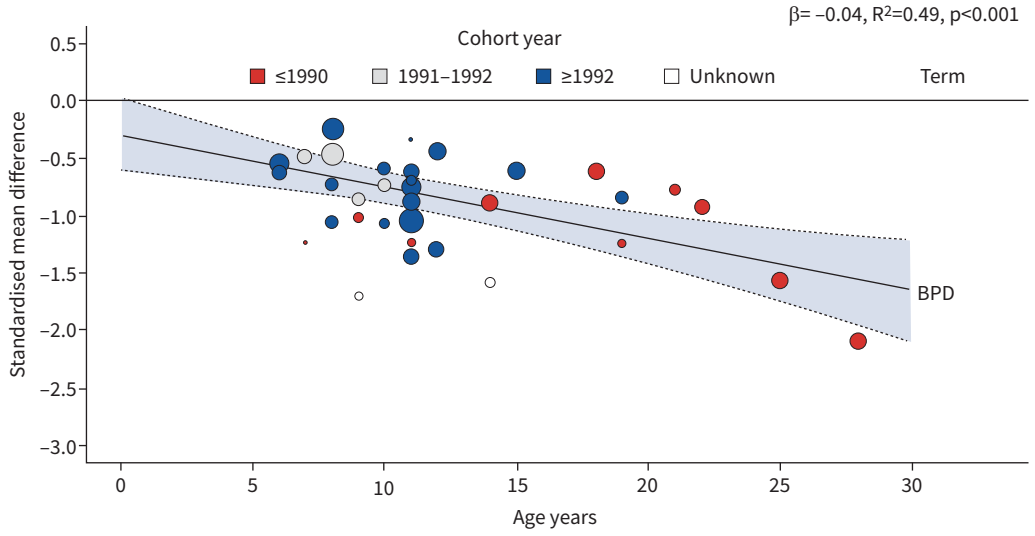

FIGURE 2 Meta-regression of forced expiratory volume in 1 s/forced vital capacity moderating for age: bronchopulmonary dysplasia (BPD) *versus* Term.

The mechanisms underpinning increasing airway obstruction following preterm birth are incompletely understood though likely multifactorial. Structural abnormalities of the airways are a well-recognised feature of BPD at birth, noted to persist into adolescence and adulthood on computed tomography imaging and on histopathology [5, 120]. Persistent inflammation is also likely to play a role in ongoing airway remodelling with evidence of CD8 T-lymphocyte predominant chronic inflammation seen in adults previously diagnosed with BPD, resembling patterns observed in COPD [121]. In addition, genetic factors may also play a role, with a significant association noted between COPD-associated genes and FEV_1 and FEV_1/FVC in preterm-born children at 5 years [122]. As our understanding of the mechanisms underlying the disease improves, it may provide opportunities to target treatments to slow, arrest or reverse any associated decline in lung function, and as such should be targeted as a priority in research moving forward.

With substantial changes in neonatal practice over the last several decades it may be anticipated that long-term respiratory outcomes may have changed, as evident by improvements in FEV_1 noted in our previous paper [4]; however after adjusting for the effects of age, birth year was not significantly associated with airway obstruction in this analysis. Interpretation of this finding is complicated, however, by the changing nature of BPD over the same few decades, as while neonatal care has improved in the "post-surfactant era", those diagnosed with BPD are now born at significantly lower gestational ages and have a different airway pathology at birth to those born in the "pre-surfactant era" [2]. It is feasible to consider that when considering the long-term respiratory consequences of preterm birth, improvements in neonatal care may have been somewhat offset by increased numbers of children surviving extreme preterm birth. Conversely, not all longitudinal cohorts in the post-surfactant era demonstrate the increase in airway obstruction described by Simpson *et al.* [6] and Doyle *et al.* [7]. In addition to their pre-surfactant era cohorts, Bårdsen *et al.* [117] also report on a post-surfactant era cohort where airway obstruction appears to improve between mid-childhood and early adulthood. Notably the pre-surfactant era cohorts in the same region show increased airway obstruction through adolescence. Ongoing follow-up of other longitudinal cohorts in the post-surfactant era will be critical to improve our understanding of any effects changes in neonatal practice have had on long-term lung health.

Limitations must be noted too in the data available for this analysis, as it reflects cross-sectional data from a highly heterogeneous group of studies across multiple decades using different laboratory equipment and populations. Additionally, as has been previously noted, there have been significant changes in neonatal care over time which have gradually changed the characteristics of preterm lung disease, most notably with "classic-" and "new-BPD", while the diagnosis of BPD has also changed significantly over the last several decades, likely contributing to the high levels of heterogeneity noted in our data. The strengths of this study parallel those described by Kotecha *et al.* [4] in that we have provided the largest analysis to date of FEV_1/FVC in those born preterm with 5511 preterm-born and 12 648 term-born individuals included in this analysis. While limiting this analysis to only include studies with term-born reference populations resulted in several studies being excluded, it also provides confidence in the accuracy of differences noted between preterm and term populations, which may not be possible if reference equations were used as a standard to measure against.

This study identifies an urgent need to understand better the lifelong lung health trajectories of those born preterm due to the implications associated with an ever-growing population of survivors of preterm birth and the potential lifelong impacts of preterm lung disease. Identification of individuals at risk for early decline in lung health trajectories will facilitate appropriate follow-up and intervention at an earlier time point, something which has been demonstrated to be essential in other forms of COPD. Additionally, there is a need to better understand the underlying mechanisms behind preterm lung disease such that we can better identify treatments to halt or reverse this trajectory towards COPD.

In conclusion, this meta-analysis provides the first comprehensive review of airway obstruction measured using spirometry in survivors of preterm birth. It raises significant concerns of progressive airway obstruction in a growing population of individuals, which is only now starting to be reflected in the adult healthcare system. It is a necessity that ongoing longitudinal follow-up of cohorts of survivors of preterm birth continue as they enter adulthood so that we can better understand the long-term respiratory consequences of prematurity, and ultimately so that we can identify treatments to halt or reverse prematurity-associated lung disease.

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