

Supplemental Online Content

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eAppendix 1. Search Strategy

eAppendix 2. Interventions Considered in the Systematic Review

eAppendix 3. Screening Form

eAppendix 4. Excluded Articles and Their Citations

eTable 1. Characteristics of Studies Studying Interventions on Severe Brain Injury in Preterm Infants

eTable 2. Summary of Meta-analysis of Interventions on Cystic Periventricular Leukomalacia (cPVL) and Severe Brain Injury

eTable 3. Summary of Sensitivity and Subgroup Analysis of Interventions on Severe Intraventricular Hemorrhage (IVH) and cPVL

eFigure 1. Study Flow Diagram Outlining Stages of Search Results and Filtering Process [as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines]

eFigure 2. Forest Plot for Comparison—Betamethasone for Lung Maturity vs. Dexamethasone for Lung Maturity for Outcome Severe IVH

eFigure 3. Forest Plot for Comparison—Antenatal Steroid for Lung Maturity: Repeat Course vs. Single Course for Outcome Severe IVH

eFigure 4. Forest Plot for Comparison—Antenatal MgSO₄ Therapy for Neuroprotection or Tocolysis vs. Placebo for the Outcome Severe IVH

eFigure 5. Forest Plot for Comparison—Antibiotics for PPRM vs. Placebo for the Outcome Severe IVH

eFigure 6. Forest Plot for Umbilical Cord Milking vs. Delayed Cord Clamping in Preterm Infants for the Outcome Severe IVH

eFigure 7. Forest Plot for Comparison—Lower FiO₂ for Resuscitation vs. Higher FiO₂ at Resuscitation for the Outcome Severe IVH

eFigure 8. Forest Plot for Comparison—Sustained Inflation During Resuscitation vs. Standard Resuscitation for the Outcome Severe IVH

eFigure 9. Forest Plot for Comparison—Delayed Cord Clamping vs. Early Cord Clamping for the Outcome Severe IVH

eFigure 10. Forest Plot for Comparison—Umbilical Cord Milking vs. Early Cord Clamping for the Outcome Severe IVH

eFigure 11. Forest Plot for Comparison—Delayed Cord Clamping With Respiratory Support vs. Delayed Cord Clamping Without Respiratory Support for the Outcome Severe IVH

eFigure 12. Funnel Plot of Indomethacin Prophylaxis for Patent Ductus Arteriosus vs. Placebo for Outcome Severe IVH

eFigure 13. Egger’s Regression Test for Assessing Publication Bias for Indomethacin Prophylaxis for Patent Ductus Arteriosus

eFigure 14. Funnel Plot of Volume Guarantee vs. Pressure Limited Ventilation for Outcome Severe IVH

eFigure 15. Egger’s Regression Test for Assessing Publication Bias for Volume Guarantee Ventilation vs. Pressure Limited Ventilation for Outcome Severe IVH

eFigure 16. Forest Plot for Comparison—Early Erythropoiesis-Stimulating Agents vs. Placebo for Outcome Severe IVH

eFigure 17. Funnel Plot of Early Erythropoiesis-Stimulating Agents vs. Placebo for Outcome Severe IVH

eFigure 18. Forest Plot for Comparison—Prophylactic Ethamsylate Administration vs. Placebo for the Outcome Severe IVH

eFigure 19. Forest Plot for Comparison—Supine Head Midline vs. Supine Head Rotated for the Outcome Severe IVH

eFigure 20. Forest Plot for Comparison—LISA vs. INSURE Method for Surfactant Administration for the Outcome Severe IVH

eFigure 21. Forest Plot for Comparison—Elective High-Frequency Oscillatory Ventilation (HFOV) vs. Conventional Ventilation Method for the Outcome Severe IVH

eFigure 22. Forest Plot for Comparison—Elective High-Frequency Jet Ventilation (HFJV) vs. Conventional Ventilation Method for the Outcome Severe IVH

eFigure 23. Forest Plot for Comparison—High Oxygen Saturation Target (91-95%) vs. Low Oxygen Saturation Target (85-89%) in NICU for the Outcome Severe IVH

eFigure 24. Forest Plot for Comparison—Permissive Hypercapnia vs. Normocapnia During Ventilation for the Outcome Severe IVH

eFigure 25. Forest Plot for Comparison—Early Extubation vs. Delayed Extubation During Ventilation for the Outcome Severe IVH

eFigure 26. Forest Plot for Comparison—Caffeine Prophylaxis or Treatment for Apnea or Post-Extubation vs. Placebo for the Outcome Severe IVH

eFigure 27. Forest Plot for Comparison—High Dose Caffeine Prophylaxis for Apnea or Post-Extubation vs. Low Dose Caffeine for the Outcome Severe IVH

eFigure 28. Forest Plot for Comparison—Sedation During Ventilation: Midazolam vs. Placebo for the Outcome Severe IVH

eFigure 29. Forest Plot for Comparison— Sedation During Ventilation: Opioid vs. Placebo for the Outcome Severe IVH

eFigure 30. Forest Plot for Comparison—Neuromuscular Paralysis During Ventilation vs. Placebo for the Outcome Severe IVH

eFigure 31. Forest Plot for Comparison—Volume Expansion vs. Inotropes for Hypotension for the Outcome Severe IVH

eFigure 32. Forest Plot for Comparison—Dopamine vs. Dobutamine for Hypotension for the Outcome Severe IVH

eFigure 33. Forest Plot for Comparison—Ibuprofen Prophylaxis for PDA vs. Placebo for the Outcome Severe IVH

eFigure 34. Forest Plot for Comparison—Indomethacin Pre-Symptomatic Treatment for PDA vs. Placebo for the Outcome Severe IVH

eFigure 35. Forest Plot for Comparison—Ibuprofen Pre-Symptomatic Treatment for PDA vs. Placebo for the Outcome Severe IVH

eFigure 36. Forest Plot for Comparison—Restrictive vs. Liberal Packed Red Cell Transfusion for Anemia for the Outcome Severe IVH

eFigure 37. Forest Plot for Comparison—Prophylactic Factor VII Administration vs. Placebo for the Outcome Severe IVH

eFigure 38. Forest Plot for Comparison—Prophylactic Antithrombin III Administration vs. Placebo for the Outcome Severe IVH

eFigure 39. Forest Plot for Comparison—Prophylactic Heparin Administration vs. Placebo for the Outcome Severe IVH

eFigure 40. Forest Plot for Comparison—Vitamin A Supplementation vs. Placebo for the Outcome Severe IVH

eFigure 41. Forest Plot for Comparison—Vitamin E Supplementation vs. Placebo for the Outcome Severe IVH

eFigure 42. Forest Plot for Comparison—Early Erythropoiesis-Stimulating Agents vs. Placebo for Outcome cPVL

eFigure 43. Forest Plot for Comparison—Elective HFJV vs. Conventional Ventilation Method for the Outcome cPVL

eFigure 44. Forest Plot for Comparison—Any Steroids for Lung Maturity vs. Placebo for the Outcome cPVL

eFigure 45. Forest Plots for Comparison—Betamethasone for Lung Maturity vs. Betamethasone for Lung Maturity for Outcome cPVL

eFigure 46. Forest Plot for Comparison—Antenatal Steroid for Lung Maturity: Repeat Course vs. Single Course for Outcome cPVL

- eFigure 47.** Forest Plot for Comparison—Antenatal MgSO₄ Therapy for Neuroprotection vs. Placebo for the Outcome cPVL
- eFigure 48.** Forest Plot for Comparison—Lower FiO₂ for Resuscitation vs. Higher FiO₂ for the Outcome cPVL
- eFigure 49.** Forest Plot for Comparison—Sustained Inflation During Resuscitation vs. Standard Resuscitation for the Outcome cPVL
- eFigure 50.** Forest Plot for Comparison—Umbilical Cord Milking vs. Early Cord Clamping for the Outcome cPVL
- eFigure 51.** Forest Plot for Comparison—Supine Head Midline vs. Supine Head Rotated for the Outcome cPVL
- eFigure 52.** Forest Plot for Comparison—Less Invasive Surfactant Administration (LISA) vs. Intubate, Surfactant, Extubate (INSURE) Method for Surfactant Administration for the Outcome Severe cPVL
- eFigure 53.** Forest Plot for Comparison—Volume Target Ventilation vs. Pressure Limited Ventilation for the Outcome Severe cPVL
- eFigure 54.** Forest Plot for Comparison—Elective HFOV vs. Conventional Ventilation Method for the Outcome cPVL
- eFigure 55.** Forest Plot for Comparison—High Oxygen Saturation Target (91-95%) vs. Low Oxygen Saturation Target (85-89%) in NICU for the Outcome cPVL
- eFigure 56.** Forest Plot for Comparison—Permissive Hypercapnia vs. Normocapnia During Ventilation for the Outcome cPVL
- eFigure 57.** Forest Plot for Comparison—Caffeine Prophylaxis or Treatment for Apnea or Post-Extubation vs. Placebo for the Outcome cPVL
- eFigure 58.** Forest Plot for Comparison—High Dose Caffeine Prophylaxis for Apnea or Post-Extubation vs. Low Dose Caffeine for the Outcome cPVL
- eFigure 59.** Forest Plot for Comparison—Sedation During Ventilation: Opioid vs. Placebo for the Outcome cPVL
- eFigure 60.** Forest Plot for Comparison—Neuromuscular Paralysis During Ventilation vs. Placebo for the Outcome cPVL
- eFigure 61.** Forest Plot for Comparison—Indomethacin Prophylaxis for PDA vs. Placebo for the Outcome cPVL
- eFigure 62.** Forest Plot for Comparison—Indomethacin Pre-Symptomatic Treatment for PDA vs. Placebo for the Outcome cPVL
- eFigure 63.** Forest Plot for Comparison—Ibuprofen Prophylaxis for PDA vs. Placebo for the Outcome cPVL

eFigure 64. Forest Plot for Comparison—Restrictive vs. Liberal Packed Red Cell Transfusion for Anemia for the Outcome cPVL

eFigure 65. Forest Plot for Comparison—Elective HFOV vs. Conventional Ventilation Method for the Outcome Severe Brain Injury

eFigure 66. Forest Plot for Comparison—Any Steroids for Lung Maturity vs. Placebo for the Outcome Severe Brain Injury

eFigure 67. Forest Plot for Comparison—Delayed Cord Clamping vs. Early Cord Clamping for the Outcome Severe Brain Injury

eFigure 68. Forest Plot for Comparison—High vs. Low Oxygen Saturation Targets for the Outcome Severe Brain Injury

eFigure 69. Forest Plot for Comparison—Caffeine Prophylaxis or Treatment for Apnea or Post-Extubation for the Outcome Severe Brain Injury

eFigure 70. Forest Plot for Comparison—Indomethacin Prophylaxis for the Outcome Severe Brain Injury

eFigure 71. Forest Plot for Comparison—Restrictive vs. Liberal Packed Red Cell Transfusion for Anemia for the Outcome Severe Brain Injury

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

eAppendix 1. Search Strategy

Database(s): Ovid MEDLINE(R) ALL: 1946 to September 08, 2022

First Search was conducted on 16th May 2020; the search has been updated on 22nd October 2021 and 8th September 2022

#	Searches	Results
1	exp Infant, Newborn/ or neonat*.mp.	804206
2	exp Infant/ or infan*.mp.	1389301
3	newborn.mp. or exp Infant, Newborn/	811062
4	exp Infant, Premature/ or preterm.mp.	119056
5	premature.mp. or exp Infant, Premature/ or exp Infant, Extremely Premature/	214615
6	premie.mp.	29
7	low birth weight.mp. or exp Infant, Low Birth Weight/	52655
8	very low birth weight.mp. or exp Infant, Very Low Birth Weight/	15158
9	extremely low birth weight.mp. or exp Infant, Extremely Low Birth Weight/	3745
10	or/1-9	1712280
11	randomized.mp. or exp Randomized Controlled Trial/	979027
12	exp Clinical Trial/ or trial.mp.	1347829
13	randomly.mp.	391699
14	controlled clinical trial.mp. or exp Controlled Clinical Trial/	673723
15	or/11-14	1832476
16	exp Cerebral Hemorrhage/ or intraventricular hemorrhage.mp.	40707
17	intraventricular hemorrhages.mp.	258
18	intra-ventricular hemorrhage.mp.	76
19	intra-ventricular hemorrhages.mp.	5
20	periventricular-intraventricular hemorrhage.mp.	166
21	periventricular-intraventricular hemorrhages.mp.	6
22	PIVH.mp.	137
23	peri-intraventricular hemorrhage.mp.	75
24	peri-intraventricular hemorrhages.mp.	13
25	periventricular leukomalacia.mp. or exp Leukomalacia, Periventricular/	2889
26	intracranial hemorrhage.mp. or exp Intracranial Hemorrhages/	84717
27	intracranial hemorrhages.mp. or exp Intracranial Hemorrhages/	78756
28	germinal matrix hemorrhage.mp.	251
29	germinal matrix hemorrhages.mp.	27
30	brain bleed.mp.	25
31	brain injury.mp. or exp Brain Injuries/	112952
32	brain injuries.mp.	69672
33	PVL.mp.	4541
34	or/16-33	199972

35	10 and 15 and 34	2169
36	exp animals/ not humans/	5043654
37	35 not 36	1951
38	limit 37 to dt=20200516-20211231	165
39	limit 37 to dt=20211231-20220910	58

Database(s): Embase Classic+Embase-1947 to 2022 September 08

First Search was conducted on 16th May 2020; the search has been updated on 22nd October 2021 and 8th September 2022.

#	Searches	Results
1	exp Infant, Newborn/ or neonat*.mp.	860637
2	exp Infant/ or infan*.mp.	1534244
3	newborn.mp. or exp Infant, Newborn/	797532
4	exp Infant, Premature/ or preterm.mp.	192597
5	premature.mp. or exp Infant, Premature/ or exp Infant, Extremely Premature/	329858
6	premie.mp.	60
7	low birth weight.mp. or exp Infant, Low Birth Weight/	80809
8	very low birth weight.mp. or exp Infant, Very Low Birth Weight/	19697
9	extremely low birth weight.mp. or exp Infant, Extremely Low Birth Weight/	5327
10	or/1-9	1896070
11	randomized.mp. or exp Randomized Controlled Trial/	1326912
12	exp Clinical Trial/ or trial.mp.	2617159
13	randomly.mp.	521230
14	controlled clinical trial.mp. or exp Controlled Clinical Trial/	940146
15	or/11-14	3122705
16	exp Cerebral Hemorrhage/ or intraventricular hemorrhage.mp.	173566
17	intraventricular hemorrhages.mp.	363
18	intra-ventricular hemorrhage.mp.	169
19	intra-ventricular hemorrhages.mp.	4
20	periventricular-intraventricular hemorrhage.mp.	195
21	periventricular-intraventricular hemorrhages.mp.	7
22	PIVH.mp.	153
23	peri-intraventricular hemorrhage.mp.	97
24	peri-intraventricular hemorrhages.mp.	14
25	periventricular leukomalacia.mp. or exp Leukomalacia, Periventricular/	7599
26	intracranial hemorrhage.mp. or exp Intracranial Hemorrhages/	175092
27	intracranial hemorrhages.mp. or exp Intracranial Hemorrhages/	172676
28	germinal matrix hemorrhage.mp.	379
29	germinal matrix hemorrhages.mp.	40
30	brain bleed.mp.	33

31	brain injury.mp. or exp Brain Injuries/	236548
32	brain injuries.mp.	13352
33	PVL.mp.	7028
34	or/16-33	406687
35	10 and 15 and 34	5489
36	exp animals/ not humans/	12275913
37	35 not 36	3476
38	limit 37 to dc=20200516-20211231	481
39	limit 37 to dc=20211231-20220831	298

Database CENTRAL, Search Name: brain injury

First Search was conducted on 16th May 2020; the search has been updated on 22nd October 2021 and 10th September (Trials other than Medline and Embase only downloaded)

ID	Search	Hits
#1	infant (Word variations have been searched)	68573
#2	preterm (Word variations have been searched)	16348
#3	premature (Word variations have been searched)	27641
#4	infan*	72420
#5	Newborn (Word variations have been searched)	31725
#6	premie (Word variations have been searched)	147
#7	low birth weight (Word variations have been searched)	9704
#8	MeSH descriptor: [Infant, Low Birth Weight] explode all trees	2332
#9	very low birth weight (Word variations have been searched)	5090
#10	MeSH descriptor: [Infant, Very Low Birth Weight] explode all trees	1038
#11	extremely low birth weight (Word variations have been searched)	1867
#12	MeSH descriptor: [Infant, Extremely Low Birth Weight] explode all trees	131
#13	{OR #1-#12}	91237
#14	intraventricular hemorrhage (Word variations have been searched)	2146
#15	"Intraventricular hemorrhage"	1923
#16	MeSH descriptor: [Infant, Newborn, Diseases] explode all trees	7713
#17	intraventricular NEAR2 hemorrhage (Word variations have been searched)	39215
#18	Cerebral NEAR2 Hemorrhage (Word variations have been searched)	64213
#19	MeSH descriptor: [Cerebral Hemorrhage] explode all trees	1113
#20	MeSH descriptor: [Cerebral Intraventricular Hemorrhage] explode all trees	22
#21	intra-ventricular hemorrhage (Word variations have been searched)	70
#22	periventricular-intraventricular hemorrhage (Word variations have been searched)	42
#23	PIVH (Word variations have been searched)	18
#24	peri-intraventricular hemorrhage (Word variations have been searched)	14
#25	periventricular NEAR2 leukomalacia	1184

#26	MeSH descriptor: [Leukomalacia, Periventricular] explode all trees	62
#27	intracranial hemorrhage (Word variations have been searched)	4093
#28	germinal matrix hemorrhage (Word variations have been searched)	41
#29	brain NEAR2 bleed (Word variations have been searched)	125581
#30	brain NEAR2 injury (Word variations have been searched)	136624
#31	PVL (Word variations have been searched)	419
#32	{OR #14-#31}	170705
#33	#13 AND #32	2197
#34	#13 AND #32 with Publication Year from 2020 to 2021, with Cochrane Library publication date Between May 2022 and Oct 2021, in Trials	427
#35	#13 AND #32 with Publication Year from 2021 to 2022, with Cochrane Library publication date Between Oct 2021 and Sep 2022, in Trials	240

Database – CINAHL

Firs Search was conducted on 16th May2020 (n=606); the search has been updated on 22nd October 2021 (n=40) and 10th September 2022 (n=31).

#	Query	Results
S24	S5 AND S9 AND S23	677
S23	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22	53,072
S22	PVL	723
S21	brain N2 injury OR brain N2 injuries	37,672
S20	brain N2 bleed OR brain N2 bleeds	26
S19	("germinal matrix" N2 (hemorrhage OR heamorrhages)) OR (germinal matrix N2 (hemorrhages OR heamorrhages))	102
S18	(intracranial N2 hemorrhage OR intracranial N2 haemorrhage) OR (intracranial N2 hemorrhages OR intracranial N2 haemorrhages)	6,438
S17	periventricular N2 leukomalacia OR MJ periventricular leukomalacia	656
S16	"peri-intraventricular" N2 hemorrhage OR "peri-intraventricular" N2 hemorrhages	28
S15	PIVH	19
S14	"periventricular-intraventricular" N2 hemorrhage OR "periventricular-intraventricular" N2 hemorrhages OR MJ periventricular-intraventricular hemorrhage	49
S13	intraventricular N2 hemorrhages OR intraventricular N2 hemorrhage OR intra-ventricular N2 hemorrhage OR intra-ventricular N2 hemorrhages	2,468
S12	intraventricular N2 hemorrhages	2,443
S11	intraventricular hemorrhages	6,967
S10	Cerebral N2 Hemorrhage OR intraventricular N2 hemorrhage	10,119
S9	(S6 OR S7 OR S8)	509,385
S8	(randomized controlled trials or rtc or randomised control trials or randomized clinical trial or randomized controlled study) OR MJ Controlled Clinical Trial	229,347
S7	Controlled Clinical Trial OR MJ Controlled Clinical Trial	37,162
S6	random*	492,224

S5	(S1 OR S2 OR S3 OR S4)	349,626
S4	premie	13,060
S3	low birth weight OR MJ very low birthweight OR extremely low birth weight	17,489
S2	(premature infants or preterm infants OR preterm) OR MJ (premature infants or preterm infants OR preterm)	51,931
S1	(infants or newborn or neonate) OR MH (infants or newborns or neonates)	338,921

eAppendix 2. Interventions Considered in the Systematic Review

ANTENATAL INTERVENTIONS:

1. Antenatal corticosteroids for lung maturity
2. Betamethasone vs. Dexamethasone for lung maturity
3. Repeat antenatal steroids vs. single course antenatal steroids
4. Magnesium sulfate for neuroprotection or tocolysis
5. Antibiotics for premature rupture of membranes
6. Cesarean section vs. vaginal delivery for preterm birth

DELIVERY ROOM INTERVENTIONS:

1. Lower vs. higher FiO₂ for resuscitation
2. Sustained inflation vs. standard resuscitation
3. Delayed cord clamping vs. early cord clamping
4. Umbilical cord milking vs. early cord clamping
5. Umbilical cord milking vs. delayed cord clamping
6. Delayed cord clamping with respiratory support vs. delayed cord clamping without respiratory support

POSTNATAL INTERVENTIONS:

1. Supine head midline vs. Supine head rotated
2. LISA vs. INSURE
3. Volume guarantee vs. pressure limited ventilation
4. Elective HFOV vs. conventional ventilation
5. Elective HFJV vs. conventional ventilation
6. Oxygen saturation target after birth: 85-89% vs. 91-95%
7. Permissive hypercapnia vs. normocapnia
8. Early extubation vs. delayed extubation
9. Caffeine prophylaxis or treatment for apnea or post-extubation
10. High dose vs. low dose caffeine for apnea or post-extubation
11. Sedation during ventilation: midazolam vs. placebo
12. Sedation during ventilation: opioids vs. placebo
13. Sedation during ventilation: phenobarbitone vs. placebo
14. Neuromuscular paralysis during ventilation vs placebo
15. Early erythropoiesis-stimulating agents vs placebo
16. Volume expansion vs. inotropes (any) for hypotension
17. Dopamine vs. dobutamine for hypotension
18. Indomethacin prophylaxis for PDA vs placebo
19. Indomethacin pre-symptomatic treatment for PDA vs placebo
20. Ibuprofen prophylaxis for PDA vs placebo
21. Ibuprofen pre-symptomatic treatment for PDA vs placebo

22. Restrictive vs. liberal packed red cell transfusion for anemia
23. Low vs. high threshold for platelet transfusion for thrombocytopenia
24. Prophylactic plasma administration vs placebo to reduce IVH/PVL
25. Prophylactic factor VII administration vs placebo to reduce IVH/PVL
26. Prophylactic antithrombin III administration vs placebo to reduce IVH/PVL
27. Prophylactic ethamsylate administration vs placebo to reduce IVH/PVL
28. Prophylactic heparin administration vs placebo to reduce IVH/PVL
29. Stem cell therapy
30. Vitamin A supplementation vs. placebo for the outcome severe IVH
31. Vitamin E supplementation vs. placebo for the outcome severe IVH
32. Vitamin K supplementation vs. placebo for the outcome severe IVH

eAppendix 3. Screening Form

INCLUSION: STUDY MUST MEET ALL FOUR STEPS TO BE INCLUDED

STEP 1: We will only include randomised or quasi-randomised clinical trials reporting at least one or more outcomes (sIVH, cPVL, and severe brain injury) identified in the systematic review

STEP 2: Preterm infants <37 weeks gestational age.

STEP 3: Must include at least one of the 44 interventions as listed above (antenatal (n=6), delivery room (n=6), and neonatal (n=32)).

STEP 4: Must report at least one of the outcomes of our interest:

- sIVH: defined as hemorrhage into the ventricles with ventricular distension, intra-parenchymal hemorrhage, or parenchymal hemorrhagic infarct (grade III or IV IVH Papile grading), identified any time before discharge on cranial ultrasound.
- cPVL: defined as white matter injury characterized by the necrosis of white matter near the lateral ventricles (must include cystic changes), identified any time before discharge on cranial ultrasound.
- Severe brain injury: defined as the presence of either sIVH or cPVL

EXCLUSION: STUDY WILL BE EXCLUDED IF IT MEETS ANY ONE OF THE FOLLOWING:

- Non-randomised studies
- Studies including term infants
- Studies evaluating interventions that are not mentioned above.

eAppendix 4. Excluded Articles and Their Citations

Study author, year	Reasons for exclusion
Abbas, 2019 ¹	Review article
Adamska, 2015 ²	No outcome of interest.
Aher, 2006 ³	Cochrane Review
Ahn, 2018 ⁴	Not an RCT.
Altaany, 2015 ⁵	Retrospective study design, not an RCT.
Ambalavanan 2015 ⁶	Follow-up study, not eligible.
Amin 2007 ⁷	Metanalysis (Review article)
Amorin 1999 ⁸	Studied effect of antenatal corticosteroid in pregnant women, not eligible.
Ankola 1993 ⁹	Not mentioned Severe IVH of cPVL, no outcome of interest.
Araki 2018 ¹⁰	Systematic Review, not eligible
Ardell 2018 ¹¹	Intervention was not considered in our study.
Askie 2017 ¹²	Cochrane Review
Abdel-Rehman ¹³	Not an RCT.
Adcock 2018 ¹⁴	Retrospective study design
Ahmed 2019 ¹⁵	Intervention not considered in our study
Airoidi 2009 ¹⁶	Case-control study, not eligible.
Bassler 2006 ¹⁷	Cochrane Review
Been 2011 ¹⁸	Meta-analysis-Review article
Bellu 2008 ¹⁹	Cochrane Review
Bhuta 1997 ²⁰	Study already considered, duplicate study
Blankenship 2019 ²¹	Not an RCT.
Boedy 2005 ²²	No outcome of interest.
Bourchier 1997 ²³	Intervention was not considered in our study.
Bowes 2004 ²⁴	Full text not found.
Bradshaw 2015 ²⁵	Study protocol.
Brion 2003 ²⁶	Cochrane Review
Brooks 1999 ²⁷	No outcome of interest.
Bruschettini 2016 ²⁸	Duplicate, the published study included
Cao 2020 ²⁹	Full text not found, although it looks like a review article.
Corbet 1995 ³⁰	A pilot study, study protocol.
Carlo 1987 ³¹	Not mentioned severe IVH of cPVL, no outcome of interest.
Carroll 2019 ³²	Retrospective cohort study, not an RCT.
Chapman 2016 ³³	Systematic review
Anand 1999 ³⁴	Duplicate data, published in two different journals, one already included

Chatzakis 2020 ¹	No outcome of interest.
Chiswick 1991 ³⁵	IVH is not classified into I to IV grade, not eligible
Clark 1996 ³⁶	Meta-analysis-Review article
Clyman 2006 ³⁷	Follow-up study.
Cooke 2003 ³⁸	Cochrane Review
Cools 2015 ³⁹	Review article
Crane 2003 ⁴⁰	Poster, no eligible.
Crowther 2012 ⁴¹	Duplicate data, published in two different journals. One already included.
Dagenais 2017 ⁴²	No outcome of interest.
Dang 2015 ⁴³	No outcome of interest.
Darlow 2016 ⁴⁴	Review article
Dilmen 2014 ⁴⁵	No outcome of interest.
Dolfin 1994 ⁴⁶	Intervention was not considered in our study.
Dogoff 2017 ⁴⁷	Study protocol, No outcome of interest.
Egarter 1996 ⁴⁸	No outcome of interest.
Elbourne 2001 ⁴⁹	Follow-up study at 2 years of age
Elimian 2013 ⁵⁰	Duplicate data, published in two different journals. One already included.
Fergusson 2012 ⁵¹	Intervention not considered in our study
Fogarty 2018 ⁵²	Not an RCT.
Fowlie 2003 ⁵³	Review article.
Foligno 2020 ⁵⁴	Studied bovine vs. porcine surfactant, not considered in our study.
Fujiwara 1990 ⁵⁵	Included preterm with grade 2 IVH, met exclusion criteria.
Gerstmann 1996 ⁵⁶	No outcome of interest.
Gork 2008 ⁵⁷	Review Article.
Grevsen 2020 ⁵⁸	Not an RCT.
Haidenn 2005 ⁵⁸	Studied EPO in anemia, not considered as an intervention in our study.
Hammerman 2008 ⁵⁹	Study protocol, poster.
Harding 2001 ⁶⁰	Follow-up study
Henderson 2010 ⁶¹	Studied Caffeine vs. Theophylline in AOP, not a comparison in our review.
Herrera 2007 ⁶²	Cochrane Review
Hodnett 1999 ⁶³	No outcome of interest.
Horton 2015 ⁶⁴	Secondary follow-up study.
How 1998 ⁶⁵	Intervention was not considered in our study.
Hutzel 2008 ⁶⁶	Review article.
Ibrahim 2000 ⁶⁷	No outcome of interest.
Ibrahim 2014 ⁶⁸	Review article

Jacqz-Aigrain1994 ⁶⁹	Did not report IVH.
Jarde 2020 ⁷⁰	Not an RCT.
Jiang 2012 ⁷¹	Did not report IVH.
Joshi 2006 ⁷²	Cochrane Review
Juul 2008 ⁷³	Study protocol, phase I/II trial, we included the final article.
Kalani 2016 ⁷⁴	Compared Indomethacin vs. Ibuprofen, we did not consider this intervention.
Kashanian 2018 ⁷⁵	Studied different Dexamethasone regimes, intervention not considered.
Keszler 1991 ⁷⁶	Duplicate data, we already considered one latest study.
Khuwuthyakorn 2018 ⁷⁷	Evaluated oral Indomethacin vs. oral Ibuprofen; we did not consider the intervention.
Klauser 2012 ⁷⁸	No outcome of interest.
Kribs 2015 ⁷⁹	No outcome of interest.
Kua 2017 ⁸⁰	Not an RCT.
Lago 1998 ⁸¹	No separate data on severe IVH, cystic PVL or severe brain injury provided
Lietich 1998 ⁸²	Meta-analysis, review article.
Leuchter 2014 ⁸³	Did not mention IVH, PVL mentioned but no data on cPVL
Li 2020 ⁸⁴	No outcome of interest.
Liao 2014 ⁸⁵	Not an RCT.
Liu 2016 ⁸⁶	Chinese article, Full text not available.
Laughon 2009 ⁸⁷	Study protocol, pilot study.
Long 1991 ⁸⁸	Intervention was not considered in our study.
Maruyama 2012 ⁸⁹	No outcome of interest.
Mirzarahimi 2018 ⁹⁰	Compared efficacy of Curosurf vs. Surfacta, innervation was not considered.
Mittendorf 2002 ⁹¹	IVH is not graded into I to IV and PVL is not defined.
Malhotra 2017 ⁹²	A prospective observational study, not an RCT.
Ment 1996 ⁹³	Duplicate data, we already considered one study.
Mercer 2016 ⁹⁴	Follow-up study
Mirzamoradi 2014 ⁹⁵	IVH and PVL are not defined, no outcome of interest.
Mitra 2016 ⁹⁶	Network meta-analysis, excluded.
Nagano 2018 ⁹⁷	Review article.
Nayeri 2014 ⁹⁸	IVH and PVL are not clearly defined.
Neary 2016 ⁹⁹	Cochrane Review.
Nguyen 2013 ¹⁰⁰	Study includes term neonates, excluded.
Nicolades 2016 ¹⁰¹	Poster presentation. No outcome of interest.
Nijman 2018 ¹⁰²	Secondary analysis excluded.
O'Sullivan 2019 ¹⁰³	Secondary analysis of prospective gathered data.
Oberthuer 2017 ¹⁰⁴	Conference abstract

Oei 2018 ¹⁰⁵	Review article.
Ohlsson 2017 ¹⁰⁶	Cochrane review.
Osborn 2003 ¹⁰⁷	IVH and PVL are not defined clearly.
Ovalle 2006 ¹⁰⁸	Only includes Antibiotics for Preterm labor, no PPROM, so excluded.
Park 2017 ¹⁰⁹	Review article about Mesenchymal stem cell transplantation, not an RCT.
Pasquier 2019 ¹¹⁰	IVH not graded, no outcome of interest.
Peng 2014 ¹¹¹	A meta-analysis, not an RCT.
Perlman 1985 ¹¹²	No outcome of interest.
Qublan 2001 ¹¹³	Prospective study but no randomisation.
Quinn 1993 ¹¹⁴	No outcome of interest.
Rennie 1986 ¹¹⁵	IVH and PVL are not defined clearly.
Reynolds 1985 ¹¹⁶	No outcome of interest.
Rezaie 2016 ¹¹⁷	Compared single vs. double Betamethasone dose, it's a study protocol and did not have any outcome of our interest.
Roberts 2017 ¹¹⁸	Cochrane Review.
Rojas 2009 ¹¹⁹	Studied the effect of Surfactant with or without ventilation, we did not consider this intervention.
Romero 1993 ¹²⁰	Antibiotics for preterm labor with intact membranes, no PPROM, so excluded.
Rook 2012 ¹²¹	Study protocol.
Ruegger 2015 ¹²²	Included all grades of IVH, so excluded.
Saugstad 2017 ¹²³	Conference abstract.
Scheller 1994 ¹²⁴	Commentary and recommendation, not an RCT.
Schmidt 2001 ¹²⁵	No outcome of interest.
Schmolzer 2018 ¹²⁶	Feasibility trial.
Schulte 2005 ¹²⁷	Long-term follow-up study.
Shah 2008 ¹²⁸	Review article.
Shankaran 1995 ¹²⁹	No outcome of interest.
Sharafutdinova 2019 ¹³⁰	A prospective observational study, not an RCT.
Shirk 2019 ¹³¹	Conference abstract.
Silver 1996 ¹³²	Studied the effect of Surfactant on IVH, we did not consider this intervention.
Simons 2006 ¹³³	Did not specify severe IVH or cPVL.
Sinha 2005 ¹³⁴	No outcome of interest.
Sluncheva 2006 ¹³⁵	Studied prevention of IVH and surfactant, not an inclusion criterion.
Skoll 2018 ¹³⁶	Review article.
Smit 2013 ¹³⁷	Studied postnatal phenobarbital on neonatal outcome, we did not include this intervention.
Smith 2007 ¹³⁸	No outcome of interest.
Sosenko 2012 ¹³⁹	Studied symptomatic PDA; we only considered prophylactic/asymptomatic PDA

Sommers 2012 ¹⁴⁰	Prospective study, not an RCT.
Stock 2012 ¹⁴¹	Review article.
Strickland 2007 ¹⁴²	Response letter, commentary to an original article.
Su 2003 ¹⁴³	Comparison between Indomethacin and Ibuprofen for treatment of PDA, not an inclusion criterion for our study.
Subhedar 2003 ¹⁴⁴	Cochrane Review.
Supapannachart 1999 ¹⁴⁵	The article did not clearly define severe IVH, cPVL, or severe brain injury, so we excluded the article.
Thomas 2005 ¹⁴⁶	Review article.
Thome 2000 ¹⁴⁷	No outcome of interest.
Thome 2018 ¹⁴⁸	Long-term follow-up study.
Unal 2017 ¹⁴⁹	No outcome of interest.
Van Teeffelen 2014 ¹⁵⁰	No outcome of interest.
Van Overmeire 2001 ¹⁵¹	Included symptomatic PDA cases; we only considered prophylactic and pre-symptomatic cases.
Veldman 2006 ¹⁵²	Study protocol.
Walti 1973 ¹⁵³	Prospective study, not an RCT.
Wang 2015 ¹⁵⁴	A meta-analysis, Review article.
Wardle 2001 ¹⁵⁵	Not defined severe IVH, no outcome of interest.
Wenstrom 2007 ¹⁵⁶	No outcome of interest.
Wheeler 2011 ¹⁵⁷	Review article.
Whyte 2011 ¹⁵⁸	Cochrane review.
Thorp 1995 ¹⁵⁹	No outcome of interest.
Weesner 1987 ¹⁶⁰	Did not mention separately grade III-IV IVH or no mention of cPVL
Wyllie 2018 ¹⁶¹	Commentary to an original article. Not an RCT.
Xu 2016 ¹⁶²	Studied Atosiban in threatened preterm labor; cases did not have PPRM
Yadav 2014 ¹⁶³	Compared oral Indomethacin vs. oral Ibuprofen in the closure of PDA, intervention was not considered in our study.
Yang 2018 ¹⁶⁴	Did not mention separately grade III-IV IVH or cPVL
Zeng 2019 ¹⁶⁵	Review article.
Sunil 2022 ¹⁶⁶	No IVH reported
McDonald 2022 ¹⁶⁷	Studied different doses of Betamethasone, not considered as an intervention
Benavides 2021 ¹⁶⁸	Follow up study of Bell 2005
Bravo 2021 ¹⁶⁹	Considered symptomatic PDA neonates, excluded.
Erdeve 2021 ¹⁷⁰	Not an RCT
Mari 2022 ¹⁷¹	Review article
Li 2021 ¹⁷²	No mention of severe IVH or cPVL.
Sabzehai 2022 ¹⁷³	No grading of IVH

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e-Table 1: Characteristics of studies studying interventions on severe brain injury in preterm infants

					Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome	Incomplete outcome	Selective reporting	Other biases
Antenatal Interventions											
Antenatal corticosteroids for lung maturity											
WHO Trial 2020	Multicenter	26-34wk	Dexa X 4, 6mg Q12hr	Placebo/NS	L	L	L	L	L	L	L
Gyamfi 2016	USA	34-36wk	Beta X 2, 12mg Q24hr	Placebo	L	L	L	L	L	L	L
Garite 2009	Multicenter	25-34wk	Beta X 2, 12mg Q24hr	Placebo	L	L	L	U	L	L	L
Peltoniemi 2007	Finland	<34wk	Beta X 2, 12mg Q24hr, Repeat course >7days	Placebo/NS	L	L	L	L	L	L	L
Lewis 1996	USA	24-34wk	Beta X 2, 12mg Q24hr	No treatment	L	L	H	U	L	L	U
Silver 1996	USA	24-29wk	Dexa X4, 5 mg 12hr	NS	L	L	L	L	H	L	U
Kari 1994	Finland	24-32wk	Dexa X 4, 6mg Q12hr	Placebo	U	U	L	U	L	L	U
Garite 1992	USA	24-28wk	Beta Acetate 6mg+ Beta phosphate 6mg , Q24hr	NS	L	U	L	U	L	L	U
Morales 1989	USA	26-34wk	Beta X 2, 12mg Q24hr	No treatment	U	U	H	U	L	L	U
Morales 1986	USA	28-33wk	Dexa X 4, 6mg Q12hr	No treatment	L	L	U	L	L	U	U
Dexamethasone vs. Betamethasone for lung maturity											
Crowther 2019	Multicenter	<34wk	Dexa X 4, 6mg Q12hr	Beta X 2, 12mg Q24hr	L	L	L	L	L	L	L
Elimian 2007	USA	24-34wk	Dexa X 4, 6mg Q12hr	Beta X 2, 12mg Q24hr	L	L	L	L	U	L	L
Chen 2005	Taiwan	24-34wk	Dexa X 4, 6mg Q12hr	Beta X 2, 12mg Q24hr	U	U	U	U	H	U	U
Subtil 2003	France	27-35wk	Dexa X 4, 6mg Q12hr	Beta X 2, 12mg Q24hr	L	U	H	H	U	L	L

Repeat antenatal steroids vs. no repeat antenatal steroids											
Garite 2009	Multicenter	25-33wk	Beta (Repeat course)	NS	L	L	L	U	L	L	L
Murphy 2008	Multicenter	25-32wk	Beta x Q14 day till 33wk	Placebo	U	L	L	U	L	L	L
Peltoniemi 2007	Finland	<34wk	Beta (Repeat)	Placebo	L	L	L	L	L	L	H
Crowther 2006	Multicenter	<32 wk	Celestone (Repeat till delivery or 32wk)	NS	L	L	L	U	L	L	L
Wapner 2006	Multicenter	23-32wk	Beta (Repeat once)	Placebo	L	L	L	L	L	L	H
Lee 2004	Multicenter	24-33wk	Beta x till 34wk	Placebo	L	L	L	U	L	L	L
Asghajafari 2002	Canada	24-30wk	Beta x till 33wk	NS	L	L	L	U	L	U	L
Guinn 2001	Multicenter	24-33wk	Beta or Dexa Q wkly till 34 wk	Single course Beta or Dexa	L	L	L	U	L	L	H
Magnesium sulfate for tocolysis or neuroprotection											
Crowther 2003	Australia	<30wk	MgSO4	NS	L	L	L	L	L	L	L
Rouse 2008 (BEAM)	USA	24-31wk	MgSO4	Placebo	L	L	L	L	L	L	L
Marret 2006 (PREMAG)	France	<33wk	MgSO4	NS	L	L	U	L	L	L	L
Parashi 2017	Iran	<33wk.	MgSO4	NS	L	L	L	L	L	L	L
Fox 1993	USA	34-37wk	MgSO4	Placebo	L	L	H	U	L	L	L
How 1998	USA	24-34wk	MgSO4	Placebo	L	U	U	U	L	U	L
Antibiotics for premature rupture of membranes											
Fuhr 2006	Multicenter	24-33wk	Mezlocillin	Placebo	U	U	L	U	L	U	U
Mercer 1997	Multicenter	24-32wk	Ampicillin+Erythromycin	Placebo	L	L	L	L	L	U	U
Grable 1996	USA	<35wk	Ampicillin	Placebo	L	L	L	L	L	U	L
Owen 1993	USA	24-34wk	Ampicillin	Not specified	L	L	H	U	L	U	L
Cesarean section vs. vaginal delivery for preterm birth											
No RCT											
Delivery Room Interventions											
Lower vs. higher FiO2 for resuscitation				FiO2	FiO2						
Oie 2017	Australia	<32 wk	21-100%	100%	L	L	H	L	U	L	L
Aguar 2013	Multicenter	<28wk	30%	60%	L	L	H	L	L	L	L
Boronat 2013	Spain	<30wk	30%	60-65%	L	L	H	L	L	L	L
Kapadia 2013	USA	24-35w	21-100%	100%	L	L	H	U	L	H	L
Vento 2009	Spain	<28wk	21-100%	100%	L	L	H	U	L	L	L
Esrig 2008	Spain	<28wk	30%	90%	L	L	H	L	U	U	L
Wang 2008	USA	23-32wk	21%	100%	U	U	H	U	L	L	L

Lundstrom 1995	Denmark	<33wk	21%	80%	U	U	H	U	L	L	L
Sustained lung inflation (SLI) vs. standard resuscitation											
Hamd 2020	Egypt	<27-32 wk	SLI 20cm for 15sec, then CPAP 5.	CPAP 5	L	U	U	U	H	H	L
Kirpalani 2019	Multicenter	23-27wk	SLI, 20cm, 15sec, later SLI 25cm 15sec.	IPPV with PEEP	L	L	H	U	L	L	U
Laverde 2019	Italy	28-31wk	SLI 25cm for 15 sec, CPAP 5.	PPV 25/5 R 40-60	U	U	U	U	L	U	L
El Fattah 2017	Egypt	<32wk	SLI 15,20cm for10,20sec each.	CPAP 5	L	U	U	U	L	L	L
Jiravisitkul 2017	Thailand	25-32wk	SLI 25cm 15s, later CPAP 6, 2 nd SLI	PIP 15-20cm, PEEP5,	L	L	H	U	L	U	L
Nagan 2017	Canada	23-33wk	2PIP 24cm 20sec 2 nd SLI 20 20sec	IPPV later CPAP 5cm	L	U	H	L	H	L	U
Schwaberger 2015	Austria	28-34wk	PIP 30cm,15sec, Rpt 1 or 2 HR <100. CPAP, HR >100.	IPPV, later CPAP	L	L	H	L	L	L	L
Lista 2015	Multicenter	25-29wk	PIP 25cm 15sec, CPAP 5.PIP 20cm 15sec	CPAP 5 or PIP	U	L	H	L	L	L	L
Linder 2015	Germany	25-29wk	SLI 25-30 sec, PIP 20cm, PEEP 4-6	CPAP 5	U	L	H	U	L	L	U
Delayed cord clamping vs. early cord clamping											
Yunis 2020	Egypt	<34wk	DCC 60sec	ECC 10sec	L	L	H	U	L	L	L
Hemmati 2020	Iran	26-34wk	DCC 30-45sec	ECC 10-15	L	U	H	L	H	L	L
Finn 2019(CUPiD)	Ireland	<32wk	DCC 60sec	ECC 20sec	L	L	H	L	L	L	L
Duley L 2018 (Cord Pilot Trial)	UK	<32wk	DCC 2min	ECC 20sec	L	L	H	L	L	L	L
Armanian 2017	Iran	<34wk	Resus bedside								
Tarnow Mordi 2017	Multicenter	<32wk	DCC 30-45sec	ECC 5-10sec	L	L	H	U	L	L	U
Backes 2016	USA	23-28wk	DCC 60sec	ECC 10sec	L	L	H	U	L	L	L
Dong 2016	China	25-32wk	DCC 30-45sec	ECC 10sec	L	L	H	L	L	L	L
			DCC with 10-20cm below	ECC 10sec	U	U	H	U	L	L	
Kugelman 2007	Israel	24-35wk	DCC 30-45sec	ECC 10sec	U	U	H	U	L	U	U
Mercer 2006	USA	24-32wk	DCC 30-45sec, 10-15 inches below	ECC <10sec	L	L	H	L	L	L	L
Mercer 2003	USA	24-32wk	DCC 30-45sec	ECC 10sec	U	U	H	L	L	L	U
Rabe 2000	Germany	<33wk	DCC 45sec	ECC 20sec	L	L	H	U	L	U	L

Hofmeyr 1998	SA	<35wk	DCC 60sec	ECC <10sec	U	U	H	L	L	L	U
Hofmeyr 1993	SA	<2000g	DCC	ECC	U	U	H	L	L	U	L
Kelly 2021	Canada	24-32wk	DCC 30-45 sec	ECC 10 sec	L	L	H	U	L	L	L
Umbilical cord milking vs. early cord clamping											
EL Naggar 2020	Canada	<32wk	UCM 10cm/s x3	ECC<10sec	L	L	H	L	L	L	L
Finn 2019(CUPiD)	Ireland	<32wk	UCM+DCC	ECC 20sec	L	L	H	L	L	L	L
Josephsen 2020	USA	24-28wk	UCMX3 2sec	ECC<10sec	U	U	H	U	L	U	U
Juan 2018	China	28-37wk	UCM 20cmX4	ECC	U	U	H	U	L	U	L
Rammohan 2018	India	<37wk	UCMX3 25cm	ECC <10sec	L	L	H	H	L	L	L
Song 2017	China	24-35wk	UCMX4 2sec below introitus (15-20sec)	ECC<10sec	L	U	H	L	L	L	L
Mercer 2016	USA	24-32wk	DCC30-40sec	ECC<10sec	U	U	H	L	L	L	U
Alan 2014	Turkey	<32wk	UCMX3, 25-30cm	ECC<10sec	U	U	H	U	L	L	L
Eliman 2014	USA	24-34wk	UCMX3, DCC 30sec	ECC <5sec	L	L	H	L	L	L	L
Katheria 2014	USA	23-32wk	UCMX3 2 sec	ECC <10sec	L	L	H	L	L	L	L
March 2013	USA	24-28wk	UCMX3	ECC <10sec	L	L	H	U	L	L	L
Hosno 2008	Japan	24-28wk	UCMX2-3	ECC <10sec	U	L	H	U	L	L	L
Umbilical cord milking vs. delayed cord clamping											
Katheria 2020	Multicenter	23-28wk	UCMX3, 20cm	DCC 60sec	L	L	H	U	L	H	H
Katheria 2019	Multicenter	23-32wk	UCMX3,20cm DCC 60sec	DCC 60sec	L	L	H	L	L	L	H
Finn 2019(CUPiD)	Ireland	<32wk	UCM	DCC	L	L	H	L	L	L	L
Katheria 2015	USA	23-32wk	UCM X4, 20cm,	DCC 45sec	L	L	H	L	L	L	U
Rabe 2011	UK	24-32wk	UCM X4, 20cm	DCC 30sec	L	L	H	U	L	L	U
Bichkar 2019	India	<32wk	UCM x4, 20cm	DCC 30sec	L	L	H	U	L	L	L
Delayed cord clamping with respiratory support vs. delayed cord clamping without respiratory support											
Katheria 2016	USA	23-32wk	DCC 60sec, CPAP/PPV	DCC	L	L	H	U	L	L	L
Postnatal Interventions											
Head midline position											
Kochan 2019	USA	<1000g	Supine head elevated 30 ⁰	Supine flat lateral	L	L	H	L	L	U	L
Al Abdi 2015	Saudi Arabia	<30wk	Flat midline head 168hrs	Supine flat lateral	U	U	H	L	L	L	H
Al Abdi 2011	Saudi Arabia	<30wk	Flat midline, chin at 90 ⁰	Supine flat lateral	L	L	H	L	L	L	U

LISA vs. INSURE											
Han 2020	Multicenter	<32wk	MISA with 5Fr gastric tube. 16G catheter marked to desired depth, X 5 bolus, Later CPAP 4Fr catheter attached to a syringe, breathing on CPAP. Spont breathing, CPAP, Surf. using thin catheter. 16G Angiocath or 6F feeding tube, Spont breathing. MISA with 5Fr gastric tube.	Surfactant via ETT	L	L	H	H	L	L	L
Bao 2015	China	28-32wk		Surfactant via ETT	U	U	H	U	L	U	L
Kribs 2015	Multicenter	23-27wk		Surfactant via ETT	L	L	H	H	L	L	L
Gopel 2011	Multicenter	26-30wk		Rescue surfactant	L	U	H	H	L	L	L
Jena 2019	India	<34 wk		Surfactant via ETT	L	L	L	U	L	U	L
Gupta 2020	India	24-34wk		Surfactant via ETT	L	L	H	U	L	L	L
Volume guarantee vs. Conventional ventilation											

Krishna 2019	India	27-34wk	SIMV+VG 5ml/kg, PEEP 4-6cm H2O	SIMV+PC, PIP 14-18, PEEP 4-6cm	L	L	U	U	L	U	U
Chowdhury	UK	<34wk	SIMV+VT 5ml/kg	SIMV	L	L	H	U	L	L	H
Güven 2013	Turkey	<32wk	SIMV+VG 4-5ml/kg	SIMV+PIP 20-25	L	U	H	U	L	U	H
Duman 2012	Turkey	<32wk	VG 4ml/kg PEEP 4-6	PLV+PIP	L	L	H	U	L	L	L
Liu 2011	China	24-32wk	SIPPV+VG 4-6ml/kg	IMV, PIP 20-25	U	U	H	U	L	U	L
Piotrowski 2007	Poland	RDS +	PRVC, VT 5-6 ml/kg	PLV, PEEP3-5	L	L	H	H	L	U	H
Singh 2006	UK	600-1500g	VG 8-10ml/kg, PEEP 3-5cm H2O	SIMV, PEEP 3-5ml/kg	L	L	H	U	L	U	U
D'Angio 2005	USA	500-1249g	PRVC, ? VT	PLV, PIP (VT 4-6)	L	L	H	U	L	U	L
Nafday 2005	USA	<1500g	PSV-VG 5ml/kg	PLV + SIMV	L	L	U	U	L	U	L
Keszler 2004	USA	<32wk	A/C+VG	A/C	L	L	H	H	L	U	L
Lista 2004	Italy	25-32wk	PSV-VG 5ml/kg PEEP 3.5-4cm H2O	PSV, PEEP 3.5-4cm H2O	L	L	H	U	L	U	H
Piotrowski 1997	Poland	<2500g	PRVC VT 5-6ml/kg	PLV PIP, PEEP 3-5cm H2O	U	L	H	L	L	U	L
Sinha 1997	USA	1200g	VT 5-8ml/kg	PLV PIP (5-8ml/kg)	U	U	H	L	L	U	U
Elective HFOV vs. Conventional ventilation											
Sun 2014	China	<32wk, <1500g	HFOV MAP 6-8 Increase gradually, 10Hz	SIMV-PSV VT 4-6, PEEP 4-6	L	U	H	U	L	H	L
Salvo 2012	Multicenter	<30wk <1500g	HFOV 15hz, MAP 6-8, AMP good wiggle.	SIPPV PIP 18-24, PEEP 5-8.	L	U	H	U	L	L	U
Lista 2008	Italy	25-32wk	HFOV MAP 8-10, 10 Hz, Amp 40%.	CV-VG 5ml/kg, PEEP 5.	L	U	H	U	L	L	L
Vento 2005	Italy	24-29wk 500-1000g	MAP 2cm > CV, 10Hz Amp 30%.	SIMV VT 4-6, PEEP 4-5.	L	L	H	U	L	L	L
Schrieber 2003	USA	23-34wk	MAP~ Lung Inflation, Hz10-12.	PIP 16-24, PEEP 4-6.	U	U	H	U	L	L	U
Craft 2003	USA	23-34wk	MAP-optimal lung vol, Hz 10-12.	PIP-good chest rise, PEEP 4-6.	L	L	H	U	L	L	U

Van Reempts 2003	Germany	<32wk	MAP 8-10, Hz 10, Amp-good wiggle.	CV-PIP 20, PEEP 4-6.	U	U	H	L	L	L	L
Courtney 2002	USA	600-1220g	MAP>2 CV, Hz 10-15, Amp good wiggle.	VT 4-7ml/kg, PEEP 4-6.	U	U	H	L	L	L	L
Johnson 2002	Multicenter	<29wk	MAP 8-10, Hz 10, Amp-good wiggle.	CV Rate 60	U	U	H	L	L	L	L
Durand 2001	USA	501-1200g	MAP>2 CV, Hz 10-15, Amp-depends on PCO2.	TV 5-6ml/kg, PEEP 4-6.	U	U	H	L	L	L	U
Moriette 2001	France	24-29wk.	MAP>2 CV, Hz 15, high vol strategy.	SIMV-PIP target TV. PEEP 4-5.	L	L	H	L	L	L	L
Plavka 1999	Czech Republic	500-1499g, <31wk	MAP-step wise increase, Hz 15.	CV-PIP chest rise, PEEP 3-5.	L	L	H	U	L	L	L
Thome 1999	Germany	24-<30wk	MAP>1-2 CV, Hz 10, Amp good wiggle.	IPPV, PIP adjust, PEEP >3, rate 60.	U	L	H	U	L	L	L
Rettwitz-Volk 1998	Multicenter	750-1500g	MAP and Amp- chest rise/Spo2, Hz 15-20.	PIP-chest rise, PEEP 3-4.	L	U	H	U	L	L	L
Gerstmann 1996	Multicenter	<35wk	MAP 1-2cm H2O>CV, I:E 0.33, 10-15Hz.	IMV, PIP 30-35, PEEP 3-7.	L	U	H	U	L	L	H
Ogawa 1993	Czech Republic	500-1499g, <31wk	MAP step wise increase HZ10-15, Amp wiggle.	CV, PIP-chest rise, PEEP 3-5.	L	L	H	U	L	L	L
HiFO study Group 1993	Multicenter	>=500g with sRDS	MAP 2-3cm > CV, Hz15 Amp-adequate.	CV-PIP chest rise, PEEP 4-6.	L	U	H	U	L	U	L
Clark 1992	USA	<35wk, <1751g	MAP 1-2cm H2O above CV, 10Hz.	CV-PIP20-27, PEEP 4-6.	L	U	H	U	L	U	L
HIFI 1989	Multicenter	750-2000g	MAP= or < CV, or 8-10cm,15Hz, AMP chest oscillation	PEEP2-5cm H2O, PIP 20-25cm.	L	U	H	U	L	L	L
Elective HFJV vs. Conventional ventilation											
Keszler 1997	Multicenter	<36wk	PEEP for recruitment, intermittent sigh breath. PEEP increased, thereby result in MAP inc 0.5-2cm H2O	CV-R 30-60/min, iT 0.3-0.4S, PEEP 4-6 cm H2O	L	L	H	U	L	L	H
Wiswell 1996	USA	<33wk	Freq 420/min, jet time 0.02sec PIP 80-90% of PIP on CV. PEEP 4-5cm H2O,5-10 back up breaths.	CV (setting not mentioned)	U	U	H	L	L	L	L

Oxygen saturation target after birth: 85-89% vs. 91-95%. Target SpO2				Target SpO2								
BOOST-II 2016	Australia	Australia	<28wk	91-95%	85-89%	L	L	L	L	L	L	U
BOOST-II UK 2016		UK	<24hr	91-95%	85-89%	L	L	L	L	L	L	U
BOOST-II NZ 2014		New Zealand	<24hr	91-95%	85-89%	L	L	L	L	L	L	L
Schmidt (COT) 2013		Multicenter	<28wk	91-95%	85-89%	L	L	L	L	L	L	L
Vaucher (Support) 2010		Multicenter	<24hr	91-95%	85-89%	L	L	L	L	L	L	L
Permissive hypercapnia vs. normocapnia												
Thome 2015		Multicenter	23-29wk	PaCO2 55-65 (1-3 days)	PaCO2 40-50 (1-3 days)	L	U	H	L	H	L	H
Thome 2006		USA	23-29wk	PaCO2 55-65 (7 days)	PaCO2 35-45 (7 days)	L	L	H	U	H	U	H
Carlo 2002		Multicenter	501-1000g	PaCO2 >52	PaCO2 <48	L	U	U	U	U	U	H
Carlo 1999		Multicenter	501-1000g	PaCO2 >52, 10 days	PaCO2 <48, 10 days	U	U	U	U	U	U	H
Mariani 1999		USA	601-1250g	PCO2 45-55, 96hr	PCO2 35-45, 96 hr	L	L	U	U	L	L	L
Early extubation vs. delayed extubation												
Denan 2008		France	24-27wk	Extubated immediately (criteria met)	Delayed extubation 36 hr	L	U	H	U	L	U	L
Caffeine prophylaxis or treatment for apnea or post-extubation												
Amaro 2018		USA	23-30wk	Caffeine L- 20mg/kg, M-5mg/kg.	NS	L	U	L	L	L	L	H
CAP Trial 2006		Multicenter	500-1250g	Caffeine L- 20mg/kg, M-5mg/kg.	NS	L	L	L	L	L	L	L
Ramin 2022		Iran	1500-2000g	Caffeine L- 20mg/kg, M-10mg/kg.	No treatment	U	U	H	U	L	L	U
High dose vs. low dose caffeine for apnea or post-extubation												

Mohd Kori 2021	Malaysia	<32wk	L-Caff 40mg/kg, M-20mg/kg.	L-Caff 20mg /kg, M-10mg/kg maintenance.	L	L	L	U	L	L	L
Vesoulis 2018	USA	<30wk	L-Caff 80mg/kg (36hr), M-10mg/kg.	L-Caff 30mg /kg (36hrs), M-10mg/kg.	L	L	L	L	L	L	L
Mohammad 2015	Egypt	<32wk	L-Caff 40mg/kg, M-20mg/kg.	L-Caff 20mg /kg, M-10mg/kg.	L	U	L	L	L	L	L
McPherson 2015	USA	24-30wk	L-Caff 40mg/kg, 20mg/kg (12hr), M-10mg/kg (24hr, 36hr).	L-Caff 20mg /kg, M-10mg/kg.	L	U	L	L	H	H	L
Gray 2010	Australia	<30wk	L-Caff 80mg/kg, M-20mg/kg .	L-Caff 20mg /kg, M-5 mg/kg.	L	L	L	U	L	L	L
Steer 2003	Australia	<32wk	L-Caff 30mg/kg, M-1mg/kg	L-Caff 3mg /kg, M-1mg/kg	L	L	L	U	U	U	H
Sedation during ventilation: opioids vs. placebo											
Anand 1999	Multicenter	24-32wk	Morphine 200mc/kg 20,40,60 mc/kg/hr maintenance.	Dextrose 10%	L	L	L	U	L	U	L
Anand 2004	Multicenter	23-32wk	Morphine 100mc/kg 10, 20,30 mc/kg/hr maintenance.	Placebo	L	L	L	L	L	L	L
Simons 2003	Netherlands	23-37wk <3days	Morphine 100mc/kg Later 10mc/kg/hr for 7 days.	Saline+5% Dextrose	L	L	L	L	L	L	L
Siwec 1999	USA	26-35wk 810-2750g	Morphine 100mc/kg Later 20mc/kg/hr 1-5 days.	NA	U	U	U	U	U	U	U
Lago 1998	Italy	26-34wk	Fentanyl 0.5-2 mcg/kg/hr	NA	U	U	H	U	L	L	L
Sedation during ventilation: midazolam vs. placebo											

Anand 1999	Multicenter	24-32wk	Midaz 200mc/kg 20,40,60 mc/kg/hr Maintenance.	Dextrose 10%	L	L	L	U	L	U	L
Sedation during ventilation: phenobarbitone vs. placebo											
No Studies											
Neuromuscular paralysis during ventilation vs. placebo											
Shaw 1993	UK	<2000g	Pancuronium 80mcg/kg IV, repeat dose if needed.	If restless, morphine IV	U	U	U	U	L	U	L
Perlman 1985	USA	750-1500g	NA	NA	U	U	U	L	L	U	L
Early erythropoiesis-stimulating agents vs. placebo											
Juul 2020 (PENUT Trial)	Multicenter	24-28wk	EPO 1000u/kg Q48hrX6, 3/wk till 32+6wk.	Saline	L	L	L	L	L	L	L
Sun 2020	China	24-32wk	EPO 500u/kg AD X2 wks, 7 dose.	Saline	L	U	U	U	L	L	H
Natalucci 2016	Switzerland	26-32wk	EPO 3000u/kgX3, 3hr, 12-18, 36-42hr	Saline	L	U	L	L	L	L	H
Song 2016	China	<32wk	EPO 500u/kg ADx2wk	Saline	L	L	H	L	L	U	L
Fauchere 2015	Multicenter	26-32wk	EPO 3000u/kgX3, 3hr, 12-18, 36-42hr	Saline	L	L	L	L	L	L	L
Peltoniemi 2017	Finland	700-1500g	Eprex 250u/kgX6 for 6 days.	Saline	L	L	L	L	L	L	L
Ohls 2013	Multicenter	500-1250g 24-32wk	EPO 400u/kgx3/ wk, Darb 10mcg/kg SC/wk	Placebo	L	L	L	L	U	L	L
Fauchere 2008	Switzerland	401g- 1250g	Epoitin beta 3000u/kg, 3- 6, 12-18, 36-42hr	Saline	L	L	L	L	L	U	L
Bierer 2006	USA	<32wk	EPO 400mcgX3/wk upto 35wk	Saline	L	U	L	U	L	U	L
Haiden 2005	Austria	<32wk		No placebo	U	L	H	U	L	U	L

Ohls 2001	Multicenter	401-1250g <32wk	EPO 300u/kg/d or 700U/kg 3x/wk. EPO 400u/kg 3x wk till 35wk or discharge.	Placebo	U	L	L	L	L	U	L
Maier 1994	Multicenter	750-1499g	EPO 250u on AD till 40- 42wk, 17doses.	No placebo	U	L	L	L	H	U	L
Volume expansion vs. inotropes (any) for hypotension											
Gill 1993	UK	<1501g	Dopa 5mcg/kg/min, inc by 2.5mcg /kg/min till 10mcg.	4.5% Alb 20ml/kg over 30min.	L	L	H	U	L	L	L
Dopamine vs. dobutamine for hypotension											
Hentschel 1995	Germany	25-36wk	Dopa 10mcg/kg/min.	Dobu 10mcg/ kg/min.	L	L	H	L	L	L	L
Klarr 1994	USA	<34wk	Dopa at 5mcg /kg/min, max 20mcg.	Dobu at 5mcg /kg/min, max 20mcg.	L	L	L	L	L	L	L
Indomethacin prophylaxis for PDA vs. placebo											
Kalani 2016	Iran	600-1250g	Indo 0.2mg/kg OD x 3 days.	Standard care	U	U	U	U	L	L	L
Scmidt 2001	Multicenter	500-999g	Indo 0.1mg/kg OD x3 doses.	Saline	L	L	L	L	L	L	L
Yaseen 1997	KSA	<1750g	Indo 0.2mg/kg OD x3 doses.	Saline	L	L	L	L	L	L	L
Couser 1996	USA	23-29wk	Indo 0.1mg/kg OD x 6 doses.	Saline	L	L	L	L	L	L	L
Ment 1994(a)	Multicenter	600-1250g	Indo 0.1mg/kg,6-8hr, ODx2doses.	Saline	L	L	L	L	L	L	L
Ment 1994(b)	Multicenter	600-1250g	Indo 0.1mg/kg,6-8hr, ODx2doses.	Saline	L	L	L	L	L	L	L
Dominaco 1994	Multicenter	600-1250g	Indo 3 doses, 0.2, 0.1,0.1mg/kg at <12hrs, 24, 36hrs.	Saline	U	L	L	L	L	U	L
Morales Suarez 1994	Mexico	<1250g	Indo 0.1mg/kg Q12hrs.	Saline	U	U	L	L	L	L	L
Bada 1989	USA	28-36wk	Indo 0.2mg/kg,6hr 0.1mg/kg, 18hr, 30hr	Placebo	U	U	L	L	L	L	L

Bandastra 1988	USA	<1500g	Indo 0.2mg/kg, 12hr, 0.1mg/kg Q12hr x 2 doses.	Placebo	L	L	L	L	L	L	L
Hanigan 1988	USA	500-1500g	Indo 0.1mg/kg 12,24,48,72hr.	Saline	L	L	L	L	L	L	L
Ment 1988	USA	500-1500g	Indo 0.1mg/kg Q24hr x 3 doses.	Saline	L	L	L	L	L	L	L
Krueger 1987	USA	600-1250g	Indo 0.2mg/kg 24hr of age.	No Treatment	U	U	H	U	L	L	L
Vincer 1987	Multicenter	750-1500g	Indo 0.2mg/kg, 12hr, Q12hr.	Saline	U	U	L	L	L	L	L
Ment 1985	USA	600-1250g	Indo 0.2mg/kg, 0.1mg/kg Q12hr for 5 doses.	Saline	L	L	L	L	L	L	L
Indomethacin pre-symptomatic treatment for PDA vs. placebo											
Kluckow 2014	Multicenter	<29wk	Indo 0.2mg/kg, then 0.1mg/kg Q24hr x2 days.	Saline	L	L	L	L	L	L	U
Ibuprofen prophylaxis for PDA vs. placebo											
Kalani 2016	Iran	<32wk <1500g	Ibup 10,5,5mg/kg Q24h for 3 days.	Standard care	U	U	U	U	L	U	L
Kanmaz 2013	Turkey	<28wk <1000g	Ibup 10mg/kg, 12-24hr, then 5mg/kg Q24hr, 48hr.	No Treatment	L	L	H	U	L	L	H
Dani 2005	Multicenter	<28wk	Ibup 10mg/kg, 6hrs then 5mg/kg after 24hr, 48hr.	Placebo	U	L	L	U	L	U	L
Gournay 2004	Multicenter	<28wk	Ibup 10/5/5 Q24hr.	Saline	U	L	L	L	L	U	L
Van Overmeire 2004	Multicenter	24-30wk	Ibup10mg/kg, 6hr then 5mg/kg Q24hr, 48hr.	Saline	L	L	L	L	L	L	L
De Carolis 2000	Italy	<31wk >500g	Ibup 10mg/kg, 2 then 5mg/kg Q24hr and 48hrs	No Treatment	U	U	H	U	L	U	L
Dani 2000	Multicenter	<34wk	Ibup 10mg/kg, 24hr, then 5mg/kg at 24hr and 48hr	No Treatment	U	L	H	U	L	U	L
Varvarigou 1996	Canada			Placebo	U	U	L	L	L	L	L

		<32wk <1500g	Ibup10mg/g, 3hr then 5mg/kg at 24hr and 48hr								
Ibuprofen pre-symptomatic treatment for PDA vs. placebo											
Roze 2020 (TRIOAPI)	Multicenter	24-27wk	Ibup 10mg/kg, then 5mg/kg 24hr, 48 hrs.	Placebo	L	L	L	L	L	L	L
Sosenko 2012	USA	23-32wk	Ibup 10mg/kg then 5mg/kg Q24hr x 2.	5% Dextrose	L	L	L	L	L	L	L
Aranda 2009	Multicenter	<30wk, 500-1000g	Ibup 10mg/kg then 5mg/kg Q24hr x 2.	Placebo	L	L	L	L	L	L	L
Restrictive vs. liberal packed red cell transfusion for anemia											
Franz 2020 (ETTNO RCT)	Multicenter	400-999g	PRBC depends on critical and non-critical health.	NA	L	L	H	L	L	L	L
Kirpalani 2020 (TOP Trial)	Multicenter	<1000g	PRBC transfusion depends on algorithm.	NA	L	L	H	U	L	L	L
Chen 2009	Taiwan	<1500g	Liberals HCT >45,40,30% (Vent, NIV, Spont breathing)	NA	L	L	H	U	L	U	L
Kirpalani 2006	Multicenter	<31wk <1000g	Restrictive HCT kept >35%, 30, 22%. BT depends upon respiratory support, age and cap/central HCT.	NA	L	L	H	L	L	L	L
Bell 2005	USA	500-1300g	PRBC given according to cap HCT value.	NA	L	L	H	L	H	H	L
Connelly 1999	Canada	<1500g	PRBC according to Hb value at various postnatal week+ resp support	NA	L	L	H	H	L	L	L
Low vs. high threshold for platelet transfusion for thrombocytopenia											
Curley 2019 (PlaNet 2)	Multicenter	<34wk Plt <50k	Plt transfusion 15ml/kg when Plt <25K.	Plt transfusion 15ml/ kg when Plt <50K.	L	U	H	L	L	L	L
Kumar 2019	India	<35wk			L	L	H	U	L	L	L

		Plt <100k	Plt transfusion to keep >100K.	Plt transfusion 15ml/kg when Plt <50K.							
Prophylactic plasma administration vs. placebo to reduce IVH/PVL											
NNI Trial group 1996	UK	<32wk	Prophylactic plasma infusion 20ml/kg.	10% Dextrose	L	L	H	H	L	U	L
Beverly 1985	UK	<1500g <32wk	FFP 10ml/kg at admission and then at 24hr of age	NA	U	H	H	L	L	U	L
Prophylactic factor VII administration vs. placebo to reduce IVH/PVL											
NO STUDIES											
Prophylactic antithrombin III administration vs. placebo to reduce IVH/PVL											
Fulia 2003	Italy	<30wk Anti III <40%	Anti III loading dose 2 ml/kg (100 U/kg) IV then 1ml/kg (50U/kg) Q8hr.	5% Dextrose	L	H	U	U	L	U	L
Schmidt 1998	Canada	750-1900g	Anti III loading dose 2 ml/kg (100 U/kg) 1ml/kg (50U/kg) Q6hr, 48hr.	1% Albumin	L	L	L	L	L	L	U
Prophylactic ethamsylate administration vs. placebo to reduce IVH/PVL											
Sanghvi 1999	India	<34wk	Etham 12.5 mg at 1 hr then Q6hr X 4 days.	Routine therapy	L	L	U	L	H	L	L
EC Trial group 1994	Multicenter	<32wk <4hr	Etham 12.5mg/kg then 15 dose Q6hr x 4 days.	Placebo	L	H	L	L	U	L	L
Chen 1993	Taiwan	<1751g	Etham 12.5mg/kg, 1 hr, then Q6hr for 4 days.	Saline	U	U	L	L	L	L	L
Amato 1992	Switzerland	Pre-term	Etham 12.5 mg/kg 4hr of birth, then Q6hr x 4 days.	Saline	U	U	U	U	L	L	L
Benson 1986	UK	<1500g	Etham 12.5 mg/kg 1 hr of birth, then Q6hr for 4 days.	Placebo	L	L	L	L	L	L	L
Morgan 1981	UK	<1500g	Etham 12.5 mg/kg 2 hr of birth, then Q6hr for 4 days.	Placebo	L	L	L	L	L	L	L

Prophylactic heparin administration vs. placebo to reduce IVH/PVL											
Chang 1997	USA	<31wk	Heparin 1U/ml through UVC.	No Heparin	U	U	L	L	L	U	U
Stem cell therapy											
No RCT											
Vitamin A supplementation vs. placebo for the outcome severe IVH											
Sun 2020	China	<28 days <96hr	Vit A 1500IU/day, until 28 days or discharge, IM.	Placebo	U	U	L	L	L	L	L
Kiatchoosakun 2014	Thailand	<1500g	Vit A 5000IU Mon, Wed, Fri for 4wk IM.	Sham Procedure	L	L	L	U	L	U	L
Mactier 2012	Glasgow	<1501g <32wk	Vit A 10,000 IU IM x 3/wk Max 12 doses.	NA	L	L	L	L	L	L	L
Ravishankar 2003	USA	<32wk 500-1500G	Vit A 50,000 IU/mL, 1, 3 and 7 days, IM.	Sham Procedure	U	L	L	L	L	U	L
Tyson 1999	Multicenter	401-1000g	Vit A 5000IU Mon, Wed, Fri for 4wk, IM.	Sham Procedure	L	L	L	L	L	L	L
Bental 1994	SA	1000-1500g, ≤34wk	Vit A 4000 units IM x 3/wk total 12 doses.	NA	L	U	U	U	L	L	U
Papagaroufalis 1991	Greece	25-29wk 560-1240g	Vit A 5000U IM AD X 8 dose over 15days.	NS	U	U	H	U	L	U	L
Vitamin E supplementation vs. placebo for the outcome severe IVH											
Barekatein 2018	Iran	<30wk	10U of Vit E oral x3 days. Vit E IM 15mg, then 10mg OD 1,2,4,6 days.	Distilled water	U	U	U	U	L	L	L
Fish 1990	USA	<1000g		Placebo	L	L	L	L	H	U	L
Phleps 1987	USA			Placebo	L	L	L	L	L	U	L

Sinha 1987	UK	<1500g <33wk	Vit E 20mg/kg IV repeated on D2, D3, Cont'd till retinal exam.	No Placebo	L	L	H	U	L	U	L
Hittner 1984	USA	≤32wk	Vit E 20mg/kg IM D0, then Q24hr and 48hr.	Placebo	L	L	L	L	L	L	L
		<1500g +RDS	Vit E 100mg/kg 24hr of age and then IM injection at 15, 10, 10, and 10 mg/kg on days 1,2,4 and 6.								
Speer 1984	USA	<1500g,	Vit E 100mg/kg via NGT, IM D1,2,4,6.	Placebo	U	U	U	L	L	U	L
Hittner 1981	USA	<1500g,	Vit E 100 mg/kg/day till stay.	Placebo	L	L	L	L	L	L	L
Vitamin K supplementation vs. placebo for the outcome severe IVH											
No RCT											

NOTE: **AD:** Alternate days, **Alb:** Albumin, **Amp:** Amplitude, **Anti III:** Antithrombin III, **Beta:** Betamethasone, **Caff:** Caffeine, **Cap:** capillary, **cm:** centimeter, **CPAP:** Continuous Positive Airway Pressure, **CV:** Conventional ventilation, **DCC:** Delayed Cord Clamping, **Dexa:** Dexamethasone, **Dobu:** Dobutamine, **Dopa:** Dopamine, **ECC:** Early Cord Clamping, **EPO:** Erythropoietin, **Etham:** Ethamsylate, **ETT:** Endotracheal Tube, **FFP:** Fresh frozen plasma. **Fr:** French, **G:** Gauge, **g:** gram, **H:** High, **Hb:** Hemoglobin, **HCT:** Hematocrit, **HFOV:** High Frequency Oscillation Ventilation, **Hz:** Hertz, **hr:** Hour, **H2O:** Water, **Ibup:** Ibuprofen, **IM:** Intramuscular, **IMV:** Intermittent mandatory ventilation, **Indo:** Indomethacin, **IPPV:** Intermittent Positive Pressure Ventilation, **IVH:** Intraventricular Hemorrhage, **IU:** International Unit, **IV:** Intravenous, **K:** Thousand, **Kg:** kilogram, **KSA:** kingdom of Saudi Arabia, **L:** Loading dose, **M:** Maintenance dose, **MAP:** Mean Airway Pressure, **L:** Low **MISA:** Minimally invasive surfactant administration, **Midaz:** Midazolam, **MgSO4:** Magnesium Sulphate, **NA:** Not Available, **NGT:** Nasogastric tube, **NIV:** Non-invasive ventilation, **NS:** Normal Saline, **OD:** Once Daily, **PC:** Pressure Control, **PEEP:** Positive End Expiratory Pressure, **PIP:** Peak Inspiratory Pressure, **PPV:** Positive Pressure Ventilation, **Plt:** Platelet, **PLV:** Pressure-limited ventilation, **PaCO2:** Partial pressure of carbon dioxide, **PRVC:** Pressure regulated volume control, **PRBC:** Packed Red blood Cell, **PSV:** Pressure support ventilation, **PVL:** Peri-ventricular leukomalacia, **Q (12,24,36,48):** Every (12,24,36,48), **SIPPV:** Synchronous intermittent positive pressure ventilation, **SIMV:** Synchronized intermittent mandatory ventilation, **SA:** South Africa, **SC:** Subcutaneous, **Sec:** Seconds, **SLI:** Sustained Lung inflation, **SpO2:** Oxygen saturation, **U:** Uncertain, **UVC:** Umbilical

Venous Catheter, **UCM:** Umbilical Cord Milking, **USA:** United States of America, **UK:** United Kingdom, **VG:** Volume Guarantee, **Vit A:** Vitamin A, **Vit E:** Vitamin E, **Vit K:** Vitamin K, **VT:** Tidal Volume, **Wk:** Week, **X:** times.

e-Table 2: Summary of meta-analysis of interventions on cystic periventricular leukomalacia and severe brain injury.

			RR (95% CI)	Heterogeneity (I ²)	GRADE
CYSTIC PVL					
Antenatal Interventions					
Antenatal corticosteroids for lung maturity	01	326	5.25(0.25, 108.51)	NA	Low ³
Betamethasone <i>vs.</i> Dexamethasone for lung maturity	01	157	0.47 (0.04, 5.07)	NA	Low ^{1, 3}
Repeat antenatal steroids <i>vs.</i> no repeat antenatal steroids	03	3113	0.98 (0.46, 2.07)	00	Moderate ¹
Magnesium sulfate for neuroprotection or tocolysis	02	1900	0.97 (0.66, 1.42)	00	High
Delivery Room Interventions					
Lower <i>vs.</i> higher FiO2 for resuscitation at birth	02	157	0.33 (0.01, 7.97)	NA	Low ^{1, 3}
Sustained inflation <i>vs.</i> standard resuscitation	05	635	0.59 (0.24, 1.44)	00	Low ^{1, 3} (
Umbilical cord milking <i>vs.</i> immediate cord clamping	01	40	0.50 (0.05, 5.08)	NA	Very low ^{1, 3}
Postnatal Interventions					
Supine head midline <i>vs.</i> Supine head rotated	02	228	3.25(0.14, 76.01)	NA	Low ^{1, 3}
LISA <i>vs.</i> INSURE	02	431	0.69 (0.30, 1.57)	75	Very low ^{1, 2, 3}
Volume guarantee <i>vs.</i> pressure limited ventilation	01	40	3.0 (0.13, 69.52)	NA	Low ^{1, 3}
Elective HFOV <i>vs.</i> conventional ventilation	04	1365	0.76 (0.49, 1.16)	00	Low ^{1, 3}
Elective HFJV <i>vs.</i> conventional ventilation	01	64	5.0 (1.19, 21.04)	NA	Low ^{1, 3}
Oxygen saturation target after birth: 85-89% <i>vs.</i> 91-95%	01	1272	1.23(0.73, 2.08)	NA	High
Permissive hypercapnia <i>vs.</i> normocapnia	01	49	1.04 (0.16, 6.81)	NA	Low ^{1, 3}
Caffeine prophylaxis or treatment for apnea or post-extubation	01	2016	0.65 (0.39, 1.07)	NA	High
High dose <i>vs.</i> low dose caffeine for apnea or post-extubation	01	246	0.48 (0.17, 1.33)	00	Low ^{1, 3}
Sedation during ventilation: opioids <i>vs.</i> no opioids	01	734	0.79 (0.49, 1.29)	NA	Moderate ³
Neuromuscular paralysis during ventilation	01	193	1.26 (0.35, 4.56)	NA	Low ^{1, 3}
Early erythropoiesis-stimulating agents	03	1551	0.59 (0.42, 0.83)	00	Low ¹
Indomethacin prophylaxis for PDA	02	289	0.36 (0.12, 1.06)	00	Moderate ³
Indomethacin pre-symptomatic treatment for PDA	01	92	1.09 (0.29, 4.10)	NA	Low ^{1, 3}
Ibuprofen prophylaxis for PDA	03	701	1.21 (0.63, 2.30)	00	Moderate ¹
Restrictive <i>vs.</i> liberal packed cell transfusion for anemia	03	1558	0.91 (0.56, 1.47)	34	Moderate ¹
SEVERE BRAIN INJURY					

Antenatal Interventions					
Antenatal corticosteroids for lung maturity	01	1530	1.78 (0.45,7.08)	NA	High
Delivery Room Interventions					
Delayed cord clamping <i>vs.</i> immediate cord clamping	02	2905	1.16 (0.80,1.69)	00	Moderate ¹
Postnatal Interventions					
Elective HFOV <i>vs.</i> conventional ventilation	04	1769	0.79 (0.63, 0.99)	00	Low ^{1,3}
Oxygen saturation target after birth: 85-89% <i>vs.</i> 91-95%	04	3348	0.94 (0.80, 1.10)	16	High
Caffeine prophylaxis or treatment for apnea or post-extubation	01	1933	0.91 (0.73, 1.14)	NA	High
Indomethacin prophylaxis for PDA	02	1215	0.85 (0.70, 1.05)	04	Moderate ³
Restrictive <i>vs.</i> liberal packed cell transfusion for anemia	03	2248	0.94 (0.78, 1.13)	40	Moderate ¹

Note: **CI:** confidence interval; **FiO₂:** fraction of inspired oxygen; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation—¹Risk of bias, ²heterogeneity, ³imprecision, ⁴publication bias, ⁵inconsistency; **HFJV:** high-frequency oscillatory ventilation; **HFOV:** high-frequency oscillatory ventilation; **INSURE:** Intubate-surfactant-extubate; **IVH:** intraventricular hemorrhage; **LISA:** less-invasive surfactant treatment; **NA:** not available; **PDA:** patent ductus arteriosus; **PVL:** periventricular leukomalacia; **RCTs:** randomized clinical trials; **RR:** relative risk, ***vs.*:** Versus.

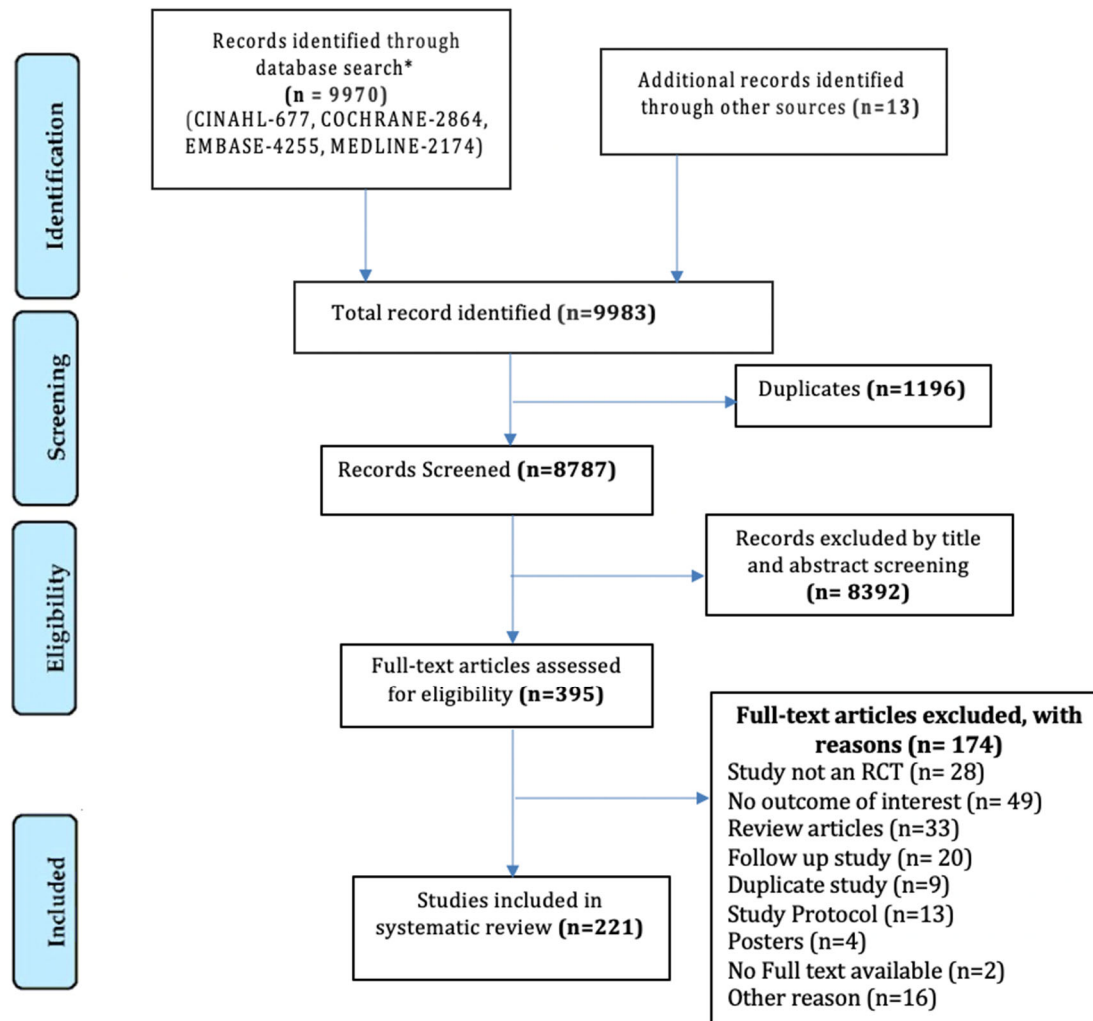
e-Table 3: Summary of sensitivity and subgroup analysis of interventions on severe intraventricular hemorrhage and cystic periventricular leukomalacia

Antenatal corticosteroids for lung maturity	NP	NP	NP	NP
Dexamethasone <i>vs.</i> Betamethasone for lung maturity	NP	NP	NP	NP
Repeat antenatal steroids <i>vs.</i> no repeat antenatal steroids	NP	NP	NP	NP
Magnesium sulfate for tocolysis or neuroprotection	NP	NP	NP	NP
Antibiotics for premature rupture of membranes	NP	NP	NP	NP
Cesarean section <i>vs.</i> vaginal delivery for preterm birth	NP	NP	NP	NP
Lower <i>vs.</i> higher FiO2 for resuscitation	NP	NP	NP	NP
Sustained inflation <i>vs.</i> standard resuscitation	NP	NP	NP	NP
Delayed cord clamping <i>vs.</i> immediate cord clamping	NP	NP	NP	NP
Umbilical cord milking <i>vs.</i> immediate cord clamping	NP	NP	NP	NP
Umbilical cord milking <i>vs.</i> delayed cord clamping	NP	NP	NP	NP
Delayed cord clamping with respiratory support <i>vs.</i> delayed cord clamping without respiratory support	NP	NP	NP	NP
Head midline position	NP	NP	NP	NP
LISA <i>vs.</i> INSURE	NP	NP	No high-quality studies	Subgroup data not available
Volume guarantee <i>vs.</i> conventional ventilation	NP	NP	NP	NP
Elective HFOV <i>vs.</i> conventional ventilation	NP	NP	NP	NP
Elective HFJV <i>vs.</i> conventional ventilation	NP	NP	NP	NP
Oxygen saturation target after birth: 85-89% <i>vs.</i> 91-95%	NP	NP	NP	NP
Permissive hypercapnia <i>vs.</i> normocapnia	NP	NP	NP	NP
Early extubation <i>vs.</i> delayed extubation	NP	NP	NP	NP
Caffeine prophylaxis or treatment for apnea or post-extubation	0.86 (0.67,1.11), I ² =NA n=1933, 1 trial (GRADE)	Subgroup data not available	NP	NP

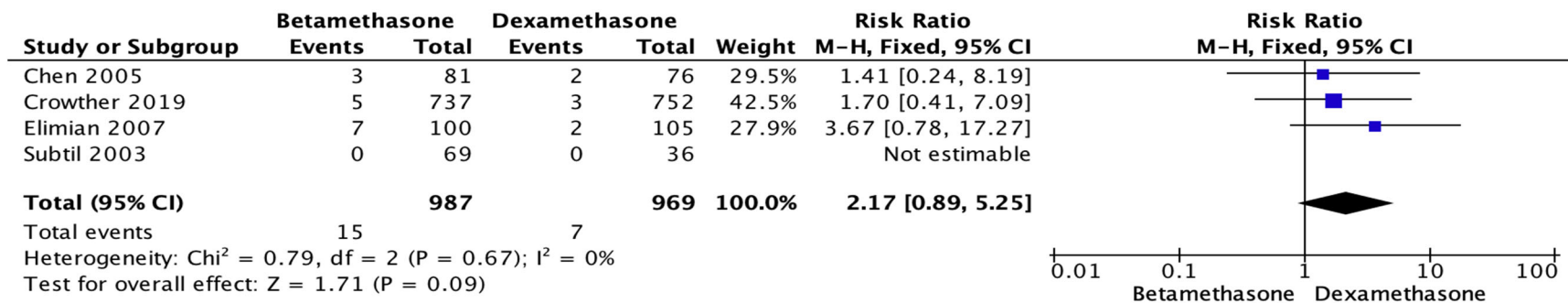
High dose <i>vs.</i> low dose caffeine for apnea or post-extubation	NP	NP	NP	NP
Sedation during ventilation: midazolam <i>vs.</i> no midazolam	NP	NP	NP	NP
Sedation during ventilation: opioids <i>vs.</i> no opioids	NP	NP	NP	NP
Sedation during ventilation: phenobarbitone <i>vs.</i> no phenobarbitone	NP	NP	NP	NP
Neuromuscular paralysis during ventilation	No high-quality studies	Subgroup data not available	NP	NP
Early erythropoiesis-stimulating agents	0.99 (0.76. 1.31), I ² =42%, n=1372, 6 trials (GRADE-low)	Subgroup data not available	NP	NP
Volume expansion <i>vs.</i> inotropes (any) for hypotension	NP	NP	NP	NP
Dopamine <i>vs.</i> dobutamine for hypotension	NP	NP	NP	NP
Indomethacin prophylaxis for PDA	NP	NP	NP	NP
Indomethacin pre-symptomatic treatment for PDA	NP	NP	NP	NP
Ibuprofen prophylaxis for PDA	NP	NP	NP	NP
Ibuprofen pre-symptomatic treatment for PDA	NP	NP	NP	NP
Restrictive <i>vs.</i> liberal packed cell transfusion for anemia	NP	NP	NP	NP
Low <i>vs.</i> high threshold for platelet transfusion for thrombocytopenia	NP	NP	NP	NP
Prophylactic plasma administration to reduce IVH/PVL	NP	NP	NP	NP
Prophylactic factor VII administration to reduce IVH/PVL	NP	NP	NP	NP
Prophylactic antithrombin III administration to reduce IVH/PVL	NP	NP	NP	NP
Prophylactic ethamsylate administration to reduce IVH/PVL	NP	NP	NP	NP
Prophylactic heparin administration to reduce IVH/PVL	NP	NP	NP	NP
Stem cell therapy	NP	NP	NP	NP
Vitamin A supplementation	NP	NP	NP	NP

Vitamin E supplementation	NP	NP	NP	NP
Vitamin K supplementation	NP	NP	NP	NP

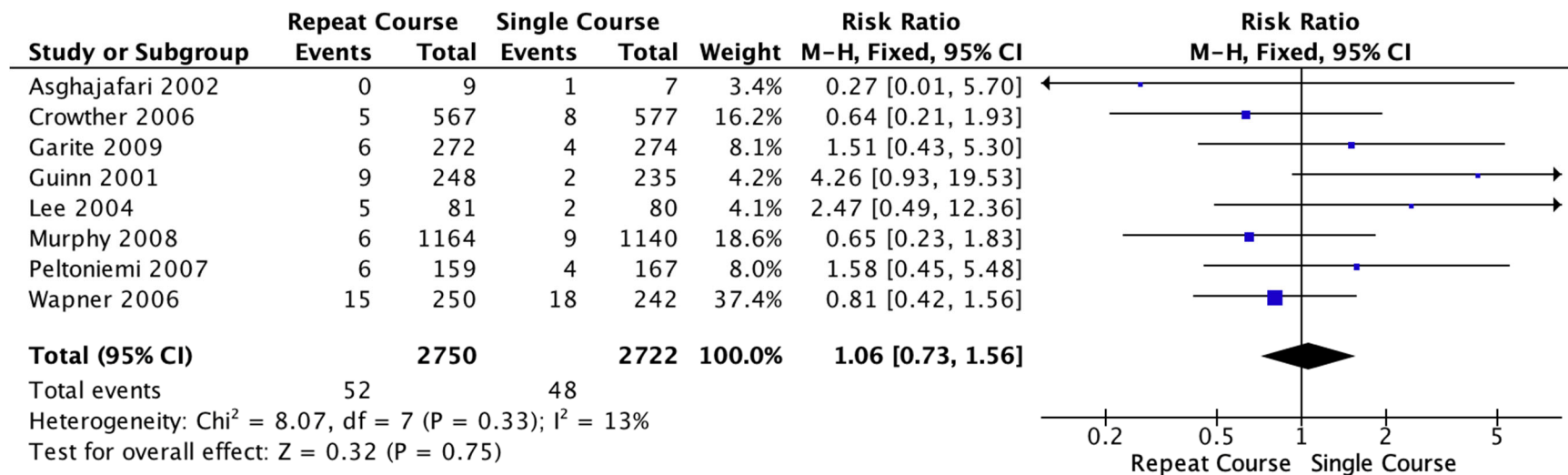
Note: **CI:** confidence interval; **FiO₂:** fraction of inspired oxygen; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation—¹Risk of bias, ²heterogeneity, ³imprecision, ⁴publication bias, ⁵inconsistency; **HFJV:** high-frequency oscillatory ventilation; **HFOV:** high-frequency oscillatory ventilation; **INSURE:** Intubate-surfactant-extubate; **IVH:** intraventricular hemorrhage; **LISA:** less-invasive surfactant treatment; **NA:** not available; **NP:** not performed (no significant heterogeneity in the main meta-analysis); **PDA:** patent ductus arteriosus; **PVL:** periventricular leukomalacia; **RCTs:** randomised clinical trials; **RR:** relative risk, **vs.:** Versus, **NP:** ??



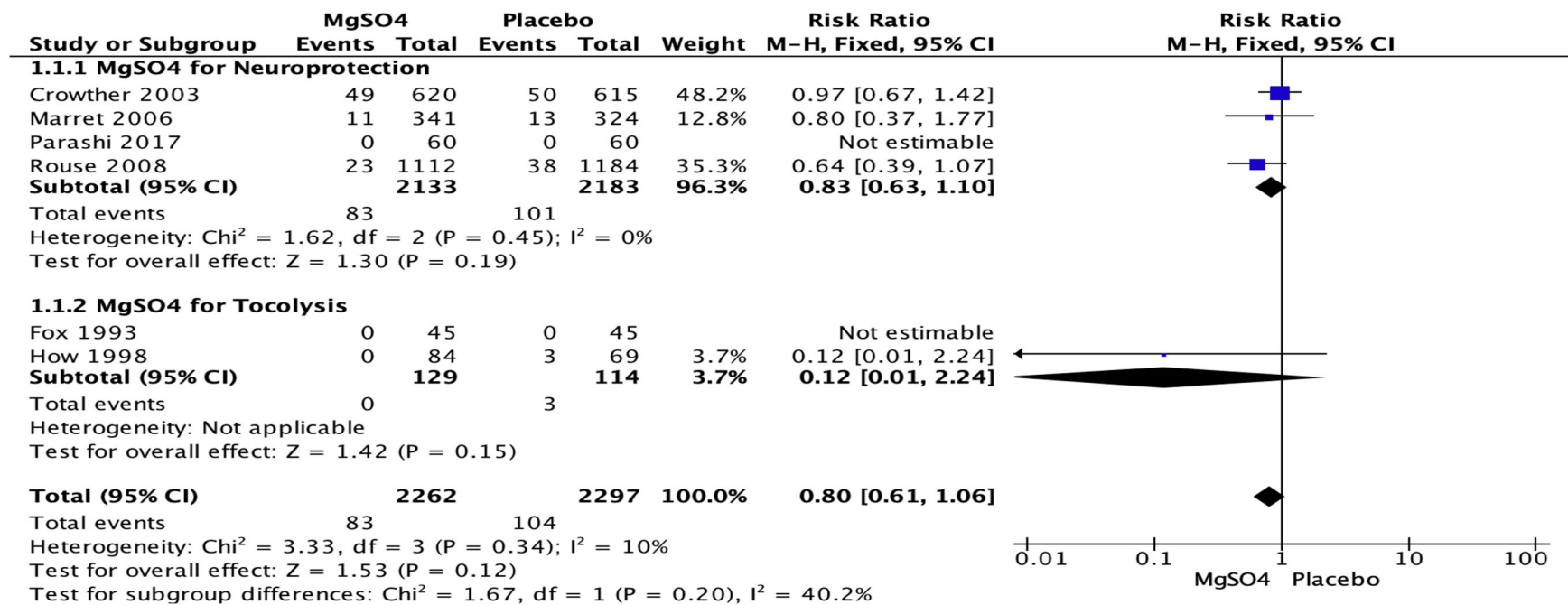
eFigure 1. Study Flow diagram outlining stages of search results and filtering process [as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines]



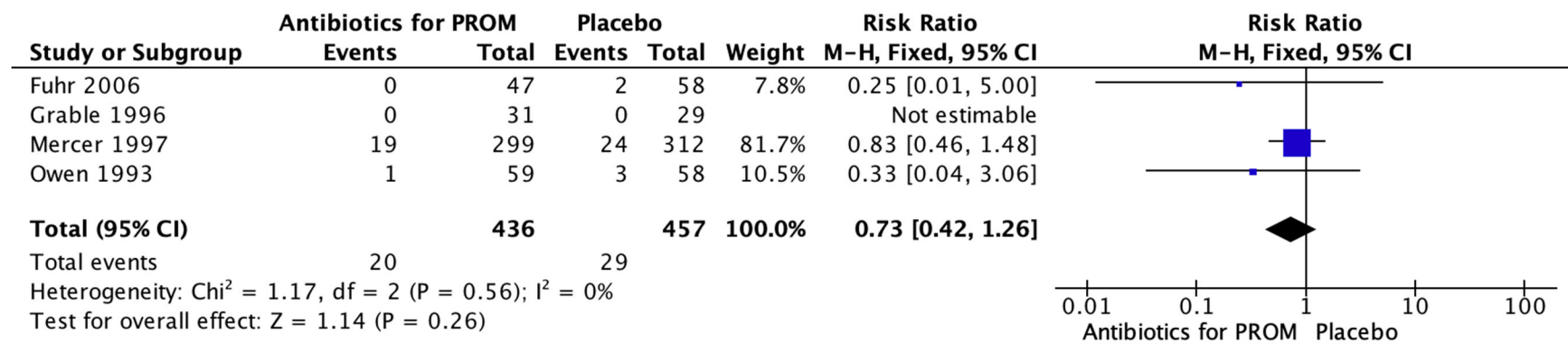
eFigure 2. Forest plot for comparison—Betamethasone for lung maturity vs Dexamethasone for lung maturity for outcome severe IVH.



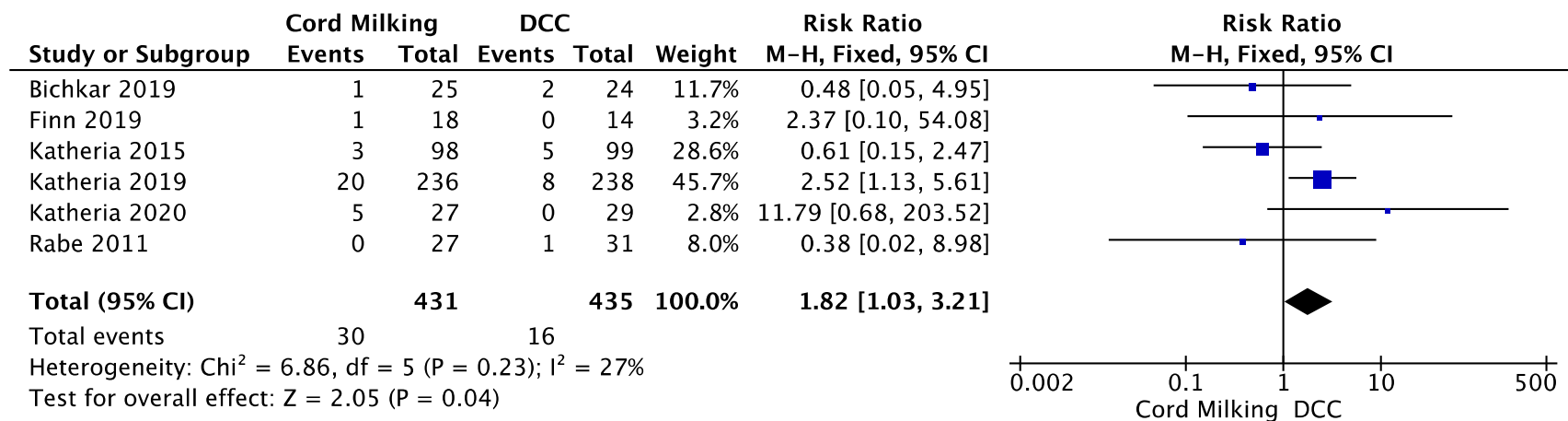
eFigure 3. Forest plot for comparison—Antenatal steroid for lung maturity: repeat course vs single course for outcome severe IVH.



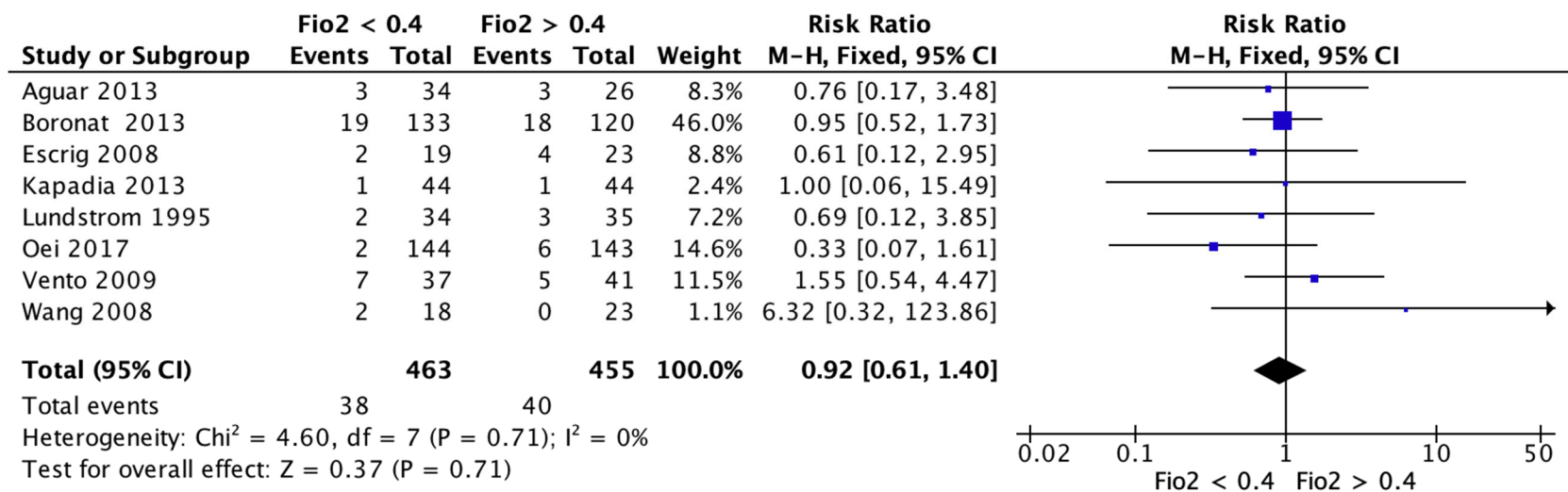
eFigure 4. Forest plot for comparison—Antenatal MgSO4 therapy for Neuroprotection or Tocolysis vs placebo for the outcome severe IVH.



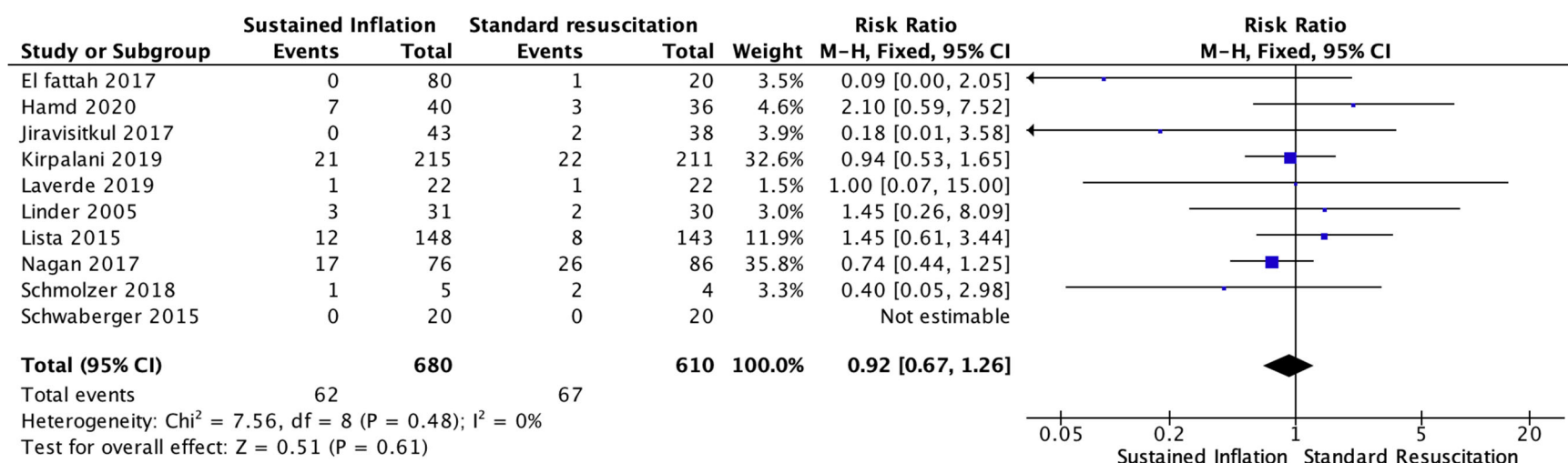
eFigure 5. Forest plot for comparison—Antibiotics for PPRM vs placebo for the outcome severe IVH.



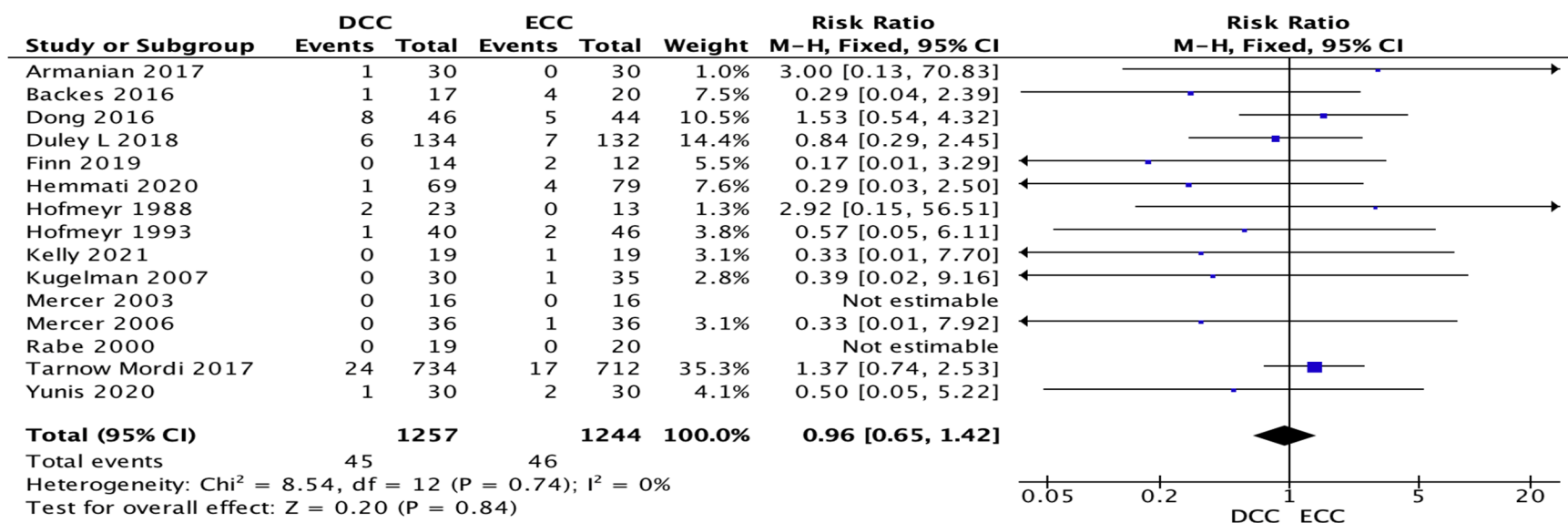
eFigure 6. Forest plot for umbilical cord milking vs. delayed cord clamping in preterm infants for the outcome severe IVH.



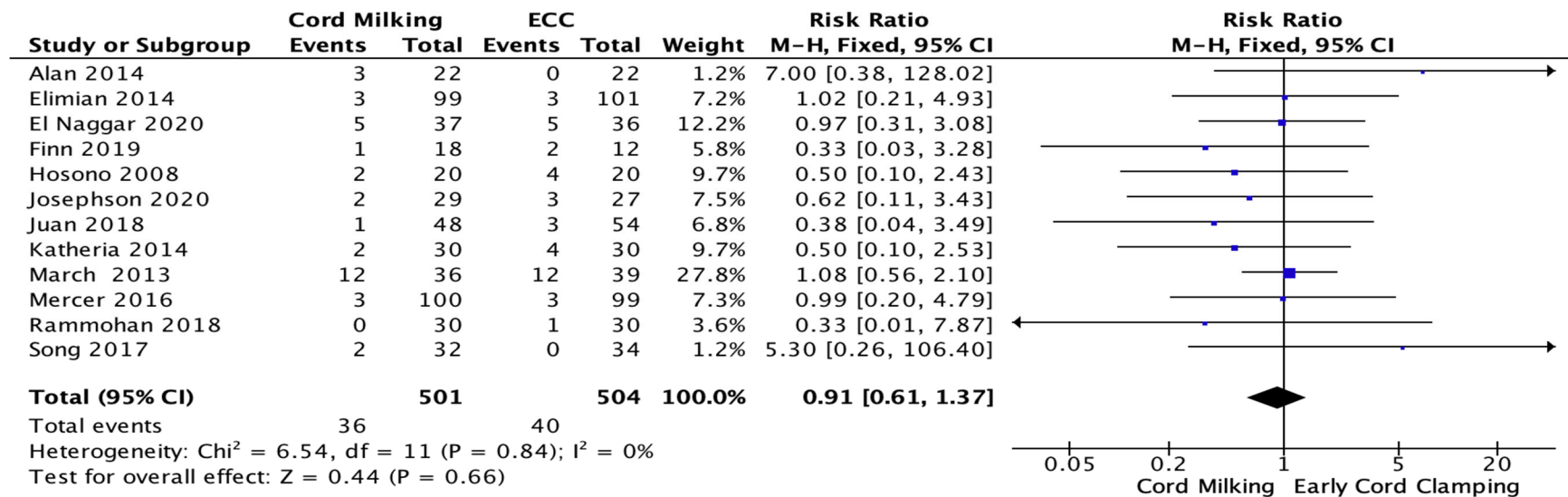
eFigure 7. Forest plot for comparison—lower FiO2 for resuscitation vs. higher FiO2 at resuscitation for the outcome severe IVH.



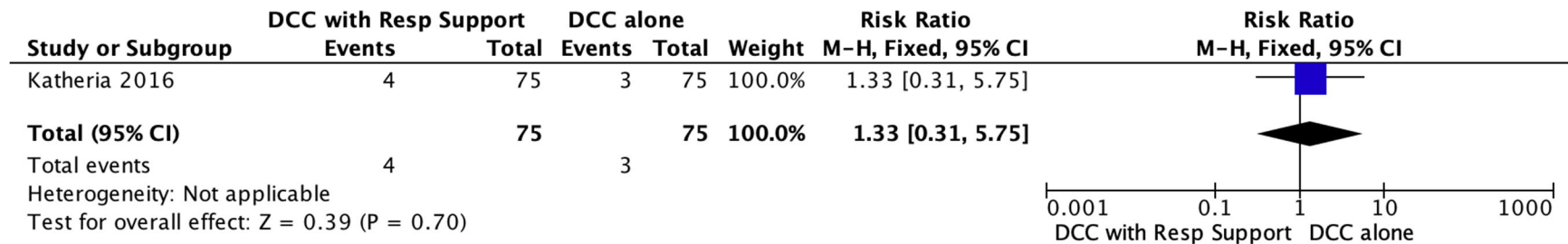
eFigure 8. Forest plot for comparison—Sustained inflation during resuscitation vs. standard resuscitation for the outcome severe IVH.



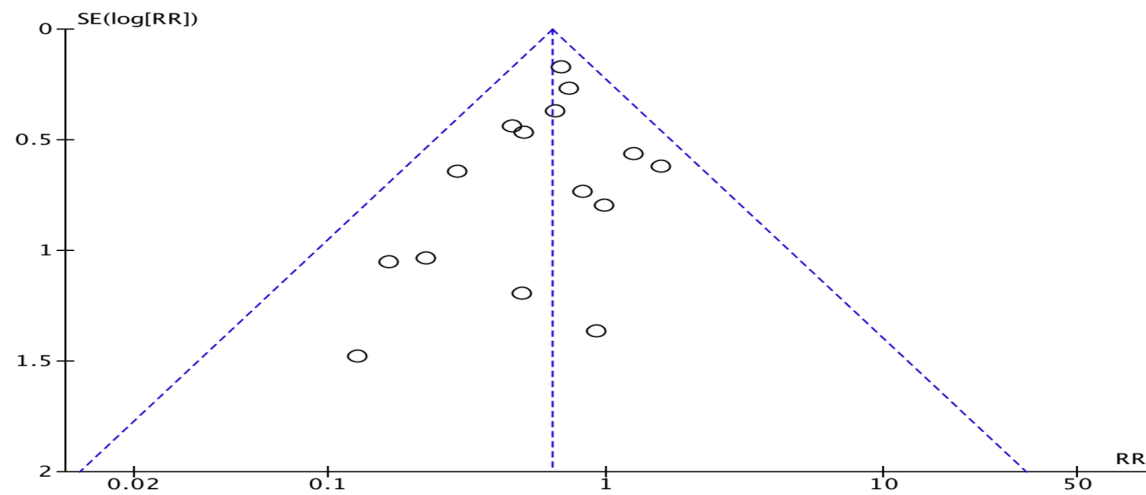
eFigure 9. Forest plot for comparison—Delayed cord clamping vs. early cord clamping for the outcome severe IVH.



eFigure 10. Forest plot for comparison—Umbilical cord milking vs. early cord clamping for the outcome severe IVH.



eFigure 11. Forest plot for comparison—Delayed cord clamping with respiratory support vs. delayed cord clamping without respiratory support for the outcome severe IVH.

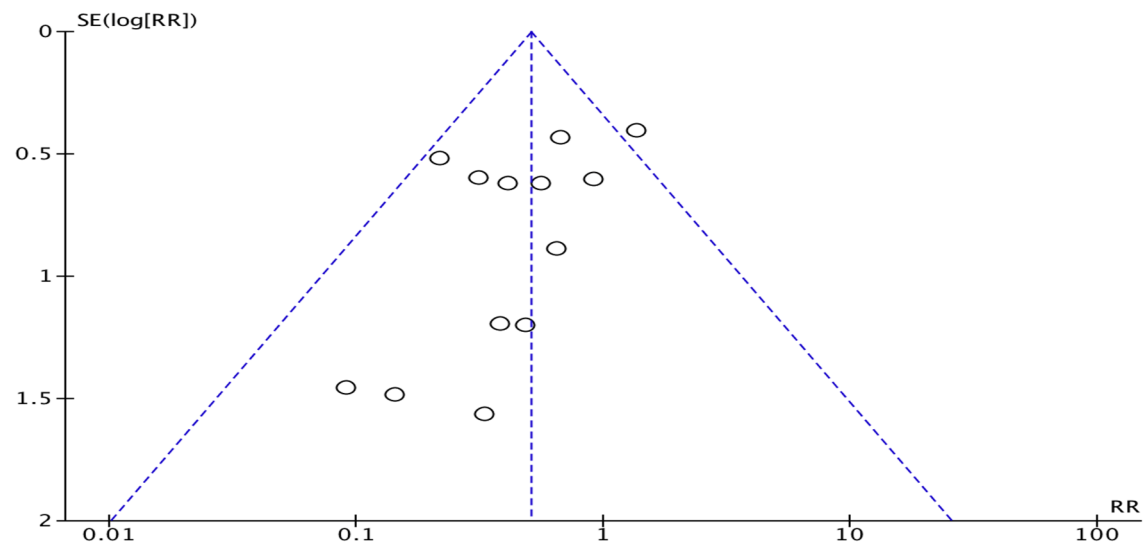


eFigure 12. Funnel plot of Indomethacin prophylaxis for patent ductus arteriosus vs. placebo for outcome severe IVH.

Egger's regression intercept

Intercept	-0.44728
Standard error	0.38610
95% lower limit (2-tailed)	-1.28140
95% upper limit (2-tailed)	0.38685
t-value	1.15845
df	13.00000
P-value (1-tailed)	0.13376
P-value (2-tailed)	0.26752

eFigure 13. Egger's regression test for assessing publication bias for indomethacin prophylaxis for patent ductus arteriosus

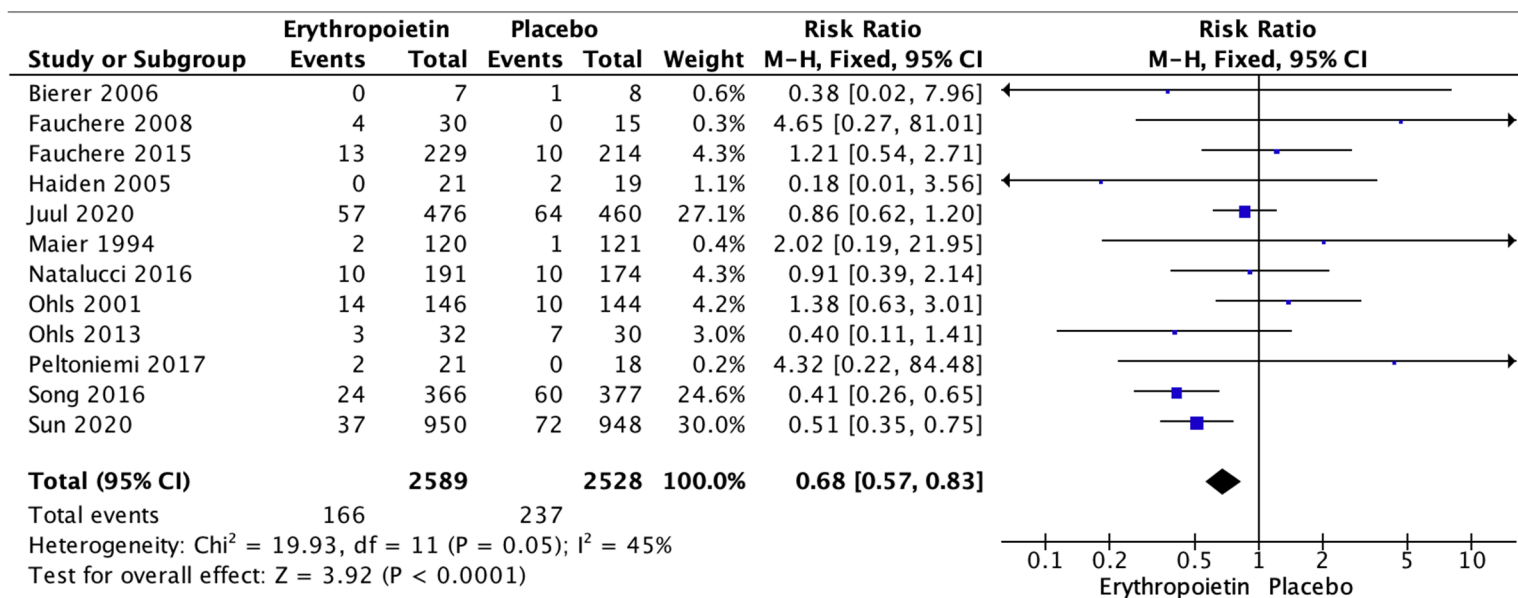


eFigure 14. Funnel plot of volume guarantee ventilation vs. pressure limited ventilation for outcome severe IVH.

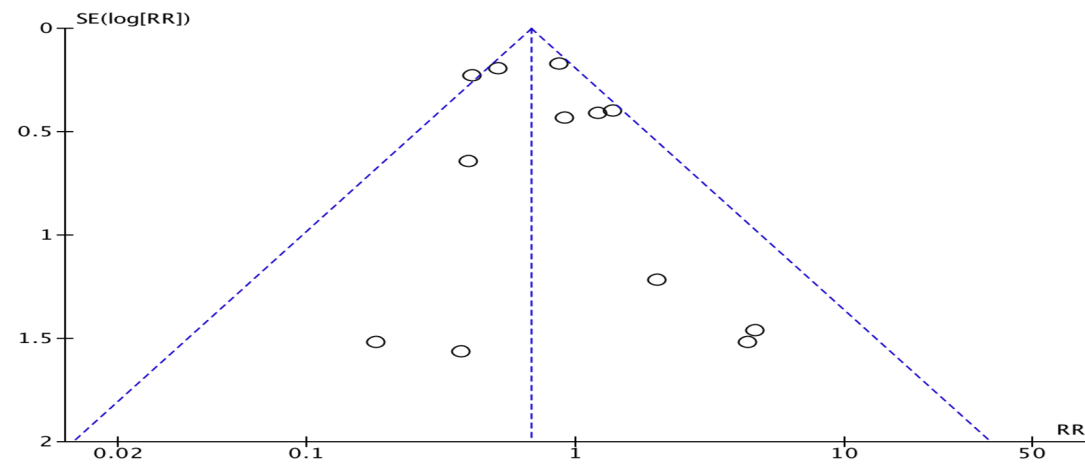
Egger's regression intercept

Intercept	-1.25674
Standard error	0.64404
95% lower limit (2-tailed)	-2.67426
95% upper limit (2-tailed)	0.16077
t-value	1.95136
df	11.00000
P-value (1-tailed)	0.03847
P-value (2-tailed)	0.07694

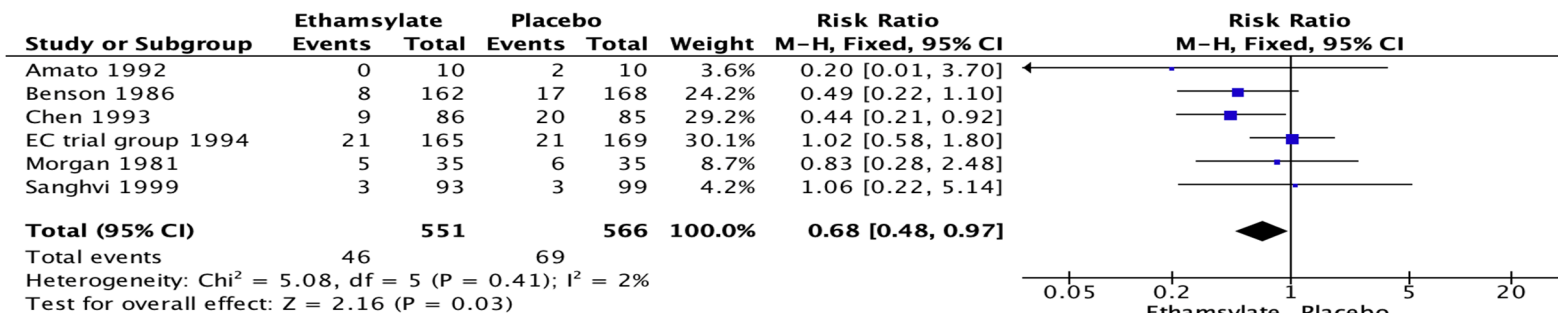
eFigure 15. Egger's regression test for assessing publication bias volume guarantee ventilation vs. pressure limited ventilation for outcome severe IVH



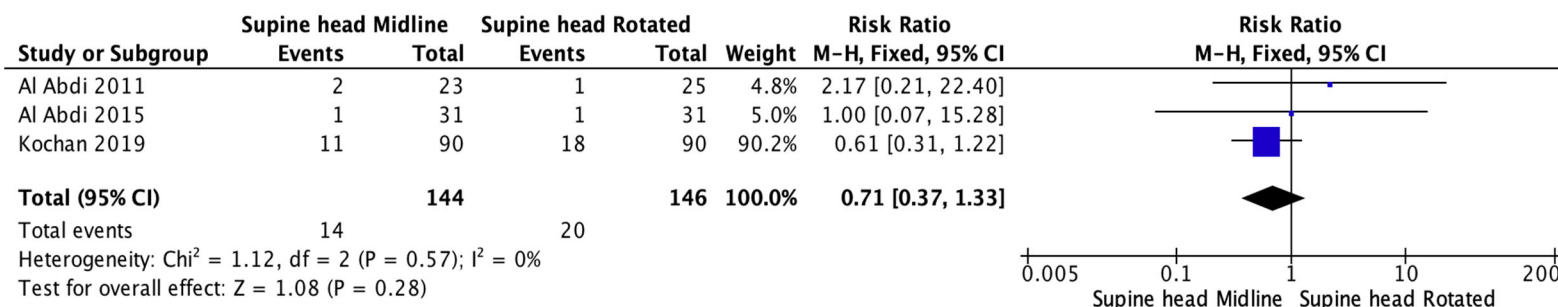
eFigure 16. Forest plot for comparison—Early erythropoiesis-stimulating agents vs. placebo for outcome severe IVH



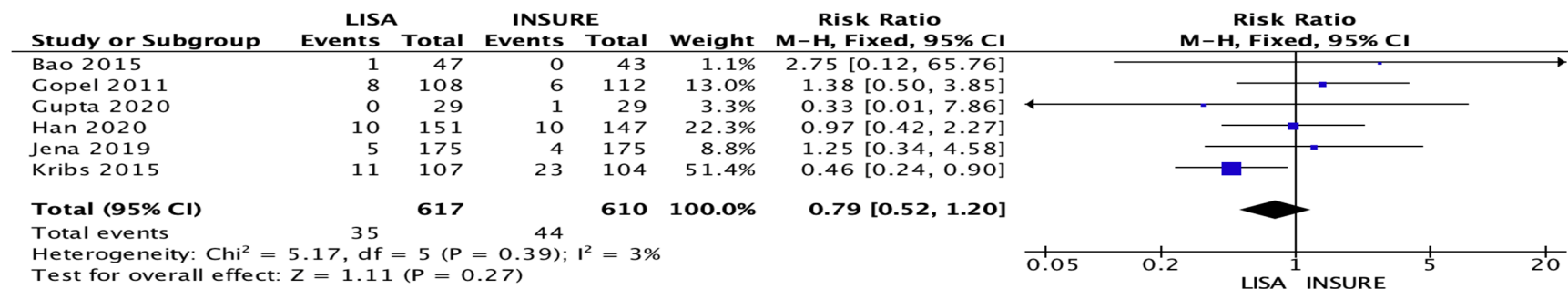
eFigure 17. Funnel plot of Early erythropoiesis-stimulating agents vs. placebo for outcome severe IVH.



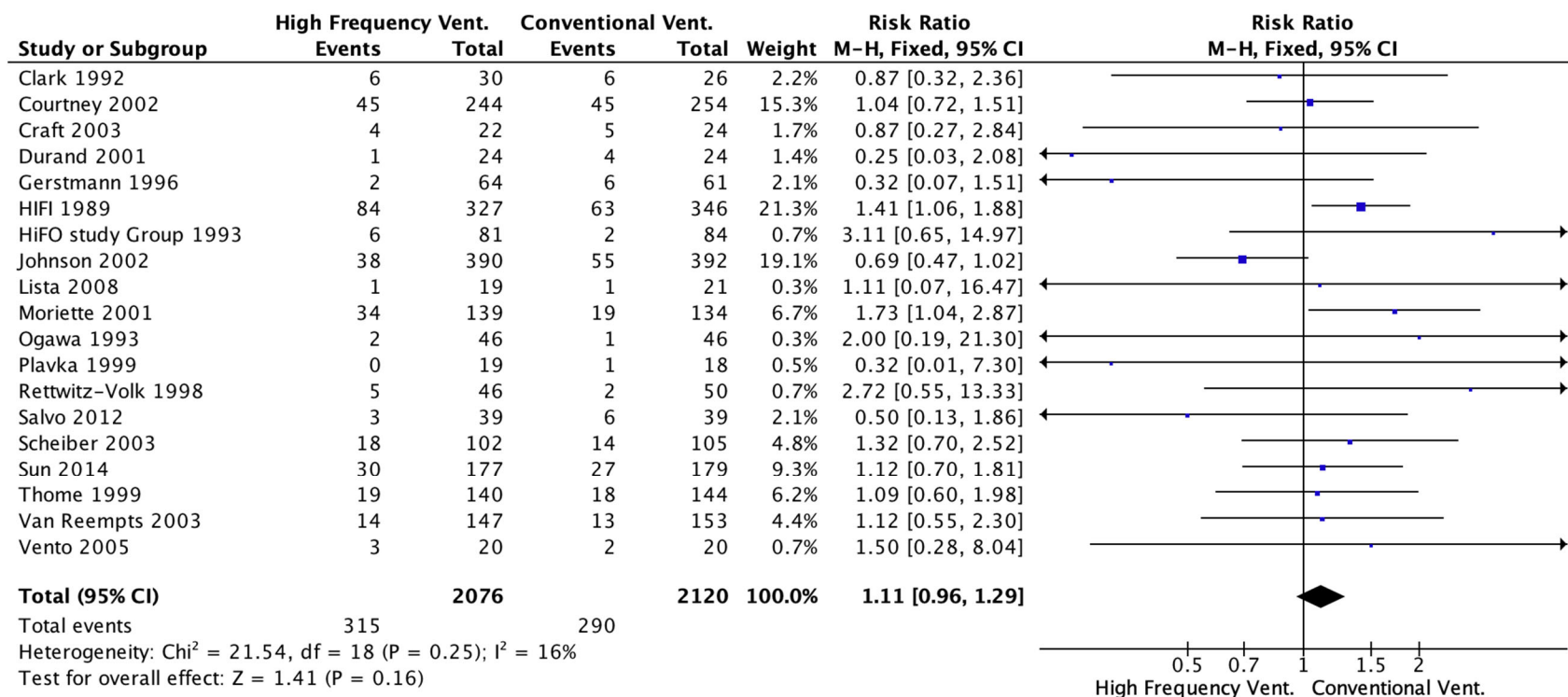
eFigure 18. Forest plot for comparison— prophylactic ethamsylate administration vs. placebo for the outcome severe IVH.



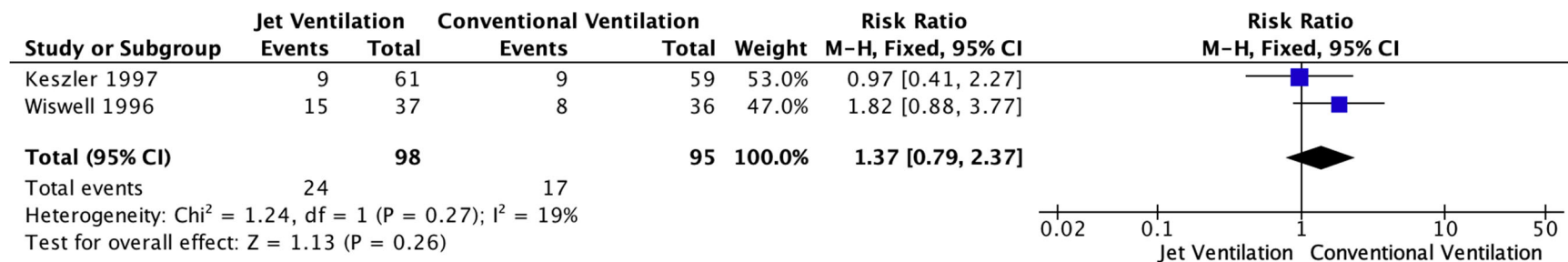
eFigure 19. Forest plot for comparison— Supine head midline vs. supine head rotated for the outcome severe IVH.



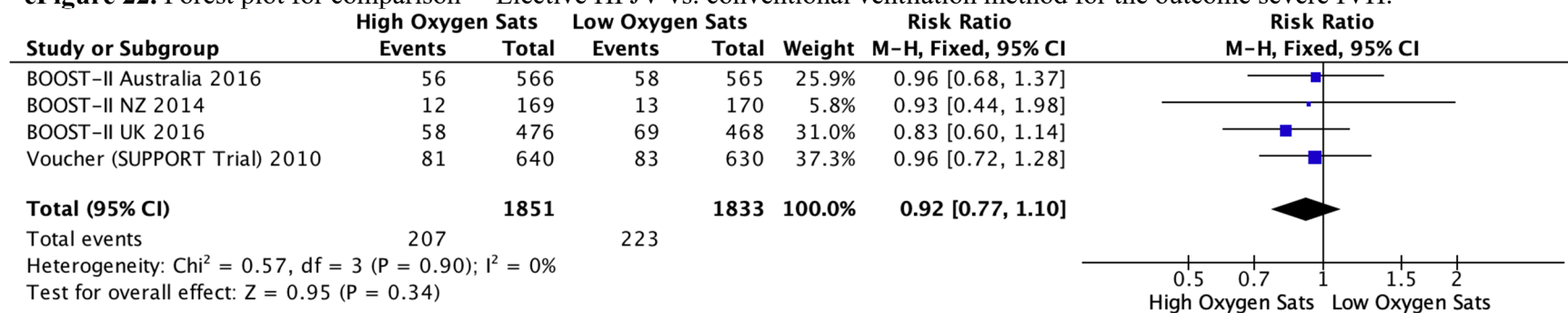
eFigure 20. Forest plot for comparison— LISA vs. INSURE method for surfactant administration for the outcome severe IVH



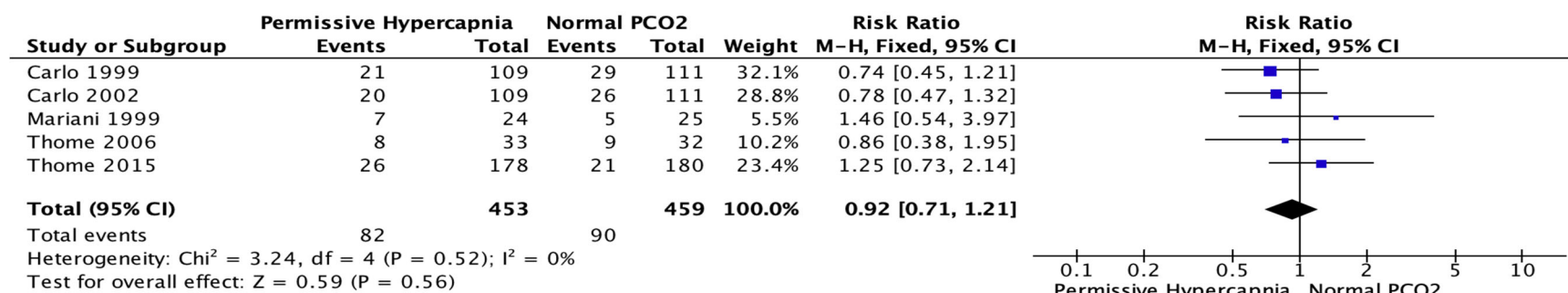
eFigure 21. Forest plot for comparison— Elective HFOV vs. conventional ventilation method for the outcome severe IVH.



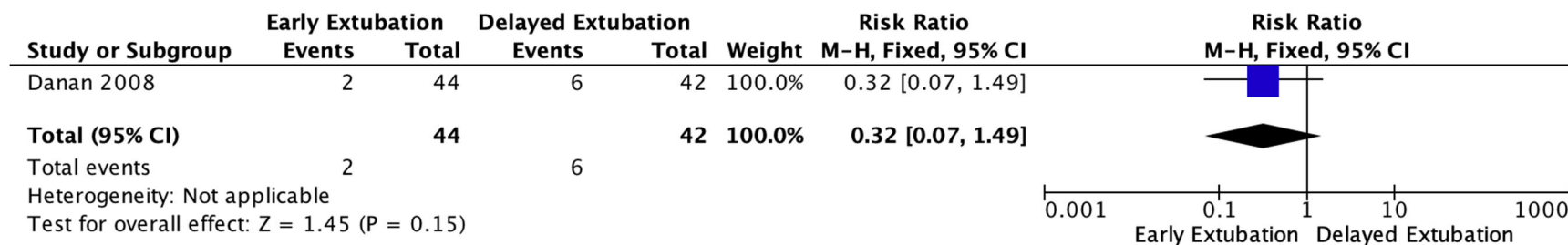
eFigure 22. Forest plot for comparison— Elective HFJV vs. conventional ventilation method for the outcome severe IVH.



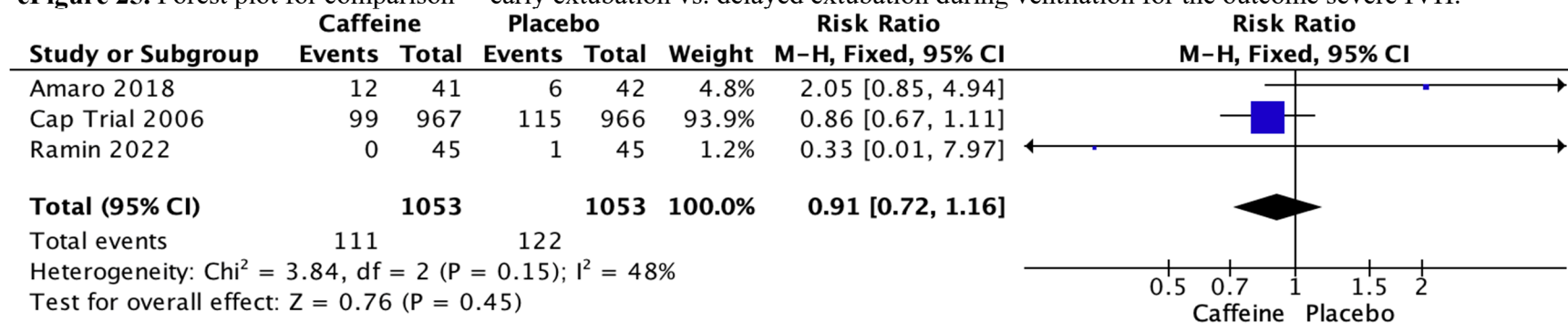
eFigure 23. Forest plot for comparison— high oxygen saturation target (91-95%) vs low oxygen saturation target (85-89%) in NICU for the outcome severe IVH.



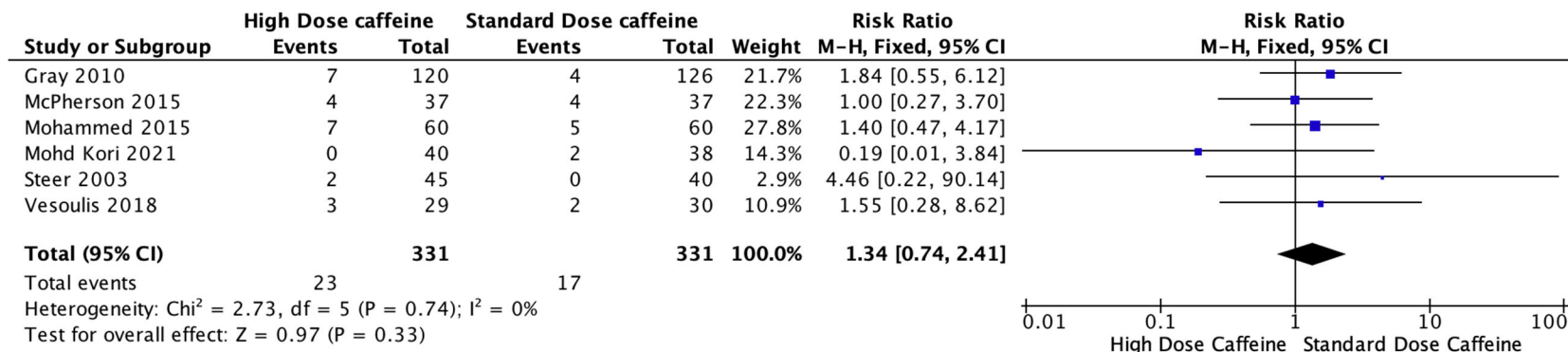
eFigure 24. Forest plot for comparison— permissive hypercapnia vs. normocapnia during ventilation for the outcome severe IVH.



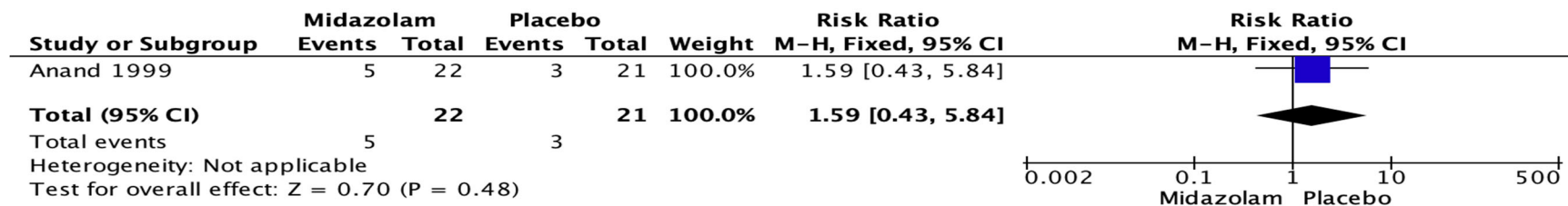
eFigure 25. Forest plot for comparison— early extubation vs. delayed extubation during ventilation for the outcome severe IVH.



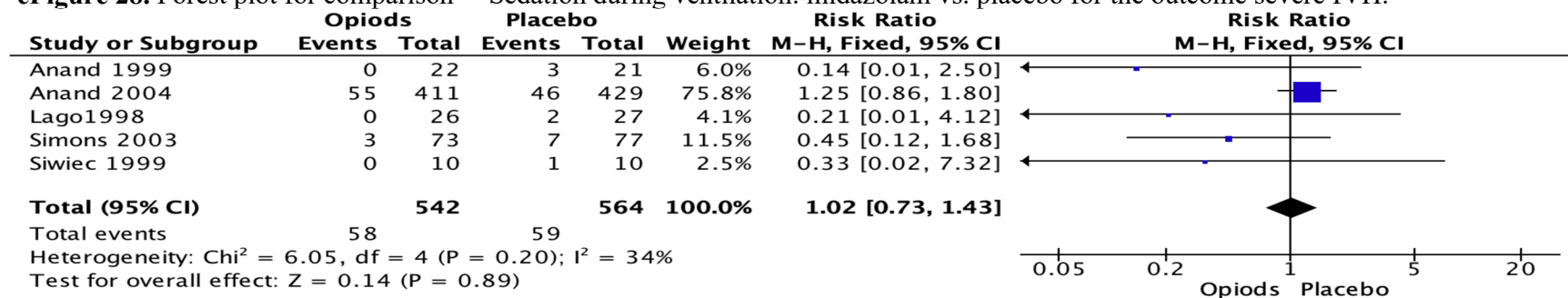
eFigure 26. Forest plot for comparison—Caffeine prophylaxis or treatment for apnea or post-extubation vs. placebo for the outcome severe IVH.



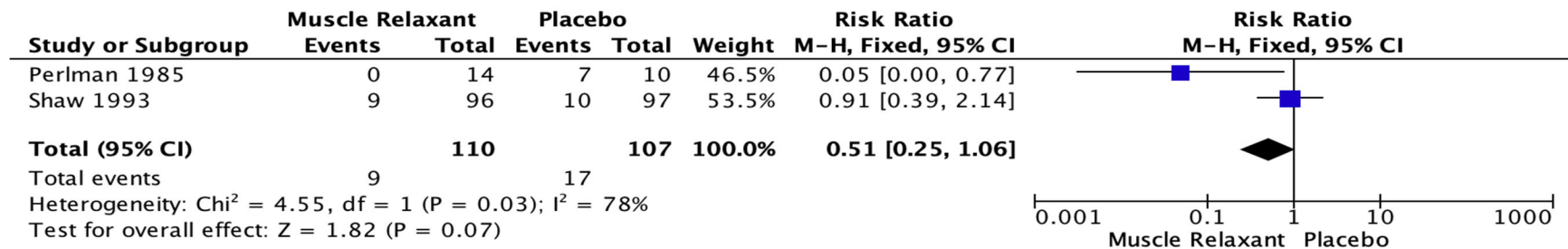
eFigure 27. Forest plot for comparison—high dose vs. low dose caffeine prophylaxis for apnea or post-extubation for the outcome severe IVH.



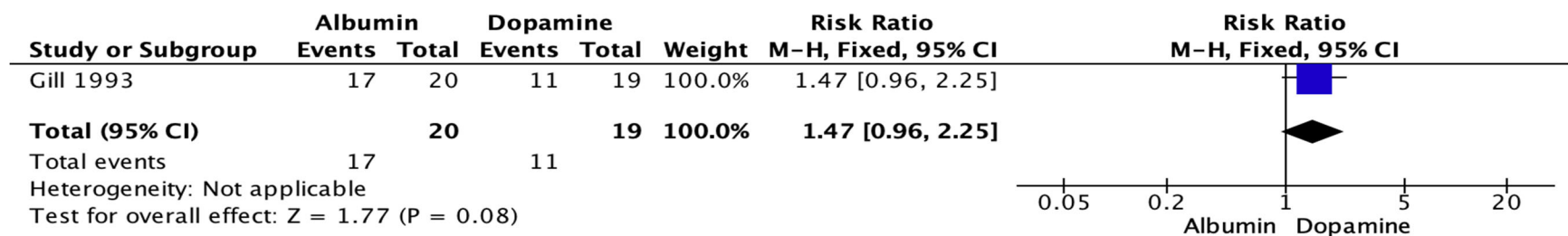
eFigure 28. Forest plot for comparison—Sedation during ventilation: midazolam vs. placebo for the outcome severe IVH.



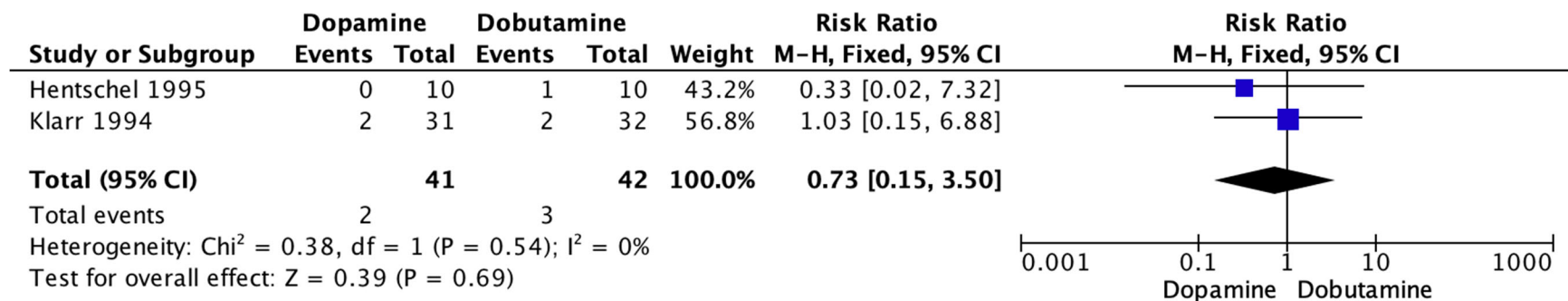
eFigure 29. Forest plot for comparison—Sedation during ventilation: opioid vs. placebo for the outcome severe IVH.



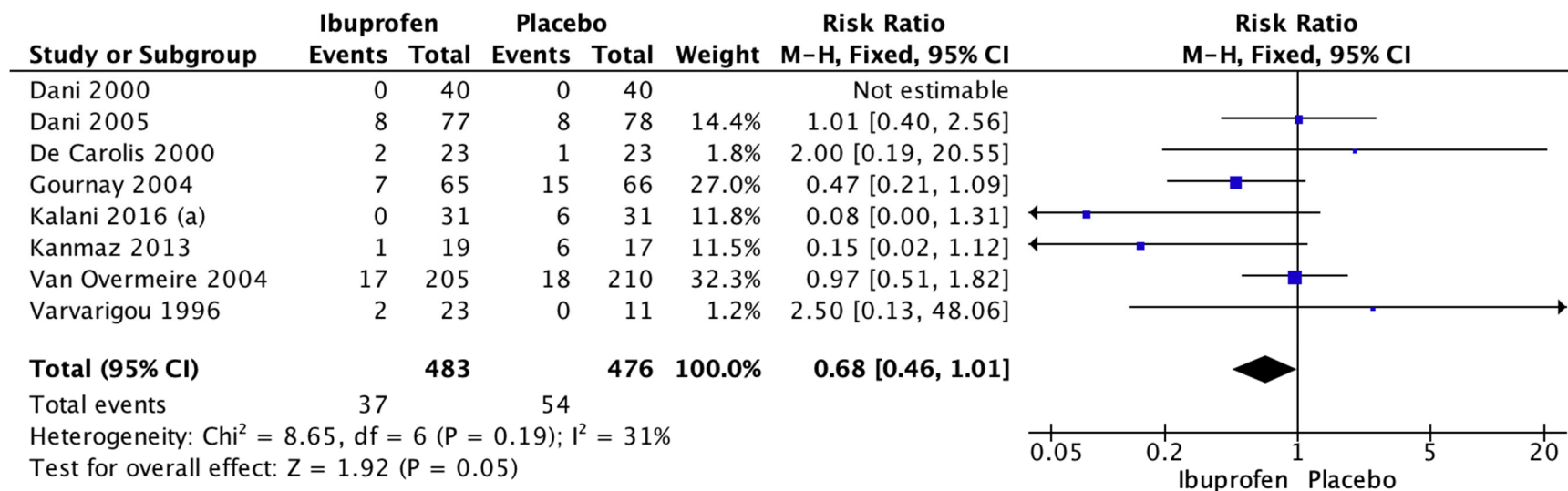
eFigure 30. Forest plot for comparison— Neuromuscular paralysis during ventilation vs. placebo for the outcome severe IVH.



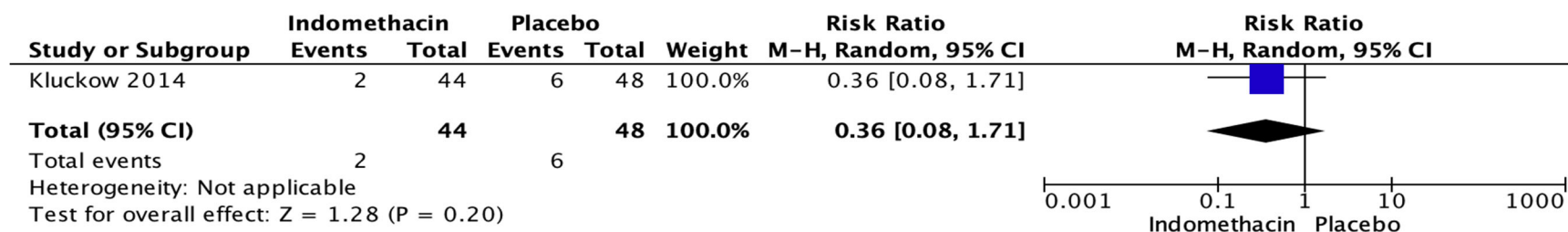
eFigure 31. Forest plot for comparison— volume expansion vs. inotropes (any) for hypotension for the outcome severe IVH.



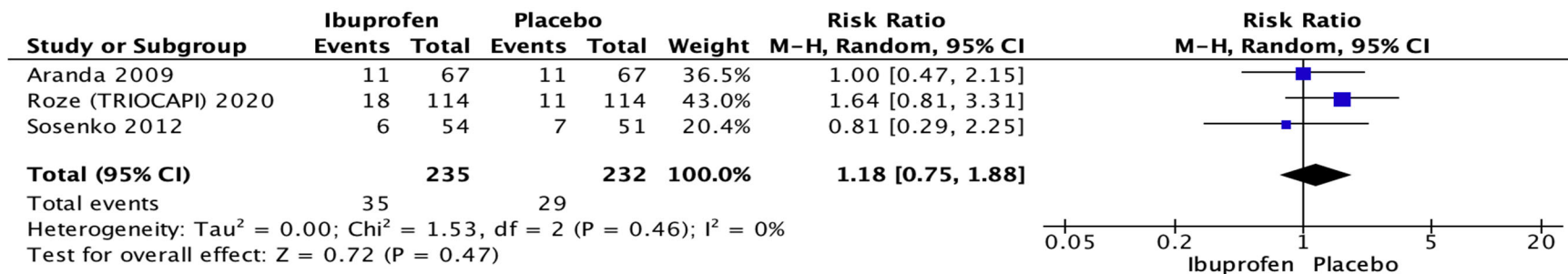
eFigure 32. Forest plot for comparison— Dopamine vs. dobutamine for hypotension for the outcome severe IVH.



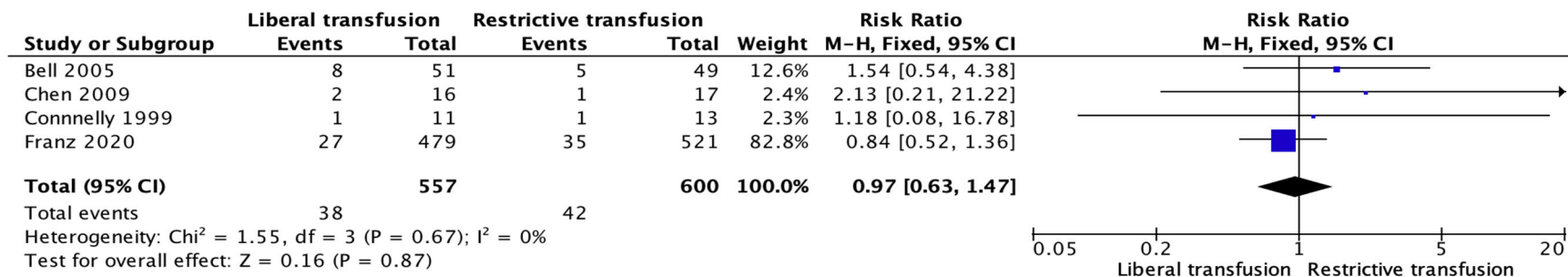
eFigure 33. Forest plot for comparison— Ibuprofen prophylaxis for PDA vs. placebo for the outcome severe IVH.



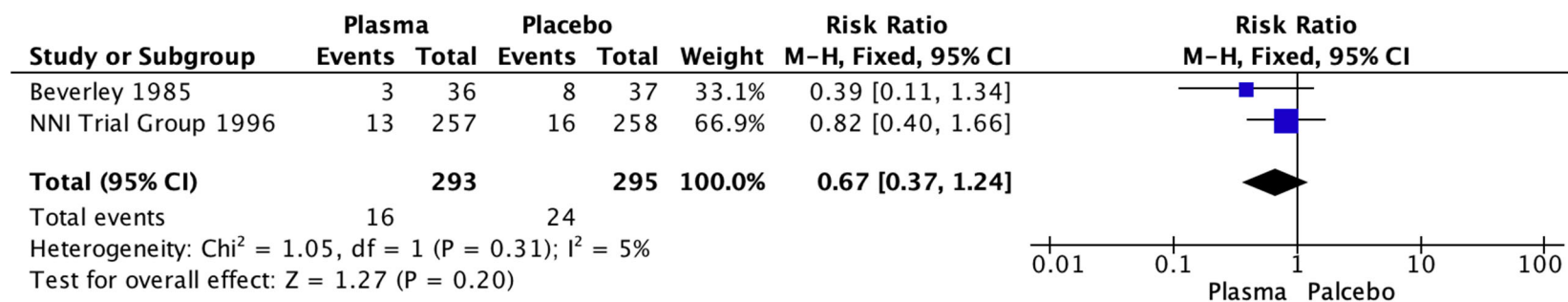
eFigure 34. Forest plot for comparison— Indomethacin pre-symptomatic treatment for PDA vs. placebo for the outcome severe IVH.



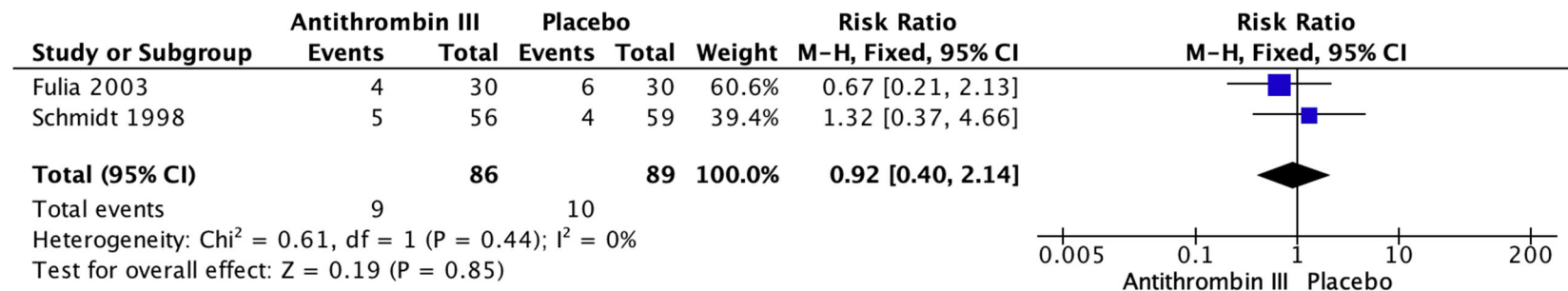
eFigure 35. Forest plot for comparison— Ibuprofen pre-symptomatic treatment for PDA vs. placebo for the outcome severe IVH.



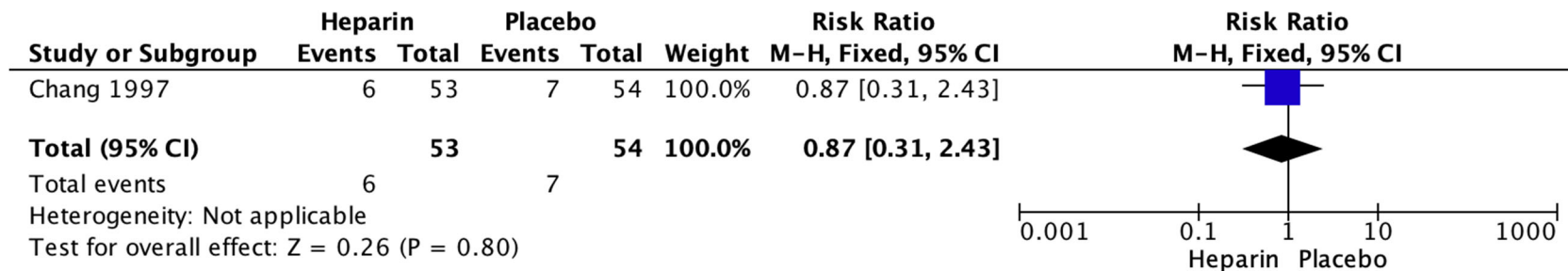
eFigure 36. Forest plot for comparison— Restrictive vs. liberal packed red cell transfusion for anemia for the outcome severe IVH.



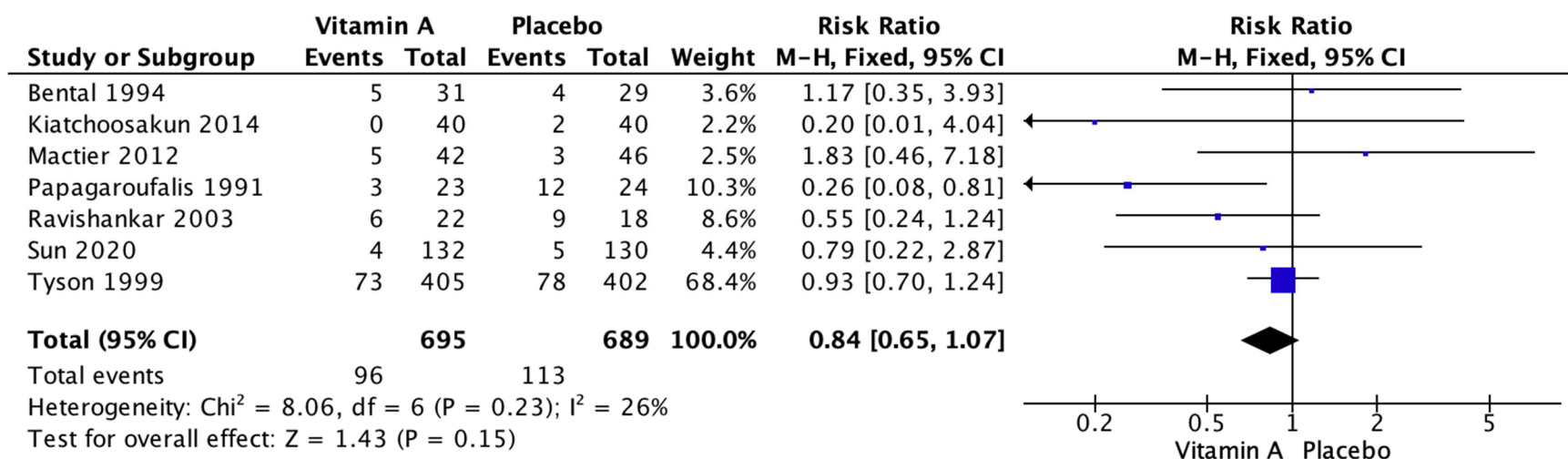
eFigure 37. Forest plot for comparison— Prophylactic plasma administration vs. placebo for the outcome severe IVH.



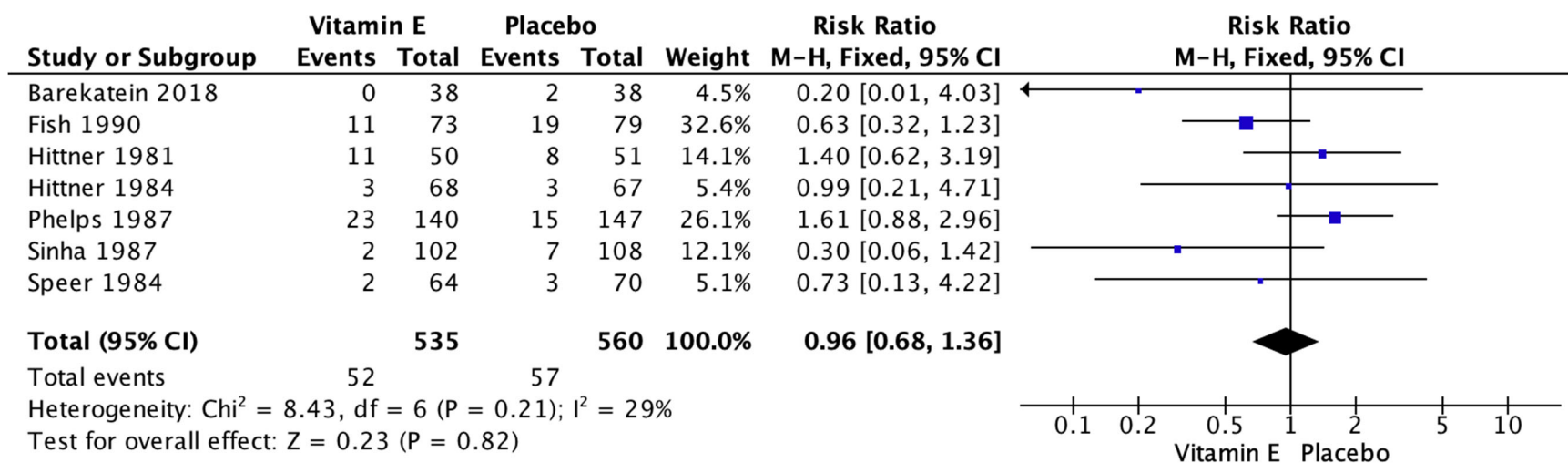
eFigure 38. Forest plot for comparison— Prophylactic antithrombin III administration vs. placebo for the outcome severe IVH.



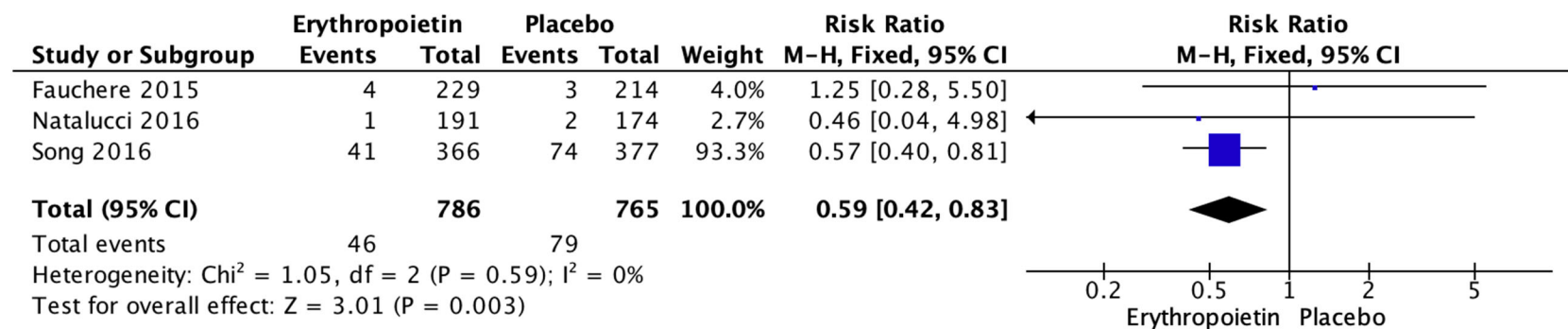
eFigure 39. Forest plot for comparison— Prophylactic heparin administration vs. placebo for the outcome severe IVH.



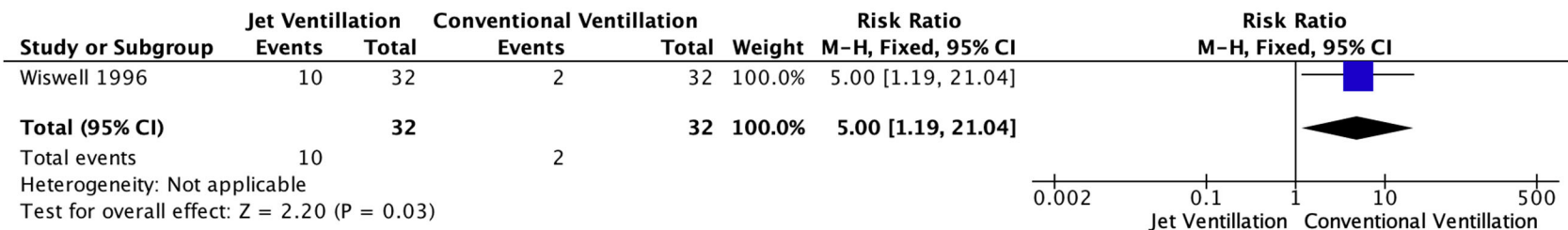
eFigure 40. Forest plot for comparison— Vitamin A supplementation vs. placebo for the outcome severe IVH.



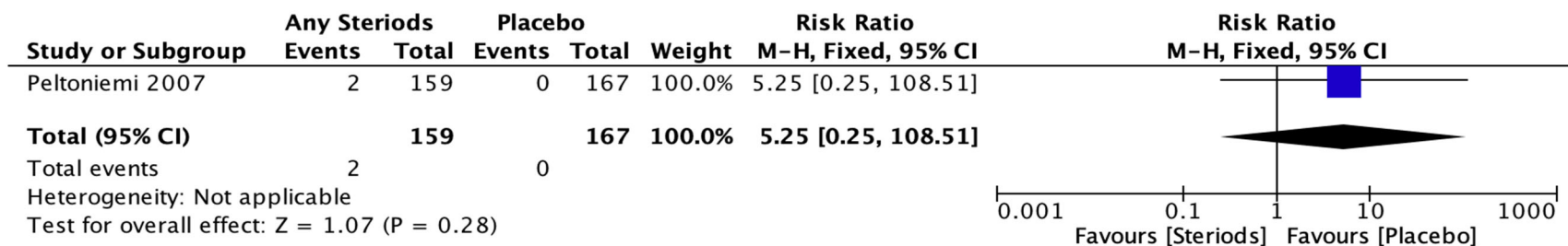
eFigure 41. Forest plot for comparison— Vitamin E supplementation vs. placebo for the outcome severe IVH.



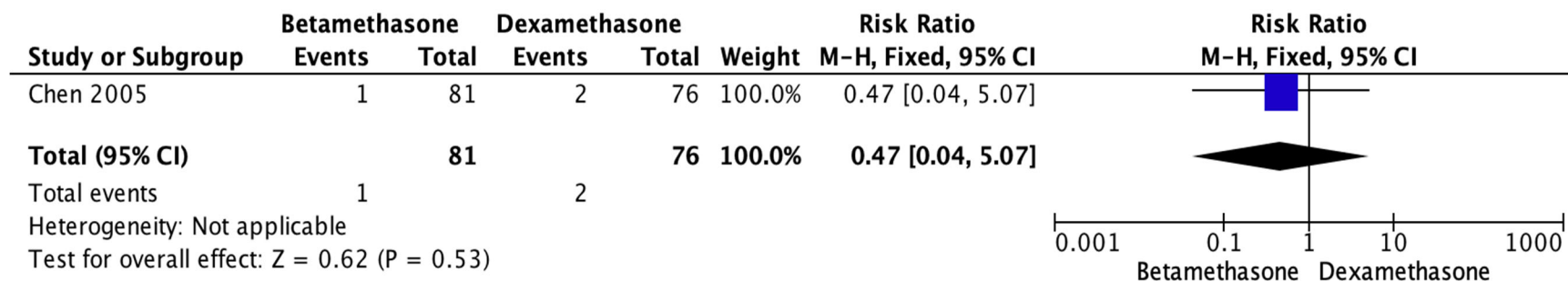
eFigure 42. Forest plot for comparison—Early erythropoiesis-stimulating agents vs. placebo for outcome cPVL



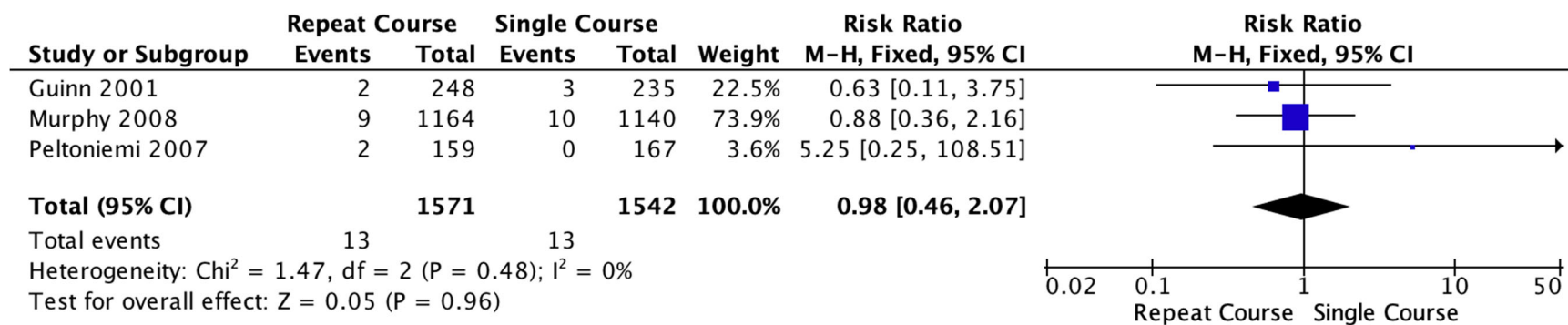
eFigure 43. Forest plot for comparison— Elective high-frequency jet ventilation vs. conventional ventilation method for the outcome cPVL.



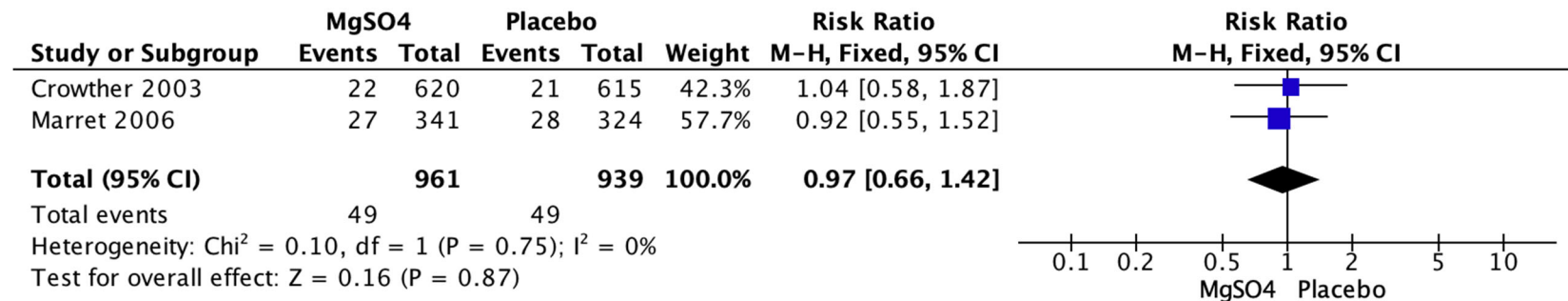
eFigure 44. Forest plot for comparison—Any steroids for lung maturity vs. placebo for the outcome cPVL.



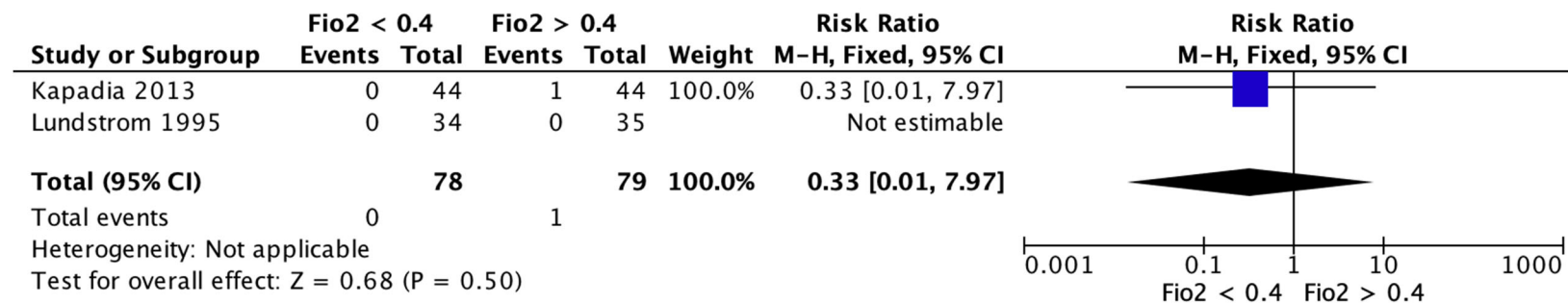
eFigure 45. Forest plots for comparison—Betamethasone for lung maturity vs. Betamethasone for lung maturity for outcome cPVL.



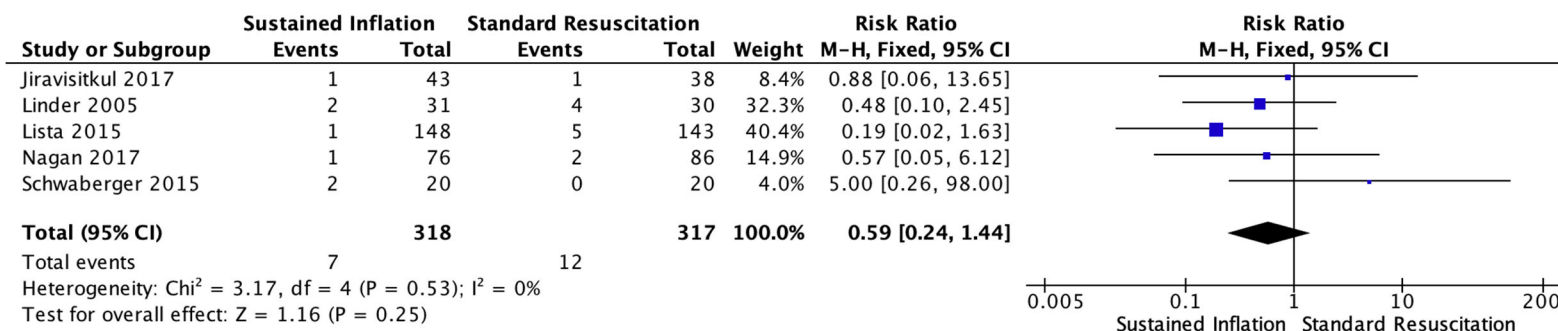
eFigure 46. Forest plot for comparison—Antenatal steroid for lung maturity: repeat course vs. single course for outcome cPVL.



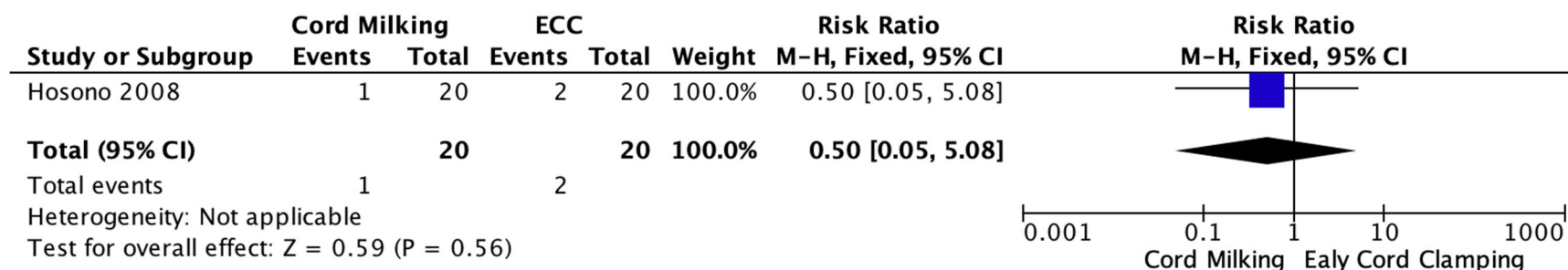
eFigure 47. Forest plot for comparison—Antenatal MgSO4 therapy for Neuroprotection vs. placebo for the outcome cPVL.



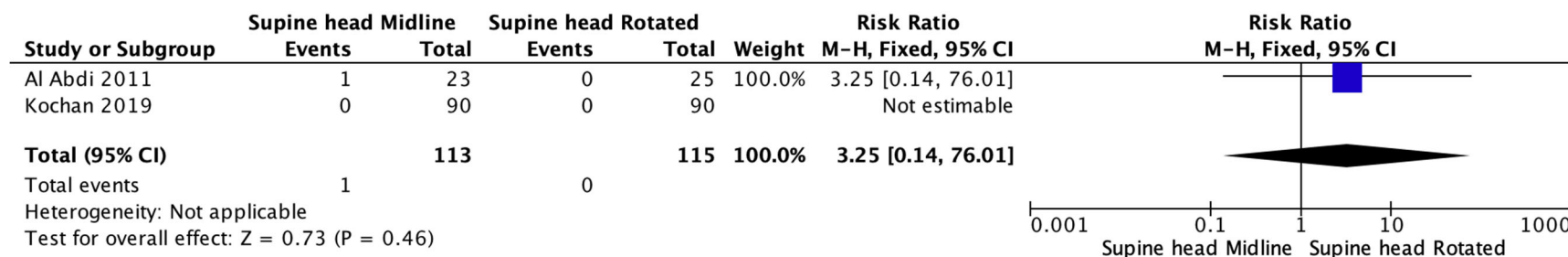
eFigure 48. Forest plot for comparison—lower Fio2 for resuscitation vs. higher Fio2 for resuscitation for the outcome cPVL.



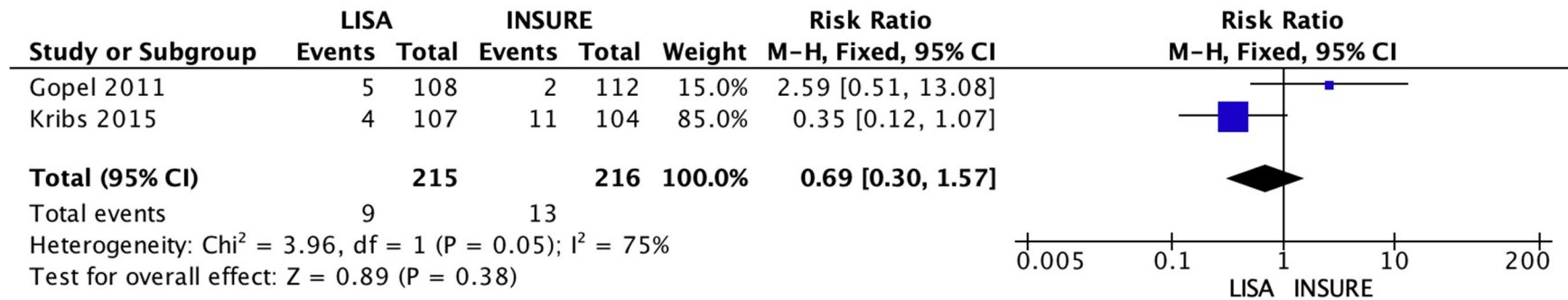
eFigure 49. Forest plot for comparison—Sustained inflation during resuscitation vs. standard resuscitation for the outcome cPVL.



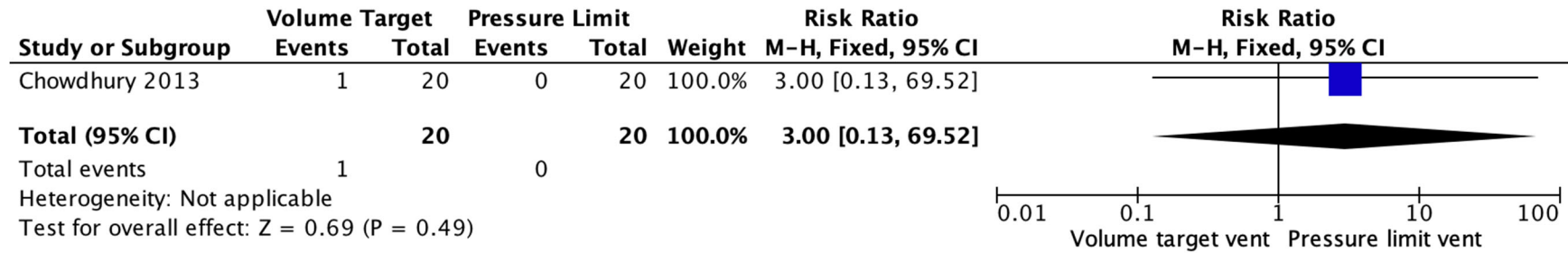
eFigure 50. Forest plot for comparison—Umbilical cord milking vs. early cord clamping for the outcome cPVL.



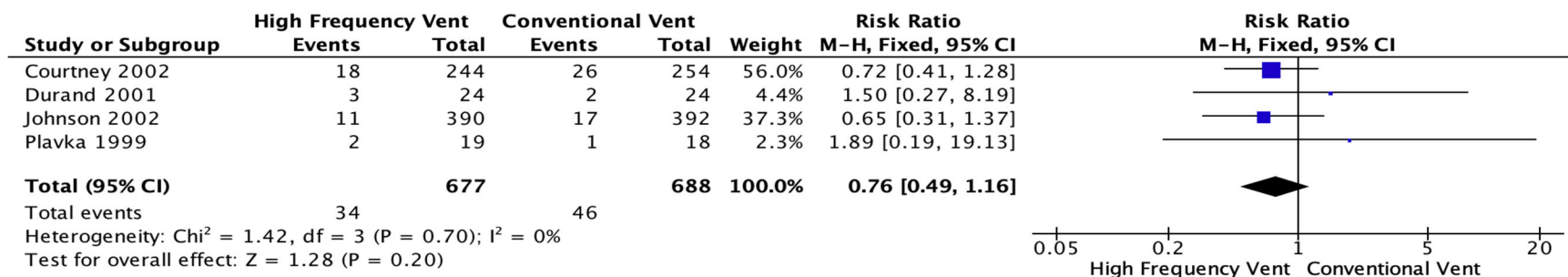
eFigure 51. Forest plot for comparison—supine head midline vs. supine head rotated for the outcome cPVL.



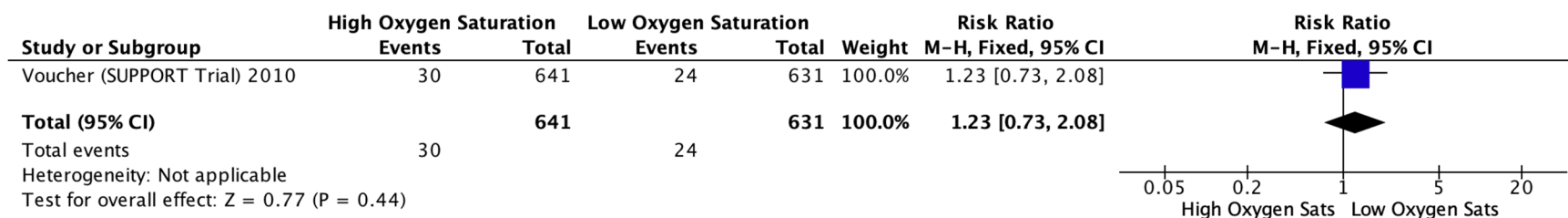
eFigure 52. Forest plot for comparison— LISA vs. INSURE method for surfactant administration for the outcome severe cPVL.



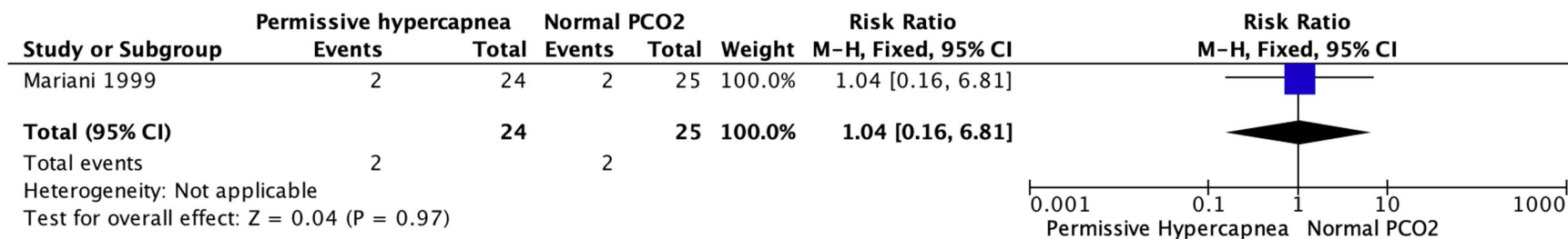
eFigure 53. Forest plot for comparison— Volume target ventilation vs. pressure limited ventilation for the outcome severe cPVL.



eFigure 54. Forest plot for comparison— Elective HFOV vs. conventional ventilation method for the outcome cPVL.



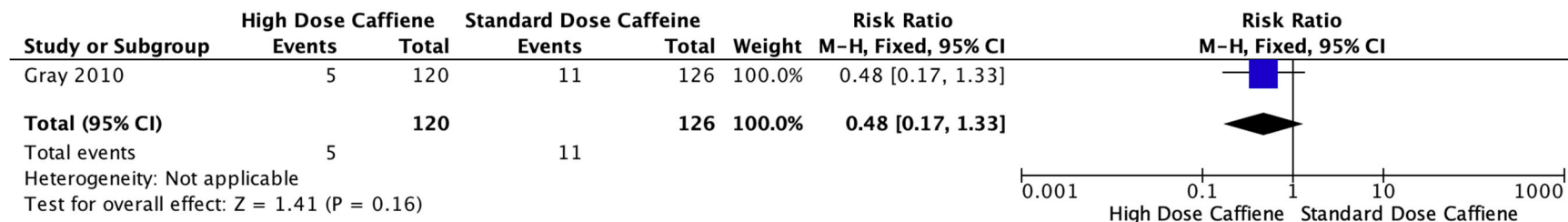
eFigure 55. Forest plot for comparison— high oxygen saturation target (91-95%) vs. low oxygen saturation target (85-89%) in NICU for the outcome cPVL.



eFigure 56. Forest plot for comparison— permissive hypercapnia vs normocapnia during ventilation for the outcome cPVL.



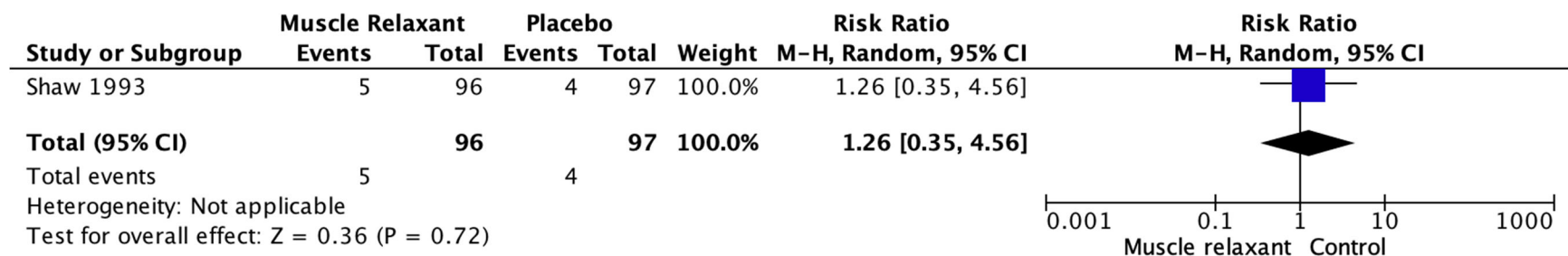
eFigure 57. Forest plot for comparison—Caffeine prophylaxis or treatment for apnea or post-extubation vs. placebo for the outcome cPVL.



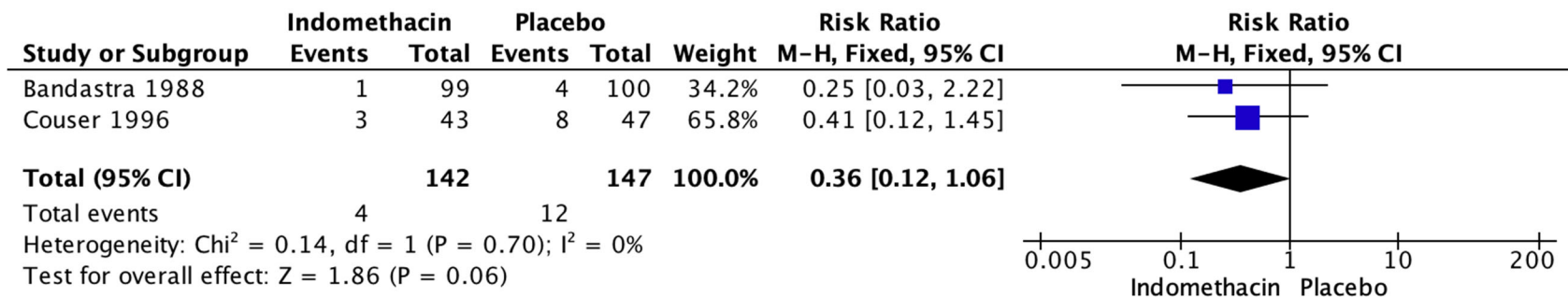
eFigure 58. Forest plot for comparison—high dose caffeine prophylaxis for apnea or post-extubation vs. low dose caffeine for the outcome cPVL.



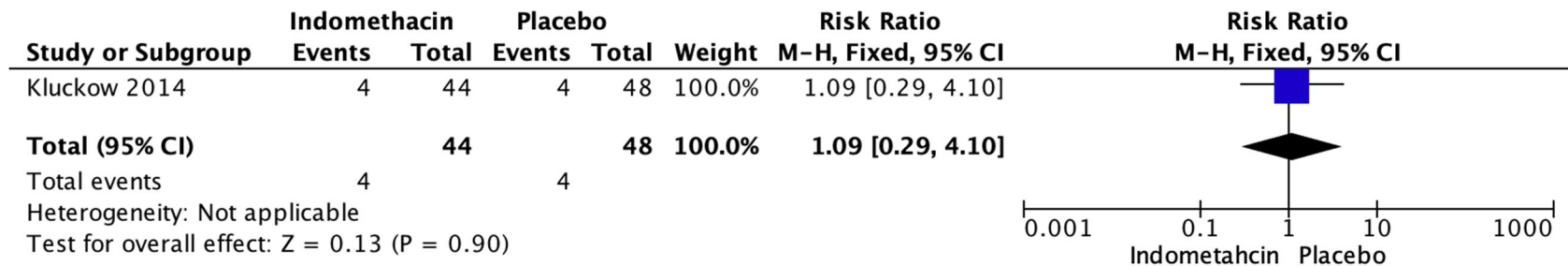
eFigure 59. Forest plot for comparison— Sedation during ventilation: opioid vs. placebo for the outcome cPVL.



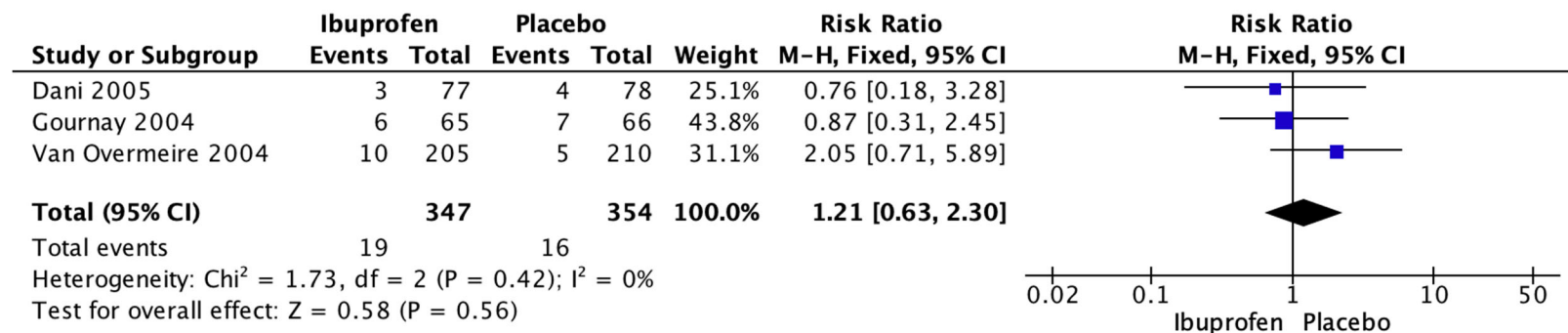
eFigure 60. Forest plot for comparison— Neuromuscular paralysis during ventilation vs. placebo for the outcome cPVL.



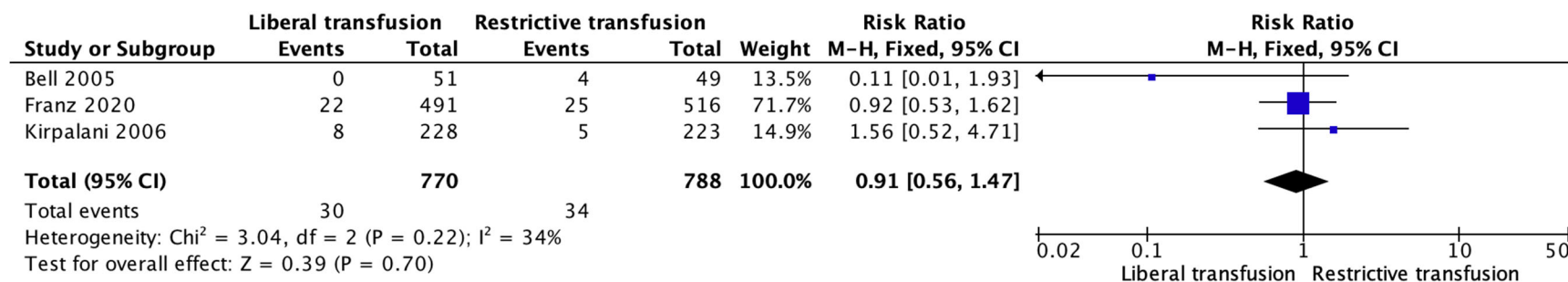
eFigure 61. Forest plot for comparison— Indomethacin prophylaxis for PDA vs. placebo for the outcome cPVL.



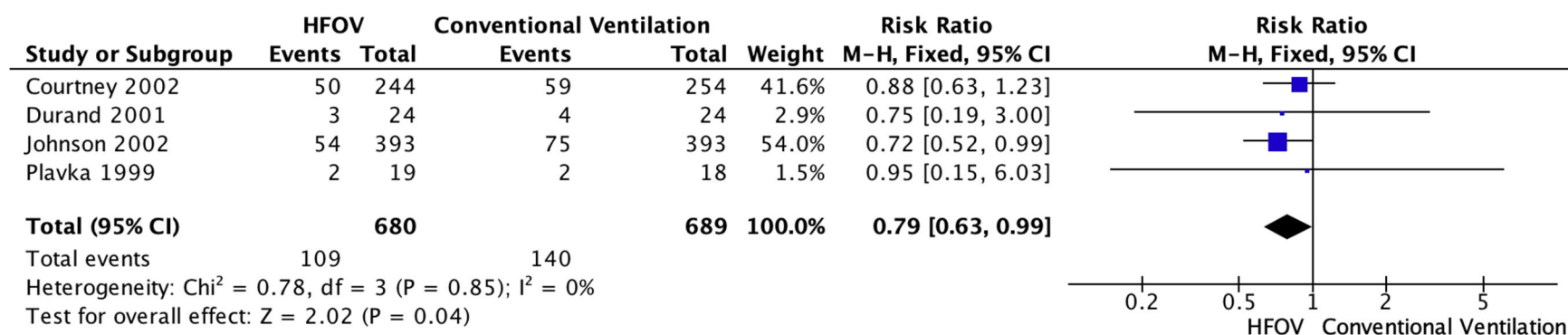
eFigure 62. Forest plot for comparison— Indomethacin pre-symptomatic treatment for PDA vs. placebo for the outcome cPVL.



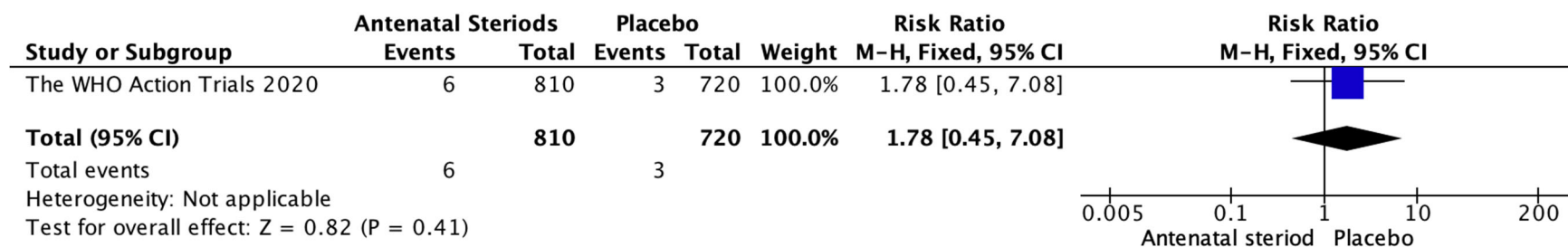
eFigure 63. Forest plot for comparison— Ibuprofen prophylaxis for PDA vs. placebo for the outcome cPVL.



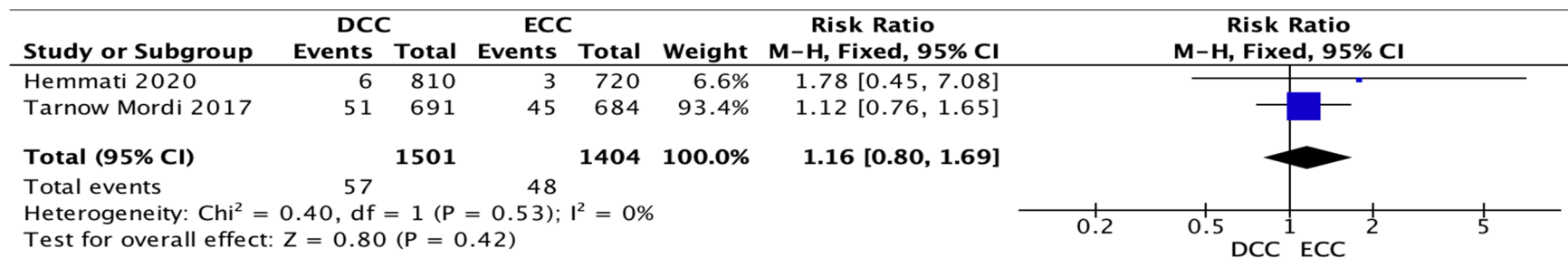
eFigure 64. Forest plot for comparison— Restrictive vs. liberal packed red cell transfusion for anemia for the outcome cPVL.



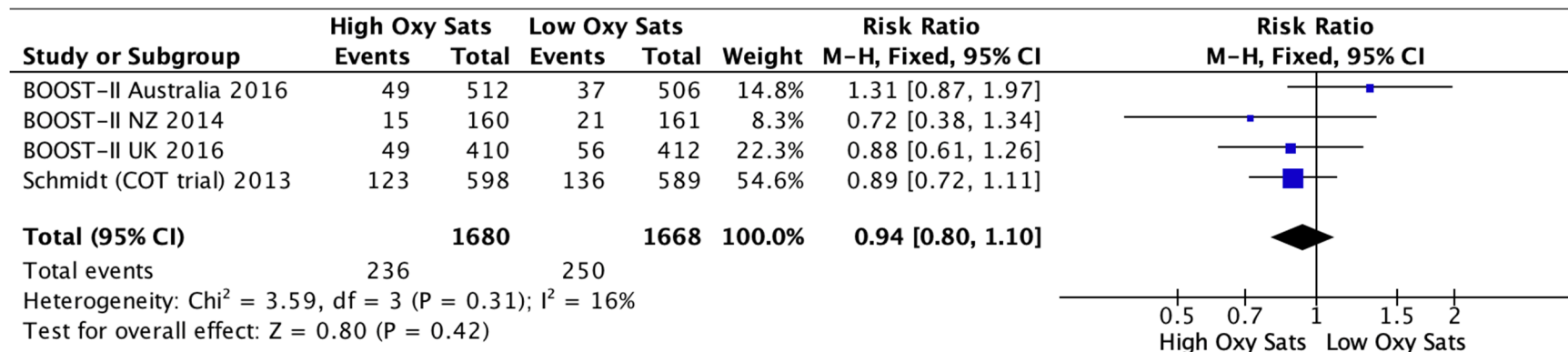
eFigure 65. Forest plot for comparison— Elective HFOV vs. conventional ventilation method for the outcome severe brain injury.



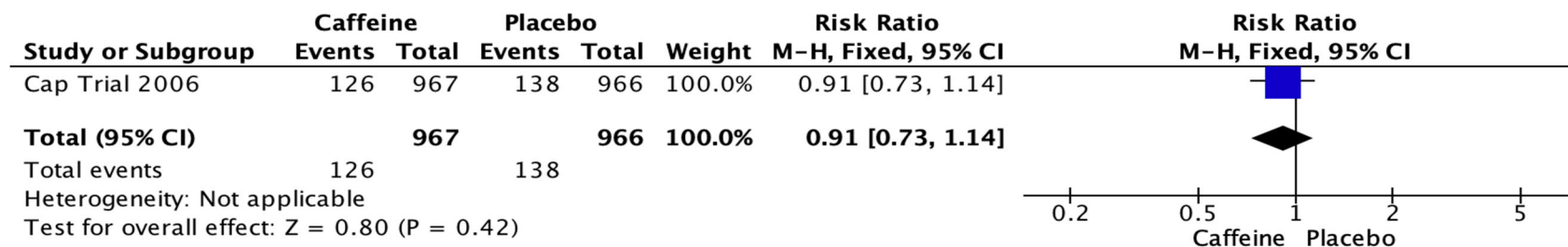
eFigure 66. Forest plot for comparison—Any steroids for lung maturity vs. placebo for the outcome severe brain injury



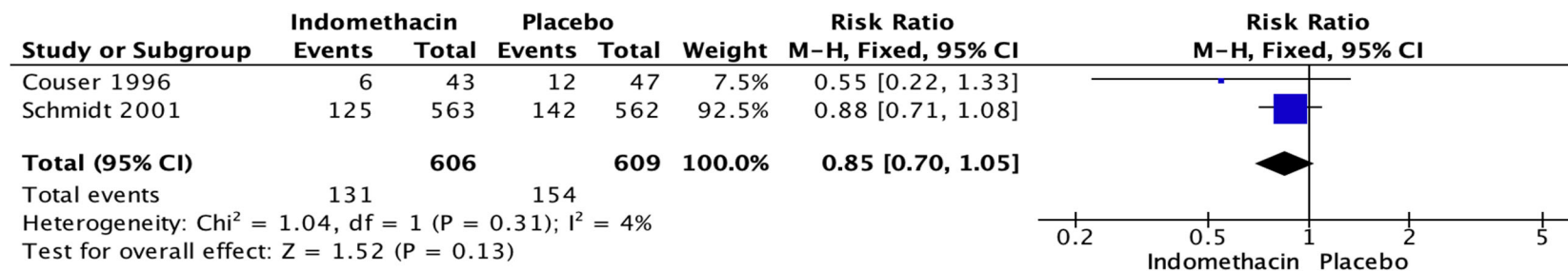
eFigure 67. Forest plot for comparison—Delayed cord clamping vs. early cord clamping for the outcome severe brain injury



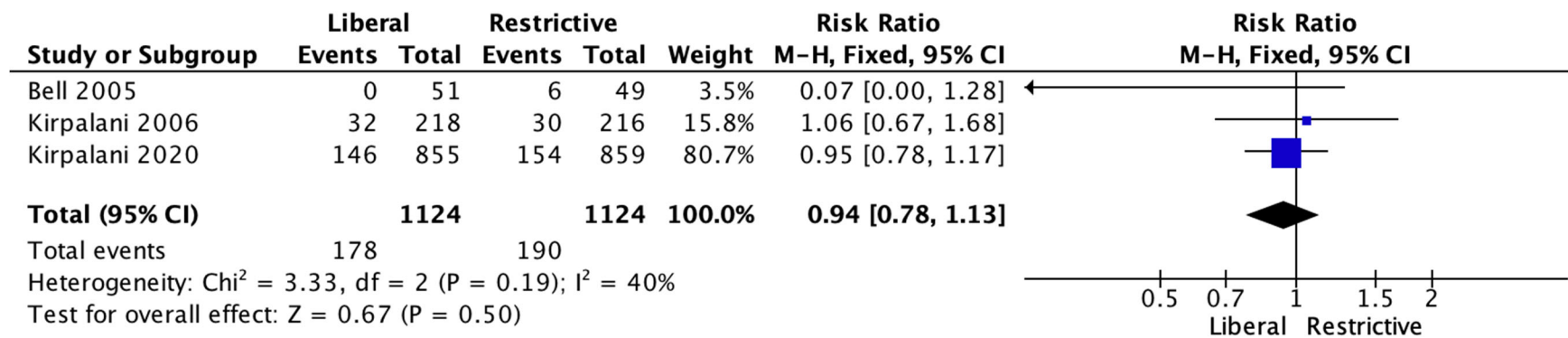
eFigure 68. Forest plot for comparison— High vs. low oxygen saturation targets for the outcome severe brain injury



eFigure 69. Forest plot for comparison-Caffeine prophylaxis or treatment for apnea/post-extubation for outcome severe brain injury



eFigure 70. Forest plot for comparison— Indomethacin prophylaxis for the outcome severe brain injury



eFigure 71. Forest plot for comparison— Restrictive vs. liberal packed red cell transfusion for anemia for the outcome severe brain injury