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The association between bronchopulmonary dysplasia and cerebral palsy in children: A meta-analysis

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The association between bronchopulmonary dysplasia and cerebral palsy in children: A meta-analysis

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Abstract

Objective: To investigate whether bronchopulmonary dysplasia (BPD) affects the neurodevelopment outcomes especially cerebral palsy (CP) and to identify the factors that may explain these differences.

Data sources: We used EMBASE, PubMed and Web of Science to conduct a meta-analysis of studies published before September 1, 2017 with English, with titles or abstracts that discussed an association between BPD and CP.

Study selection: Case-control studies and cohort studies were included.

Data extraction and synthesis: All review stages were conducted by 2 reviewers independently. Data synthesis was undertaken via meta-analysis of available evidence.

Main outcomes and measures: Neurodevelopment outcomes, especially cerebral palsy after exposure to BPD.

Results: Among 1234 initially identified studies, we selected those that addressed an association between BPD and CP according to our preselected inclusion criteria. Our meta-analysis included 11 studies. According to a random effect model, BPD was significantly associated with both cerebral palsy (ORs=2.10: 95% CI 1.57 to 2.82) in preterm infants. Factors explaining differences in the study results included study design, the definition of BPD, the time of diagnosis of CP, and whether the studies adjusted for potential confounders.

Conclusion This study suggests that BPD is a risk factor for cerebral palsy. Further studies are required to confirm these results and to detect the influence of variables across studies.

Keywords: bronchopulmonary dysplasia; cerebral palsy; neurodevelopment; infant

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Strengths and limitations of the study

*Infants exposed to bronchopulmonary dysplasia (BPD) were more likely to develop cerebral palsy (CP).

*We conducted a meta-analysis to evaluate the potential association between BPD and CP in preterm infants. Factors explaining differences in the study results included study design, the definition of BPD, the time of diagnosis of CP, and whether the studies adjusted for potential confounders.

*We failed to identify the source of heterogeneity.

*The association between BPD ad CP is recognized but whether this is because the same infants are susceptible to both adverse outcomes or whether BPD truly influence the development of CP cannot be determined from the existing literature. Further studies are required to confirm these results and to detect the influence of variables across studies.

*The number of studies included is limited, and therefore, the results of this meta-analysis should be interpreted with caution.

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Introduction

Despite advances in obstetric and neonatal care, the prevalence of cerebral palsy (CP) has been increased [1], and the etiology of CP remains poorly understood. Evidence shows that prenatal factors, including maternal age [2], education [3, 4], obesity [5-7], race [8], chorioamnionitis[9] and hypertension [10] contribute to CP. Yet, the neonatal factors play a relatively minor role.

Bronchopulmonary dysplasia (BPD) has been implicated as a potential neonatal factor of CP[11]. BPD is common in preterm and low birthweight infants born at 24 to 26 weeks of gestation[12]. The lung is in the canalicular stage from 16 to 28 weeks, and it is in the saccular stage from 28 to 36 weeks. Alveoli are not uniformly present until 36 weeks. Thus, premature birth and the initiation of pulmonary gas exchange arrest normal alveolar and distal vascular development, and subsequent BPD[12]. Maternal infection, especially maternal chorioamnionitis was associated with an increased risk of BPD[13]. The inconsistencies in the definition of BPD contribute to variation in incidence of BPD. Some studies defined as oxygen dependency at 36 weeks post-menstrual age (PMA), yet, others defined as 28 or more days duration of oxygen dependency during hospitalization [13]. Cerebral palsy, cognitive delay, and hearing loss are important and commonly reported adverse outcomes in very premature infants[14]. It is postulated that BPD can lead to neonatal brain injury and subsequent CP.

A number of studies have assessed the relationship between BPD and CP in premature infants, but most have not examined a significant association, for example, one study defined BPD as 28 days duration of oxygen dependency[15], and one study[16] evaluated the association between BPD (oxygen dependency at 36 weeks) and quadriparas and diparesis. Yet, any other studies[17, 18] showed a significant association between BPD and CP. We conducted a meta-analysis to evaluate the potential association between BPD and CP in preterm infants.

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Methods

Retrieval of studies. The PubMed, EMBASE, and Web of Science databases were searched through September 1, 2017. The search of bronchopulmonary dysplasia was performed using the following keywords and subject terms: "bronchopulmonary dysplasia", or "BPD*", or "lung dysplasia", or "Dysplasia, Bronchopulmonary", or "Bronchopulmonary Dysplasia", using "OR" to link relevant text within the search field. To acquire studies related to cerebral palsy, "OR" was used to associate the key words, which included "cerebral palsy", "Crebral pals*", "spastic*", "quadripleg*" and "CP". We combined these terms using "AND" to retrieve the studies. We restricted the search to human studies published in English.

Inclusion/exclusion criteria.

The study inclusion criteria were as follows: (1) the study evaluated the association between bronchopulmonary dysplasia (BPD) and the risk of CP in children; (2) the study was published in English; (3) case-control or cohort study design; (4) the study described the assessment of exposure and outcome; and the study reported unadjusted and/or adjusted relative ratios (RRs) and corresponding 95% confidence intervals (CIs), unadjusted and/or adjusted odds ratios (ORs) estimates and 95% CIs.

The exclusion criteria were as follows: (1) a review or meta-analysis or a case report; (2) the study was not published in English; (3) the article described an animal experiment study; (4) a study with overlapping data; (5) the study was not reported the children's CP or disability affected by BPD, and did not have useable data.

Study selection

The retrieved studies were screened by reading the titles and abstracts, and two authors (Xiaoyun Gou and Lei Yang) subsequently read the full text of the remaining publications independently and then discussed disagreements to reach a consensus.

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Data extraction. The data were independently extracted from the studies by two reviewers (Xiaoyun Gou and Lei Yang) and included the name of the first author, publication year, the country of the participants, study design, sample size, gestational age and/or birthweight, following years, BPD definition, primary outcome, and adjusted confounders.

Quality evaluation. The two reviewers (Xiaoyun Gou and Lei Yang) independently used the Newcastle-Ottawa Scale (NOS) [19] to examine all included studies for their methodological quality. The reviewers evaluated the quality score via examine the selection of the study population, comparability and evaluation of exposure and outcome, with a maximum score of nine. The reviewers resolved disagreements in the manner previously described.

Statistical analysis. The original studies included used ORs and/or RRs and 95%CIs to assess the association between BPD and the risk of CP in children. The ORs and RRs were directly considered as ORs. We pooled ORs and/or RRs of each study separately using the Der Simonian-Laird formula (random-effects model) [20]. Statistical heterogeneity [21] between the studies was assessed using the Q and I^2 statistics. Values of I^2>50% and P<0.1 indicated high heterogeneity [9]. We conducted a stratified analysis based on study design (case-control, cohort), BPD type (oxygen dependency at 36 weeks' post-menstrual age (PMA), 28 days duration of oxygen dependency during hospitalization, severe BPD including mechanical ventilation at 36 weeks, not defined BPD), diagnostic criteria for CP (Age <2 years, other), confounding variables (gestational age, unadjusted estimated). We performed sensitivity analyses by omitting one study at a time.

We used Egger's [22] and Begg's [23] tests to assess the publication bias, which was considered to be statistically significant when p<0.05. We used Stata software, version 12.0 (StataCorp, College Station, TX) to perform the statistical tests.

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Results

Literature search. We identified 1234 potential studies: 195 from PubMed, 523 from EMBASE, 515 from Web of Science and 1 additional study from the related reference. After careful screening, 11 studies that reported the association between BPD and the risk of CP in children were selected for inclusion in this study (see Figure 1). These 11 included studies are summarized in Table 1.

Characteristics and quality of the included studies. The included studies were published between 1999 and 2017. Eleven studies evaluated the association between BPD and cerebral palsy in preterm infants. Two[15, 17] of these studies reported no significant association. Eight of the included studies were cohort studies and three [15, 24, 25] of the studies were case-control studies of a high quality (NOS>5). Some of the studies defined the diagnosis of CP more than 2 years, while others defined CP less than 2 years.

Bronchopulmonary dysplasia (BPD) and cerebral palsy (CP).

When the study results were analyzed using random effects model, BPD was significantly associated with both CP (ORs, 2.10; 95%CIs, 1.57, 2.82). These infants were preterm infants.

Six studies[16, 17, 24, 26-28] evaluated the association between BPD (oxygen dependence at 36 weeks) and CP in premature infants, with only 1 reporting[17] a no significant association (Figure 2). One study[15] evaluated the association between BPD (oxygen dependence at 28 days) and CP in premature infants with no significant association (OR 1.12, 95%CI, 0.84, 1.49). Three studies[18, 25, 29] evaluated the association (OR 2.80, 95%CI, 2.08, 3.79) without mentioned BPD definition, and 2 studies[16, 30] show severe BPD or mechanical ventilation at 36 weeks (OR 3.44, 95%CI, 1.56, 7.60).

Stratified analysis

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A stratified analysis was conducted to investigate the possible sources of heterogeneity in articles of BPD in preterm infants (Table 2). The case-control studies did not produce significant summary ORs (2.13; 95%CI, 0.85, 5.34), yet, a significant association was seen in cohort studies ORs (2.15; 95%CI, 1.57,2.94).

The definition of CP differed greatly among studies of preterm infants (Table 2). Of the four studies[16-18, 26] that provided adequate information, four studies provided a minimum age of 2 years for diagnosing CP; Some studies confirm the diagnosis by performing examination, while others did not. Some studies excluded children with congenital anomalies[15, 17, 18], while others[16, 26] did not specify any exclusion criteria.

Five studies of BPD(PMA) in premature infants reported ORs controlled for gestational age. The summary ORs calculated from adjusted gestational age was not significant smaller than that derived from unadjusted estimates (ORs, 2.29; 95%CI, 1.5, 3.49; vs ORs, 2.01; 1.43, 2.83; Table 2).

Sensitivity analysis

The resulting summary ORs differed minimally after omitting each of one of the included studies at a time.

Publication bias. Asymmetry and publication bias were evaluated by Egger's and Begg's tests. The pooled results did not support the presence of significant publication bias (all $p>0.05$).

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Discussion

To our knowledge, this article is the first meta-analysis of the relationship between BPD and risk of CP in children. The results of this meta-analysis, which included 11 studies, showed evidence that BPD appears to be associated with CP in preterm infants.

BPD might affect the neurodevelopment outcome of infants through multiple pathways. A growing body evidence supports that BPD contributes to neonatal brain injury[31]. Experimental BPD with hypoxia leads to central nervous system damage, and subsequent CP[32, 33]. Indeed, the preterm infants with BPD accompany with hypoxia often had oligodendrocytes maturation arrest or injury[34-36], disruption of myelination and demyelination, and then cause white matter injury[36] and impaired neurodevelopmental outcomes[33].

To better understand the relationship between BPD and CP, it is crucial to develop consensus definitions of BPD. Most published reports do not apply specific diagnostic criteria for BPD, as a group, these studies produced heterogeneous results. The results of the stratified analysis suggest that a stronger association is seen when used severe or mechanical ventilation at 36 weeks diagnostic criteria in the studies. The studies do not include strict criteria may lead to an over-diagnosis of BPD, which may contribute to the evidence of heterogeneity.

The definition of CP varied between studies; although CP can be difficult to diagnosis in children younger than 2 years, 1 study made the diagnosis in infants younger than 12 months. A consensus definition of CP is required.

Some studies report significant associations between BPD and CP after adjust for potential confounders. Although gestational age appears to be a possible confounder, it may also lie directly in the causal pathway between BPD and CP. BPD is associated with premature delivery, and low gestational age, which is associated with a host of

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intrinsic vulnerabilities within the brain, that have been implicated in the pathogenesis of CP. Therefore, if low gestational age resulting in BPD plays a direct role in the pathogenesis of CP, then adjusting for gestational age will falsely diminish the observed association between BPD and CP. One study of BPD in premature infants reported insignificant association when controlling for the confounder variables including gestational age. It is unclear if this is because BPD does not contribute independently to CP, or perhaps because gestational age lies on the causal pathway.

Other factors may interact with BPD in the pathogenetic pathway leading to CP. For example, child sex, IVH, Apgar score at 5 minutes, small for gestational age (SGA), which may contribute to CP lies on the causal pathway. Although the studies controlled for some confounder variables, many other factors that contribute to CP may not be excluded.

Our meta-analysis is subject to limitations as follows. Firstly, we only included articles published in English. Secondly, there may be publication bias, incomplete ascertainment of published studies, and errors in data abstraction. Thirdly, the number of studies included is small, and therefore, the results of this meta-analysis should be interpreted with caution. Furthermore, the bias inherent to observational studies are not eliminated in a quantitative synthesis.

Our meta-analysis has some merits. First, the study evaluated the association between BPD and CP. Second, the study used stratified analysis to explore the heterogeneity source, yet, we failed to identify the source of heterogeneity.

In conclusion, our pooled analyses provide evidence that BPD is significantly associated with cerebral palsy in children. Future studies that consider additional factors are required to resolve this issue.

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Author contributions

XG and LY contributed to the conception and design of the study, as well as to the drafting of this article. LP contributed to the collection and analysis of the data. DX contributed to the conception and design of the study and approved the final version of the manuscript for submission for publication.

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Competing financial interests

The authors declare that they have no competing financial interests.

Data sharing statement

No additional data are available.

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Table 1. Characteristics of the included studies.

Study	Publication year	country	Study design	Gestational age/ birth weight	Sample size	BPD definition	Primary outcome	adjusted confounder variables
Gagliardi[28]	2009	Italy	Cohort study	<32 weeks and BW<1500g	1209	BPD (at 36 weeks PMA)	ORs=2.16(CI, 1.1-3.9)	GA, propensity score for prolonged ventilation, centre
Kim[15]	1999	Korea	Case-control	<37 weeks	184	BPD (oxygen dependence at 28 days)	ORs=1.12(CI, 0.85-1.5)	Apgar score at 5 min, IVH, PDA, sepsis, duration of mechanical ventilation
Lodha[29]	2011	Canada	Cohort study	<28 weeks	918	NA	ORs=2(CI, 1.2-3.2)	NA
Natarajan[27]	2012	NA	Cohort study	<27 weeks BW<1000g	1189	BPD (at 36 weeks PMA)	ORs=2.41(CI, 1.4-4.13)	GA, male gender, SGA, maternal education, surgical NEC, IVH or PVL
Palta[30]	2000	USA	Cohort study	BW<1500g	1024	Severe BPD	ORs=2.3(CI, 1.2-4.6)	NA
Schlapbach[24]	2010	Switzerland	Case-control study	<32 weeks	99	BPD (at 36 weeks PMA)	ORs=3.75(CI, 1.08-11.14)	gestational age, birth weight, postnatal growth, mechanical ventilation
Synnes[26]	2017	Canada	Cohort study	<29 weeks	3700	BPD (at 36 weeks PMA)	ORs=1.42(CI, 1.17-1.73)	NA
Tran[25]	2005	Australia	Case control	<27 weeks	150	NA home oxygen	ORs=3.4(CI, 1.2-9.4)	NA
Van Marter[16]	2011	USA	Cohort study	<28 weeks	1047	BPD (at 36 weeks PMA)	ORs=1.77(CI, 1.02-3.77) ORs=5.16(CI, 2.62-10.16)	NA

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						BPD (Mechanical ventilation at 36 weeks)		
Wang[18]	2014	China	Cohort study	GA<30 weeks and BW<1500g	5807	Not mentioned	ORs=3.14(CI, 2.61-3.85)	GA, BW, sex, ROP grade≥III, grade III/IV IVH and PVL
Bashir[17]	2016	Canada	Retrospective observational study	BW<1250g	1563	BPD (at 36 weeks PMA)	ORs=1.3(CI, 0.87-1.96)	GA, male gender, ANCS use, Apgar score<7 at 5 minutes, SGA, postnatal steroids, blood transfusion, PDA, IVH grade≥III and/ or PVL, ROP grade≥III and/ or required laser treatment and postnatal sepsis

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Table 2. Pooled results of the associations between bronchopulmonary dysplasia and cerebral palsy in children.

Variables	Studies (n)	ORs(95%CI)	I^2 (p-value for heterogeneity)
Total	11	2.10(1.57,2.82)	82.5% (0.000)
Study design			
Case-control	3	2.13 (0.85, 5.34)	82.1% (0.000)
Cohort	8	2.15 (1.57, 2.94)	73.6% (0.023)
Definition of BPD			
Oxygen dependence at 36 weeks	6	1.67(1.33,2.11)	33.2% (0.187)
Oxygen dependence at 28 days	1	1.12(0.84,1.49)	NA
Severe BPD (mechanical ventilation)	2	3.44(1.56,7.60)	63.7%(0.097)
Not mentioned BPD type	3	2.80(2.08, 3.79)	30.5% (0.237)
Diagnostic criteria for cerebral palsy			
Age≥2 years only	4	1.54(1.15,2.06)	62.4% (0.046)
Age<2 years included	6	2.31(1.61,3.32)	69.7% (0.006)
Controlling for potential confounders			
Unadjusted estimates	5	2.01(1.43,2.83)	53.4% (0.072)
Controlled for gestational age	5	2.29(1.50, 3.49)	74.3% (0.004)

NA: not available

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Figure captions

Figure 1. Flow chart for study selection

Figure 2. Analysis of BPD and CP.

Figure 3. The Egger's test for publication bias test.

Figure 4. The Begg's test for publication bias test.

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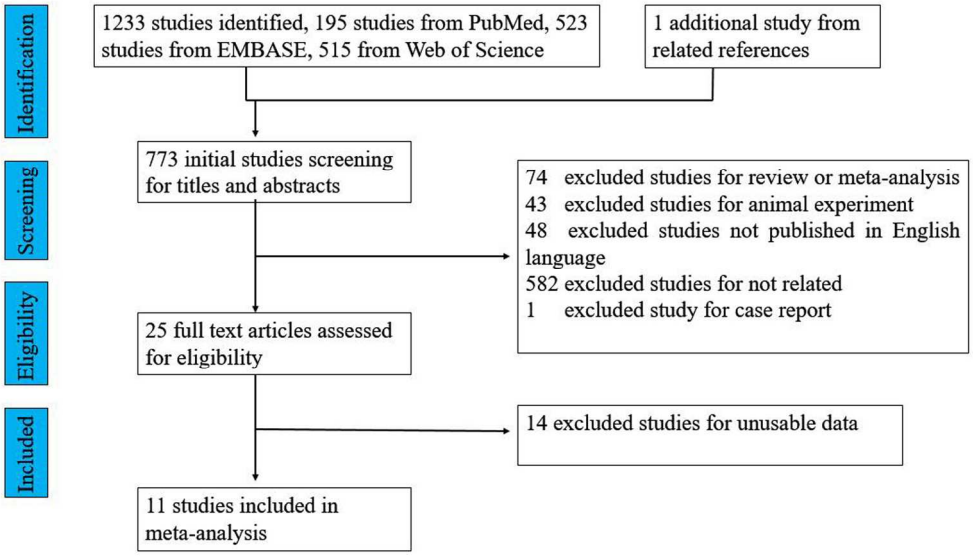

Figure 1. Flow chart for study selection

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eview only

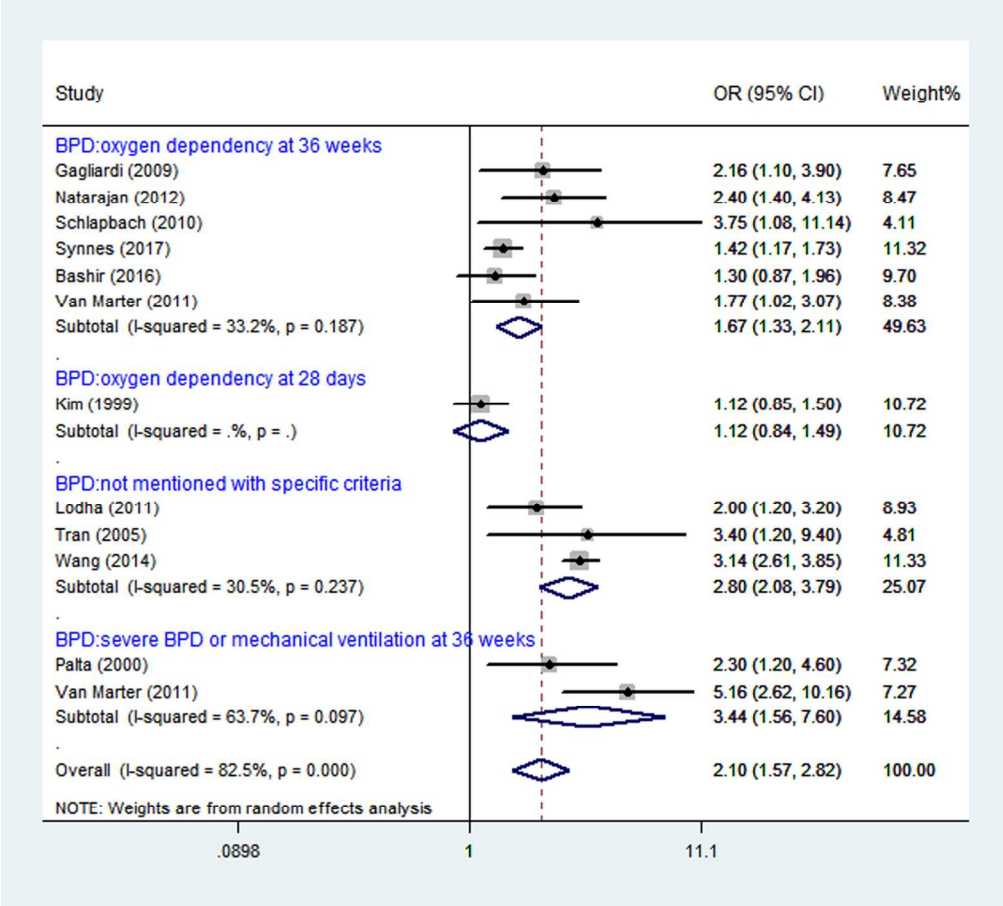

Figure 2. Analysis of BPD and CP.

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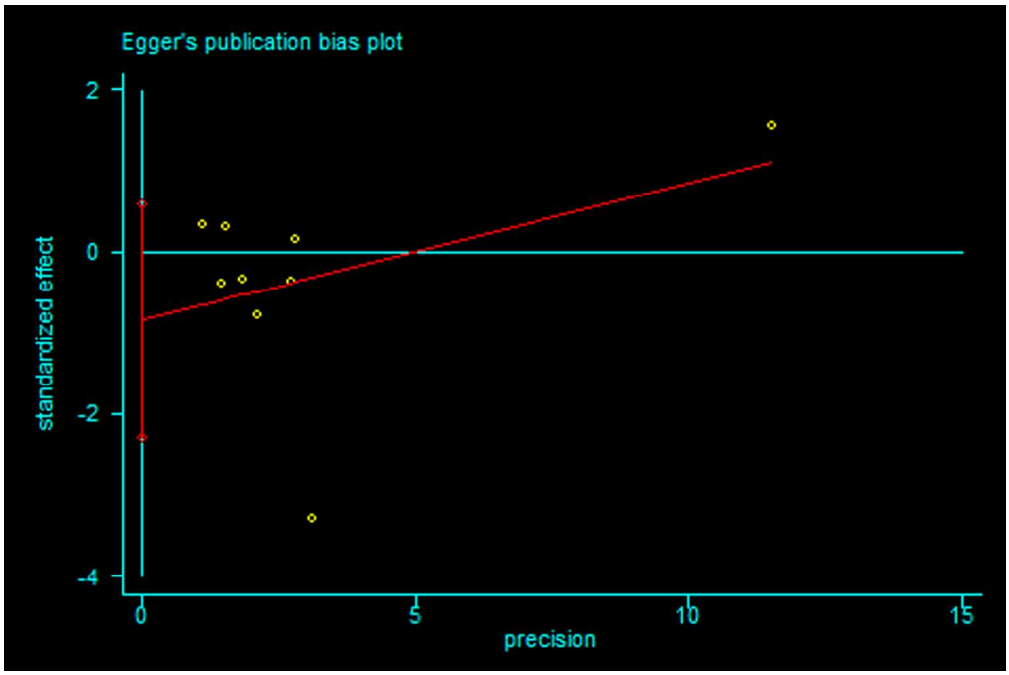

Figure 3. The Egger's test for publication bias test.

190x126mm (300 x 300 DPI)

view only

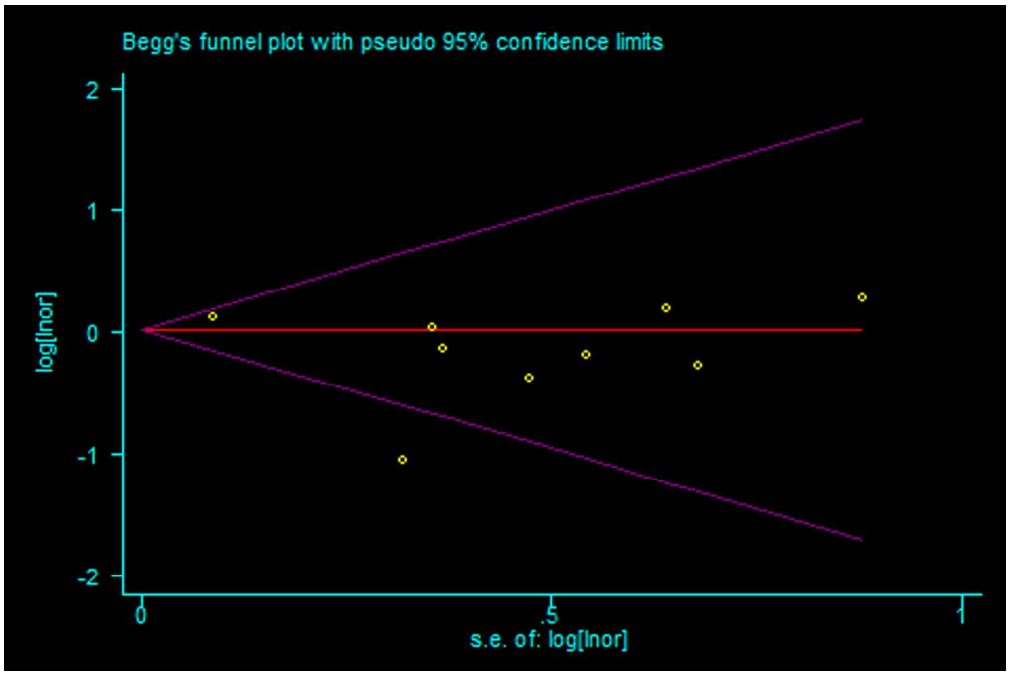

Figure 4. The Begg's test for publication bias test.

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The association between bronchopulmonary dysplasia and cerebral palsy in children: A meta-analysis

Supplement 1. Retrieval strategy of PubMed, EMBASE and Web of Science

Before 1 September 2017.

PubMed 195

Search (((((((Cerebral pals*[Title/Abstract]) OR CP[Title/Abstract]) OR spastic*[Title/Abstract]) OR Cerebral Palsy[Title/Abstract])) OR "Cerebral Palsy"[Mesh])) AND ((((((Dysplasia, Bronchopulmonary[Title/Abstract]) OR Bronchopulmonary Dysplasia[Title/Abstract]) OR BPD[Title/Abstract]) OR bronchopulmonary dysplasia[Title/Abstract])) OR "Bronchopulmonary Dysplasia"[Mesh])

EMBASE 523

Before 1 September 2017.

1 Cerebral palsy/

2 Cerebral pals$.tw.

3 Little$ disease.tw.

4 CP.tw.

5 (unilateral adj3 spastic$).tw.

6 (hemiplegi$ adj3 spastic$).tw.

7 (diplegi$ adj3 spastic$).tw.

8 (tetrapleg$ adj3 spastic$).tw.

9 (triplegi$ adj3 spastic$).tw.

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10 ((bilateral or bi-lateral) adj3 spastic$).tw.

11 (quadripleg$ adj3 spastic$).tw.

12 or/1-11

13 Bronchopulmonary Dysplasia.mp. or exp lung dysplasia/

14 BPD.tw.

15 Dysplasia, Bronchopulmonary.tw.

16 Bronchopulmonary Dysplasia.tw.

17 13 or 14 or 15 or 16

18 12 and 17

Web of science 515

Before 1 September 2017.

TS=(cerebral pals* or spastic* or quadripleg* or cerebral palsy or CP)

TS=(Bronchopulmonary Dysplasia or lung dysplasia or bronchopulmonary dysplasia or BPD or Dysplasia, Bronchopulmonary)

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Supplement 2. Newcastle - Ottawa Quality Assessment Scale results for case-control studies

Question	**Option**	Kim	Schlapbach	Tran
Is the case definition adequate?	a) yes, with independent validation * b) yes, eg record linkage or based on self reports c) no description	a	a	a
Representativeness of the cases	a) consecutive or obviously representative series of cases * b) potential for selection biases or not stated	a	b	b
Selection of Controls	a) community controls * b) hospital controls c) no description	b	b	b
Definition of Controls	a) no history of disease (endpoint)* b) no description of source	a	a	b
Comparability of cases and controls on the basis of the design or analysis	a) study controls for (Select the most important factor.* b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.) *	a	a	a

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Ascertainment of exposure	a) secure record (eg surgical records)* b) structured interview where blind to case/control status* c) interview not blinded to case/control status d) written self report or medical record only e) no description	a	a	a
Same method of ascertainment for cases and controls	a) yes* b) no	a	a	a
Non-Response rate	a) same rate for both groups* b) non-respondents described c) rate different and no designation	b	a	b

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Supplement 3. Newcastle - Ottawa Quality Assessment Scale results for cohort studies

Question	**Option**	Gagliardi	**Lodha**	Palta	Natarajan	Synnes	Van Marter	Wang	Bahir
Representativeness of the exposed cohort	a) truly representative of the average (describe) in the community * b) somewhat representative of the average in the community* c) selected group of users eg nurses, volunteered) no description of the derivation of the cohort	b	b	b	b	b	b	b	b
Selection of the Non-exposed cohort	a) drawn from the same community as the exposed cohort* b) drawn from a different source c) no description of the derivation of the non-exposed cohort	a	a	a	a	a	a	a	a
Ascertainment of exposure	a) secure record (eg surgical records)* b) structured interview* c) written self report d) no description	a	a	a	a	b	a	a	a
Demonstration that outcome of interest was not present at start of study	a) yes* b) no	a	a	a	a	a	a	a	a
Comparability of cohorts on the basis of the design or analysis	a) study controls for (select the most important factor)* b) study controls for any additional factor*	a	a	a	a	a	a	a	a

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Assessment of outcome	a) independent blind assessment* b) record linkage* c) self report d) no description	b	b	b	b	b	b	b	b
Was follow-up long enough for outcomes to occur	a) yes* b) no	b	b	b	a	a	a	a	a
Adequacy of follow up of cohort	a) complete follow up - all subjects accounted for* b) subjects lost to follow up unlikely to introduce bias - small number lost - > % (select an adequate %) follow up, or description provided of those lost) c) follow up rate < % (select an adequate %) and no description of those lost d) no statement	d	d	d	d	d	d	d	d

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Supplement 4. Egger's and Begg's test for publication bias test

Begg's Test

adj. Kendall's Score (P-Q) = 6

Std. Dev. of Score = 9.59

Number of Studies = 9

z = 0.63

Pr > |z| = 0.532

z = 0.52 (continuity corrected)

Pr > |z| = 0.602 (continuity corrected)

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.1683662	.139195	1.21	0.266	-.1607777	.49751
bias	-.8435039	.608102	-1.39	0.208	-2.281437	.5944288

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BMJ Open

The association between bronchopulmonary dysplasia and cerebral palsy in children: A meta-analysis

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Neurology
Keywords:	bronchopulmonary dysplasia, cerebral palsy, neurodevelopment, infant

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Manuscripts

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The association between bronchopulmonary dysplasia and cerebral palsy in children: A meta-analysis

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Abstract

Objective: To investigate the association between bronchopulmonary dysplasia (BPD) and the risk of cerebral palsy (CP) in children.

Data sources We used EMBASE, PubMed and Web of Science to conduct a meta-analysis of studies published before September 1 2017, written in English which titles or abstracts discussed an association between BPD and CP.

Study selection: Observational studies eg case control and cohort studies were included.

Data extraction and synthesis: All review stages were conducted by 2 reviewers independently. Data synthesis was undertaken via meta-analysis of available evidence.

Main outcomes and measures: The prevalence of developing CP was measured after exposure to BPD.

Results Among 1234 initially identified studies, we selected those that addressed an association between BPD and CP according to our preselected inclusion criteria. Our meta-analysis included 11 studies. According to a random effect model, BPD was significantly associated with cerebral palsy (ORs, 2.10; 95% CI, 1.57, 2.82) in preterm infants. Factors explaining differences in the study results included study design, the definition of BPD, the time of diagnosis of CP, and whether the studies adjusted for potential confounders.

Conclusion This study suggests that BPD is a risk factor for cerebral palsy. Further studies are required to confirm these results and to detect the influence of variables across studies.

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Keywords: bronchopulmonary dysplasia; cerebral palsy; neurodevelopment; infant

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Strengths and limitations of the study

*No consensus exists regarding the association between BPD and CP in children.

*The clear and univocal definition of BPD may explain the differences of the results of studies which evaluated the association between BPD and CP in children.

*The number of studies included is limited, and therefore, the results of the meta-analysis should be interpreted with caution.

*Observational study designs rarely can establish causality.

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Introduction

Despite advances in obstetric and neonatal care, the prevalence of developing cerebral palsy (CP) was approximately at 0.2% during the past decades[1], and the etiology of CP remains poorly understood. Evidence shows that prenatal factors, including maternal age [2], education [3 4], obesity [5-7], race [8], chorioamnionitis[1] and hypertension [9] contribute to CP.

Bronchopulmonary dysplasia (BPD) has been implicated as a potential neonatal factor of CP[10]. BPD is common in preterm and low birthweight infants born at 24 to 26 weeks of gestation[11]. The lung is in the canalicular stage from 16 to 28 weeks, and it is in the saccular stage from 28 to 36 weeks. Alveoli are not uniformly present until 36 weeks. Thus, premature birth and the initiation of pulmonary gas exchange arrest normal alveolar and distal vascular development, and subsequent BPD[11]. Maternal infection, especially maternal chorioamnionitis was associated with an increased risk of BPD[12]. The inconsistencies in the definition of BPD contribute to variation in incidence of BPD. BPD is a chronic lung disease developed after mechanical ventilation or oxygen inhalation usually occurring in certain premature neonates with respiratory distress syndrome. Some studies defined as oxygen dependency at 36 weeks post-menstrual age (PMA), yet, others defined as 28 or more days duration of oxygen dependency during hospitalization [12]. Cerebral palsy, cognitive delay, and hearing loss are important and commonly reported adverse outcomes in very premature infants[13]. It is postulated that BPD can lead to neonatal brain injury and subsequent CP[14].

A number of studies have assessed the relationship between BPD and CP in premature infants, the association between BPD and CP was inconsistent. Some of the studies have not examined a significant association[15 16]. For example, one study defined BPD as 28 days duration of oxygen dependency[15] and reported insignificant

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association between BPD and CP, additionally, another study[14] evaluated the association between BPD (oxygen dependency at 36 weeks) and quadriparas and diparesis, and reported the same result. However, any other studies[17 18] showed a significant association between BPD and CP. We conducted a meta-analysis to evaluate the potential association between BPD and CP in preterm infants.

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Methods

Retrieval of studies. The PubMed, EMBASE, and Web of Science databases were searched through September 1, 2017. The search of bronchopulmonary dysplasia was performed using the following keywords and subject terms: "bronchopulmonary dysplasia", or "BPD*", or "lung dysplasia", or "Dysplasia, Bronchopulmonary", or "Bronchopulmonary Dysplasia", using "OR" to link relevant text within the search field. To acquire studies related to cerebral palsy, "OR" was used to associate the key words, which included "cerebral palsy", "Crebral pals*", "spastic*", "quadripleg*" and "CP". We combined these terms using "AND" to retrieve the studies (Supplement 1). We restricted the search to human studies published in English. The retrieved studies were screened by reading the titles and abstracts, and two authors (Xiaoyun Gou and Lei Yang) subsequently read the full text of the remaining publications independently and then discussed disagreements to reach a consensus.

Patient and Public Involvement. Not required, a meta-analysis

Study selection. The study inclusion criteria were as follows: (1) the study evaluated the association between bronchopulmonary dysplasia (BPD) and the risk of CP in children; (2) the study was published in English; (3) case-control or cohort study design; (4) the study described the assessment of exposure and outcome, the relevant exposure included any type of BPD. Relevant outcome included any definition of CP. The association between exposure and outcome was directly reported by unadjusted and/or adjusted relative ratios (RRs) and corresponding 95% confidence intervals (CIs), unadjusted and/or adjusted odds ratios (ORs) estimates and 95% CIs.

The exclusion criteria were as follows: (1) a review or meta-analysis or a case report; (2) the study was not published in English; (3) the article described an animal experiment study; (4) a study with overlapping data; (5) the articles with unusable

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data that was reported that have allowed RRs/ORs to be calculated (e.g. number of cases of BPD events and total number of children with CP).

Data extraction. The data were independently extracted from the studies by two reviewers (Xiaoyun Gou and Lei Yang) and included the name of the first author, publication year, the country of the participants, study design, sample size, gestational age and/or birthweight, following years, BPD definition, primary outcome (the association between BPD and risk of CP), and adjusted confounders.

Quality evaluation. The two reviewers (Xiaoyun Gou and Lei Yang) independently used the Newcastle-Ottawa Scale (NOS) [19] to examine all included studies for their methodological quality. The reviewers evaluated the quality score via examine the selection of the study population, comparability and evaluation of exposure and outcome, with a maximum score of nine. The reviewers resolved disagreements in the manner previously described.

Statistical analysis. The original studies included used ORs and/or RRs and 95%CIs to assess the association between BPD and the risk of CP in children. The ORs and RRs were directly considered as ORs when the outcome is rare[1]. We pooled ORs and/or RRs of each study separately using the Der Simonian-Laird formula (random-effects model) [20]. Statistical heterogeneity [21] between the studies was assessed using the Q and I^2 statistics. Values of I^2>50% and P<0.1 indicated high heterogeneity [1]. We conducted a stratified analysis based on study design (case-control, cohort), BPD type (oxygen dependency at 36 weeks' post-menstrual age (PMA), 28 days duration of oxygen dependency during hospitalization, severe BPD including mechanical ventilation at 36 weeks, not defined BPD), diagnostic criteria for CP (Age <2 years, other), confounding variables (gestational age, unadjusted estimated).

We used Egger's [22] and Begg's [23] tests to assess the publication bias, which was considered to be statistically significant when p<0.05. We used Stata software,

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version 12.0 (Stata Corp, College Station, TX) to perform the statistical tests.

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Results

Literature search. We identified 1234 potential studies: 195 from PubMed, 523 from EMBASE, 515 from Web of Science and 1 additional study from the related reference. After careful screening, 11 studies that reported the association between BPD and the risk of CP in children were selected for inclusion in this study (see Figure 1). These 11 included studies are summarized in Table 1.

Characteristics and quality of the included studies. The included studies were published between 1999 and 2017. Eleven studies evaluated the association between BPD and cerebral palsy in preterm infants. Two[15 16] of these studies reported no significant association. Eight of the included studies were cohort studies and three [15 17 18] of the studies were case-control studies of a high quality (NOS>5, Supplement 2, Supplement 3). All the studies evaluated the association between BPD and CP in preterm neonates with ORs.

Bronchopulmonary dysplasia (BPD) and cerebral palsy (CP). When the study results were analyzed using random effects model, BPD was significantly associated with CP (Figure 2). These infants were preterm infants.

Stratified analysis. A stratified analysis was conducted to determine whether there are any significantly different results across the subgroups considered (Table 2). The case-control studies did not produce significant summary ORs (2.13; 95%CI, 0.85, 5.34, I^2=82.1%), yet, a significant association was seen in cohort studies ORs (2.15; 95%CI, 1.57, 2.94, I^2=73.6%).

Six studies[14 16 18 24-26] evaluated the association between BPD (oxygen dependence at 36 weeks) and CP in premature infants, with only 1 reporting[16] a no significant association (Figure 2). One study[15] evaluated the association between BPD

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(oxygen dependence at 28 days) and CP in premature infants with no significant association (OR 1.12, 95%CI, 0.84, 1.49). Three studies[17 27 28] evaluated the association (OR 2.80, 95%CI, 2.08, 3.79, I^2=30.5%) without mentioned BPD definition, and 2 studies[14 29] show severe BPD or mechanical ventilation at 36 weeks (OR 3.44, 95%CI, 1.56, 7.60, I^2=63.7%).

The definition of CP differed greatly among studies of preterm infants (Table 2). Of the four studies[14 16 24 28] that provided adequate information, four studies provided a minimum age of 2 years for diagnosing CP; Some studies confirm the diagnosis by performing examination, while others did not. Some studies excluded children with congenital anomalies[15 16 28], while others[14 24] did not specify any exclusion criteria.

Five studies of BPD(PMA) in premature infants reported ORs controlled for gestational age. Association between BPD and CP remains significate both adjusted or unadjusted by gestational age (ORs, 2.29; 95%CI, 1.5, 3.49; vs ORs, 2.01; 1.43, 2.83; Table 2).

Publication bias. Asymmetry and publication bias were evaluated by Egger's and Begg's tests (Figure 3, Figure 4). The pooled results did not support the presence of significant publication bias (all p>0.05, Supplement 4).

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Discussion

To our knowledge, this article is the first meta-analysis of the relationship between BPD and risk of CP in children. The results of this meta-analysis, which included 11 studies, showed evidence that BPD appears to be associated with CP in preterm infants.

BPD might affect the neurodevelopment outcome of infants through multiple pathways. A growing body evidence supports that BPD contributes to neonatal brain injury[30]. Experimental BPD with hypoxia leads to central nervous system damage, and subsequent CP[31 32]. Indeed, the preterm infants with BPD accompany with hypoxia often had oligodendrocytes maturation arrest or injury[33-35], disruption of myelination and demyelination, and then cause white matter injury[35] and impaired neurodevelopmental outcomes[32].

To better understand the relationship between BPD and CP, it is crucial to develop consensus definitions of BPD. Most published reports do not apply specific diagnostic criteria for BPD, as a group, these studies produced heterogeneous results. The results of the stratified analysis suggest that a stronger association is seen when used severe or mechanical ventilation at 36 weeks diagnostic criteria in the studies. The studies do not include strict criteria may lead to an over-diagnosis of BPD, which may contribute to the evidence of heterogeneity.

The definition of CP varied between studies; although CP can be difficult to diagnosis in children younger than 2 years, 1 study made the diagnosis in infants younger than 12 months. A consensus definition of CP is required.

Some studies report significant associations between BPD and CP after adjust for potential confounders[15 16 18 25 26 28]. Although gestational age appears to be a possible

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confounder, it may not lie directly in the causal pathway between BPD and CP. Gestational age can be considered as a confounder, as a premature baby is born at any gestational age and a lot of time later may develop BPD. The study would falsely diminish the association between BPD and CP without considering gestational age as a confounder. BPD is associated with premature delivery, and low gestational age, which is associated with a host of intrinsic vulnerabilities within the brain, that have been implicated in the pathogenesis of CP. Therefore, if low gestational age resulting in BPD plays a direct role in the pathogenesis of CP, then adjusting for gestational age will falsely diminish the observed association between BPD and CP. One study[16] of BPD in premature infants found no association when controlling for the confounder variables including gestational age. It is unclear if this is because BPD does not contribute independently to CP, or perhaps because gestational age lies on the causal pathway.

Other factors may interact with BPD in the pathogenetic pathway leading to CP. For example, child sex, IVH, Apgar score at 5 minutes, small for gestational age (SGA), which may contribute to CP lies on the causal pathway. Accordino et al. [36] demonstrated that premature spontaneous birth and iatrogenic preterm birth are significantly associated with CP. The reasons of the difference contribute to neurological damage would be related to infection. Although the studies controlled for some confounder variables, many other factors that contribute to CP may not be excluded.

Our meta-analysis is subject to limitations as follows. Firstly, we only included articles published in English. Secondly, there may be publication bias, incomplete ascertainment of published studies, and errors in data abstraction. Thirdly, the number of studies included is small, and therefore, the results of this meta-analysis should be

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interpreted with caution. Furthermore, the bias inherent to observational studies are not eliminated in a quantitative synthesis.

Our meta-analysis has some merits. First, the study evaluated the association between BPD and CP. Second, the study used stratified analysis to explore the heterogeneity source, and the different definition of BPD may contribute to the source of heterogeneity.

In conclusion, our pooled analyses provide evidence that BPD is significantly associated with cerebral palsy in children. Future studies that consider additional factors are required to resolve this issue.

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Author contributions

XG and LY contributed to the conception and design of the study, as well as to the drafting of this article. LP contributed to the collection and analysis of the data. DX contributed to the conception and design of the study and approved the final version of the manuscript for submission for publication.

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Ethical approval

Not available, a meta-analysis

Competing financial interests

The authors declare that they have no competing financial interests.

Data sharing statement

No additional data are available.

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Table 1. Characteristics of the included studies.

Study	Publication year	country	Study design	Gestational age/ birth weight	Sample size	BPD definition	Primary outcome	adjusted confounder variables	NOS score
Gagliardi[26]	2009	Italy	Cohort study	<32 weeks and BW<1500g	1209	BPD (at 36 weeks PMA)	ORs=2.16(CI, 1.1-3.9)	GA, propensity score for prolonged ventilation, centre	6
Kim[15]	1999	Korea	Case-control	<37 weeks	184	BPD (oxygen dependence at 28 days)	ORs=1.12(CI, 0.85-1.5)	Apgar score at 5 min, IVH, PDA, sepsis, duration of mechanical ventilation	7
Lodha[27]	2011	Canada	Cohort study	<28 weeks	918	NA	ORs=2(CI, 1.2-3.2)	NA	6
Natarajan[25]	2012	NA	Cohort study	<27 weeks BW<1000g	1189	BPD (at 36 weeks PMA)	ORs=2.41(CI, 1.4-4.13)	GA, male gender, SGA, maternal education, surgical NEC, IVH or PVL	7
Palta[29]	2000	USA	Cohort study	BW<1500g	1024	Severe BPD	ORs=2.3(CI, 1.2-4.6)	NA	6
Schlapbach[18]	2010	Switzerland	Case-control study	<32 weeks	99	BPD (at 36 weeks PMA)	ORs=3.75(CI, 1.08-11.14)	gestational age, birth weight, postnatal growth, mechanical ventilation	7
Synnes[24]	2017	Canada	Cohort study	<29 weeks	3700	BPD (at 36 weeks PMA)	ORs=1.42(CI, 1.17-1.73)	NA	8
Tran[17]	2005	Australia	Case control	<27 weeks	150	NA home oxygen	ORs=3.4(CI, 1.2-9.4)	NA	6
Van Marter[14]	2011	USA	Cohort study	<28 weeks	1047	BPD (at 36 weeks PMA) BPD (Mechanical ventilation at	ORs=1.77(CI, 1.02-3.77) ORs=5.16(CI, 2.62-10.16)	NA	8

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						36 weeks)			
Wang[28]	2014	China	Cohort study	GA<30 weeks and BW<1500g	5807	Not mentioned	ORs=3.14(CI, 2.61-3.85)	GA, BW, sex, ROP grade≥III, grade III/IV IVH and PVL	8
Bashir[16]	2016	Canada	Retrospective observational study	BW<1250g	1563	BPD (at 36 weeks PMA)	ORs=1.3(CI, 0.87-1.96)	GA, male gender, ANCS use, Apgar score<7 at 5 minutes, SGA, postnatal steroids, blood transfusion, PDA, IVH grade≥III and/ or PVL, ROP grade≥III and/ or required laser treatment and postnatal sepsis	8

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Table 2. Pooled results of the associations between bronchopulmonary dysplasia and cerebral palsy in children.

Variables	Studies (n)	ORs(95%CI)	I^2 (p-value for heterogeneity)
Total	11	2.10(1.57,2.82)	82.5% (0.000)
Study design			
Case-control	3	2.13 (0.85, 5.34)	82.1% (0.000)
Cohort	8	2.15 (1.57, 2.94)	73.6% (0.023)
Definition of BPD			
Oxygen dependence at 36 weeks	6	1.67(1.33,2.11)	33.2% (0.187)
Oxygen dependence at 28 days	1	1.12(0.84,1.49)	NA
Severe BPD (mechanical ventilation)	2	3.44(1.56,7.60)	63.7%(0.097)
Not mentioned BPD type	3	2.80(2.08, 3.79)	30.5% (0.237)
Diagnostic criteria for cerebral palsy			
Age≥2 years only	4	1.54(1.15,2.06)	62.4% (0.046)
Age<2 years included	6	2.31(1.61,3.32)	69.7% (0.006)
Controlling for potential confounders			
Unadjusted estimates	5	2.01(1.43,2.83)	53.4% (0.072)
Controlled for gestational age	5	2.29(1.50, 3.49)	74.3% (0.004)

NA: not available

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Figure captions

Figure 1. Flow chart for study selection

Figure 2. Analysis of BPD and CP.

Figure 3. The Egger's test for publication bias test.

Figure 4. The Begg's test for publication bias test.

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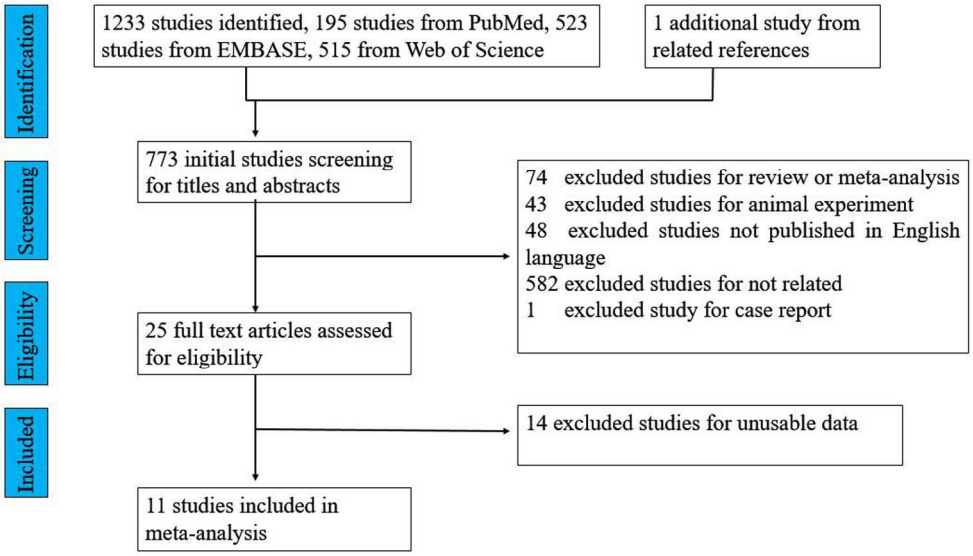

Figure 1. Flow chart for study selection

190x113mm (300 x 300 DPI)

eview only

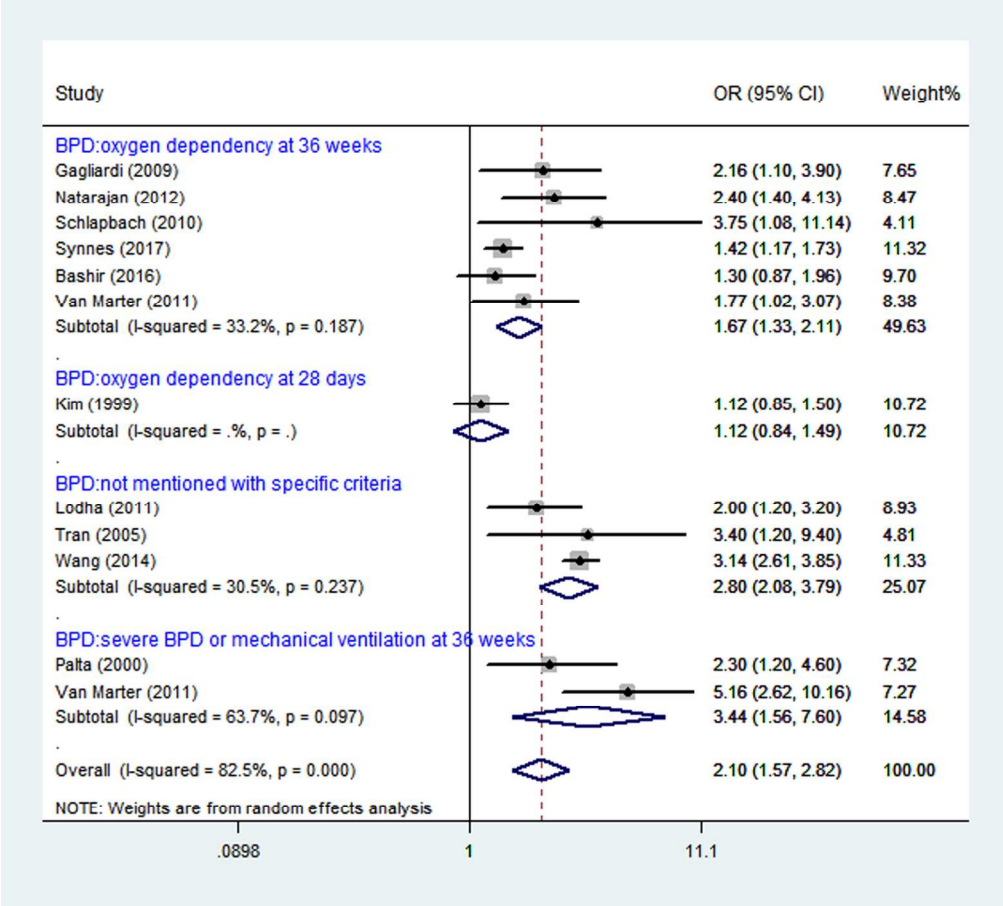

Figure 2. Analysis of BPD and CP.

190x172mm (300 x 300 DPI)

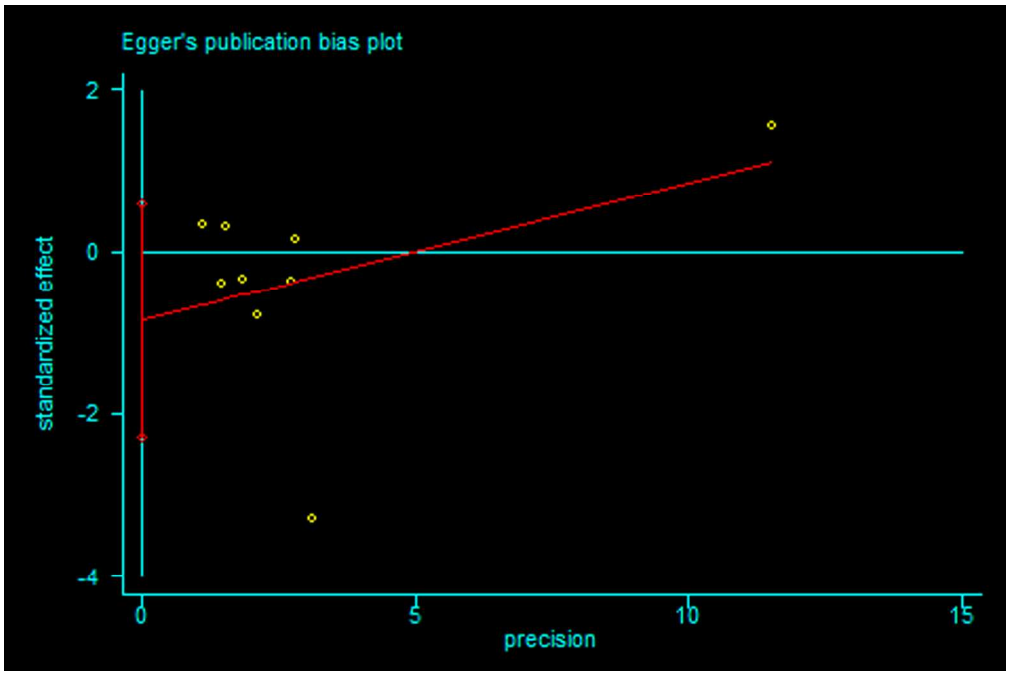

Figure 3. The Egger's test for publication bias test.

190x126mm (300 x 300 DPI)

view only

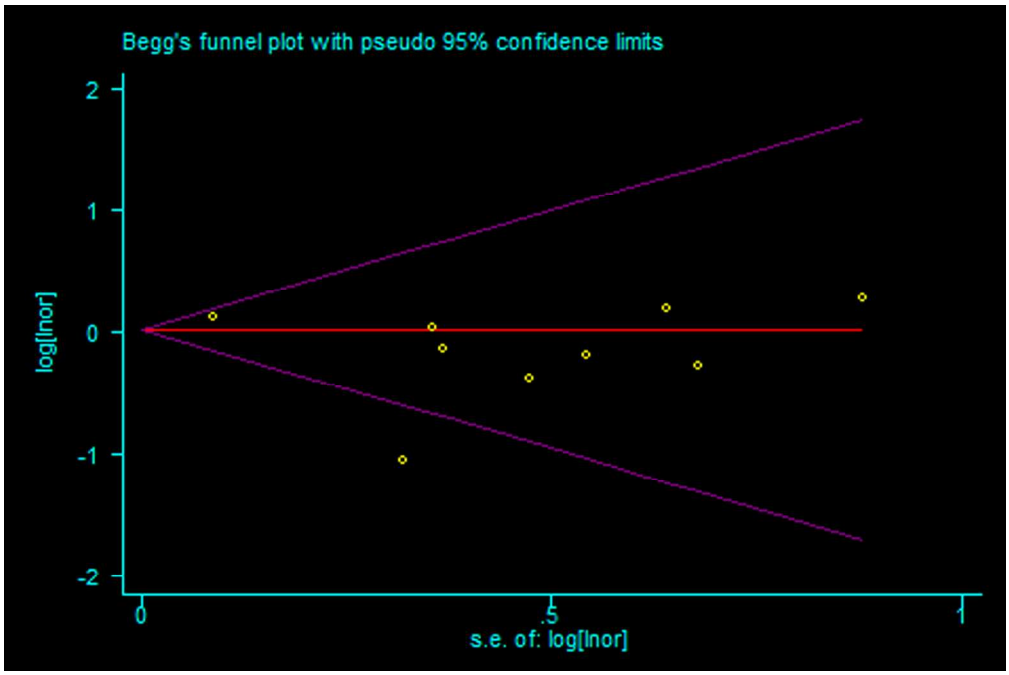

Figure 4. The Begg's test for publication bias test.

190x126mm (300 x 300 DPI)

View only

The association between bronchopulmonary dysplasia and cerebral palsy in children: A meta-analysis

Supplement 1. Retrieval strategy of PubMed, EMBASE and Web of Science

Before 1 September 2017.

PubMed 195

Search (((((((Cerebral pals*[Title/Abstract]) OR CP[Title/Abstract]) OR spastic*[Title/Abstract]) OR Cerebral Palsy[Title/Abstract])) OR "Cerebral Palsy"[Mesh])) AND ((((((Dysplasia, Bronchopulmonary[Title/Abstract]) OR Bronchopulmonary Dysplasia[Title/Abstract]) OR BPD[Title/Abstract]) OR bronchopulmonary dysplasia[Title/Abstract])) OR "Bronchopulmonary Dysplasia"[Mesh])

EMBASE 523

Before 1 September 2017.

1 Cerebral palsy/

2 Cerebral pals$.tw.

3 Little$ disease.tw.

4 CP.tw.

5 (unilateral adj3 spastic$).tw.

6 (hemiplegi$ adj3 spastic$).tw.

7 (diplegi$ adj3 spastic$).tw.

8 (tetrapleg$ adj3 spastic$).tw.

9 (triplegi$ adj3 spastic$).tw.

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10 ((bilateral or bi-lateral) adj3 spastic$).tw.

11 (quadripleg$ adj3 spastic$).tw.

12 or/1-11

13 Bronchopulmonary Dysplasia.mp. or exp lung dysplasia/

14 BPD.tw.

15 Dysplasia, Bronchopulmonary.tw.

16 Bronchopulmonary Dysplasia.tw.

17 13 or 14 or 15 or 16

18 12 and 17

Web of science 515

Before 1 September 2017.

TS=(cerebral pals* or spastic* or quadripleg* or cerebral palsy or CP)

TS=(Bronchopulmonary Dysplasia or lung dysplasia or bronchopulmonary dysplasia or BPD or Dysplasia, Bronchopulmonary)

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Supplement 2. Newcastle - Ottawa Quality Assessment Scale results for case-control studies

Question	**Option**	Kim	Schlapbach	Tran
Is the case definition adequate?	a) yes, with independent validation * b) yes, eg record linkage or based on self reports c) no description	a	a	a
Representativeness of the cases	a) consecutive or obviously representative series of cases * b) potential for selection biases or not stated	a	b	b
Selection of Controls	a) community controls * b) hospital controls c) no description	b	b	b
Definition of Controls	a) no history of disease (endpoint)* b) no description of source	a	a	b
Comparability of cases and controls on the basis of the design or analysis	a) study controls for (Select the most important factor.* b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.) *	a	a	a

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Ascertainment of exposure	a) secure record (eg surgical records)* b) structured interview where blind to case/control status* c) interview not blinded to case/control status d) written self report or medical record only e) no description	a	a	a
Same method of ascertainment for cases and controls	a) yes* b) no	a	a	a
Non-Response rate	a) same rate for both groups* b) non-respondents described c) rate different and no designation	b	a	b

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Supplement 3. Newcastle - Ottawa Quality Assessment Scale results for cohort studies

Question	**Option**	Gagliardi	**Lodha**	Palta	Natarajan	Synnes	Van Marter	Wang	Bahir
Representativeness of the exposed cohort	a) truly representative of the average (describe) in the community * b) somewhat representative of the average in the community* c) selected group of users eg nurses, volunteered) no description of the derivation of the cohort	b	b	b	b	b	b	b	b
Selection of the Non-exposed cohort	a) drawn from the same community as the exposed cohort* b) drawn from a different source c) no description of the derivation of the non-exposed cohort	a	a	a	a	a	a	a	a
Ascertainment of exposure	a) secure record (eg surgical records)* b) structured interview* c) written self report d) no description	a	a	a	a	b	a	a	a
Demonstration that outcome of interest was not present at start of study	a) yes* b) no	a	a	a	a	a	a	a	a
Comparability of cohorts on the basis of the design or analysis	a) study controls for (select the most important factor)* b) study controls for any additional factor*	a	a	a	a	a	a	a	a

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Assessment of outcome	a) independent blind assessment* b) record linkage* c) self report d) no description	b	b	b	b	b	b	b	b
Was follow-up long enough for outcomes to occur	a) yes* b) no	b	b	b	a	a	a	a	a
Adequacy of follow up of cohort	a) complete follow up - all subjects accounted for* b) subjects lost to follow up unlikely to introduce bias - small number lost - > % (select an adequate %) follow up, or description provided of those lost) c) follow up rate < % (select an adequate %) and no description of those lost d) no statement	d	d	d	d	d	d	d	d

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Supplement 4. Egger's and Begg's test for publication bias test

Begg's Test

adj. Kendall's Score (P-Q) = 6

Std. Dev. of Score = 9.59

Number of Studies = 9

z = 0.63

Pr > |z| = 0.532

z = 0.52 (continuity corrected)

Pr > |z| = 0.602 (continuity corrected)

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.1683662	.139195	1.21	0.266	-.1607777	.49751
bias	-.8435039	.608102	-1.39	0.208	-2.281437	.5944288

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a meta-analysis.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3 , 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7,8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7,8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7,8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7,8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9,10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9,10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	No

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

The association between bronchopulmonary dysplasia and cerebral palsy in children: A meta-analysis

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Neurology
Keywords:	bronchopulmonary dysplasia, cerebral palsy, neurodevelopment, infant

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The association between bronchopulmonary dysplasia and cerebral palsy in children: A meta-analysis

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Abstract

Objective: To investigate the association between bronchopulmonary dysplasia (BPD) and the risk of cerebral palsy (CP) in children.

Data sources We used EMBASE, PubMed and Web of Science to conduct a meta-analysis of studies published before September 1 2017, written in English which titles or abstracts discussed an association between BPD and CP.

Study selection: Observational studies eg case control and cohort studies were included.

Data extraction and synthesis: All review stages were conducted by 2 reviewers independently. Data synthesis was undertaken via meta-analysis of available evidence.

Main outcomes and measures: The prevalence of developing CP was measured after exposure to BPD.

Results Among 1234 initially identified studies, we selected those that addressed an association between BPD and CP according to our preselected inclusion criteria. Our meta-analysis included 11 studies. According to a random effect model, BPD was significantly associated with cerebral palsy (ORs, 2.10; 95% CI, 1.57, 2.82) in preterm infants. Factors explaining differences in the study results included study design, the definition of BPD, the time of diagnosis of CP, and whether the studies adjusted for potential confounders.

Conclusion This study suggests that BPD is a risk factor for cerebral palsy. Further studies are required to confirm these results and to detect the influence of variables across studies.

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Keywords: bronchopulmonary dysplasia; cerebral palsy; neurodevelopment; infant

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Strengths and limitations of the study

*No consensus exists regarding the association between BPD and CP in children.

*The clear and univocal definition of BPD may explain the differences of the results of studies which evaluated the association between BPD and CP in children.

*The number of studies included is limited, and therefore, the results of the meta-analysis should be interpreted with caution.

*Observational study designs rarely can establish causality.

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Introduction

Despite advances in obstetric and neonatal care, the prevalence of developing cerebral palsy (CP) was approximately at 0.2% during the past decades[1], and the etiology of CP remains poorly understood. Evidence shows that prenatal factors, including maternal age [2], education [3 4], obesity [5-7], race [8], chorioamnionitis[1] and hypertension [9] contribute to CP.

Bronchopulmonary dysplasia (BPD) has been implicated as a potential neonatal factor of CP[10]. BPD is common in preterm and low birthweight infants born at 24 to 26 weeks of gestation[11]. The lung is in the canalicular stage from 16 to 28 weeks, and it is in the saccular stage from 28 to 36 weeks. Alveoli are not uniformly present until 36 weeks. Thus, premature birth and the initiation of pulmonary gas exchange arrest normal alveolar and distal vascular development, and subsequent BPD[11]. Maternal infection, especially maternal chorioamnionitis was associated with an increased risk of BPD[12]. The inconsistencies in the definition of BPD contribute to variation in incidence of BPD. BPD is a chronic lung disease developed after mechanical ventilation or oxygen inhalation usually occurring in certain premature neonates with respiratory distress syndrome. Some studies defined as oxygen dependency at 36 weeks post-menstrual age (PMA), yet, others defined as 28 or more days duration of oxygen dependency during hospitalization [12]. Cerebral palsy, cognitive delay, and hearing loss are important and commonly reported adverse outcomes in very premature infants[13]. It is postulated that BPD can lead to neonatal brain injury and subsequent CP[14].

A number of studies have assessed the relationship between BPD and CP in premature infants, the association between BPD and CP was inconsistent. Some of the studies have not examined a significant association[15 16]. For example, one study defined BPD as 28 days duration of oxygen dependency[15] and reported insignificant

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association between BPD and CP, additionally, another study[14] evaluated the association between BPD (oxygen dependency at 36 weeks) and quadriparas and diparesis, and reported the same result. However, any other studies[17 18] showed a significant association between BPD and CP. We conducted a meta-analysis to evaluate the potential association between BPD and CP in preterm infants.

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Methods

Retrieval of studies. The PubMed, EMBASE, and Web of Science databases were searched through September 1, 2017. The search of bronchopulmonary dysplasia was performed using the following keywords and subject terms: "bronchopulmonary dysplasia", or "BPD*", or "lung dysplasia", or "Dysplasia, Bronchopulmonary", or "Bronchopulmonary Dysplasia", using "OR" to link relevant text within the search field. To acquire studies related to cerebral palsy, "OR" was used to associate the key words, which included "cerebral palsy", "Crebral pals*", "spastic*", "quadripleg*" and "CP". We combined these terms using "AND" to retrieve the studies (Supplement 1). We restricted the search to human studies published in English. The retrieved studies were screened by reading the titles and abstracts, and two authors (Xiaoyun Gou and Lei Yang) subsequently read the full text of the remaining publications independently and then discussed disagreements to reach a consensus.

Patient and Public Involvement. Not required, a meta-analysis

Study selection. The study inclusion criteria were as follows: (1) the study evaluated the association between bronchopulmonary dysplasia (BPD) and the risk of CP in children; (2) the study was published in English; (3) case-control or cohort study design; (4) the study described the assessment of exposure and outcome, the relevant exposure included any type of BPD. Relevant outcome included any definition of CP. The association between exposure and outcome was reported by unadjusted and/or adjusted relative ratios (RRs) and corresponding 95% confidence intervals (CIs), unadjusted and/or adjusted odds ratios (ORs) estimates and 95% CIs or reported that could have allowed RRs/ORs to be calculated (e.g. number of cases of BPD events and total number of children with CP).

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The exclusion criteria were as follows: (1) a review or meta-analysis or a case report; (2) the study was not published in English; (3) the article described an animal experiment study; (4) a study with overlapping data; (5) the articles with unusable data that was reported with that (e.g. neurological lesion before discharge or cerebral palsy between BPD and without BPD, we cannot know the exactly result of the association between cerebral palsy and BPD; neurodevelopmental outcomes (Neuropsychological Performance, neurodevelopmental disability) including cerebral palsy but not only cerebral palsy) was excluded.

Data extraction. The data were independently extracted from the studies by two reviewers (Xiaoyun Gou and Lei Yang) and included the name of the first author, publication year, the country of the participants, study design, sample size, gestational age and/or birthweight, following years, BPD definition, primary outcome (the association between BPD and risk of CP), and adjusted confounders.

Quality evaluation. The two reviewers (Xiaoyun Gou and Lei Yang) independently used the Newcastle-Ottawa Scale (NOS) [19] to examine all included studies for their methodological quality. The reviewers evaluated the quality score via examine the selection of the study population, comparability and evaluation of exposure and outcome, with a maximum score of nine. The reviewers resolved disagreements in the manner previously described.

Statistical analysis. The original studies included used ORs and/or RRs and 95%CIs to assess the association between BPD and the risk of CP in children. The ORs and RRs were directly considered as ORs when the outcome is rare[1]. We pooled ORs and/or RRs of each study separately using the Der Simonian-Laird formula (random-effects model) [20]. Statistical heterogeneity [21] between the studies was assessed using the Q and I^2 statistics. Values of I^2>50% and P<0.1 indicated high heterogeneity [1]. We conducted a stratified analysis based on study design (case-control, cohort), BPD type

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(oxygen dependency at 36 weeks' post-menstrual age (PMA), 28 days duration of oxygen dependency during hospitalization, severe BPD including mechanical ventilation at 36 weeks, not defined BPD), diagnostic criteria for CP (Age <2 years, other), confounding variables (gestational age, unadjusted estimated).

We used Egger's [22] and Begg's [23] tests to assess the publication bias, which was considered to be statistically significant when $p<0.05$. We used Stata software, version 12.0 (Stata Corp, College Station, TX) to perform the statistical tests. We performed a "Test of Subgroup differences" in software such as Review Manager 5.3 (Cochrane).

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Results

Literature search. We identified 1234 potential studies: 195 from PubMed, 523 from EMBASE, 515 from Web of Science and 1 additional study from the related reference. After careful screening, 11 studies that reported the association between BPD and the risk of CP in children were selected for inclusion in this study (see Figure 1). These 11 included studies are summarized in Table 1.

Characteristics and quality of the included studies. The included studies were published between 1999 and 2017. Eleven studies evaluated the association between BPD and cerebral palsy in preterm infants. Two[15 16] of these studies reported no significant association. Eight of the included studies were cohort studies and three [15 17 18] of the studies were case-control studies of a high quality (NOS>5, Supplement 2, Supplement 3). All the studies evaluated the association between BPD and CP in preterm neonates with ORs.

Bronchopulmonary dysplasia (BPD) and cerebral palsy (CP). When the study results were analyzed using random effects model, BPD was significantly associated with CP (Figure 2). These infants were preterm infants.

Stratified analysis. A stratified analysis was conducted to determine whether there are any significantly different results across the subgroups considered (Table 2). The case-control studies did not produce significant summary ORs (1.27; 95%CI, 0.98, 1.64, I^2=72%), yet, a significant association was seen in cohort studies ORs (2.09; 95%CI, 1.86, 2.34, I^2=83%). And the subgroup difference was significant when stratified by study design (ORs, 1.27; 95%CI, 0.98, 1.64; vs ORs, 2.09; 95%CI, 1.86, 2.34; p<0.05, Table 2).

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Six studies[14 16 18 24-26] evaluated the association between BPD (oxygen dependence at 36 weeks) and CP in premature infants, with only 1 reporting[16] a no significant association (Figure 2). One study[15] evaluated the association between BPD (oxygen dependence at 28 days) and CP in premature infants with no significant association (OR 1.12, 95%CI, 0.84, 1.49). Three studies[17 27 28] evaluated the association (OR 2.80, 95%CI, 2.08, 3.79, I^2=30.5%) without mentioned BPD definition, and 2 studies[14 29] show severe BPD or mechanical ventilation at 36 weeks (OR 3.44, 95%CI, 1.56, 7.60, I^2=63.7%). And the subgroup difference was significant when stratified by BPD definition (p<0.00001, Table 2)

The definition of CP differed greatly among studies of preterm infants (Table 2). Of the four studies[14 16 24 28] that provided adequate information, four studies provided a minimum age of 2 years for diagnosing CP; Some studies confirm the diagnosis by performing examination, while others did not. Some studies excluded children with congenital anomalies[15 16 28], while others[14 24] did not specify any exclusion criteria.

Five studies of BPD(PMA) in premature infants reported ORs controlled for gestational age. Association between BPD and CP remains significate both adjusted or unadjusted by gestational age (ORs, 2.64; 95%CI, 2.27, 3.08; vs ORs, 1.48; 95%CI, 1.28, 1.70; p<0.00001, Table 2).

Publication bias. Asymmetry and publication bias were evaluated by Egger's and Begg's tests (Figure 3, Figure 4). The pooled results did not support the presence of significant publication bias (all p>0.05, Supplement 4)**.**

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Discussion

To our knowledge, this article is the first meta-analysis of the relationship between BPD and risk of CP in children. The results of this meta-analysis, which included 11 studies, showed evidence that BPD appears to be associated with CP in preterm infants.

BPD might affect the neurodevelopment outcome of infants through multiple pathways. A growing body evidence supports that BPD contributes to neonatal brain injury[30]. Experimental BPD with hypoxia leads to central nervous system damage, and subsequent CP[31 32]. Indeed, the preterm infants with BPD accompany with hypoxia often had oligodendrocytes maturation arrest or injury[33-35], disruption of myelination and demyelination, and then cause white matter injury[35] and impaired neurodevelopmental outcomes[32].

To better understand the relationship between BPD and CP, it is crucial to develop consensus definitions of BPD. Most published reports do not apply specific diagnostic criteria for BPD, as a group, these studies produced heterogeneous results. The results of the stratified analysis suggest that a stronger association is seen when used severe or mechanical ventilation at 36 weeks diagnostic criteria in the studies. The studies do not include strict criteria may lead to an over-diagnosis of BPD, which may contribute to the evidence of heterogeneity.

The definition of CP varied between studies; although CP can be difficult to diagnosis in children younger than 2 years, 1 study made the diagnosis in infants younger than 12 months. A consensus definition of CP is required.

Some studies report significant associations between BPD and CP after adjust for potential confounders[15 16 18 25 26 28]. Although gestational age appears to be a possible

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confounder, it may not lie directly in the causal pathway between BPD and CP. Gestational age can be considered as a confounder, as a premature baby is born at any gestational age and a lot of time later may develop BPD. The study would falsely diminish the association between BPD and CP without considering gestational age as a confounder. BPD is associated with premature delivery, and low gestational age, which is associated with a host of intrinsic vulnerabilities within the brain, that have been implicated in the pathogenesis of CP. Therefore, if low gestational age resulting in BPD plays a direct role in the pathogenesis of CP, then adjusting for gestational age will falsely diminish the observed association between BPD and CP. One study[16] of BPD in premature infants found no association when controlling for the confounder variables including gestational age. It is unclear if this is because BPD does not contribute independently to CP, or perhaps because gestational age lies on the causal pathway.

Other factors may interact with BPD in the pathogenetic pathway leading to CP. For example, child sex, IVH, Apgar score at 5 minutes, small for gestational age (SGA), which may contribute to CP lies on the causal pathway. Accordino et al. [36] demonstrated that premature spontaneous birth and iatrogenic preterm birth are significantly associated with CP. The reasons of the difference contribute to neurological damage would be related to infection. Although the studies controlled for some confounder variables, many other factors that contribute to CP may not be excluded.

Our meta-analysis is subject to limitations as follows. Firstly, we only included articles published in English. Secondly, there may be publication bias, incomplete ascertainment of published studies, and errors in data abstraction. Thirdly, the number of studies included is small, and therefore, the results of this meta-analysis should be

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interpreted with caution. Furthermore, the bias inherent to observational studies are not eliminated in a quantitative synthesis.

Our meta-analysis has some merits. First, the study evaluated the association between BPD and CP. Second, the study used stratified analysis to explore the heterogeneity source, and the different definition of BPD may contribute to the source of heterogeneity.

In conclusion, our pooled analyses provide evidence that BPD is significantly associated with cerebral palsy in children. Future studies that consider additional factors are required to resolve this issue.

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Author contributions

XG and LY contributed to the conception and design of the study, as well as to the drafting of this article. LP contributed to the collection and analysis of the data. DX contributed to the conception and design of the study and approved the final version of the manuscript for submission for publication.

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Ethical approval

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Patients and Public Involvement statement

Patients and or Public were not involved

Competing financial interests

The authors declare that they have no competing financial interests.

Data sharing statement

No additional data are available.

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Table 1. Characteristics of the included studies.

Study	Publication year	country	Study design	Gestational age/ birth weight	Sample size	BPD definition	Primary outcome	adjusted confounder variables	NOS score
Gagliardi[26]	2009	Italy	Cohort study	<32 weeks and BW<1500g	1209	BPD (at 36 weeks PMA)	ORs=2.16(CI, 1.1-3.9)	GA, propensity score for prolonged ventilation, centre	6
Kim[15]	1999	Korea	Case-control	<37 weeks	184	BPD (oxygen dependence at 28 days)	ORs=1.12(CI, 0.85-1.5)	Apgar score at 5 min, IVH, PDA, sepsis, duration of mechanical ventilation	7
Lodha[27]	2011	Canada	Cohort study	<28 weeks	918	NA	ORs=2(CI, 1.2-3.2)	NA	6
Natarajan[25]	2012	NA	Cohort study	<27 weeks BW<1000g	1189	BPD (at 36 weeks PMA)	ORs=2.41(CI, 1.4-4.13)	GA, male gender, SGA, maternal education, surgical NEC, IVH or PVL	7
Palta[29]	2000	USA	Cohort study	BW<1500g	1024	Severe BPD	ORs=2.3(CI, 1.2-4.6)	NA	6
Schlapbach[18]	2010	Switzerland	Case-control study	<32 weeks	99	BPD (at 36 weeks PMA)	ORs=3.75(CI, 1.08-11.14)	gestational age, birth weight, postnatal growth, mechanical ventilation	7
Synnes[24]	2017	Canada	Cohort study	<29 weeks	3700	BPD (at 36 weeks PMA)	ORs=1.42(CI, 1.17-1.73)	NA	8
Tran[17]	2005	Australia	Case control	<27 weeks	150	NA home oxygen	ORs=3.4(CI, 1.2-9.4)	NA	6
Van Marter[14]	2011	USA	Cohort study	<28 weeks	1047	BPD (at 36 weeks PMA) BPD (Mechanical ventilation at	ORs=1.77(CI, 1.02-3.77) ORs=5.16(CI, 2.62-10.16)	NA	8

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						36 weeks)			
Wang[28]	2014	China	Cohort study	GA<30 weeks and BW<1500g	5807	Not mentioned	ORs=3.14(CI, 2.61-3.85)	GA, BW, sex, ROP grade≥III, grade III/IV IVH and PVL	8
Bashir[16]	2016	Canada	Retrospective observational study	BW<1250g	1563	BPD (at 36 weeks PMA)	ORs=1.3(CI, 0.87-1.96)	GA, male gender, ANCS use, Apgar score<7 at 5 minutes, SGA, postnatal steroids, blood transfusion, PDA, IVH grade≥III and/ or PVL, ROP grade≥III and/ or required laser treatment and postnatal sepsis	8

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Table 2. Pooled results of the associations between bronchopulmonary dysplasia and cerebral palsy in children.

Variables	Studies (n)	ORs(95%CI)	I^2 (p-value for heterogeneity)	*p*
Total	11	2.10(1.57,2.82)	82.5% (0.000)	
Study design				
Case-control	3	1.27 (0.98, 1.64)	72% (0.03)	*p*=0.0006
Cohort	8	2.09 (1.86, 2.34)	83% (<0.00001)	
Definition of BPD				
Oxygen dependence at 36 weeks	6	1.67(1.33,2.11)	33.2% (0.187)	*p*<0.00001
Oxygen dependence at 28 days	1	1.12(0.84,1.49)	NA	
Severe BPD (mechanical ventilation)	2	3.44(1.56,7.60)	63.7%(0.097)	
Not mentioned BPD type	3	2.80(2.08, 3.79)	30.5% (0.237)	
Diagnostic criteria for cerebral palsy				
Age≥2 years only	6	2.62(2.26, 3.05)	71% (0.004)	*p*<0.00001
Age<2 years included	4	1.42(1.22, 1.64)	64% (0.04)	
Controlling for potential confounders				
Unadjusted estimates	6	1.48(1.28, 1.70)	64% (0.02)	*p*<0.00001
Controlled for gestational age	5	2.64(2.27, 3.08)	75% (0.003)	

NA: not available

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Figure captions

Figure 1. Flow chart for study selection

Figure 2. Analysis of BPD and CP.

Figure 3. The Egger's test for publication bias test.

Figure 4. The Begg's test for publication bias test.

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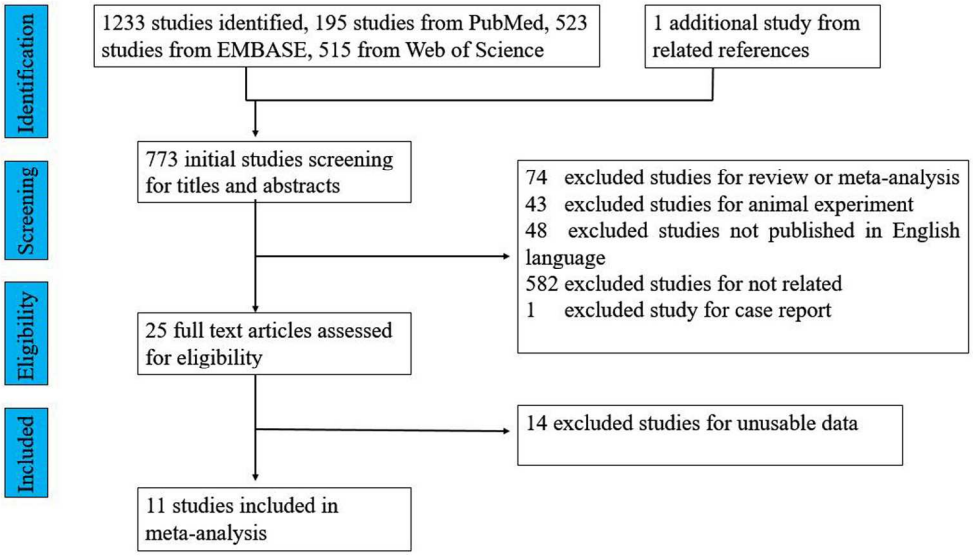

Figure 1. Flow chart for study selection

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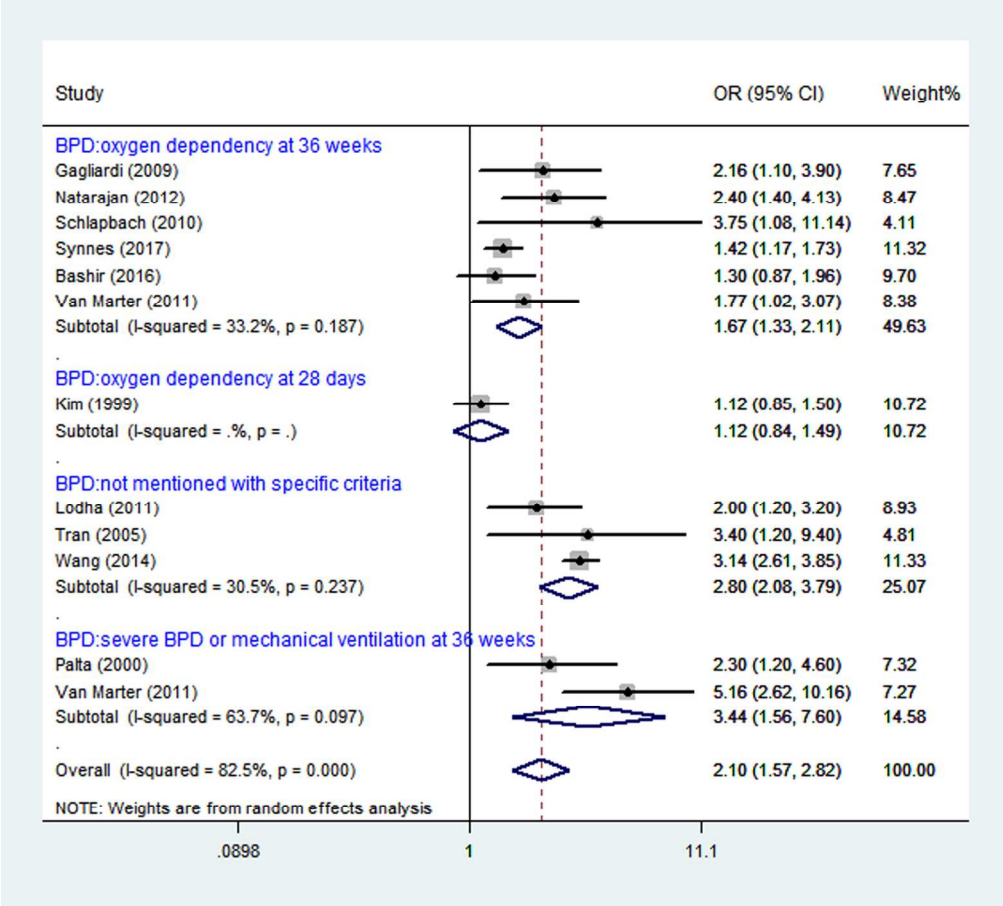

Figure 2. Analysis of BPD and CP.

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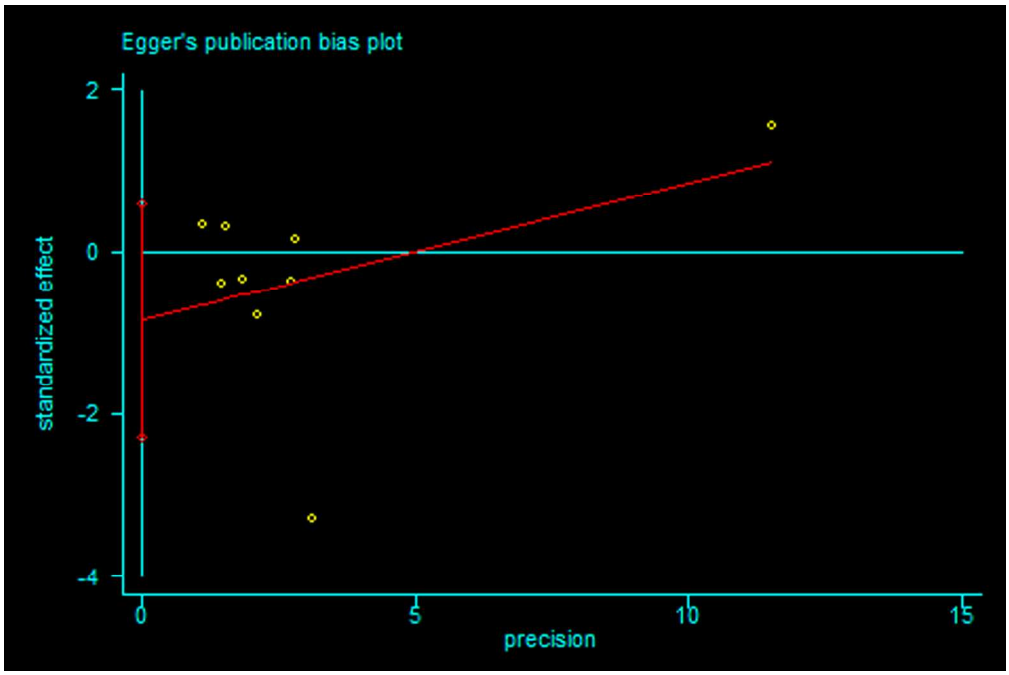

Figure 3. The Egger's test for publication bias test.

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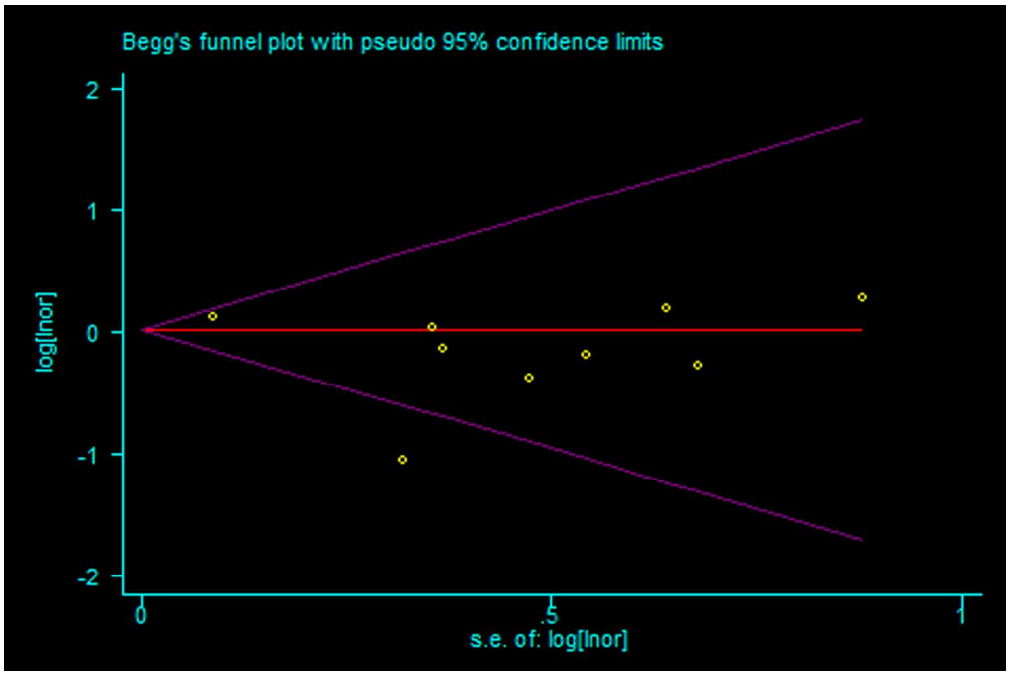

Figure 4. The Begg's test for publication bias test.

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The association between bronchopulmonary dysplasia and cerebral palsy in children: A meta-analysis

Supplement 1. Retrieval strategy of PubMed, EMBASE and Web of Science

Before 1 September 2017.

PubMed 195

Search (((((((Cerebral pals*[Title/Abstract]) OR CP[Title/Abstract]) OR spastic*[Title/Abstract]) OR Cerebral Palsy[Title/Abstract])) OR "Cerebral Palsy"[Mesh])) AND ((((((Dysplasia, Bronchopulmonary[Title/Abstract]) OR Bronchopulmonary Dysplasia[Title/Abstract]) OR BPD[Title/Abstract]) OR bronchopulmonary dysplasia[Title/Abstract])) OR "Bronchopulmonary Dysplasia"[Mesh])

EMBASE 523

Before 1 September 2017.

1 Cerebral palsy/

2 Cerebral pals$.tw.

3 Little$ disease.tw.

4 CP.tw.

5 (unilateral adj3 spastic$).tw.

6 (hemiplegi$ adj3 spastic$).tw.

7 (diplegi$ adj3 spastic$).tw.

8 (tetrapleg$ adj3 spastic$).tw.

9 (triplegi$ adj3 spastic$).tw.

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10 ((bilateral or bi-lateral) adj3 spastic$).tw.

11 (quadripleg$ adj3 spastic$).tw.

12 or/1-11

13 Bronchopulmonary Dysplasia.mp. or exp lung dysplasia/

14 BPD.tw.

15 Dysplasia, Bronchopulmonary.tw.

16 Bronchopulmonary Dysplasia.tw.

17 13 or 14 or 15 or 16

18 12 and 17

Web of science 515

Before 1 September 2017.

TS=(cerebral pals* or spastic* or quadripleg* or cerebral palsy or CP)

TS=(Bronchopulmonary Dysplasia or lung dysplasia or bronchopulmonary dysplasia or BPD or Dysplasia, Bronchopulmonary)

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Supplement 2. Newcastle - Ottawa Quality Assessment Scale results for case-control studies

Question	**Option**	Kim	Schlapbach	Tran
Is the case definition adequate?	a) yes, with independent validation * b) yes, eg record linkage or based on self reports c) no description	a	a	a
Representativeness of the cases	a) consecutive or obviously representative series of cases * b) potential for selection biases or not stated	a	b	b
Selection of Controls	a) community controls * b) hospital controls c) no description	b	b	b
Definition of Controls	a) no history of disease (endpoint)* b) no description of source	a	a	b
Comparability of cases and controls on the basis of the design or analysis	a) study controls for (Select the most important factor.* b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.) *	a	a	a

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Ascertainment of exposure	a) secure record (eg surgical records)* b) structured interview where blind to case/control status* c) interview not blinded to case/control status d) written self report or medical record only e) no description	a	a	a
Same method of ascertainment for cases and controls	a) yes* b) no	a	a	a
Non-Response rate	a) same rate for both groups* b) non-respondents described c) rate different and no designation	b	a	b

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Supplement 3. Newcastle - Ottawa Quality Assessment Scale results for cohort studies

Question	**Option**	Gagliardi	**Lodha**	Palta	Natarajan	Synnes	Van Marter	Wang	Bahir
Representativeness of the exposed cohort	a) truly representative of the average (describe) in the community * b) somewhat representative of the average in the community* c) selected group of users eg nurses, volunteered) no description of the derivation of the cohort	b	b	b	b	b	b	b	b
Selection of the Non-exposed cohort	a) drawn from the same community as the exposed cohort* b) drawn from a different source c) no description of the derivation of the non-exposed cohort	a	a	a	a	a	a	a	a
Ascertainment of exposure	a) secure record (eg surgical records)* b) structured interview* c) written self report d) no description	a	a	a	a	b	a	a	a
Demonstration that outcome of interest was not present at start of study	a) yes* b) no	a	a	a	a	a	a	a	a
Comparability of cohorts on the basis of the design or analysis	a) study controls for (select the most important factor)* b) study controls for any additional factor*	a	a	a	a	a	a	a	a

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Assessment of outcome	a) independent blind assessment* b) record linkage* c) self report d) no description	b	b	b	b	b	b	b	b
Was follow-up long enough for outcomes to occur	a) yes* b) no	b	b	b	a	a	a	a	a
Adequacy of follow up of cohort	a) complete follow up - all subjects accounted for* b) subjects lost to follow up unlikely to introduce bias - small number lost - > % (select an adequate %) follow up, or description provided of those lost) c) follow up rate < % (select an adequate %) and no description of those lost d) no statement	d	d	d	d	d	d	d	d

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Supplement 4. Egger's and Begg's test for publication bias test

Begg's Test

adj. Kendall's Score (P-Q) = 6

Std. Dev. of Score = 9.59

Number of Studies = 9

z = 0.63

Pr > |z| = 0.532

z = 0.52 (continuity corrected)

Pr > |z| = 0.602 (continuity corrected)

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.1683662	.139195	1.21	0.266	-.1607777	.49751
bias	-.8435039	.608102	-1.39	0.208	-2.281437	.5944288

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a meta-analysis.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3 , 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7,8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7,8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7,8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7,8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9,10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9,10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	No

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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