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Lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth (Review)

Lui K, Jones LJ, Foster JP, Davis PG, Ching SK, Oei JL, Osborn DA

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Lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth.
Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD010239.
DOI: 10.1002/14651858.CD010239.pub2.

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[Intervention Review]

Lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth

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Editorial group: Cochrane Neonatal Group.
Publication status and date: Edited (no change to conclusions), published in Issue 5, 2018.

Citation: Lui K, Jones LJ, Foster JP, Davis PG, Ching SK, Oei JL, Osborn DA. Lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth. *Cochrane Database of Systematic Reviews* 2018, Issue 5. Art. No.: CD010239. DOI: 10.1002/14651858.CD010239.pub2.

ABSTRACT

Background

Initial resuscitation with air is well tolerated by most infants born at term. However, the optimal fractional inspired oxygen concentration (FiO_2 - proportion of the breathed air that is oxygen) targeted to oxygen saturation (SpO_2 - an estimate of the amount of oxygen in the blood) for infants born preterm is unclear.

Objectives

To determine whether lower or higher initial oxygen concentrations, when titrated according to oxygen saturation targets during the resuscitation of preterm infants at birth, lead to improved short- and long-term mortality and morbidity.

Search methods

We conducted electronic searches of the Cochrane Central Register of Controlled Trials (13 October 2017), Ovid MEDLINE (1946 to 13 October 2017), Embase (1974 to 13 October 2017) and CINAHL (1982 to 13 October 2017); we also searched previous reviews (including cross-references), contacted expert informants, and handsearched journals.

Selection criteria

We included randomised controlled trials (including cluster- and quasi-randomised trials) which enrolled preterm infants requiring resuscitation following birth and allocated them to receive either lower ($FiO_2 < 0.4$) or higher ($FiO_2 \geq 0.4$) initial oxygen concentrations titrated to target oxygen saturation.

Data collection and analysis

Two review authors independently assessed the eligibility of studies for inclusion, extracted data and assessed methodological quality. Primary outcomes included mortality near term or at discharge (latest reported) and neurodevelopmental disability. We conducted meta-analysis using a fixed-effect model. We assessed the quality of the evidence using GRADE.

Main results

The search identified 10 eligible trials. Meta-analysis of the 10 included studies (914 infants) showed no difference in mortality to discharge between lower (FiO_2 < 0.4) and higher (FiO_2 ≥ 0.4) initial oxygen concentrations targeted to oxygen saturation (risk ratio (RR) 1.05, 95% confidence interval (CI) 0.68 to 1.63). We identified no heterogeneity in this analysis. We graded the quality of the evidence as low due to risk of bias and imprecision. There were no significant subgroup effects according to inspired oxygen concentration strata (FiO_2 0.21 versus ≥ 0.4 to < 0.6; FiO_2 0.21 versus ≥ 0.6 to 1.0; and FiO_2 ≥ 0.3 to < 0.4 versus ≥ 0.6 to 1.0). Subgroup analysis identified a single trial that reported increased mortality from use of lower (FiO_2 0.21) versus higher (FiO_2 1.0) initial oxygen concentration targeted to a lowest SpO_2 of less than 85%, whereas meta-analysis of nine trials targeting a lowest SpO_2 of 85% to 90% found no difference in mortality.

Meta-analysis of two trials (208 infants) showed no difference in neurodevelopmental disability at 24 months between infants receiving lower (FiO_2 < 0.4) versus higher (FiO_2 > 0.4) initial oxygen concentrations targeted to oxygen saturation. Other outcomes were incompletely reported by studies. Overall, we found no difference in use of intermittent positive pressure ventilation or intubation in the delivery room; retinopathy (damage to the retina of the eyes, measured as any retinopathy and severe retinopathy); intraventricular haemorrhage (any and severe); periventricular leukomalacia (a type of white-matter brain injury); necrotising enterocolitis (a condition where a portion of the bowel dies); chronic lung disease at 36 weeks' gestation; mortality to follow up; postnatal growth failure; and patent ductus arteriosus. We graded the quality of the evidence for these outcomes as low or very low.

Authors' conclusions

There is uncertainty as to whether initiating post birth resuscitation in preterm infants using lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen concentrations, targeted to oxygen saturations in the first 10 minutes, has an important effect on mortality or major morbidity, intubation during post birth resuscitation, other resuscitation outcomes, and long-term outcomes including neurodevelopmental disability. We assessed the quality of the evidence for all outcomes as low to very low. Further large, well designed trials are needed to assess the effect of using different initial oxygen concentrations and the effect of targeting different oxygen saturations.

PLAIN LANGUAGE SUMMARY

Lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth

Background

For infants born at full term, the use of air (21% oxygen) for resuscitation is generally well tolerated and may be associated with better outcomes. Infants born preterm (before 37 weeks' gestation) require more resuscitation after birth and have more problems with adaptation to life.

Review question

This review set out to investigate whether the use of lower or higher concentrations of oxygen (adjusted according to the infant's oxygen saturation, or percentage of hemoglobin binding sites in the bloodstream occupied by oxygen) are better for resuscitating preterm infants, when used in the first ten minutes after birth.

Results

We included ten trials in this review. The trials included a total of 914 infants, the majority of which were born before 32 weeks' gestation. The review found no evidence of an effect from use of a lower compared to a higher initial oxygen concentration targeted to infant oxygen saturation for resuscitation on mortality or other newborn health outcomes. There was also no difference in the rate of airway intubation (placement of a flexible plastic tube into the windpipe) during resuscitation between the infants who received lower concentrations of oxygen and those who received higher concentrations of oxygen. There was not enough information to determine the effect on long-term outcomes including neurodevelopmental disability (impairment in physical, learning, language, or behaviour areas). We judged the overall quality of the evidence to be low because of the uncertainty of the effects we found and also because we had concerns about the way in which many of the studies were carried out. The evidence in this review is current to October 2017.

Conclusions

When targeted to the infant's oxygen saturation, it is currently unclear whether the initial oxygen concentration used for resuscitation of preterm infants affects short- or long-term infant outcomes. Further trials enrolling preterm infants at birth assessing both the initial oxygen concentration and the best level of oxygen saturation to target are needed.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth

Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentrations titrated to oxygen saturations during resuscitation of preterm infants at birth

Patient or population: preterm infants
Settings: at birth
Intervention: lower oxygen concentrations (FiO_2 < 0.4) titrated to oxygen saturations during resuscitation
Comparison: higher oxygen concentrations (FiO_2 ≥ 0.4) titrated to oxygen saturations during resuscitation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration				
Mortality, near term corrected age or discharge	**Study population**		**RR 1.05** (0.68 to 1.63)	914 (10 studies)	⊕⊕⊖⊖ **low**[1,2]	Subgroup analyses: single study targeting lowest SpO_2 < 85% reported increased mortality for infants resuscitated with air compared to 100% oxygen (Oei 2016). Meta-analysis of 9 studies (627 infants) targeting lowest SpO_2 85% to 90% found no difference in mortality. No subgroup differences according to inspired oxygen concentration strata, highest SpO_2 limit, or gestational age. Quality of evidence downgraded due to risk of bias and imprecision.
	76 per 1000	**80 per 1000** (52 to 124)				
	Moderate					
	68 per 1000	**71 per 1000** (46 to 111)				
Neurodevelopmental disability Follow-up: 2 years	**Study population**		**RR 0.82** (0.49 to 1.35)	208 (2 studies)	⊕⊕⊖⊖ **low**[2,3]	Subgroup analyses: both studies compared FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0 and had a lowest SpO_2 target 85 to 90%. Quality of evidence downgraded due to inconsistency and imprecision.
	242 per 1000	**199 per 1000** (119 to 327)				
	Moderate					

	170 per 1000	**139 per 1000** (83 to 230)				
Intubation in the delivery room	**Study population**		**RR 0.98** (0.82 to 1.18)	875 (9 studies)	⊕⊕⊖⊖ **low**[1,2]	Subgroup analyses: no subgroup differences according to inspired oxygen concentration strata, lowest or highest SpO_2 target, or gestational age. Quality of evidence downgraded due to risk of bias and imprecision.
	352 per 1000	**345 per 1000** (289 to 416)				
	Moderate					
	386 per 1000	**378 per 1000** (317 to 455)				
Severe retinopathy of prematurity (≥ stage 3)	**Study population**		**RR 0.57** (0.24 to 1.36)	453 (4 studies)	⊕⊕⊖⊖ **low**[2,4]	Subgroup analyses: no subgroup differences according to inspired oxygen concentration strata, lowest SpO_2 target, or gestational age. Quality of evidence downgraded due to risk of bias and imprecision.
	58 per 1000	**33 per 1000** (14 to 79)				
	Moderate					
	70 per 1000	**40 per 1000** (17 to 95)				
Severe intraventricular haemorrhage (grade 3 or 4)	**Study population**		**RR 0.93** (0.51 to 1.71)	596 (6 studies)	⊕⊕⊖⊖ **low**[2,4]	Subgroup analyses: no subgroup differences according to inspired oxygen concentration strata, lowest or highest SpO_2 target, or gestational age. Quality of evidence downgraded due to risk of bias and imprecision.
	63 per 1000	**59 per 1000** (32 to 108)				
	Moderate					
	79 per 1000	**73 per 1000** (40 to 135)				
Necrotising enterocolitis	**Study population**		**RR 0.98** (0.51 to 1.87)	807 (8 studies)	⊕⊕⊖⊖ **low**[1,2]	Subgroup analyses: no subgroup differences according to inspired oxygen concentration strata, lowest or highest SpO_2 target, or gestational age. Quality of evidence downgraded due to risk of bias and imprecision.
	47 per 1000	**46 per 1000** (24 to 88)				
	Moderate					
	41 per 1000	**40 per 1000** (21 to 77)				

Chronic lung disease (36 weeks' corrected age)	**Study population**		**RR 0.91** (0.72 to 1.14)	862 (9 studies)	⊕⊝⊝⊝ **very low**[1,2,3]	Subgroup analyses: no subgroup differences according to inspired oxygen concentration strata, lowest or highest SpO_2 target, or gestational age. Quality of evidence downgraded due to risk of bias, inconsistency and imprecision.
	269 per 1000	**244 per 1000** (193 to 306)				
	Moderate					
	250 per 1000	**228 per 1000** (180 to 285)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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; **FiO_2:** fractional inspired oxygen;**SpO_2:** oxygen saturation

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1] Two studies at low risk of bias.
[2] Wide confidence intervals.
[3] Moderate heterogeneity.
[4] A single study at low risk of bias.

BACKGROUND

Description of the condition

Until the past decade, 100% oxygen was recommended as the gas of choice for all full term and preterm infants requiring resuscitation at birth (O'Donnell 2006; Finer 2010). Oxygen has the potential for both beneficial and deleterious effects (Duc 1992). In the minutes after birth many preterm infants, particularly the very preterm, have lung pathology that often requires respiratory assistance and supplemental oxygen. Acute asphyxia can lead to brain hypoxia and ischaemia. These physiological processes can lead to death and morbidity (Perlman 2004). For example, intraventricular haemorrhage is now thought to be caused by capillary bleeding from an abrupt alteration in cerebral blood flow and pressure. Conversely, hyperoxia has also been found to slow cerebral blood flow in term and preterm infants (Niijima 1988). In addition, the antioxidant defence system is immature in preterm infants and they are more susceptible to the effects of free oxygen radical damage (Finer 2009; Finer 2010; Silvers 1998; Varsila 1995). Oxidative stress caused by free oxygen radicals is associated with significant injury to the brain, lungs, heart, eyes (Castillo 2008; Shiao 2006; Vento 2005), and neonatal bowel (Czyrko 1991). Oxygen free radicals are released during the recovery or reperfusion period and excessive oxidative stress can lead to further tissue damage in preterm infants, such as that seen in hypoxic-ischaemic brain injury (du Plessis 1997), retinopathy of prematurity (ROP), chronic lung disease (CLD) (Finer 2009; Finer 2010), and cerebral palsy (CP) (Klinger 2005). CLD is a serious condition that results in chronic inflammation and fibrosis in the infant lung with recurring cycles of lung damage and repair that may impair alveolarization and vascularization in the developing lungs (Hayes 2010). ROP is characterised by abnormal retinal vascular development and remains a major cause of blindness and visual impairment despite improvements in neonatal care (Romagnoli 2009).

Description of the intervention

The aim of resuscitation is to prevent death and adverse long-term neurodevelopmental sequelae (Davis 2004). Accumulating evidence over the last decade has challenged clinicians to reconsider the optimal oxygen concentration for resuscitation of the newborn term infant (Vento 2001; Vento 2002; Vento 2003; Vento 2005). A number of studies have compared varying concentrations of oxygen at resuscitation without targeting a predetermined oxygen saturation range in term infants (for example: Saugstad 1998 - 21% versus 100%; Vento 2001 - 21% versus 100%; Harling 2005 - 50% versus 100%).

Several systematic reviews have compared the use of 100% and 21% oxygen during resuscitation of preterm and term infants (Davis 2004; Saugstad 2008; Tan 2005). A Cochrane review found a reduction in mortality in infants resuscitated with room air and no evidence of adverse effects (Tan 2005). However, more than a quarter of the infants randomised to 21% oxygen (room air) required supplemental oxygen. A planned subgroup analysis based on gestational age was not possible as the results of individual studies were not stratified by gestational age. One study similarly reported that the relative risk of mortality was less when 21% oxygen rather than 100% oxygen was used as the resuscitation gas (Saugstad 2008).

Recently there has been an increased interest in titrating oxygen concentrations according to oxygen saturation range. A randomised controlled trial studied oxidative stress in preterm infants who were resuscitated with 100% oxygen throughout the resuscitation (without oxygen saturation targeting) versus preterm infants who were initially given 100% oxygen and titrated according to a predetermined target oxygen saturation (90 to 95%) (Ezaki 2009). These authors concluded that oxidative stress may be reduced by titrating oxygen concentrations according to targeted oxygen saturations during resuscitation. An observational study compared preterm infants receiving 100% oxygen throughout the entire resuscitation with those that initially received 21% oxygen and then were titrated according to a predetermined target oxygen saturation (80% to 90%) (Dawson 2009). The authors also concluded that it is possible to adjust the fraction of inspired oxygen (FiO_2) to keep peripheral oxygen saturation (SpO_2) measurements within a targeted range during resuscitation. However, 92% of infants resuscitated with 21% oxygen required supplemental oxygen. Thus, this review assesses trials that have compared lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation for preterm infants at birth.

How the intervention might work

The first minutes of transition from fetal to neonatal life require a unique adjustment from lower to higher environmental oxygen exposure. Oxygen saturations are lower in utero than ex utero, and the rate of change from fetal to neonatal values has been shown to be a more gradual process than we previously believed. The natural history of the transition from fetal to neonatal blood oxygen saturations has been documented to be a slow but steady increase in the first five to 10 minutes of life (Finer 2010). Fetal oxygen partial pressures (PaO_2) are in the 15 mmHg to 30 mmHg range, resulting in a fetal SpO_2 range of 45% to 55%. After delivery, these pressures will normally rise over the next few minutes to between 50 mmHg and 80 mmHg (Kamlin 2006; Rabi 2006), depending on the status of the lungs, the pulmonary circulation, and the presence of other stressors at delivery. It has been shown that the oxygen saturation of healthy preterm infants rises gradually after birth and only reaches 90% saturation readings by a median of seven minutes of life (Kamlin 2006; Rabi 2006). It is postulated that resuscitation with oxygen titrated on the basis of targeted saturations can mimic the oxygen saturations of transitioning preterm infants not needing resuscitation, with a resultant physiological rise of oxygen saturation. Thus, the goal of oxygen saturation targeting is to reduce total oxygen load while 'normal and adequate' oxygen saturation and tissue oxygenation is maintained. Pulse oximetry allows clinicians to continuously monitor and target oxygen saturations within a defined range (Duc 1992). Thus, rather than resuscitating infants with a predetermined oxygen concentration such as 100% or 21% throughout the resuscitation, it has been proposed that titrating oxygen concentrations, for example increasing the initial concentration from 21% oxygen or decreasing initial concentration from 100% according to a predetermined oxygen saturation range, helps prevent hypoxia or hyperoxia or oxidative stress in premature infants (Dawson 2009; Ezaki 2009; Finer 2009; Finer 2010).

Why it is important to do this review

The use of oxygen during the resuscitation of preterm infants has become an increasingly controversial issue (Perlman 2006). There is a growing body of evidence that resuscitation with air is well tolerated in most term infants (Perlman 2006; Tan 2005). However, the optimal oxygen concentration for preterm infants, who often have some element of pulmonary disease and usually require more intensive resuscitation, are less clear (Perlman 2006). The question as to whether lower or higher initial oxygen concentrations that are titrated according to oxygen saturation targets during the resuscitation of preterm infants at birth would lead to improved short- and long-term mortality and morbidity remains unanswered. Therefore, it is currently difficult for clinicians to make informed decisions regarding the use of oxygen in preterm infants.

OBJECTIVES

To determine whether lower or higher initial oxygen concentrations, when titrated according to oxygen saturation targets during the resuscitation of preterm infants at birth, lead to improved short- and long-term mortality and morbidity.

Primary comparison

- Any of the lower concentrations of oxygen (21%, air; > 21% to 29%, very low; ≥ 30% to 39%, low) versus any of the higher concentrations of oxygen (≥ 40% to 59%, high; ≥ 60% to 100%, very high).

The primary comparison was analysed by the following subgroups:

- targeted oxygen saturation (lower or higher limit for oxygen saturation target range for titration < 85%; 85% to 90%; 91% to 95%; > 95%);
- type of oxygen saturation monitor (fractional or functional oxygen saturation);
- gestation (< 28 weeks; 28 weeks to 32 weeks; 33 to 36 weeks).

Secondary analyses

We did not include studies comparing two oxygen concentrations considered to be either in the lower or the higher ranges in the primary analyses. We planned to perform secondary analyses for studies comparing two groups that were both in the lower, or higher, oxygen concentration range (for example, 50% versus 100%).

METHODS

Criteria for considering studies for this review

Types of studies

We considered all published and unpublished randomised or quasi-randomised trials, including cluster-randomised trials.

Types of participants

Preterm infants < 37 weeks' gestation that required resuscitation at birth.

Types of interventions

Lower versus higher oxygen concentrations (fraction of inspired oxygen (FiO_2) < 0.4 or FiO_2 ≥ 0.4 as initial gas mixtures) to targeted oxygen saturation during resuscitation at birth. We did not include trials comparing different O_2 saturation targets.

Both groups must have had the same targeted oxygen saturation.

Trials were eligible for inclusion if the intervention groups shared similar oxygenation saturation targeting at any time during resuscitation or during initial neonatal intensive care unit (NICU) admission (or both) for the first 30 minutes.

Types of outcome measures

Primary outcomes

- Mortality, near term corrected or at discharge (latest reported).
- Neurodevelopmental disability (after at least 18 months postnatal age):
  - neurological abnormality including cerebral palsy on clinical examination, developmental delay more than two standard deviations below population mean on any standard test of development;
  - blindness (visual acuity < 6/60);
  - deafness (any hearing impairment requiring amplification).

Secondary outcomes

Response to resuscitation

- need for intermittent positive pressure ventilation (IPPV) in the delivery room;
- need for intubation in the delivery room;
- time to reach desired oxygen saturation target (seconds or minutes).
- time to reach heart rate > 100 beats per minute (bpm) (seconds or minutes).

Neonatal outcomes

- retinopathy of prematurity (ROP) (any; severe (stage ≥ 3));
- intraventricular haemorrhage (IVH) (any; severe (stage ≥ 3)) according to Papile classification (Papile 1978);
- periventricular leukomalacia (PVL) (cystic);
- hypoxic ischaemic encephalopathy (HIE) Grade 1 to 3 (Sarnat 1976);
- necrotising enterocolitis (proven = Bell stage ≥ 2) (Bell 1978);
- chronic lung disease (need for supplemental oxygen at 28 days of life; need for supplemental oxygen at 36 weeks' postmenstrual age for infants born at or before 32 weeks' gestation);
- duration of respiratory support (mechanical ventilation, continuous positive airway pressure (CPAP)) (days from birth);
- duration of supplemental oxygen administration (days from birth);
- late mortality (after at least 18 months postnatal age);
- postnatal growth failure (weight < 10th percentile at discharge); and
- duration of hospitalisation (days from birth).

Search methods for identification of studies

We used the standard search strategy of the Cochrane Neonatal Review Group (CNRG) as outlined in the *Cochrane Library*. See: Appendix 1.

Electronic searches

Two review authors performed the electronic database searches independently. This included electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (January 2017), Ovid MEDLINE (1946 to January 2017), Embase (1974 to January 2017) and CINAHL (1982 to January 2017). We updated these searches on 13 October 2017.

We searched MEDLINE, Embase and CINAHL for relevant articles using: (oxygen.mp. or exp oxygen/) AND (exp resuscitation/ or resuscitation.mp.) AND (exp prematurity/ or preterm.mp or premature.mp). Searches were limited to: MEDLINE - humans and clinical trial, all; Embase - human and (clinical trial or randomised controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial).

MeSH terms "infant, newborn" or "infant, newborn diseases" or text term "neonat*" AND Resuscitation (explode) [MeSH heading] AND Oxygen (explode) [MeSH heading].

We searched clinical trials registries for current or recently completed trials (clinicaltrials.gov; controlled-trials.com; who.int/ictrp).

Searching other resources

We also included in our search strategy communication with expert informants; searches of the bibliographies of reviews and trials for references to other trials; previous reviews including cross-references; abstracts, and conferences and symposia proceedings of the Perinatal Society of Australia and New Zealand and Pediatric Academic Societies (American Pediatric Society, Society for Pediatric Research and European Society for Pediatric Research) from 1990 to 2016. We contacted the corresponding investigator for information if we identified any unpublished trial. We considered unpublished studies or studies only reported as abstracts as eligible for inclusion in the review if methods and data could be confirmed by the author. We also contacted the corresponding authors of identified RCTs for additional information about their studies when further data was required.

Data collection and analysis

We used the standard methods of Cochrane as documented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and recommended by the Cochrane Neonatal Review Group.

Selection of studies

Two review authors (DO and LJ) independently screened titles and abstracts. Four review authors (KL, JF, DO, and LJ) independently assessed eligibility of all studies identified in the searches for inclusion in this review from full text. Any differences in opinion were resolved through discussion (KL, PD, DO).

Data extraction and management

Four review authors (KL, JF, LJ, DO) independently extracted data from the full-text articles using a specifically designed spread sheet to manage the information. Any differences in opinion were resolved by discussion. We entered the data into Review Manager software (Review Manager 2014), and cross-checked entries for accuracy. We sought unpublished data from several authors.

Assessment of risk of bias in included studies

We assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.

Review authors (KL, JF, DO and LJ) independently assessed the risk of bias of all included trials using the Cochrane 'Risk of bias' tool for the following domains (Higgins 2011):

- sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias);
- any other bias.

For each domain, we assigned a judgement of high, low, or unclear risk of bias. We resolved any disagreements by discussion or by involving another assessor. See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We analysed the results of the studies using the statistical package in Review Manager (Review Manager 2014). We summarised the data in a meta-analysis if they were sufficiently homogeneous, both clinically and statistically.

Dichotomous data

We present results as risk ratios (RRs) and risk differences (RDs) with 95% confidence intervals (CIs) for dichotomous data. We intended to calculate the number needed to treat to benefit (NNTB), or number needed to harm (NNTH), and associated 95% CI if there was a statistically significant reduction (or increase) in RD.

Continuous data

We used the mean difference (MD) for continuous data when outcomes were measured in the same way between trials. We used the standardised mean difference (SMD) to combine trials that measured the same outcome but use different methods. Where trials reported continuous data as median and interquartile range(IQR) and data passed a test of skewness, we converted mean to median and estimated the standard deviation as IQR/1.35. Where trials reported medians and ranges we used the methods reported by Hozo 2005.

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials. No cluster-randomised trials were identified.

Cluster-randomised trials

We planned to make adjustments to the standard errors using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011 section 16.3.6) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study with a similar population. If we used ICCs from other sources, we planned to report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. We consider it reasonable to combine the results from both cluster-randomised trials and individually

randomised trials if there is little heterogeneity between the study designs and the interaction between the effect of the intervention and the choice of randomisation unit is considered to be unlikely.

Dealing with missing data

We noted levels of attrition for included studies. We intended to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. We carried out analyses for all outcomes, as far as possible, on an intention-to-treat basis, that is we attempted to include all participants randomised to each group in the analyses, and we analysed all participants in the group to which they were allocated regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We used Review Manager 5 to assess the heterogeneity of treatment effects between trials (Review Manager 2014). We used the Chi^2 test to assess whether observed variability in effect sizes between studies is greater than would be expected by chance. Since this test has low power when the number of studies included in the meta-analysis is small, we set the probability at the 10% level of significance.

We used the I^2 statistic to ensure that pooling of data was valid. We considered a degree of heterogeneity less than 25% to represent no heterogeneity, 25% to 49% may represent minimal heterogeneity, 50% to 74% may represent moderate heterogeneity, and greater than 75% may represent substantial or high heterogeneity.

We assessed the source of the heterogeneity using sensitivity and subgroup analyses, looking for evidence of bias or methodological differences between trials where there is evidence of apparent or statistical heterogeneity.

Assessment of reporting biases

We assessed reporting bias by comparing the stated primary and secondary outcomes and reported outcomes. Where study protocols were available, we compared these to the full publications to determine the likelihood of reporting bias. We investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually; we did not use formal tests. We planned to perform exploratory analyses to investigate if asymmetry was detected by visual assessment.

Data synthesis

We carried out statistical analysis using Review Manager (Review Manager 2014). We used the fixed-effect model inverse variance meta-analysis for combining data where trials examined the same intervention and the populations and methods of the trials were judged to be similar. We intended to assess the possible source(s) of heterogeneity using subgroup and sensitivity analysis.

Quality of evidence

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

- mortality (near term corrected or at discharge (latest reported));
- neurodevelopmental disability (after at least 18 months postnatal age);
- intubation in the delivery room;
- retinopathy of prematurity (severe, stage ≥ 3);
- intraventricular haemorrhage (severe, stage ≥ 3);
- necrotising enterocolitis (proven, = Bell stage ≥ 2);
- chronic lung disease.

Two review authors independently assessed the quality of the evidence for each of the outcomes above. We considered evidence from randomised controlled trials as high quality but downgraded the evidence one level for serious (or 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 GRADEpro GDT to create a 'Summary of findings' table to report the quality of the evidence (GRADEpro GDT).

The GRADE approach results in an assessment of the quality of a body of evidence according to one of the following grades.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: 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: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses:

- targeted oxygen saturation (low or high upper target limit for titration, < 85%; 85% to 90%; 91% to 95%; > 95%);
- time taken to reach oxygen saturation target range (within first 10 minutes; within first 20 minutes; within first 30 minutes);
- type of oxygen saturation monitor (fractional or functional oxygen saturation);
- gestation (< 28 weeks; 28 to 32 weeks; 33 to 36 weeks).

Secondary analyses

We intended to undertake secondary analyses of studies in which infants in both the intervention and control arms were exposed to the same category (high or low) of supplemental oxygen (these studies were not included in the primary analyses).

Strategies for exploring heterogeneity

- Identification of the methodological differences between studies
- Subgroup analysis
- Meta-regression if enough data were available (Higgins 2011)

Sensitivity analysis

We explored methodological heterogeneity through the use of sensitivity analyses, where sufficient data were available. We

performed sensitivity analyses through excluding trials of high risk of bias, based on a lack of any of the following: allocation concealment, adequate randomisation, blinding of treatment, less than 10% loss to follow-up.

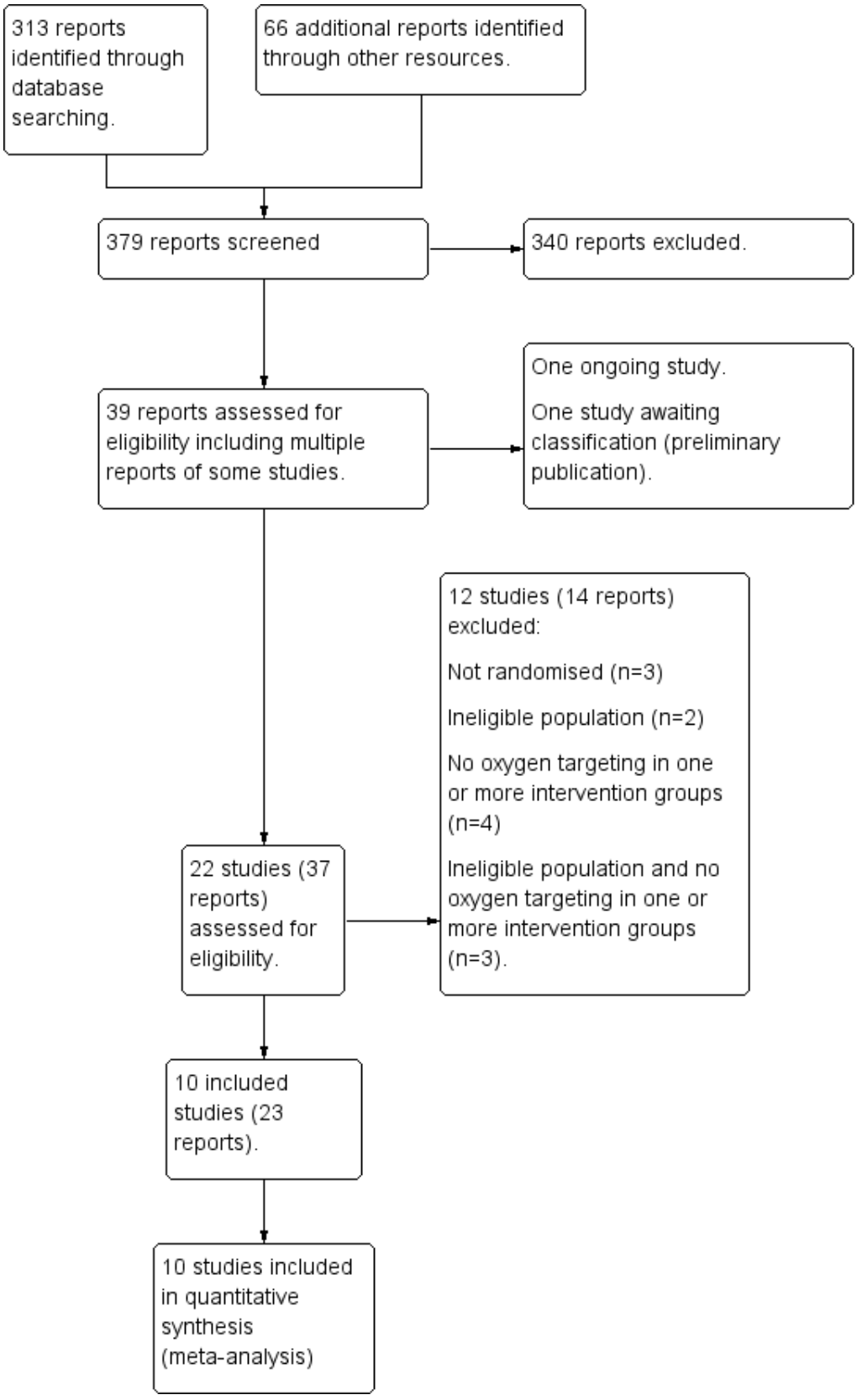
RESULTS

Description of studies

Results of the search

Refer to Figure 1 for a flow diagram of searches. The combined searches of CENTRAL, MEDLINE and Embase returned 313 records. Additional databases (WHO, Maternity and Infant Care, PAS Abstracts, www.clinicaltrials.gov and www.controlledtrials.com) returned 66 records. We assessed 39 full-text reports for eligibility, of which we excluded 12 studies (14 reports). We identified one study as ongoing, one study as awaiting assessment, and included 10 studies (23 reports) for analysis. This includes a report from our updated search on 13 October 2017, a single additional report of neurodevelopmental outcomes of two trials that are incorporated in the review (Aguar 2013; Rook 2014).

Figure 1. Study flow diagram.



Included studies

We identified 10 eligible trials studies comparing lower versus higher oxygen concentrations titrated to targeted oxygen saturations during resuscitation (Aguar 2013; Armanian 2012; Escrig 2008; Kapadia 2013; Kumar 2014; Oei 2016; Rabi 2011; Rook 2014; Vento 2009; Wang 2008). Refer to Characteristics of included studies for details.

Participants

The trials took place in a variety of perinatal treatment centres in the Netherlands, Spain, Iran, Qatar, Malaysia, Australia, USA and Canada within the last 12 years. A total of 914 infants participated. All 10 trials enrolled infants on the basis of preterm gestation corresponding to the following subgroups: extremely preterm (< 28 weeks' gestation) (Oei 2016; Aguar 2013); very preterm (28 to < 32 weeks' gestation) (Escrig 2008; Kumar 2014; Oei 2016; Rabi 2011; Rook 2014; Vento 2009); extremely to very preterm (24 to < 32 weeks' gestation) (Kapadia 2013; Wang 2008); and very preterm to preterm (28 to < 37 weeks' gestation) (Armanian 2012). Two studies excluded infants of unknown or uncertain gestational ages (Aguar 2013; Escrig 2008). No studies reported on preterm infants born at 32 to < 37 weeks. One study reported subgroups of extremely preterm (100 from 290 enrolled infants) and very preterm (10 from 19 enrolled infants) (Oei 2016). All ten trials included low birth weight infants, but only one trial enrolled infants on the basis of low birth weight (≤ 1250 g) if the precise gestational age was unclear (Oei 2016).

Interventions

Oxygen concentrations

A single study compared air (21% oxygen) with ≥ 40% to 60% (high) oxygen for resuscitation (Kumar 2014). Five studies compared air with 100% oxygen (Kapadia 2013; Kumar 2014; Oei 2016; Rabi 2011; Wang 2008). Five studies compared 30% to 40% oxygen with ≥ 60% to 100% (very high) oxygen: one compared 30% oxygen versus 60% oxygen (Aguar 2013); another compared 30% oxygen versus 100% oxygen (Armanian 2012); two studies compared 30% oxygen versus 90% oxygen (Escrig 2008; Vento 2009); and one study compared 30% oxygen versus 65% oxygen (Rook 2014).

Oxygen targeting

Oxygen saturation targeting criteria and timing varied among the included studies. In all ten studies, supplemental oxygen was adjusted to maintain the oxygen saturation (SpO_2) above a prespecified lower limit. A lower limit of oxygen saturation target range < 85% was applied in five studies (Aguar 2013; Kapadia 2013; Oei 2016; Vento 2009; Wang 2008). A lower limit of oxygen saturation target range 85% to 90% was applied in eight studies (Aguar 2013; Armanian 2012; Escrig 2008; Kumar 2014; Rabi 2011; Rook 2014; Vento 2009; Wang 2008).

In seven studies (Escrig 2008; Kapadia 2013; Kumar 2014; Oei 2016; Rabi 2011; Rook 2014; Wang 2008), supplemental oxygen was adjusted to maintain the oxygen saturation below a prespecified upper limit in the first 10 minutes of life. Three studies did not prespecify an upper limit (Aguar 2013; Armanian 2012; Vento 2009). An upper limit of oxygen saturation target range 85% to 90% was applied in two studies (Escrig 2008; Wang 2008). An upper limit of oxygen saturation target range > 91% to 95% was applied in six studies (Kapadia 2013; Kumar 2014; Oei 2016; Rabi 2011; Rook 2014; Wang 2008).

Two studies reported oxygen targeting to different SpO_2 ranges between lower and higher oxygen groups. One study, which compared 21% oxygen versus 100% oxygen, reported using interquartile values for healthy newborns for the lower limit in the low oxygen group and a lower limit of 85% in the high oxygen group (Kapadia 2013). The other study prespecified a lower limit of 80% to 85% at five minutes, then 85% to 90% after seven minutes, and an upper limit of ≤ 95% for the high oxygen group (Wang 2008).

Type of oximeter

Seven studies used functional oximeters: two studies used Masimo Radical (Escrig 2008; Kapadia 2013); four studies used Masimo Radical 7 Signal Extraction Technology (Kumar 2014; Oei 2016; Vento 2009; Wang 2008); and one study used Nellcor Oximax-N-600x (Rook 2014). Three studies did not describe the type of pulse oximeter used (Aguar 2013; Armanian 2012; Rabi 2011). No studies reported using the most recent model fractional or 'rainbow technology Co-oximeters' described by Masimo.

Outcomes

See Characteristics of included studies for details of outcome reporting for each study.

Primary Outcomes

All ten studies reported mortality. Timing of reporting varied; five studies reported mortality before hospital discharge (Aguar 2013; Kapadia 2013; Rabi 2011; Oei 2016; Escrig 2008), four studies reported neonatal mortality < 28 days from birth (Escrig 2008; Oei 2016; Vento 2009; Wang 2008), two studies reported mortality at an unspecified period (Kumar 2014; Rook 2014), one study reported mortality in early infancy (Armanian 2012), and one study reported late mortality after 18 months postnatal age (Aguar 2013). Other primary outcomes were less commonly reported. Three studies reported neurodevelopmental disability after 18 months postnatal age (Aguar 2013; Escrig 2008; Rook 2014). Two studies provided combined data for this outcome (Aguar 2013; Rook 2014). The data were calculated separately for each study in this review and recombined in meta-analysis. One study reported no difference in neuro sensorial dysfunction, but no data were provided (Escrig 2008). One study is yet to report the planned primary outcome of combined mortality or major disability (or both) at 18 to 24 months corrected age (Oei 2016).

Secondary outcomes

These were all incompletely reported. More commonly reported outcomes included intermittent positive pressure ventilation (IPPV) in the delivery room (five studies); intubation in the delivery room (eight studies), duration of respiratory support (seven studies), severe intraventricular haemorrhage (five studies), necrotising enterocolitis (six studies), and chronic lung disease (requiring oxygen at 36 weeks' postmenstrual age) (nine studies). Outcomes reported by a minority of studies included any retinopathy of prematurity (three studies), severe retinopathy of prematurity (four studies), duration of supplemental oxygen administration (three studies), all intraventricular haemorrhage (four studies), periventricular leukomalacia (three studies), late mortality at > 18 months (two studies), postnatal growth failure (weight < 10th percentile at discharge) (one study), and chronic

lung disease (requiring oxygen at 28 postnatal days) (two studies). Duration of respiratory support was variably reported. Four studies reported separate data for duration of mechanical ventilation and duration of continuous positive airway pressure (CPAP) (Escrig 2008; Kapadia 2013; Vento 2009; Wang 2008), whilst two studies reported on duration of mechanical ventilation only (Rabi 2011; Rook 2014). One study included both mechanical ventilation and CPAP in their definition of respiratory support (Vento 2009), and one combined mechanical ventilation, CPAP, high- and low-flow nasal cannula (Oei 2016).

Several continuous outcomes were reported as non-parametric data requiring conversion to parametric data for inclusion in analyses. For duration of respiratory support, three studies reported median and interquartile range (IQR) (Escrig 2008; Rook 2014; Vento 2009), and three reported median and range (Kapadia 2013; Oei 2016; Rabi 2011). Two studies reported time taken to reach the desired oxygen saturation target (Aguar 2013; Escrig 2008), with Escrig 2008 reporting median and IQR. Three studies reported on the post hoc outcome 'time taken to reach a heart rate > 100 bpm (minutes)' (Aguar 2013; Armanian 2012; Escrig 2008), with Escrig 2008 reporting median and IQR. For duration of supplemental oxygen administration (days from birth), one study reported the data as mean and standard deviation (SD) (Aguar 2013), whilst two studies reported median and IQR (Rook 2014; Vento 2009). Three studies reported duration of hospitalisation (Aguar 2013; Kapadia 2013; Rabi 2011), with two studies reporting data as median and range (Kapadia 2013; Rabi 2011).

Excluded studies

We categorised 12 studies as excluded studies (Bajaj 2005; Dawson 2009; Ezaki 2009; Gandhi 2013; Harling 2005; Lundstrom 1995; Pope 2013; Ramji 1993; Ramji 2003; Saugstad 1998; Toma 2006; Toma 2007b). See Characteristics of excluded studies for reasons for exclusion.

Ongoing studies

We are awaiting data following completion of NCT01773746. Refer to Ongoing studies for details.

Studies awaiting classification

We are awaiting an English language translation of Toma 2007b. Refer to Studies awaiting classification for details.

Risk of bias in included studies

See 'Risk of bias' graph (Figure 2) and 'Risk of bias' summary (Figure 3).

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

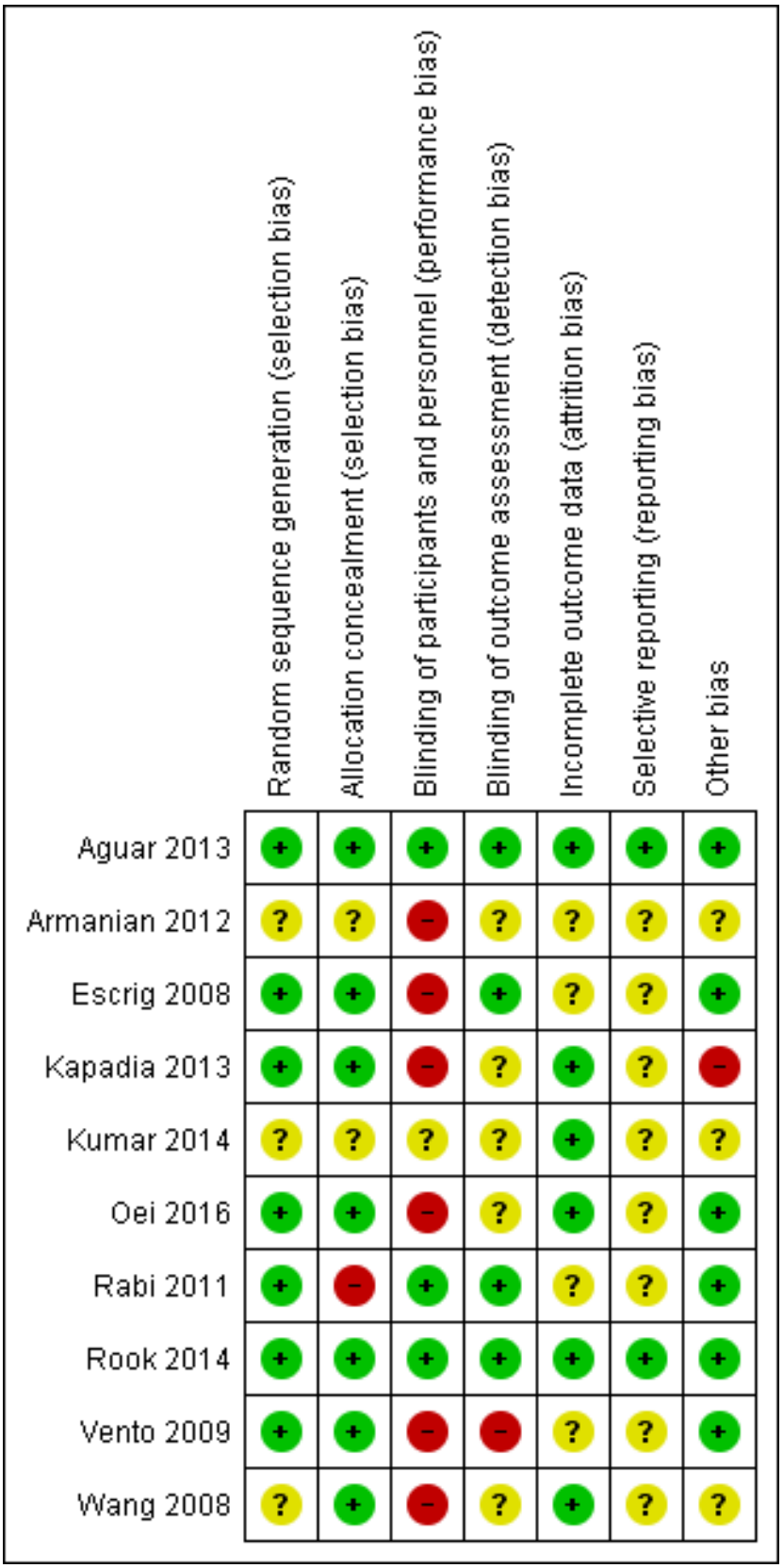
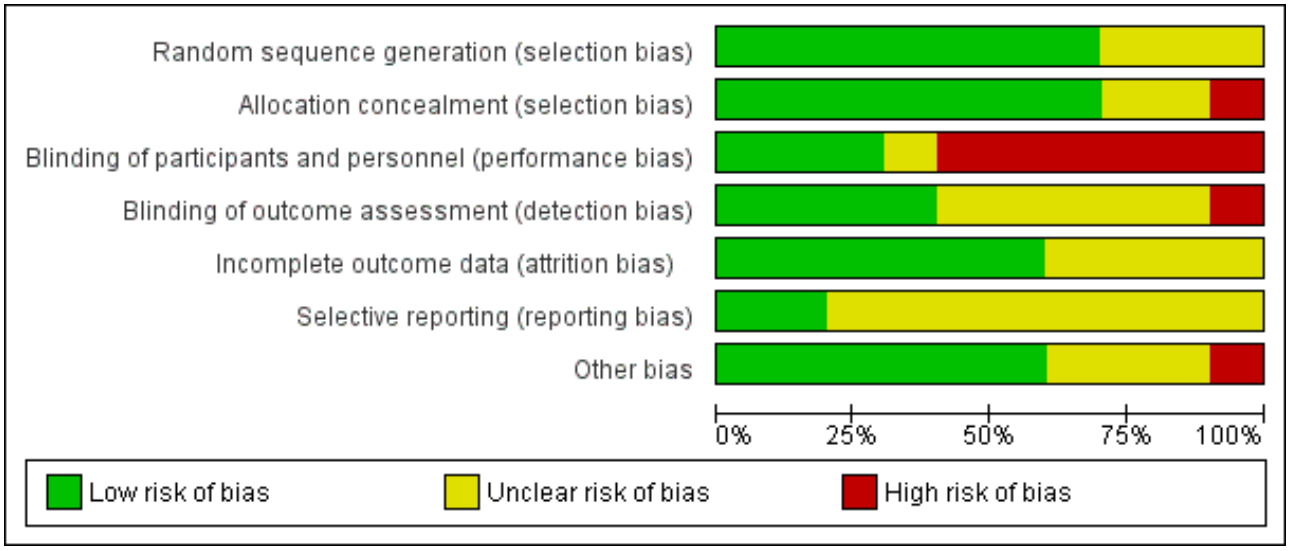


Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

We assessed three studies as having unclear risk of selection bias as they did not report the method of sequence generation (Armanian 2012; Kumar 2014; Wang 2008). We assessed one study, Rabi 2011, as having high risk of bias due to lack of allocation concealment as they allowed consent to be obtained from parents after the intervention. Two studies were at unclear risk of selection bias due to lack of reporting of allocation concealment (Armanian 2012; Kumar 2014). We judged six studies as having low risk of selection bias overall (Aguar 2013; Escrig 2008; Kapadia 2013; Oei 2016; Rook 2014; Vento 2009), three studies as having unclear risk of bias (Armanian 2012; Kumar 2014; Wang 2008), and one as having high risk of bias (Rabi 2011).

Studies at unclear or high risk of selection bias have a relatively low weight in analyses of mortality (10.1%); intubation in the delivery room (15.4%); severe retinopathy of prematurity (7.7%); severe intraventricular haemorrhage (2.3%); necrotising enterocolitis (24.7%); and chronic lung disease at 36 weeks (22.8%). Neurodevelopmental disability was reported by a single study assessed as being at low risk of selection bias (Aguar 2013).

Blinding

Six studies did not report blinding of participants or personnel (Armanian 2012; Escrig 2008; Kapadia 2013; Oei 2016; Vento 2009; Wang 2008), and in one study the blinding was unclear (Kumar 2014). One study, Vento 2009, reported not blinding outcome assessment; and blinding was unclear in five (Armanian 2012; Kapadia 2013; Kumar 2014; Oei 2016; Wang 2008). Three studies reported adequate blinding of participants, personnel and outcome assessment and we judged these to have low risk of performance and detection bias (Aguar 2013; Rabi 2011; Rook 2014).

Studies at high or unclear risk of performance and detection bias were heavily weighted in analyses of mortality; intubation in the delivery room; severe retinopathy of prematurity; severe intraventricular haemorrhage; necrotising enterocolitis; and chronic lung disease. Neurodevelopmental disability was reported by two studies assessed as having low risk of performance and detection bias (Aguar 2013; Rook 2014). Outcomes such as intubation in the delivery room were likely to be at highest risk of bias from lack of blinding of personnel.

Incomplete outcome data

Four studies were at unclear risk of attrition bias, including: Armanian 2012 (losses not reported); Escrig 2008 (losses not reported); Rabi 2011 (unclear if 103 infants (49%) were excluded pre- or post-randomisation); and Vento 2009 (18% of infants not resuscitated so 'lost to randomisation'; 2 infants not accounted for and 7 infants who died were not reported for other outcomes). We judged six studies to have low risk of attrition bias (Aguar 2013; Kapadia 2013; Kumar 2014; Oei 2016; Rook 2014; Wang 2008).

Studies that were at high or unclear risk of attrition bias have low to moderate weight in analyses of mortality (21.5%); intubation in the delivery room (39.3%); severe intraventricular haemorrhage (43.7%); necrotising enterocolitis (30%); and chronic lung disease (27.3%). Neurodevelopmental disability was reported by two studies assessed as having low risk of attrition bias (Aguar 2013; Rook 2014); and severe retinopathy of prematurity was reported by four studies which had low risk of bias (Aguar 2013; Kapadia 2013; Kumar 2014; Oei 2016).

Selective reporting

Eight studies were at unclear risk of reporting bias predominantly due to lack of protocol availability (Armanian 2012; Escrig 2008; Kapadia 2013; Kumar 2014; Oei 2016; Rabi 2011; Vento 2009; Wang 2008). We assessed three studies as having low risk of reporting bias (Aguar 2013; Rook 2014; Wang 2008).

Other potential sources of bias

We considered one study to have a substantial baseline difference between groups (breech presentation) (Kapadia 2013); and we assessed three studies as having unclear risk of bias due to

some baseline differences or failure to adequately report baseline characteristics (Armanian 2012; Kumar 2014; Wang 2008).

Effects of interventions

See: **Summary of findings for the main comparison** Lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth

Comparison 1. Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentrations

Ten studies (962 infants) compared lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth (Aguar 2013; Armanian 2012; Escrig 2008; Kapadia 2013; Kumar 2014; Oei 2016; Rabi 2011; Rook 2014; Vento 2009; Wang 2008).

Primary Outcomes

Mortality, near term corrected or discharge (latest reported) (Analysis 1.1)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (risk ratio (RR) 1.05, 95% CI 0.68 to 1.63; participants = 914; studies = 10; I^2 = 11%). We graded the quality of evidence as low, due to risk of bias and imprecision of the estimate.

Neurodevelopmental disability (Analysis 1.2)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (RR 0.82, 95% CI 0.49 to 1.35; participants = 208; studies = 2; I^2 = 53%). We identified moderate heterogeneity in this analysis.

Secondary Outcomes

Intermittent positive pressure ventilation (IPPV) in the delivery room (Analysis 1.3)

Our meta-analysis showed no significant difference in need for IPPV in the delivery room between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (RR 0.94, 95% CI 0.83 to 1.06; participants = 249; studies = 5; I^2 = 13%).

Intubation in the delivery room (Analysis 1.4)

Our meta-analysis showed no significant difference in the need for intubation in the delivery room between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (RR 0.98, 95% CI 0.82 to 1.18; participants = 875; studies = 9; I^2 = 0%). We graded the quality of evidence as low, due to risk of bias and imprecision of the estimate.

Time to reach desired oxygen saturation target (Analysis 1.5)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (MD -0.52 minutes, 95% CI -1.83 to 0.79; participants = 102; studies = 2; I^2 = 85%).

Time to reach heart rate > 100 beats per minute (not prespecified) (Analysis 1.6)

One study, Aguar 2013, reported no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (MD 0.27 minutes, 95% CI -1.21 to 1.75; participants = 60; I^2 = 0%). One of the studies, Escrig 2008, reported data as median/interquartile range (IQR) and included additional criteria for time to response (SpO_2 > 85% and good response to stimuli) so data from this study were not included in meta-analysis This outcome is reported post hoc.

Retinopathy of prematurity (any) (Analysis 1.7)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (RR 0.80, 95% CI 0.43 to 1.49; participants = 373; studies = 4; I^2 = 0%).

Severe retinopathy of prematurity (≥ stage 3) (Analysis 1.8)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (RR 0.57, 95% CI 0.24 to 1.36; participants = 453; studies = 4; I^2 = 0%). We graded the quality of evidence as low, due to risk of bias and imprecision of the estimate.

Intraventricular haemorrhage (IVH) (any) (Analysis 1.9)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (RR 0.81, 95% CI 0.46 to 1.44; participants = 271; studies = 3; I^2 = 0%).

Severe intraventricular haemorrhage (IVH) (grade 3 or 4) (Analysis 1.10)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (RR 0.93, 95% CI 0.51 to 1.71; participants = 596; studies = 6; I^2 = 0%). No individual study reported a significant effect. We graded the quality of evidence as low, due to risk of bias and imprecision of the estimate.

Periventricular leukomalacia (PVL) (Analysis 1.11)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen group (RR 0.66, 95% CI 0.09 to 4.73; participants = 130; studies = 2; I^2 = 0%).

Hypoxic ischaemic encephalopathy

Not reported by any trial.

Necrotising enterocolitis (proven) (Analysis 1.12)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (RR 0.98, 95% CI 0.51 to 1.87; participants = 807; studies = 8; I^2 = 1%). We graded the quality of evidence as low, due to risk of bias and imprecision of the estimate.

Chronic lung disease (28 days) (Analysis 1.13)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (RR 0.70, 95% CI 0.41 to 1.21; participants = 148; studies = 2; I^2 = 66%). We identified moderate heterogeneity in this analysis.

Chronic lung disease (36 weeks) (Analysis 1.14)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (RR 0.91, 95% CI 0.72 to 1.14; participants = 862; studies = 9; I^2 = 45%). We identified mimimal heterogeneity in this analysis. We graded the quality of evidence as low, due to risk of bias of included studies, lack of precision of the estimate and heterogeneity between studies detected in the analysis.

Duration of respiratory support (mechanical ventilation or CPAP) (days from birth) (Analysis 1.15)

Our meta-analysis showed infants who received lower (FiO_2 < 0.4) oxygen had a shorter duration of respiratory support (mechanical ventilation or CPAP) compared to infants on higher oxygen (FiO_2 ≥ 0.4) (MD -12.39, 95% CI -13.49 to -11.29; participants = 326; studies = 2; I^2 = 98%). We identified high heterogeneity in this analysis.

Duration of respiratory support (mechanical ventilation) (days from birth) (Analysis 1.16)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (MD 0.61, 95% CI -1.33 to 2.54; participants = 510; studies = 6; I^2 = 0%). This outcome was included post hoc.

Duration of respiratory support (continuous positive airway pressure (CPAP)) (days from birth) (Analysis 1.17)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (MD -1.60, 95% CI -5.39 to 2.19; participants = 249; studies = 4; I^2 = 0%) This outcome was included post hoc.

Duration of supplemental oxygen administration (days) (Analysis 1.18)

Our meta-analysis showed infants allocated to the lower oxygen group (FiO_2 < 0.4) had a shorter duration of supplemental oxygen administration compared to infants allocated to the higher oxygen (FiO_2 ≥ 0.4) group (MD 9.23 days, 95% CI 6.52 to 11.95; participants = 639; studies = 5; I^2 = 79%). We identified high heterogeneity in this analysis.

Mortality to follow-up (> 18 months) (Analysis 1.19)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (RR 1.00, 95% CI 0.59 to 1.70; participants = 540; studies = 3; I^2 = 65%).

Postnatal growth failure (weight < 10th percentile at discharge) (Analysis 1.20)

One study, Aguar 2013, reported no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (RR 0.86, 95% CI 0.55 to 1.33; participants = 60).

Duration of hospitalisation (days) (Analysis 1.21)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (MD -1.75, 95% CI -12.22 to 8.71; participants = 216; studies = 3; I^2 = 33%).

Patent ductus arteriosus (not prespecified) (Analysis 1.22)

Our meta-analysis showed no significant difference between lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen groups (RR 0.93, 95% CI 0.77 to 1.14; participants = 766; studies = 7; I^2 = 0%).

Subgroup analyses (Appendix 3)

The following subgroup comparisons are appended in Appendix 3:

Comparison 2. Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentrations subgrouped by FiO_2

Comparison 3. Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation target range at 5 to 10 minutes

Comparison 4. Lower versus higher oxygen concentrations — subgrouped by higher limit of oxygen saturation target range at 5 to 10 minutes

Comparison 5. Lower versus higher oxygen concentrations — subgrouped by gestational age

Comparison 6. Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration — sensitivity analysis

DISCUSSION

Summary of main results

Mortality and neurodevelopment

Overall, our meta-analysis of 10 studies (with a total of 914 infants) showed no difference in mortality to discharge. We downgraded our assessment of the quality of evidence to low, due to risk of bias and imprecision. We found no subgroup differences according to inspired oxygen concentration strata. However we did find a significant subgroup difference in mortality according to lower limit of oxygen saturation target range at 5 to 10 minutes' age. A single study targeting lowest oxygen saturation (SpO_2) < 85% reported increased mortality for infants resuscitated with air compared to those resuscitated with 100% oxygen (Oei 2016), whereas meta-analysis of nine studies (627 infants) targeting lowest SpO_2 85% to 90% showed no difference in mortality. We found no subgroup differences according to higher limit of SpO_2 target range or gestational age (≤ 28 weeks versus > 28 weeks to 32 weeks).

Meta-analysis of two studies (208 infants) showed no difference in neurodevelopmental disability at 18 to 24 months of age. Both studies compared fractional inspired oxygen (FiO_2) ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 0.65 and had a lowest SpO_2 target of 85% to 90%. We assessed the quality of evidence as low, due to inconsistency and imprecision.

Response to resuscitation

We found no overall difference in use of intermittent positive pressure ventilation or intubation in the delivery room for infants receiving lower versus higher oxygen concentrations. For intubation, subgroup analyses showed no differences between groups according to inspired oxygen concentration strata, lowest or highest SpO_2 target, or gestational age. We downgraded our assessment of the quality of evidence to low, due to risk of bias and imprecision. There were limited data that reported time to reach desired oxygen saturation target or heart rate, with no significant differences identified.

Neonatal outcomes

We found no difference between use of lower versus higher concentrations of oxygen for the following outcomes: any retinopathy, severe retinopathy (low-quality evidence), any intraventricular haemorrhage (IVH), severe IVH (low-quality evidence), periventricular leukomalacia, necrotising enterocolitis (low-quality evidence), chronic lung disease at 28 days or 36 weeks' gestation (very low-quality evidence), postnatal growth

failure, duration of hospitalisation, or patent ductus arteriosus. There were also no significant subgroup differences for these neonatal outcomes according to inspired oxygen concentration strata, lowest SpO_2 target, highest SpO_2 target, and gestational age strata (≤ 28 weeks versus > 28 weeks to 32 weeks).

Studies reported duration of respiratory support as various combinations of mechanical ventilation, continuous positive airway pressure (CPAP), and high-flow nasal cannula (HFNC). This resulted in difficulty pooling data. For our prespecified outcome, duration of positive pressure respiratory support (mechanical ventilation or CPAP), there was a mean reduction of 12.4 days (95% CI 11.3 to 13.5 days) through use of lower versus higher oxygen concentration, though this was only reported by a minority of studies (two studies, 326 infants). For outcomes that were not prespecified by this review, we found no difference in duration of mechanical ventilation (which was reported by six studies including 510 infants) or duration of CPAP (which was reported by four studies including 249 infants). There was an mean +9.2 day (95% CI 6.5 to 12.0 day) increase in duration of supplemental oxygen administration, which was reported by five studies including 639 infants. We identified high levels of heterogeneity in the analyses of duration of respiratory support and duration of supplemental oxygen. Subgroup analyses showed a decreased duration of respiratory support (mechanical ventilation or CPAP), but an increased duration of supplemental oxygen, from use of low oxygen concentrations. This was attributable to a single study (Oei 2016), which compared inspired oxygen concentrations of 0.21 versus 1.0 and had a lower SpO_2 target < 85% at 5 to 10 minutes.

Overall completeness and applicability of evidence

We included ten trials that reported outcomes for 914 infants in this review. The majority of included infants were of extreme preterm gestation, with subgroup analysis of mortality including 516 infants ≤ 28 weeks' gestation and 316 infants of 28 to 32 weeks' gestation.

The trials compared various oxygen concentrations for resuscitation. The common comparisons were air versus 100% oxygen, reported by five studies (Kapadia 2013; Kumar 2014; Oei 2016; Rabi 2011; Wang 2008). A single study compared air with 40% oxygen (Kumar 2014). Five studies used various supplemental oxygen concentrations in both groups: 30% versus 60% oxygen (Aguar 2013); 30% oxygen versus 65% oxygen (Rook 2014); 30% oxygen versus 90% oxygen (Escrig 2008; Vento 2009); and 30% oxygen versus 100% oxygen (Armanian 2012).

All trials reported mortality. Although no significant difference was found between lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentrations overall, the analysis lacks precision so is underpowered to detect an important effect. In addition, a subgroup analysis identified a single study (Oei 2016) targeting a lower limit of oxygen saturation range of < 85% that reported increased mortality in the air group compared to the 100% oxygen group. There were no other significant subgroup effects for mortality according to SpO_2 target or gestational strata (≤ 28 weeks or 28 to 32 weeks' gestation).

Reporting of other outcomes was variable among trials and not consistently reported in the same manner. Only two trials reported on neurodevelopmental disability in 208 infants. There were no significant differences in long-term effects of using lower versus higher oxygen concentrations.

Among hospital outcomes, intubation in the delivery room was reported by nine trials including 875 infants, with no significant difference between groups found. Other commonly reported outcomes were severe Intraventricular haemorrhage (IVH) (6 studies, 596 infants), necrotising enterocolitis (8 studies, 807 infants) and chronic lung disease at 36 weeks (9 studies, 862 infants). All other prespecified outcomes were reported by a minority of studies.

Duration of specific types of respiratory support was reported variably by studies. Only two studies reported our prespecified outcome (mechanical ventilation and CPAP). Duration of mechanical ventilation, duration of CPAP and duration of supplemental oxygen were more commonly reported. There was a high level of heterogeneity between studies of the effect of differing oxygen concentrations on duration of respiratory support (mechanical ventilation and CPAP) in the meta-analysis. A high level of heterogeneity was also present in the analysis of duration of supplemental oxygen administration. A single study reported a reduction in duration of respiratory support (mechanical ventilation and CPAP) but an increase in duration of supplemental oxygen (Oei 2016). No difference was found in analyses of duration of mechanical ventilation or duration of CPAP, or chronic lung disease at 36 weeks. As effects on duration of respiratory support and duration of supplemental oxygen administration are largely limited to a single study, the results should be treated with caution.

Quality of the evidence

We graded the quality of the evidence as 'low' or 'very low' for all prespecified GRADE rated outcomes. We downgraded our assessment of the quality of evidence for mortality to discharge as only two of 10 studies were at low risk of bias and had sufficiently precise estimates. Common methodological concerns were unclear or high risk of selection bias (four studies) and lack of blinding of intervention (five studies). Two studies reported neurodevelopment in 208 infants; we downgraded our assessment of the quality of this evidence due to inconsistency (moderate heterogeneity, I^2 = 53%) and imprecision. There was also inconsistency (high heterogeneity, I^2 > 75%) in analyses of duration of respiratory support (mechanical ventilation and CPAP) and duration of supplemental oxygen. Subgroup analyses identified the heterogeneity could be due to differences between studies in inspired oxygen concentrations, or differences in the lowest SpO_2 target ranges (or both). Two studies, which reported outcomes of 253 infants, were at low risk of bias and were included in sensitivity analyses (Aguar 2013; Rook 2014). The studies reported no significant differences in mortality to discharge, neurodevelopmental disability, outcomes relating to response to resuscitation and multiple neonatal morbidities. Given the findings of the sensitivity analyses, it is possible observed differences between lower and high oxygen concentration groups in specific analyses were due to bias.

Potential biases in the review process

In this review we prespecified inclusion criteria, performed an extensive search of the literature (supplemented by searches of conference abstracts and expert informants), independently and reproducibly assessed eligibility, assessed risk of bias, extracted data and graded the quality of evidence. We resolved differences by discussion. There were difficulties in extracting data for prespecified respiratory support outcomes, duration of

respiratory support, duration of supplemental oxygen and duration of hospitalisation, as the reporting in the majority of trials was not compatible. Data were variably reported as means (standard deviation (SD)), median and range or interquartile range. We converted non-parametric data to mean (SD) for inclusion in analyses. These data should be treated with caution as means (SD) were estimated and could be affected by data skew.

Agreements and disagreements with other studies or reviews

An earlier systematic review of randomised controlled trials, by Brown and colleagues (Brown 2012b), assessed the effect of lower (FiO_2 21% to 50%) versus higher (FiO_2 > 50%) oxygen concentrations for delivery room support of preterm infants. Six trials enrolling 484 infants were identified. Most participants were born before 32 weeks' gestation. Meta-analyses showed a significant reduction in death (RR 0.65, 95% CI 0.43 to 0.98). However, no effect was found when analysis was limited to the four trials with adequate allocation concealment (RR 1.0, 95% CI 0.45 to 2.24).

A recent systematic review of infants born ≤ 28 weeks and six days' gestation randomised to resuscitation with low (FiO_2 ≤ 0.3) versus high (FiO_2 ≥ 0.6) oxygen at delivery identified 504 infants enrolled in eight studies (Oei 2017). Meta-analyses found no difference in bronchopulmonary dysplasia (RR 0.88, 95% CI 0.68 to 1.14), intraventricular haemorrhage (RR 0.81, 95% CI 0.52 to 1.27), retinopathy of prematurity (RR 0.82, 95% CI 0.46 to 1.46), patent ductus arteriosus (RR 0.95, 95% CI 0.80 to 1.14) and necrotising enterocolitis (RR 1.61, 95% CI 0.67 to 3.36) and overall mortality (RR 0.99, 95% CI 0.52 to 1.91). The review reported mortality was lower in low oxygen arms of masked studies (RR 0.46, 95% CI 0.23 to 0.92; P = 0.03) and higher in low oxygen arms of unmasked studies (RR 1.94 95% CI 1.02 to 3.68, P = 0.04).

This review has been cross-checked against Oei 2017, for data accuracy. The conclusion of the review by Oei and colleagues was a finding of no difference in risk of death or other morbidity after resuscitation is initiated at delivery with lower (≤ 0.3) or higher (≥ 0.6) oxygen concentrations (Oei 2017). The need for larger, well designed studies was identified.

A recent systematic review of RCTs that enrolled babies born < 28 weeks' gestation, at birth or soon thereafter, and targeted SpO_2 ranges of either ≤ 90% or > 90% found targeting lower compared to higher SpO_2 had no significant effect on the composite outcome of death or major disability or on major disability alone, but increased the average risk of mortality by 28 per 1000 infants treated (Askie 2017). However, the findings are not directly applicable to resuscitation, since three trials enrolled infants < 24 hours' age, one trial infants < 12 hours' age and one trial required infants to be enrolled by 2 hours of age.

AUTHORS' CONCLUSIONS

Implications for practice

There is uncertainty as to whether initiating post birth resuscitation in preterm infants using lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen concentrations, targeted to oxygen saturations in the first 10 minutes, has an important effect on mortality or major morbidity, intubation during post birth resuscitation, other resuscitation outcomes, and long-term outcomes including neurodevelopmental disability. The evidence was assessed as low- to very low-quality for all outcomes.

Implications for research

Comparing initiating post birth resuscitation in preterm infants using lower (FiO_2 < 0.4) or higher (FiO_2 ≥ 0.4) oxygen concentrations, targeted to oxygen saturations in the first 10 minutes, the finding of no difference in mortality lacks precision so important differences may not have been detected. In addition, the quality of evidence we identified was compromised due to methodological concerns including the potential for selection and performance bias. Further large, well designed trials are needed to assess the effect of using different initial oxygen concentrations.

In subgroup analysis we identified a single trial that reported increased mortality from use of lower (FiO_2 0.21) versus higher (FiO_2 1.0) oxygen concentrations targeted to a lowest SpO_2 < 85%, whereas meta-analysis of nine trials targeting a lowest SpO_2 of 85% to 90% found no difference in mortality. Further large, well designed trials are needed to assess the effect of targeting different oxygen saturations in the first 10 minutes after birth. Neurodevelopmental outcomes should be reported.

ACKNOWLEDGEMENTS

None.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Aguar 2013

Methods	Multicentre randomised controlled trial from two centres in Spain
Participants	**Inclusion criteria:** infants born ≤ 28 weeks' gestation **Exclusion criteria:** unknown/uncertain gestational age; major congenital malformations; chromosomopathies
Interventions	**Higher oxygen group (n = 26):** initial inspiratory fraction of oxygen 0.6 **Lower oxygen group (n = 34):** initial inspiratory fraction of oxygen 0.3 **Target SpO_2 (both groups):** > 75% at 5 min; > 85% at 10 min **Pulse oximeter:** not reported
Outcomes	**Primary outcome:** need for intubation in the delivery room **Secondary outcomes:** 1. need for IPPV in the delivery room; 2. time to reach desired oxygen saturation target; 3. time to reach heart rate > 100 bpm; 4. duration of respiratory support (days); 5. duration of supplemental oxygen administration (days); 6. neurological abnormality (Cerebral Palsy or developmental disability); 7. late mortality (after 18 months of age); 8. survival with bronchopulmonary dysplasia; 9. retinopathy of prematurity (any and > stage 2); 10. patent ductus arteriosus; 11. intraventricular haemorrhage (any and grade 3 or 4); 12. necrotising enterocolitis; 13. bronchopulmonary dysplasia (continued oxygen requirement at 28 postnatal days); 14. bronchopulmonary dysplasia (continued oxygen requirement at 36 weeks' corrected age); 15. postnatal growth failure; 16. duration of hospitalisation. **Long-term outcomes:** Bayley Scales of Infant and Toddler Development III at 24 months Disability defined as: no disability, mild disability (defined as scores between –1 and –2 SD from the mean in any of the Bayley III scales or mild CP [I and II]), moderate disability (scores between –2 and –3 SD from the mean in any of the Bayley III scales, moderate CP [III]), and severe disability (scores less than the mean –3 SD in any of the Bayley III scales, severe CP [IV and V] or bilateral blindness or deafness)
Notes	Conference abstracts and trial registration available (unpublished data obtained from author) 24 month follow-up for two studies (Aguar 2013; Rook 2014), combined in report. Neurodevelopmental disability for Aguar 2013 as reported by author Neurodevelopmental disability for Rook 2014 calculated from combined total subtracting those infants reported by Aguar 2013.

Aguar 2013 *(Continued)*

Sample size: a reduction from 55% to 30% of intubation in the delivery room needed with an alpha of 0.05 and a beta risk of 15% a total of 66 patients per group (total = 132).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers were generated by computer programme. Babies were stratified according to gestational age in two blocks: ≤ 26 weeks; > 26 weeks.
Allocation concealment (selection bias)	Low risk	Pregnant women at risk of preterm delivery were approached prior to delivery. Informed consent was signed prior to delivery. Randomisation was performed at the time of delivery with opaque sealed envelopes opened by the non-blinded researcher in the delivery room.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blender was not visible for the resuscitation staff. One researcher was not blinded and adjusted blender according to the team leader instructions.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	NICU staff and laboratory staff were also blinded for the intervention. Patient was assigned a code that was only opened at the end of the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised infants were reported.
Selective reporting (reporting bias)	Low risk	Primary outcome stated: intubation reduction in the delivery room during stabilisation.
Other bias	Low risk	Author (personal communication) stated that baseline characteristics were similar between intervention groups.

Armanian 2012

Methods	Randomised controlled trial, conducted 2009 and 2010 in Iran
Participants	**Inclusion:** infants 29 to 34 weeks' gestation requiring resuscitation at birth **Exclusion:** major congenital anomalies, the need for chest compressions during resuscitation, endotracheal intubation and no need for resuscitation at birth **Sample size:** 32 infants (16 infants in each group)
Interventions	Low oxygen concentration (30% oxygen) versus very high oxygen concentration (100% oxygen) The desired concentration of oxygen (low or very high) was given to both groups for the first 10 seconds of resuscitation. The pulse oximeter was attached and the infant was monitored. The concentration of oxygen was measured with an oxygen analyser.

Armanian 2012 *(Continued)*

	Low oxygen group (n = 16): resuscitation commenced with 30% oxygen. The baby was checked every 60 to 90 seconds. If the heart rate was below 100, then the previous oxygen was increased by 10% and this was repeated until a heart rate >100 beats per minute and oxygen saturations > 85% were reached. Positive pressure ventilation and the desired concentration of oxygen were started in the case of no satisfactory response and spontaneous breathing. **High oxygen group (n = 16):** resuscitation commenced with 100% oxygen. The babies condition were checked every 60 to 90 seconds. The time for reaching the heart rate > 100 beats per minute and oxygen saturation > 85% were recorded. In the case of reaching > 85% oxygen saturation, the oxygen concentration was reduced by 10 to 15% from the previous FiO_2 until the heart rate reached 100 and the oxygen saturation reached 85% **Target SpO_2 (both groups):** > 85% **Pulse oximeter:** not reported
Outcomes	1. Time (min) to reach oxygen saturation > 85%; 2. time (min) to reach HR > 100 bpm; 3. mean HR and oxygen saturation at 1, 2, 3, 4 and 5 minutes after birth; 4. FiO_2 required to achieve oxygen saturation > 85%; 5. FiO_2 required to achieve heart rate > 100 beats per minute; 6. mean required FiO_2 at 1, 2, 3 4 and 5 minutes after birth; 7. number of infants with heart rate > 100 bpm at 1, 2 and 3 minutes after birth; 8. number of infants with oxygen saturations > 85% 1, 2, 3, 4 and 5 minutes after birth; 9. mortality 'in early infancy'.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported infants 'randomized' into 2 groups Method not reported
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No reporting of attempts to blind intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	Insufficient reporting of demographic and baseline data

Escrig 2008

Methods	Randomised controlled trial conducted September 2005 to February 2007 in Spain
Participants	**Inclusion criteria:** preterm infants ≤ 28 weeks' gestation requiring active resuscitation in the delivery room. Included infants who were bradycardic (heart rate ≤ 80 beats per minute, hypotonic or hyporeactive, and unable to sustain active and/or effective respiration at birth **Exclusion criteria:** uncertain gestational age, severe congenital malformations, and chromosomal abnormalities **Sample size:** 42 infants (19 low oxygen group; 23 high oxygen group)
Interventions	**Low oxygen group:** 30% oxygen **High oxygen group:** 90% oxygen Immediately after birth a preductal probe for measuring SpO_2 was attached to the infant and connected to the pulse oximeter immediately after birth. The initial FiO_2 in both groups was increased or reduced by 10% every 60 to 90 seconds according to the infant's heart rate and oxygen saturation. FiO_2 was increased by 10% when the heart rate decreased below 100 beats per minute. Additional changes were performed according to the responses obtained. Where HR remained ≥ 100, FiO_2 was reduced in a stepwise manner to keep SpO_2 at 85%. In severe situations (persistent bradycardia of ≤ 60 beats per minute for > 30 seconds) the oxygen blender was switched directly to 100% oxygen. When SpO_2 values increased very rapidly to > 90%, the FiO_2 was reduced in increments of 10% every 90 seconds. **Target SpO_2 (both groups):** 85% to 90% **Pulse oximeter:** radical pulse oximeter; Masimo — Functional
Outcomes	1. Mean FiO_2 from birth to 15 minutes (measured at minutely intervals); 2. mean HR from birth to 15 minutes (measured at minutely intervals); 3. need for mask CPAP, mask IPPV, or intubation and IPPV, in the delivery room; 4. need for mask IPPV on arrival in NICU; 5. need for IPPV via ETT on arrival in NICU; 6. time to reach heart rate > 100 beats per min; 7. FiO_2 required to achieve oxygen saturations ≧ 85%; 8. FiO_2 required to achieve heart rate ≥ 100 beats per minute; 9. proportion (%) of infants receiving room air at any time point (1 to 20 minutes after birth); 10. difference between SpO_2 values at 10 minutes after birth; 11. proportions of SpO_2 values at various time points (1 to 20 minutes after birth); 12. time to reach clinical stability (oxygen saturation > 85%; heart rate > 100 beats per minute, good response to stimuli); 13. body temperature on admission to NICU; 14. blood pH; 15. duration of mechanical ventilation (days); 16. duration of CPAP (days); 17. mortality during neonatal period; 18. mortality during hospitalisation ; 19. persistent ductus arteriosus (additional data obtained from Oei 2017); 20. necrotizing enterocolitis; 21. apneic-bradycardic syndrome;

Escrig 2008 *(Continued)*

22.intraventricular haemorrhage (> grade 2);
23.periventricular haemorrhage (grades 3 or 4);
24.bronchopulmonary dysplasia (continued oxygen requirement at 36 weeks' corrected age);
25.retinopathy of prematurity (any) (additional data obtained from Oei 2017);
26.neurosensory dysfunction.

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-based randomisation procedure was used. Twin deliveries were considered as a unit for the purpose of randomisation.
Allocation concealment (selection bias)	Low risk	'As soon as the mothers were admitted to the hospital, informed consent was obtained' 'Immediately before delivery, infants were randomly assigned .... using sealed envelopes'
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Authors confirm that blinding of outcome assessment was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses not reported
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	Groups similar at baseline

Kapadia 2013

Methods	Randomised controlled trial, conducted August 2010 to January 2011 in USA
Participants	**Inclusion criteria:** all inborn neonates of obstetrical gestational age 24 weeks 0 days to 34 weeks and 6 days for whom the high-risk resuscitation team was present at birth and who required active resuscitation **Exclusion criteria:** neonates were excluded for nonviability, prenatally diagnosed cyanotic congenital heart disease, if no active resuscitation was required, or if preductal SpO_2 could not be measured **Sample size:** 88 infants (44 low oxygen group; 44 high oxygen group)
Interventions	Resuscitation started with room air while the envelope was opened and then immediately changed to low oxygen or high oxygen. **Low oxygen group:** resuscitation was initiated with 21% oxygen

Kapadia 2013 *(Continued)*

	Supplemental oxygen was given for the following indications: 1. heart rate (HR), 100 beats per minute after 30 seconds of effective ventilation; or 2. lower limit of goal saturations not achieved. FiO_2 was adjusted by 10% in 30-second intervals to maintain target SpO_2 If HR remained < 60 beats per minute despite 30 seconds of PPV, FiO_2 was increased to 100% until recovery of HR to > 100 beats per minute **High oxygen group:** resuscitation was initiated with 100% oxygen and adjusted every 30 seconds by 10% to meet target SpO_2 **Target SpO_2 (higher oxygen group):** 85% to 94% **Target SpO_2 (lower oxygen group):** interquartile values for healthy term neonates (Dawson 2010; Kamlin 2006) **Pulse oximeter:** radical pulse oximeter; Masimo — Functional
Outcomes	**Primary outcome:** oxidative balance ratio (BAP/TH) **Secondary outcomes:** 1. admission PaO_2 > 100 mmHg; 2. change in Apgar score; 3. need for IPPV in the delivery room; 4. need for intubation in the delivery room; 5. total O_2 used during resuscitation; 6. integrated excessive O_2 (Sum [FiO_2 – 0.21] x time [min]); 7. time during resuscitation with saturations > 94%; 8. use of rescue high frequency oscillatory ventilation; 9. time on ventilation (days); 10. duration of hospital stay (days); 11. in-hospital mortality; 12. bronchopulmonary dysplasia at 28 days of life; 13. bronchopulmonary dysplasia at 36 weeks' postmenstrual age; 14. retinopathy of prematurity (severe); 15. necrotizing enterocolitis; 16. symptomatic patent ductus arteriosus; 17. intraventricular haemorrhage (grade 3 or 4); 18. cystic periventricular haemorrhage.
Notes	Initial oxygen targeting was different between groups; then targeted SpO_2 was 88% to 94% so we included study. **Sample size estimation:** based on the reported oxidative balance ratio data for preterm neonates, to detect a 15% change, 39 patients were needed for each arm using a 2-sided a level of 0.05 and a power of 0.8. Ten extra infants were recruited to accommodate a potential 10% dropout rate

Risk of bias

Bias	Authors' judgement	Support for judgement

Kapadia 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	A non-investigator used a permuted design in blocks of 8 to determine randomisation sequence and stratified participants into estimated gestation groups: 24 0/7 to 28 6/7 weeks and 29 0/7 to 34 6/7 weeks.
Allocation concealment (selection bias)	Low risk	Allocation was concealed via serially numbered, sealed, opaque envelopes that were opened sequentially by the resuscitation team when the need for resuscitation was recognised.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	High risk	Excess breech delivered infants in high oxygen group (23 versus 55%; P < 0.05)

Kumar 2014

Methods	Randomised controlled trial, conducted March 2009 to November 2010 in USA
Participants	**Inclusion criteria:** infants < 32 weeks' gestational age **Exclusion criteria:** none reported **Sample size:** 18 infants (21% n = 6; 40% n = 7; 100% n = 5)
Interventions	**Low oxygen group:** 21% oxygen **High oxygen group:** 40% oxygen **Very high oxygen group:** 100% oxygen Resuscitated as per 2004 NRP guidelines The FiO_2 determined at randomisation was kept constant for the initial 10 minutes after birth. Oxygen (21%, 40%, or 100% oxygen) was provided with the blender at flow rates of 8 L/min, via the T-piece resuscitator, and the peak inspiratory pressure was adjusted depending on chest rise, colour, or the HR. For infants breathing spontaneously with a HR >100, the study gas was used to provide free-flow oxygen if needed, until they established regular respirations. Soon after birth preductal SpO_2 were recorded (Masimo SET, Masimo, CA). For the initial 10 minutes, both the FiO_2 concentration and the SpO_2 recordings were blinded from the resuscitation team. Oxygen groups & SpO_2 were unmasked at 10 min, FiO_2 adjusted to maintain SpO_2 85% to 95%.

Kumar 2014 *(Continued)*

	We continued the study gas as long as the SpO_2 was in the target range of 85% to 95%, and transferred the infant to the neonatal intensive care unit in a transport isolette with the respiratory support required. FiO_2 was decreased for SpO_2 > 95% and increased for SpO_2 < 85%, by 10% to 20% every 60 seconds to maintain the SpO_2 target of 85% to 95%. Infants were switched to 100% oxygen (and unmasked) only if they were not responding to the study gas (HR < 100/min for > 90 seconds) despite adequate ventilation at any time after birth and were excluded from the study. However, no infant received chest compressions or crossed over to 100% oxygen during the study period. The intervention portion of the study was complete at 30 minutes of life and the FiO_2 was adjusted to maintain an SpO_2 of 88% to 94% as per NICU protocol at the time. **Target SpO_2 (both groups):** 85% to 95% from 10 minutes **Pulse oximeter:** radical pulse oximeter; Masimo — Functional
Outcomes	**Primary outcome:** glutathione to oxidized glutathione ratio (GSH/GSSG) at 24 hours of age **Secondary outcomes:** 1. mortality; 2. IPPV in the delivery room; 3. BPD (oxygen requirement at 36 weeks); 4. necrotizing enterocolitis (Bell's stage 2 or 3) (unpublished data); 5. patent ductus arteriosus; 6. intraventricular haemorrhage (any).
Notes	The study was stopped at 30% enrolment following publication of the 2010 Neonatal Resuscitation Program (NRP) guidelines. **Sample size estimation:** to detect a difference of 1.5 standard deviation in oxidative balance ratio at 24 hours with an alpha level of 0.05 and power of 80%, it was estimated that each group would require 20 patients. **Note:** no oxygen targeting for the first 10 minutes of resuscitation. Delayed SpO_2 targeting from 10 minutes — included study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not reported Oxygen groups were stratified into two subgroups (23 to 27 6/7 weeks; 28 0/7 to 31 6/7 weeks).
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as a 'double blind' study The personnel in the delivery room (and all but one of the study personnel) were blinded to the study gas FiO_2 to 10 minutes of age. Unmasked at 10 minutes but intervention not completed until 30 minutes
Blinding of outcome assessment (detection bias)	Unclear risk	No information. Certain study outcomes ((GSH/GSSG) and mortality/BPD) unlikely to be influenced

Kumar 2014 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses reported
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	Some baseline differences between groups

Oei 2016

Methods	Multicentre randomised controlled trial, conducted January 2008 to June 2014 in Australia, Malaysia and Qatar
Participants	**Inclusion criteria:** live-born infants below 32 weeks' gestation or ≤ 1250 grams birth weight (if gestation was unclear) were eligible if their mothers presented at least 6 hours before delivery and if parental or guardian consent was obtained. **Exclusion criteria:** infants were excluded at any time if they were found to have severe cardiorespiratory abnormalities that could affect oxygenation or if death was considered to be imminent or inevitable. **Sample size:** 290 infants (145 low oxygen group; 145 high oxygen group)
Interventions	Respiratory support was initiated with either; 1) room air, or 2) 100% oxygen **Room air group:** FiO_2 was increased by 10% aliquots if pre-ductal saturations continued to be < 65% before 5 minutes and < 80% after 5 minutes. FiO_2 was decreased by 10% aliquots every minute if SpO_2 readings were > 95% at any time. FiO_2 was increased immediately to 100% if the infant's heart rate remained persistently below 100bpm despite adequate ventilation, if SpO_2 was < 65% at 5 minutes, if external cardiac massage or resuscitation medications e.g. adrenaline were required or if considered necessary by the attending clinician **100% oxygen group:** decrease FiO_2 by 10% aliquots every minute if SaO_2 > 95% at any time **Target SpO_2 (both groups):** 80% to 95% at 5 minutes **Pulse oximeter:** not reported
Outcomes	**Primary outcome:** 1. Combined mortality and/or major disability at 18 to 24 months corrected age 2. Major disability defined as one or more of the following: 1. composite cognitive score < 85 and/or language score < 85 on the Bayley Scale of Infant Development III (BSID III); 2. severe visual loss (< 6/60 vision); 3. cerebral palsy with Gross Motor Function Classification System (GMFCS) level ≥ 2; 4. deafness requiring hearing aids **Secondary outcomes:** 1. ROP (grade ≥ 3); 2. bronchopulmonary dysplasia (continued oxygen requirement at 36 weeks' corrected age); 3. patent ductus arteriosus (PDA) requiring treatment; 4. necrotizing enterocolitis (NEC) requiring surgery or resulting in death; 5. severe brain injury (IVH grade III/IV) and/or periventricular leukomalacia; 6. neonatal mortality (< 28 days from birth);

Oei 2016 *(Continued)*

	7. mortality before hospital discharge.
Notes	Data obtained from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by computer-generated sequences once birth was imminent Grouped into blocks of 10 stratified by gestation (below 28 weeks' gestation and 28 to 31 weeks' gestation)
Allocation concealment (selection bias)	Low risk	Consent and alibility assessed before antenatal randomisation immediately before delivery
Blinding of participants and personnel (performance bias) All outcomes	High risk	Protocol reported as 'non-blinded'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	None reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/290 (1%) post randomisation exclusions due to congenital malformation
Selective reporting (reporting bias)	Unclear risk	Clinical trial registration published primary outcome as mortality measured at 2 years
Other bias	Low risk	Groups similar at baseline

Rabi 2011

Methods	Randomised controlled trial, conducted January 2005 to September 2007 in Canada
Participants	**Inclusion criteria:** preterm infants 32 weeks or less gestation and inborn at the study centre **Exclusion criteria:** infants with lethal anomalies, risk of persistent pulmonary hypertension (i.e., presence of oligohydramnios, meconium at delivery), antenatally diagnosed cyanotic congenital heart disease, or haemoglobinopathy **Sample size:** 106 infants reported (34 low oxygen group; 34 moderate oxygen group; 38 high oxygen group) plus 103 excluded post randomisation
Interventions	**High oxygen group:** static concentration of 100% oxygen during assisted ventilation (not included in this review) **'Moderate' oxygen group:** assisted ventilation started with 100% oxygen **Low-oxygen group:** assisted ventilation started with 21% oxygen **Target SpO_2 (both groups):** 85% to 92% **Pulse oximeter:** Datex-Ohmeda; GE Healthcare - Functional

Rabi 2011 *(Continued)*

Outcomes	**Primary outcomes:** 1. time spent in the target SpO_2 range of 85% to 92% during resuscitation; 2. time taken to reach target SpO_2 range of 85% to 92% during resuscitation. **Secondary outcomes:** 1. proportion of time spent outside target SpO_2 range of 85% to 92% during resuscitation; 2. total oxygen exposure (litres of 100% oxygen per kg); 3. FiO_2 at the end of resuscitation; 4. need for intubation in the delivery room; 5. resuscitation duration; 6. survival at discharge; 7. duration of mechanical ventilation (days); 8. duration of hospital stay (days); 9. incidence of bronchopulmonary dysplasia at 36 weeks' postmenstrual age (additional data obtained from Oei 2017); 10. treatment failure (heart rate < 100 beats per minute for > 30 seconds).
Notes	**Sample size:** calculated on the basis of the primary outcome A sample size of 108 infants (36 in each of the 3 groups) was required to detect a difference of 30% between 2 adjacent means (80%, 50% and 20% of the resuscitation time spent in the target SPO_2 range) with 80% power at the 5% level of significance (2-tailed)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used permuted-block randomisation design with random block sizes of 3 and 6 using a computer-generated randomised schedule
Allocation concealment (selection bias)	High risk	Allocation sequence was constructed by a non-clinician who was not involved in the study and maintained possession of the allocation sequence in a locked drawer. Sequentially numbered, opaque, sealed envelopes were used and opened immediately by the study investigator before the delivery of a potentially eligible infant. But "permitted to obtain consent from parents after the intervention for inclusion of collected data and ongoing monitoring until discharge."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The resuscitation and healthcare teams were blinded to the intervention. The investigator attending the delivery was not blinded to the intervention and was responsible for adjusting the oxygen during resuscitation but did not take part in resuscitation care.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessors, the statistician and data collectors were blinded to the intervention.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In text reported as "subsequent to randomisation, infants not requiring assisted ventilation during resuscitation, per Neonatal Resuscitation Program Guidelines were excluded from the analysis" (n=103/209, 49%), however in CONSORT figure reported as not randomised.
Selective reporting (reporting bias)	Unclear risk	No protocol available

Rabi 2011 *(Continued)*

Other bias	Low risk	Groups similar at baseline

Rook 2014

Methods	Randomised controlled trial, conducted August 2008 to February 2012 in The Netherlands
Participants	**Inclusion criteria:** infants < 32 weeks' gestation **Exclusion criteria:** known major congenital malformations, chromosome defects, or metabolic, endocrine or renal disorders **Sample size:** 198 infants (101 low oxygen group; 97 high oxygen group)
Interventions	**Low oxygen group:** 30% oxygen **Very high oxygen group:** 65% oxygen The FiO_2 was adjusted based on oxygen saturation measured by pulse oximetry and pulse rate (heart rate 100 beats per minute) in order to achieve a target SpO_2 of 88% to 94% at 10 minutes of life. The FiO_2 and pulse oximetry data was continuously recorded. **Target SpO_2 (both groups):** 88% to 94% at 10 minutes **Pulse oximeter:** Nellcor OxiMax N-600x; Covidien — Functional
Outcomes	**Primary outcome:** survival without BPD at 36 weeks' postmenstrual age **Secondary outcomes**: 1. Apgar score at 5 min; 2. intubation in the delivery room; 3. time taken to achieve SpO_2 > 88% following birth; 4. cumulative O_2 exposure during resuscitation; 5. glutathione synthesis and markers of oxidative stress; 6. duration of supplemental oxygen administration (days); 7. duration of mechanical ventilation; 8. retinopathy of prematurity (grade ≥ 2); 9. bronchopulmonary dysplasia at 36 weeks' postmenstrual age; 10.necrotising enterocolitis (grade ≥ 2); 11.mortality; 12.intraventricular haemorrhage (Grade III/IV); 13.neurodevelopmental outcome at 2 years of age. **Long-term outcomes:** Bayley Scales of Infant and Toddler Development III at 24 months Disability defined as: no disability, mild disability (defined as scores between –1 and –2 SD from the mean in any of the Bayley III scales or mild CP [I and II]), moderate disability (scores between –2 and –3 SD from the mean in any of the Bayley III scales, moderate CP [III]), and severe disability (scores less than the mean –3 SD in any of the Bayley III scales, severe CP [IV and V] or bilateral blindness or deafness)
Notes	**Sample size calculation:** based on the incidence of BPD shows that, with an incidence of 30% and an expected reduction of 15%, 100 infants per group were needed to find a statistically significant difference with an α of 0.05 and a power of 0.80 Additional data obtained from Oei 2017 for patent ductus arteriosus

Rook 2014 *(Continued)*

	24-month follow-up for two studies, Aguar 2013 and Rook 2014, combined in report. Neurodevelopmental disability for Aguar 2013, as reported by author Neurodevelopmental disability for Rook 2014, calculated from combined total subtracting those infants reported by Aguar 2013.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list by an individual not involved in the study.
Allocation concealment (selection bias)	Low risk	Reported 'written informed consent will be obtained antenatally. When an infant with prenatal consent is born, the physician will activate the research setting by activation of a switch just before delivery. By activating this research switch ... administered oxygen will come from the additional oxygen blender, randomised to 30% or 65% oxygen.'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Before the start of the resuscitation the study blender was activated by a switch on the resuscitation unit.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The physician remained blinded to the group assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/198 (3%) post randomisation exclusions for congenital abnormalities. 19/253 (8%) of randomised infants from Aguar 2013 and Rook 2014 lost to 24 months follow-up.
Selective reporting (reporting bias)	Low risk	Prespecified primary outcome in protocol: 'survival without bronchopulmonary dysplasia, as assessed by a physiological test at 36 weeks' postmenstrual age'.
Other bias	Low risk	Groups similar at baseline.

Vento 2009

Methods	Two-centre randomised controlled trial, conducted September 2005 to March 2008 in Spain
Participants	**Inclusion criteria:** inborn infants ≤ 28 weeks' gestation with one of the following resuscitation criteria: absence of spontaneous respiration at > 1 minute; bradycardia (< 60 beats per minute) for ≥ 2 minutes, hypoactivity, and/or hypotonia; or ineffective ventilation, as determined through auscultation and/or lack of thoracic expansion **Exclusion criteria:** uncertain gestational age; severe congenital malformations or chromosomal abnormalities **Sample size:** 87 infants randomised — 78 infants reported (37 low oxygen group; 41 high oxygen group; mortality reported for 41 low oxygen group and 44 high oxygen group)
Interventions	**Low oxygen group:** 30% oxygen **Very high oxygen group:** 90% oxygen Neonates with a heart rate of 80 to 100 beats per minute and increased work of breathing in the first 2 minutes of life initially underwent ventilation with a face mask (5 to 8 cmH_20), with a T-piece resusci-

Vento 2009 *(Continued)*

	tator. If clinical responses were insufficient, then the neonates were switched to intermittent positive pressure ventilation. For infants with gestational ages of < 27 weeks, endotracheal intubation was performed. For infants with gestational ages of 27 or 28 weeks, noninvasive ventilation was pursued for several minutes and intubation was performed only if the infants' condition did not improve. Initial parameters for intermittent positive pressure ventilation were positive inspiratory pressure of 20 cmH_2O and positive and end expiratory pressure of 5 cmH_2O. If no improvement was detected after 2 minutes, then respiratory parameters were modified to achieve the targeted objectives. Immediately after birth, an oximeter probe with sensors with 2-second averaging (Radical 7; Masimo, Irvine, CA) was set on the right wrist for preductal SpO_2 monitoring. FiO_2 was titrated to attain targeted SpO_2 values (preductal SpO_2 values of 75% at 5 minutes and 85% at 10 minutes after birth) and 60 to 90 seconds were allowed for responses after each change. Abrupt FiO_2 changes (> 10% every 30 seconds) were avoided, to prevent pulmonary vessel constriction. Heart rate indicated the effectiveness of resuscitation; if bradycardia (heart rate ≤ 60 beats per minute) lasted > 30 seconds, then FiO_2 was switched to 100%. SpO_2 was recorded continuously, and the information was downloaded and analysed once oxygen treatment was discontinued. **Target SpO_2 (both groups):** > 75% at 5 min; > 85% at 10 min **Pulse oximeter:** Radical pulse oximeter; Masimo - Functional
Outcomes	**Primary outcome:** combined neonatal mortality (death at < 28 days) and bronchopulmonary dysplasia (need for oxygen supplementation at postconceptual age of 36 weeks) **Secondary outcomes:** 1. intubation in the delivery room; 2. duration of supplementary oxygen treatment (days from birth); 3. duration of mechanical ventilation (days from birth); 4. duration of CPAP therapy (days from birth); 5. use of surfactant; 6. correlation between BPD and oxidative; stress biomarkers/pro inflammatory cytokines; 7. retinopathy of prematurity (any); 8. neonatal mortality (death at < 28 days); 9. bronchopulmonary dysplasia at 36 weeks' postmenstrual age; 10. intraventricular haemorrhage (grade III/IV).
Notes	Data obtained from authors. Additional data obtained from Oei 2017.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Used sealed envelopes. In cases of refusal, the patients were not assigned
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was not blinded with respect to the neonatologist in charge of the respiratory airway but it was with respect to the rest of the caregivers in the delivery room
Blinding of outcome assessment (detection bias) All outcomes	High risk	"This was not a blinded study"

Vento 2009 *(Continued)*

		"Interventions in the delivery room were recorded scrupulously and were analysed to evaluate possible bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	'If an infant was assigned randomly but was not resuscitated, then the data were not included in the study'. 'Of of 106 eligible neonates, 9 in the low-oxygen group and 10 in the high-oxygen group were lost to randomisation because parents declined to participate. Of the remaining subjects, 4 in the low-oxygen group and 3 in the high-oxygen group died and did not complete the study.' Two infants not accounted for in reporting. Timing of exclusions unclear with respect to randomisation.
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Low risk	Groups similar at baseline

Wang 2008

Methods	Two-centre randomised controlled trial, conducted December 2005 and March 2007 in USA
Participants	**Inclusion criteria:** inborn infants with gestational ages 23 to 31 weeks requiring resuscitation **Exclusion criteria:** neonates with known congenital malformations or chromosomal anomalies **Sample size:** 41 infants (18 very low oxygen group; 23 very high oxygen group)
Interventions	Low oxygen concentration (21%) versus very high oxygen concentration (100%) For all infants a pulse oximeter was applied within the first 30 seconds of life. All SpO_2 values obtained and recorded were from a preductal site, always on the right wrist. The base unit was turned on and the probe was applied to the infant, followed by attachment of the probe to the base unit. Radical oximeters (Masimo, Irvine, CA) were used with HiFi sensors (Masimo, Irvine, CA) which automatically set the oximeter to maximal sensitivity, and 2-second averaging. **Very high oxygen group:** resuscitation was initiated with 100% oxygen. At 5 minutes of life, oxygen treatment was weaned if the SpO_2 was consistently > 95%. **Low oxygen group:** 21% oxygen was used as the initial resuscitation gas. The goal was to maintain the SpO_2 80% to 85% at 5 minutes and 85% to 90% after 7 minutes FiO_2 was immediately increased to 100% under the following conditions: need for chest compressions or medication administration, heart rate of < 100 beats per minute at 2 minutes of life, or heart rate < 60 beats per minute for 30 seconds at any time. FiO_2 was increased in 25% increments if SpO_2 was < 70% at 3 minutes of life or < 85% at 5 minutes of life. Video recordings were linked to the analogue data on heart rate, SpO_2, FiO_2, peak inspiratory pressure, and positive end expiratory pressure, the exact time at which resuscitation events occurred, including any changes in FiO_2 and administration of positive pressure ventilation was documented in relation to the status of the infant at the time. **Target SpO_2:** Lower group 80% to 85% at 5 min, Maintain 85% to 90% after 7 min; Higher group ≤ 95% **Pulse oximeter:** radical pulse oximeter; Masimo - Functional
Outcomes	**Primary outcome:** SpO_2 values similar to those of non-resuscitated transitioning neonates **Secondary outcomes:** 1. SpO_2 levels; 2. heart rate;

Wang 2008 *(Continued)*

3. percentage of oxygen administered;
4. percentage of neonates with SpO_2 > 95%;
5. time to establish heart rate > 100 beats per minute;
6. heart rate < 100 beats per minute at 2 minutes post birth;
7. neonatal mortality (< 28 postnatal days);
8. intraventricular haemorrhage (grade III-IV);
9. oxygen therapy at adjusted age of 36 weeks;
10. duration of intubation;
11. duration of NCPAP therapy (days from birth);
12. duration of mechanical ventilation (days from birth);
13. duration of CPAP therapy (days);
14. pneumothorax;
15. surfactant treatment;
16. need for intubation in the delivery room;
17. need for chest compressions;
18. need for medications;
19. Apgar score at 1, 5 and 10 minutes;
20. cord arterial pH;
21. need for positive pressure ventilation in the delivery room;
22. need for CPAP;
23. initial pH, PCO_2, PO_2, Base deficit on arterial blood gases after resuscitation.

Notes	Sample size estimation not performed Additional data obtained from Oei 2017

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was in blocks of 10. Multiple gestations were assigned randomly according to pregnancy, not individual neonates
Allocation concealment (selection bias)	Low risk	Prenatal parental consent was obtained. When delivery was imminent, subjects were assigned randomly using sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	'The trial was not blinded, by design'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	'Although the intervention was not blinded, the analysis of data was performed in the most objective way possible'
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/43 (5%) excluded post randomisation as did not require resuscitation
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	Some baseline differences between groups

bpm: beats per minute

CPAP: continuous positive airway pressure
ETT: endotracheal tube
HR: heart rate
IPPV: intermittent positive pressure ventilation
FiO_2: fraction of inspired oxygen
NEC: necrotising enterocolitis
NICU: neonatal intensive care unit
NRP: Neonatal Resuscitation Program
O_2: oxygen
PaO_2: arterial partial pressure oxygen
PDA: patent ductus arteriosus
PPV: positive pressure ventilation
ROP: retinopathy of prematurity
SD: standard deviation
SpO_2: peripheral capillary oxygen saturation

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

Study	Reason for exclusion
Bajaj 2005	Randomised to lower versus higher oxygen. Mean gestation > 37 weeks. No oxygen saturation targeting
Dawson 2009	Observational study. No routine oxygen saturation targeting
Ezaki 2009	Only one arm of study titrated oxygen concentrations according to targeted oxygen saturation
Gandhi 2013	Prospective cohort evaluation of a change in practice
Harling 2005	No routine oxygen saturation targeting during resuscitation
Lundstrom 1995	Oxygen targeted according to heart rate and respiratory rate. No routine oxygen saturation targeting
Pope 2013	Historical control study
Ramji 1993	Randomised to lower versus higher oxygen. Mean gestation > 37 weeks. No oxygen saturation targeting
Ramji 2003	Randomised to lower versus higher oxygen. Mean gestation > 37 weeks. No oxygen saturation targeting
Saugstad 1998	No routine oxygen saturation targeting
Toma 2006	Term infants enrolled
Toma 2007b	Mean gestation of infants > 37 weeks

Characteristics of studies awaiting assessment *[ordered by study ID]*

Toma 2007a

Methods	Quasi-randomised trial
Participants	Newborn infants (n = 44) requiring resuscitation for birth asphyxia

Toma 2007a *(Continued)*

Interventions	Resuscitated at delivery with oxygen 21% (20 infants) versus resuscitation at delivery with oxygen 100% (24 infants)
Outcomes	Cerebral and mesenteric blood flow velocities, correlation between mesenteric arterial velocities and feeding intolerance
Notes	Spanish paper with English abstract reported preliminary data from 3 months of study

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

NCT01773746

Trial name or title	Study of room air versus 60% oxygen for resuscitation of premature infants (PRESOX)
Methods	Multicentre randomised controlled trial
Participants	**Inclusion Criteria:** infants with a gestational age of 23 0/7 to 28 6/7 weeks by best obstetrical estimate Infants who will receive full resuscitation as necessary, i.e. no parental request or physician decision to forego resuscitation Infants whose parents/legal guardians have provided consent for enrolment, or for whom a waiver of consent is in place Infants without known major congenital malformations prior to delivery **Exclusion Criteria:** any infant transported to the centre after delivery; infants whose parents/legal guardians refuse consent; infants born when the research apparatus/study personnel were not available; infants < 23 weeks 0 days or > 28 weeks 6 days, completed weeks of gestation
Interventions	Room air neonatal resuscitation: using continuous positive airway pressure (CPAP) or positive pressure ventilation (PPV) will be provided with 21% oxygen. Infants will remain on 21% oxygen until they have a functioning oximeter when SpO_2 will be managed as below. FiO_2 will be increased by 10% increments when the infant's SpO_2 is below the lower sat limit for 30 seconds and repeated if the SpO_2 remains outside the limit for a subsequent interval of 30 seconds as often as is necessary to bring the SpO2 within the prespecified range. The FiO_2 will be decreased by 10% increments when the SpO2 is above the upper limit for 30 seconds and repeated if the SpO_2 remains outside the limit for a subsequent interval of 30 second as often as is necessary to bring the SpO_2 within the prespecified range. 60% Group: neonatal resuscitation using CPAP or PPV will be provided with 60% oxygen. Infants will remain on 60% oxygen until they have a functioning oximeter at which time their SpO_2 will be managed as described below. FiO_2 will be increased by 10% increments when the infant's SpO_2 is below the lower sat limit for 30 seconds and repeated if the SpO_2 remains outside the limit for a subsequent interval of 30 seconds as often as is necessary to bring the SpO_2 within the pre-specified range. The FiO_2 will be decreased by 10% increments when the SpO_2 is above the upper limit for 30 seconds and repeated if the SpO_2 remains outside the limit for a subsequent interval of 30 seconds as often as is necessary to bring the SpO_2 within the prespecified range.
Outcomes	Primary outcome measures: survival with neurodevelopmental impairment 18 to 22 months. Secondary outcome measures: survival without bronchopulmonary dysplasia 36 weeks; survival without ROP 36 weeks; decreased GSSG/GSH ratio birth, 1, 3, 7 days.

NCT01773746 *(Continued)*

Starting date	August 2013
Contact information	Wade Rich, wrich@ucsd.edu
Notes	

DATA AND ANALYSES

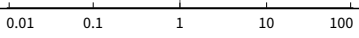
Comparison 1. Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality near term corrected age or discharge (latest reported) subgrouped by inspired oxygen concentration	10	914	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.68, 1.63]
2 Neurodevelopmental disability	2	208	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.49, 1.35]
3 IPPV in the delivery room	5	249	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.83, 1.06]
4 Intubation in the delivery room	9	875	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.82, 1.18]
5 Time to reach desired oxygen saturation target	2	102	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-1.83, 0.79]
6 Time to reach heart rate > 100 bpm (not prespecified)	1	60	Mean Difference (IV, Fixed, 95% CI)	0.27 [-1.21, 1.75]
7 Retinopathy of prematurity	4	373	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.43, 1.49]
8 Severe retinopathy of prematurity (≥ stage 3)	4	453	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.24, 1.36]
9 Intraventricular haemorrhage	3	271	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.46, 1.44]
10 Severe intraventricular haemorrhage (grade 3 or 4)	6	596	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.51, 1.71]
11 Periventricular leukomalacia	2	130	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.09, 4.73]
12 Necrotising enterocolitis	8	807	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.51, 1.87]
13 Chronic lung disease (28 days' age)	2	148	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.41, 1.21]
14 Chronic lung disease (36 weeks' corrected age)	9	862	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.14]
15 Duration of respiratory support (mechanical ventilation or CPAP) (days from birth)	2	326	Mean Difference (IV, Fixed, 95% CI)	-12.39 [-13.49, -11.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Duration of respiratory support (mechanical ventilation) (days from birth)	6	510	Mean Difference (IV, Fixed, 95% CI)	0.61 [-1.33, 2.54]
17 Duration of respiratory support (CPAP) (days from birth)	4	249	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-5.39, 2.19]
18 Duration of supplemental oxygen administration	5	639	Mean Difference (IV, Fixed, 95% CI)	9.23 [6.52, 11.95]
19 Mortality to follow up (> 18 months)	3	540	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.59, 1.70]
20 Postnatal growth failure (weight < 10th percentile at discharge)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.55, 1.33]
21 Duration of hospitalisation (days)	3	216	Mean Difference (IV, Fixed, 95% CI)	-1.75 [-12.22, 8.71]
22 Patent ductus arteriosus (not prespecified)	7	766	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.14]

Analysis 1.1. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 1 Mortality near term corrected age or discharge (latest reported) subgrouped by inspired oxygen concentration.

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	4/34	7/26		22.43%	0.44[0.14,1.34]
Armanian 2012	0/16	0/16			Not estimable
Escrig 2008	4/19	3/23		7.68%	1.61[0.41,6.34]
Kapadia 2013	2/44	3/44		8.48%	0.67[0.12,3.8]
Kumar 2014	1/6	1/12		1.89%	2[0.15,26.73]
Oei 2016	14/144	5/143		14.19%	2.78[1.03,7.52]
Rabi 2011	1/34	2/34		5.66%	0.5[0.05,5.26]
Rook 2014	6/99	10/94		29.01%	0.57[0.22,1.51]
Vento 2009	4/41	3/44		8.18%	1.43[0.34,6.01]
Wang 2008	1/18	1/23		2.48%	1.28[0.09,19.06]
Total (95% CI)	**455**	**459**		**100%**	**1.05[0.68,1.63]**
Total events: 37 (Lower oxygen), 35 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=9.03, df=8(P=0.34); I^2=11.42%					
Test for overall effect: Z=0.23(P=0.82)					



Favours lower oxygen — Favours higher oxygen

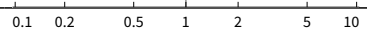
Analysis 1.2. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 2 Neurodevelopmental disability.

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	3/14	1/17		3.53%	3.64[0.42,31.27]
Rook 2014	19/95	23/82		96.47%	0.71[0.42,1.21]
Total (95% CI)	**109**	**99**		**100%**	**0.82[0.49,1.35]**
Total events: 22 (Lower oxygen), 24 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=2.11, df=1(P=0.15); I^2=52.58%					
Test for overall effect: Z=0.79(P=0.43)					

Favours lower oxygen — Favours higher oxygen

Analysis 1.3. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 3 IPPV in the delivery room.

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	34/34	26/26		29.47%	1[0.94,1.07]
Escrig 2008	13/19	18/23		16.04%	0.87[0.6,1.27]
Kapadia 2013	29/44	30/44		29.55%	0.97[0.72,1.3]
Kumar 2014	3/6	9/12		5.91%	0.67[0.28,1.58]
Wang 2008	16/18	22/23		19.03%	0.93[0.77,1.12]
Total (95% CI)	**121**	**128**		**100%**	**0.94[0.83,1.06]**
Total events: 95 (Lower oxygen), 105 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=4.6, df=4(P=0.33); I^2=13.13%					
Test for overall effect: Z=1.06(P=0.29)					

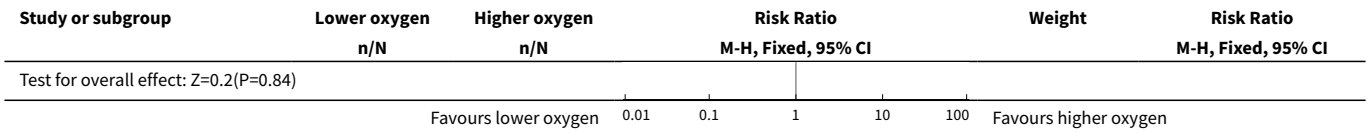


Favours lower oxygen — Favours higher oxygen

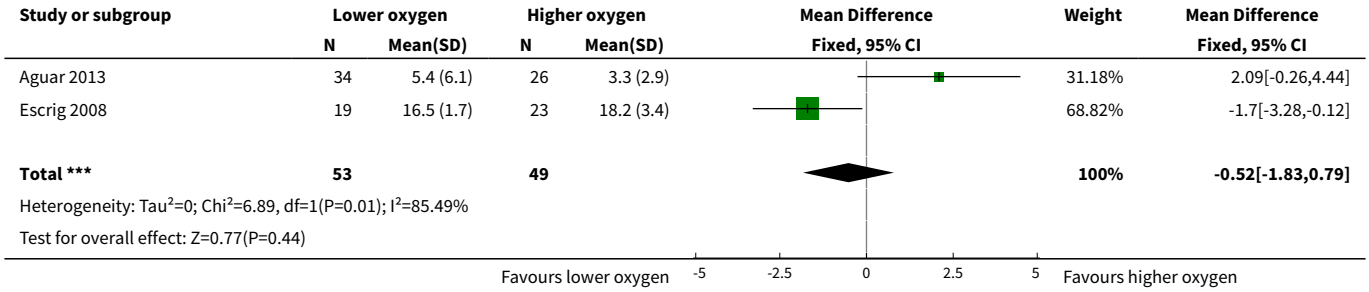
Analysis 1.4. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 4 Intubation in the delivery room.

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	11/34	5/26		3.77%	1.68[0.67,4.25]
Escrig 2008	9/19	12/23		7.23%	0.91[0.49,1.68]
Kapadia 2013	9/44	17/44		11.32%	0.53[0.27,1.06]
Kumar 2014	2/6	8/12		3.55%	0.5[0.15,1.66]
Oei 2016	43/144	41/143		27.39%	1.04[0.73,1.49]
Rabi 2011	10/34	9/34		5.99%	1.11[0.52,2.39]
Rook 2014	31/99	28/94		19.12%	1.05[0.69,1.61]
Vento 2009	21/37	25/41		15.79%	0.93[0.64,1.35]
Wang 2008	10/18	10/23		5.84%	1.28[0.69,2.38]
Total (95% CI)	**435**	**440**		**100%**	**0.98[0.82,1.18]**
Total events: 146 (Lower oxygen), 155 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=6.71, df=8(P=0.57); I^2=0%					

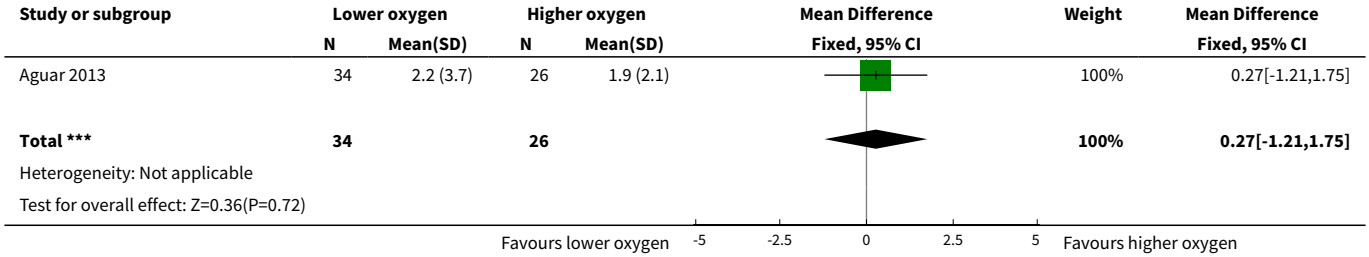
Favours lower oxygen — Favours higher oxygen



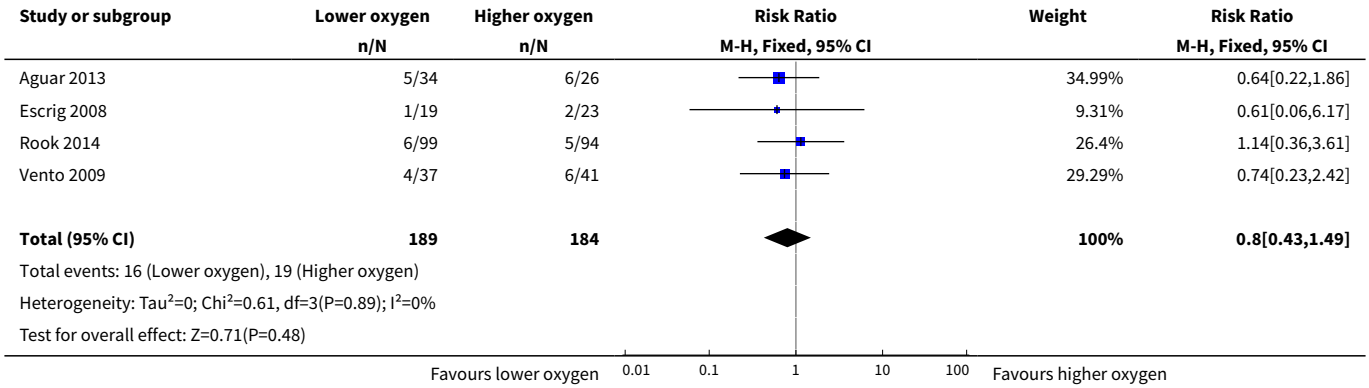
Analysis 1.5. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 5 Time to reach desired oxygen saturation target.



Analysis 1.6. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 6 Time to reach heart rate > 100 bpm (not prespecified).

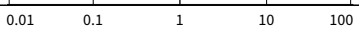


Analysis 1.7. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 7 Retinopathy of prematurity.



Analysis 1.8. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 8 Severe retinopathy of prematurity (≥ stage 3).

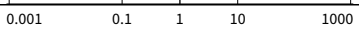
Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	2/34	0/26		4.14%	3.86[0.19,77.05]
Kapadia 2013	1/44	4/44		29.32%	0.25[0.03,2.15]
Kumar 2014	0/6	1/12		7.7%	0.62[0.03,13.28]
Oei 2016	4/144	8/143		58.85%	0.5[0.15,1.61]
Total (95% CI)	**228**	**225**		**100%**	**0.57[0.24,1.36]**
Total events: 7 (Lower oxygen), 13 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=2.19, df=3(P=0.53); I^2=0%					
Test for overall effect: Z=1.26(P=0.21)					



Favours lower oxygen — Favours higher oxygen

Analysis 1.9. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 9 Intraventricular haemorrhage.

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	10/34	8/26		43.02%	0.96[0.44,2.08]
Kumar 2014	0/6	2/12		8.3%	0.37[0.02,6.71]
Rook 2014	8/99	10/94		48.68%	0.76[0.31,1.84]
Total (95% CI)	**139**	**132**		**100%**	**0.81[0.46,1.44]**
Total events: 18 (Lower oxygen), 20 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=2(P=0.79); I^2=0%					
Test for overall effect: Z=0.71(P=0.48)					



Favours lower oxygen — Favours higher oxygen

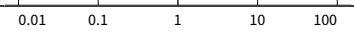
Analysis 1.10. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 10 Severe intraventricular haemorrhage (grade 3 or 4).

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	3/34	3/26		17.68%	0.76[0.17,3.48]
Escrig 2008	2/19	4/23		18.82%	0.61[0.12,2.95]
Kapadia 2013	1/44	1/44		5.2%	1[0.06,15.49]
Oei 2016	2/144	6/143		31.32%	0.33[0.07,1.61]
Vento 2009	7/37	5/41		24.67%	1.55[0.54,4.47]
Wang 2008	2/18	0/23		2.3%	6.32[0.32,123.86]
Total (95% CI)	**296**	**300**		**100%**	**0.93[0.51,1.71]**
Total events: 17 (Lower oxygen), 19 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=4.47, df=5(P=0.48); I^2=0%					
Test for overall effect: Z=0.22(P=0.82)					

Favours lower oxygen — Favours higher oxygen

Analysis 1.11. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 11 Periventricular leukomalacia.

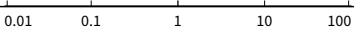
Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Escrig 2008	1/19	1/23		37.62%	1.21[0.08,18.09]
Kapadia 2013	0/44	1/44		62.38%	0.33[0.01,7.97]
Total (95% CI)	**63**	**67**		**100%**	**0.66[0.09,4.73]**
Total events: 1 (Lower oxygen), 2 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=0.37, df=1(P=0.54); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					



Favours lower oxygen — Favours higher oxygen

Analysis 1.12. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 12 Necrotising enterocolitis.

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	3/34	1/26		6.31%	2.29[0.25,20.8]
Escrig 2008	0/19	1/23		7.6%	0.4[0.02,9.29]
Kapadia 2013	1/44	6/44		33.43%	0.17[0.02,1.33]
Kumar 2014	1/6	4/12		14.86%	0.5[0.07,3.55]
Oei 2016	5/144	1/143		5.59%	4.97[0.59,41.97]
Rook 2014	4/99	3/94		17.15%	1.27[0.29,5.51]
Vento 2009	2/37	1/41		5.29%	2.22[0.21,23.45]
Wang 2008	1/18	2/23		9.78%	0.64[0.06,6.5]
Total (95% CI)	**401**	**406**		**100%**	**0.98[0.51,1.87]**
Total events: 17 (Lower oxygen), 19 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=7.06, df=7(P=0.42); I^2=0.88%					
Test for overall effect: Z=0.06(P=0.95)					



Favours lower oxygen — Favours higher oxygen

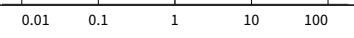
Analysis 1.13. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 13 Chronic lung disease (28 days' age).

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	10/34	6/26		28.57%	1.27[0.53,3.05]
Kapadia 2013	8/44	17/44		71.43%	0.47[0.23,0.98]
Total (95% CI)	**78**	**70**		**100%**	**0.7[0.41,1.21]**
Total events: 18 (Lower oxygen), 23 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=2.95, df=1(P=0.09); I^2=66.05%					
Test for overall effect: Z=1.28(P=0.2)					

Favours lower oxygen — Favours higher oxygen

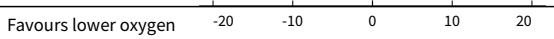
Analysis 1.14. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 14 Chronic lung disease (36 weeks' corrected age).

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	10/30	5/20		5.25%	1.33[0.54,3.32]
Escrig 2008	3/19	5/23		3.96%	0.73[0.2,2.65]
Kapadia 2013	3/44	11/44		9.63%	0.27[0.08,0.91]
Kumar 2014	1/6	6/12		3.5%	0.33[0.05,2.18]
Oei 2016	34/144	40/143		35.12%	0.84[0.57,1.25]
Rabi 2011	18/33	19/32		16.88%	0.92[0.6,1.4]
Rook 2014	23/99	14/94		12.57%	1.56[0.85,2.85]
Vento 2009	6/37	13/41		10.79%	0.51[0.22,1.21]
Wang 2008	7/18	3/23		2.3%	2.98[0.89,9.94]
Total (95% CI)	**430**	**432**		**100%**	**0.91[0.72,1.14]**
Total events: 105 (Lower oxygen), 116 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=14.42, df=8(P=0.07); I^2=44.51%					
Test for overall effect: Z=0.83(P=0.4)					



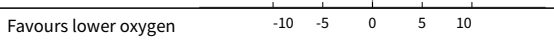
Analysis 1.15. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 15 Duration of respiratory support (mechanical ventilation or CPAP) (days from birth).

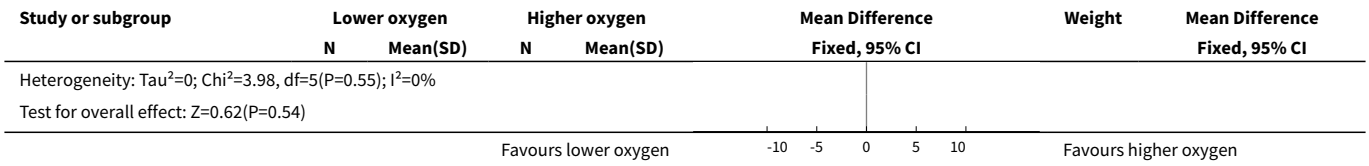
Study or subgroup	Lower oxygen N	Lower oxygen Mean(SD)	Higher oxygen N	Higher oxygen Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Aguar 2013	34	9.9 (8.8)	26	8.9 (5.8)		8.91%	1.06[-2.63,4.75]
Oei 2016	129	21.6 (2.2)	137	35.3 (6.5)		91.09%	-13.7[-14.85,-12.55]
Total ***	**163**		**163**			**100%**	**-12.39[-13.49,-11.29]**
Heterogeneity: Tau^2=0; Chi^2=56.1, df=1(P<0.0001); I^2=98.22%							
Test for overall effect: Z=22.06(P<0.0001)							



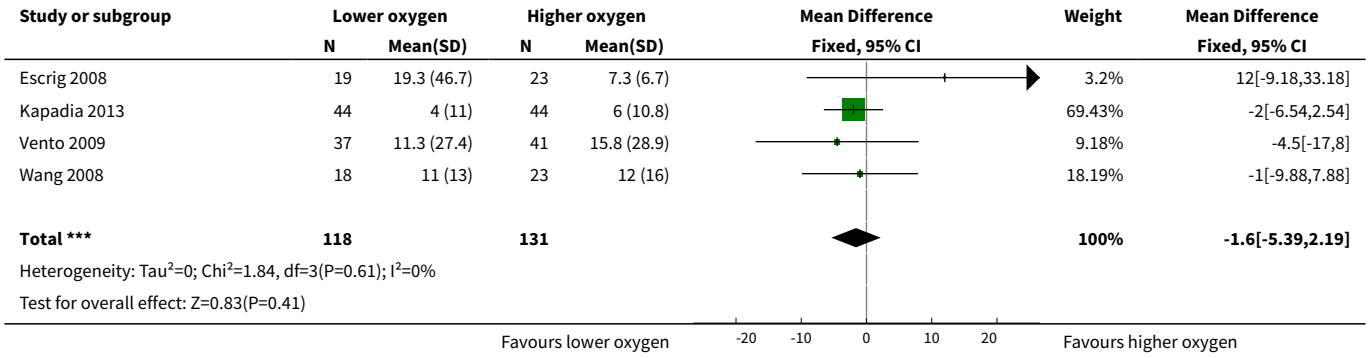
Analysis 1.16. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 16 Duration of respiratory support (mechanical ventilation) (days from birth).

Study or subgroup	Lower oxygen N	Lower oxygen Mean(SD)	Higher oxygen N	Higher oxygen Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Escrig 2008	19	25 (47.4)	23	29.8 (60)		0.35%	-4.75[-37.24,27.74]
Kapadia 2013	44	3 (16)	44	8 (24)		5.14%	-5[-13.52,3.52]
Rabi 2011	34	6.9 (11.8)	34	5.5 (10.3)		13.52%	1.4[-3.86,6.66]
Rook 2014	99	2 (8.9)	94	1 (6.7)		76.13%	1[-1.22,3.22]
Vento 2009	37	19.3 (37.8)	41	35.5 (65.2)		0.68%	-16.25[-39.63,7.13]
Wang 2008	18	2 (16.8)	23	1 (13.3)		4.16%	1[-8.48,10.48]
Total ***	**251**		**259**			**100%**	**0.61[-1.33,2.54]**

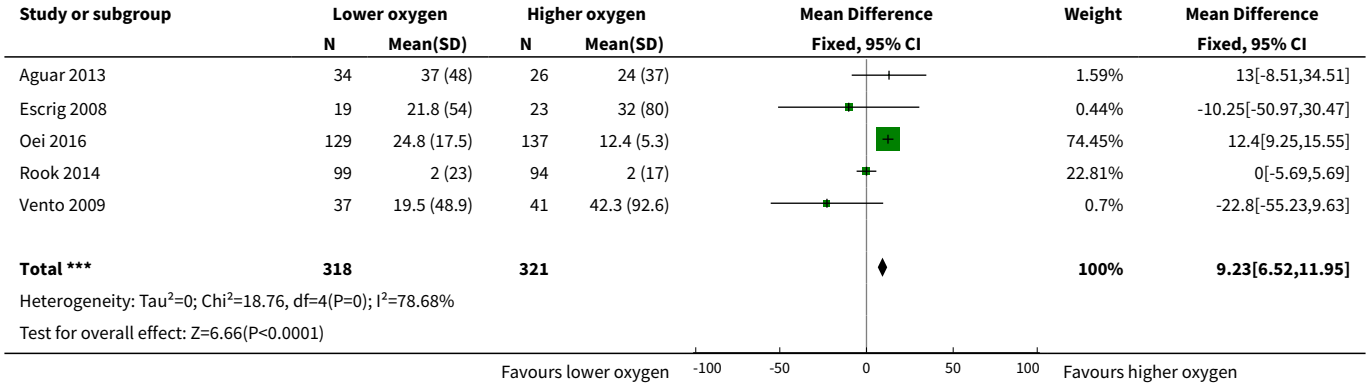




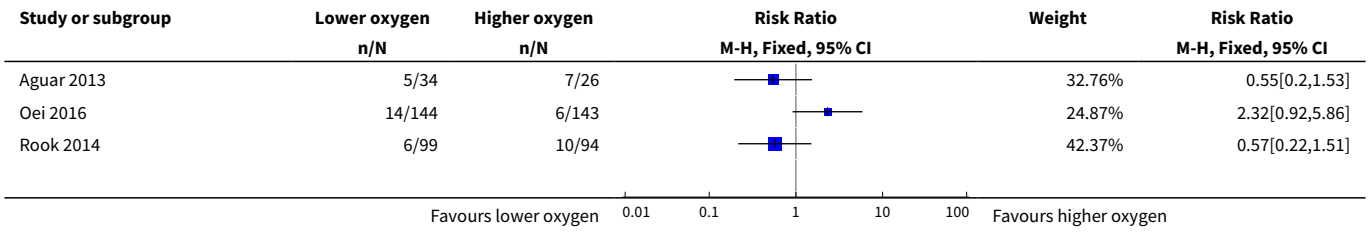
Analysis 1.17. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 17 Duration of respiratory support (CPAP) (days from birth).

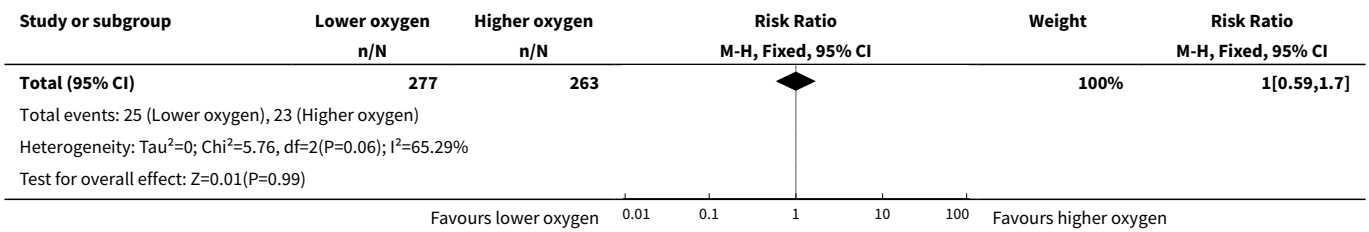


Analysis 1.18. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 18 Duration of supplemental oxygen administration.

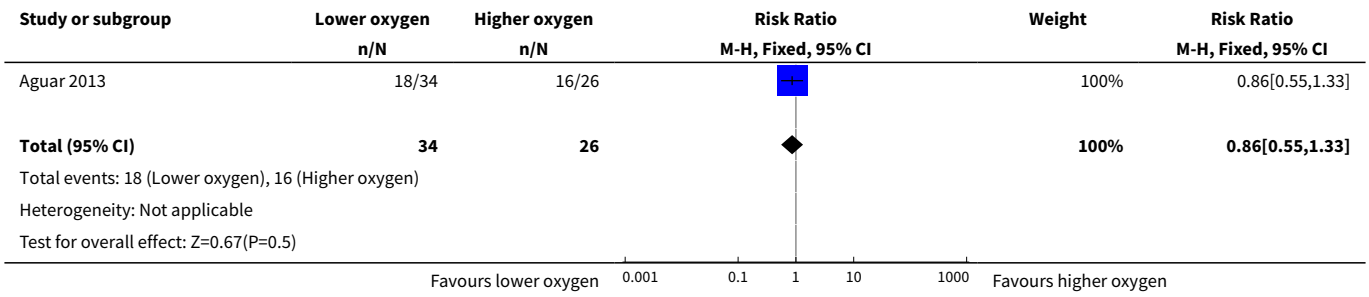


Analysis 1.19. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 19 Mortality to follow up (> 18 months).

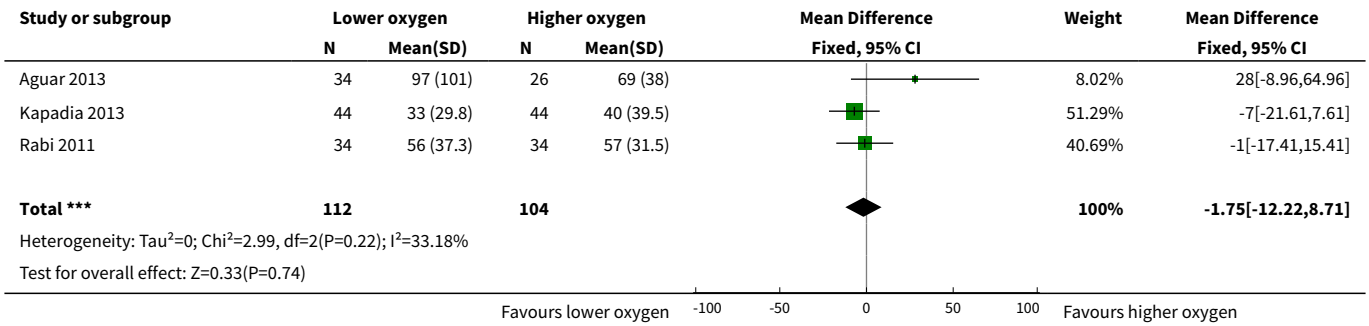




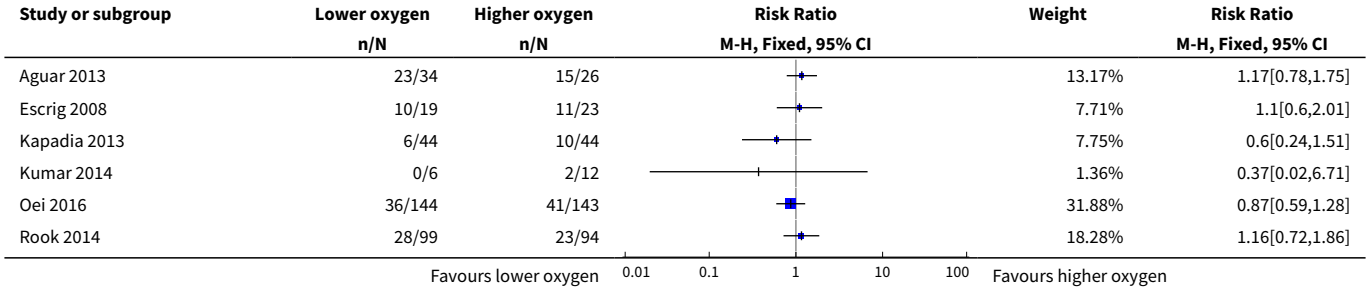
Analysis 1.20. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 20 Postnatal growth failure (weight < 10th percentile at discharge).

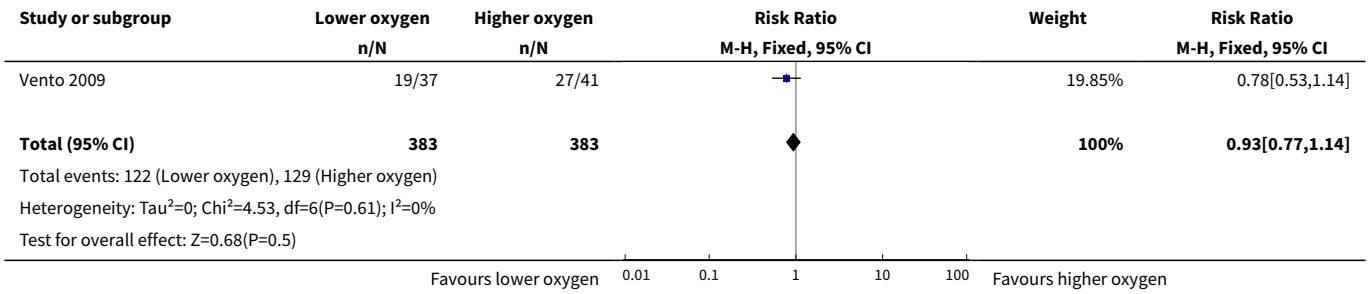


Analysis 1.21. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 21 Duration of hospitalisation (days).



Analysis 1.22. Comparison 1 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration, Outcome 22 Patent ductus arteriosus (not prespecified).





Comparison 2. Lower versus higher oxygen concentration subgrouped by FiO_2

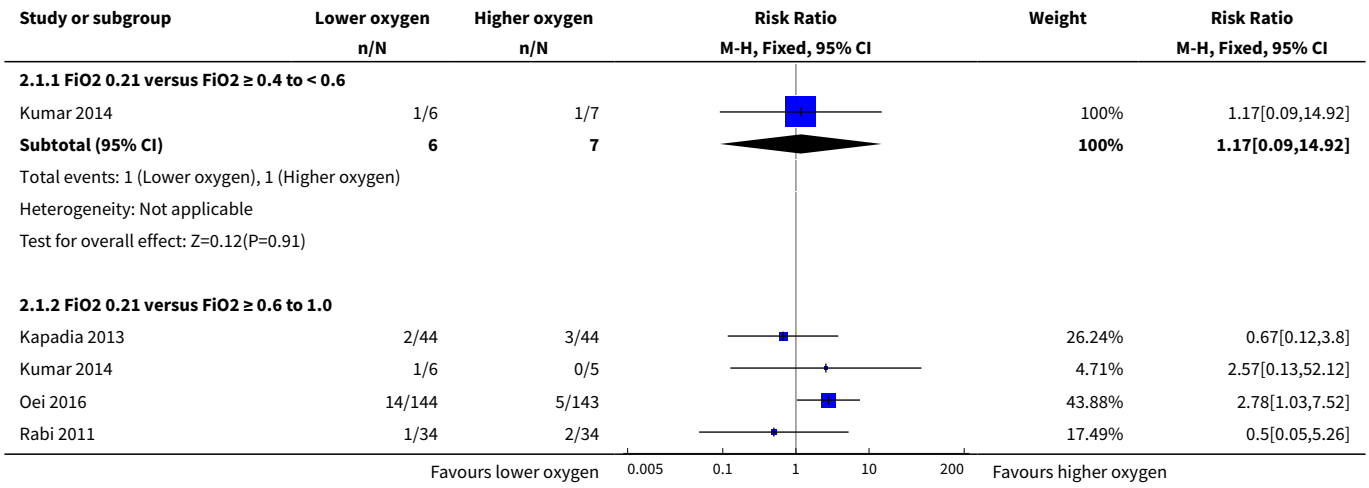
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality near term corrected age or discharge (latest reported) subgrouped by inspired oxygen concentration	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 FiO_2 0.21 versus $FiO_2 \geq 0.4$ to < 0.6	1	13	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.09, 14.92]
1.2 FiO_2 0.21 versus $FiO_2 \geq 0.6$ to 1.0	5	495	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [0.84, 3.46]
1.3 $FiO_2 \geq 0.3$ to < 0.4 versus $FiO_2 \geq 0.6$ to 1.0	5	412	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.42, 1.32]
2 Neurodevelopmental disability	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.2 $FiO_2 \geq 0.3$ to < 0.4 versus $FiO_2 \geq 0.6$ to 1.0	2	208	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.49, 1.35]
3 IPPV in the delivery room	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 FiO_2 0.21 versus $FiO_2 \geq 0.4$ to < 0.6	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.7 [0.28, 1.77]
3.2 FiO_2 0.21 versus $FiO_2 \geq 0.6$ to 1.0	3	140	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.12]
3.3 $FiO_2 \geq 0.3$ to < 0.4 versus $FiO_2 \geq 0.6$ to 1.0	2	102	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.09]
4 Intubation in the delivery room	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 FiO_2 0.21 versus $FiO_2 \geq 0.4$ to < 0.6	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.16, 2.14]
4.2 FiO_2 0.21 versus $FiO_2 \geq 0.6$ to 1.0	5	495	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.21]
4.3 $FiO_2 \geq 0.3$ to < 0.4 versus $FiO_2 \geq 0.6$ to 1.0	4	373	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.81, 1.34]
5 Time to reach desired oxygen saturation target	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

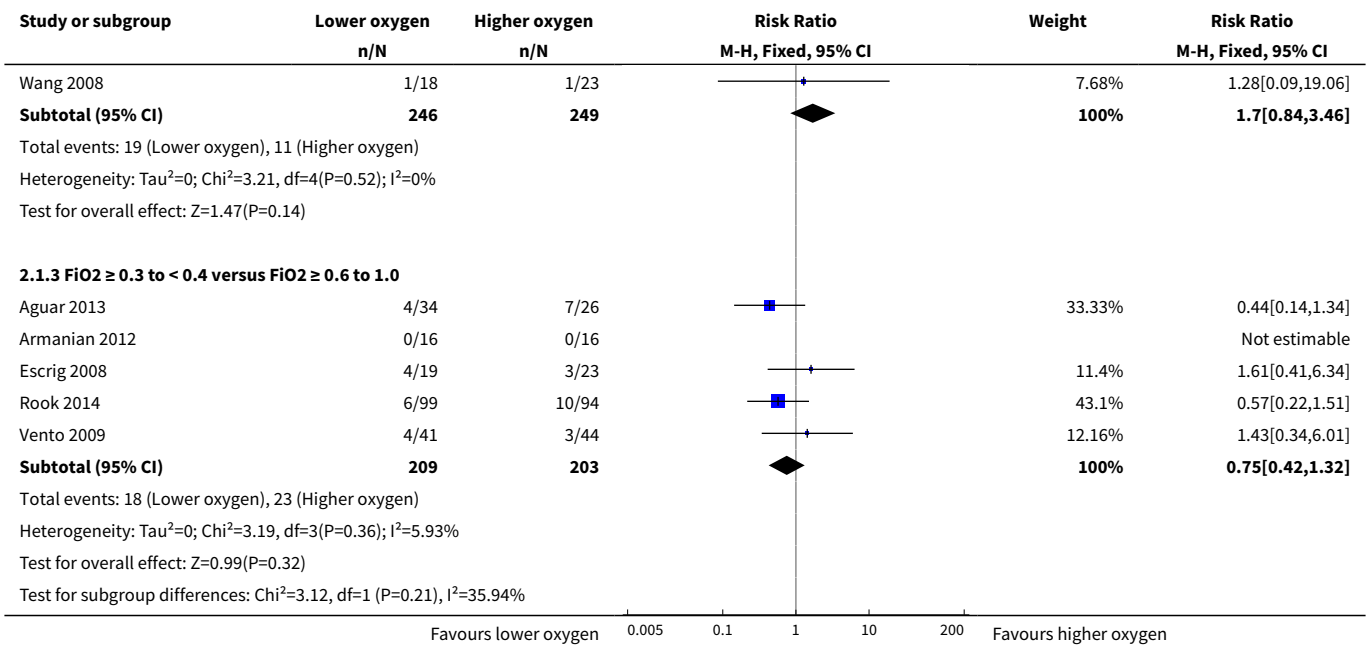
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 $FiO_2 \geq 0.3$ to < 0.4 versus $FiO_2 \geq 0.6$ to 1.0	2	102	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-1.83, 0.79]
6 Time to reach heart rate > 100 bpm (not prespecified)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 $FiO_2 \geq 0.3$ to < 0.4 versus $FiO_2 \geq 0.6$ to 1.0	1	60	Mean Difference (IV, Fixed, 95% CI)	0.27 [-1.21, 1.75]
7 Retinopathy of prematurity	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 $FiO_2 \geq 0.3$ to < 0.4 versus $FiO_2 \geq 0.6$ to 1.0	4	373	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.43, 1.49]
8 Severe retinopathy of prematurity (≥ stage 3)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 FiO_2 0.21 versus $FiO_2 \geq 0.4$ to < 0.6	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 FiO_2 0.21 versus $FiO_2 \geq 0.6$ to 1.0	3	386	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.15, 1.05]
8.3 $FiO_2 \geq 0.3$ to < 0.4 versus $FiO_2 \geq 0.6$ to 1.0	1	60	Risk Ratio (M-H, Fixed, 95% CI)	3.86 [0.19, 77.05]
9 Intraventricular haemorrhage	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 FiO_2 0.21 versus $FiO_2 \geq 0.4$ to < 0.6	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 FiO_2 0.21 versus $FiO_2 \geq 0.6$ to 1.0	1	11	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.01, 2.92]
9.3 $FiO_2 \geq 0.3$ to < 0.4 versus $FiO_2 \geq 0.6$ to 1.0	2	253	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.47, 1.53]
10 Severe intraventricular haemorrhage (grade 3 or 4)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 FiO_2 0.21 versus $FiO_2 \geq 0.6$ to 1.0	3	416	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.27, 2.24]
10.2 $FiO_2 \geq 0.3$ to < 0.4 versus $FiO_2 \geq 0.6$ to 1.0	3	180	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.49, 2.18]
11 Periventricular leukomalacia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 FiO_2 0.21 versus $FiO_2 \geq 0.6$ to 1.0	1	88	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.97]
11.2 $FiO_2 \geq 0.3$ to < 0.4 versus $FiO_2 \geq 0.6$ to 1.0	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.08, 18.09]
12 Necrotising enterocolitis	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 FiO_2 0.21 versus $FiO_2 \geq 0.4$ to < 0.6	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.07, 4.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2 FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0	4	434	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.31, 1.76]
12.3 FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0	4	373	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.52, 3.78]
13 Chronic lung disease (28 days age)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0	1	88	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.23, 0.98]
13.2 FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.53, 3.05]
14 Chronic lung disease (36 weeks' corrected age)	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 FiO_2 0.21 versus FiO_2 ≥ 0.4 to < 0.6	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.05, 2.83]
14.2 FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0	5	492	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.63, 1.09]
14.3 FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0	4	363	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.72, 1.60]
15 Duration of respiratory support (mechanical ventilation or CPAP) (days from birth)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.1 FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0	1	266	Mean Difference (IV, Fixed, 95% CI)	-13.70 [-14.85, -12.55]
15.2 FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0	1	60	Mean Difference (IV, Fixed, 95% CI)	1.06 [-2.63, 4.75]
16 Duration of respiratory support (mechanical ventilation) (days from birth)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
16.1 FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0	3	197	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-4.16, 3.93]
16.2 FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0	3	313	Mean Difference (IV, Fixed, 95% CI)	0.82 [-1.38, 3.02]
17 Duration of respiratory support (CPAP) (days from birth)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
17.1 FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0	2	129	Mean Difference (IV, Fixed, 95% CI)	-1.79 [-5.84, 2.25]
17.2 FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0	2	120	Mean Difference (IV, Fixed, 95% CI)	-0.24 [-11.00, 10.53]
18 Duration of supplemental oxygen administration	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18.1 FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0	1	266	Mean Difference (IV, Fixed, 95% CI)	12.4 [9.25, 15.55]

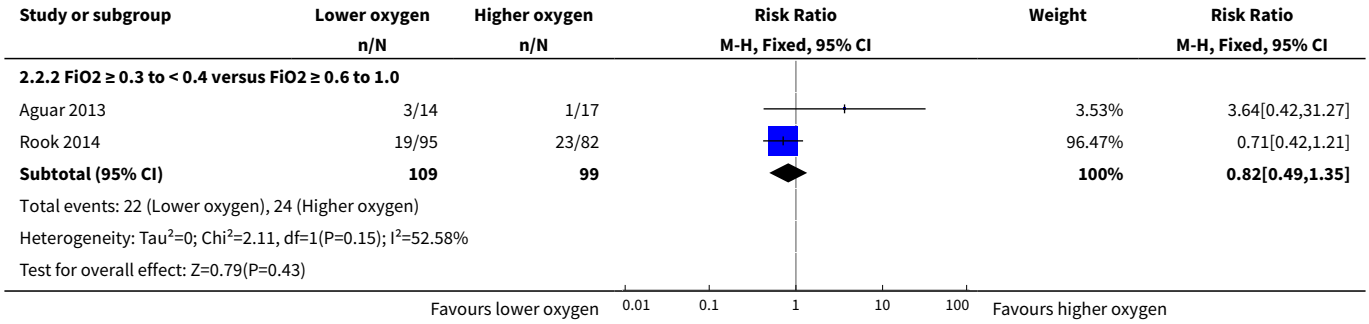
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.2 FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0	4	373	Mean Difference (IV, Fixed, 95% CI)	0.01 [-5.37, 5.38]
19 Mortality to follow up (> 18 months)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0	1	287	Risk Ratio (M-H, Fixed, 95% CI)	2.32 [0.92, 5.86]
19.2 FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0	2	253	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.28, 1.14]
20 Postnatal growth failure (weight < 10th percentile at discharge)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.55, 1.33]
21 Duration of hospitalisation (days)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
21.1 FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0	2	156	Mean Difference (IV, Fixed, 95% CI)	-4.35 [-15.26, 6.57]
21.2 FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0	1	60	Mean Difference (IV, Fixed, 95% CI)	28.0 [-8.96, 64.96]
22 Patent ductus arteriosus (not prespecified)	7	766	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.14]
22.1 FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0	3	393	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.57, 1.14]
22.2 FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0	4	373	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.82, 1.29]

Analysis 2.1. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 1 Mortality near term corrected age or discharge (latest reported) subgrouped by inspired oxygen concentration.

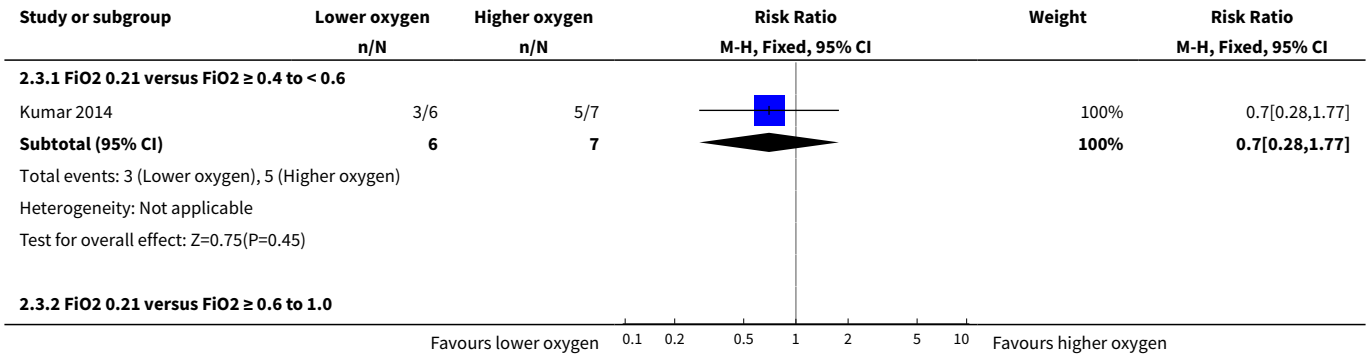


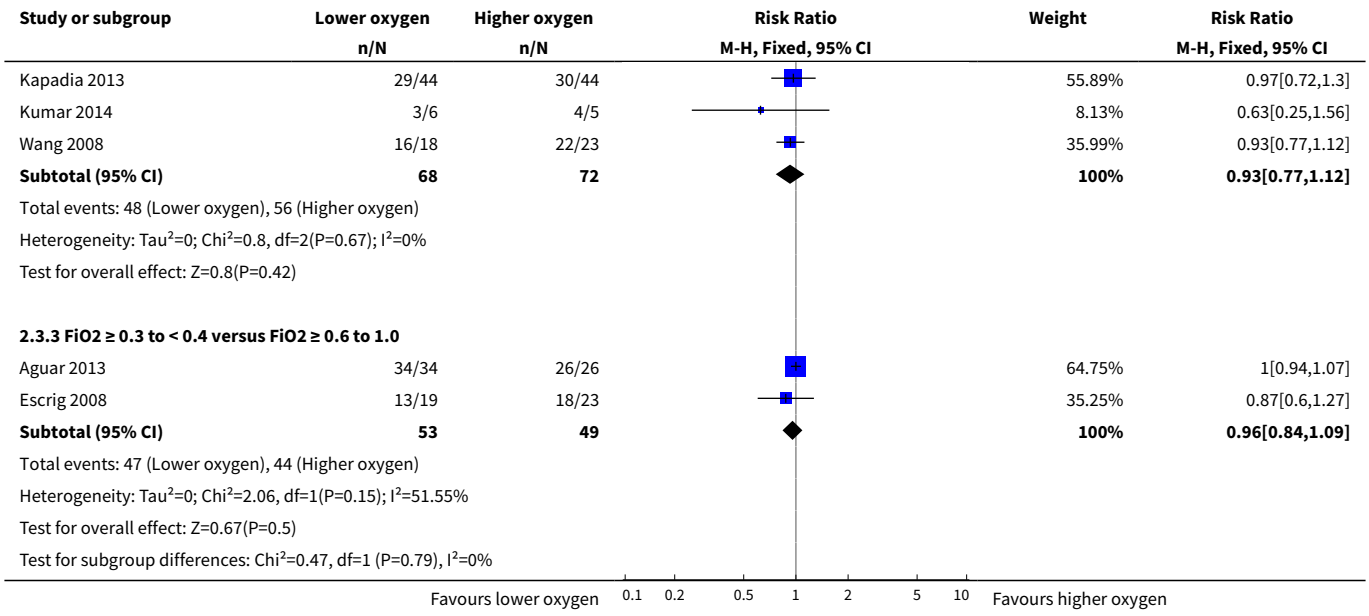


Analysis 2.2. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 2 Neurodevelopmental disability.

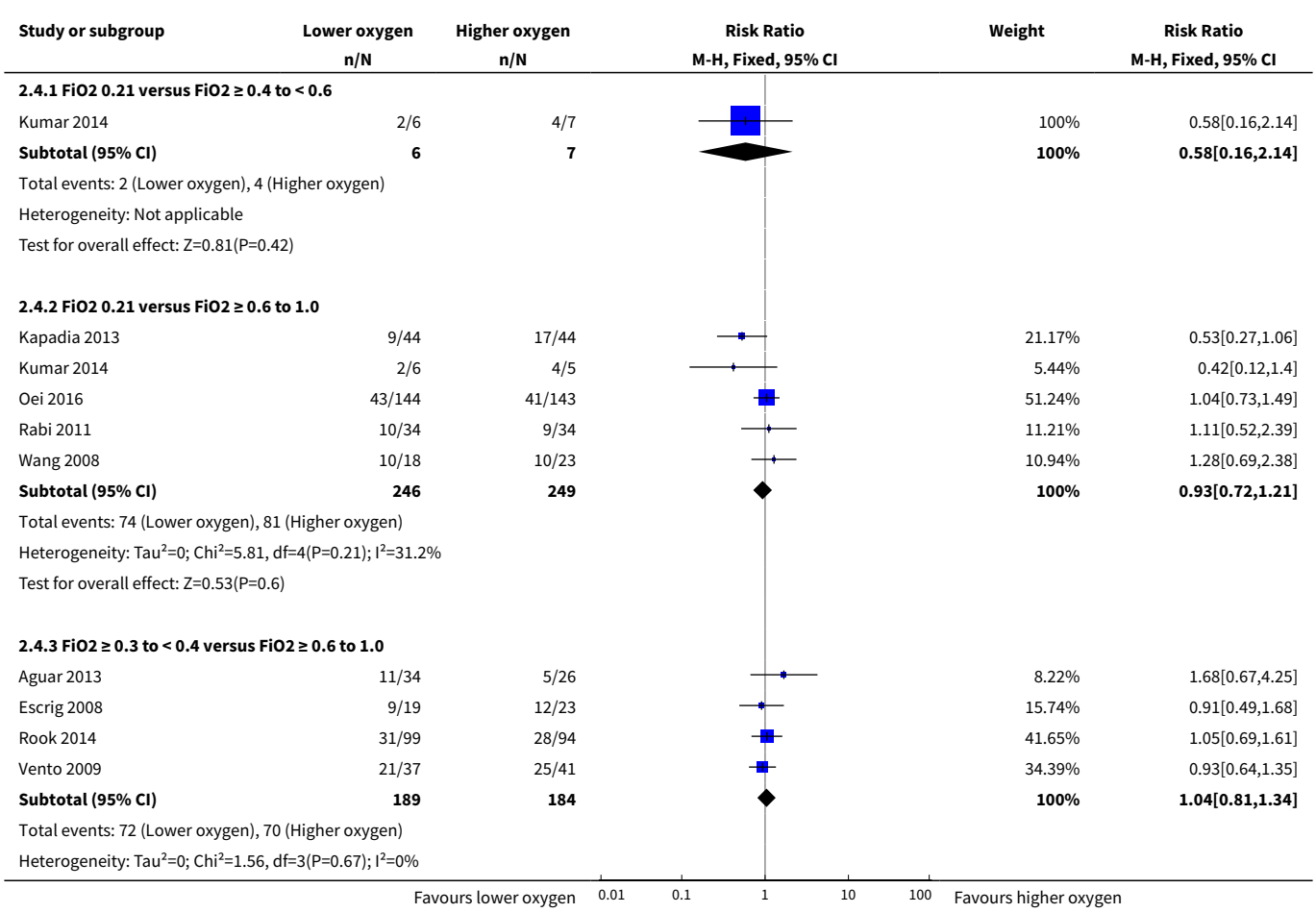


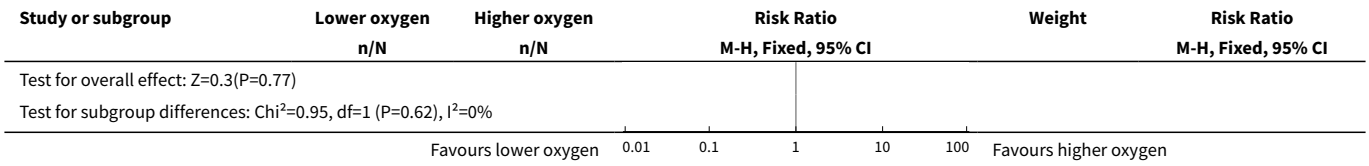
Analysis 2.3. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 3 IPPV in the delivery room.



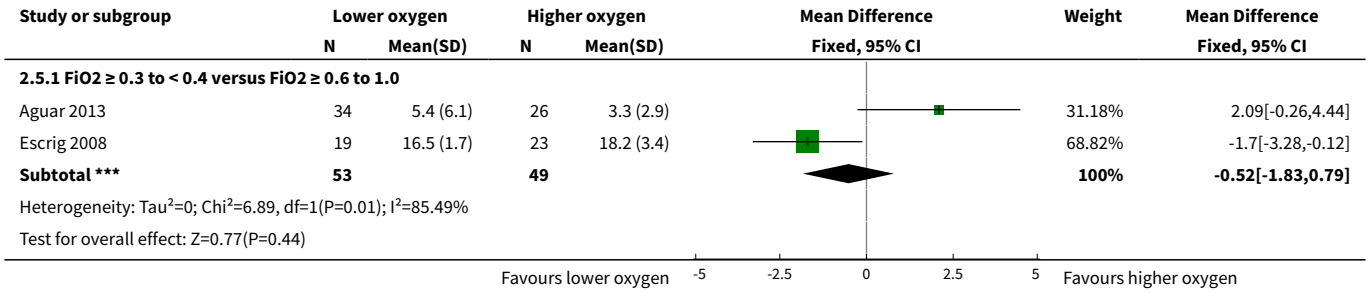


Analysis 2.4. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 4 Intubation in the delivery room.

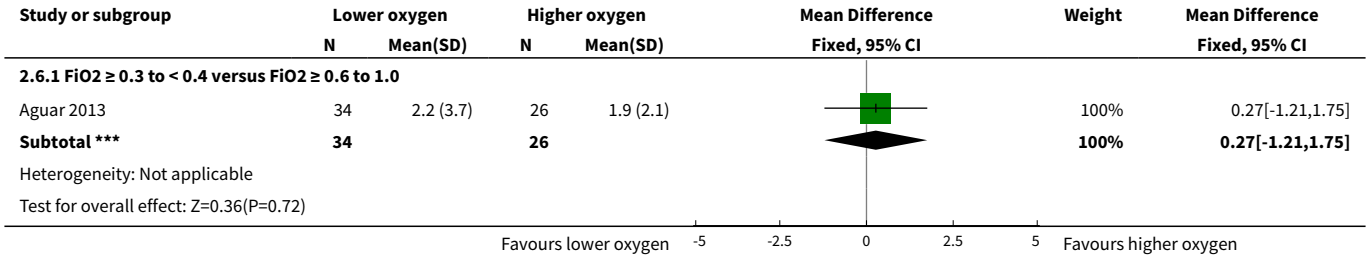




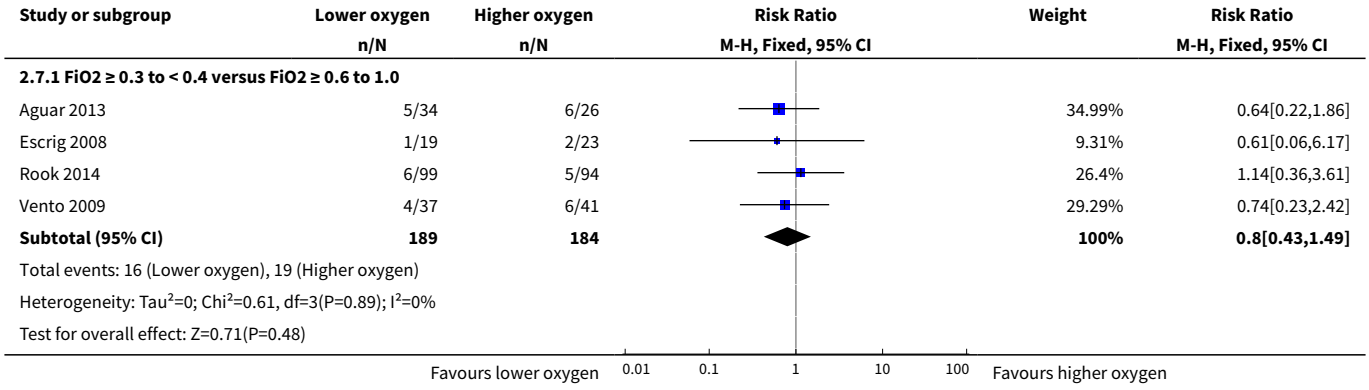
Analysis 2.5. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 5 Time to reach desired oxygen saturation target.



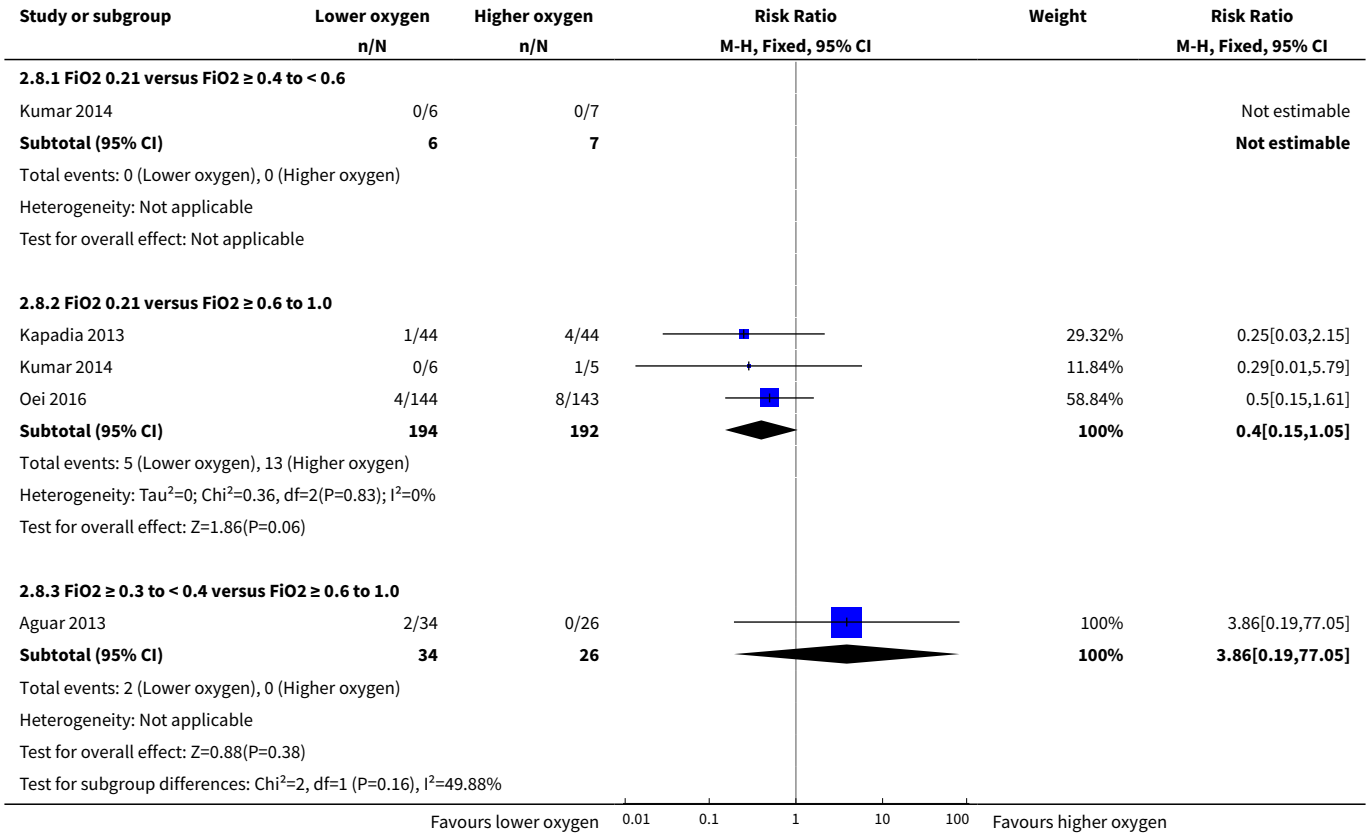
Analysis 2.6. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 6 Time to reach heart rate > 100 bpm (not prespecified).



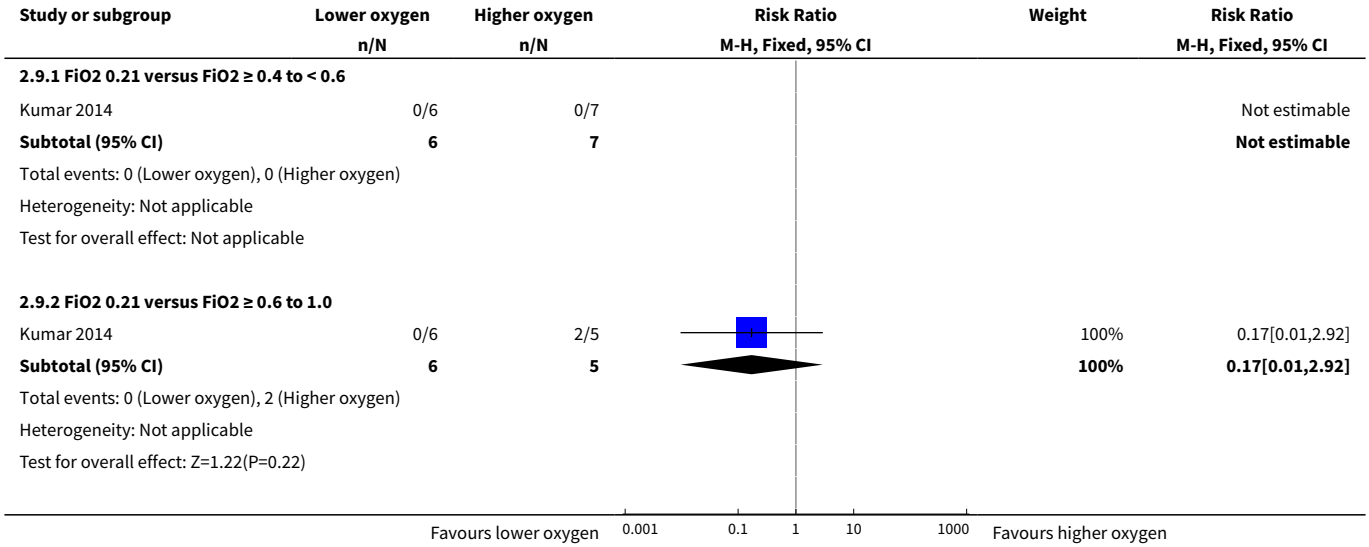
Analysis 2.7. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 7 Retinopathy of prematurity.

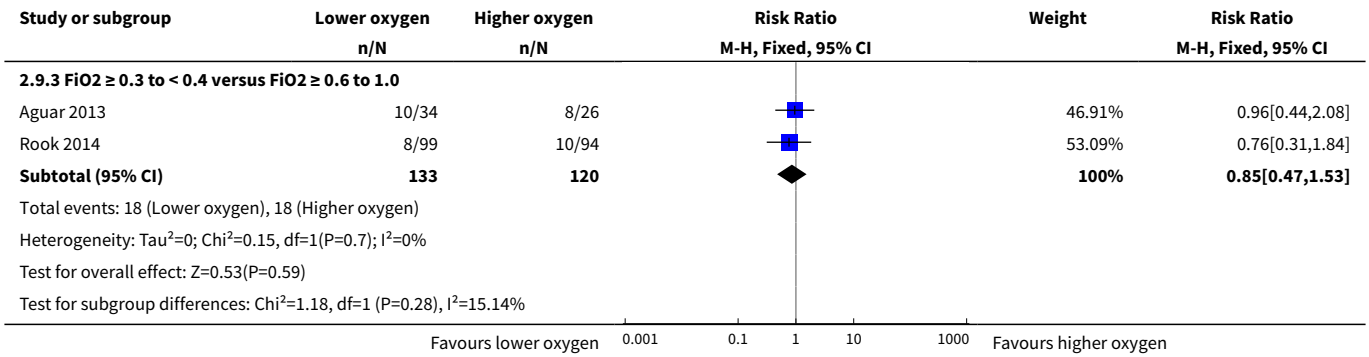


Analysis 2.8. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 8 Severe retinopathy of prematurity (≥ stage 3).

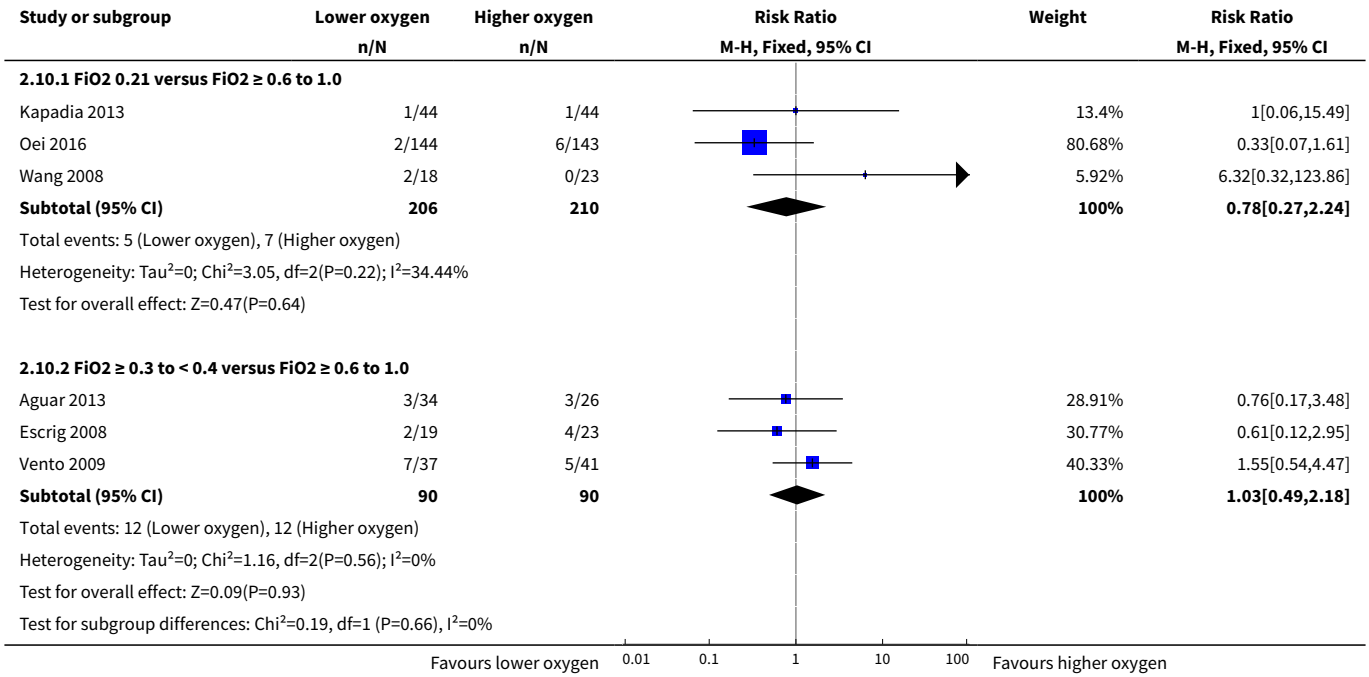


Analysis 2.9. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 9 Intraventricular haemorrhage.

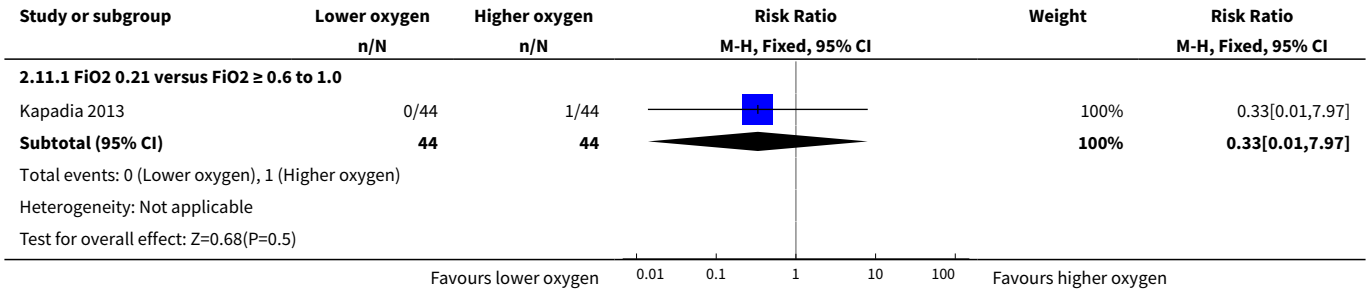


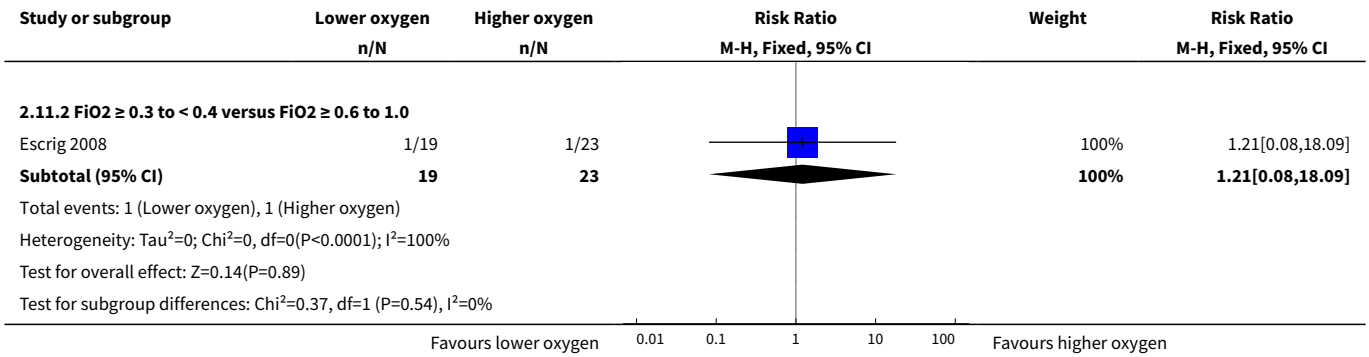


Analysis 2.10. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 10 Severe intraventricular haemorrhage (grade 3 or 4).

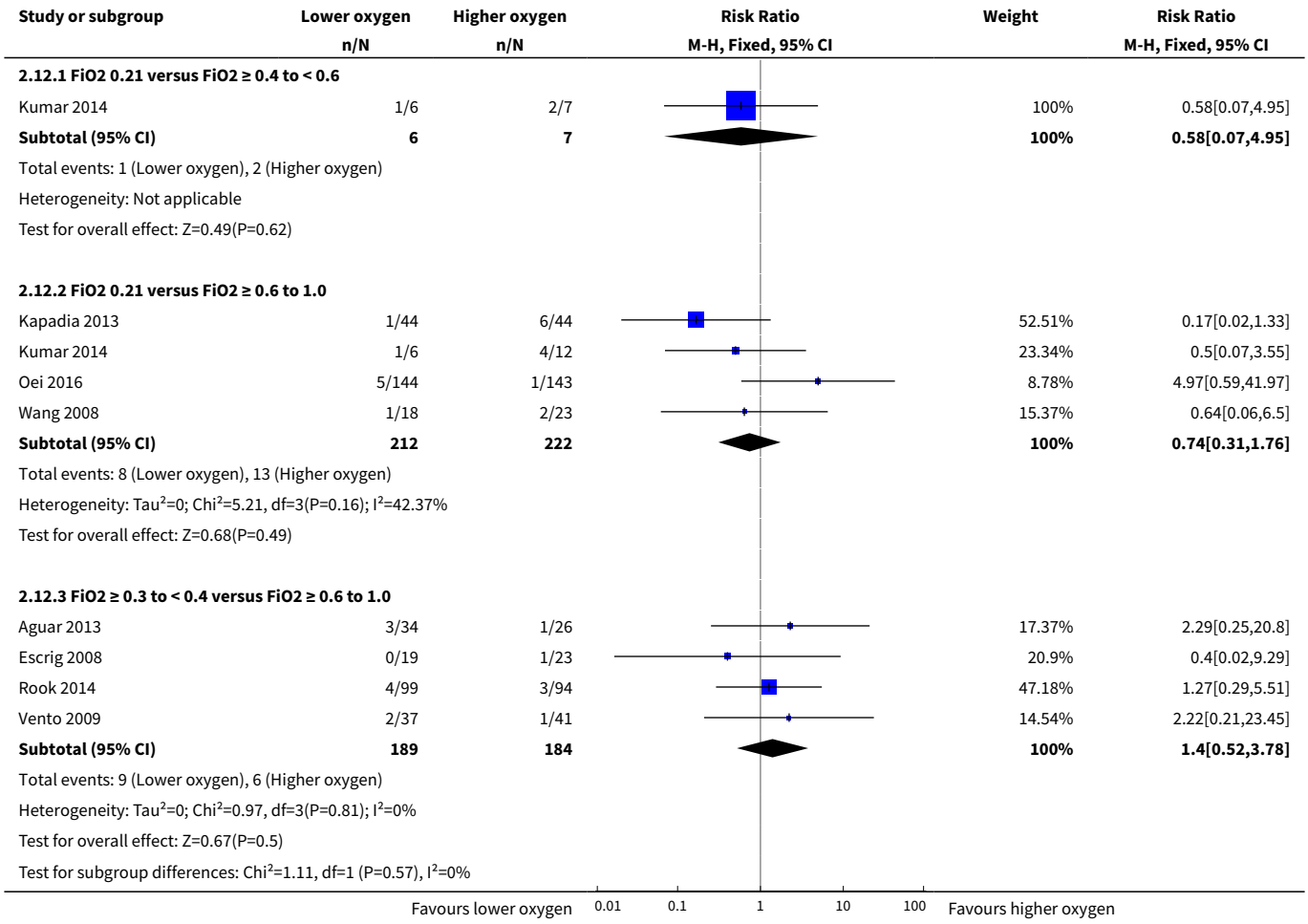


Analysis 2.11. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 11 Periventricular leukomalacia.

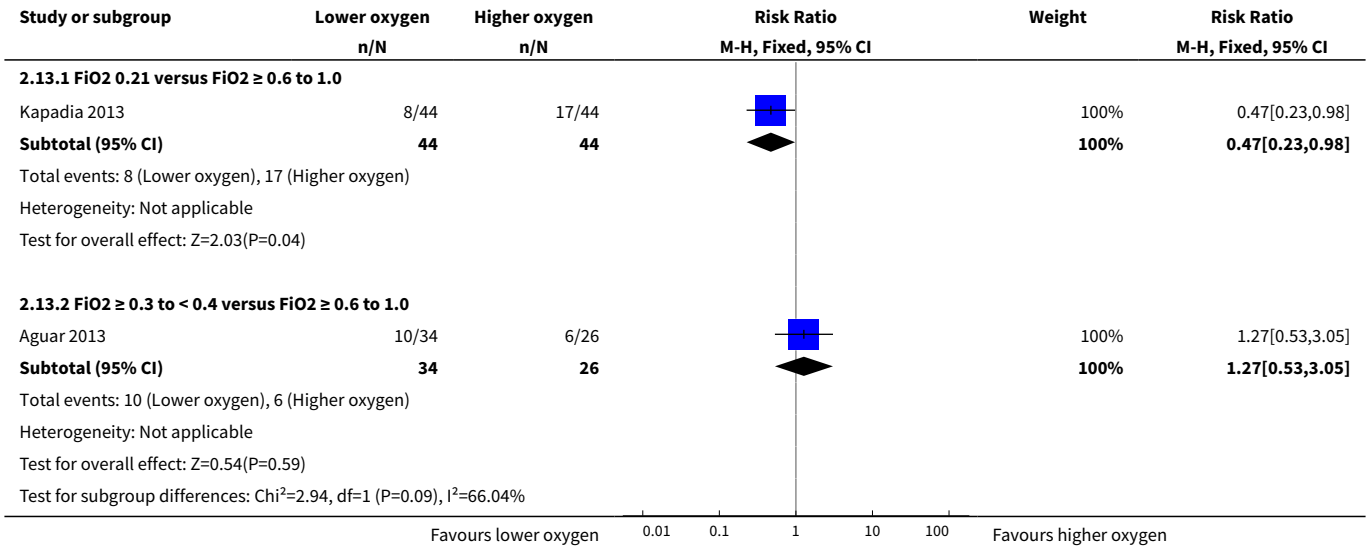




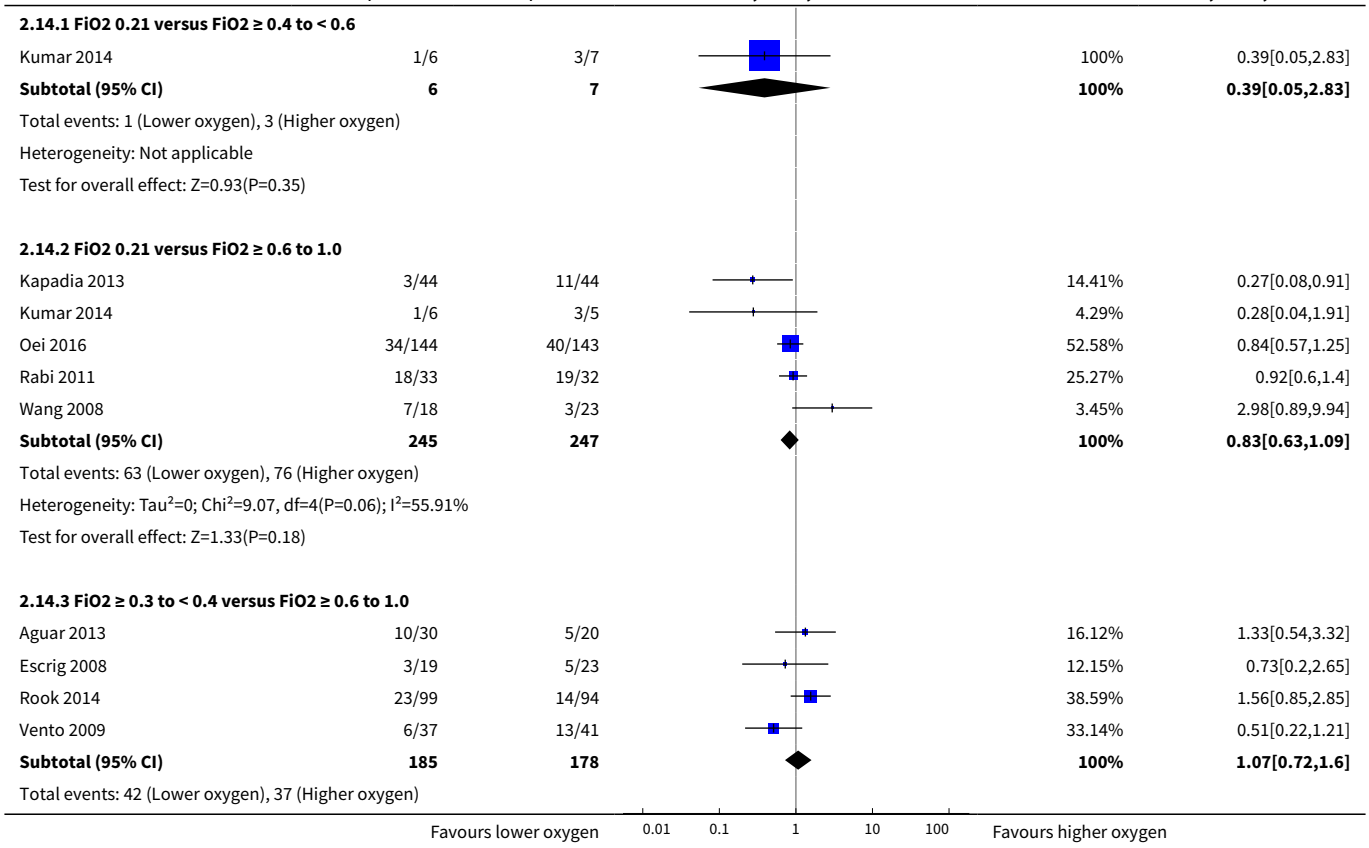
Analysis 2.12. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 12 Necrotising enterocolitis.

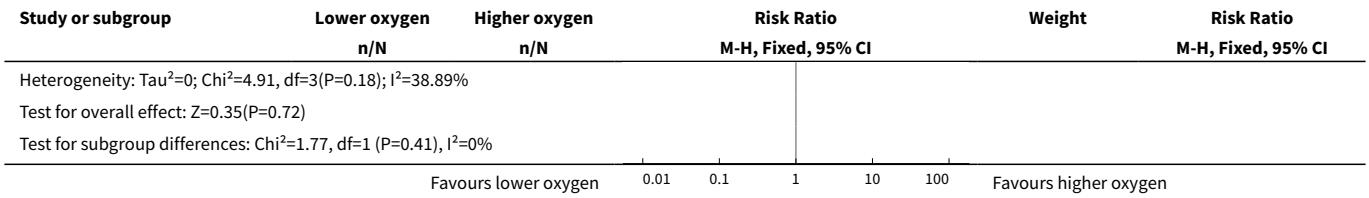


Analysis 2.13. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 13 Chronic lung disease (28 days age).

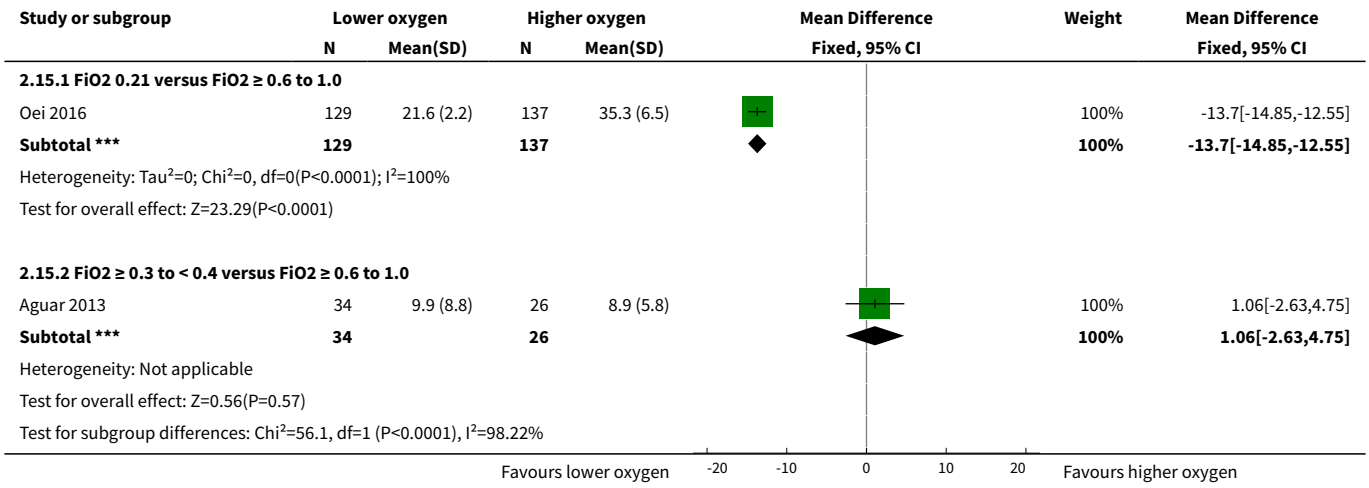


Analysis 2.14. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 14 Chronic lung disease (36 weeks' corrected age).

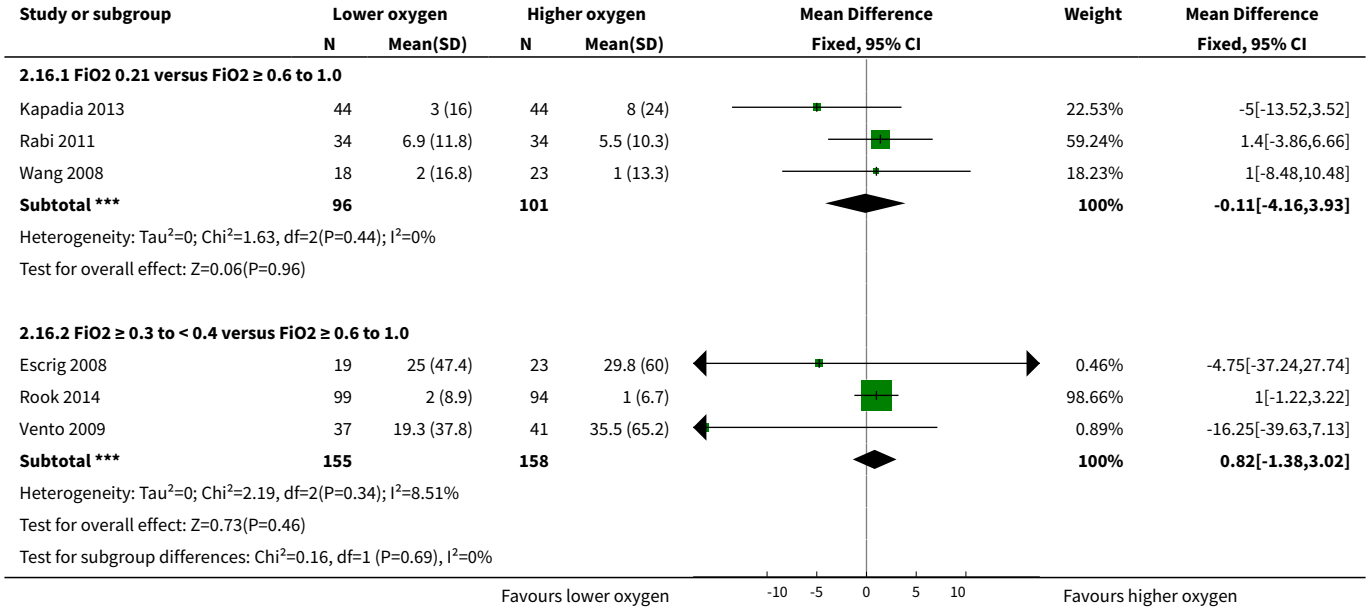




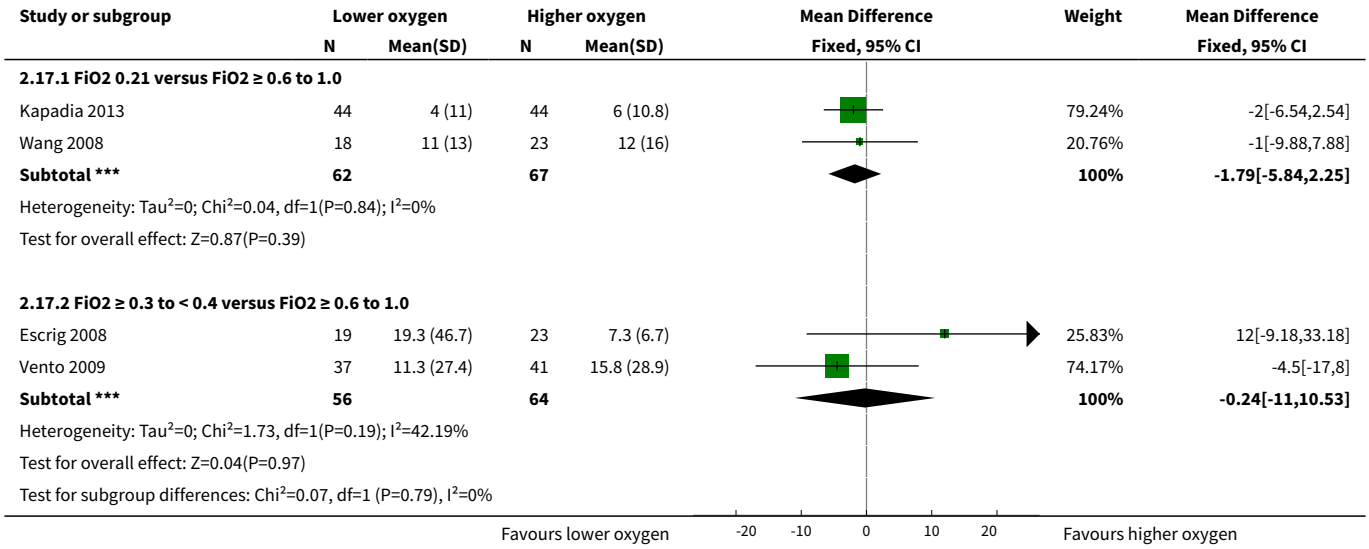
Analysis 2.15. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 15 Duration of respiratory support (mechanical ventilation or CPAP) (days from birth).



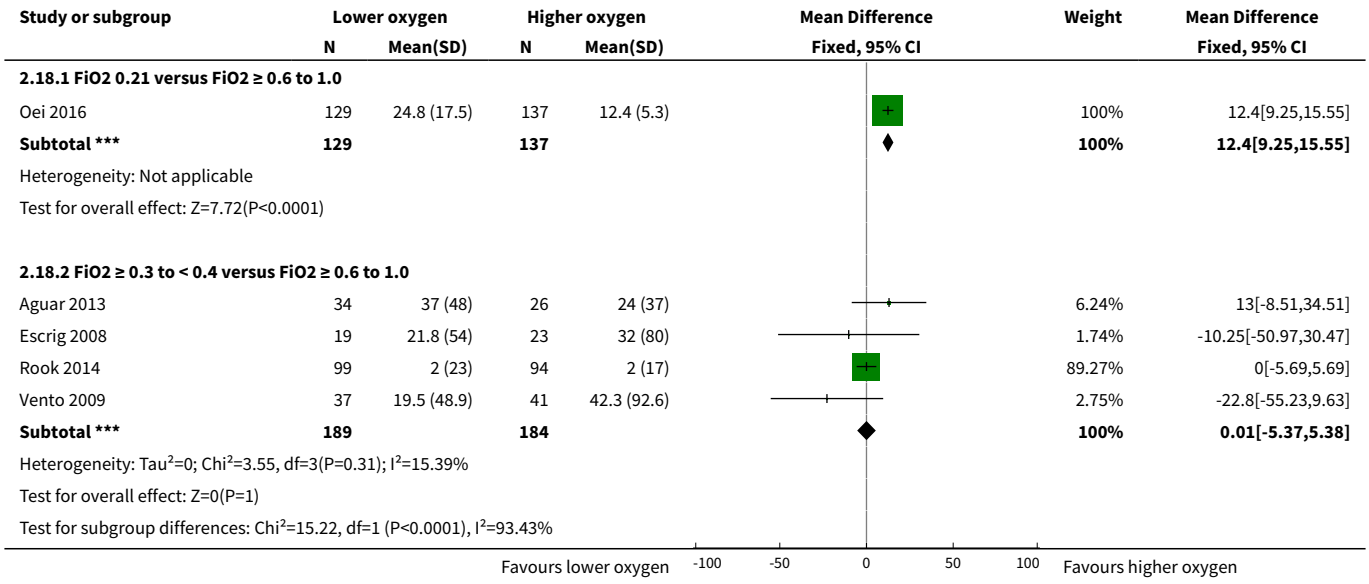
Analysis 2.16. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 16 Duration of respiratory support (mechanical ventilation) (days from birth).



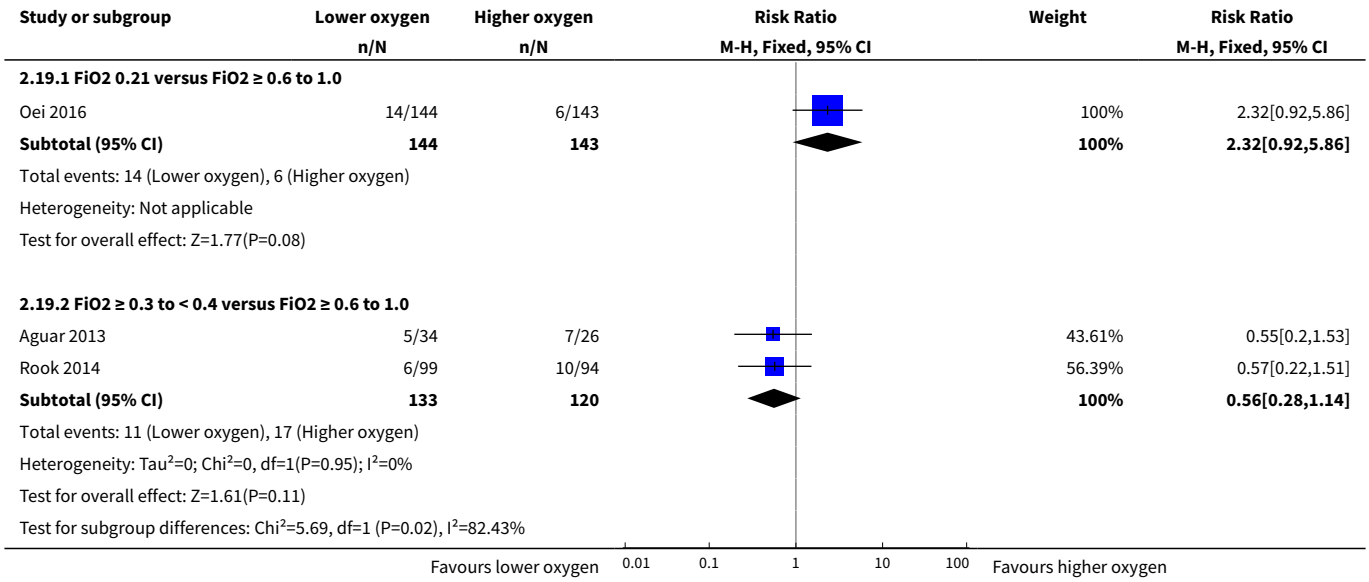
Analysis 2.17. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 17 Duration of respiratory support (CPAP) (days from birth).



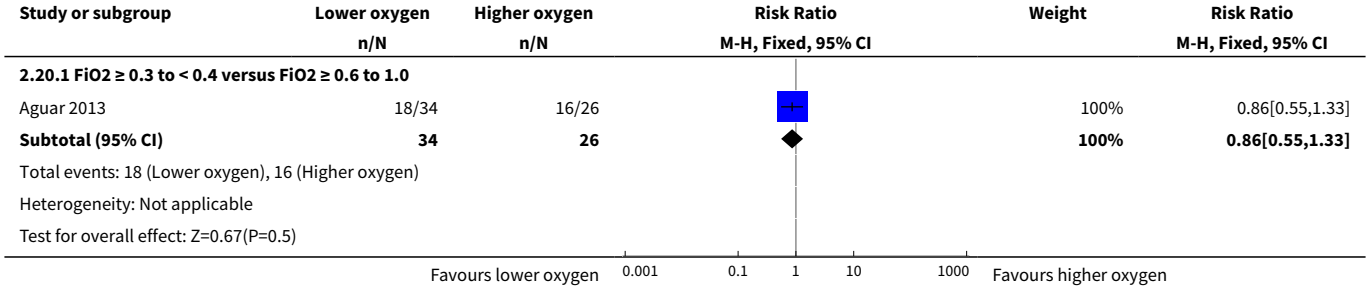
Analysis 2.18. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 18 Duration of supplemental oxygen administration.



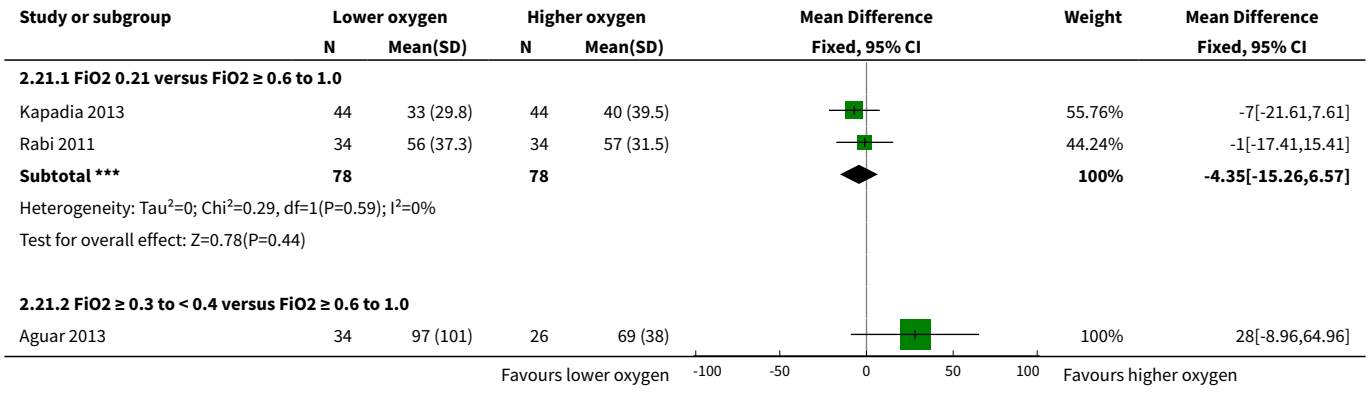
Analysis 2.19. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 19 Mortality to follow up (> 18 months).

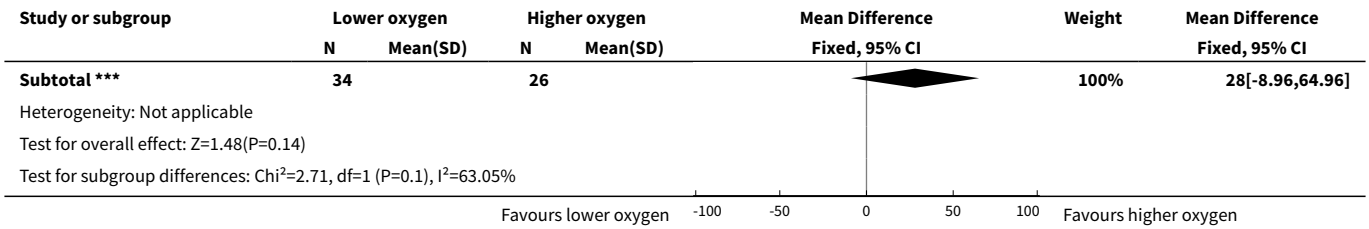


Analysis 2.20. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 20 Postnatal growth failure (weight < 10th percentile at discharge).

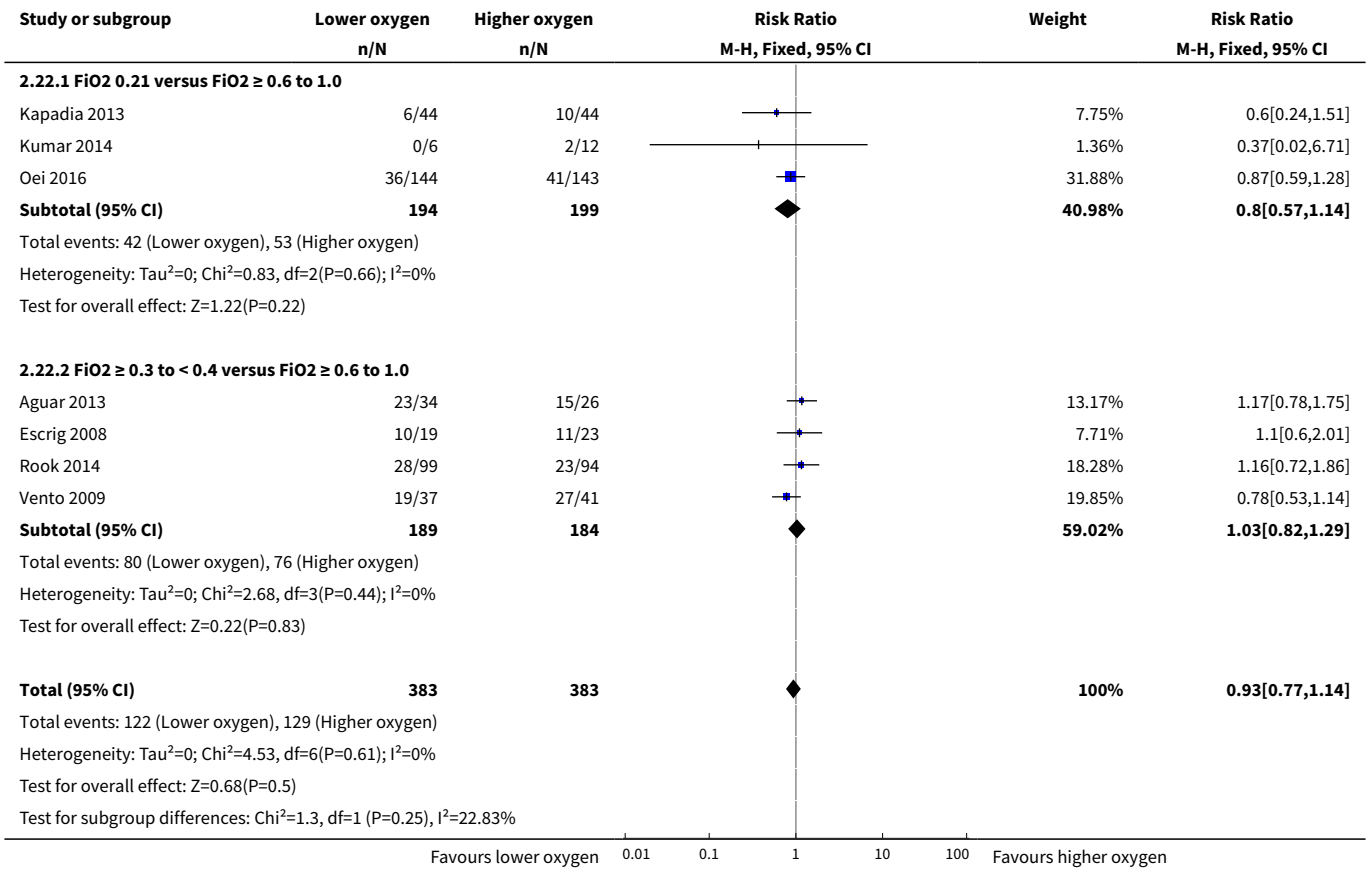


Analysis 2.21. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 21 Duration of hospitalisation (days).





Analysis 2.22. Comparison 2 Lower versus higher oxygen concentration subgrouped by FiO_2, Outcome 22 Patent ductus arteriosus (not prespecified).



Comparison 3. Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality near term corrected age or discharge (latest reported)	10	914	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.68, 1.63]
1.1 SpO_2 target < 85%	1	287	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [1.03, 7.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 SpO_2 target 85 to 90%	9	627	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.46, 1.27]
2 Neurodevelopmental disability	2	208	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.49, 1.35]
2.1 SpO_2 target 85 to 90%	2	208	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.49, 1.35]
3 IPPV in the delivery room	5	249	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.83, 1.06]
3.1 SpO_2 target 85 to 90%	5	249	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.83, 1.06]
4 Intubation in the delivery room	9	875	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.82, 1.18]
4.1 SpO_2 target < 85%	1	287	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.73, 1.49]
4.2 SpO_2 target 85 to 90%	8	588	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.78, 1.18]
5 Time to reach desired oxygen saturation target	2	102	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-1.83, 0.79]
5.1 SpO_2 target 85 to 90%	2	102	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-1.83, 0.79]
6 Time to reach heart rate > 100 bpm (not prespecified)	1	60	Mean Difference (IV, Fixed, 95% CI)	0.27 [-1.21, 1.75]
6.1 SpO_2 target 85 to 90%	1	60	Mean Difference (IV, Fixed, 95% CI)	0.27 [-1.21, 1.75]
7 Retinopathy of prematurity	4	373	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.43, 1.49]
7.1 SpO_2 target 85 to 90%	4	373	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.43, 1.49]
8 Severe retinopathy of prematurity (≥ stage 3)	4	453	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.24, 1.36]
8.1 SpO_2 target < 85%	1	287	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.15, 1.61]
8.2 SpO_2 target 85 to 90%	3	166	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.19, 2.48]
9 Intraventricular haemorrhage	3	271	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.46, 1.44]
9.1 SpO_2 target 85 to 90%	3	271	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.46, 1.44]
10 Severe intraventricular haemorrhage (grade 3 or 4)	6	596	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.51, 1.71]
10.1 SpO_2 target < 85%	1	287	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.61]
10.2 SpO_2 target 85 to 90%	5	309	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.61, 2.39]
11 Periventricular leukomalacia	2	130	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.09, 4.73]
11.1 SpO_2 target 85 to 90%	2	130	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.09, 4.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 Necrotising enterocolitis	8	807	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.51, 1.87]
12.1 SpO_2 target < 85%	1	287	Risk Ratio (M-H, Fixed, 95% CI)	4.97 [0.59, 41.97]
12.2 SpO_2 target 85 to 90%	7	520	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.36, 1.52]
13 Chronic lung disease (28 days' age)	2	148	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.41, 1.21]
13.1 SpO_2 target 85 to 90%	2	148	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.41, 1.21]
14 Chronic lung disease (36 weeks' corrected age)	9	862	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.64, 1.29]
14.1 SpO_2 target < 85%	1	287	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.57, 1.25]
14.2 SpO_2 target 85 to 90%	8	575	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.43]
15 Duration of respiratory support (mechanical ventilation or CPAP) (days from birth)	2	326	Mean Difference (IV, Fixed, 95% CI)	-12.39 [-13.49, -11.29]
15.1 SpO_2 target < 85%	1	266	Mean Difference (IV, Fixed, 95% CI)	-13.70 [-14.85, -12.55]
15.2 SpO_2 target 85 to 90%	1	60	Mean Difference (IV, Fixed, 95% CI)	1.06 [-2.63, 4.75]
16 Duration of respiratory support (mechanical ventilation) (days from birth)	6	510	Mean Difference (IV, Fixed, 95% CI)	0.78 [-1.15, 2.72]
16.1 SpO_2 target 85 to 90%	6	510	Mean Difference (IV, Fixed, 95% CI)	0.78 [-1.15, 2.72]
17 Duration of respiratory support (CPAP) (days from birth)	4	249	Mean Difference (IV, Fixed, 95% CI)	-1.83 [-5.62, 1.96]
17.1 SpO_2 target 85 to 90%	4	249	Mean Difference (IV, Fixed, 95% CI)	-1.83 [-5.62, 1.96]
18 Duration of supplemental oxygen administration	5	639	Mean Difference (IV, Fixed, 95% CI)	9.67 [6.96, 12.39]
18.1 SpO_2 target < 85%	1	266	Mean Difference (IV, Fixed, 95% CI)	12.4 [9.25, 15.55]
18.2 SpO_2 target 85 to 90%	4	373	Mean Difference (IV, Fixed, 95% CI)	1.73 [-3.64, 7.11]
19 Mortality to follow up (> 18 months)	3	540	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.59, 1.70]
19.1 SpO_2 target < 85%	1	287	Risk Ratio (M-H, Fixed, 95% CI)	2.32 [0.92, 5.86]
19.2 SpO_2 target 85 to 90%	2	253	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.28, 1.14]

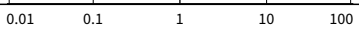
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20 Postnatal growth failure (weight < 10th percentile at discharge)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.55, 1.33]
20.1 SpO_2 target 85 to 90%	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.55, 1.33]
21 Duration of hospitalisation (days)	3	216	Mean Difference (IV, Fixed, 95% CI)	-1.75 [-12.22, 8.71]
21.1 SpO_2 target 85 to 90%	3	216	Mean Difference (IV, Fixed, 95% CI)	-1.75 [-12.22, 8.71]
22 Patent ductus arteriosus (not prespecified)	7	766	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.79, 1.15]
22.1 SpO_2 target < 85%	1	287	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.59, 1.28]
22.2 SpO_2 target 85 to 90%	6	479	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.79, 1.22]

Analysis 3.1. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 1 Mortality near term corrected age or discharge (latest reported).

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 SpO2 target < 85%					
Oei 2016	14/144	5/143		14.19%	2.78[1.03,7.52]
Subtotal (95% CI)	**144**	**143**		**14.19%**	**2.78[1.03,7.52]**
Total events: 14 (Lower oxygen), 5 (Higher oxygen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.02(P=0.04)					
3.1.2 SpO2 target 85 to 90%					
Aguar 2013	4/34	7/26		22.43%	0.44[0.14,1.34]
Armanian 2012	0/16	0/16			Not estimable
Escrig 2008	4/19	3/23		7.68%	1.61[0.41,6.34]
Kapadia 2013	2/44	3/44		8.48%	0.67[0.12,3.8]
Kumar 2014	1/6	1/12		1.89%	2[0.15,26.73]
Rabi 2011	1/34	2/34		5.66%	0.5[0.05,5.26]
Rook 2014	6/99	10/94		29.01%	0.57[0.22,1.51]
Vento 2009	4/41	3/44		8.18%	1.43[0.34,6.01]
Wang 2008	1/18	1/23		2.48%	1.28[0.09,19.06]
Subtotal (95% CI)	**311**	**316**		**85.81%**	**0.77[0.46,1.27]**
Total events: 23 (Lower oxygen), 30 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=4.01, df=7(P=0.78); I^2=0%					
Test for overall effect: Z=1.03(P=0.3)					
Total (95% CI)	**455**	**459**		**100%**	**1.05[0.68,1.63]**
Total events: 37 (Lower oxygen), 35 (Higher oxygen)					

Favours lower oxygen — Favours higher oxygen

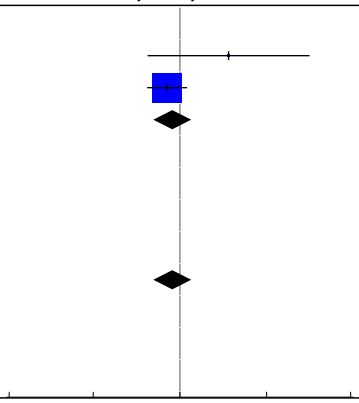
Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=9.03, df=8(P=0.34); I²=11.42%					
Test for overall effect: Z=0.23(P=0.82)					
Test for subgroup differences: Chi²=5.12, df=1 (P=0.02), I²=80.45%					



Favours lower oxygen — Favours higher oxygen

Analysis 3.2. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 2 Neurodevelopmental disability.

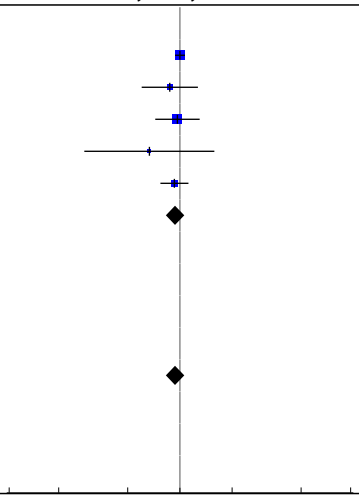
Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 SpO2 target 85 to 90%					
Aguar 2013	3/14	1/17		3.53%	3.64[0.42,31.27]
Rook 2014	19/95	23/82		96.47%	0.71[0.42,1.21]
Subtotal (95% CI)	**109**	**99**		**100%**	**0.82[0.49,1.35]**
Total events: 22 (Lower oxygen), 24 (Higher oxygen)					
Heterogeneity: Tau²=0; Chi²=2.11, df=1(P=0.15); I²=52.58%					
Test for overall effect: Z=0.79(P=0.43)					
Total (95% CI)	**109**	**99**		**100%**	**0.82[0.49,1.35]**
Total events: 22 (Lower oxygen), 24 (Higher oxygen)					
Heterogeneity: Tau²=0; Chi²=2.11, df=1(P=0.15); I²=52.58%					
Test for overall effect: Z=0.79(P=0.43)					



Favours lower oxygen — Favours higher oxygen

Analysis 3.3. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 3 IPPV in the delivery room.

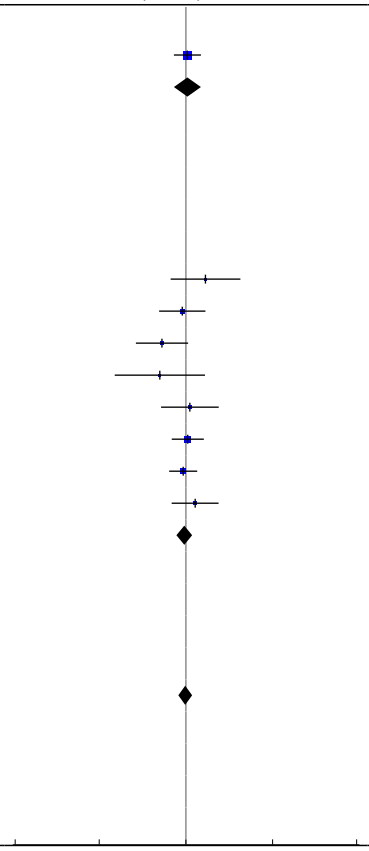
Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 SpO2 target 85 to 90%					
Aguar 2013	34/34	26/26		29.47%	1[0.94,1.07]
Escrig 2008	13/19	18/23		16.04%	0.87[0.6,1.27]
Kapadia 2013	29/44	30/44		29.55%	0.97[0.72,1.3]
Kumar 2014	3/6	9/12		5.91%	0.67[0.28,1.58]
Wang 2008	16/18	22/23		19.03%	0.93[0.77,1.12]
Subtotal (95% CI)	**121**	**128**		**100%**	**0.94[0.83,1.06]**
Total events: 95 (Lower oxygen), 105 (Higher oxygen)					
Heterogeneity: Tau²=0; Chi²=4.6, df=4(P=0.33); I²=13.13%					
Test for overall effect: Z=1.06(P=0.29)					
Total (95% CI)	**121**	**128**		**100%**	**0.94[0.83,1.06]**
Total events: 95 (Lower oxygen), 105 (Higher oxygen)					
Heterogeneity: Tau²=0; Chi²=4.6, df=4(P=0.33); I²=13.13%					
Test for overall effect: Z=1.06(P=0.29)					



Favours lower oxygen — Favours higher oxygen

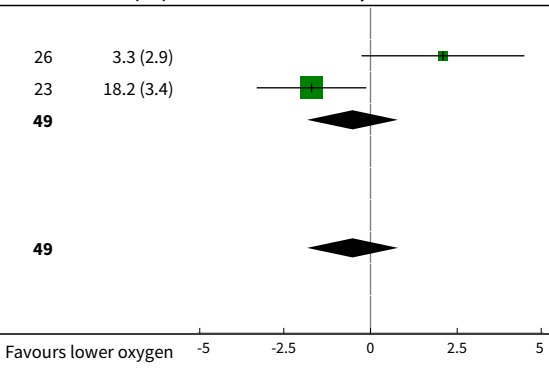
Analysis 3.4. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 4 Intubation in the delivery room.

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 SpO2 target < 85%					
Oei 2016	43/144	41/143		27.39%	1.04[0.73,1.49]
Subtotal (95% CI)	**144**	**143**		**27.39%**	**1.04[0.73,1.49]**
Total events: 43 (Lower oxygen), 41 (Higher oxygen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.22(P=0.82)					
3.4.2 SpO2 target 85 to 90%					
Aguar 2013	11/34	5/26		3.77%	1.68[0.67,4.25]
Escrig 2008	9/19	12/23		7.23%	0.91[0.49,1.68]
Kapadia 2013	9/44	17/44		11.32%	0.53[0.27,1.06]
Kumar 2014	2/6	8/12		3.55%	0.5[0.15,1.66]
Rabi 2011	10/34	9/34		5.99%	1.11[0.52,2.39]
Rook 2014	31/99	28/94		19.12%	1.05[0.69,1.61]
Vento 2009	21/37	25/41		15.79%	0.93[0.64,1.35]
Wang 2008	10/18	10/23		5.84%	1.28[0.69,2.38]
Subtotal (95% CI)	**291**	**297**		**72.61%**	**0.96[0.78,1.18]**
Total events: 103 (Lower oxygen), 114 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=6.58, df=7(P=0.47); I^2=0%					
Test for overall effect: Z=0.4(P=0.69)					
Total (95% CI)	**435**	**440**		**100%**	**0.98[0.82,1.18]**
Total events: 146 (Lower oxygen), 155 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=6.71, df=8(P=0.57); I^2=0%					
Test for overall effect: Z=0.2(P=0.84)					
Test for subgroup differences: Chi^2=0.15, df=1 (P=0.7), I^2=0%					



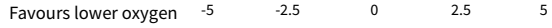
Analysis 3.5. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 5 Time to reach desired oxygen saturation target.

Study or subgroup	Lower oxygen N	Lower oxygen Mean(SD)	Higher oxygen N	Higher oxygen Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.5.1 SpO2 target 85 to 90%							
Aguar 2013	34	5.4 (6.1)	26	3.3 (2.9)		31.18%	2.09[-0.26,4.44]
Escrig 2008	19	16.5 (1.7)	23	18.2 (3.4)		68.82%	-1.7[-3.28,-0.12]
Subtotal ***	**53**		**49**			**100%**	**-0.52[-1.83,0.79]**
Heterogeneity: Tau^2=0; Chi^2=6.89, df=1(P=0.01); I^2=85.49%							
Test for overall effect: Z=0.77(P=0.44)							
Total ***	**53**		**49**			**100%**	**-0.52[-1.83,0.79]**
Heterogeneity: Tau^2=0; Chi^2=6.89, df=1(P=0.01); I^2=85.49%							
Test for overall effect: Z=0.77(P=0.44)							



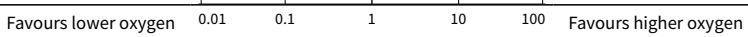
Analysis 3.6. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 6 Time to reach heart rate > 100 bpm (not prespecified).

Study or subgroup	Lower oxygen N	Lower oxygen Mean(SD)	Higher oxygen N	Higher oxygen Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.6.1 SpO2 target 85 to 90%							
Aguar 2013	34	2.2 (3.7)	26	1.9 (2.1)		100%	0.27[-1.21,1.75]
Subtotal ***	**34**		**26**			**100%**	**0.27[-1.21,1.75]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.36(P=0.72)							
Total ***	**34**		**26**			**100%**	**0.27[-1.21,1.75]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.36(P=0.72)							



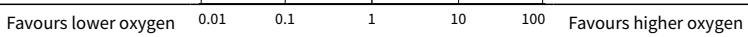
Analysis 3.7. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 7 Retinopathy of prematurity.

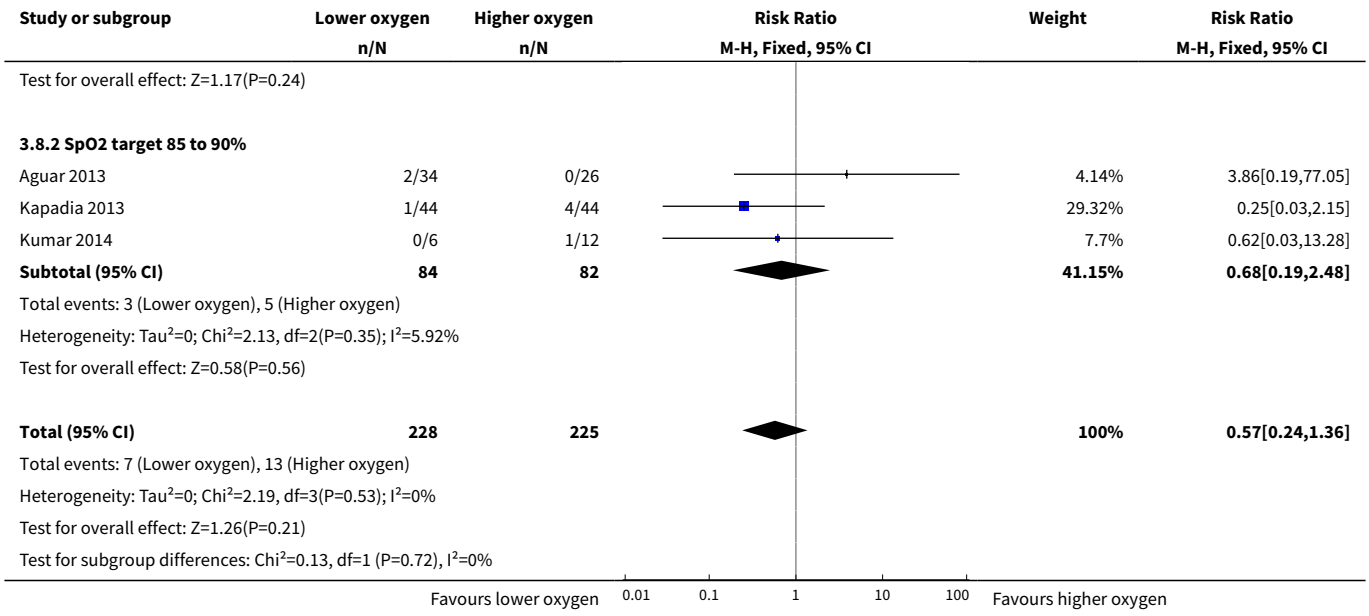
Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.7.1 SpO2 target 85 to 90%					
Aguar 2013	5/34	6/26		34.99%	0.64[0.22,1.86]
Escrig 2008	1/19	2/23		9.31%	0.61[0.06,6.17]
Rook 2014	6/99	5/94		26.4%	1.14[0.36,3.61]
Vento 2009	4/37	6/41		29.29%	0.74[0.23,2.42]
Subtotal (95% CI)	**189**	**184**		**100%**	**0.8[0.43,1.49]**
Total events: 16 (Lower oxygen), 19 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=0.61, df=3(P=0.89); I^2=0%					
Test for overall effect: Z=0.71(P=0.48)					
Total (95% CI)	**189**	**184**		**100%**	**0.8[0.43,1.49]**
Total events: 16 (Lower oxygen), 19 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=0.61, df=3(P=0.89); I^2=0%					
Test for overall effect: Z=0.71(P=0.48)					



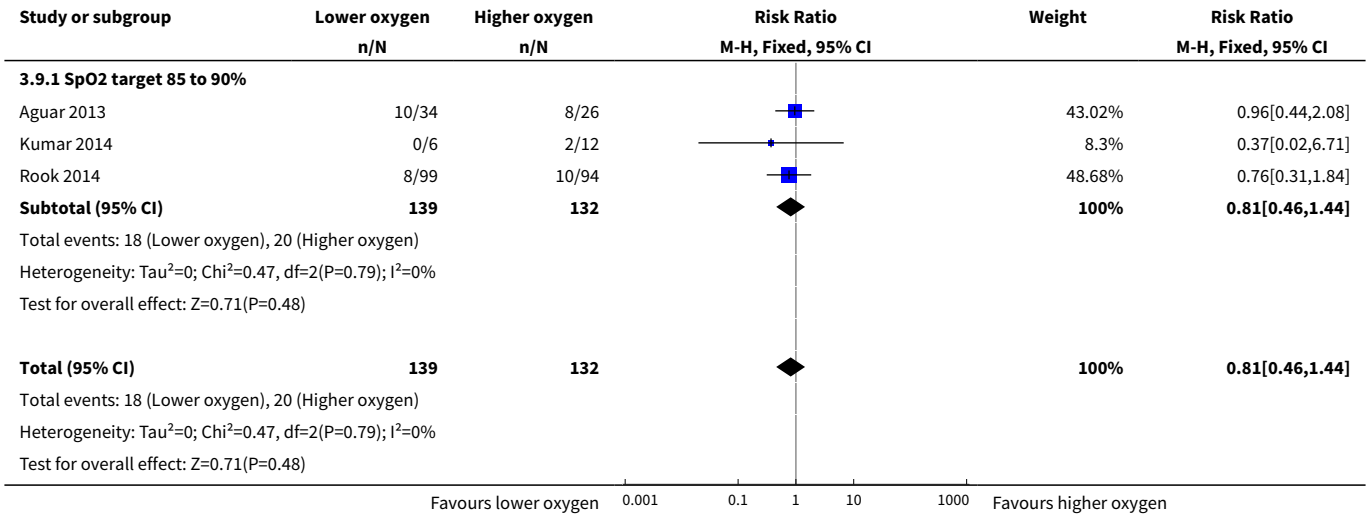
Analysis 3.8. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 8 Severe retinopathy of prematurity (≥ stage 3).

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.8.1 SpO2 target < 85%					
Oei 2016	4/144	8/143		58.85%	0.5[0.15,1.61]
Subtotal (95% CI)	**144**	**143**		**58.85%**	**0.5[0.15,1.61]**
Total events: 4 (Lower oxygen), 8 (Higher oxygen)					
Heterogeneity: Not applicable					

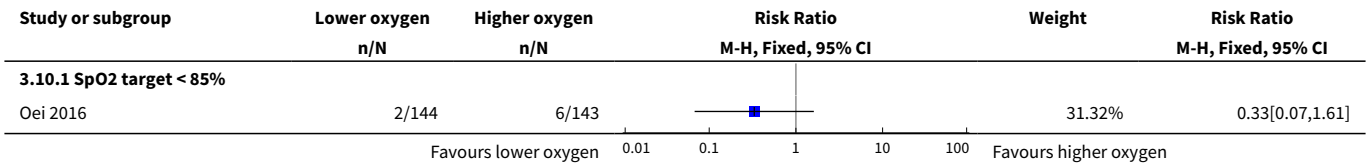


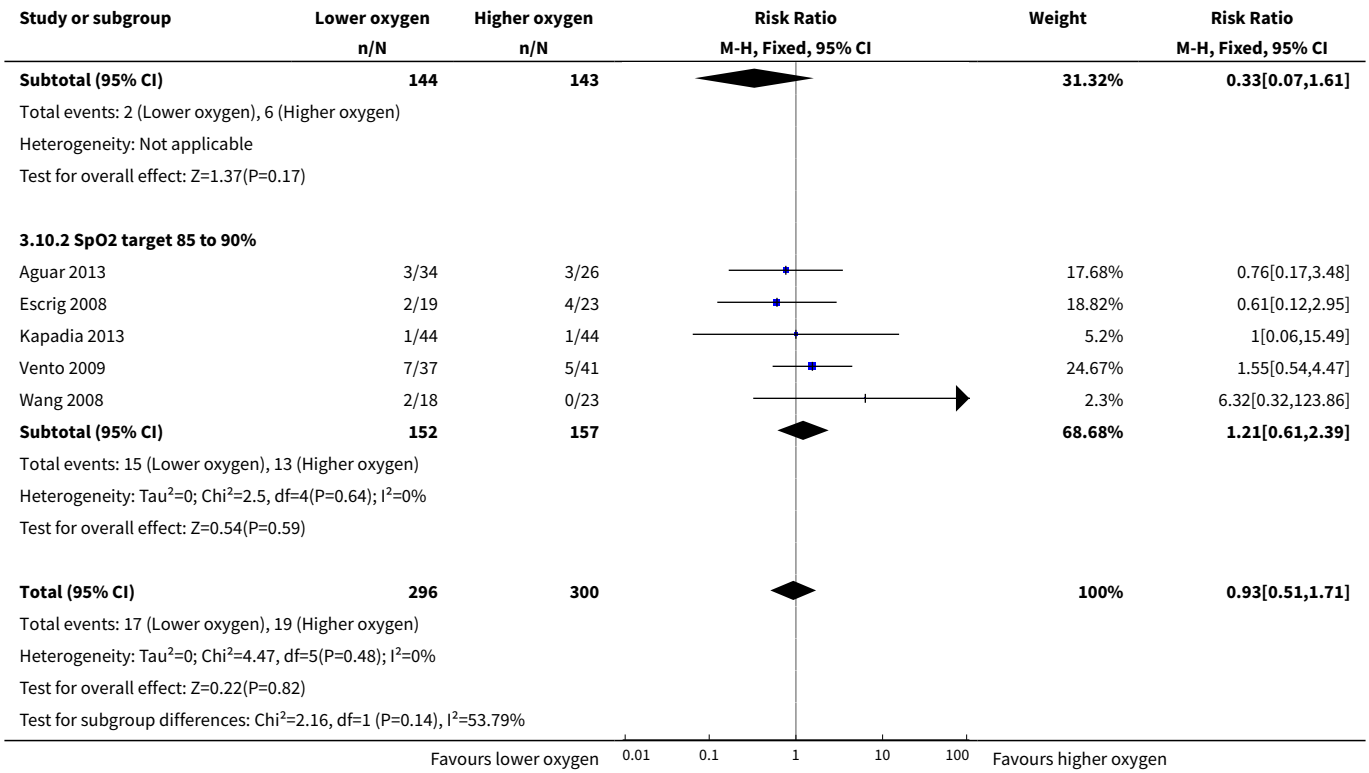


Analysis 3.9. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 9 Intraventricular haemorrhage.

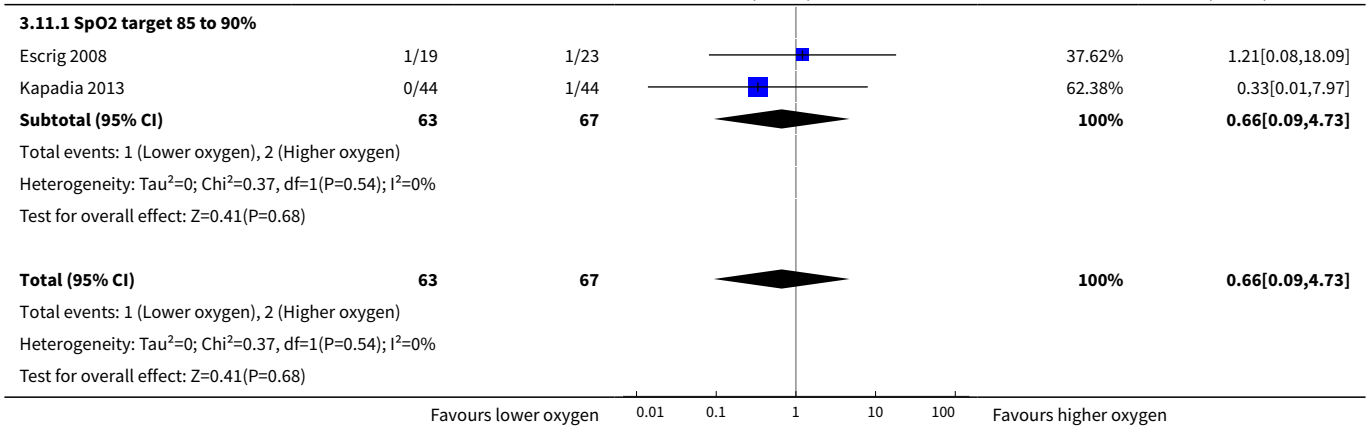


Analysis 3.10. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 10 Severe intraventricular haemorrhage (grade 3 or 4).





Analysis 3.11. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 11 Periventricular leukomalacia.



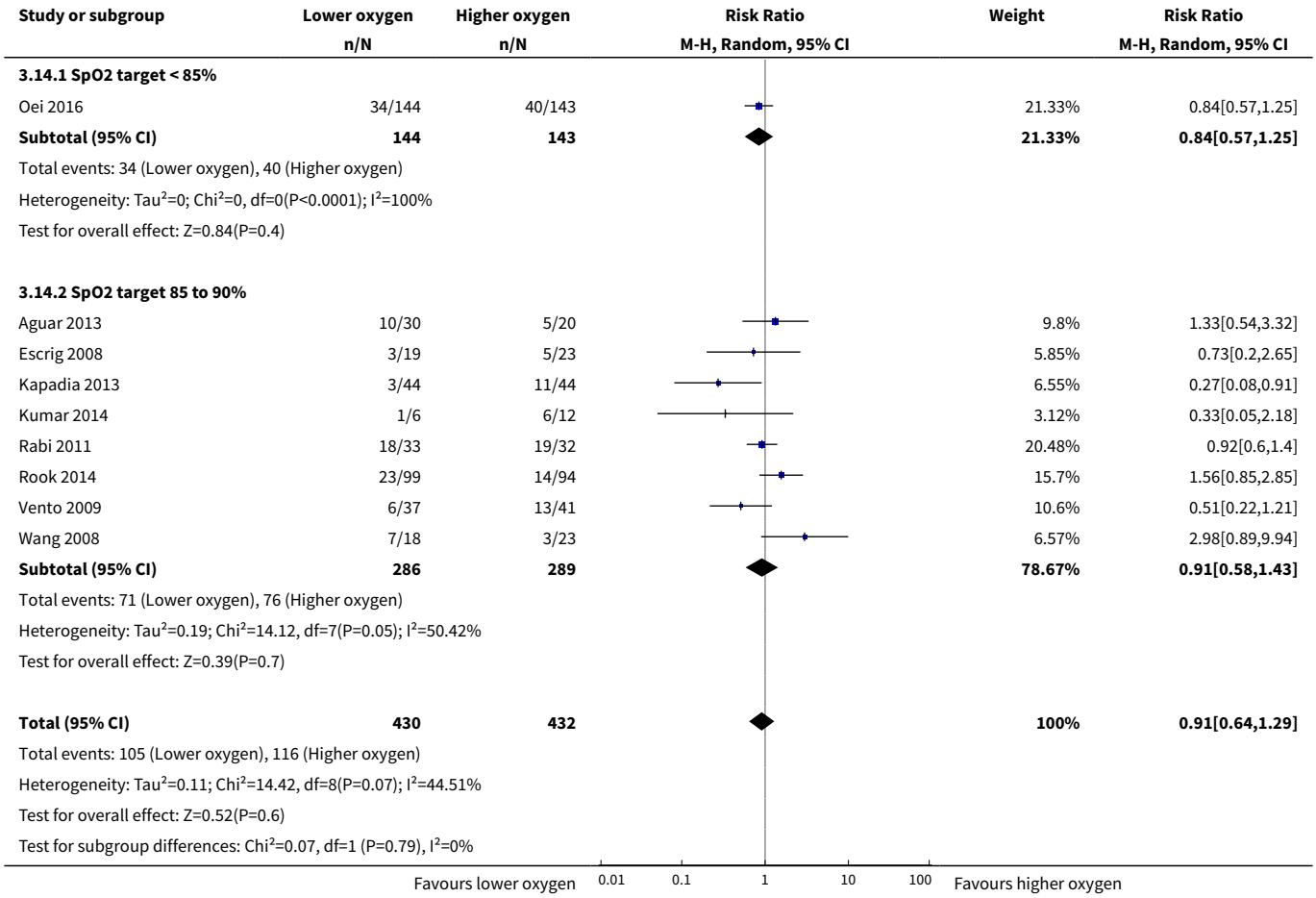
Analysis 3.12. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 12 Necrotising enterocolitis.

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.12.1 SpO2 target < 85%					
Oei 2016	5/144	1/143		5.59%	4.97[0.59,41.97]
Subtotal (95% CI)	**144**	**143**		**5.59%**	**4.97[0.59,41.97]**
Total events: 5 (Lower oxygen), 1 (Higher oxygen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.47(P=0.14)					
3.12.2 SpO2 target 85 to 90%					
Aguar 2013	3/34	1/26		6.31%	2.29[0.25,20.8]
Escrig 2008	0/19	1/23		7.6%	0.4[0.02,9.29]
Kapadia 2013	1/44	6/44		33.43%	0.17[0.02,1.33]
Kumar 2014	1/6	4/12		14.86%	0.5[0.07,3.55]
Rook 2014	4/99	3/94		17.15%	1.27[0.29,5.51]
Vento 2009	2/37	1/41		5.29%	2.22[0.21,23.45]
Wang 2008	1/18	2/23		9.78%	0.64[0.06,6.5]
Subtotal (95% CI)	**257**	**263**		**94.41%**	**0.74[0.36,1.52]**
Total events: 12 (Lower oxygen), 18 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=4.65, df=6(P=0.59); I^2=0%					
Test for overall effect: Z=0.81(P=0.42)					
Total (95% CI)	**401**	**406**		**100%**	**0.98[0.51,1.87]**
Total events: 17 (Lower oxygen), 19 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=7.06, df=7(P=0.42); I^2=0.88%					
Test for overall effect: Z=0.06(P=0.95)					
Test for subgroup differences: Chi^2=2.73, df=1 (P=0.1), I^2=63.43%					

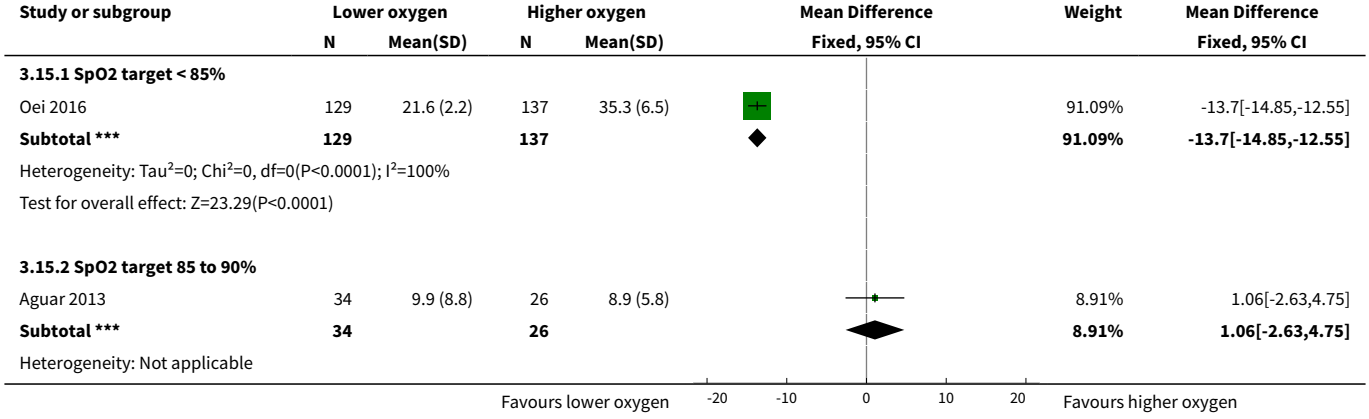
Analysis 3.13. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 13 Chronic lung disease (28 days' age).

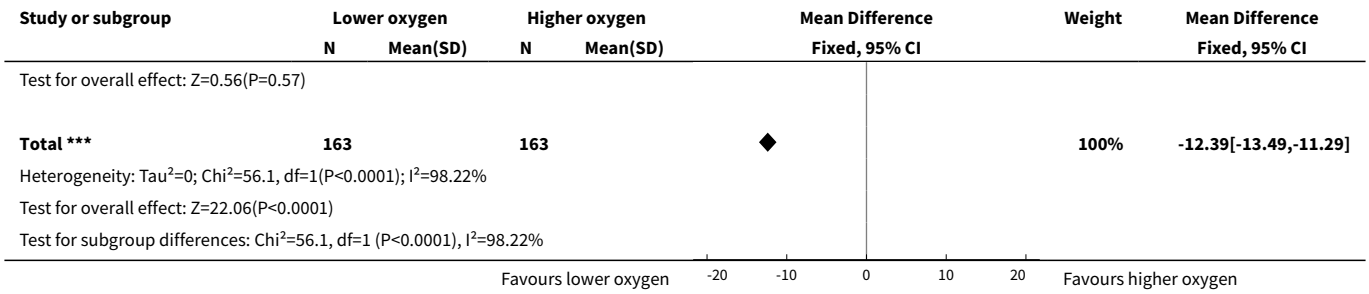
Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.13.1 SpO2 target 85 to 90%					
Aguar 2013	10/34	6/26		28.57%	1.27[0.53,3.05]
Kapadia 2013	8/44	17/44		71.43%	0.47[0.23,0.98]
Subtotal (95% CI)	**78**	**70**		**100%**	**0.7[0.41,1.21]**
Total events: 18 (Lower oxygen), 23 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=2.95, df=1(P=0.09); I^2=66.05%					
Test for overall effect: Z=1.28(P=0.2)					
Total (95% CI)	**78**	**70**		**100%**	**0.7[0.41,1.21]**
Total events: 18 (Lower oxygen), 23 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=2.95, df=1(P=0.09); I^2=66.05%					
Test for overall effect: Z=1.28(P=0.2)					

Analysis 3.14. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 14 Chronic lung disease (36 weeks' corrected age).

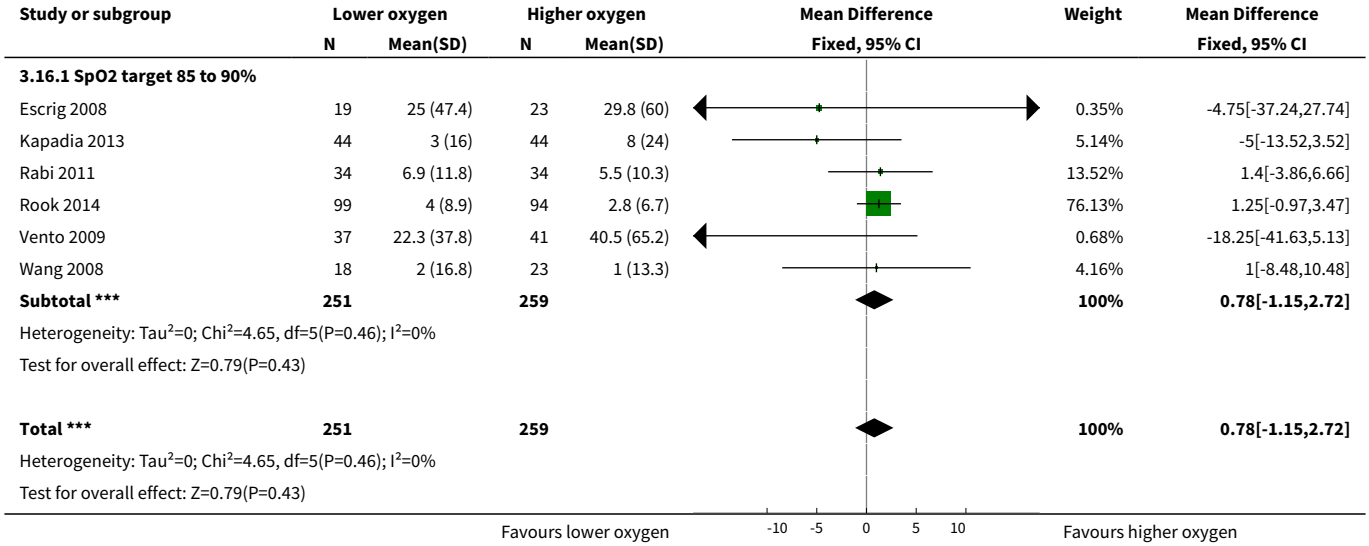


Analysis 3.15. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 15 Duration of respiratory support (mechanical ventilation or CPAP) (days from birth).

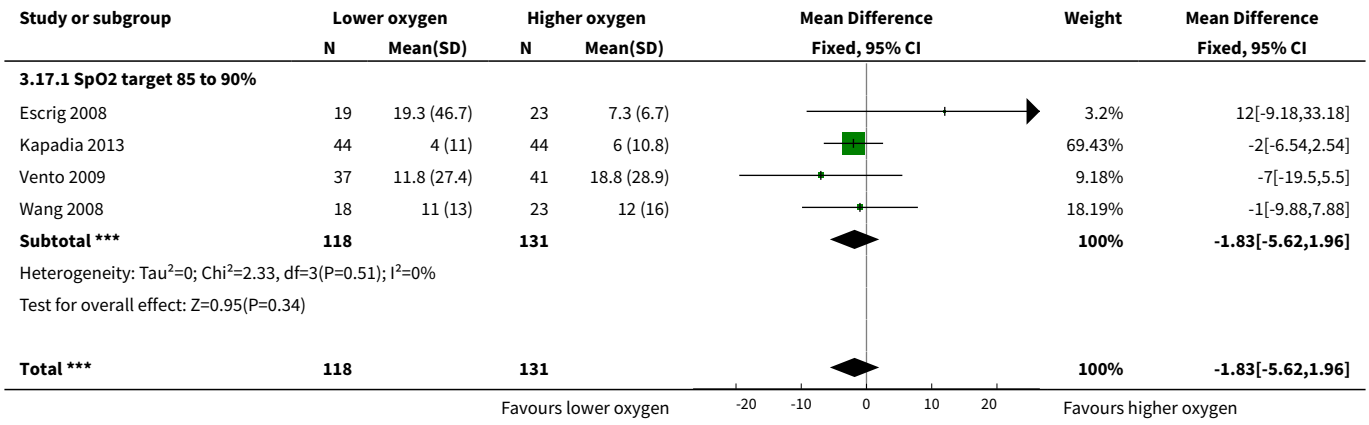


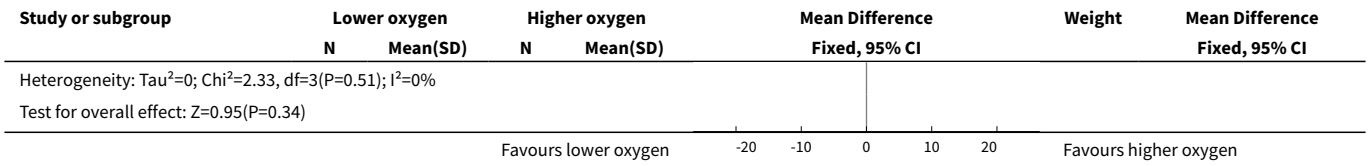


Analysis 3.16. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 16 Duration of respiratory support (mechanical ventilation) (days from birth).

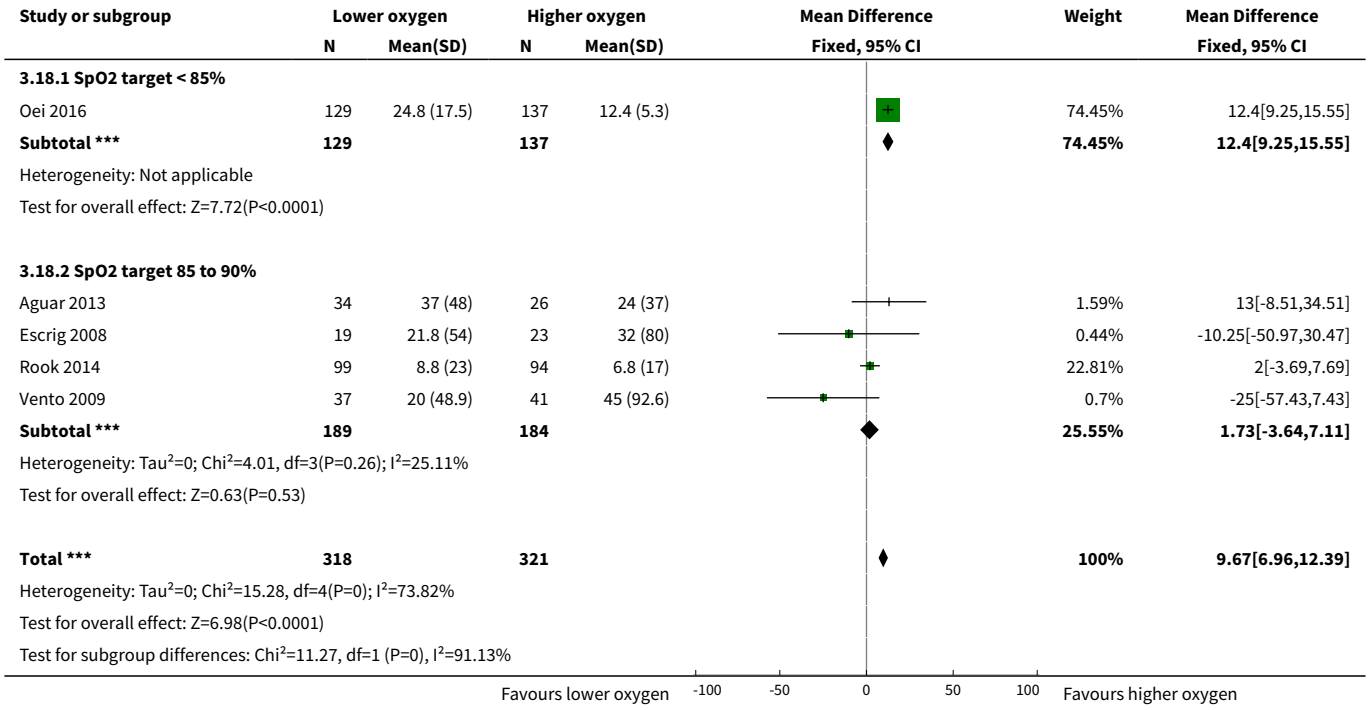


Analysis 3.17. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 17 Duration of respiratory support (CPAP) (days from birth).

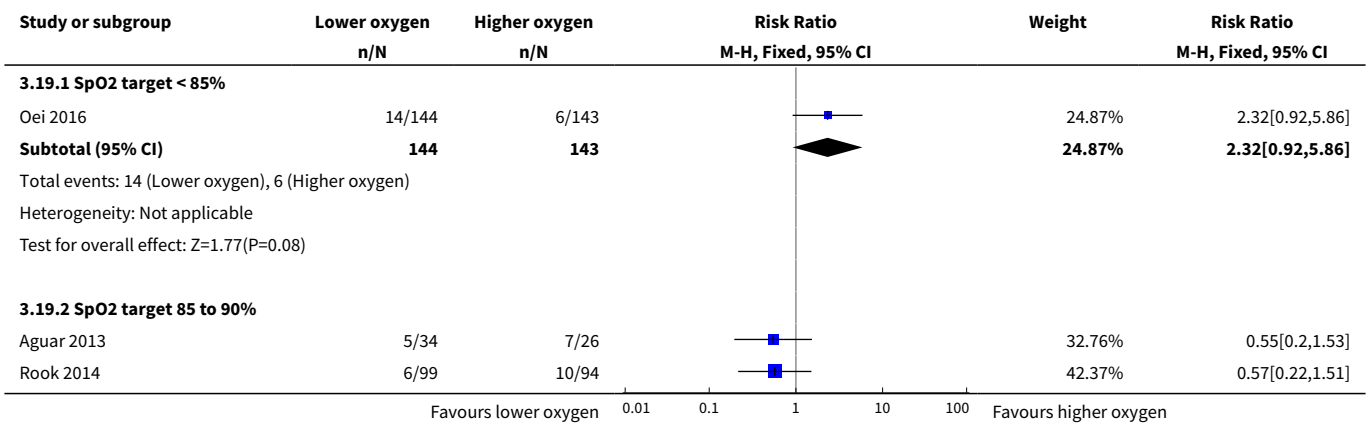


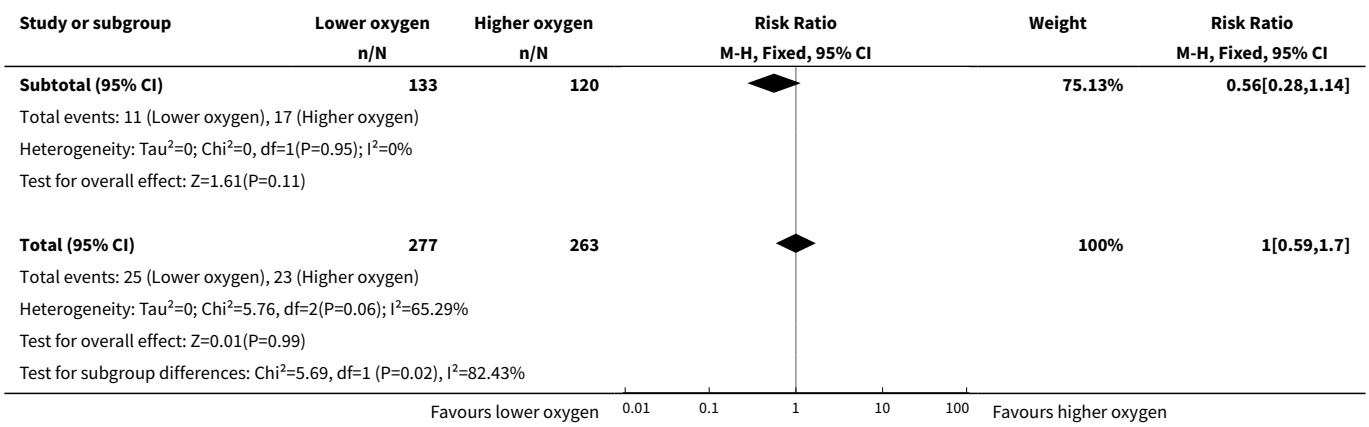


Analysis 3.18. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 18 Duration of supplemental oxygen administration.

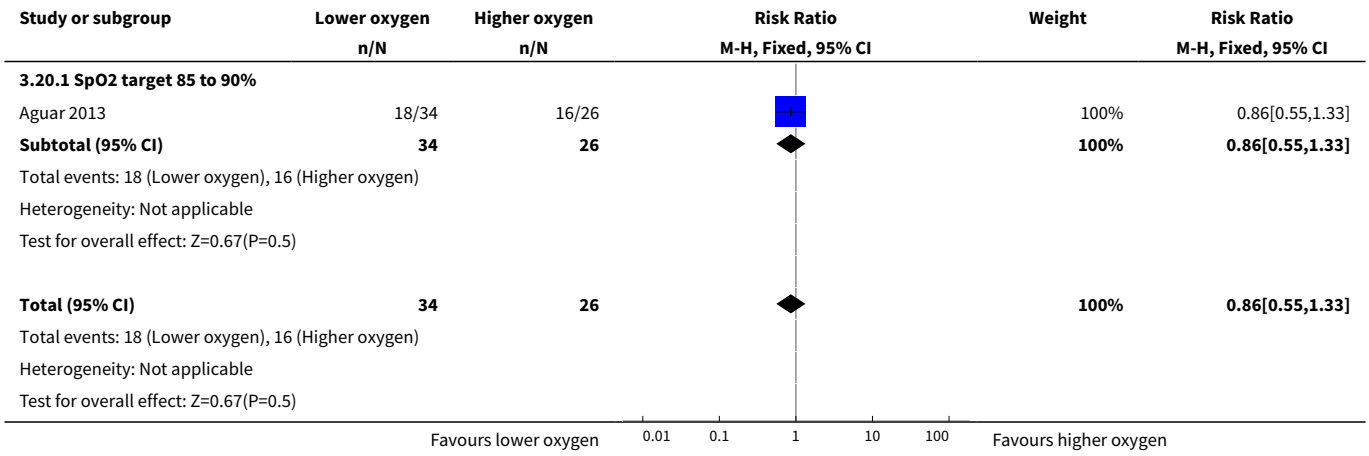


Analysis 3.19. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 19 Mortality to follow up (> 18 months).

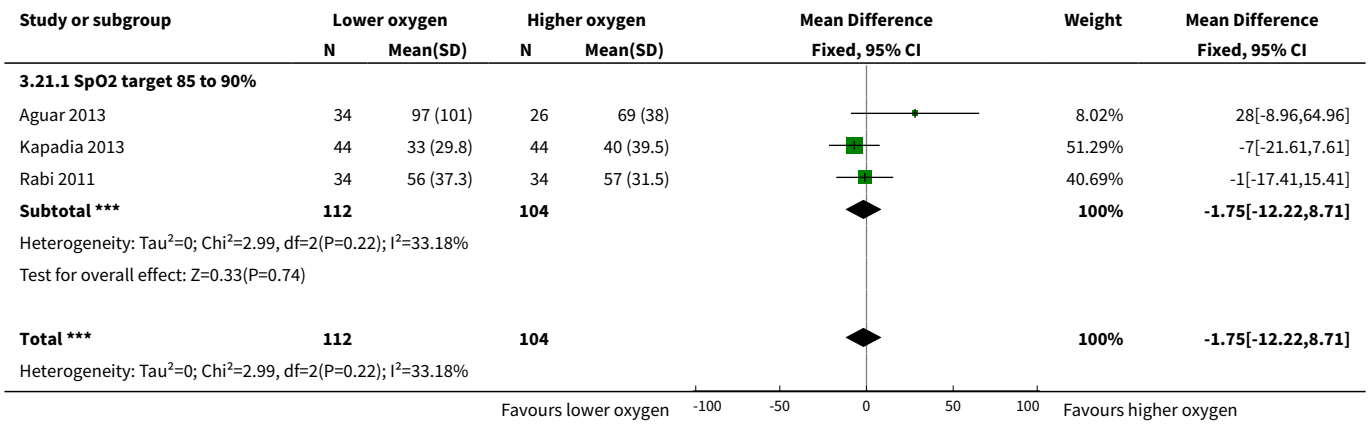


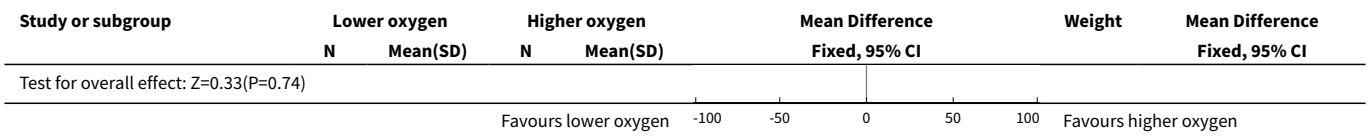


Analysis 3.20. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 20 Postnatal growth failure (weight < 10th percentile at discharge).

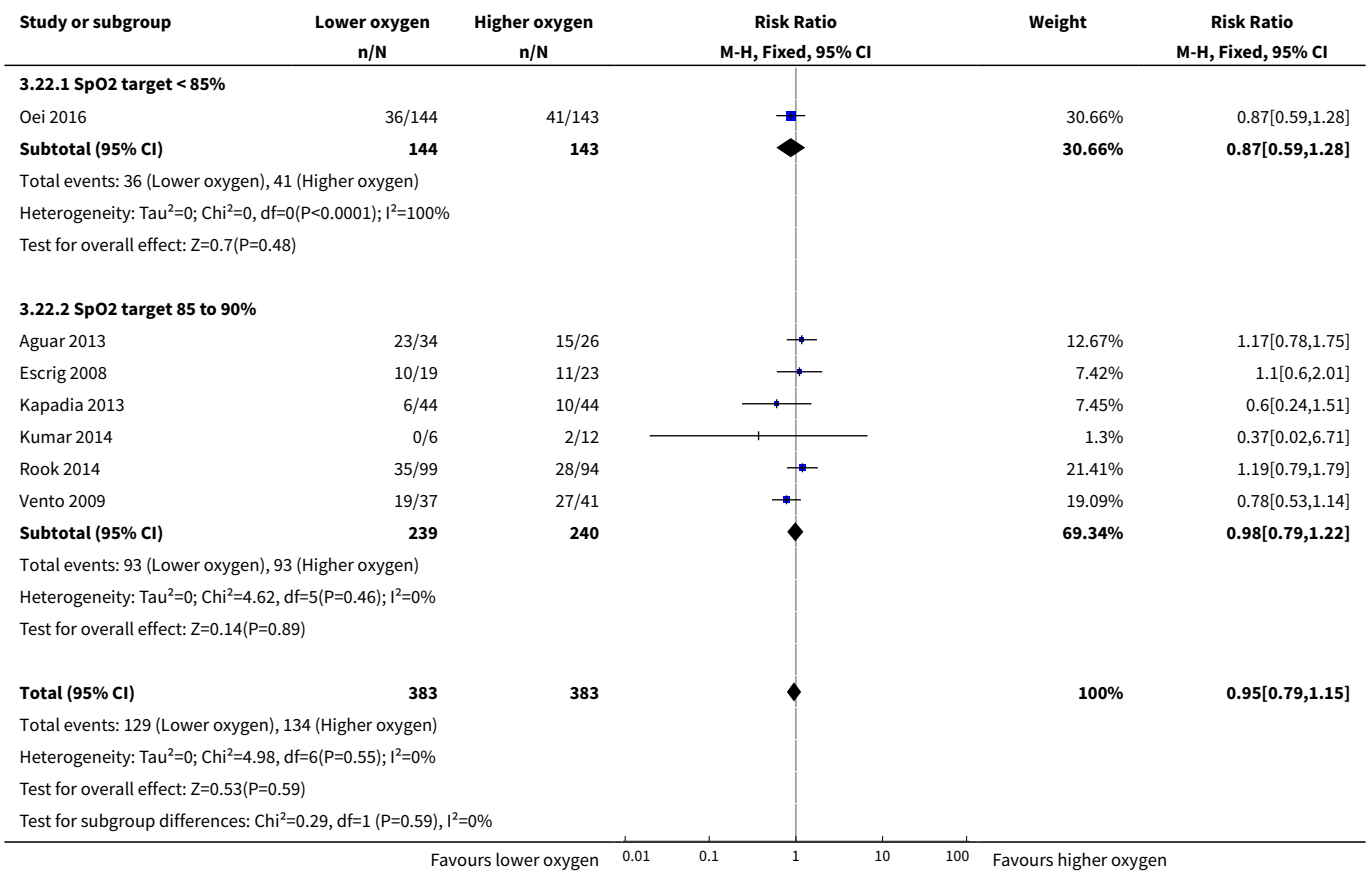


Analysis 3.21. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 21 Duration of hospitalisation (days).





Analysis 3.22. Comparison 3 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation range at 5 to 10 mintues, Outcome 22 Patent ductus arteriosus (not prespecified).



Comparison 4. Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Mortality near term corrected age or discharge (latest reported)	7	737	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.72, 2.02]
1.1 SpO_2 target 85 to 90%	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.41, 6.34]
1.2 SpO_2 target 91 to 95%	6	695	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.67, 2.01]

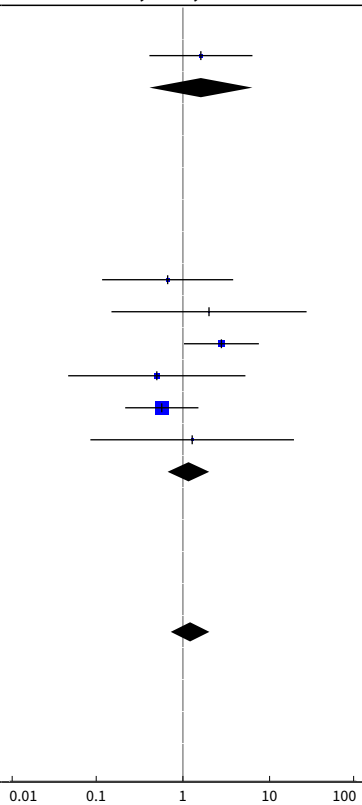
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Neurodevelopmental disability	1	177	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.42, 1.21]
2.1 SpO_2 target 91 to 95%	1	177	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.42, 1.21]
3 IPPV in the delivery room	4	189	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.77, 1.08]
3.1 SpO_2 target 85 to 90%	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.60, 1.27]
3.2 SpO_2 target 91 to 95%	3	147	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.76, 1.12]
4 Intubation in the delivery room	7	737	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.78, 1.18]
4.1 SpO_2 target 85 to 90%	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.49, 1.68]
4.2 SpO_2 target 91 to 95%	6	695	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.77, 1.20]
5 Time to reach desired oxygen saturation target	1	42	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-3.28, -0.12]
5.1 SpO_2 target 85 to 90%	1	42	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-3.28, -0.12]
6 Retinopathy of prematurity	2	235	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.36, 2.79]
6.1 SpO_2 target 85 to 90%	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.06, 6.17]
6.2 SpO_2 target 91 to 95%	1	193	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.36, 3.61]
7 Severe retinopathy of prematurity (≥ stage 3)	3	393	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.16, 1.14]
7.1 SpO_2 target 91 to 95%	3	393	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.16, 1.14]
8 Intraventricular haemorrhage	2	211	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.30, 1.64]
8.1 SpO_2 target 91 to 95%	2	211	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.30, 1.64]
9 Severe intraventricular haemorrhage (grade 3 or 4)	4	458	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.30, 1.73]
9.1 SpO_2 target 85 to 90%	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.12, 2.95]
9.2 SpO_2 target 91 to 95%	3	416	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.27, 2.24]
10 Periventricular leukomalacia	2	130	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.09, 4.73]
10.1 SpO_2 target 85 to 90%	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.08, 18.09]
10.2 SpO_2 target 91 to 95%	1	88	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.97]
11 Necrotising enterocolitis	6	669	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.39, 1.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 SpO_2 target 85 to 90%	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.02, 9.29]
11.2 SpO_2 target 91 to 95%	5	627	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.40, 1.79]
12 Chronic lung disease (28 days age)	1	88	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.23, 0.98]
12.1 SpO_2 target 91 to 95%	1	88	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.23, 0.98]
13 Chronic lung disease (36 weeks' corrected age)	7	734	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.73, 1.19]
13.1 SpO_2 target 85 to 90%	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.20, 2.65]
13.2 SpO_2 target 91 to 95%	6	692	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.74, 1.21]
14 Duration of respiratory support (mechanical ventilation or CPAP) (days from birth)	1	266	Mean Difference (IV, Fixed, 95% CI)	-13.70 [-14.85, -12.55]
14.1 SpO_2 target 91 to 95%	1	266	Mean Difference (IV, Fixed, 95% CI)	-13.70 [-14.85, -12.55]
15 Duration of respiratory support (mechanical ventilation) (days from birth)	5	432	Mean Difference (IV, Fixed, 95% CI)	0.91 [-1.02, 2.85]
15.1 SpO_2 target 85 to 90%	1	42	Mean Difference (IV, Fixed, 95% CI)	-4.75 [-37.24, 27.74]
15.2 SpO_2 target 91 to 95%	4	390	Mean Difference (IV, Fixed, 95% CI)	0.94 [-1.01, 2.88]
16 Duration of respiratory support (CPAP) (days from birth)	3	171	Mean Difference (IV, Fixed, 95% CI)	-3.11 [-7.08, 0.86]
16.1 SpO_2 target 85 to 90%	1	42	Mean Difference (IV, Fixed, 95% CI)	12.0 [-9.18, 33.18]
16.2 Higher SpO_2 target 91 to 95%	2	129	Mean Difference (IV, Fixed, 95% CI)	-3.66 [-7.71, 0.38]
17 Duration of supplemental oxygen administration	3	501	Mean Difference (IV, Fixed, 95% CI)	9.87 [7.12, 12.62]
17.1 SpO_2 target 85 to 90%	1	42	Mean Difference (IV, Fixed, 95% CI)	-10.25 [-50.97, 30.47]
17.2 SpO_2 target 91 to 95%	2	459	Mean Difference (IV, Fixed, 95% CI)	9.96 [7.21, 12.71]
18 Mortality to follow up (> 18 months)	2	480	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.65, 2.29]
18.1 SpO_2 target 91 to 95%	2	480	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.65, 2.29]
19 Duration of hospitalisation (days)	2	156	Mean Difference (IV, Fixed, 95% CI)	-4.35 [-15.26, 6.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 SpO_2 target 91 to 95%	2	156	Mean Difference (IV, Fixed, 95% CI)	-4.35 [-15.26, 6.57]
20 Patent ductus arteriosus (not prespecified)	5	628	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.75, 1.22]
20.1 SpO_2 target 85 to 90%	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.60, 2.01]
20.2 SpO_2 target 91 to 95%	4	586	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.72, 1.22]

Analysis 4.1. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 1 Mortality near term corrected age or discharge (latest reported).

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 SpO2 target 85 to 90%					
Escrig 2008	4/19	3/23		11.06%	1.61[0.41,6.34]
Subtotal (95% CI)	**19**	**23**		**11.06%**	**1.61[0.41,6.34]**
Total events: 4 (Lower oxygen), 3 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.69(P=0.49)					
4.1.2 SpO2 target 91 to 95%					
Kapadia 2013	2/44	3/44		12.23%	0.67[0.12,3.8]
Kumar 2014	1/6	1/12		2.72%	2[0.15,26.73]
Oei 2016	14/144	5/143		20.45%	2.78[1.03,7.52]
Rabi 2011	1/34	2/34		8.15%	0.5[0.05,5.26]
Rook 2014	6/99	10/94		41.81%	0.57[0.22,1.51]
Wang 2008	1/18	1/23		3.58%	1.28[0.09,19.06]
Subtotal (95% CI)	**345**	**350**		**88.94%**	**1.16[0.67,2.01]**
Total events: 25 (Lower oxygen), 22 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=6.08, df=5(P=0.3); I^2=17.73%					
Test for overall effect: Z=0.52(P=0.6)					
Total (95% CI)	**364**	**373**		**100%**	**1.21[0.72,2.02]**
Total events: 29 (Lower oxygen), 25 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=6.3, df=6(P=0.39); I^2=4.82%					
Test for overall effect: Z=0.72(P=0.47)					
Test for subgroup differences: Chi^2=0.2, df=1 (P=0.66), I^2=0%					



Analysis 4.2. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 2 Neurodevelopmental disability.

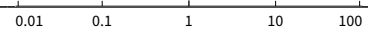
Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 SpO2 target 91 to 95%					
Rook 2014	19/95	23/82		100%	0.71[0.42,1.21]
Subtotal (95% CI)	**95**	**82**		**100%**	**0.71[0.42,1.21]**
Total events: 19 (Lower oxygen), 23 (Higher oxygen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.25(P=0.21)					
Total (95% CI)	**95**	**82**		**100%**	**0.71[0.42,1.21]**
Total events: 19 (Lower oxygen), 23 (Higher oxygen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.25(P=0.21)					

Analysis 4.3. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 3 IPPV in the delivery room.

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 SpO2 target 85 to 90%					
Escrig 2008	13/19	18/23		22.74%	0.87[0.6,1.27]
Subtotal (95% CI)	**19**	**23**		**22.74%**	**0.87[0.6,1.27]**
Total events: 13 (Lower oxygen), 18 (Higher oxygen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.7(P=0.48)					
4.3.2 SpO2 target 91 to 95%					
Kapadia 2013	29/44	30/44		41.9%	0.97[0.72,1.3]
Kumar 2014	3/6	9/12		8.38%	0.67[0.28,1.58]
Wang 2008	16/18	22/23		26.98%	0.93[0.77,1.12]
Subtotal (95% CI)	**68**	**79**		**77.26%**	**0.92[0.76,1.12]**
Total events: 48 (Lower oxygen), 61 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=0.65, df=2(P=0.72); I^2=0%					
Test for overall effect: Z=0.84(P=0.4)					
Total (95% CI)	**87**	**102**		**100%**	**0.91[0.77,1.08]**
Total events: 61 (Lower oxygen), 79 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=0.75, df=3(P=0.86); I^2=0%					
Test for overall effect: Z=1.07(P=0.28)					
Test for subgroup differences: Chi^2=0.06, df=1 (P=0.81), I^2=0%					

Analysis 4.4. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 4 Intubation in the delivery room.

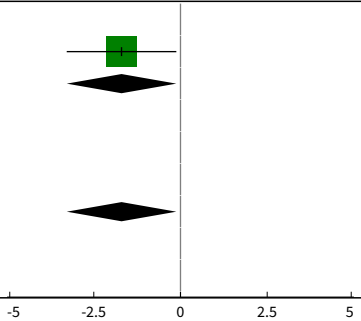
Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.4.1 SpO2 target 85 to 90%					
Escrig 2008	9/19	12/23		8.98%	0.91[0.49,1.68]
Subtotal (95% CI)	**19**	**23**		**8.98%**	**0.91[0.49,1.68]**
Total events: 9 (Lower oxygen), 12 (Higher oxygen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.31(P=0.76)					
4.4.2 SpO2 target 91 to 95%					
Kapadia 2013	9/44	17/44		14.07%	0.53[0.27,1.06]
Kumar 2014	2/6	8/12		4.41%	0.5[0.15,1.66]
Oei 2016	43/144	41/143		34.05%	1.04[0.73,1.49]
Rabi 2011	10/34	9/34		7.45%	1.11[0.52,2.39]
Rook 2014	31/99	28/94		23.77%	1.05[0.69,1.61]
Wang 2008	10/18	10/23		7.27%	1.28[0.69,2.38]
Subtotal (95% CI)	**345**	**350**		**91.02%**	**0.96[0.77,1.2]**
Total events: 105 (Lower oxygen), 113 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=5.29, df=5(P=0.38); I^2=5.52%					
Test for overall effect: Z=0.33(P=0.74)					
Total (95% CI)	**364**	**373**		**100%**	**0.96[0.78,1.18]**
Total events: 114 (Lower oxygen), 125 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=5.34, df=6(P=0.5); I^2=0%					
Test for overall effect: Z=0.4(P=0.69)					
Test for subgroup differences: Chi^2=0.03, df=1 (P=0.86), I^2=0%					



Favours lower oxygen — Favours higher oxygen

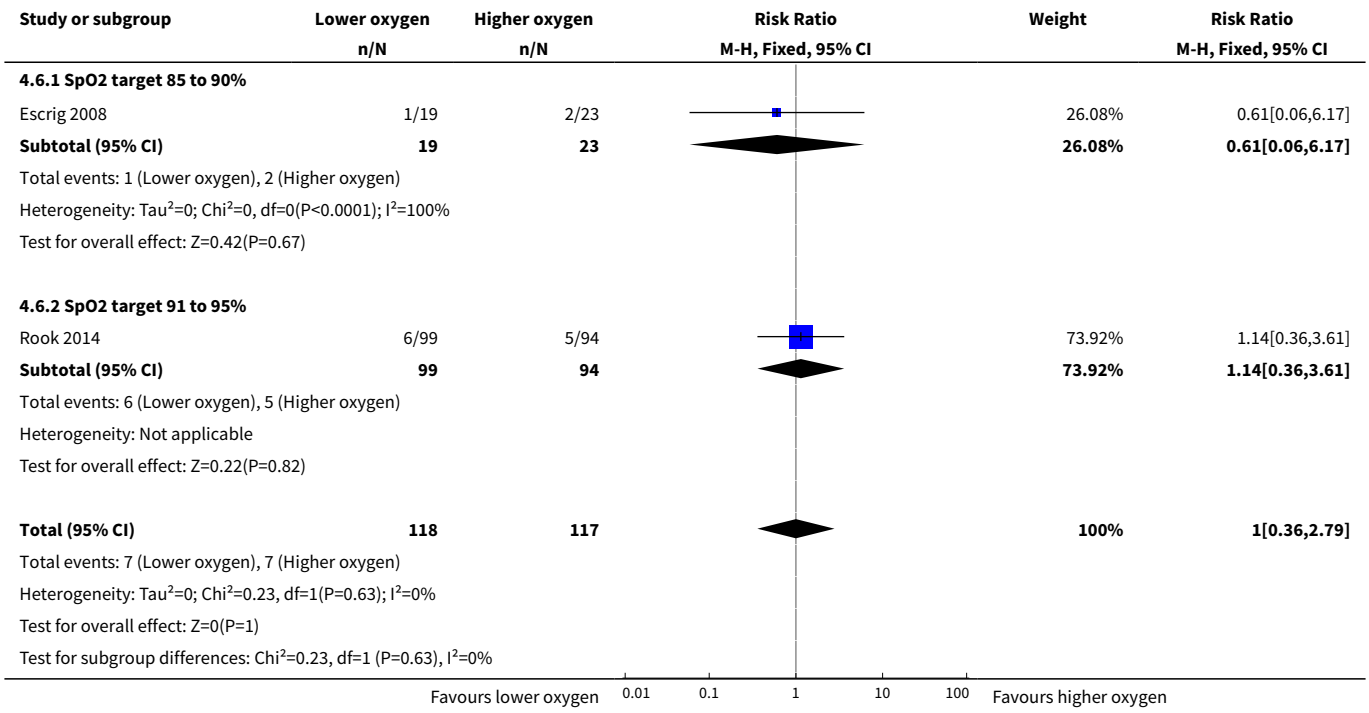
Analysis 4.5. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 5 Time to reach desired oxygen saturation target.

Study or subgroup	Lower oxygen N	Lower oxygen Mean(SD)	Higher oxygen N	Higher oxygen Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.5.1 SpO2 target 85 to 90%							
Escrig 2008	19	16.5 (1.7)	23	18.2 (3.4)		100%	-1.7[-3.28,-0.12]
Subtotal ***	**19**		**23**			**100%**	**-1.7[-3.28,-0.12]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.11(P=0.03)							
Total ***	**19**		**23**			**100%**	**-1.7[-3.28,-0.12]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.11(P=0.03)							

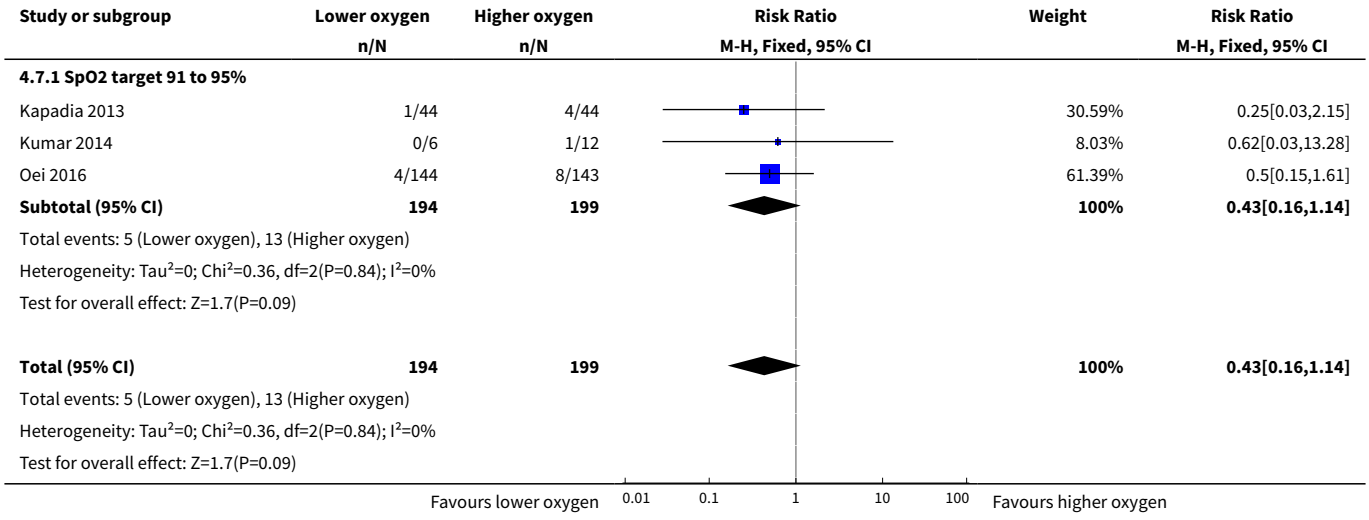


Favours lower oxygen — Favours higher oxygen

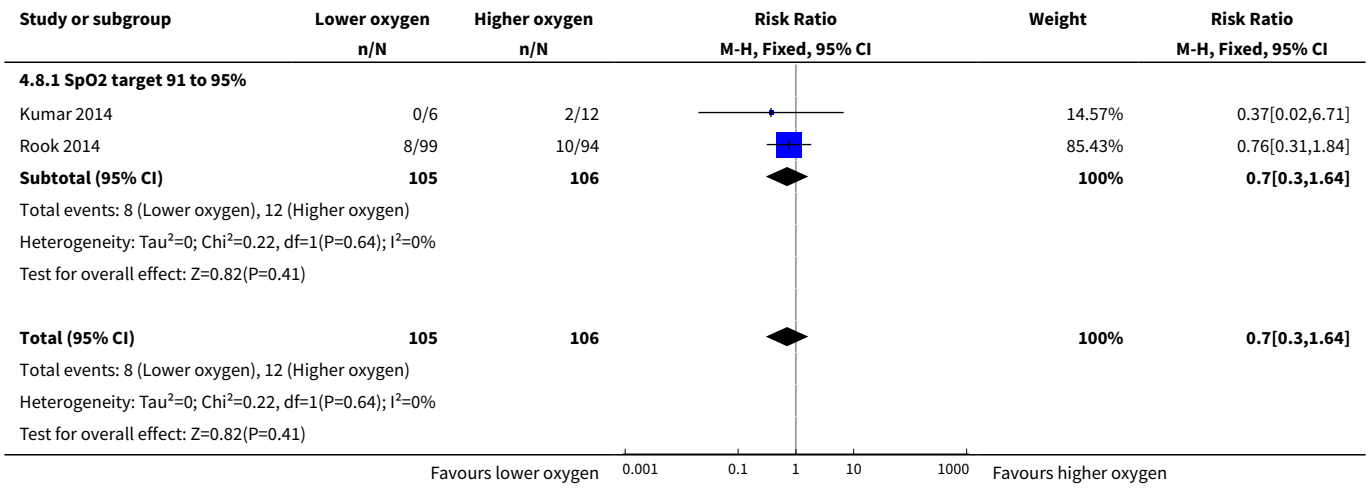
Analysis 4.6. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 6 Retinopathy of prematurity.



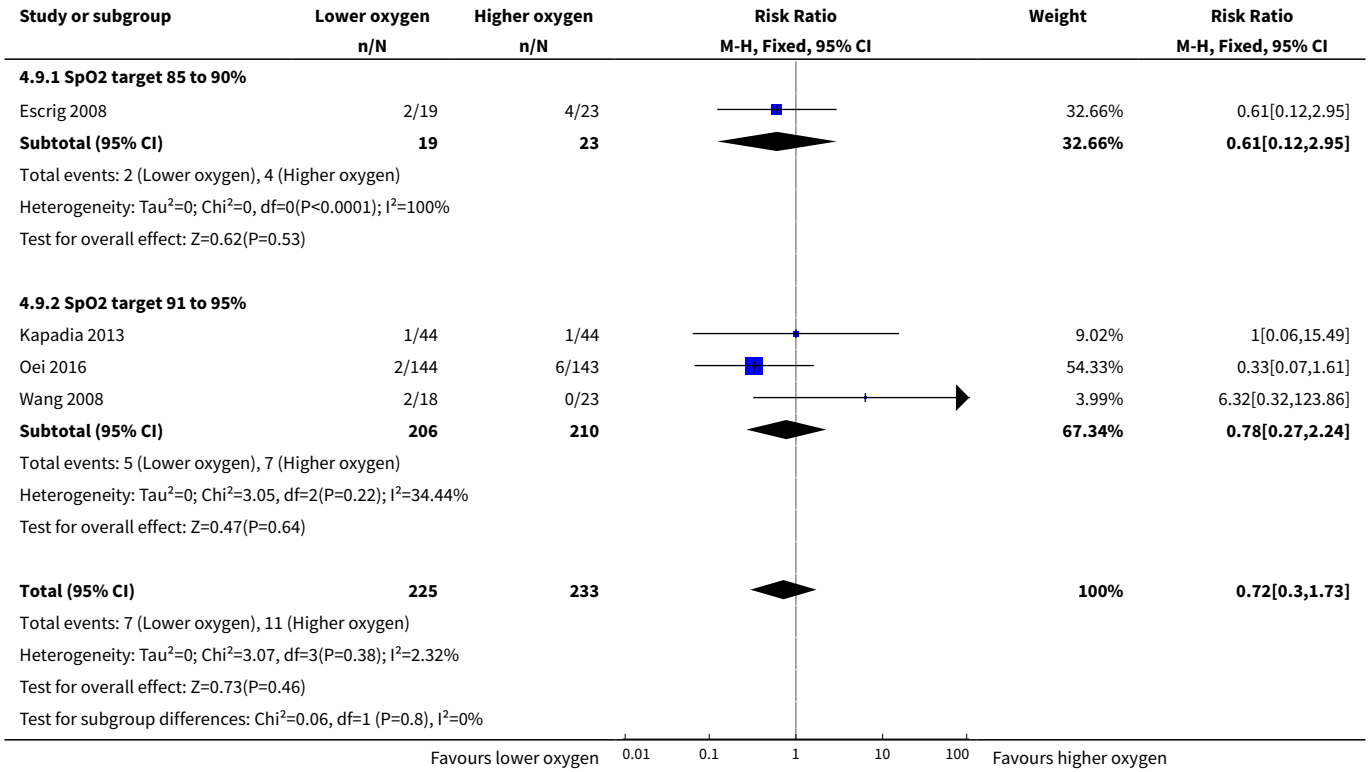
Analysis 4.7. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 7 Severe retinopathy of prematurity (≥ stage 3).



Analysis 4.8. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 8 Intraventricular haemorrhage.



Analysis 4.9. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 9 Severe intraventricular haemorrhage (grade 3 or 4).

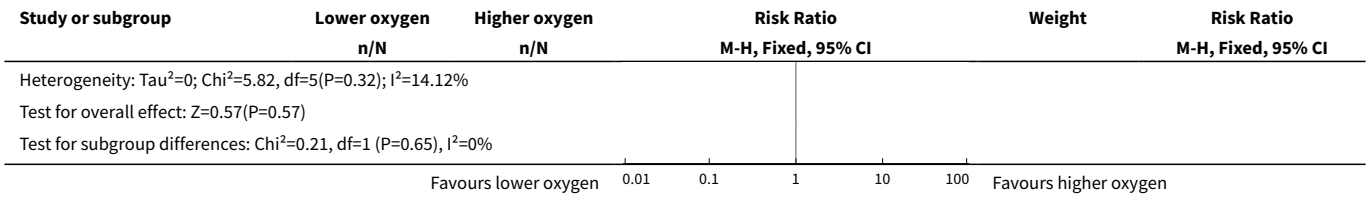


Analysis 4.10. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 10 Periventricular leukomalacia.

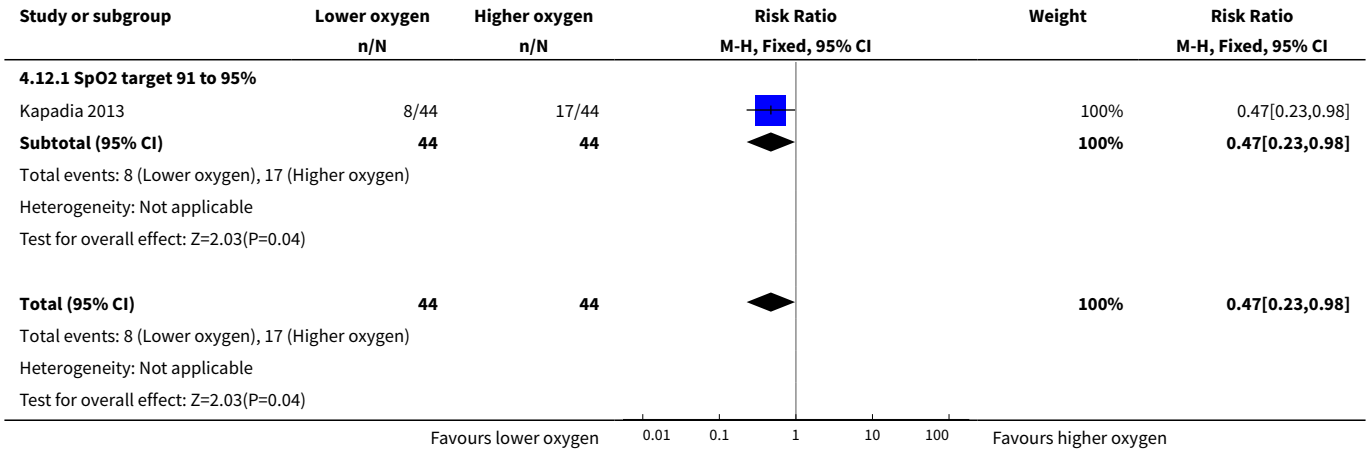
Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.10.1 SpO2 target 85 to 90%					
Escrig 2008	1/19	1/23		37.62%	1.21[0.08,18.09]
Subtotal (95% CI)	**19**	**23**		**37.62%**	**1.21[0.08,18.09]**
Total events: 1 (Lower oxygen), 1 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.14(P=0.89)					
4.10.2 SpO2 target 91 to 95%					
Kapadia 2013	0/44	1/44		62.38%	0.33[0.01,7.97]
Subtotal (95% CI)	**44**	**44**		**62.38%**	**0.33[0.01,7.97]**
Total events: 0 (Lower oxygen), 1 (Higher oxygen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					
Total (95% CI)	**63**	**67**		**100%**	**0.66[0.09,4.73]**
Total events: 1 (Lower oxygen), 2 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=0.37, df=1(P=0.54); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					
Test for subgroup differences: Chi^2=0.37, df=1 (P=0.54), I^2=0%					

Analysis 4.11. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 11 Necrotising enterocolitis.

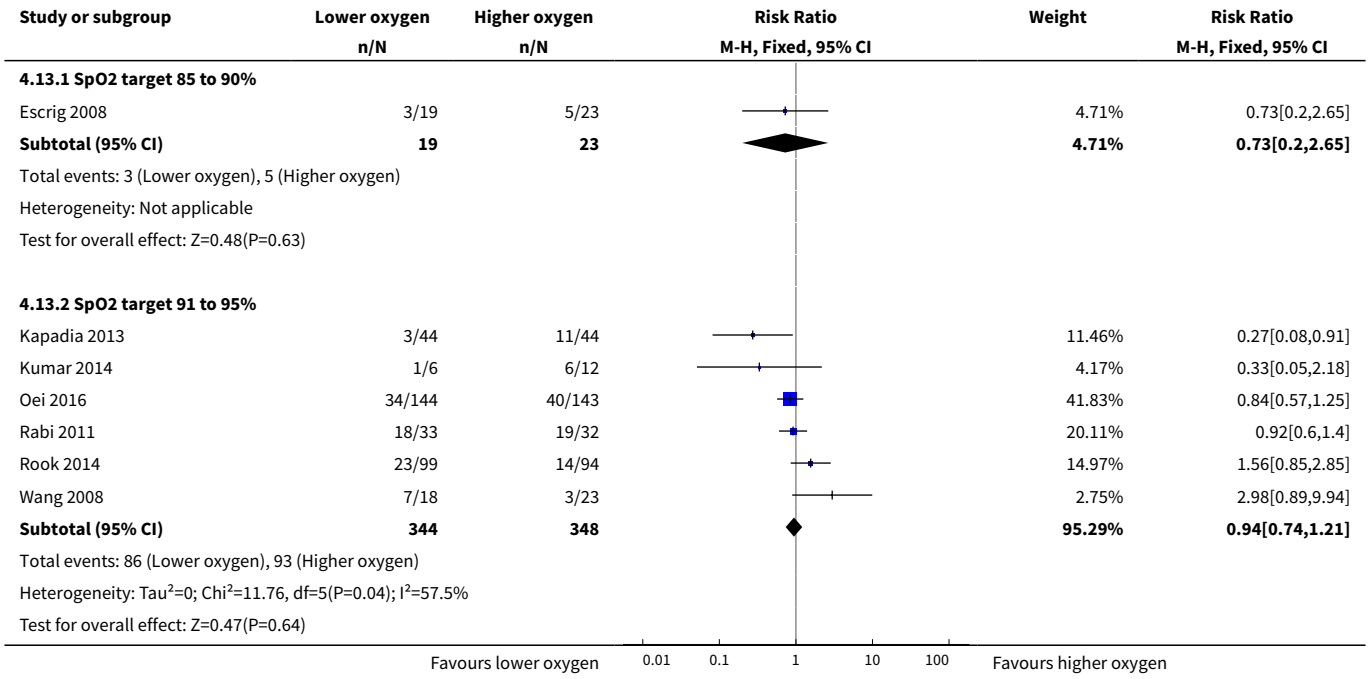
Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.11.1 SpO2 target 85 to 90%					
Escrig 2008	0/19	1/23		8.59%	0.4[0.02,9.29]
Subtotal (95% CI)	**19**	**23**		**8.59%**	**0.4[0.02,9.29]**
Total events: 0 (Lower oxygen), 1 (Higher oxygen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.57(P=0.57)					
4.11.2 SpO2 target 91 to 95%					
Kapadia 2013	1/44	6/44		37.81%	0.17[0.02,1.33]
Kumar 2014	1/6	4/12		16.81%	0.5[0.07,3.55]
Oei 2016	5/144	1/143		6.32%	4.97[0.59,41.97]
Rook 2014	4/99	3/94		19.4%	1.27[0.29,5.51]
Wang 2008	1/18	2/23		11.07%	0.64[0.06,6.5]
Subtotal (95% CI)	**311**	**316**		**91.41%**	**0.85[0.4,1.79]**
Total events: 12 (Lower oxygen), 16 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=5.62, df=4(P=0.23); I^2=28.77%					
Test for overall effect: Z=0.43(P=0.67)					
Total (95% CI)	**330**	**339**		**100%**	**0.81[0.39,1.67]**
Total events: 12 (Lower oxygen), 17 (Higher oxygen)					

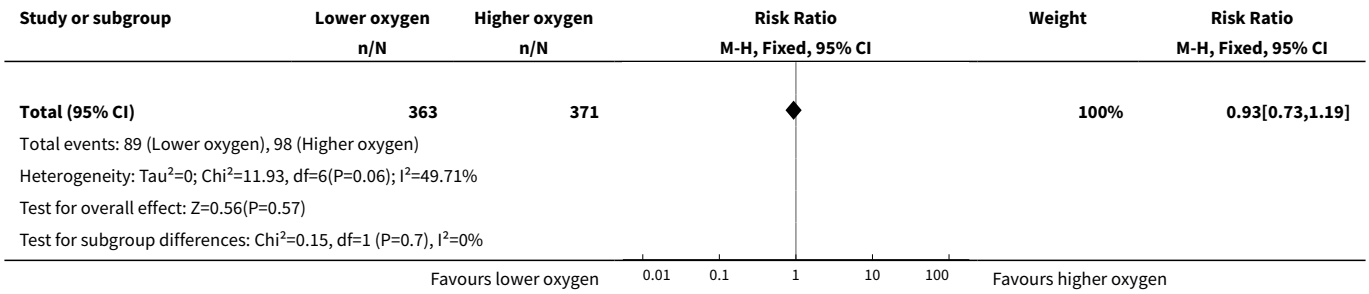


Analysis 4.12. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 12 Chronic lung disease (28 days age).

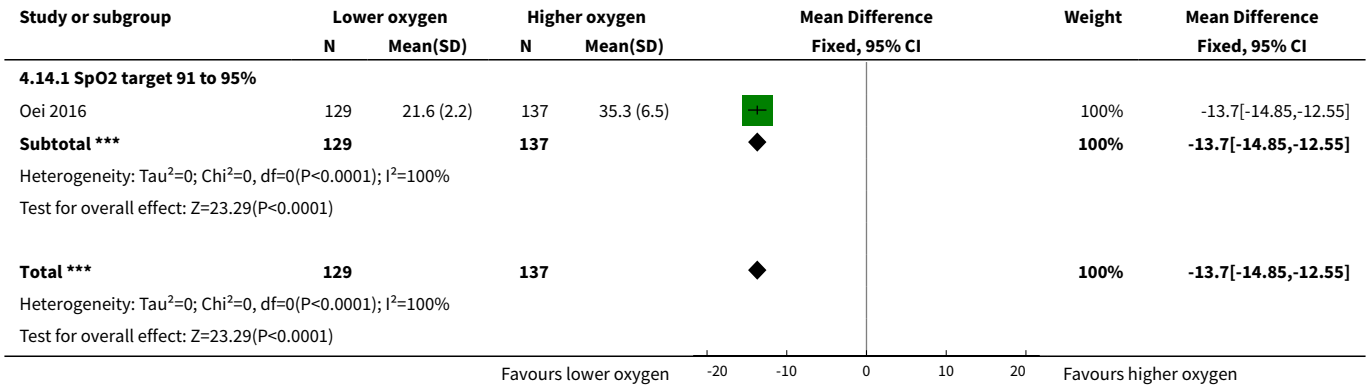


Analysis 4.13. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 13 Chronic lung disease (36 weeks' corrected age).

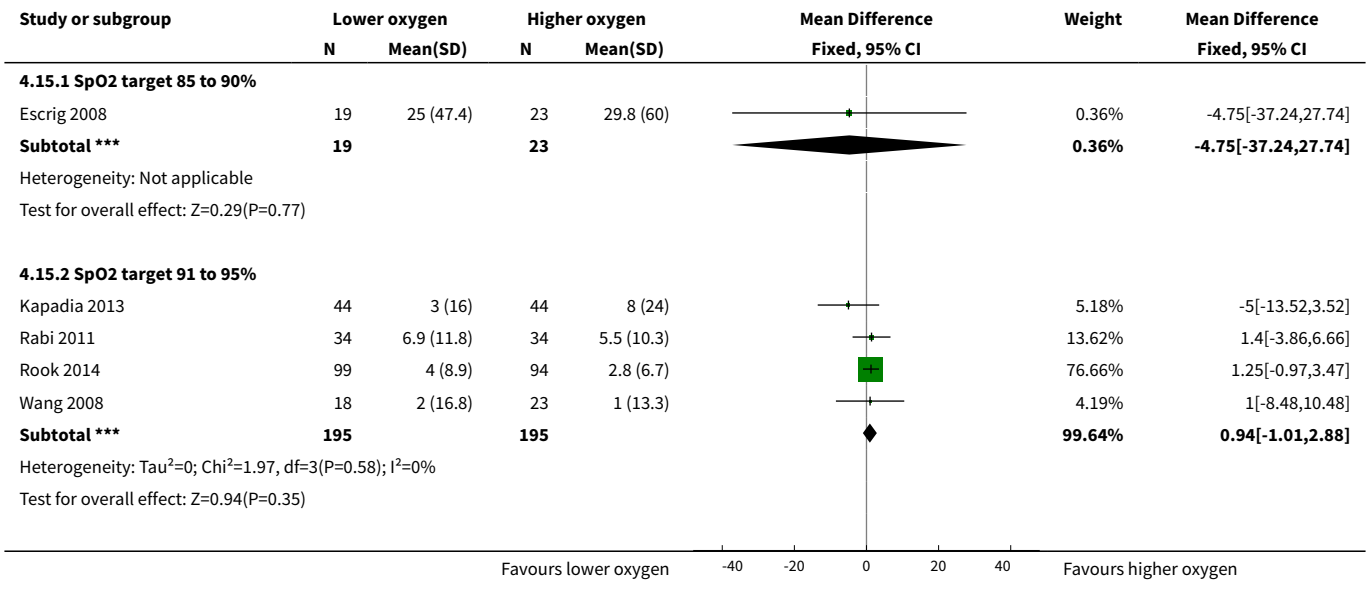


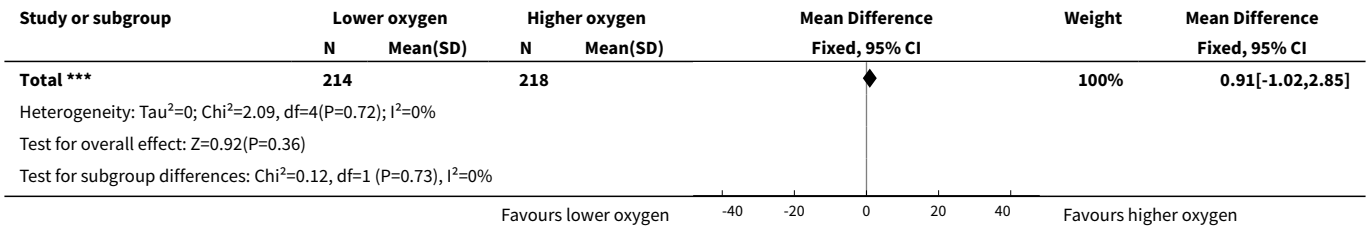


Analysis 4.14. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 14 Duration of respiratory support (mechanical ventilation or CPAP) (days from birth).

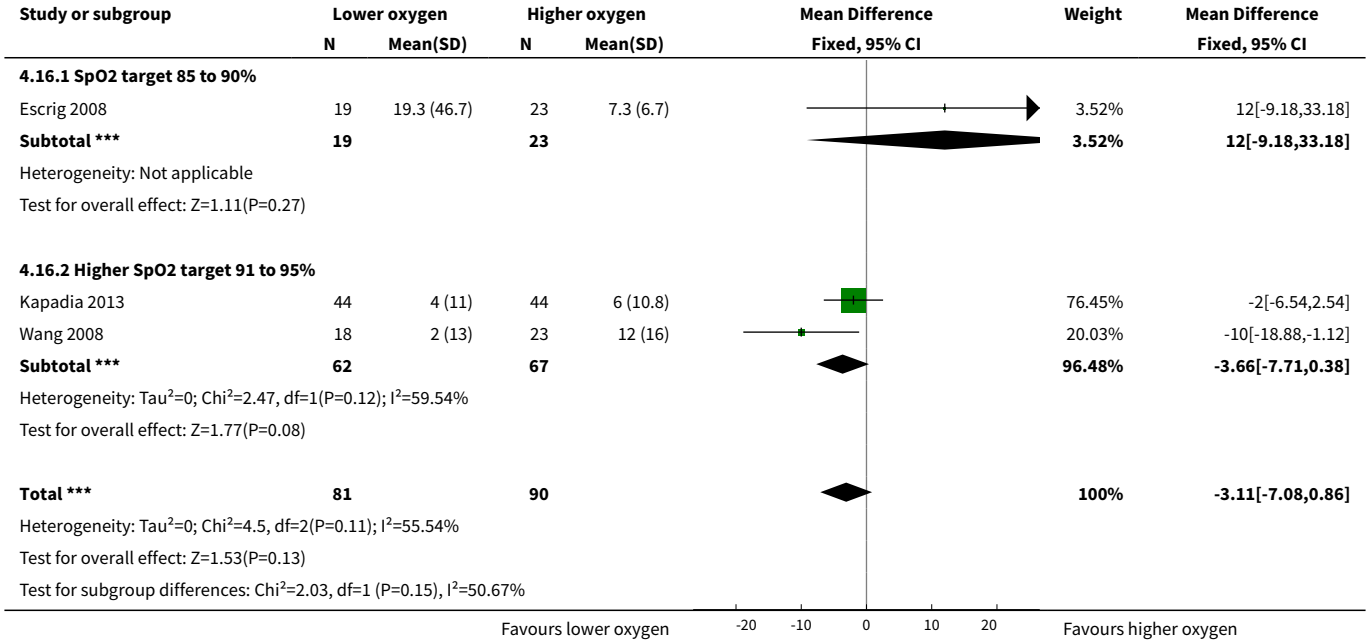


Analysis 4.15. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 15 Duration of respiratory support (mechanical ventilation) (days from birth).

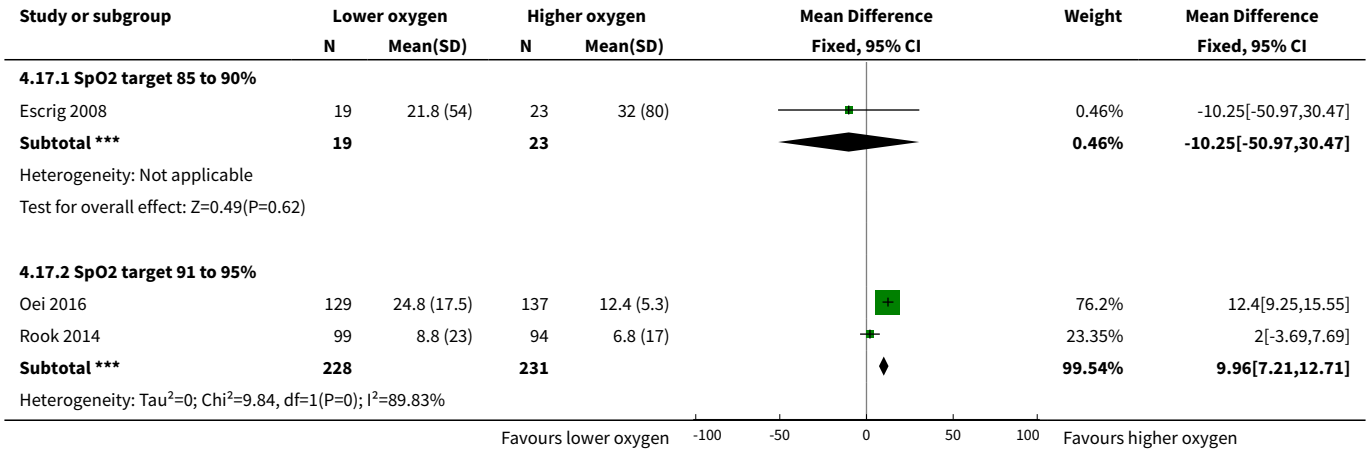


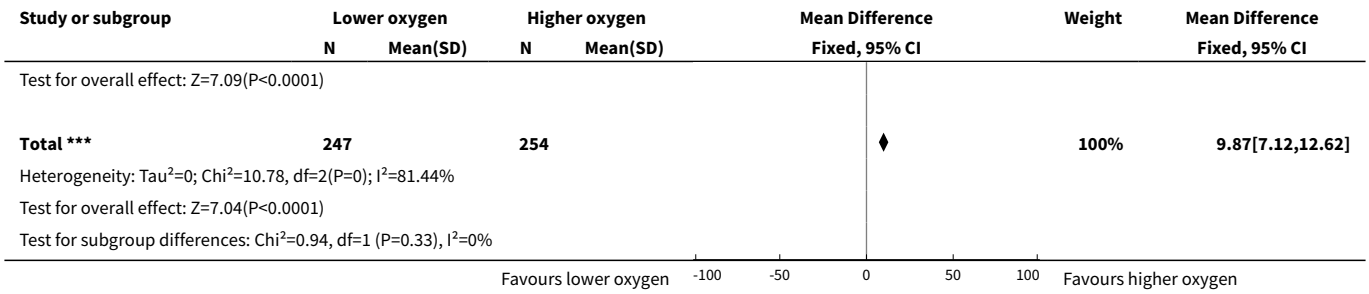


Analysis 4.16. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 16 Duration of respiratory support (CPAP) (days from birth).

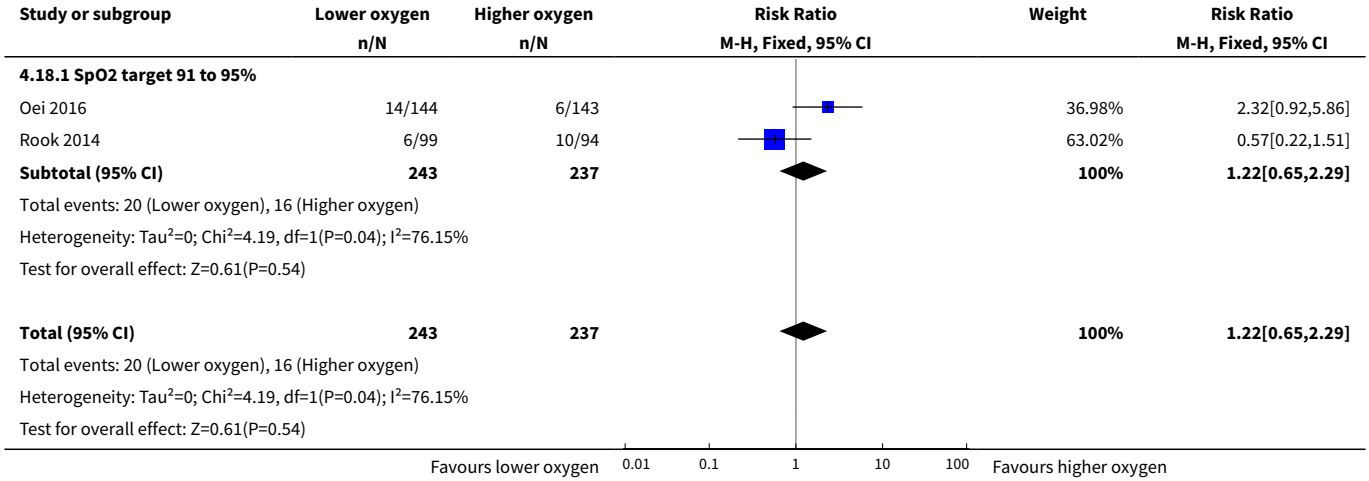


Analysis 4.17. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 17 Duration of supplemental oxygen administration.

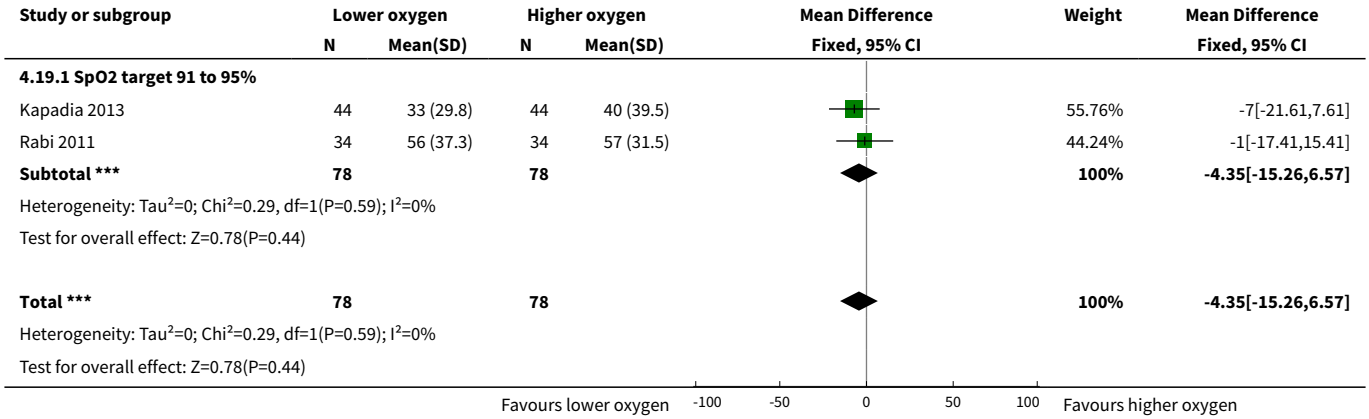




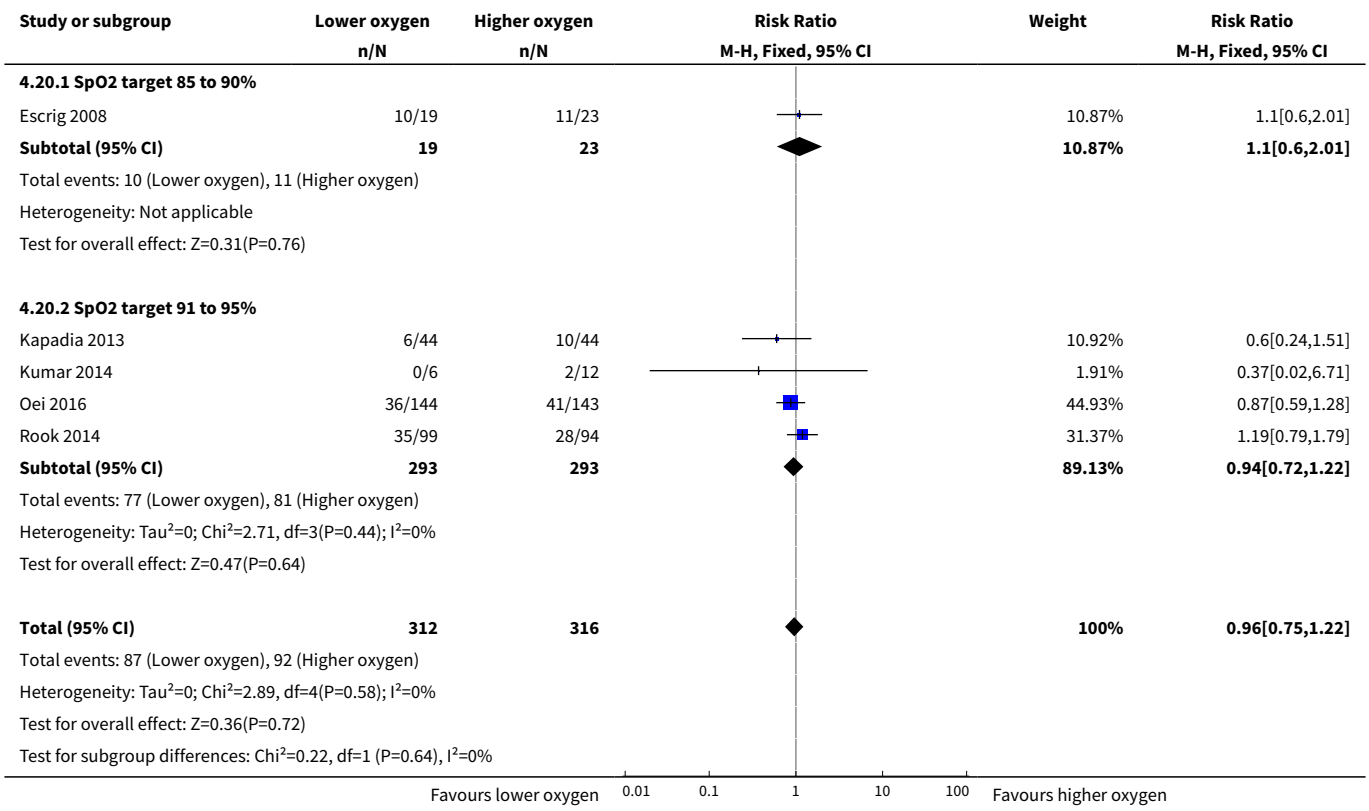
Analysis 4.18. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 18 Mortality to follow up (> 18 months).



Analysis 4.19. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 19 Duration of hospitalisation (days).



Analysis 4.20. Comparison 4 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by highest SpO_2 limit at 10 minutes, Outcome 20 Patent ductus arteriosus (not prespecified).



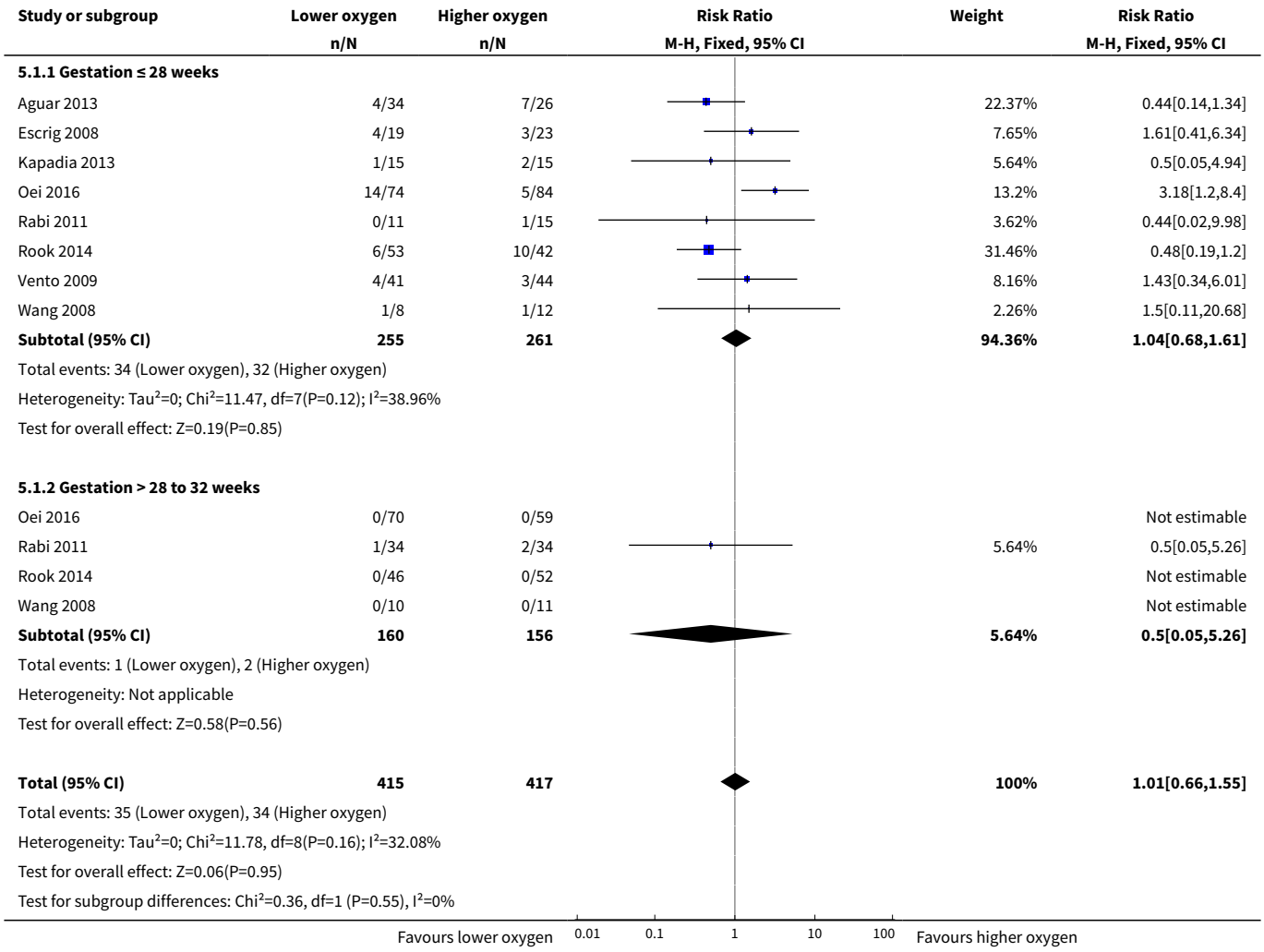
Comparison 5. Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality near term corrected age or discharge (latest reported)	8	832	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.66, 1.55]
1.1 Gestation ≤ 28 weeks	8	516	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.68, 1.61]
1.2 Gestation > 28 to 32 weeks	4	316	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.26]
2 Neurodevelopmental disability	1	31	Risk Ratio (M-H, Fixed, 95% CI)	3.64 [0.42, 31.27]
2.1 Gestation ≤ 28 weeks	1	31	Risk Ratio (M-H, Fixed, 95% CI)	3.64 [0.42, 31.27]
3 IPPV in the delivery room	2	102	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.09]
3.1 Gestation ≤ 28 weeks	2	102	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.09]
4 Intubation in the delivery room	4	467	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.85, 1.35]
4.1 Gestation ≤ 28 weeks	4	338	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.84, 1.34]

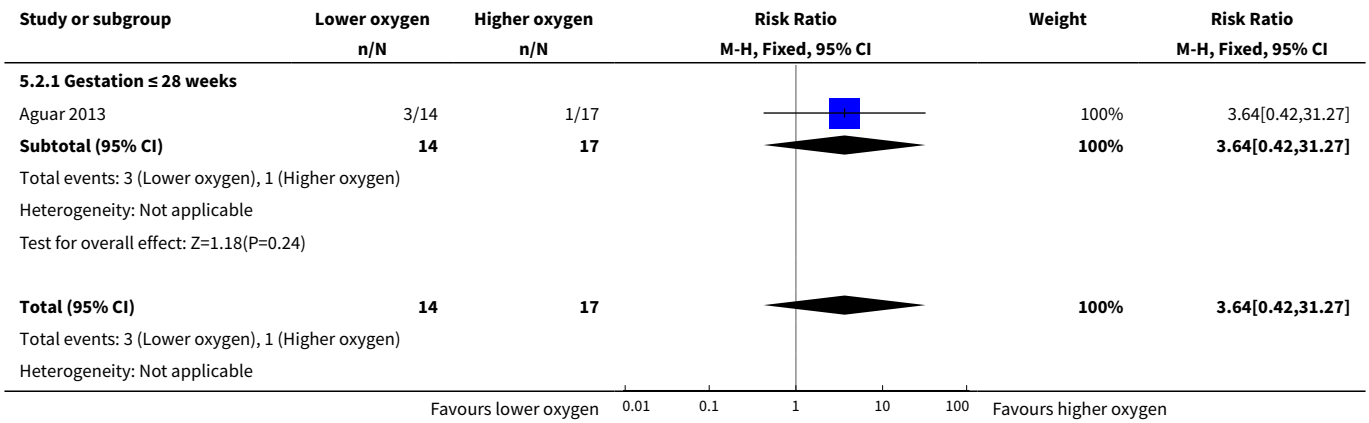
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Gestation > 28 to 32 weeks	1	129	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.49, 2.97]
5 Time to reach desired oxygen saturation target	2	102	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-1.83, 0.79]
5.1 Gestation ≤ 28 weeks	2	102	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-1.83, 0.79]
6 Time to reach heart rate > 100 bpm	1	60	Mean Difference (IV, Fixed, 95% CI)	0.27 [-1.21, 1.75]
6.1 Gestation ≤ 28 weeks	1	60	Mean Difference (IV, Fixed, 95% CI)	0.27 [-1.21, 1.75]
7 Retinopathy of prematurity	4	259	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.38, 1.33]
7.1 Gestation ≤ 28 weeks	4	259	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.38, 1.33]
8 Severe retinopathy of prematurity (≥ stage 3)	5	464	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.46, 1.89]
8.1 Gestation ≤ 28 weeks	5	317	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.43, 1.82]
8.2 Gestation > 28 to 32 weeks	1	147	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [0.09, 54.54]
9 Intraventricular haemorrhage	2	217	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.52, 1.48]
9.1 Gestation ≤ 28 weeks	2	217	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.52, 1.48]
10 Severe intraventricular haemorrhage (grade 3 or 4)	6	537	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.55, 1.87]
10.1 Gestation ≤ 28 weeks	6	388	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.51, 1.79]
10.2 Gestation > 28 to 32 weeks	2	149	Risk Ratio (M-H, Fixed, 95% CI)	3.27 [0.15, 72.23]
11 Periventricular leukomalacia	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.08, 18.09]
11.1 Gestation ≤ 28 weeks	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.08, 18.09]
12 Necrotising enterocolitis	7	731	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.78, 3.17]
12.1 Gestation ≤ 28 weeks	7	483	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.80, 4.01]
12.2 Gestation > 28 to 32 weeks	3	248	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.23, 4.47]
13 Chronic lung disease (28 days age)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.53, 3.05]
13.1 Gestation ≤ 28 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.53, 3.05]
14 Chronic lung disease (36 weeks' corrected age)	8	694	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.72, 1.13]
14.1 Gestation ≤ 28 weeks	8	411	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.72, 1.13]

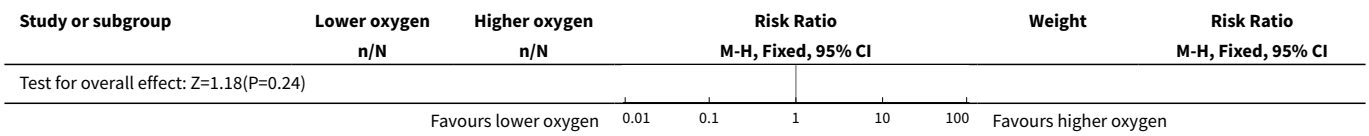
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.2 Gestation > 28 to 32 weeks	3	283	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.36, 2.33]
15 Duration of respiratory support (mechanical ventilation or CPAP) (days from birth)	1	60	Mean Difference (IV, Fixed, 95% CI)	1.06 [-2.63, 4.75]
15.1 Gestation ≤ 28 weeks	1	60	Mean Difference (IV, Fixed, 95% CI)	1.06 [-2.63, 4.75]
16 Duration of respiratory support (mechanical ventilation) (days from birth)	2	120	Mean Difference (IV, Fixed, 95% CI)	-13.64 [-32.62, 5.33]
16.1 Gestation ≤ 28 weeks	2	120	Mean Difference (IV, Fixed, 95% CI)	-13.64 [-32.62, 5.33]
17 Duration of respiratory support (CPAP) (days from birth)	2	120	Mean Difference (IV, Fixed, 95% CI)	-2.09 [-12.85, 8.67]
17.1 Gestation ≤ 28 weeks	2	120	Mean Difference (IV, Fixed, 95% CI)	-2.09 [-12.85, 8.67]
18 Duration of supplemental oxygen administration	3	180	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-16.90, 15.91]
18.1 Gestation ≤ 28 weeks	3	180	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-16.90, 15.91]
19 Mortality to follow up (> 18 months)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.20, 1.53]
19.1 Gestation ≤ 28 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.20, 1.53]
20 Postnatal growth failure (weight < 10th percentile at discharge)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.55, 1.33]
20.1 Gestation ≤ 28 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.55, 1.33]
21 Duration of hospitalisation (days)	1	60	Mean Difference (IV, Fixed, 95% CI)	28.0 [-8.96, 64.96]
21.1 Gestation ≤ 28 weeks	1	60	Mean Difference (IV, Fixed, 95% CI)	28.0 [-8.96, 64.96]
22 Patent ductus arteriosus (not prespecified)	7	710	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.81, 1.14]
22.1 Gestation ≤ 28 weeks	7	483	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.14]
22.2 Gestation > 28 to 32 weeks	2	227	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.54, 2.05]

Analysis 5.1. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 1 Mortality near term corrected age or discharge (latest reported).

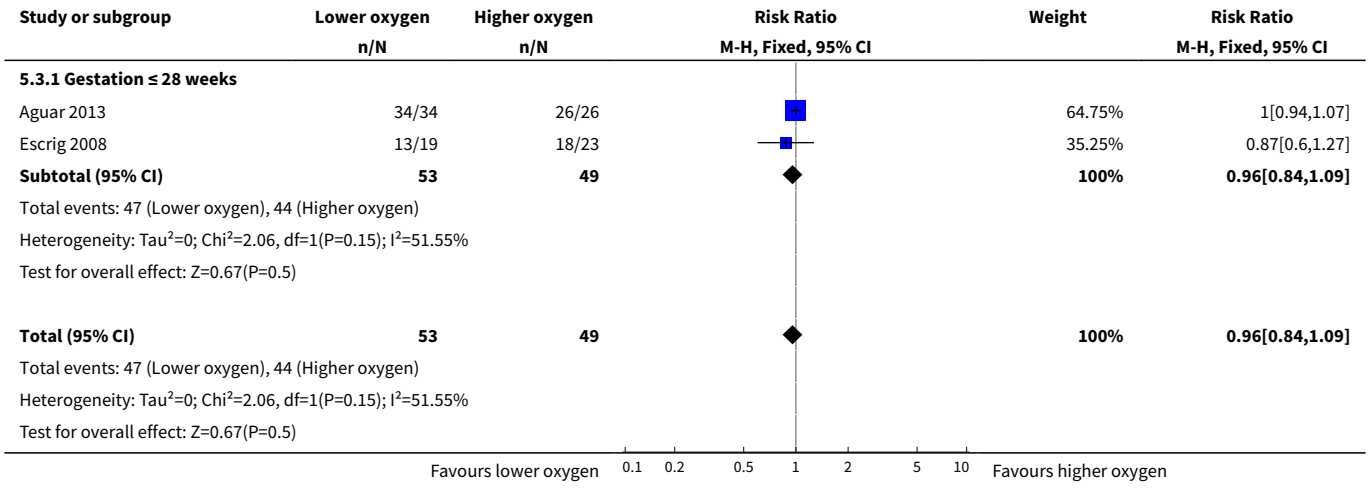


Analysis 5.2. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 2 Neurodevelopmental disability.

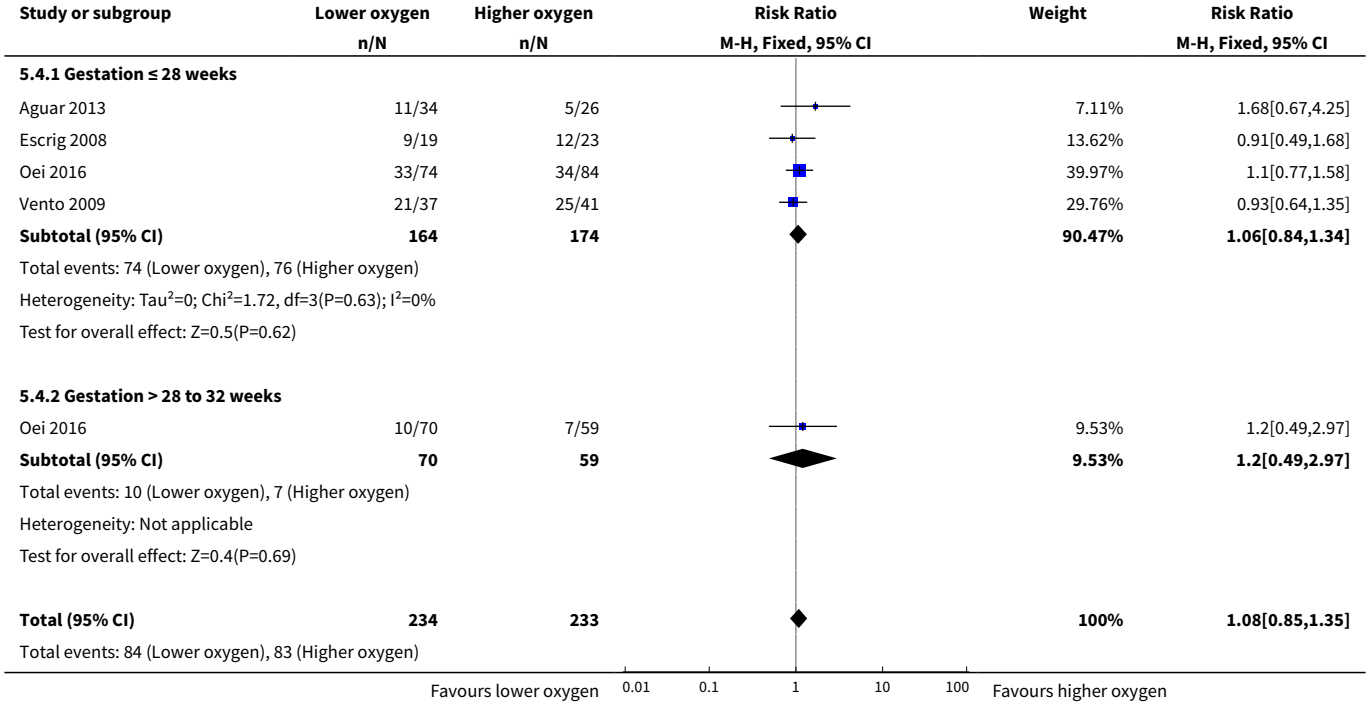


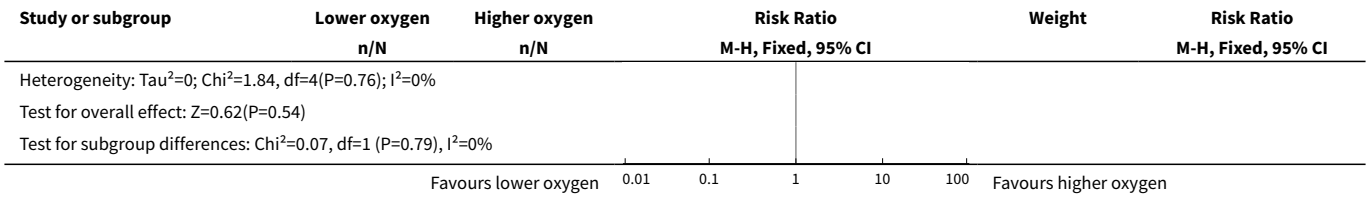


Analysis 5.3. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 3 IPPV in the delivery room.

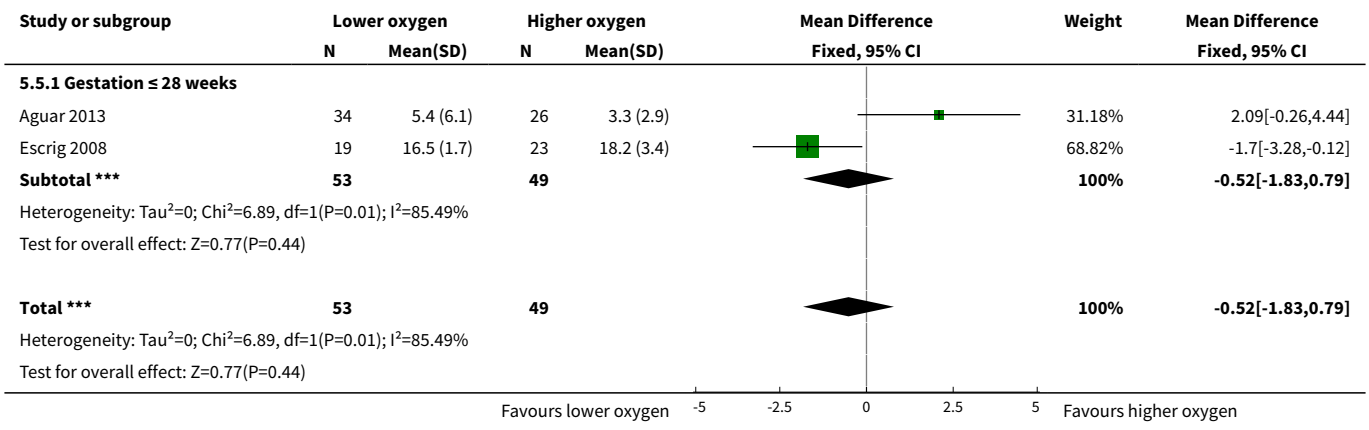


Analysis 5.4. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 4 Intubation in the delivery room.

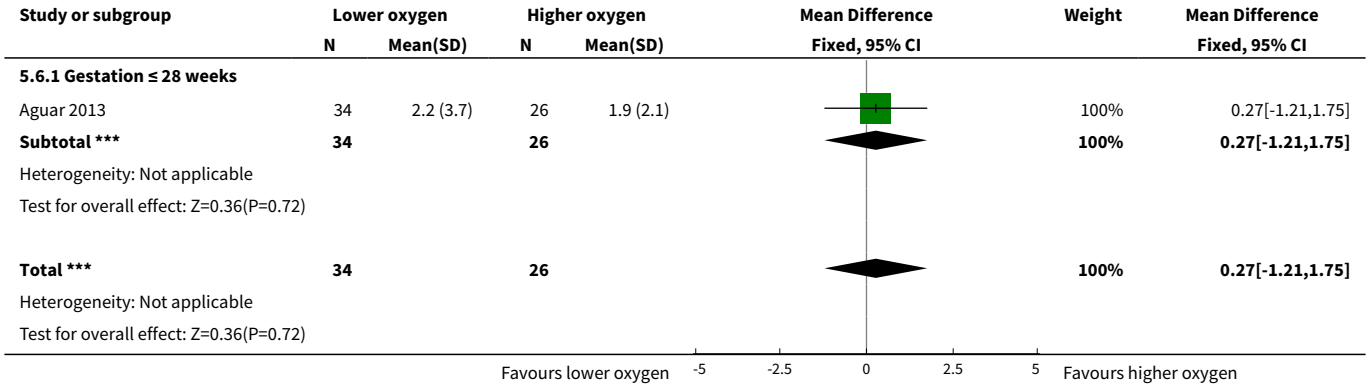




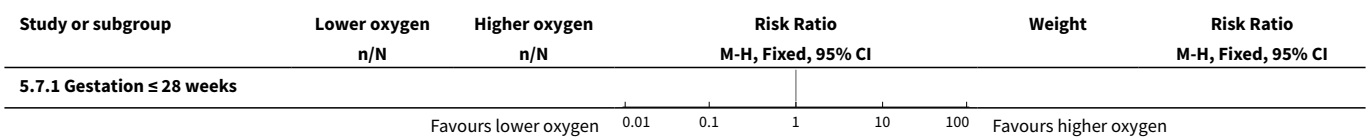
Analysis 5.5. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 5 Time to reach desired oxygen saturation target.

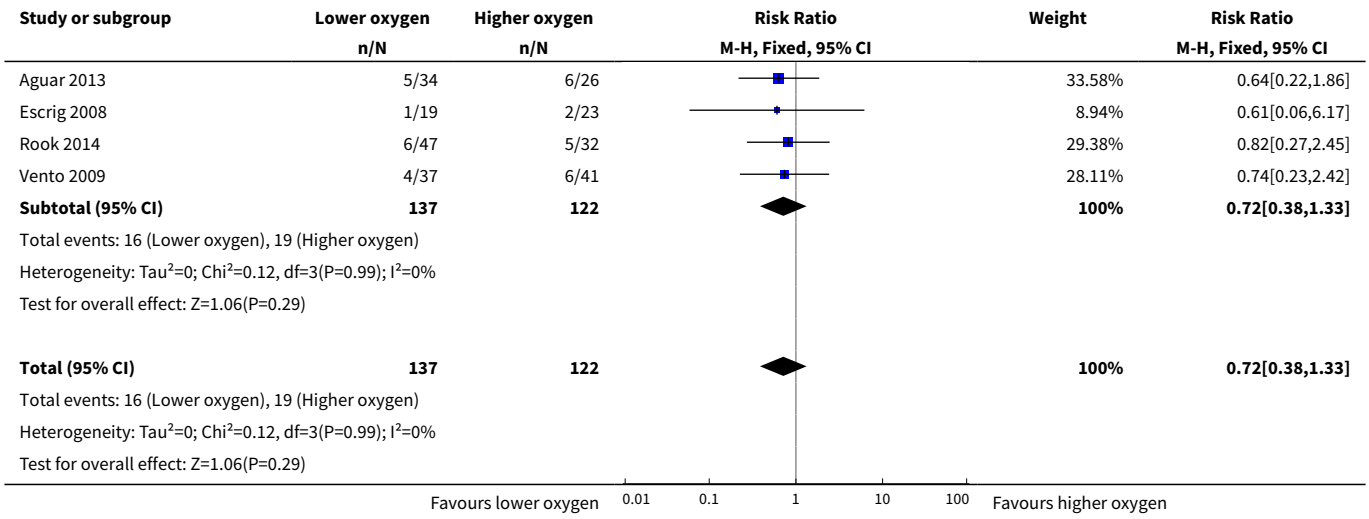


Analysis 5.6. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 6 Time to reach heart rate > 100 bpm.

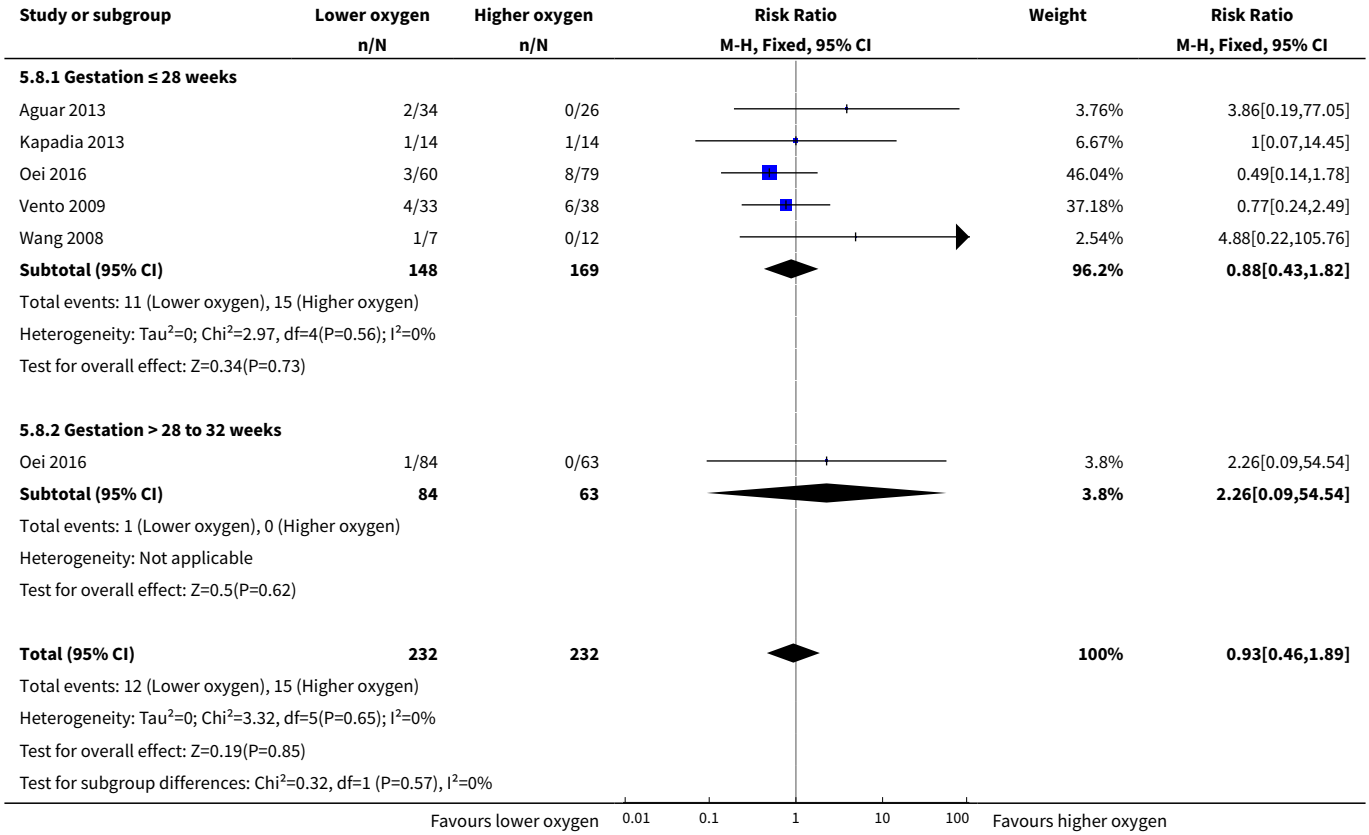


Analysis 5.7. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 7 Retinopathy of prematurity.

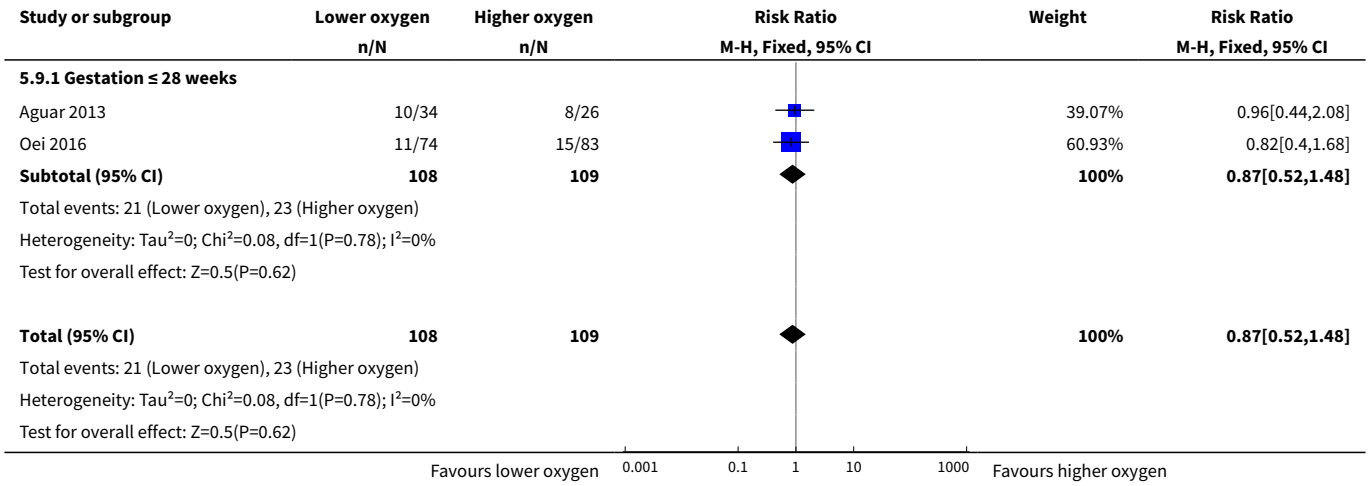




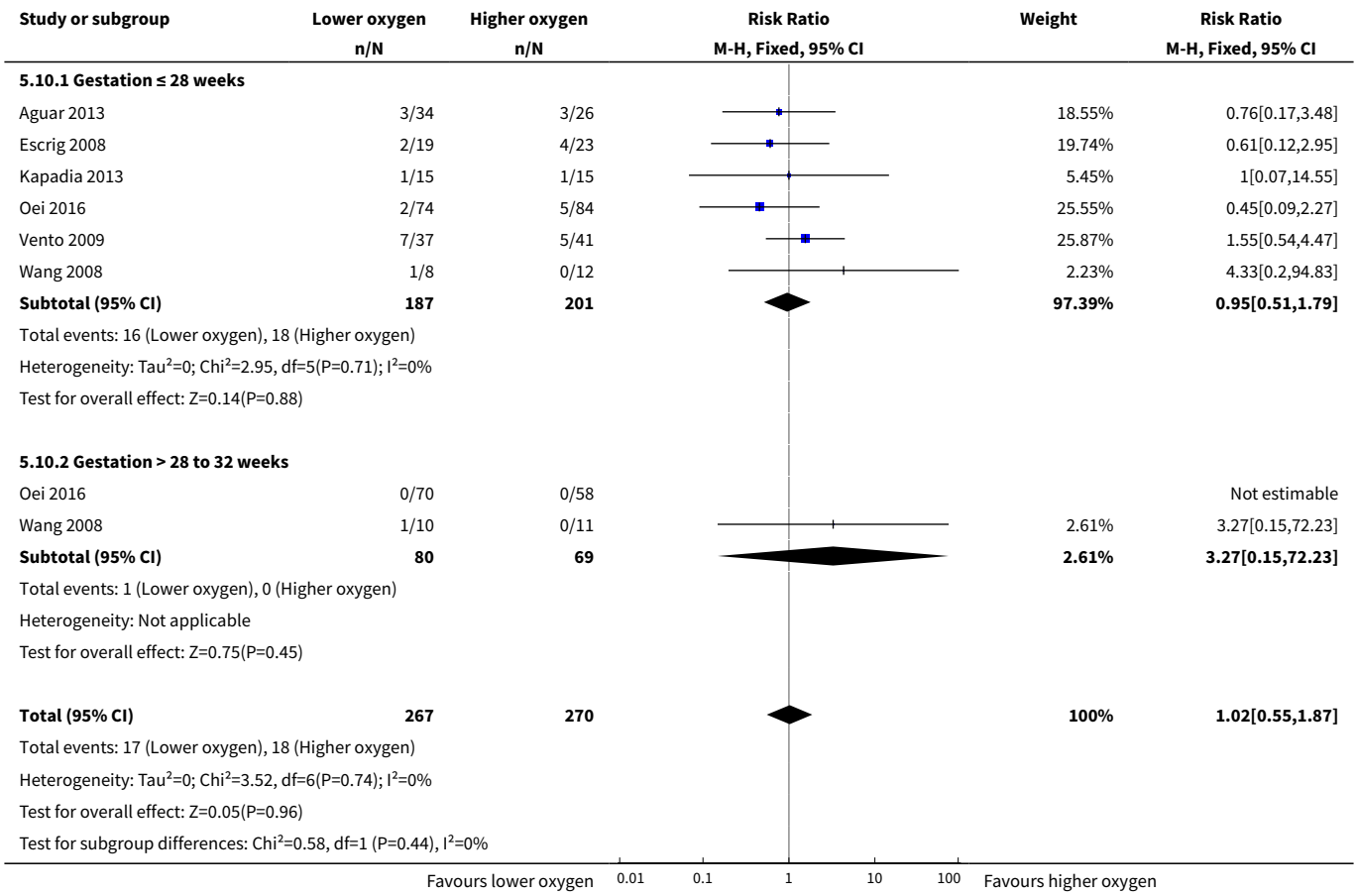
Analysis 5.8. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 8 Severe retinopathy of prematurity (≥ stage 3).



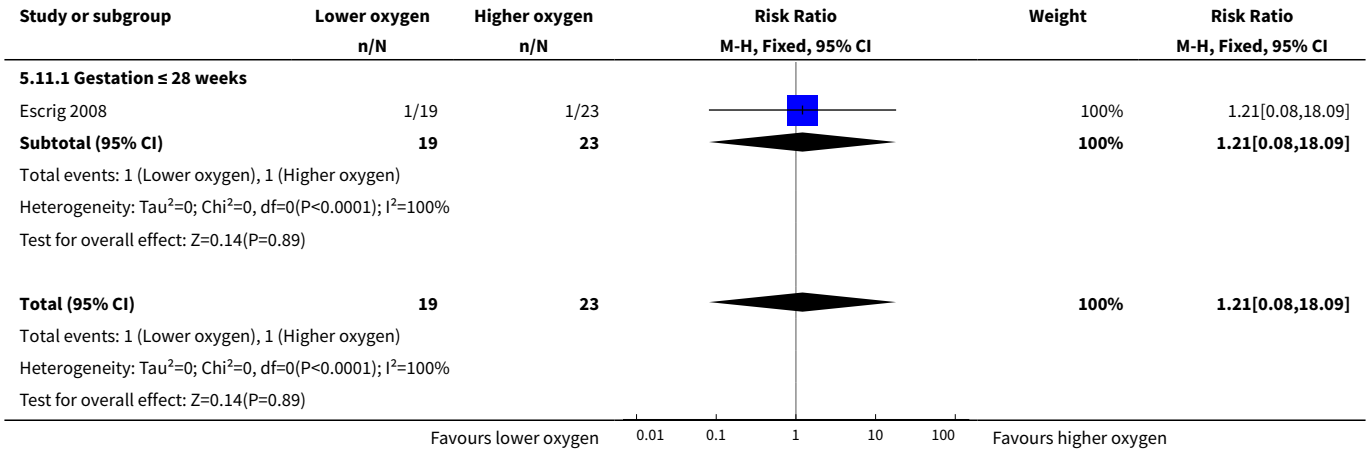
Analysis 5.9. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 9 Intraventricular haemorrhage.



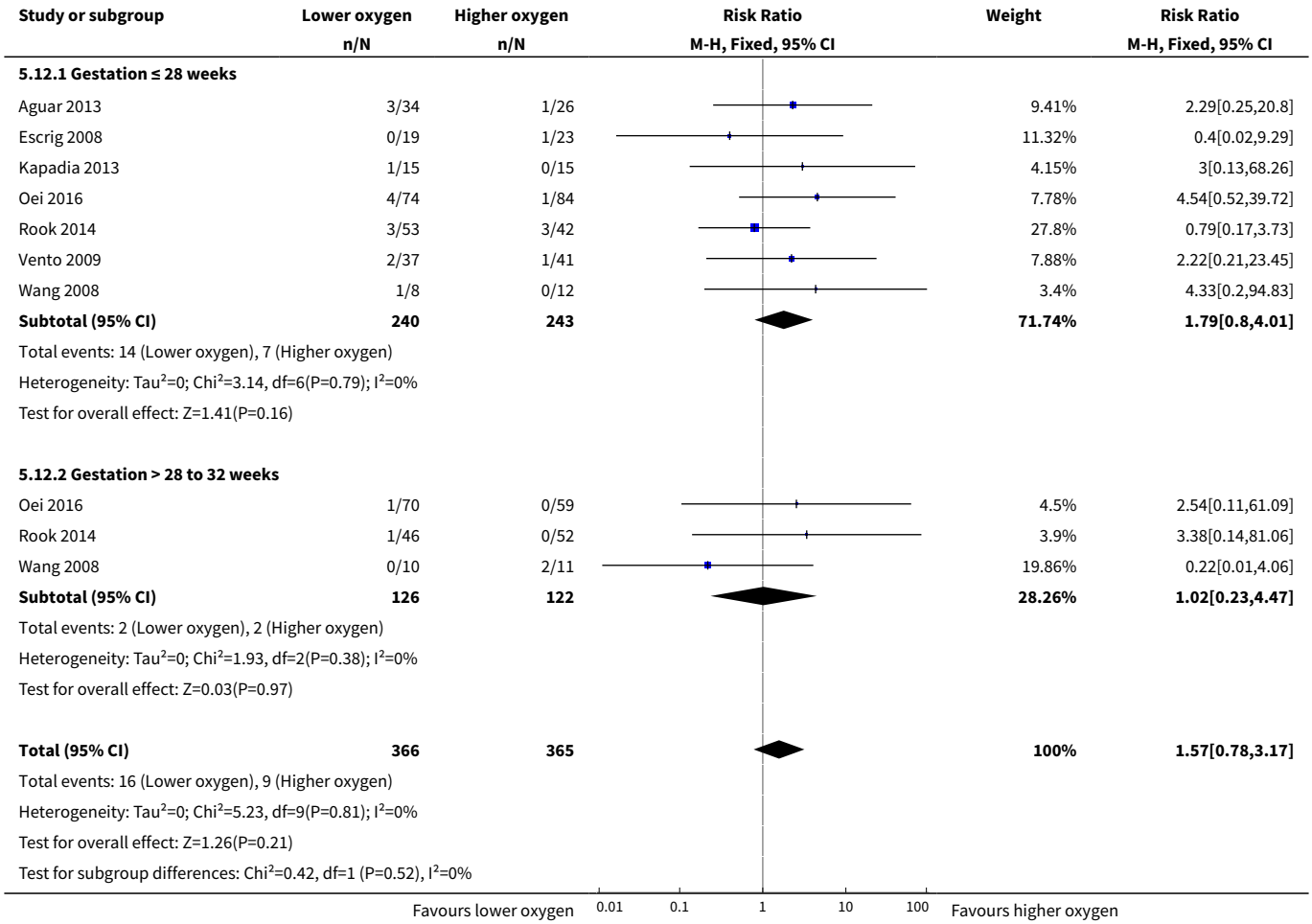
Analysis 5.10. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 10 Severe intraventricular haemorrhage (grade 3 or 4).



Analysis 5.11. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 11 Periventricular leukomalacia.

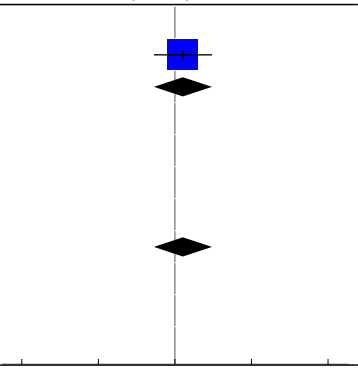


Analysis 5.12. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 12 Necrotising enterocolitis.



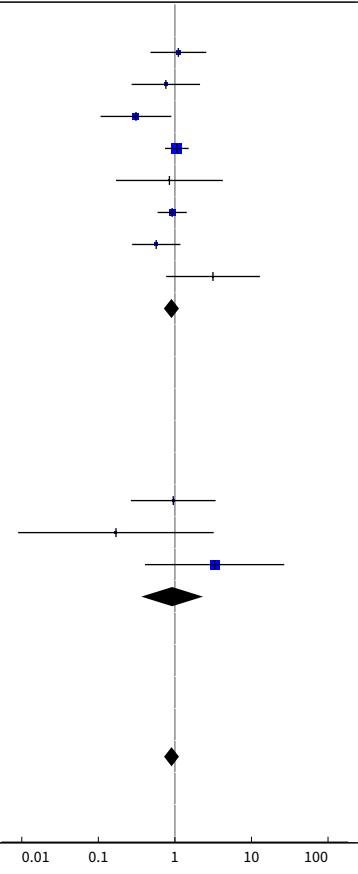
Analysis 5.13. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 13 Chronic lung disease (28 days age).

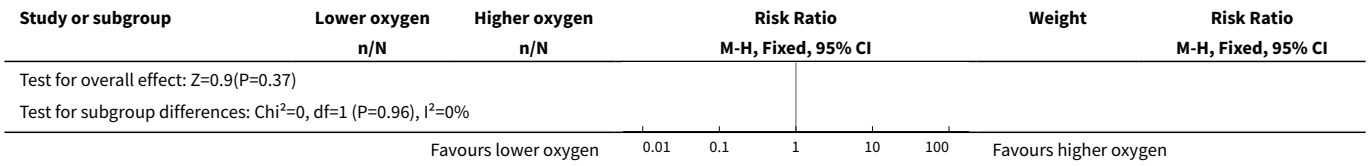
Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.13.1 Gestation ≤ 28 weeks					
Aguar 2013	10/34	6/26		100%	1.27[0.53,3.05]
Subtotal (95% CI)	**34**	**26**		**100%**	**1.27[0.53,3.05]**
Total events: 10 (Lower oxygen), 6 (Higher oxygen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					
Total (95% CI)	**34**	**26**		**100%**	**1.27[0.53,3.05]**
Total events: 10 (Lower oxygen), 6 (Higher oxygen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					



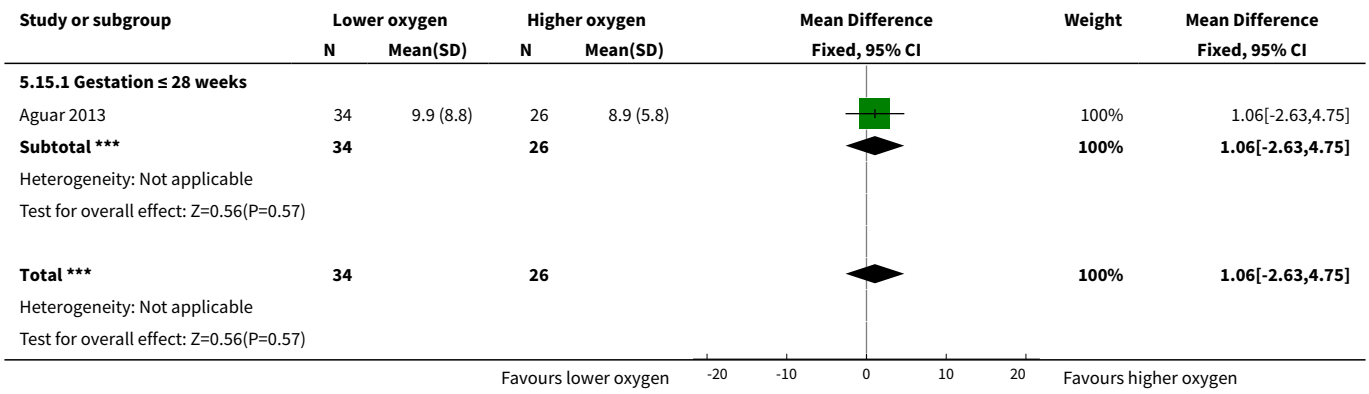
Analysis 5.14. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 14 Chronic lung disease (36 weeks' corrected age).

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
5.14.1 Gestation ≤ 28 weeks					
Aguar 2013	10/30	6/20		7.32%	1.11[0.48,2.57]
Escrig 2008	4/15	7/20		6.1%	0.76[0.27,2.13]
Kapadia 2013	3/14	9/13		9.49%	0.31[0.11,0.9]
Oei 2016	29/60	36/79		31.6%	1.06[0.74,1.51]
Rabi 2011	2/11	3/14		2.68%	0.85[0.17,4.23]
Rook 2014	23/47	17/32		20.57%	0.92[0.59,1.43]
Vento 2009	6/17	13/21		11.83%	0.57[0.28,1.18]
Wang 2008	4/7	2/11		1.58%	3.14[0.77,12.85]
Subtotal (95% CI)	**201**	**210**		**91.16%**	**0.9[0.72,1.13]**
Total events: 81 (Lower oxygen), 93 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=9.57, df=7(P=0.21); I^2=26.86%					
Test for overall effect: Z=0.9(P=0.37)					
5.14.2 Gestation > 28 to 32 weeks					
Oei 2016	5/84	4/64		4.62%	0.95[0.27,3.4]
Rook 2014	0/52	3/62		3.25%	0.17[0.01,3.21]
Wang 2008	3/10	1/11		0.97%	3.3[0.41,26.81]
Subtotal (95% CI)	**146**	**137**		**8.84%**	**0.92[0.36,2.33]**
Total events: 8 (Lower oxygen), 8 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=2.7, df=2(P=0.26); I^2=25.86%					
Test for overall effect: Z=0.17(P=0.86)					
Total (95% CI)	**347**	**347**		**100%**	**0.9[0.72,1.13]**
Total events: 89 (Lower oxygen), 101 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=12.28, df=10(P=0.27); I^2=18.58%					

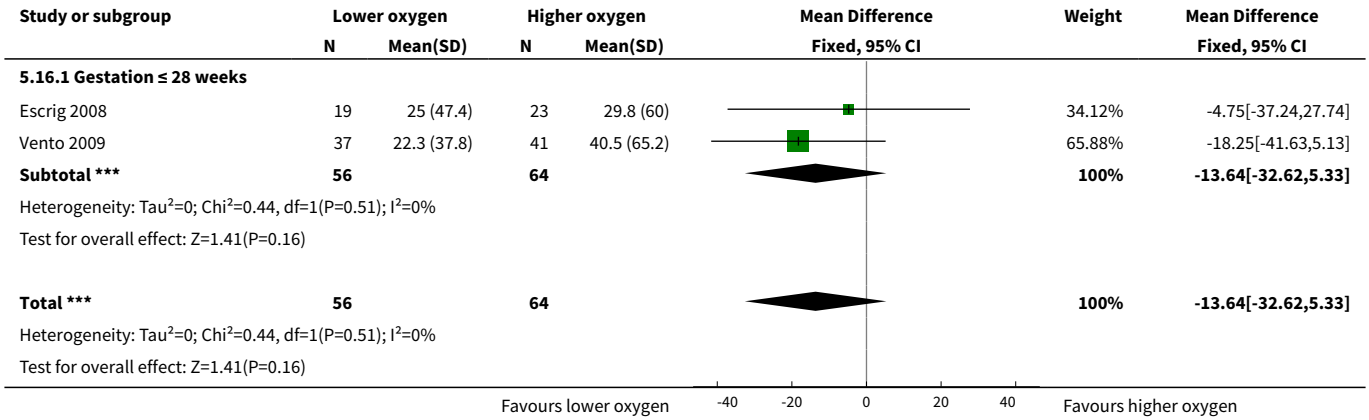




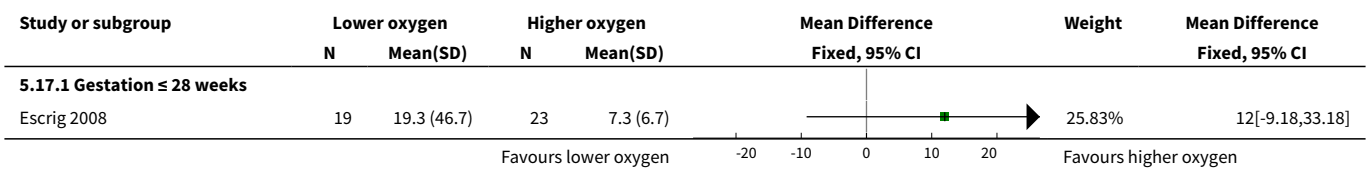
Analysis 5.15. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 15 Duration of respiratory support (mechanical ventilation or CPAP) (days from birth).

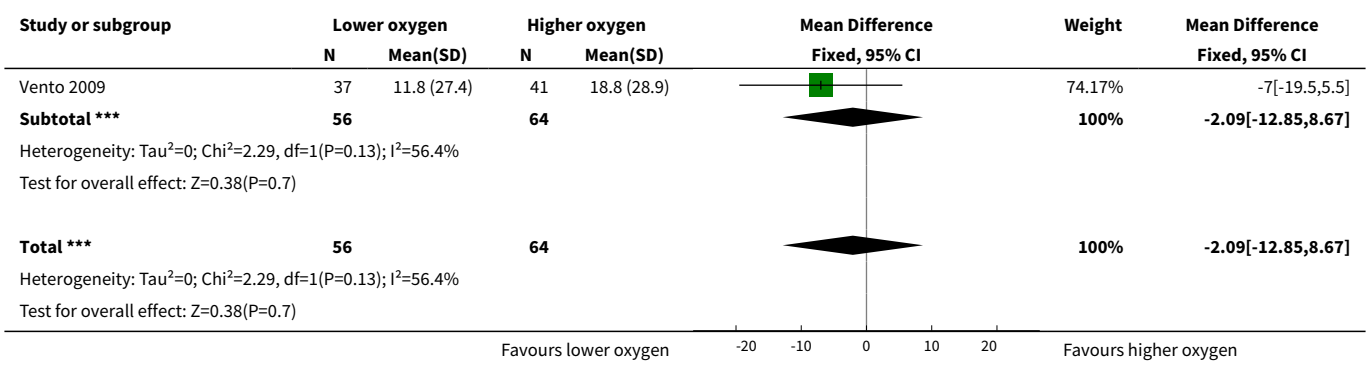


Analysis 5.16. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 16 Duration of respiratory support (mechanical ventilation) (days from birth).

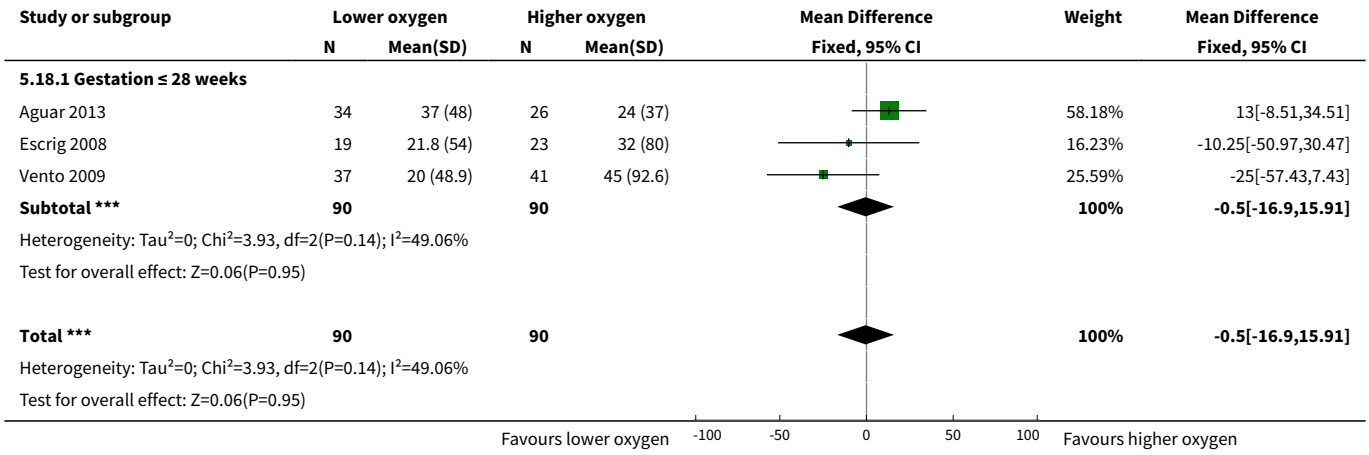


Analysis 5.17. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 17 Duration of respiratory support (CPAP) (days from birth).

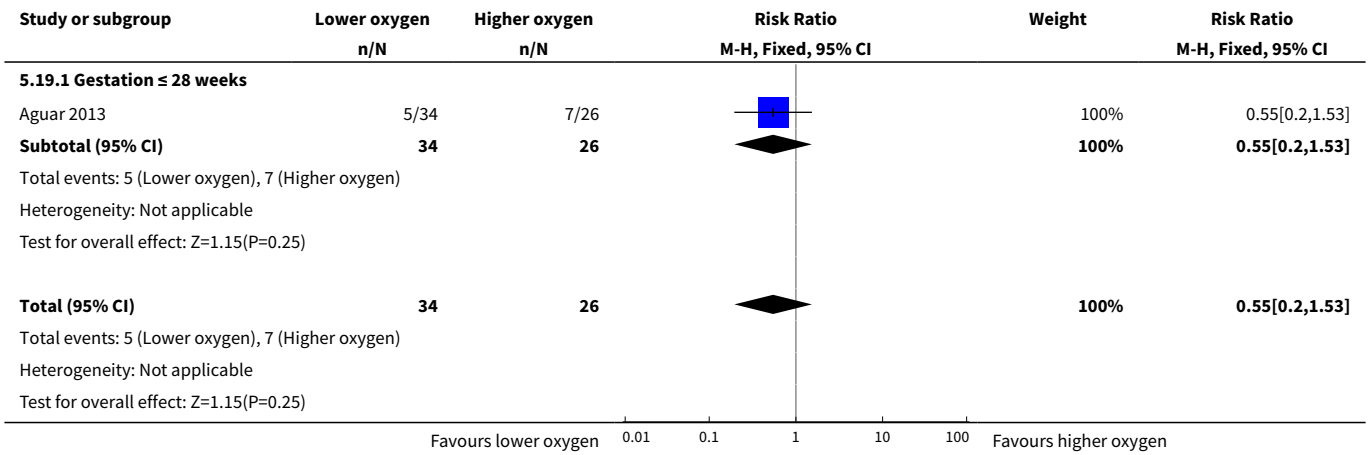




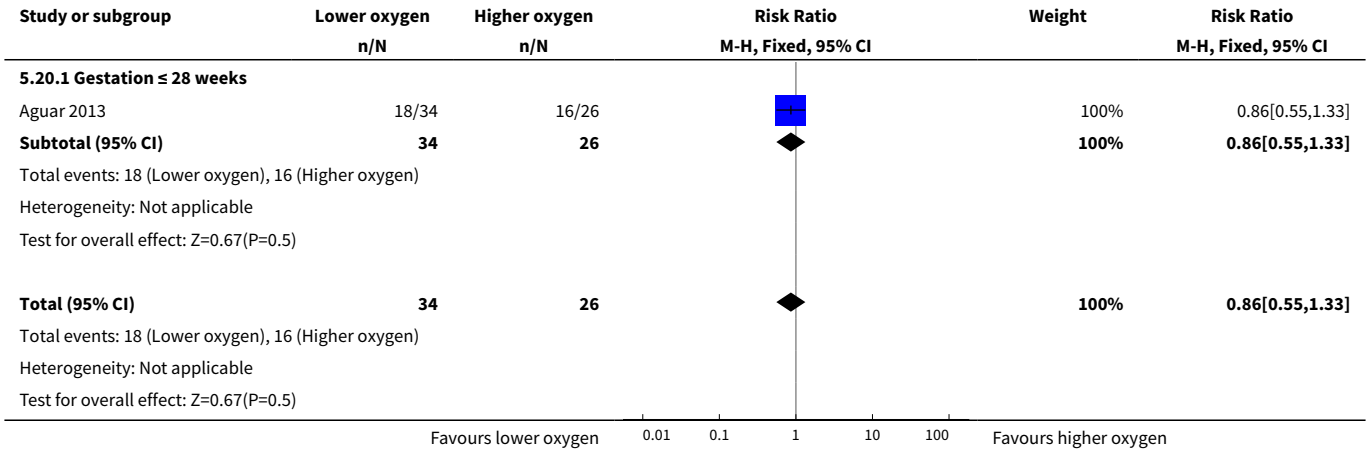
Analysis 5.18. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 18 Duration of supplemental oxygen administration.



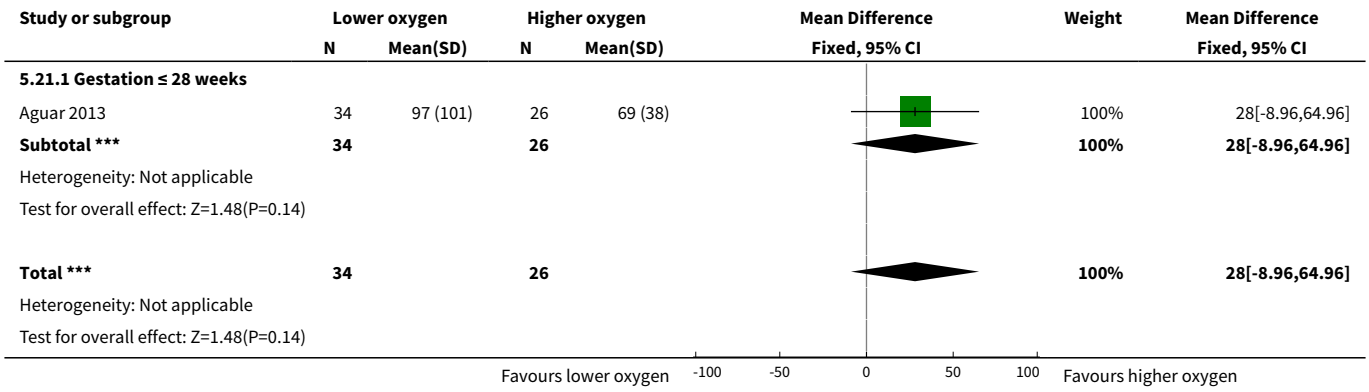
Analysis 5.19. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 19 Mortality to follow up (> 18 months).



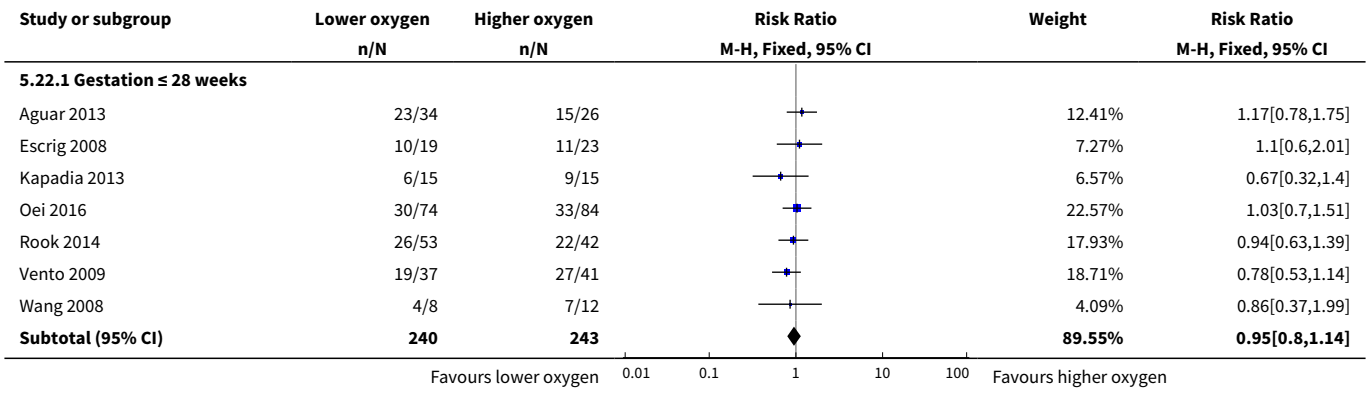
Analysis 5.20. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 20 Postnatal growth failure (weight < 10th percentile at discharge).

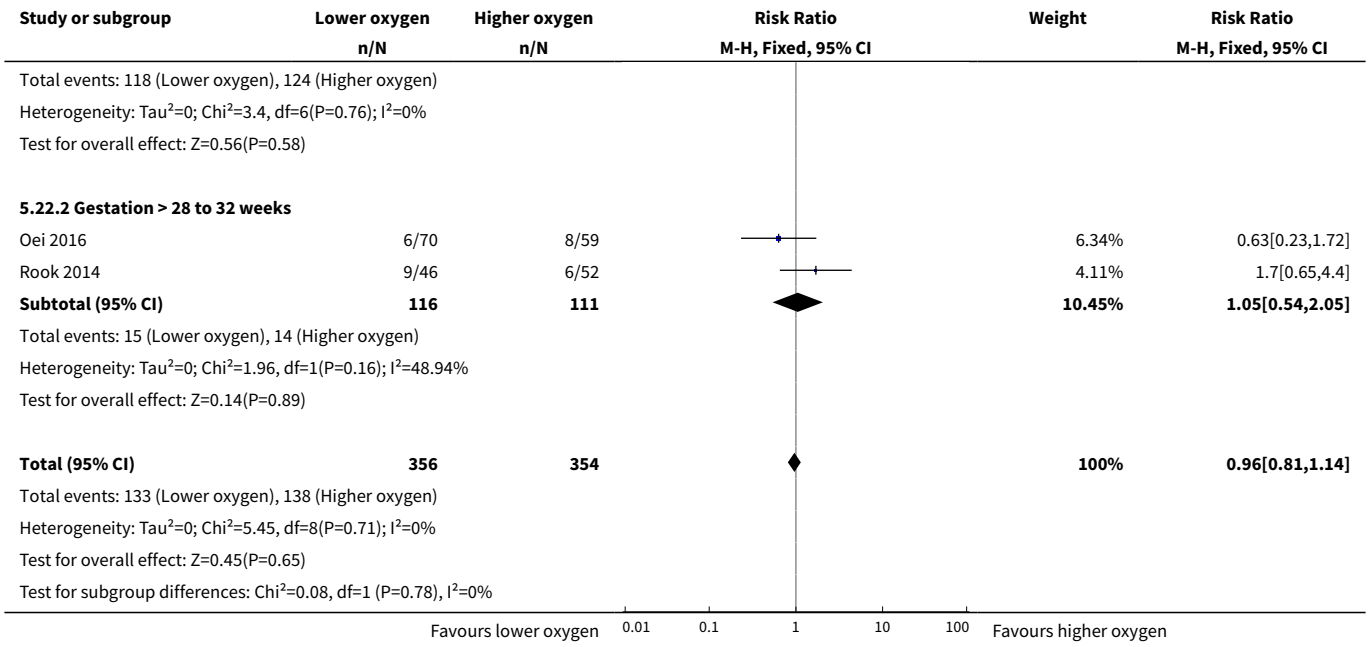


Analysis 5.21. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 21 Duration of hospitalisation (days).



Analysis 5.22. Comparison 5 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by gestational age, Outcome 22 Patent ductus arteriosus (not prespecified).





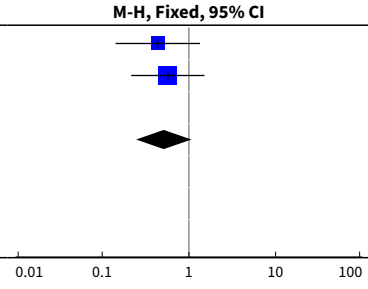
Comparison 6. Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality near term corrected age or discharge (latest reported)	2	253	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.25, 1.07]
2 Neurodevelopmental disability	2	208	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.49, 1.35]
3 IPPV in the delivery room	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.94, 1.07]
4 Intubation in the delivery room	2	253	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.79, 1.70]
5 Time to reach desired oxygen saturation target	1	60	Mean Difference (IV, Fixed, 95% CI)	2.09 [-0.26, 4.44]
6 Time to reach heart rate > 100 bpm (not prespecified)	1	60	Mean Difference (IV, Fixed, 95% CI)	0.27 [-1.21, 1.75]
7 Retinopathy of prematurity	2	253	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.39, 1.86]
8 Severe retinopathy of prematurity (≥ stage 3)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	3.86 [0.19, 77.05]
9 Intraventricular haemorrhage	2	253	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.47, 1.53]
10 Severe intraventricular haemorrhage (grade 3 or 4)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.17, 3.48]
11 Necrotising enterocolitis	2	253	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.46, 5.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 Chronic lung disease (28 days age)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.53, 3.05]
13 Chronic lung disease (36 weeks' corrected age)	2	243	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.90, 2.47]
14 Duration of respiratory support (mechanical ventilation or CPAP) (days from birth)	1	60	Mean Difference (IV, Fixed, 95% CI)	1.06 [-2.63, 4.75]
15 Duration of respiratory support (mechanical ventilation) (days from birth)	1	193	Mean Difference (IV, Fixed, 95% CI)	1.25 [-0.97, 3.47]
16 Duration of supplemental oxygen administration	2	253	Mean Difference (IV, Fixed, 95% CI)	2.72 [-2.78, 8.22]
17 Mortality to follow up (> 18 months)	2	253	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.28, 1.14]
18 Postnatal growth failure (weight < 10th percentile at discharge)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.55, 1.33]
19 Duration of hospitalisation (days)	1	60	Mean Difference (IV, Fixed, 95% CI)	28.0 [-8.96, 64.96]
20 Patent ductus arteriosus (not prespecified)	2	253	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.88, 1.59]

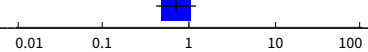
Analysis 6.1. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 1 Mortality near term corrected age or discharge (latest reported).

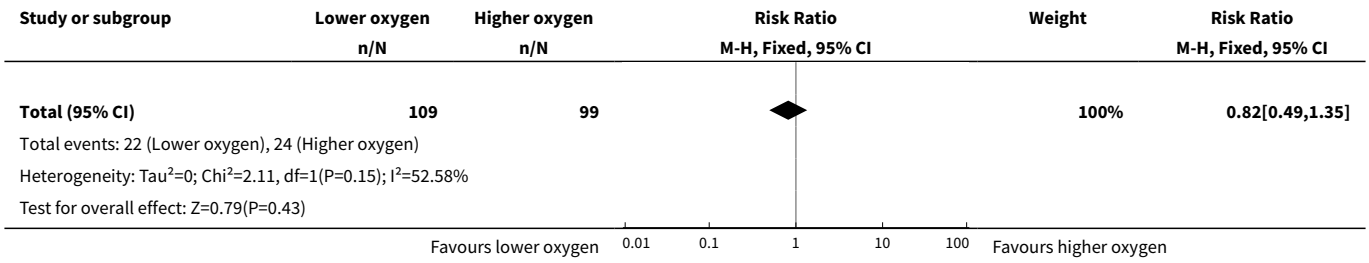
Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	4/34	7/26		43.61%	0.44[0.14,1.34]
Rook 2014	6/99	10/94		56.39%	0.57[0.22,1.51]
Total (95% CI)	**133**	**120**		**100%**	**0.51[0.25,1.07]**
Total events: 10 (Lower oxygen), 17 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=0.12, df=1(P=0.73); I^2=0%					
Test for overall effect: Z=1.79(P=0.07)					



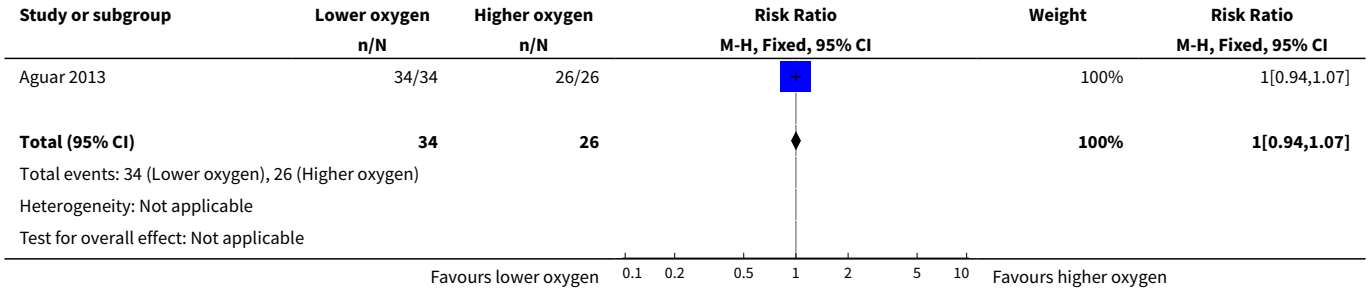
Analysis 6.2. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 2 Neurodevelopmental disability.

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	3/14	1/17		3.53%	3.64[0.42,31.27]
Rook 2014	19/95	23/82		96.47%	0.71[0.42,1.21]

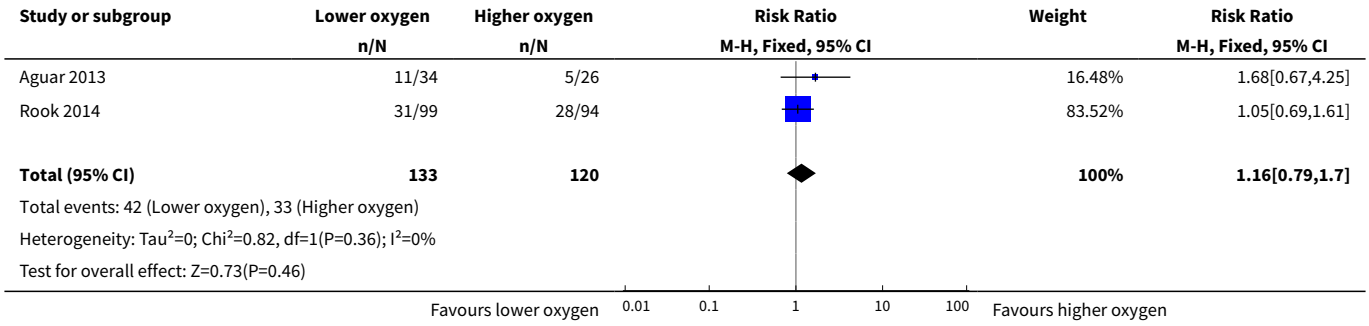




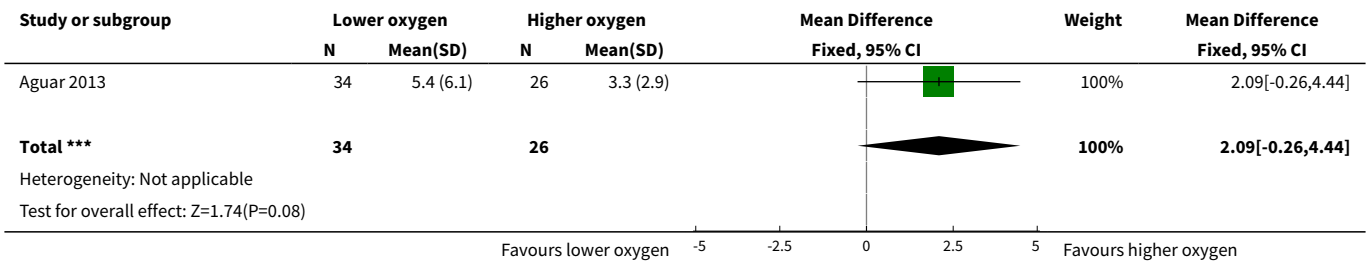
Analysis 6.3. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 3 IPPV in the delivery room.



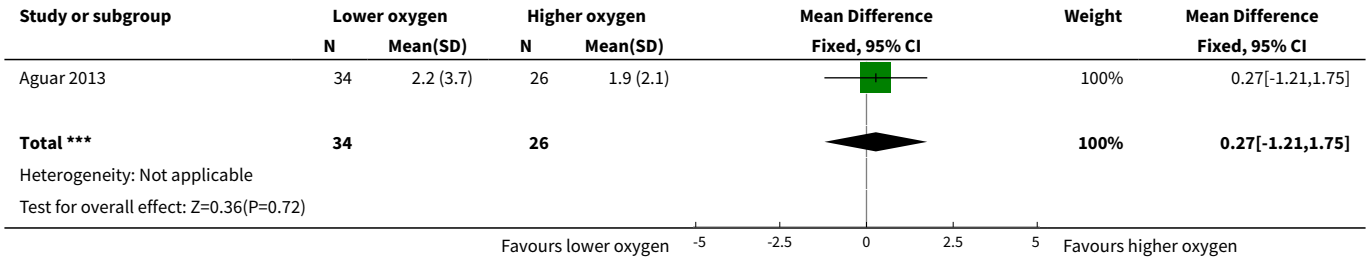
Analysis 6.4. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 4 Intubation in the delivery room.



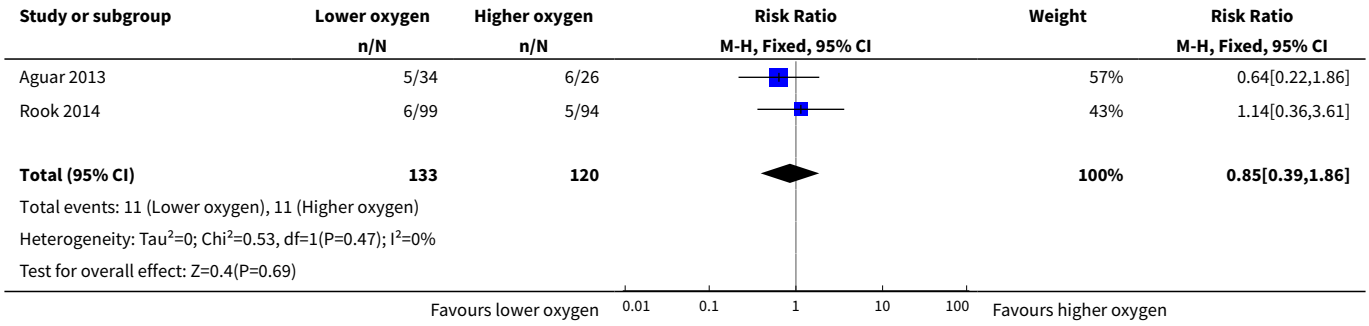
Analysis 6.5. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 5 Time to reach desired oxygen saturation target.



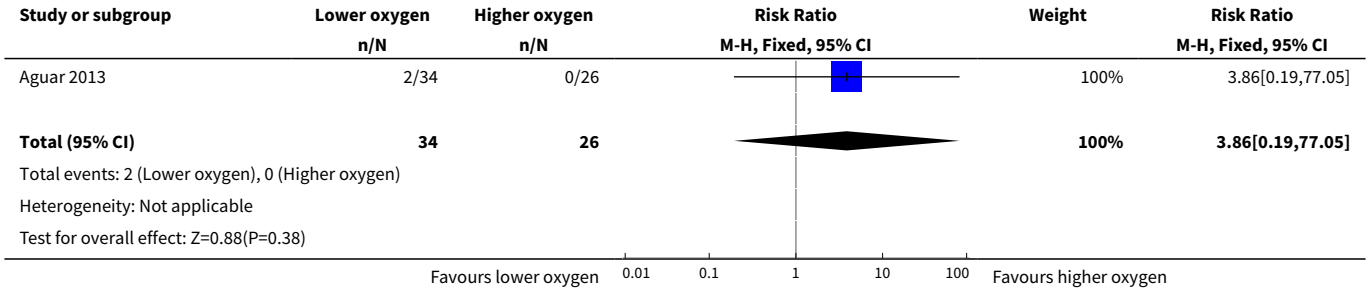
Analysis 6.6. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 6 Time to reach heart rate > 100 bpm (not prespecified).



Analysis 6.7. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 7 Retinopathy of prematurity.

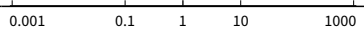


Analysis 6.8. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 8 Severe retinopathy of prematurity (≥ stage 3).



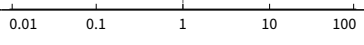
Analysis 6.9. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 9 Intraventricular haemorrhage.

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	10/34	8/26		46.91%	0.96[0.44,2.08]
Rook 2014	8/99	10/94		53.09%	0.76[0.31,1.84]
Total (95% CI)	**133**	**120**		**100%**	**0.85[0.47,1.53]**
Total events: 18 (Lower oxygen), 18 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=0.15, df=1(P=0.7); I^2=0%					
Test for overall effect: Z=0.53(P=0.59)					



Analysis 6.10. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 10 Severe intraventricular haemorrhage (grade 3 or 4).

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	3/34	3/26		100%	0.76[0.17,3.48]
Total (95% CI)	**34**	**26**		**100%**	**0.76[0.17,3.48]**
Total events: 3 (Lower oxygen), 3 (Higher oxygen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.35(P=0.73)					

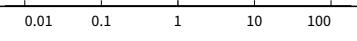


Analysis 6.11. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 11 Necrotising enterocolitis.

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	3/34	1/26		26.91%	2.29[0.25,20.8]
Rook 2014	4/99	3/94		73.09%	1.27[0.29,5.51]
Total (95% CI)	**133**	**120**		**100%**	**1.54[0.46,5.19]**
Total events: 7 (Lower oxygen), 4 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=0.19, df=1(P=0.66); I^2=0%					
Test for overall effect: Z=0.7(P=0.48)					

Analysis 6.12. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 12 Chronic lung disease (28 days age).

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	10/34	6/26		100%	1.27[0.53,3.05]
Total (95% CI)	**34**	**26**		**100%**	**1.27[0.53,3.05]**
Total events: 10 (Lower oxygen), 6 (Higher oxygen)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					



Favours lower oxygen — Favours higher oxygen

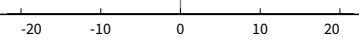
Analysis 6.13. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 13 Chronic lung disease (36 weeks' corrected age).

Study or subgroup	Lower oxygen n/N	Higher oxygen n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aguar 2013	10/30	5/20		29.47%	1.33[0.54,3.32]
Rook 2014	23/99	14/94		70.53%	1.56[0.85,2.85]
Total (95% CI)	**129**	**114**		**100%**	**1.49[0.9,2.47]**
Total events: 33 (Lower oxygen), 19 (Higher oxygen)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=1(P=0.78); I^2=0%					
Test for overall effect: Z=1.56(P=0.12)					

Favours lower oxygen — Favours higher oxygen

Analysis 6.14. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 14 Duration of respiratory support (mechanical ventilation or CPAP) (days from birth).

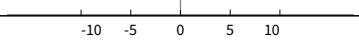
Study or subgroup	Lower oxygen N	Lower oxygen Mean(SD)	Higher oxygen N	Higher oxygen Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Aguar 2013	34	9.9 (8.8)	26	8.9 (5.8)		100%	1.06[-2.63,4.75]
Total ***	**34**		**26**			**100%**	**1.06[-2.63,4.75]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.56(P=0.57)							



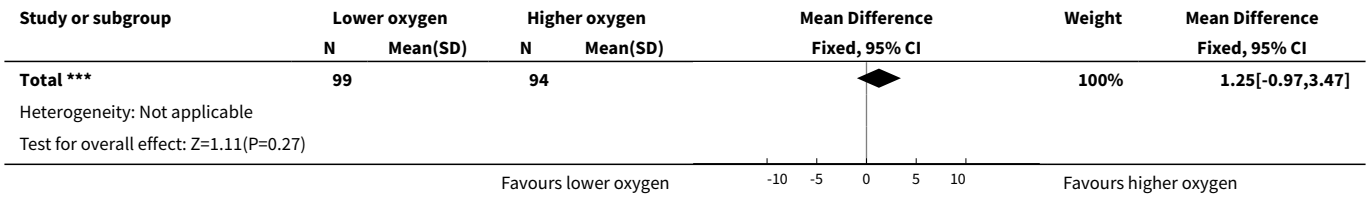
Favours lower oxygen — Favours higher oxygen

Analysis 6.15. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 15 Duration of respiratory support (mechanical ventilation) (days from birth).

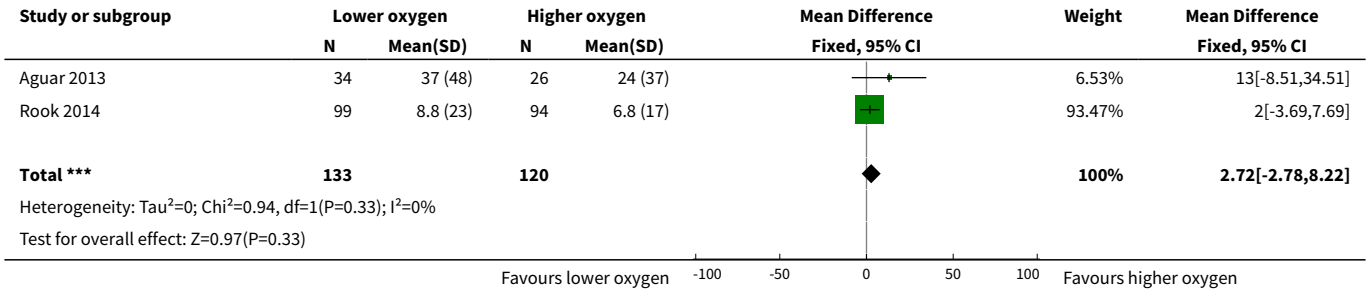
Study or subgroup	Lower oxygen N	Lower oxygen Mean(SD)	Higher oxygen N	Higher oxygen Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Rook 2014	99	4 (8.9)	94	2.8 (6.7)		100%	1.25[-0.97,3.47]



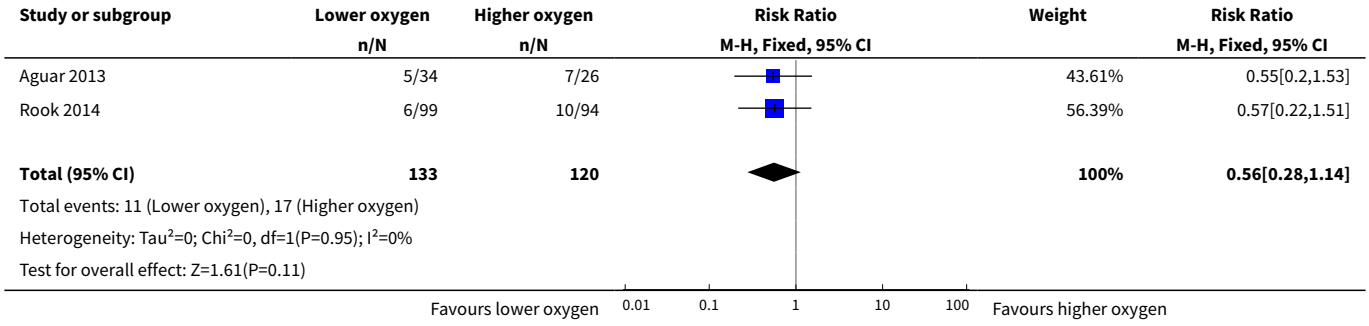
Favours lower oxygen — Favours higher oxygen



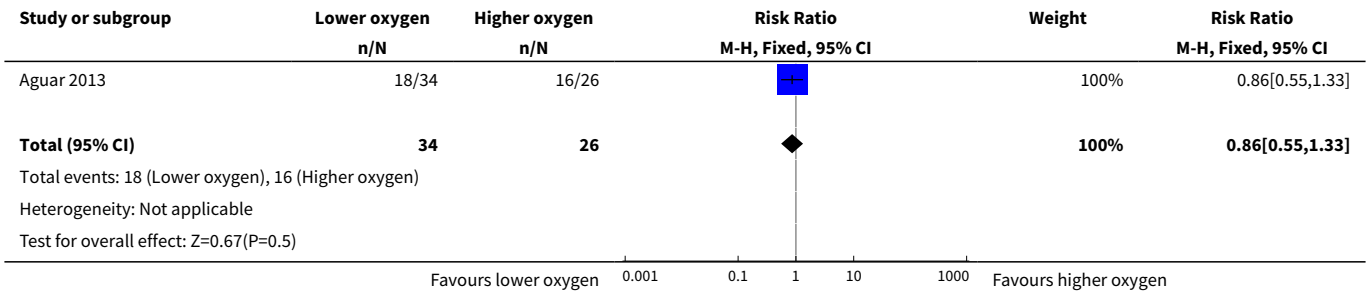
Analysis 6.16. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 16 Duration of supplemental oxygen administration.



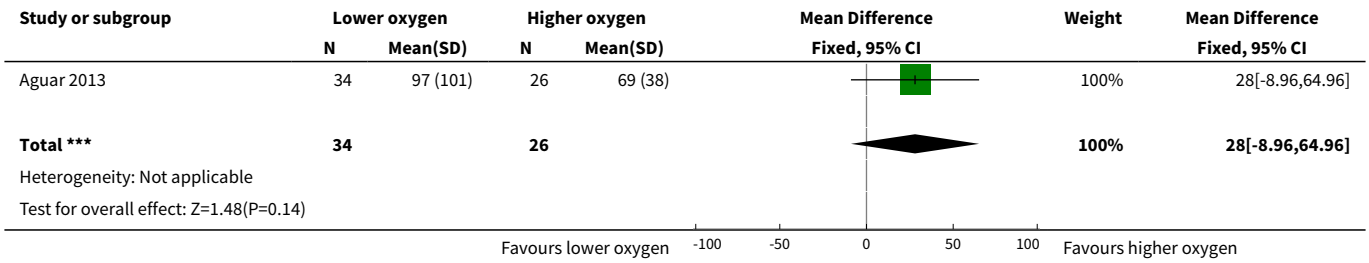
Analysis 6.17. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 17 Mortality to follow up (> 18 months).



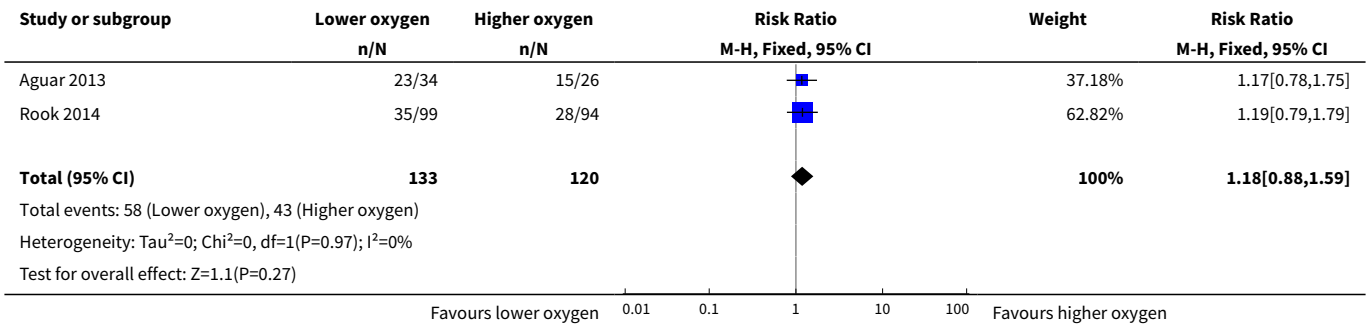
Analysis 6.18. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 18 Postnatal growth failure (weight < 10th percentile at discharge).



Analysis 6.19. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 19 Duration of hospitalisation (days).



Analysis 6.20. Comparison 6 Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration - sensitivity analysis, Outcome 20 Patent ductus arteriosus (not prespecified).



APPENDICES

Appendix 1. Search strategies

MEDLINE

Ovid MEDLINE 1946 to January 2017

1 oxygen.mp or exp oxygen/ n=480581

2 exp resuscitation/ or resuscitation.mp n=97831

3 1 and 2 n=11743

4 exp infant, premature/ or preterm.mp n=77564

5 premature.mp n=152266

6 4 or 5 n=166276

7 3 and 6 n=1048

8 limit 7 to (humans and clinical trial/all) n=262

EMBASE

Embase 1974 to January 2017

1 oxygen.mp. or exp oxygen/ or exp oxygen therapy/ n=651861

2 exp resuscitation/ or resuscitation.mp n=115208

3 1 and 2 n=10938

4 exp prematurity/ or preterm.mp n=122817

5 premature.mp n=163835

6 4 or 5 n=229047

7 3 and 6 n=562

8 limit 7 to (human and (clinical trial or randomized controlled trial or controlled clinical trial or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)) n=66

COCHRANE CENTRAL

Cochrane Central Register of Controlled Trials January 2017

1 exp Oxygen/ or oxygen.mp n=2595

2 exp Resuscitation/ or resuscitation.mp n=6001

3 1 and 2 n=1143

4 preterm.mp. or exp Infant, Premature/ n=7342

5 premature.mp n=9643

6 4 or 5 n=12485

7 3 and 6 n=203

CINAHL

1 (MH "Oxygen+") OR "oxygen" OR (MH "Oxygen Therapy+") n=30969

2 (MH "Resuscitation+") OR "resuscitation" n=27428

3 1 and 2 n=2109

4 "preterm" OR (MH "Infant, Premature") n=19360

5 "premature" n=25412

6 4 or 5 n=28658

7 3 and 6 n=243

8 7 limited to "clinical trial" or "randomized controlled trial" n=47

Appendix 2. Risk of bias tool

The following issues were evaluated and entered into the risk of bias table:

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorized the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorized the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- 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 categorized 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 categorized the methods as:

- low risk, high risk or unclear risk for participants; and
- 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 categorized the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorized the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- 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 categorized the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or
- 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:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- 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
- 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:

- low risk;
- high risk;
- unclear risk

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

Appendix 3. Subgroup Analyses

Subgroup analyses

Comparison 2. Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentrations subgrouped by FiO_2

One study was eligible for the subgroup analysis of FiO_2 0.21 versus FiO_2 ≥ 0.4 to < 0.6: it compared air (21%) with 40% oxygen (Kumar 2014).

Five studies were eligible for the subgroup analysis of FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: they compared air with 100% oxygen for resuscitation (Kapadia 2013; Kumar 2014; Oei 2016; Rabi 2011; Wang 2008).

Five studies were eligible for the subgroup analysis of FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: one study compared 30% oxygen versus 60% oxygen (Aguar 2013); one study compared 30% oxygen versus 100% oxygen (Armanian 2012); two studies compared 30% oxygen versus 90% oxygen (Escrig 2008; Vento 2009); and one study compared 30% oxygen versus 65% oxygen (Rook 2014).

Primary Outcomes

Mortality, near term corrected or discharge (latest reported) (Analysis 2.1)

FiO_2 0.21 versus FiO_2 ≥ 0.4 to < 0.6: one study reported no significant difference between groups (RR 1.17, 95% CI 0.09 to 14.92; participants = 13) (Kumar 2014).

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 1.70, 95% CI 0.84 to 3.46; participants = 495; studies = 5).

FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 0.75, 95% CI 0.42 to 1.32; participants = 412; studies = 5).

The test for subgroup differences found no significant difference between groups (P = 0.21, I^2 = 35.9%).

Neurodevelopmental disability (Analysis 2.2)

FiO_2 0.21 versus FiO_2 ≥ 0.4 to < 0.6: our meta-analysis showed no significant difference between groups (RR 0.82, 95% CI 0.49 to 1.35; participants = 208; studies = 2). Test for subgroup differences not applicable.

Secondary Outcomes

Intermittent positive pressure ventilation (IPPV) in the delivery room (Analysis 2.3)

FiO_2 0.21 versus FiO_2 0.4 to < 0.6: one study reported no significant difference between groups (RR 0.70, 95% CI 0.28 to 1.77; participants = 13) (Kumar 2014).

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 0.93, 95% CI 0.77 to 1.12; participants = 140; studies = 3).

FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 0.96, 95% CI 0.84 to 1.09; participants = 102; studies = 2).

The test for subgroup differences found no significant difference between groups (P = 0.79, I^2 = 0%).

Intubation in the delivery room (Analysis 2.4)

FiO_2 0.21 versus FiO_2 ≥ 0.4 to < 0.6: one study reported no significant difference between groups (RR 0.58, 95% CI 0.16 to 2.14; participants = 13) (Kumar 2014).

FiO2 0.21 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 0.93, 95% CI 0.72 to 1.21; participants = 495; studies = 5).

FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 1.04, 95% CI 0.81 to 1.34; participants = 373; studies = 4).

The test for subgroup differences found no significant difference between groups (P = 0.62, I^2 = 0%).

Time to reach desired oxygen saturation target (Analysis 2.5)

FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (MD -0.52 minutes, 95% CI -1.83 to 0.79; participants = 102; studies = 2). Test for subgroup differences not applicable.

Time to reach heart rate > 100 beats per minute (not prespecified) (Analysis 2.6)

FiO_2 0.21 versus FiO_2 ≥ 0.4 to < 0.6: one study reported no significant difference between groups (MD 0.27 minutes, 95% CI -1.21 to 1.75; participants = 60) (Aguar 2013). One of the studies, Escrig 2008, reported data as median/IQR and included additional criteria for time to response (SaO_2 > 85% and good response to stimuli) so data from this study were not included in meta-analysis. The test for subgroup differences was not applicable.

Retinopathy of prematurity (any) (Analysis 2.7)

FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 0.80, 95% CI 0.43 to 1.49; participants = 373; studies = 4). The test for subgroup differences was not applicable.

Severe retinopathy of prematurity (≥ stage 3) (Analysis 2.8)

FiO_2 0.21 versus FiO_2 ≥ 0.4 to < 0.6: one study reported no events in either group (Kumar 2014).

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 0.40, 95% CI 0.15 to 1.05; participants = 386; studies = 3).

FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: one study reported no significant difference between groups (RR 3.86, 95% CI 0.19 to 77.05; participants = 60) (Aguar 2013).

The test for subgroup differences found no significant difference between groups (P = 0.16, I^2 = 49.9%).

Intraventricular haemorrhage (IVH) (any) (Analysis 2.9)

FiO_2 0.21 versus FiO_2 ≥ 0.4 to < 0.6: one study reported no events in either group (Kumar 2014).

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: one study reported no significant difference between groups (RR 0.17, 95% CI 0.01 to 2.92; participants = 11) (Kumar 2014).

FiO_2 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 0.85, 95% CI 0.47 to 1.53; participants = 253; studies = 2).

The test for subgroup differences found no significant difference between groups (P = 0.28, I^2 = 15.1%).

Severe intraventricular haemorrhage (IVH) (grade 3 or 4) (Analysis 2.10)

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 0.78, 95% CI 0.27 to 2.24; participants = 416; studies = 3).

FiO_2 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 1.03, 95% CI 0.49 to 2.18; participants = 180; studies = 3).

The test for subgroup differences found no significant difference between groups (P = 0.66, I^2 = 0%).

Periventricular leukomalacia (PVL) (Analysis 2.11)

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: one study reported no significant difference between groups (RR 0.33, 95% CI 0.01 to 7.97; participants = 88) (Kapadia 2013).

FiO_2 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: one study reported no significant difference between groups (RR 1.21, 95% CI 0.08 to 18.09; participants = 42) (Escrig 2008).

The test for subgroup differences found no significant difference between groups (P = 0.54, I^2 = 0%).

Necrotising enterocolitis (proven) (Analysis 2.12)

FiO_2 0.21 versus FiO_2 ≥ 0.4 to < 0.6: one study reported no significant difference between groups (RR 0.58, 95% CI 0.07 to 4.95; participants = 13) (Kumar 2014).

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 0.74, 95% CI 0.31 to 1.76; participants = 434; studies = 4).

FiO_2 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 1.40, 95% CI 0.52 to 3.78; participants = 373; studies = 4).

The test for subgroup differences found no significant difference between groups (P = 0.57, I^2 = 0%).

Chronic lung disease (28 days) (Analysis 2.13)

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: one study reported a lower risk of chronic lung disease at 28 days of life in infants allocated to the lower oxygen group (RR 0.47, 95% CI 0.23 to 0.98; participants = 88) (Kapadia 2013).

FiO_2 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: one study reported no significant difference between groups (RR 1.27, 95% CI 0.53 to 3.05; participants = 60) (Aguar 2013).

The test for subgroup differences found no significant difference between groups (P = 0.09, I^2 = 66%).

Chronic lung disease (36 weeks) (Analysis 2.14)

FiO_2 0.21 versus FiO_2 ≥ 0.4 to < 0.6: one study reported no significant difference between groups (RR 0.39, 95% CI 0.05 to 2.83; participants = 13) (Kumar 2014).

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 0.83, 95% CI 0.63 to 1.09; participants = 492; studies = 5).

FiO_2 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 1.07, 95% CI 0.72 to 1.60; participants = 363; studies = 4).

The test for subgroup differences found no significant difference between groups (P = 0.41, I^2 = 0%).

Duration of respiratory support (mechanical ventilation or CPAP) (days from birth) (Analysis 2.15)

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: one study reported infants receiving lower (FiO_2 0.21) oxygen had a shorter duration of respiratory support (mechanical ventilation or CPAP*)* compared to infants on higher oxygen (FiO_2 1.0) (MD -13.70, 95% CI -14.85 to -12.55; participants = 266) (Oei 2016).

FiO_2 ≥ 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: one study reported no significant difference between groups (MD 1.06, 95% CI -2.63 to 4.75; participants = 60) (Aguar 2013).

Test for subgroup differences found a significant difference (P < 0.00001, I^2 = 98.2%).

Duration of respiratory support (mechanical ventilation) (days from birth) (Analysis 2.16)

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (MD -0.11, 95% CI -4.16 to 3.93; participants = 197; studies = 3).

FiO_2 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (MD 0.82, 95% CI -1.38 to 3.02; participants = 313; studies = 3).

The test for subgroup differences found no significant difference between groups (P = 0.69, I^2 = 0%).

Duration of respiratory support (continuous positive airway pressure (CPAP)) (days from birth) (Analysis 2.17)

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (MD -1.79, 95% CI -5.84 to 2.25; participants = 129; studies = 2).

FiO_2 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (MD -0.24, 95% CI -11.00 to 10.53; participants = 120; studies = 2).

The test for subgroup differences found no significant difference between groups (P = 0.79, I^2 = 0%).

Duration of supplemental oxygen administration (days) (Analysis 2.18)

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: one study reported infants who received lower (FiO_2 0.21) oxygen had a shorter duration of supplemental oxygen administration compared to infants on higher oxygen (FiO_2 1.0) (MD 12.40 days, 95% CI 9.25 to 15.55; participants = 266) (Oei 2016).

FiO_2 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (MD 0.01 days, 95% CI -5.37 to 5.38; participants = 373; studies = 4).

Test for subgroup differences found a significant difference (P < 0.00001, I^2 = 93.4%).

Mortality to follow-up (> 18 months) (Analysis 2.19)

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: one study reported no significant difference between groups (RR 2.32, 95% CI 0.92 to 5.86; participants = 287) (Oei 2016).

FiO_2 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 0.56, 95% CI 0.28 to 1.14; participants = 253; studies = 2).

The test for subgroup differences found a significant difference (P = 0.02, I^2 = 82.4%).

Postnatal growth failure (weight < 10th percentile at discharge) (Analysis 2.20)

FiO_2 0.21 versus FiO_2 ≥ 0.4 to < 0.6: one study reported no significant difference between groups (RR 0.86, 95% CI 0.55 to 1.33; participants = 60) (Aguar 2013). The test for subgroup differences was not applicable.

Duration of hospitalisation (days) (Analysis 2.21)

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (MD -4.35, 95% CI -15.26 to 6.57; participants = 156; studies = 2).

FiO_2 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: one study reported no significant difference between groups (MD 28.00, 95% CI -8.96 to 64.96; participants = 60) (Aguar 2013).

The test for subgroup differences found no significant difference between groups (P = 0.10, I^2 = 63.1%).

Patent ductus arteriosus (not prespecified) (Analysis 2.22)

FiO_2 0.21 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 0.80, 95% CI 0.57 to 1.14; participants = 393; studies = 3).

FiO_2 0.3 to < 0.4 versus FiO_2 ≥ 0.6 to 1.0: our meta-analysis showed no significant difference between groups (RR 1.03, 95% CI 0.82 to 1.29; participants = 373; studies = 4).

Test for subgroup differences found no significant difference between groups (P = 0.25, I^2 = 22.8%).

Comparison 3. Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration subgrouped by lower limit of oxygen saturation target range at 5 to 10 minutes

One study, Oei 2016, reported outcomes in infants receiving lower or higher oxygen concentrations and targeted to a lower limit of oxygen saturation target range of < 85%.

Nine studies reported outcomes for infants receiving lower or higher oxygen concentrations targeted to SpO_2 85% to 90% for postbirth resuscitation (Aguar 2013; Armanian 2012; Escrig 2008; Kapadia 2013; Kumar 2014; Rabi 2011; Rook 2014; Vento 2009; Wang 2008).

No studies reported outcomes for infants receiving lower or higher oxygen concentrations targeted to SpO_2 91% to 95% or SpO_2 > 95% for postbirth resuscitation.

Primary Outcomes

Mortality, near term corrected age or discharge (latest reported) (Analysis 3.1)

Lower oxygen group, SpO_2 target < 85%: one study reported significantly increased mortality in infants allocated to air (FiO_2 0.21) compared to infants receiving 100% oxygen (RR 2.78, 95% CI 1.03 to 7.52; participants = 287) (Oei 2016).

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (RR 0.77, 95% CI 0.46 to 1.27; participants = 627; studies = 9).

The test for subgroup differences found a significant difference (P = 0.02; I^2 = 80.5%).

Neurodevelopmental disability (Analysis 3.2)

Lower oxygen group, SpO_2 target < 85%: no study has reported data to date.

Subgroup: lower oxygen group, SpO_2 target 85 to 90%: our meta-analysis showed no significant difference between groups (RR 0.82, 95% CI 0.49 to 1.35; participants = 208; studies = 2).

Test for subgroup differences not indicated.

Secondary Outcomes

Intermittent positive pressure ventilation (IPPV) in the delivery room (Analysis 3.3)

Subgroup: lower oxygen group SpO_2 target < 85%: no study has reported data to date.

Subgroup: lower oxygen group SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (RR 0.94, 95% CI 0.83 to 1.06; participants = 249; studies = 5). Test for subgroup differences not indicated.

Intubation in the delivery room (Analysis 3.4)

Lower oxygen group, SpO_2 target < 85%: one study reported no significant difference between groups (RR 1.04, 95% CI 0.73 to 1.49; participants = 287) (Oei 2016).

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (RR 0.96, 95% CI 0.78 to 1.18; participants = 588; studies = 8). The test for subgroup differences found no significant difference between groups (P = 0.70; I^2 = 0%).

Time to reach desired oxygen saturation target (Analysis 3.5)

Subgroup: lower oxygen group SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (MD -0.52 minutes, 95% CI -1.83 to 0.79; participants = 102; studies = 2). Test for subgroup differences not indicated.

Time to reach heart rate > 100 beats per minute (Analysis 3.6)

Subgroup: lower oxygen group SpO_2 target 85% to 90%: reported no significant difference between groups (MD 0.27 minutes, 95% CI -1.21 to 1.75; participants = 60) (Aguar 2013). Test for subgroup differences not indicated.

Retinopathy of prematurity (any) (Analysis 3.7)

Subgroup: lower oxygen group SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (RR 0.80, 95% CI 0.43 to 1.49; participants = 373; studies = 4). Test for subgroup differences not indicated.

Severe retinopathy of prematurity (≥ stage 3) (Analysis 3.8)

Lower oxygen group, SpO_2 target < 85%: one study reported no significant difference between groups (RR 0.50, 95% CI 0.15 to 1.61; participants = 287) (Oei 2016).

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (RR 0.68, 95% CI 0.19 to 2.48; participants = 166; studies = 3).

The test for subgroup differences found no significant difference between groups (P = 0.72; I^2 = 0%).

Intraventricular haemorrhage (IVH) (any) (Analysis 3.9)

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (RR 0.81, 95% CI 0.46 to 1.44; participants = 271; studies = 3). Test for subgroup differences not indicated.

Severe intraventricular haemorrhage (IVH) (grade 3 or 4) (Analysis 3.10)

Lower oxygen group, SpO_2 target < 85%: one study reported no significant difference between groups (RR 0.33, 95% CI 0.07 to 1.61; participants = 287) (Oei 2016).

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (RR 1.21, 95% CI 0.61 to 2.39; participants = 309; studies = 5).

The test for subgroup differences found no significant difference (P = 0.14; I^2 = 53.8%).

Periventricular leukomalacia (PVL) (Analysis 3.11)

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (RR 0.66, 95% CI 0.09 to 4.73; participants = 130; studies = 2; I^2 = 0%). Test for subgroup differences not indicated.

Necrotising enterocolitis (proven) (Analysis 3.12)

Lower oxygen group, SpO_2 target < 85%: one study reported no significant difference between groups (RR 4.97, 95% CI 0.59 to 41.97; participants = 287) (Oei 2016).

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (RR 0.74, 95% CI 0.36 to 1.52; participants = 520; studies = 7).

The test for subgroup differences found no significant difference (P = 0.10; I^2 = 63.4%).

Chronic lung disease (28 days) (Analysis 3.13)

Subgroup: lower oxygen group, SpO_2 target 85%-90%: our meta-analysis showed no significant difference between groups (RR 0.70, 95% CI 0.41 to 1.21; participants = 148; studies = 2; I^2 = 66%). We identified moderate heterogeneity in this analysis. Test for subgroup differences not indicated.

Chronic lung disease (36 weeks) (Analysis 3.14)

Lower oxygen group, SpO_2 target < 85%: Oei 2016 reported no significant difference between groups (RR 0.84, 95% CI 0.57 to 1.25; participants = 287).

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (RR 0.91, 95% CI 0.58 to 1.43; participants = 575; studies = 8).

The test for subgroup differences found no significant difference (P = 0.79; I^2 = 0%).

Duration of respiratory support (mechanical ventilation or CPAP) (days from birth) (Analysis 3.15)

Lower oxygen group, SpO_2 target < 85%: one study reported a shorter duration of respiratory support (mechanical ventilation or CPAP) (days from birth) in infants allocated to lower (FiO_2 0.21) compared higher oxygen (FiO_2 1.0) (MD -13.70, 95% CI -14.85 to -12.55; participants = 266) (Oei 2016).

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: reported no significant difference between groups (MD 1.06, 95% CI -2.63 to 4.75; participants = 60) (Aguar 2013).

The test for subgroup differences found a significant difference (P < 0.00001; I^2 = 98.2%).

Duration of respiratory support (mechanical ventilation) (days from birth) (Analysis 3.16)

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (MD 0.78, 95% CI -1.15 to 2.72; participants = 510; studies = 6). Test for subgroup differences not indicated.

Duration of respiratory support (continuous positive airway pressure (CPAP) (days from birth) (Analysis 3.17)

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (MD -1.83, 95% CI -5.62 to 1.96; participants = 249; studies = 4). Test for subgroup differences not indicated.

Duration of supplemental oxygen administration (days) (Analysis 3.18)

Lower oxygen group, SpO_2 target < 85%: one study reported a longer duration of supplemental oxygen in infants allocated to lower (FiO_2 0.21) compared higher oxygen (FiO_2 1.0) (MD 12.40 days, 95% CI 9.25 to 15.55; participants = 266) (Oei 2016).

Subgroup: lower oxygen group SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (MD 1.73 days, 95% CI -3.64 to 7.11; participants = 373; studies = 4).

The test for subgroup differences found a significant difference (P < 0.0008; I^2 = 91.1%).

Mortality to follow-up (> 18 months) (Analysis 3.19)

Lower oxygen group, SpO_2 target < 85%: one study reported no significant difference between groups (RR 2.32, 95% CI 0.92 to 5.86; participants = 287) (Oei 2016).

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (RR 0.56, 95% CI 0.28 to 1.14; participants = 253; studies = 2).

The test for subgroup differences found a significant difference (P = 0.02; I^2 = 82.4%).

Postnatal growth failure (weight < 10th percentile at discharge) (Analysis 3.20)

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: one study reported no significant difference between groups (RR 0.86, 95% CI 0.55 to 1.33; participants = 60) (Aguar 2013). Test for subgroup differences not indicated.

Duration of hospitalisation (days) (Analysis 3.21)

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (MD -1.75, 95% CI -12.22 to 8.71; participants = 216; studies = 3). Test for subgroup differences not indicated.

Patent ductus arteriosus (not prespecified) (Analysis 3.22)

Lower oxygen group, SpO_2 target < 85%: one study reported no significant difference between groups (RR 0.87, 95% CI 0.59 to 1.28; participants = 287) (Oei 2016).

Subgroup: lower oxygen group, SpO_2 target 85% to 90%: our meta-analysis showed no significant difference between groups (RR 0.98, 95% CI 0.79 to 1.22; participants = 479; studies = 6).

Test for subgroup differences found no significant difference (P = 0.59; I^2 = 0%).

Comparison 4. Lower versus higher oxygen concentrations — subgrouped by higher limit of oxygen saturation target range at 5 to 10 minutes

One study reported outcomes in infants receiving lower or higher oxygen concentrations targeted to a higher limit of oxygen saturation target range of 85% to 90% (Escrig 2008).

Six studies reported outcomes for infants receiving lower or higher oxygen concentrations targeted to a highest SpO_2 limit of 91% to 95% (Kapadia 2013; Kumar 2014; Oei 2016; Rabi 2011; Rook 2014; Vento 2009).

Three studies did not report higher limit of oxygen saturation target ranges (Aguar 2013; Armanian 2012; Vento 2009).

No studies reported outcomes for infants receiving lower or higher oxygen concentrations targeted to a higher limit of oxygen saturation target range of < 85% or > 95% for postbirth resuscitation.

Primary Outcomes

Mortality, near term corrected age or discharge (latest reported) (Analysis 4.1)

Subgroup: higher limit of the oxygen saturation target range 85% to 90%: one study reported no significant difference between groups (RR 1.61, 95% CI 0.41 to 6.34; participants = 42) (Escrig 2008).

Subgroup: higher limit of the oxygen saturation target range 90% to 95%: our meta-analysis showed no significant difference between groups (RR 1.16, 95% CI 0.67 to 2.01; participants = 695; studies = 6).

The test for subgroup differences found no significant difference (P = 0.66; I^2 = 0%).

Neurodevelopmental disability (Analysis 4.2)

Subgroup: higher limit of the oxygen saturation target range 90% to 95%: one study reported no significant difference between lower and higher oxygen groups (RR 0.71, 95% CI 0.42 to 1.21; participants = 177) (Rook 2014). Test for subgroup differences not indicated.

Secondary Outcomes

Intermittent positive pressure ventilation (IPPV) in the delivery room (Analysis 4.3)

Subgroup: higher limit of the oxygen saturation target range 85% to 90%: one study reported no significant difference between groups (RR 0.87, 95% CI 0.60 to 1.27; participants = 42) (Escrig 2008).

Subgroup: higher limit of the oxygen saturation target range 90% to 95%: our meta-analysis showed no significant difference between groups (RR 0.92, 95% CI 0.76 to 1.12; participants = 147; studies = 3).

The test for subgroup differences found no significant difference (P = 0.81; I^2 = 0%).

Intubation in the delivery room (Analysis 4.4)

Subgroup: higher limit of the oxygen saturation target range 85% to 90%: one study reported no significant difference between groups (RR 0.91, 95% CI 0.49 to 1.68; participants = 42) (Escrig 2008).

Subgroup: higher limit of the oxygen saturation target range 91% to 95%: our meta-analysis showed no significant difference between groups (RR 0.96, 95% CI 0.77 to 1.20; participants = 695; studies = 6).

The test for subgroup differences found no significant difference (P = 0.86; I^2 = 0%).

Time to reach desired oxygen saturation target (min) (Analysis 4.5)

Subgroup: higher limit of the oxygen saturation target range 85% to 90%: one study reported a reduction in time to each desired oxygen saturation target in infants allocated to the lower (FiO_2 0.3) versus higher (FiO_2 0.9) oxygen group (MD -1.70 minutes, 95% CI -3.28 to -0.12; participants = 42) (Escrig 2008). Test for subgroup differences not indicated.

Time to reach heart rate > 100 beats per minute

No studies that reported targeting a highest SpO_2 limit reported this outcome.

Retinopathy of prematurity (any) (Analysis 4.6)

Subgroup: higher limit of the oxygen saturation target range 85% to 90%: one study reported no significant difference between groups (RR 0.61, 95% CI 0.06 to 6.17; participants = 42) (Escrig 2008).

Subgroup: highest limit of the oxygen saturation target range 91% to 95%: one study reported no significant difference between groups (RR 1.14, 95% CI 0.36 to 3.61; participants = 193) (Rook 2014).

The test for subgroup differences found no significant difference (P = 0.63; I^2 = 0%).

Severe retinopathy of prematurity (≥ stage 3) (Analysis 4.7)

Subgroup:higher limit of oxygen saturation target range 91% to 95%: our meta-analysis showed no significant difference between groups (RR 0.43, 95% CI 0.16 to 1.14; participants = 393; studies = 3). Test for subgroup differences not indicated.

Intraventricular haemorrhage (IVH) (any) (Analysis 4.8)

Subgroup: higher limit of oxygen saturation target range 91% to 95%: our meta-analysis showed no significant difference between groups (RR 0.70, 95% CI 0.30 to 1.64; participants = 211; studies = 2). Test for subgroup differences not indicated.

Severe intraventricular haemorrhage (IVH) (grade 3 or 4) (Analysis 4.9)

Subgroup: higher limit of the oxygen saturation target range 85% to 90%: one study reported no significant difference between groups (RR 0.61, 95% CI 0.12 to 2.95; participants = 42) (Escrig 2008).

Subgroup: higher limit of the oxygen saturation target range 91% to 95%: our meta-analysis showed no significant difference between groups (RR 0.78, 95% CI 0.27 to 2.24; participants = 416; studies = 3).

The test for subgroup differences found no significant difference (P = 0.80; I^2 = 0%).

Periventricular leukomalacia (Analysis 4.10)

Subgroup: higher limit of the oxygen saturation target range 85% to 90%: one study reported no significant difference between groups (RR 1.21, 95% CI 0.08 to 18.09; participants = 42) (Escrig 2008).

Subgroup: higher limit of the oxygen saturation target range 91% to 95%: one study reported no significant difference between groups (RR 0.33, 95% CI 0.01 to 7.97; participants = 88) (Kapadia 2013).

The test for subgroup differences found no significant difference (P = 0.54; I^2 = 0%).

Necrotising enterocolitis (proven) (Analysis 4.11)

Subgroup: higher limit of the oxygen saturation target range 85% to 90%: one study reported no significant difference between groups (RR 0.40, 95% CI 0.02 to 9.29; participants = 42) (Escrig 2008).

Subgroup: higher SpO_2 limit 91% to 95%: our meta-analysis showed no significant difference between groups (RR 0.85, 95% CI 0.40 to 1.79; participants = 627; studies = 5).

The test for subgroup differences found no significant difference (P = 0.65; I^2 = 0%).

Chronic lung disease (28 days) (Analysis 4.12)

Subgroup: higher SpO_2 limit 91% to 95%: one study reported a lower incidence of chronic lung disease at 28 days (RR 0.47, 95% CI 0.23 to 0.98; participants = 88) (Kapadia 2013). Test for subgroup differences not indicated.

Chronic lung disease (36 weeks) (Analysis 4.13)

Subgroup: higher SpO_2 limit 85% to 90%: one study reported no significant difference between groups (RR 0.73, 95% CI 0.20 to 2.65; participants = 42) (Escrig 2008).

Subgroup: higher SpO_2 limit 91% to 95%: our meta-analysis showed no significant difference between groups (RR 0.94, 95% CI 0.74 to 1.21; participants = 692; studies = 6).

The test for subgroup differences found no significant difference (P = 0.70; I^2 = 0%).

Duration of respiratory support (mechanical ventilation or CPAP) (days from birth) (Analysis 4.14)

Subgroup: highest limit of the oxygen saturation target range 91% to 95%: one study reported a shorter duration of respiratory support (mechanical ventilation or CPAP) in infants allocated to the 30% oxygen group compared to those in the 90% oxygen group (MD -13.70, 95% CI -14.85 to -12.55; participants = 266) (Oei 2016). The definition of respiratory support included ventilation, CPAP, high-flow nasal cannula or low-flow oxygen. Test for subgroup differences not indicated.

Duration of respiratory support (mechanical ventilation) (days from birth) (Analysis 4.15)

Subgroup: higher limit of the oxygen saturation target range 85% to 90%: one study reported no significant difference between groups (MD -4.75, 95% CI -37.24 to 27.74; participants = 42) (Escrig 2008).

Subgroup: higher limit of the oxygen saturation target range 91% to 95%: our meta-analysis showed no significant difference between groups (MD 0.94, 95% CI -1.01 to 2.88; participants = 390; studies = 4).

The test for subgroup differences found no significant difference (P = 0.73; I^2 = 0%).

Duration of respiratory support (CPAP) (days from birth) (Analysis 4.16)

Subgroup: highest limit of the oxygen saturation target range 85% to 90%: one study reported no significant difference between groups (MD 12.00, 95% CI -9.18 to 33.18; participants = 42) (Escrig 2008).

Subgroup: highest limit of the oxygen saturation target range 91% to 95%: our meta-analysis showed a shorter duration of respiratory support (CPAP) (MD -3.66 days, 95% CI -7.71 to 0.38; participants = 129; studies = 2).

The test for subgroup differences found no significant difference (P = 0.15; I^2 = 50.7%).

Duration of supplemental oxygen administration (days) (Analysis 4.17)

Subgroup: highest limit of the oxygen saturation target range 85% to 90%: one study reported no significant difference between groups (MD -10.25 days, 95% CI -50.97 to 30.47; participants = 42) (Escrig 2008).

Subgroup: highest limit of the oxygen saturation target range 91% to 95%: our meta-analysis showed a longer duration of supplemental oxygen (MD 9.96 days, 95% CI 7.21 to 12.71; participants = 459; studies = 2).

Test for subgroup differences found no significant difference (P = 0.33; I^2 = 0%).

Mortality to follow-up (> 18 months) (Analysis 4.18)

Subgroup: higher limit of the oxygen saturation target range 91% to 95%: our meta-analysis showed no significant difference between groups (RR 1.22, 95% CI 0.65 to 2.29; participants = 480; studies = 2). Test for subgroup differences not indicated.

Postnatal growth failure (weight < 10th percentile at discharge)

No study with a prespecified higher oxygen saturation limit reported this outcome.

Duration of hospitalisation (days) (Analysis 4.19)

Subgroup: higher limit of the oxygen saturation target range 91% to 95%: our meta-analysis showed no significant difference between groups (MD -4.35, 95% CI -15.26 to 6.57; participants = 156; studies = 2; I^2 = 0%). Test for subgroup differences not indicated.

Patent ductus arteriosus (not prespecified) (Analysis 4.20)

Subgroup: highest limit of the oxygen saturation target range 85% to 90%: one study reported no significant difference between groups (RR 1.10, 95% CI 0.60 to 2.01; participants = 42) (Escrig 2008).

Subgroup: highest limit of the oxygen saturation target range 91% to 95%: our meta-analysis showed no significant difference between groups (RR 0.94, 95% CI 0.72 to 1.22; participants = 586; studies = 4).

The test for subgroup differences found no significant difference (P = 0.64; I^2 = 0%).

Comparison 5. Lower versus higher oxygen concentrations — subgrouped by gestational age

Mortality, near term corrected age or discharge (latest reported) (Analysis 5.1)

Subgroup: gestation ≤ 28 weeks: our meta-analysis showed no significant difference between groups (RR 1.04, 95% CI 0.68 to 1.61; participants = 516; studies = 8).

Subgroup: gestation > 28 weeks to 32 weeks: our meta-analysis showed no significant difference between groups (RR 0.50, 95% CI 0.05 to 5.26; participants = 316; studies = 4).

The test for subgroup differences found no significant difference (P = 0.55; I^2 = 0%).

Neurodevelopmental disability at > 18 months of age (Analysis 5.2)

Subgroup: gestation ≤ 28 weeks: one study reported no significant difference between groups (RR 3.64, 95% CI 0.42 to 31.27; participants = 31) (Aguar 2013). Test for subgroup differences not indicated.

IPPV in the delivery room (Analysis 5.3)

Subgroup: gestation ≤ 28 weeks: our meta-analysis showed no significant difference between groups (RR 0.96, 95% CI 0.84 to 1.09; participants = 102; studies = 2). Test for subgroup differences not indicated.

Intubation in the delivery room (Analysis 5.4)

Subgroup: gestation ≤ 28 weeks: our meta-analysis showed no significant difference between groups (RR 1.06, 95% CI 0.84 to 1.34; participants = 338; studies = 4).

Subgroup: gestation > 28 weeks to 32 weeks: one study reported no significant difference between groups (RR 1.20, 95% CI 0.49 to 2.97; participants = 129) (Oei 2016).

The test for subgroup differences found no significant difference (P = 0.79; I^2 = 0%).

Time to reach desired oxygen saturation target [minutes] (Analysis 5.5)

Subgroup: gestation ≤ 28 weeks: our meta-analysis showed no significant difference between groups (MD -0.52 minutes, 95% CI -1.83 to 0.79; participants = 102; studies = 2). Test for subgroup differences not indicated.

Time to reach heart rate > 100 beats per minute (Analysis 5.6)

Subgroup: gestation ≤ 28 weeks: one study reported no significant difference between groups (MD 0.27 minutes, 95% CI -1.21 to 1.75; participants = 60) (Aguar 2013). Test for subgroup differences not indicated.

Retinopathy of prematurity (Analysis 5.7)

Subgroup: gestation ≤ 28 weeks: our meta-analysis showed no significant difference between groups (RR 0.72, 95% CI 0.38 to 1.33; participants = 259; studies = 4). Test for subgroup differences not indicated.

Severe retinopathy of prematurity (≥ stage 3) (Analysis 5.8)

Subgroup: gestation ≤ 28 weeks: our meta-analysis showed no significant difference between groups (RR 0.88, 95% CI 0.43 to 1.82; participants = 317; studies = 5).

Subgroup: gestation > 28 weeks to 32 weeks: one study reported no significant difference between groups (RR 2.26, 95% CI 0.09 to 54.54; participants = 147) (Oei 2016).

Test for subgroup differences found no significant difference (P = 0.57; I^2 = 0%).

Intraventricular haemorrhage (any) (Analysis 5.9)

Subgroup: gestation ≤ 28 weeks: our meta-analysis showed no significant difference between groups (RR 0.87, 95% CI 0.52 to 1.48; participants = 217; studies = 2). Test for subgroup differences not indicated.

Severe intraventricular haemorrhage (grade 3 or 4) (Analysis 5.10)

Subgroup: gestation ≤ 28 weeks: our meta-analysis showed no significant difference between groups (RR 0.95, 95% CI 0.51 to 1.79; participants = 388; studies = 6).

Subgroup: gestation > 28 weeks to 32 weeks: our meta-analysis showed no significant difference between groups (RR 3.27, 95% CI 0.15 to 72.23; participants = 149; studies = 2).

The test for subgroup differences found no significant difference (P = 0.44; I^2 = 0%).

Periventricular leukomalacia (Analysis 5.11)

Subgroup: gestation ≤ 28 weeks: one study reported no significant difference between groups (RR 1.21, 95% CI 0.08 to 18.09; participants = 42) (Escrig 2008). Test for subgroup differences not indicated.

Necrotising enterocolitis (proven) (Analysis 5.12)

Subgroup: gestation ≤ 28 weeks: our meta-analysis showed no significant difference between groups (RR 1.79, 95% CI 0.80 to 4.01; participants = 483; studies = 7).

Subgroup: gestation > 28 weeks to 32 weeks: our meta-analysis showed no significant difference between groups (RR 1.02, 95% CI 0.23 to 4.47; participants = 248; studies = 3).

Test for subgroup differences found no significant difference (P = 0.52; I^2 = 0%).

Chronic lung disease (28 days age) (Analysis 5.13)

Subgroup: gestation ≤ 28 weeks: one study reported no significant difference between groups (RR 1.27, 95% CI 0.53 to 3.05; participants = 60) (Aguar 2013). Test for subgroup differences not indicated.

Chronic lung disease (36 weeks' corrected age) (Analysis 5.14)

Subgroup: gestation ≤ 28 weeks: our meta-analysis showed no significant difference between groups (RR 0.90, 95% CI 0.72 to 1.13; participants = 411; studies = 8).

Subgroup: gestation > 28 weeks to 32 weeks: our meta-analysis showed no significant difference between groups (RR 0.92, 95% CI 0.36 to 2.33; participants = 283; studies = 3).

The test for subgroup differences found no significant difference (P = 0.96; I^2 = 0%).

Duration of respiratory support (mechanical ventilation or CPAP) (days from birth) (Analysis 5.15)

Subgroup: gestation ≤ 28 weeks: one study reported no significant difference between groups (MD 1.06, 95% CI -2.63 to 4.75; participants = 60) (Aguar 2013). Test for subgroup differences not indicated.

Duration of respiratory support (mechanical ventilation) (days from birth) (Analysis 5.16)

Subgroup: gestation ≤ 28 weeks: our meta-analysis showed no significant difference between groups (MD -13.64, 95% CI -32.62 to 5.33; participants = 120; studies = 2). Test for subgroup differences not indicated.

Duration of respiratory support (CPAP) (days from birth) (Analysis 5.17)

Subgroup: gestation ≤ 28 weeks: our meta-analysis showed no significant difference between groups (MD -2.09, 95% CI -12.85 to 8.67; participants = 120; studies = 2). Test for subgroup differences not indicated.

Duration of supplemental oxygen administration (days) (Analysis 5.18)

Subgroup: gestation ≤ 28 weeks: our meta-analysis showed no significant difference between groups (MD -0.50 days, 95% CI -16.90 to 15.91; participants = 180; studies = 3). Test for subgroup differences not indicated.

Mortality to follow up (> 18 months) (Analysis 5.19)

Subgroup: gestation ≤ 28 weeks: one study reported no significant difference between groups (RR 0.55, 95% CI 0.20 to 1.53; participants = 60) (Aguar 2013). Test for subgroup differences not indicated.

Postnatal growth failure (weight < 10th percentile at discharge) (Analysis 5.20)

Subgroup: gestation ≤ 28 weeks: one study reported no significant difference between groups (RR 0.86, 95% CI 0.55 to 1.33; participants = 60) (Aguar 2013). Test for subgroup differences not indicated.

Duration of hospitalisation (days) (Analysis 5.21)

Subgroup: gestation ≤ 28 weeks: one study reported no significant difference between groups (MD 28.00, 95% CI -8.96 to 64.96; participants = 60) (Aguar 2013). Test for subgroup differences not indicated.

Patent ductus arteriosus (not prespecified) (Analysis 5.22)

Subgroup: gestation ≤ 28 weeks: our meta-analysis showed no significant difference between groups (RR 0.95, 95% CI 0.80 to 1.14; participants = 483; studies = 7).

Subgroup: gestation > 28 weeks to 32 weeks: our meta-analysis showed no significant difference between groups (RR 1.05, 95% CI 0.54 to 2.05; participants = 227; studies = 2).

The test for subgroup differences found no significant difference (P = 0.78; I^2 = 0%).

Comparison 6. Lower (FiO_2 < 0.4) versus higher (FiO_2 ≥ 0.4) oxygen concentration — sensitivity analysis

The following sensitivity analyses report outcomes limited to trials assessed as being at low risk of bias (based on a lack of any of the following: allocation concealment, adequate randomisation, blinding of treatment, less than 10% loss to follow-up). Two studies were assessed as being at low risk of bias (Aguar 2013; Rook 2014).

Mortality, near term corrected age or discharge (latest reported) (Analysis 6.1)

Our meta-analysis showed no significant difference between groups (RR 0.51, 95% CI 0.25 to 1.07; participants = 253; studies = 2; I^2 = 0%).

Neurodevelopmental disability at > 18 months of age (Analysis 6.2)

Our meta-analysis showed no significant difference between groups (RR 0.82, 95% CI 0.49 to 1.35; participants = 208; studies = 2; I^2 = 53%).

IPPV in the delivery room (Analysis 6.3)

One study reported no significant difference between groups (RR 1.00, 95% CI 0.94 to 1.07; participants = 60) (Aguar 2013).

Intubation in the delivery room (Analysis 6.4)

Our meta-analysis showed no significant difference between groups (RR 1.16, 95% CI 0.79 to 1.70; participants = 253; studies = 2; I^2 = 0%).

Time to reach desired oxygen saturation target [minutes] (Analysis 6.5)

One study reported no significant difference between groups (MD 2.09 minutes, 95% CI -0.26 to 4.44; participants = 60) (Aguar 2013).

Time to reach heart rate > 100 bpm [minutes] (Analysis 6.6)

One study reported no significant difference between groups (MD 0.27 minutes, 95% CI -1.21 to 1.75; participants = 60) (Aguar 2013).

Retinopathy of prematurity (Analysis 6.7)

Our meta-analysis showed no significant difference between groups (RR 0.85, 95% CI 0.39 to 1.86; participants = 253; studies = 2; I^2 = 0%).

Severe retinopathy of prematurity (≥ stage 3) (Analysis 6.8)

One study reported no significant difference between groups (RR 3.86, 95% CI 0.19 to 77.05; participants = 60) (Aguar 2013).

Intraventricular haemorrhage (any) (Analysis 6.9)

Our meta-analysis showed no significant difference between groups (RR 0.85, 95% CI 0.47 to 1.53; participants = 253; studies = 2; I^2 = 0%).

Severe intraventricular haemorrhage (grade 3 or 4) (Analysis 6.10)

One study reported no significant difference between groups (RR 0.76, 95% CI 0.17 to 3.48; participants = 60) (Aguar 2013).

Necrotising enterocolitis (proven) (Analysis 6.11)

Our meta-analysis showed no significant difference between groups (RR 1.54, 95% CI 0.46 to 5.19; participants = 253; studies = 2; I^2 = 0%).

Chronic lung disease (28 days age) (Analysis 6.12)

One study reported no significant difference between groups (RR 1.27, 95% CI 0.53 to 3.05; participants = 60) (Aguar 2013).

Chronic lung disease (36 weeks' corrected age) (Analysis 6.13)

Our meta-analysis showed no significant difference between groups (RR 1.49, 95% CI 0.90 to 2.47; participants = 243; studies = 2; I^2 = 0%).

Duration of respiratory support (mechanical ventilation or CPAP) (days from birth) (Analysis 6.14)

One study (Aguar 2013) reported no significant difference between groups (MD 1.06, 95% CI -2.63 to 4.75; participants = 60).

Duration of respiratory support (mechanical ventilation) (days from birth) (Analysis 6.15)

One study reported no significant difference between groups (MD 1.25, 95% CI -0.97 to 3.47; participants = 193) (Rook 2014).

Duration of supplemental oxygen administration (days) (Analysis 6.16)

Our meta-analysis showed no significant difference between groups (MD 2.72 days, 95% CI -2.78 to 8.22; participants = 253; studies = 2; I^2 = 0%).

Mortality to follow up (> 18 months) (Analysis 6.17)

Our meta-analysis showed no significant difference between groups (RR 0.56, 95% CI 0.28 to 1.14; participants = 253; studies = 2; I^2 = 0%).

Postnatal growth failure (weight < 10th percentile at discharge) (Analysis 6.18)

One study reported no significant difference between groups (RR 0.86, 95% CI 0.55 to 1.33; participants = 60) (Aguar 2013).

Duration of hospitalisation (days) (Analysis 6.19)

One study reported no significant difference between groups (MD 28.00, 95% CI -8.96 to 64.96; participants = 60) (Aguar 2013).

Patent ductus arteriosus (not prespecified) (Analysis 6.20)

Our meta-analysis showed no significant difference between groups (RR 1.18, 95% CI 0.88 to 1.59; participants = 253; studies = 2; I^2 = 0%).

WHAT'S NEW

Date	Event	Description
5 May 2018	Amended	Author affiliation updated.

CONTRIBUTIONS OF AUTHORS

Kei Lui conceived and wrote the protocol. Jann Foster wrote the protocol and provided general advice.
Julee Oei, Peter Davis, See Kwee Ching and David Osborn provided general advice on the protocol. Lisa Jones and Jann Foster performed the initial and updated searches and extracted the data. Kei Lui, David Osborn, Jann Foster and Lisa Jones performed the eligibility assessments. Lisa Jones performed the data analyses and wrote up the results sections. David Osborn and Jann Foster cross-checked the data analyses. Lisa Jones and David Osborn wrote the text of the review. Kei Lui, Jann Foster, Lisa Jones, Peter Davis and David Osborn had input into the final version of the review.

DECLARATIONS OF INTEREST

Kei Lui and Ju lee Oei were the investigators of a randomised controlled trial titled Targeted oxygenation in the development of premature infants and their developmental outcome (the TO2RPIDO study).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Australian Satellite of the Cochrane Neonatal Review Group, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Grading of degree of heterogeneity changed to reflect that used by the Neonatal Review Group.

Methods for converting non-parametric data to parametric data documented and used.

We added the methodology and plan for 'Summary of findings' tables and GRADE recommendations, which were not included in the original protocol.

We included additional outcomes post hoc, including duration of respiratory support (mechanical ventilation), duration of respiratory support (CPAP) and patent ductus arteriosus.

The following statement was added to the inclusion criteria post hoc: 'trials were eligible for inclusion if groups had similar oxygenation saturation targeting at any time during resuscitation and NICU admission periods up to 20 (or 30) minutes'.

We performed updated searches of CENTRAL, MEDLINE, Embase and CINAHL on 13 October 2017 to obtain further reports of published literature.

INDEX TERMS

Medical Subject Headings (MeSH)

*Resuscitation [adverse effects] [methods]; Cerebral Hemorrhage [epidemiology]; Enterocolitis, Necrotizing [epidemiology]; Infant Mortality; Infant, Premature [*blood]; Intubation, Intratracheal [statistics & numerical data]; Lung Diseases [epidemiology]; Neurodevelopmental Disorders [epidemiology] [etiology]; Oxygen [*administration & dosage] [*analysis]; Randomized Controlled Trials as Topic; Retinopathy of Prematurity [epidemiology]

MeSH check words

Child, Preschool; Humans; Infant; Infant, Newborn