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REVIEW ARTICLE

WILEY Paediatric and Perinatal Epidemiology

# Identification of gaps in the current knowledge on pulmonary hypertension in extremely preterm infants: A systematic review and meta-analysis

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## Abstract

**Background**: Pulmonary hypertension complicates the clinical course of extremely preterm infants and is associated with bronchopulmonary dysplasia (BPD). However, prevalence, risk factors, and outcome of pulmonary hypertension in these infants are insufficiently known. This systematic review and meta-analysis aims to provide an up-to-date overview of available data on prevalence, risk factors, and outcome of pulmonary hypertension and to identify current knowledge gaps.

**Methods**: Medline, EMBASE, and the Cochrane Library databases were searched in July 2017. Two authors reviewed titles/abstracts and full-texts. Eligible studies reported prevalence, patient characteristics or mortality of infants with/without pulmonary hypertension. Studies were excluded if they did not include extremely preterm infants. Only similar study samples (selected infants with BPD or infants both with/without BPD) were compared in the meta-analyses.

**Results**: Of 1829 unique articles identified, 25 were eligible for inclusion. Pulmonary hypertension was observed in infants with BPD (20%, 95% confidence interval [CI] 14, 25), but also in those without BPD (2%, 95% CI 0, 8). Infants with severe BPD were most at risk of pulmonary hypertension (risk ratio [RR] 2.7, 95% CI 1.7, 4.2). Infants with pulmonary hypertension were more at risk of mortality (RR 4.7, 95% CI 2.7, 8.3).

**Conclusions**: Pulmonary hypertension occurs in particularly in infants with severe BPD, and increases risk of mortality. Due to selected study populations, heterogeneous pulmonary hypertension-definitions and poorly reported timing of pulmonary hypertension assessments, however, data available in current reports are insufficient to allow accurate assessment of true prevalence, risk factors, and time-related outcome. Prospective studies, with standardised methodology and follow-up are needed to determine these factors.

KEYWORDS
bronchopulmonary dysplasia, extremely preterm infants, meta-analysis, pulmonary hypertension, systematic review

**Clinical Trial Registration**
Prospero. Registration number: CRD42016042435.

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## 1 | INTRODUCTION

Over the past decades, advances in perinatal medicine have contributed enormously to the survival of extremely preterm infants. Nevertheless, the risk of respiratory morbidity and mortality remain high, often associated with bronchopulmonary dysplasia (BPD), a chronic lung disease of infancy first described by Northway in 1967.[1,2] Traditionally, BPD occurred predominantly in preterm infants born around 30-32 weeks requiring respiratory support and oxygen therapy at birth.[1,2] In those infants 'classic BPD' was characterised by lung damage and fibrosis due to oxygen toxicity and mechanical ventilation.

In the current era, however, BPD occurs most frequently in extremely preterm infants born between 24 to 28 weeks' gestation and, in contrast, BPD in these infants is characterised by a disordered lung development. These 'new BPD' infants show fewer severe acute respiratory symptoms and require less respiratory support than did 'classic BPD' patients in the past. Histological examination of the 'new BPD' patients suggests that an extremely preterm birth in combination with perinatal lung injury results in disrupted vascular growth and impaired alveolarisation, which in turn may result in pulmonary hypertension.[1,3-5]

Pulmonary hypertension, defined as an increased pressure in the pulmonary arterial system, substantially complicates the postnatal course of extremely preterm infants. In extremely preterm infants both early PH, occurring during the first week of life, and late PH after 36 weeks' postmenstrual age have been associated with poor outcomes. Recent reports suggested that morbidity and late mortality of PH in 'new BPD' patients is high, with a mortality rate of up to 48% 2 years after PH was diagnosed.[6] Additionally, PH has also been reported to occur in extremely preterm infants without BPD.[5]

In extremely preterm infants of less than 30 weeks' postmenstrual age, the prevalence rate of BPD is estimated to be between 30% and 60%, while the prevalence rate of PH received significantly less attention and estimates vary from 10% in infants with no BPD to 30% in infants with BPD.[5,7,8] In these studies, however, the age at which PH was diagnosed was highly variable and often unclear. The pathogenesis of BPD is complex and known risk factors for the development of severe BPD include both maternal factors, such as smoking during pregnancy, and neonatal factors, such as male gender, chorioamnionitis, low birthweight, gestational age, and acute lung injury caused by high ventilator settings and the duration of ventilation. The risk factors for the development of PH in extremely preterm infants are not well-defined.[9-11]

Knowledge on prevalence, risk factors, and time-related mortality of PH in extremely preterm infants will allow physicians to develop evidence-based screening guidelines for these infants and eventually preventive strategies. Early detection of PH will lead to early and thus potentially better treatment.

We undertook a systematic review and meta-analysis to determine prevalence of PH in extremely preterm infants, both with or without BPD. We also attempted to identify risk factors for the development of PH in extremely preterm infants and to determine the mortality of these infants.

## 2 | METHODS

### 2.1 | Search strategy

We performed a systematic review and meta-analysis of all available publications on PH in extremely preterm infants, until July 2017 (registered in the International prospective register of systematic reviews PROSPERO 2016 CRD42016042435). Since this study is a systematic literature study, review of an ethics board was not required.

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram to document the excluding process and the PRISMA checklist for performing the systematic review (Table S1).[12]

On July 25, 2017 we searched the electronic databases of Medline, EMBASE, and the Cochrane Library for studies eligible for inclusion. We focused on three domains: PH, prematurity, and a combined domain for prevalence, risk factors, and mortality rate. Table S2 in the supplemental data shows the exact search strategy. Subsequently, we scanned the reference lists of the articles selected for any additional studies we might have missed during our initial search.

### 2.2 | Study selection

Title and/or abstract reviews and full text reviews were carried out by two authors (SA and EAHZ). In case of a disagreement the authors discussed the issue until a consensus was reached.

We included prospective and retrospective observational studies. We excluded articles written in a language other than English, articles that consisted of an abstract only, case reports, animal studies, and interventional studies.

A study was deemed eligible for inclusion if it reported on at least one of the following: prevalence of PH, patient characteristics of infants with and without PH, and/or mortality after PH had been diagnosed. The studies had to report the echocardiographic PH definition used and it had to include one of the following echocardiographic findings: estimated right ventricular systolic pressure (RVSP) >40 mm Hg, RVSP/systemic systolic blood pressure ratio >0.5, presence of a cardiac shunt with bidirectional or right-to-left flow, or the presence of ventricular septal wall flattening.[5,13] In addition, if eligible studies included infants with BPD, they had to use the BPD definition and grading according to National Institutes of Health (NIH) standards.[4]

We excluded studies that did not report on very and/or extremely preterm infants (less than 32 weeks' gestation) and/or infants with very low birthweights (less than 1250 grams).[14,15] We also excluded studies that did not report how PH had been diagnosed, as well as studies that reported selectively on persistent PH of the newborn.

We used the NIH quality assessment tools to assess risk of bias.[16,17] Reports that failed the NIH assessment tools for risk of bias, due to a rating 'poor', were excluded. A sensitivity analysis including these excluded articles has been performed to ensure no important

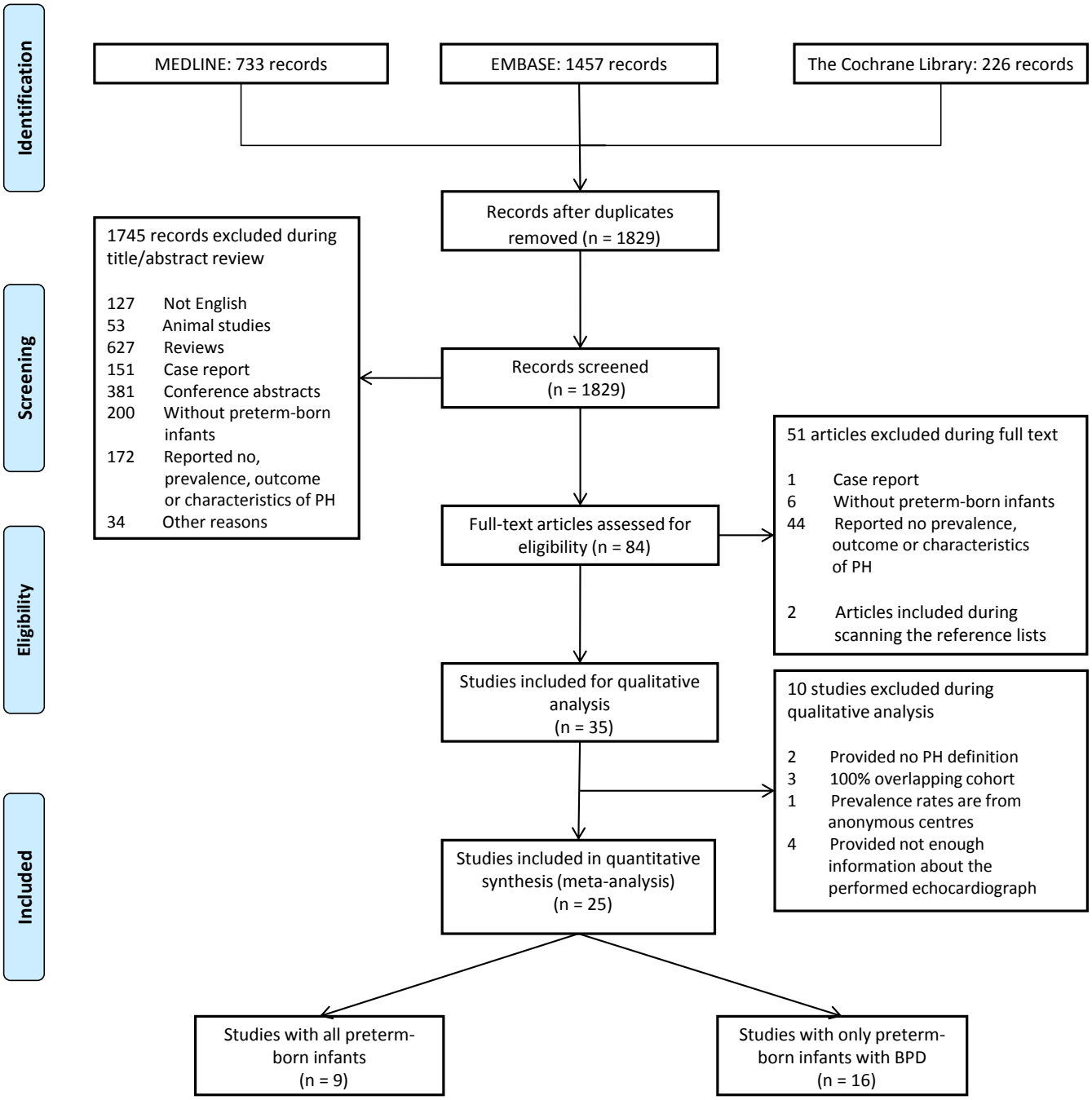


**FIGURE 1** PRISMA flow chart of the excluding process. *Legend:* Explanation abbreviations: PH=pulmonary hypertension; BPD=Bronchopulmonary dysplasia. *other reasons included: comments, editorials and letters to the editor

data would be missed. Publication bias was assessed by funnel plots. Funnel plots were only drawn if a meta-analysis existed of more than ten studies, because fewer studies decrease the power and validity of the test.[18]

## 2.3 | Outcomes

The primary objective was to determine the prevalence of PH in extremely preterm infants based on a PH definition that was concordant with proposed PH criteria.

The secondary objectives were to examine the associations between extreme preterm births and the development of PH and to determine the mortality of extremely preterm infants suffering PH.

## 2.4 | Data extraction

We extracted the reported proportions of preterms with PH from all eligible studies. Also, the various proportions of infants reported for each BPD classification were taken into consideration. In addition, we collected the available patient characteristics of all infants

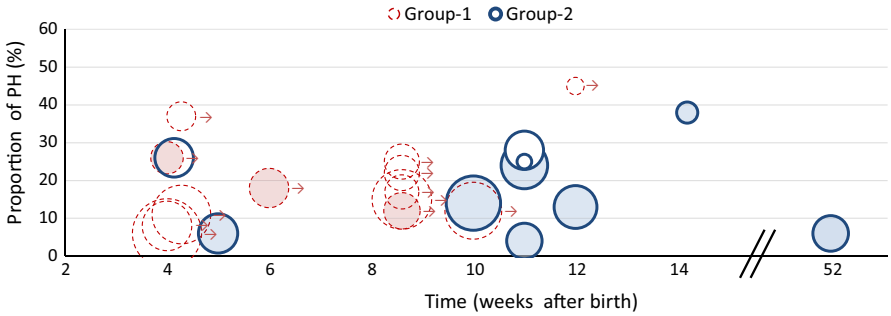


**FIGURE 2** Prevalence proportions of PH in relation to timing of PH assessment. *Legend:* Group-1: PH prevalence proportions of studies with a poorly defined time of PH assessment (→ indicates the start of the time interval in which PH was assessed). Group-2: PH prevalence proportions of studies with a well-defined time of PH assessment. The bubble's area represents the number of infants. Filled bubbles represent prospective studies. PH, pulmonary hypertension

both with PH and without PH, including maternal as well as neonatal variables. Finally, for further analyses, we collected the number, and if available, the ages of infants that had died during the study period.

### 2.5 | Data synthesis

We performed meta-analyses of the prevalences of PH reported in the included papers, associations of patient characteristics with PH, and the risk of mortality. We used STATA 14.0 statistical software for the statistical analyses.[19]

Studies that reported a prevalence of PH were eligible for the meta-analysis of the prevalence of PH. An overall prevalence of PH was estimated by using the metaprop command for the analyses of proportions in STATA. It was performed for studies restricted to only infants with BPD and separately for studies consisting of infants with and those without BPD.[20] To be certain the meta-analyses included prevalences near 0% and 100%, the Freeman-Tukey double arcsine transformation was used.[20] In addition, we estimated the prevalences of PH for each BPD classification.

Studies that reported patient characteristics of infants with and infants without PH were eligible for the meta-analysis of associations for the development of PH. To ensure the identified characteristics are in fact 'real' associations with the development of PH and not an incidental finding, characteristics had to be reported in 3 or more studies to be eligible for meta-analysis. Only characteristics of similar and not overlapping study populations were included. The metan command in STATA was used for the meta-analysis for binary outcomes for the estimation of risk ratios (RR) for the development of PH for binary variables. Hedges' g was calculated for continuous variables and subsequently used to estimate the standardised mean differences (SMDs) for the development of PH.[21] A SMD of zero was considered as no effect and a SMD greater than or equal to 0.8, or less than or equal to -0.8 was considered a high effect.[22] Hozo's method was used to convert values reported as medians with interquartile ranges to means with standard deviations.[23] These values could therefore be included in the meta-analyses.

Studies that reported mortality were eligible for the meta-analysis of mortality. An overall mortality of PH was estimated for studies that restricted to only infants with BPD and also separately for studies consisting of infants with and those without BPD. In addition, the binary meta-analysis was used to estimate a RR for mortality of infants with PH.

Because we expected a certain degree of heterogeneity between the eligible studies, we performed a random-effect analysis in all the analyses. We assessed heterogeneity with the Cochran *Q* test and the $I^2$ measure. In case of substantial heterogeneity ($I^2 > 50\%$), we examined the articles for possible methodological differences and performed a meta-regression analysis to identify possible sources of heterogeneity.

## 3 | RESULTS

### 3.1 | Study selection

The initial search identified 2416 articles and after removing duplicates 1829 remained. After reviewing the titles and/or abstracts we excluded another 1745 articles, leaving 84 articles for a full text review. Subsequently, an additional 51 articles were excluded. We included two articles by scanning the reference lists. Finally, 25 articles, 16 retrospective and 9 prospective studies, were eligible for inclusion in the study.[5-7,24-45] The flow chart of this excluding process is given in Figure 1. Examination of the baseline tables of all included studies revealed that the means and medians of the gestational ages of all the infants were below 30 weeks' gestation, indicating an extremely preterm infant sample. Table S3 shows the main characteristics of the included studies.

### 3.2 | Risk of bias

The results of the assessment of the risk of bias are shown in Table S4. Eight studies that were included provided clearly defined objectives, study populations, and outcome measures.[5,7,32,35,36,39,40,43] However, 17 of the 25 included studies had a retrospective design and included a selected study population.[6,24-31,33,34,37,38,41,42,44,45] Four studies reported on a study population of extremely preterm infants with and without BPD,[5,7,35,43] whereas 16 studies reported selectively on infants with BPD and seven studies reported selectively on a study population of infants with moderate/severe BPD.[27,28,31-33,37,42] In nine

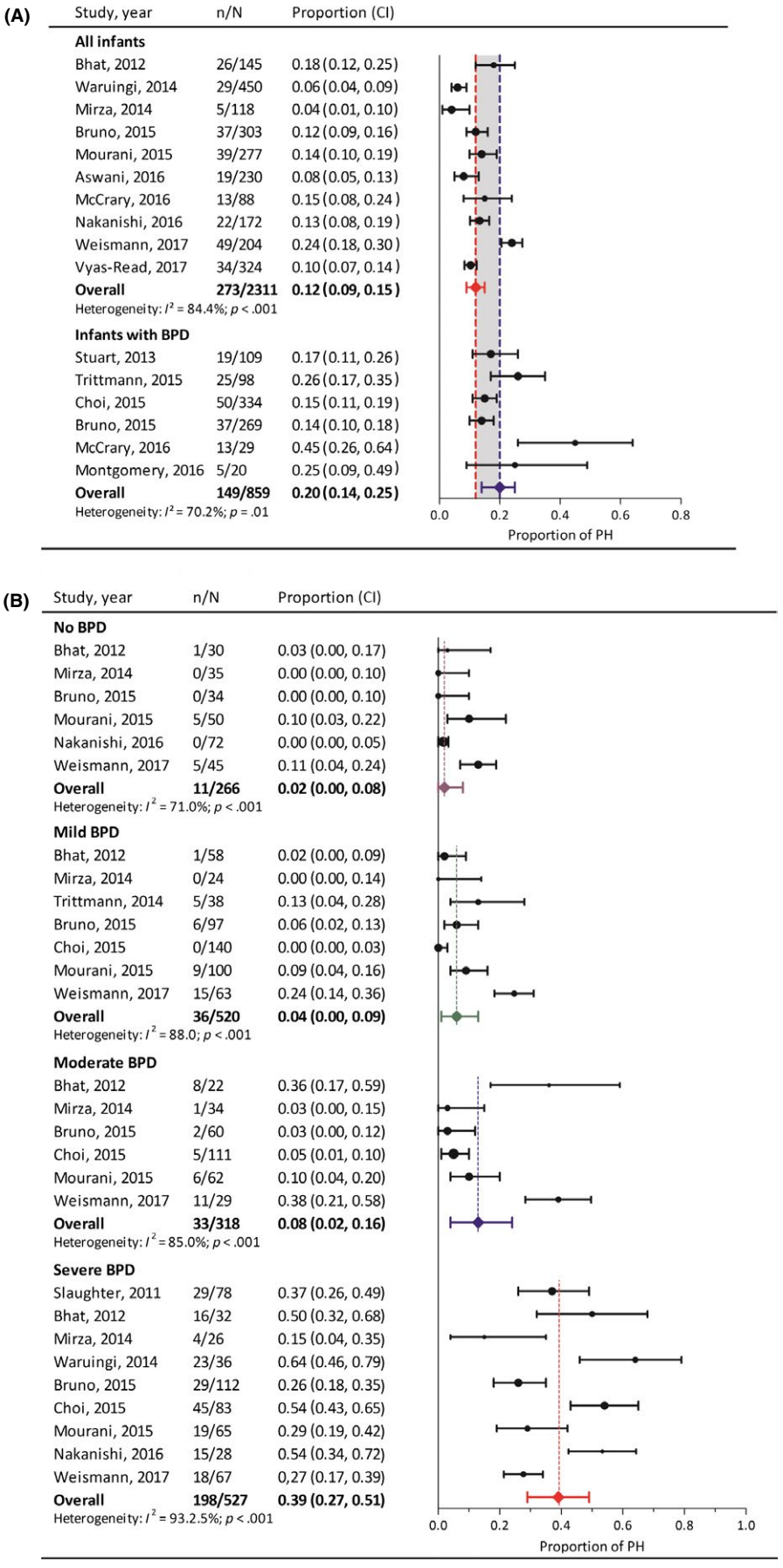


**FIGURE 3** Reported prevalence proportions in extremely preterm infants. *Legend:* (A) PH prevalence proportions of studies that included infants with/without BPD and of studies that included only BPD infants. The shaded area represents the difference between the two.(B) PH prevalence proportions per BPD classification. Heterogeneity: $I^2$. PH, pulmonary hypertension; BPD, bronchopulmonary dysplasia; CI, confidence interval

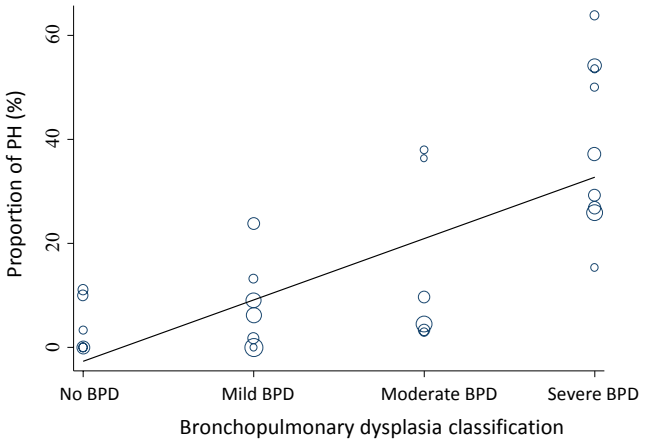


**FIGURE 4** Bubble chart of the meta-regression analysis of the prevalence proportions of PH per BPD classification. *Legend:* The area of each bubble represents the number of patients. Explanation abbreviations: PH, pulmonary hypertension; BPD, bronchopulmonary dysplasia

studies the study population partly overlapped with other included studies (Table S5).[24,27,28,31-33,39,40] Seven studies were excluded because they failed to report a clear definition of the outcome of interest (Table S4). In addition, three studies were excluded because the study population had an 100% overlap with another included study (Table S5). We could not draw funnel plots because none of the meta-analyses consisted of more than ten studies.

## 3.3 | Prevalence of PH

Figure 2 shows all reported prevalences of infants with PH at the various ages that PH was diagnosed in the respective studies. In total 25 prevalences were reported in 21 eligible studies, 10 of these 25 prevelances were reported in prospective studies,[5,7,32,35,36,39,40,43] whereas 15 of 25 prevalences were reported in retrospective studies.[24-28,31,33,34,37,38,41,44,45] Eleven prevalences were derived from studies that reported a well-defined time of PH-assessment.[5,7,27,33,35,36,39,43,45] Fourteen prevalences were derived from studies that did not report a well-defined time point of assessment of PH.[7,24-26,28,31,32,34,37,40,41,44]

Six studies provided prevalences of PH in extremely preterm infants with BPD, and meta-analyses provided an accumulative estimated prevalence of 20% (95% CI 14, 25) (Figure 3).[26,28,34,36,38,40] Ten studies reported a prevalence of PH in extremely preterm infants both with and without BPD, giving an accumulative estimated prevalence of 12% (95% CI 9, 15) after meta-analysis (Figure 3).[5,7,25,26,34,35,41,43-45] Ten studies provided prevalences of PH for each BPD classification. Meta-analysis revealed the following prevalences: 2% (95% CI 0%, 8%) in the absence of BPD, 6% (95% CI 1, 13) for mild BPD, 12% (95% CI 4, 24) for moderate BPD, and 39% (95% CI 29, 49) for severe BPD.[5,7,26,28,35,37,39,41,43,45] The meta-analyses of the prevalence of PH are shown in Figure 3. Due to substantial heterogeneity between the studies ($I^2$ > 50%), the true prevalence of PH could not be accurately estimated. Meta-regression analysis identified an association between the classification of BPD and the prevalence of PH in extremely preterm infants: slope coefficient (95% CI) 0.118 (0.0708, 0.165); Figure 4).

**TABLE 1** Clinical characteristics: associations with the presence of pulmonary hypertension

| Characteristic | Infants with and without BPD SMD (CI) | Infants with BPD only SMD (CI) |
|---|---|---|
| Birthweight | −1.0 (−1.6, −0.5)[a] | −0.4 (−0.7, −0.2)[a] |
| Gestational age | −0.6 (−1.3, 0.1)[a] | −0.4 (−0.6, −0.2) |
| Length of stay | 2.3 (−0.4, 4.9)[a] | 0.8 (0.1, 1.5)[a] |
| Apgar score at 5 min | NA | −0.4 (−0.8, 0.0)[a] |
| Days MV | NA | 0.6 (0.0, 1.1)[a] |
| **Characteristic** | **RR (CI)** | **RR (CI)** |
| Gender (male) | 1.1 (0.9, 1.3) | 0.9 (0.7, 1.2) |
| SGA | 1.8 (1.2, 2.7)[a] | 0.5 (0.1, 1.8)[a] |
| BPD | 1.3 (1.1, 1.5)[a] | NA |
| Severe BPD | 2.7 (1.7, 4.2)[a] | NA |
| ROP | 1.9 (1.3, 2.7) | 1.2 (0.8, 1.9) |
| NEC | 1.8 (0.9, 3.9)[a] | 3.4 (1.1, 10.2)[a] |
| Severe IVH | 1.7 (0.8, 3.4)[a] | NA |
| Need PDA ligation | 1.8 (1.3, 2.4)[a] | NA |
| Maternal HT | 1.2 (0.8, 2.0) | NA |
| Chorioamnionitis | 1.1 (0.7, 1.8) | NA |
| Maternal PPROM | 0.8 (0.5, 1.1) | NA |
| PDA | 1.3 (1.2, 1.5) | 1.2 (1.0, 1.5) |
| Maternal Steroids | 0.9 (0.8, 1.1) | 1.0 (0.9, 1.1) |

BPD, bronchopulmonary dysplasia; SMD, standardised mean difference; CI, confidence interval; NA, not available; MV, mechanical ventilation; RR, risk ratio; SGA, small for gestational age; ROP, retinopathy of prematurity; NEC, necrotising enterocolitis; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; HT, hypertension; PPROM, prolonged preterm born rupture of membranes.
[a]$I^2$ > 50%.

## 3.4 | Characteristics associated with PH

Table S6 shows all patient characteristics collected from the selected studies. Altogether 59 types of patient characteristics of infants with and without PH were reported, where 24 patient characteristics were reported three times or more. These are shown in Table S7. Eighteen of these characteristics were from comparable not-overlapping samples and therefore eligible for meta-analysis. Sixteen of these eligible characteristics were reported in studies that included infants with and without BPD and eleven characteristics were reported in studies that selectively included only infants with BPD. The meta-analyses of the analysed characteristics are displayed in Table 1.

Birth weight was reported in 12 nonoverlapping studies, that is five studies on infants with and without BPD and seven studies with BPD infants only.[5,7,25,26,34,36,38,40,41,43,45]

Gestational age was reported in 12 nonoverlapping studies, that is five studies on infants with and without BPD and seven studies with BPD infants only.[5,7,24-26,34,36,38,40,41,43,45]

The presence of PH was associated with a lower birthweight in both BPD- and non-BPD-infants, whereas PH was associated with lower gestational age only in the BPD infants.

Small-for-gestational age (SGA) was reported nine times in eight similar not-overlapping studies, that is five studies on infants with and without BPD and two studies only on BPD infants. Only one study reported on infants with and without BPD, and also separately on those with BPD.[5,7,25,26,39,41,43,45] SGA was associated with the occurrence of PH in patients with or without BPD, whereas such association was not found when restricted to only infants with BPD.

Information regarding the severity of BPD was reported ten times in nine comparable, not-overlapping studies, that is five studies that included both infants with and without BPD and three studies including only infants with BPD. One study reported on infants with and without BPD, and also separately on those with BPD.[5,7,24-26,39,41,43,45] The meta-analysis revealed that the occurrence of PH was associated with BPD (RR 1.3, 95% CI 1.1, 1.5), but also with the severity of BPD: this relative risk doubled for those infants with severe BPD (RR 2.7, 95% CI 1.7, 4.2).

Retinopathy of prematurity (ROP) was reported in seven similar and not-overlapping studies, that is four times by studies on infants with and without BPD and three times by studies on BPD infants only.[5,7,24-26,28,39,45] The meta-analysis identified a moderate association between ROP and PH (RR of 1.9, 95% CI 1.3, 2.7).

Necrotising enterocolitis (NEC) was reported eight times in seven similar and not-overlapping studies, that is three studies on infants with and without BPD, three studies on infants with BPD only and one study on both infants with and without BPD as infants with BPD only..[5,7,24,25,36,43,45] Meta-analysis with BPD infants only identified a strong association between the presence of NEC and PH (RR 3.4, 95% CI 1.1, 10.2).

Information regarding a patent ductus arteriosus (PDA) was reported ten times in nine similar and not-overlapping studies, that is four studies on infants with and without BPD, four studies on BPD infants only and one study reported on infants with and without BPD, and separately on those with BPD only.[5,24-26,40,41,43,45] A weak association between the presence of PDA as well as the need for its ligation and the presence of PH was identified in infants with and without BPD (RR 1.3, 95% CI 1.2, 1.5 and RR 1.8, 95% CI 1.3, 2.4, respectively).

Information regarding the length of stay at the NICU was reported in six similar and not-overlapping studies, that is three studies on infants with and without BPD and three studies on BPD infants only.[5,7,24,25,43,45] Meta-analysis identified a strong association between the length of stay and PH in BPD infants (SMD 0.8, 95% CI 0.1, 1.5).

Information regarding the total days of ventilation was reported in four similar and not-overlapping studies on BPD-infants.[24,43,45] Meta-analysis identified an association between the total days of ventilation and PH (SMD 0.6 95% CI 0.0, 1.1).

No association was found between the occurrence of PH and the remaining characteristics - gender, maternal hypertension, chorioamnionitis, maternal prolonged preterm born rupture of membranes, maternal steroids, Apgar score at 5 minutes and severe interventricular hemorrhage.

### 3.5 | Mortality and PH

Five studies provided a proportion of mortality prior to discharge of infants with PH and infants with and without BPD. This resulted in an accumulative estimated mortality rate of 16% (95% CI 7, 28).[5,7,25,41,43] No precise timing of death was reported in these studies. Another three studies reported a mortality rate during a 2-year follow-up study of PH in preterm infants with BPD, resulting in an accumulative estimated mortality rate of 40% (95% CI 26, 54).[6,29,30] However, these latter studies include only infants that had survived one or 2 months after birth.

Meta-analysis of six studies that included infants with and without BPD, showed that the presence of PH was strongly associated with mortality (RR 4.7 (95% CI 2.7, 8.3)).[5,7,25,41,43,45]

### 3.6 | Sensitivity analyses

With regards to the prevalence of PH in total five articles of the excluded articles could be included in the meta-analyses, that is three studies on the prevalence of PH in infants with and without BPD, and two on the prevalence of PH in infants with severe BPD. Supporting Information References S1-S5. Giving an unchanged prevalence of PH in infants with and without BPD of 12% (95% CI, 9-15), and a slightly lower prevalence of PH in infants with severe BPD of 33% (95% CI, 16-52).

With regards to the clinical characteristics associated with the development of PH, in total one of the excluded articles could be included in the additional meta-analyses. Supporting Information Reference S4. For a total of 4 characteristics additional analyses could be performed: male gender with an unchanged RR of 1.1 (95% CI 0.9, 1.2), and slightly less strong RR's for the presence of NEC (RR of 1.7 (95% CI 0.8, 3.5)), severe IVH (RR 1.5 (95% CI 0.8, 2.9)) and the need for PDA ligation (RR of 1.8 (95% CI 1.3, 2.4)).

With regards to the mortality of PH none of the excluded articles could be included in the additional meta-analyses.

## 4 | COMMENT

### 4.1 | Principal findings

To the best of our knowledge, this is the first systematic review to report prevalence, associations, and mortality rates of PH covering samples of extremely preterm infants, including both those with and without BPD.

The primary finding is that current publications do not provide sufficient data for an accurate assessment of the true prevalence, risk factors and outcome of PH in extremely preterm infants. This is mainly due to substantial heterogeneity caused by the nature of reported

study designs that were predominantly retrospective and suffered from significant selection bias regarding patient inclusion and from variability in definition of PH as well as timing of PH-assessments.

## 4.2 | Interpretation

Nevertheless, these reports did reveal that PH occurred most prevalent in extremely preterm infants with severe BPD. Also, severe BPD was found to be the factor most strongly associated with the development of PH in these extremely preterm infants. Furthermore, mortality was significantly higher in infants with PH in comparison to infants without PH. These results strongly underscore the need for better prevention, screening, and treatment strategies in order to improve survival in this vulnerable group of infants. To develop such strategies, better insight in the occurrence of PH in these infants, its clinical course and confirmed risk factors is highly needed.

The results of the current review further show that PH may also occur in infants with no or mild BPD. A substantial variety of PH prevalences was reported for these infants, ranging from 0%-10%.[5,7,26,35,41,43] Only 9 of 25 studies reported on PH in extremely preterm infants with BPD bus also in those without BPD,[5,7,25,26,35,41,43-45] while the other 16 studies focused exclusively on PH in infants with BPD.[6,24,27-34,36-40,42] Moreover, 2 of 9 studies on infants both with and without BPD, selectively only reported characteristics of the infants with BPD.[44,45] We conclude that the extremely preterm infant with no or mild BPD is a seriously understudied infant population with respect to pulmonary vascular disease. Therefore, within the population of extremely preterm infants a substantial number of infants with PH might be missed. Hence, although severe BPD is a major risk factor for the presence of PH in preterm infants, for developing screening strategies, prevention and early treatment, the focus should not be limited to infants with BPD only. Prospective cohort studies will need to include a broader study population of unselected infants with and without BPD not only to identify the true prevalence rate of PH in extremely preterm infants but also to arrive at a clearer understanding of the association between BPD and the subsequent (or preceding) development of PH.

The current results showed that aside from BPD, also SGA, low birthweight, the presence of ROP, NEC or PDA were associated with the development of PH. Importantly, these factors are also known risk factors for the development of BPD.[11,46] Since BPD is strongly associated with the presence of PH, it is of crucial importance to study also preterm infants without BPD who develop PH in order to be able to distinguish whether or not the conditions associated with PH identified in current meta-analyses are also independent risk factors for PH. For instance, the presence of early PH, at 7 days of age, has been reported to be associated with the development of BPD.[5] Unfortunately, in none of the studies this was reported separately for infants without BPD and for infants with BPD. Due to insufficient data on preterms with PH without BPD, currently known conditions associated with PH in preterm infants cannot be assessed independently from BPD as a risk factor for the development of PH.

The results further showed that infants with PH have a higher risk for mortality than infants without PH. However, only three studies reported the age of death of the infants.[6,29,30] The remaining five studies reporting on mortality, provided no data on timing of death other than that the infants had died prior to discharge.[5,7,25,41,43] So, an accurate mortality rate estimate was not possible. Also, a mortality proportion of infants with PH, but without BPD, could not be estimated from the available reports. Therefore, well-designed follow-up studies of unselected cohorts of preterm infants both with and without PH are urgently needed.

## 4.3 | Limitations of available data

We found important differences regarding the moment of PH-assessment amongst the studies selected for the meta-analysis. This time of screening varied from 28 days after birth, at 36 weeks' post menstrual age to more than 2 months of age. Due to this variation, no accurate estimate of the presence of PH in relation to age could be made using meta-analysis. We were unable to determine with certainty the age at which PH was assessed for an important number of the reported prevalences (Group 1 in Figure 2) since the age of assessment was not clearly stated or could vary over weeks to months. Some studies, for instance, solely reported that PH was assessed "after 36 weeks' postmenstrual age". A more standardised prospective follow up for screening of PH, starting early after birth, is needed for an accurate estimate of the current prevalence of PH and its development over time in extremely preterm infants. In addition, these infants will have to be followed up over a longer period of time. Only one of the included studies reported an echocardiographic screening for PH at the age of 1 year.[43] Unfortunately, currently no other patient cohorts have been reported with a long follow-up of extremely preterm infants with and without BPD. As a result the time course of PH in preterm infants, whether PH may arise or resolve at a later age are insufficiently known, nor are its longer term effects on morbidity and mortality.

Finally, the interpretation of the available literature on PH in extremely preterm infants and of the current meta-analyses is further hampered by the lack of a robust definition of PH in the reported studies, associated with the intrinsic limitations of echocardiography in defining PH.[47] Although, we included only studies that used one of our pre-defined echocardiographic definitions of PH, a high variety among the studies existed. Although echocardiography is the mainstay for detecting PH in preterm infants, currently no perfect echocardiographic definition for the presence of PH in extremely preterm infants is available.[48] Invasive cardiac catheterisation is regarded the gold standard to confirm the presence of PH (mPAP >25 mm Hg) in older children and adults. In the vulnerable population of preterm infants, the relative shortcomings of non-invasive echocardiography should be weighted to the risks of invasive cardiac catheterisation.

In the current analyses on patient characteristics associated with the occurrence of PH we have chosen to include characteristics that were reported by three or more studies, in order to increase the robustness of the found associations, and to reduce the chance to

identify co-incidental associations. A limitation of this approach is that incidentally reported characteristics are not included in the analysis.

### 4.4 | Strengths of the study

A strength of this study was that we provided an up-to-date synthesis of all current publications on PH including samples of extremely preterm infants with but also without BPD. We achieved this by carrying out an extensive systematic search consisting of three domains. In addition, we carefully selected the studies and assessed them on their quality and risk of bias. Only those studies we found to have the lowest risk of bias by using the NIH quality assessment tool were included for further meta-analysis (Table S5).[16,17] Another strength in comparison to previous meta-analyses was our meticulous selection of studies for the respective meta-analyses.[49,50] We only compared studies that had comparable study populations. For instance, studies on infants with solely severe or moderate BPD were not compared with studies on infants with all BPD classifications. In doing so we avoided potential bias, because infants with severe or moderate BPD may be at greater risk of developing PH than infants with no, or mild, BPD. Previous performed meta-analyses did not consider these differences among the included studies. In addition, we included also infants without BPD into our analyses in contrast to previous performed meta-analyses.

This systematic review and meta-analysis identified the high need for standardised prospective cohort studies in this population. Standardised research methodology will eventually lead to a systematic review and meta-analysis that will enable researchers to arrive at an accurate estimate of prevalence, risk factors, and outcome of PH, allowing for optimalisation of prevention-, screening- and treatment strategies.

## 5 | CONCLUSIONS

Pulmonary hypertension occurs in extremely preterm infants, and most frequently but not exclusively in infants with severe BPD. Severe BPD is a prominent risk factor for the development of PH. Additional risk factors for PH include birthweight and SGA, and are also known to be risk factors for BPD. The presence of PH significantly increases the risk of mortality.

However, current available data on the occurrence of PH in extremely preterm infants are insufficient and do not allow for accurate estimation of true prevalence rates, identification of independent risk factors or predict outcome after term age. Properly designed prospective studies, including unselected cohorts of extremely preterm infants (with and without those who develop BPD), with PH-assessments using well defined criteria and at standardised time points, from the first weeks after birth and during long-term follow-up are needed.

### CONFLICT OF INTEREST

None.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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