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Annex N° 2.
Charts and tables

Table3. Description of studies included in this analysis.

Bueno Campana 2014 Campaña MB, Ortiz JO, Muñoz CN, Lucas MR, Rincón AF, Hernández OP, et al. *High flow therapy versus hypertonic saline in bronchiolitis: randomised controlled trial. Archives of Disease in Childhood*. 1 jun 2014;99(6):511-5.	
Type of study/participants	Randomized-controlled clinical trial from October 1, 2010 to December 31, 2012 in two secondary pediatric hospitalization units in Madrid (Spain). Children aged 6 months or less presenting with moderate bronchiolitis (as defined by McConnochie20) and metadmission criteria were eligible for inclusion in the study. Moderate respiratory distress was defined by a Respiratory Stress Assessment Instrument score of 4 or higher (see Table S1). 21 Exclusion criteria were as follows: history of prematurity (gestational age less than or equal to 37 weeks), chronic lung disease, cystic fibrosis, congenital heart disease, neuromuscular disease, airway abnormalities, immunodeficiency, and those requiring immediate intubation and ventilation. Informed consent was obtained from parents prior to enrollment. The study was terminated at discharge or if, at any time, the clinical condition necessitated transfer to PICU
Interventions	Once included in the trial, participants received a nebulization of 0.5 ml/kg (maximum 3 ml) of epinephrine 1/1000 plus 2 ml of normal saline (NS) (0.9%), if they had not previously received it. Then, the investigators used a computer-generated list 22 for simple allocation of participants into two groups (1: 1 ratio): (1) HSS group: nebulized epinephrine 1/1000 plus 2 ml of HS (3%) every 4 h. (2) HHHFNC group: HHHFNC with flow depending on weight (tidal volume × respiratory rate (RR) × 9) 12 and nebulized epinephrine 1/1000 plus 2 ml of NS (0.9%) every 4 h. Other treatments provided were intravenous fluids and oxygen supplementation titrated to achieve an oxygen saturation (SatO2) of 92–96%. No other bronchodilators, antibiotics, or steroids were used. In the HSS group, oxygen supplementation was administered by conventional nasal prongs, with a flow rate of no more than 3 bpm. In the HHHFNC group, the flow rate was between 6 and 8 bpm. Attending physicians were free to prescribe additional nebulization or change the patient's study group if deemed clinically necessary. Precision Flow (Vapotherm Inc., Stevensville, MD, USA) and RT329 (Fisher and Paykel Healthcare, Auckland, New Zealand) were the devices used to administer HHHFNC depending on availability. Depending on age, two different Fisher and Paykel nasal cannulae were used in both devices, with different internal clearance and maximum admitted flow of 6 and 8 bpm, respectively. Air leakage around the cannula into the

	nares was allowed.
Outcomes	The variable for the primary outcome was the difference in mean RACS between the groups at the assessment points (RACS0 - RACS5). For the first secondary outcome, it was the difference in mean comfort score during the monitoring period (Comfort1-Comfort6). Other secondary outcome variables were LOS in days and PICU admission (rate) in both groups.
Notes	The study was funded by the Spanish Department of Health, Social Policy and Equality, Grant EC11-437 and approved by the Medical Ethics Committee of both centers.

PICU: pediatric intensive care unit.

SatO2: oxygen saturation.

HHHFNC: heated, humidified high-flow nasal cannulae.

HFNC: humidified high-flow nasal cannulae.

HSS: hypertonic saline solution.

Franklin 2018.

Franklin D, Babl FE, Schlapbach LJ, Oakley E, Craig S, Neutze J, et al. A Randomized Trial of High-Flow Oxygen Therapy in Infants with Bronchiolitis. New England Journal of Medicine [Internet]. March 21, 2018 [cited 2020 Nov 11]; Available from: https://www.nejm.org/doi/10.1056/NEJMoa1714855.

Methods	Methods In this multicenter, randomized, controlled trial, we assigned infants younger than 12 months who had bronchiolitis and needed supplemental oxygen therapy to receive high-flow oxygen therapy (high-flow group) or standard oxygen therapy (standard therapy group). Infants in the standard therapy group could receive high-flow rescue oxygen therapy if their condition met criteria for treatment failure. A computer-generated randomization sequence with a block size of 10 was used, and infants were stratified according to participating center. Sequentially numbered, sealed, opaque envelopes containing treatment assignment (in a 1: 1 ratio) were opened when eligibility criteria were met. Masking of the assigned

	treatment was not possible, given the visually obvious differences between the two interventions. Although the intervention could not be masked, all investigators remained unaware of the trial outcome until all data were locked at the end of the trial in December 2016, following analysis of data from all enrolled patients.
Participants	Infants younger than 12 months of age were eligible for inclusion for presentation to an emergency department or inpatient unit if they had clinical signs of bronchiolitis and the need for supplemental oxygen therapy to maintain the oxygenation level in the range of 92 to 98% (or 94 to 98% in the 11 hospitals with higher saturation thresholds for hypoxemia intervention, in alignment with their institutional practice). Bronchiolitis in an infant was defined according to American Academy of Pediatrics criteria 20 as symptoms of respiratory distress associated with symptoms of a viral respiratory tract infection.5 We excluded critically ill infants who had an immediate need for respiratory support and admission to the ICU; infants with cyanotic heart disease, basal skull fracture, upper airway obstruction, or craniofacial malformation; and infants who were receiving home oxygen therapy.
Interventions	Infants in the high-flow group received heated and humidified high-flow oxygen at a rate of 2 L/kg of body weight/min, delivered by the Optiflow system with the use of an age-appropriate Optiflow Junior cannula and the Airvo 2 high flow (Fisher and Paykel Healthcare). The fraction of inspired oxygen (Fio2) for high-flow use was adjusted to obtain oxygen saturation levels in the range of 92 to 98% (or 94 to 98% in the 11 hospitals with higher saturation thresholds). Fio2 was allowed to wean to room air level (0.21) at any time to provide the lowest percentage of oxygen possible to maintain an oxygen saturation level of at least 92% (or ≥94% at the 11 specified hospitals). High-flow oxygen therapy was stopped after 4 h of receiving a Fio2 of 0.21 while oxygen levels were maintained in the expected range. Infants in the standard therapy group received supplemental oxygen through a nasal cannula, up to a maximum of 2 L/min, to maintain an oxygen saturation level in the range of 92 to 98% (or 94 to 98%, depending on the institution). Weaning from supplemental oxygen was allowed at any time to provide the lowest possible oxygen level to maintain an oxygen saturation level of at least 92% (or ≥94%).
Outcomes	The primary outcome was escalation of care due to treatment failure (defined as meeting ≥ 3 of 4 clinical criteria: persistent tachycardia, tachypnea, hypoxemia, and medical review triggered by a hospital early warning tool). Secondary outcomes included length of hospital stay, duration of oxygen therapy, and rates of transfer to a tertiary hospital, ICU admission, intubation, and adverse events.

Notes	Emergency departments and general pediatric inpatient units at 17 tertiary and regional hospitals in Australia and New Zealand participated in the trial. The human research ethics committee at each participating site approved the trial. The protocol, available with the full text of this article at NEJM.org, has been published previously [19]. The trial was overseen by a steering committee with a principal investigator at each site. The authors attest to the accuracy and completeness of the data and the fidelity of the trial to the protocol. Early drafts of the manuscript were written by the first and last authors with input from all authors. Although the intervention could not be masked, all investigators remained unaware of the outcome of the trial until all data were locked at the end of the trial in December 2016, following analysis of data from all Emergency departments and general pediatric inpatient units at 17 tertiary and regional hospitals in Australia and New Zealand participated in the trial. The human research ethics committee at each participating site approved the trial. The protocol, available with the full text of this article at NEJM.org, has been published previously [19]. The trial was overseen by a steering committee with a principal investigator at each site. The authors attest to the accuracy and completeness of the data and the fidelity of the trial to the protocol. Early drafts of the manuscript were written by the first and last authors with input from all authors. Although the intervention could not be masked, all investigators remained unaware of the outcome of the trial until all data were locked at the end of the trial in December 2016, following analysis of data from all patients enrolled patients enrolled

Fio2: fraction of inspired oxygen.

HIlliard 2012

Hilliard TN, Archer N, Laura H, Heraghty J, Cottis H, Mills K, et al. Pilot study of vapotherm oxygen delivery in moderately severe bronchiolitis. Archives of Disease in Childhood. 2012 Feb 1;97(2):182-3.

Methods	Prospective, randomized, single-center pilot study in the United Kingdom.
Participants	Newborn infants with clinical diagnosis of bronchiolitis admitted to the Department of Pediatric Respiratory Medicine, Bristol Children's Hospital Recruited: 21 infants (one excluded with onset of apnea and one excluded with decreased oxygen requirement) Randomized: 19 infants, median age 3.0 months, range 0.3 to 11.3 months. Intervention group: 11 infants, age in days: median 49 (range 8 to 334). Control group: 8 infants, age in days: median 125 (range 12 to 343). Inclusion criteria: infants younger than 12 months admitted to a general pediatric ward with a clinical diagnosis of bronchiolitis (cough, tachypnea, chest retraction, and crackles on auscultation); moderately severe disease defined as a head box oxygen requirement of at least 35%, moderate to severe tachypnea, increased breathing effort and in whom feeding was discontinued. Exclusion

	criteria: congenital cyanotic heart disease, repeated severe apneas, or severe hypercapnia with acidosis on pH blood gas analysis.
Interventions	High-flow nasal cannula therapy via the Vapotherm 2000i device, with a 1 to 8 L/min pediatric cartridge and infant-sized nasal cannulae (TV), started at a flow rate of 4 L/min with 100% oxygen, at 37 °C and flow rate increased by 0.5 L every 5 min up to 8 L/min if tolerated to achieve target SpO2 over 24 h. If clinically stable, Fio2 decreased in 10% steps at 4-h intervals, with the same control of target SpO2: conventional head oxygen therapy (HBO).
Outcomes	Primary: SpO2 at 8 h after randomization heart rate, respiratory rate, blood pressure, Fio2, combined bronchiolitis severity score (maximum of 7). Recorded outcomes: 4, 8, 12, 24, 36, and 48 h. Additional recorded outcomes: duration of time to switch to dry oxygen, time receiving oxygen therapy after randomization, total oxygen therapy time, time until enteral feedings were started, time to discharge, and total hospital length of stay, Reported outcomes: SpO2 at 8 h, Fio2 at 8 h, SpO2 at 12 h, Fio2 at 12 h, SpO2 at 24 h, Fio2 at 24 h, time to dry O2 (hours), total time on O2 (hours), time to feedings (hours), time to discharge (hours), and total length of stay (hours).

SpO2: oxygen saturation measured by pulse oximeter.

Source: Data contributed by the authors and extracted from the review by Beggs et al.

Kepreotes 2017.

Kepreotes E, Whitehead B, Attia J, Oldmeadow C, Collison A, Searles A, et al. High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial. The Lancet. March 4, 2017;389(10072):930-9.

Methods	We conducted a phase 4, open-label, randomized controlled trial from July 16, 2012, to May 1, 2015, in the emergency department of John Hunter Hospital and the medical unit of John Hunter Children's Hospital in the Hunter New England Local Health District of New South Wales (NSW), Australia.
Participants	Infants younger than 24 months who presented to the emergency department or were admitted to the ward were eligible for inclusion if they had a clinical diagnosis of bronchiolitis that was assessed as moderate severity using the NSW Health clinical practice guideline [15] and required supplemental oxygen. Infants with chronic neonatal lung disease on home oxygen could be included but were weaned to their home oxygen index rather than to room air.

Interventions	Standard therapy incorporated 100% cold wall oxygen through infant nasal cannulae at low flow up to a maximum of 2 L/min. This approach has been practiced in Australian hospitals for more than 20 years and is considered standard therapy in most developed countries. Estimates of standard therapy FiO2 are difficult to establish in children, but a range of 0–30 to 0–3,818 was reported in healthy adults. The emergency department does not add humidification to standard therapy, but the wards use Aquapak bubble humidifiers (Hudson RCI301; Hudson RCI Teleflex; Temecula, CA, USA) to add moisture to the cold wall gas by bubbling it through sterile water before it reaches the patient. In the experimental arm, HFWHO was delivered via age-appropriate Optiflow Junior nasal cannulae and MR850 humidifier (Fisher and Paykel Healthcare, Auckland, New Zealand) using a maximum flow rate of 1 L/kg/min up to a limit of 20 L/min using 1:1 air-to-oxygen ratio, resulting in a maximum FiO2 of 0.6. OptiflowJunior nasal cannulae allowed all children in the experimental arm to start at a flow rate of 1 L/kg/min.
Outcomes	Primary outcome oxygen weaning time (time from randomization to first sustained observation of room air after oxygen), time from randomization to first sustained observation of room air after oxygen, and time from randomization to first sustained observation of room air after oxygen. Secondary safety outcomes were time from randomization to treatment failure, proportion of treatment failure, proportion of serious adverse events, transfer to ICU. Secondary outcomes of effectiveness length of hospital stay.
Notes	

HFWHO RCT: high-flow warm humidified oxygen.

NSW: New South Wales.

FiO2: fractional percentage of inspired oxygen.

ICU: intensive care unit.

Milani 2016	
Methods	Clinical trial, open-label, where the control group were those for whom high flow was not available. A prospective study was performed from January 2014 to March 2014 in the Pediatric Emergency Department. Prospective non-randomized study.
Participants	Inclusion criteria were admission for a diagnosis of moderate or severe bronchiolitis, need for oxygen supplementation (peripheral oxygen saturation < 92% on room air), younger than 12 months, gestational age >34 weeks, absence of underlying disease or any condition at risk for bronchiolitis complications, and written informed consent signed by the parents. Bronchiolitis was defined as acute onset of respiratory distress with cough and diffuse crackles on auscultation. On

	admission, a severity score was assigned according to our standard procedure (Table S1): a score of 4 or more moderate to severe bronchiolitis identified. Exclusion criteria included a gestational age of 34 weeks, admission to a neonatal intensive care unit at birth, history of previous bronchiolitis or wheezing episodes, chronic respiratory disease, congenital airway anomalies, craniofacial malformations, hemodynamically significant cardiac disease, underlying neurologic disease, or admission to the PICU according to previously defined criteria
Interventions	Two high-flow nasal cannula nasal cannula devices were available at our institution, and were used in a non-formalized randomized fashion, which was dependent on availability, as previously described by Aminalai et al. If an HFNC device was not available, standard low-flow oxygen delivery therapy was provided. In subjects treated with HFNC, Airvo 2 (Fisher and Paykel Healthcare, Auckland, New Zealand) delivered oxygen supplementation via appropriately sized nasal cannulae with humidified and heated flow (L/min = 8 ml/kg 9 respiratory rate 9 0.3). In infants treated with low-flow oxygen delivery, oxygen supplementation was delivered via standard nasal prongs. Oxygen supplementation volumes were chosen.
Outcomes	Respiratory rate, respiratory effort, and feeding capacity were assessed according to the criteria described previously and recorded at regular time points. The total duration of oxygen supplementation and length of hospital stay were also analyzed. Adverse events and failed treatments, including admission to the PICU, were recorded. Admission to PICU implied withdrawal from the study. However, the difference in respiratory rate and effort and feeding capacity between the two groups was also analyzed, including data from withdrawn subjects obtained before admission to the PICU.
Notes	

PICU: pediatric intensive care unit.

HFNC: humidified high-flow nasal cannula.

Ergul 2018.

Ergul AB, Calıskan E, Samsa H, Gokcek I, Kaya A, Zararsiz GE, et al. Using a high-flow nasal cannula provides superior results to OxyMask delivery in moderate to severe bronchiolitis: a randomized controlled study. Eur J Pediatr. Aug 1, 2018;177(8):1299-307.

Methods	Single-center, open-label, phase 4, randomized controlled clinical trial comparing oxygen therapy administered with a diffusing mask with the use of an HFNC in children younger than 24 months who were diagnosed with moderate to severe bronchiolitis and admitted to the pediatric ICU of the Emergency Department of Kayseri Emel Mehmet Tarman Children's Hospital, Kayseri Teaching Hospital and University of Medical Sciences, between March and December 2016. Randomization 1:1 using a block of four, with stratification by sex.

Participants	Sixty patients who were aged between 1 and 24 months and had been diagnosed with moderate or severe acute bronchiolitis were included. Patients requiring immediate respiratory support, those already admitted to the ICU due to respiratory failure, those with chronic lung disease or cardiovascular disorders, those with upper respiratory tract obstructions, and those with cranial malformations were excluded. The severity of bronchiolitis in all the children admitted. The severity of bronchiolitis in all children admitted to the ICU was assessed by a clinical scoring system that included general health status, respiratory rate, heart rate, and the presence of chest retractions.
Interventions	*Oxygen diffusing mask*: Patients received oxygen therapy (10–15 L/min) from an OxyMask (Southmedic, Inc.) to maintain SpO2 >94%. Weaning from supplemental oxygen was allowed at any time for delivery of as little oxygen as possible while maintaining an oxygen saturation level of at least >94%. Oxygen therapy was stopped if SpO2 was maintained at a level >94% for more than 4 h. In such cases, the oxygen flow rate was decreased to 2 L/min and the patient was monitored. The patient was then transferred to a ward. *HNFC group*: Patients received oxygen therapy at a high flow rate from a Precision Flow nasal cannula (Vapotherm, Inc., Stevensville, MD, USA). A 1.9-mm pediatric cannula, which can dispense 1 to 20 L/min of oxygen, the initial oxygen flow was 1 L/kg/min, up to a maximum of 20 L/min. Oxygen was delivered at air: oxygen ratio of 1:1, resulting in a maximum FiO2 of 60%. FiO2 was then reduced to 20%. HFNC therapy was stopped if SpO2 was maintained at a level >94% for more than 4 h at a FiO2 value of 20%. The patient was then transferred to a ward.
Outcomes	**Primary**: treatment failure. Defined as meeting at least two of three clinical criteria and the requirement for escalation of care. The clinical criteria are as follows: 1. No change or increase in respiratory rate compared to baseline 2. 2. No change or increase in heart rate compared to baseline. 3. Persistently low SpO2 measurements (< 92%) despite adequate oxygen flow rate and FiO2 in the HFNC group or an oxygen flow rate of 15 L/min in the mask group. **Secondary**: differences in time to weaning from oxygen therapy, length of ICU stay length of hospital stay, heart rate and respiratory rate, pH, partial pressure of carbon dioxide (pCO2) and oxygen saturation (SpO2). treatment failure. Defined as meeting at least two of three clinical criteria and the requirement for escalation of care. The clinical criteria.
Notes	According to protocol, in the group of patients with diffusing mask, when oxygen therapy failed, the HFNC treatment protocol was applied. And it was indicated to implement noninvasive mechanical ventilation if there was a treatment failure in the patients in the HFNC group.

ICU: intensive care unit.

PICU: pediatric intensive care unit.

HFNC: humidified high-flow nasal cannula.

SpO2: oxygen saturation measured by pulse oximeter.

FiO2: fractional percentage of inspired oxygen.

Table 4. Studies excluded after evaluation of the full text, with reasons for exclusion.

Bressan 2013 Bressan S, Balzani M, Krauss B, Pettenazzo A, Zanconato S, Baraldi E. High-flow nasal cannula oxygen for bronchiolitis in a pediatric ward: a pilot study. Eur J Pediatr. 2013 Dec;172(12):1649-56. doi: 10.1007/s00431-013-2094-4. Epub 2013 Jul 31. PMID: 23900520; PMCID: PMC7087157.	Non-randomized study, no control branch
Franklin 2019 Franklin D, Shellshear D, Babl FE, Schlapbach LJ, Oakley E, Borland ML, Hoeppner T, George S, Craig S, Neutze J, Williams A, Acworth J, McCay H, Wallace A, Mattes J, Gangathimn V, Wildman M, Fraser JF, Moloney S, Gavranich J, Waugh J, Hobbins S, Fahy R, Grew S, Gannon B, Gibbons K, Dalziel S, Schibler A; PARIS and PREDICT. Multicentre, randomised trial to investigate early nasal high-flow therapy in paediatric acute hypoxaemic respiratory failure: a protocol for a randomised controlled trial-a Paediatric Acute respiratory Intervention Study (PARIS 2). BMJ Open. 2019 Dec 18;9(12):e030516. doi: 10.1136/bmjopen-2019-030516. PMID: 31857300; PMCID: PMC6937038.	Sub-study of the PARIS study, which compared two high-flow forms with and without oxygen with saturation less and greater than 85%

Maitland 2017 Maitland K, Kiguli S, Opoka RO, Olupot-Olupot P, Engoru C, Njuguna P, Bandika V, Mpoya A, Bush A, Williams TN, Grieve R, Sadique Z, Fraser J, Harrison D, Rowan K. Children's Oxygen Administration Strategies Trial (COAST): A randomised controlled trial of high flow versus oxygen versus control in African children with severe pneumonia. Wellcome Open Res. 2018 Jan 9;2:100. doi: 10.12688/wellcomeopenres.12747.2. PMID: 29383331; PMCID: PMC5771148.	Population of any age with pneumonia
Daverio 2019 Daverio M, Da Dalt L, Panozzo M, Frigo AC, Bressan S. A two-tiered high-flow nasal cannula approach to bronchiolitis was associated with low admission rate to intensive care and no adverse outcomes. Acta Paediatr. 2019 Nov;108(11):2056-2062. doi: 10.1111/apa.14869. Epub 2019 Jun 13. PMID: 31102551.	Retrospective study
Mayfield 2014 Mayfield S, Bogossian F, O'Malley L, Schibler A. High-flow nasal cannula oxygen therapy for infants with bronchiolitis: pilot study. J Paediatr Child Health. 2014 May;50(5):373-8. doi: 10.1111/jpc.12509. Epub 2014 Feb 25. PMID: 24612137.	Observational study with historical control

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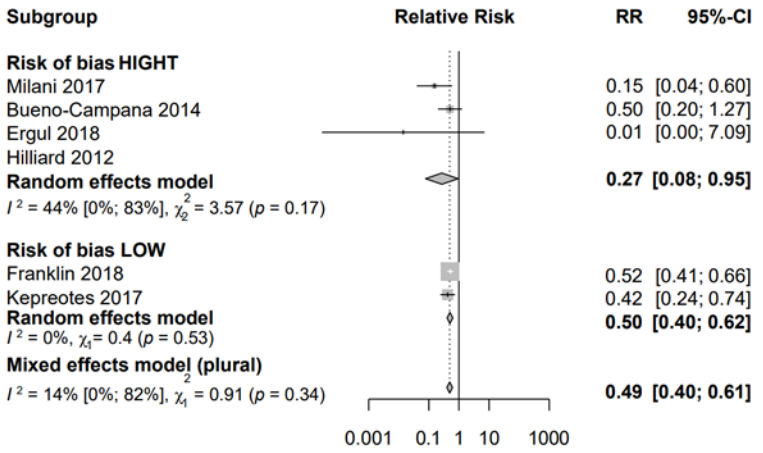
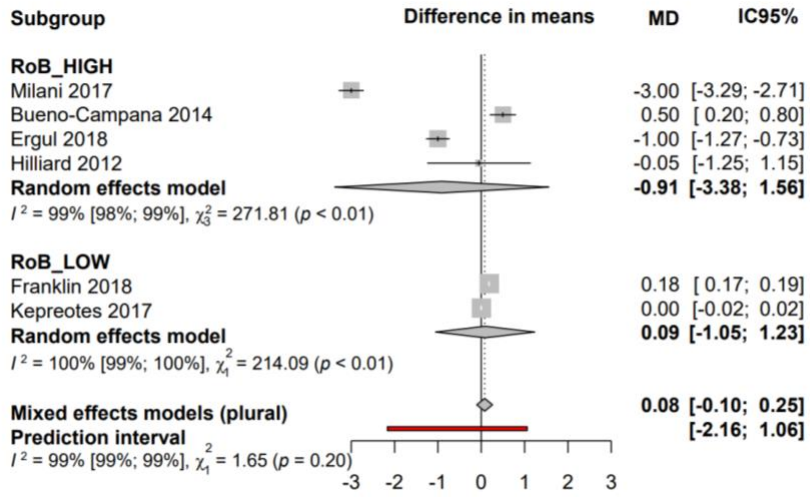
Figure 5. Forest plot of high-flow oxygen cannula versus low-flow oxygen. Unlink: treatment failure.



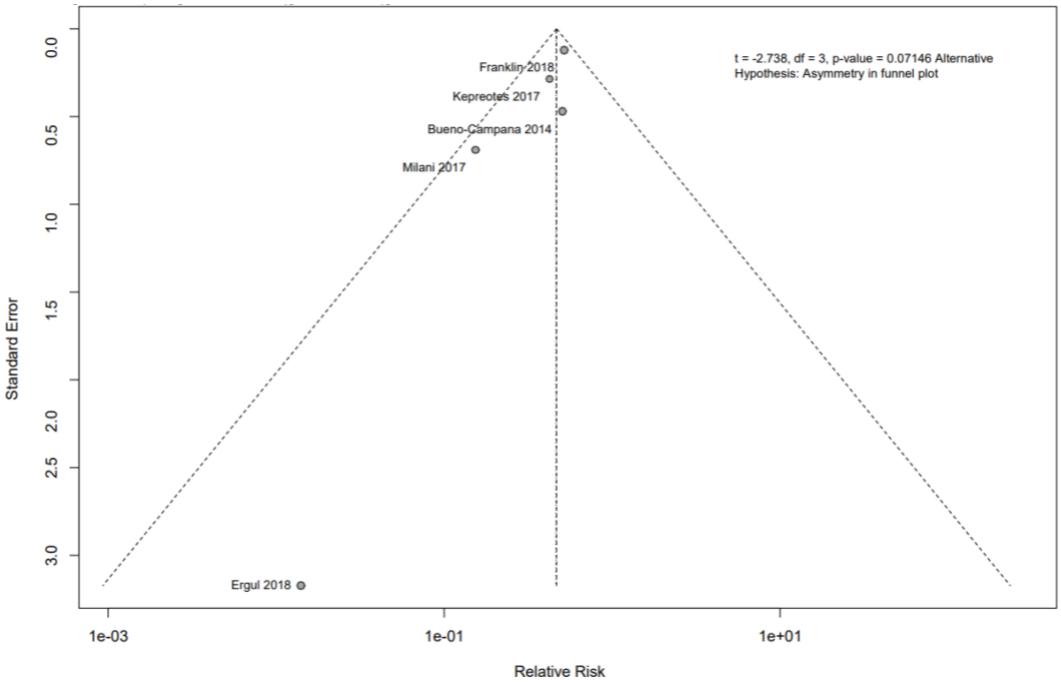
Subgroups: high risk of bias (RoB_HIGH) versus low risk of bias (RoB_LOW).

Figure 6. Forest plot of high-flow oxygen cannula versus low-flow oxygen. Outcome: mean number of days of hospitalization.



Subgroups: high risk of bias (RoB_HIGH) versus low risk of bias (RoB_LOW).
SD: standard error.
MD: mean difference.
95%CI: 95% confidence interval.

Figure 7. High-flow cannulated oxygen funnel plot versus low-flow oxygen for treatment of acute infant bronchiolitis.



t = -2,738.
df = 3.
p-value = 0.07146.
Alternative hypothesis: funnel plot asymmetry.

Figure 8. Contour funnel plot: high-flow versus low-flow cannulated oxygen for treatment of acute infant bronchiolitis.