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Non-invasive high-frequency ventilation in newborn infants with respiratory distress (Review)

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[Intervention Review]

Non-invasive high-frequency ventilation in newborn infants with respiratory distress

Mohamed E Abdel-Latif[1,2,3], Olive Tan[4], Michelle Fiander[5], David A Osborn[6,7]

[1]Discipline of Neonatology, School of Medicine and Psychology, College of Health and Medicine, Australian National University, Acton, ACT, Australia. [2]Department of Neonatology, Centenary Hospital for Women and Children, Canberra Hospital, Garran, ACT, Australia. [3]Department of Public Health, La Trobe University, Bundoora, VIC, Australia. [4]Department of Neonatology, Centenary Hospital for Women and Children, Canberra Hospital, Garran, ACT, Australia. [5]Cochrane Neonatal Group, Halifax, Canada. [6]Central Clinical School, School of Medicine, The University of Sydney, Sydney, Australia. [7]Department of Neonatology, Royal Prince Alfred Hospital, Camperdown, Australia

Contact: Mohamed E Abdel-Latif, abdel-latif.mohamed@act.gov.au.

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ABSTRACT

Background

Respiratory distress occurs in up to 7% of newborns, with respiratory support (RS) provided invasively via an endotracheal (ET) tube or non-invasively via a nasal interface. Invasive ventilation increases the risk of lung injury and chronic lung disease (CLD). Using non-invasive strategies, with or without minimally invasive surfactant, may reduce the need for mechanical ventilation and the risk of lung damage in newborn infants with respiratory distress.

Objectives

To evaluate the benefits and harms of nasal high-frequency ventilation (nHFV) compared to invasive ventilation via an ET tube or other non-invasive ventilation methods on morbidity and mortality in preterm and term infants with or at risk of respiratory distress.

Search methods

We searched CENTRAL, MEDLINE, Embase, CINAHL and three trial registries in April 2023.

Selection criteria

Randomised controlled trials (RCTs), cluster- or quasi-RCTs of nHFV in newborn infants with respiratory distress compared to invasive or non-invasive ventilation.

Data collection and analysis

Two authors independently selected the trials for inclusion, extracted data, assessed the risk of bias, and undertook GRADE assessment.

Main results

We identified 33 studies, mostly in low- to middle-income settings, that investigated this therapy in 5068 preterm and 46 term infants.

nHFV compared to invasive respiratory therapy for initial RS

We are very uncertain whether nHFV reduces mortality before hospital discharge (RR 0.67, 95% CI 0.20 to 2.18; 1 study, 80 infants) or the incidence of CLD (RR 0.38, 95% CI 0.09 to 1.59; 2 studies, 180 infants), both very low-certainty. ET intubation, death or CLD, severe intraventricular haemorrhage (IVH) and neurodevelopmental disability (ND) were not reported.

nHFV vs nasal continuous positive airway pressure (nCPAP) used for initial RS

We are very uncertain whether nHFV reduces mortality before hospital discharge (RR 1.00, 95% CI 0.41 to 2.41; 4 studies, 531 infants; very low-certainty). nHFV may reduce ET intubation (RR 0.52, 95% CI 0.33 to 0.82; 5 studies, 571 infants), but there may be little or no difference in CLD (RR 1.35, 95% CI 0.80 to 2.27; 4 studies, 481 infants); death or CLD (RR 2.50, 95% CI 0.52 to 12.01; 1 study, 68 participants); or severe IVH (RR 1.17, 95% CI 0.36 to 3.78; 4 studies, 531 infants), all low-certainty evidence. ND was not reported.

nHFV vs nasal intermittent positive-pressure ventilation (nIPPV) used for initial RS

nHFV may result in little to no difference in mortality before hospital discharge (RR 1.86, 95% CI 0.90 to 3.83; 2 studies, 84 infants; low-certainty). nHFV may have little or no effect in reducing ET intubation (RR 1.33, 95% CI 0.76 to 2.34; 5 studies, 228 infants; low-certainty). There may be a reduction in CLD (RR 0.63, 95% CI 0.42 to 0.95; 5 studies, 307 infants; low-certainty). A single study (36 infants) reported no events for severe IVH. Death or CLD and ND were not reported.

nHFV vs high-flow nasal cannula (HFNC) used for initial RS

We are very uncertain whether nHFV reduces ET intubation (RR 2.94, 95% CI 0.65 to 13.27; 1 study, 37 infants) or reduces CLD (RR 1.18, 95% CI 0.46 to 2.98; 1 study, 37 participants), both very low-certainty. There were no mortality events before hospital discharge or severe IVH. Other deaths, CLD and ND, were not reported.

nHFV vs nCPAP used for RS following planned extubation

nHFV probably results in little or no difference in mortality before hospital discharge (RR 0.92, 95% CI 0.52 to 1.64; 6 studies, 1472 infants; moderate-certainty). nHFV may result in a reduction in ET reintubation (RR 0.42, 95% CI 0.35 to 0.51; 11 studies, 1897 infants) and CLD (RR 0.78, 95% CI 0.67 to 0.91; 10 studies, 1829 infants), both low-certainty. nHFV probably has little or no effect on death or CLD (RR 0.90, 95% CI 0.77 to 1.06; 2 studies, 966 infants) and severe IVH (RR 0.80, 95% CI 0.57 to 1.13; 3 studies, 1117 infants), both moderate-certainty. We are very uncertain whether nHFV reduces ND (RR 0.92, 95% CI 0.37 to 2.29; 1 study, 74 infants; very low-certainty).

nHFV versus nIPPV used for RS following planned extubation

nHFV may have little or no effect on mortality before hospital discharge (RR 1.83, 95% CI 0.70 to 4.79; 2 studies, 984 infants; low-certainty). There is probably a reduction in ET reintubation (RR 0.69, 95% CI 0.54 to 0.89; 6 studies, 1364 infants), but little or no effect on CLD (RR 0.88, 95% CI 0.75 to 1.04; 4 studies, 1236 infants); death or CLD (RR 0.92, 95% CI 0.79 to 1.08; 3 studies, 1070 infants); or severe IVH (RR 0.78, 95% CI 0.55 to 1.10; 4 studies, 1162 infants), all moderate-certainty. One study reported there might be no difference in ND (RR 0.88, 95% CI 0.35 to 2.16; 1 study, 72 infants; low-certainty).

nHFV versus nIPPV following initial non-invasive RS failure

nHFV may have little or no effect on mortality before hospital discharge (RR 1.44, 95% CI 0.10 to 21.33); or ET intubation (RR 1.23, 95% CI 0.51 to 2.98); or CLD (RR 1.01, 95% CI 0.70 to 1.47); or severe IVH (RR 0.47, 95% CI 0.02 to 10.87); 1 study, 39 participants, all low- or very low-certainty. Other deaths or CLD and ND were not reported.

Authors' conclusions

For initial RS, we are very uncertain if using nHFV compared to invasive respiratory therapy affects clinical outcomes. However, nHFV may reduce intubation when compared to nCPAP.

For planned extubation, nHFV may reduce the risk of reintubation compared to nCPAP and nIPPV. nHFV may reduce the risk of CLD when compared to nCPAP.

Following initial non-invasive respiratory support failure, nHFV when compared to nIPPV may result in little to no difference in intubation.

Large trials, particularly in high-income settings, are needed to determine the role of nHFV in initial RS and following the failure of other non-invasive respiratory support. Also, the optimal settings of nHVF require further investigation.

PLAIN LANGUAGE SUMMARY

Non-invasive high-frequency ventilation (nHFV) in newborn infants with respiratory distress

Key messages

What is respiratory distress?

Respiratory distress is a breathing problem that frequently affects newborn babies. The causes vary depending on the baby's gestation (the length of time that a baby spends in the womb before delivery). The most common cause in babies born before their due date (preterm) is a lack of the lung's natural compound (surfactant) that prevents the air sacs (alveoli) from opening and closing easily. The commonest cause in babies born after 37 weeks gestation (term) is a condition called transient tachypnoea of the newborn (or wet lungs), which results from a delay in the clearance of lung fluid after birth, which leads to respiratory distress and fast breathing. There are many other cases of respiratory distress.

How is respiratory distress treated?

The usual treatment involves providing breathing support (mechanical ventilation), oxygen and administering a medication called surfactant directly into the newborn infant's breathing pipe (trachea).

Respiratory support can be provided via a tube called an endotracheal tube inserted into the infant's trachea (invasive ventilation) or via a mask or prong situated at the nose (non-invasive ventilation). Invasive ventilation is associated with an increased risk of lung damage called chronic lung disease. Non-invasive ventilation, with or without surfactant treatment, may reduce the need for mechanical ventilation and the risk of chronic lung disease in newborn infants with respiratory distress.

What is non-invasive high-frequency ventilation?

High-frequency ventilation delivers very small breaths at a very fast rate (6 to 15 hertz, equal to 360 to 900 breaths per minute). High-frequency ventilation helps with the opening of collapsed lung tissue by providing constant positive pressure in the trachea. High-frequency ventilation is usually delivered via an endotracheal tube. Non-invasive high-frequency ventilation is delivered via a mask or prong situated in the nose.

Why is non-invasive high-frequency ventilation important for newborn infants?

Non-invasive high-frequency ventilation in newborn infants is a relatively newer method of non-invasive ventilation compared to other forms of non-invasive ventilation that also use nasal prongs such as nasal continuous airway pressure, nasal intermittent positive-pressure ventilation, or heated humidified high-flow nasal cannula. Continuous positive airway pressure provides constant distending pressure to the infant's airway. Intermittent positive-pressure ventilation provides normal breaths, typically at the infant's normal breathing rate (30 to 60 breaths per minute). A high-flow nasal cannula delivers heated humidified air or oxygen at flow rates between three and eight litres per minute.

What did we want to find out?

We wanted to find out if non-invasive high-frequency ventilation compared to other forms of non-invasive ventilation via nasal prongs (e.g. nasal continuous airway pressure; nasal intermittent positive-pressure ventilation; heated humidified high flow nasal cannula) and invasive ventilation via an endotracheal tube could improve survival and reduce the rate of the need for an endotracheal tube and other outcomes in term and premature infants with or at risk of respiratory distress syndrome. We also wanted to determine if non-invasive high-frequency ventilation use had unwanted effects.

What did we do?

We searched for studies that compared non-invasive high-frequency ventilation to nasal continuous airway pressure, nasal intermittent positive-pressure ventilation, heated humidified high-flow nasal cannula, and invasive ventilation via an endotracheal tube in preterm infants with or at risk of respiratory distress syndrome. We compared and summarised the results of the included studies and rated our confidence in the evidence based on factors such as study method and size.

What did we find?

We identified 33 studies, mostly in low- to middle-income settings, that investigated this therapy in 5068 preterm and 46-term infants. For preterm infants with respiratory distress, the initial use of non-invasive high-frequency ventilation probably reduces the risk of intubation and ventilation compared to the use of nasal continuous airway pressure. For preterm infants with planned extubation following intubation and surfactant, using non-invasive high-frequency ventilation probably reduces the risk of endotracheal reintubation compared to nasal continuous airway pressure and nasal intermittent positive-pressure ventilation. Compared to nasal continuous airway pressure, using non-invasive high-frequency ventilation probably also reduces the risk of chronic lung disease. No differences were found in deaths or other newborn outcomes. Long-term outcomes were either not reported or only reported by a small trial. Large trials are needed to compare non-invasive high-frequency ventilation and nasal intermittent positive-pressure ventilation for initial respiratory support and planned extubation to determine the optimal respiratory support strategies for newborn infants.

Given the encouraging results from these trials, the use of non-invasive high-frequency ventilation in very preterm infants with or at risk of respiratory distress syndrome in selected clinical situations is justified.

What are the limitations of the evidence?

Large trials, particularly in high-income settings, are needed to determine the role of non-invasive high-frequency ventilation in initial respiratory support and following the failure of other types of non-invasive respiratory support. Therefore, further research trials are needed to identify optimal ventilation strategies and settings with non-invasive high-frequency ventilation.

How up-to-date is this evidence?

The evidence is up-to-date until 9 April 2023.

SUMMARY OF FINDINGS

Summary of findings 1. nHFV compared to invasive respiratory therapy for initial respiratory support

nHFV compared to invasive respiratory therapy for initial respiratory support

Patient or population: preterm infants with respiratory distress
Settings: neonatal intensive care
Intervention: nasal high-frequency ventilation (nHFV)
Comparison: invasive respiratory therapy (mechanical ventilation via endotracheal tube)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Invasive respiratory therapy	nHFV				
Mortality before hospital discharge	150 per 1000	101 per 1000 (30 to 327)	RR 0.67 (0.20 to 2.18)	80 (1 study)	⊕⊖⊖⊖ very low[1,2]	
Endotracheal intubation or reintubation To discharge	See comment	See comment	Not estimable	0 (0)	See comment	Not reported
Chronic lung disease Follow-up: 36 weeks	67 per 1000	25 per 1000 (6 to 106)	RR 0.38 (0.09 to 1.59)	180 (2 studies)	⊕⊖⊖⊖ very low[1,2,3]	
Death or chronic lung disease Follow-up: 36 weeks	See comment	See comment	Not estimable	0 (0)	See comment	Not reported
Intraventricular haemorrhage, Papile grade 3/4 Follow-up: 14 days	See comment	See comment	Not estimable	0 (0)	See comment	Not reported
Neurodevelopmental disability Follow-up: ≥ 18 months	See comment	See comment	Not estimable	0 (0)	See comment	Not reported

*The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; **RR**: Risk ratio

GRADE Working Group certainty of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded one level for high risk of bias
[2] Downgraded two levels for imprecision due to a single small study and wide confidence intervals
[3] Downgraded two levels for serious imprecision due to few events, and confidence intervals include appreciable benefit or harm

Summary of findings 2. nHFV compared to nCPAP used for initial respiratory support

nHFV compared to nCPAP used for initial respiratory support

Patient or population: newborn (term* and preterm) infants with respiratory distress for initial respiratory support
Settings: neonatal intensive care
Intervention: nasal high-frequency ventilation (nHFV)
Comparison: nasal continuous positive airway pressure (nCPAP)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	nCPAP	nHFV				
Mortality before hospital discharge	34 per 1000	34 per 1000 (14 to 82)	RR 1.00 (0.41 to 2.41)	531 (4 studies)	⊕⊖⊖⊖ very low[1,2]	
Endotracheal intubation To discharge	165 per 1000	86 per 1000 (54 to 135)	RR 0.52 (0.33 to 0.82)	571 (5 studies)	⊕⊕⊖⊖ low[1,3,5]	Subgroup analyses according to gestation, nHFV mean airway pressure, and nHFV frequency found no statistically significant subgroup differences.
Chronic lung disease Follow-up: 36 weeks	91 per 1000	123 per 1000 (73 to 202)	RR 1.35 (0.80 to 2.27)	481 (4 studies)	⊕⊕⊖⊖ low[1,3]	
Death or chronic lung disease Follow-up: 36 weeks	59 per 1000	147 per 1000 (31 to 706)	RR 2.50 (0.52 to 12.01)	68 (1 study)	⊕⊕⊖⊖ low[2,4]	

Intraventricular haemorrhage, Papile grade 3/4 Follow-up: 14 days	19 per 1000	22 per 1000 (7 to 71)	RR 1.17 (0.36 to 3.78)	531 (4 studies)	⊕⊕⊖⊖ low[1,3]	
Neurodevelopmental disability Follow-up: ≥ 18 months	See comment	See comment	Not estimable	0 (0)	See comment	Not reported

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group certainty of evidence
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Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded one level for risk of bias
[2] Downgraded two levels for serious imprecision because of wide confidence intervals and few events
[3] Downgraded one level for imprecision due to confidence intervals, including appreciable benefit or harm
[4] Single small study
[5] Subjective outcome measure
* A single study enroled 46 term infants (De La Roque 2011).

Summary of findings 3. nHFV compared to nIPPV used for initial respiratory support

nHFV compared to nIPPV used for initial respiratory support

Patient or population: preterm infants with respiratory distress for initial respiratory support
Settings: neonatal intensive care
Intervention: nasal high-frequency ventilation (nHFV)
Comparison: nasal intermittent positive pressure ventilation (nIPPV)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	NIPPV	nHFV				
Mortality before hospital discharge	163 per 1000	303 per 1000 (147 to 623)	RR 1.86 (0.90 to 3.83)	84 (2 studies)	⊕⊕⊖⊖	

					low[1,2]	
Endotracheal intubation To discharge	144 per 1000	192 per 1000 (104 to 284)	RR 1.33 (0.76 to 2.34)	228 (5 studies)	⊕⊕⊖⊖ low[1,2,4]	
Chronic lung disease Follow-up: 36 weeks	276 per 1000	174 per 1000 (116 to 262)	RR 0.63 (0.42 to 0.95)	307 (5 studies)	⊕⊕⊖⊖ low[1,2]	
Death or chronic lung disease Follow-up: 36 weeks	See comment	See comment	Not estimable	0 (0)	See comment	Not reported
Intraventricular haemorrhage, Papile grade 3/4 Follow-up: 14 days	See comment	See comment	Not estimable	36 (1 study)	⊕⊖⊖⊖ very low[1,3]	No events
Neurodevelopmental disability Follow-up: ≥ 18 months	See comment	See comment	Not estimable	0 (0)	See comment	Not reported

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

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Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded one level for risk of bias
[2] Downgraded one level for imprecision due to wide confidence intervals
[3] Downgraded two levels for serious imprecision due to a single small study with no/few events
[4] Subjective outcome measure

Summary of findings 4. nHFV compared to HFNC for initial respiratory support

nHFV compared to HFNC for initial respiratory support

Patient or population: preterm infants with respiratory distress for initial respiratory support
Settings: neonatal intensive care
Intervention: nasal high-frequency ventilation (nHFV)

Comparison: heated humidified high-flow nasal cannula (HFNC)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	HFNC	nHFV				
Mortality before hospital discharge	See comment	See comment	Not estimable	37 (1 study)	⊕⊖⊖⊖ very low[1,2]	No events
Endotracheal intubation or reintubation To discharge	100 per 1000	294 per 1000 (65 to 1000)	RR 2.94 (0.65 to 13.27)	37 (1 study)	⊕⊖⊖⊖ very low[1,2,3]	
Chronic lung disease Follow-up: 36 weeks	300 per 1000	354 per 1000 (138 to 894)	RR 1.18 (0.46 to 2.98)	37 (1 study)	⊕⊖⊖⊖ very low[1,2]	
Death or chronic lung disease Follow-up: 36 weeks	See comment	See comment	Not estimable	0 (0)	See comment	Not reported
Intraventricular haemorrhage, Papile grade 3/4 Follow-up: 14 days	See comment	See comment	Not estimable	37 (1 study)	⊕⊖⊖⊖ very low[1,2]	No events
Neurodevelopmental disability Follow-up: ≥ 18 months	See comment	See comment	Not estimable	0 (0)	See comment	Not reported

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group certainty of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
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Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded one level for risk of bias
[2] Downgraded two levels for serious imprecision due to a single small study with few/no events

[3] Subjective outcome measure

Summary of findings 5. nHFV compared to nCPAP for respiratory support following planned extubation

nHFV compared to nCPAP for respiratory support following planned extubation

Patient or population: ventilated preterm infants with planned extubation
Settings: neonatal intensive care
Intervention: nasal high-frequency ventilation (nHFV)
Comparison: nasal continuous positive airway pressure (nCPAP)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	NCPAP	nHFV				
Mortality before hospital discharge	32 per 1000	30 per 1000 (17 to 53)	RR 0.92 (0.52 to 1.64)	1427 (6 studies)	⊕⊕⊕⊖ moderate[1]	
Endotracheal reintubation To discharge	306 per 1000	128 per 1000 (107 to 156)	RR 0.42 (0.35 to 0.51)	1897 (11 studies)	⊕⊕⊖⊖ low[2,3,4]	Subgroup analyses according to gestation, nHFV mean airway pressure, and nHFV frequency found no statistically significant subgroup differences.
Chronic lung disease Follow-up: 36 weeks	284 per 1000	222 per 1000 (190 to 259)	RR 0.78 (0.67 to 0.91)	1829 (10 studies)	⊕⊕⊖⊖ low [1,3]	
Death or chronic lung disease Follow-up: 36 weeks	394 per 1000	355 per 1000 (304 to 418)	RR 0.90 (0.77 to 1.06)	966 (2 studies)	⊕⊕⊕⊖ moderate[1]	
Intraventricular haemorrhage, Papile grade 3/4 Follow-up: 14 days	116 per 1000	93 per 1000 (66 to 132)	RR 0.80 (0.57 to 1.13)	1117 (3 studies)	⊕⊕⊕⊖ moderate[1]	
Neurodevelopmental disability Follow-up: ≥18 months	211 per 1000	194 per 1000 (78 to 482)	RR 0.92 (0.37, 2.29)	74 (1 study)	⊕⊖⊖⊖ very low[2,5]	

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group certainty of evidence
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Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
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[1] Downgraded one level for imprecision because of wide confidence intervals
[2] Downgraded one level for risk of bias
[3] Downgraded one level for publication bias
[4] Subjective outcome measure
[5] Downgraded two levels for serious imprecision due to a single study with few events, and confidence intervals included appreciable benefit or harm

Summary of findings 6. nHFV compared to nIPPV for respiratory support following planned extubation

nHFV compared to nIPPV for respiratory support following planned extubation

Patient or population: ventilated preterm infants with planned extubation
Settings: neonatal intensive care
Intervention: nasal high-frequency ventilation (nHFV)
Comparison: nasal intermittent positive pressure ventilation (nIPPV)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	NIPPV	nHFV				
Mortality before hospital discharge	12 per 1000	22 per 1000 (9 to 58)	RR 1.83 (0.70 to 4.79)	984 (2 studies)	⊕⊕⊖⊖ low[1,2]	
Endotracheal reintubation To discharge	179 per 1000	123 per 1000 (96 to 159)	RR 0.69 (0.54 to 0.89)	1364 (6 studies)	⊕⊕⊕⊖ moderate[1,3]	Subgroup analyses according to gestation, nHFV mean airway pressure, and nHFV frequency found no statistically significant

						subgroup differences.
Chronic lung disease Follow-up: 36 weeks	336 per 1000	296 per 1000 (252 to 349)	RR 0.88 (0.75 to 1.04)	1236 (4 studies)	⊕⊕⊕⊖ moderate[2]	
Death or chronic lung disease Follow-up: 36 weeks	387 per 1000	356 per 1000 (306 to 418)	RR 0.92 (0.79 to 1.08)	1070 (3 studies)	⊕⊕⊕⊖ moderate[2]	
Intraventricular haemorrhage, Papile grade 3/4 Follow-up: 14 days	115 per 1000	90 per 1000 (63 to 127)	RR 0.78 (0.55 to 1.10)	1162 (4 studies)	⊕⊕⊕⊖ moderate[2]	
Neurodevelopmental disability Follow-up: ≥ 18 months	222 per 1000	196 per 1000 (78 to 480)	RR 0.88 (0.35 to 2.16)	72 (1 study)	⊕⊕⊖⊖ low[1,2]	

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

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[1] Downgraded one level for risk of bias
[2] Downgraded one level for imprecision due to confidence intervals, including appreciable benefit or harm
[3] Subjective outcome measure

Summary of findings 7. nHFV compared to nIPPV following failure of initial non-invasive respiratory support

nHFV compared to nIPPV following failure of initial non-invasive respiratory support

Patient or population: ventilated preterm infants with failure of initial non-invasive respiratory support
Settings: neonatal intensive care
Intervention: nasal high frequency ventilation (nHFV)
Comparison: nasal intermittent positive pressure ventilation (nIPPV)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Assumed risk	Corresponding risk				
	NIPPV	nHFV				
Mortality before hospital discharge	43 per 1000	63 per 1000 (4 to 927)	RR 1.44 (0.10 to 21.33)	39 (1 study)	⊕⊕⊖⊖ low[1]	
Endotracheal intubation To discharge	304 per 1000	374 per 1000 (155 to 907)	RR 1.23 (0.51 to 2.98)	39 (1 study)	⊕⊖⊖⊖ very low[1,2]	
Chronic lung disease Follow-up: 36 weeks	739 per 1000	747 per 1000 (517 to 1000)	RR 1.01 (0.70 to 1.47)	39 (1 study)	⊕⊕⊖⊖ low[1]	
Death or chronic lung disease Follow-up: 36 weeks	See comment	See comment	Not estimable	0 (0)	See comment	Not reported
Intraventricular haemorrhage, Papile grade 3/4 Follow-up: 14 days	43 per 1000	20 per 1000 (1 to 473)	RR 0.47 (0.02 to 10.87)	39 (1 study)	⊕⊕⊖⊖ low[13]	
Neurodevelopmental disability Follow-up: ≥ 18 months	See comment	See comment	Not estimable	0 (0)	See comment	Not reported

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group certainty of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded two levels for serious imprecision due to a single small study with few events, and confidence intervals included appreciable benefit or harm
[2] Downgraded one level for risk of bias (unblinded study/subjective outcome measure)
[3] A single event of Intraventricular haemorrhage, Papile grade 3/4, was reported amongst the nasal intermittent positive pressure ventilation (nIPPV) group.

BACKGROUND

Description of the condition

Respiratory distress

Respiratory distress occurs in 7% of newborn infants (Reuter 2014). Causes vary between preterm and term infants. Respiratory distress syndrome (RDS) and infection are responsible for around half of the cases in preterm infants, and infection, pulmonary hypoplasia, meconium aspiration syndrome (MAS), congenital heart disease, and diaphragmatic hernia contribute to half of all cases of respiratory distress in term infants (Reuter 2014). Respiratory distress syndrome is a disease that occurs predominantly in preterm infants and is associated with surfactant deficiency, dysfunction, or inactivation (Pfister 2009; Soll 2010). The term 'hyaline membrane disease' is used synonymously with 'respiratory distress syndrome' to describe respiratory distress in preterm infants (Stedman 2000). Transient tachypnoea of the newborn (TTN) is a common cause of respiratory distress in term infants, particularly after caesarean section.

Management of respiratory distress and its complications

Despite varied causes, the goals of managing respiratory distress include maintaining airway patency and providing respiratory support to deliver oxygen and remove carbon dioxide. In severe respiratory distress, mechanical ventilation often achieves these goals (Sarnaik 2011). Bronchopulmonary dysplasia (BPD) is one of the sequelae of mechanical ventilation of most significant concern. The term 'BPD' is used interchangeably with 'chronic lung disease (CLD)' (Jobe 2001). BPD is a chronic pulmonary condition caused by incomplete resolution or abnormal lung injury repair during the neonatal period. A factor that contributes to BPD is when mechanical ventilation leads to volutrauma and barotrauma, causing fluid and protein transudation in the alveoli (Jobe 2001). Insufficiently opened lung areas may be damaged by shear forces during the respiratory cycle through repetitive opening and closing of alveoli (atelectotrauma). These different traumas, in turn, stimulate the release of pro-inflammatory cytokines and an inflammatory cascade, causing biotrauma to the lungs. In addition, high-inspired oxygen can cause oxidative stress and inflammation (Neumann 2014). Furthermore, the endotracheal (ET) tube used in mechanical ventilation causes trauma during the introduction, leading to loss of defence mechanisms, including mucociliary clearance, and increasing the risk for bacterial colonisation and respiratory infection (Aly 2008). Prolonged use of the ET tube can lead to subglottic stenosis and oedema, resulting in subsequent failure to extubate.

Description of the intervention

Non-invasive ventilation techniques have the potential to minimise BPD caused by invasive endotracheal ventilation and have been reported to reduce BPD in some cases (DiBlasi 2011). Several methods of non-invasive ventilation can be used, including nasal continuous positive airway pressure (nCPAP) (Ho 2020a; Ho 2020b; Rojas-Reyes 2012; Subramaniam 2021); nasal intermittent positive-pressure ventilation (nIPPV) (Davis 2003; Lemyre 2023); and humidified high-flow nasal cannula (HFNC) (Hodgson 2023).

Non-invasive high-frequency ventilation (nHFV) is another non-invasive strategy that addresses some disadvantages of mechanical ventilation. Three modes of high-frequency ventilation (HFV) are used (Allan 2010):

1. non-invasive high-frequency oscillatory ventilation (nHFOV);
2. non-invasive high-frequency percussive ventilation (nHFPV);
3. non-invasive high-frequency jet ventilation (nHFJV).

High-frequency jet ventilation delivers tidal volumes of 1 to 3 mL/kg at respiratory rates between 240 and 660 breaths per minute. Exhalation during jet HFV is passive, which is similar to that of conventional mechanical ventilation. Jet HFV is a more effective means of treating pulmonary interstitial emphysema (Keszler 1991), and decreasing CLD in infants with severe respiratory distress (Keszler 1997), than rapid-rate conventional mechanical ventilation. Oscillatory HFV differs from jet HFV in that smaller volumes are delivered at a faster respiratory rate of about 8 to 15 hertz (Hz) (Donn 2009). Percussive HFV involves small pulses of gas at ≥ 60 breaths/minute that accumulate to form a 'low-frequency' tidal volume breath; this technique was initially used in burn units and may have an application in neonatal ventilation (Allan 2010).

It has been postulated that coupling HFV with a non-invasive nasal delivery method may produce a synergistic effect that enhances the benefit of HFV. In a single case report, nHFV was shown to be effective in managing pulmonary emphysema in a premature infant (Al Tawil 2011). Non-invasive delivery of HFV to newborn infants has been achieved successfully using nasal prongs (De Luca 2010), and a nasopharyngeal tube (Colaizy 2008); benefits for CO_2 removal have been observed. In a newborn mannequin model, nHFV was superior to nIPPV for lung CO_2 elimination. However, it is unclear how nHFV achieves more effective CO_2 elimination or whether it provides adequate gas exchange in neonates (Mukerji 2013).

nHFV may be used similarly to HFV in several scenarios (Bhuta 1998; Cools 2009; Cools 2010; Rojas-Reyes 2015). It may be used:

1. as initial respiratory support;
2. for respiratory support following extubation; or
3. following the failure of initial non-invasive therapy.

nHFV has some potential problems. The pressure amplitude in nHFV is dampened by varying diameters of the circuit, nasopharyngeal tube, and airways; this makes it difficult to estimate the extent of the dampening variable. Resulting leakages and changes in airway patency may cause sudden undesirable changes in pressure delivery, leading to under-ventilation or over-ventilation (Carlo 2008).

How the intervention might work

Non-invasive high-frequency ventilation operates at high frequency and low tidal volumes to allow gas exchange; this distinguishes it from conventional ventilation, which relies on large changes in pressure and volume (Ghazanshahi 1986; Habre 2010). In animal models, this ventilation method has been reported to result in more uniform lung inflation, improve oxygenation, and reduce the severity of lung pathology produced by conventional ventilation (Yoder 2000). The expiration phase in jet HFV is passive; this allows jet HFV to be used with lower mean airway pressure without risk of airway collapse (Brown 2011). In contrast, the expiration phase in oscillatory HFV is active, reducing expiratory time and preventing air trapping (Wheeler 2007).

Nasal high-frequency ventilation introduced via a less invasive interphase (e.g. nasal or nasopharyngeal tube) may achieve adequate gas exchange and may prevent intubation in newborn infants with respiratory distress or prevent extubation failure. Observational studies reported the feasibility of nHFV in preventing intubation or facilitating extubation (Cao 2020; Czernik 2012; Mukerji 2015).

Why it is important to do this review

Applying positive-pressure ventilation for an extended duration increases the likelihood of BPD (Ramanathan 2008). Despite significant advances in neonatal intensive care, BPD remains challenging. Newborn infants surviving BPD are at increased risk of respiratory infection, asthma-like disease, and pulmonary hypertension. They are more likely to be admitted to hospital during the first two years of life for lower respiratory tract infection (Greenough 2002), and they suffer more deficits in somatic growth and neurodevelopmental follow-up (Reiterer 2013). Preterm infants with BPD who survive to adulthood have been shown to have general impairment and poorer respiratory health when compared with adults born at term (Gough 2012). Neurodevelopmental impairment is also strongly associated with neonatal BPD (Singer 1997; Singer 2001; Vohr 2000).

Furthermore, coupling non-invasive modes of ventilation, such as nHFV, with non-invasive or minimally surfactant administration methods may potentially reduce the need for intubation and endotracheal surfactant administration (Abdel-Latif 2011a; Abdel-Latif 2011b; Abdel-Latif 2012; Abdel-Latif 2021).

The use of nHFV is on the rise. A European survey of neonatal intensive care units (NICUs) (n = 172) in five European countries revealed that nHFV was used in 17% of the units, most frequently in premature infants < 1500 g with nCPAP failure (Fischer 2015).

Although the comparison between modes of ventilation delivered by non-invasive means such as nCPAP and nIPPV following extubation in preterm infants has been the topic of various Cochrane Reviews (Davis 2003; Lemyre 2023), to date, no other systematic review has compared nHFV with other ventilation techniques.

This systematic review will gather evidence for using nHFV in newborn infants compared with other ventilation modes delivered invasively or non-invasively. Furthermore, we will gather evidence on subgroups of gestation, mean airway pressure, frequency and interphase used to deliver nHFV, and different types of nHFV if data allow (Subgroup analysis and investigation of heterogeneity).

OBJECTIVES

To evaluate the benefits and harms of nHFV compared to invasive ventilation via an ET tube or other non-invasive ventilation methods on morbidity and mortality in preterm and term infants with or at risk of respiratory distress.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel interventional trials, randomised or quasi-randomised, regardless of the allocation unit (individual or cluster). Cross-over trials were not eligible for inclusion as outcomes required longitudinal follow-up of parallel groups, and there is a likelihood of carry-over in some outcomes as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023).

Types of participants

We included term and preterm infants with or at risk of respiratory distress during their initial hospitalisation.

Types of interventions

Intervention

Non-invasive high-frequency ventilation (nHFV).

We also planned to compare different types of nHFV (oscillatory, percussive, and jet) with one another.

Types of comparisons

nHFV was compared in separate comparisons to the following comparator (control) groups as below:

1. Invasive respiratory support (with or without surfactant therapy) via an ET including:
   a. conventional ventilation, such as synchronised intermittent positive-pressure ventilation (SIPPV) and synchronised intermittent mechanical ventilation (SIMV);
   b. high-frequency ventilation, such as high-frequency oscillation ventilation (HFOV) or high-frequency jet ventilation (HFJV);
   c. neurally adjusted ventilatory assist (NAVA).
2. Non-invasive respiratory support including:
   a. nasal continuous positive airway pressure (nCPAP);
   b. nasal intermittent positive airway pressure (nIPPV);
   c. heated humidified high-flow nasal cannula (HFNC);
   d. non-invasive neurally adjusted ventilatory assist (nNAVA).

For trials of nHFV versus other methods of non-invasive respiratory support, we did not consider trials that included differential surfactant treatment regimens between groups.

nHFV or non-invasive respiratory support could be delivered by any interface, including unilateral or bilateral nasal prongs, short or long nasal prongs, nasopharyngeal tube, face mask, and laryngeal mask airway.

We considered nasal biphasic continuous positive airway pressure (BP-CPAP), bilevel positive airway pressure (BiPAP), and duo positive airway pressure (DuoPAP) as equivalent strategies to nIPPV.

The above comparisons were further separated according to indications for respiratory support as below:

1. nHFV for initial respiratory support

In this category, nHFV is used as an initial respiratory support after birth/after resuscitation at delivery (if needed).

2. nHFV for respiratory support following planned extubation

In this category, nHFV is used as an alternative to other non-invasive respiratory support following extubation.

3. nHFV following the failure of initial non-invasive therapy

In this category, nHFV is used as an alternative to ET ventilation following the failure of other forms of non-invasive respiratory support.

Types of outcome measures

The critical outcomes that we have graded and presented in the summary of findings' tables are in bold text.

Primary outcomes

1. **Mortality before hospital discharge (all causes);**
2. **Endotracheal intubation or reintubation** during admission.

Secondary outcomes

We intended to include the following secondary outcomes.

Measures of the safety of the nHFV

1. Trauma to the nostrils and upper airway (whilst on allocated mode of support).

Measures of respiratory support

1. Failure of respiratory support or failure of extubation as defined by respiratory support failure criteria (e.g. partial pressure of carbon dioxide (PCO_2) ≥ 60 mm Hg or blood pH < 7.20, or both; increased oxygen requirement; apnoea that is frequent or severe, leading to additional ventilatory support), or as defined by trial authors;
2. Duration of respiratory support (days);
3. Duration of oxygen therapy (days).

Outcomes during the first hospitalisation

1. All-cause mortality at 28 days;
2. **Chronic lung disease (CLD)** is defined as the need for oxygen or respiratory support at 36 weeks' postmenstrual age (PMA) (Shennan 1988);
3. **Death or CLD** reported at 36 weeks' PMA;
4. Patent ductus arteriosus (PDA) (treated medically or surgically);
5. Pulmonary air leak syndromes, including pulmonary interstitial emphysema (PIE) and gross extrapulmonary air leak (such as pneumothorax);
6. Proven sepsis;
7. Necrotising enterocolitis (NEC) (any Bell stage; Bell 1978);
8. NEC (Bell stage ≥ 2; Bell 1978);
9. Spontaneous intestinal perforation;
10. Intraventricular haemorrhage (IVH) (any Papile grade; Papile 1978);
11. **Severe IVH** (Papile grade 3/4; Papile 1978);
12. Periventricular leukomalacia;
13. Retinopathy of prematurity (ROP) (any stage; International Committee 2005);
14. ROP (stage ≥ 3; International Committee 2005);
15. Length of hospital stay (days);
16. Discharge on home oxygen.

Postdischarge outcomes

1. All-cause mortality to follow-up (≥ 1 year of age);
2. **Neurodevelopmental disability at least 18 months' postnatal age or later** (defined as neurological abnormality including cerebral palsy on clinical examination or developmental delay more than two standard deviations (SD) below the population mean on a standardised test of development, for instance, the Denver developmental screening test); blindness (visual acuity < 6/60); or deafness (any hearing impairment requiring amplification) at any time after term corrected.

Search methods for identification of studies

Search strategies were developed by an Information Specialist (MF). We used controlled vocabulary and keywords and combined them with methodological filters to restrict retrieval to RCTs and systematic reviews. We conducted searches without language, publication year, publication type, or publication status restrictions.

Electronic searches

We searched the following databases in April 2023.

1. Cochrane Central Register of Controlled Trials (CENTRAL), via Wiley, Issue 4, 2023;
2. Ovid MEDLINE(R) All, 1946 to 8 April 2023;
3. OVID Embase 1974 to 8 April 2023;
4. CINAHL (Cumulative Index to Nursing and Allied Health Literature; 1982 to 8 April 2023;
5. Epistemonikos https://www.epistemonikos.org.

The search strategies are available: Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5.

Searching other resources

We conducted additional searches of the following sources in 28 April 2023.

1. Ongoing trials at the following trial registries:
   a. ClinicalTrials.gov (U.S. National Institutes of Health);
   b. ISRCTN;
   c. Australian New Zealand Clinical Trials Registry;
   d. International Clinical Trials Registry Platform (ICTRP).

These search strategies are available in Appendix 6.

Other searches:

1. Abstracts from the following conferences:
   a. Proceedings of the Pediatric Academic Societies (PAS) and European Society for Paediatric Research (ESPR) from 1990 to 2022 in the journal of *Pediatric Research* and via the PAS website (https://www.pas-meeting.org/past-abstracts/).
   b. Proceedings of the European Academy of Paediatric Societies (EAPS), including EAPS 2020; EAPS 2021; EAPS 2022; the European Academy of Paediatrics (EAP), and the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) from 2003 to 2022 from Abstracts Online.
   c. Proceedings of the Perinatal Society of Australia and New Zealand (PSANZ) from 1996 to 2022 (handsearch).
2. Reference lists: we also screened the reference lists of relevant manuscripts after reading studies that examined the effects of

nHFV on morbidity or mortality, or both, in newborn infants at risk of respiratory distress to identify other relevant studies.

3. Personal communications; we planned to contact:
   a. the corresponding investigator for information if we had identified any potentially relevant unpublished trials;
   b. the corresponding authors of identified RCTs for additional information about their studies when data provided in the studies were deemed insufficient;
   c. study authors who published in this field to ask about possible unpublished articles;
   d. medical ventilator companies that develop high-frequency ventilators to ask about possible unpublished studies using their product.

Data collection and analysis

We collected information regarding the method of randomisation, blinding, intervention, stratification, and whether the trial was single or multicentre for each included study. We noted information regarding trial participants, interventions and outcomes as detailed under Data extraction and management. We analysed the clinical outcomes mentioned above in Types of outcome measures. We entered and cross-checked data using Review Manager (RevMan 2024).

Where studies have multiple publications, we collated the reports of the same study so that each study, rather than each report, was the unit of interest for the review, and such studies have a single identifier with multiple references.

Selection of studies

We used Covidence for screening (Covidence 2023). Two review authors (MEA and DAO) independently reviewed the titles and abstracts of potentially relevant studies identified by the literature searches. Two review authors (MEA and DAO) independently reviewed full texts of the studies included based on the title abstract. At any point in the screening process, we resolved disagreements between review authors by discussion. We documented our reasons for excluding studies during the review of full texts in the Characteristics of excluded studies table. We collated multiple reports of the same study so that each study, rather than each report or reference, was the unit of interest in the review; related reports were grouped under a single study ID. We also provided any information we could obtain about ongoing studies in the Characteristics of ongoing studies table. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009).

Data extraction and management

One review author (MEA) extracted and entered the data into Cochrane's statistical software for data entry (RevMan 2024). A second review author (DAO) independently checked the data. We resolved disagreements through discussion. We contacted study investigators/authors for clarification in cases requiring additional data.

We extracted the following characteristics from each included study in the Characteristics of included studies table and Table 1; Table 2; Table 3; Table 4.

1. Administrative details: study author(s); published or unpublished; year of publication; year in which the study was conducted; the presence of vested interest by study authors; details of other relevant papers cited;
2. Study characteristics: study registration, study design type, study setting, number of study centres and location; informed consent; ethics approval, details of any 'run-in' period (if applicable), completeness of follow-up (e.g. greater than 80%);
3. Participants: number randomised, number lost to follow-up/ withdrawn, number analysed, mean gestational age (GA), GA age range, mean chronological age (CA), CA age range, sex, diagnostic criteria, inclusion criteria and exclusion criteria;
4. Interventions: indication and timing, type, settings (mean airway pressure (MAP), frequency, rate, interface), surfactant co-administration;
5. Outcomes: as mentioned above under Types of outcome measures.

We described ongoing studies identified by our search and documented available information such as the primary author, research question(s), methods, and outcome measures, together with an estimate of the anticipated reporting date in the Characteristics of ongoing studies table. We replaced any standard error of the mean (SEM) with the corresponding SD.

Assessment of risk of bias in included studies

Two review authors (MEA and DO) independently assessed study quality and risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (RoB1) for the following domains (Higgins 2011).

1. Sequence generation (selection bias);
2. Allocation concealment (selection bias);
3. Blinding of participants and personnel (performance bias);
4. Blinding of outcome assessment (detection bias);
5. Attrition bias:
   a. Incomplete outcome data; and
   b. Incomplete long-term outcome data;
6. Selective reporting (reporting bias);
7. Any other bias.

We resolved any disagreements by discussion or by consultation with a third assessor. See Appendix 7 for a more detailed description of the risk of bias domains.

Measures of treatment effect

We analysed the results of the included studies using the statistical package Review Manager (RevMan 2024). We used the standard methods of Cochrane Neonatal. We used a fixed-effect model for meta-analysis. In assessing treatment effects for dichotomous data or categorical data, we reported the risk ratio (RR) or the risk difference (RD), respectively, along with the 95% confidence interval (CI). If the RD was statistically significant, we calculated the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH) (1/RD). For outcomes measured on a continuous scale, we reported the mean difference (MD) and the 95% CI.

Unit of analysis issues

For parallel-group trial designs by which infants were randomised to receive one or more different types of ventilation (nHFV, invasive

ventilation, or an alternative type of non-invasive ventilation such as nCPAP, nIPPV, HFNC), the unit of analysis for both short-term and long-term outcomes was the infant by group of assignment (intention-to-treat (ITT)).

Cluster-randomised trials

The unit of analysis for cluster-randomised trials was planned to be the randomised treating centre or cluster. We planned to include cluster-randomised trials in the analyses, using an estimate of the intra-cluster correlation coefficient (ICC) derived from the trial (if possible) or from another source, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023). If ICCs from other sources were used, we planned to report this and conduct sensitivity analyses to investigate the effects of variation in the ICC. We planned to synthesise the relevant information if we identified both cluster-randomised and individually randomised trials. We considered that it was reasonable to combine the results of both studies if we noted little heterogeneity between study designs and if the interaction between effects of the intervention and choice of randomisation unit was considered unlikely.

Dealing with missing data

In the case of missing data, we described the number of participants with missing data in the Results section and the Characteristics of included studies table. We performed an ITT meta-analysis using reconstructed denominators, when possible. We discussed the implications of data missing from the review, as appropriate.

Assessment of heterogeneity

We used Review Manager to assess the heterogeneity of treatment effects between trials (RevMan 2024). We used two formal statistical approaches to assess the presence of statistical heterogeneity.

1. The Chi^2 test for homogeneity: because this test has low power when the number of studies included in the meta-analysis is small, we set the level of significance at 10% probability ($P < 0.1$) (Higgins 2023).
2. The I^2 statistic: the I^2 statistic describes the percentage of total variation across studies due to heterogeneity rather than sampling error. It is thus a measure of the validity of data pooling for meta-analysis. We graded the degree of heterogeneity as follows: ≤ 24%, no heterogeneity; 25% to 49%, low heterogeneity; 50% to 74%, moderate heterogeneity; and ≥ 75%, high heterogeneity.

When we noted evidence of apparent or statistical heterogeneity, we assessed the source of heterogeneity by using sensitivity and subgroup analyses to look for evidence of bias or methodological differences between trials.

Assessment of reporting biases

We attempted to obtain the study protocols of all included studies and compare outcomes reported in the protocol versus those reported in the findings for each of the included studies. If reporting bias was suspected, we attempted to contact the study authors to ask them for further information. When this was impossible and missing data were thought to introduce serious bias, we examined the impact of including/excluding such studies in the overall assessment of results by performing a sensitivity analysis.

We investigated non-reporting (including publication) bias by visually assessing funnel plot asymmetry and by using Egger's test in meta-analyses if data from at least ten trials contributing events were available (Egger 1997).

Data synthesis

We performed meta-analyses using the standard methods of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023). We used a fixed-effect model. When studies were statistically heterogenous, we examined study characteristics, including design and quality. When appropriate, we performed a sensitivity analysis, including only trials with higher methodological rigour.

We did not pool trials that included different comparison groups (see Types of interventions).

Subgroup analysis and investigation of heterogeneity

Where sufficient data were available, we explored potential sources of clinical heterogeneity by analysing whether results differed for newborn infants:

1. gestational age ≥ 37 weeks (term), < 37 weeks (preterm), < 32 weeks (very preterm), or < 28 weeks (extremely preterm);
2. ventilated with nHFV using lower (< 10 cm H_2O) versus higher mean airway pressures (≥ 10 cm H_2O);
3. ventilated with nHFV using lower (< 10 Hz) versus higher frequencies (≥ 10 Hz);
4. interface used to deliver nHFV: unilateral or bilateral and short or long nasal prongs, nasopharyngeal tube, face mask, laryngeal mask airway;
5. different types of nHFV (oscillatory, percussive, and jet).

Sensitivity analysis

When sufficient data were available, we explored methodological heterogeneity by performing sensitivity analyses to assess any change in the direction of effect caused by the inclusion of studies of lower quality. We assessed studies as having low quality based on a lack of any of the following: sequence generation, allocation concealment and if the loss to follow-up was greater than 10%. As the intervention is unlikely to be adequately blinded, we did not include blinding as a criterion in the sensitivity analyses for objective outcomes (e.g. death). However, we included blinding as a criterion in the sensitivity analyses for subjective outcomes (endotracheal intubation and endotracheal reintubation).

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook, to assess the certainty of evidence for the following (clinically relevant) outcomes (Schünemann 2013).

1. Mortality before hospital discharge;
2. Endotracheal intubation or reintubation;
3. Chronic lung disease at 36 weeks;
4. Death or chronic lung disease at 36 weeks;
5. Intraventricular haemorrhage, Papile grade 3/4;
6. Neurodevelopmental disability at least 18 months postnatal age or later.

Two review authors (MEA and DO) independently assessed the certainty of evidence for each of the outcomes above. We considered evidence from RCTs as high certainty, but downgraded the evidence by one level for serious (or by two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We used the GRADEpro GDT Guideline Development Tool to create seven summary of findings tables to report the certainty of the evidence for the following comparisons.

1. nHFV compared to invasive respiratory therapy for initial respiratory support (Summary of findings 1);
2. nHFV compared to nCPAP used for initial respiratory support (Summary of findings 2);
3. nHFV compared to nIPPV used for initial respiratory support (Summary of findings 3);
4. nHFV compared to HFNC for initial respiratory support (Summary of findings 4);
5. nHFV compared to nCPAP for respiratory support following planned extubation (Summary of findings 5);
6. nHFV compared to nIPPV for respiratory support following planned extubation (Summary of findings 6);
7. nHFV compared to nIPPV following failure of initial non-invasive respiratory support (Summary of findings 7).

The GRADE approach results in an assessment of the certainty of a body of evidence as belonging to one of four grades.

1. High certainty: further research is very unlikely to change our confidence in the estimate of effect;
2. Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;
3. Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
4. Very low certainty: we are very uncertain about the estimate.

We justified all decisions to downgrade the certainty of the evidence using footnotes and made comments to aid the reader's understanding of the review, where necessary. For precision of estimates, we considered whether the confidence intervals included or excluded clinically important differences and whether the confidence intervals were influenced by a 'few events' (< 10 events).

RESULTS

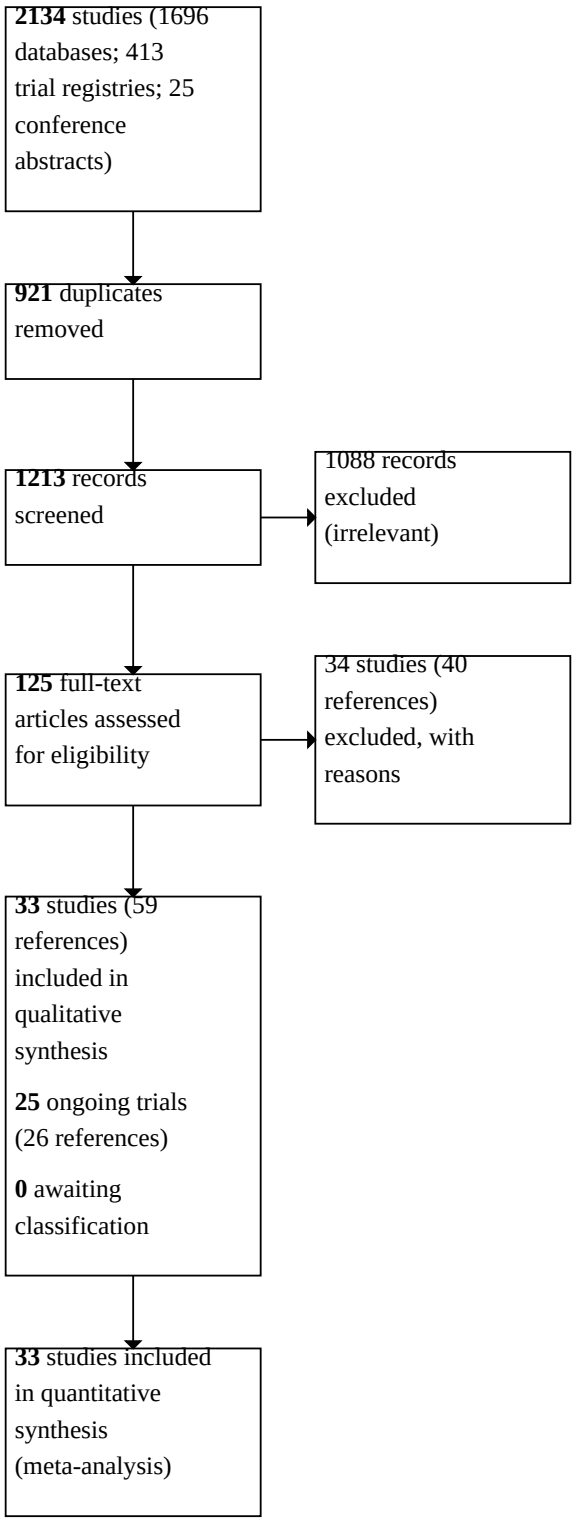
Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

Searches of databases, trial registries, and conference proceedings identified 2134 references. After removing 921 duplicates, 1213 records were available for screening. We excluded 1088 based on title/abstract and reviewed 125 full texts, trial registration records or conference abstracts. We excluded 34 studies (40 references); identified 25 ongoing studies (26 references); classified 0 as awaiting assessment; and included 33 studies (59 references). For details, see Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies. Details of the selection are available in Figure 1.

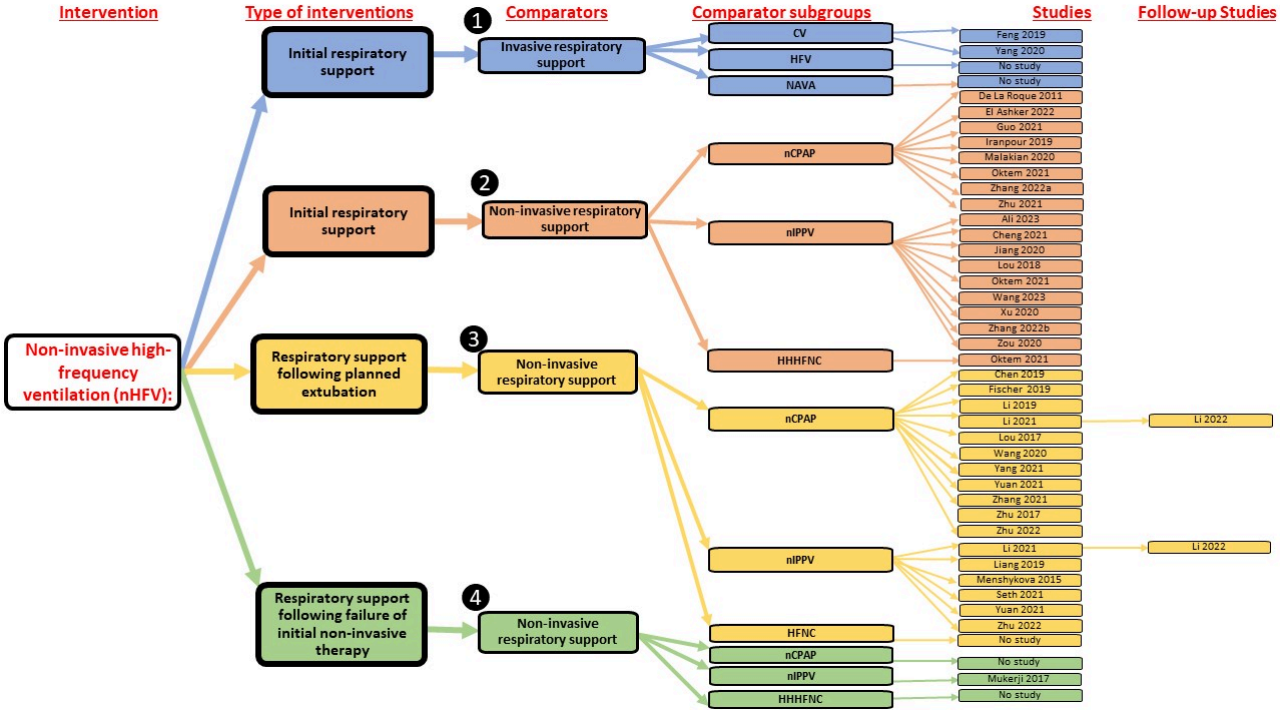
Figure 1. Study flow diagram. Updated search April 2023.



Included studies

A description of all the included studies is detailed in the Characteristics of included studies, and summarised in Figure 2 and Table 1, Table 2, Table 3, and Table 4.

Figure 2. Studies included in the review were categorised by comparison group. CV denotes invasive conventional ventilation; InSurE: Intubate, Surfactant, Extubate; HFV: invasive high-frequency ventilation; HHHFNC: Heated humidified high-flow nasal cannula; NAVA: invasive Neurally Adjusted Ventilatory Assist; nCPAP: nasal continuous positive airway pressure; nHFV: non-invasive high-frequency ventilation; nIPPV: non-invasive intermittent positive-pressure ventilation



Population

We identified 33 studies mostly in low- to middle-income settings that investigated this therapy in 5068 preterm (Ali 2023; Chen 2019; Cheng 2021; El Ashker 2022; Feng 2019; Fischer 2019; Guo 2021; Iranpour 2019; Jiang 2020; Li 2019; Li 2021; Lou 2017; Lou 2018; Malakian 2020; Menshykova 2015; Mukerji 2017; Oktem 2021; Seth 2021; Wang 2020; Wang 2023; Xu 2020; Yang 2020; Yang 2021; Yuan 2021; Zhang 2021; Zhang 2022a; Zhang 2022b; Zhenyu 2019; Zhu 2017; Zhu 2021; Zhu 2022; Zou 2020), and 46 term infants (De La Roque 2011).

The studies were primarily conducted in low- to middle-income settings as follows: Canada (n = 1), China (n = 23), Egypt (n = 1), France (n = 1), Germany (n = 1), India (n = 1), Iran (n = 2), Pakistan (n = 1), Turkey (n = 1) and Ukraine (n = 1). Only three studies enroling 78 term or preterm infants were conducted in high-income settings (De La Roque 2011; Fischer 2019; Mukerji 2017).

Interventions and comparisons

We categorised the included studies into four separate comparisons based on the comparison group as follows:

1. Comparison 1: nHFV versus invasive respiratory therapy used for initial respiratory support

a. nHFV versus invasive conventional ventilation: Two studies enroled 180 preterm infants with respiratory distress and allocated them to nHFV versus conventional ventilation as the initial treatment for respiratory distress (Feng 2019; Yang 2020).

b. nHFV versus invasive high-frequency ventilation: no studies were identified in this comparison.

c. nHFV versus invasive neurally adjusted ventilatory assist (iNAVA) ventilation: no studies were identified in this comparison.

2. Comparison 2: nHFV versus other non-invasive respiratory therapy modalities used for initial respiratory support

a. nHFV versus nCPAP: this comparison included eight studies enroling a total of 851 infants and compared nHFV versus CPAP for initial respiratory management (De La Roque 2011; El Ashker 2022; Guo 2021; Iranpour 2019; Malakian 2020; Oktem 2021; Zhang 2022a; Zhu 2021). A single study enroled 46 term infants (> 37 weeks gestation) with mild respiratory distress consistent with transient tachypnoea of the newborn and allocated them to nHFV versus nCPAP as the initial treatment for respiratory distress (De La Roque

2011). The other seven studies enroled a total of 805 preterm infants.

b. nHFV versus nIPPV: this comparison included nine studies enroling a total of 513 infants (Ali 2023; Cheng 2021; Jiang 2020; Lou 2018; Oktem 2021; Wang 2023; Xu 2020; Zhang 2022b; Zou 2020). Of these, four studies included surfactant administration in both arms. Ali 2023 (Pakistan, 48 preterm infants) compared nHFV with InSurE versus nIPPV with InSurE. Three studies (Cheng 2021 (China, 60 preterm infants); Jiang 2020 (China, 82 preterm infants); Wang 2023 (China, 43 preterm infants)) compared nHFV with non-invasive surfactant versus nIPPV with non-invasive surfactant. The other studies did not report the use of a minimally invasive surfactant as an adjunct to non-invasive respiratory support. Three studies enroling 190 preterm infants used nasal biphasic continuous positive airway pressure (BP-CPAP), bilevel positive airway pressure (BiPAP) or duo positive airway pressure (DuoPAP) considered equivalent strategies to nIPPV (Jiang 2020; Lou 2018; Wang 2023). The other studies used standard nIPPV. A single study (Zhang 2022b) enroled 82 newborn infants with persistent pulmonary hypertension of the newborn (PPHN) with a mean gestation of 34 to 35 weeks. The other studies enroled preterm or low birthweight infants.

c. nHFV versus HFNC: a single study enroling 37 preterm infants compared nHFV versus HFNC for initial respiratory management (Oktem 2021).

d. nHFV versus non-invasive neurally adjusted ventilatory assist (nNAVA): no studies were identified in this comparison.

3. Comparison 3: nHFV versus other non-invasive respiratory therapy modalities used for respiratory support following planned extubation

a. nHFV versus nCPAP: this comparison included 11 studies involving 2026 preterm infants with planned extubation after intubation and surfactant and compared nHFV versus nCPAP (Chen 2019; Fischer 2019; Li 2019; Li 2021; Lou 2017; Wang 2020; Yang 2021; Yuan 2021; Zhang 2021; Zhu 2017; Zhu 2022). Two studies used InSurE procedures with extubation to the allocated intervention (Yuan 2021; Zhu 2017).

b. nHFV versus nIPPV: this comparison included six studies that enroled 1448 preterm infants (Li 2021; Menshykova 2015; Seth 2021; Yuan 2021; Zhenyu 2019; Zhu 2022).

c. nHFV versus HFNC: no studies were identified in this comparison.

d. nHFV versus nNAVA: no studies were identified in this comparison.

4. Comparison 4: nHFV vs other non-invasive respiratory therapy modalities following the failure of initial non-invasive respiratory support

a. nHFV versus nCPAP: no studies were identified in this comparison.

b. nHFV versus nIPPV: this comparison included a single study that enroled 39 preterm infants who had failed nCPAP treatment and allocated them to nHFV versus nIPPV (Mukerji 2017).

c. nHFV versus HFNC: no studies were identified in this comparison.

d. nHFV vs nNAVA: no studies were identified in this comparison.

The ventilatory setting and interphase used in the intervention group (nHFV) and control groups (invasive respiratory support, nCPAP, nIPPV, BP-CPAP, BiPAP, and DuoPAP) were broad variables between the studies and are summarised in the above-mentioned tables.

Outcomes

The included studies reported a wide range of outcomes, and the prevalence of these depends on the type of population studied (preterm, borderline preterm or extremely preterm infants). The mean gestational age and birthweight of each trial are summarised in the above-mentioned tables.

Primary outcomes

1. 14 studies reported mortality before discharge (Ali 2023; Chen 2019; Feng 2019; Fischer 2019; Iranpour 2019; Li 2019; Lou 2017; Malakian 2020; Menshykova 2015; Mukerji 2017; Oktem 2021; Zhu 2017; Zhu 2021; Zhu 2022).
2. 24 studies reported endotracheal intubation or reintubation (Ali 2023; Chen 2019; Cheng 2021; De La Roque 2011; Fischer 2019; Iranpour 2019; Li 2019; Li 2021; Lou 2017; Malakian 2020; Menshykova 2015; Mukerji 2017; Oktem 2021; Seth 2021; Wang 2020; Wang 2023; Yang 2021; Yuan 2021; Zhang 2021; Zhang 2022b; Zhenyu 2019; Zhu 2017; Zhu 2021; Zhu 2022).

Secondary outcomes

1. Reporting of the majority of secondary outcomes was incomplete.
2. Continuous outcomes, including duration of respiratory support, oxygen therapy, and hospitalisation, were incomplete and variably reported as means (SD) and non-parametric data (medians and interquartile range or range). We converted non-parametric data to parametric data, where available, for inclusion in the meta-analysis.

Excluded studies

We excluded 34 studies.

We excluded five cross-over RCTs (Bottino 2018; Gaertner 2021; Klotz 2018; Renesme 2020; Ruegger 2018). No other randomised, cluster-randomised or quasi-RCTs were identified for exclusion from the review.

We identified and excluded 30 observational non-randomised and non-controlled studies (See Characteristics of excluded studies for more details).

Ongoing studies

See Characteristics of ongoing studies.

We identified 25 ongoing trials. The recruiting status of these trials is as follows:

1. **Finished recruiting but not published** (IRCT2016111930964N1; IRCT20180915041040N3; IRCT20190416043290N2; IRCT20201222049795N1);

2. **Still recruiting (**DRKS00005387; DRKS00023438; NCT03206489; NCT04905732; NCT05141435; NCT05493527; NCT05706428);
3. **Active but not recruiting (**ChiCTR1900028092; ChiCTR2100045446; CTRI/2021/10/037681; NCT03558737; NCT04323397; NCT04914715);
4. **Recruitment pending** (IRCT20221120056556N1);
5. **Terminated, withdrawn or suspended** (NCT01277874; NCT01852916; NCT03711565);
6. **Unknown status**: (NCT02543125; NCT03006354; NCT03842462; NCT04282369).

Studies awaiting classification

There are no studies awaiting classification.

Risk of bias in included studies

The risk of bias for studies included in this review based on the review authors' judgements is reported in the Characteristics of included studies and summarised in Figure 3 and Figure 4.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

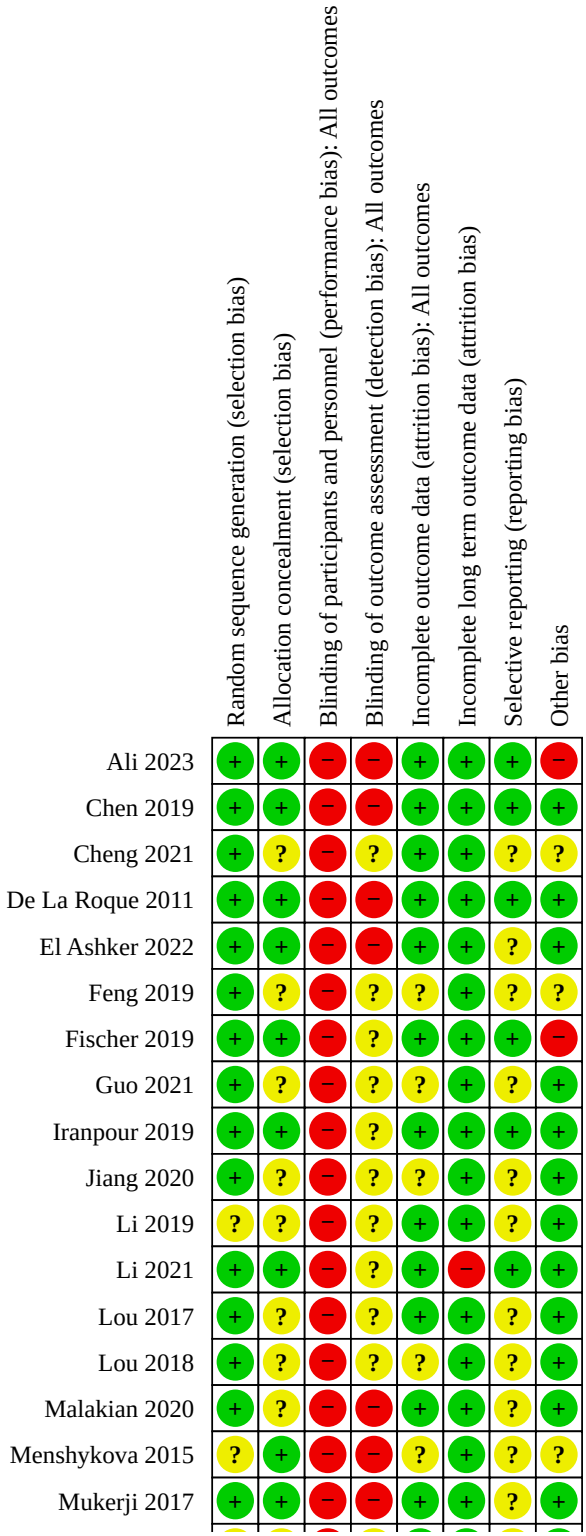
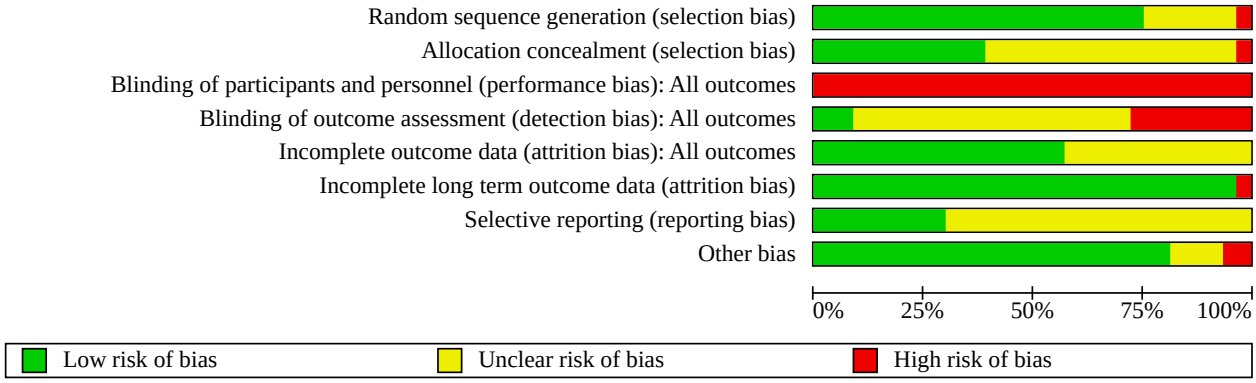


Figure 3. (Continued)

Figure 4.



Nine studies were assessed as having low risk of selection and attrition bias and were included in sensitivity analyses (Chen 2019; De La Roque 2011; Fischer 2019; Li 2021; Mukerji 2017; Seth 2021; Zhu 2017; Zhu 2021; Zhu 2022).

Allocation

Random sequence generation

One study reported quasi-random allocation using odd and even admission dates, so it was considered at high risk of selection bias (Yang 2021). Seven studies did not report the method of random sequence generation, so they were at unclear risk of selection bias (Li 2019; Menshykova 2015; Oktem 2021; Xu 2020; Yuan 2021; Zhang 2022a; Zou 2020). The remaining 25 studies were assessed as having a low risk of selection bias from random sequence generation.

Allocation concealment

Thirteen studies were assessed as having low risk of selection bias due to adequate allocation concealment (Ali 2023; Chen 2019; De La Roque 2011; El Ashker 2022; Fischer 2019; Iranpour 2019; Li 2021; Menshykova 2015; Mukerji 2017; Seth 2021; Zhu 2017; Zhu 2021; Zhu 2022). One study was at high risk of selection bias from predictable allocation (Yang 2021). The remaining 19 studies did not report

methods of allocation concealment, so were considered at unclear risk of selection bias.

Blinding

Blinding of participants

No study reported blinding of participants. However, given the nature of the interventions, blinding was unlikely and so all studies were assessed as being at high risk of performance bias. Twelve studies reported the participants were unblinded, which reflects the quality of reporting (Chen 2019; De La Roque 2011; Li 2021; Malakian 2020; Menshykova 2015; Mukerji 2017; Oktem 2021; Seth 2021; Yuan 2021; Zhu 2017; Zhu 2021; Zhu 2022). The other 21 studies did not report whether the study was blinded.

Blinding of outcome assessment

Three studies reported blinding of outcome assessment (low risk of bias: Seth 2021; Wang 2023; Zhu 2022). Nine studies reported that outcome assessment was not blinded (high risk of bias: Ali 2023; Chen 2019; De La Roque 2011; El Ashker 2022; Malakian 2020; Menshykova 2015; Mukerji 2017; Zhu 2017; Zhu 2021). The other 21 studies did not report whether the outcome assessment was blinded (unclear risk of bias).

Incomplete outcome data

Twenty studies reported no or minimal losses (< 10%) to follow-up, so were considered to be at low risk of attrition bias (Ali 2023; Chen 2019; Cheng 2021; De La Roque 2011; El Ashker 2022; Fischer 2019; Iranpour 2019; Li 2019; Li 2021; Lou 2017; Malakian 2020; Mukerji 2017; Oktem 2021; Seth 2021; Wang 2023; Yuan 2021; Zhu 2017; Zhu 2021; Zhu 2022; Zou 2020). For the other 13 studies, the reporting of losses was unclear.

A single study reporting neurodevelopmental disability had a 26.2% loss to follow-up at 24 months corrected age, so it was assessed as being at high risk of attrition bias for long-term outcomes (Li 2019).

Selective reporting

Ten studies were assessed as having a low risk of reporting bias either from the availability of a trial protocol or prospective trial registration (Ali 2023; Chen 2019; De La Roque 2011; Fischer 2019; Iranpour 2019; Li 2021; Seth 2021; Wang 2023; Zhu 2021; Zhu 2022). Trial protocols and prospective trial registrations were unavailable for the other 23 studies, so they were assessed as having an unclear risk of selective reporting bias.

Other potential sources of bias

Fischer 2019 prematurely stopped the trial for feasibility and low number of enrolments and so was considered at high risk of bias. Four studies did not provide sufficient information, including baseline characteristics of groups, so they were considered at unclear risk of other sources of bias (Cheng 2021; Feng 2019; Menshykova 2015; Zhenyu 2019). Ali 2023 reported baseline differences between groups for spontaneous vaginal delivery, gestational age and birthweight, so it was considered at high risk of other bias. The other 27 studies had no other biases identified in the assessment and were considered at low risk of bias.

Effects of interventions

See: **Summary of findings 1** nHFV compared to invasive respiratory therapy for initial respiratory support; **Summary of findings 2** nHFV compared to nCPAP used for initial respiratory support; **Summary of findings 3** nHFV compared to nIPPV used for initial respiratory support; **Summary of findings 4** nHFV compared to HFNC for initial respiratory support; **Summary of findings 5** nHFV compared to nCPAP for respiratory support following planned extubation; **Summary of findings 6** nHFV compared to nIPPV for respiratory support following planned extubation; **Summary of findings 7** nHFV compared to nIPPV following failure of initial non-invasive respiratory support

We identified 33 studies in 5068 preterm and 46 term infants.

Comparison 1: nHFV versus invasive respiratory therapy used for initial respiratory support

1.a nHFV versus invasive conventional ventilation used for initial respiratory support

For details, see Summary of findings 1.

Two studies enroled 180 preterm infants with respiratory distress and allocated them to nHFV versus conventional ventilation as the initial treatment for respiratory distress (Feng 2019; Yang 2020).

Primary outcomes

Mortality before hospital discharge

One study reported this outcome (Feng 2019). We are very uncertain whether nHFV reduces mortality before hospital discharge compared with invasive conventional ventilation used for initial respiratory support (RR 0.67, 95% CI 0.20 to 2.18; RD -0.05, 95% CI -0.19 to 0.09; I^2 = not applicable (NA); 1 study, 80 participants; very low-certainty evidence; Analysis 1.1).

Endotracheal intubation or reintubation

None of the studies in this comparison reported this outcome.

Secondary outcomes

Measures of respiratory support

Duration of respiratory support (days)

One study reported this outcome (Feng 2019). We are very uncertain whether nHFV reduces the duration of respiratory support compared with invasive conventional ventilation used for initial respiratory support (MD -0.43 days, 95% CI -0.59 to -0.27; I^2 = NA; 1 study, 80 participants; Analysis 1.2).

Outcomes during the first hospitalisation

Chronic lung disease (CLD), defined as the need for oxygen or respiratory support at 36 weeks' postmenstrual age (PMA)

Two studies reported this outcome (Feng 2019; Yang 2020). We are very uncertain whether nHFV reduces CLD at 36 weeks compared with invasive conventional ventilation used for initial respiratory support (RR 0.38, 95% CI 0.09 to 1.59; I^2 = 0%; RD -0.04, 95% CI -0.11 to 0.02; I^2 = 0%; 2 studies, 180 participants; very low-certainty evidence; Analysis 1.3).

Pulmonary air leak syndromes, including pulmonary interstitial emphysema (PIE) and gross extrapulmonary air leak (such as pneumothorax)

Two studies reported this outcome (Feng 2019; Yang 2020). We are very uncertain whether nHFV reduces pulmonary air leak syndromes compared with invasive conventional ventilation used for initial respiratory support (RR 0.25, 95% CI 0.05 to 1.14; I^2 = 0%; 2 studies, 180 participants; Analysis 1.4).

Length of hospital stay (days)

One study reported this outcome (Feng 2019). We are very uncertain whether nHFV reduces the length of hospital stay compared with invasive conventional ventilation used for initial respiratory support (MD -6.68 days, 95% CI -8.08 to -5.28; I^2 = NA; 1 study, 80 participants; Analysis 1.5).

Other secondary outcomes

None of the studies in this comparison reported the following outcomes.

1. Trauma to the nostrils and upper airway;
2. Failure of respiratory support as defined by respiratory support failure criteria or as defined by trial authors;
3. Duration of oxygen therapy (days);
4. All-cause mortality at 28 days;
5. Death or CDL reported at 36 weeks' PMA or discharge on home oxygen;
6. Patent ductus arteriosus (PDA) (treated medically or surgically);
7. Proven sepsis;
8. Necrotising enterocolitis (NEC) (any Bell stage);
9. NEC (Bell stage ≥ 2);
10. Spontaneous intestinal perforation;
11. Intraventricular haemorrhage (IVH) (any Papile grade);
12. IVH (Papile grade 3/4);
13. Periventricular leukomalacia;
14. Retinopathy of prematurity (ROP) (any stage);
15. ROP (stage ≥ 3);
16. Discharge on home oxygen;
17. All-cause mortality to follow-up (≥ one year of age);
18. Neurodevelopmental disability at least 18 months postnatal age (PNA) or later.

Subgroup analyses

Data were not available to conduct these analyses.

Sensitivity analyses

Data were not available to conduct these analyses.

1.b nHFV versus invasive high-frequency ventilation used for initial respiratory support

We did not find any RCT that compared nHFV with invasive high-frequency ventilation for initial respiratory support.

1.c nHFV versus invasive neurally adjusted ventilatory assist (iNAVA) ventilation used for initial respiratory support

We did not find any RCT that compared nHFV with NAVA for initial respiratory support.

Comparison 2: nHFV versus other non-invasive respiratory therapy modalities used for initial respiratory support

2.a nHFV versus nCPAP used for initial respiratory support

For details, see Summary of findings 2.

Eight studies enroling a total of 851 infants compared nHFV versus nCPAP for initial respiratory management (De La Roque 2011; El Ashker 2022; Guo 2021; Iranpour 2019; Malakian 2020; Oktem 2021; Zhang 2022a; Zhu 2021).

Primary outcomes

Mortality before hospital discharge

Four studies reported this outcome (Iranpour 2019; Malakian 2020; Oktem 2021; Zhu 2021). We are very uncertain whether nHFV reduces mortality before hospital discharge compared with nCPAP (RR 1.00, 95% CI 0.41 to 2.41; I^2 = 0%; RD -0.00, 95% CI -0.03 to 0.03; I^2 = 0%; 4 studies, 531 participants; very low-certainty evidence; Analysis 2.1).

Endotracheal intubation or reintubation

Five studies reported this outcome (De La Roque 2011; Iranpour 2019; Malakian 2020; Oktem 2021; Zhu 2021). Using nHFV probably reduces endotracheal intubation compared to nCPAP (RR 0.52, 95% CI 0.33 to 0.82; I^2 = 0%; RD -0.08, 95% CI -0.13 to -0.03; I^2 = 0%; NNTB = 13, 95% CI 7 to 37; 5 studies, 571 participants; low-certainty evidence; Analysis 2.2).

Secondary outcomes

Measures of the safety of nHFV

Trauma to the nostrils and upper airway

Two studies reported this outcome (Malakian 2020; Oktem 2021). We are very uncertain whether nHFV reduces trauma to the nostrils and upper airway compared with nCPAP used for initial respiratory support (RR 1.03, 95% CI 0.72 to 1.47; I^2 = 86%; 2 studies, 161 participants; Analysis 2.3).

Measures of respiratory support

Failure of respiratory support as defined by respiratory support failure criteria or as defined by trial authors

Three studies reported this outcome (Malakian 2020; Oktem 2021; Zhu 2021). nHFV, compared with nCPAP used for initial respiratory support, may reduce failure of respiratory support (RR 0.57, 95% CI 0.36 to 0.90; I^2 = 0%; RD -0.08, -0.14 to -0.02; I^2 = 0%; 3 studies, 463 participants; Analysis 2.4).

Duration of respiratory support (days)

Six studies reported this outcome (Guo 2021; Iranpour 2019; Malakian 2020; Oktem 2021; Zhang 2022a; Zhu 2021). nHFV, compared with nCPAP used for initial respiratory support, may reduce the duration of respiratory support (MD -0.48 days, 95% CI -0.55 to -0.40; I^2 = 91%; 6 studies, 707 participants; Analysis 2.5).

Duration of oxygen therapy (days)

Three studies reported this outcome (De La Roque 2011; Malakian 2020; Zhu 2021). nHFV, compared with nCPAP used for initial respiratory support, may have little or no effect on the duration of oxygen therapy (MD 0.03 days, 95% CI -0.05 to 0.11; I^2 = 95%; 3 studies, 466 participants; Analysis 2.6).

Outcomes during the first hospitalisation

CLD, defined as the need for oxygen or respiratory support at 36 weeks' PMA

Four studies reported this outcome (Guo 2021; Iranpour 2019; Oktem 2021; Zhu 2021). nHFV, compared with nCPAP used for initial respiratory support, may have little or no effect on CLD (RR 1.35, 95% CI 0.80 to 2.27; I^2 = 0%; RD 0.03, 95% CI -0.02 to 0.09; I^2 = 0%; 4 studies, 481 participants; low-certainty evidence; Analysis 2.7).

Death or CLD reported at 36 weeks' PMA or discharge on home oxygen

One study reported this outcome (Iranpour 2019). We are very uncertain whether nHFV compared with nCPAP used for initial respiratory support, reduces death or CLD reported at 36 weeks (RR 2.50, 95% CI 0.52 to 12.01; I^2 = NA; 1 study, 68 participants; low-certainty evidence; Analysis 2.8).

PDA (treated medically or surgically)

Two studies reported this outcome (Iranpour 2019; Oktem 2021). We are very uncertain whether nHFV, compared with nCPAP used for initial respiratory support, reduces PDA (RR 0.68, 95% CI 0.29 to 1.62; I^2 = 0%; 2 studies, 105 participants; Analysis 2.9).

Pulmonary air leak syndromes, including PIE and gross extrapulmonary air leak (such as pneumothorax)

Six studies reported this outcome (De La Roque 2011; Guo 2021; Iranpour 2019; Malakian 2020; Oktem 2021; Zhu 2021). nHFV, compared with nCPAP used for initial respiratory support, may have little or no effect on pulmonary air leak syndromes (RR 2.01, 95% CI 0.70 to 5.75; I^2 = 0%; 6 studies, 645 participants; Analysis 2.10).

Proven sepsis

Two studies reported this outcome (De La Roque 2011; Oktem 2021). One study reported no events amongst the study groups (De La Roque 2011). We are very uncertain whether nHFV, compared with nCPAP used for initial respiratory support, reduces proven sepsis (RR 0.88, 95% CI 0.38 to 2.04; I^2 = NA; I^2 = NA; 2 studies, 77 participants; Analysis 2.11).

NEC (any Bell stage)

Three studies reported this outcome (Iranpour 2019; Oktem 2021; Zhu 2021). nHFV, compared with nCPAP used for initial respiratory support, may have little or no effect on NEC (RR 1.19, 95% CI 0.52 to 2.69; I^2 = 37%; 3 studies, 407 participants; Analysis 2.12).

IVH (any Papile grade)

Three studies reported this outcome (Guo 2021; Iranpour 2019; Oktem 2021). nHFV, compared with nCPAP used for initial respiratory support, may have little or no effect on IVH (any Papile grade) (RR 0.42, 95% CI 0.16 to 1.13; I^2 = 0%; I^2 = 54%; 3 studies, 179 participants; Analysis 2.15).

IVH (Papile grade 3/4)

Four studies reported this outcome (Iranpour 2019; Malakian 2020; Oktem 2021; Zhu 2021). nHFV, compared with nCPAP used for initial respiratory support, may have little or no effect on IVH Papile grade 3/4 (RR 1.17, 95% CI 0.36 to 3.78; I^2 = 0%; RD 0.00, 95% CI -0.02 to 0.03; I^2 = 0%; 4 studies, 531 participants; low-certainty evidence; Analysis 2.16).

ROP (any stage)

One study reported this outcome (Guo 2021). We are very uncertain whether nHFV, compared with nCPAP used for initial respiratory support, reduces ROP (any stage) (RR 0.70, 95% CI 0.12 to 3.97; I^2 = NA; 1 study, 74 participants; Analysis 2.18).

ROP (stage ≥ 3)

One study reported this outcome (Zhu 2021). We are very uncertain whether nHFV, compared with nCPAP used for initial respiratory support, reduces ROP ≥ 3 (RR 0.77, 95% CI 0.29 to 2.01; I^2 = NA; 1 study, 302 participants; Analysis 2.19).

Length of hospital stay (days)

Four studies reported this outcome (Guo 2021; Malakian 2020; Zhang 2022a; Zhu 2021). nHFV, compared with nCPAP used for initial respiratory support, may have little or no effect on the length of hospital stay (MD -4.07 days, 95% CI -4.46 to -3.67; I^2 = 93%; 4 studies, 602 participants; Analysis 2.20).

Other secondary outcomes

None of the studies in this comparison reported the following outcomes.

1. All-cause mortality at 28 days;
2. NEC (Bell stage ≥ 2);
3. Discharge on home oxygen;
4. All-cause mortality to follow-up (≥ one year of age);
5. Neurodevelopmental disability at least 18 months postnatal age (PNA) or later.

Subgroup analyses

The following GRADE outcomes are reported for gestation (term or near-term versus preterm), nHFV mean airway pressure (≥ 10 cm H_2O versus < 10 cm H_2O) and nHFV frequency (≥ 10 Hz versus < 10 Hz) subgroup analyses:

Mortality before hospital discharge(Analysis 3.1)

1. Gestation: term or near-term infants: no studies. Analysis of studies enroling preterm infants found no difference (RR 1.00, 95% CI 0.41 to 2.41; I^2 = 0%; 4 studies, 531 participants). The test for subgroup differences was not performed.
2. nHFV mean airway pressure: analysis of studies using nHFV MAP ≥ 10 cm H_2O found no studies. Analysis of studies using nHFV MAP < 10 cm H_2O found no difference (RR 1.00, 95% CI 0.41 to 2.41; I^2 = 0%; 4 studies, 531 participants). The test for subgroup differences was not performed.

3. nHFV frequency: analysis of studies using nHFV Hz ≥ 10 found no difference (RR 0.39, 95% CI 0.02 to 8.97; I^2 = 0%; 2 studies, 105 participants). Analysis of studies using nHFV Hz < 10 found no difference: (RR 0.73, 95% CI 0.17 to 3.11; I^2 = NA; 1 study, 124 participants). The subgroup differences test was not significant (Chi^2 = 0.13; df = 1; P = 0.72; I^2 = 0%).

Endotracheal intubation(Analysis 3.2)

1. Gestation: term or near-term infants - De La Roque 2011 reported no intubation in either group (40 participants).
2. Analysis of studies enroling preterm infants found a reduction (RR 0.52, 95% CI 0.33 to 0.82; I^2 = 0%; 4 studies, 531 participants). The test for subgroup differences was not performed.
3. Mean airway pressure: analysis of studies using HFV MAP ≥ 10 cm H_2O found no studies. Analysis of studies using nHFV MAP < 10 cm H_2O found a reduction (RR 0.52, 95% CI 0.33 to 0.82; I^2 = 0%; 5 studies, 571 participants). The test for subgroup differences was not performed.
4. Frequency: analysis of studies using nHFV Hz ≥ 10 found no difference (RR 0.50, 95% CI 0.21 to 1.18; I^2 = 43%; 2 studies, 105 participants). Analysis of studies using nHFV Hz < 10 found a reduction (RR 0.43, 95% CI 0.14 to 1.32; I^2 = NA; 2 studies, 164 participants). The subgroup differences test was not significant (Chi^2 = 0.04; df = 1; P = 0.84; I^2 = 0).

Failure of respiratory support (Analysis 3.3)

1. Gestation: term or near-term infants - no studies. Analysis of studies enroling preterm infants found a reduction (RR 0.57, 95% CI 0.36 to 0.90; I^2 = 0%; 3 studies, 463 participants). The test for subgroup differences was not performed.
2. Mean airway pressure: analysis of studies using HFV MAP ≥ 10 cm H_2O found no studies. Analysis of studies using nHFV MAP < 10 cm H_2O found a reduction (RR 0.57, 95% CI 0.36 to 0.90; I^2 = 0%; 3 studies, 463 participants).
3. Frequency: analysis of studies using nHFV Hz ≥ 10 found a single study (Oktem 2021). That study reported no difference (RR 0.74, 95% CI 0.30 to 1.83; 1 study, 37 participants). A single study (Malakian 2020) used nHFV Hz < 10. This study reported no difference (RR 0.43, 95% CI 0.14 to 1.32; I^2 = NA; 1 study, 124 participants). The subgroup differences test was not significant (Chi^2 = 0.53, df = 1; P = 0.47; I^2 = 0%).

CLD at 36 weeks (Analysis 3.4)

1. Gestation: term or near-term infants - no studies. Analysis of studies enroling preterm infants found no difference (RR 1.35, 95% CI 0.80 to 2.27; I^2 = 0%; 4 studies, 481 participants). The test for subgroup differences was not performed.
2. Mean airway pressure: No study used nHFV MAP ≥ 10 cm H_2O. Analysis of studies using nHFV MAP < 10 cm H_2O found no difference (RR 1.43, 95% CI 0.84 to 2.44; I^2 = 0%; 3 studies, 407 participants). The test for subgroup differences was not performed.
3. Frequency: analysis of studies using nHFV Hz ≥ 10 found no difference (RR 2.41, 95% CI 0.91 to 6.38; I^2 = 0%; 2 studies, 105 participants). Analysis of studies using nHFV Hz < 10 found no studies. The test for subgroup differences was not performed.

Death or CLD at 36 weeks(Analysis 3.5).

A single study reported data for a single subgroup (Iranpour 2019). The test for subgroup differences was not performed.

IVH, Papile grade 3/4(Analysis 3.6)

1. Gestation: term or near-term infants - no studies. Analysis of studies enroling preterm infants found no difference (RR 1.17, 95% CI 0.36 to 3.78; I^2 = 0%; 4 studies, 531 participants). The test for subgroup differences was not performed.
2. Mean airway pressure: analysis of studies using HFV MAP ≥ 10 cm H_2O found no studies. Analysis of studies using nHFV MAP < 10 cm H_2O found no difference (RR 1.17, 95% CI 0.36 to 3.78; I^2 = 0%; 4 studies, 531 participants). The test for subgroup differences was not performed.
3. Frequency: analysis of studies using nHFV Hz ≥ 10 found two studies that reported no events in either group (Iranpour 2019; Oktem 2021; 105 participants). Analysis of a single study using nHFV Hz < 10 found no difference (Malakian 2020); (RR 0.65, 95% CI 0.11 to 3.73; I^2 = NA; 1 study, 124 participants). The test for subgroup differences was not performed.

Neurodevelopmental disability at least 18 months' PNA or later

No studies reported this outcome.

Sensitivity analyses

Three studies were assessed as having a low risk of selection and attrition bias (De La Roque 2011; Iranpour 2019; Zhu 2021).

Mortality before hospital discharge

Sensitivity analyses found no difference in mortality before hospital discharge (RR 1.48, 95% CI 0.43 to 5.14; I^2 = 0%; 2 studies, 370 participants; Analysis 5.1).

Endotracheal intubation

Sensitivity analyses found reduced endotracheal reintubation (RR 0.50, 95% CI 0.28 to 0.89; I^2 = 18%; 3 studies, 410 participants = 410; Analysis 5.2).

Failure of respiratory support

A single study reported no difference in extubation failure (Zhu 2021) (RR 0.57, 95% CI 0.31 to 1.03; 1 study, 302 participants; Analysis 5.3).

CLD at 36 weeks

The analysis found no difference in CLD at 36 weeks (RR 1.28, 95% CI 0.70 to 2.33; I^2 = 0%; 2 studies, 370 participants; Analysis 5.4).

Death or CLD at 36 weeks

A single study reported no difference in death or CLD at 36 weeks (Iranpour 2019); (RR 2.50, 95% CI 0.52 to 12.01; 1 study, 68 participants; Analysis 5.5).

IVH, Papile grade 3/4

The analysis found no difference in IVH, Papile grade 3/4 (RR 1.97, 95% CI 0.37 to 10.61; I^2 = NA; 2 studies, 370 participants; Analysis 5.6).

Neurodevelopmental disability at least 18 months' PNA or later

No studies reported this outcome.

2.b nHFV versus nIPPV used for initial respiratory support

For details, see Summary of findings 3.

Nine studies enroled 513 infants comparing nHFV versus nIPPV for initial respiratory management (Ali 2023; Cheng 2021; Jiang 2020; Lou 2018; Oktem 2021; Wang 2023; Xu 2020; Zhang 2022b; Zou 2020).

Primary outcomes

Mortality before hospital discharge

Two studies reported this outcome (Ali 2023; Oktem 2021). Oktem 2021 reported no mortality before discharge (participants = 36). Ali 2023 reported a total of 20 deaths before hospital discharge (participants = 48). nHFV may result in little to no difference in mortality before hospital discharge compared with nIPPV used for initial respiratory support (RR 1.86, 95% CI 0.90 to 3.83; I^2 = NA; RD 0.14, 95% CI -0.02 to 0.30; I^2 = 88%; 2 studies, 84 participants; low-certainty evidence; Analysis 2.1).

Endotracheal intubation or reintubation

Five studies reported this outcome (Ali 2023; Cheng 2021; Oktem 2021; Wang 2023; Zhang 2022b). Using nHFV probably has no effect in reducing endotracheal intubation compared to nIPPV (RR 1.33, 95% CI 0.76 to 2.34; I^2 = 15%; RD 0.05, 95% CI -0.04 to 0.14; I^2 = 38%; 5 studies, 228 participants; low-certainty evidence; Analysis 2.2).

Secondary outcomes

Measures of the safety of nHFV

Trauma to the nostrils and upper airway

Two studies reported this outcome (Jiang 2020; Oktem 2021). We are very uncertain whether nHFV reduces trauma to the nostrils and upper airway compared with nIPPV used for initial respiratory support (RR 0.98, 95% CI 0.68 to 1.40; I^2 = 0%; 2 studies, 118 participants; Analysis 2.3).

Measures of respiratory support

Failure of respiratory support or failure of extubation as defined by respiratory support failure criteria or as defined by trial authors

One study reported this outcome (Oktem 2021). We are very uncertain whether nHFV compared with nIPPV used for initial respiratory support reduces failure of respiratory support (RR 2.79, 95% CI 0.62 to 12.57; I^2 = NA; RD 0.19, -0.07 to 0.45; I^2 = NA; 1 study, 37 participants; very low-certainty evidence; Analysis 2.4).

Duration of respiratory support (days)

Five studies reported this outcome (Ali 2023; Cheng 2021; Jiang 2020; Oktem 2021; Wang 2023). nHFV, compared with nIPPV used for initial respiratory support, may have little or no effect on the duration of respiratory support (MD 0.22 days, 95% CI -0.58 to 1.01; I^2 = 56%; 5 studies, 269 participants; Analysis 2.5).

Duration of oxygen therapy (days)

Three studies reported this outcome (Cheng 2021; Jiang 2020; Wang 2023). nHFV, compared with nIPPV used for initial respiratory support, may reduce the duration of oxygen therapy (MD -0.65 days, 95% CI -1.13 to -0.17; I^2 = 0%; 3 studies, 185 participants; Analysis 2.6).

Outcomes during the first hospitalisation

CLD, defined as the need for oxygen or respiratory support at 36 weeks' PMA

Five studies reported this outcome (Ali 2023; Cheng 2021; Oktem 2021; Wang 2023; Zou 2020). nHFV, compared with nIPPV used for initial respiratory support, may reduce CLD (RR 0.63, 95% CI 0.42 to 0.95; I^2 = 0%; RD -0.10, 95% CI -0.19 to -0.02; I^2 = 56%; NNTB 10, 95% CI% 5 to 91; 5 studies, 307 participants; low-certainty evidence; Analysis 2.7).

PDA (treated medically or surgically)

Two studies reported this outcome (Ali 2023; Oktem 2021). Ali 2023 reported no events amongst the study groups. We are very uncertain whether nHFV compared with nIPPV used for initial respiratory support reduces PDA (RR 0.67, 95% CI 0.19 to 2.40; I^2 = NA; 2 studies, 84 participants; Analysis 2.9).

Pulmonary air leak syndromes, including PIE and gross extrapulmonary air leak (such as pneumothorax)

Five studies reported this outcome (Ali 2023; Jiang 2020; Oktem 2021; Xu 2020; Zhang 2022b). nHFV, compared with nIPPV used for initial respiratory support, may have little or no effect on pulmonary air leak syndromes (RR 0.66, 95% CI 0.27 to 1.66; I^2 = 0%; 5 studies, 267 participants; Analysis 2.10).

Proven sepsis

One study reported this outcome (Oktem 2021). We are very uncertain whether nHFV, compared with nIPPV used for initial respiratory support, reduces proven sepsis (RR 0.75, 95% CI 0.34 to 1.66; I^2 = NA; 1 study, 36 participants; Analysis 2.11).

NEC (any Bell stage)

Two studies reported this outcome (Ali 2023; Oktem 2021). We are very uncertain whether nHFV, compared with nIPPV used for initial respiratory support, reduces NEC (RR 0.63, 95% CI 0.09 to 4.64; I^2 = 0%; 2 studies, 84 participants; Analysis 2.12).

NEC (Bell stage ≥ 2)

A single study reported no events amongst the study groups (Wang 2023: 43 participants; Analysis 2.13).

Spontaneous intestinal perforation

A single study reported no events amongst the study groups (Ali 2023: 48 participants; Analysis 2.14).

IVH (any Papile grade)

Five studies reported this outcome (Ali 2023; Oktem 2021; Wang 2023; Zhang 2022b; Zou 2020). nHFV, compared with nCPAP used for initial respiratory support, may have little or no effect on IVH (any Papile grade) (RR 0.61, 95% CI 0.30 to 1.22; I^2 = 0%; 5 studies, 288 participants; Analysis 2.15).

IVH (Papile grade 3/4)

A single study reported no events amongst the study groups (36 participants; very low-certainty evidence; Analysis 2.16; Oktem 2021).

Periventricular leukomalacia

A single study reported no difference in periventricular leukomalacia (RR 0.95, 95% CI 0.44 to 2.07; I^2 = NA; 43 participants; Analysis 2.17; Wang 2023).

ROP (any stage)

Two studies reported this outcome (Ali 2023; Zou 2020). nHFV compared with nIPPV used for initial respiratory support may reduce ROP at any stage (RR 0.54, 95% CI 0.30 to 0.98; I^2 = 0%; RD -0.13, 95% CI -0.25 to -0.01; I^2 = 0%; NNTB 8, 95% CI 4 to 140; 2 studies, 168 participants; Analysis 2.18).

Length of hospital stay (days)

Two studies reported this outcome (Jiang 2020; Wang 2023). nHFV, compared with nCPAP used for initial respiratory support, may reduce the length of hospital stay (MD -4.34 days, 95% CI -6.22 to -2.47; I^2 = 0%; 2 studies, 125 participants; Analysis 2.20).

Other secondary outcomes

None of the studies in this comparison reported the following outcomes.

1. All-cause mortality at 28 days;
2. Death or CDL reported at 36 weeks' PMA or discharge on home oxygen;
3. ROP (stage ≥ 3);
4. Discharge on home oxygen;
5. All-cause mortality to follow-up (≥ one year of age);
6. Neurodevelopmental disability at least 18 months postnatal age (PNA) or later.

Subgroup analyses

The following GRADE outcomes were reported for gestation (term or near-term versus preterm): nHFV mean airway pressure (≥ 10 cm H_2O versus < 10 cm H_2O) and nHFV frequency (≥ 10 Hz versus < 10 Hz) subgroup analyses.

Mortality before hospital discharge (Analysis 4.1)

1. Gestation: term or near-term infants - no studies. Analysis of studies enroling preterm infants found no difference (RR 1.86, 95% CI 0.90 to 3.83; I^2 = NA; 2 studies, 84 participants). The test for subgroup differences was not performed.
2. nHFV mean airway pressure: nHFV MAP ≥ 10 cm H_2O - no studies. Analysis of studies using nHFV MAP < 10 cm H_2O found no difference (RR 1.86, 95% CI 0.90 to 3.83; I^2 = NA; 2 studies, 84 participants). The test for subgroup differences was not performed.
3. nHFV frequency: a single study using nHFV Hz ≥ 10 reported no events (participants = 36). nHFV Hz < 10 - no studies. The test for subgroup differences was not performed (Oktem 2021).

Endotracheal intubation(Analysis 4.2)

1. Gestation: term or near-term infants - Zhang 2022b reported no difference (RR 0.10, 95% CI 0.01 to 1.78, 1 study, 41 participants). Analysis of studies enroling preterm infants found no difference (RR 1.58, 95% CI 0.84 to 3.00; I^2 = 9%; 4 studies, 187 participants). The test for subgroup differences was not significant (Chi^2 = 3.37; df = 1; P = 0.07; I^2 = 70.3%).
2. Mean airway pressure: HFV MAP ≥ 10 cm H_2O - no studies. Analysis of studies using nHFV MAP < 10 cm H_2O found no difference (RR 1.29, 95% CI 0.68 to 2.44; I^2 = 58%; 3 studies, 125 participants; Analysis 4.2). The test for subgroup differences was not performed.
3. Frequency: Oktem 2021, using nHFV Hz ≥ 10, reported no difference (RR 2.79, 95% CI 0.62 to 12.57; 1 study, 36 participants; Analysis 4.2). nHFV Hz < 10 - no studies. The test for subgroup differences was not performed.

Failure of respiratory support (Analysis 4.3)

A single study reported on failure of respiratory support (Oktem 2021).

1. Gestation: term or near-term infants - no studies. A single study enroling preterm infants reported no difference (RR 2.79, 95% CI 0.62 to 12.57; 1 study, 36 participants). The test for subgroup differences was not performed.
2. Mean airway pressure: HFV MAP ≥ 10 cm H_2O - no studies. A single study using nHFV MAP < 10 cm H_2O reported no difference (RR 2.79, 95% CI 0.62 to 12.57; 36 participants). The test for subgroup differences was not performed.
3. Frequency: a single study using nHFV Hz ≥ 10 reported no difference (RR 2.79, 95% CI 0.62 to 12.57; 1 study, 36 participants). nHFV Hz < 10 - no studies. The test for subgroup differences was not performed.

CLD at 36 weeks (Analysis 4.4)

1. Gestation: term or near-term infants - no studies. Analysis of studies enroling preterm infants found a reduction (RR 0.63, 95% CI 0.42 to 0.95; I^2 = 0%; 5 studies, 307 participants). The test for subgroup differences was not performed.
2. Mean airway pressure: HFV MAP ≥ 10 cm H_2O - no studies. Analysis of studies using nHFV MAP < 10 cm H_2O found no difference (RR 0.79, 95% CI 0.37 to 1.66; I^2 = 0%; 2 studies, 84 participants). The test for subgroup differences was not performed.
3. Frequency: a single study using nHFV Hz ≥ 10 reported no difference (RR 3.35, 95% CI 0.78 to 14.44; 1 study, 36 participants). nHFV Hz < 10 - no studies. The test for subgroup differences was not performed.

Death or CLD at 36 weeks

No studies reported this outcome.

IVH, Papile grade 3/4 (Analysis 4.5)

A single study (36 participants) reported no events (Oktem 2021). The test for subgroup differences was not performed.

Neurodevelopmental disability at least 18 months' PNA or later

No studies reported this outcome.

Sensitivity analyses

No study was considered to have a low risk of bias.

2.c nHFV versus HFNC used for initial respiratory support

For details, see Summary of findings 4.

A single study enroling 37 preterm infants compared nHFV versus HFNC for initial respiratory management (Oktem 2021).

Primary outcomes

Mortality before hospital discharge

Oktem 2021 reported no mortality in nHFV and HFNC arms before hospital discharge (37 participants; very low-certainty evidence; Analysis 2.1).

Endotracheal intubation or reintubation

We are very uncertain whether nHFV, compared with HFNC used for initial respiratory support, reduces endotracheal intubation (RR 2.94, 95% CI 0.65 to 13.27; I^2 = NA; RD 0.19, 95% CI -0.06 to 0.45; I^2 = NA; 1 study, 37 participants; very low-certainty evidence; Analysis 2.2).

Secondary outcomes

Measures of the safety of nHFV

Trauma to the nostrils and upper airway

nHFV compared with HFNC used for initial respiratory support may increase trauma to the nostrils and upper airway (RR 2.35, 95% CI 1.25 to 4.45; I^2 = NA; RD 0.47, 0.20 to 0.75; I^2 = NA; NNTB 3, 95% CI 1 to 5; 1 study, 37 participants; Analysis 2.3).

Measures of respiratory support

Failure of respiratory support or failure of extubation as defined by respiratory support failure criteria or as defined by trial authors

We are very uncertain whether nHFV compared with HFNC used for initial respiratory support reduces failure of respiratory support (RR 2.94, 95% CI 0.65 to 13.27; I^2 = NA; RD 0.19, -0.06 to 0.45; I^2 = NA; 1 study, 37 participants; Analysis 2.4).

Duration of respiratory support (days)

We are very uncertain whether nHFV, compared with HFNC used for initial respiratory support, reduces the duration of respiratory support (MD -6.40 days, 95% CI -14.74 to 1.94; I^2 = NA; 1 study, 37 participants; Analysis 2.5).

Outcomes during the first hospitalisation

CLD, defined as the need for oxygen or respiratory support at 36 weeks' PMA

We are very uncertain whether nHFV, compared with HFNC used for initial respiratory support, reduces CLD (RR 1.18, 95% CI 0.46 to 2.98; I^2 = NA; RD 0.05, 95% CI -0.25 to 0.36; I^2 = NA; 1 study, 37 participants; very low-certainty evidence; Analysis 2.7).

PDA (treated medically or surgically)

We are very uncertain whether nHFV, compared with HFNC used for initial respiratory support, reduces PDA (RR 1.18, 95% CI 0.27 to 5.09; I^2 = NA; 1 study, 37 participants; Analysis 2.9).

Pulmonary air leak syndromes, including PIE and gross extrapulmonary air leak (such as pneumothorax)

We are very uncertain whether nHFV, compared with HFNC used for initial respiratory support, reduces pulmonary air leak syndromes (RR 3.50, 95% CI 0.15 to 80.71; I^2 = NA; 1 study, 37 participants; Analysis 2.10).

Proven sepsis

We are very uncertain whether nHFV, compared with HFNC used for initial respiratory support, reduces proven sepsis (RR 1.01, 95% CI 0.42 to 2.43; I^2 = NA; 1 study, 37 participants; Analysis 2.11).

NEC (any Bell stage)

We are very uncertain whether nHFV, compared with HFNC used for initial respiratory support, reduces NEC (any Bell stage) (RR 0.23, 95% CI 0.01 to 4.55; I^2 = NA; 1 study, 37 participants; Analysis 2.12).

IVH (any Papile grade)

We are very uncertain whether nHFV, compared with HFNC used for initial respiratory support, reduces IVH (any Papile grade) (RR 0.23, 95% CI 0.01 to 4.55; I^2 = NA; 1 study, 37 participants; Analysis 2.15).

IVH (Papile grade 3/4)

Oktem 2021 reported no IVH Papile grade 3/4 in both nHFC and HFNC arms (37 participants; very low-certainty evidence; Analysis 2.16).

Other secondary outcomes

None of the studies in this comparison reported the following outcomes.

1. Duration of oxygen therapy (days);
2. All-cause mortality at 28 days;
3. Death or CLD reported at 36 weeks' PMA;
4. NEC (Bell stage ≥ 2);
5. Spontaneous intestinal perforation;
6. Periventricular leukomalacia;
7. ROP (any stage);
8. ROP (stage ≥ 3);
9. Length of hospital stay (days);
10. Discharge on home oxygen;
11. All-cause mortality to follow-up (≥ one year of age);
12. Neurodevelopmental disability at least 18 months' PNA or later.

Subgroup analyses

These were not performed as only a single study was included in this comparison (Oktem 2021).

Sensitivity analyses

No study was at low risk of bias.

2.d nHFV versus non-invasive neurally adjusted ventilatory assist (nNAVA) ventilation used for initial respiratory support

No studies assessed this comparison.

Comparison 3: nHFV versus other non-invasive respiratory therapy modalities used for respiratory support following planned extubation

3.a nHFV versus nCPAP used for respiratory support following planned extubation

For details, see Summary of findings 5.

Eleven studies enroled 2026 preterm infants with planned extubation after intubation and surfactant, and compared nHFV versus nCPAP (Chen 2019; Fischer 2019; Li 2019; Li 2021; Lou 2017; Wang 2020; Yang 2021; Yuan 2021; Zhang 2021; Zhu 2017; Zhu 2022).

Two studies used InSurE procedures with extubation to the allocated intervention (Yuan 2021; Zhu 2017).

Primary outcomes

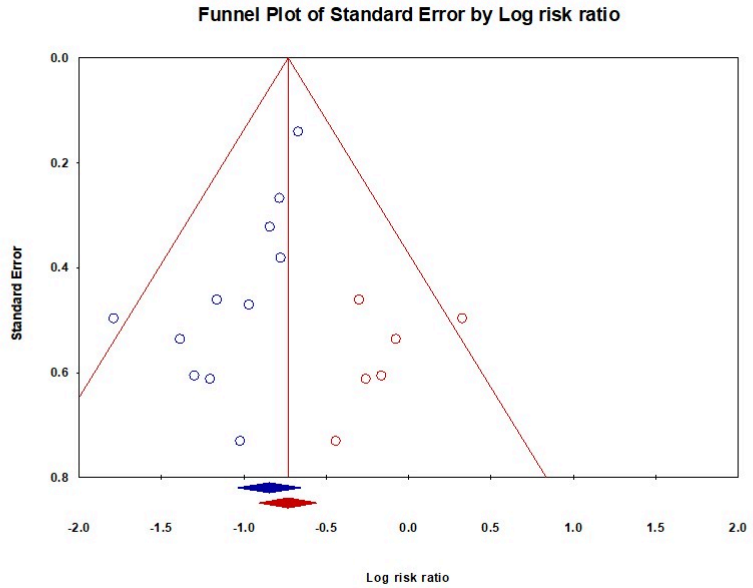
Mortality before hospital discharge

Six studies reported this outcome (Chen 2019; Fischer 2019; Li 2019; Lou 2017; Zhu 2017; Zhu 2022). nHFV probably does not reduce mortality before hospital discharge compared with nCPAP (RR 0.92, 95% CI 0.52 to 1.64; I^2 = 0%; RD -0.00, 95% CI -0.02 to 0.02; I^2 = 0%; 6 studies, 1472 participants; moderate-certainty evidence; Analysis 6.1).

Endotracheal intubation or reintubation

Eleven studies reported this outcome (Chen 2019; Fischer 2019; Li 2019; Li 2021; Lou 2017; Wang 2020; Yang 2021; Yuan 2021; Zhang 2021; Zhu 2017; Zhu 2022). nHFV results in a reduction in endotracheal intubation or reintubation compared with nCPAP (RR 0.42, 95% CI 0.35 to 0.51; I^2 = 0%; RD -0.18, 95% CI -0.21 to -0.14; I^2 = 55%; NNTB 6, 95% CI 5 to 7; 11 studies, 1897 participants; low-certainty evidence; Analysis 6.2). There was statistically significant evidence of funnel plot asymmetry consistent with trials favouring controls missing from the meta-analysis (Egger test for bias, P = 0.002; Figure 5).

Figure 5. Funnel plot: Trials comparing nHFV with nCPAP for respiratory support following planned extubation: Outcome 6.2 Endotracheal reintubation. Current studies are depicted as blue, and imputed studies are red. Egger test P = 0.002



Secondary outcomes

Measures of the safety of nHFV

Trauma to the nostrils and upper airway

Four studies reported this outcome (Chen 2019; Li 2021; Yuan 2021; Zhu 2022). nHFV, compared with nCPAP for respiratory support following planned extubation, may have little or no effect on trauma to the nostrils and upper airway (RR 0.96, 95% CI 0.64 to 1.44; I^2 = 60%; RD-0.00, 95% CI -0.03 to 0.02; I^2 = 72%; 4 studies, 1418 participants; Analysis 6.3).

Measures of respiratory support

Failure of respiratory support or failure of extubation as defined by respiratory support failure criteria or as defined by trial authors

One study reported this outcome (Fischer 2019). We are very uncertain whether nHFV, compared with nCPAP for respiratory support following planned extubation, reduces failure of respiratory support (RR 0.60, 95% CI 0.22 to 1.65; I^2 = NA; RD -0.50, 95% CI -1.11 to 0.11; I^2 = NA; 1 study, 6 participants; Analysis 6.4).

Duration of respiratory support (days)

Seven studies reported this outcome (Fischer 2019; Li 2019; Li 2021; Lou 2017; Yang 2021; Zhang 2021; Zhu 2022). nHFV compared with nCPAP for respiratory support following planned extubation may reduce the duration of respiratory support (MD -0.11 days, 95% CI -0.20 to -0.03 days; I^2 = 69%; 7 studies, 1371 participants; Analysis 6.5).

Duration of oxygen therapy (days)

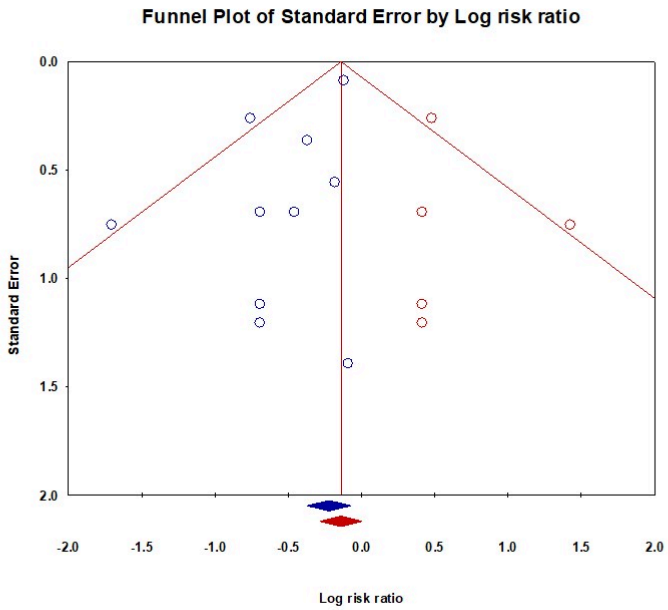
Four studies reported this outcome (Fischer 2019; Li 2021; Yuan 2021; Zhu 2022). nHFV compared with nCPAP for respiratory support following planned extubation may reduce the duration of respiratory support (MD -2.38 days, 95% CI -3.48 to -1.28 days; I^2 = 0%; 4 studies, 1218 participants; Analysis 6.6).

Outcomes during the first hospitalisation

CLD, defined as the need for oxygen or respiratory support at 36 weeks' PMA

Ten studies reported this outcome (Chen 2019; Fischer 2019; Li 2019; Li 2021; Lou 2017; Wang 2020; Yuan 2021; Zhang 2021; Zhu 2017; Zhu 2022). nHFV may reduce CLD compared with nCPAP for respiratory support following planned extubation (RR 0.78, 95% CI 0.67 to 0.91; I^2 = 16%; RD -0.06, 95% CI -0.10 to -0.03; I^2 = 34%; NNTB 16, 95% CI 10 to 42; 10 studies, 1829 participants; low-certainty evidence; Analysis 6.7). There was no evidence of funnel plot asymmetry consistent with trials favouring controls missing from the meta-analysis (Egger test for bias, P = 0.050; Figure 6).

Figure 6. Funnel plot: Trials comparing nHFV with nCPAP for respiratory support following planned extubation: Outcome 6.7 Chronic lung disease at 36 weeks. Current studies are depicted as blue, and imputed studies are red. Egger test = 0.050



Death or CLD reported at 36 weeks' PMA

Two studies reported this outcome (Fischer 2019; Zhu 2022). nHFV probably has little or no effect on death or CLD compared with nCPAP for respiratory support following planned extubation (RR 0.90, 95% CI 0.77 to 1.06; I^2 = 0%; RD -0.04, 95% CI -0.10 to 0.02; I^2 = 0%; 2 studies, 966 participants; moderate-certainty evidence; Analysis 6.8).

PDA (treated medically or surgically)

Three studies reported this outcome (Chen 2019; Li 2021; Zhu 2022). There is probably little or no difference in PDA (RR 0.99, 95% CI 0.84 to 1.16; I^2 = 0%; 3 studies, 1258 participants; Analysis 6.9).

Pulmonary air leak syndromes, including PIE and gross extrapulmonary air leak (such as pneumothorax)

Eight studies reported this outcome (Chen 2019; Li 2021; Lou 2017; Wang 2020; Yuan 2021; Zhang 2021; Zhu 2017; Zhu 2022). There is probably little or no difference in pulmonary air leak syndrome (RR

0.60, 95% CI 0.31 to 1.15; I^2 = 19%; 8 studies, 1673 participants; Analysis 6.10).

Proven sepsis

One study reported this outcome (Zhu 2022). We are very uncertain whether nHFV, compared with nCPAP for respiratory support following planned extubation, reduces proven sepsis (RR 0.85, 95% CI 0.38 to 1.87; I^2 = NA; 1 study, 960 participants; Analysis 6.11).

NEC (any Bell stage)

Four studies reported this outcome (Chen 2019; Li 2021; Lou 2017; Yuan 2021). nHFV compared with nCPAP used for initial respiratory support may have little or no effect on NEC (RR 0.83, 95% CI 0.47 to 1.45; I^2 = 43%; 4 studies, 523 participants; Analysis 6.12).

NEC (Bell stage ≥ 2)

Three studies reported this outcome (Li 2019; Yang 2021; Zhu 2022). nHFV, compared with nCPAP used for initial respiratory support, may have little or no effect on NEC Bell stage ≥ 2 (RR 1.32, 95% CI 0.82 to 2.10; I^2 = 0%; 3 studies, 1142 participants; Analysis 6.13).

Intraventricular haemorrhage (any Papile grade)

Seven studies reported this outcome (Chen 2019; Li 2021; Wang 2020; Yuan 2021; Zhang 2021; Zhu 2017; Zhu 2022). nHFV probably has little or no effect on intraventricular haemorrhage, any Papile grade, compared with nCPAP for respiratory support following planned extubation (RR 0.92, 95% CI 0.69 to 1.21; I^2 = 5%; 7 studies, 1644 participants; Analysis 6.14).

IVH (Papile grade 3/4)

Three studies reported this outcome (Li 2021; Lou 2017; Zhu 2022). nHFV compared with nCPAP for respiratory support following planned extubation probably has little or no effect on IVH Papile grade 3/4 (RR 0.80, 95% CI 0.57 to 1.13; I^2 = 0%; RD -0.02, 95% CI -0.06 to 0.01; I^2 = 25%; 3 studies, 1117 participants; moderate-certainty evidence; Analysis 6.15).

ROP (any stage)

Four studies reported this outcome (Chen 2019; Li 2021; Lou 2017; Yuan 2021). nHFV compared with nCPAP for respiratory support following planned extubation may reduce ROP, any stage (RR 0.76, 95% CI 0.58 to 0.99; I^2 = 36%; RD -0.04, 95% CI -0.07 to -0.00; I^2 = 55%; NNTB 28, 95% CI 14 to 951; 4 studies, 1418 participants; Analysis 6.17).

ROP (stage ≥ 3)

Two studies reported this outcome (Li 2021; Zhu 2022). nHFV compared with nCPAP for respiratory support following planned extubation may have little or no effect on ROP stage ≥ 3 (RR 0.81, 95% CI 0.61 to 1.08; I^2 = 0%; 2 studies, 1052 participants; Analysis 6.18).

Length of hospital stay (days)

Five studies reported this outcome (Chen 2019; Li 2019; Li 2021; Yang 2021; Yuan 2021). nHFV compared with nCPAP for respiratory support following planned extubation may reduce the length of hospital stay (MD -1.14 days, 95% CI -2.01 to -0.27 days; I^2 = 77%; 5 studies, 640 participants; Analysis 6.19).

Postdischarge outcomes

Neurodevelopmental disability at least 18 months' PNA or later

One study reported this outcome (Li 2021). We are very uncertain whether nHFV, compared with nCPAP for respiratory support following planned extubation, reduces neurodevelopmental disability (RR 0.92, 95% CI 0.37 to 2.29; I^2 = NA; RD -0.02, 95% CI -0.20 to 0.17; I^2 = NA; 1 study, 72 participants; very low-certainty evidence; Analysis 6.20).

Other secondary outcomes

None of the studies in this comparison reported the following outcomes:

1. All-cause mortality at 28 days;
2. Spontaneous intestinal perforation;
3. Periventricular leukomalacia;
4. Discharge on home oxygen;
5. All-cause mortality to follow-up (≥ one year of age).

Subgroup analyses

Mortality before hospital discharge (Analysis 7.1)

1. Gestation: term or near-term infants - no studies. Analysis of studies enroling preterm infants found no difference (RR 0.92, 95% CI 0.52 to 1.64; I^2 = 0%; 6 studies, 1427 participants). The test for subgroup differences was not performed.
2. Mean airway pressure: analysis of studies using HFV MAP ≥ 10 cm H_2O found no difference (RR 0.67, 95% CI 0.19 to 2.29; I^2 = NA; 1 study, 206 participants). Analysis of studies using nHFV MAP < 10 cm H_2O found no difference (RR 0.60, 95% CI 0.15 to 2.40; I^2 = 0%; 3 studies, 147 participants). The subgroup differences test was not significant (Chi^2 = 0.01, df = 1; P = 0.91; I^2 = 0%).
3. Frequency: analysis of studies using nHFV Hz ≥ 10 found no difference (RR 0.68, 95% CI 0.25 to 1.85; I^2 = 0%; 2 studies, 282 participants). Analysis of studies using nHFV Hz < 10 found no difference (RR 1.60, 95% CI 0.53 to 4.86; I^2 = NA; 2 studies, 968 participants). The subgroup differences test was not significant (Chi^2 = 1.26, df = 1; P = 0.26; I^2 = 20.6%).

Endotracheal intubation(Analysis 7.2)

1. Gestation: Wang 2020, enroling term or near-term infants, reported a reduction (RR 0.31, 95% CI 0.13 to 0.77; 1 study; 80 participants). Analysis of studies enroling preterm infants found a reduction (RR 0.42, 95% CI 0.35 to 0.52; I^2 = 0%; 10 studies, 1817 participants). The test for subgroup differences was not significant (Chi^2 = 0.42, df = 1; P = 0.52; I^2 = 0%).
2. Mean airway pressure: analysis of studies using HFV MAP ≥ 10 cm H_2O found a reduction (RR 0.34, 95% CI 0.21 to 0.53; I^2 = 70%; 2 studies, 298 participants). Analysis of studies using nHFV MAP < 10 cm H_2O found a reduction (RR 0.41, 95% CI 0.25 to 0.67; I^2 = 0%; 3 studies, 147 participants). The subgroup differences test was not significant (Chi^2 = 0.30, df = 1; P = 0.58; I^2 = 0%).
3. Frequency: analysis of studies using nHFV Hz ≥ 10 found a reduction (RR 0.45, 95% CI 0.30 to 0.67; I^2 = 0%; 2 studies, 282

participants). Analysis of studies using nHFV Hz < 10 found a reduction (RR 0.51, 95% CI 0.39 to 0.67; I^2 = 0%; 2 studies, 699 participants). The subgroup differences test was not significant (Chi^2 = 0.27, df = 1; P = 0.61; I^2 = 0%).

Failure of extubation(Analysis 7.3)

This outcome was reported by a single study (Fischer 2019). The test for subgroup differences was not performed.

CLD at 36 weeks (Analysis 7.4)

1. Gestation: Wang 2020, enroling term or near-term infants, reported no difference (RR 0.50, 95% CI 0.05 to 5.30; 1 study, 80 participants). Analysis of studies enroling preterm infants found a reduction (RR 0.78, 95% CI 0.67 to 0.91; I^2 = 24%; 9 studies, 1749 participants). The subgroup differences test was not significant (Chi^2 = 0.14, df = 1; P = 0.71; I^2 = 0%).
2. Mean airway pressure: analysis of studies using HFV MAP ≥ 10 cm H_2O found a reduction (RR 0.47, 95% CI 0.29 to 0.77; I^2 = 0%; 2 studies, 298 participants). Analysis of studies using nHFV MAP < 10 cm H_2O found a reduction (RR 0.65, 95% CI 0.22 to 1.90; I^2 = 0%; 2 studies, 147 participants). The test for subgroup differences was not significant (Chi^2 = 0.27, df = 1; P = 0.60; I^2 = 0%).
3. Frequency: analysis of studies using nHFV Hz ≥ 10 found a reduction (RR 0.56, 95% CI 0.21 to 1.46; I^2 = 0%, 2 studies, 282 participants). Analysis of studies using nHFV Hz < 10 found no difference (RR 0.88, 95% CI 0.75 to 1.04; I^2 = 0%; 2 studies, 966 participants). The subgroup differences test was not significant (Chi^2 = 0.84, df = 1; P = 0.36; I^2 = 0%).

Death or CLD at 36 weeks(Analysis 7.5)

1. Gestation: term or near-term infants - no studies. Analysis of studies enroling preterm infants found no difference (RR 0.90, 95% CI 0.77 to 1.06; I^2 = 0%; 2 studies, 966 participants). The test for subgroup differences was not performed.
2. Mean airway pressure: HFV MAP ≥ 10 cm H_2O was not reported. Fischer 2019, using nHFV MAP < 10 cm H_2O, found no difference (RR 0.50, 95% CI 0.06 to 4.47; I^2 = 0%; 1 study, 6 participants). The test for subgroup differences was not performed.
3. Frequency: nHFV Hz ≥ 10 found no studies. Analysis of studies using nHFV Hz < 10 found no difference (RR 0.90, 95% CI 0.77 to 1.06; I^2 = 0%; 2 studies, 966 participants). The test for subgroup differences was not performed.

IVH, Papile grade 3/4(Analysis 7.6)

1. Gestation: term or near-term infants - no studies. Analysis of studies enroling preterm infants found no difference (RR 0.80, 95% CI 0.57 to 1.13; I^2 = 0%; 3 studies, 1117 participants). The test for subgroup differences was not performed.
2. Mean airway pressure: Li 2021, using HFV MAP ≥ 10 cm H_2O, reported no difference (RR 2.09, 95% CI 0.20 to 22.24; 1 study, 92 participants). Lou 2017, using nHFV MAP < 10 cm H_2O, reported no difference (RR 1.82, 95% CI 0.17 to 19.13; 1 study, 65 participants). The test for subgroup differences was not significant (Chi^2 = 0.01, df = 1; P = 0.94; I^2 = 0%).
3. Frequency: nHFV Hz ≥ 10 was not reported. Zhu 2022, using nHFV Hz < 10, reported no difference (RR 0.76, 95% CI 0.54 to 1.09; 1 study, 960 participants). The test for subgroup differences was not performed.

Neurodevelopmental disability at least 18 months' PNA or later (Analysis 7.7)

This outcome was reported by a single study (Li 2021). The test for subgroup differences was not performed.

Sensitivity analyses

Six studies comparing **nHFV versus nCPAP** for respiratory support following planned extubation were assessed as having low risk of selection and attrition bias (Chen 2019; Fischer 2019; Li 2021; Zhang 2021; Zhu 2017; Zhu 2022).

Mortality before hospital discharge

Sensitivity analyses found no difference in mortality before hospital discharge (RR 1.01, 95% CI 0.49 to 2.09; I^2 = 0%; 4 studies; 1248 participants; Analysis 9.1).

Endotracheal intubation

Sensitivity analyses found reduced endotracheal reintubation (RR 0.45, 95% CI 0.36 to 0.56; I^2 = 19%; 5 studies, 1340 participants; Analysis 9.2).

Failure of respiratory support

Fischer 2019, reported no difference in extubation failure (RR 0.60, 95% CI 0.22 to 1.65; 1 study, 6 participants; Analysis 9.3).

CLD at 36 weeks

The analysis found no difference in CLD at 36 weeks (RR 0.82, 95% CI 0.70 to 0.95; I^2 = 36%; 5 studies, 1340 participants; Analysis 9.4).

Death or CLD at 36 weeks

The analysis found no difference in death or CLD at 36 weeks (RR 0.90, 95% CI 0.77 to 1.06; I^2 = 0%; 2 studies, 966 participants; Analysis 9.5).

IVH, Papile grade 3/4

The analysis found no difference in IVH Papile grade 3/4 (RR 0.78, 95% CI 0.55 to 1.11; I^2 = 0%; 2 studies, 1052 participants; Analysis 9.6).

Neurodevelopmental disability at least 18 months' PNA or later

Survival with neurosensory disability at least 18 months postnatal age was not reported.

3.b nHFV versus nIPPV used for respiratory support following planned extubation

For details, see Summary of findings 6.

Six studies enroled 1448 preterm infants with planned extubation after intubation and surfactant and compared nHFV versus nIPPV (Li 2021; Menshykova 2015; Seth 2021; Yuan 2021; Zhenyu 2019; Zhu 2022).

Primary outcomes

Mortality before hospital discharge

Two studies reported this outcome (Menshykova 2015; Zhu 2022). nHFV compared with nIPPV for respiratory support following planned extubation may have little or no effect on mortality before hospital discharge (RR 1.83, 95% CI 0.70 to 4.79; I^2 = 0%; RD 0.01, 95% CI -0.01 to 0.03; I^2 = 0%; 2 studies, 984 participants; low-certainty evidence; Analysis 6.1).

Endotracheal intubation or reintubation

Six studies reported this outcome (Li 2021; Menshykova 2015; Seth 2021; Yuan 2021; Zhenyu 2019; Zhu 2022). nHFV results in a reduction in endotracheal intubation or reintubation compared with nIPPV (RR 0.69, 95% CI 0.54 to 0.89; I^2 = 2%; RD -0.06, 95% CI -0.09 to -0.02; I^2 = 32%; NNTB 19, 95% CI 11 to 57; 6 studies, 1364 participants; moderate-certainty evidence; Analysis 6.2).

Secondary outcomes

Measures of the safety of nHFV

Trauma to the nostrils and upper airway

Four studies reported this outcome (Li 2021; Yuan 2021; Zhenyu 2019; Zhu 2022). nHFV, compared with nIPPV for respiratory support following planned extubation, may have little or no effect on trauma to the nostrils and upper airway (RR 1.01, 95% CI 0.66 to 1.53; I^2 = 11%; RD -0.00, 95% CI -0.03 to 0.03; I^2 = 19%; 4 studies, 1254 participants; Analysis 6.3).

Duration of respiratory support (days)

Two studies reported this outcome (Li 2021; Zhu 2022). nHFV, compared with nIPPV for respiratory support following planned extubation, may reduce the duration of respiratory support (MD -2.09 days, 95% CI -3.32 to -0.85; I^2 = 0%; 2 studies, 1052 participants; Analysis 6.5).

Duration of oxygen therapy (days)

Three studies reported this outcome (Li 2021; Yuan 2021; Zhu 2022). nHFV, compared with nIPPV for respiratory support following planned extubation, may have little or no effect on the duration of respiratory support (MD -0.57 days, 95% CI -1.59 to 0.45; I^2 = 0%; 3 studies, 1212 participants; Analysis 6.6).

Outcomes during the first hospitalisation

CLD, defined as the need for oxygen or respiratory support at 36 weeks' PMA

Four studies reported this outcome (Li 2021; Menshykova 2015; Yuan 2021; Zhu 2022). nHFV probably has little or no effect on CLD compared with nIPPV for respiratory support following planned extubation (RR 0.88, 95% CI 0.75 to 1.04; I^2 = 0%; RD -0.04, 95% CI -0.09 to 0.01; I^2 = 0%; 4 studies, 1236 participants; moderate-certainty evidence; Analysis 6.7).

Death or CLD reported at 36 weeks' PMA or discharge on home oxygen

Three studies reported this outcome (Menshykova 2015; Seth 2021; Zhu 2022). nHFV probably has little or no effect on death or CLD compared with nIPPV for respiratory support following planned extubation (RR 0.92, 95% CI 0.79 to 1.08; I^2 = 0%; RD -0.03, 95% CI -0.09 to 0.03; I^2 = 0%; 3 studies, 1070 participants; moderate-certainty evidence; Analysis 6.8).

PDA (treated medically or surgically)

Three studies (Li 2021; Menshykova 2015; Zhu 2022). There is probably little or no difference in PDA (RR 0.88, 95% CI 0.74 to 1.05; I^2 = 0%; 3 studies, 1076 participants; Analysis 6.9).

Pulmonary air leak syndrome, PIE and gross extrapulmonary air leak (such as pneumothorax)

Five studies reported this outcome (Li 2021; Menshykova 2015; Seth 2021; Yang 2021; Zhu 2022). There is probably little or no difference in pulmonary air leak syndrome (RR 0.83, 95% CI 0.36 to 1.91; I^2 = 58%; 5 studies, 1322 participants; Analysis 6.10).

Proven sepsis

Two studies reported this outcome (Li 2021; Zhenyu 2019; Menshykova 2015; Seth 2021; Yuan 2021; Zhu 2022). We are very uncertain whether nHFV, compared with nIPPV for respiratory support following planned extubation, reduces proven sepsis (RR 1.00, 95% CI 0.50 to 2.00; I^2 = 0%; 2 studies, 984 participants; Analysis 6.11).

NEC (any Bell stage)

Four studies reported this outcome (Li 2021; Menshykova 2015; Yuan 2021; Zhenyu 2019; Zhu 2022). nHFV, compared with nIPPV used for initial respiratory support, may have little or no effect on NEC (RR 1.02, 95% CI 0.32 to 3.24; I^2 = 0%; 4 studies, 318 participants; Analysis 6.12).

NEC (Bell stage ≥ 2)

Two studies reported this outcome (Menshykova 2015; Zhu 2022). nHFV, compared with nIPPV used for initial respiratory support, may have little or no effect on NEC Bell stage ≥ 2 (RR 0.92, 95% CI 0.58 to 1.44; I^2 = 0%; 2 studies, 984 participants; Analysis 6.13).

Intraventricular haemorrhage (any Papile grade)

Four studies reported this outcome (Li 2021; Menshykova 2015; Seth 2021; Zhu 2022). nHFV probably has little or no effect on intraventricular haemorrhage, any Papile grade compared with nIPPV for respiratory support following planned extubation (RR 0.99, 95% CI 0.73 to 1.34; I^2 = 52%; 4 studies, 1236 participants; Analysis 6.14).

Intraventricular haemorrhage (Papile grade 3/4)

Four studies reported this outcome (Li 2021; Zhenyu 2019; Menshykova 2015; Seth 2021; Zhu 2022). nHFV probably has little or no effect on intraventricular haemorrhage, any Papile grade 3/4, compared with nIPPV for respiratory support following planned extubation (RR 0.78, 95% CI 0.55 to 1.10; I^2 = 0%; RD -0.03, 95% CI -0.06 to 0.01; I^2 = 0%; 4 studies, 1162 participants; moderate-certainty evidence; Analysis 6.15).

Periventricular leukomalacia

One small study (Menshykova 2015), reported no difference in periventricular leukomalacia (RR 7.00, 95% CI 0.40 to 122.44, 1 study, 24 participants; Analysis 6.16).

ROP (any stage)

Four studies reported this outcome (Li 2021; Menshykova 2015; Yuan 2021; Zhu 2022). nHFV probably has little or no effect on ROP, any stage compared with nIPPV for respiratory support following planned extubation (RR 0.85, 95% CI 0.64 to 1.13; I^2 = 0%; 4 studies, 1236 participants; Analysis 6.17).

ROP (stage ≥ 3)

Two studies reported this outcome (Li 2021; Zhu 2022). nHFV, compared with nIPPV for respiratory support following planned extubation, may have little or no effect on ROP stage ≥ 3 (RR 0.86, 95% CI 0.64 to 1.15; I^2 = 0%; 2 studies, 1052 participants; Analysis 6.18).

Length of hospital stay (days)

Three studies reported this outcome (Li 2021; Menshykova 2015; Yuan 2021). nHFV, compared with nIPPV for respiratory support following planned extubation, may have little or no effect on the length of hospital stay (MD -1.05 days, 95% CI -3.34 to 1.24; I^2 = 0%; 3 studies, 276 participants; Analysis 6.19).

Postdischarge outcomes

Neurodevelopmental disability at least 18 months' PNA or later

Li 2021, reported no difference in neurodevelopmental disability (RR 0.88, 95% CI 0.35 to 2.16; I^2 = NA; RD -0.03, 95% CI -0.22 to 0.16; I^2 = NA; 1 study, 72 participants; low-certainty evidence; Analysis 6.20).

Other secondary outcomes

None of the studies in this comparison reported the following outcomes:

1. Failure of respiratory support as defined by respiratory support failure criteria or as defined by trial authors;
2. All-cause mortality at 28 days;
3. Spontaneous intestinal perforation;
4. Discharge on home oxygen;
5. All-cause mortality to follow-up (≥ one year of age).

Subgroup analyses

Mortality before hospital discharge(Analysis 8.1)

1. Gestation: term or near-term infants - no studies. Analysis of studies enroling preterm infants found no difference (RR 1.83, 95% CI 0.70 to 4.79; I^2 = 0%; 2 studies, 984 participants). The test for subgroup differences was not performed.
2. Mean airway pressure: HFV MAP ≥ 10 cm H_2O was not reported. Menshykova 2015, using HFV MAP < 10 cm H_2O, reported no difference (RR 1.50, 95% CI 0.30 to 7.43; 1 study, 24 participants). The test for subgroup differences was not performed.
3. Frequency: Menshykova 2015, using HFV Hz ≥ 10 cm H_2O, reported no difference (RR 1.50, 95% CI 0.30 to 7.43; 1 study, 24 participants). Zhu 2022, using HFV Hz < 10 cm H_2O, reported no difference (RR 2.00, 95% CI 0.61 to 6.60; 1 study, 960 participants). The test for subgroup differences was not significant (Chi^2 = 0.08, df = 1; P = 0.78; I^2 = 0%).

Endotracheal reintubation(Analysis 8.2)

1. Gestation: term or near-term infants - no studies. Analysis of studies enroling preterm infants found a reduction (RR 0.69, 95% CI 0.54 to 0.89; I^2 = 2%; 6 studies, 1364 participants). The test for subgroup differences was not performed.
2. Mean airway pressure: analysis of studies using HFV MAP ≥ 10 cm H_2O found a reduction (RR 0.27, 95% CI 0.11 to 0.68; I^2 = 0%; RD -0.20, 95% CI -0.33 to -0.08; I^2 = 0%; NNTB 5, 95% CI 3 to 12.5; 2 studies, 134 participants). Analysis of studies using HFV MAP < 10 cm H_2O found no difference (RR 0.92, 95% CI 0.47 to 1.80; I^2 = 0%; 2 studies, 110 participants). The subgroup differences test was significant (Chi^2 = 4.41, df = 1; P = 0.04; I^2 = 77.3%).
3. Frequency: analysis of studies with nHFV Hz ≥ 10 found no difference (RR 0.92, 95% CI 0.47, 1.80; I^2 = 0%; 2 studies, 110 participants). Analysis of studies nHFV Hz < 10 found a borderline difference (RR 0.75, 95% CI 0.55 to 1.01; I^2 = NA; 1 study, 960 participants). The subgroup differences test was not significant (Chi^2 = 0.31, df = 1; P = 0.58; I^2 = 0%).

Failure of extubation

No studies reported this outcome.

CLD at 36 weeks (Analysis 8.3)

1. Gestation: term or near-term infants - no studies. Analysis of studies enroling preterm infants found no difference (RR 0.88, 95% CI 0.75 to 1.04; I^2 = 0%; 4 studies, 1236 participants). The test for subgroup differences was not performed.
2. Mean airway pressure: Li 2021, using HFV MAP ≥ 10 cm H_2O, reported no difference (RR 0.80, 95% CI 0.44 to 1.45; 1 study, 92 participants). Menshykova 2015, using HFV MAP < 10 cm H_2O, reported no difference (RR 1.00, 95% CI 0.39 to 2.58; 1 study, 24 participants). The subgroup differences test was not significant (Chi^2 = 0.16, df = 1; P = 0.69; I^2 = 0%).
3. Frequency: Menshykova 2015, with nHFV Hz ≥ 10, reported no difference (RR 1.00, 95% CI 0.39 to 2.58; 1 study, 24 participants). Zhu 2022, with nHFV Hz < 10, reported no difference (RR 0.90, 95% CI 0.76 to 1.06; 1 study, 960 participants). The subgroup differences test was not significant (Chi^2 = 0.05, df = 1; P = 0.82; I^2 = 0%).

Death or CLD at 36 weeks(Analysis 8.4)

1. Gestation: term or near-term infants - no studies. Analysis of studies enroling preterm infants found no difference (RR 0.92, 95% CI 0.79 to 1.08; I^2 = 0%; 3 studies, 1070 participants). The test for subgroup differences was not performed.
2. Mean airway pressure: HFV MAP ≥ 10 cm H_2O was not reported. Analysis of studies using HFV MAP < 10 cm H_2O found no difference (RR 0.95, 95% CI 0.60 to 1.52; I^2 = 0%; 2 studies, 110 participants). The test for subgroup differences was not performed.
3. Frequency: analysis of studies nHFV Hz ≥ 10 found no difference (RR 0.95, 95% CI 0.60 to 1.52; I^2 = 0%; 2 studies, 110 participants).

Zhu 2022, using nHFV Hz < 10, reported no difference (RR 0.92, 95% CI 0.78 to 1.08; 1 study, 960 participants). The subgroup differences test was not significant (Chi^2 = 0.02, df = 1; P = 0.89; I^2 = 0%).

IVH, Papile grade 3/4 (Analysis 8.5)

1. Gestation: term or near-term infants - no studies. Analysis of studies enroling preterm infants found no difference (RR 0.78, 95% CI 0.55 to 1.10; I^2 = 0%; 4 studies, 1162 participants).
2. Mean airway pressure: Li 2021, using HFV MAP ≥ 10 cm H_2O, reported no difference (RR 0.70, 95% CI 0.12 to 3.97; 1 study, 92 participants). Analysis of studies using HFV MAP V 10 cm H_2O found no difference (RR 0.40, 95% CI 0.08 to 1.92; I^2 = 0%; 2 studies, 110 participants). The subgroup differences test was not significant (Chi^2 = 0.21, df = 1; P = 0.64; I^2 = 0%).
3. Frequency: analysis of studies using nHFV Hz ≥ 10 found no difference (RR 0.40, 95% CI 0.08 to 1.92; I^2 = 0%; 2 studies, 110 participants). A single study of nHFV Hz < 10 reported no difference (RR 0.81, 95% CI 0.57 to 1.17; 1 study, 960 participants). The subgroup differences test was not significant (Chi^2 = 0.75, df = 1; P = 0.39; I^2 = 0%).

Death or survival with neurosensory disability at least 18 months' PNA(Analysis 8.6)

This outcome was reported by a single study (Li 2021). The test for subgroup differences was not performed.

Sensitivity analyses

Three studies comparing **nHFV versus nIPPV** for respiratory support following planned extubation were assessed as being at low risk of selection and attrition bias (Li 2021; Seth 2021; Zhu 2022).

Mortality before hospital discharge

Zhu 2022 reported no difference in mortality before hospital discharge (RR 2.00, 95% CI 0.61 to 6.60; 1 study, 960 participants; Analysis 9.1).

Endotracheal intubation

The analysis found reduced endotracheal reintubation (RR 0.71, 95% CI 0.54 to 0.94; I^2 = 3%; 3 studies, 1138 participants; Analysis 9.2).

Failure of respiratory support

No studies reported this outcome.

CLD at 36 weeks

The analysis found no difference in CLD at 36 weeks (RR 0.89, 95% CI 0.75 to 1.04; I^2 = 0%; 2 studies, 1052 participants; Analysis 9.4).

Death or CLD at 36 weeks

The analysis found no difference in death or CLD at 36 weeks (RR 0.92, 95% CI 0.78 to 1.07; I^2 = 0%; 2 studies, 1046 participants; Analysis 9.5).

IVH, Papile grade 3/4

The analysis found no difference in IVH Papile grade 3/4 (RR 0.80, 95% CI 0.56 to 1.13; I^2 = 0%; 3 studies, 1138 participants; Analysis 9.6).

Neurodevelopmental disability at least 18 months' PNA or later

No studies reported this outcome.

3.c nHFV versus HFNC used for respiratory support following planned extubation

No studies assessed this comparison.

3.d nHFV versus non-invasive neurally adjusted ventilatory assist (nNAVA) ventilation used for respiratory support following planned extubation

No studies assessed this comparison.

Comparison 4: nHFV versus other non-invasive respiratory therapy modalities following initial non-invasive respiratory support failure

4.a nHFV versus nCPAP following initial non-invasive respiratory support failure

No studies assessed this comparison.

4.b nHFV versus nIPPV following initial non-invasive respiratory support failure

See Summary of findings 7.

A single study enroled 39 preterm infants who had failed nCPAP treatment and were therefore allocated to nHFV versus nIPPV (Mukerji 2017).

Primary outcomes

Mortality before hospital discharge

One study reported this outcome (Mukerji 2017). nHFV compared with nIPPV following the failure of initial non-invasive respiratory support may have little or no effect on mortality before hospital discharge (RR 1.44, 95% CI 0.10 to 21.33; I^2 = NA; RD 0.02, 95% CI -0.13 to 0.16; I^2 = NA; 1 study, 39 participants; low-certainty evidence; Analysis 10.1).

Endotracheal intubation or reintubation

One study reported this outcome (Mukerji 2017). nHFV compared with nIPPV following the failure of initial non-invasive respiratory support may have little or no effect on endotracheal intubation (RR 1.23, 95% CI 0.51 to 2.98; I^2 = NA; RD 0.07, 95% CI -0.23 to 0.37; I^2 = NA; 1 study, 39 participants; very low-certainty evidence; Analysis 10.2).

Secondary outcomes

Measures of respiratory support

Failure of respiratory support or failure of extubation as defined by respiratory support failure criteria or as defined by trial authors

One study reported this outcome (Mukerji 2017). nHFV compared with nIPPV following the failure of initial non-invasive respiratory support may have little or no effect on endotracheal intubation (RR

0.57, 95% CI 0.29 to 1.16; I^2 = NA; RD -0.28, 95% CI -0.58 to 0.03; I^2 = NA; 1 study, 39 participants; Analysis 10.3).

Duration of oxygen therapy (days)

One study reported this outcome (Mukerji 2017). nHFV compared with nIPPV following the failure of initial non-invasive respiratory support may have little or no effect on the duration of respiratory support (MD 24.00 days, 95% CI -8.18 to 56.18; I^2 = NA; 1 study, 39 participants; Analysis 10.4).

Outcomes during the first hospitalisation

CLD, defined as the need for oxygen or respiratory support at 36 weeks' PMA

One study reported this outcome (Mukerji 2017). nHFV compared with nIPPV following the failure of initial non-invasive respiratory support may have little or no effect on CLD (RR 1.01, 95% CI 0.70 to 1.47; I^2 = NA; RD 0.01, 95% CI -0.27 to 0.29; I^2 = NA, 1 study, 39 participants; low-certainty evidence; Analysis 10.5).

Pulmonary air leak syndromes, including PIE and gross extrapulmonary air leak (such as pneumothorax)

Mukerji 2017 reported no infant had a pulmonary air leak syndrome (no estimate, 39 participants; Analysis 10.6).

NEC (any Bell stage)

One study reported this outcome (Mukerji 2017). nHFV compared with nIPPV following the failure of initial non-invasive respiratory support may have little or no effect on endotracheal intubation (RR 0.47, 95% CI 0.02 to 10.87; I^2 = NA; 1 study, 39 participants; Analysis 10.7).

Spontaneous intestinal perforation

Mukerji 2017 reported no infant had spontaneous intestinal perforation (no estimate, 39 participants; Analysis 10.8).

IVH (Papile grade 3/4)

One study reported this outcome (Mukerji 2017). A single event of IVH (Papile grade 3/4) was reported amongst the nasal intermittent positive pressure ventilation (nIPPV) group. nHFV compared with nIPPV following the failure of initial non-invasive respiratory support may have little or no effect on Papile grade 3/4 (RR 0.47, 95% CI 0.02 to 10.87; I^2 = NA; RD -0.04, 95% CI -0.17 to 0.08; I^2 = NA, 1 study, 39 participants; low-certainty evidence; Analysis 10.9).

Periventricular leukomalacia

No infant was reported to have periventricular leukomalacia (no estimate, 1 study, 39 participants; Analysis 10.10).

ROP (any stage)

One study reported this outcome (Mukerji 2017). nHFV compared with nIPPV following the failure of initial non-invasive respiratory support may have little or no effect on ROP stage ≥ 3 (RR 9.88, 95% CI 0.55 to 179.12; I^2 = NA, 1 study, 39 participants; Analysis 10.11).

Other secondary outcomes

None of the studies in this comparison reported the following outcomes:

1. Trauma to the nostrils and upper airway;
2. Duration of respiratory support (days);
3. All-cause mortality at 28 days;
4. Death or CDL reported at 36 weeks' PMA or discharge on home oxygen;
5. Patent ductus arteriosus (PDA) (treated medically or surgically);
6. Proven sepsis;
7. NEC (Bell stage ≥ 2);
8. Spontaneous intestinal perforation;
9. IVH (Papile grade 3/4);
10. ROP (stage ≥ 3);
11. Length of hospital stay (days);
12. Discharge on home oxygen;
13. All-cause mortality to follow-up (≥ one year of age);
14. Neurodevelopmental disability at least 18 months postnatal age (PNA) or later.

Subgroup analyses

These analyses were not performed, as only one study was included in this comparison.

Sensitivity analyses

Mukerji 2017 was at low risk of selection and attrition bias. Analyses were reported, as above.

4.c nHFV versus HFNC following initial non-invasive respiratory support failure

No studies assessed this comparison.

4.d nHFV versus non-invasive neurally adjusted ventilatory assist (nNAVA) ventilation following initial non-invasive respiratory support failure

No studies assessed this comparison.

DISCUSSION

Summary of main results

We identified 33 studies, mostly in low- to middle-income settings, that investigated this therapy in 5068 preterm and 46-term infants.

nHFV versus invasive respiratory therapy used for initial respiratory support

Two studies enroled 180 preterm infants with respiratory distress and allocated them to nHFV versus conventional ventilation as the initial treatment for respiratory distress. For primary outcomes, a single study reported there may be little or no difference in mortality before discharge (very low-certainty evidence). Endotracheal intubation was not reported. For secondary outcomes, a single study reported there may be a small reduction in the duration of respiratory support (MD -0.43 days, 95% CI -0.59 to -0.27) and a larger reduction in length of hospital stay for infants on nHFV (MD -6.68 days, 95% CI -8.08 to -5.28) from the use of nHFV, but little or no difference in chronic lung disease (very

low-certainty evidence) and pulmonary air leak syndromes. Other neonatal morbidities and longer-term outcomes were not reported.

nHRV versus other non-invasive respiratory therapy used for initial respiratory support

nHFV versus nCPAP used for initial respiratory support

Eight studies enroling 851 infants compared nHFV versus CPAP for initial respiratory management. For primary outcomes, there may be little or no difference in mortality before discharge (very low-certainty evidence), but the use of nHFV may reduce endotracheal intubation compared to nCPAP (RD -0.08, 95% CI -0.13 to -0.03; NNTB 13, 95% CI 7 to 37; low-certainty evidence). For secondary outcomes, the use of nHFV may reduce failure of respiratory support and result in a small reduction in the duration of respiratory support (MD -0.48 days, 95% CI -0.55 to -0.40) and a moderate reduction in the length of hospital stay (MD -4.07 days, 95% CI -4.46 to -3.67). However, there may be little or no difference in chronic lung disease (low-certainty evidence) and no differences found for other neonatal morbidities. Longer-term outcomes were not reported.

Subgroup analyses (Analysis 3) according to gestation (term and near-term versus preterm), mean airway pressure (≥ 10 cm H_2O versus < 10 cm H_2O), and nHFV frequency (≥ 10 Hz versus < 10 Hz) found no statistically significant subgroup differences.

nHFV versus nIPPV used for initial respiratory support

Nine studies enroling a total of 513 compared nHFV versus nIPPV for initial respiratory management. For primary outcomes, there may be little or no difference in mortality before discharge (low-certainty evidence). For secondary outcomes, there may be little or no difference in endotracheal intubation (very low-certainty), and a single small study reported there may be little or no difference in failure of respiratory support. Duration of respiratory support did not differ, but a reduction in the duration of oxygen therapy was found (MD -0.65 days, 95% CI -1.13 to -0.17) and there may be a reduction in chronic lung disease at 36 weeks from use of nHFV compared to nIPPV (RD -0.10, 95% CI -0.19 to -0.02; NNTB 10, 95% CI% 5 to 50; low-certainty evidence). There may also be a reduction in the length of hospital stay (MD -4.34 days, 95% CI -6.22 to -2.47). There were no differences found for other neonatal morbidities. Longer-term outcomes were not reported.

Subgroup analyses (Analysis 4) according to gestation (term and near-term versus preterm), mean airway pressure (≥ 10 cm H_2O versus < 10 cm H_2O), and nHFV frequency (≥ 10 Hz versus < 10 Hz) found no subgroup differences.

nHFV versus HFNC used for initial respiratory support

A single small study enroling 37 preterm infants compared nHFV versus HFNC for initial respiratory management. The study reported no mortality before hospital discharge and no difference in endotracheal intubation (both very low-certainty evidence). nHFV was reported to increase trauma to the nostrils and upper airways compared to HFNC (RD 0.47, 95% CI 0.20 to 0.75; NNTB 3, 95% CI 1 to 5). No difference was reported for other measures of respiratory support or neonatal morbidities. However, periventricular leukomalacia, retinopathy of prematurity, length of hospital stay, discharge on home oxygen, mortality up to follow-up and neurodevelopmental disability were not reported.

nHFV versus nCPAP for respiratory support following planned extubation

Eleven studies that enroled 2026 preterm infants with planned extubation after intubation and surfactant compared nHFV versus nCPAP. For primary outcomes, there is probably little or no difference in mortality before hospital discharge (moderate-certainty evidence), but there maybe a reduction in endotracheal reintubation from the use of nHFV compared to nCPAP for respiratory support following planned extubation (RD -0.18, 95% CI -0.21 to -0.14; NNTB 6, 95% CI 5 to 7; low-certainty evidence). For secondary outcomes, there may be small reductions in the duration of respiratory support (MD -0.11 days, 95% CI -0.20 to -0.03), duration of oxygen therapy (MD -2.38 days, 95% CI -3.48 to -1.28) and length of hospital stay (MD -1.14 days, 95% CI -2.01 to -0.27). There may be a reduction in chronic lung disease reported at 36 weeks (RD -0.06, 95% CI -0.10 to -0.03; NNTB 17, 95% CI 10 to 33; low-certainty evidence). However, there is probably little or no difference in death or chronic lung disease reported at 36 weeks (RR 0.90, 95% CI 0.77 to 1.06; moderate-certainty evidence). There was no difference in other neonatal morbidities other than a possible reduction in retinopathy of prematurity at any stage (RD -0.04, 95% CI -0.07 to -0.00; NNTB 28, 95% CI 14 to 950). Discharge on home oxygen and mortality up to follow-up were not reported. A single small study reported there may be no difference in neurodevelopmental disability (very low-certainty evidence).

Subgroup analyses (Analysis 7) according to gestation (term and near-term versus preterm), mean airway pressure (≥ 10 cm H_2O versus < 10 cm H_2O), and nHFV frequency (≥ 10 Hz versus < 10 Hz) found no statistically significant subgroup differences.

nHFV versus nIPPV used for respiratory support following planned extubation

Six studies enroled 1448 preterm infants with planned extubation after intubation and surfactant and compared nHFV versus nIPPV. For primary outcomes, there is probably little or no difference in mortality before hospital discharge (low-certainty evidence). There is probably a reduction in endotracheal reintubation from the use of nHFV compared to nIPPV for respiratory support following planned extubation (RD -0.06, 95% CI -0.09 to -0.02; NNTB 19, 95% CI 11 to 57; moderate-certainty evidence). For secondary outcomes, there may be a moderate reduction in the duration of respiratory support (MD -2.09 days, 95% CI -3.32 to -0.85) but little or no effect on the duration of oxygen therapy and hospital stay. There is probably little or no effect on chronic lung disease at 36 weeks (moderate-certainty evidence) and death or chronic lung disease at 36 weeks (moderate-certainty evidence). There was no difference found for other neonatal morbidities. Discharge on home oxygen and mortality up to follow-up were not reported. A single study reported there may be no difference in neurodevelopmental disability (low-certainty).

For endotracheal reintubation, subgroup analyses (Analysis 8.2) according to mean airway pressure (≥ 10 cm H_2O versus < 10 cm H_2O) found a significant difference (P = 0.04). Analysis of studies using HFV MAP ≥ 10 cm H_2O found a reduction in reintubation (RD -0.20, 95% CI -0.33 to -0.08; NNTB 5, 95% CI 3 to 12.5) compared to analysis of studies using HFV MAP < 10 cm H_2O which found no difference (RR 0.92, 95% CI 0.47 to 1.80).

Subgroup analyses (Analysis 8) for other outcomes and according to gestation (term and near-term versus preterm) and nHFV frequency (≥ 10 Hz versus < 10 Hz) found no other statistically significant subgroup differences.

nHFV versus nIPPV following the failure of initial non-invasive respiratory support

A small study enroled 39 preterm infants who had failed nCPAP treatment and allocated them to nHFV versus nIPPV. The study reported there may be little or no difference in mortality before hospital discharge (low-certainty evidence) and endotracheal intubation (low-certainty evidence). For secondary outcomes, the study reported there may be no difference in the duration of oxygen therapy and chronic lung disease (low-certainty evidence). Death or chronic lung disease was not reported, and a single infant in the nIPPV was reported with intraventricular haemorrhage Papile grade 3/4. Other neonatal outcomes were not different or not reported. Discharge on home oxygen, mortality up to follow-up and neurodevelopmental disability at least 18 months postnatal age or later were not reported.

Overall completeness and applicability of evidence

This review included infants with different indications for respiratory support and multiple comparisons of invasive and non-invasive support. Comparisons of nHFV versus nCPAP and nIPPV for initial respiratory support and following planned extubation had the most studies and participants. Several comparisons had few studies and infants, including use of nHFV compared to invasive respiratory therapy as initial respiratory support, and nHFV compared to HFNC for initial respiratory support. Several comparisons had no studies including use of nHFV compared to NAVA for any indication, and nFHV versus HFNC for planned extubation. In addition, outcomes were often incompletely reported, especially those postdischarge from hospital, so analyses often lacked precision.

The comparison of nHFV versus invasive respiratory therapy used for initial respiratory support included two studies that enroled 180 preterm infants with respiratory distress. Many outcomes were not reported. The analysis was incomplete and imprecise. Term and near-term infants were not enroled.

The comparison of nHFV versus nCPAP used for initial respiratory support included eight studies enroling 851 infants. A single study enroled 46 term infants > 37 weeks with mild respiratory distress consistent with transient tachypnoea of the newborn (De La Roque 2011). The other seven studies enroled 805 preterm infants, so results broadly apply to preterm infants with respiratory distress syndrome without preceding surfactant administration. Primary outcomes and GRADE outcomes were reported. However, longer-term outcomes were not reported.

The comparison of nHFV versus nIPPV used for initial respiratory support included nine studies enroling 513 infants. Of these, four studies (233 preterm infants) included surfactant administration in both arms. Ali 2023 (Pakistan, 48 preterm infants) compared nHFV with InSurE versus nIPPV with InSurE. Cheng 2021 (China, 60 preterm infants), Jiang 2020 (China, 82 preterm infants) and Wang 2023 (China, 43 preterm infants) compared nHFV with non-invasive surfactant versus nIPPV with non-invasive surfactant. The other studies did not report the use of a minimally invasive surfactant as an adjunct to non-invasive respiratory support. Three studies enroling 190 preterm infants used nasal biphasic continuous positive airway pressure (BP-CPAP), bilevel positive airway pressure (BiPAP) or duo positive airway pressure (DuoPAP) considered equivalent strategies to nIPPV (Jiang 2020; Lou 2018; Wang 2023). The other studies used standard nIPPV. A single study enroled 82 newborn infants with persistent pulmonary hypertension of the newborn (PPHN) with mean gestation of 34 to 35 weeks (Zhang 2022b). The other studies enroled preterm or low birthweight infants without preceding surfactant administration, so results broadly apply to preterm infants with respiratory distress syndrome without preceding surfactant administration. Most primary outcomes and most GRADE outcomes were reported. However, death or chronic lung disease, and longer-term outcomes were not reported.

A single study enroling 37 preterm infants compared nHFV versus HFNC for initial respiratory support (Oktem 2021). Most primary outcomes and most GRADE outcomes were reported. However, death or chronic lung disease, and longer-term outcomes were not reported. The analyses had a serious lack of precision.

The comparison of nHFV versus nCPAP used for respiratory support following planned extubation after intubation and surfactant included 11 studies that enroled 2026 preterm infants. Two studies used InSurE procedures with extubation to the allocated intervention (Yuan 2021; Zhu 2017). Primary outcomes and GRADE outcomes were reported. However, longer-term outcomes were reported by a single study. The results broadly apply to preterm infants with respiratory distress syndrome with planned extubation after surfactant administration.

The comparison of nHFV versus nIPPV used for respiratory support following planned extubation included six studies that enroled 1448 preterm infants. Primary and GRADE outcomes were mainly reported apart from the failure of respiratory support. However, longer-term outcomes were reported by a single study. The results largely apply to preterm infants with respiratory distress syndrome with planned extubation after surfactant administration.

No studies compared nHFV versus HFNC used for respiratory support following planned extubation.

A small study enroling 39 preterm infants compared nHFV to nIPPV following initial non-invasive respiratory support failure (Mukerji 2017). Many outcomes, including longer-term outcomes, were not reported. The analysis was incomplete and imprecise. Term and near-term infants were not enroled.

This review conducted subgroup analyses, where possible, for studies that enroled term and near-term infants versus preterm infants; studies that used nHFV mean airway pressures ≥ 10 cm H_2O versus < 10 cm H_2O; and studies that used nHFV frequencies ≥ 10 Hz versus < 10 Hz. Few studies enroled term or near-term infants, so subgroup analyses according to gestation either lacked power or were unable to be performed. The results of this review broadly apply to preterm infants. For subgroup analyses according to nHFV mean airway pressure and frequency, tests of subgroup difference were statistically not significant, except for the comparison of nHFV versus nIPPV for respiratory support following planned extubation, which found that the use of nHFV mean airway pressures ≥ 10 cm H_2O reduced endotracheal reintubation.

Most of the trials included in this review used oscillatory nHFOV except for one trial which used percussive nHFV (nHFPV) (De La Roque 2011), and two ongoing trials of jet nHFV (nHFJV) (NCT03558737; NCT03006354). As such, the results of this review are mainly applicable to oscillatory nHFOV.

Quality of the evidence

Twelve of the 33 studies were assessed as having low risk of selection and attrition bias and were included in sensitivity analyses. However, many studies were considered at unclear risk due to inadequate reporting of methods. This was particularly the case for studies published in Chinese journals. Journals must enforce CONSORT Statement 2011 guidelines for reporting RCTs.

Only two analyses had at least 10 studies reporting specific outcomes. Both of these analyses (comparing nHFV with nCPAP for respiratory support following planned extubation) found statistical evidence of publication bias through use of funnel plots and Egger tests (see Analysis 6.2; Analysis 6.7). GRADE assessments were downgraded accordingly for these outcomes (endotracheal reintubation and chronic lung disease at 36 weeks). However, it was not possible to statistically explore the potential of publication bias for other comparisons due to the limited number of studies available.

Most GRADE outcomes across the comparisons were assessed as having low or very low certainty of evidence due to the risk of bias and lack of precision. However, several analyses were evaluated as having high or moderate certainty of evidence, including the following comparisons:

- nHFV compared to nCPAP used for initial respiratory support, assessed as moderate certainty for a reduction in endotracheal intubation;
- nHFV compared to nCPAP for respiratory support following planned extubation, assessed as moderate certainty for no difference in mortality, death or chronic lung disease and intraventricular haemorrhage grade 3 or 4, moderate certainty for a reduction in chronic lung disease and high certainly for a reduction in endotracheal intubation;
- nHFV compared to nIPPV for respiratory support following planned extubation was assessed as high-certainty evidence for a reduction in endotracheal intubation and moderate-certainty evidence for no difference in chronic lung disease, death or chronic lung disease and intraventricular haemorrhage grade 3 or 4.

Potential biases in the review process

This review was conducted to a prespecified Cochrane protocol (Chan 2017), and included extensive searches for published and unpublished literature and supplemented with cross-checking of citations of included studies and reviews. Furthermore, we searched additional databases: Epistemonikos and the Chinese language articles from China/Asia On Demand (CAOD). The eligibility, characteristics of included studies, risk of bias and data extraction were conducted independently by at least two review authors, except for Chinese language articles. Chinese language articles were translated by a single author (OT) under the supervision of a senior author (MEA). Differences were reconciled through the consensus of all authors.

Sensitivity and subgroup analyses were prespecified and performed where sufficient data were available. We removed blinding as a criterion in the sensitivity analysis for objective outcomes as the intervention was unlikely to be able to be adequately blinded. However, for endotracheal intubation and reintubation, we considered these subjective outcomes and downgraded risk of bias assessments for these outcomes.

These post hoc changes might be considered potential biases in the review process.

We included subgroup analyses even when only one study was available because weight and gestation groups are commonly used in guideline development.

Some outcomes may only be relevant for certain groups within the study population. For instance, BPD is more relevant for extremely preterm infants (28 weeks' gestation or less) than preterm (33 to 36 weeks' gestation). Subgroup analyses were performed only for GRADE outcomes. Data were limited, particularly for term infants.

We identified 33 studies, mostly in low- to middle-income settings, that investigated this therapy in 5068 preterm and 46 term infants. Only three studies, enroling a total of 78 term or preterm infants, were conducted in high-income settings (De La Roque 2011; Fischer 2019; Mukerji 2017).

Agreements and disagreements with other studies or reviews

The findings of our systematic review are consistent in part with recently published meta-analyses (De Luca 2021; Haidar 2021; Li 2019; Li 2022). They differ from the findings of previously published meta-narrative reviews, which did not include more recent studies (Mukerji 2016; Yoder 2016).

A systematic review of nHFOV versus nCPAP as primary respiratory support strategies for respiratory distress syndrome in preterm infants included four RCTs involving 570 participants and reported that compared with nCPAP, nHFV resulted in less intubation (RR 0.44; 95% CI 0.29 to 0.67, P = 0.0002) (Li 2022). The review concluded that nHFV decreased the intubation rate compared with nCPAP as a primary respiratory supporting strategy in preterm infants suffering from RDS. Future research should assess whether NHFOV can reduce the incidence of BPD and intubation rate in preterm infants with BPD. This review agrees with the findings of our comparison of nHFV to nCPAP used for initial respiratory support.

A Cochrane systematic review of non-invasive respiratory support for the management of transient tachypnoea of the newborn included three trials (150 infants) comparing either CPAP to free-flow oxygen, nasal intermittent mandatory ventilation to nCPAP, or nasal high-frequency percussive ventilation versus nCPAP (Moresco 2020). However, only the single trial included in our review (De La Roque 2011), compared nHFV to nCPAP and reported that no cases of mechanical ventilation or pneumothorax occurred (46 participants), but the duration of tachypnoea was reduced in the nHFV group (MD -4.53, 95% CI -5.64 to -3.42; 1 study, 46 participants).

Two previous systematic reviews of nHFV as respiratory support in preterm infants with respiratory distress included four RCTs involving 218 infants (Yang 2018), and eight RCTs involving 463 infants (Li 2019), so they provided imprecise estimates of effect.

Both reviews concluded that nHFV reduced intubation compared to nCPAP with no differences in clinical morbidities.

AUTHORS' CONCLUSIONS

Implications for practice

For initial respiratory support, we are uncertain if using nHFV compared to invasive respiratory therapy affects clinical outcomes. However, nHFV may reduce endotracheal intubation when compared to nCPAP.

For planned extubation following intubation and surfactant, nHFV may reduce the risk of endotracheal reintubation compared to nCPAP and nIPPV. nHFV may reduce the risk of CLD when compared to nCPAP.

Following initial non-invasive respiratory support failure, nHFV versus nIPPV may result in little to no difference in endotracheal intubation.

Given these results, using nHFV in very preterm infants with or at risk of respiratory distress syndrome may be justified for initial respiratory support and planned extubation following intubation and surfactant to reduce the rate of intubation and risk of CLD.

Subgroup analyses identified that using nHFV MAP ≥ 10 cm H_2O compared to < 10 cm H_2O may reduce reintubation of preterm infants following extubation. Studies predominately used oscillatory nHFV. Too few term infants were enroled in trials for subgroup analyses according to gestation to be meaningful.

Implications for research

Large trials are needed, particularly in high-income settings and term infants, to determine the role of nHFV in initial respiratory support, following planned extubation, and following the failure of other non-invasive respiratory support.

The role of different nHFV types (oscillatory, percussive and jet) for different indications (initial support, following planned extubation and following the failure of initial non-invasive respiratory support) needs further research.

Also, the optimal setting of nHVF (MAP < 10 versus ≥ 10 cm H_2O and frequency < 10 versus ≥ 10 Hz) requires further investigation.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ali 2023

Study characteristics	
Methods	**Design**: randomised controlled trial
	Country: Pakistan

Ali 2023 *(Continued)*

	Single site/multiple sites: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between 01 January 2021 and 27 August 2021
Participants	48 preterm infants with planned extubation were included in the trial. **Inclusion criteria** 1. GA 27 to 34 weeks (estimated on postmenstrual date and early gestational ultrasonography findings) 2. RDS based on clinical manifestations (tachypnoea, nasal flaring, and/or grunting) or RDS Silverman score > 5 3. Moderate–severe RDS based on arterial to alveolar PO_2 (a/A PO_2) ratio and Silverman score within the first hour of life (a/A PO_2 ratio 0.30 or Silverman score > 6) **Exclusion criteria** 1. Any baby intubated for resuscitation or other reasons 2. Birthweight less than 600 g 3. Major congenital malformations such as cystic adenomatous malformations, sequestration, diaphragmatic hernia; or pulmonary hypoplasia; or known complex congenital heart disease 4. Pulmonary haemorrhage 5. Grade 4 intraventricular haemorrhage 6. Cardiopulmonary arrest needing prolonged resuscitation 7. Transferred out of the NICU before randomisation
Interventions	When the neonate had fulfilled the inclusion criteria, nHFOV or nIPPV was started based on the group assignment within 6 hours of life after surfactant administration by InSurE technique: 1. **nHFOV (n = 24):** nHFOV delivered by a high-frequency ventilator (CNO Medin, Germany) via nasal mask with the following starting parameters a. MAP 6 (range 6–0) cm H_2O; b. Frequency of 8 (range 8–12) Hz; c. Amplitude of 7 (range 7–10) cm H_2O; d. FiO_2 regulated in order to maintain oxygen saturation (SpO_2) from 90% to 94% in preterm < 30 weeks' GA and > 89 % to 94% in neonates > 30 weeks' GA by pulse oximeter. 2. **nIPPV (n = 24):** nIPPV delivered via ventilator (CNO Medin, Germany), through nasal mask. The settings were a. PEEP 6 cm H_2O (can be raised in steps of 1 cm H_2O to max 8 cm H_2O, according to the oxygenation); b. Peak inspiratory pressure: 15 cm H_2O (can be raised in steps of 1 cm H_2O to max 25 cm H_2O, according to oxygenation, $PaCO_2$ levels and chest expansion); c. Inspiratory time 0.40 s (according to clinicians' evaluation of leaks and the appearance of the pressure curve: a small pressure plateau is required, and flow may be set accordingly); d. Respiratory rate started at 40 breaths/min (bpm) (can be raised in steps of 5 bpm to max 60 bpm, according to $PaCO_2$ levels); e. FiO_2 regulated in order to maintain oxygen saturation (SpO_2) from 90% to 94% in preterm < 30 weeks' GA and > 89% to 94% in neonates > 30 weeks' GA by pulse oximeter. **For both intervention and control groups** 1. Neonates with moderate-to-severe respiratory RDS were given Surfactant curosurf (Poractant alfa, Chiesi Pharmaceuticals, Parma, Italy) at a dose of 2.5 mL/kg via the InSurE method before initiation of the study intervention or control. In the InSurE technique, surfactant was administered via an endotracheal tube and after a brief period of positive pressure ventilation, the patient was extubated via the assigned mode. 2. Infants undergoing the InSurE method were not considered as having received IMV.

Ali 2023 *(Continued)*

3. Second doses of surfactant 1.5 mL/kg may be given using the InSurE technique within 12 hours if the FiO_2 requirement is > 0.40 to maintain target oxygen saturation (SpO_2 89%–93%) for preterm with < 30 weeks' (90%–94%) for > 30 weeks' GA.
4. Respiratory support was delivered using an appropriate size nasal mask that fits the nares without blanching the surrounding skin, based on the diameter of the nares (small, medium, large size) as per the manufacturer's recommendations.
5. An oro-gastric tube was placed in the stomach to minimise gastric distention, and gas was periodically aspirated.
6. Pacifiers were used to reduce the air leaks from the mouth.
7. A caffeine citrate injection (Chiesi Pharmaceuticals, Parma, Italy) was administered via the intravenous site when infants present with moderate apnoea (defined as 3 or more episodes in 24 hours or a single episode requiring resuscitation and bag and mask ventilation). The initial loading dose was 20 mg/kg, and the maintenance dose was 10 mg/kg per day till completion of postconception GA 34 weeks.
8. The criteria for failure of the intervention and control group, i.e. intubation and invasive mechanical ventilation, were as follows
   a. severe respiratory acidosis ($PaCO_2$ > 65 mm Hg with pH < 7.20);
   b. severe apnoea and bradycardia (defined as recurrent apnoea with more than 3 episodes per hour associated with a heart rate less than 100/min or a single episode of apnoea that requires bag and mask ventilation);
   c. hypoxaemia (FiO_2 < 0.5 with PaO_2 < 50 mm Hg from an arterial blood gas sample);
   d. severe respiratory distress, pulmonary haemorrhage, and cardiopulmonary arrest needing chest compressions.
9. The criteria for weaning the intervention and control group were as follows
   a. minimal or no signs of respiratory distress;
   b. mean airway pressure < 6 cm H_2O; and
   c. fraction inspired oxygen (FiO_2 < 0.25) to achieve target oxygen saturation (SpO_2).

Outcomes

Primary outcomes

Requirement for invasive mechanical ventilation during the first 7 days of life. The following criteria were used to assess the need for invasive mechanical ventilation.

1. Severe respiratory acidosis ($PaCO_2$ > 65 mm Hg with pH < 7.20) in arterial ABGs;
2. Severe apnoea and bradycardia on clinical examination and by oxygen and heart rate monitor;
3. Hypoxaemia (FiO_2 > 0.5 with PaO_2 < 50 mm Hg from an arterial blood gas sample);
4. Severe respiratory distress, pulmonary haemorrhage, and cardiopulmonary arrest needing chest compressions assessed by clinical examination.

Secondary outcomes

1. Air leak on x-ray chest during first 7 days of life;
2. Number of days of hospitalisation;
3. Use of surfactant via InSurE technique;
4. Second doses of surfactant given during the first 3 days of life;
5. Oxygen saturation assessed by an oxygen monitor during the first 3 days of life;
6. PDA assessed by EEG during the first 7 days of life;
7. Spontaneous intestinal perforation assessed by clinical exam and abdominal X-ray during the first 7 days of life;
8. IVH was assessed by brain ultrasound during the first 7 days;
9. Mortality from birth till hospital discharge;
10. Days of non-invasive ventilation during the first 7 days of life;
11. Days of supplementary oxygen during the first 7 days of life;
12. ROP assessed by an ophthalmologist (all neonates born at < 30 weeks' GA or weigh < 1.5 kg at birth, neonates with GA < 30 weeks and birthweight < 1.5 kg at birth with moderate-to-severe respiratory distress syndrome, will be assessed at 4–6 weeks after birth);

Ali 2023 *(Continued)*

	13.BPD assessed by the need for oxygen supplements; 14.Mean airway pressure during the first 7 days of life; 15.NEC assessed by Bell staging clinical criteria.
Notes	**Study conducted in**: a lower-middle-income country (Pakistan) **Disclosures:** no information was provided. **Funding:** no information was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used random table (author communication)
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed, opaque envelopes opened within 6 hours of birth by an attending paediatric registrar not involved in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open (masking not used)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open (masking not used)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All allocated infants reported
Incomplete long term outcome data (attrition bias)	Low risk	No losses reported (no long-term data included)
Selective reporting (reporting bias)	Low risk	The study was registered retrospectively at the Australian New Zealand Clinical Trials Registry (ANZCTR) https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12622000291785(Identifier: ACTRN12622000291785) on 16 February 2022 (submitted on 26 August 2021; trial conducted between January 2021 and August 2021).
Other bias	High risk	Groups dissimilar at baseline for spontaneous vaginal delivery, gestation and birthweight. Achieved prespecified sample size

Chen 2019

Study characteristics

Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit

Chen 2019 *(Continued)*

	Study dates: between May 2017 and May 2018
Participants	206 preterm infants with planned extubation were included in the trial. **Inclusion criteria** 1. GA less than 37 weeks 2. Diagnosed with RDS- or ARDS-associated respiratory failure, or both, and supported by invasive ventilation with synchronised intermittent mandatory ventilation or HFOV 3. No IVH grade 3 or 4 4. The first extubation and subsequent noninvasive ventilation were ready to be carried out 5. Parents written informed consent **Exclusion criteria** 1. Parents' decision not to participate 2. Major congenital anomalies
Interventions	When the neonate had fulfilled the extubation criteria, nHFOV or nCPAP was immediately started on the basis of the group assignment. Other care was at the discretion of the attending neonatologist. 1. **nHFOV for extubation (n = 103):** nHFOV delivered via SLE5000 (SLE 5000, SLE UK, Croyden, UK) with the following starting parameters: a. Frequency of 10 Hz (subsequent regulation range, 8-12, in steps of 1 Hz); b. Inspiratory time of 50% (1:1); c. Oscillation amplitude of 35 cm H_2O (subsequent regulation range, 25–50, in steps of 5 cm H_2O). Oscillation amplitude would be regulated according to the level of PCO_2. Visible chest oscillation was not necessary; d. MAP of 10 cm H_2O (subsequent regulation range, 5-16, in steps of 1 cm H_2O). MAP was regulated according to an open lung recruitment strategy; e. FiO_2 regulated from 0.21 to 0.40 (target value ≤ 30%) in order to maintain SpO_2 from 90% to 95%. 2. **nCPAP for extubation (n = 103):** nCPAP delivered via a bubble CPAP system (Fritz Stephan GmbH): • Initiated at a pressure of 6 cm H_2O (subsequent regulation range, 4–8, in steps of 1 cm H_2O); • FiO_2 from 0.21 to 0.40 (target value ≤ 30%) to maintain SpO_2 from 90% to 95%. All respiratory support was delivered using appropriate size short binasal prongs. To minimise gastric distention, an oro-gastric tube was placed in the stomach and gas was periodically aspirated in both groups. To reduce neonates' discomfort and gas leak, nursing, pacifiers, and positioning were used. No oral or injected sedation was applied.
Outcomes	**Primary outcomes** 1. Endotracheal intubation and ventilation within 1 week. The criteria for reintubation and mechanical ventilation were met with the occurrence of any one of the following conditions: a. Cardiorespiratory arrest or any type of pulmonary haemorrhage; b. Respiratory acidosis with $PaCO_2$ > 70 mm Hg and pH < 7.2 for 2 hours; c. Hypoxia with PO_2 < 50 mm Hg, FiO_2 less than 0.6, and maximal pressures given (8 and 16 cm H_2O in the nCPAP group and nHFOV group, respectively) < 7.2 for 2 hours; d. Apnoea occurring 3 or more times per hour and a heart rate less than 100/min; e. Requirement for mask ventilation in any case; f. Persistent low blood pressure without response to liquid resuscitation and vasoactive agents. 2. Level of PCO_2 within 6 hours of treatment. PCO_2 levels were determined by arterial or arterialised blood gas analysis. **Secondary outcomes** 1. Incidence of BPD; 2. PDA;

Chen 2019 *(Continued)*

3. ROP;
4. NEC;
5. IVH;
6. Length of hospital stay;
7. Abdominal distension;
8. Nasal trauma.

Notes	**Study conducted in**: an upper-middle-income country (China) **Disclosures**: "Financial/non-financial disclosures: none declared." **Funding:** The study was supported by The Social Livelihood Program of Chongqing Science and Technology Commission, China (No. cstc2018jscx-msybX0040): "The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Quote: "After documenting parental consent, the infants with invasive ventilation were randomly assigned to either non-invasive high-frequency oscillatory ventilation (NHFOV) or nasal continuous positive airway pressure (NCPAP), using a table of random numbers and sealed opaque envelopes when they were eligible for extubation".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding to doctor was not possible due to the nature of the intervention.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding to doctor was not possible, due to the nature of the intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited newborns completed the study.
Incomplete long term outcome data (attrition bias)	Low risk	No losses reported (no long-term data included)
Selective reporting (reporting bias)	Low risk	The study was registered at https://www.clinicaltrials.gov (ClinicalTrials.gov; Identifier: NCT03140891) on 3 May 2017 (trial conducted between May 2017 and May 2018).
Other bias	Low risk	• The care of infants before and during the trial was standardised (e.g. gastric tube use, etc.). The study set standard criteria for escalation or de-escalation of treatment, weaning of treatment, termination of study, etc. • Groups similar at baseline. Achieved prespecified sample size

Cheng 2021

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between October 2017 and October 2019
Participants	60 neonates with respiratory distress syndrome: **Inclusion criteria** 1. Preterm, gestation age 28–34 weeks; 2. Diagnosed as respiratory distress syndrome; 3. Not needing mechanical ventilation after birth. **Exclusion criteria** 1. Major congenital malformation or pulmonary malformation; 2. Acute and severe cardiovascular diseases such as respiratory and cardiac arrest; 3. Upper gastrointestinal haemorrhage, upper airway injury or obstruction; 4. IVH.
Interventions	Neonates with respiratory distress syndrome were randomised into: 1. **nHFOV for initial treatment of respiratory distress (n = 28):** nHFOV delivered via Leoni Plus. The setting of nHFPV was as follows: a. MAP 6–12 cm H_2O; b. high-frequency ventilator at 61–2 Hz; c. amplitude settings with 2 times the MAP with visible chest oscillation; d. itime 0.3–0.5 s; e. FiO_2 between 0.21–0.40 according to transcutaneous SO_2 monitoring; f. ventilator weaning indication: MAP < 6 cm H_2O, FiO_2 < 30%. 2. **NIPPV for initial treatment of respiratory distress (n = 32):** nCPAP was delivered via Leoni Plus. NIPPV setting was: a. PIP 15–25 cm H_2O; b. PEEP 4–6 cm H_2O; c. itime 0.3–0.5 s; d. FiO_2 0.21–0.40 according to transcutaneous SO_2 monitoring; e. respiratory rate settings between 15–40 breaths/min; f. ventilator weaning indication: FiO_2 < 30%, PIP < 14 cm H_2O, PEEP < 4 cm H_2O and respiratory rate < 15 breath/min. Infants for both groups were given 100 mg/kg surfactant via minimally invasive method with the whole procedure connected to either nHFOV or NIPPV circuits. **Criteria for intubation** 1. $PaCO_2$ > 60 mm Hg, pH < 7.2; 2. FiO_2 > 60%, PaO_2 < 50 mm Hg or transcutaneous saturation < 85%; 3. Frequent apnoea events a. Apnoea episodes not needing stimulation of > 3/hour or apnoea episodes needing intervention of 1 episode per day;

Cheng 2021 *(Continued)*

	4. 4. Pulmonary haemorrhage or upper gastrointestinal tract bleeding.
Outcomes	**Primary outcomes** 1. Arterial blood gas indexes, including pH, PaO_2, $PaCO_2$, OI at 6, 12, 24 hours after receiving respiratory support. **Secondary outcomes** 1. Duration of non-invasive ventilation; 2. Total duration of oxygen inhalation; 3. Utilisation rate of invasive ventilation; 4. Incidence of VAP; 5. Incidence of BPD.
Notes	**Study conducted in**: an upper-middle-income country (China) **Disclosures: no information provided** **Funding:** no information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table method
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 recruited infants did not complete the study, 1 with supraventricular tachycardia and 1 self discharged from the hospital).
Incomplete long term outcome data (attrition bias)	Low risk	No losses reported (no long-term data included)
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Unclear risk	The study and control groups were similar at baseline. Achieved prespecified sample size

De La Roque 2011

Study characteristics

De La Roque 2011 *(Continued)*

Methods	**Design**: randomised controlled trial **Country**: France **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between November 2007 and September 2009
Participants	46 term infants as initial treatment of respiratory distress: **Inclusion criteria** 1. Birthweight ≥ 2000 g; 2. GA ≥ 37 weeks; 3. Transcutaneous oxygen saturation < 90% in room air; 4. Simplified Silverman score: (chest movement, expiratory grunt, and nares dilation) ≥ 5; 5. Diagnosis of TTN. **Exclusion criteria** 1. Major congenital malformation or pulmonary malformation; 2. Meconium aspiration; 3. Neonatal infection with haemodynamic alteration; 4. Neonatal asphyxia (pH < 7.1); 5. Clinical signs of chest wall retraction (that could be a differential diagnosis of TTN such as HMD); 6. Newborn infants with secondary diagnosis of HMD were discontinued from the study.
Interventions	Term infants with respiratory distress were randomised to initial treatment with: 1. **nHFOV for initial treatment of respiratory distress (n = 23):** nHFOV delivered via high-frequency percussive (nHFPV; pressure limited, time-cycled, high frequency mode) ventilator (VDR3, Percussionaire, Bird technologies, Sandpoint, ID). The setting of nHFPV was as follows: a. pressure of 5 cm H_2O; b. high-frequency ventilator at 5 Hz. 2. **nCPAP for initial treatment of respiratory distress (n = 23):** nCPAP was delivered via a conventional time cycled, pressure limited ventilator (Babylog 8000; Drager, Telford, PA). NCPAP setting was: a. PEEP started at 5 cm H_2O. All respiratory support was delivered using a heated humidified nasal probe of appropriate size. FiO_2 was adjusted by an investigating physician to obtain a targeted SpO_2 of 90%–96%. The HFPV and nCPAP setting were not changed during the procedure.
Outcomes	**Primary outcomes** Duration of respiratory distress. **Secondary outcomes** 1. Duration and level of oxygen supplementation; 2. Incidence of pneumothorax; 3. Pulmonary infections.
Notes	**Study conducted in**: a high-income country (France) **Disclosures**: manuscript stated "none reported." **Funding**: none reported

De La Roque 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Infants born consecutively were assigned using a table of random numbers.
Allocation concealment (selection bias)	Low risk	Infants were assigned using sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 of 46 infants (13%) excluded post randomisation with diagnosis of hyaline membrane disease (HMD) or asphyxia
Incomplete long term outcome data (attrition bias)	Low risk	No losses reported (no long-term data included)
Selective reporting (reporting bias)	Low risk	• The study was registered at https://www.clinicaltrials.gov (ClinicalTrials.gov; Identifier: NCT00556738) on 12 November 2007 (trial conducted between November 2007 and September 2009). • The inclusion criteria differ slightly between the published manuscript (gestation ≥ 37 weeks) and the registered protocol (gestation ≥ 35 weeks).
Other bias	Low risk	• 2 different ventilators were used for the intervention and control: nHFOV delivered via VDR3, Percussionaire, Bird technologies, Sandpoint, ID (high-frequency percussive ventilation (nHFPV)) for intervention and nCPAP delivered via Babylog 8000; Drager, Telford, PA ventilator for the control. • The disease studied was transient tachypnoea of the newborn (TTN) which is a self-limiting condition. • Groups similar at baseline. Achieved prespecified sample size

El Ashker 2022

Study characteristics

Methods	**Design**: randomised controlled trial **Country**: Egypt **Single site/multiple sites**: multiple centres (2) **Setting**: neonatal intensive care units **Study dates**: May 2019 to June 2020
Participants	**Target sample size:** 60 **Inclusion criteria**

El Ashker 2022 *(Continued)*

	1. Appropriate weight for the GA; 2. Preterm infants between 28 + 0 and 33 + 6 weeks of gestation determined by the New Ballard Score (Ballard 1991), data from the LMP or ultrasound measurement of the foetus; 3. RDS diagnosis was made on the basis of the combination of clinical features and radiological features. **Exclusion criteria** 1. Full-term neonates; 2. Causes other than RDS for respiratory distress; 3. Need for intubation for mechanical ventilation during resuscitation or on the first 2 days of life; 4. Major congenital malformations; 5. Intrauterine growth retardation.
Interventions	Eligible infants were randomised to either: 1. **nCPAP** via binasal prongs (ventilator: SMedin CNO, medin Medical Innovations GmbH, Olching, Germany or SLE 1000, SLE Limited, UK); 2. **nHFOV** via nasopharyngeal tube (ventilator: SLE5000, UK). For both intervention and control groups: 1. Natural bovine lung surfactant (Alveofact, Lyomark Pharma GmbH, Germany) was administered when available at a dose of 54 mg/kg (1.2 mL/kg) via the InSurE method if an infant presented with the following: ≤ 30 weeks' GA when FiO_2 requirement > 0.30 or > 30 weeks' GA when FiO_2 requirement > 0.40; 2. Caffeine citrate injection (Caffeinospire, Inspire Pharmaceutical Co., Egypt) was administered when infants presented with moderate apnoea (defined as 3 or more episodes in 24 hours or a single episode requiring resuscitation and bag and mask ventilation). The initial loading dose was 20 mg/kg, and the maintenance dose was 5 mg/kg per day; 3. Other neonatal care and follow-up were the same for both study groups.
Outcomes	**Primary outcome** 1. Failure of technique and need for intubation and surfactant. When possible, surfactant to be administered through InSurE. **Secondary outcomes** 1. Duration of non-invasive respiratory support; 2. Invasive ventilation; 3. Duration of respiratory support; 4. Duration of hospital stay; 5. Partial pressure of carbon dioxide clearance.
Notes	**Study conducted in**: a lower middle-income country (Egypt) **Disclosures**: no information was provided. **Funding:** no information was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Simple randomization using a randomization table created by a computer software program"
Allocation concealment (selection bias)	Low risk	Quote: "Sealed opaque envelopes"

El Ashker 2022 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Open-label (Masking Not Used)"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote:"Open-label (Masking Not Used)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses reported
Incomplete long term outcome data (attrition bias)	Low risk	No losses reported (no long-term data included)
Selective reporting (reporting bias)	Unclear risk	**Registered retrospectively with:** Pan African Clinical Trials Registry (PACTR): https://pactr.samrc.ac.za/; ID: PACTR202207646279984 on 22 July 2022 (trial conducted between May 2019 to June 2020)
Other bias	Low risk	• The care of infants before and during the trial was standardised (e.g. surfactant, caffeine use, monitoring etc.). The study set standard criteria for surfactant administration etc. • Groups similar at baseline. Achieved prespecified sample size • The nCPAP was delivered via binasal prongs while nHFOV was delivered via nasopharyngeal tube.

Feng 2019

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between May 2017 and April 2018
Participants	80 infants with neonatal respiratory distress syndrome were included in the trial. **Inclusion criteria** 1. Needing respiratory support within 12 hours of delivery; 2. Chest x-ray changes: uniform fine particles, ground glass appearance; blood gas changes: pH, PaO_2, HCO_3 decreasing and increasing $PaCO_2$; Grade III–IV NRDS; 3. Research committee approval and parental written consent. **Exclusion criteria** 1. Major cardiac malformation or pulmonary malformation; 2. Severe neonatal infection, congenital pneumonia, wet lung, meconium aspiration causing respiratory distress; 3. No parental consent.

Feng 2019 *(Continued)*

Interventions	Infants were randomised into: 1. **Conventional ventilation combined with pulmonary surfactant therapy (n = 40)** a. PIP 15–25 cm H_2O; b. PEEP 4 –6 cm H_2O; c. FiO_2 50%–80%; d. Respiratory rate 40–60 breaths/min. 2. **Non-invasive high-frequency oscillatory ventilation combined with pulmonary surfactant therapy (n = 40**) a. Pmean 10–12 cm H_2O; b. High-frequency ventilator at 12–15 Hz; c. Amplitude settings 30–45 cm H_2O; d. itime 0.33 s; e. FiO_2 between 40%–60%. Infants are weaned from ventilation support if the Pmean < 8 cm H_2o, FiO_2 < 30%, stable respiratory status, improvement in chest x-ray, blood gas results within the limit of ceasing ventilation. Criteria for failure of non-invasive ventilation support: 1. FiO_2 > 60%; 2. PaO_2 < 50 mm Hg; 3. pH < 7.20; 4. $PaCO_2$ > 60 mm Hg; 5. Apnoeic events > 3/hour despite given caffeine.
Outcomes	1. To compare the effective rate of treatment for both groups, defined as: a. Very effective: 12 hours post treatment, respiratory status stable, chest x-ray improvement with good expansion, SaO_2 > 85% with no other symptoms of respiratory distress; b. Effective: 12 hours post treatment, SaO_2 > 70%-80%, some improvement in respiratory distress, lesser ground glass appearance on chest x-ray; c. Not effective: 12 hours post treatment, SaO_2 < 70%, no improvement in respiratory distress or deterioration and no changes in chest x-ray appearance; d. Total effective rate: (very effective + effective)/number of treatments x 100%; 2. Ventilation support duration, symptom relief time and hospital stay length; 3. Comparing arterial blood gas indexes (PaO_2, pH, $PaCO_2$, FiO_2, Oxygen index, MAP) at 24 hours; 4. Other complications: pneumothorax, pulmonary haemorrhage, bronchopulmonary dysplasia, pneumonia.
Notes	**Study conducted in**: an upper-middle-income country (China) **Disclosures**: no information provided **Funding:** Shaanxi Provincial Department of Health (No. 2015JM40186)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple number generator
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described

Feng 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Unclear risk	• 2 different ventilators were used for the intervention and control: nHFOV via Stephanie (Servo-1) and conventional delivered via Maquet, Germany. • The study and control groups were similar at baseline. Achieved prespecified sample size

Fischer 2019

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: Germany **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between January 2015 and 31 December 2017
Participants	Aimed to include 68 preterm infants undergoing planned extubation. However, the study was terminated after recruiting 6 participants. **Inclusion criteria** 1. GA < 32 + 0 weeks; 2. Birthweight < 1500 g; 3. Received mechanical ventilation via an endotracheal tube for ≥ 120 hours; 4. Caffeine treatment according to unit guidelines; 5. $paCO_2$ < 65 mm Hg with pH > 7.2; 6. FiO_2 25%-40% to maintain SpO_2 at 90%–94%; 7. Ventilated using: a. Time-cycled, pressure-controlled ventilation: PIP ≤ 22 cm H_2O, PEEP ≤ 6 cm H_2O; or b. Volume guarantee ventilation: working Ppeak ≤ 22 cm H_2O, PEEP ≤ 6 cm H_2O; or c. High frequency oscillation ventilation: Pmean ≤ 12 cm H_2O, amplitude ≤ 30 cm H_2O. 8. Decision of the attending clinician to extubate. **Exclusion criteria**

Fischer 2019 *(Continued)*

1. Major congenital malformation requiring surgery;
2. Duct-dependent congenital heart disease;
3. Neuromuscular disease;
4. Participation in another randomised controlled trial;
5. Death before reaching the eligibility criteria;
6. Hydrocortisone treatment at the time of enrolment;
7. Chronological age > 28 days.

Interventions	Infants at planned extubation were randomised to: 1. **nHFOV for extubation (n = 4):** nHFOV settings were as follows: a. Pmean 8 cm H_2O; b. Frequency 9–10 Hz; c. Amplitude 20–30 cm H_2O; d. I:E ratio 33:66. 2. **nCPAP for extubation (n = 2):** nCPAP settings were: a. PEEP 8 cm H_2O; b. Flow 7–8 L/min. After extubation, appropriately sized binasal prongs were applied to the patient (Infant Nasal Prongs, Fisher & Paykel Healthcare Ltd., Auckland, New Zealand) and connected to a heated humidifier (MR850, Fisher & Paykel) and a neonatal ventilator (VN500, Drägerwerk AG, Lübeck, Germany, or Leoni Plus, Heinen & Löwenstein, Bad Ems, Germany) using the manufacturer approved heated-wire ventilatory circuit. The ventilator remained the same before and after extubation. The FiO_2 was set to maintain SpO_2 at 90%–94%. Within the limits, the physician was free to adjust ventilator settings.
Outcomes	**Primary outcomes** 1. $PaCO_2$ at 72 hours after extubation (time frame: 64 hours to 80 hours) **Secondary outcomes** 1. Blood gas analysis results at 2 hours after extubation: pH, PaO_2, $PaCO_2$ and base excess; 2. Blood gas analysis results at 72 hours after extubation: pH, PaO_2 and base excess; 3. Successful extubation within 72 hours; 4. Airway obstruction due to highly viscous secretions within 72 hours; 5. Treatment failure within 7 days, defined as meeting at least 1 of the following criteria: a. A sustained PCO_2 > 80 mm Hg and pH < 7.20 confirmed by arterial or capillary blood gas analysis despite maximum ventilator support; b. An FiO_2 > 0.6 to maintain SpO_2 at 90%–94%; c. Reintubation. 6. Reintubation within 7 days; 7. Total duration of mechanical ventilation until discharge; 8. Total duration of supplemental oxygen until discharge; 9. Rescue treatment (if the nCPAP infants developed treatment failure but did not need immediate reintubation, nHFOV was provided as ‘rescue treatment’. In the HFOV group, any non-invasive rescue treatment could be provided); 10. Blood gas analysis results at 2 hours after switch to "Rescue Treatment": pH, PaO_2, $PaCO_2$ and base excess; 11. Incidence of common adverse effects of prematurity (IVH III°- IV° (Papile 1978), surgical NEC, pneumothorax, pulmonary interstitial emphysema, PDA requiring surgical closure, ROP requiring laser treatment or injection of bevacizumab, or both, death or moderate-to-severe BPD (Jobe 2001), at 36 weeks' GA, PVL).
Notes	**Study was conducted** in: a high-income country (Germany)

Fischer 2019 *(Continued)*

Slow recruitment: the main reason for slow recruitment was because few participants fulfilled the study eligibility criteria of receiving ≥ 120 hours of endotracheal mechanical ventilation and requiring a FiO_2 of 25%–40% at extubation. This was thought to be due to the introduction of new treatment strategies to avoid endotracheal mechanical ventilation, such as LISA at the study centre.

Disclosures: "The authors declare that they have no competing interests." The corresponding author's organisation is Charité, Universitäts-medizin Berlin which "is a corporate member of Freie Universität Berlin, Humboldt-Universitätzu Berlin, and the Berlin Institute of Health."

Funding: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An independent statistician and a study nurse performed random sequence generation using a 1:1 ratio and variable block sizes.
Allocation concealment (selection bias)	Low risk	Numbered opaque envelopes opened immediately prior to extubation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited newborns completed the study.
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Low risk	The study was registered at https://www.clinicaltrials.gov (ClinicalTrials.gov; Identifier: NCT02340299) on 16 January 2015 (trial conducted between January 2015 and 31 December 2017).
Other bias	High risk	Premature stopping for feasibility and low number of enrolments. Enroled 6 infants of planned sample size of 68 participants

Guo 2021

Study characteristics

Methods

Design: randomised controlled trial

Country: China

Single site/multiple sites: single-centre

Setting: tertiary neonatal intensive care unit

Study dates: between January 2018 and December 2019

Guo 2021 *(Continued)*

Participants	74 neonates with respiratory distress syndrome were included in the trial. **Inclusion criteria** 1. Grade III–IV RDS: 2. Within 12 hours of delivery, they noted difficulty breathing, tachypnoea, respiratory rate > 60 breaths/min; 3. Chest x-ray with respiratory distress syndrome changes; 4. Needing ventilation support. **Exclusion criteria** 1. Severe liver, kidney dysfunction; 2. Severe immune dysfunction; 3. Genetic or metabolic disorder; 4. Congenital heart disease; 5. Congenital pulmonary disease; 6. Neonatal infection; 7. Abnormal gastrointestinal tract.
Interventions	All neonates with respiratory distress syndrome were given pulmonary surfactant (Curosurf) 200 mg/kg via InSurE technique and randomised into: 1. **Non-invasive high-frequency ventilation group (NHFV) (n = 36)** (Germany, 3090 Medin CNO) a. MAP 8–12 cm H_2O; b. FiO_2 30%–40%; c. Frequency 7–12 Hz; d. Amplitude 2–3 times the MAP value with visible chest oscillation. 2. **Non-invasive continuous positive pressure ventilation (nCPAP) (n = 38)** a. FiO_2 30%–60%; b. PEEP 5–7 cm H_2O; c. Flow 5 L/min. Criteria for failure of non-invasive ventilation: 1. MAP > 14 cm H_2O or FiO_2 > 50% to maintain normal saturation; 2. $PaCO_2$ > 70 mm Hg; 3. Frequent apnoeic episode: more than 6 episodes in 24 hours or more than 2 episodes requiring IPPV. Criteria for weaning ventilation support: 1. Minimal ventilation settings; 2. Able to breathe above the ventilator support; 3. SpO_2 > 90%.
Outcomes	**Outcomes** 1. PO_2, A/APO_2 and SaO_2 at 12, 24, 48, 72 hours after corresponding treatment; 2. Complications such as air leakage, persistent pulmonary hypertension, BDP, retinopathy, pulmonary haemorrhage, intracranial haemorrhage and other complications; 3. Duration of ventilator use; 4. Total hospital length.
Notes	**Study conducted in**: an upper-middle-income country (China) **Disclosures**: no statements provided

Guo 2021 *(Continued)*

Funding: "The key project of natural science research in colleges and universities of Anhui Province (KJ2019A0342)".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table method
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	Groups similar at baseline

Iranpour 2019

Study characteristics

Methods	**Design**: randomised controlled trial **Country**: Iran **Single site/multiple sites**: multi-centre (2) **Setting**: tertiary neonatal intensive care units **Study dates**: from October 2017 to March 2018
Participants	68 preterm infants as initial treatment of respiratory distress: **Inclusion criteria** 1. GA at birth between 30 and 36 weeks and 6 days; 2. Appropriate weight for the gestational age; 3. Spontaneous breathing and clinical signs and symptoms of RDS. **Exclusion criteria**

Iranpour 2019 *(Continued)*

1. Major congenital abnormalities such as diaphragmatic hernia, cyanotic heart disease;
2. Intrauterine growth retardation;
3. Intubation and mandatory ventilation on the first day of life;
4. Perinatal asphyxia (umbilical cord pH < 7 and umbilical cord bicarbonate < 12 mEq/L).

Interventions	Infants were randomised to initial mode of respiratory support: 1. **nHFOV for initial treatment of respiratory distress (n = 34):** nHFOV with initial settings: a. Pmean 8 cm H_2O. Adjustments to the MAP were not permitted; b. Frequency 10–20 Hz. Adjustments to the frequency were not permitted; c. The amplitude was set at 20 cm H_2O and adjusted (±2 cm H_2O every 2 minutes), to maintain transcutaneous carbon dioxide ($tcCO_2$) levels (40–60 mm Hg). 2. **nCPAP for initial treatment of respiratory distress (n = 34)** nCPAP initial settings: a. PEEP 6-7 cm H_2O; b. Flow 7-8 L/min. A Fabian ventilator (Fabian, Autromic Medical Systems AG, Hirzel, Zurich, Switzerland) and binasal midline prongs (Fisher & Paykel Healthcare, New Zealand) were used for both groups. The FiO_2 was set to maintain SpO_2 at 89%–95%.
Outcomes	**Primary outcomes** The duration of using nCPAP or nHFOV. **Secondary outcomes** 1. Failure of treatment defined as apnoea or pH < 7.2 and $PaCO_2$ > 60 mm Hg; 2. Need for intubation and ventilator when FiO_2 levels > 35% to maintain the desired oxygen saturation levels; 3. PDA; 4. Pulmonary haemorrhage; 5. NEC; 6. IVH; 7. CLD; 8. Pneumothorax; 9. Pulmonary haemorrhage; 10. Time to full enteral feeding.
Notes	**Study conducted in**: an upper-middle-income country (Iran) **Disclosures:** "Competing interests: none declared." **Funding:** "This project is sponsored by the Isfahan University of Medical Sciences," Isfahan, Iran.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequentially numbered computerised randomisation algorithm
Allocation concealment (selection bias)	Low risk	The allocation to treatment was concealed until study entry.
Blinding of participants and personnel (performance bias)	High risk	Not reported. Different modes and settings of ventilation

Iranpour 2019 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited newborns completed the study.
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Low risk	The study was registered at https://en.irct.ir/search (IRCT; Identifier: IRCT2017062734782N1) on 9 September 2017 (trial conducted between October 2017 to March 2018).
Other bias	Low risk	Groups similar at baseline. Achieved prespecified sample size

Jiang 2020

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between January 2017 to April 2019
Participants	82 preterm infants after thin catheter administration of surfactant **Inclusion criteria** 1. Met RDS diagnostic criteria set in the 2016 European Guidelines for the Prevention and Treatment of Neonatal Respiratory Distress Syndrome (Sweet 2017); 2. GA < 3 7 weeks; 3. Hospitalised within 12 hours after birth; 4. Progressive dyspnoea at 6 hours after birth. **Exclusion criteria** 1. Children with heart and liver disease; 2. Intrauterine infection; 3. Aspiration pneumonia; 4. Wet lungs; 5. Congenital genetic disease; 6. Congenital malformations.
Interventions	Infants after thin catheter surfactant administration were randomised to: 1. **nHFOV for initial treatment of respiratory distress (n = 41):** nHFOV delivered via SLE baby 5000 ventilator (SLE 5000, SLE UK, Croyden, UK) with inial settings as follows: a. MAP 8 cm H_2O;

Jiang 2020 *(Continued)*

b. Frequency: 7–12 HZ;
c. Amplitude set at 2–3 times MAP and adjusted according to the degree of oscillation of the chest of the child, which was preferably at 8–9 ribs on the chest radiograph;
d. FiO_2: 30%–40%;
e. Ventilator weaning indication: MAP < 6 cm H_2O, FiO_2 < 30%, and PaO_2 > 90%.

2. **nIPPV for initial treatment of respiratory distress (n = 41):** BiPAP delivered via a Fabian ventilator (Fabian, Autromic Medical Systems AG, Hirzel, Zurich, Switzerland) with the parameters set as follows:
a. PIP: 12–15 cm H_2O;
b. PEEP: 5 cm H_2O;
c. Respiratory rate: 30–40 times/minute;
d. FiO_2: 30%–40%;
e. Ventilator weaning indication: PEEP ≤ 3 cm H_2O, FiO_2 < 30%, PIP ≤ 5 cm H_2O, PaO_2 > 90%.

Both groups received pulmonary surfactant (Poractant alfa; Curosurf, Chiesi Pharmaceutical Co., Ltd., Germany) via a thin catheter before initiation of the treatment. Nasal interface not reported

Outcomes

Primary outcomes

1. The duration of using nCPAP or nHFOV

Secondary outcomes

1. Failure of treatment, defined as apnoea or pH < 7.2 and partial pressure of CO_2 > 60 mm Hg;
2. Need for intubation and ventilator when FiO_2 levels > 35% to maintain the desired oxygen saturation levels;
3. PDA;
4. Pulmonary haemorrhage;
5. NEC;
6. IVH;
7. CLD;
8. Pneumothorax;
9. Time to full enteral feeding.

Notes

Study conducted in: an upper-middle-income country (China)

Disclosures: authors stated "none."

Funding: no information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The infants were divided into 2 groups using the random number table method.
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported

Jiang 2020 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	2 different ventilators were used for the intervention and control: nHFOV delivered via SLE baby 5000, UK ventilator and bilevel positive airway pressure (BiBAP) delivered via a Fabian ventilator (Fabian, Autromic Medical Systems AG, Hirzel, Zurich, Switzerland). Groups similar at baseline. No sample size calculation reported

Li 2019

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between January 2017 to January 2019
Participants	114 preterm infants with: **Inclusion criteria** 1. Gestational age 26 + 0 weeks to 31 + 6 weeks; 2. Birthweight of < 1500 g; 3. Met the criteria of intubation and requiring invasive mechanical ventilation of any mode on admission for > 7 days; 4. Only the first extubation from invasive ventilation was included in this study; 5. Fulfil extubation criteria: prior to extubation, caffeine loaded with 20 mg/kg initially, and continued on 5 mg/kg daily dose; low breathing support parameters and able to maintain blood gas of pH > 7.20, PO_2 50 mm Hg to 60 mm Hg; 6. Informed consent was obtained from a guardian. **Exclusion criteria** 1. Major life-threatening congenital malformations; 2. Surgical conditions requiring surgery before extubation (e.g. congenital diaphragmatic hernia and complex congenital heart disease except for ligation of PDA and surgical NEC; 3. Grade IV IVH before extubation; 4. Other conditions such as genetics or trisomy conditions.
Interventions	Infants undergoing planned extubation were randomised to 2 arms:

Li 2019 *(Continued)*

1. **nHFOV for extubation (n = 56):** nHFOV delivered via SLE5000 HFO machine with inial settings as follows:
   a. MAP prior to extubation MAP level + 2 cm H_20 (range 8–14);
   b. Frequency: 10 (range 8–12) HZ;
   c. Amplitude: depending on visible chest oscillation (range 20–35) cm H_2O;
   d. FiO_2: 0.21 to 0.40, similar to value prior to extubation.
2. **nCPAP for extubation (n = 58):** nCPAP delivered (China GuangZhou) with the parameters set as follows:
   a. PEEP: 6 (range 6 –8) cm H_2O;
   b. FiO_2: 0.21 to 0.40 with similar value prior to extubation.

Outcomes

Primary outcomes

1. The rate of reintubation within 7 days of extubation

Secondary outcomes

1. Duration of non-invasive ventilation;
2. Length of hospital stay;
3. Number of deaths;
4. Pneumothorax;
5. NEC: stage II and higher;
6. IVH: Papile grade III and higher;
7. BPD.

Notes

Study conducted in: an upper-middle-income country (China)

Disclosures "The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest."

Funding: "This study was funded by the Guangxi Clinical Research Center for Pediatric Diseases and the Guangxi Medical and Health Key Discipline Program. Funds received for open access publication fees are provided by the Guangxi Clinical Research Center for Pediatric Diseases."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised by envelope extraction
Allocation concealment (selection bias)	Unclear risk	Randomised by envelope extraction
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses reported

Li 2019 *(Continued)*

Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	Groups similar at baseline. Achieved prespecified sample size

Li 2021

Study characteristics	
Methods	***Li 2021 publication:*** **Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between 1 April 2017 and 31 October 2018 ***Li 2022 publication:*** **Follow-up**: post hoc 12- and 24-month CA follow-up analysis of the original trial ***(Li 2021)***
Participants	***Li 2021 publication:*** 149 preterm infants **Inclusion criteria** 1. GA 25 + 0 weeks to 33 + 6 weeks; 2. Birthweight of < 1500 g; 3. Met the criteria of intubation and requiring invasive mechanical ventilation of any mode on admission; 4. Only the first extubation from invasive ventilation was included in this study; 5. Informed consent was obtained from a guardian. **Exclusion criteria** 1. Major life-threatening congenital malformations; 2. Died within 24 hours after admission; 3. Abnormal upper airway structure (e.g. Pierre–Robin's syndrome and choanal atresia); 4. Surgical conditions requiring surgery before extubation (e.g. congenital diaphragmatic hernia and complex congenital heart disease with the exception of ligation PDA and surgical NEC); 5. Grade IV IVH before extubation; 6. Other conditions such as congenital pulmonary hypoplasia and surfactant protein B deficiency. ***Li 2022 publication:*** **Follow-up** The follow-up study reported 12- and 24-month CA outcomes for surviving infants among the original study participants (n = 149). Inclusion and exclusion criteria for the primary trial were as above.

Li 2021 *(Continued)*

	All infants from the primary trial who were alive at 12 months (n = 113) and 24 months (n = 110) were eligible for follow-up. Of the total cohort of 149 infants: 1. 10 did not complete the study; 2. 4 died before12-month CA; 3. 22 lost to follow-up at 12-month CA, and 113 were assessed; 4. 3 lost to follow-up at 24-month CA, and 110 were assessed.
Interventions	Infants undergoing planned extubation were randomised to 3 arms: 1. **nHFOV for extubation (n = 47):** nHFOV delivered via Fabian HFO machine (Acutronic Medical System AG, Hirzel, Switzerland) with inial settings as follows: a. MAP 10 (range 6–12) cm H_2O; b. Frequency: 10 (range 6–12) HZ; c. Amplitude: 25 (range 25–50) cm H_2O. Visible chest oscillation was not always necessary; d. Inspiration time of 33%; e. FiO_2: 0.21 to 0.40 to maintain a target SpO_2 of 90% to 95%. 2. **nIPPV for extubation (n = 51):** nIPPV delivered via Comen NV8 machine (Shenzhen Comen Medical Instruments Co. Ltd., Shenzhen, China) with the parameters set as follows: a. PIP: 15 (range 15–25) cm H_2O; b. PEEP: 4 (range 4–8) cm H_2O; c. Inspiratory time of 0.45 to 0.5 sec; d. Respiratory rate: 30 (range 15–40) times/minute; e. FiO_2: 0.21 to 0.40 to maintain a target SpO_2 of 90% to 95%. 3. **nCPAP for extubation (n = 51):** nCPAP delivered via a Fabian HFO machine (Acutronic Medical System AG, Hirzel, Switzerland) with the parameters set as follows: a. PEEP: 5 (range 3 –8) cm H_2O; b. FiO_2: 0.21 to 0.40 to maintain a target SpO_2 of 90% to 95%. Ventilation delivered via appropriate size bi-nasal prongs (NeoJet System; Lowenstein Medical GmbH & Co. KG, Bad Ems, Germany).
Outcomes	***Li 2021 publication:*** **Primary outcomes** 1. The rate of reintubation within 7 days of extubation **Secondary outcomes** 1. The oxygenation index (OI = MAP x FiO_2 x 100/PaO_2) post-extubation; 2. Duration of non-invasive ventilation; 3. Duration of O_2 supplementation; 4. Duration of parenteral nutrition; 5. Length of hospital stay; 6. VAP; 7. Pneumothorax; 8. PDA; 9. NEC: stage II and higher; 10. IVH: Papile grade III and higher; 11. BPD; 12. ROP stage II and higher; 13. Nasal injury; 14. Girth (measurements were taken at 48 and 96 hours after non-invasive ventilation). ***Li 2022 publication:***

Li 2021 *(Continued)*

Primary outcomes

The primary outcome was neurodevelopmental impairment at 24-month CA (including CP, motor or cognition delay, and language delay).

1. Neurodevelopmental impairment includes: CP, motor or cognition delay, and language delay;
2. The severity of CP categorised by GMFCS;
3. Motor and cognition development was measured with GDS; DQ below 75 was considered motor and cognition delay;
4. Language delay refers to language development that does not achieve the level corresponding to their age assessed with S - S relations.

Secondary outcomes

1. Pulmonary function tests performed at 12-month CA;
2. Respiratory diseases occurring within 12- and 24-month CA.

Notes

Study conducted in: an upper-middle-income country (China)

Li 2021 publication:

Disclosures:

"The authors declare that the research was conducted in the absence of any commerical or financial relationships that could be construed as a potential conflict of interest".

Funding: "This study was funded by the Guangxi Clinical Research Center for Pediatric Diseases and the Guangxi Medical and Health Key Discipline Program. Funds received for open access publication fees are provided by the Guangxi Clinical Research Center for Pediatric Diseases".

Li 2022 publication

Disclosures: "The authors declare that there is no conflict of interest".

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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated random numbers list was devised by an independent statistician (design 1:1:1).
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed opaque envelopes containing a card indicating the arm of randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was blinded to parents, but blinding to the doctors was not possible owing to the nature of the intervention. All respiratory management was performed by clinicians who did not belong to the study team. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Losses not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 (6.7%) infants were lost to follow-up for various reasons (e.g. transfer to another centre for surgery).

Li 2021 *(Continued)*

Incomplete long term outcome data (attrition bias)	High risk	39/149 (26.2%) lost to follow-up at 24 months corrected age so considered high risk of attrition bias for longer-term outcomes (Li 2022 (DOI: 10.3389/fped.2022.865057))
Selective reporting (reporting bias)	Low risk	Li 2021 [low risk] The study registered at the Chinese Clinical Trials Register, http://www.chictr.org.cn (Identifier: ChiCTR1900024289) on 5 July 2017 (trial conducted between 1 April 2017 and 31 October 2018). Li 2022 [unclear risk] The trial protocol was not available for review and was not prospectively registered with any trial registry.
Other bias	Low risk	Li 2021 [low risk] • The study set standard criteria for intubation at birth, extubation to intervention/control, failure of intervention (reintubation), escalation or de-escalation of treatment, weaning of treatment, termination of study ...etc. • 2 different ventilators were used for the intervention and control: nHFOV and nCPAP delivered via Fabian HFO machine (Acutronic Medical System AG, Hirzel, Switzerland) and nIPPV delivered via Comen NV8 machine (Shenzhen Comen Medical Instruments Co. Ltd., Shenzhen, China). • Groups similar at baseline. Achieved prespecified sample size. Li 2022 [high risk] • The initial design of the study did not include the planning of a follow-up study as this was a post-hoc analysis of the original trial. • Ethical approval for the follow-up data collection seems to obtained at the same time as the original study. • Some data (eg. history of respiratory diseases) were collected from parents via phone interview and was subject to re-collection bias. • Follow-up assessment was done by different examiners who were not blinded. • Follow-up examinations were carried out by different examiners which may result in some variability. • Furthermore, the study was not powered to assess differences in neurodevelopment.

Lou 2017

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between July 2015 and September 2016
Participants	65 infants between 28–45 weeks' gestation with severe NRDS needing mechanical ventilation for more than 48 hours and extubated within 3 weeks of age planned for extubation

Lou 2017 *(Continued)*

	Inclusion criteria 1. After birth, neonates noted to have respiratory distress, nasal flaring, grunting, tachypnoea, recession, cyanosis or decreased chest sounds bilaterally with chest x-ray changes consistent with NRDS Grade III–IV 2. Persistent respiratory distress despite surfactant administration 3. Indications for mechanical ventilation **Exclusion criteria** 1. Respiratory distress symptoms caused by infection, meconium aspiration, wet lungs or perinatal asphyxia 2. Severe congenital abnormalities or congenital heart disease 3. Death within 24 hours of admission
Interventions	Preterm infants were randomised to extubation on: 1. **nHFOV (n = 34):** nHFOV delivered via SLE baby 5000, Germany; with inial settings as follows: a. MAP: 2–4 cm H_2O; b. Frequency: 6–12 Hz; c. Amplitude: 2 to 3 times MAP; with visible chest wall oscillation; d. Chest x-ray with 8–9 ribs expansion; e. FiO_2: addition 5%–10% from the original FiO_2 settings prior to extubation; f. Criteria to wean from nHFOV: (can wean to oxygen or high flow nasal prongs): i. MAP < 6 cm H_2O; ii. FiO_2 < 0.30; iii. SpO_2 > 90%. 2. **nCPAP (n = 31):** nCPAP: Stephan, Germany with the parameters set as follows: a. PEEP: 4–6 cm H_2O; b. Flow: 8~10 L/min; c. FiO_2: 0.30–0.40; d. Criteria to wean for nCPAP: i. PEEP 2 cm H_2O; ii. FiO_2 < 0.3 with no symptoms of respiratory distress; iii. SpO_2 > 90%. Extubation failure is defined as: within 72 hours of extubation neonates developed: 1. Apnoea > 4 times in 24 hours; 2. Unable to maintain SpO_2 within 85%–95%; 3. PaO_2 < 50 mm Hg or $PaCo_2$ > 60 mm Hg. Ventilation delivered via appropriate size short bi-nasal prongs Both groups received pulmonary surfactant (Poractant alfa; Curosurf) 200 mg/kg via intubation and maintained on mechanical ventilation mode of A/C or SIMV +PSV.
Outcomes	**Primary outcomes** 1. Successful extubation within 72 hours; 2. Reasons for extubation failure. **Secondary outcomes** 1. Duration of non-invasive respiratory support; 2. Total mechanical ventilation length; 3. Pneumothorax;

Lou 2017 *(Continued)*

4. BPD;
5. NEC;
6. IVH > Grade III;
7. Death.

Notes	**Study conducted in**: an upper-middle-income country (China) **Disclosures:** No information provided **Funding:** "Xinxiang Science and Technology Research Project (CXGG16052)"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table used
Allocation concealment (selection bias)	Unclear risk	Informed consent obtained. Timing not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	Groups similar at baseline

Lou 2018

Study characteristics

Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between June 2016 and May 2017
Participants	65 preterm infants (initial treatment of respiratory distress) randomised to:

Lou 2018 *(Continued)*

	Inclusion criteria 1. Gestational age 28–35 weeks; 2. RDS requiring respiratory support; 3. Informed consent was obtained from a guardian. **Exclusion criteria** 1. Major life-threatening congenital malformations; 2. Heart failure.
Interventions	Preterm infants were randomised to: 1. **nHFOV (n = 33):** nHFOV delivered via SLE baby 5000, Germany; with inial settings as follows: a. MAP: 6–12 cm H_2O; b. Frequency: 6 –12 Hz; c. Amplitute: 2–3 times MAP; d. FiO_2: 0.30–0.40 to maintain a target SpO_2 of 90% to 95%. 2. **BP-CPAP (n = 32):** nIPPV delivered via Fabian, Swiss with the parameters set as follows: a. PIP: range 12–15 cm H_2O; b. PEEP: 5 cm H_2O; c. Inspiratory time of 0.5 sec; d. Respiratory rate: 30 –40 times/minute; e. FiO_2: 0.30–0.40 to maintain a target SpO_2 of 90% to 95%. Ventilation delivered via appropriate size short bi-nasal prongs Surfactant (Poractant alfa; Curosurf) was administered via InSurE method to certain criteria.
Outcomes	**Primary outcomes** 1. PaO_2, $PaCO_2$ and (OI before and 1, 12, 24, 48, and 72 hours after non-invasive respiratory support. **Secondary outcomes** 1. Rate of respiratory support within 72 hours; 2. Rate of intubation; 3. Duration of non-invasive ventilation; 4. Duration of O_2 supplementation; 5. Pneumothorax; 6. NEC; 7. IVH; 8. BPD; 9. PVL; 10. Mortality.
Notes	**Study conducted in**: an upper-middle-income country (China) **Disclosures:** "This article has no conflict of interest." **Funding:** "Xinxiang City Science and Technology Research Project (CXGG16052)."

Risk of bias

Bias	Authors' judgement	Support for judgement

Lou 2018 *(Continued)*

Random sequence generation (selection bias)	Low risk	Random number table method
Allocation concealment (selection bias)	Unclear risk	Informed parental consent obtained. Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	Groups similar at baseline

Malakian 2020

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: Iran **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: from 5 June 2016 to 20 November 2016
Participants	124 preterm infants as initial treatment for respiratory distress **Inclusion criteria** 1. GA at birth between 28 and 34 weeks; 2. Birthweight between 1000 and 2000 grams; 3. Respiratory distress and a Silverman–Anderson retraction score of 6 or 7. **Exclusion criteria** 1. Significant morbidity (apart from RDS) including cardiac disease, congenital malformations, upper airway anomalies, suspected metabolic disorders, severe cardiovascular instability, and babies who had: a. severe asphyxia (Apgar score 3 at 1 and 5 min); b. IVH on admission.
Interventions	Infants were randomised to:

Malakian 2020 *(Continued)*

	1. **nHFOV for initial treatment of respiratory distress (n = 63):** nHFOV delivered via flow-driver combined with nasal high frequency oscillatory ventilation (CNO NCPAP driver with NHFOV, Medin Medical Innovations, Germany) with inial settings as follows: a. FiO_2 0.4–0.6; b. Pmean 8 cm H_2O; c. Frequency 5 Hz; d. Amplitude 3–7 cm H_2O. 2. **nCPAP for initial treatment of respiratory distress (n = 61):** nCPAP delivered via a flow-driver (Sindi NCPAP driver, Medin Medical Innovations, Germany). The settings were: a. PEEP 4 –8 cm H_2O; b. FiO_2 0.4–0.6. Ventilation delivered via appropriate size binasal prongs as interface (CNO NCPAP driver with NHFOV, Medin Medical Innovations, Germany) for both groups
Outcomes	**Primary outcomes** 1. The need for intubation or meeting non-invasive ventilatory failure (pH 7.20 and $PaCO_2$ 60 mm Hg, PaO_2 50 mm Hg with FiO_2 of 0.6 or recurrent apnoea with 3 episodes per hour associated with bradycardia, or a single episode of apnoea that required bag-and-mask ventilation) within the first 72 hours of life. **Secondary outcomes** 1. Duration of respiratory support; 2. Duration of oxygen with hood; 3. Duration of hospitalisation; 4. Time to full spoon-feeds; 5. Air leaks; 6. IVH: grade III and IV; 7. BPD; 8. Tauma of nasal skin and mucosa; 9. Feed intolerance included pre-feed gastric aspirates > 30% of feed volume for volumes > 6 mL, and abdominal distention.
Notes	**Study conducted in**: an upper-middle-income country (Iran) **Disclosures/funding:** "This paper is part of a thesis of Neonatology subspecialty degree (project code: NRC-9418). All expenses of this study were provided by research vice-chancellor of Ahvaz Jundishapur University of Medical Sciences. All authors affirm that there are no conflicts of interest. The corresponding author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned (and registered with) have been explained. The reporting of this work is compliant with CONSORT guidelines."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A (quote): "Random numbers. First, 6 modes were considered, including AABB, ABAB, ABBA, BABA, BAAB, BBAA. Each mode was given a code between 1 and 6. We randomly select number between 1 and 6 to create a random sequence. A was considered for NHFOV and B for NCPAP."
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described

Malakian 2020 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded study. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Non-blinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited newborns completed the study.
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	The study was registered retrospectively at Registry of Clinical Trials https://www.irct.ir/ (IRCT; Identifier: IRCT2016111930964N1) on 30 December 2016 after completing recruitment (trial conducted between 5 June 2016 to 20 November 2016).
Other bias	Low risk	• The care of infants before and during the trial was standardised (e.g. open oro-gastric tube etc.). • The study set standard criteria for surfactant administration via InSurE. • Groups similar at baseline. Achieved prespecified sample size

Menshykova 2015

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: Ukraine **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: dates not reported
Participants	24 preterm infants with planned extubation **Inclusion criteria** 1. Gestation ≤ 32 weeks; 2. Birth between ≤ 1500 grams; 3. Diagnosed with respiratory distress; 4. Treated with mechanical ventilation and extubated before day 7. **Exclusion criteria** 1. None reported.
Interventions	Infants were extubated at pre-defined criteria (FiO_2 < 35%; PIP < 20 and PEEP < 5 cm H_2O; rate < 30 breath per min; $PaCO_2$ < 60 mm Hg) and randomised to:

Menshykova 2015 *(Continued)*

1. **nHFOV for extubation (n = 12):** nHFOV delivered via CNO driver, Medin Medical Innovations, Germany with initial settings as follows:
   a. Pmean 6 –8 cm H_2O;
   b. Frequency 10 Hz;
   c. The amplitude appropriate for visible chest oscillation;
   d. Inspiration time of 33%;
   e. FiO_2: appropriate to maintain a target SpO_2 of 90%–95%.
2. **nIPPV for extubation (n = 12):** nIPPV delivered via Servo-I (Maquet Medical Systems, Wayne, NJ) and Leoni-2 (Heinen-Lowenstein, Germany). The settings were:
   a. PEEP 4 –8 cm H_2O;
   b. PIP 2 –4 cm H_2O above the PEEP;
   c. Rate 15– 25 breaths per min;
   d. FiO_2: appropriate to maintain a target SpO_2 of 90%–95%.

Ventilation delivered via appropriate size long or short binasal prongs or masks as interface for both groups

Outcomes

Primary outcomes

1. The need for intubation within the first 72 hours of life.

Secondary outcomes

1. BPD;
2. Mortality;
3. Duration of MV;
4. Duration of oxygen therapy;
5. Length of stay;
6. Neonatal morbidities.

Notes

Study conducted in: a lower-middle income country (Ukraine)

Disclosures: no statements found

Funding: no statements found

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not reported
Allocation concealment (selection bias)	Low risk	Randomisation was performed using non-transparent envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Pilot open randomised trial. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Pilot open randomised trial
Incomplete outcome data (attrition bias)	Unclear risk	Losses not reported

Menshykova 2015 *(Continued)*

All outcomes

Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Unclear risk	No sample size calculation reported. Some baseline differences between groups in severity of respiratory distress syndrome (RDS) stage

Mukerji 2017

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: Canada **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between July 2013 and 2015
Participants	26 preterm infants failing nCPAP treatment **Inclusion criteria** 1. Birthweight < 1250 g; 2. Current weight < 2000 g; 3. Age > 72 hours old; 4. Supported by CPAP; 5. Met any of the pre-defined CPAP failure criteria: a. Respiratory acidosis with pH between 7.21 and 7.25; b. Increase in spells including apnoeas, bradycardias or desaturations despite an optimised caffeine-citrate dose of 5 mg/kg; c. Increased work of breathing (intercostal recession and accessory muscle use) with respiratory rate > 75 breaths/minute. Increase in spells were defined as > 2 spells/hour for 3 hours, > 3 spells/hour for 2 hours, or > 4 spells/hour for 1 hour over a preceding 6-hour baseline. The spells were defined as those which required some form of intervention by the bedside nurse (such as increase in supplemental oxygen or provision of stimulation), rather than any set numerical cut-offs. There was no minimum CPAP pressure level required before confirming CPAP failure, but NICU guideline for maximum CPAP pressure was 8 cm H_2O. CPAP was delivered with the use of an Infant-Flow device (SiPAP, Carefusion, USA) using nasal masks or short bi-nasal prongs. **Exclusion criteria** 1. Congenital/acquired abnormality of upper airways; 2. Severe congenital anomalies; 3. Severe nasal excoriation/injury preventing use of NIV interface.
Interventions	Following failure of nCPAP (based on specific predefined criteria above) infants were randomised to: 1. **nHFOV following nCPAP failure (n = 17):** nHFOV delivered via VN500 ventilator (Drager, Lubeck, Germany) with the following settings: a. Frequency 5–14 Hz; b. Amplitude was set to achieve palpable/visible chest vibrations;

Mukerji 2017 *(Continued)*

c. MAP 8–10 cm H_2O. Adjustments to the MAP were as per predefined guidelines based on FiO_2 requirement.

2. **Biphasic nCPAP (BP-nCPAP) following nCPAP failure (n = 23):** BP-CPAP delivered via Infant-Flow device (SiPAP, Carefusion, USA) with the following settings:
   a. Lower PEEP 5 (range 7–10) cm H_2O;
   b. Higher PEEP level of 8 (range 7–10) cm H_2O (1 s/cycle);
   c. Cycle rate of 20 (max 30) per min;
   d. Adjustments to the BP-CPAP were as per predefined guidelines based on FiO_2 requirement. Further adjustments based on work of breathing were as per the medical team.

Both modes were delivered via short binasal prongs or nasal masks using sizes as per manufacturer (Fisher-Paykel, Auckland, NZ). Cross-over was not allowed during the trial.

Outcomes

Primary outcomes

1. Failure of nHFOV or BP-CPAP within 72 hours.

Secondary outcomes

1. Intubation rates at 72 hours and 7 days post randomisation;
2. Comparison of the number of apnoeic spells within 7 days;
3. $PaCO_2$ levels at time of initiation;
4. Total number of days on endotracheal mechanical ventilation;
5. Rates of adverse outcomes between the 2 groups;
6. Time to discharge from hospital;
7. $PaCO_2$ 1 hour post NIV mode;
8. Time to re-intubation within 7 days;
9. Rates of IVH;
10. Rates of BPD.

Notes

Study conducted in: a high-income country (Canada)

Disclosures/funding: "The authors declare no conflict of interest. Sources of funding/grants from Sandra Schmirler Foundation."

Note: we considered biphasic (BP) nCPAP (BiBAP/BP-nCPAP) to be an equivalent strategy to nIPPV.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated random-numbers list devised by an independent statistician
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed opaque envelopes containing a card indicating arm of randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither bedside clinicians nor study investigators were blinded to the intervention.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Neither bedside clinicians nor study investigators were blinded to the intervention. Different modes and settings of ventilation

Mukerji 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	1 infant excluded post allocation from nHFOV group by medical team
Incomplete long term outcome data (attrition bias)	Low risk	No losses reported
Selective reporting (reporting bias)	Unclear risk	The study was registered retrospectively at https://www.clinicaltrials.gov (ClinicalTrials.gov; Identifier: NCT02051491) on 16 January 2015 after completing recruitment (trial conducted between July 2013 and 2015).
Other bias	Low risk	• The care of infants before and during the trial was standardised (e.g. open oro-gastric tube etc.). • The study set standard criteria for rescue non-invasive respiratory support failure, failure of intervention, escalation or de-escalation of treatment, weaning of treatment etc. • Two different ventilators were used for the intervention and control: nHFOV delivered via VN500 ventilator (Drager, Lubeck, Germany) and bi-level pressure continuous positive airway pressure (BP-CPAP) delivered via Infant-Flow device (SiPAP, Carefusion, USA). • Groups similar at baseline. Study prematurely stopped due to low enrolment rate. Enroled 40 of planned 60

Oktem 2021

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: Turkey **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: from December 2015 and February 2017
Participants	76 preterm infants as initial treatment for respiratory distress **Inclusion criteria** 1. GA at birth < 32 weeks; 2. Diagnosed with respiratory distress syndrome. **Exclusion criteria** 1. Required mechanical ventilation at birth; 2. Infants with congenital malformations or inherited metabolic diseases.
Interventions	Infants on nCPAP at admission to NICU were randomised to: 1. **nHFOV for initial treatment (n = 17):** nHFOV delivered via high-frequency oscillation ventilator (Drager Babylog 8000; Lübeck, Germany), through short binasal prongs used as an interface (Optiflow Junior 2 nasal cannula). The inial settings as follows: a. Pmean 6 cm H_2O; b. Frequency 10 Hz; c. Delta P 100%;

Oktem 2021 *(Continued)*

2. **nCPAP for initial treatment (n = 20):** nCPAP delivered via a CPAP system (Fisher & Paykel Healthcare, Auckland, New Zealand) through short binasal prongs used as an interface (Optiflow Junior 2 nasal cannula). The settings were:
   a. PEEP 5–6 cm H_2O;
3. **nIPPV for initial treatment (n = 20):** nIPPV delivered via conventional ventilator device (Drager Babylog 8000; Lübeck, Germany), through short binasal prongs used as an interface (Optiflow Junior 2 nasal cannula). The settings were:
   a. PEEP 5–6 cm H_2O;
   b. peak inspiratory pressure: 15 –20 cm H_2O;
   c. Inspiratory time 0.4–0.5 s;
   d. Respiratory rate 25–30 breaths/min;
4. **HFNC for initial treatment (n = 20):** Heated humidified high-flow nasal cannula (HFNC) a precision flow device (Precision Flow, Vapotherm, Inc, Exeter, NH, USA), applied through the small bore cannula in the Vapothermas, an interface. The initial parameters were:
   a. Flow: 5 L/min;
   b. Temperature: 37 °C.

The fraction of inspired oxygen (FiO_2) was set in all the arms with the target pulse oximeter 90%–95%.

Outcomes

Primary outcomes

1. The need for intubation during non-invasive ventilation support.

Secondary outcomes

1. Duration of non-invasive ventilation (days);
2. Air leak syndrome;
3. Abdominal distension;
4. Intraventricular haemorrhage;
5. NEC;
6. Nasal injury;
7. Increased secretions;
8. Agitation measured by N-PASS;
9. Mortality rate.

Notes

Study conducted in: an upper-middle-income country (Turkey)

Disclosures: no statements provided

Funding: no statements provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not reported
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different modes and settings of ventilation
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported

Oktem 2021 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All allocated infants reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	Groups similar at baseline. Achieved prespecified sample size

Seth 2021

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: India **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between from July 2019 to September 2020
Participants	42 preterm infants with planned extubation **Inclusion criteria** 1. Gestational age 26–36 + 6 weeks; 2. With respiratory distress; 3. Presenting within 15 days of life; 4. Requiring invasive ventilatory support for at least 12 hours. **Exclusion criteria** 1. Major congenital malformation; 2. Known/suspected chromosomal anomalies; 3. Upper airway anomalies; 4. Severe perinatal asphyxia; 5. Born outside the study centre.
Interventions	Following extubation (based on specific predefined criteria), infants were randomised to: 1. **nHFOV for extubation (n = 43):** nHFOV delivered via SLE 6000 ventilator (Surrey, UK) with the following initial settings: a. Frequency 10–12 Hz; b. I:E ratio 1:1; c. Amplitude 25–35 cm H_2O (titrated based on visible chest oscillations and PCO_2); d. Pmean 8 –10 cm H_2O (titrated on oxygenation). 2. **nIPPV for extubation (n = 43):** nIPPV delivered via Dragger Babylog 8000 plus ventilator (Lübeck, Germany) with the following initial settings: a. PIP 2 cm H_2O above the pre-extubation set PIP on mechanical ventilation;

Seth 2021 *(Continued)*

b. PEEP 4–6 cm H_2O or identical to PEEP during mechanical ventilation;
c. Ti 0.30–0.45 s;
d. Pmean 8–10 cm H^2O;
e. RR 40–50 breaths/min;
f. Flow 8–10 L/min.

The study had specified criteria for weaning, discontinuation, up gradation and failure of the intervention/control.

Both modes were delivered via Fisher Paykel FlexiTrunkTM interface using sizes as per manufacturer (Fisher-Paykel, Auckland, NZ). Cycling of prongs and masks was done every 4 h. Chin straps were not used. The FiO_2 adjusted to maintain SpO_2 between 90% and 95%

Outcomes

Primary outcomes

1. Extubation failure within 72 hours

Secondary outcomes

1. Reintubation rate;
2. Invasive ventilator-free days;
3. SpO_2/FiO_2 ratio;
4. Composite duration of oxygen supplementation/ventilation support;
5. PCO_2 and pH 12 hours post intervention;
6. IVH (above grade 3);
7. Composite BPD/mortality;
8. Rate of feeding intolerance;
9. Time taken to full enteral feeds;
10. Pulmonary air leaks.

Notes

Study conducted in: a lower-middle-income country (India)

Disclosures: "The authors declare no competing interests."

Funding: no information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done by computer-generated random sequence number (Research Randomiser version 4.0); stratified by gestational age (26–31 + 6weeks and 32–36 + 6 weeks) with allocation ratio of 1:1.
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed, opaque envelopes completed by a person not involved in the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	The infants and personnel could not be blinded due to the nature of intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessor was blinded.
Incomplete outcome data (attrition bias)	Low risk	All allocated infants reported

Seth 2021 *(Continued)*

All outcomes		
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Low risk	The study was registered at the Clinical trial registry of India https://www.ctri.nic.in (Identifier: CTRI/2019/07/020055) on 5 July 2019 (trial conducted between July 2019 and September 2020).
Other bias	Low risk	Groups similar at baseline. Achieved prespecified sample size

Wang 2020

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: from February 2018 to October 2019
Participants	80 neonates with neonatal respiratory distress syndrome **Inclusion criteria** 1. Meeting criteria for neonatal respiratory distress syndrome; 2. Able to cooperate with this study; 3. No drop off. **Exclusion criteria** 1. Meconium aspiration; 2. Other infection; 3. Death within one day of hospitalisation; 4. Congenital anomalies; 5. Does not meet criteria for mechanical ventilation.
Interventions	Infants while intubated were given 200 mg/kg of surfactant prior to starting mechanical ventilation, and once they met extubation criteria, they were randomly divided into 2 groups: **Non-invasive high frequency oscillatory ventilation (nHFOV) (n = 40)** 1. Amplitude 2.5–3 times the value for MAP; 2. MAP 2–4 cm H_2O higher than MAP prior to extubation; 3. Frequency 6–1 2 Hz; 4. FiO_2 5%–10% more than prior to extubation; 5. Criteria for stopping nHFOV: (switch to oxygen or high flow nasal cannula): a. MAP < 6 cm H_2O; b. FiO_2 < 0.3; c. SpO_2 > 90%. **Continuous positive airway pressure ventilation (CPAP) (n = 40)**

Wang 2020 *(Continued)*

1. FiO_2 0.3–0.4 cm H_2O;
2. PEEP 4–6 cm H_2O;
3. Flow 8–10 L/min;
4. Criteria for stopping CPAP:
   a. $FiO_2 < 0.3$;
   b. PEEP < 2 cm H_2O;
   c. $SpO_2 > 90\%$.

Outcomes	Compared in both groups 1. Ventilation time; 2. Success rate from weaning ventilation mode; 3. Other complications (pneumothorax, BPD, IVH); 4. Oxygenation indexes.
Notes	**Study conducted in**: an upper-middle-income country (China) **Disclosures**: no information provided **Funding**: no information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly divided
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	Reported that groups were similar at baseline

Wang 2023

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: from January 2020 to November 2022
Participants	43 neonates with neonatal respiratory distress syndrome **Inclusion criteria** 1. Meeting specific criteria for neonatal respiratory distress syndrome: a. Presents with breathing problems at birth that progressively worsen, flaring nostrils, rapid breathing, grunting sounds when breathing, and chest retractions and cyanosis; b. RDS based on chest x-ray, with grade I and II RDS classified as mild, and grades III and IV RDS classified as severe; c. Arterial oxygen partial pressure/fraction of inspiration O_2 (PaO_2/FiO_2) ratio of < 300 (PaO_2 < 60 mm Hg); 2. Born before 36 weeks of gestation; 3. Required respiratory support and received 1 dose of surfactant regardless of exposure to antenatal corticosteroids. **Exclusion criteria** 1. Infection from 6 hours to 3 days (defined as white blood cells ≥ 30 x 10^9; C-reactive protein ≥ 3 mg/L within 6 hours, or C-reactive protein ≥ 5 mg/L within 6–12 hours); 2. Anaemia (neonatal venous blood ≤ 130 g/L within 2 weeks); 3. Dyspnoea caused by pulmonary haemorrhage; 4. Congenital malformations, including PDA (ductus arteriosus was still not closed 72 hours after birth by bedside ultrasound examination, and the left-to-right shunt flow was more than 50%); 5. Heart failure; 6. Unsmooth crying and heart rate < 100 beats/minute, initial resuscitation management was given, and T-Piece positive pressure ventilation.
Interventions	Infants, while on NIV, were given 200 mg/kg of surfactant (Poractant Alfa) via thin catheter prior to being randomly divided into 2 groups: **Non-invasive high frequency oscillatory ventilation (nHFOV) (n = 22)** 1. NHFV ventilator (SLEbaby 5000; SLE Limited, South Croydon Surrey, UK); 2. Amplitude 2–3 times the value for MAP; 3. MAP 6 –12 cm H_2O; 4. Frequency 6–12 Hz; 5. FiO_2 0.30 –0.40; 6. Criteria for stopping nHFOV: (switch to nasal cannula oxygen therapy if required) a. MAP < 6 cm H_2O; b. FiO_2 < 0.3; c. SpO_2 > 90%. **Duo positive airway pressure (DuoPAP; Bilevel positive airway pressure) (n = 21)** 1. Using DuoPAP (ACUTRONIC Medical Systems AG, Hirzel, Zurich, Switzerland); 2. FiO_2 0.3–0.4 cm H_2O;

Wang 2023 *(Continued)*

3. PEEP 5 cm H_2O;
4. PIP 12–15 cm H_2O;
5. Inspiratory time 0.5 sec;
6. Respiratory rate 30–40 breaths/minute;
7. Criteria for stopping DuoPAP:
   a. $FiO_2 < 0.3$;
   b. PEEP ≤ 3 cm H_2O;
   c. PIP ≤ 5 cm H_2O without respiratory distress;
   d. $SpO_2 > 90\%$;
   e. No abnormalities on blood gas analysis.

The nasal interface was not specified for both groups.

Outcomes	**Primary outcomes** 1. PaO_2; 2. $PaCO_2$; 3. OI at 12 and 24 hours after the start of NIV. **Secondary outcomes** 1. The incidences of IVH, PVL, NEC, BPD, and apnoea during the first 72 hours; 2. Duration of NIV; 3. Duration of nasal cannula oxygen therapy; 4. Length of hospital stay; 5. Time to full feeding.
Notes	Study conducted in: an upper-middle-income country (China) **Funding/disclosures:** the manuscript stated, "The authors have no funding and conflicts of interest to disclose".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A (quote:) “random number table randomization” was used.
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The (quote:) "assessment results were blinded to the assessor".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited newborns completed the study.

Wang 2023 *(Continued)*

Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Low risk	This protocol has been registered on the National Medical Research Registration Platform of China (No. MR-34-21-010666).
Other bias	Low risk	Both groups similar at baseline

Xu 2020

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: from January 2017 to January 2020
Participants	60 neonates with neonatal respiratory distress syndrome **Inclusion criteria** 1. Diagnosed with respiratory distress syndrome based on chest x-ray; 2. Neonate needing mechanical ventilation for respiratory distress within 12 hours of life; 3. Parental consent. **Exclusion criteria** 1. Congenital anomalies of the airways or congenital heart disease; 2. Other cause for respiratory distress: wet lung, congenital pneumonia, meconium aspiration etc.; 3. Serious liver or kidney injury.
Interventions	Infants were divided into 2 groups. **Non-invasive positive pressure ventilation (NIPPV) and surfactant (n = 30)** 1. PIP 15–25 cm H_2O; 2. PEEP 4–6 cm H_2O; 3. itime 0.3–0.4 s; 4. FiO_2 21%–40%. **NHFOV and surfactant (n = 30)** • Amplitude 30–40 cm; • MAP 8–12 cm H_2O; • Inspired to expired time 50:50; • Frequency 10–15 Hz; • FiO_2 21%–40%. Surfactant of 200 mg/kg were given via InSurE technique for both groups.
Outcomes	**Outcomes**

Xu 2020 *(Continued)*

1. To compare the therapeutic effect of both groups, defined as:
   a. very effective: 12 hours post treatment, respiratory status stable, chest x-ray improvement with good expansion, SaO_2 > 89% with no other symptoms of respiratory distress;
   b. effective: 12 hours post treatment, SaO_2 > 85%–89%, some improvement in respiratory distress, lesser ground glass appearance on chest x-ray;
   c. Not effective: 12 hours post treatment, SaO_2 < 85%, no improvement in respiratory distress and no changes in chest x-ray appearance;
2. To compare MAP, PaO_2, PCO_2, FiO_2 and OI of both groups;
3. Other complications including pneumonia, pneumothorax and pulmonary haemorrhage.

Notes	**Study conducted in**: an upper-middle-income country (China) **Disclosures**: no information provided **Funding**: no information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Infants were selected and randomly divided into 2 groups.
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	Groups similar at baseline

Yang 2020

Study characteristics

Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre

Yang 2020 *(Continued)*

	Setting: tertiary neonatal intensive care unit **Study dates**: from January 2018 to December 2019
Participants	100 infants with neonatal respiratory distress syndrome were included in this study. **Inclusion criteria** 1. Combination of typical clinical symptoms, signs, and blood gases analysis and chest x-ray to meet NRDS clinical diagnostic criteria; 2. Needing mechanical ventilation within 12 hours of birth; 3. Parental consent. **Exclusion criteria** 1. Congenital disease or deformities; 2. Serious complications of the liver, heart, kidneys and other organs; 3. Other cause for respiratory distress: congenital pneumonia, wet lungs, congenital diaphragmatic hernia etc.
Interventions	Infants were divided into 2 groups 1. **nHFOV (n = 50)** (Medin CNO, Germany) with initial settings of • Frequency 7–10 Hz; • Amplitude 4–10; • MAP 5–10 cm H_2O; • FiO_2 21%–40%; • inspired time to expired time of 1:2. 2. **Conventional mechanical ventilation (n = 50)** (Drager Babylog VN 500, Germany) Commonly use AC/VG mode ventilation with initial settings of: a. Respirator rate 30–40 breaths/min; b. PIP 15–25 cm H_2O; c. PEEP 4–8 cm H_2O; d. FiO_2 21%–40%.
Outcomes	**Outcomes** 1. Treatment efficacy: a. very effective: resolution of all symptoms within 12 hours, improvement on chest x-ray, PaO_2 > 90%; b. effective: improvement in symptoms within 12 hours, improvement on chest x-ray, PaO_2 80% – 89%; c. not effective: no improvement or worsening in respiratory symptoms; d. total effectiveness = very effective + effective. 2. Arterial blood gas analysis indexes (PaO_2, $PaCo_2$, OI) before treatment and 12 hours after treatment; 3. Other complications such as pneumonia, pulmonary haemorrhage, pneumothorax and BPD.
Notes	**Study conducted in**: an upper-middle-income country (China) **Disclosures**: no statements provided **Funding**: no statements provided

Risk of bias

Bias	Authors' judgement	Support for judgement

Yang 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	Random number table method
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	Reported that groups were similar at baseline

Yang 2021

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: from April 2017 to October 2019
Participants	68 intubated preterm infants were included. Specific inclusion and exclusion criteria not reported
Interventions	Infants that were weaning from mechanical ventilation were randomised into 2 groups according to the odd and even number of admission date: 1. **High-frequency oscillatory ventilation (n = 34)** a. Frequency 10 Hz (range 8–12 Hz); b. MAP level prior to extubation + 2 cm H_2O (range 8–14 cm H_2O); c. Amplitude: visible chest wall oscillation (range 20–35 cm H_2O); d. FiO_2 range from 0.21–0.40. 2. **Nasal CPAP (n = 34)** a. PEEP 6 cm H_2O (range from 6–8 cm H_2O);

Yang 2021 *(Continued)*

b. FiO_2 range from 0.21–0.40.

Outcomes	**Outcomes** 1. The need for reintubation 1 week after extubation; 2. Duration of non-invasive ventilation; 3. Length of hospital stay; 4. IVH grade > II, NEC grade > II.
Notes	**Study conducted in**: an upper-middle-income country (China) **Disclosures**: no information provided **Funding**: no information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-random allocation using odd and even dates of admission
Allocation concealment (selection bias)	High risk	Allocation sequence predictable
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	Reported that groups were similar at baseline

Yuan 2021

Study characteristics

Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit

Yuan 2021 *(Continued)*

	Study dates: from January 2016 to June 2019
Participants	240 preterm infants (120: < 32 weeks and 120: 32–36 + 6 weeks gestation) after intubation and surfactant: **Inclusion criteria** 1. GA at birth < 37 weeks; 2. Diagnosed with respiratory distress syndrome based on chest X-ray and by an experienced physician. **Exclusion criteria** 1. Congenital heart disease; 2. Genetic disorders; 3. Other respiratory diseases; 4. Failure of important organs; 5. Congenital disabilities; 6. Surgery immediately after birth; 7. Allergic to drugs adopted in the study; 8. Lack of parental consent.
Interventions	Infants after intubation and surfactant were randomised to: 1. **nHFOV for extubation (n = 80):** nHFOV delivered via Löwenstein Leoni plus ventilator. The inial settings were as follows: a. MAP 8 (range 6–12) cm H_2O; b. Amplitude 2–3 times the mean airway pressure with visible oscillation in neck and thorax; c. Frequency 6–12 Hz. 2. **nCPAP for extubation (n = 80):** nCPAP delivered via a CPAP system (F.STEPHAN GmbH Medizintechnik). The settings were: a. PEEP 4 –6 cm H_2O. 3. **nIPPV for extubation (n = 80):** nIPPV delivered via COMEN NV8 ventilator. The settings were: a. PEEP 5–6 cm H_2O; b. Peak inspiratory pressure: 10 cm H_2O; c. Inspiratory time 0.4–0.5 s; d. Respiratory rate 25–30 breaths/min. The study had specified criteria for weaning, adjustment and failure of the intervention/control. Nasal interface not reported. After surfactant application (through ETT) and extubation from invasive ventilation, non-invasive ventilation was started. The fraction of inspired oxygen (FiO_2) was set in all the arms with the target pulse oximeter rate of 90%–94%.
Outcomes	**Outcomes** 1. Blood gas parameters (PaO_2, $PaCO_2$, PaO_2/FiO_2 (P/F)) at specified time before and after surfactant administration; 2. Duration of oxygen therapy; 3. Duration of non-invasive ventilation; 4. Number of apnoea; 5. Requirement for repeat surfactant; 6. Episodes of intubation during study; 7. Total gastrointestinal feeding time; 8. Length of stay; 9. Hospitalisation costs;

Yuan 2021 *(Continued)*

	10.Complications (gas leakage, abdominal distension, NEC, intracranial haemorrhage, retinopathy of preterm infant, BPD, nasal injury).
Notes	**Study conducted in:** an upper-middle-income country (China) **Disclosures**: no information provided **Funding**: no information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified by gestational age (GA) as < 32 weeks and GA 32 to 36 + 6 weeks. Method of sequence generation not specified
Allocation concealment (selection bias)	Unclear risk	Not reported. Institutional ethical approval and informed parental consent were obtained.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Intervention not able to be blinded. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All allocated infants reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	Groups similar at baseline. No sample size calculation reported

Zhang 2021

Study characteristics

Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between September 2021 and March 2021
Participants	70 preterm infants **Inclusion criteria**

Zhang 2021 *(Continued)*

1. Infants born at 32–36 weeks;
2. Needing Invasive mechanical ventilation for more than 48 hours;
3. First extubation in the first 2 weeks of life;
4. Meeting extubation criteria:
   a. improvement in condition and baby is able to breathe by themselves;
   b. pulse oximetry 90%–95%, blood gases values within normal range;
   c. extubation ventilation settings: RR < 30 breaths/min, FiO_2 < 40%, MAP 6–8 cm H_2O.

Exclusion criteria

1. Upper airway abnormalities (severe nasal injuries, congenital tracheomalacia, choanal atresia);
2. Infant needing surgery prior to extubation (congenital diaphragmatic hernia, NEC, congenital heart disease etc.);
3. Grade IV IVH diagnosed prior to extubation;
4. Infants with genetic or metabolic disorders.

Interventions	Infants after extubation were randomised into:
	1. **nHFOV** (SLE5000) with initial settings of: (n = 35)
	   a. Frequency: 10 Hz (range 8–12 Hz);
	   b. MAP: with MAP level prior to extubation + 2 cm H_2O (range 8–14 cm H_2O);
	   c. Amplitude: depending on visible chest oscillation (range 20–35) cm H_2O;
	   d. FiO_2 (range 0.21–0.40).
	2. **nCPAP** (NV8) with initial settings of: (n = 35)
	   a. PEEP 5 cm H_2O (range 3–8 cm H_2O);
	   b. FiO_2 range 0.21–0.40.

Outcomes	**Primary outcome** 1. Rate of successful extubation within 72 hours; 2. Non-invasive respiratory ventilation support time. **Secondary outcomes** 1. Incidence of pneumothorax; 2. Incidence of BPD; 3. IVH.
Notes	**Study conducted in**: an upper-middle-income country (China) **Funding:** "Science and Technology Plan Project of Jianjin District, Chongqing (Y2018042)" **Disclosures:** no information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised digital table
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias)	High risk	Not reported. Different modes and settings of ventilation

Zhang 2021 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	Groups similar at baseline

Zhang 2022a

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between February 2019 to February 2021
Participants	102 infants were selected. **Inclusion criteria** 1. NRDS Grade III–IV; 2. 12 hours after birth, noted respiratory distress or apnaeic chest x-ray; 3. Gestational age 26–42 weeks; 4. Needing ventilatory support; 5. Parent consented for ventilatory support and then were given a choice between non-invasive continuous positive pressure or non-invasive high-frequency oscillatory ventilation. **Exclusion criteria** 1. Congenital pneumonia, wet lungs, meconium aspiration causing respiratory distress; 2. Infants with immunodeficiency, severe liver or kidney dysfunction; 3. Neonatal infection or gastrointestinal tract anomalies; 4. Infants with genetic disorders; 5. Contraindications for non-invasive ventilation.
Interventions	Infants meeting criteria were randomised into 1. **nHFOV (SLE5000) (n = 51) - the settings were:** a. MAP 8–12 cm H_2O; b. FiO_2 30%–40%; c. Frequency 7–12 Hz.

Zhang 2022a *(Continued)*

2. **CPAP (n = 51) - the settings were:**
   - PEEP 5–7 cm H_2O;
   - FiO_2 30%–40%.

Neonates for both groups were given surfactant 100 mg/kg via InSurE method prior to starting non-invasive ventilation.

Criteria for weaning non-invasive ventilation:

1. SpO_2 > 90%;
2. Not in respiratory distress;
3. FiO_2 < 30%;
4. PEEP < 3 cm H_20.

Outcomes	1. Treatment efficacy a. Very effective: stable respiratory status, respiratory rate of 40–45 breaths/min; b. Effective: mild respiratory distress, respiratory rate of 45–60 breaths/min; c. Not effective: did not meet the above criteria; d. Total effectiveness = very effective + effective/total infants 100%. 2. The improvement rate of respiratory distress a. respiratory rate 40–60 breaths/min; 3. Ventilation time and length of hospital stay; 4. $PaCO_2$ and PaO_2 were measured before treatment and 24 hours after treatment.
Notes	**Study conducted in:** an upper-middle-income country (China) **Disclosures**: no information provided **Funding:** no information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Infants were randomly divided into 2 groups. However, in the methods it was mentioned that (quote:) "Parents were given a choice for non-invasive continuous positive pressure or non-invasive high-frequency oscillatory ventilation".
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included

Zhang 2022a *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	Groups similar at baseline

Zhang 2022b

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between January 2020 and May 2021
Participants	41 newborns with PPHN: **Inclusion criteria** 1. Neonates diagnosed with PPHN; 2. Parental consent. **Exclusion criteria** 1. Other serious complications (i.e. diaphragmatic hernia, congenital tracheo-esophageal fistula, congenital heart disease); 2. Diagnosed with IVH Grade III–IV prior to extubation; 3. Infants with genetic or metabolic disorders; 4. Neonatal demise on admission.
Interventions	After extubation by invasive ventilation, infants were randomised into: **1. nIPPV (N = 22)** 1. FiO_2 25%–40%; 2. PIP 15–20cm H_2O; 3. PEEP 4–6 cm H_2O; 4. RR 25–50 breaths per min. **2. nHFOV (N = 19)** • FiO_2 25%–40%; • Frequency 6–12 Hz; • MAP 6–10 cm H_2O; • Amplitude: 2–3 times the MAP.
Outcomes	**Primary outcome** 1. To compare the $PaCo_2$ and PaO_2 of the 2 groups at 1, 6 and 24 hours post extubation. **Secondary outcome** 1. Extubation failure within 72 hours;

Zhang 2022b *(Continued)*

2. Pulmonary haemorrhage;
3. IVH;
4. Pneumothorax.

Notes	**Study conducted in**: an upper-middle-income country (China) **Funding**: Hui Zhou Science and Technology Plan Project (2020Y237) **Disclosures**: no information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Infants were randomly divided into 2 groups.
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	Groups similar at baseline

Zhenyu 2019

Study characteristics

Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between March 2015 to September 2018
Participants	42 children with NRDS who underwent invasive high-frequency oscillator ventilation were included in the trial.

Zhenyu 2019 *(Continued)*

	1. **Inclusion criteria** a. NRDS Grade II–III, within 12 hours after birth noted to be in respiratory distress; chest x-ray showed grade II-III NRDS changes; b. PaO_2 < 50 mm Hg, $PaCO_2$ > 45 mm Hg. 2. **Exclusion criteria** • Severe respiratory acidosis, $PaCO_2$ > 60 mm Hg; • Combined with pneumothorax, pulmonary haemorrhages, congenital heart disease, congenital anomalies of the gastrointestinal tract or respiratory tract. Neonates must meet extubation criteria: • MAP < 8 mm H_2O; • FiO_2 < 40%; • SpO_2 85%–95%.
Interventions	Neonates were divided into 2 groups after extubation: 1. **Nasal intermittent positive pressure ventilation (NIPPV) (n = 21)** a. RR 40 breaths/min; b. FiO_2 25%–40%; c. PIP 15–20 cm H_2O; d. PEEP 4–6 cm H_20. 2. **Non-invasive high frequency ventilation (NHFV) (n = 21)** a. MAP < 14 cm H_2O; b. Amplitude set at visible oscillation noted at neck and chest area; c. FiO_2 25%–40%. Neonates will be reintubated if they meet the following criteria: 1. 6 serious apnoeic events within 24 hours; 2. Needing IPPV resuscitation more than twice in 24 hours; 3. After NIPPV started, PaO_2 < 50 mm Hg, $PaCO_2$ > 60 mm Hg; 4. After nHFOV started, MAP > 12 cm H_2O or FiO_2 > 40%, $PaCO_2$ > 60 mm Hg.
Outcomes	1. Success rate of weaning; 2. Occurrence of apnoea; 3. The level of partial pressure of carbon dioxide ($PaCO_2$); 4. Incidence of complications.
Notes	**Study conducted in**: in an upper-middle-income country (China) **Disclosures**: no information provided **Funding**: no information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table method
Allocation concealment (selection bias)	Unclear risk	The family members of the children were informed and agreed to the treatment and signed the informed consent. Letter of intent, approved by the ethics committee. Unclear timing

Zhenyu 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Unclear risk	Baseline characteristics of groups not reported

Zhu 2017

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between May 2016 and March 2017
Participants	81 preterm infants after intubation and surfactant **Inclusion criteria** 1. GA between 28 and 34 weeks; 2. Moderate-to-severe RDS treated with surfactant. The diagnosis of moderate-severe RDS was based on arterial to alveolar PO_2 (a/A PO_2) ratio and Silverman score within the first hour of life (a/A PO_2 ratio > 0.30 or Silverman score > 6, or both). **Exclusion criteria** 1. Major congenital anomalies; 2. Severe RDS requiring early intubation.
Interventions	Infants after intubation and surfactant randomised to: 1. **nHFOV for extubation (n = 39)** nHFOV delivered via CNO, Medin, Germany via binasal prongs (Medin, Germany) with the following starting parameters: a. MAP 6 cm H_2O; b. Frequency of 10 Hz; c. Amplitude adjusted until infant's chest showed slight oscillations. 2. **nCPAP for extubation (n = 42):** nCPAP delivered via a bubble CPAP system (Fritz Stephan GmbH):

Zhu 2017 *(Continued)*

a. PEEP 6 cm H_2O.

After surfactant replacement (through InSurE) and extubation from invasive ventilation, non-invasive ventilation was started. All respiratory support was delivered using binasal prongs of appropriate size (Medin, Germany). The FiO_2 was set in all the arms with the target pulse oximeter rate of 90%–94%. If infants needed FiO_2 > 0.40 to maintain the target SpO_2, a repeat dose of surfactant was allowed at the discretion of the clinical care team.

To minimise gastric distention, an oro-gastric tube was placed and gas was periodically aspirated in both groups.

Outcomes	**Primary outcomes** 1. Endotracheal intubation and ventilation during the first 7 days after birth at set criteria of: a. severe respiratory acidosis ($PaCO_2$ > 60 mm Hg with pH < 7.20); b. severe apnoea and bradycardia (defined as recurrent apnoea with > 3 episodes per hour associated with heart rate < 100/min); c. single episode of apnoea that required bag and mask ventilation); d. hypoxia (FiO_2 > 0.5 with PaO_2 < 50 mmHg); e. severe respiratory distress; f. pulmonary haemorrhage. **Secondary outcomes** 1. Air leak syndrome; 2. IVH ≥ grade 2; 3. BPD; 4. Mortality.
Notes	**Study conducted in**: an upper-middle-income country (China) **Disclosures:** no statement provided **Funding:** Technological Innovation Projects of Chongqing Social Undertakings and People's Livelihood Guarante **Note**: same Clinicaltrials.gov identifier as Zhu 2021 study. Zhu 2017 reported as pilot study by Zhu 2021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias)	Low risk	5 infants (6%) discontinued study as transferred out of unit

Zhu 2017 *(Continued)*
All outcomes

Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	The study was registered retrospectively at https://www.clinicaltrials.gov (ClinicalTrials.gov; Identifier: NCT03099694) on 4 April 2017 after completing recruitment (trial conducted between May 2016 and March 2017).
Other bias	Low risk	The care of infants before and during the trial was standardised (e.g. gastric tube use etc.). The study set standard criteria for escalation or de-escalation of treatment, weaning of treatment, termination of study etc. Groups similar at baseline. No sample size calculation reported

Zhu 2021

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: multi-centre (18) **Setting**: tertiary neonatal intensive care units **Study dates**: between May 2016 and March 2017
Participants	340 preterm infants as initial treatment for respiratory distress **Inclusion criteria** 1. GA between 26 + 7 to 33 + 7 weeks; 2. Diagnosis of RDS and Silverman score > 5; 3. Signed informed parental consent obtained before delivery. **Exclusion criteria** 1. Intubated for resuscitation or for other reasons prior to randomisation; 2. Major congenital malformations or known complex congenital heart disease; 3. Pulmonary haemorrhage; 4. Cardiopulmonary arrest needing prolonged resuscitation; 5. Transferred out of the NICU before randomisation.
Interventions	Infants received a treatment mode of either: 1. **nHFOV as initial treatment of respiratory distress (n = 170):** nHFOV delivered via high-frequency ventilator (CNO, Medin, Germany or SLE5000, UK) via binasal prongs (Medin, Germany) with the following starting parameters: a. CNO, Medin, Germany: i. MAP 6 (range 6–10) cm H_2O; ii. Frequency of 8 (range 8–12) Hz; iii. Amplitude 7 (range 7–10). b. For the SLE5000: i. MAP 6 (range 6–10) cm H_2O; ii. Frequency of 8 (range 8–12) Hz;

Zhu 2021 *(Continued)*

iii. Inspiratory time 50% (1:1);
iv. Amplitude 20 (range 20–35) cm H_2O.

2. **nCPAP as initial treatment of respiratory distress (n = 170):** nCPAP delivered via CNO Medin, Germany, SLE5000, UK, or Carefusion, USA:
   a. PEEP 6 (range 6 –8) cm H_2O.

All respiratory support was delivered using binasal prongs of appropriate size. The fraction of inspired oxygen (FiO_2) was set in all the arms with the target pulse oximeter rate of 89% to 93% in infants < 30 weeks' GA and from 90% to 94% in infants ≥ 30 weeks' GA.

Surfactant was administered via the InSurE method if the FiO_2 requirement > 0.30 for GA ≤ 30 weeks or the FiO_2 requirement > 0.4 for GA > 30 weeks.

To minimise gastric distention, an oro-gastric tube was placed and gas was periodically aspirated in both groups. Pacifiers were used whenever possible to decrease air leaks from the mouth.

Outcomes

Primary outcomes

1. Need for invasive mechanical ventilation during the first 7 days after birth at set criteria of:
   a. severe respiratory acidosis ($PaCO_2$ > 65 mm Hg with pH < 7.20);
   b. severe apnoea and bradycardia (defined as recurrent apnoea with > 3 episodes per hour associated with heart rate < 100/min);
   c. single episode of apnoea that required bag and mask ventilation);
   d. hypoxia (FiO_2 > 0.5 with PaO_2 < 50 mm Hg);
   e. severe respiratory distress;
   f. pulmonary haemorrhage;
   g. cardiopulmonary arrest needing chest compressions.

Secondary outcomes

1. Days of hospitalisation;
2. Duration of NIV;
3. Days on supplemental oxygen;
4. Predischarge mortality;
5. The need for surfactant;
6. The need for caffeine;
7. Rate of ROP > stage II;
8. Rate of BPD;
9. Rate of air leaks;
10. Rate of intraventricular haemorrhage (IVH) ≥ grade 3;
11. NEC ≥ stage II;
12. Thick secretions;
13. The Bayley Scales of Infant Development at 18–24 months of corrected age (when available).

Notes

Disclosures: none of the authors have declared conflicts of interest in participating in this trial. Medin Medical Innovations GmbH and SLE Limited are industries producing neonatal ventilators. These companies were not involved at all in the study and didll not have any role in the conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, approval of the manuscript; or decision to submit it for publication.

Funding: "the trial was initiated and planned by the researchers and funded by the Scientific Research Projects unit of Chongqing (Project-cstc2016shms-ztzx13001). Only this public funding will be used for the study, teleconferences, international panel meeting, and for publication costs. This is a [non-promoted] study, and investigators did not receive and will not receive any fee from any industry. In no way, industry or commercially interested subjects will have access to the data before their publication. The study has not received any grant or support from any commercial company/organization. The study only received public funding from the Chongqing Government."

Zhu 2021 *(Continued)*

Note: same Clinicaltrials.gov identifier as Zhu 2017 study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence with variable block sizes was used. Infants born from multiple gestations were assigned by individual randomisation.
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed opaque envelopes in each site after verification of eligibility
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	38 (11%) excluded as consent withdrawn
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Low risk	The study was registered at https://www.clinicaltrials.gov (ClinicalTrials.gov; Identifier: NCT03099694) on 4 April 2017 (trial conducted between July 2017 and June 2018).
Other bias	Low risk	The care of infants before and during the trial was standardised (e.g. gastric tube use etc.). The study set standard criteria for escalation or de-escalation of treatment, weaning of treatment, termination of study etc. Groups similar at baseline. Exceeded prespecified sample size

Zhu 2022

Study characteristics

Methods	**Design**: parallel randomised controlled trial **Country**: China **Single site/multiple sites**: multi-centre (69) **Setting**: tertiary neonatal intensive care units **Study dates**: from December 2017 and May 2021
Participants	1493 preterm infants with planned extubation **Inclusion criteria** 1. GA between 25 + 0 and 32 + 6 weeks;

Zhu 2022 *(Continued)*

2. Assisted with any type of endotracheal ventilation;
3. Post conceptional age < 36 weeks;
4. Ready to be extubated for the first time (extubation readiness required meeting specific criteria).

Exclusion criteria

1. Neonates who never needed intubation and IMV;
2. Neonates who were randomised but not extubated within 1 hr;
3. Major congenital anomalies or chromosomal abnormalities;
4. Neuromuscular diseases;
5. Upper respiratory tract abnormalities;
6. Need for surgery known before the first extubation;
7. Grade IV IVH occurring before the first extubation;
8. Birthweight < 600 g;
9. Suspected congenital lung diseases (such as genetic anomalies of surfactant metabolism) or malformations (such as cystic adenomatous malformations, sequestration, diaphragmatic hernia) or pulmonary hypoplasia.

Interventions	Infants were randomised to: 1. **nHFOV for extubation (n = 497):** nHFOV delivered by a high-frequency ventilator using piston/membrane and able to provide an active expiratory phase (that is, Acutronic FABIAN-III, SLE 5000, Loweinstein Med LEONI+, Sensormedics 3100A). Other ventilators providing high frequency ventilation using other technologies were not used. The initial settings were as follows: a. MAP 5–16 cm H_2O; b. Amplitude titrated according to $PaCO_2$; c. Frequency 8–15 Hz. 2. **nCPAP for extubation (n = 501):** nCPAP delivered via a CPAP system (either variable flow or continuous flow devices). The settings were: a. PEEP 5–8 cm H_2O. 3. **nIPPV for extubation (n = 495):** nIPPV delivered via any type of neonatal ventilator able to generate enough pressure according to the protocol. The settings were: a. PEEP 5–8 cm H_2O; b. PIP: 10–25 cm H_2O; c. Inspiratory time 0.4–0.5 s; d. Respiratory rate 30–50 breaths/min. The study had specified criteria for weaning, adjustment and failure of the intervention/control. Interface short binasal prongs. After extubation from invasive ventilation, non-invasive ventilation was started. The fraction of inspired oxygen (FiO_2) was set in all the arms with the target pulse oximeter rate of 90%–95%.
Outcomes	**Primary outcomes** 1. Duration of IMV (days) from the randomisation; 2. Ventilator-free days; 3. The number of reintubations (at specific criteria). **Secondary outcomes** 1. Air leaks (pneumothorax and/or pneumomediastinum) occurring after extubation; 2. BPD, defined according to the NICHD definition; 3. Haemodynamically significant PDA, defined according to local NICU protocols; 4. ROP > 2nd stage; 5. NEC ≥ 2nd stage; 6. IVH > 2nd grade;

Zhu 2022 *(Continued)*

7. Need for postnatal steroids;
8. In-hospital mortality;
9. Composite mortality/BPD;
10. Weekly weight gain (in grams/d) for the first 4 weeks of life or until NICU discharge, whichever comes first.

Notes	**Study conducted in**: an upper-middle-income country (China) **Disclosures:** "Declaration of Interest: Daniele De Luca has received research support, travel grants and/or consultancy fees from Vyaire, Philips and Getinge independently of this study. These companies produce neonatal ventilators. They were in no way involved in the study and played no part in its conduct: collection, management, analysis, and interpretation of the data; preparation, review, approval of the manuscript or decision to submit it for publication. Xingwang Zhu, Hongbo Qi, ZhIchun Feng and Yuan Shi have nothing to disclose." **Funding:** "Scientific Research Projects unit of Chongqing (Grant n. Projectcstc2016shms-ztzx13001)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised in a 1:1:1 ratio by simple randomisation using a computer-generated random number table. Twins were to be allocated to the same treatment group. Cross-over was not permitted.
Allocation concealment (selection bias)	Low risk	Randomisation was performed on a secured website and accessed when extubation was imminent.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of caregivers was impossible and blinding of the patients made no sense. Different modes and settings of ventilation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes' assessors and investigators performing the final statistical analyses were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	53 (4%) infants did not complete study because their parents/guardians withdrew consent.
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Low risk	The study was registered at https://www.clinicaltrials.gov (ClinicalTrials.gov; Identifier: NCT03181958) on 9 June 2017 (trial conducted between December 2017 and May 2021)
Other bias	Low risk	The care of infants before and during the trial was standardised (e.g. gastric tube use, sedation with sucrose etc.). The study set standard criteria for escalation or de-escalation of treatment, weaning of treatment, termination of study etc. Groups similar at baseline. Achieved prespecified sample size

Zou 2020

Study characteristics	
Methods	**Design**: randomised controlled trial **Country**: China **Single site/multiple sites**: single-centre **Setting**: tertiary neonatal intensive care unit **Study dates**: between June 2017 and June 2019
Participants	120 very low birthweight/extremely low birthweight infants were included in this study: **Inclusion criteria** 1. Infants born < 31 weeks; 2. Birthweight < 1500 g; 3. Meeting criteria for diagnosis of RDS. **Exclusion criteria** 1. Severe respiratory distress needing invasive mechanical ventilation; 2. IVH; 3. Congenital heart disease; 4. Lung malformations; 5. Other congenital anomalies.
Interventions	Infants were divided into 2 groups: 1. **Non-invasive positive pressure ventilation (NIPPV) and surfactant (n = 60);** 2. **nHFOV and surfactant (n = 60).** Details of the interventions were not reported.
Outcomes	1. The efficacy was compared by pH value, partial pressure of carbon dioxide and oxygen partial pressure of blood gas before and after 6 hours of treatment. 2. Other complications: apnoea, BPD, pulmonary haemorrhage, intracranial haemorrhage, ROP and abdominal distention.
Notes	**Study conducted in**: an upper-middle-income country (China) **Disclosures**: no information provided **Funding:** Jiangxi Provincial Health and Family Planning Commission Science and Technology Plan Project (20185420)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Infants were randomly divided into 2 groups. Method not reported
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not described
Blinding of participants and personnel (performance bias)	High risk	Not reported. Different modes and settings of ventilation

Zou 2020 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Incomplete long term outcome data (attrition bias)	Low risk	No long-term data published/included
Selective reporting (reporting bias)	Unclear risk	Study registration/protocol not available
Other bias	Low risk	Groups similar at baseline

a/A PO_2:arterial/alveolar oxygen ratio
ABG: arterial blood gas
AC/VG: assist control/volume guarantee
APGAR: appearance, pulse, grimace, activity, and respiration
ARDS: acute respiratory distress syndrome
BDP: bronchopulmonary dysplasia
BiPAP: bilevel positive airway pressure
BP-CPAP: bi-level pressure continuous positive airway pressure
BPD: bronchopulmonary dysplasia
bpm: beats per minute
CA: corrected age
CLD: chronic lung disease
CNO: MedicinCNO device manufacturer
CONSORT: Consolidated Standards of Reporting Trials
CP: cerebral palsy
CPAP: continuous positive airway pressure
DQ: Developmental quotient
DuoPAP: Duo positive airway pressure
EEG: electrocardiograph
ETT: endotracheal tube
FiO_2: fraction of inspiration oxygen
g: grams
GA: gestational age
GDS: Gesell Development Scale
GMFCS: gross motor function classification system
H_2O: water
HCO_3: bicarbonate
HFNC: High-flow nasal cannula
HFOV: high-frequency oscillatory ventilation
HFPV: high-frequency percussive ventilation
HMD: hyaline membrane disease
HR: heart rate
Hz: hertz
IMV: invasive mechanical ventilation
I:E: inspiratory to expiratory ratio
InSurE: Intubate, Surfactant, Extubate
IMV: intermittent mandatory ventilation
IPPV: intermittent positive pressure ventilation
IQR: interquartile range
itime: inspiratory time
IVH: intraventricular haemorrhage

L: litre
LISA: less invasive surfactant administration
LMP: last menstrual period
MAP: mean airway pressure
max: maximum
Min: minutes
MV: mechanical ventilation
nCPAP: nasal continuous positive airway pressure
NEC: necrotising enterocolitis
nHFJV: non-invasive high frequency jet ventilation
nHFV: non-invasive high frequency ventilation
nHFOV: non-invasive high-frequency oscillatory ventilation
nHFPV: non-invasive high frequency percussive ventilation
NICHD: National Institute of Child Health and Human Development
NICU: neonatal intensive care unit
nIPPV: non-invasive intermittent positive-pressure ventilation
NIV: non-invasive ventilation
N-PASS: neonatal pain agitation and sedation scale
NR: not reported
NRDS: neonatal respiratory distress syndrome
OI: oxygenation index
$PaCO_2$: arterial partial pressure of carbon dioxide
PDA: patent ductus arteriosus
PEEP: positive end-expiratory pressure
PIP: positive inspiratory pressure
PaO_2: arterial partial pressure of oxygen
Pmean: mean airway pressure
PO_2: oxygen partial pressure
PPHN: Persistent pulmonary hypertension of the newborn
PVL: periventricular leukomalacia
RDS: respiratory distress syndrome
ROP: retinopathy of prematurity
RR: respiratory rate
s or sec: seconds
SaO_2: oxygen saturation of arterial blood
s/cycle: seconds per cycle
SD: standard deviation
SiPAP: synchronised intermittent positive airway pressure
SLE: specialised laboratory equipment
SpO_2: oxygen saturation
S - S: Sign - Significate
$tcCO_2$: transcutaneous carbon dioxide
Ti: inspiratory time
TTN: Transient tachypnoea of the newborn
VAP: ventilator-associated pneumonia

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aktas 2016	Case report of 3 premature cases who were ventilated with nHFOV
Al Tawil 2011	Observational study
Ali 2020	Observational study
Bottino 2018	Cross-over trial to 4 alternating periods of nHFV versus nCPAP

Study	Reason for exclusion
Cao 2020	Observational study
Colaizy 2008	Observational study
Cools 2009	Study protocol for systematic review with meta-analysis based on individual patient data
Czernik 2012	Observational study
Gaertner 2021	Cross-over trial of nHFOV versus nCPAP
He 2022	Controlled study. No mention of randomisation
Hoehn 2000	Observational study
Keel 2021	Observational study
Klotz 2018	Cross-over study of nHFOV versus nCPAP
Kohlhauser 2005	Observational study
Kugelman 2016	Observational study
Kugelman 2017	Observational study
Lai 2022	Observational study
Lin 2021	Reported "Infants in the 3 groups were intubated by a respiratory tube". Randomly assigned into HFOV group (receiving conventional therapy and HFOV), the nCPAP group (conventional therapy and nCPAP), and the conventional group (receiving conventional therapy). Reporting unclear
Liu 2021	Reported "Infants randomly assigned into nasal non-invasive HFOV with sequential heating and humidification high flow nasal catheter ventilation (HFNC) group (receiving HFNC but no mention of HFOV settings) and nCPAP group". Reporting unclear
Loniewska 2019	Observational study
Mukerji 2015	Observational study
NCT01506401	Ineligible age group (16 years to 85 years old)
NCT04327466	Study on high-frequency oscillatory high-flow nasal cannula (Osciflow)
Renesme 2020	Cross-over trial of nCPAP/nHFOV versus nHFOV/nCPAP
Ruegger 2018	Cross-over trial of nHFOV versus nCPAP
Shi 2020	Observational study
Teng 2022	Retrospective observational analysis
Thatrimontrichai 2020	Observational study
Van der Hoeven 1998	Observational study
Wang 2017	Observational study

Study	Reason for exclusion
Wu 2021	RCT comparing nHFOV versus nCPAP postoperatively in infants after congenital heart surgery
Yang 2021b	Prospective cohort study
Zhang 2020	Ineligible comparator. Trial of nHFOV and inhaled budesonide versus nCPAP alone
Zheng 2020	Controlled study. No mention of randomisation

HFNC: high-flow nasal cannula
HFOV: high-frequency oscillation ventilation
nCPAP: nasal continuous airway pressure
nHFOV: nasal high-frequency oscillation ventilation
RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR1900028092

Study name	Clinical study for multiple ventilation methods on graded respiratory support in neonates with respiratory distress syndrome
Methods	1. Allocation: randomised 2. Intervention model: sequential assignment 3. Masking: not stated 4. Primary purpose: treatment
Participants	**Target sample size:** 500 **Inclusion criteria** 1. Foetal age ≤ 37 weeks; 2. Those who meet the RDS Diagnostic Standards for Practical Neonatology (4th edition); 3. With the guardian's informed consent of the infants; 4. The infant's guardian agrees to receive pulmonary surfactant replacement therapy or mechanically assisted ventilation if necessary. **Exclusion criteria** 1. Congenital malformations of the respiratory system, complex congenital heart disease, severe intrauterine infection, severe instability of the circulatory system, congenital genetic metabolic diseases and chromosomal diseases; 2. Family members refuse to participate; 3. Those who fail to complete the study and cannot provide complete data.
Interventions	Eligible infants are randomised to either control or 1 of 4 arms interventions: 1. Invasive ventilation 2. HFNC 3. nCPAP 4. nIPPV 5. nHFOV
Outcomes	**Primary outcomes** 1. Blood gas analysis 2. Intubation in 72 hours

ChiCTR1900028092 *(Continued)*

	3. Intubation in 72 hours –7 days 4. Oxygen time 5. Ventilation time; 6. BPD 7. ROP 8. NEC 9. Air leak 10.IVH 11.Number of deaths 12.PDA **Secondary outcomes** 1. None stated
Starting date	**Anticipated or actual date of first enrolment:** 13 December 2019 **Recruitment status of this study:** "Pending" as of 16 December 2019
Contact information	Gao Weiwei and Chen Jia, 13 West Guangyuan Road, Yuexiu District, Guangzhou, Guangdong, China; Tel: +86 13580538573; Email: 745750964@qq.com
Notes	**Registered prospectively with:** Chinese Clinical Trials Registry (ChiCTR): https://www.chictr.org.cn/; ID: ChiCTR1900028092) on 11 December 2019

ChiCTR2100045446

Study name	Application of high frequency oscillatory ventilation in premature infants
Methods	1. Allocation: randomised 2. Intervention model: parallel 3. Masking: not stated 4. Primary purpose: treatment
Participants	**Target sample size:** 400 **Inclusion criteria** 1. GA 25–34 weeks; 2. Patients with neonatal respiratory failure diagnosed within 1 hour after birth and requiring non-invasive assisted ventilation. **Exclusion criteria** 1. Severe asphyxia (1 minute Apgar < 4 at 1 minute, or cord blood pH < 7.0); 2. cCHD 3. Maxillofacial developmental abnormalities (cleft palate, distorted nasal septum, atresia of posterior foramen); 4. Chromosomal disease, genetic metabolic disease; 5. Shock; 6. Give up treatment within 7 days of admission; 7. Infants who needed tracheal intubation and mechanical ventilation within 1 hour after birth.
Interventions	Eligible infants are randomised to either: 1. Bipap;

ChiCTR2100045446 *(Continued)*

	2. nHFOV.
Outcomes	**Primary outcome** 1. MV rate required for ETT **Secondary outcomes:** 1. Changes of pCO_2 before and after ventilation; 2. Oxygenation index; 3. SpO_2 distribution; 4. BPD.
Starting date	**Anticipated or actual date of first enrolment:** 14 May 2021 **Recruitment status of this study:** "Pending" as of 29 November 2021
Contact information	Chen Wenqian, 18 Daoshan Road, Gulou Distr+86 18960938870; Email: chwenqian@163.com
Notes	**Registered prospectively with:** Chinese Clinical Trials Registry (ChiCTR): https://www.chictr.org.cn/; ID: ChiCTR2100045446) on 15 April 2021

CTRI/2021/10/037681

Study name	Comparison of non-invasive ventilation in CPAP failure preterm infants with respiratory distress as a rescue mode
Methods	Allocation: stratified block randomisation 1. Allocation concealment: sequentially numbered, sealed, opaque envelopes 2. Intervention model: parallel 3. Masking: no 4. Primary purpose: treatment
Participants	**Target sample size:** 96 **Inclusion criteria** 1. Preterm infants born before 34 weeks' GA; 2. Having respiratory distress before 6 hours of life; 3. Requiring nasal CPAP for their management. **Exclusion criteria** 1. Neonate with major congenital anomalies; 2. Hydrops; 3. Systemic signs of shock requiring inotropic support (> 2 inotropes or > 10 mcg/kg/min of any inotrope); 4. IVH > grade 2; 5. Cystic PVL > grade 2; 6. Poor respiratory efforts/encephalopathy; 7. Tension pneumothorax- requiring ICD insertion; 8. Critical congenital heart disease.
Interventions	Eligible infants who fail CPAP treatment will be randomised to either:

CTRI/2021/10/037681 *(Continued)*

	1. **nIMV**: nMV will be generated by neonatal ventilators (SLE 6000 and Acutronic) using nasal prongs or mask; 2. **nHFOV** generated by neonatal ventilators (SLE 6000, Acutronic) using nasal prongs or mask.
Outcomes	**Primary outcome** 1. Proportion of preterm infants with RD requiring mechanical ventilation in the first 7 days of life when nHFOV is used as rescue mode alternative to nIMV for CPAP failures. **Secondary outcomes** 1. Mortality - death before discharge; 2. Respiratory morbidities: a. Requirement of MV in first 72 hours of life; b. Duration of non-invasive respiratory support; c. Duration of invasive ventilation; d. Total duration of respiratory support; e. Incidence of pneumothorax; f. BPD. 3. HSPDA; 4. NEC - more than Stage 2A; 5. ROP requiring laser treatment; 6. IVH more than Grade 2; 7. PVL more than Grade 2.
Starting date	**Anticipated or actual date of first enrolment:** 1 January 2021 **Recruitment status of this study:** "Not Yet Recruiting" as of 24 November 2021.
Contact information	Tejopratap Oleti, Fernandez Hospital 3-6-282, Hyderguda Basheerbaug road, AP housing board, Hyderguda Hyderabad Telangana 500029 India; Tel: 9989372490; Email: tejopratap@gmail.com
Notes	**Registered prospectively with:** Clinical Trials Registry- India (CTRI): https://www.ctri.nic.in/; ID: CTRI/2021/10/037681 on 29 October 2021

DRKS00005387

Study name	**NAS**: randomised cross-over trial of different nasal support systems for the treatment of apnoea of prematurity
Methods	1. Allocation: randomised 2. Endpoint classification: efficacy study 3. Intervention model: parallel assignment 4. Masking: blinding (assessor) 5. Primary purpose: treatment
Participants	**Target sample size:** 37 **Inclusion criteria** 1. GA at birth = 34 0/7 weeks; 2. Ages at study performance = 38 0/7 weeks; 3. Persistent apnoea despite administration of caffeine; 4. Apnoea score = 6; 5. Parental approval and written informed parental consent.

DRKS00005387 *(Continued)*

	Exclusion criteria 1. Congenital severe dysplasia; 2. Symptomatic apnoea due to sepsis, epileptic seizure, hypoglycaemia or intracerebral haemorrhage, neuromuscular, muscular or skeletal disease; 3. Necessity of changing the doses of caffeine or doxapram; 4. Necessity of intubation and mechanical ventilation.
Interventions	Eligible infants are randomised to either: 1. nCPAP via variable flow device (Infant Flow; Electro Medical Equipment, Brighton, UK) (PEEP 6 cm H_2O); 2. nCPAP with additional background support: nCPAP using conventional respirator (Stephanie; Stephan, Gackenbach, Germany) with application of respiratory support by Hudson prongs and additional background support, synchronisation via Graseby Respiration Sensor placed on the abdomen (SIMV f = 20/min, P insp.: 15 cm H_2O, PEEP: 6 cm H_2O); 3. nCPAP using a conventional respirator (Stephanie; Stephan, Gackenbach, Germany) with application of respiratory support by Hudson prongs and additional background support via high-frequency ventilation (variable amplitude, P osz.: 15 cm H_2O, MAP: 6 cm H_2O).
Outcomes	**Primary outcomes** 1. Combined rate of intermittent hypoxia (SpO_2 < 80%) and bradycardia (pulse rate < 80 bpm) per hour **Secondary outcomes** 1. Mean FiO_2; 2. Mean $tcPCO_2$; 3. Change of abdominal girth during the particular 8-hour interval.
Starting date	**Anticipated or actual date of first enrolment:** 16 December 2013 **Recruitment status of this study:** "Recruiting ongoing" as of December 2014
Contact information	Anette Poets, Calwerstr. 7 72076 Tübingen Germany; Tel: 07071-2980877; Email: anette.poets@med.uni-tuebingen.de
Notes	**Registered prospectively with:** German Clinical Trial Register: https://www.drks.de/; ID: DRKS00005387 on 12 November 2013

DRKS00023438

Study name	Influence of non-invasive positive pressure ventilation versus nasal high-frequency oscillation ventilation on parameters of oxygenation and ventilation in premature infants in the weaning phase after respiratory distress syndrome
Methods	1. Study type: interventional 2. Allocation: randomised controlled trial 3. Blinding: open (masking not used) 4. Control: active control (effective treatment of control group) 5. Purpose: treatment 6. Assignment: cross-over
Participants	**Target sample size:** 48

DRKS00023438 *(Continued)*

Inclusion criteria

1. Premature babies with a gestational age < 32 weeks of gestation and a birthweight < 1500 g;
2. At least 72 hours old;
3. Requirement for non-invasive ventilation (CPAP/NIPPV);
4. FiO_2 under CPAP/nIPPV 21%–60% with a PEEP of 5-8 cm H_20;
5. At least 4 hypoxaemias (< 80% SpO_2) or apnoeas/bradycardias in the 12 hours prior to study entry;
6. In the 12 hours prior to study entry, the number of intervention-requiring events (defined as SpO_2 < 70% for > 1 min or heart rate < 100/min for > 30 seconds) does not lead to an escalation of the non-invasive ventilation;
7. Written consent of the legal guardian is given.

Exclusion criteria

1. Premature babies and newborns with severe malformations that significantly impair respiratory regulation (severe CNS malformations), lung function (e.g. pulmonary hypoplasia, acute extra-alveolar air such as pneumothorax and pulmonary interstitial emphysema, diaphragmatic hernias) or the circulatory function (congenital cyanotic heart disease, septic shock);
2. Postnatal age < 72 hours of life (often acute deterioration in the early phase of respiratory distress syndrome and to protect the minimal handling principle in the critical phase to prevent intraventricular bleeding);
3. Start of treatment for an acute clinical infection < 72 hours before study entry;
4. FiO_2 under CPAP/nIPPV > 60% or PEEP > 8 cm H_20;
5. Escalation of non-invasive ventilation in the 12 hours before study entry due to the number of intervention-requiring events (defined as SpO_2 < 70% for > 1 min or heart rate < 100/min for > 30 seconds);
6. Planned blood transfusion or surgery during the study phase.

Interventions	Eligible infants are randomised to either: 1. nIPPV; 2. nHFOV.
Outcomes	**Primary outcomes** 1. The absolute time as a percentage of oxygen saturation (SpO_2) measured by pulse oximetry in the target oxygen saturation range (88%–96%). **Secondary outcomes** 1. Number and duration of episodes with SpO_2 < 80% and < 70%, number and duration of episodes with SpO_2 > 96% with oxygen demand during each study period; 2. Number of long and very long hypoxic and hyperoxic episodes outside the SpO_2 target range (defined as episodes lasting > 60 seconds and > 180 seconds; 3. Mean oxygen concentration in the inspiratory air (FiO_2) during each study period; 4. Median and mean SpO_2 values as well as SpO_2 variability (coefficient of variation) during each study period; 5. Measurement of cerebral tissue oxygenation ($SctO_2$) a. Individual $SctO_2$ median for each child during each study period; b. Area below the curve above and below the individual $SctO_2$ median of each child during each study period; 6. Mean transcutaneous PCO_2 and standard deviation during each study period; 7. Collection of the Silverman score at the beginning, after 4 hours, and at the end of each study period; 8. Measurement of the waist circumference at the beginning and at the end of each study period;

DRKS00023438 *(Continued)*

	9. Number of children who meet the pre-defined dropout criteria at which point in time and in which phase of study; 10. Non-invasive measurement of regional lung ventilation using EIT.
Starting date	**Anticipated or actual date of first enrolment:** 15 September2020 **Recruitment status of this study:** "Recruiting ongoing" as of 05 November 2021
Contact information	Harald Ehrhardt, Feulgenstr. 12; 35392 Giessen; Germany. Telephone: +4964198558964; Email: harald.ehrhardt at paediat.med.uni-giessen.de
Notes	**Registered retrospectively with:** German Clinical Trial Register: https://www.drks.de/; ID: DRKS00023438 on 05 November 2021

IRCT2016111930964N1

Study name	Study of two non-invasive ventilation methods in the treatment of acute respiratory distress syndrome of infants
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: open (masking not used) 4. Primary purpose: treatment
Participants	**Target sample size:** 128 **Inclusion criteria** 1. GA of 28 to 34 weeks; 2. Weight between 1000 and 2000 grams; 3. RDS; 4. Silverman-Anderson retraction score 6–7. **Exclusion criteria** 1. Congenital malformation; 2. Cardiac disease; 3. Severe asphyxia (Apgar score ≤ 3 at 1 and 5 minutes or pH ≤ 7.12); 4. Parents' unwillingness to participate in the study.
Interventions	Eligible infants are randomised to either: 1. nCPAP; 2. Oscillatory nCPAP (combination of nHFOV and nCPAP).
Outcomes	**Primary outcome** 1. Non-invasive ventilatory failure within 72 hours **Secondary outcomes** 1. Milk intolerance rate; 2. Pneumothorax; 3. IVH.
Starting date	**Anticipated or actual date of first enrolment:** 22 August 2016

IRCT20161111930964N1 *(Continued)*

	Recruitment status of this study: "Completed on 20/11/2016"
Contact information	Arash Malekian, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; Email: malekia-narash@gmail.com
Notes	**Registered retrospectively with:** Iranian Registry of Clinical Trials (IRCT): https://www.irct.ir/; ID: IRCT20161111930964N1 on 30 December 2016

IRCT20180915041040N3

Study name	Comparison of the effectiveness of nasal continuous positive airway pressure (NCPAP) therapy with combination of high-frequency oscillations and NCPAP in treatment of respiratory distress syndrome in infants
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: blinding (assessor and parents of participant) 4. Primary purpose: treatment
Participants	**Target sample size:** 40 **Inclusion criteria** 1. Gestation < 35 weeks; 2. Diagnosed with RDS. **Exclusion criteria** 1. Death during study; 2. Chromosomal anomaly; 3. Congenital heart defect; 4. IVH Grade 2 and above.
Interventions	Eligible infants are randomised to either: nCPAP; Combination of nHFOV and nCPAP.
Outcomes	**Primary outcome** 1. Duration of hospitalisation **Secondary outcomes** 1. Not stated
Starting date	**Anticipated or actual date of first enrolment:** 22 August 2016 **Recruitment status of this study:** "Completed on 20/5/2018"
Contact information	Roya Choopani, Shahre-kord University of Medical Sciences, Parastar Street, Sharekord, Iran; Email: choopani.r@skums.ac.ir; dr.choopani@yahoo.com
Notes	**Registered retrospectively with:** Iranian Registry of Clinical Trials (IRCT): https://www.irct.ir/; ID: IRCT20180915041040N3 on 17 August 2019

IRCT20190416043290N2

Study name	Comparison of the consequences of using two methods of "continuous positive airway pressure" and "high frequency oscillation" in the treatment of respiratory distress in premature neonates
Methods	1. Allocation: block randomisation 2. Intervention model: parallel assignment 3. Masking: open (masking not used) 4. Primary purpose: treatment
Participants	**Target sample size:** 78 **Inclusion criteria** 1. Gestation 28–34 weeks; 2. Birthweight < 2000 g; 3. Hospitalised due to RDS within the first 24 hours of life. **Exclusion criteria** 1. Severe asphyxia (Apgar of 5 minutes less than or equal to 6); 2. Positive blood culture upon arrival at the neonatal intensive care unit; 3. Congenital malformations (whether pulmonary or extrapulmonary).
Interventions	Eligible infants are randomised to either: 1. **nCPAP** using single prong 3–4 centimetres inside the nose; 2. **nHFOV.** Surfactant administration through InSurE is allowed in both groups.
Outcomes	**Primary outcome** 1. Success or failure (using specific criteria) of any method within 3 days **Secondary outcomes** 1. Not stated
Starting date	**Anticipated or actual date of first enrolment:** 5 December 2020 **Recruitment status of this study:** "Completed on 5/6/2021"
Contact information	Tahereh Esmaeilnia, Tehran University of Medical Sciences, Iran; Email: tesmaeilnia@sina.tums.ac.ir
Notes	**Registered retrospectively with:** Iranian Registry of Clinical Trials (IRCT): https://www.irct.ir/; ID: IRCT20190416043290N2 on 17 December 2020

IRCT20201222049795N1

Study name	A comparison of the effect of nasal continuous positive airway pressure (NCPAP) vs nasal high-frequency oscillation (NHFO) in the treatment of respiratory distress in preterm infants
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: single-blinded (parents of participant)

IRCT20201222049795N1 *(Continued)*

	4. Primary purpose: treatment
Participants	**Target sample size:** 20 **Inclusion criteria** 1. GA between 25–35 weeks; 2. Moderate-to-severe RDS. **Exclusion criteria** 1. Patients with congenital anomalies; 2. Patients needed endotracheal intubation.
Interventions	Eligible infants are randomised to either: 1. nCPAP; 2. Combination of nHFOV and nCPAP.
Outcomes	**Primary outcomes** 1. Not stated **Secondary outcomes** 1. O_2 therapy; 2. Duration of O_2 therapy; 3. Duration of MV; 4. The infant's age at the time of use of MV; 5. Apnoea; 6. The infant's age at the time of apnoea; 7. Surfactant; 8. Age of infants at surfactant indication; 9. Pneumothorax; 10.Age of infants at pneumothorax incidence; 11.IVH; 12.Age of infants at IVH; 13.CLD.
Starting date	**Anticipated or actual date of first enrolment:** 30 September 2020 **Recruitment status of this study:** "Completed on 20/12/2020"
Contact information	Maryam Jandaghi, Islamic Azad University, Semnan, Iran; Email: M.Jandaghi73@gmail.com
Notes	**Registered retrospectively with:** Iranian Registry of Clinical Trials (IRCT): https://www.irct.ir/; ID: IRCT20201222049795N1 on 9 January 2021

IRCT20221120056556N1

Study name	Comparison of the effect of (NSIMV) nasal synchronized intermittent mandatory ventilation with (NHFOV) nasal high frequency oscillatory ventilation in neonates requiring non-invasive mechanical ventilation in Mofid Pediatric Hospital
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment

IRCT20221120056556N1 *(Continued)*

3. Masking: double-blinded
4. Primary purpose: treatment

Participants	**Target sample size:** 180 **Inclusion criteria** 1. Premature babies hospitalised in the intensive care unit; 2. GA of more than 26 weeks; 3. Respiratory support; 4. Informed consent of the baby's parents. **Exclusion criteria** 1. Babies who were intubated for resuscitation or for another reason before randomisation; 2. Cardio-pulmonary arrest requiring prolonged resuscitation; 3. Lack of consent of the baby's parents; 4. Transferring the baby out of the neonatal intensive care unit before randomisation; 5. Contraindication of non-invasive mechanical ventilation, such as infants with oesophageal atresia or diaphragmatic hernia within 10 to 14 days after surgery; 6. Babies with head and face anomalies that do not allow ventilation inside the baby's nose, such as cleft lip and palate; 7. Intraventricular haemorrhage grade 3 and 4.
Interventions	1. nSIMV 2. nHFOV
Outcomes	**Primary outcome** 1. Duration of MV **Secondary outcomes** 1. BPD 2. IVH 3. PDA 4. ROP 5. NEC
Starting date	**Anticipated or actual date of first enrolment:** 22 August 2016 **Recruitment status of this study:** "Completed on 20/11/2016"
Contact information	Minoo Fallahi, 7th Floor, Bldg No.2 SBUMS, Arabi Ave, Daneshjoo Blvd, Velenjak, Tehran 1546815514, Iran; Tel: +98 21 2292 2828; Email: minou_fallahi@sbmu.ac.ir
Notes	**Registered prospectively with:** Iranian Registry of Clinical Trials (IRCT): https://www.irct.ir/; IRCTID: IRCT20221120056556N1 on 24 January 2023

NCT01277874

Study name	Oscillatory versus non-oscillatory nasal continuous airway pressure neonatal respiratory support
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: open-label

NCT01277874 *(Continued)*

	4. Primary purpose: treatment
Participants	**Target sample size:** 246 **Inclusion criteria** 1. Newborn (0–28 days of age) admitted to NICU; 2. Ordered respiratory treatment of nCPAP. **Exclusion criteria** 1. Major congenital defect; 2. Known or suspected chromosomal disorder.
Interventions	Eligible infants are randomised to either: 1. **nCPAP** delivered via nasal prongs placed into infant's nares. It may be delivered via ventilator or by bubble; 2. **nHFOV** delivered via Bird Industries pneumatic diaphragm is attached to the nCPAP patient circuit to provide oscillations.
Outcomes	**Primary outcomes** 1. Physiologic respiratory stability of oscillating versus non-oscillating nCPAP; 2. Need for mechanical ventilation following the initiation of nCPAP. **Secondary outcomes** 1. Total duration of non-invasive and invasive respiratory support in each study group; 2. Total amount of oxygen exposure in each study group.
Starting date	**Anticipated or actual date of first enrolment:** December 2014 **Recruitment status of this study:** "Withdrawn (PI has left Institution)" as of 13 March 2017
Contact information	Donald Null, Madera, California, United States, 93636; Email: Donald.Null@imail.org
Notes	**Registered prospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT01277874 on 13 January 2011

NCT01852916

Study name	Nasal high frequency oscillatory ventilation (NHFOV) versus nasal continuous positive airway pressure (NCPAP) ventilation: a pilot trial
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: open-label 4. Primary purpose: treatment
Participants	**Target sample size:** 20 **Inclusion criteria** 1. Newborn less than 28 weeks' gestation at birth; 2. Intubated and ventilated in the first 24 hours of life; 3. Extubated in the first week of life;

NCT01852916 *(Continued)*

	4. Parental consent. **Exclusion criteria** 1. Lack of parental consent; 2. Major congenital malformation; 3. Severe perinatal asphyxia; 4. Airway abnormalities; 5. Pneumothorax.
Interventions	Eligible infants are randomised to either: 1. nCPAP delivered via Infant flow; 2. nHFOV delivered via Dräger Babylog® VN500 ventilator.
Outcomes	**Primary outcome** 1. Extubation failure within 7 days **Secondary outcomes** 1. Changes in capillary PCO_2 after extubation; 2. Pneumothorax; 3. IVH; 4. Feeding tolerance.
Starting date	**Anticipated or actual date of first enrolment:** September 2013 **Recruitment status of this study:** "Suspended (Poor recruitment rate)" as of 5 August 2015
Contact information	Dr. Yaser Ali, University of Manitoba, Winnipeg, Manitoba, Canada, R2H 2A6
Notes	**Registered prospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT01852916 on 14 May 2013

NCT02543125

Study name	Nasal high frequency oscillatory versus nasal intermittent positive pressure ventilation in neonate after extubation
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: open-label 4. Primary purpose: treatment
Participants	**Target sample size:** 75 **Inclusion criteria** 1. Birthweight > 1000 g; 2. GA > 28 weeks; 3. Have respiratory distress syndrome and need invasive ventilation. **Exclusion criteria** 1. Birthweight < 1000 g; 2. GA < 28 weeks;

NCT02543125 *(Continued)*

	3. Infants with abnormalities of upper and lower airways; 4. Infants have contraindications for non-invasive ventilation.
Interventions	Eligible infants are randomised to either: 1. nIPPV via SLE 5000; 2. nHFOV via SLE 5000.
Outcomes	**Primary outcome:** 1. Reintubation rate within 72 hours **Secondary outcomes:** 1. Significant apnoea; 2. Air leaks; 3. BPD; 4. NEC.
Starting date	**Anticipated or actual date of first enrolment:** February 2016 **Recruitment status of this study:** "Unknown" as of 4 May 2023
Contact information	Zhang Tao, Guangdong Women and Children's Hospital and Health Institute, Guangdong, China; Email: 929796361@qq.com
Notes	**Registered prospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT02543125 on 7 September 2015

NCT03006354

Study name	Nasal high frequency oscillatory ventilation versus nasal continuous positive airway pressure in late-preterm and term infants with transient tachypnea of the newborn: a randomized controlled trial
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: open-label 4. Primary purpose: treatment
Participants	**Target sample size:** 440 **Inclusion criteria** 1. GA at birth between 34 and 42 weeks of gestation; 2. Admission to Bursa Yüksek Ihtisas Teaching Hospital, NICU during the first 24 hours of life; 3. Diagnosis of TTN within the first 24 hours of life. **Exclusion criteria** 1. GA at birth less than 34 weeks or greater than 42 weeks at birth; 2. Chest x-ray or lung ultrasound finding indicating another respiratory disorder; 3. Additional infant diagnosis of major cardiac disease; 4. Additional infant diagnosis of major pulmonary disease other than TTN; 5. Additional infant diagnosis of major congenital anomaly with the potential to affect respiratory status in the neonatal period;

NCT03006354 *(Continued)*

	6. Additional infant diagnosis of infectious disease process potentially affecting respiratory status in the neonatal period.
Interventions	Eligible infants are randomised to either: 1. nCPAP via Leoni-Plus Ventilator, Heinen-Lowenstein, Germany; 2. nHFOV via Leoni-Plus Ventilator, Heinen-Lowenstein, Germany.
Outcomes	**Primary outcome** 1. Time to cessation of non-invasive positive pressure respiratory support within 72 hours **Secondary outcomes** 1. Pneumothorax; 2. Time to cessation of supplemental oxygen; 3. Time to discharge from hospital.
Starting date	**Anticipated or actual date of first enrolment:** 1 February 2017 **Recruitment status of this study:** "Unknown" as of 4 May 2023
Contact information	Emre Baldan, University of Health Sciences, Bursa Yuksek Ihtisas Teaching Hospital, Turkey; Email: emrebaldan@e-mail.com.tr
Notes	**Registered prospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT03006354 on 7 September 2015

NCT03206489

Study name	Nasal high frequency oscillation for respiratory distress syndrome in preterm twin infants
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: double (investigator, outcomes assessor) 4. Primary purpose: treatment
Participants	**Target sample size:** 200 **Inclusion criteria** 1. GA is from 26 to 37 weeks; 2. Diagnosis of RDS. The diagnosis of RDS will be based on clinical manifestations (tachypnoea, nasal flaring and or grunting) and chest x-ray findings; 3. RDS Silverman score > 5; 4. Informed parental consent has been obtained. **Exclusion criteria** 1. Severe RD requiring early intubation according to the American Academy of Pediatrics guidelines for neonatal resuscitation; 2. Major congenital malformations or complex congenital heart disease; 3. Group B haemolytic streptococcus pneumonia, septicaemia, pneumothorax, pulmonary haemorrhage; 4. Cardiopulmonary arrest needing prolonged resuscitation; 5. Transferred out of the NICU without treatment.

NCT03206489 *(Continued)*

Interventions	Eligible infants are randomised to either: 1. nCPAP used as a primary mode of ventilation; 2. nHFOV used as a primary mode of ventilation.
Outcomes	**Primary outcome:** 1. Reintubation within 7 days **Secondary outcomes:** 1. BPD; 2. Bayley Scales of Infant Development.
Starting date	**Anticipated or actual date of first enrolment:** 1 February 2017 **Recruitment status of this study:** "Recruiting" as of 16 February 2021
Contact information	Chen Long, Daping Hospital and the Research Institute of Surgery of the Third Military Medical University, China; Email: 476679422@qq.com
Notes	**Registered prospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT03206489 on 2 July 2017

NCT03558737

Study name	Nasal high-frequency jet ventilation (nHFJV) following extubation in preterm infants
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: none (open-label) 4. Primary purpose: treatment
Participants	**Target sample size:** 40 **Inclusion criteria** 1. 24 0/7 to 28 6/7 weeks' GA; 2. Intubated within 24 hours of life to SIMV or high-frequency ventilation (HFV, includes HFOV or HFJV); 3. Plan for extubation within 72 hours of life; 4. Infants intubated for surfactant replacement therapy via InSurE method; 5. Consent obtained from parent/legal guardian. **Exclusion criteria** 1. Major congenital and/or chromosomal anomalies; 2. Upper oropharyngeal anomalies.
Interventions	Eligible infants are randomised to either: 1. nIPPV delivered via a conventional ventilator through Hudson prongs; 2. nHFJV delivered via Bunnell Life Pulse high-frequency JET ventilator through a Rusch latex nasopharyngeal airway.
Outcomes	**Primary outcomes:**

NCT03558737 *(Continued)*

	1. 72-hour rate of reintubation to invasive mechanical ventilation; 2. 7-day rate of reintubation to invasive mechanical ventilation; 3. Total number of days of invasive mechanical ventilation (time frame: through hospital discharge, an average of 5 months). The total number of days of infants are intubated and require MV. **Secondary outcomes:** 1. Rates of moderate-to-severe BPD.
Starting date	**Anticipated or actual date of first enrolment:** 1 Apr 2019 **Recruitment status of this study:** "Active, not recruiting" as of 4 May 2023
Contact information	Bradley Yoder, University of Utah, USA
Notes	**Registered prospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT03558737 on 15 June 2018

NCT03711565

Study name	Oscillatory versus non-oscillatory nasal continuous airway pressure neonatal respiratory support
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: open-label 4. Primary purpose: treatment
Participants	**Target sample size:** not stated **Inclusion criteria** 1. Newborn (0–28 days of age) admitted to NICU; 2. Ordered respiratory treatment of nasal nCPAP respiratory support. **Exclusion criteria** 1. Major congenital defect; 2. Known or suspected chromosomal disorder.
Interventions	Eligible infants are randomised to either: 1. nCPAP delivered via a conventional ventilator through nasal prongs placed into infant's nares; 2. nHFOV delivered via high-frequency device through nasal prongs.
Outcomes	**Primary outcomes** 1. RSI at 72 hours after initiation of support. RSI scale is scored based on FiO_2 (0 ≤ 30%, 1 = 30%-39%, 2 = 40%–49%, 3 = > or equal to 50%), CPAP/Paw (0 = < 6, 1 = 6-7, 2 = 7-8, 3 ≥ 8), spontaneous respiratory rate (RR) (0 ≤ 40, 1 = 40–59, 2 = 60-79, 3 = ≥ to 80), retractions (0 = none, 1 = mild, 2 = moderate, 3 = severe), and apnoea (0 = none, 1 = 1/2/2015, 2 = 3/4/2015, 3 ≥ 4).
Starting date	**Anticipated or actual date of first enrolment:** 19 September 2016 **Recruitment status of this study:** "Withdrawn (the research equipment was not available for more than a year after the study was submitted. A new trial was being done during delivery of patients that competed with the study)" as of 4 May 2023.

NCT03711565 *(Continued)*

Contact information	University of California Davis Health, Sacramento, California, United States, 95817
Notes	**Registered prospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT03711565 on 6 April 2021

NCT03842462

Study name	NHFOV vs NIPPV vs nCPAP in preterm infants with respiratory distress syndrome
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: open-label 4. Primary purpose: treatment
Participants	**Target sample size:** 684 **Inclusion criteria** 1. GA of less than 30 weeks or birth weight < 1500 g; 2. Clinical diagnosis of RDS; 3. Parental consent. **Exclusion criteria** 1. Intubated for resuscitation or other reasons at birth; 2. Major congenital malformations or known complex congenital heart disease; 3. No parental consent.
Interventions	Eligible infants are randomised to either (cross-over not allowed): 1. nCPAP; 2. nIPPV; 3. nHFOV.
Outcomes	**Primary outcome** 1. Treatment failure within 72 hours after randomisation: need for invasive mechanical ventilation **Secondary outcomes** 1. Rate of air leaks (pneumothorax or pneumomediastinum, or both) occurred during non-invasive respiratory support; 2. Rate of BPD; 3. Rate of ROP; 4. Rate of NEC; 5. Rate of IVH; 6. Rate of thick secretions causing an airway obstruction; 7. Days of hospitalisation; 8. Duration of non-invasive respiratory support; 9. Days on supplemental oxygen; 10. Need for surfactant and caffeine treatment; 11. In-hospital mortality; 12. Rate of nasal trauma.
Starting date	**Anticipated or actual date of first enrolment:** 1 November 2020

NCT03842462 *(Continued)*

	Recruitment status of this study: "Unknown" as of the last update posted: 18 November 2020
Contact information	Xingwang Zhu, Jiulongpo No.1 People's Hospital; China; Phone Number:15084335697; Email: 15084335697@163.com
Notes	**Registered prospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT03842462 on 15 February 2019

NCT04282369

Study name	Evaluation of the efficacy of four different non-invasive ventilation modes performed in the delivery room
Methods	1. Allocation: randomised 2. Intervention model: single-group assignment 3. Masking: open-label 4. Primary purpose: supportive care
Participants	**Target sample size:** 100 **Inclusion criteria** 1. Late preterm and term infants with RD **Exclusion criteria** 1. Intubation for RD; 2. Major abnormalities.
Interventions	Eligible infants are randomised to either: 1. HFNC; 2. nCPAP; 3. nIPPV; 4. nHFOV.
Outcomes	**Primary outcome** 1. Silverman Score **Secondary outcomes** 1. N-PASS score (evaluation of the comfort of the four different non-invasive ventilation modes)
Starting date	**Anticipated or actual date of first enrolment:** 18 February 2018 **Recruitment status stated on the registry:** Unknown **Last updated on the registry:** 24 February 2020
Contact information	Ilker Gönen; Kanuni Sultan Suleyman Training and Research Hospital; Istanbul, Turkey, 34065; Tel: +905322054822; Email: ilkergonen81@hotmail.com.
Notes	**Registered prospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT04282369 on 17 February 2020

NCT04323397

Study name	Nasal high frequency oscillatory versus synchronized intermittent positive pressure ventilation in neonate following extubation: randomized controlled cross-over study
Methods	1. Allocation: randomised 2. Intervention model: cross-over assignment 3. Masking: none (open-label) 4. Primary purpose: treatment
Participants	**Target sample size:** 150 **Inclusion criteria** 1. 24 0/7 to 28 6/7 weeks' GA; 2. Intubated within 24 hours of life to SIMV or HFV (HFV, includes HFOV or HFJV); 3. Plan for extubation within 72 hours of life; 4. Infants intubated for surfactant replacement therapy via InSurE method; 5. Consent obtained from parent/legal guardian. **Exclusion criteria** 1. Major congenital or chromosomal anomalies, or both; 2. Upper oropharyngeal anomalies.
Interventions	Eligible infants are randomised to either: - nHFO delivered via SLE6000 infant ventilators, UK using binasal prongs; - nSIPPV delivered via SLE6000 infant ventilators, UK using bi-nasal prongs.
Outcomes	**Primary outcome** 1. PCO_2 **Secondary outcomes** 1. Extubation failure
Starting date	**Anticipated or actual date of first enrolment:** 1 April 2019 **Recruitment status of this study:** "Active, not recruiting" as of 10 November 2021
Contact information	Anucha Thatrimontrichai, Songklanagarind Hospital, Prince of Songkla University, Hat-Yai, Songkhla, Thailand, 90110
Notes	**Registered prospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT04323397 on 26 March 2020

NCT04905732

Study name	Nasal high-frequency oscillatory ventilation (NHFOV) vs nasal continuous positive airway pressure(NCPAP) for ventilated newborn infants with BPD: a randomized controlled trial
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: double (investigator, outcomes assessor)

NCT04905732 *(Continued)*

	4. Primary purpose: treatment
Participants	**Target sample size:** 200 **Inclusion criteria** 1. GA is less than 32 weeks; 2. Diagnosed with BPD and needs invasive ventilation; 3. Extubation and subsequent non-invasive ventilation is ready to be carried out. **Exclusion criteria** 1. IVH grades 3 or 4; 2. Major congenital anomalies; 3. Parents' decision not to participate.
Interventions	Eligible infants are randomised to either: 1. nCPAP; 2. nHFOV.
Outcomes	**Primary outcomes** 1. Reintubation within 7 days; 2. Death; 3. Level of carbon dioxide. **Secondary outcomes** 1. NEC; 2. Intraventricular haemorrhage(IVH).
Starting date	**Anticipated or actual date of first enrolment:** 20 May 2021 **Recruitment status of this study:** "Recruiting" as of 28 May 2021
Contact information	Chen Long, Daping Hospital and the Research Institute of Surgery of the Third Military Medical University and Children's Hospital of Chongqing Medical University, China; Email: neurocl-long@126.com
Notes	**Registered retrospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT04905732 on 28 May 2021

NCT04914715

Study name	Effectiveness of non-invasive high frequency oscillatory ventilation (nHFOV) versus invasive conventional ventilation for preterm neonates with respiratory distress syndrome
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: none (open-label) 4. Primary purpose: treatment
Participants	**Target sample size:** 1200 **Inclusion criteria**

NCT04914715 *(Continued)*

	1. Inborn preterm 26–34 weeks gestation admitted to NICU with diagnosis of RDS; 2. Babies who were initially started on high-flow oxygen therapy/nCPAP but were unable to maintain saturation > 90% on Fio_2 of 40% in the first 6 hours of life; 3. Capillary PCO_2 of > 70 or arterial PCO_2 > 65 on 2 repeated samples within 4 hours; 4. Neonates whose parents consented to participate. **Exclusion criteria** 1. Gestation below < 26 weeks or above 34 weeks; 2. Neonates requiring endotracheal intubation within the labour room/operating theatre or within 1st hour of life for respiratory support; 3. Neonates diagnosed as having congenital pneumonia or sepsis; 4. Patient with poor respiratory drive due to any reasons: neurological or central causes; 5. Diaphragmatic hernia or any other thoracic anomaly; 6. Pleural effusion unilateral or bilateral congenital cystic pulmonary malformation; 7. Underlying cyanotic heart disease; 8. Acynotic heart disease causing pulmonary oedema; 9. Cleft lip and cleft palate or any other surgical condition.
Interventions	Eligible infants are randomised to either: 1. nHFOV; 2. Conventional invasive ventilation (SIMV).
Outcomes	**Primary outcomes** 1. Respiratory support escalation within the first 24 hours of intervention; 2. Oxygen requirement within first 24 hours of intervention; 3. Weaning from assigned respiratory support within 1–2 weeks. **Secondary outcomes** 1. Number of surfactants needed within the first 3 days of assignment; 2. Respiratory support duration up to 2 weeks; 3. Complications related to respiratory support within 1 week after respiratory support discontinuation; 4. Complication related to prematurity within 1 week.
Starting date	**Anticipated or actual date of first enrolment:** 1 July 2021 **Recruitment status of this study:** "Not yet recruiting" as of 7 June 2021
Contact information	Vikram VK Kessani, the Indus Hospital and Health Network, Pakistan; Email: vikram.kumar@tih.org.pk
Notes	**Registered prospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT03206489 on 2 July 2017

NCT05141435

Study name	NHFOV as primary support in very preterm infants with RDS
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: open-label

NCT05141435 *(Continued)*

	4. Primary purpose: treatment
Participants	**Target sample size:** 340 **Inclusion criteria** 1. GA between 24 + 0/7 and 28 + 6/7 weeks; 2. Diagnosis of RDS. The diagnosis of RDS will be based on clinical manifestations (tachypnoea, nasal flaring and or grunting) and a FiO_2 greater than 0.25 for target SpO_2 89%– 94%; 3. Age less than 2 hours. **Exclusion criteria** 1. Major congenital malformations or known complex congenital heart disease; 2. No parental consent.
Interventions	Eligible infants are randomised to either: 1. nCPAP provided by either variable flow or continuous flow devices; 2. nHFOV provided via piston/membrane oscillators (Acutronic FABIAN-III, SLE5000, Lowenstein Med LEONI+, Sensormedics 3100A).
Outcomes	**Primary outcome** 1. Treatment failure within 72 hours after randomisation (need for invasive mechanical ventilation) **Secondary outcomes** 1. Rate of BPD; 2. Rate of ROP ≥ 2nd stage; 3. Rate of NEC ≥ 2nd stage; 4. Rate of IVH ≥ 3rd grade; 5. Rate of thick secretions causing an airway obstruction; 6. In-hospital mortality; 7. Rate of nasal trauma; 8. Composite mortality/BPD; 9. Weekly weight gain; 10. Overall duration of non-invasive respiratory assistance; 11. Surfactant treatment; 12. Overall duration of hospitalisation; 13. PDA.
Starting date	**Anticipated or actual date of first enrolment:** 1 August 2022 **Recruitment status of this study:** "Recruiting" as of 17 January 2023
Contact information	Xingwang Zhu; Department of Neonatology, Chongqing Medical University Affiliated Children's Hospital, Chongqing, China; Tel: +86150843335697; Email: 15084335697@163.com
Notes	**Registered prospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT05141435 on 2 December 2021

NCT05493527

Study name	Non-invasive high-frequency oscillatory ventilation as a post-extubation respiratory support in neonates

NCT05493527 *(Continued)*

Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: single (outcomes assessor) 4. Primary purpose: treatment
Participants	**Target sample size:** 60 **Inclusion criteria** 1. Preterm neonates with GA ≤ 35 weeks; 2. Neonates that were on invasive mechanical ventilation for at least 48 hours are eligible for extubation. **Exclusion criteria** 1. Patients with major upper or lower airway anomalies; 2. Patients with significant congenital anomalies, including cardiac, abdominal or respiratory.
Interventions	Eligible infants are randomised post extubation to either: 1. nIPPV delivered by ventilator generating the targeted pressures; 2. nHFOV delivered via time-cycled, pressure-limited, and continuous-flow neonatal ventilator (SLE6000; SLE).
Outcomes	**Primary outcome** 1. Re-intubation rate **Secondary outcomes** 1. Days on the assigned non-invasive respiratory support; 2. Days on supplemental oxygen; 3. Duration of admission; 4. Mortality rate; 5. Lung ultrasound score; 6. Co_2 change; 7. Oxygen requirement; 8. Incidence of feeding intolerance; 9. Days to reach full intake; 10. Intracranial haemorrhage; 11. Pneumothorax; 12. Incidence of occurrence of nasal trauma; 13. Incidence of BPD; 14. Severity of RD; 15. Need for postnatal steroids; 16. Chest x-ray change.
Starting date	**Anticipated or actual date of first enrolment:** 1 February 2021 **Recruitment status of this study:** "Recruiting" as of 9 August 2022
Contact information	Sondos Ahmed Salaheldin Ahmed, Neonatal Intensive Care Units (NICUs), Ain Shams University, Cairo, Abbasia, Egypt, 11517; Tel 01094407204 ext 202; Email sondosahmed@med.asu.edu.eg
Notes	**Registered retrospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT05493527 on 9 August 2022

NCT05706428

Study name	Cardiorespiratory effects of nasal high frequency ventilation in neonates
Methods	1. Allocation: randomised 2. Intervention model: parallel assignment 3. Masking: single (outcomes assessor) 4. Primary purpose: treatment
Participants	**Target sample size:** 100 **Inclusion criteria** 1. Moderate and late preterm infants born between 32 + 0 to 36 + 6 weeks gestation (according to WHO definitions of preterm birth); 2. Admitted to the NICU with spontaneous breathing and clinical manifestations of RDS (tachypnoea, nasal flaring, intercostal and subcostal retraction and or grunting). **Exclusion criteria** 1. Any baby intubated for resuscitation or other reasons; 2. Obvious major congenital malformations or known complex congenital heart disease; 3. Pulmonary haemorrhage; 4. Cardiopulmonary arrest needing prolonged resuscitation.
Interventions	Eligible infants are randomised post extubation to either: 1. nIPPV delivered by ventilator generating the targeted pressures; 2. nHFOV delivered via time-cycled, pressure-limited, and continuous-flow neonatal ventilator (SLE6000; SLE).
Outcomes	**Primary outcomes** 1. Duration of the non-invasive respiratory support; 2. Need for invasive ventilation in the first 72 hours; 3. Short-term complications such as: a. air leak syndromes; b. pulmonary haemorrhage; c. IVH; d. Nasal trauma; 4. Haemodynamic changes during the period of non-invasive ventilation: a. superior vena cava blood flow in mL/kg/min; b. right ventricular output in mL/kg/min; c. left ventricular output in mL/kg/min; d. peak systolic velocity in anterior cerebral artery in cm/sec. **Secondary outcomes** 1. Need for surfactant administration; 2. Days on invasive mechanical ventilation; 3. Days on supplemental oxygen; 4. Duration of hospital stay; 5. Mortality rate.
Starting date	**Anticipated or actual date of first enrolment:** 1 January 2022 **Recruitment status of this study:** "Recruiting" as of 6 February 2023

NCT05706428 *(Continued)*

Contact information	Marwa Mohamed Farag, Neonatal Intensive Care Unit (NICU), Alexandria University Maternity Hospital, Alexandria, Egypt; Tel: 01288681788 ext 02; Email: d.marwa.farag@gmail.com
Notes	**Registered retrospectively with:** ClinicalTrial.gov Trial Registry: https://clinicaltrials.gov/; ID: NCT05706428 on 31 January 2023

Apgar: score of five measures of the condition of a newborn: Activity, Pulse, Grimace, Appearance, Respiration (from 1 to 10)
Bipap: bilevel positive airway pressure
BPD: bronchopulmonary dysplasia
bpm: breaths per minute
cCHD: cyanotic congenital heart disease
CLD: chronic lung diease
cm: centimetre
CNS: central nervous system
CO_2:
CPAP: continuous positive airway pressure
EIT: electronic impedance tomography
ETT: endotracheal intubation
FiO_2: fractional inspired oxygen
g: gram
GA: gestational age
H_2O:
HFJV: high-frequency jet ventilationn
HFV: high frequency ventilation
HFNC: high flow nasal cannula
HSPDA: haemodynamically significant patent ductus arteriosus
ICD: intercostal drain
IVH: intraventricular haemorrhage
InSurE: Intubation-Surfactant-Extubation
MAP: mean airway pressure
mcg/kg/min: microgram per kilogram per minute
min: minute
MV: mechanical ventilation
nCPAP: nasal continuous positive airway pressure
NEC: necrotising enterocolitis
nHFJV: nasal high-frequency jet ventilation
NHFO: nasal high-frequency oscillation
nHFOV: nasal high-frequency oscillation ventilation
NICU: neonatal intensive care unit
nIMV:non-invasive intermittent mandatory ventilation
nIPPV: nasal intermittent positive airway pressure
nMV: nasal mandatory ventilation
nSIMV:nasal synchronised intermittent mandatory ventilation
Paw: airway pressure
PCO_2: partial pressure carbon dioxide
PDA: patent ductus arteriosus
PEEP: positive end expiratory pressure
P osz: oscillation pressure
PVL: periventricular leukomalacia
RD: respiratory distress
RDS: respiratory distress syndrome
ROP: retinopathy of prematurity
RR: respiratory rate
RSI: respiratory index score
$SctO_2$: cutaneous oxygen saturation
SIMV: synchronised intermittent mandatory ventilation
SpO_2: pulse oximetry
$tcPCO_2$: transcutaneous carbon dioxide

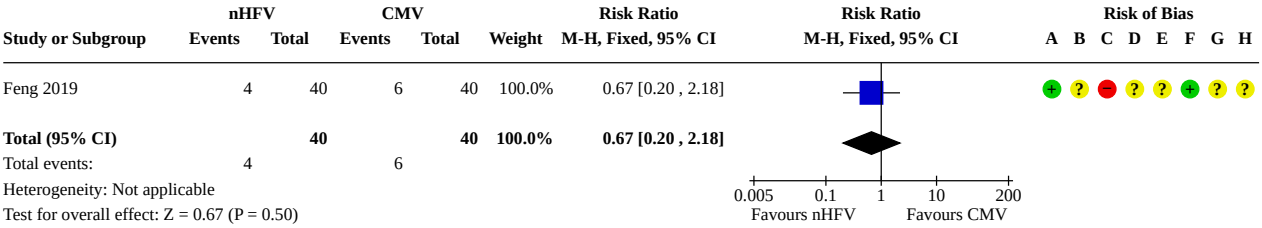
TTN: transient tachypnoea of the newborn
vs: versus
WHO: World Health Organization

DATA AND ANALYSES

Comparison 1. Initial respiratory support: nHFV vs invasive respiratory therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Mortality before hospital discharge	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.20, 2.18]
1.2 Duration of respiratory support, days	1	80	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.59, -0.27]
1.3 Chronic lung disease at 36 weeks	2	180	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.09, 1.59]
1.4 Pulmonary air leak syndromes	2	180	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.05, 1.14]
1.5 Length of hospital stay, days	1	80	Mean Difference (IV, Fixed, 95% CI)	-6.68 [-8.08, -5.28]

Analysis 1.1. Comparison 1: Initial respiratory support: nHFV vs invasive respiratory therapy, Outcome 1: Mortality before hospital discharge

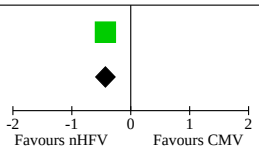


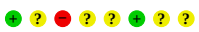
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.2. Comparison 1: Initial respiratory support: nHFV vs invasive respiratory therapy, Outcome 2: Duration of respiratory support, days

Study or Subgroup	nHFV Mean	nHFV SD	nHFV Total	CMV Mean	CMV SD	CMV Total	Weight	Mean Difference IV, Fixed, 95% CI
Feng 2019	3.5	0.35	40	3.93	0.4	40	100.0%	-0.43 [-0.59 , -0.27]
Total (95% CI)			**40**			**40**	**100.0%**	**-0.43 [-0.59 , -0.27]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.12 (P < 0.00001)
Test for subgroup differences: Not applicable





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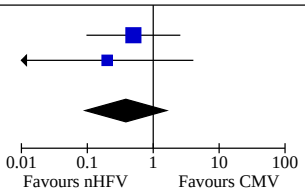
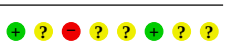
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.3. Comparison 1: Initial respiratory support: nHFV vs invasive respiratory therapy, Outcome 3: Chronic lung disease at 36 weeks

Study or Subgroup	nHFV Events	nHFV Total	CMV Events	CMV Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Feng 2019	2	40	4	40	61.5%	0.50 [0.10 , 2.58]
Yang 2020	0	50	2	50	38.5%	0.20 [0.01 , 4.06]
Total (95% CI)		**90**		**90**	**100.0%**	**0.38 [0.09 , 1.59]**
Total events:	2		6			

Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable





Risk of bias legend
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(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
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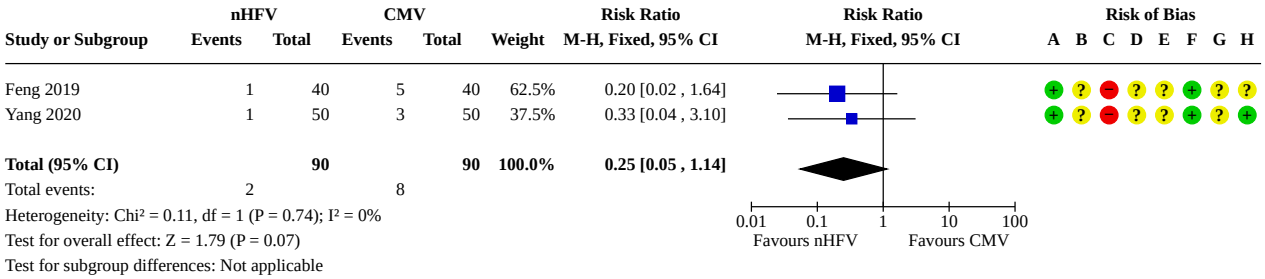
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.4. Comparison 1: Initial respiratory support: nHFV vs invasive respiratory therapy, Outcome 4: Pulmonary air leak syndromes



Risk of bias legend
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(C) Blinding of participants and personnel (performance bias): All outcomes
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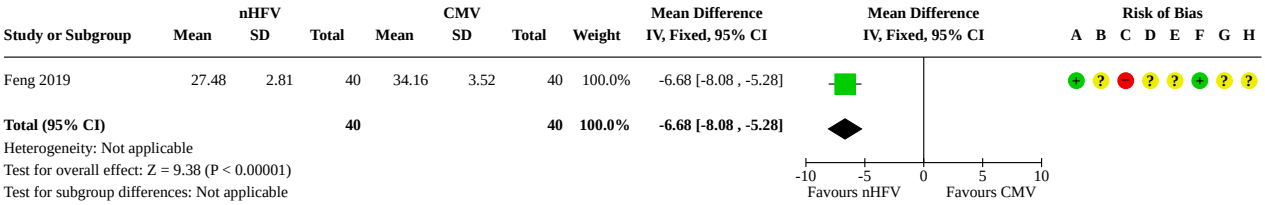
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.5. Comparison 1: Initial respiratory support: nHFV vs invasive respiratory therapy, Outcome 5: Length of hospital stay, days



Risk of bias legend
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(G) Selective reporting (reporting bias)
(H) Other bias

Comparison 2. Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities

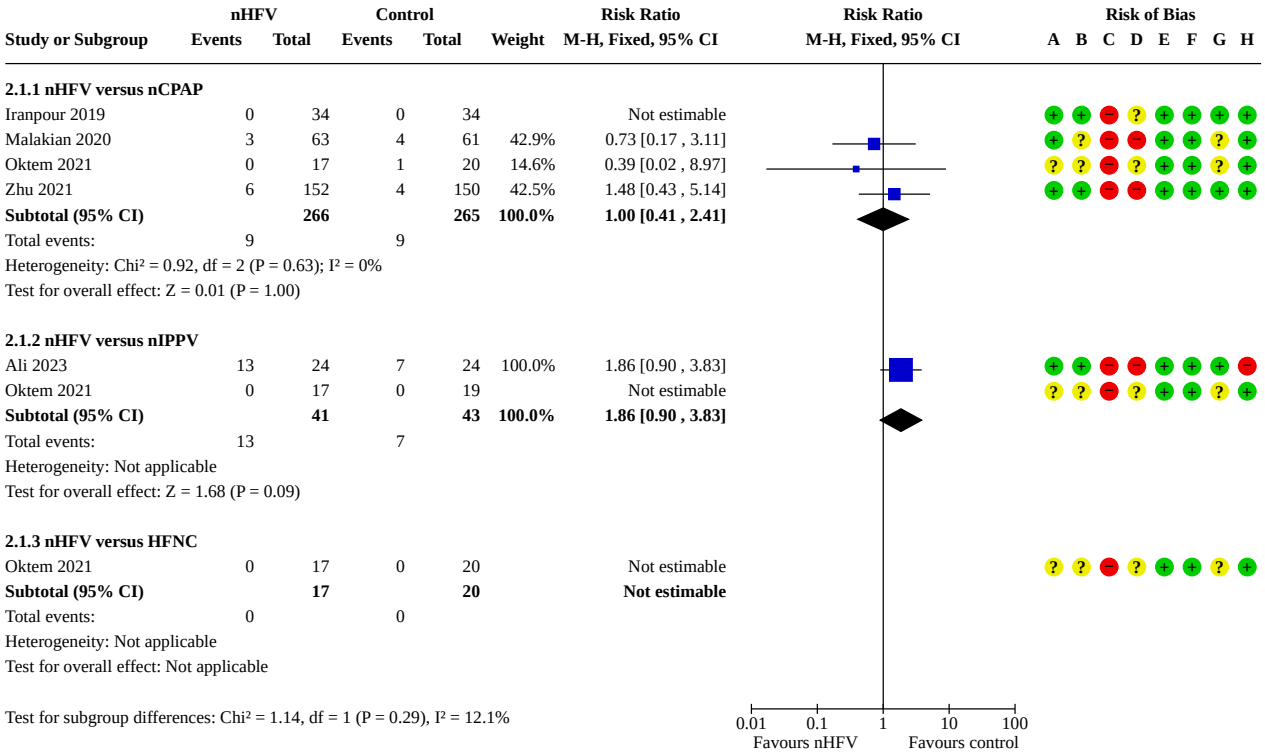
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Mortality before hospital discharge	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1.1 nHFV versus nCPAP	4	531	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.41, 2.41]
2.1.2 nHFV versus nIPPV	2	84	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [0.90, 3.83]
2.1.3 nHFV versus HFNC	1	37	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Endotracheal intubation	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.1 nHFV versus nCPAP	5	571	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.33, 0.82]
2.2.2 nHFV versus nIPPV	5	228	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.76, 2.34]
2.2.3 nHFV versus HFNC	1	37	Risk Ratio (M-H, Fixed, 95% CI)	2.94 [0.65, 13.27]
2.3 Trauma to the nostrils and upper airway	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.3.1 nHFV versus nCPAP	2	161	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.72, 1.47]
2.3.2 nHFV versus nIPPV	2	118	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.68, 1.40]
2.3.3 nHFV versus HFNC	1	37	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [1.25, 4.45]
2.4 Failure of respiratory support	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.4.1 nHFV versus nCPAP	3	463	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.36, 0.90]
2.4.2 nHFV versus nIPPV	1	36	Risk Ratio (M-H, Fixed, 95% CI)	2.79 [0.62, 12.57]
2.4.3 nHFV versus HFNC	1	37	Risk Ratio (M-H, Fixed, 95% CI)	2.94 [0.65, 13.27]
2.5 Duration of respiratory support, days	10		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.5.1 nHFV vs nCPAP	6	707	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.55, -0.40]
2.5.2 nHFV versus nIPPV	5	269	Mean Difference (IV, Fixed, 95% CI)	0.22 [-0.58, 1.01]
2.5.3 nHFV versus HFNC	1	37	Mean Difference (IV, Fixed, 95% CI)	-6.40 [-14.74, 1.94]
2.6 Duration of oxygen therapy, days	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.6.1 nHFV versus nCPAP	3	466	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.05, 0.11]
2.6.2 nHFV versus nIPPV	3	185	Mean Difference (IV, Fixed, 95% CI)	-0.65 [-1.13, -0.17]
2.7 Chronic lung disease at 36 weeks	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.7.1 nHFV versus nCPAP	4	481	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.80, 2.27]
2.7.2 nHFV versus nIPPV	5	307	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.42, 0.95]
2.7.3 nHFV versus HFNC	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.46, 2.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.8 Death or chronic lung disease at 36 weeks	1	68	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [0.52, 12.01]
2.8.1 nHFV versus nCPAP	1	68	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [0.52, 12.01]
2.9 Patent ductus arteriosus	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.9.1 nHFV versus nCPAP	2	105	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.29, 1.62]
2.9.2 nHFV versus nIPPV	2	84	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.19, 2.40]
2.9.3 nHFV versus HFNC	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.27, 5.09]
2.10 Pulmonary air leak syndromes	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.10.1 nHFV versus nCPAP	6	645	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [0.70, 5.75]
2.10.2 nHFV versus nIPPV	5	267	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.27, 1.66]
2.10.3 nHFV versus HFNC	1	37	Risk Ratio (M-H, Fixed, 95% CI)	3.50 [0.15, 80.71]
2.11 Proven sepsis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.11.1 nHFV versus nCPAP	2	77	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.38, 2.04]
2.11.2 nHFV versus nIPPV	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.34, 1.66]
2.11.3 nHFV versus HFNC	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.42, 2.43]
2.12 Necrotising enterocolitis	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.12.1 nHFV versus nCPAP	3	407	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.52, 2.69]
2.12.2 nHFV versus nIPPV	2	84	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.09, 4.64]
2.12.3 nHFV versus HFNC	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 4.55]
2.13 Necrotising enterocolitis (NEC) (Bell stage ≥ 2)	1	43	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.13.1 nHFV versus nIPPV	1	43	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.14 Spontaneous intestinal perforation	1	48	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.14.1 nHFV versus nIPPV	1	48	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.15 Intraventricular haemorrhage, any	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.15.1 nHFV versus nCPAP	3	179	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.16, 1.13]
2.15.2 nHFV versus nIPPV	5	288	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.30, 1.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.15.3 nHFV versus HFNC	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 4.55]
2.16 Intraventricular haemorrhage, Papile grade 3/4	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.16.1 nHFV versus nCPAP	4	531	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.36, 3.78]
2.16.2 nHFV versus nIPPV	1	36	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.16.3 nHFV versus HFNC	1	37	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.17 Periventricular leukomalacia	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.44, 2.07]
2.17.1 nHFV versus nIPPV	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.44, 2.07]
2.18 Retinopathy of prematurity, any	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.18.1 nHFV versus nCPAP	1	74	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.12, 3.97]
2.18.2 nHFV versus nIPPV	2	168	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.30, 0.98]
2.19 Retinopathy of prematurity, stage ≥ 3	1	302	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.29, 2.01]
2.19.1 nHFV versus nCPAP	1	302	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.29, 2.01]
2.20 Length of hospital stay, days	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.20.1 nHFV versus nCPAP	4	602	Mean Difference (IV, Fixed, 95% CI)	-4.07 [-4.46, -3.67]
2.20.2 nHFV versus nIPPV	2	125	Mean Difference (IV, Fixed, 95% CI)	-4.34 [-6.22, -2.47]

Analysis 2.1. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 1: Mortality before hospital discharge



Risk of bias legend

(A) Random sequence generation (selection bias)
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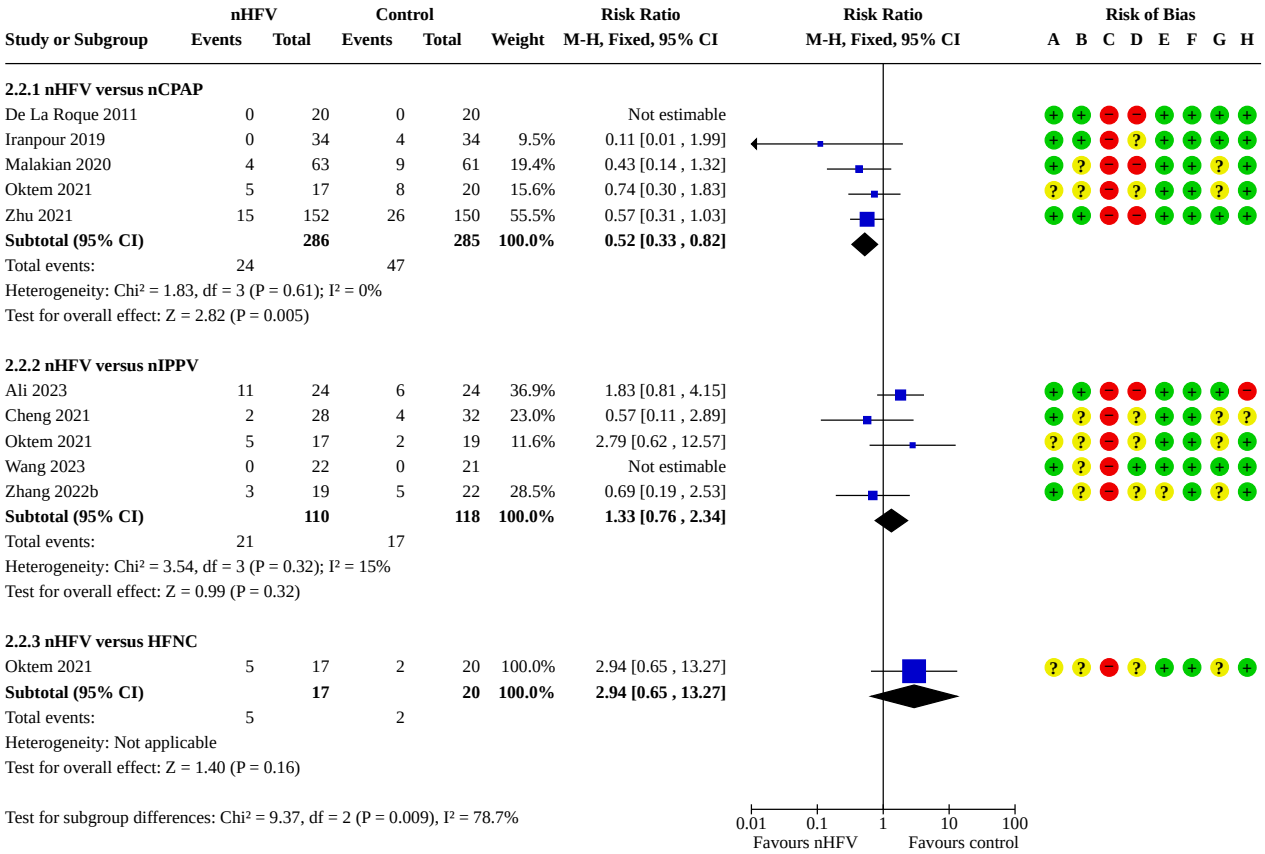
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.2. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 2: Endotracheal intubation



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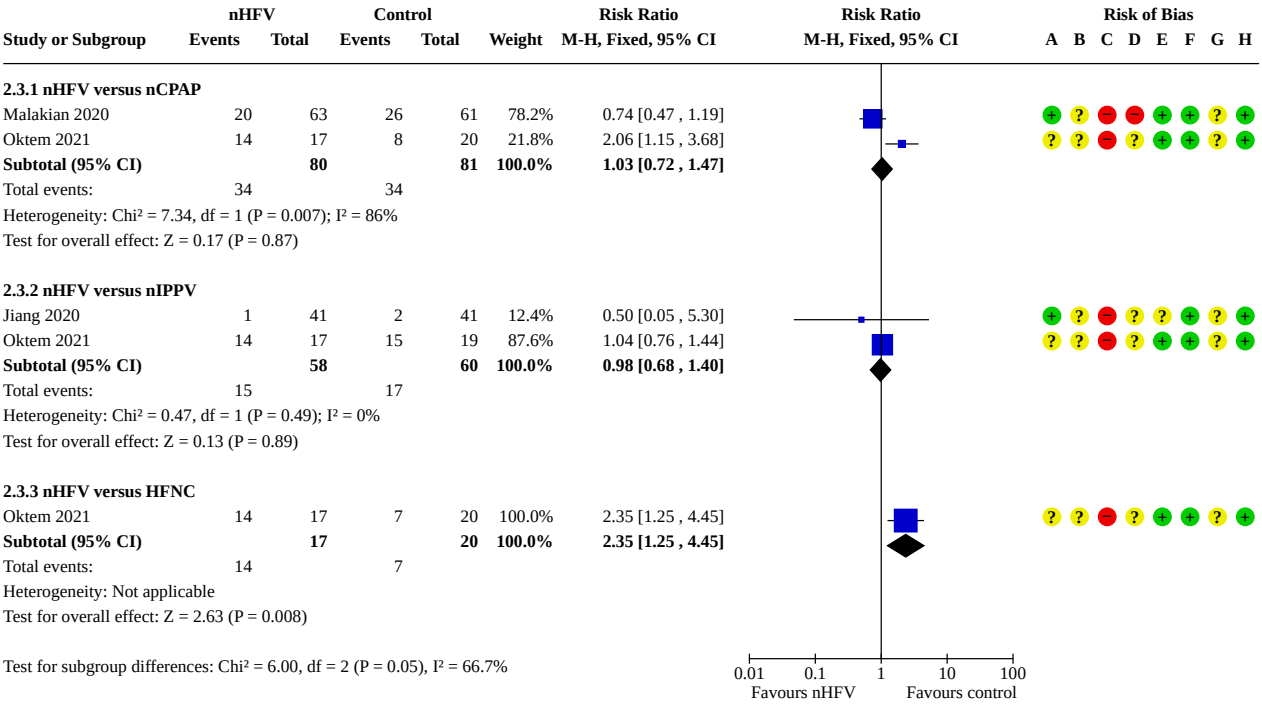
(H) Other bias

Analysis 2.3. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 3: Trauma to the nostrils and upper airway



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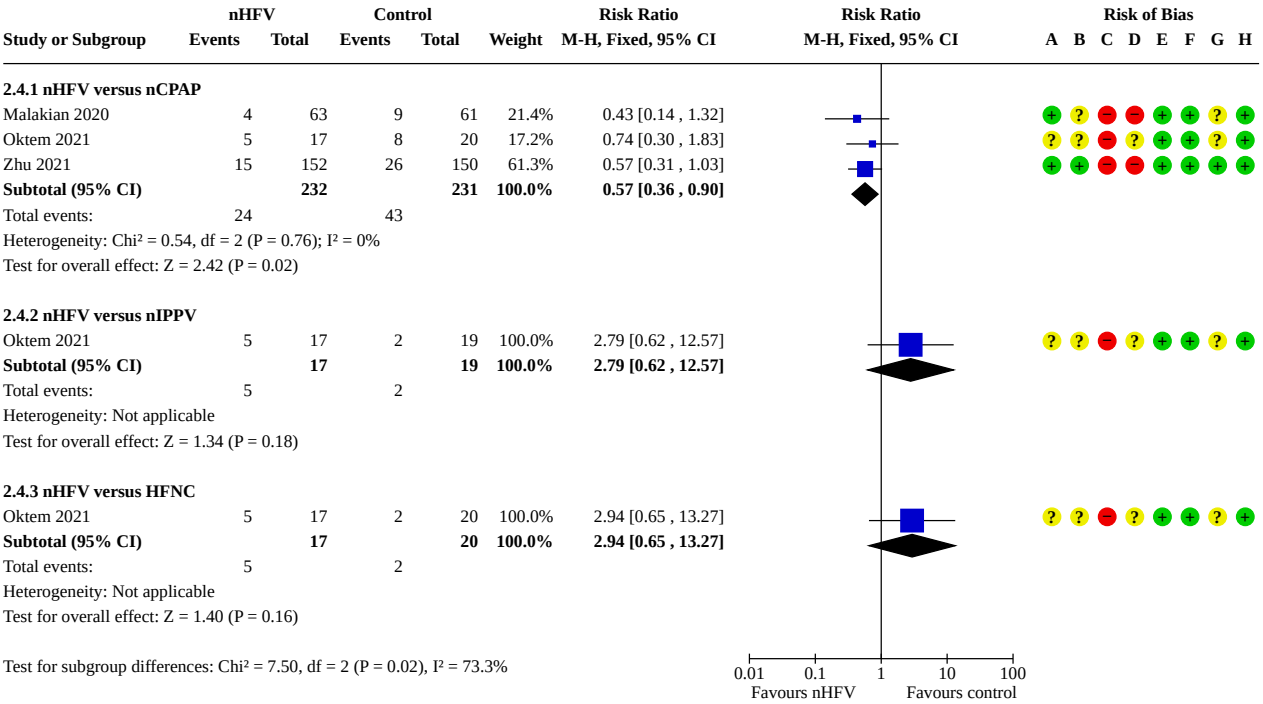
(H) Other bias

Analysis 2.4. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 4: Failure of respiratory support



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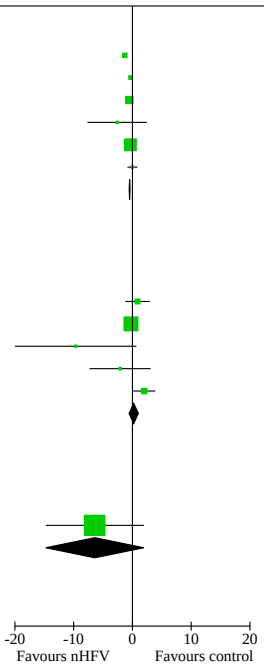
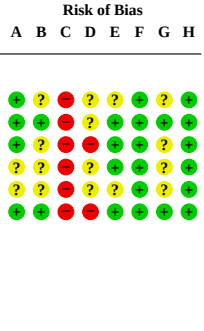
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.5. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 5: Duration of respiratory support, days

Study or Subgroup	nHFV Mean	nHFV SD	nHFV Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
2.5.1 nHFV vs nCPAP								
Guo 2021	3.81	0.49	36	5.08	0.5	38	10.7%	-1.27 [-1.50 , -1.04]
Iranpour 2019	0.8	0.3	34	1.1	0.7	34	8.3%	-0.30 [-0.56 , -0.04]
Malakian 2020	1.6	0.4	63	2.1	0.4	61	27.3%	-0.50 [-0.64 , -0.36]
Oktem 2021	4.7	4.8	17	7.3	10.3	20	0.0%	-2.60 [-7.66 , 2.46]
Zhang 2022a	2.49	0.24	51	2.83	0.28	51	52.9%	-0.34 [-0.44 , -0.24]
Zhu 2021	4	3.6	152	4	3.9	150	0.8%	0.00 [-0.85 , 0.85]
Subtotal (95% CI)			**353**			**354**	**100.0%**	**-0.48 [-0.55 , -0.40]**
Heterogeneity: Chi² = 58.34, df = 5 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 12.71 (P < 0.00001)								
2.5.2 nHFV versus nIPPV								
Ali 2023	6.5	4.375	24	5.625	2.83	24	14.6%	0.88 [-1.21 , 2.96]
Cheng 2021	4.19	1.95	28	4.44	1.95	32	64.7%	-0.25 [-1.24 , 0.74]
Jiang 2020	85.46	22.32	41	95.12	25.31	41	0.6%	-9.66 [-19.99 , 0.67]
Oktem 2021	4.7	4.8	17	6.8	10.4	19	2.3%	-2.10 [-7.30 , 3.10]
Wang 2023	6.29	1.33	22	4.28	4.21	21	17.8%	2.01 [0.13 , 3.89]
Subtotal (95% CI)			**132**			**137**	**100.0%**	**0.22 [-0.58 , 1.01]**
Heterogeneity: Chi² = 8.99, df = 4 (P = 0.06); I² = 56%								
Test for overall effect: Z = 0.54 (P = 0.59)								
2.5.3 nHFV versus HFNC								
Oktem 2021	4.7	4.8	17	11.1	18.3	20	100.0%	-6.40 [-14.74 , 1.94]
Subtotal (95% CI)			**17**			**20**	**100.0%**	**-6.40 [-14.74 , 1.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.50 (P = 0.13)								
Test for subgroup differences: Chi² = 4.85, df = 2 (P = 0.09), I² = 58.8%								





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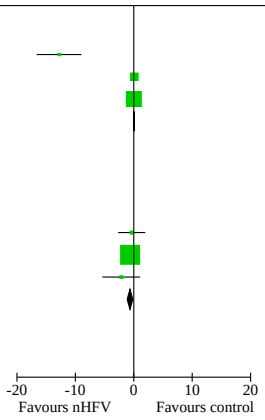
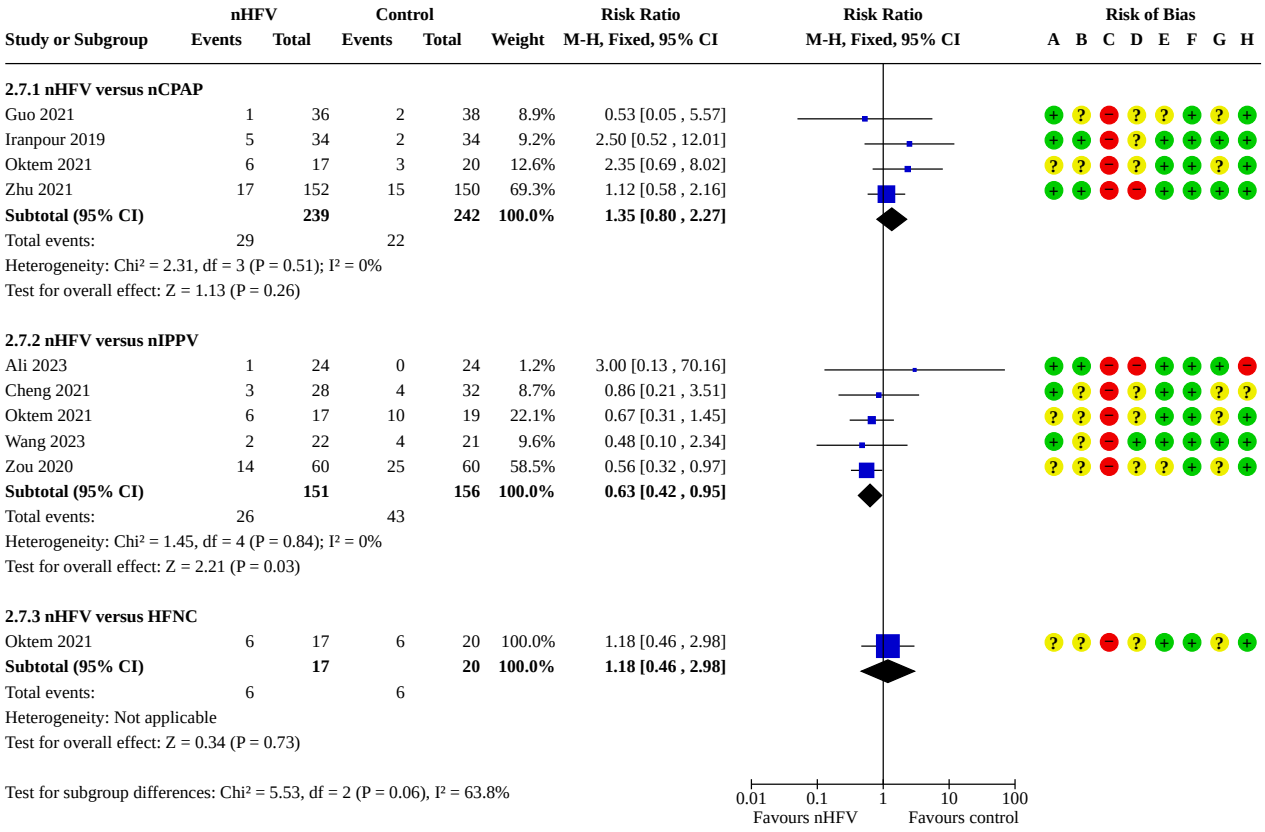
Analysis 2.6. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 6: Duration of oxygen therapy, days



Study or Subgroup	nHFV Mean	nHFV SD	nHFV Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
2.6.1 nHFV versus nCPAP									
De La Roque 2011	6.3	3.3	20	19.1	8.1	20	0.0%	-12.80 [-16.63 , -8.97]	+ + − − + + + +
Malakian 2020	1.8	0.3	63	1.7	0.5	61	28.7%	0.10 [-0.05 , 0.25]	+ ? − − + + ? +
Zhu 2021	0.4	0.41	152	0.39	0.41	150	71.3%	0.01 [-0.08 , 0.10]	+ + − − + + + +
Subtotal (95% CI)			**235**			**231**	**100.0%**	**0.03 [-0.05 , 0.11]**	
Heterogeneity: Chi² = 44.10, df = 2 (P < 0.00001); I² = 95%									
Test for overall effect: Z = 0.77 (P = 0.44)									
2.6.2 nHFV versus nIPPV									
Cheng 2021	10.93	4.82	28	11.28	4.29	32	4.2%	-0.35 [-2.67 , 1.97]	+ ? − ? + + ? ?
Jiang 2020	3.96	1.05	41	4.59	1.23	41	93.6%	-0.63 [-1.13 , -0.13]	+ ? − ? ? + ? +
Wang 2023	5.15	2.46	22	7.3	7.17	21	2.2%	-2.15 [-5.38 , 1.08]	+ ? − + + + + +
Subtotal (95% CI)			**91**			**94**	**100.0%**	**-0.65 [-1.13 , -0.17]**	
Heterogeneity: Chi² = 0.90, df = 2 (P = 0.64); I² = 0%									
Test for overall effect: Z = 2.67 (P = 0.008)									
Test for subgroup differences: Chi² = 7.59, df = 1 (P = 0.006), I² = 86.8%									

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.7. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 7: Chronic lung disease at 36 weeks

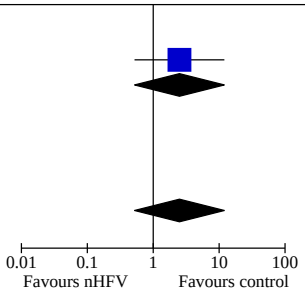


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.8. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 8: Death or chronic lung disease at 36 weeks

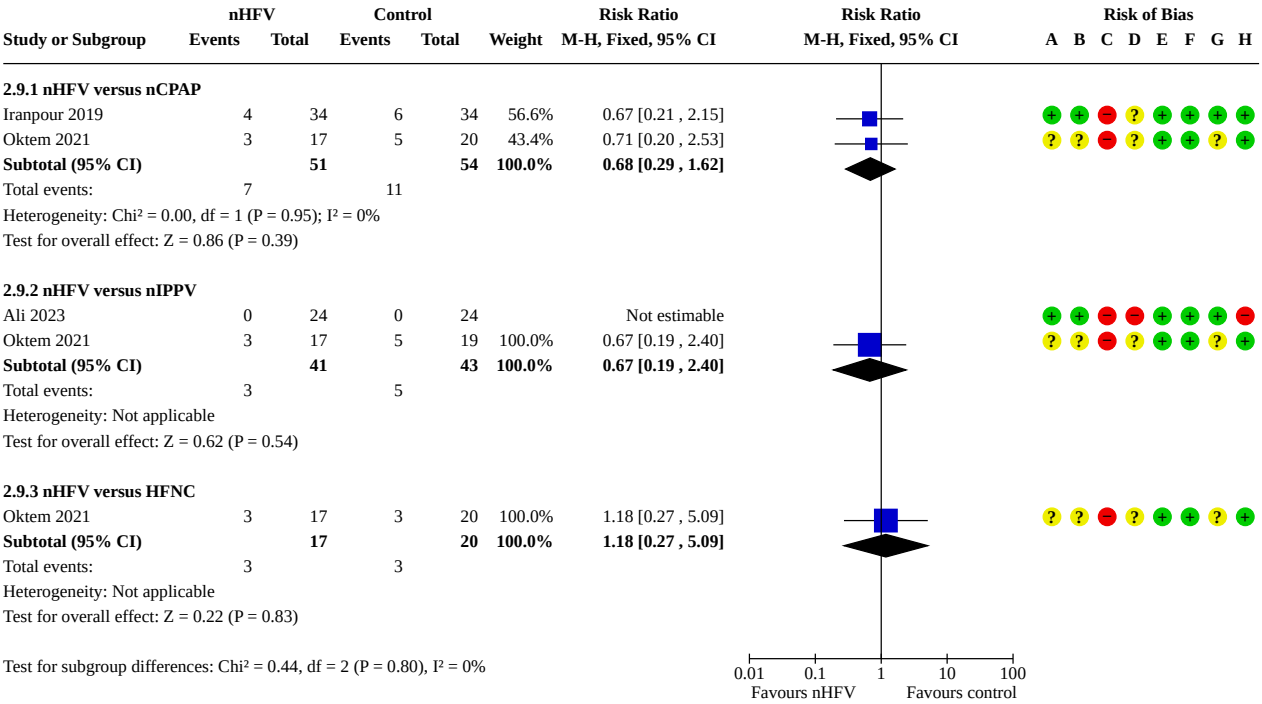
Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.8.1 nHFV versus nCPAP						
Iranpour 2019	5	34	2	34	100.0%	2.50 [0.52 , 12.01]
Subtotal (95% CI)		**34**		**34**	**100.0%**	**2.50 [0.52 , 12.01]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.25)						
Total (95% CI)		**34**		**34**	**100.0%**	**2.50 [0.52 , 12.01]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.25)						
Test for subgroup differences: Not applicable						



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

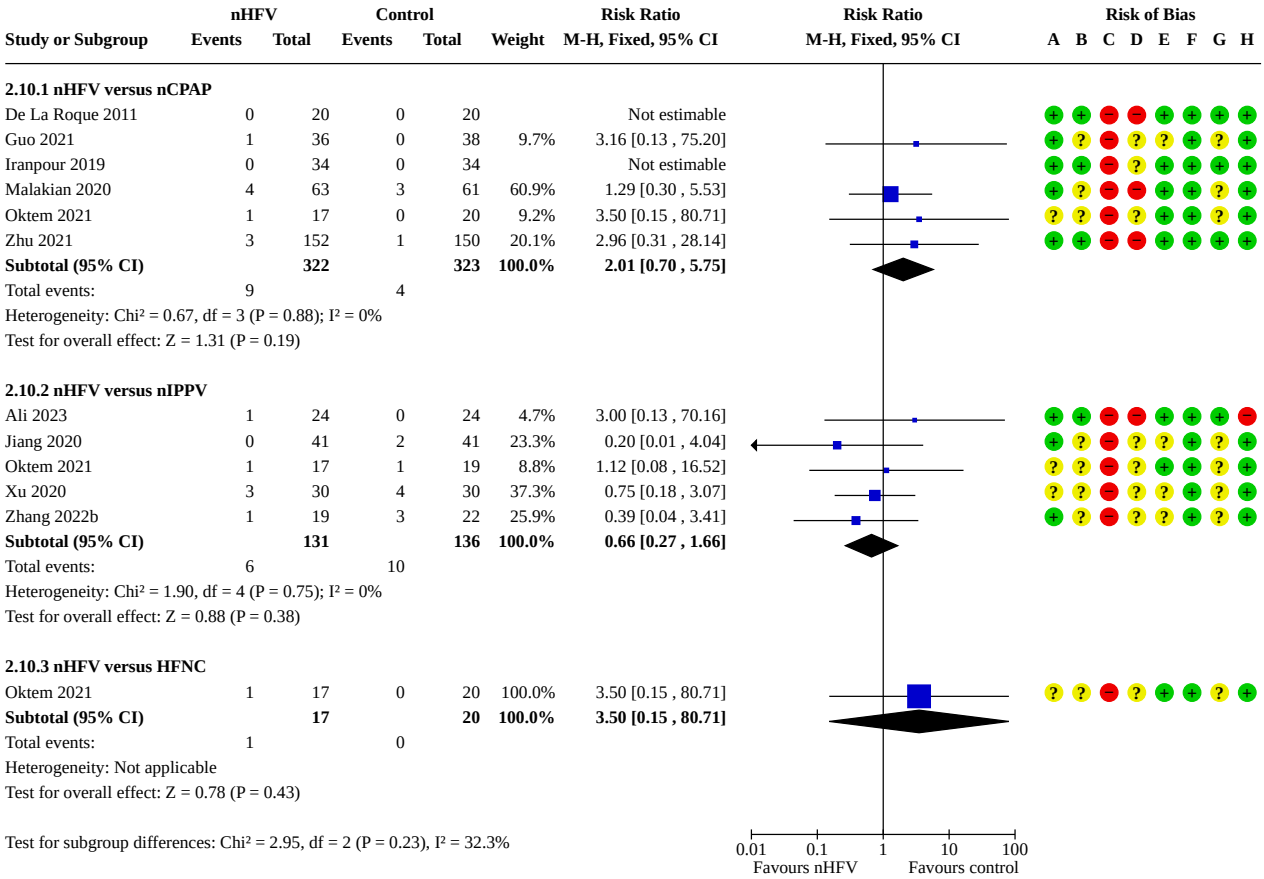
Analysis 2.9. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 9: Patent ductus arteriosus



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.10. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 10: Pulmonary air leak syndromes

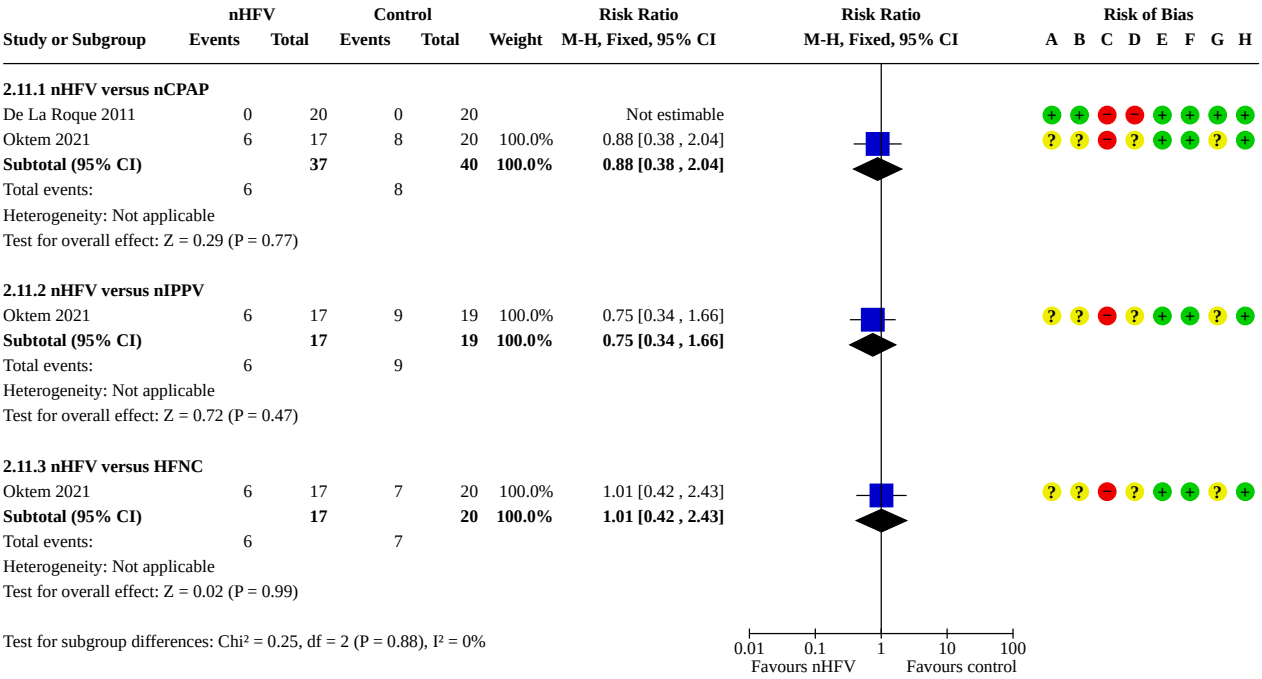


Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.10.1 nHFV versus nCPAP						
De La Roque 2011	0	20	0	20		Not estimable
Guo 2021	1	36	0	38	9.7%	3.16 [0.13 , 75.20]
Iranpour 2019	0	34	0	34		Not estimable
Malakian 2020	4	63	3	61	60.9%	1.29 [0.30 , 5.53]
Oktem 2021	1	17	0	20	9.2%	3.50 [0.15 , 80.71]
Zhu 2021	3	152	1	150	20.1%	2.96 [0.31 , 28.14]
Subtotal (95% CI)		**322**		**323**	**100.0%**	**2.01 [0.70 , 5.75]**
Total events:	9		4			
Heterogeneity: Chi² = 0.67, df = 3 (P = 0.88); I² = 0%						
Test for overall effect: Z = 1.31 (P = 0.19)						
2.10.2 nHFV versus nIPPV						
Ali 2023	1	24	0	24	4.7%	3.00 [0.13 , 70.16]
Jiang 2020	0	41	2	41	23.3%	0.20 [0.01 , 4.04]
Oktem 2021	1	17	1	19	8.8%	1.12 [0.08 , 16.52]
Xu 2020	3	30	4	30	37.3%	0.75 [0.18 , 3.07]
Zhang 2022b	1	19	3	22	25.9%	0.39 [0.04 , 3.41]
Subtotal (95% CI)		**131**		**136**	**100.0%**	**0.66 [0.27 , 1.66]**
Total events:	6		10			
Heterogeneity: Chi² = 1.90, df = 4 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.88 (P = 0.38)						
2.10.3 nHFV versus HFNC						
Oktem 2021	1	17	0	20	100.0%	3.50 [0.15 , 80.71]
Subtotal (95% CI)		**17**		**20**	**100.0%**	**3.50 [0.15 , 80.71]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.43)						
Test for subgroup differences: Chi² = 2.95, df = 2 (P = 0.23), I² = 32.3%						

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

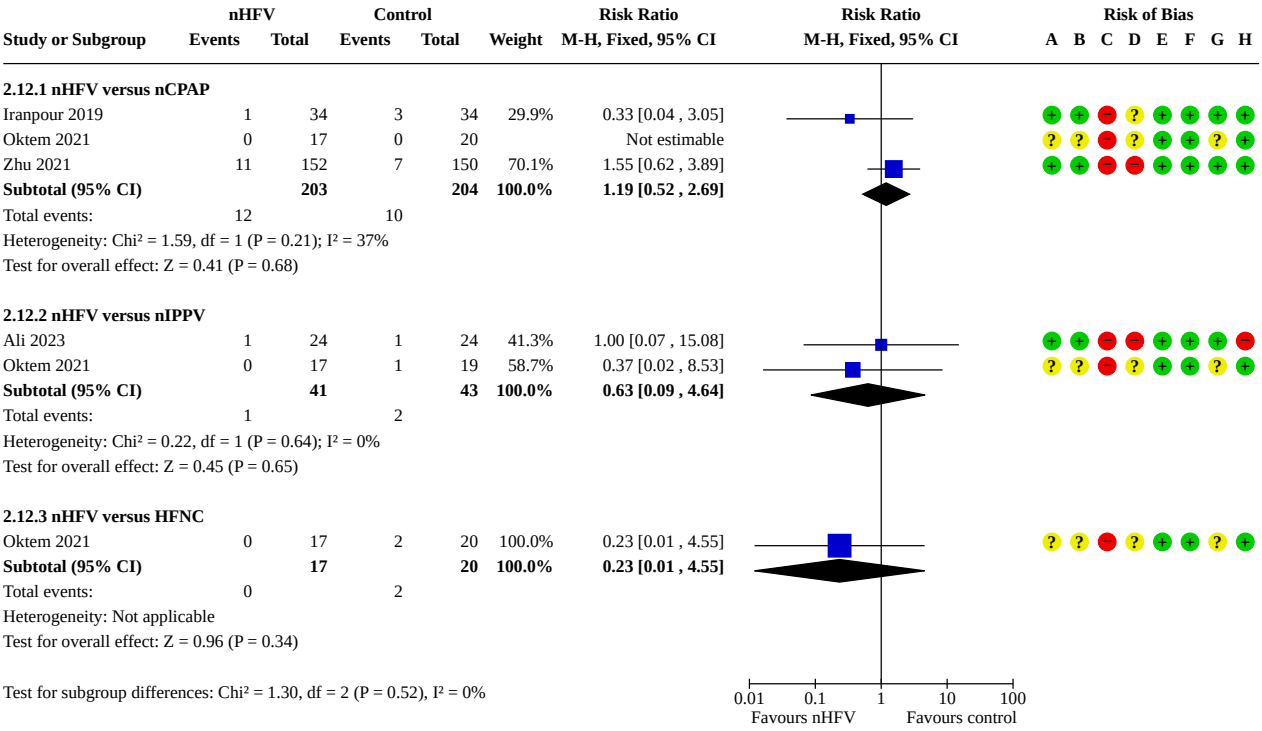
Analysis 2.11. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 11: Proven sepsis



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.12. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 12: Necrotising enterocolitis

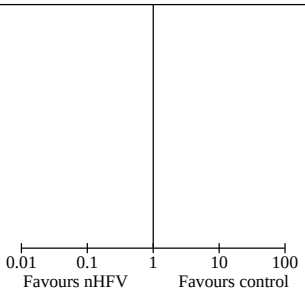


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.13. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 13: Necrotising enterocolitis (NEC) (Bell stage ≥ 2)

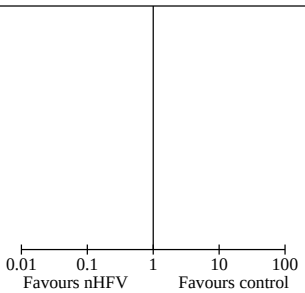
Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F	G	H
2.13.1 nHFV versus nIPPV														
Wang 2023	0	22	0	21		Not estimable	+	?	−	+	+	+	+	+
Subtotal (95% CI)		**22**		**21**		**Not estimable**								
Total events:	0		0											
Heterogeneity: Not applicable														
Test for overall effect: Not applicable														
Total (95% CI)		**22**		**21**		**Not estimable**								
Total events:	0		0											
Heterogeneity: Not applicable														
Test for overall effect: Not applicable														
Test for subgroup differences: Not applicable														



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

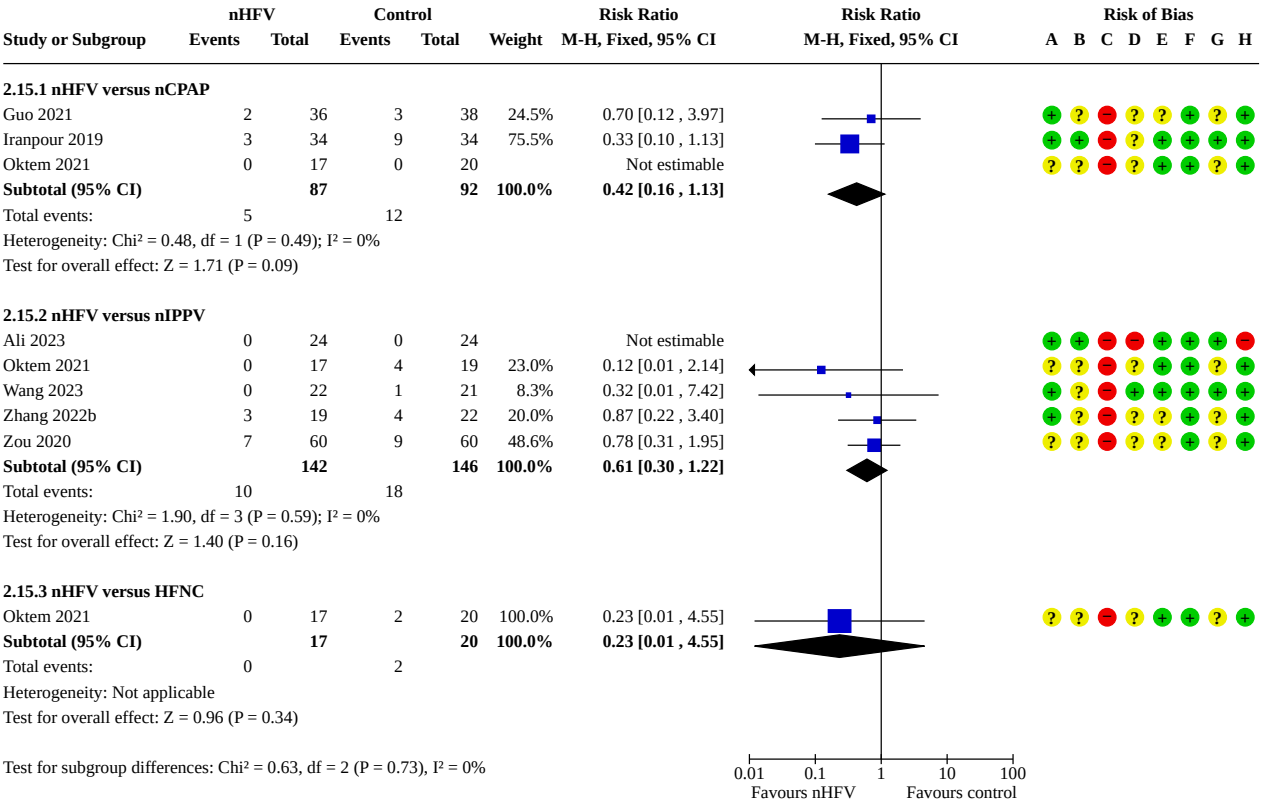
Analysis 2.14. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 14: Spontaneous intestinal perforation

Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F	G	H
2.14.1 nHFV versus nIPPV														
Ali 2023	0	24	0	24		Not estimable	+	+	−	−	+	+	+	−
Subtotal (95% CI)		**24**		**24**		**Not estimable**								
Total events:	0		0											
Heterogeneity: Not applicable														
Test for overall effect: Not applicable														
Total (95% CI)		**24**		**24**		**Not estimable**								
Total events:	0		0											
Heterogeneity: Not applicable														
Test for overall effect: Not applicable														
Test for subgroup differences: Not applicable														



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

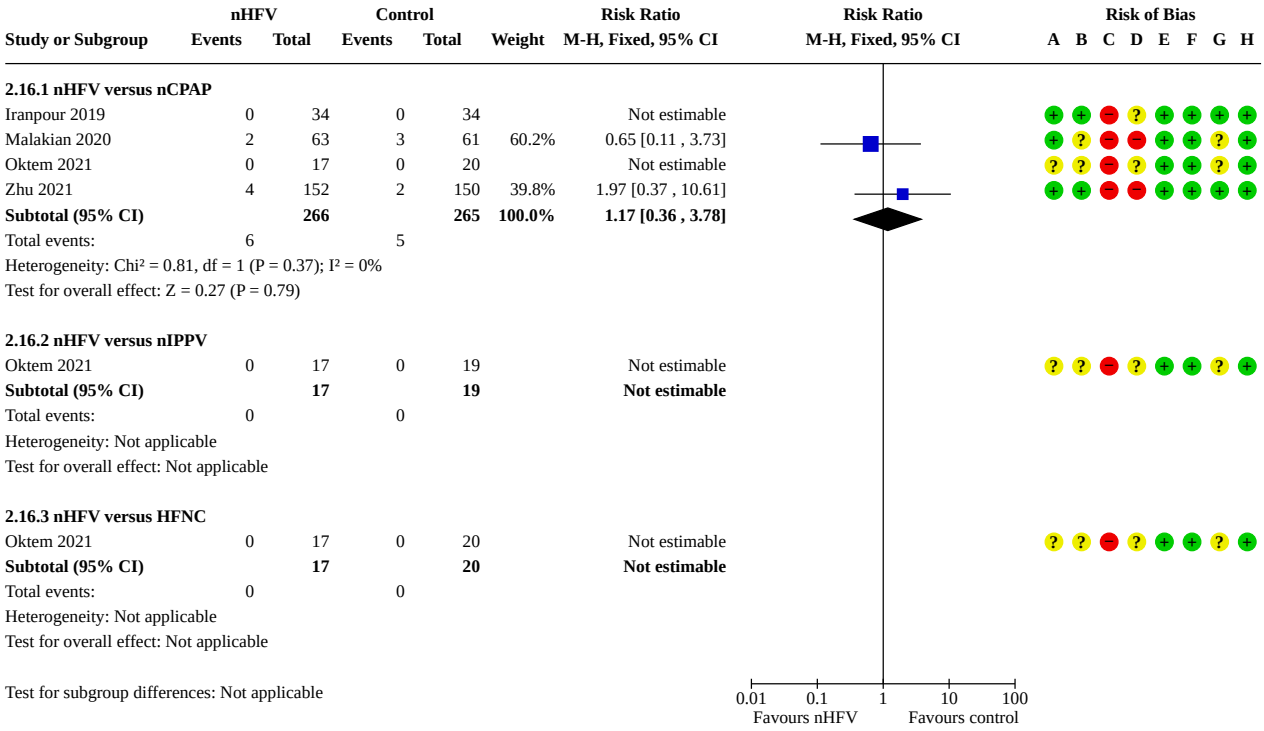
Analysis 2.15. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 15: Intraventricular haemorrhage, any



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

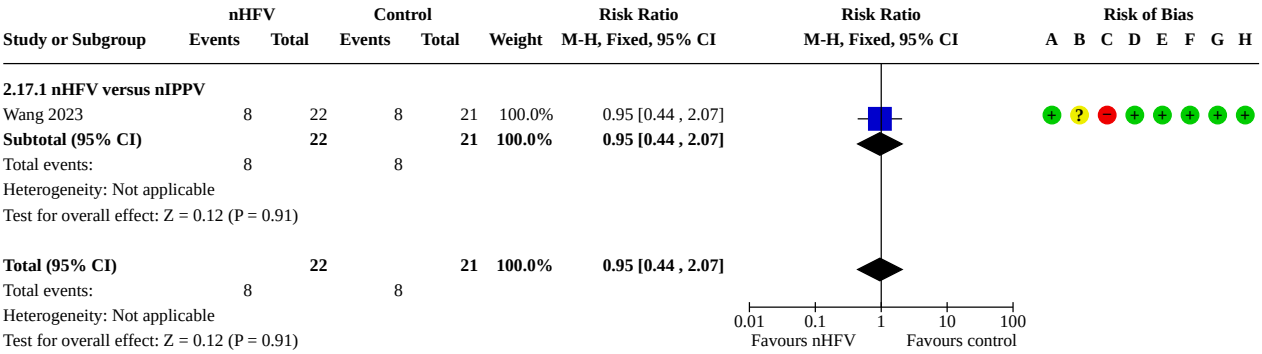
Analysis 2.16. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 16: Intraventricular haemorrhage, Papile grade 3/4



Risk of bias legend

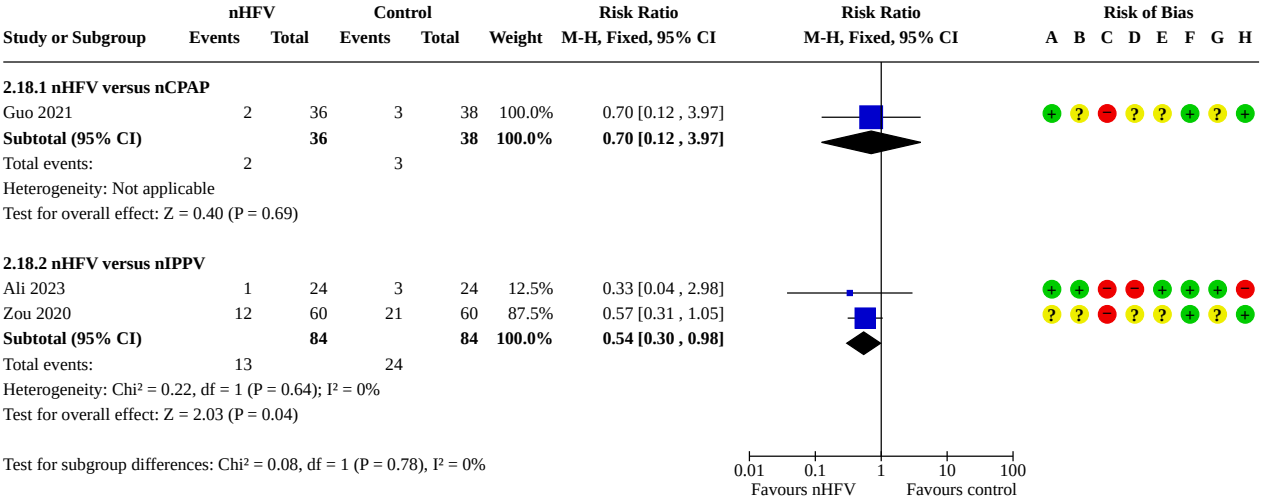
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.17. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 17: Periventricular leukomalacia



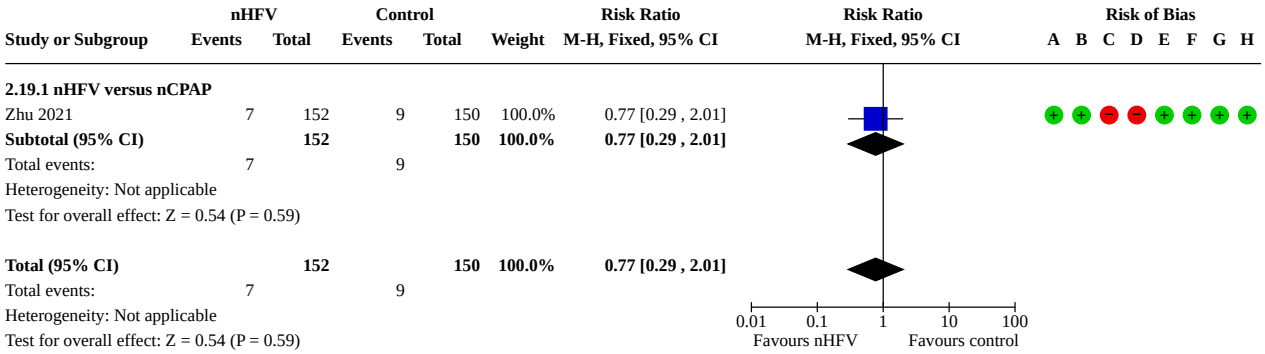
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.18. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 18: Retinopathy of prematurity, any



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

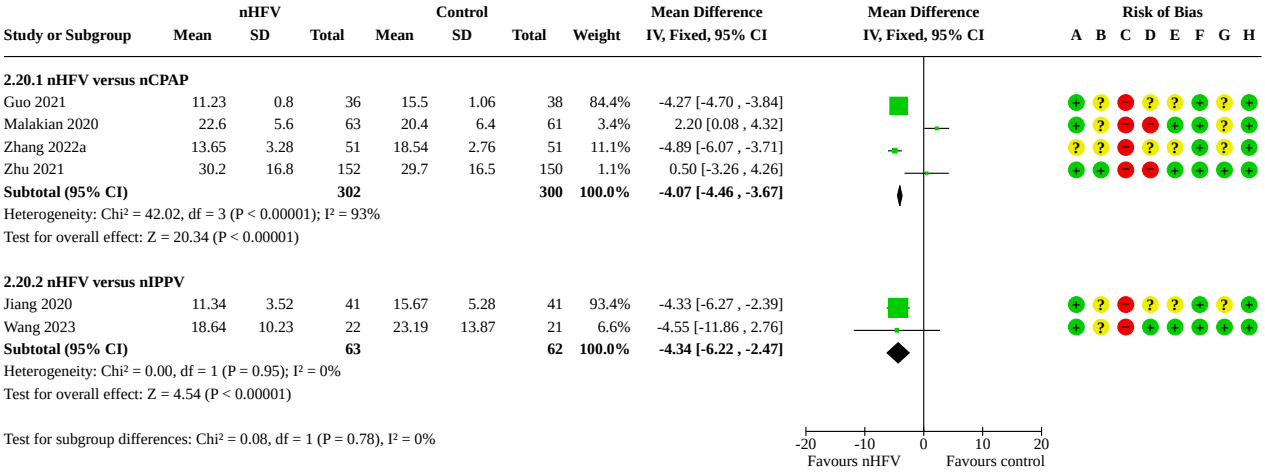
Analysis 2.19. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 19: Retinopathy of prematurity, stage ≥ 3



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 2.20. Comparison 2: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities, Outcome 20: Length of hospital stay, days



Risk of bias legend

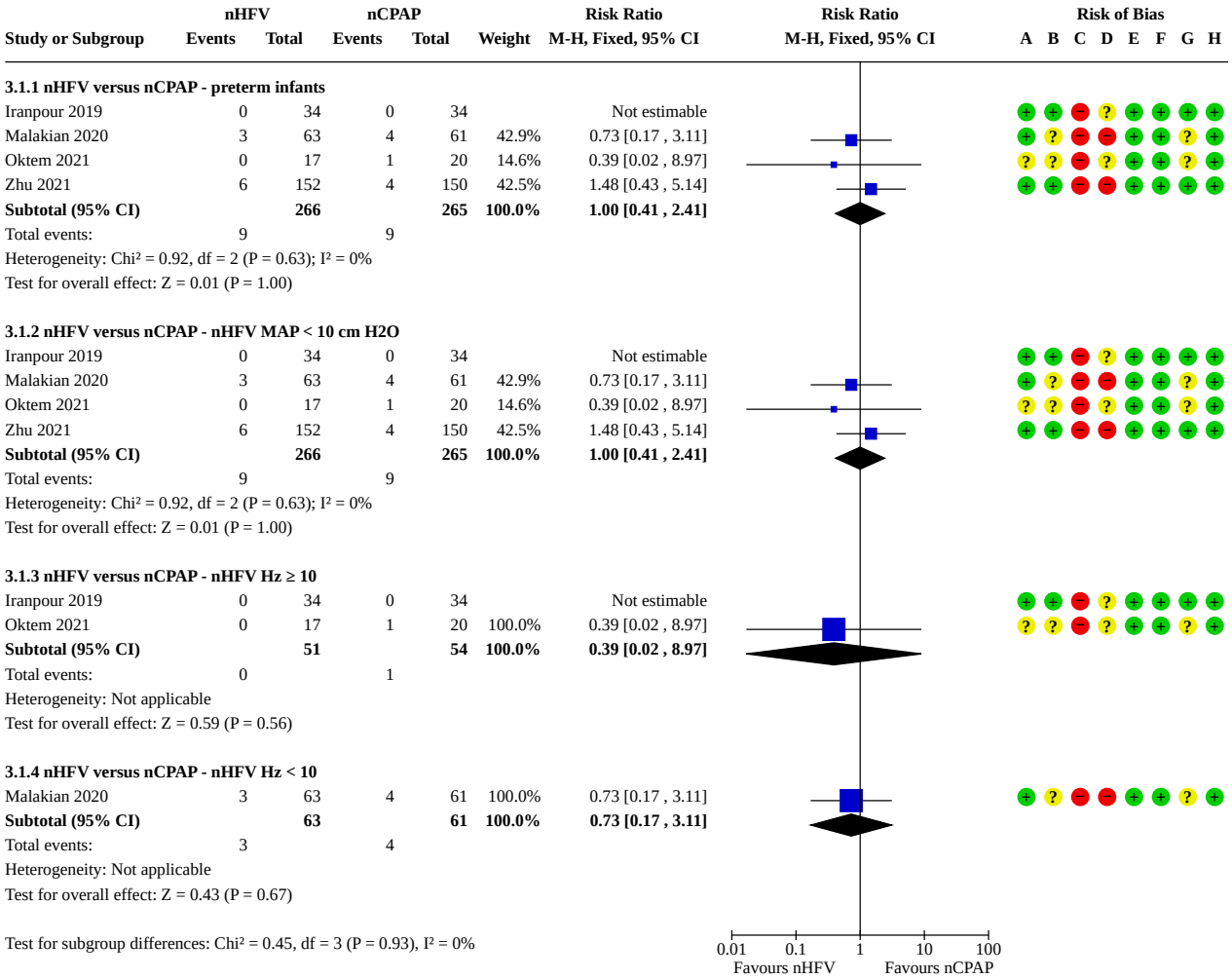
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Comparison 3. Initial respiratory support: nHFV vs nCPAP - subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Mortality before hospital discharge	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1.1 nHFV versus nCPAP - preterm infants	4	531	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.41, 2.41]
3.1.2 nHFV versus nCPAP - nHFV MAP < 10 cm H2O	4	531	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.41, 2.41]
3.1.3 nHFV versus nCPAP - nHFV Hz ≥ 10	2	105	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.02, 8.97]
3.1.4 nHFV versus nCPAP - nHFV Hz < 10	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.17, 3.11]
3.2 Endotracheal intubation	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.2.1 nHFV versus nCPAP - term or near-term infants	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2.2 nHFV versus nCPAP - preterm infants	4	531	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.33, 0.82]
3.2.3 nHFV versus nCPAP - nHFV MAP < 10 cm H2O	5	571	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.33, 0.82]
3.2.4 nHFV versus nCPAP - nHFV Hz ≥ 10	2	105	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.21, 1.18]
3.2.5 nHFV versus nCPAP - nHFV Hz < 10	2	164	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.14, 1.32]
3.3 Failure of respiratory support	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.3.1 nHFV versus nCPAP - preterm infants	3	463	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.36, 0.90]
3.3.2 nHFV versus nCPAP - nHFV MAP < 10 cm H2O	3	463	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.36, 0.90]
3.3.3 nHFV versus nCPAP - nHFV Hz ≥ 10	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.30, 1.83]
3.3.4 nHFV versus nCPAP - nHFV Hz < 10	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.14, 1.32]
3.4 Chronic lung disease at 36 weeks	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.4.1 nHFV versus nCPAP - preterm infants	4	481	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.80, 2.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4.2 nHFV versus nCPAP - nHFV MAP < 10 cm H2O	3	407	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.84, 2.44]
3.4.3 nHFV versus nCPAP - nHFV Hz ≥ 10	2	105	Risk Ratio (M-H, Fixed, 95% CI)	2.41 [0.91, 6.38]
3.5 Death or chronic lung disease at 36 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.5.1 nHFV versus nCPAP - preterm infants	1	68	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [0.52, 12.01]
3.5.2 nHFV versus nCPAP - nHFV MAP < 10 cm H2O	1	68	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [0.52, 12.01]
3.5.3 nHFV versus nCPAP - nHFV Hz ≥ 10	1	68	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [0.52, 12.01]
3.6 Intraventricular haemorrhage, Papile grade 3/4	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.6.1 nHFV versus nCPAP - preterm infants	4	531	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.36, 3.78]
3.6.2 nHFV versus nCPAP - nHFV MAP < 10 cm H2O	4	531	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.36, 3.78]
3.6.3 nHFV versus nCPAP - nHFV Hz ≥ 10	2	105	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.6.4 nHFV versus nCPAP - nHFV Hz < 10	1	124	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.11, 3.73]

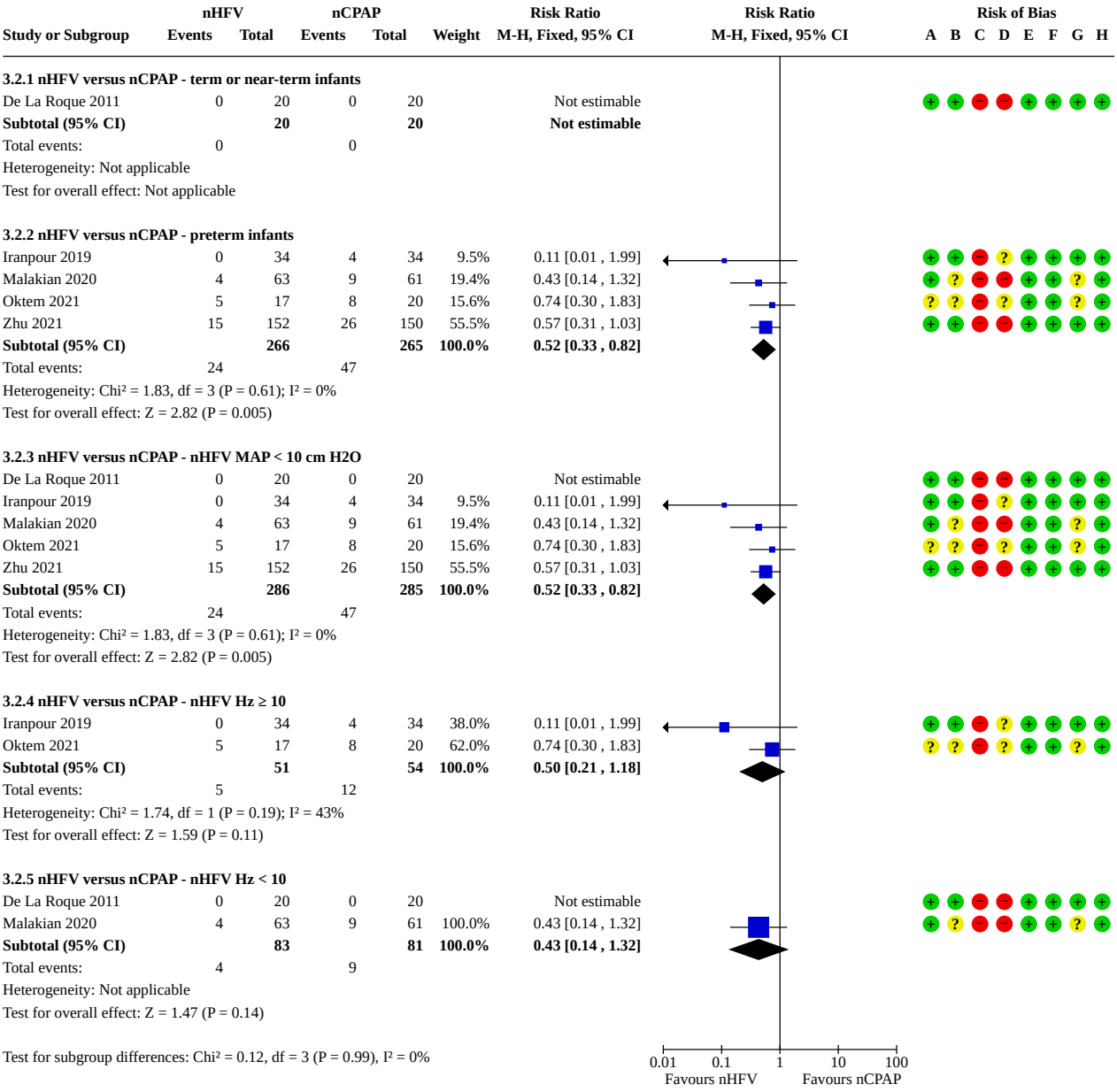
Analysis 3.1. Comparison 3: Initial respiratory support: nHFV vs nCPAP - subgroup analyses, Outcome 1: Mortality before hospital discharge



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

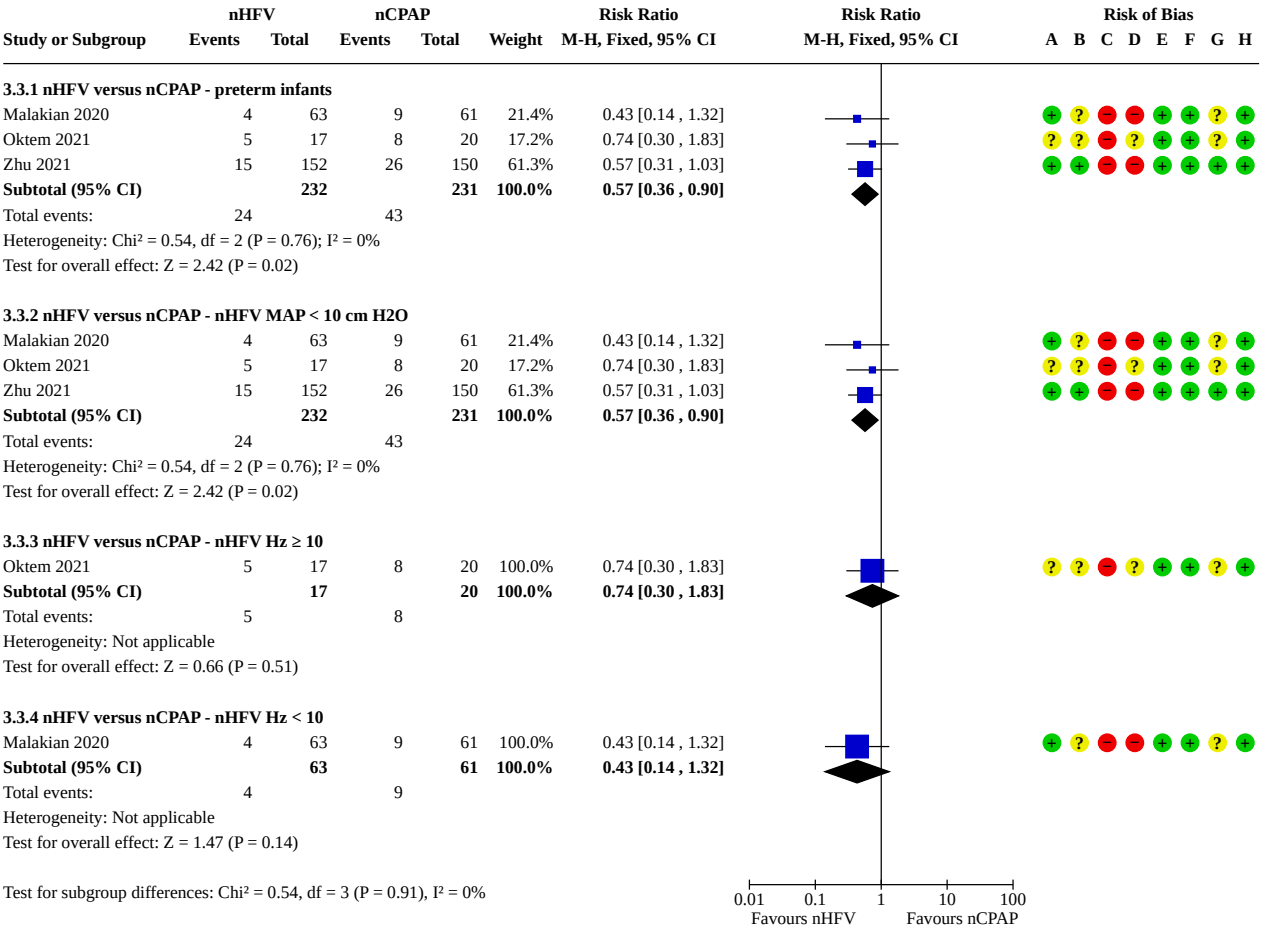
Analysis 3.2. Comparison 3: Initial respiratory support: nHFV vs nCPAP - subgroup analyses, Outcome 2: Endotracheal intubation



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

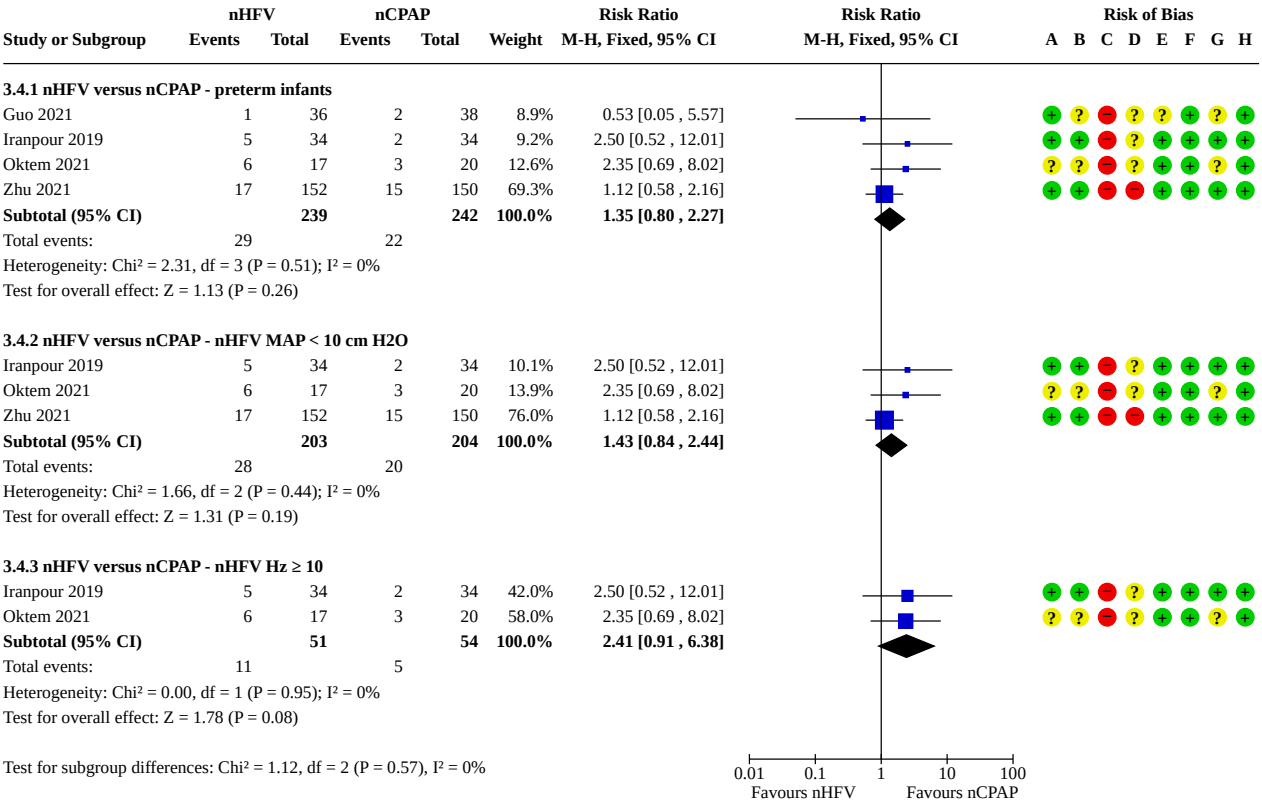
Analysis 3.3. Comparison 3: Initial respiratory support: nHFV vs nCPAP - subgroup analyses, Outcome 3: Failure of respiratory support



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

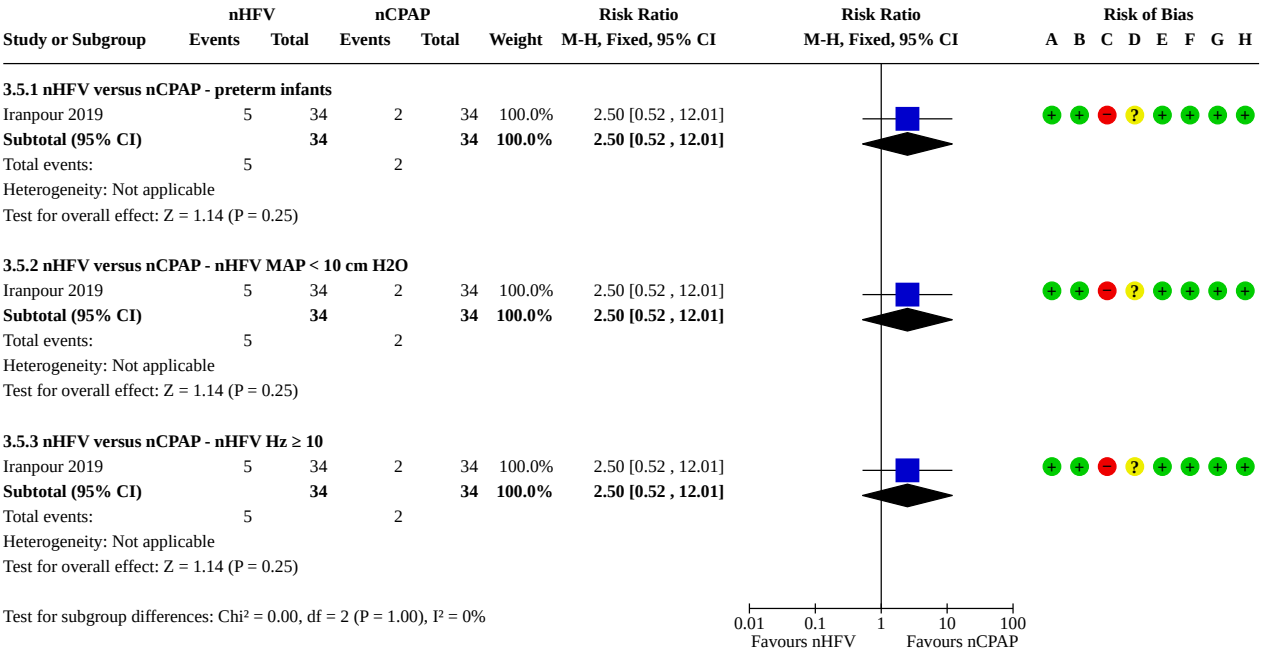
Analysis 3.4. Comparison 3: Initial respiratory support: nHFV vs nCPAP - subgroup analyses, Outcome 4: Chronic lung disease at 36 weeks



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

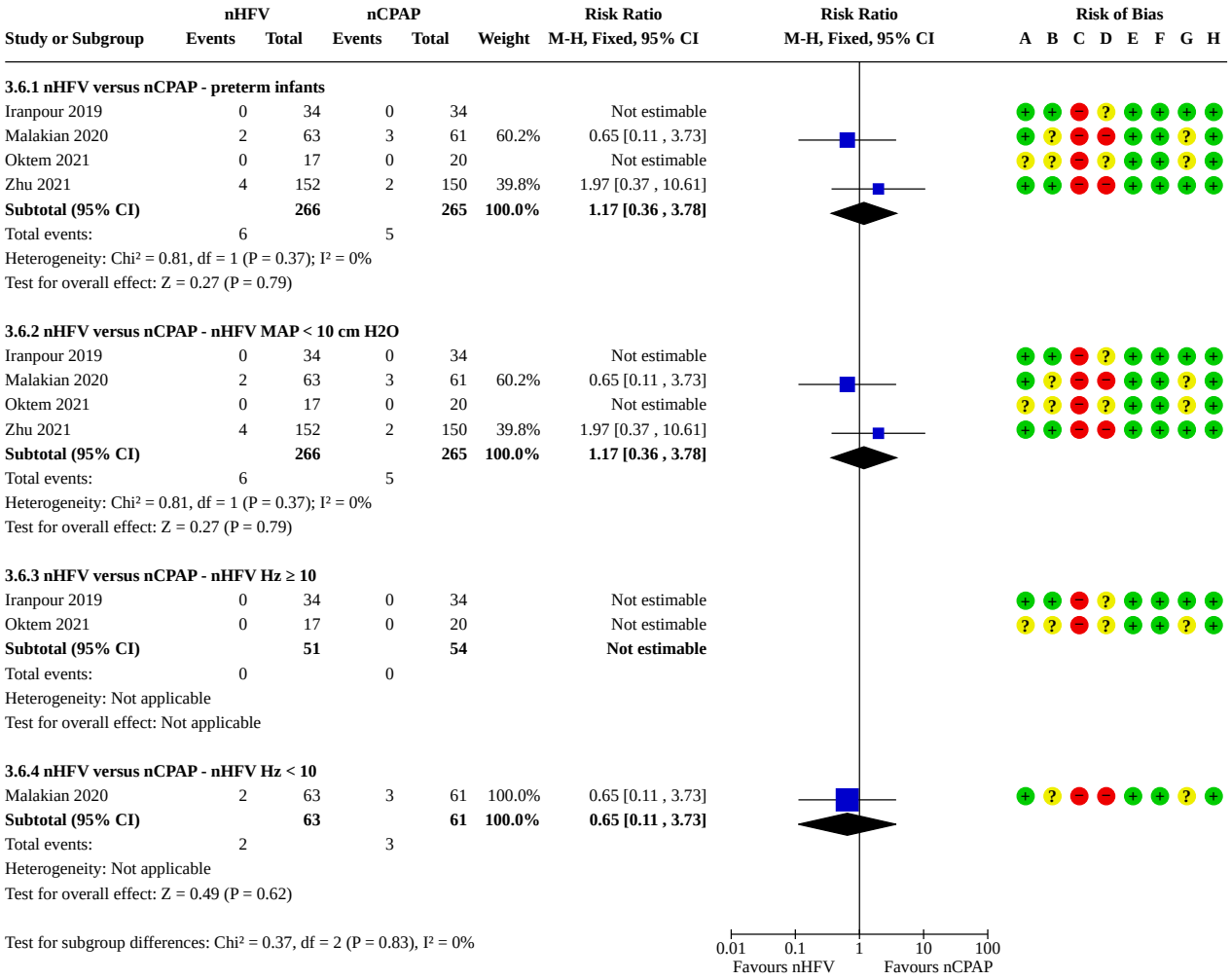
Analysis 3.5. Comparison 3: Initial respiratory support: nHFV vs nCPAP - subgroup analyses, Outcome 5: Death or chronic lung disease at 36 weeks



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 3.6. Comparison 3: Initial respiratory support: nHFV vs nCPAP - subgroup analyses, Outcome 6: Intraventricular haemorrhage, Papile grade 3/4



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

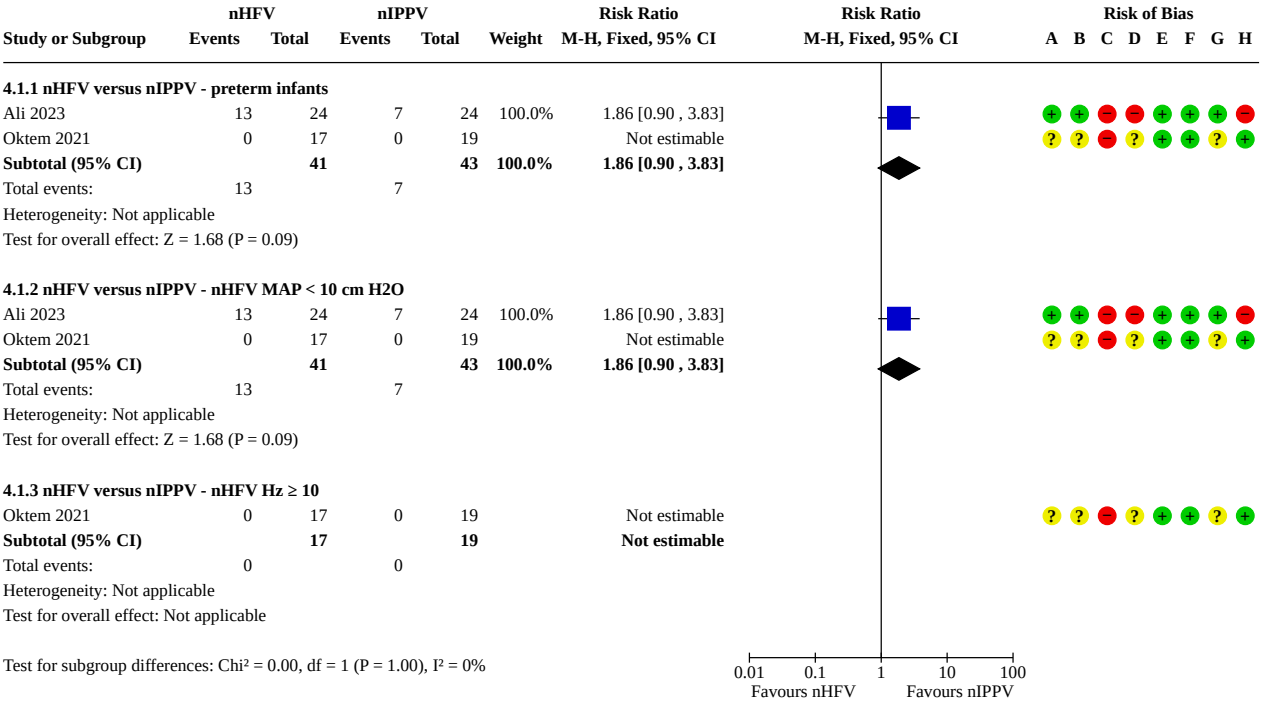
Comparison 4. Initial respiratory support: nHFV vs nIPPV - subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Mortality before hospital discharge	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1.1 nHFV versus nIPPV - preterm infants	2	84	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [0.90, 3.83]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.2 nHFV versus nIPPV - nHFV MAP < 10 cm H2O	2	84	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [0.90, 3.83]
4.1.3 nHFV versus nIPPV - nHFV Hz ≥ 10	1	36	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Endotracheal intubation	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.2.1 nHFV versus nIPPV - term or near-term infants	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.78]
4.2.2 nHFV versus nIPPV- preterm infants	4	187	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.84, 3.00]
4.2.3 nHFV versus nIPPV - nHFV MAP < 10 cm H2O	3	125	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.68, 2.44]
4.2.4 nHFV versus nIPPV - nHFV Hz ≥ 10	1	36	Risk Ratio (M-H, Fixed, 95% CI)	2.79 [0.62, 12.57]
4.3 Failure of respiratory support	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.3.1 nHFV versus nIPPV- preterm infants	1	36	Risk Ratio (M-H, Fixed, 95% CI)	2.79 [0.62, 12.57]
4.3.2 nHFV versus nIPPV - nHFV MAP < 10 cm H2O	1	36	Risk Ratio (M-H, Fixed, 95% CI)	2.79 [0.62, 12.57]
4.3.3 nHFV versus nIPPV - nHFV Hz ≥ 10	1	36	Risk Ratio (M-H, Fixed, 95% CI)	2.79 [0.62, 12.57]
4.4 Chronic lung disease at 36 weeks	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.4.1 nHFV versus nIPPV - preterm infants	5	307	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.42, 0.95]
4.4.2 nHFV versus nIPPV - nHFV MAP < 10 cm H2O	2	84	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.37, 1.66]
4.4.3 nHFV versus nIPPV - nHFV Hz ≥ 10	1	36	Risk Ratio (M-H, Fixed, 95% CI)	3.35 [0.78, 14.44]
4.5 Intraventricular haemorrhage, Papile grade 3/4	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.5.1 nHFV versus nIPPV - preterm infants	1	36	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.5.2 nHFV versus nIPPV - nHFV MAP < 10 cm H2O	1	36	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.5.3 nHFV versus nIPPV - nHFV Hz ≥ 10	1	32	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

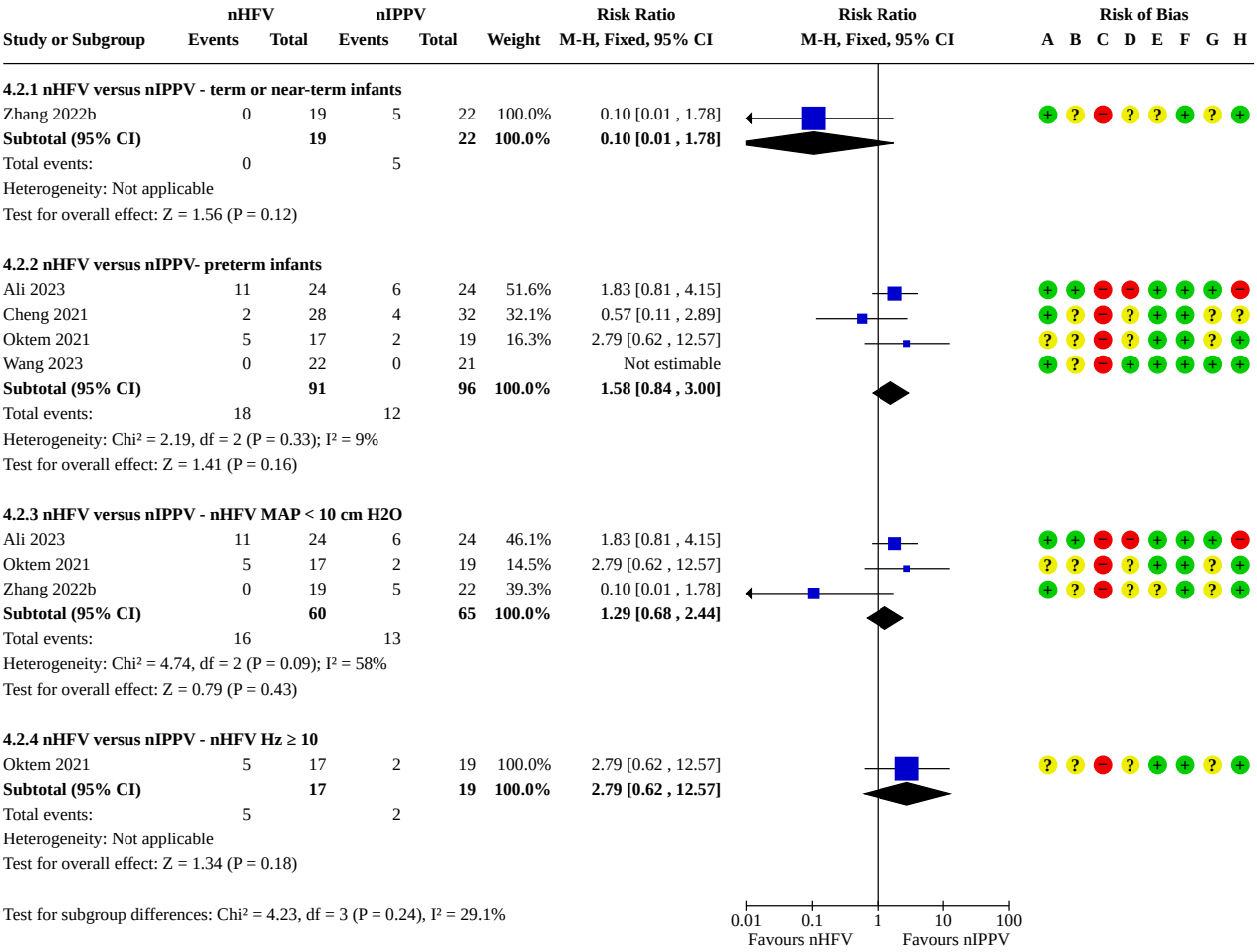
Analysis 4.1. Comparison 4: Initial respiratory support: nHFV vs nIPPV - subgroup analyses, Outcome 1: Mortality before hospital discharge



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 4.2. Comparison 4: Initial respiratory support: nHFV vs nIPPV - subgroup analyses, Outcome 2: Endotracheal intubation



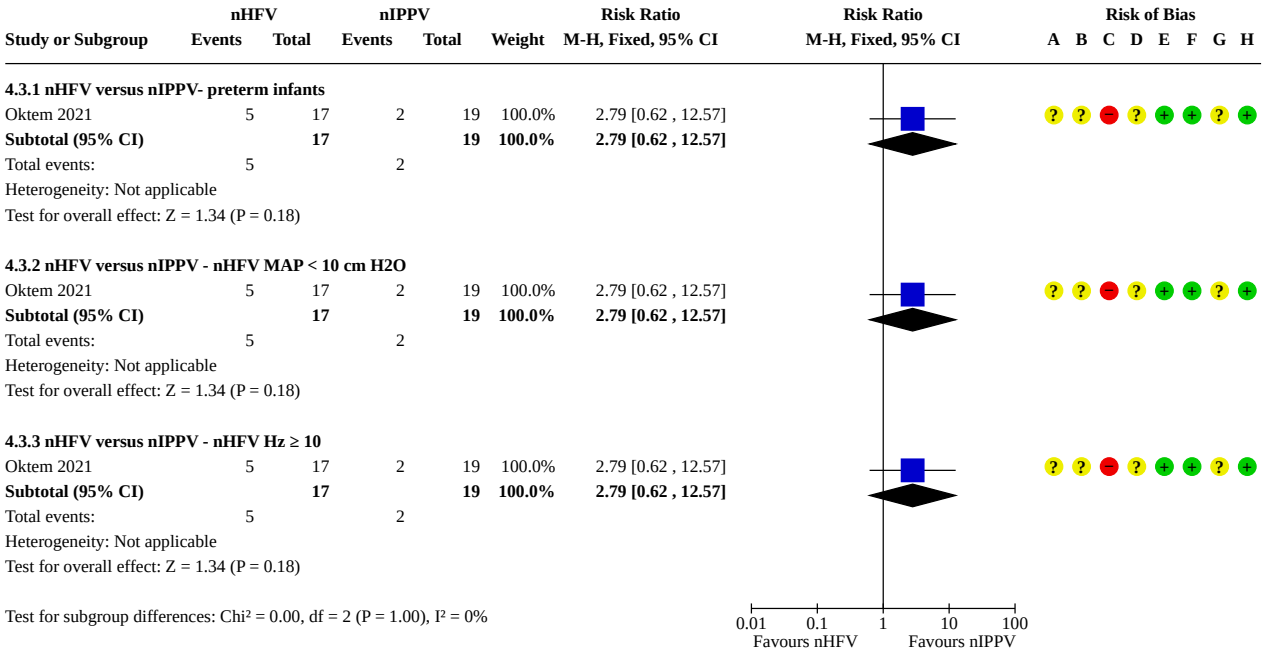
Study or Subgroup	nHFV Events	nHFV Total	nIPPV Events	nIPPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 nHFV versus nIPPV - term or near-term infants						
Zhang 2022b	0	19	5	22	100.0%	0.10 [0.01 , 1.78]
Subtotal (95% CI)		**19**		**22**	**100.0%**	**0.10 [0.01 , 1.78]**
Total events:	0		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.56 (P = 0.12)						
4.2.2 nHFV versus nIPPV- preterm infants						
Ali 2023	11	24	6	24	51.6%	1.83 [0.81 , 4.15]
Cheng 2021	2	28	4	32	32.1%	0.57 [0.11 , 2.89]
Oktem 2021	5	17	2	19	16.3%	2.79 [0.62 , 12.57]
Wang 2023	0	22	0	21		Not estimable
Subtotal (95% CI)		**91**		**96**	**100.0%**	**1.58 [0.84 , 3.00]**
Total events:	18		12			
Heterogeneity: Chi² = 2.19, df = 2 (P = 0.33); I² = 9%						
Test for overall effect: Z = 1.41 (P = 0.16)						
4.2.3 nHFV versus nIPPV - nHFV MAP < 10 cm H2O						
Ali 2023	11	24	6	24	46.1%	1.83 [0.81 , 4.15]
Oktem 2021	5	17	2	19	14.5%	2.79 [0.62 , 12.57]
Zhang 2022b	0	19	5	22	39.3%	0.10 [0.01 , 1.78]
Subtotal (95% CI)		**60**		**65**	**100.0%**	**1.29 [0.68 , 2.44]**
Total events:	16		13			
Heterogeneity: Chi² = 4.74, df = 2 (P = 0.09); I² = 58%						
Test for overall effect: Z = 0.79 (P = 0.43)						
4.2.4 nHFV versus nIPPV - nHFV Hz ≥ 10						
Oktem 2021	5	17	2	19	100.0%	2.79 [0.62 , 12.57]
Subtotal (95% CI)		**17**		**19**	**100.0%**	**2.79 [0.62 , 12.57]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.34 (P = 0.18)						

Test for subgroup differences: Chi² = 4.23, df = 3 (P = 0.24), I² = 29.1%

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 4.3. Comparison 4: Initial respiratory support: nHFV vs nIPPV - subgroup analyses, Outcome 3: Failure of respiratory support



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
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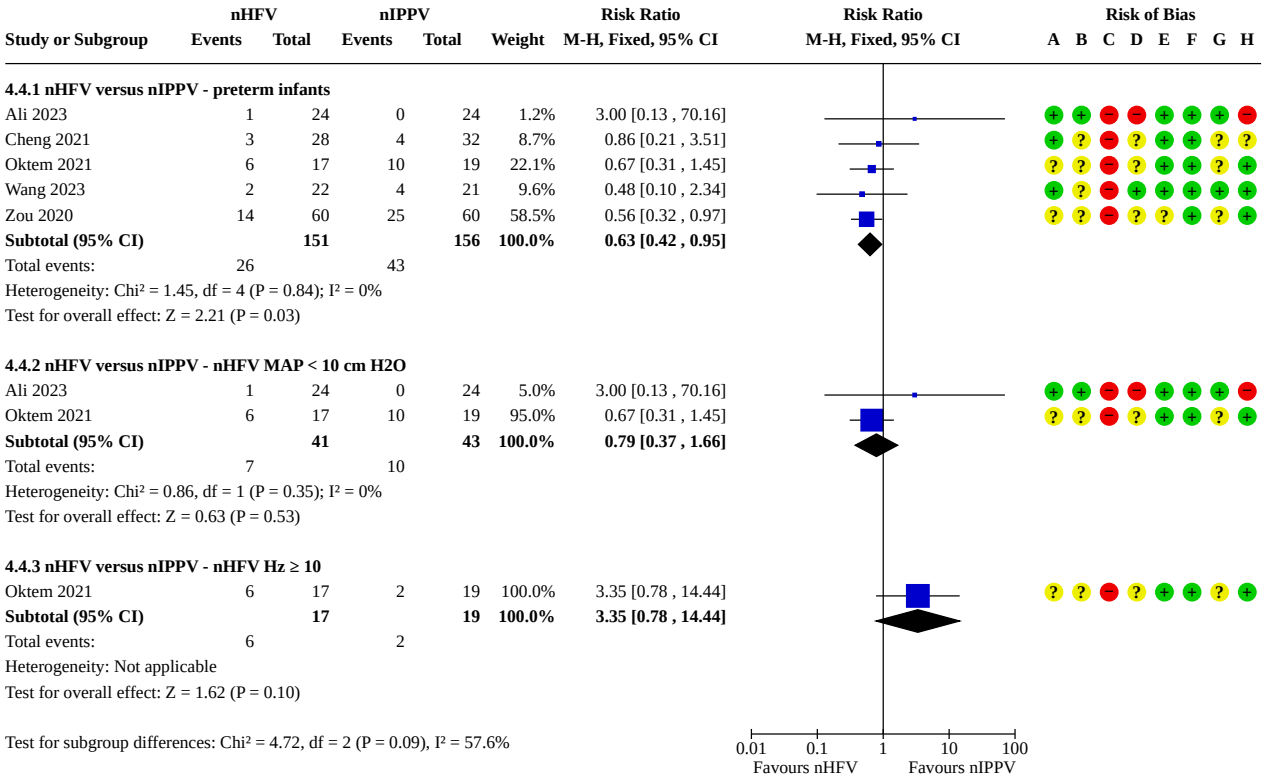
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

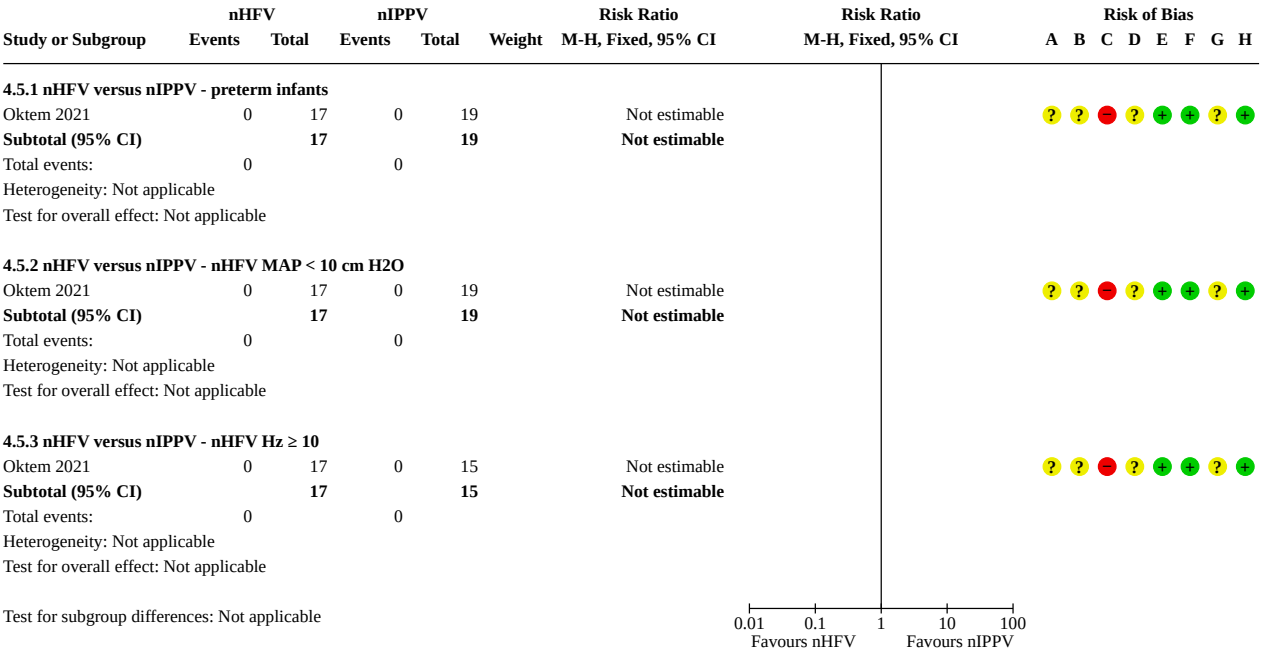
Analysis 4.4. Comparison 4: Initial respiratory support: nHFV vs nIPPV - subgroup analyses, Outcome 4: Chronic lung disease at 36 weeks



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 4.5. Comparison 4: Initial respiratory support: nHFV vs nIPPV - subgroup analyses, Outcome 5: Intraventricular haemorrhage, Papile grade 3/4



Risk of bias legend

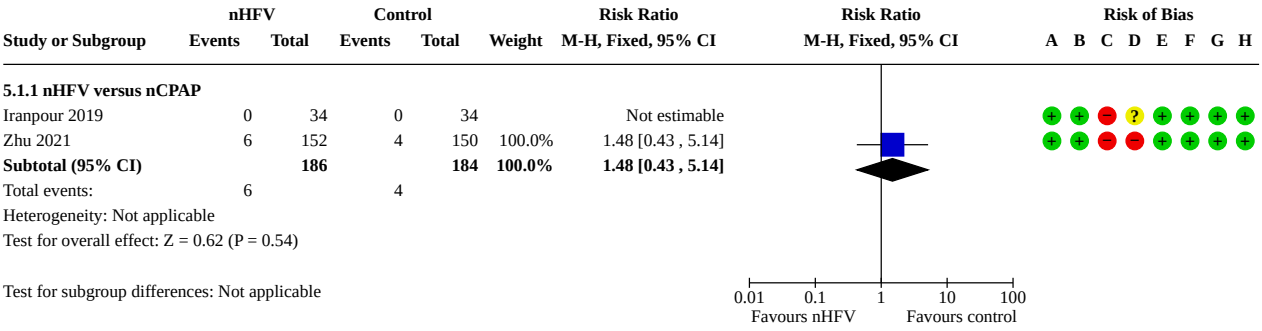
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Comparison 5. Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities - sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Mortality before hospital discharge	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1.1 nHFV versus nCPAP	2	370	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.43, 5.14]
5.2 Endotracheal intubation	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.2.1 nHFV versus nCPAP	3	410	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.28, 0.89]
5.3 Failure of respiratory support	1	302	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.31, 1.03]
5.3.1 nHFV versus nCPAP	1	302	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.31, 1.03]
5.4 Chronic lung disease at 36 weeks	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.4.1 nHFV versus nCPAP	2	370	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.70, 2.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.5 Death or chronic lung disease at 36 weeks	1	68	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [0.52, 12.01]
5.5.1 nHFV versus nCPAP	1	68	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [0.52, 12.01]
5.6 Intraventricular haemorrhage, Papile grade 3/4	2	370	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [0.37, 10.61]
5.6.1 nHFV versus nCPAP	2	370	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [0.37, 10.61]

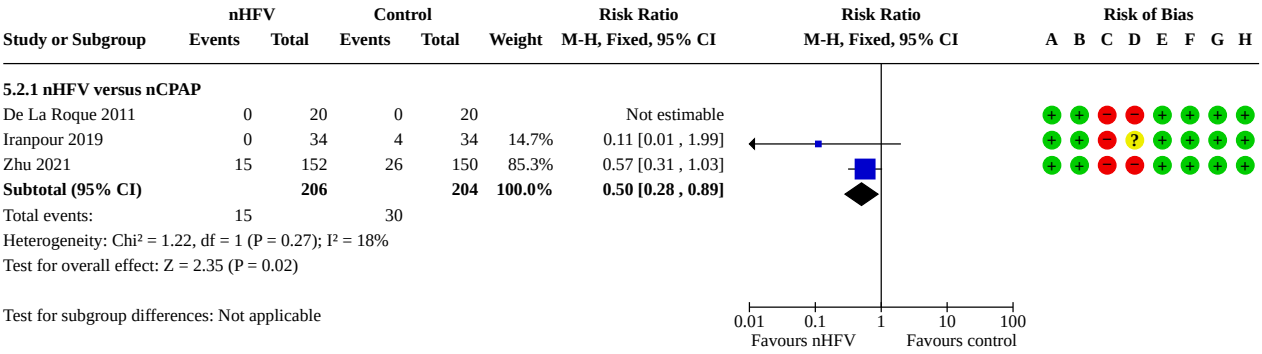
Analysis 5.1. Comparison 5: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities - sensitivity analyses, Outcome 1: Mortality before hospital discharge



Risk of bias legend

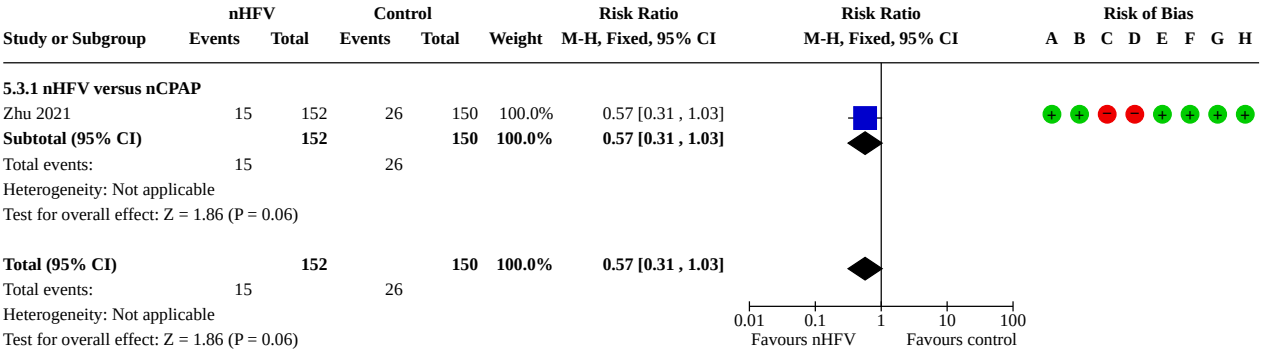
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 5.2. Comparison 5: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities - sensitivity analyses, Outcome 2: Endotracheal intubation



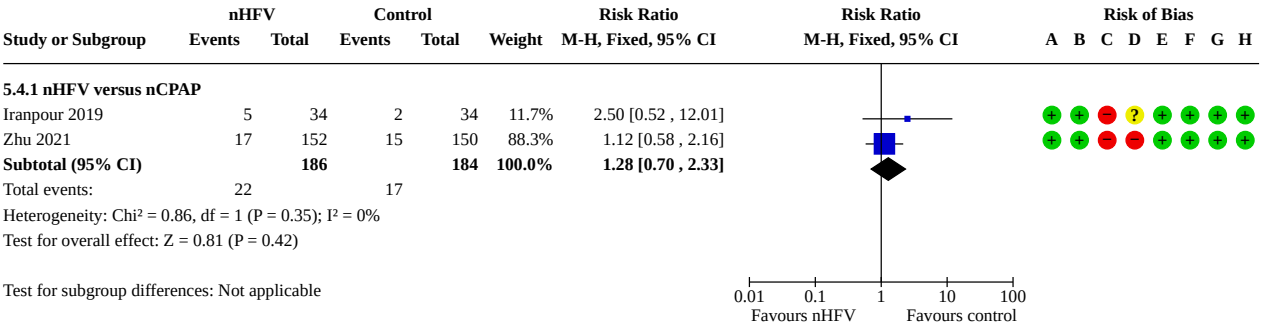
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 5.3. Comparison 5: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities - sensitivity analyses, Outcome 3: Failure of respiratory support



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 5.4. Comparison 5: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities - sensitivity analyses, Outcome 4: Chronic lung disease at 36 weeks



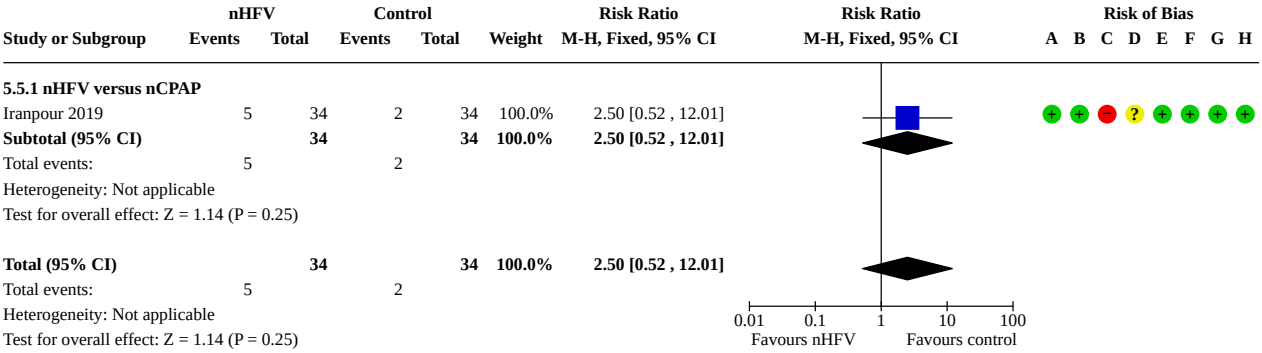
Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.4.1 nHFV versus nCPAP						
Iranpour 2019	5	34	2	34	11.7%	2.50 [0.52 , 12.01]
Zhu 2021	17	152	15	150	88.3%	1.12 [0.58 , 2.16]
Subtotal (95% CI)		**186**		**184**	**100.0%**	**1.28 [0.70 , 2.33]**
Total events:	22		17			

Heterogeneity: Chi² = 0.86, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)

Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 5.5. Comparison 5: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities - sensitivity analyses, Outcome 5: Death or chronic lung disease at 36 weeks



Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.5.1 nHFV versus nCPAP						
Iranpour 2019	5	34	2	34	100.0%	2.50 [0.52 , 12.01]
Subtotal (95% CI)		**34**		**34**	**100.0%**	**2.50 [0.52 , 12.01]**
Total events:	5		2			

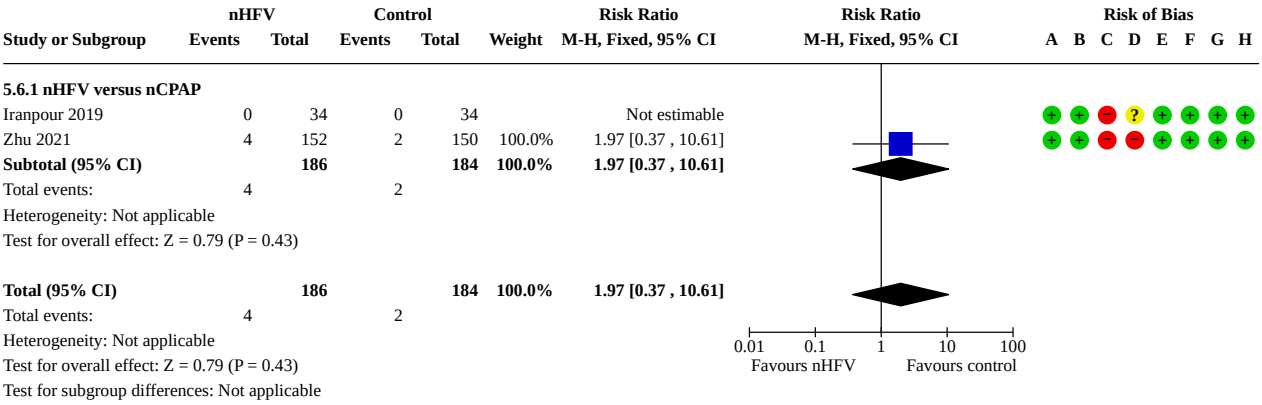
Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)

Total (95% CI)		**34**		**34**	**100.0%**	**2.50 [0.52 , 12.01]**
Total events:	5		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 5.6. Comparison 5: Initial respiratory support: nHFV vs other non-invasive respiratory therapy modalities - sensitivity analyses, Outcome 6: Intraventricular haemorrhage, Papile grade 3/4



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

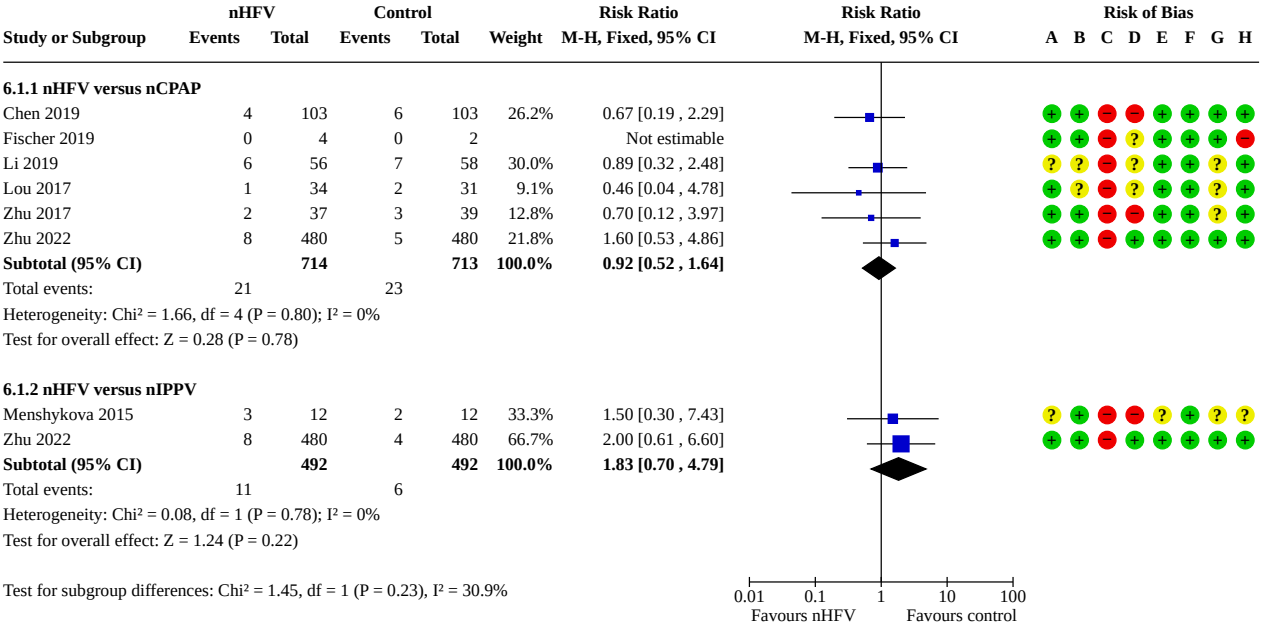
Comparison 6. Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Mortality before hospital discharge	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1.1 nHFV versus nCPAP	6	1427	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.52, 1.64]
6.1.2 nHFV versus nIPPV	2	984	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.70, 4.79]
6.2 Endotracheal reintubation	14		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.2.1 nHFV versus nCPAP	11	1897	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.35, 0.51]
6.2.2 nHFV versus nIPPV	6	1364	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.54, 0.89]
6.3 Trauma to the nostrils and upper airway	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.3.1 nHFV versus nCPAP	4	1418	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.64, 1.44]
6.3.2 nHFV versus nIPPV	4	1254	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.66, 1.53]
6.4 Failure of extubation	1	6	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.22, 1.65]
6.4.1 nHFV versus nCPAP	1	6	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.22, 1.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.5 Duration of respiratory support, days	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.5.1 nHFV versus nCPAP	7	1371	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.20, -0.03]
6.5.2 nHFV versus nIPPV	2	1052	Mean Difference (IV, Fixed, 95% CI)	-2.09 [-3.32, -0.85]
6.6 Duration of oxygen therapy, days	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.6.1 nHFV versus nCPAP	4	1218	Mean Difference (IV, Fixed, 95% CI)	-2.38 [-3.48, -1.28]
6.6.2 nHFV versus nIPPV	3	1212	Mean Difference (IV, Fixed, 95% CI)	-0.57 [-1.59, 0.45]
6.7 Chronic lung disease at 36 weeks	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.7.1 nHFV versus nCPAP	10	1829	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.67, 0.91]
6.7.2 nHFV versus nIPPV	4	1236	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.75, 1.04]
6.8 Death or chronic lung disease at 36 weeks	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.8.1 nHFV versus nCPAP	2	966	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.06]
6.8.2 nHFV versus nIPPV	3	1070	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.79, 1.08]
6.9 Patent ductus arteriosus	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.9.1 nHFV versus nCPAP	3	1258	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.84, 1.16]
6.9.2 nHFV versus nIPPV	3	1076	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.74, 1.05]
6.10 Pulmonary air leak syndromes	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.10.1 nHFV versus nCPAP	8	1673	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.31, 1.15]
6.10.2 nHFV versus nIPPV	5	1322	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.36, 1.91]
6.11 Proven sepsis	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.11.1 nHFV versus nCPAP	1	960	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.38, 1.87]
6.11.2 nHFV versus nIPPV	2	984	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.50, 2.00]
6.12 Necrotising enterocolitis	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.12.1 nHFV versus nCPAP	4	523	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.47, 1.45]
6.12.2 nHFV versus nIPPV	4	318	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.32, 3.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.13 Necrotising enterocolitis, Bell stage ≥ 2	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.13.1 nHFV versus nCPAP	3	1142	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.82, 2.10]
6.13.2 nHFV versus nIPPV	2	984	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.58, 1.44]
6.14 Intraventricular haemorrhage, any	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.14.1 nHFV versus nCPAP	7	1644	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.69, 1.21]
6.14.2 nHFV versus nIPPV	4	1236	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.73, 1.34]
6.15 Intraventricular haemorrhage, Papile grade 3/4	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.15.1 nHFV versus nCPAP	3	1117	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.57, 1.13]
6.15.2 nHFV versus nIPPV	4	1162	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.55, 1.10]
6.16 Periventricular leukomalacia	1	24	Risk Ratio (M-H, Fixed, 95% CI)	7.00 [0.40, 122.44]
6.16.1 nHFV versus nIPPV	1	24	Risk Ratio (M-H, Fixed, 95% CI)	7.00 [0.40, 122.44]
6.17 Retinopathy of prematurity, any	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.17.1 nHFV versus nCPAP	4	1418	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.58, 0.99]
6.17.2 nHFV versus nIPPV	4	1236	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.64, 1.13]
6.18 Retinopathy of prematurity, stage ≥ 3	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.18.1 nHFV versus nCPAP	2	1052	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.61, 1.08]
6.18.2 nHFV versus nIPPV	2	1052	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.64, 1.15]
6.19 Length of hospital stay, days	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.19.1 nHFV versus nCPAP	5	640	Mean Difference (IV, Fixed, 95% CI)	-1.14 [-2.01, -0.27]
6.19.2 nHFV versus nIPPV	3	276	Mean Difference (IV, Fixed, 95% CI)	-1.05 [-3.34, 1.24]
6.20 Neurodevelopmental disability at least 18 months' postnatal age or later	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.20.1 nHFV versus nCPAP	1	74	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.37, 2.29]
6.20.2 nHFV versus nIPPV	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.35, 2.16]

Analysis 6.1. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 1: Mortality before hospital discharge



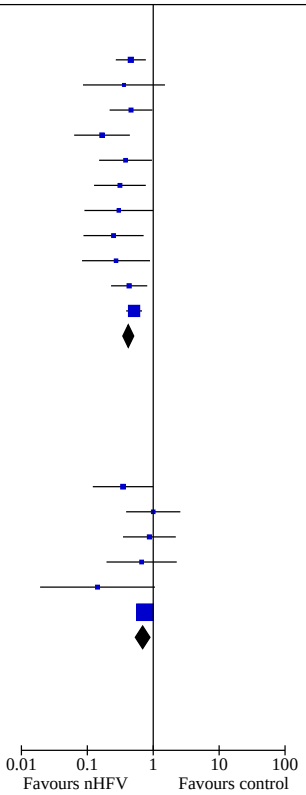
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.2. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 2: Endotracheal reintubation

Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G H
6.2.1 nHFV versus nCPAP							
Chen 2019	16	103	35	103	12.1%	0.46 [0.27 , 0.77]	+ + − − + + + +
Fischer 2019	1	4	2	2	1.1%	0.36 [0.09 , 1.51]	+ + − ? + + + −
Li 2019	8	56	18	58	6.1%	0.46 [0.22 , 0.97]	? ? − ? + + ? +
Li 2021	4	45	25	47	8.4%	0.17 [0.06 , 0.44]	+ + − ? + − + +
Lou 2017	5	34	12	31	4.3%	0.38 [0.15 , 0.96]	+ ? − ? + + ? +
Wang 2020	5	40	16	40	5.5%	0.31 [0.13 , 0.77]	+ ? − ? ? + ? +
Yang 2021	3	34	10	34	3.4%	0.30 [0.09 , 1.00]	− − − ? ? + ? +
Yuan 2021	4	80	16	80	5.5%	0.25 [0.09 , 0.72]	? ? − ? + + ? +
Zhang 2021	3	35	11	35	3.8%	0.27 [0.08 , 0.89]	+ ? − ? ? + ? +
Zhu 2017	9	37	22	39	7.4%	0.43 [0.23 , 0.81]	+ + − − + + ? +
Zhu 2022	63	480	123	480	42.4%	0.51 [0.39 , 0.68]	+ + − + + + + +
Subtotal (95% CI)		**948**		**949**	**100.0%**	**0.42 [0.35 , 0.51]**	
Total events:	121		290				
Heterogeneity: Chi² = 7.87, df = 10 (P = 0.64); I² = 0%							
Test for overall effect: Z = 8.96 (P < 0.00001)							
6.2.2 nHFV versus nIPPV							
Li 2021	4	45	12	47	9.6%	0.35 [0.12 , 1.00]	+ + − ? + − + +
Menshykova 2015	5	12	5	12	4.1%	1.00 [0.39 , 2.58]	? + − − ? + ? ?
Seth 2021	7	43	8	43	6.6%	0.88 [0.35 , 2.20]	+ + − + + + + +
Yuan 2021	4	80	6	80	4.9%	0.67 [0.20 , 2.27]	? ? − ? + + ? +
Zhenyu 2019	1	21	7	21	5.8%	0.14 [0.02 , 1.06]	+ ? − ? ? + ? ?
Zhu 2022	63	480	84	480	69.0%	0.75 [0.55 , 1.01]	+ + − + + + + +
Subtotal (95% CI)		**681**		**683**	**100.0%**	**0.69 [0.54 , 0.89]**	
Total events:	84		122				
Heterogeneity: Chi² = 5.12, df = 5 (P = 0.40); I² = 2%							
Test for overall effect: Z = 2.84 (P = 0.005)							

Test for subgroup differences: Chi² = 9.52, df = 1 (P = 0.002), I² = 89.5%

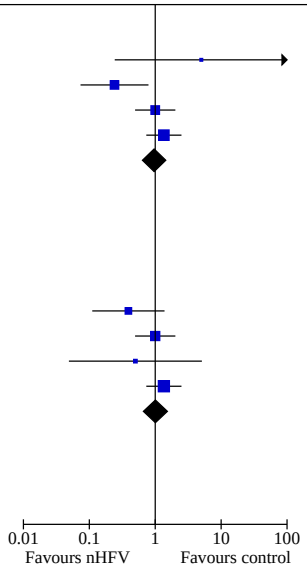


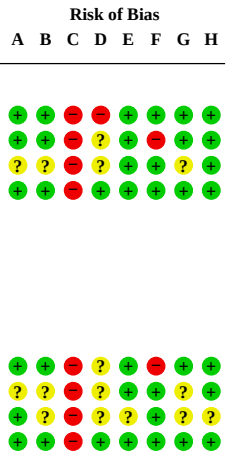
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.3. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 3: Trauma to the nostrils and upper airway

Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.3.1 nHFV versus nCPAP						
Chen 2019	2	103	0	103	1.2%	5.00 [0.24 , 102.88]
Li 2021	3	45	13	47	29.4%	0.24 [0.07 , 0.79]
Yuan 2021	13	80	13	80	30.1%	1.00 [0.49 , 2.02]
Zhu 2022	23	480	17	480	39.3%	1.35 [0.73 , 2.50]
Subtotal (95% CI)		**708**		**710**	**100.0%**	**0.96 [0.64 , 1.44]**
Total events:	41		43			
Heterogeneity: Chi² = 7.56, df = 3 (P = 0.06); I² = 60%						
Test for overall effect: Z = 0.19 (P = 0.85)						
6.3.2 nHFV versus nIPPV						
Li 2021	3	45	8	47	19.7%	0.39 [0.11 , 1.38]
Yuan 2021	13	80	13	80	32.6%	1.00 [0.49 , 2.02]
Zhenyu 2019	1	21	2	21	5.0%	0.50 [0.05 , 5.10]
Zhu 2022	23	480	17	480	42.7%	1.35 [0.73 , 2.50]
Subtotal (95% CI)		**626**		**628**	**100.0%**	**1.01 [0.66 , 1.53]**
Total events:	40		40			
Heterogeneity: Chi² = 3.39, df = 3 (P = 0.34); I² = 11%						
Test for overall effect: Z = 0.03 (P = 0.98)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						

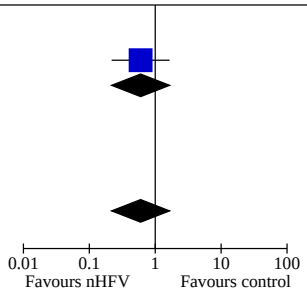




Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.4. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 4: Failure of extubation

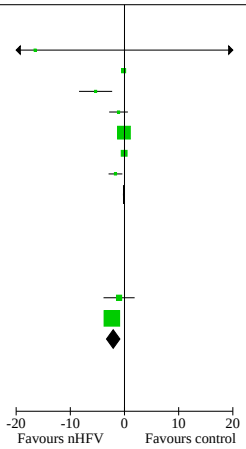
Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.4.1 nHFV versus nCPAP						
Fischer 2019	2	4	2	2	100.0%	0.60 [0.22 , 1.65]
Subtotal (95% CI)		**4**		**2**	**100.0%**	**0.60 [0.22 , 1.65]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
Total (95% CI)		**4**		**2**	**100.0%**	**0.60 [0.22 , 1.65]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.5. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 5: Duration of respiratory support, days

Study or Subgroup	nHFV Mean	nHFV SD	nHFV Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
6.5.1 nHFV versus nCPAP									
Fischer 2019	30.5	42.59019	4	47	24.80368	2	0.0%	-16.50 [-70.57 , 37.57]	+ + - ? + + + -
Li 2019	3.09	0.63	56	3.25	0.67	54	11.9%	-0.16 [-0.40 , 0.08]	? ? - ? + + ? +
Li 2021	10.33333333	5.360589	45	15.66666667	9.176832	47	0.1%	-5.33 [-8.39 , -2.28]	+ + - ? + - + +
Lou 2017	4.4	3.1	34	5.5	3.9	31	0.2%	-1.10 [-2.82 , 0.62]	+ ? - ? + + ? +
Yang 2021	3.13	0.22	34	3.23	0.22	34	64.6%	-0.10 [-0.20 , 0.00]	- - - ? ? + ? +
Zhang 2021	3.2	0.34	35	3.26	0.41	35	22.7%	-0.06 [-0.24 , 0.12]	+ ? - ? ? + ? +
Zhu 2022	11	9.66624	480	12.66666667	10.4098	480	0.4%	-1.67 [-2.94 , -0.40]	+ + - + + + + +
Subtotal (95% CI)			**688**			**683**	**100.0%**	**-0.11 [-0.20 , -0.03]**	
Heterogeneity: Chi² = 19.12, df = 6 (P = 0.004); I² = 69%									
Test for overall effect: Z = 2.60 (P = 0.009)									
6.5.2 nHFV versus nIPPV									
Li 2021	10.33333333	5.360589	45	11.33333333	8.412096	47	18.6%	-1.00 [-3.87 , 1.87]	+ + - ? + - + +
Zhu 2022	11	9.66624	480	13.33333333	11.89691	480	81.4%	-2.33 [-3.70 , -0.96]	+ + - + + + + +
Subtotal (95% CI)			**525**			**527**	**100.0%**	**-2.09 [-3.32 , -0.85]**	
Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² = 0%									
Test for overall effect: Z = 3.30 (P = 0.0010)									

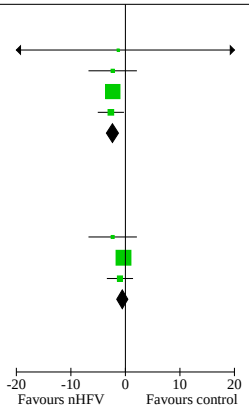


Test for subgroup differences: Chi² = 9.73, df = 1 (P = 0.002), I² = 89.7%

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.6. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 6: Duration of oxygen therapy, days

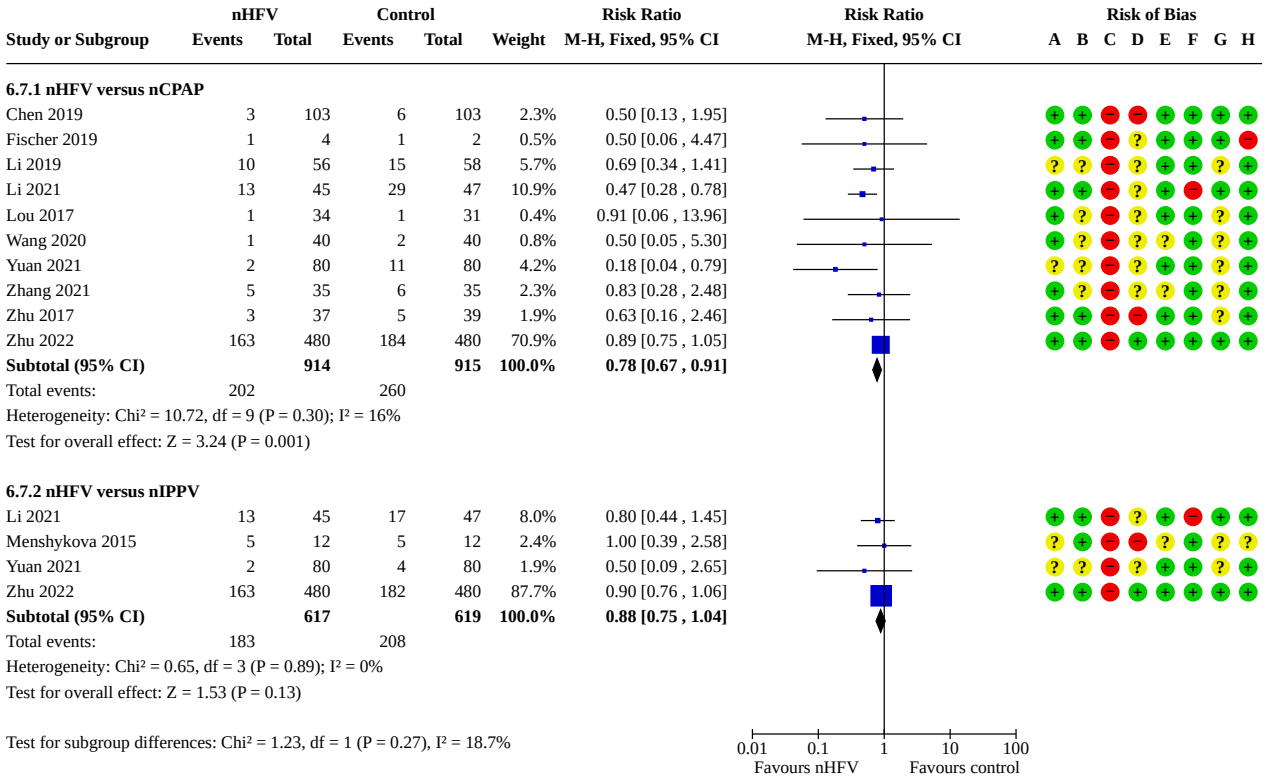
Study or Subgroup	nHFV Mean	nHFV SD	nHFV Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G H
6.6.1 nHFV versus nCPAP									
Fischer 2019	79.66666667	73.16776	4	81	3.543383	2	0.0%	-1.33 [-73.20 , 70.54]	+ + - ? + + + -
Li 2021	24.33333333	12.25277	45	26.66666667	9.176832	47	6.2%	-2.33 [-6.77 , 2.11]	+ + - ? + - + +
Yuan 2021	9.45	3.5518	80	11.75	4.731	80	72.6%	-2.30 [-3.60 , -1.00]	? ? - ? + + ? +
Zhu 2022	23.33333333	19.33248	480	26	18.58892	480	21.2%	-2.67 [-5.07 , -0.27]	+ + - + + + + +
Subtotal (95% CI)			**609**			**609**	**100.0%**	**-2.38 [-3.48 , -1.28]**	
Heterogeneity: Chi² = 0.07, df = 3 (P = 1.00); I² = 0%									
Test for overall effect: Z = 4.22 (P < 0.0001)									
6.6.2 nHFV versus nIPPV									
Li 2021	24.33333333	12.25277	45	26.66666667	9.176832	47	5.3%	-2.33 [-6.77 , 2.11]	+ + - ? + - + +
Yuan 2021	9.45	3.5518	80	9.8	3.9594	80	76.6%	-0.35 [-1.52 , 0.82]	? ? - ? + + ? +
Zhu 2022	23.33333333	19.33248	480	24.33333333	18.58892	480	18.1%	-1.00 [-3.40 , 1.40]	+ + - + + + + +
Subtotal (95% CI)			**605**			**607**	**100.0%**	**-0.57 [-1.59 , 0.45]**	
Heterogeneity: Chi² = 0.87, df = 2 (P = 0.65); I² = 0%									
Test for overall effect: Z = 1.10 (P = 0.27)									



Test for subgroup differences: Chi² = 5.55, df = 1 (P = 0.02), I² = 82.0%

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.7. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 7: Chronic lung disease at 36 weeks

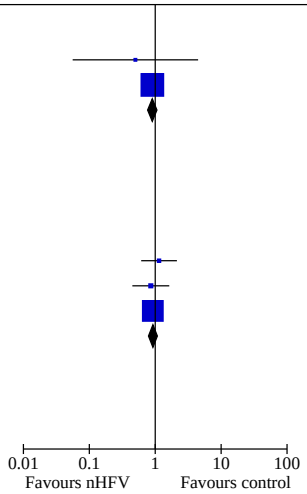


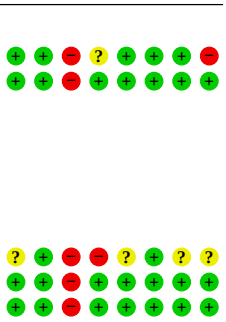
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.8. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 8: Death or chronic lung disease at 36 weeks

Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.8.1 nHFV versus nCPAP						
Fischer 2019	1	4	1	2	0.7%	0.50 [0.06 , 4.47]
Zhu 2022	171	480	189	480	99.3%	0.90 [0.77 , 1.07]
Subtotal (95% CI)		**484**		**482**	**100.0%**	**0.90 [0.77 , 1.06]**
Total events:	172		190			
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.22)						
6.8.2 nHFV versus nIPPV						
Menshykova 2015	8	12	7	12	3.4%	1.14 [0.61 , 2.13]
Seth 2021	12	43	14	43	6.8%	0.86 [0.45 , 1.63]
Zhu 2022	171	480	186	480	89.9%	0.92 [0.78 , 1.08]
Subtotal (95% CI)		**535**		**535**	**100.0%**	**0.92 [0.79 , 1.08]**
Total events:	191		207			
Heterogeneity: Chi² = 0.50, df = 2 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%						

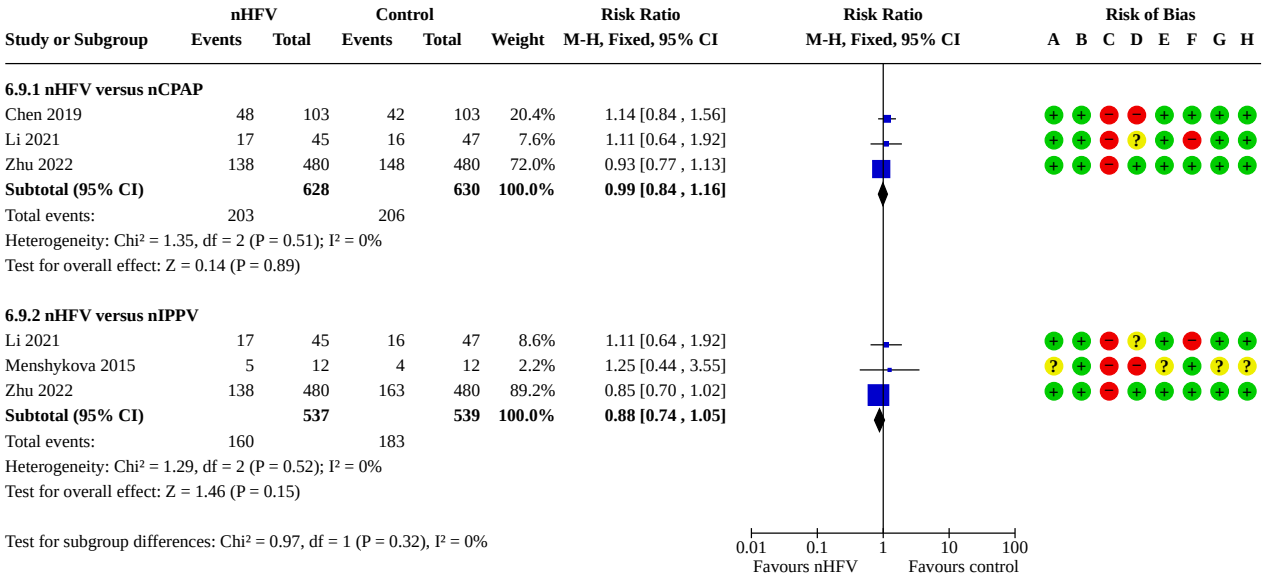




Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.9. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 9: Patent ductus arteriosus



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
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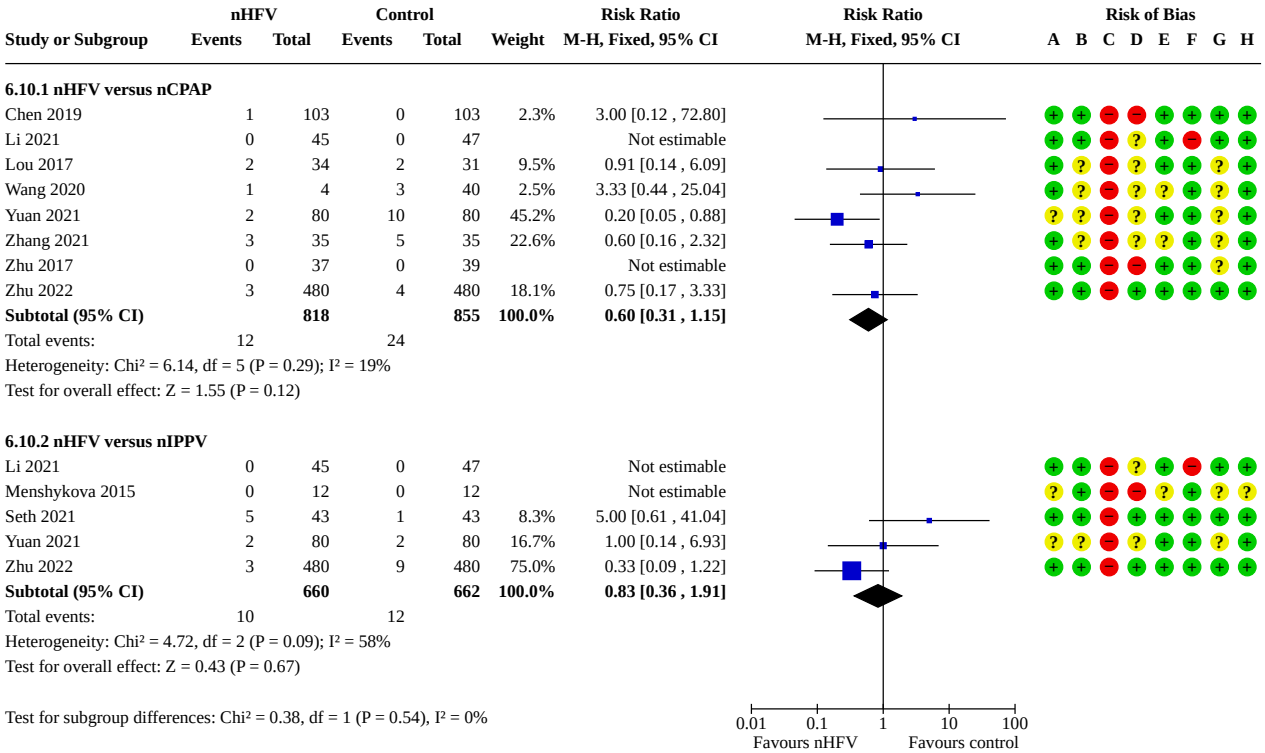
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

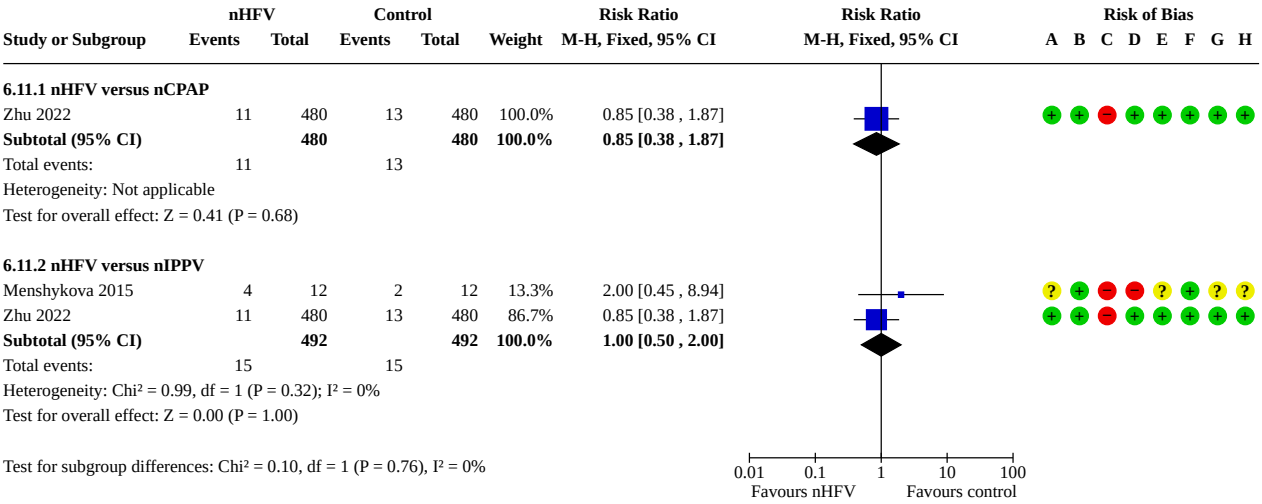
Analysis 6.10. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 10: Pulmonary air leak syndromes



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

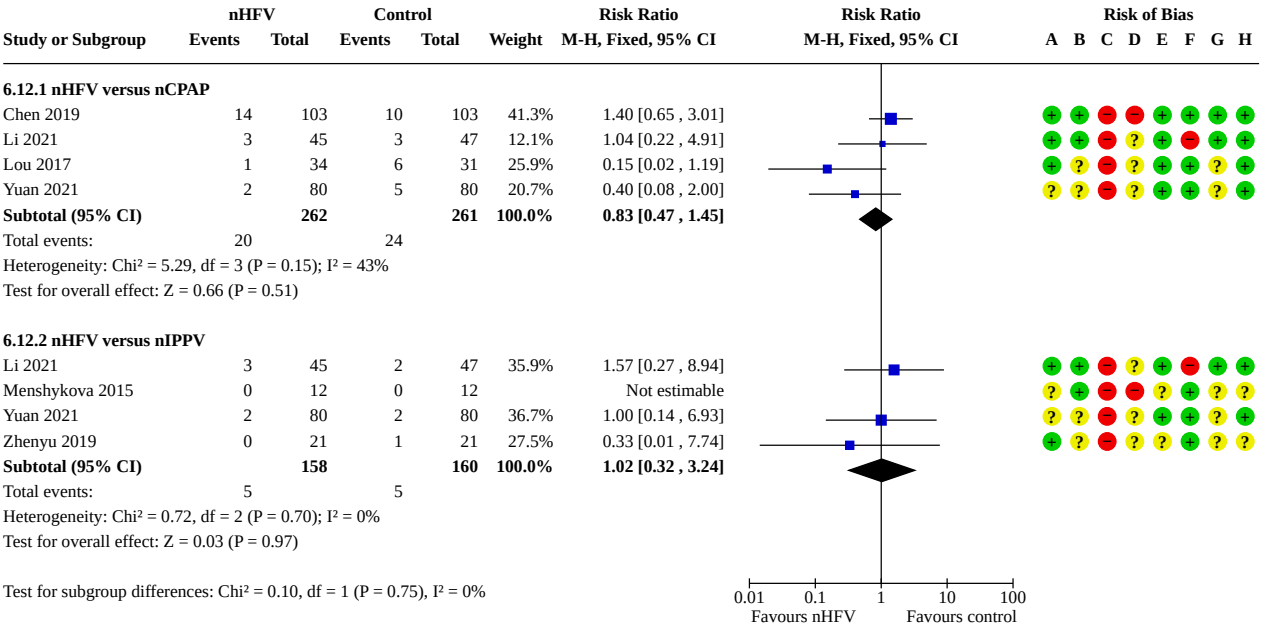
Analysis 6.11. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 11: Proven sepsis



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

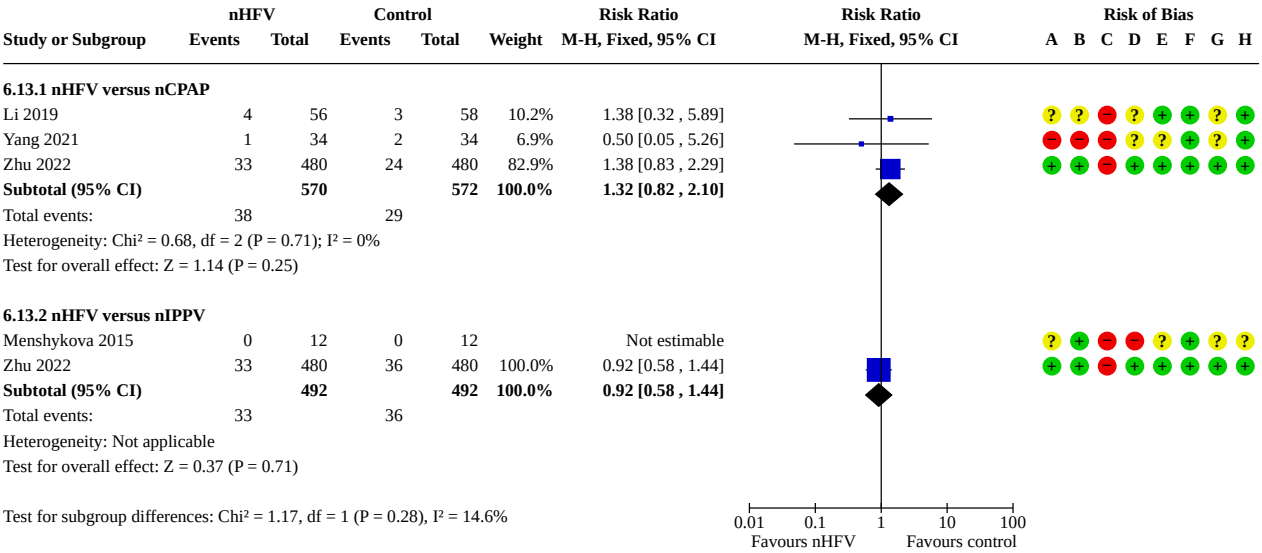
Analysis 6.12. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 12: Necrotising enterocolitis



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

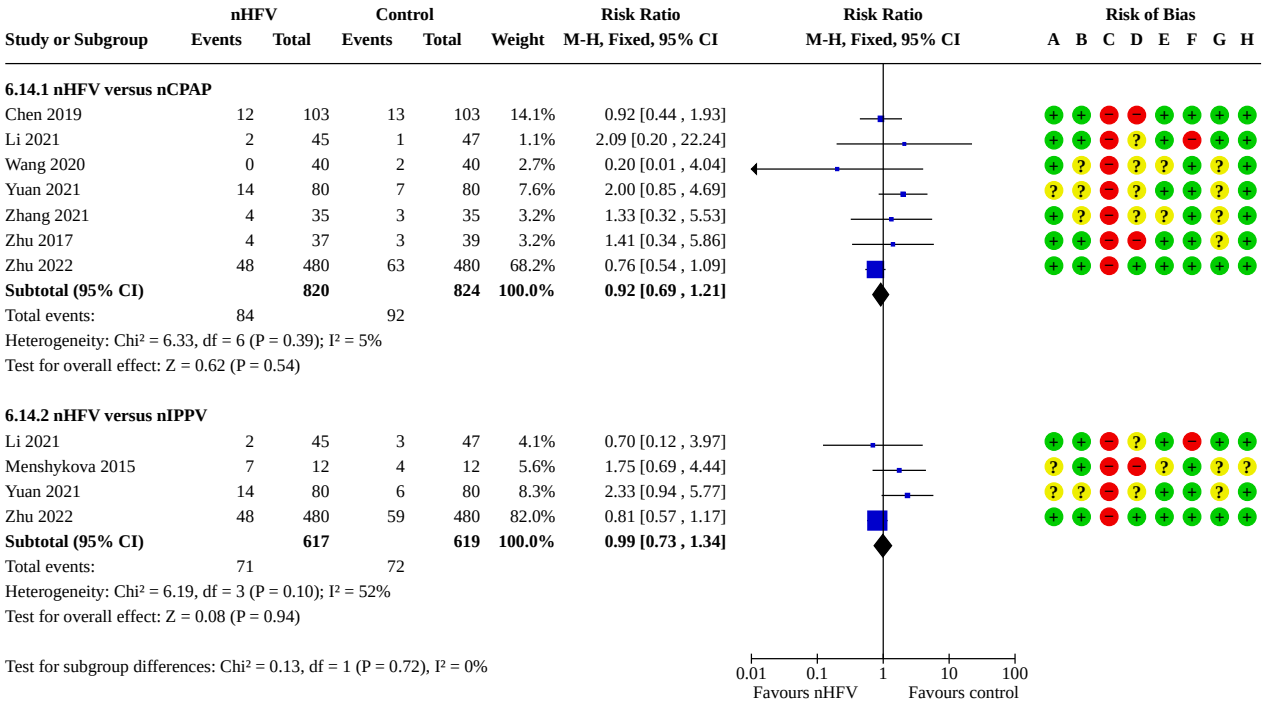
Analysis 6.13. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 13: Necrotising enterocolitis, Bell stage ≥ 2



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.14. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 14: Intraventricular haemorrhage, any

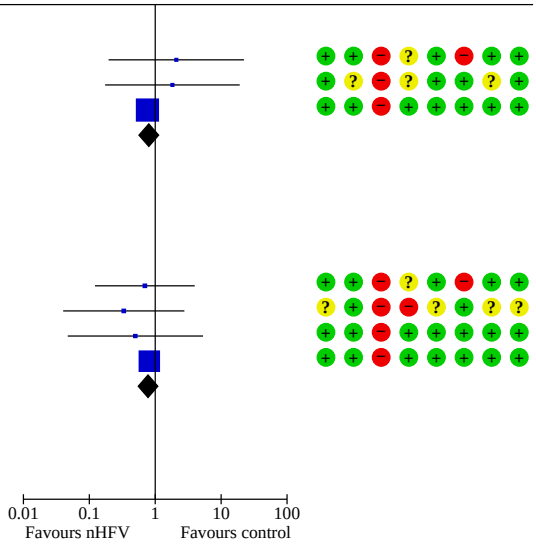


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.15. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 15: Intraventricular haemorrhage, Papile grade 3/4

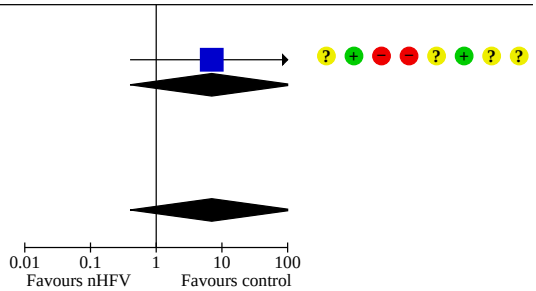
Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.15.1 nHFV versus nCPAP						
Li 2021	2	45	1	47	1.5%	2.09 [0.20 , 22.24]
Lou 2017	2	34	1	31	1.6%	1.82 [0.17 , 19.13]
Zhu 2022	48	480	63	480	96.9%	0.76 [0.54 , 1.09]
Subtotal (95% CI)		**559**		**558**	**100.0%**	**0.80 [0.57 , 1.13]**
Total events:	52		65			
Heterogeneity: Chi² = 1.18, df = 2 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.28 (P = 0.20)						
6.15.2 nHFV versus nIPPV						
Li 2021	2	45	3	47	4.4%	0.70 [0.12 , 3.97]
Menshykova 2015	1	12	3	12	4.5%	0.33 [0.04 , 2.77]
Seth 2021	1	43	2	43	3.0%	0.50 [0.05 , 5.31]
Zhu 2022	48	480	59	480	88.1%	0.81 [0.57 , 1.17]
Subtotal (95% CI)		**580**		**582**	**100.0%**	**0.78 [0.55 , 1.10]**
Total events:	52		67			
Heterogeneity: Chi² = 0.83, df = 3 (P = 0.84); I² = 0%						
Test for overall effect: Z = 1.44 (P = 0.15)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%						

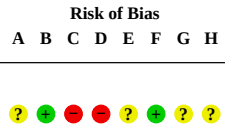


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.16. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 16: Periventricular leukomalacia

Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.16.1 nHFV versus nIPPV						
Menshykova 2015	3	12	0	12	100.0%	7.00 [0.40 , 122.44]
Subtotal (95% CI)		**12**		**12**	**100.0%**	**7.00 [0.40 , 122.44]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.33 (P = 0.18)						
Total (95% CI)		**12**		**12**	**100.0%**	**7.00 [0.40 , 122.44]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.33 (P = 0.18)						
Test for subgroup differences: Not applicable						

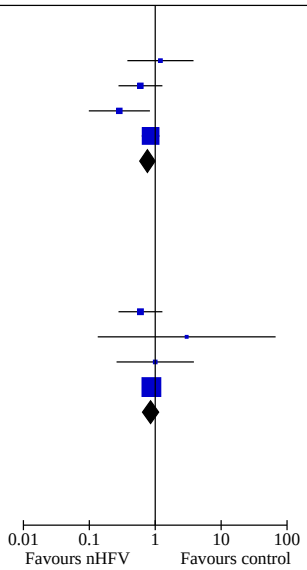


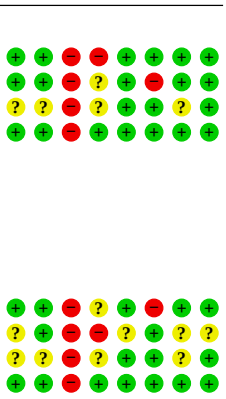


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.17. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 17: Retinopathy of prematurity, any

Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.17.1 nHFV versus nCPAP						
Chen 2019	6	103	5	103	4.7%	1.20 [0.38 , 3.81]
Li 2021	8	45	14	47	12.8%	0.60 [0.28 , 1.28]
Yuan 2021	4	80	14	80	13.1%	0.29 [0.10 , 0.83]
Zhu 2022	63	480	74	480	69.4%	0.85 [0.62 , 1.16]
Subtotal (95% CI)		**708**		**710**	**100.0%**	**0.76 [0.58 , 0.99]**
Total events:	81		107			
Heterogeneity: Chi² = 4.72, df = 3 (P = 0.19); I² = 36%						
Test for overall effect: Z = 2.00 (P = 0.05)						
6.17.2 nHFV versus nIPPV						
Li 2021	8	45	14	47	15.2%	0.60 [0.28 , 1.28]
Menshykova 2015	1	12	0	12	0.6%	3.00 [0.13 , 67.06]
Yuan 2021	4	80	4	80	4.4%	1.00 [0.26 , 3.86]
Zhu 2022	63	480	72	480	79.8%	0.88 [0.64 , 1.20]
Subtotal (95% CI)		**617**		**619**	**100.0%**	**0.85 [0.64 , 1.13]**
Total events:	76		90			
Heterogeneity: Chi² = 1.54, df = 3 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%						



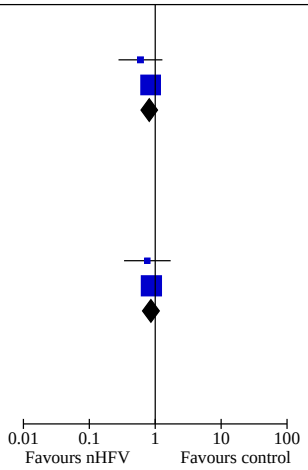


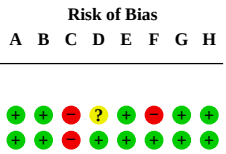
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.18. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 18: Retinopathy of prematurity, stage ≥ 3

Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.18.1 nHFV versus nCPAP						
Li 2021	8	45	14	47	15.6%	0.60 [0.28 , 1.28]
Zhu 2022	63	480	74	480	84.4%	0.85 [0.62 , 1.16]
Subtotal (95% CI)		**525**		**527**	**100.0%**	**0.81 [0.61 , 1.08]**
Total events:	71		88			
Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 1.42 (P = 0.16)						
6.18.2 nHFV versus nIPPV						
Li 2021	8	45	11	47	13.0%	0.76 [0.34 , 1.71]
Zhu 2022	63	480	72	480	87.0%	0.88 [0.64 , 1.20]
Subtotal (95% CI)		**525**		**527**	**100.0%**	**0.86 [0.64 , 1.15]**
Total events:	71		83			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						

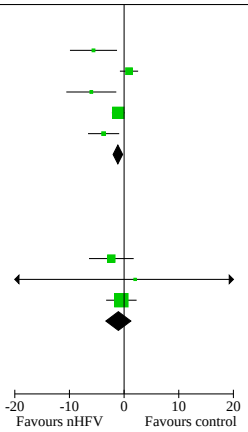


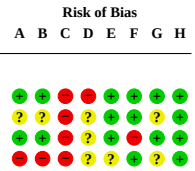


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.19. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 19: Length of hospital stay, days

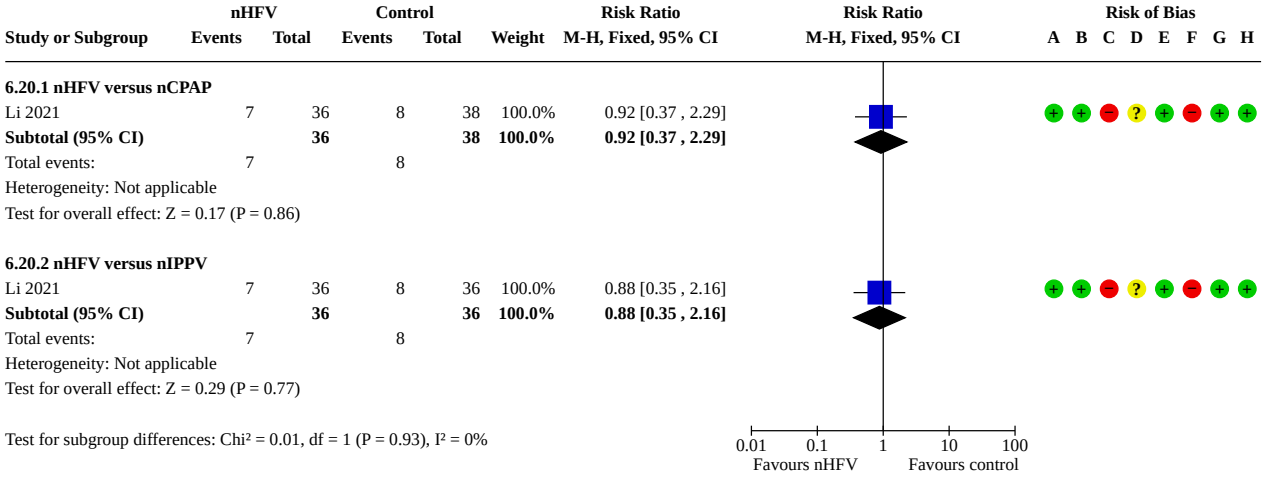
Study or Subgroup	nHFV Mean	nHFV SD	nHFV Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
6.19.1 nHFV versus nCPAP								
Chen 2019	22	14.3	103	27.6	17.1	103	4.1%	-5.60 [-9.90 , -1.30]
Li 2019	32.2	5	56	31.3	4	58	27.4%	0.90 [-0.77 , 2.57]
Li 2021	37.33333333	12.25277	45	43.33333333	9.941568	47	3.6%	-6.00 [-10.57 , -1.43]
Yang 2021	31.54	2.5	34	32.6	2.43	34	55.4%	-1.06 [-2.23 , 0.11]
Yuan 2021	23.95	8.7042	80	27.7	9.6636	80	9.4%	-3.75 [-6.60 , -0.90]
Subtotal (95% CI)			**318**			**322**	**100.0%**	**-1.14 [-2.01 , -0.27]**
Heterogeneity: Chi² = 17.47, df = 4 (P = 0.002); I² = 77%								
Test for overall effect: Z = 2.56 (P = 0.01)								
6.19.2 nHFV versus nIPPV								
Li 2021	37.33333333	12.25277	45	39.66666667	6.882624	47	31.4%	-2.33 [-6.42 , 1.75]
Menshykova 2015	61	32.64	12	59	24.12	12	1.0%	2.00 [-20.96 , 24.96]
Yuan 2021	23.95	8.7042	80	24.45	9.2595	80	67.6%	-0.50 [-3.28 , 2.28]
Subtotal (95% CI)			**137**			**139**	**100.0%**	**-1.05 [-3.34 , 1.24]**
Heterogeneity: Chi² = 0.60, df = 2 (P = 0.74); I² = 0%								
Test for overall effect: Z = 0.90 (P = 0.37)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%								





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 6.20. Comparison 6: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities, Outcome 20: Neurodevelopmental disability at least 18 months' postnatal age or later



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

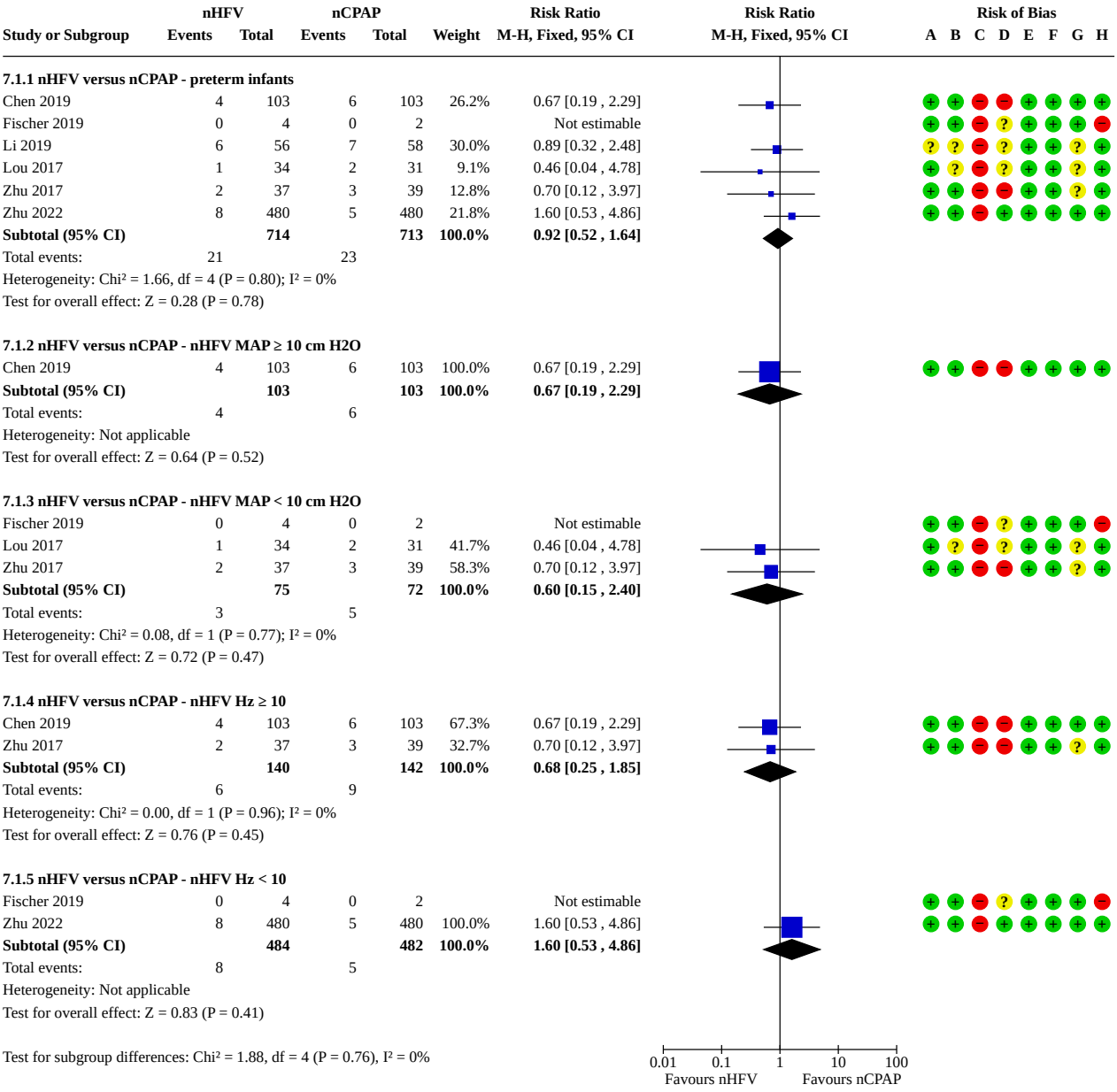
Comparison 7. Respiratory support following planned extubation: nHFV vs nCPAP - subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Mortality before hospital discharge	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1.1 nHFV versus nCPAP - preterm infants	6	1427	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.52, 1.64]
7.1.2 nHFV versus nCPAP - nHFV MAP ≥ 10 cm H2O	1	206	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.19, 2.29]
7.1.3 nHFV versus nCPAP - nHFV MAP < 10 cm H2O	3	147	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.15, 2.40]
7.1.4 nHFV versus nCPAP - nHFV Hz ≥ 10	2	282	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.25, 1.85]
7.1.5 nHFV versus nCPAP - nHFV Hz < 10	2	966	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.53, 4.86]
7.2 Endotracheal reintubation	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.2.1 nHFV versus nCPAP - term or near-term infants	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.13, 0.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2.2 nHFV versus nCPAP - preterm infants	10	1817	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.35, 0.52]
7.2.3 nHFV versus nCPAP - nHFV MAP ≥ 10 cm H2O	2	298	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.21, 0.53]
7.2.4 nHFV versus nCPAP - nHFV MAP < 10 cm H2O	3	147	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.25, 0.67]
7.2.5 nHFV versus nCPAP - nHFV Hz ≥ 10	2	282	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.30, 0.67]
7.2.6 nHFV versus nCPAP - nHFV Hz < 10	2	966	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.39, 0.67]
7.3 Failure of extubation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.3.1 nHFV versus nCPAP - preterm infants	1	6	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.22, 1.65]
7.3.2 nHFV versus nCPAP - nHFV MAP < 10 cm H2O	1	6	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.22, 1.65]
7.3.3 nHFV versus nCPAP - nHFV Hz < 10	1	6	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.22, 1.65]
7.4 Chronic lung disease at 36 weeks	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.4.1 nHFV versus nCPAP - term or near-term infants	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.30]
7.4.2 nHFV versus nCPAP - preterm infants	9	1749	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.67, 0.91]
7.4.3 nHFV versus nCPAP - nHFV MAP ≥ 10 cm H2O	2	298	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.29, 0.77]
7.4.4 nHFV versus nCPAP - nHFV MAP < 10 cm H2O	3	147	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.22, 1.90]
7.4.5 nHFV versus nCPAP - nHFV Hz ≥ 10	2	282	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.21, 1.46]
7.4.6 nHFV versus nCPAP - nHFV Hz < 10	2	966	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.75, 1.04]
7.5 Death or chronic lung disease at 36 weeks	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.5.1 nHFV versus nCPAP - preterm infants	2	966	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.5.2 nHFV versus nCPAP - nHFV MAP < 10 cm H2O	1	6	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.06, 4.47]
7.5.3 nHFV versus nCPAP - nHFV Hz < 10	2	966	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.06]
7.6 Intraventricular haemorrhage, Papile grade 3/4	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.6.1 nHFV versus nCPAP - preterm infants	3	1117	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.57, 1.13]
7.6.2 nHFV versus nCPAP - nHFV MAP ≥ 10 cm H2O	1	92	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [0.20, 22.24]
7.6.3 nHFV versus nCPAP - nHFV MAP < 10 cm H2O	1	65	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.17, 19.13]
7.6.4 nHFV versus nCPAP - nHFV Hz < 10	1	960	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.54, 1.09]
7.7 Neurodevelopmental disability at least 18 months' postnatal age or later	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.7.1 nHFV versus nCPAP - preterm infants	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.35, 2.16]
7.7.2 nHFV versus nCPAP - nHFV MAP ≥ 10 cm H2O	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.35, 2.16]

Analysis 7.1. Comparison 7: Respiratory support following planned extubation: nHFV vs nCPAP - subgroup analyses, Outcome 1: Mortality before hospital discharge

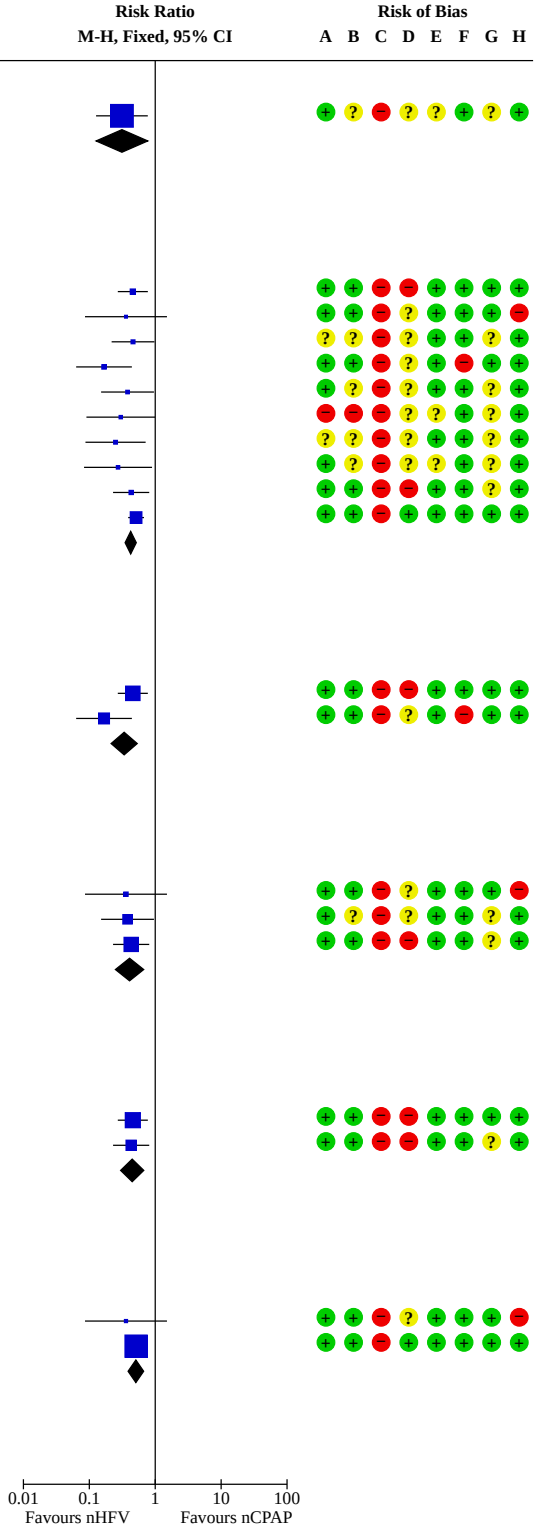


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 7.2. Comparison 7: Respiratory support following planned extubation: nHFV vs nCPAP - subgroup analyses, Outcome 2: Endotracheal reintubation

Study or Subgroup	nHFV Events	nHFV Total	nCPAP Events	nCPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 nHFV versus nCPAP - term or near-term infants						
Wang 2020	5	40	16	40	100.0%	0.31 [0.13 , 0.77]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**0.31 [0.13 , 0.77]**
Total events:	5		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.52 (P = 0.01)						
7.2.2 nHFV versus nCPAP - preterm infants						
Chen 2019	16	103	35	103	12.8%	0.46 [0.27 , 0.77]
Fischer 2019	1	4	2	2	1.1%	0.36 [0.09 , 1.51]
Li 2019	8	56	18	58	6.4%	0.46 [0.22 , 0.97]
Li 2021	4	45	25	47	8.9%	0.17 [0.06 , 0.44]
Lou 2017	5	34	12	31	4.6%	0.38 [0.15 , 0.96]
Yang 2021	3	34	10	34	3.6%	0.30 [0.09 , 1.00]
Yuan 2021	4	80	16	80	5.8%	0.25 [0.09 , 0.72]
Zhang 2021	3	35	11	35	4.0%	0.27 [0.08 , 0.89]
Zhu 2017	9	37	22	39	7.8%	0.43 [0.23 , 0.81]
Zhu 2022	63	480	123	480	44.9%	0.51 [0.39 , 0.68]
Subtotal (95% CI)		**908**		**909**	**100.0%**	**0.42 [0.35 , 0.52]**
Total events:	116		274			
Heterogeneity: Chi² = 7.37, df = 9 (P = 0.60); I² = 0%						
Test for overall effect: Z = 8.60 (P < 0.00001)						
7.2.3 nHFV versus nCPAP - nHFV MAP ≥ 10 cm H2O						
Chen 2019	16	103	35	103	58.9%	0.46 [0.27 , 0.77]
Li 2021	4	45	25	47	41.1%	0.17 [0.06 , 0.44]
Subtotal (95% CI)		**148**		**150**	**100.0%**	**0.34 [0.21 , 0.53]**
Total events:	20		60			
Heterogeneity: Chi² = 3.29, df = 1 (P = 0.07); I² = 70%						
Test for overall effect: Z = 4.66 (P < 0.00001)						
7.2.4 nHFV versus nCPAP - nHFV MAP < 10 cm H2O						
Fischer 2019	1	4	2	2	8.4%	0.36 [0.09 , 1.51]
Lou 2017	5	34	12	31	33.8%	0.38 [0.15 , 0.96]
Zhu 2017	9	37	22	39	57.7%	0.43 [0.23 , 0.81]
Subtotal (95% CI)		**75**		**72**	**100.0%**	**0.41 [0.25 , 0.67]**
Total events:	15		36			
Heterogeneity: Chi² = 0.08, df = 2 (P = 0.96); I² = 0%						
Test for overall effect: Z = 3.56 (P = 0.0004)						
7.2.5 nHFV versus nCPAP - nHFV Hz ≥ 10						
Chen 2019	16	103	35	103	62.0%	0.46 [0.27 , 0.77]
Zhu 2017	9	37	22	39	38.0%	0.43 [0.23 , 0.81]
Subtotal (95% CI)		**140**		**142**	**100.0%**	**0.45 [0.30 , 0.67]**
Total events:	25		57			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 3.90 (P < 0.0001)						
7.2.6 nHFV versus nCPAP - nHFV Hz < 10						
Fischer 2019	1	4	2	2	2.5%	0.36 [0.09 , 1.51]
Zhu 2022	63	480	123	480	97.5%	0.51 [0.39 , 0.68]
Subtotal (95% CI)		**484**		**482**	**100.0%**	**0.51 [0.39 , 0.67]**
Total events:	64		125			
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 4.88 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.10, df = 5 (P = 0.68), I² = 0%						



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

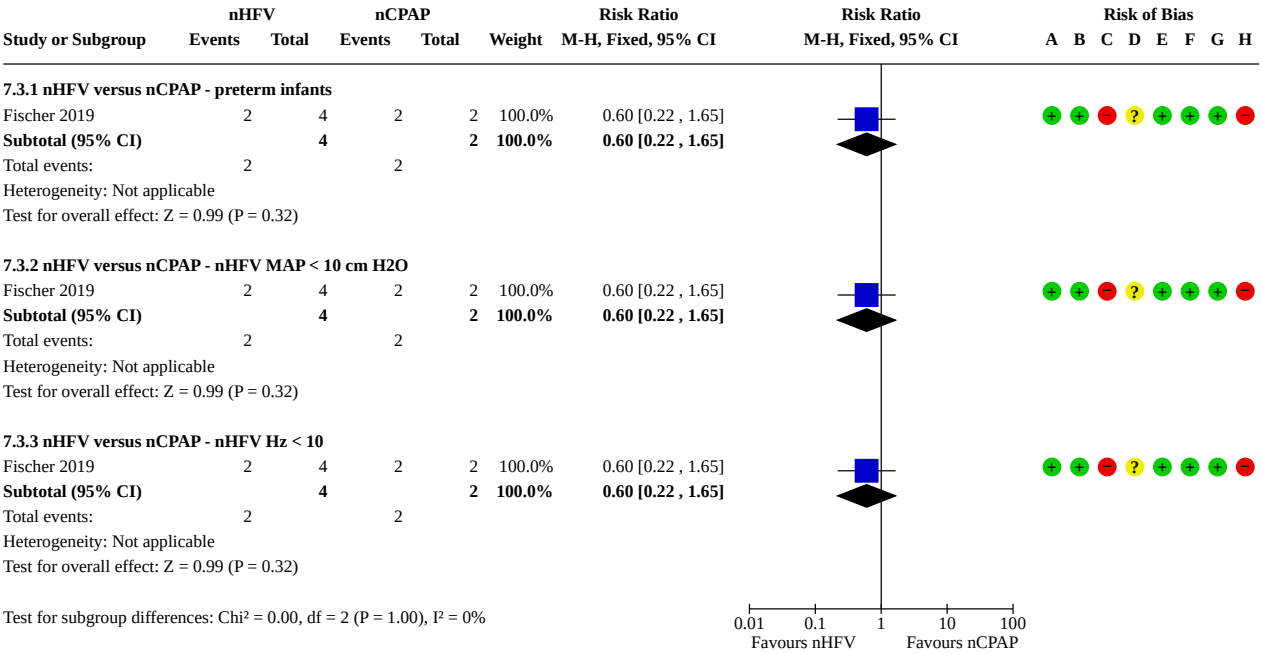
(C) Blinding of participants and personnel (performance bias): All outcomes

(D) Blinding of outcome assessment (detection bias)

Analysis 7.2. (Continued)

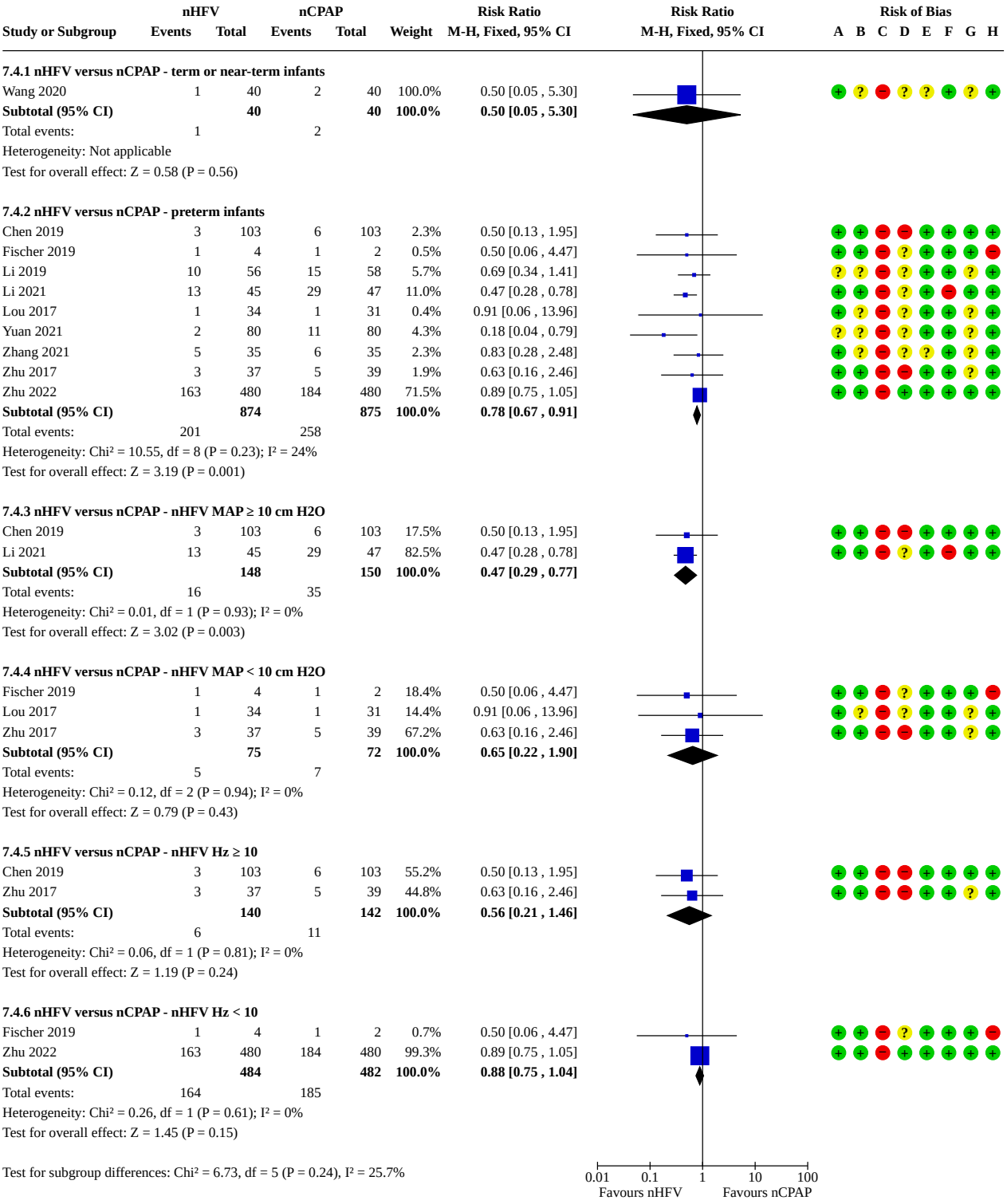
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 7.3. Comparison 7: Respiratory support following planned extubation: nHFV vs nCPAP - subgroup analyses, Outcome 3: Failure of extubation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 7.4. Comparison 7: Respiratory support following planned extubation: nHFV vs nCPAP - subgroup analyses, Outcome 4: Chronic lung disease at 36 weeks



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias): All outcomes

(D) Blinding of outcome assessment (detection bias)

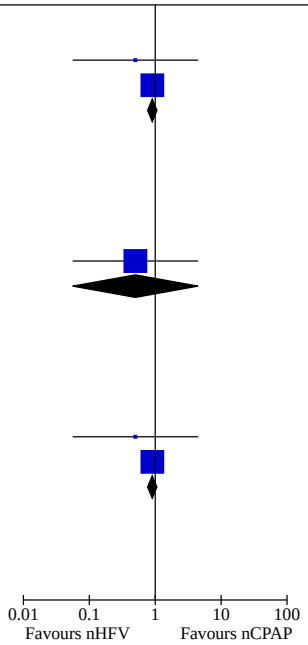
(E) Incomplete outcome data (attrition bias)

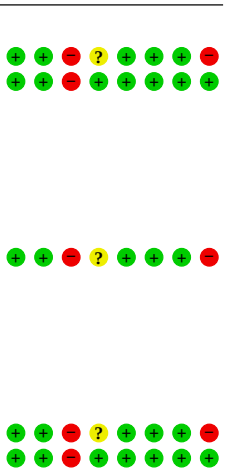
Analysis 7.4. (Continued)

(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 7.5. Comparison 7: Respiratory support following planned extubation: nHFV vs nCPAP - subgroup analyses, Outcome 5: Death or chronic lung disease at 36 weeks

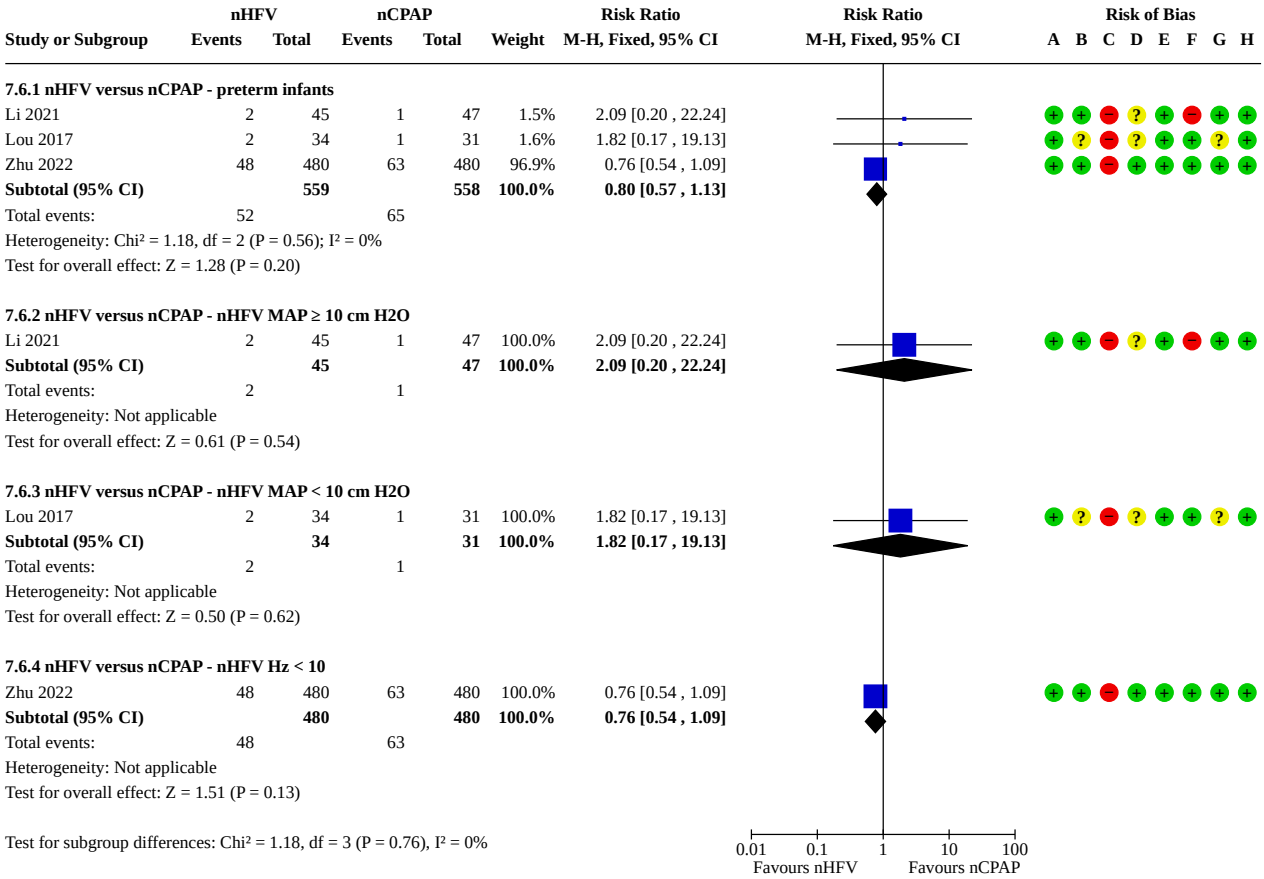
Study or Subgroup	nHFV Events	nHFV Total	nCPAP Events	nCPAP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.5.1 nHFV versus nCPAP - preterm infants						
Fischer 2019	1	4	1	2	0.7%	0.50 [0.06 , 4.47]
Zhu 2022	171	480	189	480	99.3%	0.90 [0.77 , 1.07]
Subtotal (95% CI)		**484**		**482**	**100.0%**	**0.90 [0.77 , 1.06]**
Total events:	172		190			
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.22)						
7.5.2 nHFV versus nCPAP - nHFV MAP < 10 cm H2O						
Fischer 2019	1	4	1	2	100.0%	0.50 [0.06 , 4.47]
Subtotal (95% CI)		**4**		**2**	**100.0%**	**0.50 [0.06 , 4.47]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.54)						
7.5.3 nHFV versus nCPAP - nHFV Hz < 10						
Fischer 2019	1	4	1	2	0.7%	0.50 [0.06 , 4.47]
Zhu 2022	171	480	189	480	99.3%	0.90 [0.77 , 1.07]
Subtotal (95% CI)		**484**		**482**	**100.0%**	**0.90 [0.77 , 1.06]**
Total events:	172		190			
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.22)						
Test for subgroup differences: Chi² = 0.28, df = 2 (P = 0.87), I² = 0%						





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

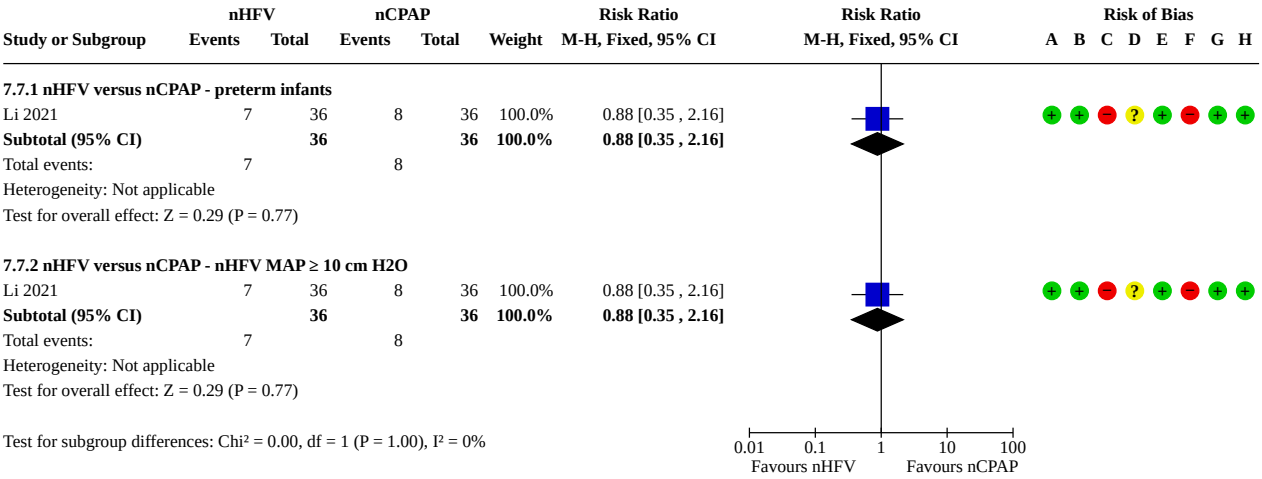
Analysis 7.6. Comparison 7: Respiratory support following planned extubation: nHFV vs nCPAP - subgroup analyses, Outcome 6: Intraventricular haemorrhage, Papile grade 3/4



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 7.7. Comparison 7: Respiratory support following planned extubation: nHFV vs nCPAP - subgroup analyses, Outcome 7: Neurodevelopmental disability at least 18 months' postnatal age or later



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

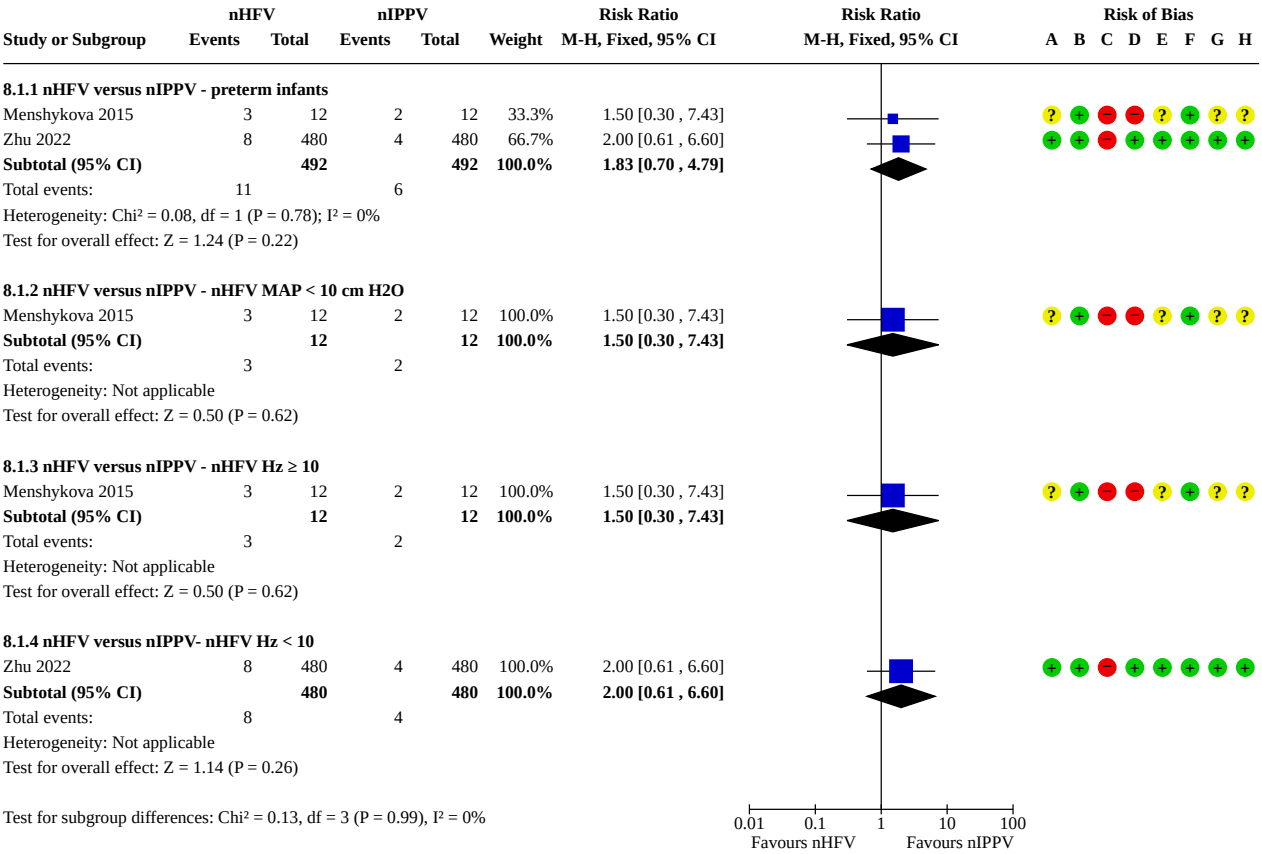
Comparison 8. Respiratory support following planned extubation: nHFV vs nIPPV - subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Mortality before hospital discharge	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1.1 nHFV versus nIPPV - preterm infants	2	984	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.70, 4.79]
8.1.2 nHFV versus nIPPV - nHFV MAP < 10 cm H2O	1	24	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.30, 7.43]
8.1.3 nHFV versus nIPPV - nHFV Hz ≥ 10	1	24	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.30, 7.43]
8.1.4 nHFV versus nIPPV- nHFV Hz < 10	1	960	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.61, 6.60]
8.2 Endotracheal reintubation	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.2.2 nHFV versus nIPPV - preterm infants	6	1364	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.54, 0.89]
8.2.3 nHFV versus nIPPV - nHFV MAP ≥ 10 cm H2O	2	134	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.11, 0.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2.4 nHFV versus nIPPV - nHFV MAP < 10 cm H2O	2	110	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.47, 1.80]
8.2.5 nHFV versus nIPPV - nHFV Hz ≥ 10	2	110	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.47, 1.80]
8.2.6 nHFV versus nIPPV- nHFV Hz < 10	1	960	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.55, 1.01]
8.3 Chronic lung disease at 36 weeks	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.3.2 nHFV versus nIPPV - preterm infants	4	1236	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.75, 1.04]
8.3.3 nHFV versus nIPPV - nHFV MAP ≥ 10 cm H2O	1	92	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.44, 1.45]
8.3.4 nHFV versus nIPPV - nHFV MAP < 10 cm H2O	1	24	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.39, 2.58]
8.3.5 nHFV versus nIPPV - nHFV Hz ≥ 10	1	24	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.39, 2.58]
8.3.6 nHFV versus nIPPV- nHFV Hz < 10	1	960	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.76, 1.06]
8.4 Death or chronic lung disease at 36 weeks	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.4.1 nHFV versus nIPPV - preterm infants	3	1070	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.79, 1.08]
8.4.2 nHFV versus nIPPV - nHFV MAP < 10 cm H2O	2	110	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.60, 1.52]
8.4.3 nHFV versus nIPPV - nHFV Hz ≥ 10	2	110	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.60, 1.52]
8.4.4 nHFV versus nIPPV- nHFV Hz < 10	1	960	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.78, 1.08]
8.5 Intraventricular haemorrhage, Papile grade 3/4	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.5.2 nHFV versus nIPPV - preterm infants	4	1162	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.55, 1.10]
8.5.3 nHFV versus nIPPV - nHFV MAP ≥ 10 cm H2O	1	92	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.12, 3.97]
8.5.4 nHFV versus nIPPV - nHFV MAP < 10 cm H2O	2	110	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 1.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.5.5 nHFV versus nIPPV - nHFV Hz ≥ 10	2	110	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 1.92]
8.5.6 nHFV versus nIPPV- nHFV Hz < 10	1	960	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.57, 1.17]
8.6 Neurodevelopmental disability at least 18 months' postnatal age or later	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.6.1 nHFV versus nIPPV - preterm infants	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.35, 2.16]
8.6.2 nHFV versus nIPPV - nHFV MAP ≥ 10 cm H2O	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.35, 2.16]

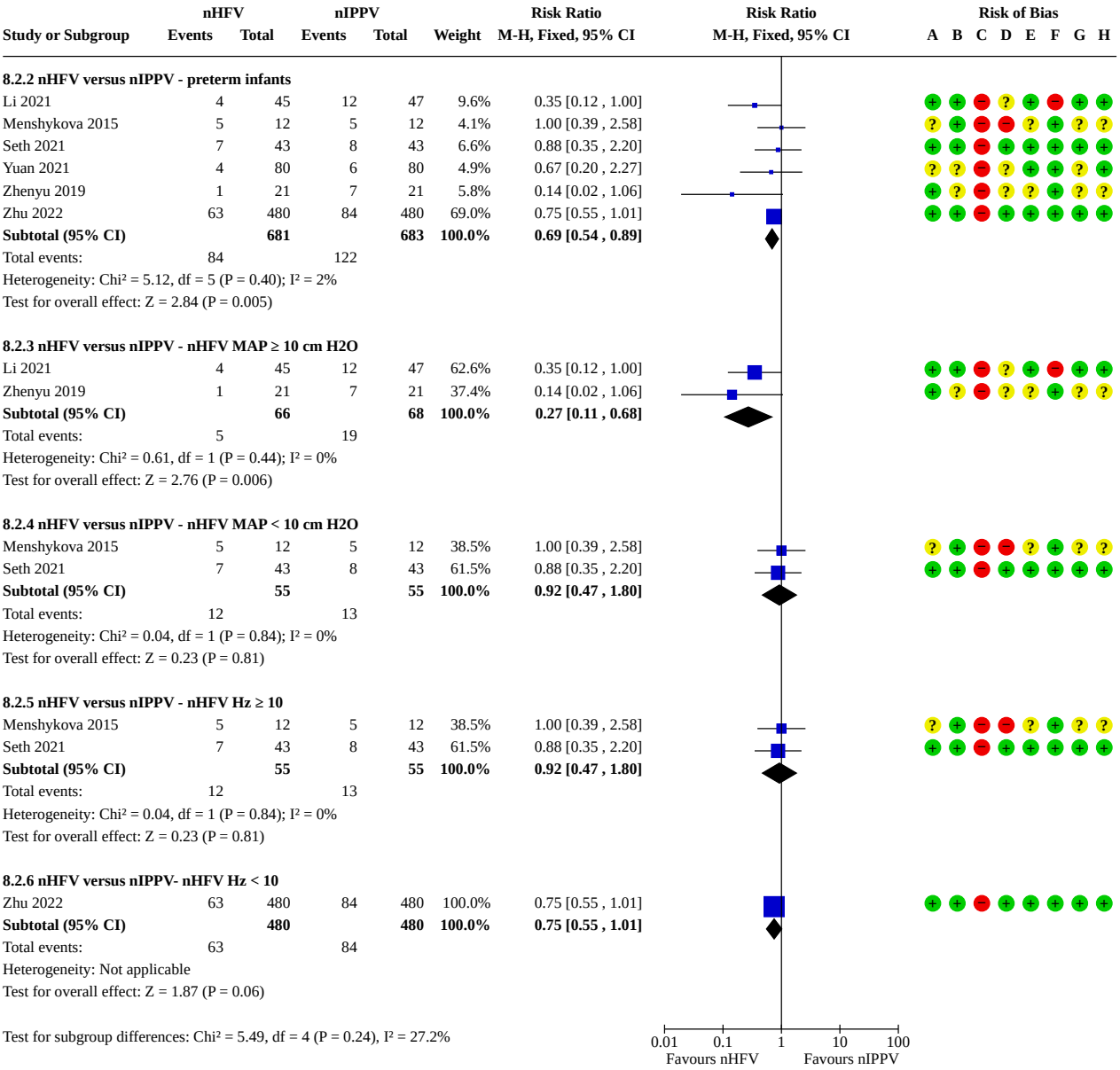
Analysis 8.1. Comparison 8: Respiratory support following planned extubation: nHFV vs nIPPV - subgroup analyses, Outcome 1: Mortality before hospital discharge



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

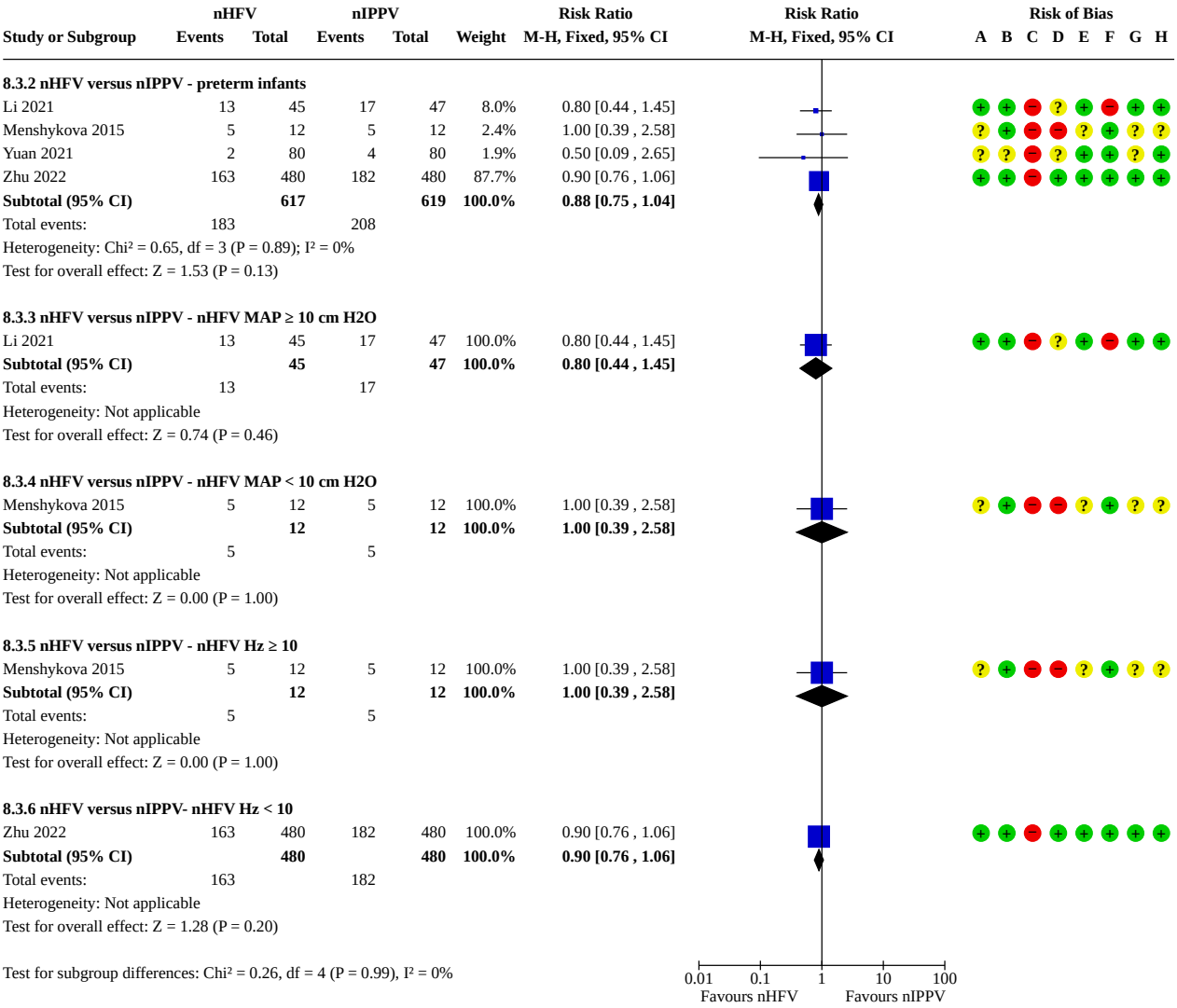
Analysis 8.2. Comparison 8: Respiratory support following planned extubation: nHFV vs nIPPV - subgroup analyses, Outcome 2: Endotracheal reintubation



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

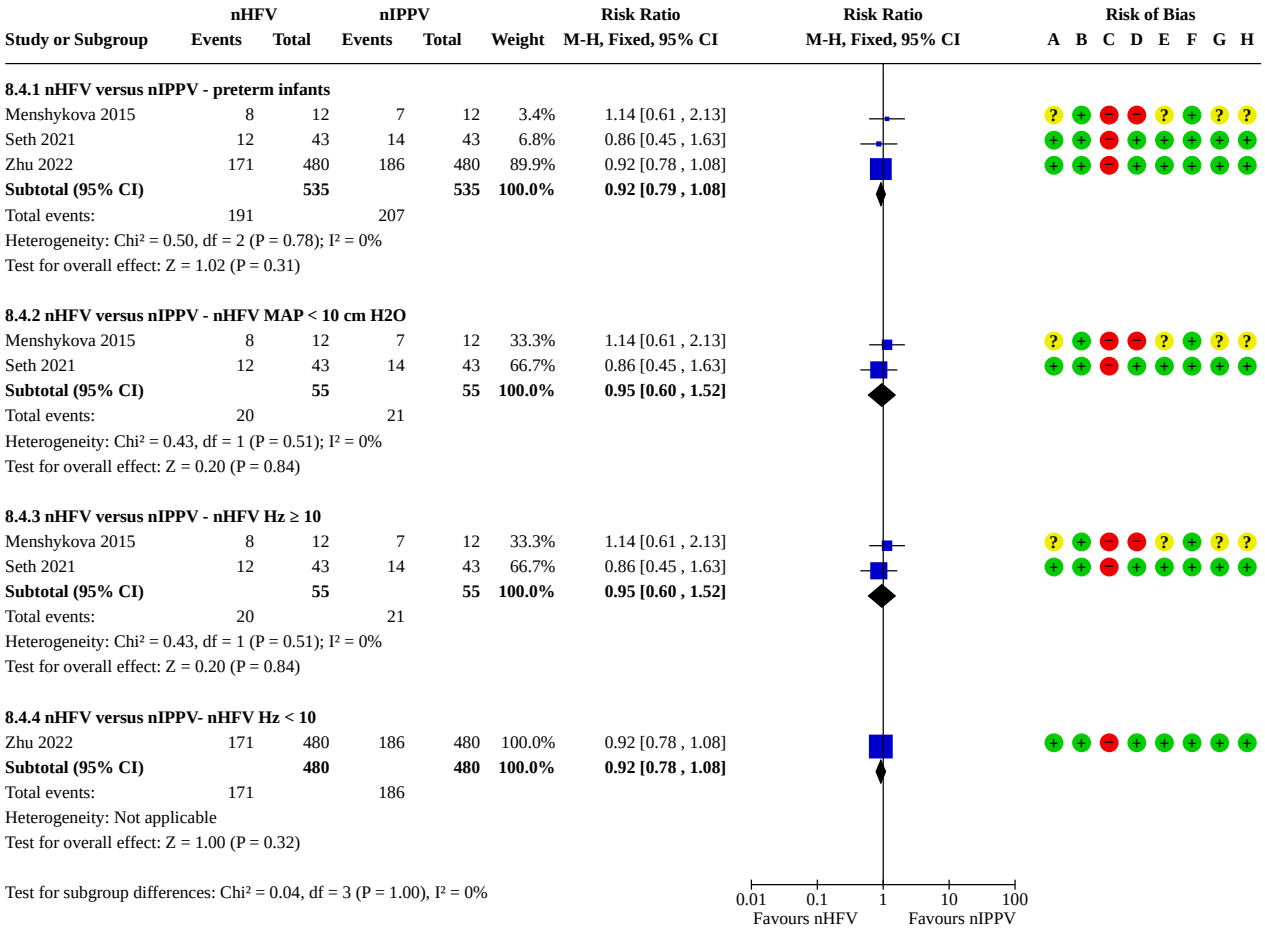
Analysis 8.3. Comparison 8: Respiratory support following planned extubation: nHFV vs nIPPV - subgroup analyses, Outcome 3: Chronic lung disease at 36 weeks



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

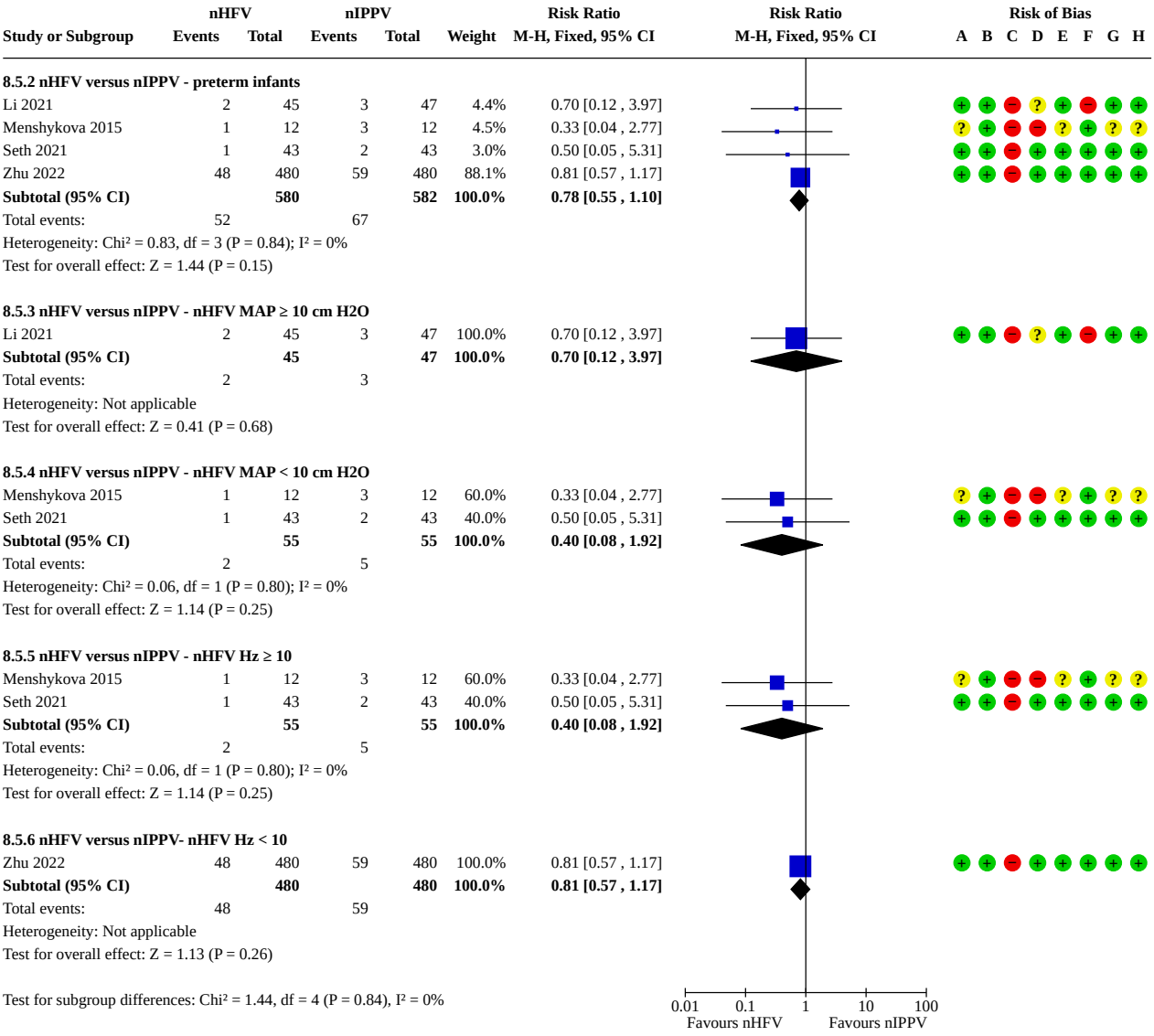
Analysis 8.4. Comparison 8: Respiratory support following planned extubation: nHFV vs nIPPV - subgroup analyses, Outcome 4: Death or chronic lung disease at 36 weeks



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

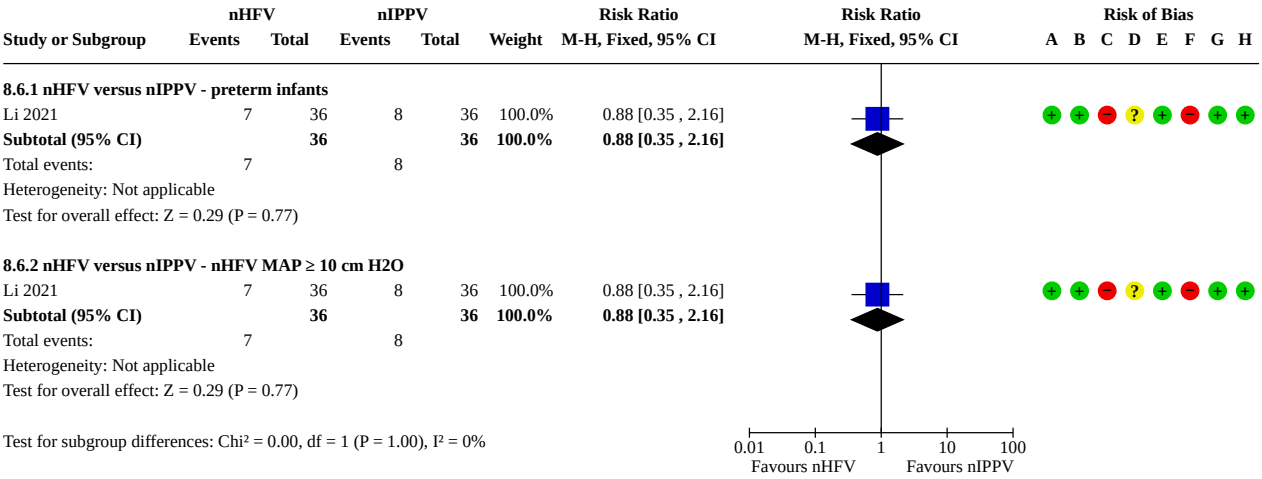
Analysis 8.5. Comparison 8: Respiratory support following planned extubation: nHFV vs nIPPV - subgroup analyses, Outcome 5: Intraventricular haemorrhage, Papile grade 3/4



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 8.6. Comparison 8: Respiratory support following planned extubation: nHFV vs nIPPV - subgroup analyses, Outcome 6: Neurodevelopmental disability at least 18 months' postnatal age or later



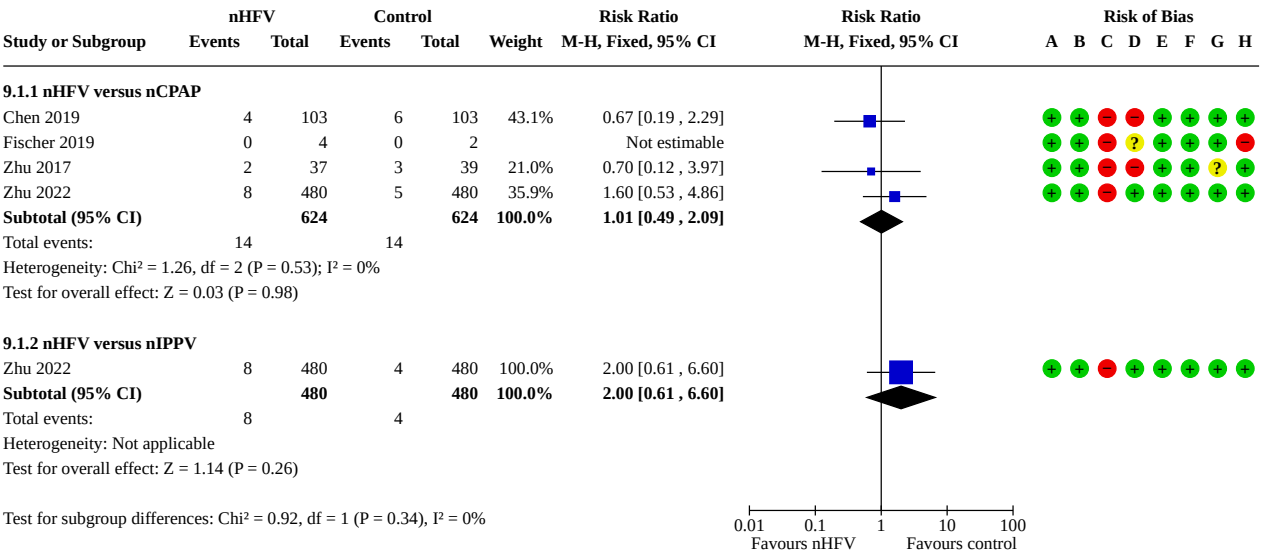
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Comparison 9. Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities - sensitivity analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Mortality before hospital discharge	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1.1 nHFV versus nCPAP	4	1248	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.49, 2.09]
9.1.2 nHFV versus nIPPV	1	960	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.61, 6.60]
9.2 Endotracheal reintubation	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.2.1 nHFV versus nCPAP	5	1340	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.36, 0.56]
9.2.2 nHFV versus nIPPV	3	1138	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.54, 0.94]
9.3 Failure of extubation	1	6	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.22, 1.65]
9.3.1 nHFV versus nCPAP	1	6	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.22, 1.65]
9.4 Chronic lung disease at 36 weeks	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.4.1 nHFV versus nCPAP	5	1340	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.70, 0.95]
9.4.2 nHFV versus nIPPV	2	1052	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.5 Death or chronic lung disease at 36 weeks	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.5.1 nHFV versus nCPAP	2	966	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.06]
9.5.2 nHFV versus nIPPV	2	1046	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.78, 1.07]
9.6 Intraventricular haemorrhage, Papile grade 3/4	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.6.1 nHFV versus nCPAP	2	1052	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.55, 1.11]
9.6.2 nHFV versus nIPPV	3	1138	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.56, 1.13]

Analysis 9.1. Comparison 9: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities - sensitivity analyses, Outcome 1: Mortality before hospital discharge

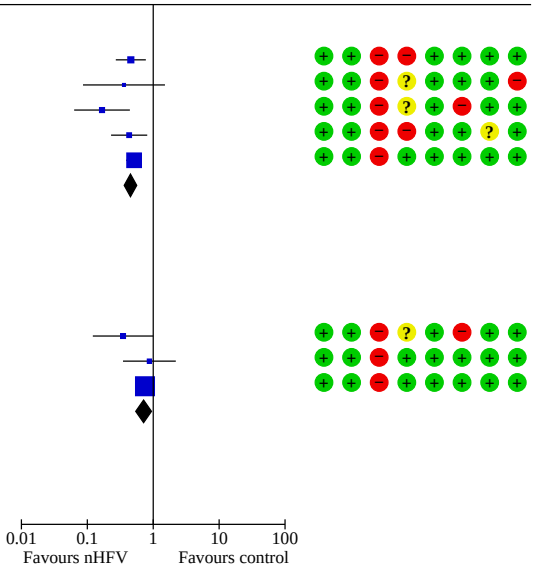


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 9.2. Comparison 9: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities - sensitivity analyses, Outcome 2: Endotracheal reintubation

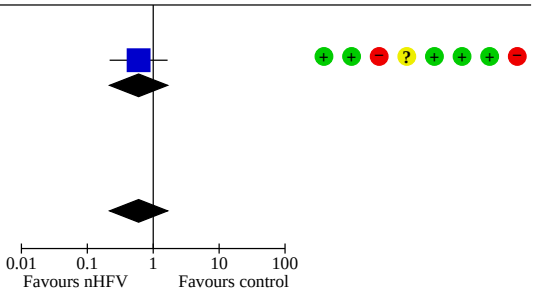
Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.2.1 nHFV versus nCPAP						
Chen 2019	16	103	35	103	16.9%	0.46 [0.27 , 0.77]
Fischer 2019	1	4	2	2	1.5%	0.36 [0.09 , 1.51]
Li 2021	4	45	25	47	11.8%	0.17 [0.06 , 0.44]
Zhu 2017	9	37	22	39	10.3%	0.43 [0.23 , 0.81]
Zhu 2022	63	480	123	480	59.4%	0.51 [0.39 , 0.68]
Subtotal (95% CI)		**669**		**671**	**100.0%**	**0.45 [0.36 , 0.56]**
Total events:	93		207			
Heterogeneity: Chi² = 4.93, df = 4 (P = 0.29); I² = 19%						
Test for overall effect: Z = 7.13 (P < 0.00001)						
9.2.2 nHFV versus nIPPV						
Li 2021	4	45	12	47	11.3%	0.35 [0.12 , 1.00]
Seth 2021	7	43	8	43	7.7%	0.88 [0.35 , 2.20]
Zhu 2022	63	480	84	480	81.0%	0.75 [0.55 , 1.01]
Subtotal (95% CI)		**568**		**570**	**100.0%**	**0.71 [0.54 , 0.94]**
Total events:	74		104			
Heterogeneity: Chi² = 2.07, df = 2 (P = 0.36); I² = 3%						
Test for overall effect: Z = 2.40 (P = 0.02)						
Test for subgroup differences: Chi² = 6.55, df = 1 (P = 0.01), I² = 84.7%						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 9.3. Comparison 9: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities - sensitivity analyses, Outcome 3: Failure of extubation

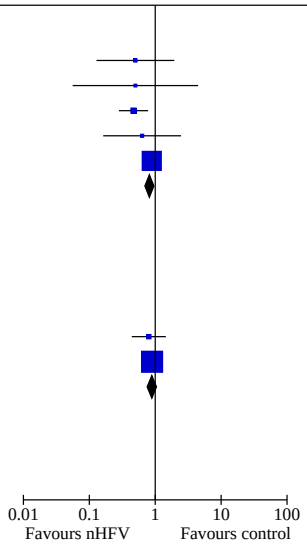
Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.3.1 nHFV versus nCPAP						
Fischer 2019	2	4	2	2	100.0%	0.60 [0.22 , 1.65]
Subtotal (95% CI)		**4**		**2**	**100.0%**	**0.60 [0.22 , 1.65]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
Total (95% CI)		**4**		**2**	**100.0%**	**0.60 [0.22 , 1.65]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

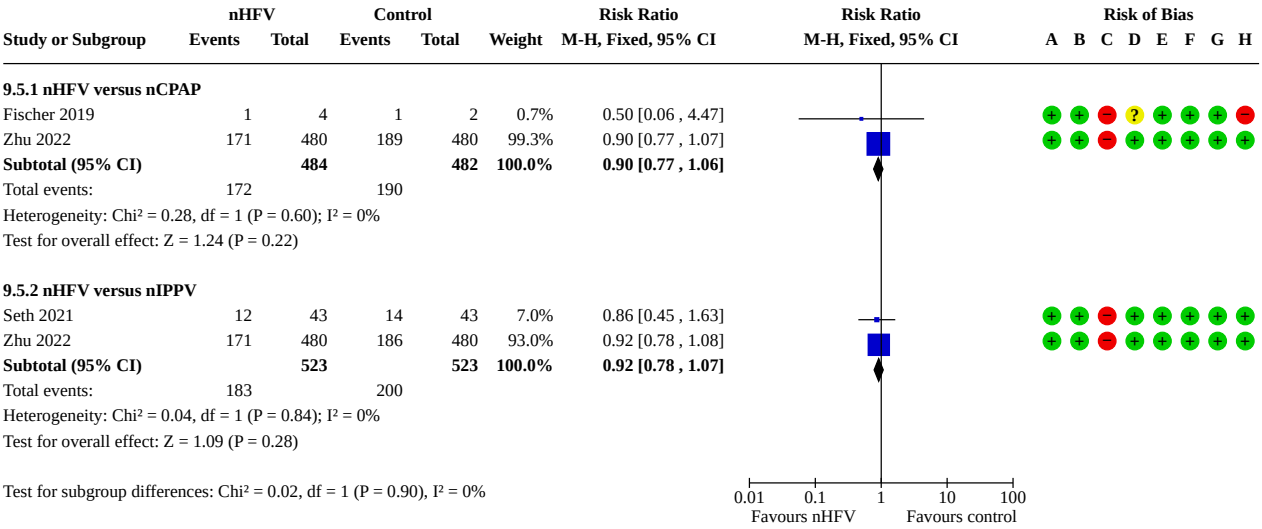
Analysis 9.4. Comparison 9: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities - sensitivity analyses, Outcome 4: Chronic lung disease at 36 weeks

Study or Subgroup	nHFV Events	nHFV Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F	G	H
9.4.1 nHFV versus nCPAP														
Chen 2019	3	103	6	103	2.7%	0.50 [0.13 , 1.95]	+	+	−	−	+	+	+	+
Fischer 2019	1	4	1	2	0.6%	0.50 [0.06 , 4.47]	+	+	−	?	+	+	+	−
Li 2021	13	45	29	47	12.6%	0.47 [0.28 , 0.78]	+	+	−	?	+	−	+	+
Zhu 2017	3	37	5	39	2.2%	0.63 [0.16 , 2.46]	+	+	−	−	+	+	?	+
Zhu 2022	163	480	184	480	81.9%	0.89 [0.75 , 1.05]	+	+	−	+	+	+	+	+
Subtotal (95% CI)		**669**		**671**	**100.0%**	**0.82 [0.70 , 0.95]**								
Total events:	183		225											
Heterogeneity: Chi² = 6.29, df = 4 (P = 0.18); I² = 36%														
Test for overall effect: Z = 2.55 (P = 0.01)														
9.4.2 nHFV versus nIPPV														
Li 2021	13	45	17	47	8.4%	0.80 [0.44 , 1.45]	+	+	−	?	+	−	+	+
Zhu 2022	163	480	182	480	91.6%	0.90 [0.76 , 1.06]	+	+	−	+	+	+	+	+
Subtotal (95% CI)		**525**		**527**	**100.0%**	**0.89 [0.75 , 1.04]**								
Total events:	176		199											
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%														
Test for overall effect: Z = 1.44 (P = 0.15)														
Test for subgroup differences: Chi² = 0.54, df = 1 (P = 0.46), I² = 0%														



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

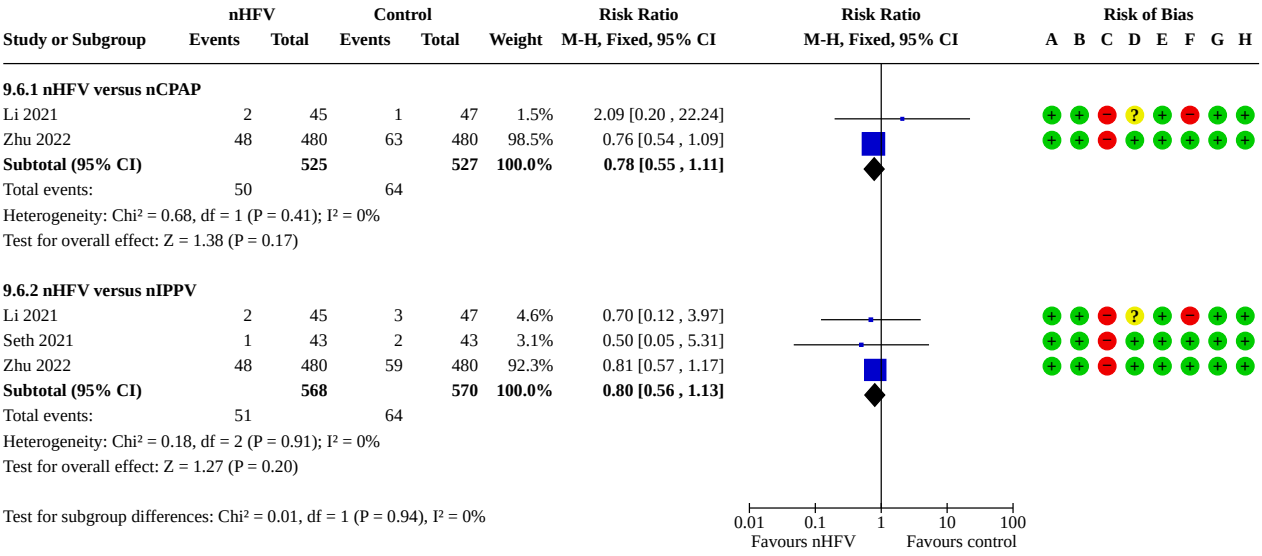
Analysis 9.5. Comparison 9: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities - sensitivity analyses, Outcome 5: Death or chronic lung disease at 36 weeks



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 9.6. Comparison 9: Respiratory support following planned extubation: nHFV vs other non-invasive respiratory therapy modalities - sensitivity analyses, Outcome 6: Intraventricular haemorrhage, Papile grade 3/4



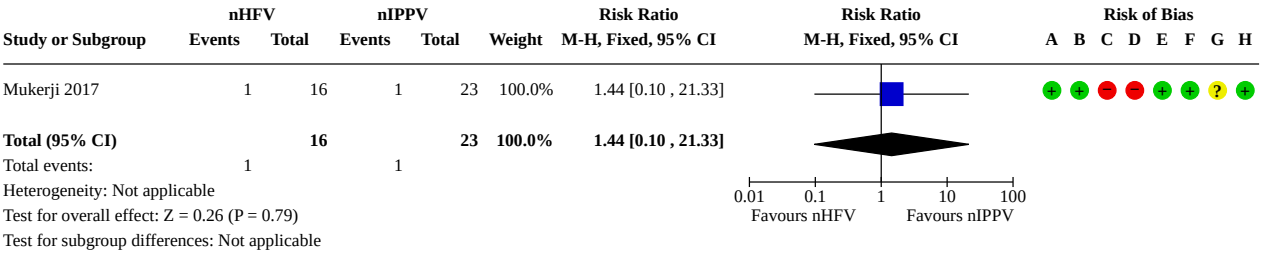
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Comparison 10. Respiratory support following initial non-invasive respiratory support failure: nHFV vs nIPPV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Mortality before hospital discharge	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.10, 21.33]
10.2 Endotracheal intubation	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.51, 2.98]
10.3 Failure of respiratory support	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.29, 1.16]
10.4 Duration of oxygen therapy, days	1	39	Mean Difference (IV, Fixed, 95% CI)	24.00 [-8.18, 56.18]
10.5 Chronic lung disease at 36 weeks	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.70, 1.47]
10.6 Pulmonary air leak syndromes	1	39	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.7 Necrotising enterocolitis	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.02, 10.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.8 Spontaneous intestinal perforation	1	39	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.9 Intraventricular haemorrhage, Papile grade 3/4	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.02, 10.87]
10.10 Periventricular leukomalacia	1	39	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.11 Retinopathy of prematurity, stage ≥ 3	1	39	Risk Ratio (M-H, Fixed, 95% CI)	9.88 [0.55, 179.12]

Analysis 10.1. Comparison 10: Respiratory support following initial non-invasive respiratory support failure: nHFV vs nIPPV, Outcome 1: Mortality before hospital discharge



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
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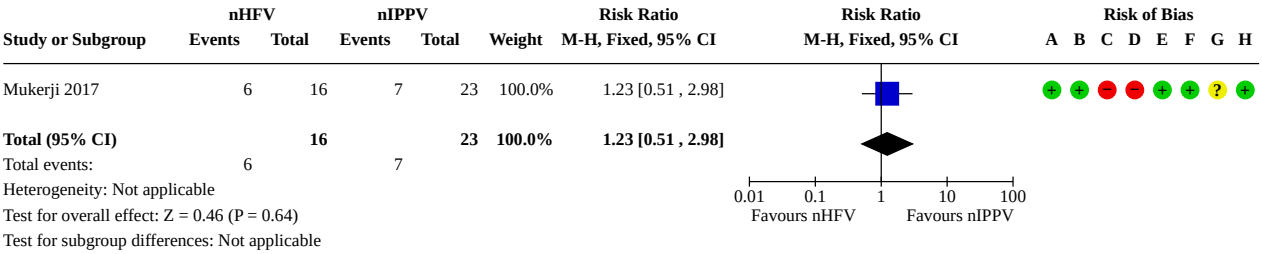
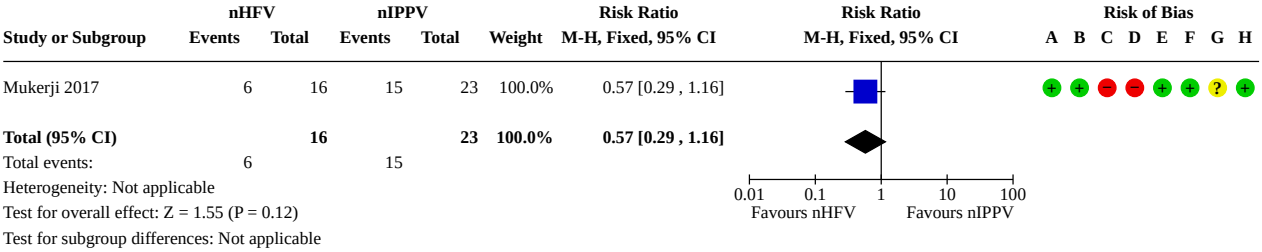
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 10.2. Comparison 10: Respiratory support following initial non-invasive respiratory support failure: nHFV vs nIPPV, Outcome 2: Endotracheal intubation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 10.3. Comparison 10: Respiratory support following initial non-invasive respiratory support failure: nHFV vs nIPPV, Outcome 3: Failure of respiratory support

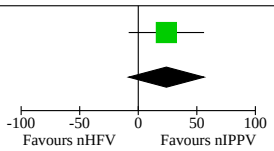


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 10.4. Comparison 10: Respiratory support following initial non-invasive respiratory support failure: nHFV vs nIPPV, Outcome 4: Duration of oxygen therapy, days

Study or Subgroup	nHFV Mean	nHFV SD	nHFV Total	nIPPV Mean	nIPPV SD	nIPPV Total	Weight	Mean Difference IV, Fixed, 95% CI
Mukerji 2017	62	51.48	16	38	48.89	23	100.0%	24.00 [-8.18 , 56.18]
Total (95% CI)			**16**			**23**	**100.0%**	**24.00 [-8.18 , 56.18]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Not applicable

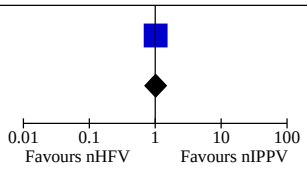


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 10.5. Comparison 10: Respiratory support following initial non-invasive respiratory support failure: nHFV vs nIPPV, Outcome 5: Chronic lung disease at 36 weeks

Study or Subgroup	nHFV Events	nHFV Total	nIPPV Events	nIPPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mukerji 2017	12	16	17	23	100.0%	1.01 [0.70 , 1.47]
Total (95% CI)		**16**		**23**	**100.0%**	**1.01 [0.70 , 1.47]**
Total events:	12		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.08 (P = 0.94)
Test for subgroup differences: Not applicable

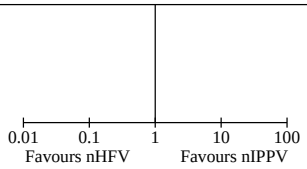


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 10.6. Comparison 10: Respiratory support following initial non-invasive respiratory support failure: nHFV vs nIPPV, Outcome 6: Pulmonary air leak syndromes

Study or Subgroup	nHFV Events	nHFV Total	nIPPV Events	nIPPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G H
Mukerji 2017	0	16	0	23		Not estimable	+ + − − + + ? +
Total (95% CI)		**16**		**23**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

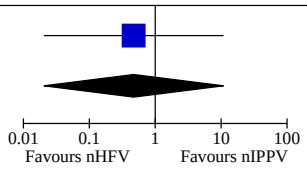


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 10.7. Comparison 10: Respiratory support following initial non-invasive respiratory support failure: nHFV vs nIPPV, Outcome 7: Necrotising enterocolitis

Study or Subgroup	nHFV Events	nHFV Total	nIPPV Events	nIPPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G H
Mukerji 2017	0	16	1	23	100.0%	0.47 [0.02 , 10.87]	+ + − − + + ? +
Total (95% CI)		**16**		**23**	**100.0%**	**0.47 [0.02 , 10.87]**	
Total events:	0		1				

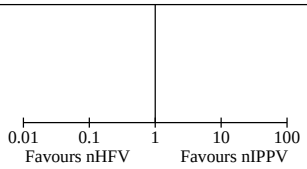
Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 10.8. Comparison 10: Respiratory support following initial non-invasive respiratory support failure: nHFV vs nIPPV, Outcome 8: Spontaneous intestinal perforation

Study or Subgroup	nHFV Events	nHFV Total	nIPPV Events	nIPPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G H
Mukerji 2017	0	16	0	23		Not estimable	+ + − − + + ? +
Total (95% CI)		**16**		**23**		**Not estimable**	
Total events:	0		0				

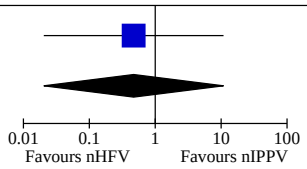


Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 10.9. Comparison 10: Respiratory support following initial non-invasive respiratory support failure: nHFV vs nIPPV, Outcome 9: Intraventricular haemorrhage, Papile grade 3/4

Study or Subgroup	nHFV Events	nHFV Total	nIPPV Events	nIPPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G H
Mukerji 2017	0	16	1	23	100.0%	0.47 [0.02 , 10.87]	+ + − − + + ? +
Total (95% CI)		**16**		**23**	**100.0%**	**0.47 [0.02 , 10.87]**	
Total events:	0		1				



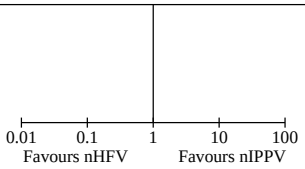
Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 10.10. Comparison 10: Respiratory support following initial non-invasive respiratory support failure: nHFV vs nIPPV, Outcome 10: Periventricular leukomalacia

Study or Subgroup	nHFV Events	nHFV Total	nIPPV Events	nIPPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G H
Mukerji 2017	0	16	0	23		Not estimable	+ + − − + + ? +
Total (95% CI)		**16**		**23**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

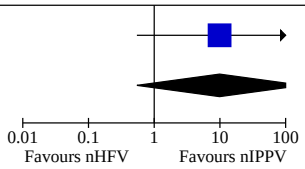


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 10.11. Comparison 10: Respiratory support following initial non-invasive respiratory support failure: nHFV vs nIPPV, Outcome 11: Retinopathy of prematurity, stage ≥ 3

Study or Subgroup	nHFV Events	nHFV Total	nIPPV Events	nIPPV Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G H
Mukerji 2017	3	16	0	23	100.0%	9.88 [0.55 , 179.12]	+ + − − + + ? +
Total (95% CI)		**16**		**23**	**100.0%**	**9.88 [0.55 , 179.12]**	
Total events:	3		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): All outcomes
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Incomplete long term outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

ADDITIONAL TABLES

Table 1. Summary of included studies - nHFV versus invasive respiratory support for initial respiratory management

Study	Country/total participants	Eligibility criteria	Gestational age weeks/ birthweight g		Intervention group		Control group		Interface (in both intervention and control groups)
			Intervention group	Control group	Mode	Settings	Mode	Settings	
Feng 2019	China 80	RDS	30.46 +/- 1.35 weeks	30.37 +/- 1.31 weeks	nHFOV with surfactant	**Ventilator:** Stephanie, Servo-a **MAP:** 10 to 12 cm H_2O **Frequency:** 12 to 15 Hz **Amplitude:** 30 to 45 cm H_2O	Invasive respiratory support (conventional mechanical ventilation) with surfactant	**Ventilator:** Maquet **PIP:** 15 to 25 cm H_2O **PEEP:** PEEP 4 to 6 cm H_2O **Respiratory Rate:** 40 to 60 bpm	Not reported
Yang 2020	China 100	RDS	31.05 +/- 1.26 (range 25 to 35) weeks	31.02+/-1.24 (range 28 to 35) weeks	nHFOV	**Ventilator:** Medin CNO, Germany **MAP:** 5 to 10 cm H_2O **Frequency:** 7 to 10 Hz **Amplitude:** 4 to 10 cm H_2O	Invasive respiratory support (conventional mechanical ventilation)	**Ventilator:** Drager Babylog VN500 **PIP:** 15 to 25 cm H_2O **PEEP:** 4 to 8 cm H_2O **Respiratory rate:** 30 to 40 bpm	Not reported

bpm: breaths per minute; **hz**: hertz; **MAP**: mean airway pressure; **nHFOV**: non-invasive high-frequency oscillatory ventilation; **PEEP**: positive end-expiratory pressure; **PIP**: positive inspiratory pressure; **RDS**: respiratory distress syndrome

Table 2. Summary of included studies - nHFV versus other forms of non-invasive respiratory support for initial respiratory management

Study	Country total participants	Gestation and weight eligibility criteria	Gestational age weeks/ birthweight g		Intervention group		Control group		Interface (in both intervention and control groups)
			Intervention group	Control group	Mode	Settings	Mode	Settings	

Table 2. Summary of included studies - nHFV versus other forms of non-invasive respiratory support for initial respiratory management *(Continued)*

De La Roque 2011	France 46	≥ 37 weeks ≥ 2000 g	38 +/- 0.5 weeks 3004 +/- 116 g	37 +/- 0.5 weeks 3375 +/- 160 g	nHFPV	**Ventilator:** Percussionaire **MAP:** 5 cm H_2O **Frequency:** 5 Hz **Amplitude:** 2 to 35 cm H_2O	nCPAP	**Ventilator:** Babylog 8000 **PEEP:** 5 cm H_2O	Single heated humidified nasal probe
El Ashker 2022	Egypt 60	GA between 28 + 0 and 33 + 6 weeks	Not stated	Not stated	nHFOV	**Ventilator:** SLE5000, UK **MAP:** NS **Frequency:** NS **Amplitude:** NS	nCPAP	**Ventilator:** Medin CNO, medin Medical Innovations GmbH, Olching, Germany) or (SLE 1000, SLE Limited, UK) **PEEP:** NS	**nCPAP** via binasal prongs **nHFOV** via nasopharyngeal tube
Iranpour 2019	Iran 68	30 to 36 + 6/7 weeks	33 (IQR 30–34) weeks 1959 (613) g	33 (IQR 31–35) weeks 2161 (764) g	nHFOV	**Ventilator:** Fabian **MAP:** 8 cmH_2O **Frequency:** 10 to 20 Hz **Amplitude:** 20 cm H_2O	nCPAP	**Ventilator:** Fabian **PEEP:** 6 to 7 cm H_2O	Short binasal prongs
Iranpour 2019	Iran 124	28 to 34 weeks	31.08 ± 2.9 weeks 1486 ± 470 g	31.07 ± 2.8 weeks 1506 ± 490 g	nHFOV	**Ventilator:** CNO driver **MAP:** 8 cm H_2O **Frequency:** 5 Hz **Amplitude:** 3 to 7 cm H_2O	nCPAP	**Ventilator:** Flow-driver (Sindi NCPAP driver) **PEEP:** 4 to 8 cm H_2O	Short binasal prongs
Guo 2021	China 74	RDS	NR	NR	nHFOV	**Ventilator:** Medin CNO **MAP:** 8 to 12 cm H_2O **Frequency:** 7 to 12 Hz **Amplitude:** 2 to 3 times MAP with visible chest oscillation	nCPAP	**PEEP:** 5 to 7 cm H_2O	Not reported
Oktem 2021*	Turkey 37	< 32 weeks	Median 29 (range 27 to 34) weeks	Median 28 (range 26 to 32) weeks	nHFOV	**Ventilator:** Babylog 8000 **MAP:** 6 cm H_2O	nCPAP	**Ventilator:** bubble CPAP system	Short binasal prongs

Table 2. Summary of included studies - nHFV versus other forms of non-invasive respiratory support for initial respiratory management *(Continued)*

			Median 1250 (range 800 to 2240) g	Median 1240 (range 580 to 2010) g		**Frequency:** 10 Hz **Amplitude:** deltaP 100%		**PEEP:** 5 to 6 cm H_2O	
Zhang 2022a	China 102	26 to 42 weeks	26 to 42 (34.52 +/- 2.98) weeks	26-39 (34.25 +/- 3.14)	nHFOV	**Ventilator:** SLE 5000 **MAP:** 8 to 12 cm H_20 **Frequency:** 7 to 12 Hz **Amplitude** not reported	nCPAP	**Ventilator:** NV8 **PEEP:** 5 to 7 cm H_2O	Not reported
Zhu 2021	China 340	26 to 33 + 6/7 weeks	30.6 +/- 1.7 weeks 1564 +/- 367 g	30.9 +/- 1.8 weeks 1582 +/- 343 g	nHFOV	**Ventilator:** CNO **MAP:** 6 [6 to 10] cm H_2O **Frequency:** 8 [8 to 12] Hz **Amplitude:** level 7 (range 7 to 10) **or** **Ventilator:** SLE5000 **MAP:** 6 [6 to 10] cm H_2O **Frequency:** 8 [8 to 12] Hz **Amplitude:** 20 [20 to 35) cm H_2O	nCPAP	**Ventilator:** CNO or SLE5000 **PEEP:** 6 [6 to 8] cm H_2O	Short binasal prongs
Lou 2018	China 65	28 to 35 weeks	33.5 ± 1.5 weeks 1790 ± 330 g	34.2 ± 1.6 weeks 1840 ± 420 g	nHFOV	**Ventilator:** SLE Baby 5000, Germany **MAP:** 6 to 12 cm H_2O **Frequency:** 6 to 12 Hz **Amplitude:** 2 to 3 times MAP	BP-CPAP (considered to be equivalent to nIPPV)	**Ventilator:** Fabian, Swiss **PIP:** 12 to 15 cm H_2O **PEEP:** 5 cm H_2O **Rate:**	Short binasal prongs
Jiang 2020	China 82	< 37 weeks	33.2 ± 1.4 weeks 1820 ± 330 g	33.5 ± 1.5 weeks 1840 ± 410 g	nHFOV with thin-catheter surfactant	**Ventilator:** SLE5000 **MAP:** 8 cm H_2O **Frequency:** 7 to 12 Hz **Amplitude:** 16 to 24 cm H_2O	BiPAP (considered to be equivalent to nIPPV) with thin-	**Ventilator:** Fabian **PIP:** 12 to 15 cm H_2O **PEEP:** 5 cm H_2O **Rate:** 30 to 40 bpm	Not reported

Table 2. Summary of included studies - nHFV versus other forms of non-invasive respiratory support for initial respiratory management *(Continued)*

							catheter surfactant		
Xu 2020	China 60	RDS	30.73 +/- 1.31 weeks	30.46 +/- 1.35 weeks	nHFOV	**Ventilator:** Sophie **MAP:** 8 to 12 cm H_2O **Frequency:** 10 to 15 Hz **Amplitude:** 30 to 40 cm	nIPPV	**Ventilator:** Sophie **PIP:** 15 to 25 cm H_20 **PEEP:** 4 to 6 cm H_20	Not reported
Zou 2020	China 120	< 31 weeks < 1500 g	28.56 ± 1.23 weeks 1150 ± 135 g	28.71 ± 1.18 weeks 1188 ± 142 g	nHFOV	Not reported	nIPPV	Not reported	Not reported
Ali 2023	Pakistan 48	27 to 34 weeks	29.96 ± 2.38 weeks 1347 ± 458 g	43.58 ± 61.03 weeks 1672 ± 534 g	nHFOV with surfactant administration via InSurE	**Ventilator:** CNO Medin **MAP:** 6 (range 6-10) cm H_2O **Frequency:** 8 (range 8-12) Hz **Amplitude:** 7 (range 7-10) cm H_2O	nIPPV with surfactant administration via InSurE	**Ventilator:** CNO Medin **PIP:** 15 (range 1-25) H_2O **PEEP:** 6 (range 1-8) cm H_2O **Rate:** 40 (range 5-60) bpm **Inspiratory time (IT):** 0.40 s	Nasal mask
Cheng 2021	China 60	28 to 34 weeks	31.38 ± 1.60 weeks 1656 ± 423 g	31.78 ± 1.55 weeks 1572 ± 370 g	nHFOV with non-invasive surfactant	**Ventilator:** Leoni Plus **MAP:** 6 to 12 cm H_2O **Frequency:** 6 to 12 Hz **Amplitude:** 2 times MAP with visible chest oscillation	nIPPV with non-invasive surfactant	**Ventilator:** Leoni Plus **PIP:** 15 to 25 cm H_2O **PEEP:** 4 to 6 cm H_2O **Rate:** 15 to 30 bpm	Not reported
Oktem 2021*	Turkey 37	< 32 weeks	Median 29 (range 27 to 34) weeks	Median 28 (26 to 32) weeks	nHFOV	**Ventilator:** Babylog 8000 **MAP:** 6 cm H_2O	nIPPV	**Ventilator:** Babylog 8000	Short binasal prongs

Table 2. Summary of included studies - nHFV versus other forms of non-invasive respiratory support for initial respiratory management *(Continued)*

			Median 1250 (range 800 to 2240) g	Median 1130 (range 530 to 2550) g		**Frequency:** 10 Hz **Amplitude:** deltaP 100%		**PIP:** 15 to 20 cm H_2O **PEEP:** 5 to 6 cm H_2O **Rate:** 25 to 30 bpm	
Zhang 2022b	China 41	Newborns with PPHN	35.0 +/- 1.8 weeks 1900 +/- 300 g	34.2 +/- 2.0 weeks 1800 +/- 200 g	nHFOV	**MAP:** 6 to 10 cm H_2O **Frequency:** 6 to 12 Hz **Amplitude:** 2 to 3 times the MAP	nIPPV	**PIP:** 15 to 20 cm H_2O **PEEP:** 4 to 6 cm H_2O **Rate:** 25 to 50 bpm	Not reported
Wang 2023	China 43	< 36 weeks	32.82 ± 1.87 weeks/ 2088.86 ± 583.37 g	32.57 ± 2.69 weeks/ 2125.24 ± 781.48 g	nHFOV with non-invasive surfactant	**MAP:** 6 to 12 cm H_2O **Frequency:** 6 to 12 Hz **Amplitude:** 2 to 3 times the MAP	Duo positive airway pressure (DuoPAP; Bilevel positive airway pressure) with non-invasive surfactant (considered to be equivalent to nIPPV)	**PIP:** 12 to 15 cm H_2O **PEEP:** 5 cm H_2O **Rate:** 30 to 40 bpm	Not reported
Oktem 2021*	Turkey 37	< 32 weeks	Median 29 (range 27 to 34) weeks Median 1250 (range 800 to 2240) g	Median 28 (range 26 to 32) weeks Median 1190 (range 600 to 2010) g	nHFOV	**Ventilator:** Babylog 8000 **MAP:** 6 cm H_2O **Frequency:** 10 Hz **Amplitude:** deltaP 100%	HFNC	**Ventilator:** Precision Flow, Vapotherm (5 L/min)	Short binasal prongs

BiPAP: bilevel positive airway pressure; **BP-CPAP:** bi-level pressure continuous positive airway pressure; **bpm:** beats per minute**; CNO:** MedicinCNO device manufacturer**; DuoPAP:** Duo positive airway pressure; **GA**: gestational age; **InSurE**: Intubate, Surfactant, Extubate; **IQR**: interquartile range; **IT:** Inspiratory time**; MAP**: mean airway pressure; **MV:** mechanical ventilation; **HFNC**: Heated humidified high-flow nasal cannula; **nCPAP**: nasal continuous positive airway pressure; **nHFOV**: non-invasive high-frequency oscillatory ventilation; **nHFPV**: non-invasive high-frequency percussive ventilation; **nIPPV**: non-invasive intermittent positive-pressure ventilation; **NR**: not reported; **NS:** not stated; **PEEP**: positive end-expiratory pressure; **PIP**: positive inspiratory pressure; **PPHN**: Persistent pulmonary hypertension of the newborn; **RDS**: respiratory distress syndrome.

*4-arm trial (nHFOV versus NIPPV versus nCPAP versus HFNC)

Table 3. Summary of included studies - nHFV versus other forms of non-invasive respiratory support for respiratory support following planned extubation

Study	Country total participants	Eligibility criteria	Gestational age weeks/ birthweight g		Intervention group		Control group		Interface (in both intervention and control groups)
			Intervention group	Control group	Mode	Settings	Mode	Settings	
Lou 2017	China 65	Ventilated infants with respiratory distress	32.5 ± 1.3 weeks 1790 ± 350 g	32.4 ± 1.4 weeks 1850 ± 410 g	nHFOV	**Ventilator:** SLE baby 5000, Germany **MAP:** 5 to 7 cm H_2O **Frequency:** 6 to 12 Hz **Amplitude:** 2 to 3 times MAP	nCPAP	**Ventilator:** Stephan, Germany **PEEP:** 4 to 6 cm H_2O	Short binasal prongs
Zhu 2017	China 81	Ventilated infants 28 to 34 weeks	31.7 ± 1.7 weeks 1670 ± 353 g	32.0 ± 1.9 weeks 1735 ± 327 g	nHFOV	**Ventilator:** CNO driver **MAP:** 6 cm H_2O **Frequency:** 10 Hz **Amplitude:** visible chest oscillation	nCPAP	**Ventilator:** Bubble CPAP system **PEEP:** 6 cm H_2O	Short binasal prongs
Chen 2019	China 206	Ventilated infants < 37 weeks	32.4 +/- 2.4 weeks 1859 +/- 569 g	32.8 +/- 2.4 weeks 1917 +/- 478 g	nHFOV	**Ventilator:** SLE5000 **MAP:** 10 cm H_2O **Frequency:** 10 Hz **Amplitude:** 35 cm H_2O	nCPAP	**Ventilator:** Bubble CPAP system **PEEP:** 6 to 8 cm H_2O	Short binasal prongs
Fischer 2019	Germany 6	Ventilated infants < 32 weeks < 1500 g	25 (range 23 + 4/7 to 26 + 3/7) weeks 503 (420 to 568) g	24 (range 23 + 6/7 to 24 + 6/7) weeks 668 (550 to 786) g	nHFOV	**Ventilator:** SLE5000 **MAP:** 8 cm H_2O **Frequency:** 9 to 10 Hz **Amplitude:** 20 to 30 cm H_2O	nCPAP	**Ventilator:** SLE 5000 **PEEP:** 8 cm H_2O	Short binasal prongs

Table 3. Summary of included studies - nHFV versus other forms of non-invasive respiratory support for respiratory support following planned extubation *(Continued)*

Li 2019	China 114	Ventilated infants 26 to 31 + 6/7 weeks < 1500 g	30.6 +/- 1.3 weeks 1257 +/- 340 g	30.8 +/- 1.4 weeks 1282 +/- 354 g	nHFOV	**Ventilator:** SLE5000 **MAP:** 8 to 14 cm H_2O **Frequency:** 8 to 12 Hz **Amplitude:** 20 to 35 cm H_2O	nCPAP	**PEEP:** 6 to 8 cm H_2O	Binasal prongs
Wang 2020	China 80	Ventilated infants with RDS	3330 ± 240 g (range 2500 to 4200) g	3410 ± 180 g (range 2600 to 4600) g	nHFOV	**MAP:** 2 to 4 cm H_2O higher than MAP prior to extubation **Frequency:** 6 to 12 Hz **Amplitude:** 2.5 to 3 times the value for MAP	nCPAP	**PEEP:** 4 to 6 cm H_2O	Not reported
Li 2021*	China 98	Ventilated infants 25 to 33 + 6/7 weeks < 1500 g	29.0 +/- 1.9 weeks 1118 +/- 202 g	29.0 +/- 1.7 weeks 1132 +/- 203 g	nHFOV	**Ventilator:** Fabian HFO **MAP:** 10 cm H_2O **Frequency:** 10 [6 to 12] Hz **Amplitude:** 25 [25 to 50] cm H_2O	nCPAP	**Ventilator:** Fabian **PEEP:** 5 [3 to 8] cm H_2O	Short binasal prongs
Yang 2021	China 68	Ventilated preterm infants	28.42 +/- 1.15 weeks	28.36 +/- 1.24 weeks	nHFOV	**MAP:** Range 8 to 14 cm H_2O **Frequency:** 8 to 12 Hz **Amplitude:** 20 to 35 cm H_2O	nCPAP	**PEEP:** 6 to 8 cm H_2O	Not reported
Yuan 2021*	China 240	Ventilated infants < 37 weeks	31.02 ± 1.88 weeks 1440 ± 300 g	30.31 ± 1.58 weeks 1390 ± 320 g	nHFOV	**Ventilator:** Löwenstein Leoni plus **MAP:** 8 [6 to 12] cm H_2O **Frequency:** 6 to 12 Hz **Amplitude:** 2 to 3 times MAP with visible chest oscillation	nCPAP	**Ventilator:** F.STEPHAN **PEEP:** 4 to 6 cm H_2O	Not reported
Zhang 2021	China 70	Ventilated infants 32 to 36 weeks	33.8 +/- 0.8 weeks 1985 +/- 246 g	33.6 +/- 1.1 weeks 1878 +/- 325 g	nHFOV	**Ventilator:** SLE5000 **MAP:** range 8 to 14 cm H_2O **Frequency:** 8 to 12 Hz	nCPAP	**Ventilator:** NV8 **PEEP:** 3 to 8 cm H_2O	Not reported

Table 3. Summary of included studies - nHFV versus other forms of non-invasive respiratory support for respiratory support following planned extubation *(Continued)*

						Amplitude: 20 to 35 cm H_2O			
Zhu 2022*	China 998	Ventilated infants 25 to 32 + 6/7 weeks	29.4 +/- 1.8 weeks 1334 +/- 366 g	29.5 +/- 1.7 weeks 1341 +/- 318 g	nHFOV	**Ventilator:** Piston/membrane oscillator **MAP:** 5 to 16 cm H_2O **Frequency:** 8 to 10 Hz **Amplitude:** titrated to $PaCO_2$	nCPAP	**Ventilator:** **PEEP:** 5 to 8 cm H_2O	Short binasal prongs
Menshykova 2015	Ukraine 24	Ventilated infants ≤ 32 weeks ≤ 1500 g	27.75 +/- 2.41 weeks 918 +/- 227 g	27.66 +/- 1.66 weeks 1034 +/- 177 g	nHFOV	**Ventilator:** CNO driver **MAP:** 6 to 8 cm H_2O **Frequency:** 10 Hz **Amplitude:** visible chest oscillation	nIPPV	**Ventilator:** Servo-I **PIP:** 6 to 12 cm H_2O **PEEP:** 4 to 8 cm H_2O **Rate:** 15 to 25 bpm	Long or short binasal prongs or mask
Zhenyu 2019	China 42	Ventilated infants with RDS	30.86 +/- 3.01 weeks	31.02 +/- 3.23 weeks	nHFOV	**MAP:** < 14 cm H_2O **Amplitude:** Amplitude set at visible oscillation noted at neck and chest area	nIPPV	**PIP:** 15 to 20 cm H_2O **PEEP:** 4 to 6 cm H_20 **Rate:** 40 bpm	Not reported
Li 2021*	China 98	Ventilated infants 25 to 33 + 6/7 weeks < 1500 g	29.0 +/- 1.9 weeks 1118 +/- 202 g	28.9 +/- 2.0 weeks 1088 +/- 154 g	nHFOV	**Ventilator:** Fabian HFO **MAP:** 10 cm H_2O **Frequency:** 10 [6 to 12] Hz **Amplitude:** 25 [25 to 50] cm H_2O	nIPPV	**Ventilator:** Comen NV8 **PIP:** 15 [15 to 25] cm H_2O **PEEP:** 4 [4 to 8] cm H_2O **Rate:** 30 [15 to 40] bpm	Short binasal prongs

Table 3. Summary of included studies - nHFV versus other forms of non-invasive respiratory support for respiratory support following planned extubation *(Continued)*

Seth 2021	India 42	Ventilated infants 26 to 36 + 6/7 weeks	Median 32 (IQR 28 to 35) weeks Median 1500 (1120 to 2140) g	Median 31 (IQR 29 to 35) weeks Median 1495 (980 to 2214) g	nHFOV	**Ventilator:** SLE6000 **MAP:** 8 to 10 cm H_2O **Frequency:** 10 to 12 Hz **Amplitude:** 25 to 35 cm H_2O with visible chest oscillation	nIPPV	**Ventilator:** Dragger Babylog 8000 **PIP:** 2 cm H_2O above pre-extubation PIP **PEEP:** 4 to 6 cm H_2O **Rate:** 40 to 50 bpm	Short binasal prongs or masks
Yuan 2021*	China 240	Ventilated infants < 37 weeks	31.02 ± 1.88 weeks 1440 ± 300 g	30.82 ± 1.60 weeks 1430 ± 330 g	nHFOV	**Ventilator:** Löwenstein Leoni plus **MAP:** 8 [6 to 12] cm H_2O **Frequency:** 6 to 12 Hz **Amplitude:** 2 to 3 times MAP with visible chest oscillation	nIPPV	**nIPPV** **Ventilator:** COMEN NV8 **PIP:** 10 cm H_2O **PEEP:** 5 to 6 cm H_2O **Rate:** 25 to 30 bpm	Not reported
Zhu 2022*	China 992	Ventilated infants 25 to 32 + 6/7 weeks			nHFOV	**Ventilator:** Piston/membrane oscillator **MAP:** 5 to 16 cm H_2O **Frequency:** 8 to 10 Hz **Amplitude:** titrated to $PaCO_2$	nIPPV	**nIPPV** **Ventilator:** any neonatal ventilator **PIP:** 10 to 25 cm H_2O **PEEP:** 5 to 8 cm H_2O **Rate:** 30 to 40 bpm	Short binasal prongs

CNO: MedicinCNO device manufacturer**; IQR**: interquartile range; **MAP**: mean airway pressure; **MV:** mechanical ventilation; **nCPAP**: nasal continuous positive airway pressure; **nHFOV**: non-invasive high-frequency oscillatory ventilation; **nIPPV**: non-invasive intermittent positive-pressure ventilation; **NR**: not reported; **$PaCO_2$:** arterial partial pressure of carbon dioxide**; PEEP**: positive end-expiratory pressure; **PIP**: positive inspiratory pressure; **RDS**: respiratory distress syndrome

*3-arm trials (nHFOV versus NIPPV versus nCPAP)

Table 4. Summary of included studies - nHFV versus other non-invasive respiratory therapy following failure of initial non-invasive respiratory support

Study	Country total participants	Eligibility criteria	Gestational age weeks/birthweight g		Intervention group		Control group		Interface (in both intervention and control groups)
			Intervention group	Control group	Mode	Settings	Mode	Settings	
Mukerji 2017	Canada 26	Birthweight < 1250 g Current weight < 2000 g Failed nCPAP	26.1 +/- 1.3 weeks gestation Birthweight 832 +/- 150 g PMA 28.6 +/- 1.5 weeks	26.5 +/- 1.6 weeks gestation Birthweight 878 +/- 198 g PMA 29.0 +/- 2.3 weeks	nHFOV	**Ventilator:** Drager VN500, Lubeck, Germany **MAP:** 8 to 10 cm H_2O **Frequency:** 5 to 14 Hz **Amplitude:** visible chest oscillation	BP-CPAP (considered to be equivalent to nIPPV)	**Ventilator:** Infant-Flow device **PIP:** 8 [7 to 10] cm H_2O **PEEP:** 5 [7 to 10] cm H_2O **Rate:** 20 to 30 bpm	Short binasal prongs or masks

bpm: breaths per minute; **BP-CPAP:** bi-level pressure continuous positive airway pressure; **MAP**: mean airway pressure; **nCPAP**: nasal continuous positive airway pressure; **nHFOV:** non-invasive high-frequency oscillatory ventilation**; niPPV:** nasal intermittent positive-pressure ventilation**; PEEP**: positive end-expiratory pressure; **PIP**: positive inspiratory pressure; **PMA**: postmenstrual age

APPENDICES

Appendix 1. Search strategy: Cochrane Library

Cochrane Library (Wiley)

April 8, 2023

ID	Search	Hits
#1	MeSH descriptor: [High-Frequency Jet Ventilation] explode all trees	58
#2	(((highfrequenc* or high-frequenc*) NEAR/4 ventilat*) or HF ventilation):ti,ab,kw	951
#3	(HFPPV or HFJV or HFO or nHFV or HFV):ti,ab,kw	236
#4	#1 OR #2 OR #3	1046
#5	MeSH descriptor: [Respiration, Artificial] explode all trees	8194
#6	(high frequenc* or highfrequenc*):ti,ab,kw	23,854
#7	((highfrequenc* or high-frequenc*) NEAR/2 (breath* or respirat* or oscillat* or oxygen* or support*)):ti,ab,kw	537
#8	(#5 AND #6) OR #7	799
#9	MeSH descriptor: [Respiratory Distress Syndrome, Newborn] explode all trees	1948
#10	(hyaline* NEAR/2 membrane?):ti,ab,kw	209
#11	((transient* or transitory) NEAR/2 (tachypne* or tachypnoe*)):ti,ab,kw	189
#12	(Meconium NEAR/2 Aspiration):ti,ab,kw	323
#13	#10 OR #11 OR #12	701
#14	MeSH descriptor: [Infant, Newborn] explode all trees	20,344
#15	MeSH descriptor: [Intensive Care, Neonatal] this term only	375
#16	MeSH descriptor: [Intensive Care Units, Neonatal] this term only	1019
#17	(baby* or babies or infant or infants or infant? or infantile or infancy or low birth weight or low birthweight or neonat* or newborn* or new born or new borns or newly born or premature or prematures or prematurity or preterm or preterms or pre term or preemie or preemies or premies or premie or VLBW or LBW or ELBW or NICU):ti,ab,kw	116,020
#18	#14 OR #15 OR #16 OR #17	116,020
#19	(#4 OR #8) AND (#13 OR #18)	500

Appendix 2. Search strategy: MEDLINE

	Ovid MEDLINE(R) All	
	April-08-2023	
#	Searches	Results
1	high-frequency ventilation/ or high-frequency jet ventilation/	2989
2	(((highfrequenc* or high-frequenc*) adj4 ventilat*) or HF ventilation).ti,ab,k-w,kf.	3957
3	(HFPPV or HFJV or HFO or nHFV or HFV).ti,ab,kw,kf.	2502
4	or/1-3 [HFV]	6385
5	exp Respiration Artificial/ and (high frequenc* or highfrequenc*).ti,ab,kw,kf.	3561
6	((highfrequenc* or high-frequenc*) adj2 (breath* or respirat* or oscillat* or oxygen* or support*)).ti,ab,kw,kf.	4588
7	or/5-6 [HF Respiration additional terms]	6520
8	respiratory distress syndrome, newborn/ or hyaline membrane disease/ or "transient tachypnea of the newborn"/ or Meconium Aspiration Syndrome/	16,974
9	(hyaline* adj2 membrane?).ti,ab,kw,kf.	2846
10	((transient* or transitory) adj2 (tachypne* or tachypnoe*)).ti,ab,kw,kf.	633
11	(Meconium adj2 Aspiration).ti,ab,kw,kf.	1703
12	or/8-11 [Neonate specific respiratory distress]	19,124
13	exp infant, newborn/ or Intensive Care, Neonatal/ or Intensive Care Units, Neonatal/	670,915
14	(baby* or babies or infant or infants or infant? or infantile or infancy or low birth weight or low birthweight or neonat* or newborn* or new born or new borns or newly born or premature or prematures or prematurity or preterm or preterms or pre term or preemie or preemies or premies or premie or VLBW or LBW or ELBW or NICU).ti,ab,kw,kf.	1,008,368
15	or/13-14 [Filter: Neonatal Population 2021--MEDLINE]	1,292,266
16	randomized controlled trial.pt.	590,453
17	controlled clinical trial.pt.	95,257
18	(randomized or randomised).ti,ab.	774,478
19	placebo.ab.	237,263
20	drug therapy.fs.	2,580,323

(Continued)

21	randomly.ab.	405,774
22	trial.ab.	643,173
23	groups.ab.	2,500,584
24	(quasirandom* or quasi-random*).ti,ab.	5531
25	exp animals/ not humans/	5,110,173
26	(or/16-24) not 25 [RCT Filter-Based on Cochrane- https://handbook-5-1-cochrane-org.ezproxy.uvm.edu/chapter_6/box_6_4_c_cochrane_hsss_2008_sensmax_ovid.htm]	4,941,897
27	meta-analysis/ or "systematic review"/ or network meta-analysis/ [/ finds same as.pt. syntax]	308,190
28	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.	310,486
29	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.	38,056
30	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.	39,375
31	(hand search* or handsearch*).ti,ab,kf,kw.	11,017
32	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.	34,976
33	meta-analysis as topic/ or network meta-analysis/	26,742
34	(met analy* or metanaly* or meta regression* or metaregression*).ti,ab,kf,kw.	14,981
35	(medline or cochrane or pubmed or medlars or embase or cinahl).ab.	326,463
36	(cochrane or systematic review?).jw.	19,969
37	or/27-36 [SR filter-Medline; based on CADTH https://www-cadth-ca.ezproxy.uvm.edu/strings-attached-cadths-database-search-filterss]	576,701
38	(or/4,7) and (or/12,15) [HFV & neonate: results before filters]	2051
39	38 and 26 [RCT Results]	586
40	(38 and 37) not 39 [SR Results]	22
41	or/39-40 [All results MEDLINE]	608

Appendix 3. Search strategy: Embase

	Embase 1974 to 2023 April 07

(Continued)

#	Searches	Results
1	high-frequency ventilation/	3986
2	((highfrequenc* or high-frequenc*) adj4 ventilat*).ti,ab,kw.	5271
3	(HFPPV or HFJV or HFO or nHFV or HFV or HF ventilation).ti,ab,kw.	3404
4	or/1-3 [HFV]	8743
5	artificial ventilation/ and (high frequenc* or highfrequenc*).ti,ab,kw.	2641
6	((highfrequenc* or high-frequenc*) adj2 (breath* or respirat* or oscillat* or oxygen* or support*)).ti,ab,kw.	6345
7	or/5-6 [HF Respiration additional terms]	7685
8	hyaline membrane disease/ or neonatal respiratory distress syndrome/ or Meconium Aspiration Syndrome/	14,969
9	(hyaline* adj2 membrane?).ti,ab,kw.	2886
10	((transient* or transitory) adj2 (tachypne* or tachypnoe*)).ti,ab,kw.	1029
11	(Meconium adj2 Aspiration).ti,ab,kw.	2373
12	or/8-11 [Neonate specific respiratory distress]	17,730
13	newborn/ or prematurity/ or newborn intensive care/ or newborn care/	682,533
14	(infant or infants or infant? or infantile or infancy or newborn* or new born or new borns or newly born or neonat* or baby* or babies or premature or premature or prematures or prematurity or preterm or preterms or pre term or preemie or preemies or premies or low birth weight or low birthweight or VLBW or LBW or ELBW or NICU).ti,ab,kw.	1,204,713
15	or/13-14 [Filter: Neonatal Population 2021-OVID EMBASE]	1,430,925
16	Randomized controlled trial/ or Controlled clinical study/	970,549
17	random$.ti,ab,kw.	1,955,873
18	Randomization/	98,704
19	placebo.ti,ab,kw.	364,000
20	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab,kw.	272,695
21	double blind procedure/	209,015
22	(controlled adj7 (study or design or trial)).ti,ab,kw.	446,672
23	parallel group$1.ti,ab.	31,934
24	(crossover or cross over).ti,ab.	123,710

(Continued)

25	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.	411,333
26	(open adj label).ti,ab.	107,923
27	or/16-26 [Terms based on Cochrane Central strategy-https://www-cochranelibrary-com.ezproxy.uvm.edu/central/central-creation]	2,764,988
28	(exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) and (human/ or normal human/ or human cell/)	25,335,665
29	exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/	32,551,602
30	29 not 28 [Animal Exclusion-Anne Eisinga, Cochrane UK]	7,215,937
31	27 not 30 [Filter: RCT-EMBASE]	2,475,979
32	meta-analysis/ or "systematic review"/ or "meta analysis (topic)"/ [EMTREE]	597,806
33	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kw.	391,610
34	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kw.	55,117
35	(data synthes* or data extraction* or data abstraction*).ti,ab,kw.	49,873
36	(hand search* or handsearch*).ti,ab,kw.	13,629
37	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kw.	47,154
38	(met analy* or metanaly* or meta regression* or metaregression*).ti,ab,kw.	19,977
39	(medline or cochrane or pubmed or medlars or embase or cinahl).ab.	426,393
40	(cochrane or systematic review?).jn,jx.	31,775
41	(overview adj2 reviews).ti.	137
42	or/32-41 [SR Filter: EMBASE based on CADTH filter: https://www-cadth-ca.ezproxy.uvm.edu/strings-attached-cadths-database-search-filters]	858,974
43	(or/4,7) and (or/12,15) [HFV & neonate: results before filters]	3079
44	43 and 31 [RCT Results]	457
45	43 and 42 [SR Results]	155
46	or/44-45 [All results EMBASE]	518

Appendix 4. Search: CINAHL

	CINAHL EbscoHost	
	April-08-2023	
	Boolean/Phrase	
S46	S44 OR S45	40
S45	S42 AND S43	40
S44	S33 AND S43	4
S43	(S5 OR S9) AND (S15 OR S19)	781
S42	S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41	262,497
S41	AB (medline or cochrane or pubmed or medlars or embase OR CINAHL)	123,777
S40	(TI met analy* or metanaly* or meta regression* or metaregression*)) OR (AB met analy* or metanaly* or meta regression* or metaregression*))	5208
S39	AB (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*)	9973
S38	AB (hand search* or handsearch*)	5013
S37	(TI (data synthes* or data extraction* or data abstraction*)) OR (AB (data synthes* or data extraction* or data abstraction*))	14,815
S36	(TI ((integrative N3 (review* or overview*)) or (collaborative N3 (review* or overview*)) or (pool* N3 analy*))) OR (AB ((integrative N3 (review* or overview*)) or (collaborative N3 (review* or overview*)) or (pool* N3 analy*)))	19,777
S35	(TI ((systematic* N3 (review* or overview*)) or (methodologic* N3 (review* or overview*)))) OR (AB ((systematic* N3 (review* or overview*)) or (methodologic* N3 (review* or overview*))))	150,681
S34	(MH "Meta Analysis")	68,757
S33	(MH "Systematic Review")	119,809
S32	S28 NOT s31	1,299,461
S31	S29 NOT S30	126,930
S30	(MH "Human")	2,671,832
S29	(MH "Animal Studies")	152,166
S28	S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27	1,339,981
S27	TI (quasirandom* or quasi-random*) OR AB (quasirandom* or quasi-random*)	2237
S26	AB groups	917,693
S25	AB (trial)	346,303

(Continued)

S24	AB placebo	66,875
S23	AB randomly	109,097
S22	TI (randomized or randomised) OR AB (randomized or randomised) OR SU (randomized or randomised)	344,152
S21	(MH "Clinical Trials+")	350,381
S20	(MH "Single-Blind Studies") OR (MH "Triple-Blind Studies") OR (MH "Randomized Controlled Trials+") OR (MH "Double-Blind Studies")	177,945
S19	S16 OR S17 OR S18	582,094
S18	TI ((baby* or babies or infant or infants or infant? or infantile or infancy or low birth weight or low birthweight or neonat* or newborn* or new born or new borns or newly born or premature or prematures or prematurity or preterm or preterms or pre term or preemie or preemies or premies or premie or VLBW or LBW or ELBW or NICU)) OR AB ((baby* or babies or infant or infants or infant? or infantile or infancy or low birth weight or low birthweight or neonat* or newborn* or new born or new born ...	581,979
S17	(MH "Intensive Care, Neonatal+") OR (MH "Intensive Care Units, Neonatal")	20,805
S16	(MH "Infant, Newborn+") OR (MH "Infant, Large for Gestational Age") OR (MH "Infant, Low Birth Weight+") OR (MH "Infant, Postmature") OR (MH "Infant, Premature")	159,371
S15	S10 OR S11 OR S12 OR S13 OR S14	1295
S14	TI (Meconium N2 Aspiration) OR AB (Meconium N2 Aspiration) OR SU (Meconium N2 Aspiration)	722
S13	TI (((transient* or transitory) N2 (tachypne* or tachypnoe*))) OR AB (((transient* or transitory) N2 (tachypne* or tachypnoe*))) OR SU (((transient* or transitory) N2 (tachypne* or tachypnoe*)))	260
S12	TI (hyaline* N2 membrane*) OR AB (hyaline* N2 membrane*) OR SU (hyaline* N2 membrane*)	366
S11	(MH "Meconium Aspiration")	505
S10	(MH "Hyaline Membrane Disease")	219
S9	(S6 AND S7) OR S8	1368
S8	TI (((highfrequenc* or high-frequenc*) N2 (breath* or respirat* or oscillat* or oxygen* or support*))) OR AB (((highfrequenc* or high-frequenc*) N2 (breath* or respirat* or oscillat* or oxygen* or support*))) OR SU (((highfrequenc* or high-frequenc*) N2 (breath* or respirat* or oscillat* or oxygen* or support*)))	1108
S7	TI ((high frequency OR highfrequency)) OR AU ((high frequency OR highfrequency)) OR SU ((high frequency OR highfrequency))	3611
S6	(MH "Respiration, Artificial")	25,492
S5	S1 OR S2 OR S3 OR S4	1925

(Continued)

S4	TI ((HFPPV or HFJV or HFO or nHFV or HFV)) OR AB ((HFPPV or HFJV or HFO or nHFV or HFV)) OR SU ((HFPPV or HFJV or HFO or nHFV or HFV))	346
S3	TI HF ventilation OR AB HF ventilation OR SU HF ventilation	1
S2	TI ((highfrequenc* or high-frequenc*) N4 ventilat*) OR AB ((highfrequenc* or high-frequenc*) N4 ventilat*) OR SU ((highfrequenc* or high-frequenc*) N4 ventilat*)	1797
S1	(MH "Jet Ventilation, High Frequency") OR (MH "Ventilation, High Frequency")	1228

Appendix 5. Search strategy: Epistemonikos

Epistemonikos	
April-08-2023	
Title/Abstract: (high frequency ventilation OR jet ventilation) AND (infant* or neonate* OR newborn*)	30

Appendix 6. Search strategy: Trial registries

Date	Source	Terms	Results
April-08-2023	ctgov	Other terms: (high-frequency OR jet) AND (infant OR neonate OR newborn)	209
April-08-2023	ctgov	Other terms field: (high-frequency OR jet) AND ventilation; limit Child (birth-17)	148
April-08-2023	ctgov	Other terms: (HFPPV or HFJV or HFO or nHFV or HFV) ; with or without Child limit.	0
April-08-2023	ICTRP	Title: infant OR neonate OR newborn AND Intervention: (high-frequency OR jet) AND ventilation	0
April-08-2023	ICTRP	Title: infant OR neonate OR newborn AND Intervention: (high-frequency OR jet)	1
April-08-2023	ICTRP	Main search screen: (high-frequency OR jet) AND (neonate OR infant OR newborn)	38
April-08-2023	ANZCTR	Main search page: high frequency ventilation AND (neonate OR infant OR newborn)	3
April-08-2023	ISRCTN	Main search page: (high frequency ventilation OR jet ventilation) AND (neonate OR infant OR newborn)	14

(Continued)

Appendix 7. Risk of bias (RoB) 1 tool

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

1. low risk (any truly random process e.g. random number table; computer random number generator);
2. high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
3. unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

1. low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
2. high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
3. unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

1. low risk, high risk or unclear risk for participants; and
2. low risk, high risk or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

1. low risk for outcome assessors;
2. high risk for outcome assessors; or
3. unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

1. low risk (< 20% missing data);
2. high risk (≥ 20% missing data); or
3. unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

1. low risk (where it is clear that all the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);

2. high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
3. unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

1. low risk;
2. high risk; or
3. unclear risk.

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

HISTORY

Protocol first published: Issue 7, 2017

CONTRIBUTIONS OF AUTHORS

Mohamed E Abdel-Latif conceived and wrote the draft of the review. He contributed independently (and equally) to study selection, data extraction, risk of bias assessment, data analysis and evidence synthesis.

Olive Tan translated, completed characteristics of included studies, risk of bias assessments and extracted data for Chinese language articles.

Michelle Fiander wrote search strategies, methods, results of search, and developed the PRISMA diagram.

David A Osborn contributed independently (and equally) to study selection, data extraction, risk of bias assessment, data analysis and evidence synthesis.

All review authors provided feedback on the content of the draft and the final manuscript.

We acknowledge Jocelyn Chan and Lisa J Jones' contribution to the protocol (Chan 2017). Jocelyn Chan helped develop the first draft of the protocol.

DECLARATIONS OF INTEREST

Mohamed E Abdel-Latif is an Associate Editor with the Cochrane Neonatal Group, but was not involved in the editorial acceptance or assessment of this review.

Olive Tan does not have any interests to disclose at this time.

Michelle Fiander is an Information Specialist and Managing Editor with the Cochrane Neonatal Group, but was not involved in the editorial acceptance or assessment of this review.

David A Osborn is a Senior Editor with the Cochrane Neonatal Group, but was not involved in the editorial acceptance or assessment of this review.

SOURCES OF SUPPORT

Internal sources

- None., Other

  None.

External sources

- Vermont Oxford Network, USA

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol (Chan 2017):

1. We replaced the term 'respiratory support' in the objective section with 'invasive ventilation via an ET tube or other non-invasive ventilation methods' based on the reviewers' feedback.
2. We updated the methods section as the methods for Cochrane reviews have evolved.
3. We removed blinding as a criterion in the sensitivity analysis for objective outcomes (e.g. death) as the intervention is unlikely to be able to be adequately blinded. However, blinding was included in the sensitivity analyses for subjective outcomes (such as endotracheal intubation and endotracheal reintubation).
4. We searched additional databases: Epistemonikos and the Chinese language articles from China/Asia On Demand (CAOD).
5. The review has been expanded to include additional ventilatory modalities, including (i) invasive neurally adjusted ventilatory assist (iNAVA) and (ii) non-invasive neurally adjusted ventilatory assist (nNAVA).
6. We added more secondary outcomes, including (i) death or chronic lung disease at 36 weeks' postmenstrual age; (ii) necrotising enterocolitis (NEC); (iii) discharge on home oxygen; (iv) spontaneous intestinal perforation; (v) duration of respiratory support (days); and (vi) duration of oxygen therapy (days).
7. Additional subgroup comparisons were added, including (i) the interface used to deliver nHFV and (ii) modes of nHFV, including oscillatory, percussive, and jet.
8. We excluded cross-over trials from the review as outcomes required longitudinal follow-up of parallel groups, and there is a likelihood of carry-over in some outcomes as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023).
9. We restated the types of participants to reflect better the review intention from: 'Preterm and term newborn infants with or at risk of respiratory distress requiring ventilation as initial support, following extubation or as a rescue mode' to 'We included term and preterm infants with or at risk of respiratory distress in their initial hospitalisation.'
10. We did not report 'Failure of respiratory support or failure of extubation' in the SoF table as it was either not reported or grossly under-reported by trials. 'Endotracheal intubation or reintubation' was reliably reported by trials, so it remains in the SoF table.