Supplemental Online Content

Villamor E, van Westering-Kroon E, Gonzalez-Luis GE, Bartoš F, Abman SH, Huizing MJ. Patent ductus arteriosus and bronchopulmonary dysplasia—associated pulmonary hypertension: a bayesian meta-analysis. *JAMA Netw Open.* 2023;6(11):e2345299. doi:10.1001/jamanetworkopen.2023.45299

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Supplemental Methods

1.1. Search strategy

Pubmed

 $(pulmonary\ hypertension\ [MESH]\ OR\ pulmonary\ hypertension\ [tiab])$

AND

(bronchopulmonary dysplasia [MESH] OR bronchopulmonary dysplasia [tiab] OR BPD [tiab] OR chronic lung disease [tiab] OR CLD [tiab] OR ductus arteriosus [MESH] OR ductus arteriosus [tiab] OR PDA [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 Infants [tiab] OR preterm infant [MESH] OR Premature Infant [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 very low birth weight infants [MESH] OR Extremely Low Birth Weight Infants)

EMBASE

('chronic lung disease'/exp OR 'chronic lung disease') AND ('pulmonary hypertension'/exp OR 'pulmonary hypertension') AND ('ductus arteriosus'/exp OR 'ductus arteriosus') AND (premature infant or Neonatal Prematurity or Infants, Premature or Prematurity or Neonatal or Preterm Infants)

Web of Science

((bronchopulmonary dysplasia OR BPD OR chronic lung disease) AND ("pulmonary hypertension") AND ("ductus arteriosus" OR PDA))

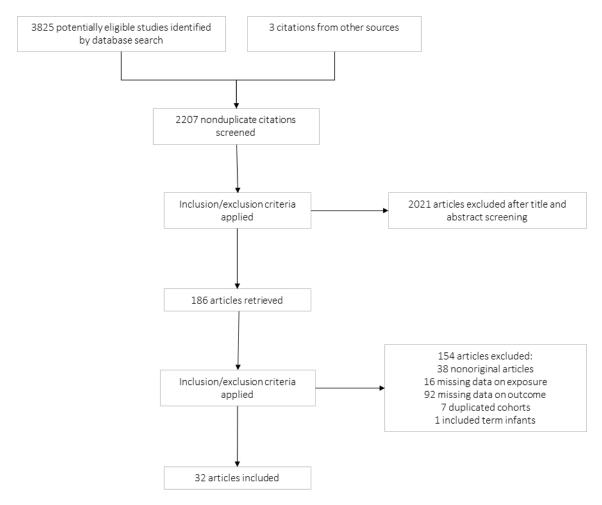
No language limits were set. Narrative reviews, systematic reviews, case reports, letters, editorials, and commentaries were excluded, but read to identify potential additional studies. Additional strategies to identify studies included manual review of reference lists from key articles that fulfilled 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 Robust Bayesian meta-analysis (RoBMA)

We used RoBMA to assess the robustness of the results to the potential presence of publication bias.^{2,3} RoBMA extends the Bayesian model-averaged meta-analysis by the two major publication bias adjustment techniques: selection models (adjusting for the publication bias operating on p-values)⁴ and precision-effect test and precision-effect estimate with standard errors (PET-PEESE, adjusting for the relationship between effect sizes and standard errors).⁵ The resulting RoBMA ensemble contains 36 models composed of the following assumptions about the presence vs. absence of the effect (2) x presence vs. absence of between-study heterogeneity (2) x presence vs. absence of publication bias adjustment models (6 selection models, PET, PEESE, and no bias). We used RoBMA with the same prior distributions for the effect and heterogeneity as in BMA and the default prior distributions for the publication bias adjustment part.

eAppendix 2. Supplemental Results

2.1. Supplementary Figures



eFigure 1. Flow Diagram of the Systematic Search

A Medically treated PDA (k=6)

Study name	Expose	ed/ Total	Statistics 1	for each st	udy	Log odds ratio and 95% credible interval
	BPD-PH Yes	BPD-PH No	Log odds ratio	Lower limit	Upper limit	
DeVries et al, ¹⁷ 2017	5 / 18	284 / 559	-0.99	-2.03	0.06	-
Kawai et al, ²⁰ 2022	4/9	63 / 122	-0.29	-1.65	1.07	-+
Mourani et al, ²⁷ 2015	17/39	101/238	0.05	-0.64	0.73	+
Gentle et al, 18 2023	20/82	19 / 138	0.70	0.00	1.40	=
Ali et al,6 2013	9 / 17	20/57	0.73	-0.36	1.83	+-
Cartón-Sánchez, 13 2016	18/22	33/62	1.37	0.18	2.57	
Fixed effects			0.27	-0.09	0.62	•
Random effects			0.23	-0.33	0.79	👆
Averaged			0.25	-0.27	0.75	
						-6 -3 0 3 6
						Decreased risk Increased risk

B Any treatment of PDA (k=8)

Study name	Expose	ed/ Total	Statistics	for each st	udy
	BPD-PH Yes	BPD-PH No	Log odds ratio	Lower limit	Upper limit
Khemani et al, ²¹ 2007	10 / 18	16/24	-0.47	-1.73	0.79
Kunjunju et al,23 2017	10/22	18/34	-0.30	-1.38	0.78
Bhat et al, ¹⁰ 2012	3 / 26	17 / 119	-0.25	-1.55	1.06
Madden et al, ²⁶ 2022	7 / 22	15 / 42	-0.17	-1.27	0.92
Lodha et al, ²⁵ 2022	37 / 52	120 / 202	0.52	-0.14	1.18
Arattu et al,8 2021	12/22	61 / 160	0.67	-0.23	1.56
Choi et al, ¹⁵ 2015	48 / 50	129/144	1.03	-0.49	2.54
Cartón-Sánchez, 13 2016	18/22	33 / 62	1.37	0.18	2.57
Fixed effects			0.31	-0.03	0.66
Random effects			0.28	-0.20	0.73
Averaged			0.30	-0.11	0.69

eFigure 2. Bayesian Model Averaged Meta-Analysis on the Association Between Bronchopulmonary Dysplasia-Associated Pulmonary Hypertension and (A) Medically Treated Patent Ductus Arteriosus (PDA), and (B) Medically or Surgically Treated PDA

2.2. Supplementary Tables

eTable 1. Characteristics of the Included Studies

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First author, year	Country	Prospective?	Total infants	Centers	GA of cohort (weeks)	PDA group	NOS Selection	NOS Comparability	NOS Outcome/Exp.	NOS Total
Ali, 2013 ⁶	Denmark	No	392	1	26.7	MedPDA SurgPDA	4	2	3	9
An, 2010 ⁷	Korea	No	116	1	26.3	SurgPDA	4	1	3	8
Arattu, 20218	UK	No	182	1	25.9	TreatPDA	4	1	3	8
Aswani, 2016 ⁹	USA	No	230	1	25.9	SurgPDA	4	1	3	8
Bhat, 2012 10	USA	Yes	145	1	26	TreatPDA	4	2	3	9
Blanca, 2018 11	NL	Yes	69	1	25.6	Any PDA	3	1	3	7
Bruno, 2015 12	USA	No	303	1	26.6	Any PDA SurgPDA	4	2	3	9
Cartón, 2016 ¹³	Spain	Yes	84	1	27.0	MedPDA SurgPDA TreatPDA	4	2	3	9
Check, 2013 14	USA	No	138	1	26.1	Any PDA SurgPDA	3	1	3	7
Choi, 2015 15	Korea	No	194	1	26.5	TreatPDA	4	1	3	8
Dasgupta, 2018 ¹⁶	USA	Yes	36	1	26.6	HsPDA MedPDA	4	2	3	9
DeVries, 2017 17	USA	No	577	1	26.6	MedPDA	4	2	2	8
Gentle, 2023 18	USA	Yes	220	1	25.7	Any PDA HsPDA	4	2	3	9

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First author, year	Country	Prospective?	Total infants	Centers	GA of cohort (weeks)	PDA group	NOS Selection	NOS Comparability	NOS Outcome/Exp.	NOS Total
						MedPDA ProlPDA TimePDA				
Kanaan, 2018 ¹⁹	USA	No	1340	1	27.8	SurgPDA	4	2	3	9
Kawai, 2022 ²⁰	Japan	No	131	1	26.0	MedPDA SurgPDA	4	2	3	9
Khemani, 2007 ²¹	USA	No	42	3	26.0	TreatPDA	3	1	3	7
Kim, 2012 ²²	Korea	No	98	1	26.8	Any PDA	4	1	3	8
Kunjunju, 2017 ²³	Australia	No	56	1	26.0	TreatPDA	3	1	3	7
Lagatta, 2018 ²⁴	USA	No	1677	23	25.0	SurgPDA TimePDA	3	2	3	8
Lodha, 2022 ²⁵	USA	No	254	1	25.8	TreatPDA	3	2	3	8
Madden 2022 ²⁶	USA	No	64	1	26.2	TreatPDA	4	1	3	8
Mourani, 2015 ²⁷	USA	Yes	274	2	27.0	Any PDA MedPDA SurgPDA	4	1	3	8
Nawaytou, 2022 ²⁸	USA	Yes	256	1	26.2	SurgPDA ProlPDA TimePDA	4	1	3	8
Philip 2021 ²⁹	USA	No	100	1	24	ProlPDA	3	1	3	7
Ra, 2013 ³⁰	Korea	No	85	1	28.0	Any PDA	3	1	3	7

First author, year	Country	Prospective?	Total infants	Centers	GA of cohort (weeks)	PDA group	NOS Selection	NOS Comparability	NOS Outcome/Exp.	NOS Total
Sallmon, 2022 ³¹	Germany	Yes	34	1	24.7	SurgPDA	4	2	3	9
Sheth, 2020 32	USA	No	220	1	25.9	HsPDA SurgPDA	4	2	3	9
Slaughter, 2011 ³³	USA	No	78	3	25	SurgPDA ProlPDA	4	2	2	8
Trittmann, 2014 ³⁴	USA	Yes	140	1	28	Any PDA	4	2	3	9
Vyas-Read, 2017 ³⁵	USA	No	556	2	26.1	Any PDA HsPDA	4	2	3	9
Wang, 2022 ³⁶	China	no	268	1	28.2	SurgPDA ProlPDA	4	1	3	8
Weismann, 2017 ³⁷	USA	Yes	159	1	25.6	AnyPDA SurgPDA ProlPDA	4	2	3	9

AnyPDA: any ductal shunt detected by echocardiography; HsPDA: hemodynamically significant PDA; MedPDA: medically treated PDA; SurgPDA: surgically-ligated or catheter-occludded PDA; TreatPDA: medically treated and/or surgically ligated/catheter occluded PDA; ProlPDA: exposure to PDA beyond 4 weeks postpartum or 36 weeks postmenstrual age. TimePDA: time of exposure to PDA.

eTable 2. Criteria for Echocardiographic Assessment of Pulmonary Hypertension in the Different Studies

Study	Age at echocardiography	Criteria for echocardiographic assessment of pulmonay hypertenion
Ali, 2013 ⁶	>4 weeks	TR (>30 mmHg), flat and left-deviated IVS, RV hypertrophy or dilation, steep PA flow curve (AT/ET ratio < 0.3)
An, 2010 ⁷	>2 months	TR (≥3 m/s in the absence of PS), flat or left-deviated IVS, RV hypertrophy and dilation
Arattu, 2021 ⁸	>28 days	TR (>3 m/s) In the absence of TR: flattened or left deviated IVS, right to left shunting across a PFO, ASD, VSD or PDA, RV hypertrophy or RV dysfunction.
Aswani, 2016 ⁹	>4 weeks	TR (>3 m/s, RVSP/SBP ratio >0.5), IVS flattening.
Bhat, 2012 10	4-6 weeks	TR (>? in the absence of PS), RV hypertrophy, IVS flattening,
Blanca, 2018 11	6 months	TR (≥2.8 m/s in the absence of PS), flat or left-deviated IVS
Bruno, 2015 12	>36 weeks PMA	TR (> 25 mmHg), RV hypertrophy, IVS flattening
Cartón, 2016 13	>2 months	TR (>2,9 m/s)
Check, 2013 14	>36 weeks PMA	TR (RVSP/SBP ratio >0.33) Without TR at least two of the following: RV enlargement, RV hypertrophy, IVS flattening and/or abnormal PA Doppler (sawtooth pattern or shortened AT).
Choi, 2015 15	>2 months	TR (≥ 3 m/s in the absence of PS) or flat or left-deviated IVS and RV hypertrophy with chamber dilation
Dasgupta, 2018 16	36 weeks PMA	TR (>25 mmHg), IVS flattening and/or RV hypertrophy.
DeVries, 2017 17	>28 days	TR (>40 mmHg or RVSP/SBP ratio >0.5) Any cardiac shunt with bidirectional or right-to-left flow, or IVS flattening
Gentle, 2023 18	>28 days	TR (\geq 35 mmHg), bidirectional flow through the PFO or PDA, or IVS flattening (EI >1.0)
Kanaan, 2018 ¹⁹	>28 days	TR (>3 m/s or >36 mm Hg), elevated PI end-diastolic velocity (>1.5 m/s or >9 mm Hg), right to left shunting, RV dilation, RV hypertrophy, RV dysfunction
Kawai, 2022 ²⁰	>36 weeks PMA	TR (>?), IVS flattening, AT/ET ratio of PA flow, RV wall thickness and PH score.
Khemani, 2007 ²¹	>2 months	TR (>?), RV hypertrophy, IVS flattening or leftward deviation.
Kim, 2014 ³⁸	unknown	TR (≥ 3 m/s in the absence of PS), or flat or left-deviated IVS and RV hypertrophy and dilation

Study	Age at echocardiography	Criteria for echocardiographic assessment of pulmonay hypertenion
Kunjunju, 2017 ²³	36 weeks PMA	TR (≥ 2.8 m/s), IVS flattening or leftward deviation (EI >0.81), right-to left PDA shunting >30% of cardiac cycle, TPV/RVETc <0.31, TR/VTI ≥ 0.14.
Lagatta, 2018 ²⁴	≥34 weeks PMA	Undefined
Lodha, 2022 ²⁵	36 weeks PMA	TR (>?), IVS flattening, main PA dilation.
Madden 2022 ²⁶	36 weeks PMA	TR (RVSP/SBP ratio >0.5), right-to-left or bidirectional shunting at any level (ASD, VSD, or PDA) or IVS flattening.
Mourani, 2015 ²⁷	36 weeks PMA	TR (> 40 mmHg or RVSP/SBP ratio > 0.5), IVS flattening, or any cardiac shunt with bidirectional or right-to-left flow.
Nawaytou, 2022 ²⁸	after 36 weeks PMA	TR (>2.9 m/s), PDA systolic flow velocity (>35 mmHg), IVS flattening (EI>1.0)
Philip 2021 ²⁹	>4 weeks	Cardiac catheterization: PVRi ≥ 3WU*m²
Ra, 2013 ³⁰	>1 month	TR (≥ 3 m/s in the absence of PS), or flat or left-deviated IVS and RV hypertrophy and dilation
Sallmon, 2022 ³¹	>3 months	TR (> 2.5 m/s) in the absence of RVOT obstruction
Sheth, 2020 32	36 weeks PMA	TR (>40 mmHg or RVSP/SBP ratio >0.5); any VSD or PDA with bidirectional or right-to-left shunting. If no TR or shunt two out of following three criteria: IVS flattening, RV dilation and/or RV hypertrophy.
Slaughter, 2011 ³³	> 30 days	TR (RVSP/SBP ratio > 0.5), IVS flattening, RV hypertrophy and/or right to left shunt.
Trittmann, 2014 ³⁴	>28 days	TR (>?) in the absence of PIS, IVS flattening, RV hypertrophy
Vyas-Read, 2017 ³⁵	>30 days	TR (> 32 mmHg), IVS flattening, RV hypertrophy, RV dilation, PDA with bidirectional or right-to-left shunting
Wang, 2022 36	> 36 weeks PMA	TR (RVSP/SBP ratio > 0.5), IVS flattened or left-deviated, bidirectional or right-to-left shunt at the PFO or PDA.
Weismann, 2017 ³⁷	36-38 weeks PMA	TR (>36 mmHg) or IVS flattening.

The numbers in parentheses correspond to the thresholds used to define PH in the different studies. In the case of TR, the value of the jet velocity (m/s) or the estimated RVSP value (mmHg) based on this velocity is given.

ASD = atrial septal defect; AT = acceleration time; EI = eccentricity index; ET = ejection time; IVS = interventricular septum; LV = left ventricular; PA = pulmonary artery; PAP = pulmonary artery pressure; PDA = patent ductus arteriosus; PFO = patent foramen ovale; PH = pulmonary hypertension; PI = pulmonary insufficiency; PMA = postmenstrual age; PR = pulmonary regurgitation; PS = pulmonary stenosis; PVR = pulmonary vascular resistance; RV = right ventricular ventricular ejection time; RVOT = right ventricular outflow tract; RVSP = right ventricular systolic pressure; SBP = systemic blood pressure; TPV = time to peak velocity; TR = tricuspid valve regurgitation; VSD = ventricular septal defect; VTI = velocity time integral.

eTable 3. Data on Heterogeneity of the Bayesian Model-Averaged Meta-Analysis (BMA)

Meta-analysis	K	Heterog eneity (Tau)	Standard deviation		redible erval	BFrf	Evidence for		P-value Heterogeneity
		(1au)		Lower Limit	Upper Limit		Random effects	Fixed effect	Frequentist Analysis
Any PDA	10	0.399	0.181	0.144	0.847	2.20	weak		0.090
Hemodinamically significant PDA	3	0.631	0.427	0.183	1.666	6.03	moderate		0.012
Medically treated PDA	6	0.541	0.300	0.161	1.284	2.19	weak		0.034
Surgically ligated or catheter occluded PDA	16	0.587	0.158	0.349	0.958	>106	extreme		<0.0001
Medically treated and/or surgically ligated/catheter occluded PDA	8	0.395	0.202	0.131	0.888	0.82		weak	0.249
Prolonged PDA	6	1.373	0.594	0.550	2.826	1872.5	extreme		<0.0001
Time of exposure to PDA	3	0.241	0.178	0.070	0.723	0.54		weak	0.382

BF: Bayes factor; K: number of studies; PDA: patent ductus arteriosus.

eTable 4. Analysis of Publication Bias by Robust Bayesian Meta-Analysis (RoBMA)

Meta-analysis	K	BF ₁₀	$\mathbf{BF}_{\mathbf{rf}}$	BFbias	Evidence bias
Any PDA	10	2.05	2.16	0.58	weak/undecided against
Hemodinamically significant PDA	3	1.76	4.98	1.68	weak/undecided for
Medically treated PDA	6	0.42	1.26	1.47	weak/undecided for
Surgically ligated or catheter occluded PDA	16	23.6	>106	0.46	weak/undecided against
Medically treated and/or surgically ligated/catheter occluded PDA	8	0.69	0.71	0.61	weak/undecided against
Prolonged PDA	6	2.80	794.4	2.29	weak/undecided for
Time of exposure to PDA	3	27.2	0.54	1.37	weak/undecided for

BF: Bayes factor; K: number of studies; PDA: patent ductus arteriosus.

eTable 5. Adjusted Effect Sizes

Study	PDA group	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjustment covariates
Sheth, 2020 32	HsPDA	1.18 (0.65-2.14)	0.92 (0.79-1.72)	BW, sex
	SurgPDA	2.20 (1.09-4.46)	1.90 (0.91-3.95)	
Gentle, 2023 18	Any PDA	2.94 (1.62-5.35)	4.29 (1.89-9.77)	BW, GA, white race, sex, invasive respiratory support at postnatal day 28, FiO ₂ at postnatal
	HsPDA	4.01 (2.08-7.73)	4.15 (1.78-9.64)	day 28

AnyPDA: any ductal shunt detected by echocardiography; BW: birth weight; CI: confidence interval; GA: gestational age; HsPDA: hemodynamically significant PDA; OR: odds ratio; PDA: patent ductus arteriosus; SurgPDA: surgically-ligated or catheter-occludded PDA.

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