Lung volumes, gas transfer and oscillometry after preterm birth: systematic review and meta-analysis

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Substantial physiological abnormalities persist following preterm birth when lung function is measured using static lung volumes, gas transfer and oscillometry. https://bit.ly/4kl67fU

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Abstract

Background Small airway and lung parenchymal abnormalities frequently occur following preterm birth but are commonly missed by spirometry. Static lung volumes, diffusing capacity of the lung for carbon monoxide (D_{LCO}) and oscillometry provide a more precise characterisation of these conditions. We hypothesised that differences in these measures exist between individuals born preterm and at term and we aimed to systematically review the literature to identify and quantify these differences in lung function.

Methods This systematic review and meta-analysis, registered with PROSPERO (CRD42022320775) and guided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards, searched six databases up to 29 December 2024. We included studies comparing lung function between preterm subjects and term controls *via* static lung volumes, gas transfer or oscillometry. Differences in lung function were analysed using random-effects meta-analysis to compute the standardised mean difference (SMD).

Results From 12 143 titles, we analysed 52 cohorts with static lung volumes, 37 with gas transfer and 18 with oscillometry data. While total lung capacity was similar between preterm and term cohorts (SMD −0.08, 95% CI −0.17 to 0.004), preterm participants showed increased residual volume (SMD 0.32, 95% CI 0.19 to 0.44) and residual volume/total lung capacity (SMD 0.45, 95% CI 0.28 to 0.63). D_{LCO} was lower in preterm cohorts (SMD −0.51, 95% CI −0.64 to −0.38). Preterm cohorts also demonstrated increased airway resistance at 5/6 Hz (SMD 0.44, 95% CI 0.22 to 0.67), difference between airway resistance at 5/6 Hz and 20 Hz (SMD 0.51, 95% CI 0.07 to 0.96), resonant frequency (SMD 0.63, 95% CI 0.12 to 1.15) and area under the reactance curve (SMD 0.62, 95% CI 0.35 to 0.88).

Interpretation We demonstrate that preterm birth is linked to notable abnormalities in static lung volumes, gas transfer and oscillometry, underscoring the necessity of employing comprehensive pulmonary function tests beyond spirometry to monitor and address long-term respiratory outcomes effectively.

Introduction

Preterm birth is associated with enduring respiratory consequences [1]. Life-sustaining interventions such as mechanical ventilation and supplemental oxygen use can injure the developing lung, while premature exposure to the extrauterine environment disrupts normal alveolar development [2]. Particularly vulnerable are those born at very (<32 weeks') or extremely (<28 weeks') early gestational ages, and those diagnosed with bronchopulmonary dysplasia (BPD) during infancy. However, prematurity-associated lung disease (also referred to as post-prematurity respiratory disease) is not isolated to this group, with even those born moderate-late preterm demonstrating abnormalities in lung health [3]. Increased rates of wheezing, pulmonary hypertension and respiratory-related hospitalisation are well documented in this population [4–6]. Recent studies have also highlighted preterm birth as a significant risk factor for early-onset COPD [7].

Despite preterm birth representing possibly the earliest origin of chronic respiratory disease, it remains unclear how best to monitor this group using lung function techniques commonly available in clinical practice [8].

Our recent systematic reviews demonstrated persistent lung function deficits measured by spirometry in preterm-born individuals, with decreases in forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratios when compared to term-born populations [9, 10]. Additionally, meta-regression analyses support previous findings of longitudinal cohort studies showing a decline in FEV_1/FVC with increasing age. Together, these studies suggest increasing airway obstruction throughout life, particularly in those with an infant diagnosis of BPD [11, 12]. Spirometry, however, has inherent limitations in elucidating the intricate changes that preterm birth inflicts on lung parenchyma, the pulmonary vascular bed and the peripheral airways. Enlarged, simplified, thick-walled alveoli with dysmorphic growth of the pulmonary vascular bed are consistently reported in histological studies [2, 13], while gas trapping, often suggestive of small airway disease, has also been reported on imaging studies [14].

Alternative pulmonary function tests may offer a more granular perspective of the pathophysiological changes occurring in the lungs following preterm birth and allow for earlier diagnosis of ongoing abnormalities. Total body plethysmography and inert gas washout can assess static lung volumes, offering insights into restrictive lung disease, gas trapping and ventilation inhomogeneity [15]. The diffusing capacity of the lungs for carbon monoxide (D_{LCO}) test assesses gas transfer, signalling changes in alveolar permeability and pulmonary capillary blood volume [16]. Oscillometry, meanwhile, can evaluate respiratory system mechanics and provide insight into the respiratory system's resistance and compliance [17]. Each of these tools has promise in the assessment of the peripheral lung, including in the smaller airways that are often labelled "the silent zone" but are increasingly recognised as an important indicator of early lung disease [18].

We systematically reviewed the literature to test our hypothesis that preterm-born individuals have abnormalities in static lung volumes, gas transfer and respiratory mechanics measured using oscillometry. In doing so, we provide a comprehensive assessment of respiratory function in survivors of preterm birth to better characterise the pathophysiological changes observed in this disease and highlight the tools with the most potential for diagnosing and monitoring prematurity-associated lung disease in clinical practice across the lifespan.

Methods

The protocol for this systematic review and meta-analyses was developed according to the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and registered prospectively using PROSPERO (CRD42022320775, supplement 1) [19]. Our primary aim was to determine if lung function measured using static lung volumes, gas transfer or oscillometry significantly differed between preterm-born individuals and those born at term. Secondary aims were to investigate if extremely/very/moderate-late preterm birth, a diagnosis of BPD, era of neonatal care and/or age at lung function test affected lung function.

The search strategy was designed to locate articles that assessed lung function through static lung volumes, gas transfer or oscillometry in groups with a history of preterm birth, including those with or without a history of BPD. Additionally, search terms were included to capture articles reporting on cardiopulmonary exercise testing in preterm cohorts, which has been reported on separately [20]. Key words were chosen within these two broad categories with appropriate Medical Subject Headings identified (supplement 1, section 3.2.3). Six databases were searched: Embase, MEDLINE, CINAHL, Scopus, Proquest Academic and Web of Science. The databases were searched to include all results up to 29 April 2022 and again on 29 November 2024 for articles published between 1 January 2022 and 29 November 2024. Articles of all languages were accepted, seeking translations if required. Duplicate results were identified and removed first using EndNote's inbuilt "Find Duplicates" feature, then manually using ordered lists.

Studies were eligible for inclusion within this analysis if they defined both a preterm (<37 weeks' gestation) and a healthy term (⩾37 weeks' gestation) control cohort and reported any of the following: static lung volumes by plethysmography or inert gas washout; gas transfer by D_{LCO}; or oscillometry measured by either impulse oscillometry or pseudo-random noise-based oscillometry techniques. Studies were excluded from the analysis if term and preterm cohort data could not be separated; cohorts had comorbidities, other than BPD, which may significantly affect respiratory health; or cohorts included data from children younger than 3 years. A 3-year cut-off was chosen based on differences in technique and

equipment typically found in measuring infant lung function. If required, authors were contacted for additional summary estimates of data where possible.

Titles and abstracts identified in searches were independently screened by two reviewers with backgrounds in medical research (J.T.D. Gibbons, M.L. Beaven, C.W. Course, S.J. Kotecha, M. Zuidersma, T. Hixson). Where either reviewer indicated the title may fit the above predefined eligibility criteria, the full manuscript was obtained and again independently reviewed by two reviewers, with a third reviewer (S.J. Simpson) mediating any disagreements. Where articles were not written in English, translations were sought. Where cohorts had data published in multiple manuscripts, the most complete data set was chosen for each of lung volumes, gas transfer and oscillometry to avoid over-representation within meta-analyses.

Risk of bias was assessed using a modified version of the Newcastle-Ottawa Quality Assessment Scale [21], with each study given a rating of low, medium or high risk of bias based on Agency of Healthcare Research and Quality standards (supplement 1, section 7.1). Subgroup analysis was performed using meta-regression to compare if studies given a rating of low risk of bias differed significantly from those of medium or high risk of bias. Publication bias was assessed if 10 or more cohorts were identified using Funnel plots and Egger's test [22].

Demographic and lung function data for each cohort were extracted into a Research Electronic Data Capture (REDCap) database into predefined fields (supplement 1, section 4.4.2) by a single reviewer (J.T.D. Gibbons, M.L. Beaven, C.W. Course, S.J. Kotecha) [23], with results validated by a second reviewer (J.T.D. Gibbons, M.L. Beaven, C.W. Course, S.J. Kotecha). Preterm cohorts were grouped by BPD status and banded into gestational age groups (extremely preterm: <28 weeks'; very preterm: 28–32 weeks'; moderate-late preterm: >32 weeks') based on the reported mean/median gestational age. Lung function data were extracted in order of preference as standard (Z) scores, per cent predicted or non-standardised data.

Statistical analysis was performed in R (version 4.3.2, www.r-project.org) using the *meta*, *metafor* and *dmetar* packages with previously documented techniques [24]. Where necessary, summary statistics from reported study groups were pooled such that a single group was represented for each of all individuals born preterm, all preterm individuals diagnosed with BPD as infants and all preterm individuals not diagnosed with BPD [25]. If variances were presented as standard error, 95% confidence intervals (95% CI) or interquartile range (IQR), these data were converted into standard deviations (SD) [26]. Where data were presented as medians and not significantly skewed [27], an estimate of the SD was calculated [28, 29].

Random-effects models were chosen for all meta-analyses owing to expected high levels of heterogeneity with variations in the techniques used for lung function testing and changes in the characteristics of prematurity-associated lung disease over time. For our primary outcome, standardised mean differences (SMDs) were calculated comparing preterm and term control groups for all lung function measures. For our secondary outcomes, where possible, the analyses were repeated with preterm groups analysed according to BPD status or banded into gestational age groups (<28 weeks', 28–32 weeks' or >32 weeks') based on the mean/median gestational age.

To analyse the impact of age and changes in neonatal care over time, we used meta-regression moderating lung function against the average age and birth year of the cohort, with significance determined by F-tests. A minimum of 10 cohorts per predictor was required for all meta-regression analyses to avoid over-fitting meta-regression models [25].

Where different techniques were used to measure lung volumes (plethysmography or inert gas washout) and respiratory mechanics using oscillometry (impulse oscillometry or pseudorandom noise), subgroup analyses using meta-regression were performed to determine if substantial differences in results existed between techniques. If the technique for measuring lung volumes was not specified, or if a combination of plethysmography and inert gas washout was used, the cohort was included in the overall analysis comparing lung volumes between preterm and term groups, but not in the subgroup analysis. Oscillometry values for resistance and reactance at 5 and 6 Hz were pooled, under the premise of their equivalence for analytical purposes.

Results

In total, 12 143 titles were identified from our combined searches, with 1243 articles identified for full review (figure 1). In total, 240 articles met inclusion criteria, comprising 68 unique cohorts (supplement 2, table E1), with 53 reporting static lung volumes or ventilation inhomogeneity (34 measuring plethysmography, 25 measuring inert gas washout) [14, 30–81], 38 reporting gas transfer [7, 14, 31, 35,

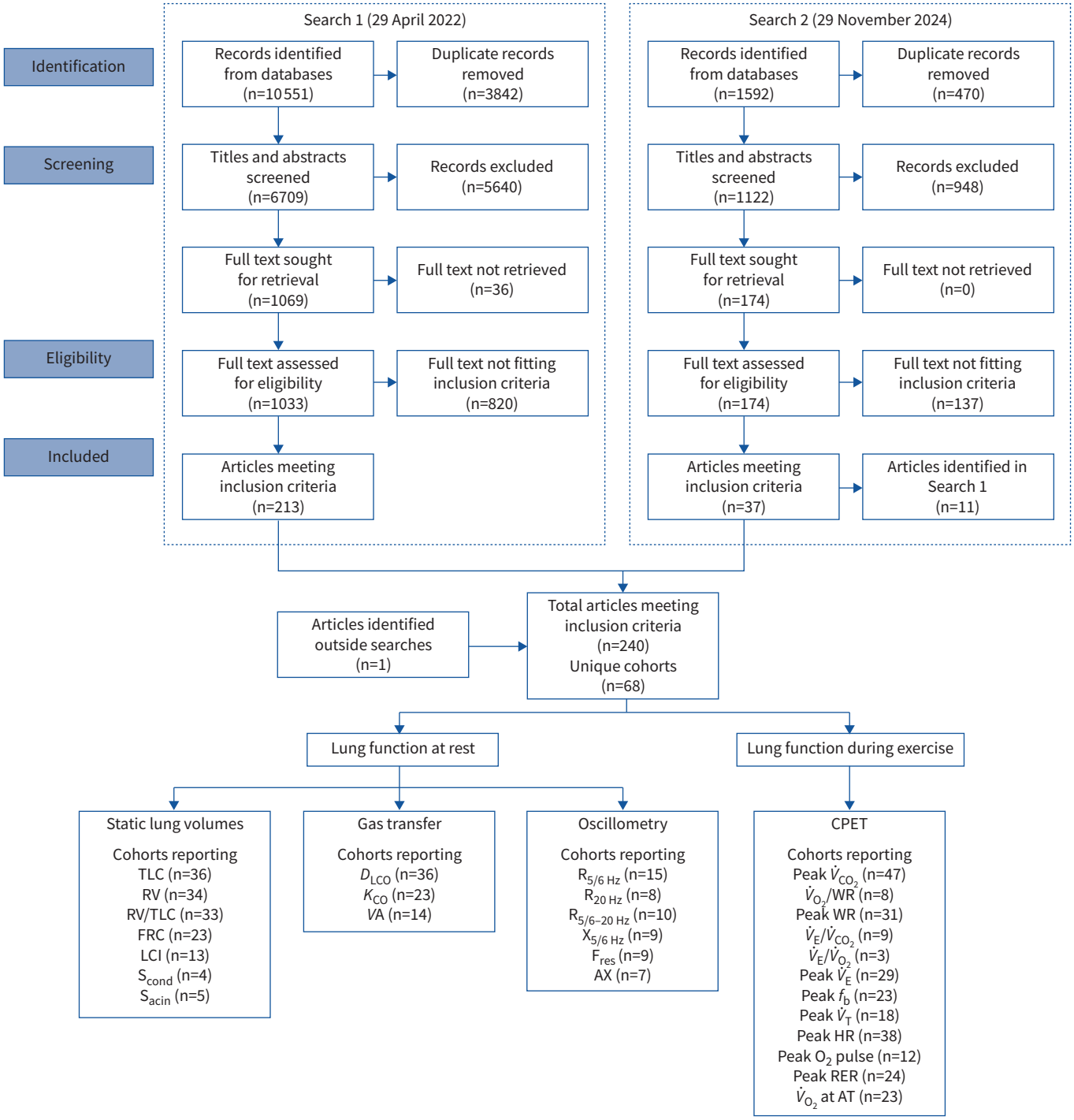

FIGURE 1 Flow diagram of search strategy. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram outlining search strategy for systematic review. Cardiopulmonary exercise testing (CPET) results discussed separately in Beaven *et al.* [20]. TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; LCI: lung clearance index; S_{cond}: conductive ventilation heterogeneity; S_{acin}: acinar ventilation heterogeneity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient for carbon monoxide; V_A: alveolar volume; $R_{5/6\ Hz}$: airway resistance at 5/6 Hz; $R_{5/6-20\ Hz}$: difference between airway resistance at 5/6 Hz and 20 Hz; $X_{5/6\ Hz}$: airway reactance at 5/6 Hz; F_{res}: resonant frequency; AX: area under the reactance curve; $\dot{V}_{CO_2}$: carbon dioxide production; $\dot{V}_{O_2}$: oxygen production; WR: work rate; $\dot{V}_E$: minute ventilation; f_b: breathing frequency; V_T: tidal volume; HR: heart rate; RER: respiratory exchange ratio; AT: aerobic threshold.

36, 39, 42–44, 46, 47, 49–52, 54, 56, 57, 59, 60, 64, 66–68, 71, 73–76, 81–90] and 18 reporting oscillometry outcomes [14, 46, 60, 73, 91–104]. In addition, 47 unique cohorts reported cardiopulmonary exercise testing and are discussed in the backing manuscript by Beaven *et al.* [20].

Characteristics of included studies are reported in supplement 2, table E2. Definitions of BPD varied widely, with diagnosis variably based on duration of supplemental oxygen or ventilation requirements, radiological abnormalities and/or clinical findings. Because we have previously shown minimal variation in FEV_1 outcomes across different diagnoses of BPD [9], we accepted the authors' reported definition of BPD. The birth year of participants ranged from 1961 to 2014, and gestational age ranged between 22 and 36 weeks. Lung function testing was conducted between 4 and 52 years of age. Study quality varied substantially, though did not appear to have any effect on the results (supplement 2, tables E4 and E5). Publication bias was evident for analyses performed on residual volumes (RVs), RV to total lung capacity (TLC) ratio and D_{LCO}, although notably was nonsignificant once BPD status was considered (supplement 3).

Summarised results of the primary analysis, including the number of eligible cohorts for each specific lung function test, are presented in figure 2, with differences between preterm and term-control groups expressed as SMD (95% CI). Spirometry values from our previous systematic review and meta-analysis are

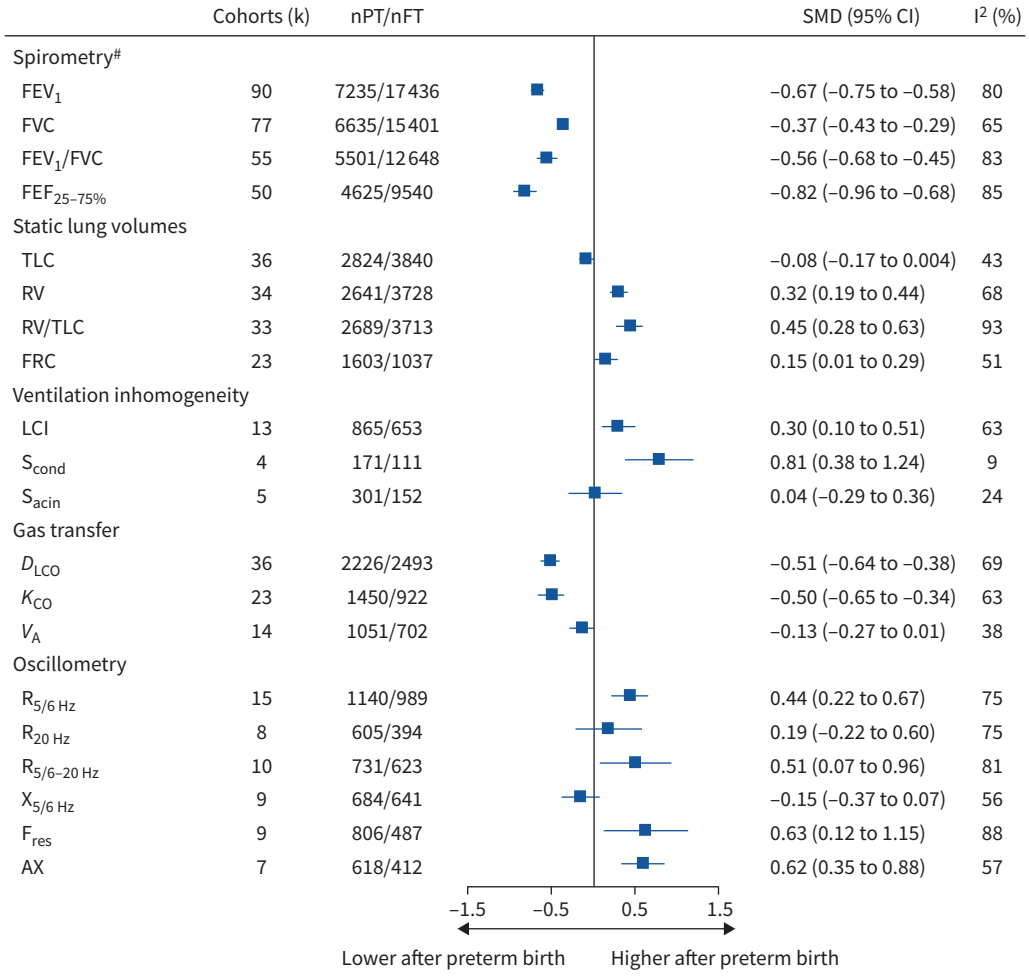

FIGURE 2 Summary of meta-analyses comparing the lung function of preterm and term-born cohorts. k: number of cohorts; nPT: number of preterm individuals in analysis; nFT: number of full-term controls in analysis; SMD: standardised mean difference; 95% CI: 95% confidence interval; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of FVC; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; LCI: lung clearance index; S_{cond}: conductive ventilation heterogeneity; S_{acin}: acinar ventilation heterogeneity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient for carbon monoxide; V_A: alveolar volume; $R_{5/6\ Hz}$: airway resistance at 5/6 Hz; $R_{20\ Hz}$: airway resistance at 20 Hz; $R_{5/6–20\ Hz}$: difference between airway resistance at 5/6 Hz and 20 Hz; $X_{5/6\ Hz}$: airway reactance at 5/6 Hz; F_{res}: resonant frequency; AX: area under the reactance curve. #: spirometry data provided for context [9, 10].

provided for context [10]. Results of secondary analyses assessing the impact of BPD and gestational age on lung function are presented in tables 1 and 2, respectively. Forest plots of individual meta-analyses are shown in supplement 4.

Preterm groups had altered static lung volumes and ventilation inhomogeneity compared to term controls, evidenced by higher RV (SMD 0.32, 95% CI 0.19 to 0.44), RV/TLC (SMD 0.45, 95% CI 0.28 to 0.63) and functional residual capacity (FRC) (SMD 0.15, 95% CI 0.01 to 0.29). Differences in all three lung function measures were greater in the preterm groups with BPD compared to preterm groups without BPD and term control groups. TLC, however, was not different between preterm and term groups and was not influenced by BPD status (table 1) or gestational age (table 2). Extremely preterm groups had significantly larger differences compared to term controls for RV and for RV as a percentage of TLC than did very preterm groups, although not different to moderate-late preterm groups. It should be noted, however, that fewer studies were available for analysis for the moderate-late preterm groups. No differences were observed between static lung volumes measured by plethysmography or inert gas washout (supplement 2, table E6).

Evidence of ventilation inhomogeneity was detected, with an elevated lung clearance index (LCI) seen in preterm groups (SMD 0.30, 95% CI 0.10 to 0.51). There were more pronounced differences observed in BPD groups (SMD 0.58, 95% CI 0.31 to 0.85) and groups born extremely preterm (SMD 0.54, 95% CI 0.16 to 0.92) when compared with term controls. Conductive ventilation heterogeneity (S_{cond}) was increased in preterm compared to term control groups (SMD 0.81, 95% CI 0.38 to 1.24). No significant differences were noted in acinar ventilation heterogeneity between preterm- and term-born groups.

Reduced gas transfer, as measured by D_{LCO} (SMD −0.51, 95% CI −0.64 to −0.38) and the transfer coefficient for carbon monoxide (K_{CO}) (SMD −0.50, 95% CI −0.65 to −0.34), were observed in those born preterm compared to term controls. The reduction in D_{LCO}, but not K_{CO}, was more pronounced in

TABLE 1 Summary of meta-analyses comparing lung function of preterm cohorts with and without a diagnosis of BPD with term cohorts

	BPD *versus* Term			No BPD *versus* Term		
	k (nPT/nFT)	SMD (95% CI)	I^2 (%)	k (nPT/nFT)	SMD (95% CI)	I^2 (%)
Static lung volumes						
TLC	29 (952/1435)	−0.06 (−0.16 to 0.03)	19	24 (1135/1281)	−0.04 (−0.15 to 0.07)	35
RV	26 (880/1282)	**0.49 (0.30 to 0.67)**	66	22 (1050/1155)	**0.21 (0.05 to 0.37)**	55
RV/TLC	24 (855/1261)	**0.69 (0.50 to 0.89)**	69	23 (1128/1216)	**0.33 (0.17 to 0.48)**	58
FRC	15 (497/603)	**0.29 (0.11 to 0.48)**	39	13 (530/543)	0.12 (−0.04 to 0.28)	19
Ventilation inhomogeneity						
LCI	9 (318/299)	**0.58 (0.31 to 0.85)**	51	9 (265/309)	0.30 (−0.08 to 0.68)	66
S_{cond}	4 (116/112)	**0.61 (0.47 to 0.75)**	0	5 (143/150)	0.44 (−0.04 to 0.93)	51
S_{acin}	4 (116/115)	0.40 (−0.22 to 1.01)	40	4 (99/114)	0.02 (−0.74 to 0.77)	66
Gas transfer						
D_{LCO}	24 (680/877)	**−0.67 (−0.88 to −0.47)**	65	24 (873/839)	−0.43 (−0.63 to −0.24)	60
K_{CO}	17 (517/631)	**−0.55 (−0.76 to −0.35)**	51	16 (565/566)	−0.50 (−0.75 to −0.25)	66
V_A	9 (339/418)	−0.10 (−0.33 to 0.13)	38	10 (426/433)	0.02 (−0.11 to 0.15)	0
Oscillometry						
$R_{5/6\ Hz}$	7 (372/391)	**0.88 (0.42 to 1.34)**	72	6 (224/472)	**0.57 (0.19 to 0.94)**	58
$R_{20\ Hz}$	3 (109/120)	0.68 (−2.39 to 3.74)	92	3 (94/120)	0.64 (−0.45 to 1.73)	67
$R_{5/6–20\ Hz}$	5 (261/366)	0.97 (−0.02 to 1.97)	83	3 (102/110)	0.43 (−0.07 to 0.93)	0
$X_{5/6\ Hz}$	2 (75/59)	−0.63 (−2.85 to 1.60)	0	3 (115/307)	−0.25 (−0.97 to 0.47)	36
F_{res}	5 (218/224)	**1.53 (0.45 to 2.61)**	85	5 (191/224)	0.75 (−0.02 to 1.53)	80
AX	5 (292/282)	**0.87 (0.57 to 1.17)**	16	3 (93/73)	**0.61 (0.51 to 0.72)**	0

Bold values indicate results where the 95% confidence interval does not cross zero. BPD: bronchopulmonary dysplasia; k: number of cohorts; nPT: number of preterm individuals in analysis; nFT: number of full-term individuals in analysis; SMD: standardised mean difference; 95% CI: 95% confidence interval; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; LCI: lung clearance index; S_{cond}: conductive ventilation heterogeneity; S_{acin}: acinar ventilation heterogeneity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient for carbon monoxide; V_A: alveolar volume; $R_{5/6\ Hz}$: airway resistance at 5/6 Hz; $R_{20\ Hz}$: airway resistance at 20 Hz; $R_{5/6–20\ Hz}$: difference between airway resistance at 5/6 Hz and 20 Hz; $X_{5/6\ Hz}$: airway reactance at 5/6 Hz; F_{res}: resonant frequency; AX: area under the reactance curve.

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TABLE 2 Summary of meta-analyses comparing lung function of preterm cohorts separated by degree of prematurity with term cohorts

	EP *versus* Term			VP *versus* Term			MLP *versus* Term		
	k (nPT/nFT)	SMD (95% CI)	I^2 (%)	k (nPT/nFT)	SMD (95% CI)	I^2 (%)	k (nPT/nFT)	SMD (95% CI)	I^2 (%)
Static lung volumes									
TLC	20 (1257/995)	−0.10 (−0.24 to 0.05)	47	19 (1268/930)	−0.11 (−0.25 to 0.04)	55	5 (249/285)	−0.05 (−0.28 to 0.18)	0
RV	20 (1440/953)	**0.37 (0.21 to 0.54)**	58	17 (1078/862)	**0.24 (0.07 to 0.41)**	53	5 (208/241)	**0.51 (0.004 to 1.02)**	64
RV/TLC	20 (1430/1010)	**0.61 (0.43 to 0.79)**	66	17 (1189/822)	**0.41 (0.22 to 0.60)**	61	6 (269/282)	**0.53 (0.11 to 0.94)**	63
FRC	11 (813/432)	**0.25 (0.07 to 0.44)**	40	10 (722/428)	0.18 (−0.04 to 0.41)	44	6 (240/271)	0.14 (−0.57 to 0.85)	67
Ventilation inhomogeneity									
LCI	6 (321/227)	**0.54 (0.16 to 0.92)**	67	5 (384/206)	**0.34 (0.25 to 0.43)**	0	3 (194/176)	0.02 (−0.29 to 0.34)	0
S_{cond}	2 (42/57)	0.89 (−0.93 to 2.72)	0	2 (65/57)	0.81 (−1.79 to 3.41)	11	[#]	[#]	
S_{acin}	2 (47/56)	0.16 (−2.84 to 3.16)	21	2 (67/56)	0.00 (0.00 to 0.00)	0	[#]	[#]	
Gas transfer									
D_{LCO}	17 (1019/588)	**−0.66 (−0.91 to −0.42)**	71	21 (924/756)	**−0.54 (−0.73 to −0.35)**	58	6 (435/1419)	−0.15 (−0.36 to 0.06)	30
K_{CO}	13 (948/493)	**−0.54 (−0.78 to −0.29)**	64	14 (682/486)	**−0.46 (−0.68 to −0.24)**	54	2 (147/141)	0.10 (−1.93 to 2.13)	30
V_A	7 (673/311)	−0.04 (−0.20 to 0.13)	0	8 (546/364)	−0.06 (−0.23 to 0.12)	1	2 (147/141)	−0.38 (−1.47 to 0.72)	0
Oscillometry									
$R_{5/6\ Hz}$	6 (543/334)	**0.62 (0.37 to 0.88)**	40	6 (542/302)	**0.46 (0.03 to 0.90)**	81	5 (284/430)	0.15 (−0.10 to 0.39)	3
$R_{20\ Hz}$	3 (306/136)	0.77 (−2.02 to 3.56)	91	3 (181/140)	0.45 (−0.94 to 1.83)	81	3 (215/164)	−0.03 (−0.68 to 0.62)	42
$R_{5/6–20\ Hz}$	5 (483/313)	**0.65 (0.25 to 1.05)**	50	5 (294/222)	0.32 (−0.01 to 0.66)	43	2 (76/89)	−0.05 (−0.46 to 0.36)	0
$X_{5/6\ Hz}$	3 (110/109)	−0.31 (−1.47 to 0.85)	74	5 (465/229)	−0.24 (−0.63 to 0.14)	61	4 (249/414)	−0.05 (−0.45 to 0.36)	39
F_{res}	3 (339/117)	1.32 (−0.69 to 3.33)	80	5 (505/252)	**0.50 (0.01 to 0.99)**	70	2 (188/145)	0.06 (−2.87 to 2.98)	74
AX	4 (227/236)	**0.70 (0.35 to 1.05)**	19	4 (292/133)	**0.60 (0.56 to 0.64)**	0	1 (49/70)	0.08 (−0.28 to 0.45)	N/A

Bold values indicate results where the 95% confidence interval does not cross zero. EP: extremely preterm (<28 weeks' gestation); VP: very preterm (28–32 weeks' gestation); MLP: moderate-late preterm (32–37 weeks' gestation); k: number of cohorts; nPT: number of preterm individuals in analysis; nFT: number of full-term individuals in analysis; SMD: standardised mean difference; 95% CI: 95% confidence interval; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; LCI: lung clearance index; S_{cond}: conductive ventilation heterogeneity; S_{acin}: acinar ventilation heterogeneity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient for carbon monoxide; V_A: alveolar volume; $R_{5/6\ Hz}$: airway resistance at 5/6 Hz; $R_{20\ Hz}$: airway resistance at 20 Hz; $R_{5/6–20\ Hz}$: difference between airway resistance at 5/6 Hz and 20 Hz; $X_{5/6\ Hz}$: airway reactance at 5/6 Hz; F_{res}: resonant frequency; AX: area under the reactance curve. [#]: S_{cond} and S_{acin} not included because there were insufficient cohorts to perform analyses for these tests.

those with a history of BPD (SMD −0.67, 95% CI −0.88 to −0.47) compared with those without BPD (SMD −0.43, 95% CI −0.63 to −0.24). Extremely preterm (SMD −0.66, 95% CI −0.91 to −0.42) and very preterm (SMD −0.54, 95% CI −0.73 to −0.35) birth were associated with substantial reductions in D_{LCO}, but this was not evident in those born moderate-late preterm. Alveolar volume (V_A) was not different between preterm- and term-born groups.

Analysis of respiratory system mechanics measured using oscillometry showed that resistance at 5/6 Hz was greater in preterm cohorts than term cohorts (SMD 0.44, 95% CI 0.22 to 0.67), particularly in those with BPD (SMD 0.88, 95% CI 0.42 to 1.34) or with a history of extremely preterm birth (SMD 0.62, 95% CI 0.37 to 0.88). Area under the reactance curve (AX) was also elevated in preterm (SMD 0.62, 95% CI 0.35 to 0.88), BPD (SMD 0.87, 95% CI 0.57 to 1.17) and extremely preterm groups (SMD 0.70, 95% CI 0.35 to 1.05) compared to term controls, while resonant frequency was elevated in preterm cohorts (SMD 0.63, 95% CI 0.12 to 1.15) and more substantially in BPD groups (SMD 1.53, 95% CI 0.45 to 2.61). The difference between airway resistance at 5/6 Hz and 20 Hz ($R_{5/6\text{-}20\ Hz}$) was also higher in preterm cohorts compared with term cohorts (SMD 0.51, 95% CI 0.07 to 0.96). Airway reactance at 5/6 Hz trended lower in those born preterm (SMD −0.15, 95% CI −0.37 to 0.07), although a degree of uncertainty remained. No other measures of oscillometry were different between preterm and term cohorts. No differences were noted on subgroup analysis comparing airway resistance at 5/6 Hz ($R_{5/6\ Hz}$) collected using impulse oscillometry and pseudorandom noise (p=0.98).

For lung function measures where meta-regression analysis was possible (TLC, RV, RV/TLC, FRC, LCI, D_{LCO}, K_{CO}, V_A, $R_{5/6}$), we did not identify any association between age or birth year (supplement 2, table E7). This suggests that alterations in these measures of lung function do not change with age, nor have they improved or declined across different eras of neonatal care.

Discussion

This systematic review and meta-analysis expands on our previous reviews of spirometry outcomes [10], providing the first overview of static lung volumes, gas transfer and oscillometry in survivors of preterm birth. We found preterm birth to be associated with gas trapping on static lung volumes (increased RVs, FRC and RV/TLC), ventilation inhomogeneity (elevated LCI and S_{cond}), impaired gas transfer (reductions in D_{LCO} and K_{CO}) and altered respiratory mechanics suggestive of small airways disease (increased $R_{5/6}$, $R_{5/6–20}$ and AX). These disparities were often exacerbated where there was a history of either BPD or extremely preterm birth. Unlike our previous reviews of spirometry outcomes, we did not observe temporal changes in lung function, either as age-related changes or with changes in birth year across different eras of neonatal care.

Gas trapping has been recognised as a hallmark feature in obstructive lung diseases such as asthma and COPD [105], and with our findings of increased RVs, FRCs and RV/TLC ratios following preterm birth, this review suggests it warrants similar consideration as a feature of prematurity-associated lung disease. Large airway obstruction, evidenced by the reductions in FEV_1/FVC we have previously reported, offers one likely explanation for gas trapping following preterm birth [106]. However, alternative mechanisms, such as small airway dysfunction and parenchymal alterations, should also be explored to understand the complexities of gas trapping in the context of prematurity-associated lung disease. Indeed, signs of small airways disease were also evident in reported cohorts, with elevations in LCI on multiple breath washout and increased $R_{5/6\ Hz}$, $R_{5/6–20\ Hz}$ and AX observed using oscillometry in the preterm group. These findings also align with imaging studies showing small airways dysfunction and parenchymal alterations in survivors of preterm birth aged 9–11 years, which depicted bronchial wall thickening alongside areas of collapse/consolidation, emphysema and bronchiectasis [14]. With worsening airway obstruction observed in many preterm survivors as they age, it may have been expected that we would detect a similar progression in markers of gas trapping; however, no such signal was observed in this study and cohort studies reporting static lung volumes longitudinally are lacking. As concern grows of early-onset COPD in the preterm-born population [1], however, systematic monitoring of pulmonary function in clinical settings may become increasingly important. By focusing on the early identification and management of gas trapping, we can potentially mitigate the risk of developing early-onset COPD and other chronic respiratory conditions in these individuals.

Our analysis also identified impairment in alveolar gas transfer to the pulmonary vasculature following preterm birth, as indicated by significantly lower D_{LCO} and K_{CO} values. In the absence of changes to V_A, this could indicate that abnormalities in gas exchange are driven by pulmonary vascular impairments, emphysematous change (with preservation of lung volumes) or anaemia [106]. While there are no reports of persisting anaemia in later life in survivors of preterm birth, emphysematous changes have been

described in the previously mentioned computed tomography imaging studies [14]. Likewise, histological samples taken from the lungs of preterm-born individuals often have both a larger simplified alveolar appearance akin to emphysema and impaired capillary growth [2, 13]. This implies that both pulmonary vascular impairments and vascular disease contribute to reductions in gas transfer following preterm birth. To determine which may have a greater impact on gas transfer, techniques have been employed to partition D_{LCO} into its constituent components: pulmonary capillary blood volume and pulmonary membrane diffusing capacity. However, results from the limited studies have thus far been conflicting for survivors of preterm birth [107, 108]. We did not identify any age-related improvement or decline in gas transfer measurements in this study, matching what has been reported in longitudinal follow-up [108]. The clinical significance of D_{LCO} measurement in prematurity-associated lung disease is not yet fully established; however, given that a diminished D_{LCO} is recognised as a predictive marker for pulmonary hypertension in COPD [109], it potentially serves as a vital indicator for the necessity of comprehensive cardiopulmonary assessment in the preterm-born population.

BPD is recognised as an indicator of increased disease severity in neonatal and early childhood respiratory diseases, with our study findings reinforcing the association of BPD with more pronounced abnormalities in gas trapping, small airway resistance and impaired gas transfer. First identified over half a century ago, the definition of BPD has undergone significant evolution and remains a subject of ongoing debate. Previously we have identified that the specific definition of BPD employed did not significantly influence subsequent lung function outcomes [9]. Consequently, in this analysis, we intentionally avoided distinguishing between various definitions of BPD, aiming for a pragmatic assessment of the association between an early-life BPD diagnosis and later impaired lung function. Although BPD correlated with more significant lung function changes, our observations also showed lung function variations in preterm infants without BPD. Similarly, while lower gestational ages were also associated with more substantial impacts on lung function, even individuals born moderate-late preterm demonstrated persistent lung function abnormalities with signs of gas trapping and reduced gas transfer. This implies that preterm birth itself, irrespective of BPD or degree of prematurity, remains a critical risk factor for long-term respiratory complications, highlighting the need for comprehensive monitoring and tailored interventions for all preterm infants.

The strengths of this study lie in its ability to pool lung function data presented in different formats (Z-score, per cent predicted or raw) to maximise the number of studies included within each meta-analysis. Additionally, by performing meta-analyses on lung volumes, gas transfer and oscillometry in this systematic review, and consolidating them with our recent systematic review on spirometry, we have provided a comprehensive overview of the summarised lung function seen following preterm birth and interpreted each finding in the context of term-born controls. Limitations include the exclusion of cohorts without a term-born control population, and the lack of data from children aged under 3 years. Infant lung function techniques were considered too different to techniques beyond infancy and were thus omitted from this systematic review. Furthermore, while some cohorts did report on data longitudinally, analysing these data was outside the scope of this review. Additionally, moderate-high levels of heterogeneity were generally observed across the analyses, which may limit the ability to draw significant conclusions, particularly where fewer cohorts were available for analysis. Factors that may have contributed to heterogeneity include variations in the pathology of preterm lung disease across multiple decades, varying definitions of BPD and differences in methodology in the collection of pulmonary function tests.

In summary, here we have provided the first systematic review and meta-analyses on static lung volumes, gas transfer and oscillometry. When combined with our previous reviews on spirometry, these present the most comprehensive assessment of lung function in survivors of preterm birth to date. While spirometry is the most-performed lung function test, we demonstrate that the use of alternative lung function tests to assess the small airways, lung parenchyma and/or pulmonary vasculature offers valuable insight when diagnosing or monitoring the long-term sequelae of preterm birth. Early markers of respiratory disease are critical to prevent disease progression, and tests like those described in this review that assess the “silent zone” are often used as early markers in asthma and COPD. The concept of pre-COPD, in which individuals develop early physiological dysfunction before developing detectable airway obstruction by spirometry, is particularly relevant here because these individuals may develop reduced D_{LCO} or signs of gas trapping as the earliest manifestations of disease [110]. Currently, definitive studies establishing how such measures present or progress longitudinally in prematurity-associated lung disease are lacking, although our systematic review suggests that a signal should be expected. Coupled with the underpinning pathophysiology of simplified alveolar structure (a reduced number of larger alveoli) and abnormal pulmonary vascular development, we suggest that these specialised lung function tests should be considered in a clinical setting to identify specific “treatable traits” in survivors of preterm birth.

Points for clinical practice

- Consider incorporating comprehensive pulmonary function testing beyond spirometry where available. Static lung volumes, diffusing capacity of the lung for carbon monoxide and oscillometry may help detect gas trapping, small airways dysfunction and impaired gas transfer in preterm survivors that could be missed by spirometry alone.
- Long-term respiratory follow-up is recommended for preterm survivors, including those born moderate-late preterm. Regular monitoring may help to detect early signs of COPD, particularly in individuals with persistent gas trapping or reduced gas transfer.
- Consider prioritising more frequent monitoring for high-risk groups, particularly those with a history of bronchopulmonary dysplasia or born extremely preterm (<28 weeks), because these individuals often show more pronounced lung function abnormalities and may benefit from closer monitoring and earlier intervention.

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