Early Human Development 180 (2023) 105756

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Respiratory and non-respiratory outcomes of bronchopulmonary dysplasia in adolescents: A systematic review

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ARTICLE INFO

Keywords:
Bronchopulmonary dysplasia (BPD)
Adolescent
Patient outcome assessment
Spirometry
Quality of life

ABSTRACT

Background: There is lack of evidence synthesis on the global consequences of bronchopulmonary dysplasia (BPD) in adolescence.
Aim: Assess the impact of bronchopulmonary dysplasia on respiratory and non-respiratory outcomes in adolescents.
Methods: A systematic review of studies assessing the outcomes of adolescents aged 10 to 19 years-old with BPD was conducted. We independently screened studies published until 6th March 2023 in PubMed® and Scopus® databases. Data on methodologic design, sample descriptive and findings were extracted from each study. Risk of bias was assessed using quality assessment tools.
Results: Thirty-one studies were included. Adolescents with a history of BPD present with more respiratory symptoms (wheezing, respiratory exacerbations, need for respiratory medication) and twenty-five studies showed a reduction in pulmonary function, with varying impact according to BPD severity and no differences before and after the surfactant era. Spirometry evaluation throughout the years is not consensual, but methacholine and salbutamol response in BPD groups is increased compared to non-BPD groups. Markers of eosinophilic airway inflammation are not increased as in asthma patients. Exercise potential is identical, but data regarding physical capacity and activity are inconsistent. More frequent radiologic abnormalities translate into higher high-resolution computed tomography scores, with linear (72.2 %) and triangular subpleural opacities (58.3 %) as the most common findings. There is a higher risk for special needs in education, but quality of life seems to be equal to non-BPD adolescents.
Conclusions: BPD negatively impacts both pulmonary and non-pulmonary outcomes in adolescents.

1. Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease associated with extremely premature (EP) birth [1]. Although recent new BPD classifications have been proposed, the most used definition for preterm infants with a gestational age of 32 weeks or younger is the need for supplemental oxygen for at least 28 days. BPD can be further classified into mild, moderate, or severe BPD at 36 weeks of postmenstrual age [1,2]. The incidence varies according to the used definition and gestational age, and the intercenter variability in disease

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https://doi.org/10.1016/j.earlhumdev.2023.105756
Received 2 February 2023; Received in revised form 17 March 2023; Accepted 17 March 2023
Available online 21 March 2023

management adds further difficulty in determining true BPD incidence (10–89 %) [2,3].

The advent of antepartum lung maturation with corticosteroids, postpartum surfactant administration and new ventilation strategies has shifted the pathophysiology of BPD [3]. In the pre-surfactant era, the "old" BPD was mainly a consequence of barotrauma and supplemental oxygen toxicity [4]. Today, the "new" BPD is marked by an arrest in lung development [1]. However, both of these phenotypes still occur today and there are no objective diagnostic criteria to separate them. Improved neonatal care has enhanced survival following preterm birth, but lung morbidity remains a problem. Understanding the respiratory long-term morbidity is crucial to assure an appropriate follow-up of ex-preterm adolescents and prepare them for adulthood [5].

The most reported long-term outcome of BPD is impaired lung function [6]. Studies of school age children with BPD show a decrease in FEV_1% and in FEV_1%/FVC, raising concerns of a persistent obstructive pattern that might evolve to chronic obstructive pulmonary disease (COPD) in adulthood [6]. However, the functional impact of this decline in lung function is still controversial. Some studies on exercise capacity reported no differences between survivors of preterm birth with and without BPD while others showed a reduction in exercise performance [6–9]. BPD is also related to poorer neurodevelopmental outcomes in children. Motor and neurological deficits have been reported, and there is lower cognitive performance in BPD children compared with non-BPD subjects. [10–13]

Systematic reviews focusing on adolescent morbidity have not yet been reported in literature. The only systematic review on long-term respiratory and non-respiratory morbidity analyzed an adult population in 2012 [14]. In 2013, a systematic review assessed the effect of preterm birth in late FEV_1, in patients aged 5 to 23 years-old [15]. So, there is lack of evidence synthesis on the global consequences of the BPD in adolescence.

The aim of this systematic review was to assess the impact of BPD in adolescents on both respiratory (respiratory symptoms, lung function impairment, exercise capacity and radiographic patterns) and non-respiratory outcomes (quality of life, educational performance and healthcare use) comparing with adolescents that had not developed this pathology.

2. Methods

This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [16]. We accessed PubMed and Scopus databases to perform the literature searches, with no limit of time. The used search query is listed in Table 1.

Table 1
Search query used in this systematic review.

Search query
"bronchopulmonary dysplasia"[MeSH Terms] AND ("follow up studies"[MeSH Terms] OR ("follow up"[All Fields] AND "studies"[All Fields]) OR "follow up studies"[All Fields] OR ("follow"[All Fields] AND "up"[All Fields] AND "studies"[All Fields]) OR "follow up studies"[All Fields] OR ("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "morbidity"[All Fields] OR "morbidity"[MeSH Terms] OR "morbid"[All Fields] OR "morbidities"[All Fields] OR "morbids"[All Fields]) OR ("respiratory physiological phenomena"[MeSH Terms] OR ("respiratory"[All Fields] AND "physiological"[All Fields] AND "phenomena"[All Fields]) OR "respiratory physiological phenomena"[All Fields] OR ("lung"[All Fields] AND "function"[All Fields]) OR "lung function"[All Fields]) OR ("respiratory function tests"[MeSH Terms] OR ("respiratory"[All Fields] AND "function"[All Fields] AND "tests"[All Fields]) OR "respiratory function tests"[All Fields]) OR ("outcome"[All Fields] OR "outcomes"[All Fields]) OR ("exercise"[MeSH Terms] OR "exercise"[All Fields] OR "exercises"[All Fields] OR "exercise therapy"[MeSH Terms] OR ("exercise"[All Fields] AND "therapy"[All Fields]) OR "exercise therapy"[All Fields] OR "exercise s"[All Fields] OR "exercised"[All Fields] OR "exerciser"[All Fields] OR "exercisers"[All Fields] OR "exercising"[All Fields]) OR "growth and development"[MeSH Terms]) AND "adolescent"[MeSH Terms] AND "humans"[MeSH Terms]

Two reviewers (MC and PS) independently performed the screening of the studies, and disagreements were resolved by discussion with a third independent reviewer (MFM).

Primary studies published until 6th March 2023 assessing outcomes in adolescents between 10 and 19 years-old with BPD were included. Review articles and other secondary studies were excluded. No language restrictions were applied. The citation pool was further supplemented from manual assessment of the reference lists of the retrieved articles and from other publications identified as being relevant for further review. A final count of 31 studies were included. A flow diagram describing the selection process is shown in Fig. 1.

Data were extracted from each study (MC and PS) and double-checked for accuracy and completeness (MFM). The information obtained was the following: author name(s), year of publication, study location, objective, study design, birth year of the participants, age of participants at the time of the study, sample descriptive with birthweight and gestational age, outcome measures, BPD definitions used, and conclusions. All results reported in this systematic review derive from adolescent participants included in the selected primary studies.

The study quality was assessed using the "Quality assessment tool for observational cohort and cross-sectional studies" for twenty-nine studies, the "Quality assessment of Controlled Intervention Studies" for one study and the "Quality assessment of case-control studies" for another, all from National Heart, Lung and Blood Institute (NIH) [17].

3. Results

3.1. Study selection

The search strategy retrieved 252 titles and abstracts after removal of duplicates. Of these, 216 were excluded (Fig. 1). Then, after reading the 36 full manuscripts, 10 more articles were excluded. Assessment of references yielded 5 more articles. Therefore, 31 studies (Table 2) were included in the final review.

3.2. Study characteristics

The included studies consisted of: 25 cohort studies [18–42], four cross sectional studies [43–46], one case control study [47] and one randomized controlled trial [48]. Overall, the studies compared the outcomes between preterm born adolescents with or without the diagnosis of BPD, born between 1978 and 2005. Some included studies had term control groups. One study did not have a control group (neither preterm nor full term infants) [36]. The most commonly used BPD definition was that from the *National Institute of Child Health and Human Development (NICHD)* [1] (27 studies). Some studies only used mild, while others considered moderate/severe grades of the NICHD definition, or the use of ventilatory support [49], as detailed in Table 3. Two studies did not specify the BPD definition used [18,37].

3.3. Risk of bias across studies

The major biases found were the lack of sample size justification or power description, failure to discern BPD severity, not blinding the outcome assessor for BPD status, and loss to follow-up of 20 % or more cases (Tables 4, 5 and 6). Only 13 studies detailed BPD severity. Five studies [18,26,36,43,46] did not adjust variables to potential confounders (gender, gestational age, birthweight, maternal smoking during pregnancy, number of days on mechanical ventilation or with supplemental oxygen were the most analyzed confounders).

3.4. Respiratory symptoms and management

Wheezing was reported in three studies [25,28,42] showing that 22–28 % of BPD-adolescents had recurrent wheezing versus 0–12 % of

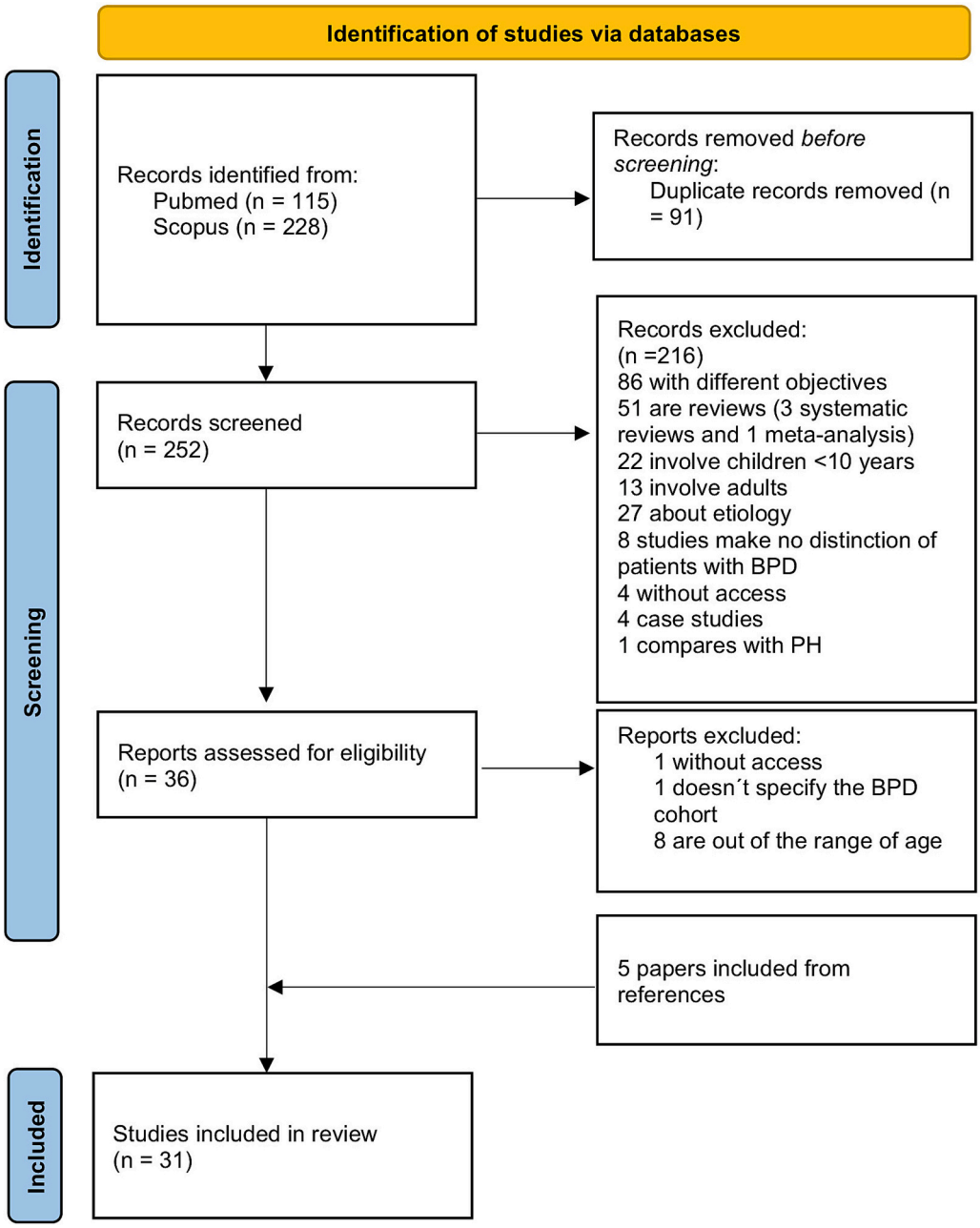

Fig. 1. PRISMA flow diagram of the literature selection.
BPD - bronchopulmonary dysplasia; PH - pulmonary hypertension.

non-BPD. Hadchouel, et al. [29] reported higher prevalence of wheezing in BPD-adolescents, despite the lack of statistical significance (18 % vs 13 %). Fillipone, et al. [27] reported respiratory disturbances in the previous two years in 70 % of BPD-adolescents versus 44 % of non-BPD (15 % vs 1 % referred cough and 38 % vs 33 % exercise-associated symptoms). There was a higher incidence of pneumonia in preterm adolescents compared to controls (58 % vs. 27 %), one study specifying BPD-patients with 66 % vs 8 % of non-BPD [31,44].

Two studies [25,31] showed an increased use of respiratory medication: more beta agonists or inhaled steroids in preterm adolescents (17–25 %) than in term controls (2–11 %); another study showed increased use of respiratory medication in adolescents with BPD (50 %) compared to non-BPD adolescents (11 %) [27].

The prevalence of a current diagnosis of asthma was not consensual between studies. Four studies showed a non-significant difference between BPD-adolescents versus non-BPD ex-preterm [42,44,45,47]. Only one study reported a higher prevalence in BPD-adolescents (25 %) versus 13 % of preterm controls [25]. However, Doyle, et al. [23] showed similar prevalence in both groups (18 % in BPD versus 19 % in non-BPD).

3.5. Pulmonary function

Twenty-five studies evaluated pulmonary function with spirometry [19–23,25–33,36,39–48]. All showed reduction in one or more spirometry measures in BPD-adolescents compared to controls (preterm infants without BPD or term controls). The six studies that conducted BPD severity analysis of pulmonary function reported that severe BPD was associated with worse spirometry results [31–33,39,40,45].

Seven studies evaluated lung function trajectory throughout the years [22,23,26,28,33,39,40]; five showed worsening of spirometry parameters and only one showed no differences [40]. Doyle, et al. [23]

Table 2
Description of included studies.

Study (author, year, country)	Objective	Study design	Birth year Age(y)	Sample descriptive with GA and BW (mean, SD/IQR)	Outcomes measure	Conclusions
Aukland, Norway, 2006 [18]	Use a scoring system for HRCT in the evaluation of radiologic findings in young people born extremely preterm and to examine the reproducibility of this scoring system.	Cohort	1982–1985: 18 1991–1992: 10	72 PT (<28 w or BW 991 g (191 g) (56 BPD) 1980s: 40 1990s: 32	High Resolution CT (HRCT)	Abnormal radiologic findings in 81.3 % of the patients at age 10 years and 92.5 % at age 18 years. Linear, triangular, and sub-pleural opacities were the most common.
Aukland et al., Norway 2009 [19]	Investigate if, and in what way, neonatal factors were associated with subsequent abnormalities on pulmonary high-resolution CT (HRCT) scanning and if pulmonary function was related to these abnormalities.	Cohort	1982–1985: 18 1991–1992: 10	74 PT (<28w or BW ≤ 1000 g) Non-BPD: 18 (BW 1121.4 g (160.6)) Mild BPD: 35 (BW 968.0 g (201.3)) M/s BPD: 21 (BW 852.4 g (169.7))	High Resolution CT (HRCT), plethysmography, spirometry	In EP infants, prolonged oxygen requirement is associated with lung abnormalities and worse pulmonary function, and these two outcomes are related.
Clemm, Norway, 2012 [20]	Compare aerobic capacity and exercise performance of children and adolescents born EP and at term, and to relate findings to medical history and lifestyle factors.	Two cohorts	1982–1985 and 1991–1992 10.6 and 17.6	75 PT (<28 w or BW ≤ 1000 g) 32 mild BPD (26.5–27.1 w, BW 927–1023 g) 24 m/s BPD (25.8–27.0 w, BW 851–887 g) 75 term controls	Standardized maximal treadmill exercise and pulmonary function tests	Exercise capacity is relatively normal between preterm and term subjects.
Clemm, Norway, 2015 [21]	Whether exercise capacity at 18 years of age was associated with neonatal factors, current lung function or reported exercise habits. We also wanted to see whether changes in exercise capacity between the ages of 10 and 18 differed between the groups born preterm and at term.	Cohort study	1991–92 10 and 18	26 EP (≤28 w or ≤ 1000 g) 10 mild BPD (BW 973 g (710–1370)) 11 moderate/ severe BPD (BW 866 g (570–1200)) 5 No BPD (BW 996 g (930–1126))	Spirometry and cardiopulmonary treadmill exercise test	Exercise capacity is relatively normal in EP adolescents.
Doyle, Australia, 2017 [22]	To compare airflow at 8 and 18 years and changes between 8 and 18 years of EP/ELBW survivors with normal birth weight controls, and within the EP/ELBW group, to determine the association of the newborn period, and of active smoking in adolescence with airflow.	Prospective cohort	1991–1992 8 and 18	297 EP/ELBW (<28 w, BW 888 g (161)) 121 BPD 260 term controls (39.2 w, BW 3386 g (438))	Spirometry	Airway obstruction increased between 8 and 18 years, especially in those with BPD. Smoking in adolescence is a risk factor for worse lung function.
Doyle et al., Australia, 2001 [23]	An additional aim was to compare the respiratory health of preterm children with and without BPD.	Prospective cohort	1977–1980 14	86 PT (BW 500-999 g, 27.5 w) (33 BPD) 124 PT (BW 1000-1500 g, 29.6 w) (9 BPD) 60 controls (BW > 2499 g, 39.9 w)	Current respiratory health, spirometry and lung volumes	The respiratory health of children of birth weight < 1501 g at 14 years of age is comparable to that of term controls.
Drummond et al., 2019, France [24]	Evaluate the consequences of BPD on academic outcome and healthcare use in adolescents born very preterm.	Prospective cohort	1997 15	55 PT BPD (26–29 w, BW 870 g (780–1060)) 249 PT non-BPD (29–31 w, BW 1370 g (1050–1640)) 47 controls (39 w, BW 3430 g (3210–3710))	Questionnaire about academic performance, current medical follow-up, and family characteristics	History of BPD was associated with a higher risk to attend a school for children with special needs ($p < 0.05$), to have repeated a grade ($p = 0.01$) and higher attendance to medical consultations.

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Table 2 (*continued*)

Study (author, year, country)	Objective	Study design	Birth year Age(y)	Sample descriptive with GA and BW (mean, SD/IQR)	Outcomes measure	Conclusions
Fawke et al., United Kingdom, 2010 [25]	Assess the degree of respiratory morbidity and functional impairment at 11 years in children born EP.	Prospective cohort	1995 11	182 EP (<25w, BW 750 g (120)) (129 BPD) 161 term controls matched for age (within 3 mo), sex, and ethnic origin	Spirometry, questionnaire from ISAAC, physical examination	Impaired lung function and increased respiratory morbidity persist in early adolescence, especially among those with BPD.
Filippone research letter, Italy, 2009 [26]	The evolution of lung function in long-term survivors of BPD	Prospective cohort	1990–1991 9 and 14–15 years	17 BPD (28 w, BW <1250 g) 17 PT Non-BPD 34 Term Controls	Spirometry	Lung function is affected by preterm delivery, but to a less extent than by BPD.
Filippone et al., Italy, 2012 [27]	Assess airway oxidative stress at long-term after preterm birth.	Cohort	1987–1994 14.9	34 PT BPD (27–30 w, BW 990 (847–1157)) 9 mild BPD 25 mod/severe BPD 18 PT non-BPD (26–30 w, BW 940 g (840–990)) 34 term controls (38–40 w, BW 3350 g (3000–3600))	8-isoprostane concentrations in exhaled breath condensate (EBC), spirometry, FeNO, Skin prick tests	Regardless of a history of BPD, the ex-premature adolescents had higher EBC 8-isoprostane levels than the controls. Forced expiratory volume in 1 s was lower in the BPD group than in the pre-term non-BPD individuals. FeNO was similar in the three groups ($p = 0.55$).
Fortuna et al., Italy, 2016 [28]	Provide longitudinal data on lung function of an EP cohort with an extremely low birth weight in the post-surfactant era.	Longitudinal prospective study	1999–2002 8 and 12	48 EP (<28 w, BW <1000 g) (20 BPD) 27 term controls	Spirometry, FeNO, questionnaire about respiratory symptoms	There is an impairment in lung function in preterm infants, especially those with BPD, and a deterioration over time.
Hadchouel et al., France, 2017 [29]	Lung function in relation to asthma symptoms from birth in adolescents born very preterm and in controls.	Prospective observational cohort	1997 15	304 PT (24–32 w, 89 with <1000 g, 100 with >1500 g) (55 BPD) 47 term controls (39–49 w)	International Study of Asthma and Allergies in Childhood (ISAAC) auto-questionnaire, spirometry	In models including BPD, asthma at each age and confounding factors in the preterm group, BPD and preschool wheeze were the only independent variables associated with FEV1.
Halvorsen, Norway, 2005 [30]	Relation between BPD and asthma-like symptoms and airway hyper-responsiveness (AHR).	Two cohorts	1982–1985 and 1991–1992 10.6 and 17.6	81 PT (≤28 w or BW ≤ 1000 g) 38 mild BPD (BW 981.0 g (200.2)) 24 m/s BPD (BW 868.8 g (166.0)) 10 non-BPD (BW 1115.1 g (158.5)) 81 term controls (BW 3494 g (300))	Methacholine provocation test, tests for exercise induced asthma (EIA) and reversibility to salbutamol, spirometry	A BPD history and the higher length of oxygen supplementation are strong risk factors for airway hyperreactivity.
Halvorsen et al., Norway, 2004 [31]	Determine respiratory health and lung function status in cohort of young preterms approaching adulthood.	Retrospective cohort	1982–1985 17.7	46 PT Mild BPD: 24 (27 w, BW 1013 g (193)) M/s BPD: 12 (27 w, BW 887 g (126)) Non-BPD: 10 (28.3 w, BW 1171 g (150)) 46 term controls	Spirometry, plethysmography, reversibility test to salbutamol and methacholine bronchial provocation test, skin prick test, questionnaire from the International Study of Asthma and Allergy in Childhood (ISAAC)	A doctor's diagnosis of asthma and use of asthma inhalers were significantly more prevalent among preterms than controls. Peak expiratory flow (PEF) and forced expiratory volume in 1 s (FEV1) were decreased and the discrepancies relative to controls increased parallel to increased severity of BPD.
Halvorsen et al., Norway, 2006 [32]	Assess whether lung function in late childhood had improved in subjects born EP with old or new BPD.	Cohort	1982–1985 17.7 (mean) 1991–1992 10.6 (mean)	1982–1985 cohort 46 PT 10 non-BPD (28.3 w, BW 1171 (150)) 24 mild BPD (27.0 w, BW 1013 (193)) 12 m/s BPD (27.0 w, 887 /126))	Spirometry	Preterms born in the "old" BPD or "new" BPD eras had similar long-term decreases in lung function.

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Table 2 (*continued*)

Study (author, year, country)	Objective	Study design	Birth year Age(y)	Sample descriptive with GA and BW (mean, SD/IQR)	Outcomes measure	Conclusions
				1991–1992 cohort 35 PT 9 non-BPD (28.3 w, BW 1053 (153)) 14 mild BPD (26.5 w, BW 927 (208)) 24 m/s BPD (25.8 w, BW 851 (202))		
Hirata et al., 2017, Japan [33]	Assess lung function and long-term respiratory outcomes in extremely low birthweight (ELBW) survivors.	Retrospective study	1990–2002 8 and 12	89 ELBW (26.7 w, BW 786 g (618, 866)) 54 none/mild BPD (25.8–28.7 w) 26 moderate BPD (26.6–27.1 w) 9 severe BPD (24.1–25.3 w)	Spirometry.	Lung function in ELBW subjects deteriorated from 8 to 12 years and was lower than the normal values, especially in severe BPD patients.
Holsti et al., Sweden, 2018 [34]	Evaluate the impact of BPD, brain injuries and severe ROP on adolescents who were born EPT.	Prospective cohort	1992–1998 10.1–15.6 (interval)	149 EP (23–25 w, BW 718 g (129)) (62 BPD)	Questionnaire for Identifying Children with Chronic Conditions (QUICCC) which has 3 domains: functional limitations, dependence on compensatory aids and need for extra services not routinely required by children	BPD and brain injuries were associated with high rates of chronic conditions, with functional limitations and special healthcare needs in adolescence.
Kuint et al., Israel, 2017 [35]	To evaluate the impact of major neonatal morbidities on the risks for rehospitalization in children and adolescents born of very low birth weight, including BPD	Prospective cohort	1995–2012 0–18	6385 VLBW (BW ≤1500 g) (573 BPD)	Hospitalization rates and adjusted relative risk (aRR) for hospitalizations.	The effect of BPD in hospitalization rates was significatively higher until 10 years, but not between 11 and 18 years.
Moschino et al., Italy, 2018 [36]	Longitudinally analyze the evolution of lung function in moderate-to-severe BPD from birth to early adult life.	Prospective cohort	1991–1993 0–24 (interval)	17 moderate/severe BPD (<31 w, BW 930 (570–1220))	Spirometry	The findings showed a tracking of airway function in subjects with moderate-to-severe BPD from early infancy into adulthood, with a significant flow limitation persisting at 24 years of age.
Narayanan, UK, 2013 [37]	Asses if alveolar damage in extreme-preterm survivors persists into early adolescence.	Cohort	1985–2005 10–14	18 EP (<32w) with CLD (BW 36.0 (20–56))[a] 19 EP (<32 w) without CLD (BW 63.4 (34–78)) 21 mild preterm (32–36 w) 61 term born	Hyperpolarized helium-3 magnetic resonance.	Alveolar size is comparable between preterm and term adolescents.
Sriram et al., USA, 2018 [38]	To compare neurocognitive, language, executive function, academic achievement, neurologic and behavioral outcomes, and quality of life at age 10 years in children born EP who developed BPD to children who did not develop BPD.	Prospective study	2002–2004 10	883 ELGA (<28w, 100 ELGA <750 g and 101ELGA >1000 g) 372 moderate BPD 78 severe BPD 413 non-BPD	Assessments of cognition (Differential Ability Scales II [DAS II], $n = 863$), executive function (NEuroPSYchological Assessment II [NEPSY II], $n = 834$), academic achievement (Wechsler Individual Achievement Test-III [WIAT III], $n = 854$, Oral and Written Language Scales [OWLS], $n = 842$) limitations, quality of life (Pediatric Quality of Life Inventory [PedsQL], $n = 848$), assessments of social functions (Social Responsiveness Scale [SRS]	Those who had BPD were at increased risk of cognitive, language, and executive dysfunctions; academic achievement limitations; social skill deficits; and low scores on assessments of health-related quality of life.
Um-Bergström et al., 2017, Sweden [39]	Evaluate the influence of BPD severity on exercise capacity and lung function and assess change of lung function from	Prospective cohort	1992–1997 14.5 (mean)	28 BPD (24-30w, BW 1003 g, 597–1520 g) 17 mild	Spirometry, impulse oscillometry (IOS), plethysmography, and ergospirometry	Results of spirometry and IOS measures in the BPD groups compared to the non-BPD group suggest

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Table 2 (*continued*)

Study (author, year, country)	Objective	Study design	Birth year Age(y)	Sample descriptive with GA and BW (mean, SD/IQR)	Outcomes measure	Conclusions
	7 to 14 years of age in relation to BPD severity.			7 moderate 4 severe 23 non-BPD (28–31 w, BW 1425, 845–2094 g)		airway obstruction including involvement of peripheral airways. The longitudinal result of a decrease in FEV1/FVC in the group with severe BPD might implicate a route towards chronic airway obstruction in adulthood.
Vollsæter et al., Norway, 2012 [40]	Assess the development of spirometric lung function variables from mid-childhood to adulthood after EP birth.	Two prospective cohorts	1982–1985: 10.5y 1991–1992: 17.8y	1982–1985 cohort: 11 EP non-BPD (27–32 w, BW 1151 (960–1480)) 24 EP mild BPD (23–28 w, BW 1013 (580–1340)) 13 EP m/s BPD (26–30 w, BW 892 (670–1080)) 46 term controls (BW 3441 (3000–4000)) 1991–1992 cohort: 9 EP non-BPD (26–31 w, BW 1053 g (930–1400)) 14 EP mild BPD (24–28 w, BW 927 (620–1370)) 12 EP m/s BPD (23–28 w, BW 851 (570–1200)) 35 term controls (BW 3564 (3010–4000))	Spirometry	Airway obstruction was present from mid-childhood to adulthood after extreme preterm birth, most evident after neonatal BPD. Lung function indices were tracking similarly in the preterm and term-born groups.
Welsh et al., United Kingdom, 2010 [41]	Evaluate exercise capacity at 11 years in children born EP.	Prospective cohort.	1995 11	38 EP (<25w, BW 740 (107)) (27 BPD) 38 controls (40w, 3360 (527))	Spirometry, body plethysmography, gas transfer testing, peak exercise test and accelerometry.	Despite marked differences in peakVO2, there were no differences in any physical activity measures between groups.
Harris et al., United Kingdom, 2022 [42]	Assess if a previous diagnosis of bronchopulmonary dysplasia (BPD) was associated with poorer lung function at 16 to 19 years of age.	Prospective cohort.	1998–2001 16–19 (interval)	150 PT (<29w) 78 BPD (BW 829 g (208)) 72 non-BPD (BW 981 g (203))	Spirometry, plethysmography, impulse oscillometry, diffusing capacity for carbon monoxide of the lungs, lung clearance index using sulfur hexafluoride and sprint test (exercise capacity).	The young people who had had BPD had significantly poorer mean airway function. There was no significant relationship between exercise distance and BPD.
Carraro et al., Italy, 2010 [43]	To measure exhaled breath temperature in BPD survivors by comparison with asthmatic cases and healthy controls.	Cross-sectional study	1990–1994 14.5 (BPD)	17 BPD (<31w, BW 1011 g (222) 17 asthmatic patients (>37w) 17 controls (>37w)	Exhaled air temperature measurement, FENO measurement, and spirometry	Exhaled breath temperatures and exhaled nitric oxide concentrations are significantly lower in BPD survivors than in asthmatic cases.
Giacoia, USA, 1997 [44]	To investigate the outcome of school-age children with BPD in terms of nutrition, pulmonary function, and intelligence, and to compare the results with a preterm cohort matched for gestational age and birth weight, and with a term control group.	Cross-sectional	1978 and 1986 12	12 BPD (29 w, BW 1015 g (222)) 12 PT (30.3 w, BW 1162 g (216)) 12 Term controls (40.07 w, BW 3663 g (777))	Illness history, anthropometric measurements, socioeconomic status, resting energy expenditure, Body composition, level of physical activity, dietary records, pulmonary function, developmental assessment	BPD is related with impaired lung function, but lower intelligence scores may be due to prematurity itself rather than BPD.
Pérez-Tarazona et al., 2021, Spain [45]	Evaluate the respiratory outcomes of "new" BPD in adolescents who were born preterm.	Cross-sectional study	2003–2005 14.2 (mean)	92 EP BPD (<28w, BW 839 g, 188) (51 high severity,	Global Asthma Network [GAN] written questionnaire, Kiddo-KINDL questionnaire, spirometry, bronchodilator	EP adolescents with "new" BPD had poorer pulmonary function than EP adolescents without BPD or

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Table 2 (*continued*)

Study (author, year, country)	Objective	Study design	Birth year Age(y)	Sample descriptive with GA and BW (mean, SD/IQR)	Outcomes measure	Conclusions
				41 low severity) 92 EP non-BPD (BW 1004 g, 220) 102 MLP (32–37 w, BW 1983 g, 526)	testing, total body plethysmography, lung diffusion, skin prick testing	moderate-late preterm adolescents. These adolescents did not have a higher prevalence of asthma symptoms or a poorer quality of life.
Bozzetto et al., Italy, 2016 [46]	Assess HRQOL (health related quality of life) in adolescents with BPD.	Cross-sectional study	—————— 14.3	27 BPD (27–30 w, BW 1020 g (855–1190 g) 27 age and sex-matched asthmatic patients 27 age and sex-matched controls	Short Form 36 (SF-36) questionnaire for health-related quality of life (HRQOL), spirometry	BPD patients have an HRQOL similar to that of their healthy peers, despite their persistent airflow limitation, and they have a better HRQOL than those of asthmatic patients
Vanhaverbeke, Belgium, 2021 [47]	Assess BPD using FRI and to correlate these findings with the clinical presentation.	Case-control study	1999–2002 13–16	15 PT (26–30.6 w, BW 1240 (637–1904)) 22 BPD (24.9–30.3 w, BW 973 (469–1640)) 3 mild 19 m/s	Questionnaire, spirometry, body plethysmography, nitrogen multiple-breath washout testing (N2MBW), single-breath carbon monoxide diffusion test, CT imaging, functional respiratory imaging	FRI analysis showed higher lobar volumes in BPD patients, indicating air trapping and reduced inspiratory capacity.
Zivanovic et al., United Kingdom, 2017 [48]	Assess whether pulmonary artery pressures differed between children born prematurely with or without BPD.	Randomized control trial	1998–2001 11–14 (interval)	190 PT (26.9 w, BW 894 g (203)) (106 BPD) 110 term controls (39.9w, BW 3510 g (434))	Two-dimensional echocardiography, spirometry	Pulmonary artery pressures were estimated to be greater in adolescents born extremely prematurely compared with those born at term, specifically in those with BPD.

BPD: Bronchopulmonary dysplasia; EP: Extreme preterm; FRI: Functional respiratory imaging; PT: Preterm; M/s: Moderate/severe; BW: Birthweight; CLD: Chronic lung disease; ELGA: Extremely low gestational age; ELWB: Extremely low weight at birth; VLWB: Very low weight at birth; ROP: Retinopathy of prematurity.
[a] Birthweight in centile with interquartile range.

Table 3
Definitions of bronchopulmonary dysplasia used in the selected studies.

Definitions
Need for supplemental oxygen at ≥28 days (mild BPD by NICHHD) [23,26,36,43,46]
NICHD according to severity [19–22,30–33,39,40,45,47]
Requirement for supplemental oxygen at 36 weeks postmenstrual age. (m/s BPD) [25,27,28,34,41,42,48]
Need for supplemental oxygen and/or ventilatory support at 36 weeks of post-menstrual age. (m/s BPD) [24,29,38,44]
Scale defined by the authors, including clinical and radiological criteria [23,27,35,44]
BPD- Bronchopulmonary dysplasia; NICHHD- *National Institute of Child Health and Human Development*

reported that between 8 and 14 years of age the lung function of all preterm mostly improved, despite reductions in FEV_1 and FEV_1/FVC being more frequently reported in BPD than in non-BPD adolescents.

Seven studies [22,25,27,29,36,45,47] showed a positive bronchodilator (BD) response, with a significantly higher post-FEV_1 in the BPD group (7–35 % vs 7–17 % of positive BD responders), despite remaining lower than the reference values, suggesting an incipient obstructive lung pattern. Also, Fawke, et al. [25] reported that the positive bronchodilator response was more pronounced in adolescents born EP (27 %) than in classmates (8 %), and in BPD-adolescents born EP (32 %) than in non-BDP (16 %). On the contrary, Halvorsen, et al. showed no significant bronchodilator response in preterm adolescents; however, the cohort from this study was the oldest among studies evaluating bronchodilator response [31].

Response to methacholine was mentioned in three studies [30–32]: all showed an increase in responsivity to methacholine in preterm adolescents versus term controls (2.6–32.5 vs 1.2–1.6, geometric means). An increased response with increasing severity of BPD was only significant in one study of the three that evaluated this parameter (3.9 in non-BPD, 5.9 in mild, 15.6 in moderate/severe (geometric means)) [30].

Two studies compared older and newer cohorts of BPD-patients. Vollsæter, et al. [40] outlined that both were similar, except for lower z-FVC (z-FVC difference: −1.01) and higher z-FEV_1/FVC (z-FEV1/FVC difference: 1.02) in the moderate/severe BPD group of the older BPD cohort, suggesting a more restrictive pattern in the latter. Halvorsen, et al. [32] reported similar decrease in lung function, though a diagnosis of moderate/severe BPD had stronger effect in reduction of FEF75 in the newer BPD group [41.6 vs 36.2, $p = 0.020$ (group mean differences between preterm and individually matched controls in percent of predicted)].

3.6. Exercise capacity

Five studies evaluated exercise capacity and overall reported no difference between BPD versus non-BPD adolescents, but with some discrepancies [20,21,39,41,42]. Clemm, et al. [21] found that the mean peak oxygen volume (VO_2) was 7–11 % lower (weight adjusted and raw values) and the treadmill distance run in meters was 10 % lower in adolescents born EP compared to term controls, although still within the normal range. Maximum minute ventilation and ventilatory reserve capacity did not differ. There was no association between exercise capacity and BPD history or the BPD strata. In another study by Clemm, et al., individuals were evaluated at 10 and 18 years old. Exercise capacity at the age of 10 significantly predicted exercise capacity at the age of 18, both in preterm and in term groups. There was a positive association between reported leisure-time exercise and peak VO_2 in both groups, although participation was significantly lower among those born preterm (21 % of those invited) [20]. Neonatal BPD and current

Table 4
Quality assessment for observational cohort and cross-sectional studies.

Criteria	Yes	No	Other (NA, NR)
1. Was the research question or objective in this paper clearly stated?	97 % (28/29)	3 % (1/29)	
2. Was the study population clearly specified and defined?	97 % (28/29)	3 % (1/29)	
3. Was the participation rate of eligible persons at least 50 %?	76 % (22/29)	17 % (5/29)	NR: 7 % (2/29)
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?	97 % (28/29)	3 % (1/29)	
5. Was a sample size justification, power description, or variance and effect estimates provided?	62 % (18/29)	38 % (11/29)	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	86 % (25/29)	14 % (4/29)	
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	86 % (25/29)	14 % (4/29)	
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	45 % (13/29)	55 % (16/29)	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	97 % (28/29)	3 % (1/29)	
10. Was the exposure(s) assessed more than once over time?			NA:100 % (29/29)
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	97 % (28/29)	3 % (1/29)	
12. Were the outcome assessors blinded to the exposure status of participants?	31 % (9/29)	45 % (13/29)	NR–24 % (7/29)
13. Was loss to follow-up after baseline 20 % or less?	45 % (13/29)	34 % (10/29)	NA-14 % (4/29); NR 7 % (2/29)
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	83 % (24/29)	17 % (5/29)	

NA: Not applicable; NR: Not reported

FEV_1 had no impact in peak VO_2, suggesting a comparable training potential in the two groups. Um-Bergström, et al. [39] also evaluated the influence of BPD severity on exercise capacity and lung function at a mean age of 14.5 years and did not find significant differences in VO_2. Harris, et al. [42] similarly found no significant association between exercise distance and BPD before or after adjustment for potential confounders and no evidence of relationship with self-reported exercise. The EPICURE [41] study, however, found that those born EP had significantly lower peak VO_2 during exercise (mean difference − 297), adopted a shallower and tachypneic breathing pattern and achieved a significantly lower peak workload (~20 % lower workload). Nevertheless, reports and measures of physical activity by accelerometer over a 7-day period showed no differences between groups, contrary to the individuals' own perception.

Table 5
Quality assessment of controlled intervention studies.

Criteria	Yes	No	Other (NA, NR)
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	X		
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?	X		
3. Was the treatment allocation concealed (so that assignments could not be predicted)?	X		
4. Were study participants and providers blinded to treatment group assignment?	X		
5. Were the people assessing the outcomes blinded to the participants' group assignments?	X		
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	X		
7. Was the overall drop-out rate from the study at endpoint 20 % or lower of the number allocated to treatment?		X	
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	X		
9. Was there high adherence to the intervention protocols for each treatment group?	X		
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	X		
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	X		
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80 % power?	X		
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	X		
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?		X	

NA: Not applicable; NR: Not reported

3.7. Airway inflammation and gas transfer

Five studies [27,28,43,45,47] assessed gas transfer and/or airway eosinophilic inflammation. Carraro, et al. [43] compared the exhaled air temperature (EAT) and exhaled nitric oxide (FeNO) among BPD survivors, asthmatics and healthy controls. They found a significantly lower EAT in BPD survivors than in asthmatic patients (26.7 °C vs 29.6 °C) and no significant difference between BPD survivors and healthy controls. They found similar FeNO in BPD survivors (10.6 ppb) compared to healthy controls (11.7 ppb), with FeNO in both of these groups lower than asthmatics (29.9 ppb). These findings suggest a different pathogenesis behind BPD and asthma.

Filippone, et al. [27] also compared the 8-isoprostane concentrations in exhaled breath condensate in BPD-adolescents versus preterm born adolescents without BPD and found similar results, but these values were higher than term control group. Similarity in 8-isoprostane between those with and without BPD suggests long-term airway oxidative stress is a feature of prematurity itself, regardless of BPD. They also measured FeNO levels and no differences emerged between groups, in agreement with findings from Fortuna, et al. [28].

Pérez-Tarazona, et al. reported no differences in lung volume or diffusion measurements [45]. However, a significantly lower diffusing capacity of the lung for carbon/alveolar volume ratio was reported in BPD adolescents by two other studies [41,47].

3.8. Lung imaging

Four studies reported lung imaging findings [18,19,37,47]. Aukland, et al. [18,19] studied a cohort of 130 subjects born at ≤28 weeks or with

Table 6
Quality assessment of case-control studies.

Criteria	Yes	No	Other (NA, NR)
1. Was the research question or objective in this paper clearly stated and appropriate?	X		
2. Was the study population clearly specified and defined?	X		
3. Did the authors include a sample size justification?		X	
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	X		
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	X		
6. Were the cases clearly defined and differentiated from controls?		X	
7. If <100 % of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA
8. Was there use of concurrent controls?		X	
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	X		
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	X		
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	X		
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	X		

NA: Not applicable; NR: Not reported

a birth weight ≤ 1000 g in Norway, in two different periods (1982–85 and 1991–92, the latter having surfactant available) over 20 years. They used high-resolution computed tomography (HRCT) to evaluate the imaging outcomes at a median age of 18 years and found abnormalities in 87.5 % of the overall cohort: linear opacities (72.2 %) and triangular subpleural opacities (58.3 %) were the most frequent findings, followed by air trapping (26.4 %), mosaic perfusion (13.1 %), bronchiectasis (9.7 %), thickening of interlobar septa (9.7 %), peribronchial thickening (5.6 %), collapse or consolidation (4.2 %), and bullae (4.2 %). However, there were no significant differences between BPD versus non-BPD status. Also, there was no evidence of pathologic bronchus-to-bronchial artery diameter ratio, mucus plugging, or emphysema. There were no differences in distribution between the right and left lungs, but lower lobes were more often affected than the upper ones. A modified Bhalla scoring system was used and the mean total HRCT score was 6.9 (95 % CI 5.3–8.6), with no differences according to gender; BPD-adolescents had higher mean and median total scores, but these differences were not significant. Compared to subjects without BPD or with mild BPD, subjects with moderate/severe BPD had a significantly higher total HRCT score (mean 3.0 vs 5.2, $p = 0.009$) as well as more opacities ($p = 0.035$) and hypoattenuated areas ($p = 0.007$). All lung function variables (FEV1, FEF50, forced expiratory flow 25 % to 75 % (FEF25–75) and RV/TLC) were significantly associated with linear/ triangular opacities and with total HRCT score. In logistic regression model, only the number of days with oxygen treatment and the number of days with ventilator treatment were significant, explaining 33.3 % of the variability in total HRCT score. When the number of days with ventilator treatment was removed from the model, the number of days with oxygen treatment still explained 31 % of the variability in total HRCT score, thus appearing the most important explanatory variable [19].

Vanhaverbeke, et al. found higher lobar volumes in all lobes in BPD patients using functional residual capacity, indicating air trapping ($p < 0.01$) [47]. In their model, BPD status and birthweight could explain 39 % of variability in air trapping on FRI analysis, suggesting that FRI might be a more sensitive detection method than HRCT.

Narayanan, et al. [37] compared alveolar dimensions in adolescents born at term, mild preterm, EP, and EP with BPD using hyperpolarized helium-3 magnetic resonance. They found similar alveolar dimensions in all groups, indicating that histologic abnormalities found in the alveoli of children with BPD in early childhood may be compensated by later alveolarization.

3.9. Pulmonary artery pressure

Only one study [48] reported pulmonary artery pressure in early adolescence. Peak tricuspid regurgitation velocity (MD -0.25), peak (MD -4.3) and mean right ventricular-right atrial gradient (MD -2.39), estimated right atrial pressure (MD -2.08), calculated systolic pulmonary artery pressures (MD -4.6) and mean pulmonary artery pressures (MD -2.31) were significantly higher in adolescents born prematurely compared with term controls. Comparing BPD preterm versus non-BPD, only peak tricuspid regurgitation velocity (2.25 in BPD vs 2.15 non-BPD, $p = 0.023$) and left ventricle ejection fraction (67 % in BPD vs 71 % non-BPD, $p = 0.006$) were significantly higher.

3.10. Psychosocial outcomes

Six studies reported psychosocial outcomes [24,34,35,38,45,46]. Quality of life was mentioned in three studies [38,45,46], but only one reported lower quality of life in BPD-adolescents [38]. Two studies [24,38] reported that BPD-adolescents were at increased risk of cognitive, language, and executive dysfunctions, academic achievement limitations and social skill deficits. After adjustment for potential confounders, Drummond, et al. [24] reported that history of BPD was associated with special education needs and grade repetition.

One study showed that BPD-adolescents required more healthcare attendance with psychomotor therapists, speech therapists, and psychologists or psychiatrists [19]. Kuint, et al. showed a non-significant higher adjusted relative risk for hospitalization in BPD-adolescents 1.15 at 11th–14th years (95 % CI 0.75–1.75) and 1.26 at 15th–18th years (95 % (CI 0.67–2.39)), showing a decrease in the risk observed at 10 years of age (1.35, 95 % CI 1.01–1.78) [35].

Holsti, et al. applied the Questionnaire for Identifying Children with Chronic Conditions (QUICCC questionnaire) and showed that BPD was associated with at least one functional limitation (65 % vs 37 %, $p = 0.003$), even if outlying the neurosensory impaired group [34].

4. Discussion

This systematic review showed that BPD has an impact in adolescence respiratory and non-respiratory outcomes. These BPD-adolescents had more respiratory symptoms, such as wheezing [25,28,29], respiratory exacerbations [27,31,44] and need for respiratory medication use and medical visits [25,31]. All reports indicated a reduction in, at least, one pulmonary function measure [19–23,25–33,36,39–48], varying according to BPD severity [31–33,39,40,45]. Studies including longitudinal changes in the parameters measured by spirometry reported conflicting results [22,23,26,28,33,39,40]. An association between BPD and increased prevalence of asthma was not unanimously reported [23,31,33,44,45,47,50], but there can be an increase in methacholine [30–32] and salbutamol [22,25,27,29,36,45,47] response in BPD groups. Exercise potential appeared to be the same, but there were conflicting results regarding exercise capacity and physical activity [20,21,39,41]. No differences were reported in airway eosinophilic inflammation, as opposed to the eosinophilia found in asthmatics [27,28,43,45,47]. Radiologic abnormalities were only more prevalent in moderate/severe BPD-adolescents, especially higher HRCT scores [18,19]. An increase in lobar volumes suggested the presence of air

trapping [18]. Reports on the quality of life were not consistent [38,45,46] but there was higher risk for special needs in education [24,38]. Hospitalization rates were higher, but differences were not as substantial as in childhood [35].

The majority of studies assessed pulmonary function measures and all of them showed an obstructive pattern with reduction of FEV_1, FVC, FEV_1/FVC and FEF25–75 %. Um-Bergtröm, et al. assessed impulse oscillometry (IOS) which is thought to represent complex functions of the lung such as small airway obstruction and airway mechanics [39]. This study showed that severe BPD-adolescents had peripheral airway involvement, compared with non-BPD subjects. Halvorsen, et al. found evidence suggesting an accelerated decline in FEV_1 in BPD-adolescents caused by structural sequelae rather than inflammation, but these findings may be influenced by higher prevalence of asthma, childhood pneumonia and bronchial hyperreactivity in the BPD group, which also expedite lung function decay [30]. Monitoring lung function in BPD-adolescents may predict the risk for developing COPD and thus allowing for preventive care [47]. Fortuna, et al. [28] also reported a decrease in lung function with increasing age in BPD-patients, but noted an interindividual heterogeneity of lung function evolution, suggesting that factors other than BPD alone may influence the lung trajectory throughout the years. When alveolar volume was considered, Vanhaverbeke, et al. [47] and Welsh, et al., [41] found a reduction in carbon diffusing capacity of the lung, suggesting an impairment in alveolar structures. The existence of structural abnormalities (more evident in severe BPD-patients) may be one of the reasons for lower lung function in BPD-adolescents, but it appears that other factors such as genetics or the environment at which children are exposed will influence the potential lung recovery and trajectory. Advice regarding smoking avoidance is also paramount as there is evidence of partial reversibility in airway obstruction of adolescents with BPD, which is less significant in smokers [22].

The only study regarding pulmonary artery pressure in early adolescence showed a significantly greater increase in peak tricuspid regurgitation velocity and left ventricle ejection fraction in those with BPD, indicating a trend towards emerging pulmonary hypertension [48]. However, only one ex-preterm fulfilled the criteria for pulmonary hypertension and clinical repercussions of these results were not assessed. This suggests that there might be an underlying common mechanism of injury both in vascular and pulmonary airways, such as an inflammatory process. However, this assumption should be cautiously interpreted, and additional studies should include inflammatory markers. Moreover, studies regarding pulmonary artery pressures with confirmatory gold standard cardiac catheterization are necessary [51].

Studies including cohorts born in the "new" BPD era also reported an association between the severity of BPD and airflow limitation in adolescence [22,25,26,28,32,33,36,39,40,45,47]. Like older BPD cohorts, newer cohorts also appear to be related to abnormalities in the airway, since flow impairment is found in both [30,32]. High oxygen concentrations, used to treat BPD patients, cause lung injury [50,52], so prolonged treatment periods (even if lower concentrations of oxygen are used) are an important factor for small airway obstruction in the newer BPD cohorts. The benefit versus harm of oxygen supplementation is an ongoing area of research, as is selective targeting of inflammatory cells that can minimize hyperoxia induced-lung impairment [53].

The pathophysiology of BPD is clearly different from the pathophysiology of asthma. Studies evaluating oxidative stress and airway inflammation by either FeNO or EAT showed lower values than to those found in asthmatic patients [27,28,43,45]. Oxidative stress appears to be related to prematurity and not to BPD history. The existence of more wheezing symptoms in BPD-patients appears to be related to airway hyperresponsiveness and chronic airflow obstruction. Airway hyperresponsiveness seen in BPD adolescents seems to be mostly associated to neonatal BPD and prolonged oxygen treatment [30]. There is no association between BPD and the prevalence of asthma in adolescents; this conclusion is also supported by a recent systematic review [54]. Therefore, wheezing in BPD is not related to asthma. Nevertheless, patients with symptoms and positive bronchodilator response should be adequately managed, as they might be undertreated [25]. However, BPD treatment is not well established and varies among clinicians and centers. Defining the best therapeutic approach through clinical trials should be a priority to improve long-term outcomes.

Although BPD-adolescents may be less physically active, their exercise capacity and trainability seem similar to healthy individuals [20]. However, these results may be biased by the fact that these studies excluded patients with significant cognitive and motor morbidities often found in ex-preterm adolescents. It is important to promote exercise practice in these adolescents to improve outcomes [53].

The duration of supplemental oxygen therapy appears to be the most significant contributor [19] to the HRCT abnormalities more commonly found in patients with moderate or severe BPD [18]. Combined methods assessing both imaging and function also demonstrated differences [47], suggesting an influence of lung abnormalities as opacities (possible fibrosis and atelectasis) and hypoattenuated areas (possible hypoperfusion) in its function. Despite lung volume reductions observed in histologic analysis of children with BPD who died, there were no differences in alveolar dimensions determined by magnetic resonance of adolescents with and without BPD, suggesting that there is a process of alveolarization that occurs beyond childhood [37]. As imaging techniques further develop, we can hope to better understand the long-term structural implications of BPD.

The higher reported respiratory disturbances in BPD-patients might be explained by the structural abnormalities in association with an altered innate immunoregulatory pathway [52]. However, increased risk of hospitalization in BPD-adolescents [53] is lower than in childhood [35], which might be due to the continued catch-up alveolarization hypothesised in adolescence.

There is lack of evidence regarding non-respiratory consequences of BPD in adolescents. BPD possibly had an independent neurologic and psychiatric impact in adolescents, regardless of respiratory morbidity [24,46]. These individuals appeared to have more educational challenges, which may impact their socioeconomic status and overall lower quality of life. However, out of the three studies [38,45,46] evaluating the quality of life, only one documented a decrease in BPD patients [38]. In fact, neurodevelopment is influenced by many factors such as gestational age and the use of postnatal corticosteroids [55,56], so attributing this impairment to only BPD requires caution.

4.1. Limitations

The major factors contributing to the divergent results of the different studies were likely the range of gestational ages included, the varying definitions of BPD, and the different time periods. In fact, the use of postnatal corticosteroids appeared to have the greatest long-term impact on the FEV_1 [40] and on the exercise capacity [21]. Older cohorts are different from more recent ones, but this is likely mostly due to inclusion of infants born extremely preterm who are now surviving; the incidence of BPD has actually increased over time [3]. Therefore, most studies performed on cohorts born in the 1980's may not be applicable to current adolescents who were born in the surfactant era. Some studies used cohorts born in the transition to modern neonatal care and made distinctions according to corticosteroid exposure [39]. The Norwegian cohort of 130 individuals is particularly significant for including two different birth-cohorts, before and after surfactant was available [18,19,30–32]. One limitation of this review was the absence of protocol registration.

The high methodologic quality score of most of the included studies makes this systematic review particularly relevant. However, the fact that some studies [24,25,41,43,46] compared EP infants to healthy controls without specifying BPD severity limited some conclusions. On the other hand, most studies which did stratify by BPD severity ended up with small samples in each group, compromising statistical power

[21,33,39,47]. As new studies with larger sample sizes emerge, a meta-analysis of their results may be of interest in the future to better quantify the impact of BPD in adolescents.

5. Conclusion

A history of BPD negatively impacts both pulmonary and non-pulmonary outcomes in adolescents, despite some contradictory findings in need of further evaluation. There is scarce information regarding treatment or preventive options for the consequences described [57,58]. We hope this systematic review contributes to raising awareness of the implications of BPD in adolescents, encouraging further investigation and proper follow-up of these patients.

CRediT authorship contribution statement

Mariana Carregã: Conceptualization, Methodology, Data Curation, Writing - Original Draft; Patrícia Sousa: Data Curation, Writing - Original Draft; Gustavo Rocha: Conceptualization, Writing - Review & Editing, Validation; Manuel Ferreira-Magalhães: Conceptualization, Methodology, Writing - Review & Editing; Inês Azevedo: Conceptualization, Writing - Review & Editing.

All authors read and approved the final version of the manuscript.

Ethics approval

Ethics approval was not required as this is a systematic review using previously published studies and no new patients were implied.

Funding declaration

This systematic review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Congresses

This paper was presented as poster at the Congress “Jornadas da Sociedade Portuguesa de Pneumologia Pediátrica e do Sono” that was held in Aveiro (Portugal) on 20th of May 2022.

Declaration of competing interest

The authors declare no conflict of interests.

Data availability

All data used in this study is available as can be requested to the corresponding author.

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