

Supplementary Material

Male Disadvantage in Oxidative Stress-Associated Complications of Prematurity: A Systematic Review, Meta-analysis and Meta-regression

Elke van Westering-Kroon, Maurice J Huizing, Eduardo Villamor-Martínez and Eduardo Villamor

Supplementary Table 1. Search strategy

Pubmed

(Sex[MESH] OR Sex Characteristics[MESH] OR Sex Distribution[MESH] OR "Sex Characteristic*" [tiab] OR "Gender Difference*" [tiab] OR "Sex Dimorphism*" [tiab] OR "Gender Characteristic*" [tiab] OR "Sex Difference*" [tiab] OR "Sex Distribution*" [tiab] OR "Gender Distribution*" [tiab] OR "Male Disadvantage" [tiab] OR "Female Advantage" [tiab])
AND
(
(Premature Infant[MESH] OR Extremely Premature Infant[MESH] OR Premature Birth[MESH] OR Low Birth Weight Infant[MESH] OR Very Low Birth Weight Infant[MESH] OR "Premature Infant*" [tiab] OR "Preterm Infant*" [tiab] OR "Preterm Infant" [tiab] OR "Premature Infants" [tiab] OR "Neonatal Prematurity" [tiab] OR "Low-Birth-Weight Infant*" [tiab] OR "Infants, Low-Birth-Weight" [tiab] OR "Low Birth Weight Infant" [tiab] OR "Low-Birth-Weight Infants" [tiab] OR "Low Birth Weight*" [tiab])
OR
(Retinopathy of Prematurity[mesh] OR Prematurity Retinopathies[tiab] OR Prematurity Retinopathy[tiab] OR Retrolental Fibroplasia[tiab] OR Retrolental Fibroplasia* [tiab])
OR
(Necrotizing enterocolitis[mesh] OR Necrotizing enterocolitis[tiab])
OR
(Periventricular Leukomalacia [mesh] OR Leukomalacia* [tiab] OR Periventricular Encephalomalacia* [tiab] OR Periventricular Leukomalacia* [tiab] OR Neonatal Cerebral Leukomalacia* [tiab] OR Cystic Periventricular Leukomalacia* [tiab])
OR
(Bronchopulmonary Dysplasia [mesh] OR Bronchopulmonary Dysplasia[tiab] OR "Chronic Lung Disease" [tiab])
OR
(Cerebral Intraventricular Hemorrhage [mesh] OR Intraventricular Hemorrhage[tiab] OR Intraventricular Haemorrhage[tiab] OR Intracranial Hemorrhage[tiab] OR Intracranial Haemorrhage[tiab])
)

Embase

(
(exp Sex Characteristics/ OR exp Sex Distribution / OR exp Sex Factors/)
OR ("male disadvantage" or "female advantage" or gender or sex or "gender difference" or "gender differences" or "sex difference" or "sex differences" or "gender differential" or "gender differentials" or "sex differential" or "sex differentials" or "sexual dimorphism" or "sexually dimorphic")
)
AND
(
(exp Premature infant/ OR exp Premature Birth OR exp Low Birth Weight Infant/ OR Extremely Low Birth Weight Infant/)
OR
(bronchopulmonary dysplasia/ OR enterocolitis, necrotizing/ OR Cerebral Intraventricular Hemorrhage/ OR "Intraventricular Hemorrhage" OR Leukomalacia, Periventricular/ OR "Retinopathy of Prematurity"/)
)

Supplementary Table 2. Characteristics of the included studies

First author	Year	Country	Total n	Male to female ratio	Gestational age (weeks)	Median year cohort	Prospective?	Singleton/Twins	Obstetric and perinatal variables	Postnatal variables and outcomes	NOS Selection	NOS Comparability	NOS Outcome	NOS Total
Bertino ¹	2009	Italy	262	0,87	30.4	1997	No	Both	BW, GA, SGA (P10)	BPD36, LOS, PDA	4	2	3	9
Binet ²	2012	Canada	2744	1,17	25.7	2003	No	Both	ACS, Outborn	BPD36, IVH 3-4, Mortality, NEC>1, sROP	4	1	3	8
Boghossian ³	2018	USA	205731	1,12	26.0	2011	No	Both	BW, ACS, Chorio, HDP, Intubation birth, Prenatal care	BPD36, EOS, IVH 3-4, LOS, Mortality, NEC>1/LIP, PDA, Pneumothorax, Postnatal steroids, RDS, Surfact	4	1	3	8
Chen ⁴	2018	China	370	1,96	33.1	2011	No	Both	Abruption, ACS, BW, C-section, Fetal distress, GA, HDP, Mat diabetes, PremROM	Mortality, Mec Ventil, RDS, Surfact	4	2	3	9
Derzbach ⁵	2005	Hungary	140	0,94	29.0	2003	No	Both	BW, GA	IVH 1-4, Hypotension, NEC, PDA, RDS, UOS	3	2	3	8
Deulofeut ⁶	2007	USA	497	0,94	27.0	2001	No	Both	ACS, BW, C-section, GA, Prenatal care, SGA(P10)	IVH 1-4, BPD36, IVH 3-4, Mortality, PVL, ROP (all), sROP	4	2	3	9
Elsmen ⁷	2004	Sweden	236	1,23	26.4	1997	No	Both	ACS, BW, C-section,GA, HDP, Intubation birth, SGA(P10), Spont pregnancy	BPD36, Hypotension, PDA, Surfact	4	1	3	8
Gagliardi ⁸	2021	Network	20924	1,13	26.9	2011	No	Twins	BW, ACS, C-section, GA, Outborn, SGA (P10)	BPD36, IVH 3-4/PVL, sROP	3	2	3	8
Garfinkle ⁹	2018	Canada	59523	0,94	26.0	2012	No	Both	Apgar5<7, C-section, GA, HDP, Mat age, Mat diabetes, Outborn, SGA(P10)	BPD36, IVH 3-4/PVL, LOS, Mortality, NEC>1, sROP	4	2	3	9
Griesmaier ¹⁰	2014	Austria	156	1,20	30.5	2010	No	Both	ACS, BW, GA, SGA(P10)	BPD28, EOS, LOS, NEC, PDA, PremROM,	4	1	3	8
Harris ¹¹	2019	UK	319	1,03	26.9	1999	No	Both	ACS, BW, GA, Mat age, Smoking	BPD28, BPD36, NEC (all), PDA, Pneumothorax, Postnatal steroids, Pulm Hem	3	1	3	7
Hintz ¹²	2006	USA	2553	0,91	25.4	1999	Yes	Both	ACS, BW, Apgar5<5, C-section, GA, Intubation birth, Mat age, Outborn, ProlROM, Resuscit, SGA(P10)	BPD36, EOS, IVH3-4, LOS, NEC>1, PDA, Postnatal steroids, PVL, sROP, Surfact	4	2	3	9
Huang ¹³	2012	Taiwan	195	1,50	28.4	2002	No	Both		PVL, sROP	4	1	3	8
Ito ¹⁴	2017	Japan	38023	1,04	28.0	2008	No	Both	ACS, BW, Chorio, Gest diabetes, HDP, Mat age, PremROM	BPD28, BPD36, LIP, IVH 1-4, Mortality, NEC, PDA, PVL, RDS, sROP	4	1	3	8
Jennische ¹⁵	2003	Sweden	64	1,29	28.9	1988	No	Both	BW, GA, SGA(P10), Resuscit	BPD28, PDA, Pneumothorax, RDS, UOS	4	2	3	9
Jones ¹⁶	2007	Canada	3117	1,27	27.4	1997	Yes	Both	ACS, ,Outborn, SGA(P10)	BPD36, EOS, IVH 3-4, LOS, M vent, Mortality, NEC>1, PDA, sROP	4	2	3	9
Kent ¹⁷	2012	Australia	2549	1,21	26.3	2001	No	Both	ACS, Apgar5<7, C-section, Fetal Distress, HDP, Intrapartum hemo, IUGR, Outborn, ProlROM, SGA(P10)	BPD36, IVH 3-4, Mortality, NEC (all), PDA, Pneumothorax, Postnatal steroids, sROP, Surfact	4	2	3	9
Lauterbach ¹⁸	2001	USA	51	0,70	32.3	1990	No	Both	BW, C-section, GA, Gest diabetes, HDP, Mat age	BPD28, Hypotension, PDA, Pneumothorax, Postnatal steroids, UOS, Surfact	3	1	3	7
Lavoie ¹⁹	1989	Canada	22	0,83	27.0	1988	No	Both	BW, C-section, GA	BPD28, BPD36, IVH 1-4, Mec Ventil, Surfact	3	1	3	7
Mansson ²⁰	2015	Sweden	398	1,20	31.4	2006	No	Both	Mat age, SGA (-2SD)	BPD36, IVH3-4/PVL, NEC (all), sROP	4	2	3	9

First author	Year	Country	Total n	Male to female ratio	Gestational age (weeks)	Median year cohort	Prospective?	Singleton/Twins	Obstetric and perinatal variables	Postnatal variables and outcomes	NOS Selection	NOS Comparability	NOS Outcome	NOS Total
Melamed ²¹	2009	Israel	5408	0,97	35.0	2001	No	Twins	BW, C-section, GA, HDP, Mat age, BW, GA, Mat diabetes, Mother>35, SGA(P10)	IVH 1-4, NEC (all), RDS	3	2	3	8
Mohamed ²²	2010	USA	104847	1,03	VLBW	2000	No	Both	HDP, PDA,	IVH 1-4, IVH 3-4, Mortality, NEC (all), Pulm hem, PVL, RDS	4	2	3	9
Neubauer ²³	2012	Austria	408	1,18	31.0	2006	No	Both	ACS, Apgar1<3, Apgar5<3, C-section, ProlROM, Outborn, SGA(P10), Smoking	BPD36, EOS, LOS, NEC>1, PDA, sROP, Surfact	4	1	3	8
Peacock ²⁴	2012	UK	797	1,16	26.5	2000	No	Both		IVH 3-4, sROP,	3	1	3	7
Ramos Navarro ²⁵	2020	Spain	389	1,48	28.5	2015	Yes	Both	Intubation birth	BPD36, Mec vent, Mortality, Pneumothorax, Surfact	4	1	3	8
Shim ²⁶	2017	Korea	2163	1,07	27.2	2014	No	Both	ACS, BW, Chorio, C-section, GA, HDP, Mat diabetes, Outborn, SGA(P10)	BPD36, IVH 3-4, Mortality, NEC>1, PVL, sROP	4	1	3	8
Shinwell ²⁷	2007	Israel	8858	1,08	28.6	1999	No	Both	ACS, BW, Chorio, C-section, GA, Infertility therapy, Intrapartum hemo, PremROM, prenatal care, Preterm Labor	BPD36, IVH 3-4, Mortality, Pneumothorax, PVL, RDS, sROP	4	2	3	9
Skiold ²⁸	2014	Sweden	107	1,28	25.5	2006	No	Both		IVH 1-4, IVH 3-4,sROP	4	1	3	8
Spinillo ²⁹	2009	Italy	754	1,09	30.3	1997	No	Both	Abruption, ACS, BW, Chorio, C-section, Fetal distress, GA, HDP, Mat age, Placenta previa, PremROM, SGA(P10), Smoking	IVH 1-4, IVH 3-4, PVL	4	2	3	9
Stark ³⁰	2009	Australia	43	1.15	29	2007	Yes	Single	ACS, Chorio, C-section, HDP, SGA(P10)		4	1	3	8
Stark ³¹	2011	Australia	60	1,07	29	2009	Yes	Both	SGA (P10)	IVH 3-4, Mortality, PDA	4	1	3	8
Steen ³²	2013	Sweden	2419	1,18	30	2002	No	Twins	HDP,	BPD36, IVH 3-4, Pneumothorax, RDS, UOS	3	1	3	7
Stevenson ³³	2000	USA	6738	0,99	28.5	1992	No	Both	ACS, Adol mother, Ant AB, Intrapartum hemo, Apgar1<3, Apgar5<3, C-section, Intubation birth, Mother Married, Mother>35, PremROM, prenatal care, ProlROM, Resuscit	IVH 1-4, BPD28,BPD36, Mec Ventil, Meningitis, Mortality, NEC>1, PDA, PVL, RDS, UOS, IVH 3-4, Surfact, Urine Infect	4	1	3	8
Stimac ³⁴	2019	Croatia	159	1,12	30	2013	No	Both	C-section, HDP, Mat diabetes	IVH 1-4, RDS	4	0	3	7
Tioseco ³⁵	2006	USA	874	1,00	30.9	1998	No	Both		BPD36, IVH 1-4, IVH 3-4, Mortality, NEC (all), PDA, PVL, ROP (all), UOS	4	2	3	9
Tottman ³⁶	2020	New Zealand	478	1,22	28	2007	Yes	Both	ACS , Outborn, ProlROM,	BPD36, Mortality, IVH 3-4, NEC>1, UOS, sROP	4	1	3	8
Walker ³⁷	2012	Canada	262	1,15	28.6	2005	No	Single	C-section, HDP, SGA(P10), SGA(P3)		4	1	3	8
Wang ³⁸	2018	Taiwan	3507	NA	<32	2011	No	Both		BPD36, PVL, sROP	4	1	3	8
Zhao ³⁹	2017	USA	114960	1,00	<37	2000	No	Twins	Apgar5<7	Mortality, Mec Ventil, RDS	3	2	3	8
Zisk ⁴⁰	2011	USA	12807	1,10	29.4	2005	No	Both	Apgar5<3, SGA(p10)	BPD36, IVH 3-4, Mortality, NEC (all), PDA Pneumothorax, Postnatal steroids, sROP, Surfact, UOS	4	2	3	9

First author	Year	Country	Total n	Male to female ratio	Gestational age (weeks)	Median year cohort	Prospective?	Singleton/Twins	Obstetric and perinatal variables	Postnatal variables and outcomes	NOS Selection	NOS Comparability	NOS Outcome	NOS Total
Zozaya ⁴¹	2019	Spain	21768	1,10	28.6	2010	No	Both	ACS, C-section, SGA(-2SD)	BPD36, LOS, Mortality, NEC>1, PDA, ROP (all), PVL	4	1	3	8

ACS: antenatal corticosteroids; Adol: adolescent; Ant: antenatal; BPD28: BPD defined as oxygen requirement on postnatal day 28; BPD36: defined as oxygen requirement at the postmenstrual age of 36 weeks; BW: birth weight; Chorio: chorioamnionitis; EOS: early onset sepsis; Gest: gestational; HDP: hypertensive disorders of pregnancy; Hemo: hemorrhage; Infect: infection; IUGR: intrauterine growth restriction; IVH: intraventricular hemorrhage; LIP: local intestinal perforation; LOS: late onset sepsis; Mat: maternal; Mec Ventil: mechanical ventilation; NEC: necrotizing enterocolitis; NOS: Newcastle Ottawa Scale; P3: 3rd percentile; P10: 10th percentile; PDA: patent ductus arteriosus; PremROM: premature rupture of membranes; ProlROM: prolonged rupture of membranes; Pulm hem: pulmonary hemorrhage; PVL: periventricular leukomalacia; RDS: respiratory distress syndrome; Resuscit: resuscitation at birth; ROP: retinopathy of prematurity; SD: standard deviation; SGA: small for gestational age; Single: singleton; Spont: spontaneous; sROP: severe ROP; Surfact: surfactant; UOS: undefined onset sepsis.

Supplementary Table 3. Subgroup analyses based on continent

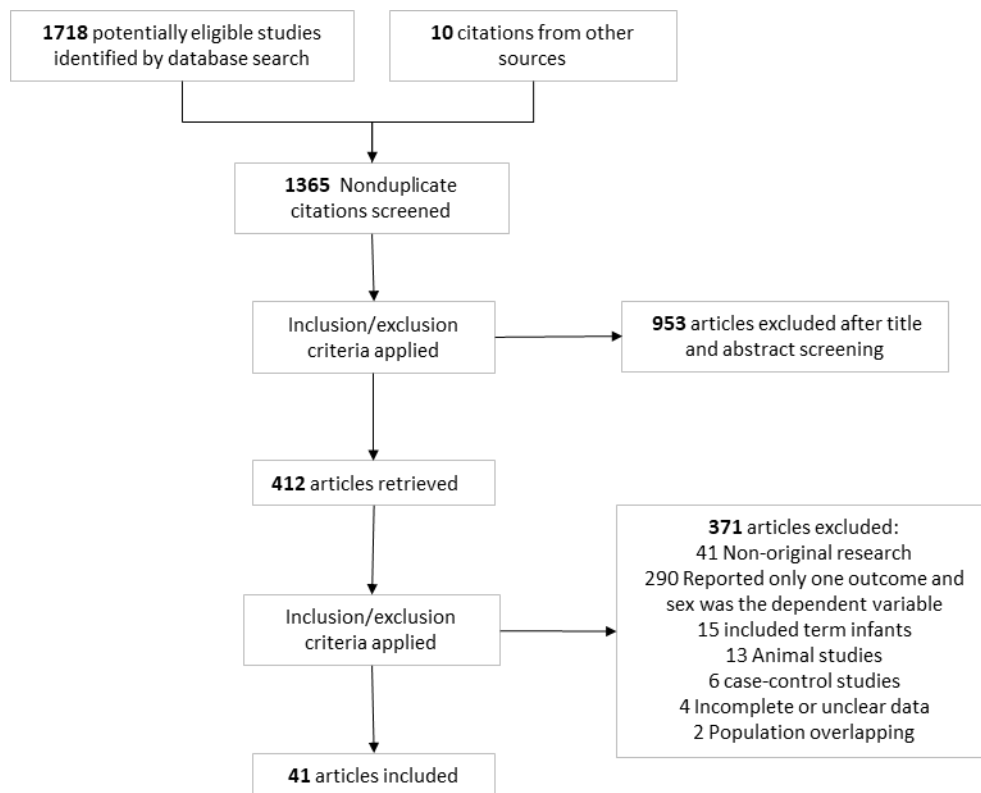
Meta-analysis	Criteria for subgrouping	K	RR	95% CI		P	Heterogeneity		Meta-regression	
				Lower limit	Upper limit		I ² (%)	P	P-value	R ² analog
BPD36	America	11	1.183	1.143	1.224	<0.001	45.7	0.048	0.145	0.0
	Asia	4	1.305	1.159	1.469	<0.001	82.7	0.001		
	Europe	8	1.346	1.203	1.506	<0.001	25.4	0.226		
	Oceania	2	1.066	0.950	1.197	0.274	0.0	0.486		
Any IVH	America	6	1.173	1.142	1.205	<0.001	0.0	0.701	0.516	0.0
	Asia	2	1.150	1.069	1.237	<0.001	6.1	0.302		
	Europe	4	1.081	0.898	1.301	0.410	0.0	0.395		
Severe IVH	America	10	1.248	1.169	1.333	<0.001	60.5	0.007	0.747	0.0
	Asia	2	1.342	1.212	1.485	<0.001	0.0	0.469		
	Europe	4	1.391	1.105	1.752	0.005	0.0	0.427		
	Oceania	3	1.105	0.621	1.965	0.735	40.9	0.184		
PVL	America	6	0.939	0.796	1.108	0.456	48.1	0.086	0.048	0.5
	Asia	5	1.208	1.032	1.414	0.018	58.4	0.047		
	Europe	2	1.303	0.980	1.731	0.068	16.8	0.273		
Severe ROP	America	8	1.121	1.038	1.212	0.004	68.4	0.002	0.827	0.0
	Asia	5	1.229	0.936	1.612	0.137	93.5	<0.001		
	Europe	5	1.096	0.908	1.324	0.338	15.2	0.318		
	Oceania	2	1.252	0.993	1.580	0.058	0.0	0.350		
Any NEC	America	4	1.127	0.994	1.279	0.062	77.1	0.004	0.256	0.17
	Asia	2	1.289	0.974	1.706	0.076	70.3	0.066		
	Europe	4	0.933	0.653	1.332	0.703	0.0	0.0		
	Oceania	1	1.003	0.768	1.312	0.980	0.0	1.000		
Mortality	America	11	1.242	1.152	1.338	<0.001	90.8	<0.001	0.947	0.0
	Asia	4	1.200	1.087	1.325	<0.001	50.9	0.106		
	Europe	2	1.228	1.152	1.308	<0.001	0.0	0.443		
	Oceania	3	1.238	1.069	1.434	0.004	0.0	0.679		

BPD36: bronchopulmonary dysplasia defined as oxygen requirement at the postmenstrual age of 36 weeks; GA: gestational age; IVH: intraventricular hemorrhage; K: number of studies; NEC: necrotizing enterocolitis; PVL: periventricular leukomalacia; ROP: retinopathy of prematurity.

Supplementary Table 4. Meta-regression analysis (continuous covariates)

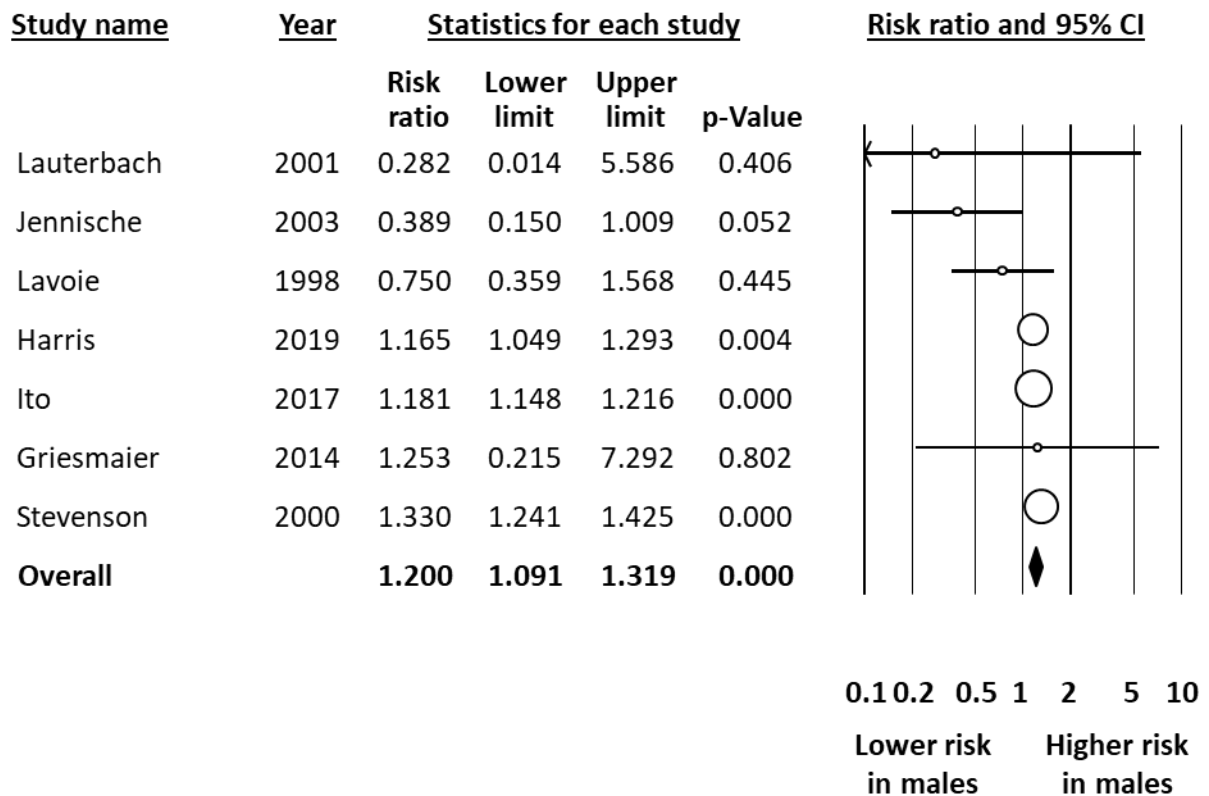
Meta-analysis	Covariate	K	Coefficient	Standard Error	P	R ² analog
BPD36	GA cohort (weeks)	25	0.025	0.013	0.065	0.05
	Median year of cohort	26	-0.005	0.003	0.076	0.01
Any IVH	GA cohort (weeks)	11	0.033	0.019	0.079	0.0
	Median year of cohort	12	-0.002	0.003	0.531	0.0
Severe IVH	GA cohort (weeks)	18	-0.014	0.024	0.567	0.0
	Median year of cohort	19	0.002	0.005	0.725	0.0
PVL	GA cohort (weeks)	11	0.038	0.063	0.546	0.0
	Median year of cohort	13	0.009	0.010	0.380	0.0
Severe ROP	GA cohort (weeks)	19	0.005	0.017	0.761	0.0
	Median year of cohort	20	0.001	0.007	0.901	0.0
Any NEC	GA cohort (weeks)	10	-0.012	0.023	0.594	0.0
	Median year of cohort	11	0.029	0.015	0.052	0.33
Mortality	GA cohort (weeks)	18	0.051	0.014	<0.001	0.75
	Median year of cohort	20	-0.009	0.004	0.019	0.37

Random effects (method of moments), univariate meta-regression. Coefficient indicates the change in the log of the RR of the association between male sex and the corresponding outcome for a unit change in the predictor covariate. R² analog: total between-study variance explained by the moderator. BPD36: bronchopulmonary dysplasia defined as oxygen requirement at the postmenstrual age of 36 weeks; GA: gestational age; IVH: intraventricular hemorrhage; K: number of studies; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity.



Supplementary Figure 1. Flow diagram of the systematic search.

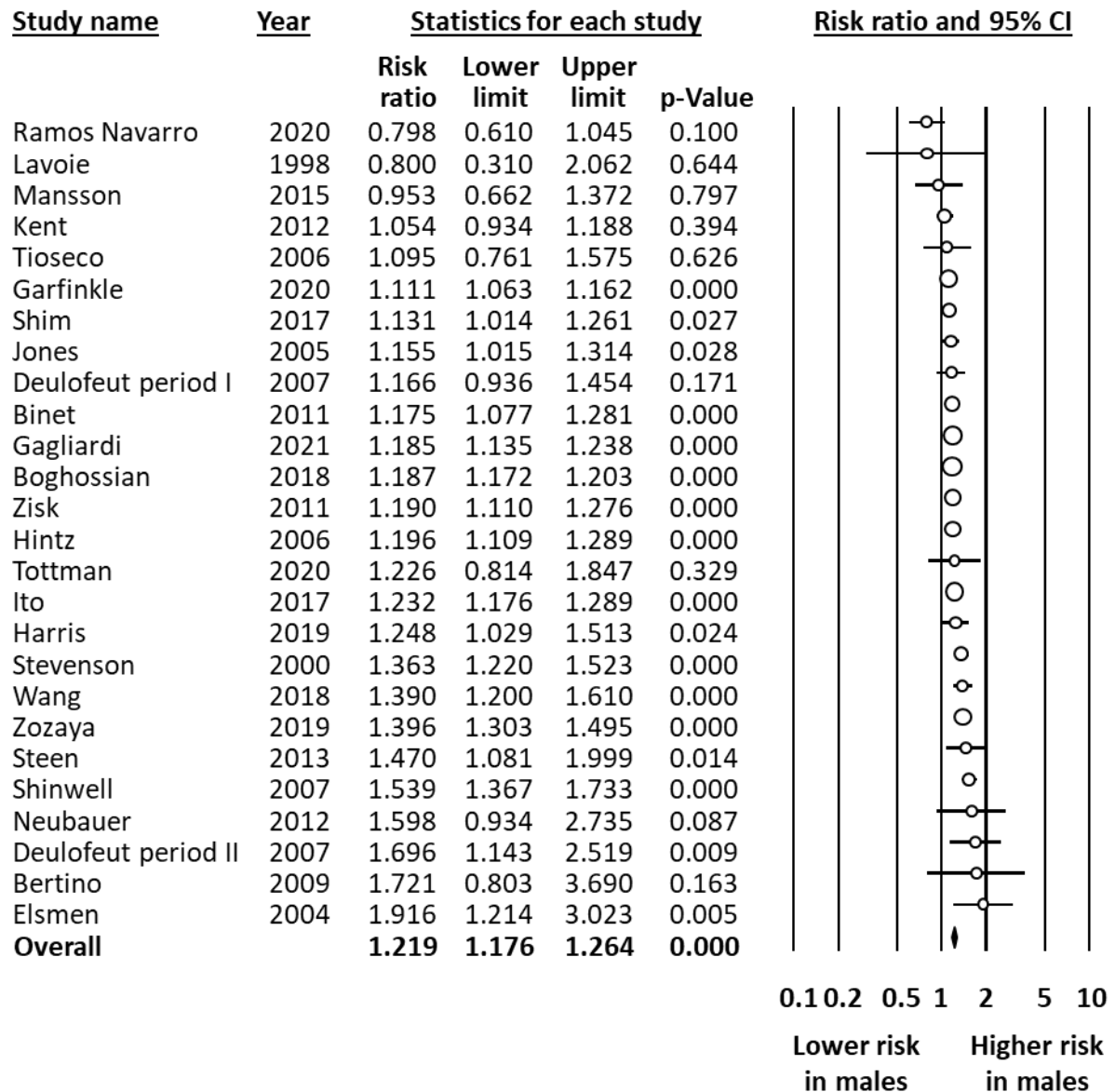
Any BPD



Supplementary Figure 2. Meta-analysis of the association between male sex of preterm infants and risk of bronchopulmonary dysplasia (BPD), defined as oxygen requirement on postnatal day 28.

CI: confidence interval.

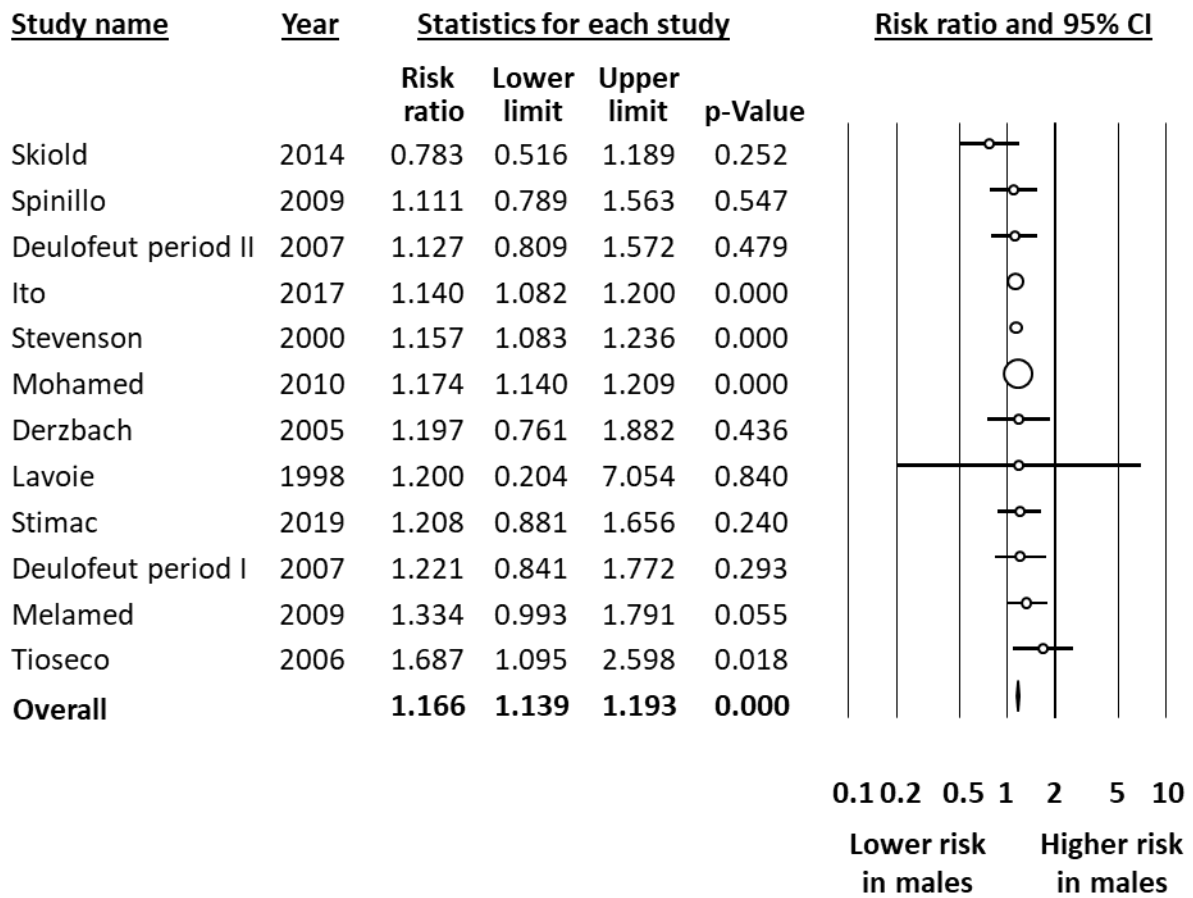
Moderate/severe BPD



Supplementary Figure 3. Meta-analysis of the association between male sex of preterm infants and risk of bronchopulmonary dysplasia (BPD), defined as oxygen requirement at the postmenstrual age of 36 weeks.

CI: confidence interval.

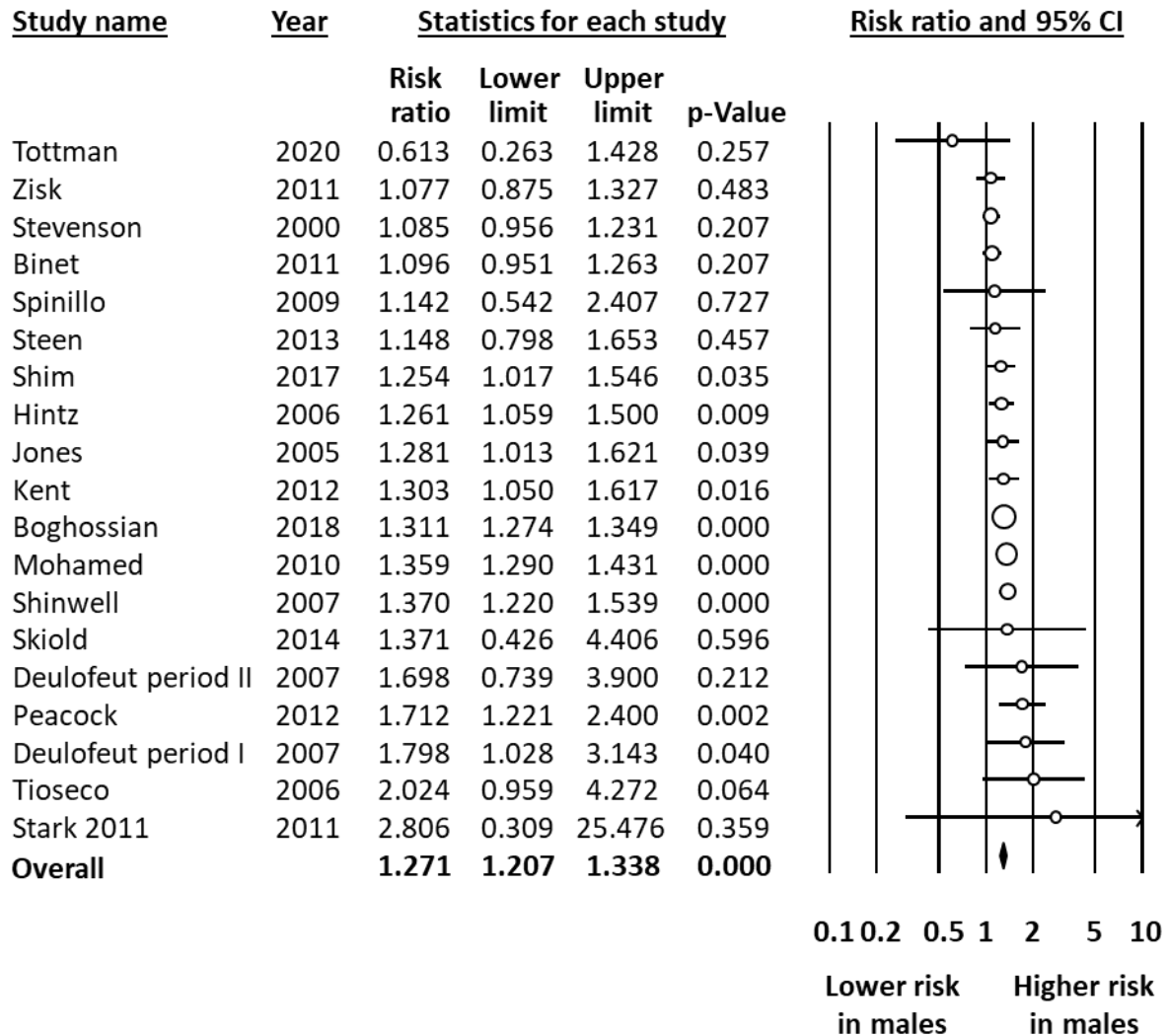
Any IVH



Supplementary Figure 4. Meta-analysis of the association between male sex and risk of intraventricular hemorrhage (IVH, grade 1-4) in preterm infants.

CI: confidence interval.

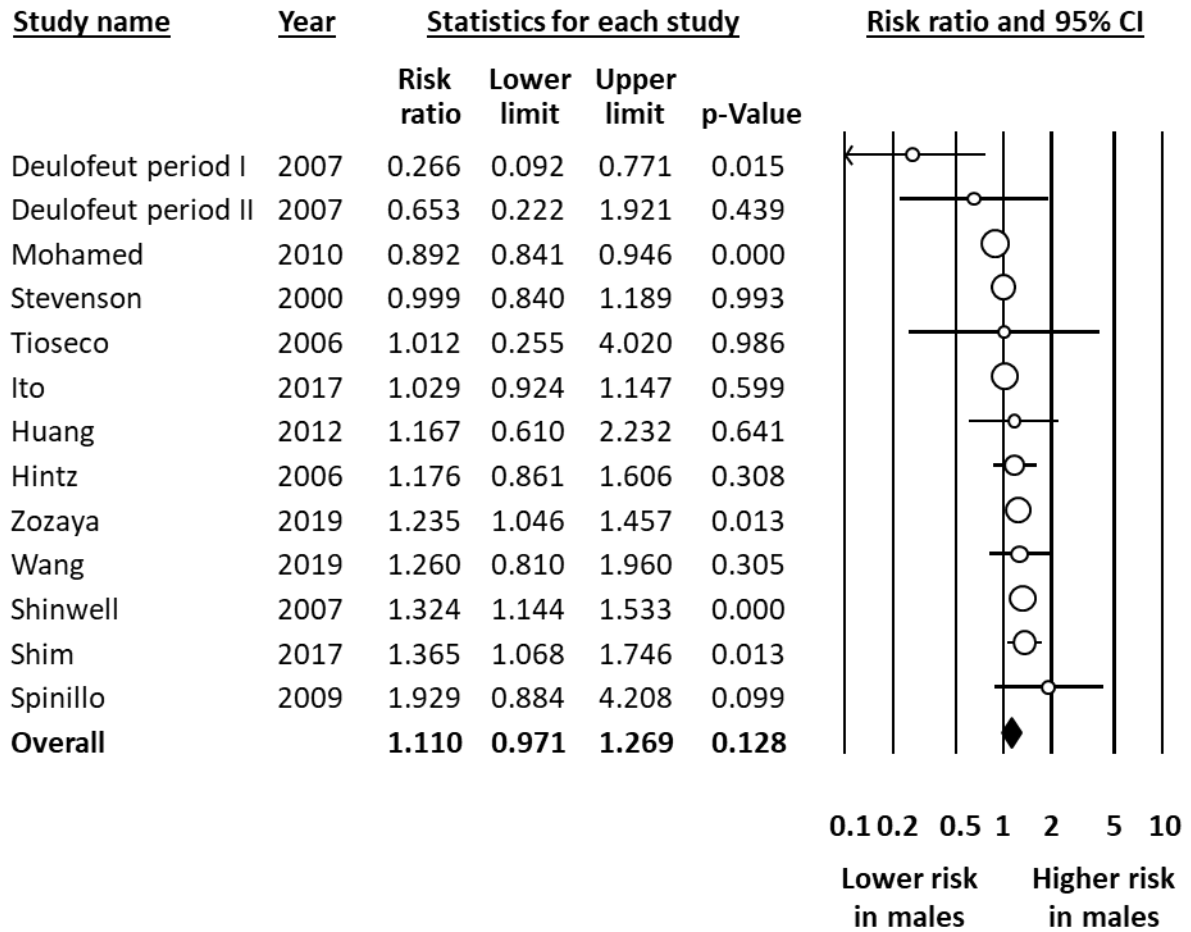
Severe IVH



Supplementary Figure 5. Meta-analysis of the association between male sex and risk of severe intraventricular hemorrhage (IVH grade 3-4) in preterm infants.

CI: confidence interval.

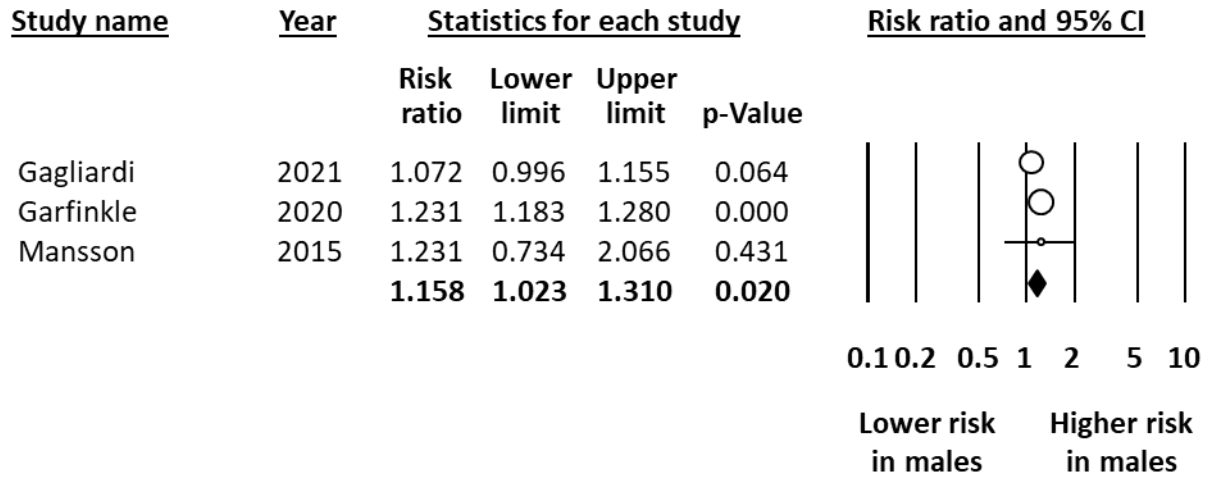
PVL



Supplementary Figure 6. Meta-analysis of the association between male sex and risk of periventricular leukomalacia (PVL) in preterm infants.

CI: confidence interval.

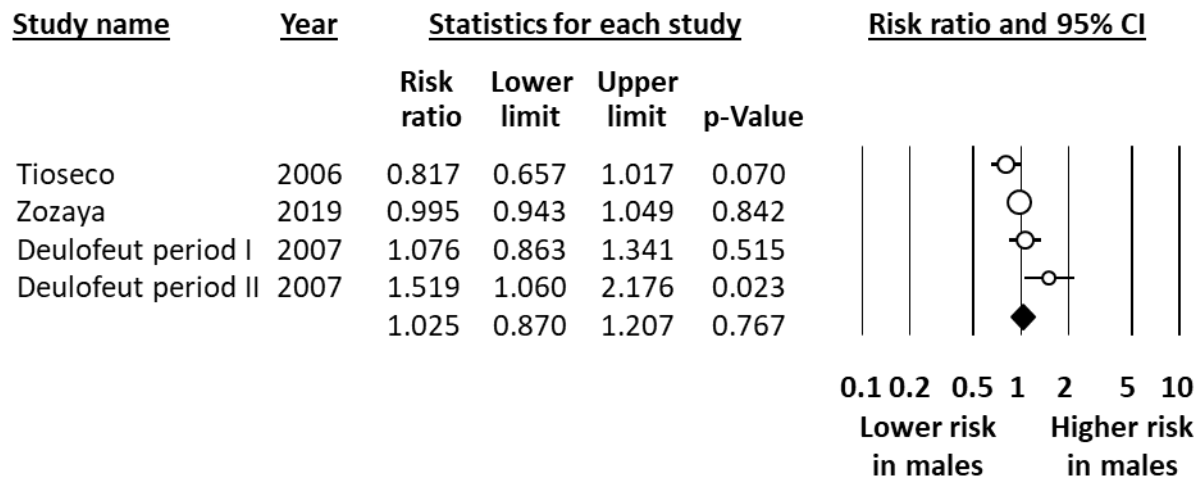
Severe IVH/PVL



Supplementary Figure 7. Meta-analysis of the association between male sex of preterm infants and risk of severe intraventricular hemorrhage (IVH grade 3-4) or periventricular leukomalacia (PVL).

CI: confidence interval.

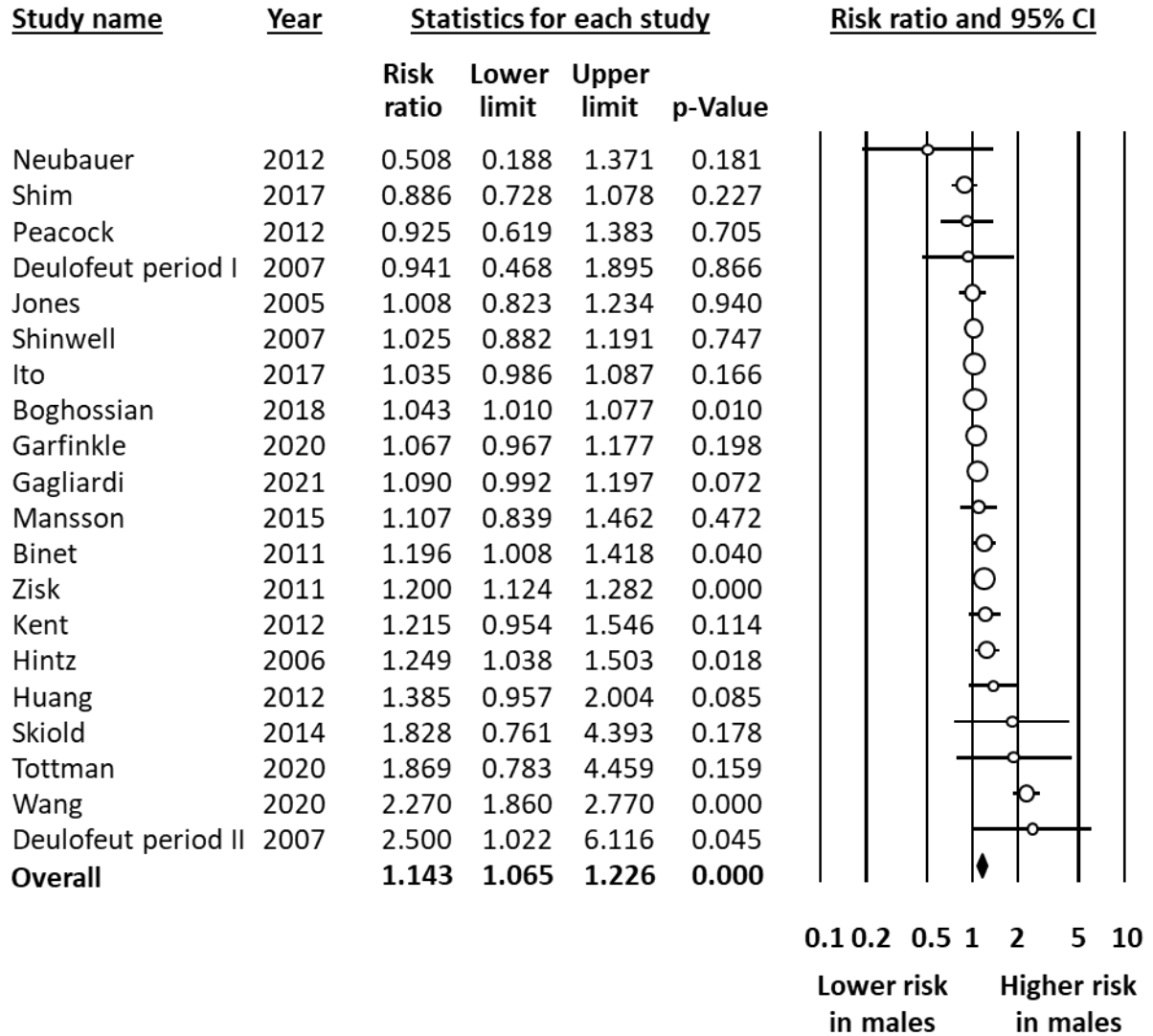
Any ROP



Supplementary Figure 8. Meta-analysis of the association between male sex of preterm infants and risk of retinopathy of prematurity (ROP, any stage).

CI: confidence interval.

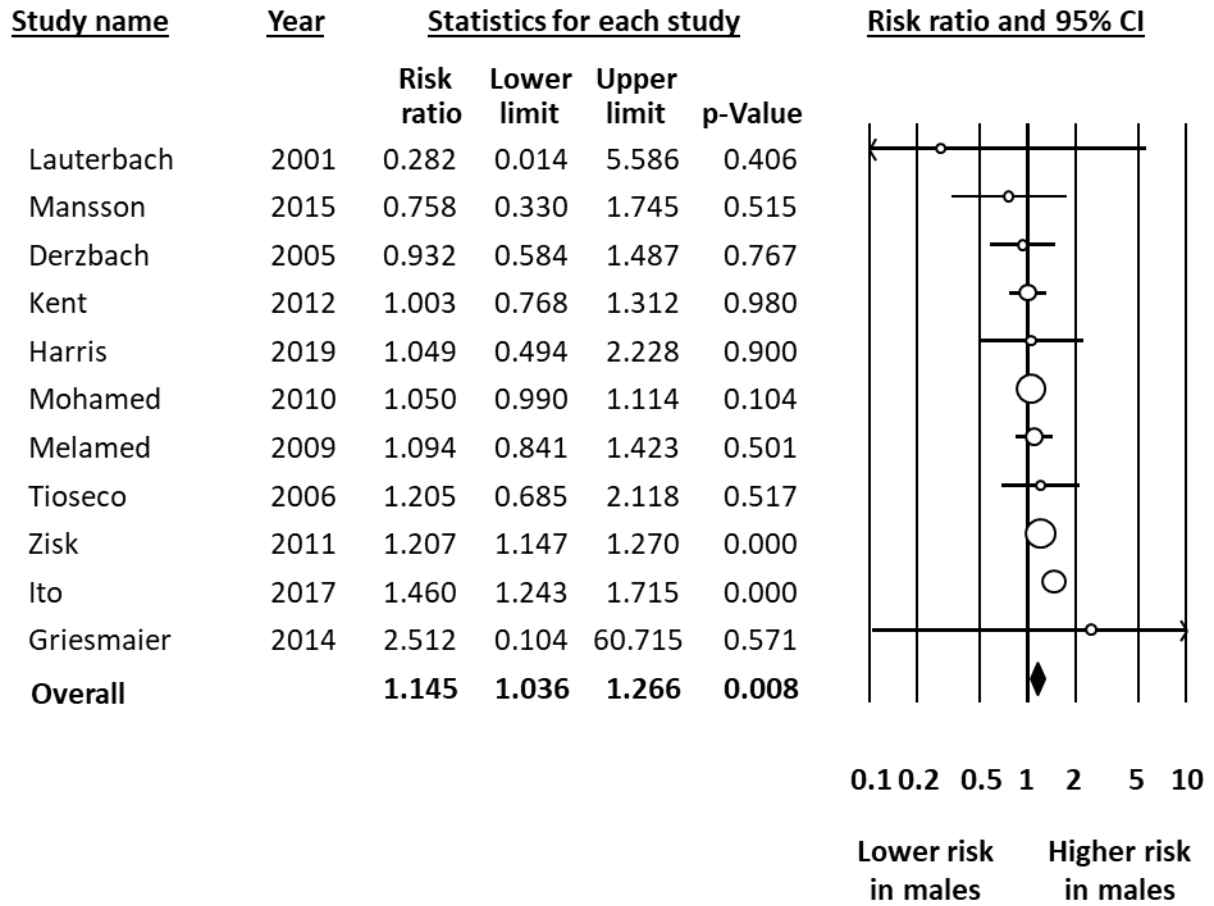
Severe ROP



Supplementary Figure 9. Meta-analysis of the association between male sex in preterm infants and risk of severe retinopathy of prematurity (ROP grade \geq 3 or requiring treatment).

CI: confidence interval.

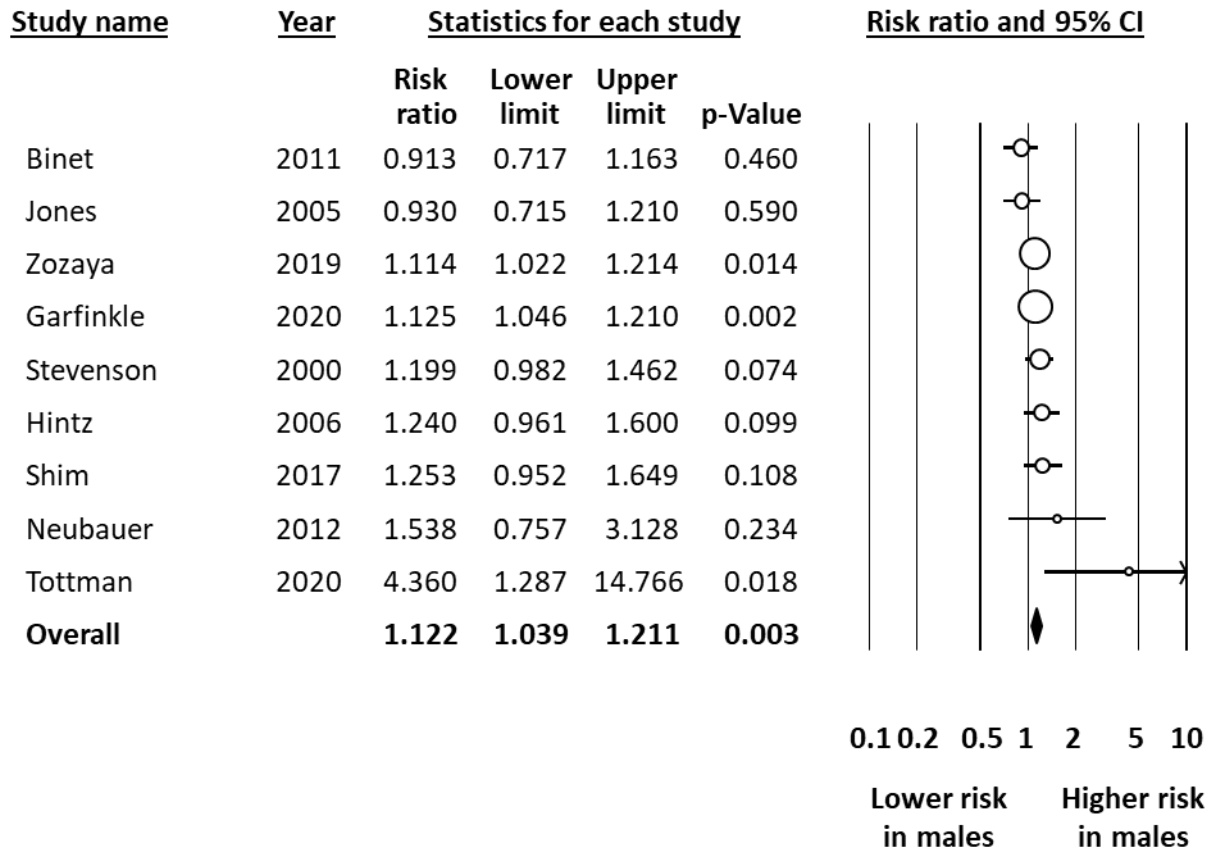
Any NEC



Supplementary Figure 10. Meta-analysis of the association between male sex and risk of necrotizing enterocolitis (NEC, any stage) in preterm infants.

CI: confidence interval.

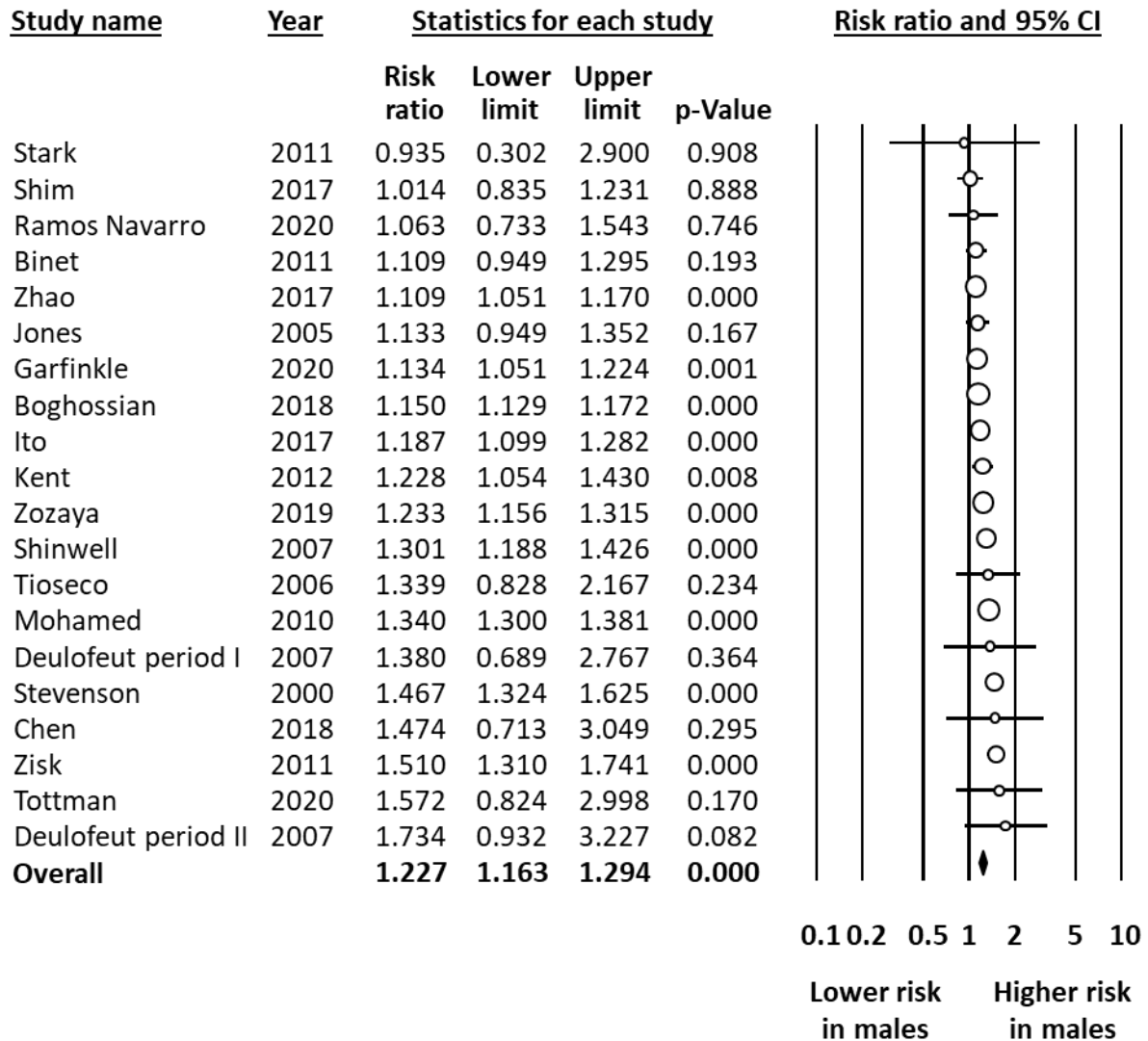
NEC stage ≥ II



Supplementary Figure 11. Meta-analysis of the association between male sex and risk of necrotizing enterocolitis (NEC, stage ≥ II) in preterm infants.

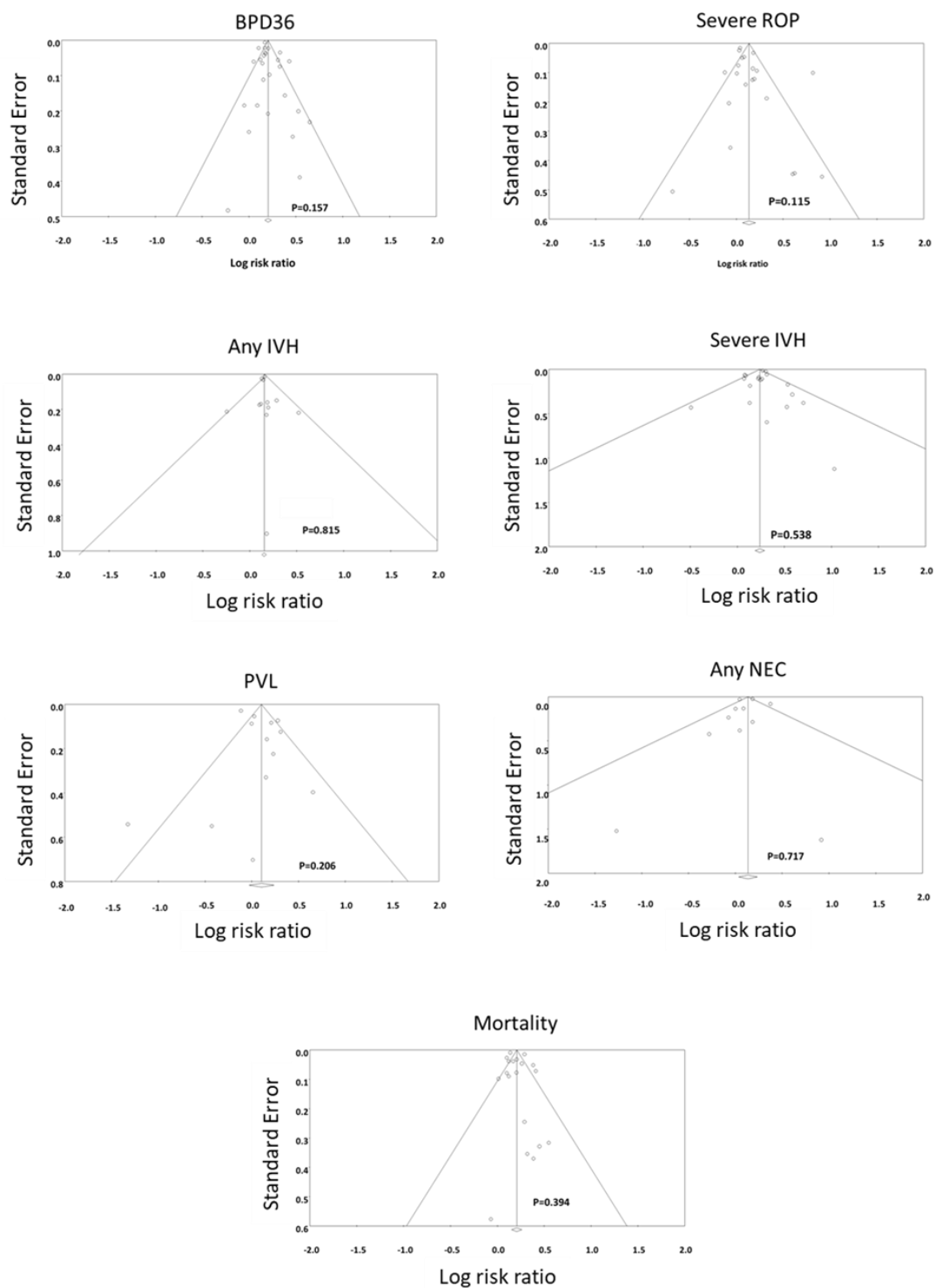
CI: confidence interval.

Mortality



Supplementary Figure 12. Meta-analysis of the association between male sex and risk of mortality before discharge in preterm infants.

CI: confidence interval.



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

BPD36: bronchopulmonary dysplasia defined as oxygen requirement at the postmenstrual age of 36 weeks; ROP: retinopathy of prematurity; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; NEC: necrotizing enterocolitis. P-value represents Egger's regression test for funnel plot asymmetry.

List of included studies

1. Bertino E, Coscia A, Boni L, et al. Weight growth velocity of very low birth weight infants: role of gender, gestational age and major morbidities. *Early human development*. 2009;85(6):339-347.
2. Binet M-E, Bujold E, Lefebvre F, Tremblay Y, Piedboeuf B, Network CN. Role of gender in morbidity and mortality of extremely premature neonates. *American journal of perinatology*. 2012;29(03):159-166.
3. Boghossian NS, Geraci M, Edwards EM, Horbar JD. Sex differences in mortality and morbidity of infants born at less than 30 weeks' gestation. *Pediatrics*. 2018;142(6).
4. Chen C, Tian T, Liu L, Zhang J, Fu H. Gender-related efficacy of pulmonary surfactant in infants with respiratory distress syndrome: A STROBE compliant study. *Medicine*. 2018;97(17).
5. Derzbach L, Treszl A, Balogh Á, Vásárhelyi B, Tulassay T. Gender dependent association between perinatal morbidity and estrogen receptor-alpha PvuII polymorphism. *Journal of perinatal medicine*. 2005;33(5):461-462.
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