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Association of the dysfunctional placentation endotype of prematurity with bronchopulmonary dysplasia: a systematic review, meta-analysis and meta-regression

Maria Pierro,[1,2] Eduardo Villamor-Martinez,[1] Elke van Westering-Kroon,[1] Maria Alvarez-Fuente,[3] Steven H Abman,[4] Eduardo Villamor [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Eduardo Villamor, Pediatrics, Maastricht University Medical Centre+, Maastricht, Netherlands 6229 HX, Netherlands;
e.villamor@mumc.nl

MP and EV-M contributed equally.

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ABSTRACT

Background Antenatal pathological conditions are key in the pathogenesis of bronchopulmonary dysplasia (BPD). Pathophysiological pathways or endotypes leading to prematurity and perinatal lung injury can be clustered into two groups: infection and dysfunctional placentation, which include hypertensive disorders of pregnancy (HDP) and intrauterine growth restriction (IUGR). We conducted a systematic review of observational studies exploring the association between the dysfunctional placentation endotype and BPD.

Methods MEDLINE, Embase and Web of Science databases were searched up to February 2020 for studies reporting data on the diagnosis of HDP, IUGR or small for gestational age (SGA) and BPD risk. BPD was classified as BPD28 (supplemental oxygen on day 28), BPD36 (oxygen at 36 weeks postmenstrual age), severe BPD (≥ 30% oxygen or mechanical ventilation), BPD36/death and BPD-associated pulmonary hypertension.

Results Of 6319 studies screened, 211 (347 963 infants) were included. Meta-analysis showed an association between SGA/IUGR and BPD36 (OR 1.56, 95% CI 1.37 to 1.79), severe BPD (OR 1.82, 95% CI 1.36 to 2.29) and BPD/death (OR 1.91, 95% CI 1.55 to 2.37). Exposure to HDP was not associated with BPD but was associated with decreased odds of BPD/death (OR 0.77, 95% CI 0.64 to 0.94). Both HDP (OR 1.41, 95% CI 1.10 to 1.80) and SGA/IUGR (OR 2.37, 95% CI 1.86 to 3.02) were associated with BPD-associated pulmonary hypertension.

Conclusion When placental vascular dysfunction is accompanied by fetal growth restriction or being born SGA, it is associated with an increased risk of developing BPD and pulmonary hypertension. The placental dysfunction endotype of prematurity is strongly associated with the vascular phenotype of BPD.

Prospero registration number Review protocol was registered in PROSPERO database (ID=CRD42018086877).

Key messages

What is the key question?

► Is the dysfunctional placentation endotype of prematurity, as represented by hypertensive disorders of pregnancy and intrauterine growth restriction, associated with an increased risk of developing bronchopulmonary dysplasia?

What is the bottom line?

► When placental vascular dysfunction is accompanied by fetal growth restriction or being born small for gestational age, it is associated with an increased risk of developing bronchopulmonary dysplasia and bronchopulmonary dysplasia-associated pulmonary hypertension.

Why read on?

► This meta-analysis review combines data from 211 studies (347 963 infants) and provides evidence that the placental dysfunction endotype of prematurity is strongly associated with the vascular phenotype of bronchopulmonary dysplasia.

INTRODUCTION

Very preterm birth is defined by a gestational age (GA) of less than 32 weeks, and extremely preterm birth by a GA of less than 28 weeks.[1 2] This degree of prematurity is the leading cause of neonatal mortality and morbidity due to a combination of organ immaturity and iatrogenic injury.[1 2] Preterm birth is always the result of a pathological process, which may not only contribute to early delivery but may also adversely impact neonatal outcomes.[3–6] The pathogenic pathways leading to very and extremely preterm birth can be clustered into two main groups: (1) intrauterine infection/inflammation and (2) dysfunctional placentation.[3–6] The first group is related to histological chorioamnionitis and placental microbial invasion, whereas the second group is associated with hypertensive disorders of pregnancy (HDP), and the entity identified as fetal indication/intrauterine growth restriction (IUGR).[3–6]

Characterisation of these two groups provides strong rationale for establishing each as a distinct endotype that impacts the risk and outcome of prematurity. The term endotype was coined by Anderson to cluster asthmatic patients not only by their clinical characteristics but also by the pathophysiological features of the disease.[7] The term has subsequently been extended to other conditions in an attempt to identify the subtypes of a disease defined by a unique or distinctive functional or pathophysiological mechanism.[8–10] The use of

endotypes is highly valuable to more fully describe specific biological pathways or biomarkers underlying clinical observations expressing the phenotype, which can enhance clinical care and research.[8–10]

Bronchopulmonary dysplasia (BPD), the chronic lung disease of prematurity, is the most common complication of very and extreme preterm birth.[11–14] Low GA at birth is the greatest single predictor of the risk for BPD. However, BPD is increasingly recognised as the result of an aberrant reparative response to both antenatal and postnatal injury to the developing lung.[11–15] Antenatal stresses, including chorioamnionitis, HDP and IUGR are frequently identified as risk factors for BPD.[11–17] However, it is very difficult to unravel which part of their pathogenic action is due to the alterations that these conditions induce in lung development and which part is due to their role as triggers of prematurity.

Intrauterine and postnatal injury to a developing lung can affect any number, if not all, of the three main lung compartments: (1) airways, (2) alveoli and adjacent lung parenchyma and (3) pulmonary vasculature.[18–21] A growing body of evidence indicates that these compartments are variably affected within each patient, which leads to different clinical phenotypes.[18–21] In particular, the 'vascular phenotype' of BPD is being increasingly recognised and BPD-associated pulmonary hypertension (PH) is a strong contributor to poor survival.[18–24] Our understanding of the risk factors and natural history of BPD-associated PH continues to grow but already the first reports on the condition suggested a strong association with both IUGR and HDP.[25 26]

Refining BPD risk according by endotypes and clinical phenotypes may be valuable for developing personalised medicine approaches that can potentially improve outcomes and lead to better-designed clinical trials. In a recent systematic review, we analysed the association between the paradigmatic example of the infectious/inflammatory endotype of prematurity (ie, chorioamnionitis) and BPD.[16] Meta-analysis showed that exposure to chorioamnionitis was associated with higher risk of BPD. However, GA in the chorioamnionitis-exposed group was ~1.2 weeks lower than in the 'control' group and meta-regression analysis showed that this difference in GA significantly modulated the association between chorioamnionitis and BPD.[16] The aim of this systematic review is to further address these questions by performing a comprehensive analysis to determine the association between the endotype of placental dysfunction, as represented by HDP and IUGR, and the risk of developing BPD and/or BPD-associated PH. In addition, through the use of meta-regression, we aimed to unravel the role of GA in the association between the placental dysfunction endotype and BPD.

METHODS

The methodology for this study was based on our recently published experience on performing meta-analyses to study the associations between chorioamnionitis and BPD,[16] and between IUGR and patent ductus arteriosus.[27] Detailed information on methods is provided as online supplemental material. The study was performed and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and meta-analysis of observational studies in epidemiology (MOOSE) guidelines.[28] The Population, Exposure, Comparison and Outcome question was: Do preterm infants (P) exposed to HDP or IUGR during pregnancy (E) have a higher risk of developing BPD or BPD-associated PH (O) than preterm infants with no history of exposure (C)?

Sources and search strategy

A comprehensive literature search was undertaken using the PubMed, EMBASE and Web of Science databases. No language limit was applied. The literature search was updated up to February 2020. The search strategy is detailed in online supplemental material.

Study selection

Studies were included if they examined preterm (GA <37 weeks) or very low birth weight (BW) (<1500 g) infants and reported primary data that could be used to measure the association between exposure to HDP or IUGR and the development of BPD or BPD-associated PH. Studies defining IUGR based on BW were also included. Since small for GA (SGA) is not necessarily synonymous with IUGR,[29–32] the group will be referred to as SGA/IUGR.

Data extraction, definitions, and quality assessment

Two reviewers (MP and MA-F) extracted data from relevant studies and three reviewers (EV-M, EvW-K and EV) checked data extraction for accuracy and completeness. Discrepancies were resolved by consulting the primary report. Outcomes considered in meta-analysis were: (1) BPD28, defined as oxygen requirement on postnatal day 28; (2) BPD36, defined as oxygen requirement at the postmenstrual age (PMA) of 36 weeks; (3) BPD36 or death; (4) Severe BPD, defined as need for ≥30% oxygen and/or positive pressure at 36 weeks PMA; (5) BPD-associated PH, defined by any echocardiographic criteria as long as the evaluation was performed at a postnatal age >4 weeks. Using these definition criteria, BPD28 was considered to include all severities of BPD, whereas BPD36 was considered to include a combination of moderate and severe BPD.[16 33] With regard to exposures, any definition of HDP or SGA/IUGR was accepted but we performed subgroup analysis based on the different definitions (Any HDP, pre-eclampsia, pre-eclampsia-hemolysis elevated liver enzymes and low platelets (HELLP) syndrome, BW <P10, BW <P5, BW <P3 or −2SD and IUGR defined by assessment of fetal growth). This subgroup analysis was only performed for the analysis including at least 10 studies. When a study used different BW threshold percentiles to define SGA, data from the lowest percentile were included. When a study did not specify the threshold percentile used, it was grouped together with the studies that used the 10th percentile.

Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohort or case–control studies.[34] This scale assigns a maximum of nine points (four for selection, two for comparability and three for exposure or outcome). NOS scores ≥7 were considered high-quality studies (low risk of bias), and scores of 5–6 denoted moderate quality (moderate risk of bias).[34]

Statistical analysis

Studies were combined and analysed using Comprehensive Meta-Analysis V.3.0 software (Biostat, Englewood, New Jersey, USA). Summary statistics were calculated with a random-effects model and subgroups were combined with a mixed-effects model.[35] For dichotomous outcomes, the OR with 95% CI was calculated. For continuous outcomes (eg, GA), the mean difference with 95% CI was calculated. Statistical heterogeneity was assessed by Cochran's Q statistic and by the I^2 statistic. Potential sources of heterogeneity were assessed through subgroup analysis and/or random effects (method of moments) univariate meta-regression analysis.[36] For both categorical and continuous covariates, the R^2 analogue, defined as the total between-study variance explained by the moderator, was calculated based on the meta-regression matrix.[36] We used the Egger's regression test and funnel plots to assess publication bias. A probability value of less than 0.05 (0.10 for heterogeneity) was considered statistically significant.

RESULTS

The PRISMA flow diagram of the search process is shown in online supplemental eFigure 1. Of 6319 potentially relevant studies, 211

Table 1 Main meta-analyses

Outcome	Exposure/insult		K	OR	95% CI		P value	Heterogeneity	
					Lower limit	Upper limit		I^2 (%)	P value
All BPD (BPD28)	Hypertensive disorders of pregnancy (HDP)	Any HDP	13	0.927	0.636	1.352	0.695	62.8	0.001
		Pre-eclampsia	14	1.058	0.756	1.482	0.742	59.4	0.002
		Pre-eclampsia/HELLP	6	0.771	0.465	1.279	0.314	64.7	0.015
		HDP overall	33	0.949	0.757	1.188	0.645	61.9	<0.001
	SGA/IUGR	BW <P10	27	0.823	0.618	1.096	0.182	64.7	<0.001
		BW <P3 or −2SD	4	1.234	0.599	2.541	0.569	82.9	0.001
		IUGR	2	1.267	0.532	3.018	0.535	0.0	0.546
		IUGR/SGA overall	33	0.898	0.696	1.158	0.408	66.2	<0.001
Moderate/severe BPD (BPD36)	HDP	Any HDP	27	1.066	0.914	1.243	0.810	68.9	<0.001
		Pre-eclampsia	31	1.093	0.869	1.375	0.448	83.8	<0.001
		Pre-eclampsia/HELLP	3	1.022	0.762	1.372	0.882	75.8	0.017
		HDP overall	61	1.066	0.948	1.198	0.288	79.8	<0.001
	SGA/IUGR	BW <P10	57	1.550	1.308	1.837	<0.001	85.7	<0.001
		BW <P5	2	1.651	0.659	4.138	0.284	0.0	0.674
		BW <P3 or −2SD	23	1.460	1.130	1.884	0.004	87.8	<0.001
		IUGR	9	2.251	1.537	3.297	<0.001	80.0	<0.001
		SGA/IUGR overall	91	1.564	1.369	1.785	<0.001	85.5	<0.001
Severe BPD	HDP	HDP overall*	8	0.940	0.582	1.517	0.799	41.8	0.100
	SGA/IUGR	BW <P10	11	1.491	1.001	2.220	0.049	34.5	0.123
		BW <P3	4	2.277	1.296	4.031	0.005	0.0	0.788
		IUGR	2	2.285	1.220	4.290	0.010	71.6	0.061
		SGA/IUGR overall	17	1.821	1.363	2.288	<0.001	24.5	0.171
BPD or death	HDP	HDP overall*	8	0.771	0.635	0.937	0.009	38.9	0.120
	SGA/IUGR	BW <P10	12	1.792	1.387	2.315	<0.001	90.5	<0.001
		BW <P5	1	2.970	0.899	9.814	0.074	0.0	1.000
		BW <P3 or −2SD	2	2.538	1.323	4.869	0.005	54.1	0.140
		IUGR	3	1.934	1.126	3.323	0.017	87.7	<0.001
		SGA/IUGR overall	18	1.914	1.545	2.373	<0.001	88.7	<0.001
BPD-associated pulmonary hypertension	HDP	Any HDP	11	1.408	1.034	1.917	0.030	38.3	0.094
		Pre-eclampsia	9	1.418	0.944	2.128	0.092	0.0	0.554
		HDP overall	20	1.412	1.104	1.805	0.006	18.3	0.227
	SGA/IUGR	BW <P10	17	2.275	1.771	2.922	<0.001	40.8	0.041
		BW <P3 or −2SD	3	4.418	1.689	11.556	0.002	0.0	0.390
		SGA/IUGR overall	20	2.373	1.862	3.023	<0.001	38.7	0.040

Mixed effects analysis. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect.
*Studies were not divided into subgroups because K<10 . OR >1 indicates association with increased risk of the outcome and OR <1 indicates association with decreased risk of the outcome.
BPD28, BPD defined as oxygen requirement on postnatal day 28; BPD36, BPD defined as oxygen requirement at the postmenstrual age of 36 weeks; BPD, bronchopulmonary dysplasia; BW, birth weight; IUGR, intrauterine growth restriction (defined on the basis of fetal growth assessment); K, number of studies; P3, third percentile; P5, 5th percentile; P10, 10th percentile; SGA, small for gestational age.

met inclusion criteria. These studies included 347 963 preterm infants. Characteristics of the studies are summarised in online supplemental table 1. In 76 studies, the exposure (HDP or SGA/IUGR) was the independent variable and the outcome (BPD) was the dependent variable. In 135 studies, the outcome was the independent variable and the exposure the dependent variable. Fifty-seven studies reported data on BPD28, 129 studies on BPD36, 19 studies on severe BPD, 23 studies on BPD/death and 27 on BPD-associated PH. The NOS score of each study is depicted in online supplemental table 1. All studies received at least six points indicating a low to moderate risk of bias.

The main results of the meta-analysis are summarised in table 1 and figure 1. The raw count data are depicted in online supplemental tables 4 to 13. Meta-analysis did not find a significant association between exposure to either HDP (figure 1, online supplemental figure S2) or SGA/IUGR (figure 1, online supplemental figure S3) and risk of developing BPD28. Exposure to HDP was also not associated with the risk of developing BPD36 (figure 1, online supplemental figrue S4). In contrast, exposure to SGA/IUGR was significantly associated with an increased risk of BPD36 (figure 1, online supplemental figure S5 and S6). When subdividing by definition of SGA/IUGR, the association with BPD36 remained significant for SGA

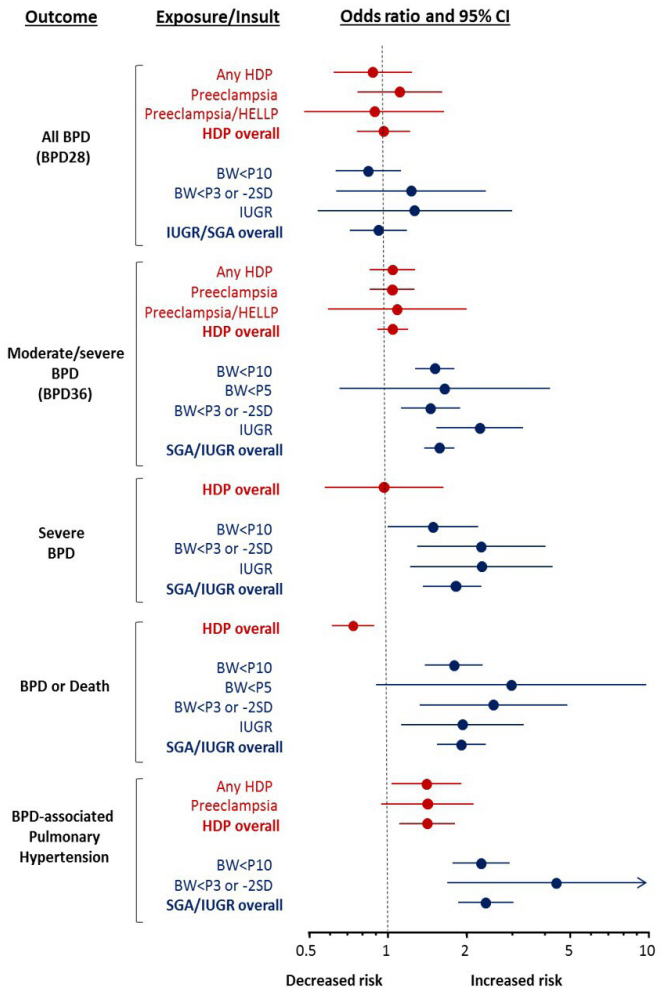

Figure 1 Summary of meta-analyses on the association between the dysfunctional placentation endotype ofprematurity and bronchopulmonary dysplasia (BPD). BPD28: BPD defined as oxygen requirement onpostnatal day 28; BPD36: defined as oxygen requirement at the postmenstrual age of 36 weeks; (defined on the basis of fetal growth assessment); BW, birthweight; HDP, hypertensive disorders of pregnancy; IUGR, intrauterine growthrestriction; P3, 3rd percentile; P10, 10th percentile; SGA, small for gestational age.

defined as BW <P10, as BW <P3 or −2SD or for IUGR, as defined by assessment of fetal growth (figure 1, online supplemental figure S5 and S6). Meta-regression analysis did not show significant differences in the association between SGA/IUGR and BPD36 depending on the criteria used to define SGA/IUGR (p=0.672).

For the outcome of severe BPD, meta-analysis showed a significant association with exposure to SGA/IUGR but did not demonstrate a significant association with exposure to HDP (figure 1, online supplemental figure S7 and S8). HDP was associated with a lower risk of developing the combined outcome BPD36 or death while SGA/IUGR was associated with a higher risk of developing this outcome (figure 1, online supplemental figure S9 and S10). Finally, both HDP and SGA/IUGR were significantly associated with an increased risk of developing BPD-associated PH (figure 1, online supplemental figure S11 and S12).

Neither visual inspection of funnel plots (online supplemental figure S13) nor Egger's test suggested publication or selection bias for any of the associations analysed.

To investigate the potential sources of heterogeneity, we conducted additional meta-analyses exploring the differences in baseline and clinical characteristics (GA, sex, exposure to antenatal corticosteroids, rate of respiratory distress syndrome (RDS)) between the groups exposed and non-exposed to HDP or SGA/IUGR. We also performed meta-regression and subgroup analysis. These latest analyses were limited to BPD36, the outcome with the largest number of studies.

Infants exposed to HDP had a significantly higher GA than the unexposed (table 2). Meta-regression showed that the difference in GA between the HDP-exposed and -unexposed groups significantly correlated with the effect size of the association between HDP and BPD36 (figure 2A, online supplemental table 2). The difference in GA was associated with 95% (R^2 analogue=0.95) of the variance in the association between HDP and BPD36 across studies (figure 2A, online supplemental table 2). To further assess the effect of GA on the association between HDP and BPD36, we carried out a meta-analysis of studies where the difference in mean GA was non-significant (p>0.05). In this subgroup of studies, HDP was significantly associated with risk of developing BPD36 (table 3).

The group of SGA/IUGR infants also showed a significantly higher GA (table 2). Meta-regression showed that the difference in GA between the SGA/IUGR-exposed and unexposed groups significantly correlated with the effect size of the association between SGA/IUGR and BPD36 (figure 2B, online supplemental table 2). However, this

Table 2 Meta-analyses of other covariates

Exposure/Insult	Meta-analysis (effect size)	K	Effect size	95% CI		P value	Heterogeneity	
				Lower limit	Upper limit		I^2 (%)	P value
Hypertensive disorders of pregnancy (HDP)	GA (MD in weeks)	33	0.613	0.399	0.826	<0.001	97.0	<0.001
	Male sex (OR)	27	0.755	0.714	0.798	<0.001	7.4	0.354
	Antenatal corticosteroids (OR)	21	1.124	0.974	1.297	0.109	85.0	<0.001
	IUGR/SGA (OR)	21	5.618	4.765	6.623	<0.001	80.0	<0.001
	RDS (OR)	20	1.164	0.907	1.494	0.234	80.6	<0.001
SGA/IUGR	GA (MD in weeks)	48	0.358	0.106	0.564	0.001	97.0	<0.001
	Male sex (OR)	27	0.921	0.818	1.037	0.173	68.668	<0.001
	Antenatal corticosteroids (OR)	20	1.123	0.908	1.388	0.286	80.4	<0.001
	HDP (OR)	22	4.858	3.365	7.013	<0.001	97.6	<0.001
	RDS (OR)	23	0.842	0.724	0.979	0.026	81.9	<0.001

GA, gestational age; HDP, hypertensive disorders of pregnancy; IUGR, intrauterine growth restriction (defined on the basis of fetal growth assessment); K, number of studies; MD, mean difference; RDS, respiratory distress syndrome; SGA, small for gestational age.

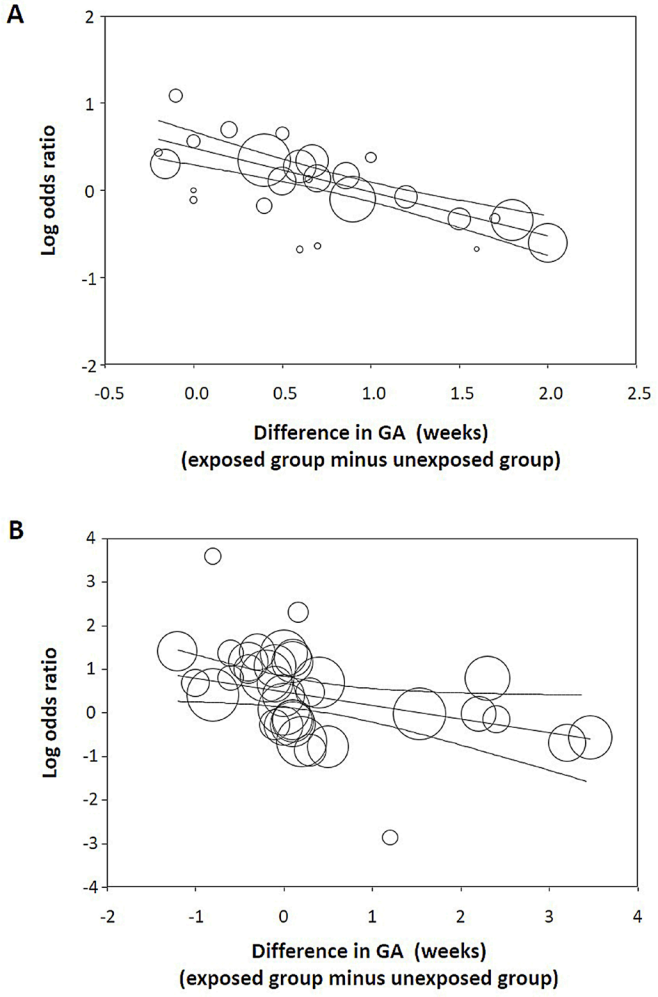

Figure 2 Meta-regression plot showing the correlation between the association of the dysfunctional placentation endotype of prematurity with moderate/severe bronchopulmonary dysplasia (BPD) and the difference in gestational age (GA) between exposed and non-exposed groups. (A) Univariate regression model correlating the difference in GA between hypertensive disorders of pregnancy (HDP)-exposed and HDP-unexposed infants. A total of 24 studies were included (coefficient, −0.50; 95% CI −0.65 to −0.35; p<0.001; R^2 analogue, 0.95). Each week that HDP-exposed infants were born later than control infants resulted in a decrease in BPD36 log OR of 0.50 (the equivalent of going from an OR of 1.00 to an OR of 0.61). (B) Univariate regression model correlating the difference in GA between small for GA (SGA)/intrauterine growth restriction (IUGR)-exposed and SGA/IUGR-unexposed infants. A total of 35 studies were included (coefficient, −0.31; 95% CI −0.57 to −0.05; p=0.002; R^2 analogue, 0.08). Log OR=lognOR.

difference in GA was only associated with 8% (R^2 analogue=0.08) of the variance in the association between HDP and BPD36 across studies (figure 2B, online supplemental table 2). In the subgroup of studies in which the GA was significantly (p<0.05) higher in the SGA/IUGR group, meta-analysis did not show any significant association between SGA/IUGR and BPD36 (table 3).

The GA of the entire cohort was also analysed as potential source of heterogeneity. The GA (mean or median) of each cohort did not correlate with the effect size of the association between HDP and BPD36 or SGA/IUGR and BPD36 (online supplemental table 2). In addition, when we conducted a subgroup analysis in which we separated studies that only included extreme preterm infants (GA <28 weeks), we observed that this criterion of subgrouping significantly affected the association between SGA/IUGR and BPD36 but not the association between HDP and BPD36 (table 3).

Additional meta-analyses showed that exposure to HDP was negatively associated with male sex of the newborn but did not find any significant association between HDP or SGA/IUGR and risk of receiving antenatal corticosteroids (table 2). Meta-regression did not show any significant correlation between risk of male sex, antenatal corticosteroids or RDS in the HDP-exposed infants and the effect size of the association between HDP and BPD36 (online supplemental table2). SGA/IUGR was negatively associated with the risk of developing RDS (table 2). Meta regression did not show any significant correlation between risk of male sex, antenatal corticosteroids or RDS in the SGA/IUGR-exposed infants and the effect size of the association between SGA/IUGR and BPD36 (online supplemental table2). As expected, meta-analyses showed a strong association between HDP and SGA/IUGR (table 2). This association was observed for all definitions of HDP and for all definitions of SGA/IUGR (online supplemental table 3).

Another potential sources of heterogeneity were the geographical location (continent) of the studies and the period of time in which they were conducted. The positive association between SGA/IUGR and BPD36 remained present in studies from America and Europe but was not observed in studies from Asia (table 3). The median year in which the study was conducted was not significantly associated with the effect size of the association between HDP or SGA/IUGR and BPD36 (online supplemental table 2).

Due to the homogeneous good quality of the studies (online supplemental table 1), we did not perform a sensitivity analysis based on the NOS scores. However, in order to investigate the role of the study design on the results of the meta-analysis, we conducted subgroup analyses in which studies were grouped depending on three criteria: (1) prospective versus retrospective; (2) cohort versus case–control and (3) exposure versus outcome as independent variable (table 3). Meta-regression did not show any significant differences among these subgroups (table 3).

DISCUSSION

This is the first meta-analysis that comprehensively addresses how two conditions related to the endotype of placental dysfunction are associated with the risk of BPD. Our data suggest that when placental vascular dysfunction is accompanied by fetal growth restriction or being born SGA, the condition is associated with an increased risk of developing moderate/severe BPD, severe BPD, BPD or death, and BPD-associated PH. The analysis also shows that preterm infants with a history of intrauterine exposure to HDP or growth restriction tended to be older at birth than their respective controls. Meta-regression analysis showed that this higher GA significantly affected the association of BPD with HDP and IUGR.

Several mechanisms have been proposed to explain the association between placental dysfunction and BPD. The main etiopathogenic hypotheses are based on the interference of chronic hypoxia and/or an imbalance between proangiogenic and antiangiogenic factors with alveolar and pulmonary vascular development.[13 14 24 37–41] Poor placentation in early stages of pregnancy that is associated with vascular underperfusion may develop into different clinical presentations: (1) maternal (HDP), (2) fetal (IUGR) or (3) both.[42 43] Different placental lesions, whether from maternal or fetal origin, are associated with the corresponding clinical presentation.[42–45] However, the correlation of these pathological conditions with a specific profile of angiogenic factors is controversial. Preliminary studies showed that HDP and IUGR of placental origin have similar proangiogenic

Table 3 Subgroup analyses

Meta-analysis	Criteria for subgrouping	K	OR	95% CI		P value	Heterogeneity		Meta-regression	
				Lower limit	Upper limit		I^2 (%)	P value	P value	R^2 analogue
HDP and BPD36	America	21	0.877	0.683	1.124	0.300	54.0	0.002	0.088*	0.0
	Asia	15	0.974	0.765	1.241	0.832	79.0	<0.001		
	Europe	17	1.182	0.947	1.474	0.139	71.5	<0.001		
	GA significantly higher in HDP group	13	0.890	0.723	1.097	0.276	81.2	<0.001	<0.001	0.53
	GA no significantly different	11	1.440	1.281	1.618	<0.001	63.0	0.006		
	Inclusion GA <28 weeks	9	1.223	0.943	1.585	0.129	63.0	0.006	0.201	0.22
	Inclusion GA >28 weeks	45	0.972	0.848	1.113	0.678	71.1	<0.001		
	Cohort	50	1.034	0.906	1.180	0.618	82.3	<0.001	0.233	0.0
	Case-control	11	1.301	0.964	1.775	0.085	34.1	0.126		
	Prospective	36	1.130	0.975	1.310	0.105	60.5	<0.001	0.300	0.0
	Retrospective	25	1.007	0.824	1.230	0.946	88.3	<0.001		
	Independent variable: Exposure	25	1.123	0.941	1341	0.197	87.4	<0.001	0.404	0.0
	Independent variable: Outcome	36	1.010	0.852	1.198	0.907	63.1	<0.001		
SGA/IUGR and BPD36	America	31	1.651	1.318	2.068	<0.001	89.6	<0.001	0.077*	0.0
	Asia	12	1.000	0.662	1.510	0.999	82.9	<0.001		
	Europe	46	1.655	1.373	1.997	<0.001	79.6	<0.001		
	GA significantly higher in SGA/IUGR group	7	0.964	0.628	1.482	0.869	88.2	<0.001	0.052	0.0
	GA no significantly different	26	1.590	1.219	2.074	0.001	69.9	<0.001		
	Inclusion GA <28 weeks	10	2.244	1.568	3.213	<0.001	95.2	<0.001	0.034	0.00
	Inclusion GA >28 weeks	81	1.477	1.280	1.703	<0.001	81.1	<0.001		
	Cohort	76	1.535	1.331	1.770	<0.001	87.9	<0.001	0.122	0.0
	Case-control	15	2.050	1.419	2.960	<0.001	50.4	0.013		
	Prospective	57	1.674	1.411	1.986	<0.001	87.0	<0.001	0.281	0.0
	Retrospective	34	1.479	1.197	1.828	<0.001	83.7	<0.001		
	Independent variable: exposure	34	1.884	1.539	2.306	<0.001	87.9	<0.001	0.060	0.0
	Independent variable: outcome	57	1.397	1.168	1.671	<0.001	85.0	<0.001		

Subgroups were compared using univariate, random effects (method of moments) meta-regression analysis. The R^2 analogue, defined as the total between-study variance explained by the moderator, was calculated based on the meta-regression matrix.
*Reference group: Asia.
GA, gestational age; HDP, hypertensive disorders of pregnancy; IUGR, intrauterine growth restriction (defined on the basis of fetal growth assessment); K, number of studies; SGA, small for gestational age.

and antiangiogenic profiles.[46] In contrast, later studies on placental pathology showed that lesions of maternal vascular underperfusion are more frequently associated with decreased cord blood angiogenic factors, as well as increased risk of both BPD and BPD-associated PH, than placental vascular lesions from fetal origin.[39 45 47]

Regardless of the origin of the placental lesions, the data from our analysis suggest that the increased risk of BPD may be predominantly associated with placental vascular dysfunction that is sufficiently severe to impair fetal growth. The relevance of the presence of growth restriction was particularly evidenced in the analysis of the combined outcome of BPD36 or death. Thus, HDP exposure had a 'protective' effect on this outcome while SGA/IUGR was associated with a higher risk of BPD/death. Interestingly, BPD-associated PH was the only condition associated with both SGA/IUGR and HDP. As mentioned in the introduction, the presence of PH is the most relevant feature of the 'vascular phenotype' of BPD. The data from this meta-analysis confirm the association between this vascular phenotype and the placental dysfunction endotype reinforcing the hypothesis that antenatal mechanisms that promote an anti-angiogenic fetal environment contribute to high risk for BPD and PH.[13 24 39–41]

A constant in our analyses was the presence of high statistical heterogeneity. We attempted to discern the sources of this heterogeneity through subgroup analysis and meta-regression. Since very and extremely preterm birth is by definition a pathological condition, a major problem when analysing the association between triggers and complications of prematurity is the absence of a healthy 'control' group. If a preterm infant is born to a mother with pre-eclampsia, the infant will be less likely to have chorioamnionitis and vice versa.[48] In fact, the studies included in our meta-analysis are comparing infants exposed to the placental dysfunction endotype with infants most likely belonging to the infectious/inflammatory endotype. Accordingly, the present results are in part a mirror image of the findings of our previous meta-analysis on the association between chorioamnionitis and BPD.[16] Herein, GA was significantly higher in the HDP and SGA/IUGR groups than in their respective control groups, while chorioamnionitis-exposed infants were born significantly earlier than non-exposed infants.[16] In all three cases (chorioamnionitis, HDP and SGA/IUGR), meta-regression showed a significant correlation between the difference in GA and the risk of developing BPD. However, this should not be interpreted as a call to adjust for GA. Although widely used, conditioning on GA in studies of prenatal exposures and their association to postnatal outcomes may not reduce but actually lead to bias through overadjustment and selection bias.[48]

The GA was also a relevant moderator in a previous meta-analysis on the association between HDP and BPD conducted by Razak *et al*.[17] They included only nine studies and did not find a significant association between HDP and risk of BPD36. However, the association was present in the subgroup analysis that included the three studies involving infants below 29 weeks' gestation.[17] Our data do not confirm those findings. Subgroup analysis of studies that only included extremely preterm newborns (GA <28 weeks) did not show a significant association between HDP and BPD but confirmed the association between SGA/IUGR and BPD. Interestingly, the studies that exclusively included infants with GA <28 weeks showed a significantly higher association between SGA/IUGR and BPD36 than the studies that also included infants above 28 weeks of gestation (table 3). Nevertheless, meta-regression did not demonstrate the presence of linear correlation between the mean GA of the infants included in the studies and the effect size of the associations between BPD and HDP or SGA/IUGR (online supplemental table 2). In another meta-analysis, including 15 studies, Bi *et al* found an association between HDP and BPD[49] that we could not confirm in our meta-analysis with a larger number of studies.

Besides the difference in GA, infants with a history of prenatal exposure to HDP or growth restriction differed from the 'control' group in other important characteristics that may have affected the association with BPD. Exposure to HDP was associated with female sex (table 2). Interestingly, mortality and several complications of prematurity, including BPD, are reported to occur at higher rates in preterm boys than girls.[50 51] Nevertheless, meta-regression did not demonstrate that sex differences affected the associations that we analysed (table 3). We also found that growth restriction, but not exposure to HDP, was associated with a decreased risk of RDS. These data would support that placental insufficiency may accelerate pulmonary maturation through chronic intrauterine stress.[52] However, this lower rate of acute respiratory morbidity in children with IUGR is followed by a higher incidence of BPD and BPD-associated PH.

Heterogeneity in the definitions of both exposures and outcomes is one of the main limitations of meta-analyses of observational studies. The controversy regarding how to best define BPD has occupied neonatologists for decades and still seems far from resolved.[11–14] Most of the studies included in this meta-analysis used the criterion of the need for oxygen or respiratory support at 36 weeks of PMA (ie, BPD36). This means that the categories of moderate and severe BPD were grouped, which does not allow differentiating those children who are sicker and at greater risk of respiratory sequelae. In addition, the current BPD definitions do not differentiate between the possible causes of respiratory support requirements (ie, the BPD phenotype). Moreover, the classical definitions of BPD do not take into consideration those children with severe respiratory problems who die before reaching 36 weeks of PMA as required for making the formal diagnosis of BPD and its severity. Finally, regarding BPD-associated PH, controversies persist regarding which echocardiography-derived measurements are best for assessing the condition and when is the optimal time for screening.[53]

Similarly, despite the publication of periodically updated consensus documents on the classification and diagnostic criteria for HDP,[54] marked heterogeneity remains among obstetricians regarding the application of these criteria. In addition, an emerging concept is that pre-eclampsia may have several subtypes, the final clinical manifestation being the result of the maternal response to either abnormal placental function or abnormal placentation.[53] Regarding IUGR, in the absence of placental pathology examination, it is uncertain whether placental vascular malperfusion was the aetiology for the growth restriction in all of the infants. In addition, the majority of the studies in this report are actually defining SGA, even though the terms SGA and IUGR are not synonymous.[29–32] SGA is a statistical definition based on BW, with the 10th percentile as the most commonly used threshold, and also encompasses constitutionally small but healthy infants at lower risk of complications. On the other hand, growth restricted infants who have a BW above the 10th percentile may be falsely classified as normally grown.[29–32 55]

CONCLUSIONS

In addition to inducing very and extremely preterm birth, the placental dysfunction and the infectious/inflammatory endotypes can each disrupt normal fetal growth and development and are strongly associated with BPD. As neither of these two endotypes is desirable, further research is necessary to prevent preterm birth and develop novel interventions in both settings. Altogether, the data from the present and our previous meta-analysis[16] suggest that the infectious/inflammatory endotype has a greater overall impact on BPD risk as it is the most frequent endotype in the lower and more vulnerable GA. However, when the endotype of placental dysfunction is accompanied by fetal growth restriction or being born SGA, it is strongly associated with higher rates of BPD even though newborns are more mature. Moreover, BPD associated with placental vascular dysfunction may have a greater component of vascular disease manifested as PH. In other words, the placental dysfunction endotype of prematurity is associated with increased risk of developing the vascular phenotype of BPD. However, neither endotypes of prematurity nor BPD phenotypes are discrete and there are cases in which the placenta may combine lesions of infection/inflammation and vascular dysfunction.[44] Nevertheless, it is necessary to recognise BPD as a heterogeneous condition and therefore prevention and treatment strategies should be targeted to the particular endotype and phenotype of each infant.

Author affiliations
[1]Pediatrics, Maastricht University Medical Centre, School for Oncology and Developmental Biology (GROW), Maastricht, The Netherlands
[2]Neonatal and Paediatric Intensive Care Unit, Maurizio Bufalini Hospital, Cesena, Italy
[3]Pediatric Cardiology, Hospital Universitario Ramón y Cajal, Madrid, Spain
[4]Pediatric Heart Lung Center, Department of Pediatrics, University of Colorado - Anschutz Medical Campus, Aurora, Colorado, USA

Contributors EV conceived and designed the study with input from the other authors. MP, EV-M, EvW-K and MA-F designed and executed the literature search, screened and reviewed the search results and abstracted the data. EV designed and conducted the analysis with input from MP, EV-M and MA-F. All authors contributed to the interpretation of analysis. MP, EV-M, EvW-K, and EV made the figures and tables. EV drafted the manuscript with input from the other authors. All authors reviewed the manuscript and provided important intellectual content. EV, MP and EV-M take responsibility for the article as a whole.

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Patient consent for publication Not required.

Ethics approval As this systematic review and meta-analysis did not involve animal subjects or personally identifiable information on human subjects, ethics review board approval and patient consent were not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iD
Eduardo Villamor http://orcid.org/0000-0003-1949-9123

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Supplementary Material

Association of the Dysfunctional Placentation Endotype of Prematurity with Bronchopulmonary Dysplasia: A Systematic Review, Meta-analysis and Meta-regression

1. Methods

1.1. Search strategy

Pubmed

1	((((((outcome AND preterm)) OR (risk factor AND preterm))) AND (((((((case control) OR Case-Control Study) OR Case-Base Studies) OR cohort study) OR Observational study) OR RCT) OR Randomized controlled trial))) AND ((((((((((premature infant [mesh]) OR premature infant [tiab]) OR premature infant) OR Neonatal Prematurity) OR Infants) OR Premature) OR Prematurity) OR Neonatal) OR Neonatal) OR before 37 completed weeks of gestation))) AND ((((pre-eclampsia AND preterm))) OR (((EPH AND preterm AND preterm)) OR (hellp syndrome AND preterm)) OR (gestational hypertensive disorder AND preterm)) OR (pre-existing hypertension AND preterm)) OR (eclampsia AND preterm)) OR (toxemia AND preterm)) OR (pregnancy toxemia AND preterm)) OR (edema proteinuria hypertension gestosis AND preterm)) OR (hypertensive disorders of pregnancy AND preterm)) OR (maternal hypertension AND preterm))))
2	(bronchopulmonary dysplasia [MESH] OR bronchopulmonary dysplasia [tiab] OR BPD [tiab] OR chronic lung disease [tiab] OR CLD [tiab] OR pulmonary hypertension [MESH] OR pulmonary hypertension [tiab]) AND (preterm infant [tiab] OR Premature Infant [tiab] OR Premature Infants [tiab] OR preterm infants [tiab] OR neonatal prematurity [tiab] OR very low birth weight infant [tiab] OR Very-Low-Birth-Weight Infant [tiab] OR Very-Low-Birth-Weight Infants [tiab] OR very low birth weight infants [tiab] OR Extremely Low Birth Weight Infant [tiab] OR Extremely Low Birth Weight Infants [tiab] OR preterm infant [MESH] OR Premature Infant [MESH] OR Premature Infants [MESH] OR preterm infants [MESH] OR neonatal prematurity [MESH] OR very low birth weight infant [MESH] OR Very-Low-Birth-Weight Infant [MESH] OR Very-Low-Birth-Weight Infants [MESH] OR very low birth weight infants [MESH] OR Extremely Low Birth Weight Infant [MESH] OR Extremely Low Birth Weight Infants) AND (cohort [MESH] OR Incidence Studies [MESH] OR Incidence Study [MESH] OR concurrent studies [MESH] OR concurrent studies [MESH] OR cohort analysis [MESH] OR observational studies [MESH] OR observational study [MESH] OR case control study [MESH] OR case control studies [MESH] OR case control [MESH] OR cohort [tiab] OR Incidence Studies [tiab] OR Incidence Study [tiab] OR concurrent studies [tiab] OR concurrent studies [tiab] OR cohort analysis [tiab] OR observational studies [tiab] OR observational study [tiab] OR case control study [tiab] OR case control studies [tiab] OR case control [tiab])

3	(fetal growth restriction [tiab] OR intrauterine growth [tiab] OR absent end diastolic [tiab] OR reversed end diastolic [tiab] OR small for gestational age [tiab] OR SGA [tiab] OR small for date [tiab] OR IUGR [tiab] OR fetal growth restriction [MESH] OR intrauterine growth [MESH] OR absent end diastolic [MESH] OR reversed end diastolic [MESH] OR small for gestational age [MESH] OR SGA [MESH] OR small for date [MESH] OR IUGR [MESH]) AND (preterm infant [tiab] OR Premature Infant [tiab] OR Premature Infants [tiab] OR preterm infants [tiab] OR neonatal prematurity [tiab] OR very low birth weight infant [tiab] OR Very-Low-Birth-Weight Infant [tiab] OR Very-Low-Birth-Weight Infants [tiab] OR very low birth weight infants [tiab] OR Extremely Low Birth Weight Infant [tiab] OR Extremely Low Birth Weight Infants [tiab] OR preterm infant [MESH] OR Premature Infant [MESH] OR Premature Infants [MESH] OR preterm infants [MESH] OR neonatal prematurity [MESH] OR very low birth weight infant [MESH] OR Very-Low-Birth-Weight Infant [MESH] OR Very-Low-Birth-Weight Infants [MESH] OR very low birth weight infants [MESH] OR Extremely Low Birth Weight Infant [MESH] OR Extremely Low Birth Weight Infants [MESH]) AND (cohort [MESH] OR Incidence Studies [MESH] OR Incidence Study [MESH] OR concurrent studies [MESH] OR concurrent studies [MESH] OR cohort analysis [MESH] OR observational studies [MESH] OR observational study [MESH] OR case control study [MESH] OR case control studies [MESH] OR case control [MESH] OR cohort [tiab] OR Incidence Studies [tiab] OR Incidence Study [tiab] OR concurrent studies [tiab] OR concurrent studies [tiab] OR cohort analysis [tiab] OR observational studies [tiab] OR observational study [tiab] OR case control study [tiab] OR case control studies [tiab] OR case control [tiab])

EMBASE

1	(pre-eclampsia or preeclampsia or EPH or hellp syndrome or gestational hypertensive disorder or pre-existing hypertension or eclampsia or toxemia or pregnancy toxemia or edema proteinuria hypertension gestosis or maternal hypertension or pregnancy-induced hypertension).af.
2	(premature infant or Neonatal Prematurity or Infants, Premature or Prematurity or Neonatal or Preterm Infants).af.
3	(case control or Case-Control Study or Case-Base Studies or cohort study or RCT).af.
4	(risk factors or outcome or risk factor).af.
5	1 and 2 and 3 and 4
6	('chronic lung disease'/exp OR 'chronic lung disease') AND ('intrauterine growth retardation'/exp OR 'intrauterine growth retardation')
7	('chronic lung disease'/exp OR 'chronic lung disease' OR 'pulmonary hypertension') AND ('prematurity'/exp OR 'prematurity') AND ('cohort analysis'/exp OR 'cohort analysis' OR 'case control study'/exp OR 'case control study')
8	('intrauterine growth retardation'/exp OR 'intrauterine growth retardation') AND ('prematurity'/exp OR 'prematurity') AND ('cohort analysis'/exp OR 'cohort analysis' OR 'case control study'/exp OR 'case control study')

Web of Science

1	**TOPIC:** (pre-eclampsia or preeclampsia or EPH or hellp syndrome or gestational hypertensive disorder or hypertensive disorders of pregnancy or pre-existing hypertension or eclampsia or toxemia or pregnancy toxaemia or edema proteinuria hypertension gestosis or maternal hypertension or pregnancy-induced hypertension) *AND* **TOPIC:** (premature infant or Neonatal Prematurity or Infants, Premature or Prematurity or Neonatal or Preterm Infants) *AND* **TOPIC:** (case control or Case-Control Study or Case-Base Studies or cohort study or observational) *AND* **TOPIC:** (risk factors or outcome or risk factor)
2	((bronchopulmonary dysplasia OR BPD OR chronic lung disease) AND ("preterm infant" OR "Premature Infant" OR "Premature Infants" OR "preterm infants" OR "neonatal prematurity" OR "very low birth weight" OR "Extremely Low Birth Weight" OR Extremely Low Birth Weight Infants) AND (cohort OR "Incidence Studies" OR "Incidence Study" OR "concurrent studies" OR "concurrent studies" OR "cohort analysis" OR "observational studies" OR "observational study" OR case control))

3	((“fetal growth restriction” OR “intrauterine growth retardation” or “intrauterine growth restriction” OR “small for gestational age”) AND (“preterm infant” OR “Premature Infant” OR “Premature Infants” OR “preterm infants” OR “neonatal prematurity” OR “very low birth weight” OR “Extremely Low Birth Weight” OR Extremely Low Birth Weight Infants) AND (cohort OR Incidence Studies OR Incidence Study OR concurrent studies OR concurrent studies OR cohort analysis OR observational studies OR observational study OR case control study OR case control studies OR case control))

No language limits were set. Narrative reviews, systematic reviews, case reports, letters, editorials, and commentaries were excluded, but read to identify potential additional studies. Additional strategies to identify studies included manual review of reference lists from key articles that fulfilled our eligibility criteria, use of “related articles” feature in PubMed, and use of the “cited by” tool in Web of Science and Google scholar. Two reviewers independently screened the results of the searches, and included studies according to the inclusion criteria using EndNote (RRID:SCR_014001), using the methodology described by Bramer et al.[1]

1.2. Supplementary information on methods

Study selection

Studies were included if they examined preterm (gestational age, GA <37 weeks) or very low birth weight (<1500g) infants and reported primary data that could be used to measure the association between exposure to hypertensive disorders of pregnancy (HDP) or small for GA (SGA)/intrauterine growth restriction (IUGR) and the development of BPD. Therefore, we selected cohort or case-control studies in which the exposure (HDP or SGA/IUGR) was the independent variable and the outcome (BPD) the dependent variable as well as studies in which the outcome was the independent variable and the exposure the dependent variable. Studies that exclusively included late preterm infants (GA ≥34 weeks) or that combined preterm and term infants were excluded. The absence of a clear definition of BPD was also an exclusion criterion. Due to the high number of included studies, no additional efforts were made to clarify the definitions or other data with the authors. Abstracts and unpublished studies were also excluded. To identify relevant studies, two reviewers (M.P., M. A-F) independently screened the results of the searches and applied inclusion criteria using a structured form. Discrepancies were resolved through discussion or consultation with two other reviewers (E. V-M, E.V.).

Data extraction

Data extracted from each study included citation information, language of publication, location where research was conducted, time period of the study, study objectives, study design, inclusion/exclusion criteria, definition criteria for HDP, IUGR, SGA, BPD, and BPD-PH, patient characteristics, and results (including raw numbers or summary statistics when raw numbers were not available). Outcomes considered in meta-analysis were: 1) BPD28, defined as oxygen requirement on postnatal day 28; 2) BPD36, defined as oxygen requirement at the postmenstrual age (PMA) of 36 weeks; 3) BPD36 or death; 4) Severe BPD, defined as need for ⩾ 30% oxygen and/or positive pressure at 36 weeks PMA; 5) BPD-associated PH, defined by any echocardiographic criteria as long as the evaluation was performed at a postnatal age>4 weeks. Any definition of HDP or SGA/IUGR was accepted but we performed sub-group analysis based on the different definitions. When a study used more than one definition criteria for growth restriction, definitions based on assessment of fetal growth prevailed over definitions based on BW. When a study used different BW threshold percentiles to define SGA, data from the lowest percentile were included. When a study did not specify the threshold percentile used, it was grouped together with the studies that used the 10^{th} percentile.

Statistical analysis

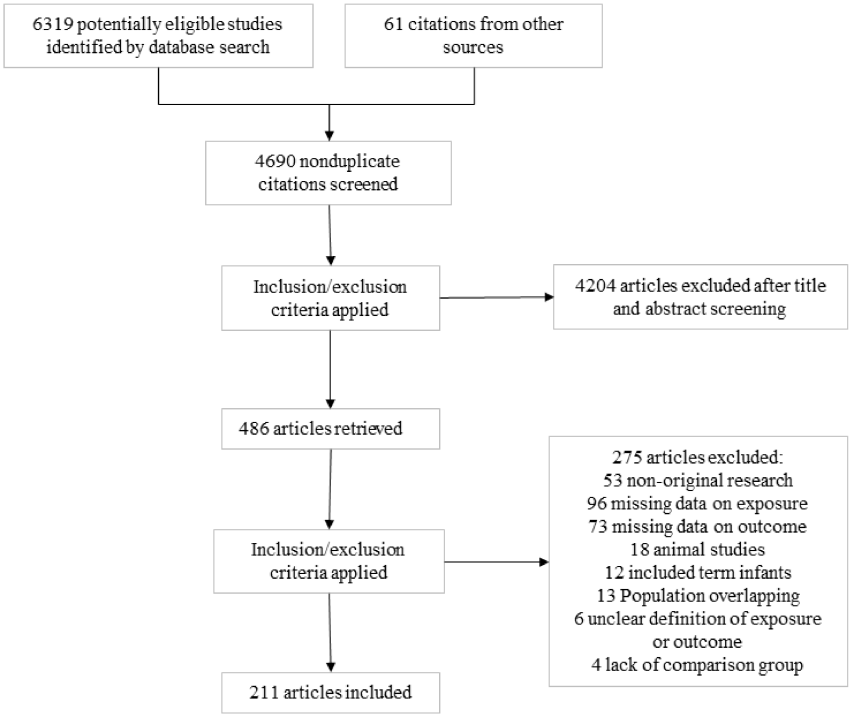
Studies were combined and analyzed using COMPREHENSIVE META-ANALYSIS V3.0 software (Biostat Inc., Englewood, NJ, USA). For dichotomous outcomes, the odds ratio (OR) with 95% confidence interval (CI) was calculated from the data provided in the studies. Reported OR were included when studies reported them and did not include the numerical data for its calculation. For continuous outcomes (example: gestational age), the mean difference (MD) with 95% CI was calculated. When studies reported continuous variables as median and range or interquartile range, we estimated the mean and standard deviation using the method of Wan et al. and the calculator they provided.[2]

Due to anticipated heterogeneity, summary statistics were calculated with a random-effects model. This model accounts for variability between studies as well as within studies. Subgroup analyses were conducted according to the mixed-effects model.[3] In this model, a random-effects model is used to combine studies within each subgroup, and a fixed-effect model is used to combine subgroups and yield the overall effect. The study-to-study variance (tau-squared) is not assumed to be the same for all subgroups. This value is computed within subgroups and not pooled across subgroups. Statistical heterogeneity was assessed by Cochran's Q statistic and by the I^2 statistic, which is derived from Q and describes the proportion of total variation that is due to heterogeneity beyond chance.[4] The I^2 statistic was interpreted as follows: low heterogeneity ($25\% \leq I^2 < 50\%$), moderate heterogeneity ($50\% \leq I^2 < 75\%$), and high heterogeneity ($I^2 \geq 75\%$). We used the Egger's regression test and funnel plots to assess publication bias. A probability value of less than 0.05 (0.10 for heterogeneity) was considered statistically significant.

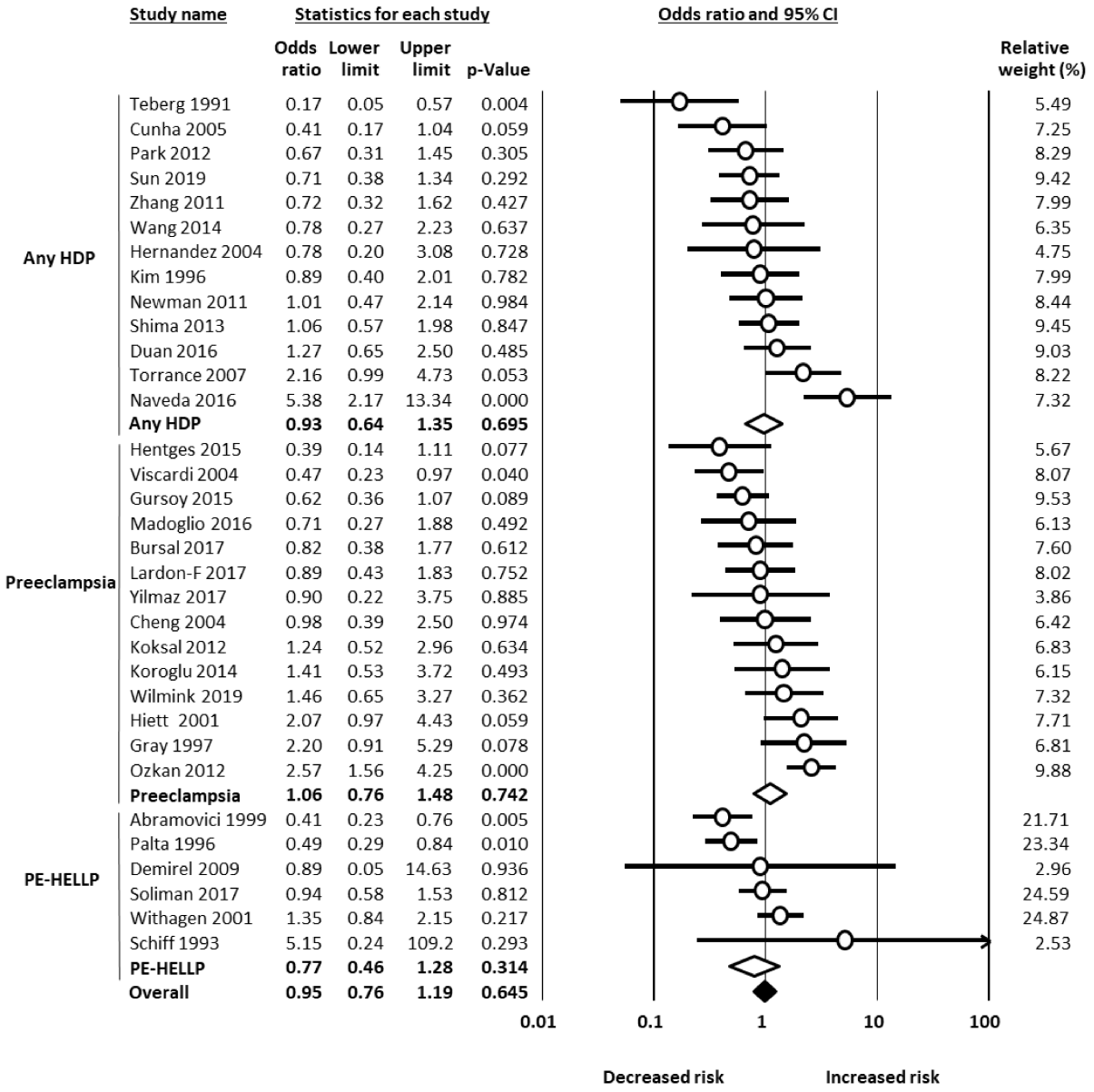
Potential sources of heterogeneity were assessed through subgroup analysis and/or random effects (method of moments) univariate meta-regression analysis.[5] For continuous covariates (examples: mean gestational age of the cohort, difference in mean gestational age between infants exposed and unexposed to HDP) we used meta-regression analyses to test whether there was a significant relationship between the covariate and effect size, as indicated by a Z-value and an associated p-value. Meta-regression coefficient indicates the change in the log of the OR of the association between BPD and the corresponding exposure for a unit change in the predictor covariate. Subgroups were compared using meta-regression for categorical covariates. For both categorical and continuous covariates, the R^2 analog, defined as the total between-study variance explained by the moderator, was calculated based on the meta-regression matrix. [5] Covariates defined a priori were: 1) Continuous: mean or median GA of the entire cohort, study time (median year of cohort inclusion), differences between exposed and unexposed infants on GA, sex, rate of use of antenatal corticosteroids, and rate of respiratory distress syndrome (RDS); 2) Categorical: HDP type, SGA/IUGR type, study included only infants with GA<28 weeks (yes/no), DM of GA between exposed and unexposed infants statistically significant (P<0.05, yes/no), and geographical location (continent) of the study. The clinical covariates were selected based on their relevance on the pathogenesis of BPD. On the basis of the recommendation of an anonymous reviewer, we added three categorical covariates related to the design of the studies: Prospective vs. Retrospective; Cohort vs. Case-control; and Exposure vs. Outcome as independent variable.

2. Results

2.1. Supplementary Figures

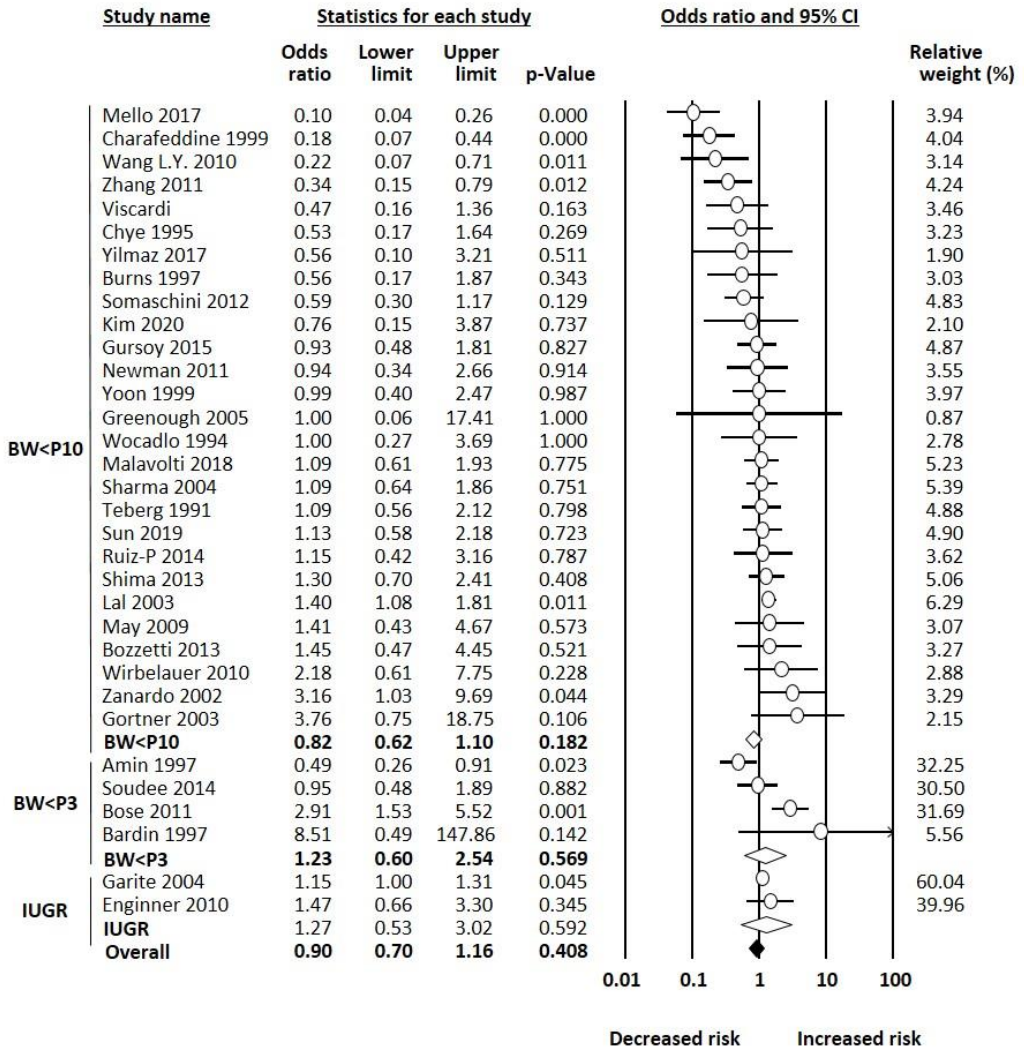


Supplementary Figure 1. Flow diagram of the systematic search.



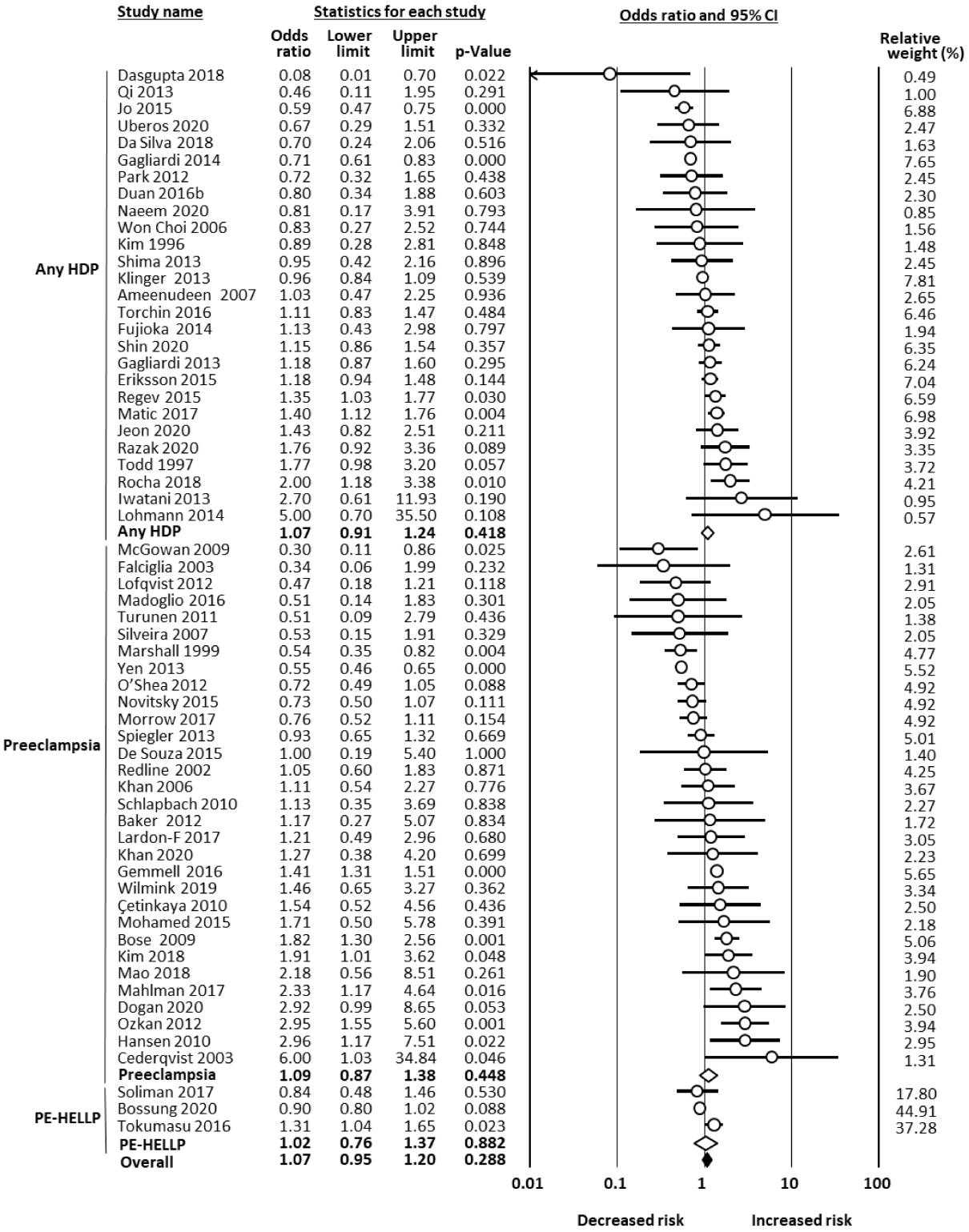
Supplementary Figure 2. Meta-analysis of hypertensive disorders of pregnancy (HDP) and bronchopulmonary dysplasia, defined as oxygen requirement on postnatal day 28 (BPD28).

CI: confidence interval; PE: preeclampsia.



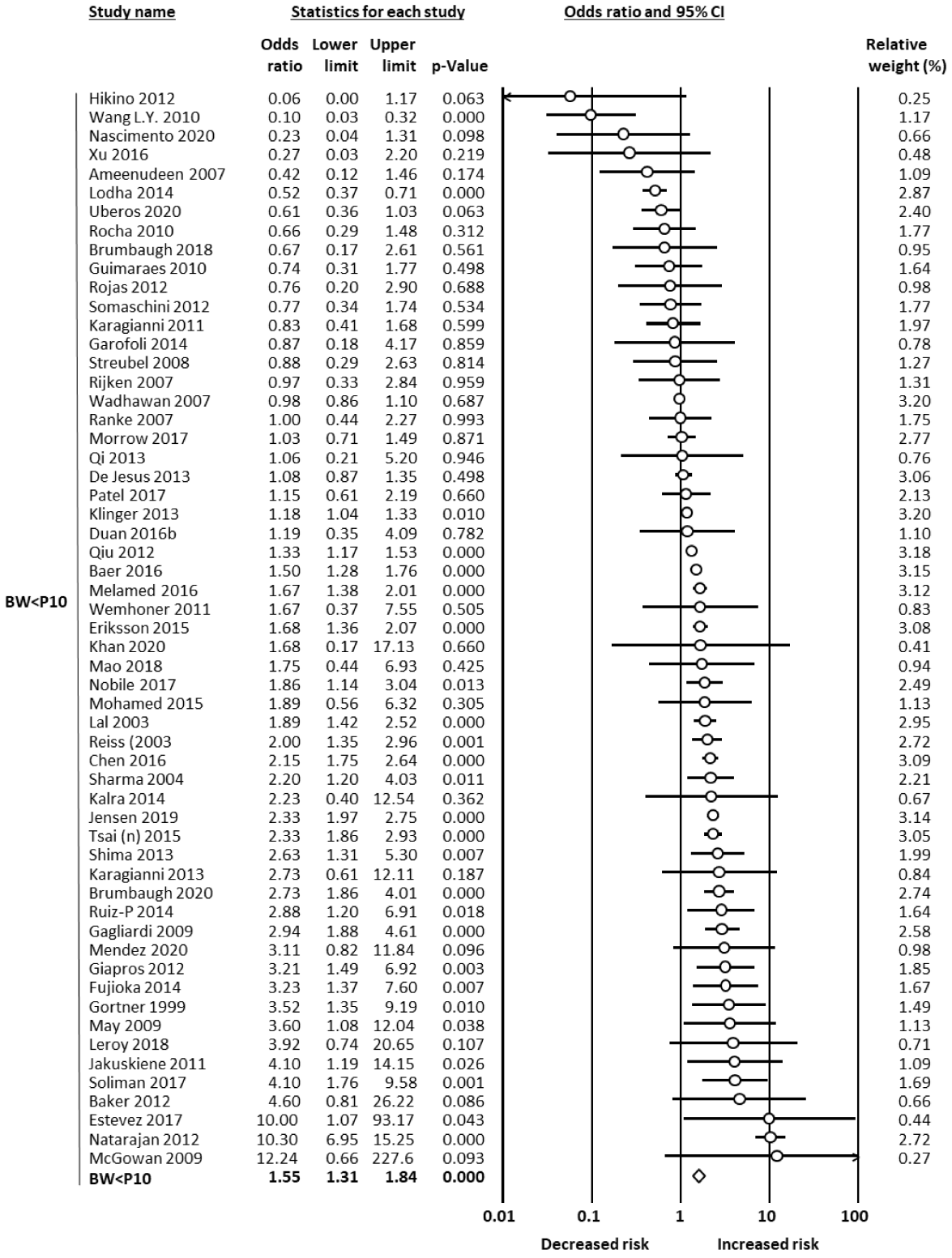
Supplementary Figure 3. Meta-analysis of small for gestational age/intrauterine growth restriction and bronchopulmonary dysplasia, defined as oxygen requirement on postnatal day 28 (BPD28).

BW: birth weight; CI: confidence interval; IUGR: intrauterine growth restriction (defined on the basis of fetal growth assessment); P3: 3rd percentile; P10: 10th percentile.

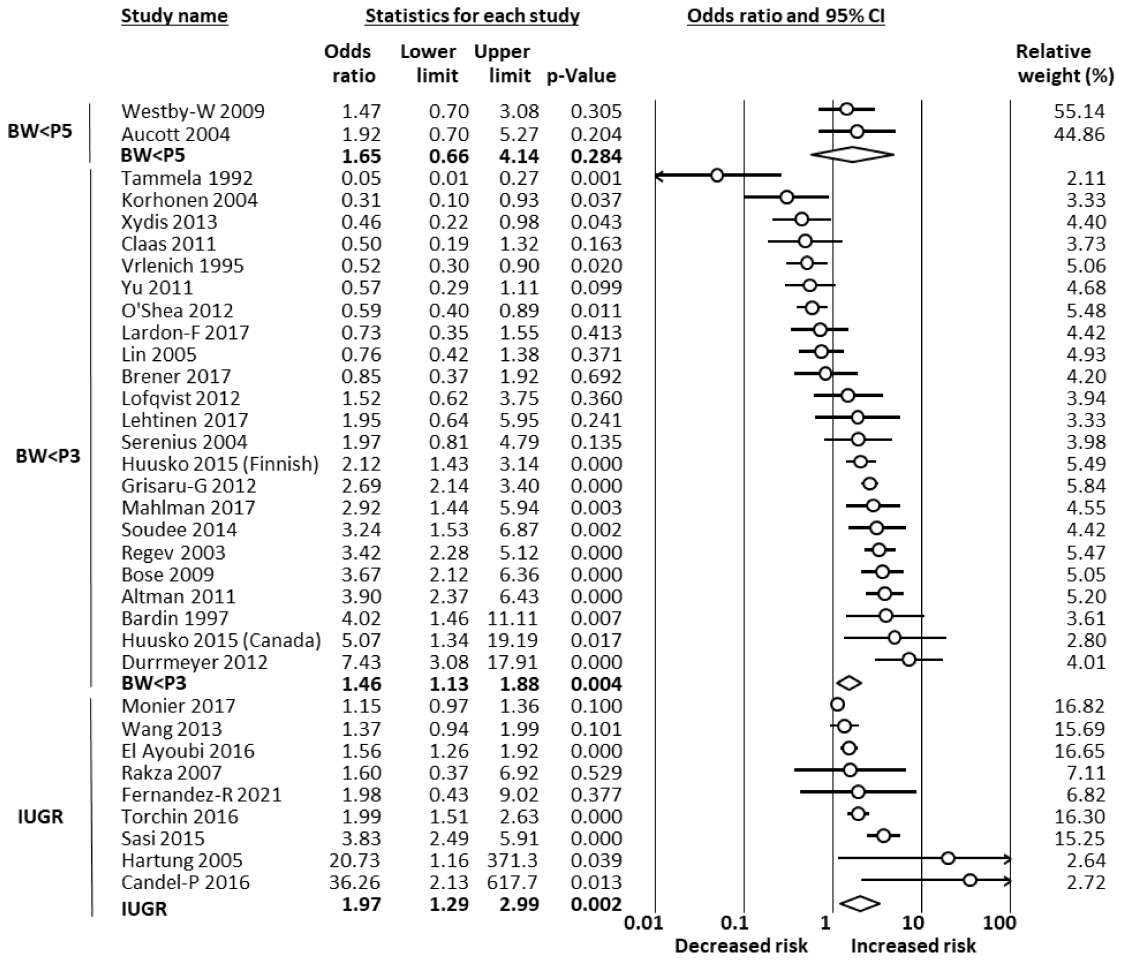


Supplementary Figure 4. Meta-analysis of hypertensive disorders of pregnancy (HDP) and bronchopulmonary dysplasia, defined as oxygen requirement at the postmenstrual age of 36 weeks (BPD36).

CI: confidence interval; PE: preeclampsia.

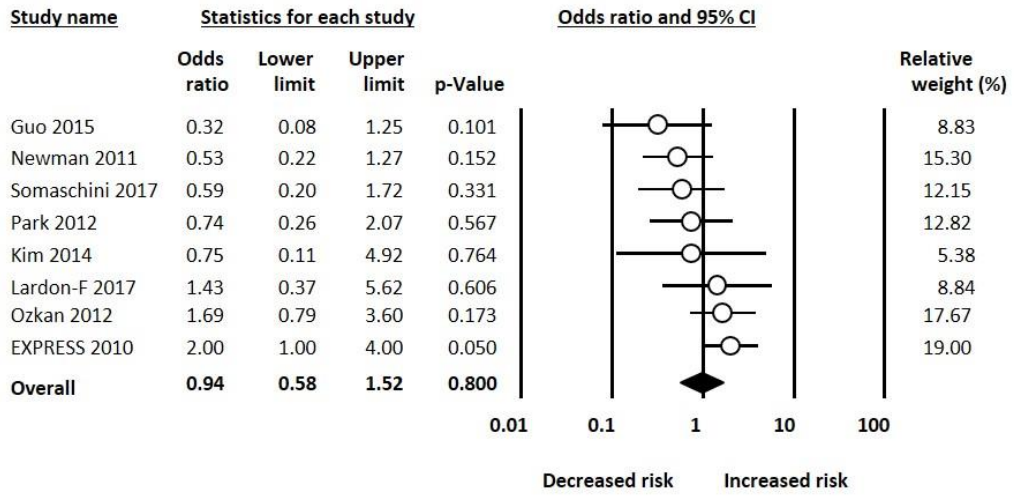


Supplementary Figure 5. Meta-analysis of the association between birth weight (BW) below the 10th percentile and bronchopulmonary dysplasia, defined as oxygen requirement at the postmenstrual age of 36 weeks (BPD36).



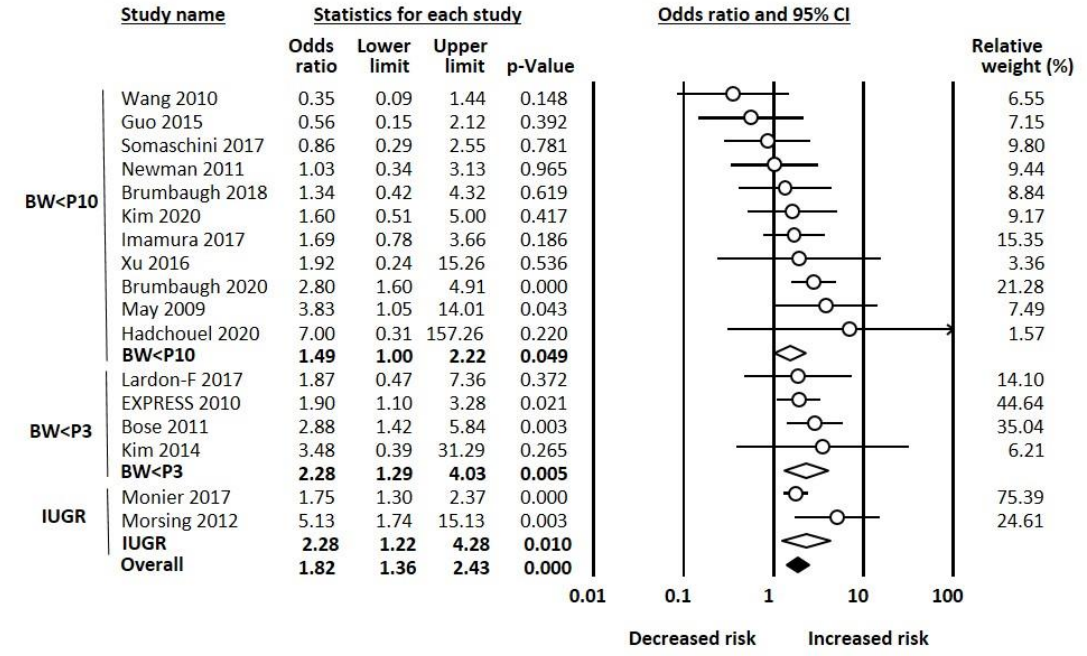
Supplementary Figure 6. Meta-analysis of the association between small for gestational age/intrauterine growth restriction and bronchopulmonary dysplasia, defined as oxygen requirement at the postmenstrual age of 36 weeks (BPD36).

BW: birth weight; CI: confidence interval; IUGR: intrauterine growth restriction (defined on the basis of fetal growth assessment); P5: 5th percentile; P10: 10th percentile.



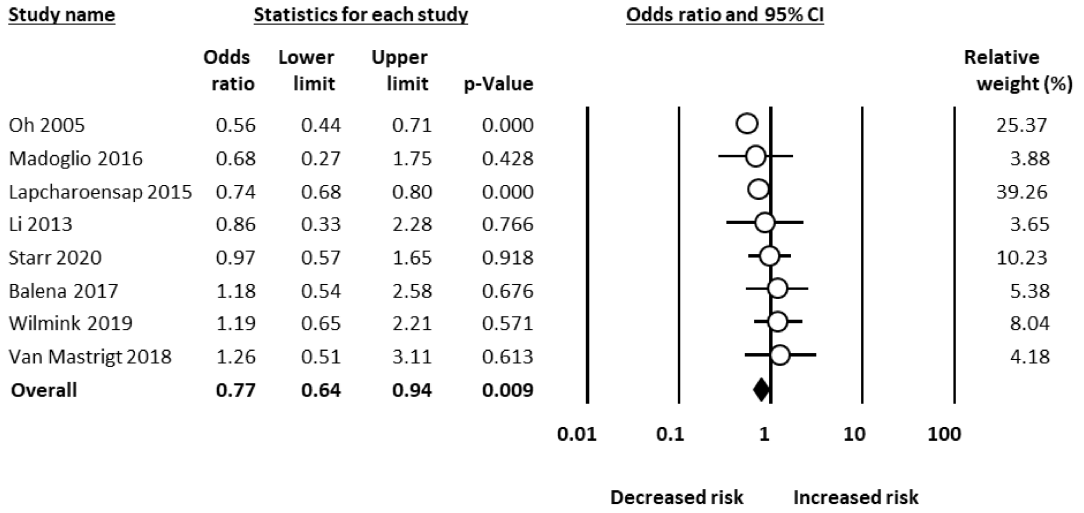
Supplementary Figure 7. Meta-analysis of hypertensive disorders of pregnancy and severe bronchopulmonary dysplasia.

CI: confidence interval.

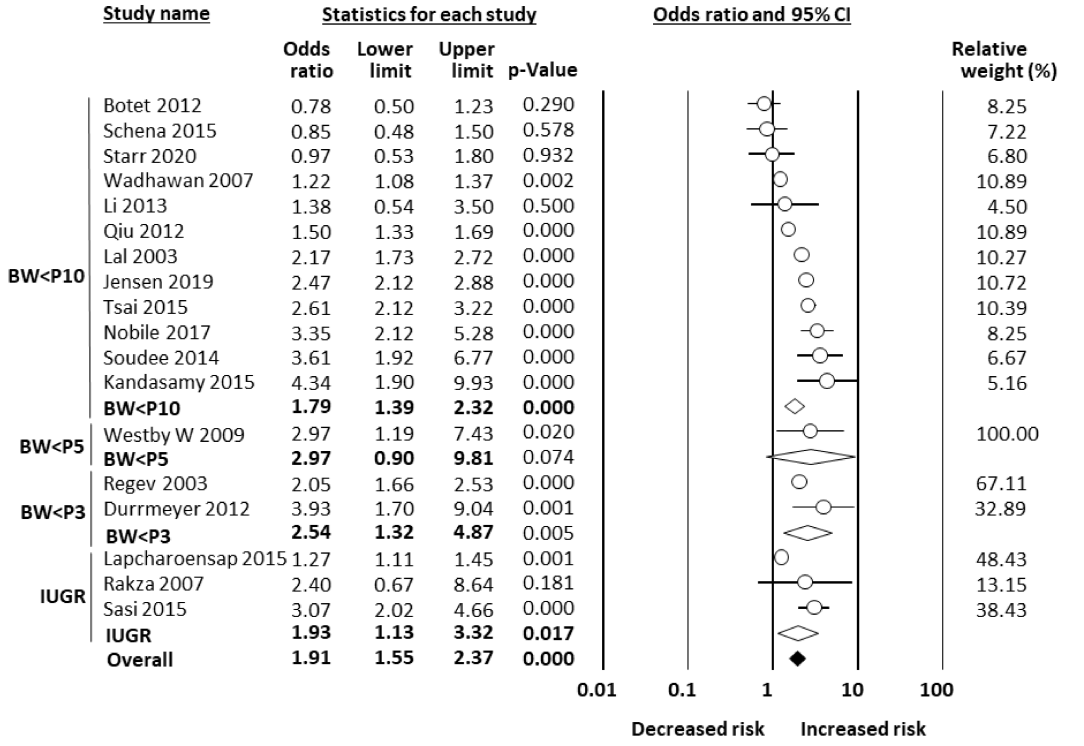


Supplementary Figure 8. Meta-analysis of small for gestational age/intrauterine growth restriction and severe bronchopulmonary dysplasia.

BW: birth weight; CI: confidence interval; IUGR: intrauterine growth restriction (defined on the basis of fetal growth assessment); P3: 3rd percentile; P10: 10th percentile.

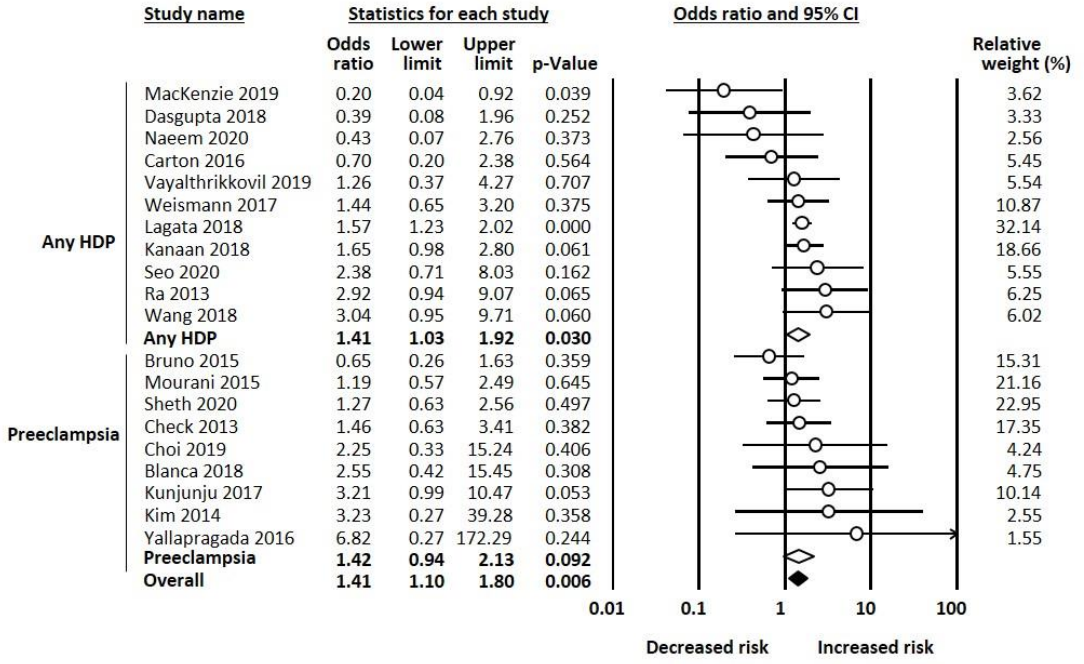


Supplementary Figure 9. Meta-analysis of hypertensive disorders of pregnancy and the combined outcome bronchopulmonary dysplasia or death.



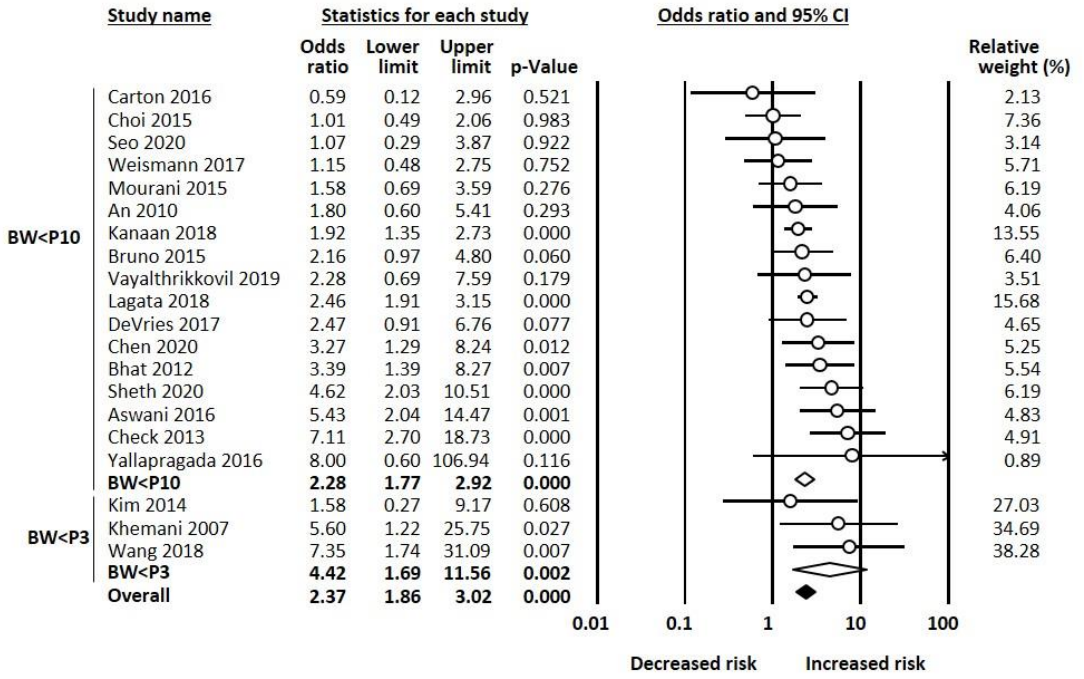
Supplementary Figure 10. Meta-analysis of small for gestational age/intrauterine growth restriction and the combined outcome bronchopulmonary dysplasia or death.

BW: birth weight; CI: confidence interval; IUGR: intrauterine growth restriction (defined on the basis of fetal growth assessment); P3: 3rd percentile; P5: 5th percentile; P10: 10th percentile.



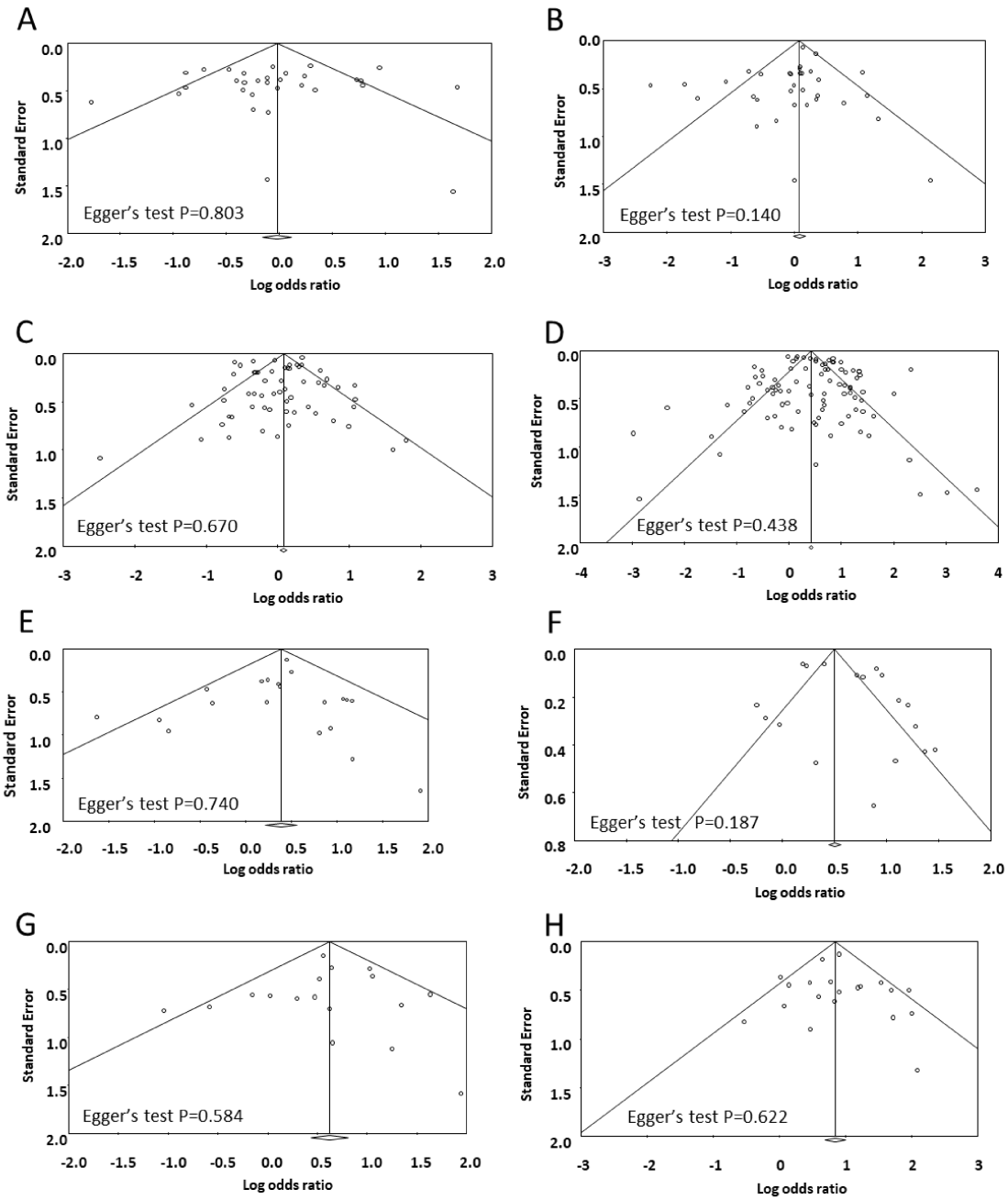
Supplementary Figure 11. Meta-analysis of hypertensive disorders of pregnancy (HDP) and bronchopulmonary dysplasia-associated pulmonary hypertension.

CI: confidence interval.



Supplementary Figure 12. Meta-analysis of small for gestational age/intrauterine growth restriction and bronchopulmonary dysplasia-associated pulmonary hypertension.

BW: birth weight; CI: confidence interval; IUGR: intrauterine growth restriction (defined on the basis of fetal growth assessment); P3: 3rd percentile; P10: 10th percentile.



Suplementary Figure 13. Funnel plot for publication bias analysis for the studies included in the different meta-analyses.

A: Meta-analysis of hypertensive disorders of pregnancy (HDP) and BPD28. B: Meta-analysis of small for gestational age (SGA)/intrauterine growth restriction (IUGR) and BPD28. C: Meta-analysis of HDP and BPD36. D: Meta-analysis of SGA/IUGR and BPD36. E: Meta-analysis of SGA/IUGR and severe BPD. F: Meta-analysis of SGA/IUGR and BPD or death. G: Meta-analysis of HDP and BPD-associated pulmonary hypertension. H: Meta-analysis of SGA/IUGR and BPD-associated pulmonary hypertension.

Supplementary Table 1. Characteristics of the included studies

First author, year	Country	Design	Prospective?	Total infants	Centers	GA of cohort (weeks)	Independent variable	Exposures	Outcomes (% of incidence in total group)	NOS Selection	NOS Comparability	NOS Outcome/Exposure	NOS Total
Abramovici, 1999 [6]	USA	cohort	no	2524	1	<36	Exposure	PE-HELLP	BPD28 (64)	3	1	3	7
Altman, 2011 [7]	Sweden	Cohort	yes	6674	Network	33.1	Exposure	BW<P3	BPD36 (1)	4	1	3	8
Ameenudeen, 2007 [8]	Malaysia	Cohort	yes	244	1	29.7	Outcome	Any HDP BW<P10	BPD36 (15)	4	2	3	9
Amin, 1997 [9]	Canada	Ca-Co	no	186	1	28.3	Exposure	BW<P3	BPD28 (54)	4	1	3	8
An, 2010 [10]	Korea	Cohort	no	116	1	26.3	Outcome	BW<P10	BPD-PH (25)	4	1	3	8
Aswani, 2016 [11]	USA	Cohort	No	230	1	25.9	Outcome	BW<P10	BPD-PH (8)	4	1	3	8
Aucott, 2004 [12]	USA	Ca-Co	no	95	1	28.4	Exposure	BW<P5	BPD36 (21)	4	1	3	8
Baer, 2016 [13]	USA	Cohort	no	78647	Network	33.0	Exposure	BW<P10	BPD36 (2)	4	1	3	8
Baker, 2012 [14]	USA	cohort	yes	62	1	31.6	Outcome	PE BW<P10	BPD36 (21)	4	1	3	8
Balena, 2017 [15]	USA	cohort	yes	113	1	27.9	Outcome	Any HDP	BPD/Death (36)	4	2	3	9
Bardin, 1997 [16]	Canada	Cohort	yes	115	1	25.3	Exposure	BW<P3	BPD28 (86) BPD36 (37)	3	1	3	7
Bhat, 2012 [17]	USA	Cohort	yes	145	1	26	Outcome	BW<P10	BPD-PH (18)	4	2	3	9
Blanca, 2018 [18]	The Netherlands	Cohort	yes	69	1	25.6	Outcome	PE	BPD-PH (12)	3	1	3	7
Bose, 2009 [19]	USA	Cohort	yes	1241	14	<28	Outcome	PE BW<P3	BPD36 (52)	4	2	3	9
Bose, 2011 [20]	USA	Cohort	yes	932	14	<28	Outcome	BW<P3	BPD28 (52) sBPD (11)	4	2	3	9
Bossung, 2020 [21]	Germany	Cohort	yes	16035	62	28.2	Exposure	PE-HELLP	BPD36 (15)	4	2	3	9
Botet, 2012 [22]	Spain	Cohort	no	415	1	27.0	Outcome	BW<P10	BPD/Death (28)	4	2	3	9
Bozzetti, 2013 [23]	Italy	Cohort	yes	310	1	29.7	Exposure	BW<P10	BPD28 (9)	4	2	3	9

First author, year	Country	Design	Prospective?	Total infants	Centers	GA of cohort (weeks)	Independent variable	Exposures	Outcomes (% of incidence in total group)	NOS Selection	NOS Comparability	NOS Outcome/Exposure	NOS Total
Brener, 2017 [24]	Argentina	Cohort	no	203	1	29.4	Outcome	BW<P3	BPD36 (22)	4	2	3	9
Brumbaugh, 2018 [25]	USA	Cohort	no	151	1	26.6	Outcome	BW<P10	BPD36 (83) sBPD (55)	4	2	3	9
Brumbaugh, 2020 [26]	USA	Cohort	yes	2310	Network	24.9	Outcome	BW<P10	BPD36 (48) sBPD (5)	4	2	3	9
Bruno, 2015 [27]	USA	Cohort	no	303	1	26.6	Outcome	PE BW<P10	BPD-PH (12)	4	2	3	9
Burns, 1997 [28]	Australia	Ca-Co	no	117	5	28.2	Outcome	BW<P10	BPD28 (55)	4	2	3	9
Bursal, 2017 [29]	Turkey	cohort	no	284	1	31.2	Exposure	PE	BPD28 (10)	2	1	3	7
Candel, 2016 [30]	Spain	Ca-Co	yes	129	1	33.8	Exposure	IUGR	BPD36 (13)	4	1	3	8
Cartón, 2016 [31]	Spain	Cohort	yes	84	1	27.0	Outcome	Any HDP BW<P10	BPD-PH (26)	4	2	3	9
Cederqvist, 2003 [32]	Finland	cohort	yes	32	1	27.8	Outcome	PE	BPD36 (56)	4	1	3	8
Çetinkaya, 2010 [33]	Turkey	Ca-Co	no	84	1	31.3	Exposure	PE	BPD36 (23)	2	1	3	6
Charafeddine, 1999 [34]	USA	Cohort	yes	123	1	27.8	Outcome	BW<P10	BPD28 (72)	4	2	3	9
Check, 2013 [35]	USA	Cohort	no	138	1	26.1	Outcome	PE BW<P10	BPD-PH (28)	3	1	3	7
Chen, 2020 [36]	USA	Cohort	yes	188	1	26.7	Outcome	BW<P10	BPD-PH (32)	4	2	3	9
Chen, 2016 [37]	Switzerland	Cohort	yes	8899	Network	29.2	Outcome	BW<P10	BPD36 (10)	4	2	3	9
Cheng, 2004 [38]	Taiwan	Ca-Co	no	89	1	28.3	Exposure	PE	BPD28 (36)	4	1	2	7
Choi, 2015 [39]	Korea	Cohort	no	194	1	26.5	Outcome	BW<P10	BPD-PH (26)	4	1	3	8
Choi, 2019 [40]	Korea	Cohort	no	81	1	25.7	Outcome	PE	BPD-PH (25)	4	1	3	8
Chye, 1995 [41]	Australia	Ca-Co	yes	156	1	28.4	Outcome	BW<P10	BPD28 (50)	4	1	3	8
Claas, 2011 [42]	The Netherlands	Cohort	no	101	1	28.0	Exposure	BW<P3	BPD36 (56)	4	1	3	8

First author, year	Country	Design	Prospective?	Total infants	Centers	GA of cohort (weeks)	Independent variable	Exposures	Outcomes (% of incidence in total group)	NOS Selection	NOS Comparability	NOS Outcome/Exposure	NOS Total
Cunha, 2005 [43]	Brazil	cohort	yes	86	1	28.9	Outcome	Any HDP	BPD28 (52)	4	1	3	8
Da Silva, 2018 [44]	Brazil	Cohort	yes	67	3	29.1	Outcome	Any HDP	BPD36 (33)	4	2	3	9
Dasgupta, 2018 [45]	USA	Cohort	yes	52	1	26.6	Outcome	Any HDP	BPD36 (69) BPD-PH (15)	4	2	3	9
De Jesus, 2013 [46]	USA	Cohort	no	2971	Network	25.0	Exposure	BW<P10	BPD36 (36)	4	2	3	9
De Souza, 2015 [47]	Brazil	Ca-Co	yes	60	1	30.0	Exposure	PE	BPD36 (10)	4	2	3	9
Demirel, 2009 [48]	Turkey	Ca-Co	yes	106	1	30.4	Outcome	PE-HELLP	BPD28 (53)	4	2	3	9
DeVries, 2017 [49]	USA	Cohort	no	577	1	26.6	Outcome	BW<P10	BPD-PH (3)	4	2	2	8
Dogan, 2020 [50]	Turkey	Cohort	no	78	1	28.6	Outcome	PE	BPD36 (41)	4	1	3	8
Duan, 2016 [51]	China	Cohort	yes	243	1	30.0	Outcome	Any HDP	BPD28 (29)	4	2	3	9
Duan, 2016b [52]	China	Cohort	yes	147	1	29.5	Outcome	Any HDP BW<P10	BPD36 (41)	4	2	3	9
Durrmeyer, 2012 [53]	France	Cohort	yes	265	1	26.0	Outcome	BW<P3	BPD36 (15) BPD/Death (25)	4	1	3	8
El Ayoub, 2016 [54]	Europe	Cohort	yes	4585	Network	28.0	Exposure	IUGR	BPD36 (14)	4	2	3	9
Enginner, 2010 [55]	UK	Ca-Co	no	121	1	<36	Exposure	IUGR	BPD28 (29)	4	1	3	8
Eriksson, 2015 [56]	Sweden	Ca-Co	no	2255	Network	30.0	Outcome	Any HDP BW<P10	BPD36 (24)	4	2	3	9
Estevez, 2017 [57]	Spain	Cohort	no	110	1	29.2	Exposure	BW<P10	BPD36 (5)	4	1	3	8
EXPRESS group, 2010 [58]	Sweden	Cohort	yes	497	Network	25.0	Outcome	PE BW<P3	sBPD (25)	4	2	3	9
Falciglia, 2003 [59]	USA	Cohort	yes	46	1	29.5	Exposure	PE	BPD36 (50)	3	2	3	8
Fernandez-Rodriguez, 2021 [60]	Spain	Cohort	no	95	1	31.4	Exposure	IUGR	BPD36 (9)	3	2	3	8
Fujioka, 2014 [61]	Japan	Cohort	no	97	1	28.0	Outcome	Any HDP	BPD36 (57)	4	1	3	8

First author, year	Country	Design	Prospective?	Total infants	Centers	GA of cohort (weeks)	Independent variable	Exposures	Outcomes (% of incidence in total group)	NOS Selection	NOS Comparability	NOS Outcome/Exposure	NOS Total
								BW<P10					
Gagliardi, 2009 [62]	Italy	Cohort	yes	1209	14	28.7	Outcome	BW<P10	BPD36 (16)	4	2	3	9
Gagliardi, 2013 [63]	Italy	Cohort	yes	2085	Network	28.7	Exposure	Any HDP	BPD36 (13)	4	2	3	9
Gagliardi, 2014 [64]	Italy	Cohort	no	3606	82	27.2	Exposure	Any HDP	BPD36 (25)	4	2	3	9
Garite, 2004 [65]	USA	Cohort	no	24249	124	29.9	Exposure	IUGR	BPD28 (18)	3	2	3	8
Garofoli, 2014 [66]	Italy	Cohort	no	76	1	31.7	Exposure	BW<P10	BPD36 (9)	4	1	3	8
Gemmell, 2016 [67]	International	Cohort	no	27846	Network	26.5	Exposure	PE	BPD36 (35)	4	2	3	9
Giapros, 2012 [68]	Greece	Cohort	no	168	1	28.5	Exposure	BW<P10	BPD36 (35)	4	2	3	9
Gortner, 1999 [69]	Germany	Cohort	yes	317	6	29.6	Exposure	BW<P10	BPD36 (6)	4	1	3	8
Gortner, 2003 [70]	Germany	Ca-Co	yes	148	1	34.0	Exposure	BW<P10	BPD28 (6)	4	0	3	7
Gray, 1997 [71]	Australia	Cohort	yes	189	1	27.3	Exposure	PE	BPD28 (49)	4	2	3	9
Greenough, 2005 [72]	UK	Ca-Co	yes	34	1	28.5	Outcome	BW<P10	BPD28 (50)	4	2	3	9
Grisaru-G, 2012 [73]	Israel	Cohort	yes	9756	Network	28.5	Exposure	BW<P3	BPD36 (15)	4	2	3	9
Guimaraes, 2010 [77]	Portugal	Cohort	yes	256	5	28.0	Outcome	BW<P10	BPD36 (18)	4	1	3	8
Guo, 2015 [75]	Taiwan	Cohort	no	75	1	27.6	Outcome	Any HDP BW<P10	sBPD (63)	4	1	3	8
Gursoy, 2015 [76]	Turkey	Cohort	no	652	1	29.4	Outcome	PE BW<P10	BPD28 (23)	4	2	3	9
Hadchouel, 2020 [77]	France	Ca-Co	no	19	3	26.7	Outcome	BW<P10	sBPD (58)	3	1	3	7
Hansen, 2010 [78]	UK	Cohort	yes	107	1	29.0	Outcome	PE	BPD36 (25)	4	2	3	9
Hartung, 2005 [79]	Germany	Ca-Co	no	88	1	31.0	Exposure	IUGR	BPD36 (9)	4	1	3	8
Hentges, 2015 [80]	Brazil	Cohort	yes	88	1	30.1	Exposure	PE	BPD28 (26)	4	2	3	9
Hernandez, 2004 [81]	Mexico	Ca-Co	yes	44	1	31.1	Outcome	Any HDP	BPD28 (50)	4	1	3	8

First author, year	Country	Design	Prospective?	Total infants	Centers	GA of cohort (weeks)	Independent variable	Exposures	Outcomes (% of incidence in total group)	NOS Selection	NOS Comparability	NOS Outcome/Exposure	NOS Total
Hiett, 2001 [82]	USA	Ca-Co	no	116	2	27.1	Exposure	PE	BPD28 (60)	4	2	3	9
Hikino, 2012 [83]	Japan	Cohort	yes	26	1	29.0	Outcome	BW<P10	BPD36 (50)	4	1	3	8
Huusko, 2015 [84]	Finland, Canada en Hungary	Ca-Co	yes	772	8	27.8	Outcome	BW<P3	BPD36 (28)	4	2	3	9
Imamura, 2017 [85]	Japan	Cohort	no	169	1	26.0	Outcome	BW<P10	sBPD (40)	4	2	3	9
Iwatani, 2013 [86]	Japan	Cohort	no	51	1	25.7	Outcome	Any HDP	BPD36 (51)	4	2	3	9
Jakuskiene, 2011 [87]	Lithuania	Cohort	yes	238	1	27.4	Outcome	BW<P10	BPD36 (6)	4	1	3	8
Jensen, 2019 [88]	USA	Cohort	no	6708	Network	28.6	Exposure	BW<P10	BPD36 (29) BPD/Death (35)	4	1	3	8
Jeon, 2020 [89]	Korea	Cohort	yes	521	1	27.4	Outcome	Any HDP	BPD36 (48)	4	1	3	8
Jo, 2015 [90]	Korea	Cohort	no	2386	55	29.0	Outcome	Any HDP	BPD36 (32)	4	2	3	9
Kalra, 2014 [91]	USA	Ca-Co	yes	60	2	27.0	Outcome	BW<P10	BPD36 (55)	4	1	3	8
Kanaan, 2018 [92]	USA	Cohort	no	1340	1	27.8	Outcome	Any HDP BW<P10	BPD-PH (12)	4	2	3	9
Kandasamy, 2015 [93]	USA	Cohort	yes	152	1	25.2	Outcome	BW<P10	BPD/Death (23)	4	1	3	8
Karagianni, 2011 [94]	Greece	Cohort	yes	219	1	29.1	Outcome	BW<P10	BPD36 (28)	4	1	3	8
Karagianni, 2013 [95]	Greece	Ca-Co	yes	61	1	32.0	Outcome	BW<P10	BPD36 (46)	4	1	3	8
Khan, 2006 [96]	USA	Cohort	no	306	2	26.7	Outcome	PE	BPD36 (45)	4	2	3	9
Khan, 2020 [97]	USA	Cohort	yes	68	1	27.0	Outcome	PE BW<P10	BPD36 (65)	4	2	3	9
Khemani, 2007 [98]	USA	Cohort	no	42	3	26.0	Outcome	BW<P3	BPD-PH (43)	3	1	3	7
Kim, 2014 [99]	Korea	Ca-Co	no	56	1	26.1	Outcome	PE BW<P3	sBPD (66) BPD-PH (27)	4	1	3	8

First author, year	Country	Design	Prospective?	Total infants	Centers	GA of cohort (weeks)	Independent variable	Exposures	Outcomes (% of incidence in total group)	NOS Selection	NOS Comparability	NOS Outcome/Exposure	NOS Total
Kim, 1996 [100]	USA	Ca-Co	no	117	1	28	Exposure	Any HDP	BPD28 (48) BPD36 (15)	3	1	3	7
Kim, 2018 [101]	Korea	cohort	no	199	1	28.9	Exposure	PE	BPD36 (31)	4	2	3	9
Kim, 2020 [102]	Korea	Cohort	no	117	1	28.8	Outcome	BW<P10	BPD28 (91) sBPD (18)	3	1	3	7
Klinger, 2013 [103]	Isreal	Cohort	yes	12139	28	29.0	Outcome	Any HDP BW<P10	BPD36 (14)	4	2	3	9
Köksal, 2012 [104]	Turkey	Cohort	yes	102	1	28.6	Outcome	PE	BPD28 (30)	4	1	3	8
Korhonen, 2004 [105]	Finland	Cohort	yes	68	1	27.5	Outcome	BW<P3	BPD36 (50)	4	1	2	7
Koroglu, 2013 [106]	Turkey	Ca-Co	yes	41	1	28.9	Outcome	PE	BPD28 (43)	3	2	3	8
Kunjunju, 2017 [107]	Australia	Cohort	no	56	1	26.0	Outcome	PE	BPD-PH (39)	3	1	3	7
Lagatta, 2018 [108]	USA	Cohort	No	1677	23	25.0	Outcome	Any HDP BW<P10	BPD-PH (22)	3	2	3	8
Lal, 2003 [109]	UK	Cohort	yes	2838	Network	29.9	Outcome	BW<P10	BPD28 (23) BPD36 (14) BPD/Death (23)	4	1	3	8
Lapcharoensap, 2015 [110]	USA	Cohort	no	15052	132	27.0	Outcome	Any HDP IUGR	BPD/Death (47)	4	2	3	9
Lardon-Fdz, 2017 [111]	Spain	Cohort	no	129	1	28.7	Outcome	PE BW<P3	BPD28 (47) BPD36 (19) sBPD (7)	3	1	3	7
Lehtinen, 2017 [112]	Finland	Cohort	yes	53	1	29.0	Outcome	BW<P3	BPD36 (40)	4	2	3	9
Leroy, 2018 [113]	Canada	Cohort	yes	62	1	27.0	Outcome	BW<P10	BPD36 (52)	4	1	3	8
Li, 2013 [114]	China	Cohort	yes	160	1	30.9	Outcome	PE BW<P10	BPD/Death (36)	4	2	3	9
Lin, 2005 [115]	Taiwan	Ca-Co	yes	224	1	26.7	Outcome	BW<P3	BPD36 (50)	4	1	3	8

First author, year	Country	Design	Prospective?	Total infants	Centers	GA of cohort (weeks)	Independent variable	Exposures	Outcomes (% of incidence in total group)	NOS Selection	NOS Comparability	NOS Outcome/Exposure	NOS Total
Lodha, 2014 [116]	Canada	Cohort	yes	586	1	28.5	Outcome	BW<P10	BPD36 (25)	4	1	2	7
Löfqvist, 2012 [117]	Sweden	Cohort	yes	108	2	27.2	Outcome	PE BW<P3	BPD36 (54)	4	2	3	9
Lohmann, 2014 [118]	USA	Cohort	yes	22	1	27.2	Outcome	Any HDP	BPD36 (45)	4	1	3	8
MacKenzie, 2020 [119]	Canada	Cohort	No	87	1	25.9	Outcome	Any HDP	BPD-PH (28)	3	1	3	7
Madoglio, 2016 [120]	Brazil	Cohort	yes	73	1	28.7	Exposure	PE	BPD28 (36) BPD36 (18) BPD/Death (46)	3	1	3	7
Mahlman, 2017 [121]	Finland	Ca-Co	yes	174	5	27.4	Outcome	PE BW<P3	BPD 36 (34)	4	1	3	8
Malavolti, 2018 [122]	Switzerland	Cohort	no	610	1	27.9	Outcome	BW<P10	BPD28 (59)	4	2	3	9
Mao, 2018 [124]	China	Ca-Co	yes	39	1	29.6	Outcome	PE BW<P10	BPD36 (49)	4	1	3	8
Marshall, 1999 [124]	USA	Cohort	yes	865	13	28.9	Outcome	PE	BPD36 (26)	3	2	3	8
Matic, 2017 [125]	Australia and UK	Cohort	no	2549	10	26.7	Exposure	Any HDP	BPD36 (30)	4	2	3	9
May, 2009 [126]	UK	Cohort	yes	80	1	28.0	Outcome	BW<P10	BPD28 (58) BPD36 (39) sBPD (16)	4	1	3	8
McGowan, 2009 [127]	USA	Ca-Co	no	98	1	26.3	Outcome	PE BW<P10	BPD36 (50)	4	2	3	9
Melamed, 2016 [128]	Canada	Cohort	no	6567	Network	29.8	Exposure	BW<P10	BPD36 (12)	4	2	3	9
Mello, 2017 [129]	Brasil	Cohort	yes	112	1	29.5	Outcome	BW<P10	BPD28 (44)	4	2	2	8
Méndez-Abad, 2020 [130]	Spain	Cohort	yes	101	1	29.0	Outcome	BW<P10	BPD36 (15)	4	1	3	8
Mohamed, 2015 [131]	Canada	Cohort	yes	99	1	26.4	Outcome	PE BW<P10	BPD36 (66)	4	1	3	8

First author, year	Country	Design	Prospective?	Total infants	Centers	GA of cohort (weeks)	Independent variable	Exposures	Outcomes (% of incidence in total group)	NOS Selection	NOS Comparability	NOS Outcome/Exposure	NOS Total
Monier, 2017 [132]	France	Cohort	yes	5919	Network	29.0	Exposure	IUGR	BPD36 (48) sBPD (7)	4	2	3	9
Morrow, 2017 [133]	USA	Cohort	yes	587	5	27.0	Outcome	PE BW<P10	BPD36 (41)	4	2	3	9
Morsing, 2012 [134]	Sweden	Ca-Co	yes	62	1	27.0	Exposure	IUGR	sBPD (50)	3	1	3	7
Mourani, 2015 [135]	USA	Cohort	yes	277	2	27.0	Outcome	PE BW<P10	BPD-PH (14)	4	1	3	8
Naeem, 2020 [136]	USA	Cohort	yes	26	N	26.1	Outcome	Any HDP	BPD36 (72) BPD-PH (17)	4	1	3	8
Nascimento, 2020 [137]	UK	Cohort	yes	40	1	28.0	Outcome	BW<P10	BPD36 (53)	4	1	3	8
Natarajan, 2012 [138]	USA	Cohort	yes	1159	Network	25.7	Outcome	BW<P10	BPD36 (13)	4	2	3	9
Naveda, 2016 [139]	Venezuela	Ca-Co	yes	144	1	33.0	Outcome	Any HDP	BPD28 (25)	3	2	3	8
Newman, 2011 [140]	USA	Cohort	no	156	1	28.6	Outcome	Any HDP BW<P10	BPD28 (51) sBPD (31)	4	2	3	9
Nobile, 2017 [141]	Italy	Cohort	no	515	1	28.0	Exposure	IUGR BW<P10	BPD36 (22) BPD/Death (38)	4	2	3	9
Novitsky, 2015 [142]	USA	Cohort	no	906	1	28.2	Outcome	PE	BPD36 (20)	3	2	3	8
O'Shea, 2012 [143]	Australia	Cohort	no	751	Network	26.6	Outcome	PE BW<P3	BPD36 (44)	4	2	3	9
Oh, 2005 [144]	USA	Cohort	no	1382	Network	26.0	Outcome	Any HDP	BPD/Death (58)	4	2	3	9
Ozkan, 2012 [145]	Turkey	Cohort	yes	332	1	29.2	Exposure	PE	BPD28 (26) BPD36 (14) sBPD (8)	4	2	3	9
Palta, 1996 [146]	USA	Cohort	no	632	7	28.7	Exposure	PE-HELLP	BPD28 (24)	3	1	3	7
Park, 2012 [147]	Korea	Cohort	no	191	1	29.4	Exposure	Any HDP	BPD28 (36) BPD36 (29)	4	1	3	8

First author, year	Country	Design	Prospective?	Total infants	Centers	GA of cohort (weeks)	Independent variable	Exposures	Outcomes (% of incidence in total group)	NOS Selection	NOS Comparability	NOS Outcome/Exposure	NOS Total
Patel, 2017 [148]	USA	Cohort	yes	254	1	27.9	Outcome	BW<P10	BPD36 (30)	4	2	3	9
Qi, 2013 [149]	China	Cohort	yes	60	1	29.5	Outcome	Any HDP BW<P10	BPD36 (42)	4	1	3	8
Qiu, 2012 [150]	Canada	Cohort	no	11909	Network	28.8	Exposure	BW<P10	BPD36 (21) BPD/Death (30)	4	2	3	9
Ra, 2013 [151]	Korea	Cohort	no	85	1	28.0	Outcome	Any HDP	BPD-PH (21)	3	1	3	7
Rakza, 2007 [152]	France	Cohort	yes	48	1	29.1	Exposure	IUGR	BPD36 (21) BPD/Death (29)	4	1	3	8
Ranke, 2007 [153]	Germany	Cohort	yes	97	1	29.0	Exposure	BW<P10	BPD36 (39)	4	1	2	7
Razak 2020[154]	Canada	Ca-Co	no	237	1	29.2	Exposure	Any HDP	BPD36 (20)	4	2	3	9
Redline, 2002 [155]	USA	cohort	no	371	1	27.6	Outcome	PE	BPD36 (30)	4	1	3	8
Regev, 2015 [156]	Israel	cohort	yes	2139	28	29.7	Exposure	Any HDP	BPD36 (12)	4	1	3	8
Regev, 2003 [157]	Israel	Cohort	yes	2764	Network	27.9	Exposure	BW<P3	BPD36 (22) BPD/Death (43)	4	2	3	9
Reiss, 2003 [158]	Germany	Cohort	yes	1365	1	28.8	Exposure	BW<P10	BPD36 (14)	4	2	3	9
Rijken, 2007 [159]	The Netherlands	Cohort	yes	158	1	28.8	Exposure	BW<P10	BPD36 (22)	4	2	3	9
Rocha, 2018 [160]	Portugal	Cohort	yes	494	11	27.3	Exposure	Any HDP	BPD36 (24)	4	2	3	9
Rocha, 2010 [161]	Portugal	Cohort	yes	205	1	29.0	Outcome	BW<P10	BPD36 (22)	4	1	3	8
Rojas, 2012 [162]	Colombia	Ca-Co	no	212	8	29.2	Outcome	BW<P10	BPD36 (30)	4	2	3	9
Ruiz-Pelaez, 2014 [163]	Colombia	Cohort	yes	416	12	31.9	Outcome	BW<P10	BPD28 (54) BPD36 (17)	3	1	3	7
Sasi, 2015 [164]	Australia	Cohort	no	459	1	28.7	Exposure	IUGR	BPD36 (27) BPD/Death (30)	4	1	3	8
Schena, 2015 [165]	Italy	Cohort	no	242	1	26.3	Outcome	BW<P10	BPD/Death (43)	4	1	3	8

First author, year	Country	Design	Prospective?	Total infants	Centers	GA of cohort (weeks)	Independent variable	Exposures	Outcomes (% of incidence in total group)	NOS Selection	NOS Comparability	NOS Outcome/Exposure	NOS Total
Schiff, 1993 [166]	USA	Ca-Co	yes	138	1	33.8	Exposure	PE-HELLP	BPD28 (1)	4	2	3	9
Schlapbach, 2010 [167]	Switzerland	Ca-Co	yes	99	1	29.3	Exposure	PE	BPD36 (14)	4	1	3	8
Seo, 2020 [168]	Korea	Cohort	no	81	1	26.4	Outcome	Any HDP BW<P10	BPD-PH (30)	4	1	2	7
Serenius, 2004 [169]	Sweden	Cohort	no	140	2	24.2	Outcome	BW<P3	BPD36 (36)	4	2	3	9
Sharma, 2004 [170]	USA	Cohort	no	2364	1	31.2	Exposure	BW<P10	BPD28 (?) BPD36 (?)	4	1	3	8
Sheth, 2020 [171]	USA	Ca-Co	no	220	1	25.9	Outcome	PE BW<P10	BPD-PH (27)	4	2	3	9
Shima, 2013 [172]	Japan	Cohort	no	306	1	29.0	Outcome	Any HDP BW<P10	BPD28 (42) BPD36 (17)	3	1	3	7
Shin, 2020 [173]	Korea	Cohort	yes	1827	Network	27.4	Exposure	Any HDP	BPD36 (42)	4	2	3	9
Silveira, 2007 [174]	Brazil	Cohort	yes	86	1	30.9	Exposure	PE	BPD36 (14)	3	1	3	7
Soliman, 2017 [175]	Canada	Cohort	yes	319	1	28.8	Exposure	PE-HELLP BW<P10	BPD28 (39) BPD36 (25)	4	1	3	8
Somaschini, 2012 [176]	Italy	Cohort	no	366	12	28.5	Outcome	Any HDP BW<P10	BPD 28 (39) BPD 36 (21) sBPD (10)	3	1	3	7
Soudee, 2014 [177]	France	Ca-Co	no	293	1	28.5	Exposure	BW<P3	BPD28 (57) BPD36 (24) BPD/Death (37)	4	2	3	9
Spiegler, 2013 [178]	Germany	Cohort	no	1577	28	29.2	Exposure	PE	BPD36 (12)	3	1	3	7
Starr, 2020 [179]	USA	Cohort	no	546	24	27.9	Outcome	Any HDP BW<P10	BPD/Death (45)	4	2	3	9
Streubel, 2008 [180]	USA	Cohort	yes	133	1	26.6	Outcome	BW<P10	BPD36 (29)	4	1	3	8
Sun, 2019 [181]	China	Cohort	no	296	1	30.0	Outcome	Any HDP BW<P10	BPD28 (49)	4	1	3	8

First author, year	Country	Design	Prospective?	Total infants	Centers	GA of cohort (weeks)	Independent variable	Exposures	Outcomes (% of incidence in total group)	NOS Selection	NOS Comparability	NOS Outcome/Exposure	NOS Total
Tammela, 1992 [182]	Finland	Cohort	yes	46	1	31.7	Outcome	BW<P3	BPD36 (50)	4	1	3	8
Teberg, 1991 [183]	USA	Cohort	yes	236	1	30.4	Outcome	Any HDP BW<P10	BPD28 (25)	4	2	3	9
Todd, 1997 [184]	Australia	Ca-Co	yes	296	1	28.0	Outcome	Any HDP	BPD36 (50)	3	1	3	7
Tokumasu, 2016 [185]	Japan	Cohort	no	4518	79	26.1	Exposure	PE-HELLP	BPD36 (25)	4	1	3	8
Torchin, 2016 [186]	France	Cohort	yes	2638	?	29.7	Exposure	Any HDP IUGR	BPD36 (10)	4	1	3	8
Torrance, 2007 [187]	Netherlands	Cohort	no	187	1	30.4	Exposure	Any HDP	BPD28 (23)	4	2	3	9
Tsai, 2015 [188]	Taiwan	Cohort	yes	1680	21	28.3	Exposure	BW<P10	BPD36 (32) BPD/Death (47)	4	2	3	9
Turunen, 2011 [189]	Finland	Ca-Co	yes	46	1	26.9	Exposure	PE	BPD36 (70)	4	2	3	9
Uberos, 2020 [190]	Spain	Cohort	no	389	1	29.0	Outcome	Any HDP BW<P10	BPD36 (41)	4	2	3	9
Van Mastright , 2018 [191]	The Netherlands	Cohort	yes	111	1	28.0	Outcome	PE	BPD/Death (40)	4	2	3	9
Vayalthrikkovil, 2019 [192]	Canada	Cohort	Yes	126	1	26.2	Outcome	Any HDP BW<P10	BPD-PH (19)	3	1	3	7
Viscardi, 2004 [193]	USA	Cohort	yes	262	2	28.0	Outcome	PE BW<P10	BPD28 (58)	4	2	3	9
Vrlenich, 1995 [194]	USA	Cohort	yes	406	10	30.3	Outcome	BW<P3	BPD36 (23)	4	1	2	7
Wadhawan, 2007 [195]	USA	Cohort	no	9461	19	26.0	Exposure	BW<P10	BPD36 (42) BPD/Death (55)	4	1	3	8
Wang, 2014 [196]	China	Cohort	yes	73	1	30.5	Outcome	Any HDP	BPD28 (33)	3	1	3	7
Wang, 2018 [197]	China	Cohort	no	191	1	28.2	Outcome	Any HDP BW<P3	BPD-PH (19)	3	1	3	7
Wang, 2013 [198]	USA	Ca-Co	no	1649	Network	27.0	Outcome	IUGR	BPD36 (52)	4	2	3	9

First author, year	Country	Design	Prospective?	Total infants	Centers	GA of cohort (weeks)	Independent variable	Exposures	Outcomes (% of incidence in total group)	NOS Selection	NOS Comparability	NOS Outcome/Exposure	NOS Total
Wang, 2010 [199]	Taiwan	Cohort	yes	72	2	28.3	Outcome	BW<P10	BPD28 (78) BPD36 (52) sBPD (36)	4	2	3	9
Weismann, 2017 [200]	USA	Cohort	yes	159	1	25.6	Outcome	Any HDP BW<P10	BPD-PH (28)	4	2	3	9
Wemhöner, 2011 [201]	Austria	Cohort	no	95	1	27.7	Outcome	BW<P10	BPD36	4	1	3	8
Westby Wold, 2009 [202]	Norway	Cohort	no	365	15	26.0	Exposure	BW<P5	BPD36 (40) BPD/Death (60)	4	1	3	8
Wilmink 2019 [203]	The Netherlands	Cohort	no	273	1	29.3	Exposure	PE	BPD28 (24) BPD36 (11) BPD/Death (19)	4	2	3	9
Wirbelauer, 2010 [204]	Germany	Cohort	yes	49	1	27.7	Exposure	BW<P10	BPD28 (29)	4	1	3	8
Withagen, 2001 [205]	Netherlands	Ca-Co	no	666	1	30.7	Exposure	PE-HELLP	BPD28 (13)	4	2	3	9
Wocadlo, 1994 [206]	Australia	Cohort	yes	36	1	27.6	Exposure	BW<P10	BPD28 (50)	4	1	2	7
Won Choi, 2006 [207]	Korea	Cohort	yes	75	1	28.5	Outcome	Any HDP	BPD36 (35)	3	1	3	7
Xu, 2016 [208]	China	Cohort	no	42	1	28.0	Outcome	BW<P10	BPD36 (76) sBPD (36)	3	1	3	7
Xydis, 2013 [209]	Greece	Cohort	yes	205	1	32.9	Exposure	BW<P3	BPD36 (59)	4	2	3	9
Yallapragada, 2016 [210]	USA	Ca-Co	yes	14	1	26.2	Outcome	PE BW<P10	BPD-PH (50)	4	1	3	8
Yen, 2013 [211]	Taiwan	Cohort	no	5753	21	30.0	Exposure	PE	BPD36 (35)	3	1	3	7
Yilmaz, 2017 [212]	Turkey	Cohort	yes	40	1	30.2	Outcome	PE BW<P10	BPD28 (35)	4	1	3	8
Yoon, 1999 [213]	Korea	Cohort	yes	203	1	31.0	Outcome	BW<P10	BPD28 (17)	4	2	3	9
Yu, 2011 [214]	Korea	Cohort	no	415	1	26.2	Exposure	BW<P3	BPD36 (37)	4	2	3	9
Zanardo, 2002 [215]	Italy	Ca-Co	no	100	1	27.7	Outcome	BW<P10	BPD28 (50)	3	1	3	7

First author, year	Country	Design	Prospective?	Total infants	Centers	GA of cohort (weeks)	Independent variable	Exposures	Outcomes (% of incidence in total group)	NOS Selection	NOS Comparability	NOS Outcome/Exposure	NOS Total
Zhang, 2011 [216]	China	cohort	no	116	1	30.2	Outcome	Any HDP BW<P10	BPD28 (48)	3	1	3	7

BPD28: BPD defined as oxygen requirement on postnatal day 28; BPD36: defined as oxygen requirement at the postmenstrual age of 36 weeks; BPD-PH: BPD-associated pulmonary hypertension; BW: birth weight; HDP: hypertensive disorders of pregnancy; IUGR: intrauterine growth restriction (defined on the basis of fetal growth assessment); NOS: Newcastle Ottawa Scale; P3: 3rd percentile; P5: 5th percentile; P10: 10th percentile; PE: preeclampsia; sBPD: severe BPD (⩾ 30% oxygen or mechanical ventilation at the postmenstrual age of 36 weeks); SGA: small for gestational age. The number in parentheses after the outcome indicates the outcome rate in the study.

Supplementary Table 2. Meta-regression analysis (continuous covariates)

Association	Covariate	Covariate unit	K	Coefficient	95% CI		P	R^2 analog
					Lower limit	Upper limit		
HDP and BPD36	MD in GA (exposed minus unexposed)	week	24	-0.500	-0.651	-0.349	<0.001	0.95
	GA total cohort (weeks)	week	55	-0.077	-0.197	0.043	0.112	0.29
	Male sex (logOR)	logOR	20	0.190	-0.670	1.050	0.665	0.00
	ACS (logOR)	logOR	17	-0.148	-0.578	0.282	0.501	0.00
	RDS (logOR)	logOR	12	0.266	-0.185	0.716	0.248	0.00
	Median year of cohort	year	60	0.008	-0.018	0.035	0.426	0.00
SGA/IUGR and BPD36	MD in GA (exposed minus unexposed)	week	35	-0.311	-0.571	-0.051	0.002	0.08
	GA total cohort	week	91	-0.039	-0.133	0.056	0.295	0.00
	Male sex (logOR)	logOR	21	-0.222	-1.374	0.930	0.705	0.02
	ACS (logOR)	logOR	18	-0.371	-0.742	0.000	0.050	0.08
	RDS (logOR)	logOR	16	0.354	-0.288	0.997	0.280	0.00
	Median year of cohort	year	89	0.021	-0.001	0.042	0.056	0.01

Random effects (method of moments), univariate meta-regression. Coefficient indicates the change in the log of the OR of the association between BPD36 and the corresponding exposure for a unit change in the predictor covariate. R^2 analog: total between-study variance explained by the moderator. ACS: antenatal corticosteroids; BPD36: bronchopulmonary dysplasia defined as oxygen requirement at the postmenstrual age of 36 weeks; BW: birth weight; CI: confidence interval; GA: gestational age; HDP: hypertensive disorders of pregnancy; IUGR: intrauterine growth restriction (defined on the basis of fetal growth assessment); K: number of studies; OR: odds ratio; SGA: small for gestational age.

Supplementary table 3. Meta-analyses on the association between SGA/IUGR and HDP

Meta-analysis	Subgroup	K	OR	95% CI		P	Heterogeneity	
				Lower limit	Upper limit		I^2 (%)	P
Exposure: SGA/IUGR Outcome: HDP	BW<P10	12	5.00	3.96	6.31	<0.001	87.1	<0.001
	BW<P5	2	8.31	4.53	15.23	<0.001	0.0	0.645
	BW<P3 or -2SD	3	6.78	4.29	10.70	<0.001	0.0	0.670
	IUGR	4	5.71	4.23	7.71	<0.001	73.4	0.010
	SGA/IUGR overall	**21**	**5.62**	**4.77**	**6.62**	**<0.001**	**80.0**	**<0.001**
Exposure: HDP Outcome: SGA/IUGR	Any HDP	3	6.22	2.32	13.79	<0.001	80.3	0.006
	Preeclampsia	16	4.06	2.65	6.22	<0.001	98.0	<0.001
	Preeclampsia -HELLP	3	11.07	3.84	31.94	<0.001	91.8	<0.001
	HDP overall	**22**	**4.86**	**3.36**	**7.01**	**<0.001**	**97.6**	**<0.001**

Mixed effects analysis. A random effects model is used to combine studies within each subgroup. A fixed effect model is used to combine subgroups and yield the overall effect. OR>1 indicates association with increased risk of the outcome and OR<1 indicates association with decreased risk of the outcome.
CI: confidence interval; GA: gestational age; HDP: hypertensive disorders of pregnancy; IUGR: intrauterine growth restriction (defined on the basis of fetal growth assessment); K: number of studies; OR: odds ratio; SGA: small for gestational age.

Supplementary table 4. Raw count data of the meta-analysis on the association between HDP and BPD28.

Study Name	BPD28-yes/total		Study Name	BPD28-yes/total	
	HDP-yes	HDP-no		HDP-yes	HDP-no
Abramovici 1999 [6]	21/47	277/419	Naveda 2016 [139]	29/76	7/68
Bursal 2017 [29]	13/140	16/144	Newman 2011 [140]	18/35	62/121
Cheng 2004 [38]	10/28	22/61	Ozkan 2012 [145]	45/117	42/215
Cunha 2005 [43]	11/29	34/57	Palta 1996 [146]	18/121	134/511
Demirel 2009 [48]	1/2	55/104	Park 2012 [147]	11/38	58/153
Duan 2016 [51]	16/48	55/195	Schiff 1993 [166]	2/69	0/69
Gray 1997 [71]	17/26	61/132	Shima 2013 [172]	21/48	109/258
Gursoy 2015 [76]	18/108	132/544	Soliman 2017 [175]	39/102	86/217
Hentges 2015 [80]	6/37	17/51	Sun 2019 [181]	20/48	124/248
Hernandez 2004 [81]	5/11	17/33	Teberg 1991 [183]	3/44	57/189
Hiett 2001 [82]	40/58	30/58	Torrance 2007 [187]	33/120	10/67
Kim 1996 [100]	16/35	34/70	Viscardi 2004 [193]	15/36	136/226
Koksal 2012 [104]	12/36	19/66	Wang 2014 [196]	7/24	17/49
Koroglu 2014 [106]	10/20	37/89	Wilmink 2019 [203]	23/90	36/157
Lardon-F 2017 [111]	21/47	39/82	Withagen 2001 [205]	33/222	51/444
Madoglio 2016-[120]	10/32	16/41	Yilmaz 2017 [212]	4/12	10/28
			Zhang 2011 [216]	14/33	42/83

Supplementary table 5. Raw count data of the meta-analysis on the association between SGA/IUGR and BPD28.

Study Name	BPD28-yes/total		Study Name	BPD28-yes/total	
	SGA/IUGR yes	SGA/IUGR no		SGA/IUGR yes	SGA/IUGR no
Amin 1997 [9]	26/62	74/124	Newman 2011 [140]	8/16	72/140
Bardin 1997 [16]	20/20	79/95	Ruiz-P 2014 [163]	OR 1.09 (95% CI 0.42-3.16)	
Bose 2011 [20]	39/52	447/880	Sharma 2004 [170]	OR 1.09 (95% CI 0.64-1.86)	
Bozzetti 2013 [23]	4/32	25/278	Shima 2013 [172]	23 /48	107/258
Burns 1997 [28]	5/12	59/105	Somaschini 2012 [176]	13/46	128/320
Charafeddine 1999 [34]	7/36	81/141	Soudee 2014 [177]	22/39	120/208
Chye 1995 [41]	5/14	73/142	Sun 2019 [181]	21/41	123/255
Enginner 2010 [55]	15/44	20/77	Teberg 1991 [183]	16/60	44/176
Garite 2004 [65]	287/1451	4068/22978	Viscardi 2004 [193]	6/15	145/247
Gortner 2003 [70]	7/74	2/74	Wang L.Y. 2010 [199]	15/25	41/47
Greenough 2005 [72]	1/2	16/32	Wirbelauer 2010 [204]	7/18	7/31
Gursoy 2015 [76]	12/55	138/597	Wocadlo 1994 [206]	9/18	9/18
Kim 2020 [102]	17/19	90/98	Xydis 2013 [209]	3/33	13/172
Lal 2003 [109]	96/333	497/2212	Yilmaz 2017 [212]	2/8	12/32
Malavolti 2018 [122]	32/53	325/557	Yoon 1999 [213]	7/42	27/161
May 2009 [126]	9/14	37/66	Zanardo 2002 [215]	13/18	37/82
Mello 2017 [129]	8/49	41/63	Zhang 2011 [216]	11/36	45/80

Supplementary table 6. Raw count data of the meta-analysis on the association between HDP and BPD36.

Study Name	BPD36-yes/total		Study Name	BPD36-yes/total	
	HDP-yes	HDP-no		HDP-yes	HDP-no
Ameenudeen 2007 [8]	11/74	23/159	Mao 2018 [123]	8/13	11/26
Baker 2012 [14]	3/13	10/49	Marshall 1999 [124]	31/178	193/687
Bose 2009 [19]	108/167	538/1074	Matic 2017 [125]	137/379	624/2170
Bossung [21]	368/2562	2030/13383	McGowan 2009 [127]	6/22	41/74
Cederqvist 2003 [32]	9/11	9/21	Mohamed 2015 [131]	12/16	51/80
Çetinkaya 2010 [33]	13/51	6/33	Morrow 2017 [133]	56/154	186/433
Da Silva 2018 [44]	7/25	15/42	Naeem 2020 [136]	17/24	9/12
Dasgupta 2018 [45]	20/35	16/17	Novitsky 2015 [142]	42/252	140/654
De Souza 2015 [47]	3/30	3/30	O'Shea 2012[143]	52/138	280/613
Dogan 2020 [50]	11/18	21/60	Ozkan 2012 [145]	26/117	19/215
Duan 2016b [51]	10/27	51/120	Park 2012 [147]	9/38	46/153
Eriksson 2015 [56]	139/534	395/1721	Qi 2013 [149]	3/11	22/49
Falciglia 2003 [59]	2/7	21/39	Razak 2020 [154]	21/79	27/158
Fujioka 2014 [61]	13/22	42/75	Redline 2002 [155]	22/71	90/300
Gagliardi 2013 [63]	63/441	204/1644	Regev 2015 [156]	146/929	105/864
Gagliardi 2014 [64]	459/2096	428/1510	Rocha 2018 [160]	27/75	92/419
Gemmell 2016 [67]	1523/3625	8235/24221	Schlapbach 2010 [167]	5/33	9/66
Hansen 2010 [78]	12/29	15/78	Shima 2013 [172]	8/48	45/258
Iwatani 2013 [86]	7/10	19/41	Shin 2020 [173]	91/203	673/1624
Jeon 2020 [89]	31/55	221/466	Silveira 2007 [174]	4/40	8/46
Jo 2015 [90]	106/446	583/1690	Soliman 2017[175]	23/102	56/217
Khan 2006 [96]	16/34	121/272	Spiegler 2013 [178]	48/353	134/922
Khan 2020 [97]	11/16	33/52	Todd 1997 [184]	35/57	113/239
Kim 1996 [100]	5/35	11/70	Tokumasu 2016 [185]	136/331	1003/2887
Kim 2018 [101]	24/59	37/140	Torchin 2016 [186]	79/605	180/1506
Klinger 2013 [103]	329/2470	1334/9669	Turunen 2011 [189]	11/21	21/25
Lardon-F 2017 [111]	10/47	15/82	Uberos 2020 [190]	9/28	150/361
Löfqvist 2012 [117]	9/23	49/85	Wilmink 2019[203]	12/90	15/157
Lohmann 2014 [118]	5/7	5/15	Won Choi 2006 [207]	6/19	20/56
Madoglio 2016 [120]	4/32	9/41	Yen 2013 [211]	204/847	1802/4906
Mahlman 2017 [121]	23/47	37/127			

Supplementary table 7. Raw count data of the meta-analysis on the association between SGA/IUGR and BPD36.

Study Name	BPD36-yes/total		Study Name	BPD36-yes/total	
	SGA/IUGR yes	SGA/IUGR no		SGA/IUGR yes	SGA/IUGR no
Altman 2011 [7]	24/840	44/5834	Mahlman 2017 [121]	23/43	37/131
Ameenudeen 2007 [8]	3/40	31/193	Mao 2018 [123]	7/12	12/27
Aucott 2004 [12]	9/31	11/64	May 2009 [126]	9/14	22/66
Baer 2016 [13]	179/8418	1004/70233	McGowan 2009 [127]	5/5	44/93
Baker 2012 [14]	3/6	10/56	Melamed 2016 [128]	164/918	652/5649
Bardin 1997 [16]	13/20	30/95	Mendez 2020 [130]	4/13	11/88
Bose 2009 [19]	60/77	579/1181	Mohamed 2015 [131]	13/17	50/79
Brener 2017 [24]	9/45	36/158	Monier 2017 [132]	362/720	1028/2199
Brumbaugh 2018 [25]	10/13	115/138	Morrow 2017 [133]	66/158	176/429
Brumbaugh 2020 [26]	92/131	1010/2179	Nascimento 2020 [137]	2/8	19/32
Candel 2016 [30]	17/72	0/57	Natarajan 2012 [138]	71/151	80/1008
Chen 2016 [37]	OR 2.15 (95% CI 1.75-2.64)		Nobile 2017 [141]	31/98	83/417
Claas 2011 [42]	9/21	48/80	O'Shea 2012 [143]	43/127	289/624
De Jesus 2013 [46]	145/385	928/2586	Patel 2017 [148]	18/55	59/199
Duan 2016b [51]	5/11	56/136	Qi 2013 [149]	3/7	22/53
Durrmeyer 2012 [53]	12/23	42/328	Qiu 2012 [150]	322/1249	2201/10660
El Ayoubi 2016 [54]	110/446	511/4139	Rakza 2007 [152]	4/14	6/30
Eriksson 2015 [56]	185/482	476/1757	Ranke 2007 [153]	20/51	18/46
Estevez 2017 [57]	4/34	1/76	Regev 2003 [157]	OR 3.42 (95% CI 2.28-5.12)	
Fernandez-Rodriguez, 2021 [60]	3/23	5/71	Reiss 2003 [158]	40/183	145/1182
Fujioka 2014 [61]	31/43	24/54	Rijken 2007 [159]	5/23	30/135
Gagliardi 2009 [62]	33/100	159/1109	Rocha 2010 [161]	9/53	36/152
Garofoli 2014 [66]	3/35	4/41	Rojas 2012 [160]	3/12	61/200
Giapros 2012 [68]	20/35	39/133	Ruiz-P 2014 [163]	OR 2.88 (95% CI 1.20-6.91)	
Gortner 1999 [69]	9/59	11/258	Sasi 2015 [164]	69/153	54/306
Grisaru-G 2012 [73]	106/408	865/7505	Serenius 2004 [169]	OR 1.97 (95% CI 0.81-4.79)	
Guimaraes 2010 [74]	7/47	40/209	Sharma 2004 [170]	OR 2.20 (95% CI 1.20-4.03)	
Hartung 2005 [79]	9/44	0/44	Shima 2013 [172]	15/48	38/258
Hikino 2012 [83]	0/5	13/21	Soliman 2017 [175]	13/24	66/295
Huusko 2015 [84] (Canada)	11/14	47/112	Somaschini 2012 [176]	8/46	68/318
Huusko 2015 [84] (Finland)	56/156	103/493	Soudee 2014 [177]	16/35	40/194
Jakuskiene 2011 [87]	OR 4.10 (95% CI 1.19-14.15)		Streubel 2008 [180]	5/19	33/114
Jensen 2019 [88]	288/631	1494/5633	Tammela 1992 [182]	2/17	21/29
Kalra 2014 [91]	5/7	28/53	Torchin 2016 [186]	90/481	169/1630
Karagianni 2011 [94]	13/52	48/167	Tsai 2015 [188]	230/451	306/992
Karagianni 2013 [95]	6/9	22/52	Uberos 2020 [190]	25/79	134/310
Khan 2020 [97]	3/4	41/64	Vrlenich 1995 [194]	20/125	75/281
Klinger 2013 [103]	384/2515	1279/9624	Wadhawan 2007 [195]	517/1248	3452/8213
Korhonen 2004 [105]	6/20	28/48	Wang 2013 [198]	72/122	783/1527
Lal 2003 [109]	74/348	274/2195	Wang L.Y. 2010 [199]	10/25	41/47
Lardon-Fdz 2017 [111]	18/40	47/89	Wemhoner 2011 [201]	3/8	23/87
Lehtinen 2017 [112]	12/25	9/28	Westby W 2009 [202]	15/31	130/334

Leroy 2018 [113]	7/9	25/53	Xu 2016 [208]	2/4	30/38
Lin 2005 [115]	28/62	84/162	Xydis 2013 [209]	14/33	106/172
Lodha 2014 [116]	78/183	500/847	Yu 2011 [214]	13/49	142/366
Lofqvist 2012 [117]	16/26	42/82			

Supplementary table 8. Raw count data of the meta-analysis on the association between HDP and severe BPD.

Study Name	Severe BPD yes/total		Study Name	Severe BPD yes/total	
	HDP-yes	HDP-no		HDP-yes	HDP-no
EXPRESS 2010 [58]	OR 2.00 (95% CI 1.00-4.00)		Newman 2011[140]	8/35	40/111
Guo 2015 [75]	4/10	44/65	Ozkan 2012 [145]	14/117	16/215
Kim 2014 [99]	3/5	34/51	Park 2012 [147]	5/31	33/160
Lardon-F 2017 [111]	4/47	5/82	Somaschini 2017 [176]	4/62	32/304

Supplementary table 9. Raw count data of the meta-analysis on the association between SGA/IUGR and severe BPD.

Study Name	Severe BPD yes/total		Study Name	Severe BPD yes/total	
	SGA/IUGR yes	SGA/IUGR no		SGA/IUGR yes	SGA/IUGR no
Bose 2011 [20]	11/52	75/880	Lardon-F 2017 [111]	4/40	5/89
Brumbaugh 2018 [25]	8/13	75/138	May 2009 [126]	5/14	9/71
Brumbaugh 2020 [26]	16/131	103/2179	Monier 2017 [132]	72/720	131/2199
EXPRESS 2010 [58]	OR 1.90 (95% CI 1.10-3.28)		Morsing [134]	21/30	10/32
Guo 2015 [75]	5/11	43/67	Newman 2011[140]	5/16	43/140
Hadchouel 2020 [77]	3/3	8/16	Somaschini 2017 [176]	4/46	32/320
Imamura 2017 [85]	16/32	51/137	Wang 2010 [199]	3/15	17/41
Kim 2014 [99]	6/7	31/49	Xu 2016 [208]	2/4	13/38
Kim 2020 [102]	5/21	16/98			

Supplementary table 10. Raw count data of the meta-analysis on the association between HDP and BPD36 or death.

Study Name	BPD36 or death yes/total		Study Name	BPD36 or death yes/total	
	HDP-yes	HDP-no		HDP-yes	HDP-no
Balena 2017 [15]	25/66	16/47	Oh 2005 [144]	166/354	631/1028
Lapcharoensap 2015 [110]	1172/2864	5909/12188	Starr 2020 [179]	28/63	218/483
Li 2013 [114]	7/21	51/139	Van Mastrigt 2018 [191]	11/25	33/86
Madoglio 2016 [120]	13/32	20/40	Wilmink 2019[203]	21/99	32/174

Supplementary table 11. Raw count data of the meta-analysis on the association between SGA/IUGR and BPD36 or death.

Study Name	BPD36 or death-yes/total		Study Name	BPD36 or death-yes/total	
	SGA/IUGR yes	SGA/IUGR no		SGA/IUGR yes	SGA/IUGR no
Botet 2012 [22]	37/149	79/266	Rakza 2007 [152]	7/17	7/31
Durrmeyer 2012 [53]	13/24	86/372	Regev 2003 [156]	235/406	1019/2538
Jensen 2019 [88]	400/743	1826/5695	Sasi 2015 [164]	70/153	66/306
Kandasamy 2015 [93]	16/35	19/117	Schena 2015 [165]	28/69	77/173
Lapcharoensap 2015 [110]	483/919	6598/14133	Soudee 2014 [177]	32/51	77/242
Li 2013 [114]	9/21	49/139	Starr 2020 [179]	20/45	226/501
Lal 2003 [109]	147/401	512/2433	Tsai 2015 [188]	349/560	434/1120
Nobile 2017 [141]	60/98	134/418	Wadhawan 2007 [195]	743/1248	4496/8213
Qiu 2012 [150]	471/1249	3068/10660	Westby 2009 [202]	25/31	195/334

Supplementary table 12. Raw count data of the meta-analysis on the association between HDP and BPD-associated pulmonary hypertension.

Study Name	BPD-associated PH yes/total		Study Name	BPD-associated PH no/total	
	HDP-yes	HDP-no		HDP-yes	HDP-no
Blanca 2018 [18]	2/10	5/56	MacKenzie 2019 [119]	2/21	22/63
Bruno 2015 [27]	6/67	31/236	Mourani 2015 [135]	12/74	27/193
Carton 2016 [31]	4/19	18/65	Naeem 2020 [136]	3/17	3/9
Check 2013 [35]	11/32	28/106	Ra 2013 [151]	7/19	11/66
Choi 2019 [39]	3/5	14/35	Seo 2020 [168]	6/13	18/68
Dasgupta 2018 [45]	3/20	5/16	Sheth 2020 [171]	15/49	44/171
Kanaan 2018 [92]	19/106	144/1234	Vayalthrikkovil 2019 [192]	4/18	19/103
Kim 2014 [99]	2/3	13/34	Wang 2018 [197]	6/13	31/141
Kunjunju 2017 [107]	10/17	12/39	Weismann 2017 [200]	12/36	32/124
Lagata 2018 [108]	123/437	247/1240	Yallapragada 2016 [210]	2/2	5/12

Supplementary table 13. Raw count data of the meta-analysis on the association between SGA/IUGR and BPD-associated pulmonary hypertension.

Study Name	BPD-associated PH yes/total		Study Name	BPD-associated PH no/total	
	SGA/IUGR yes	SGA/IUGR no		SGA/IUGR yes	SGA/IUGR no
An 2010 [10]	6/17	23/99	Khemani 2007 [98]	8/11	10/31
Aswani 2016 [11]	9/39	10/191	Kim 2014 [99]	3/6	12/31
Bhat 2012 [17]	12/26	24/119	Lagata 2018 [108]	141/403	229/1274
Bruno 2015 [27]	10/49	27/254	Mourani 2015 [135]	9/47	30/230
Carton 2016 [31]	2/11	20/73	Seo 2020 [168]	4/13	20/68
Check 2013 [35]	15/23	24/115	Sheth 2020 [171]	16/28	43/192
Chen 2020 [36]	12/21	49/169	Vayalthrikkovil 2019 [192]	5/14	19/97
Choi 2015 [39]	15/52	35/122	Wang 2018 [197]	6/9	31/145
De Vries 2017 [49]	6/100	12/477	Weismann 2017 [200]	9/30	35/129
Kanaan 2018 [92]	55/302	108/1038	Yallapragada 2016 [210]	4/5	3/9

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