

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The association between bronchopulmonary dysplasia and cerebral palsy in children: A meta-analysis
AUTHORS	Gou, Xiaoyun; Yang, Lei; Pan, Lingli; Xiao, Dongqiong

VERSION 1 – REVIEW

REVIEWER	Federica Accordino San Gerardo Hospital, University of Milano- Bicocca, Milan, Italy
REVIEW RETURNED	21-Dec-2017

GENERAL COMMENTS	<p>Hypothesis about the relationship between BDP and CP are well known, so I think that t conclusions of this paper don't give new information or prospective.</p> <p>Among prematurity we know that the ethiology of neurological damage in case of premature spontaneous birth and iatrogenic preterm birth is really different, this difference is not clear explained. The clear and univocal definition of BPD, in my opinion, has to be considered to evaluete the relationship with neurological outcome.</p>
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REVIEWER	Pablo Brener Dik Hospital Italiano de Buenos Aires, Argentina
REVIEW RETURNED	09-Feb-2018

GENERAL COMMENTS	<p>I have elaborated any NO answer of the checklist, and also made other suggestions highlighted on the file attached (manuscript)</p> <p>2-Abstract (as the paper) needs an idiomatic review. Objective on abstract and manuscript should be alike; they are not: "to identify the factors that may explain these differences" does not appear in the manuscript's objective.</p> <p>5- Meta analysis do not necessarily need previous ethical approval by any Review Board, as these 3 cites: Cochrane Database 2016, Issue 6. Art. No.: CD00124 3 ; BMJ 2013;347:f5980; Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.: CD000143. However a statment like this could help: "Ethical approval: Not required"</p> <p>6-Main outcomes and measures are only stated in the abstract nor in the manuscript. Besides, on the abstract appears as this: neurodevelopment outcomes specially CP, but last one is the only one assesed. Definitely outcomes, as other variables studied, were not clearly defined.</p> <p>8- For example 1st refference is unappropriate. It is better elaborated on the file attached. Many sentences in the manuscript are not accurately referenced</p> <p>15- Despite English is not my native language, I have noticed several mistakes so a critical idiomatic review must be performed.</p>
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REVIEWER	Rebecca Wilson King's College London, UK
REVIEW RETURNED	12-Mar-2018

GENERAL COMMENTS	With regard to the statistical analysis, the methods are appropriate, sound and generally well described. On page 6, spell out ORs, RRs and CIs on line 24/25 as this is the first time they are used. On line 26/27, "the ORs and RRs were directly considered as ORs" whilst this is fine, I would provide a justification for doing this and/or provide a reference to support this. Otherwise, the analysis section is thorough and well reported.
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REVIEWER	Sarah Nevitt University of Liverpool, United Kingdom
REVIEW RETURNED	12-Mar-2018

GENERAL COMMENTS	<p>I have provided a statistical review of the manuscript "The association between bronchopulmonary dysplasia and cerebral palsy in children: A meta-analysis."</p> <p>The authors have performed a mostly well conducted meta-analysis with difficult sources of evidence and results are interpreted appropriately. I have a few minor comments for the attention of the authors.</p> <p>Page 4, line 31: "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." Perhaps I am missing something here as I am not a clinical expert but leading on from the previous paragraphs, I do not understand oxygen dependency relates to BPD?</p> <p>Page 4, line 42-52: "A number of studies have ... any other studies showed a significant association between BPD and CP." I'm not following this paragraph - does this mean that individual studies have shown different results and used different definitions?</p> <p>Page 5, Inclusion / Exclusion Criteria: Criteria 4 – were studies also included if data were 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)? Related comment on Figure 1 – 14 studies were excluded for 'unusable data,' could the authors expand on this? Which data were published which were unusable?</p> <p>Page 6, Data extraction: Please clarify that 'Primary outcome' here refers to the 'primary' outcome of this meta-analysis (i.e. the association between BPD and risk of CP), which I assume may not have been the specified primary outcome of the original study? Also I note that no outcomes are explicitly defined for this meta-analysis. I suggest adding a brief section on this to the methods for complete clarity.</p> <p>Page 6, Statistical Analysis: "We performed sensitivity analyses by omitting one study at a time." I do not recommend this type of sensitivity analysis. Such an analysis is highly selective and will penalize studies of large sample sizes. Any exclusions should be made for clearly justified reasons (e.g. studies are of low quality or have a lot of missing data) to</p>
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	<p>examine whether any problems with included studies could have influenced the overall meta-analysis results. I suggest removing all references to this sensitivity analysis (I note that results were consistent anyway).</p> <p>Page 7-8, Results: Please also make reference to the high levels of heterogeneity present within the analyses in the main text and the OR quoted in the abstract to aid interpretations (e.g. quote I-squared statistics after odds ratios).</p> <p>Page 8: “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”).</p> <p>Please note that the stratified analyses presented here are not testing differences in the subgroups. In other words, these results show a significant OR from adjusted estimates and a significant OR from unadjusted estimates but the information presented does not show whether the unadjusted estimates are significantly smaller (or larger) than the adjusted estimates. Please either reword this or consider performing a ‘test of subgroups’ to determine whether there are any significantly different results across the subgroups considered.</p> <p>Page 10, line 40: “Second, the study used stratified analysis to explore the heterogeneity source, yet, we failed to identify the source of heterogeneity.” I think the authors are being harsh on themselves here. I’m not entirely sure what the authors mean by ‘failing’ to find the source – looking at Table 2 and Figure 2 I’d certainly say that the Definition of BPD seems to be a major source of heterogeneity and within some of these sub-categories the results seem more consistent. As the authors state in the previous paragraph, there is inherent bias and likely heterogeneity (including unknown sources of heterogeneity) associated with observational studies so I think the authors have done all they can and interpreted their results appropriately – i.e. that there appears to be an association but the size of the association is unknown due to the heterogeneity. No ‘failure’ here in my view.</p> <p>Figure 3 and Figure 4: Please refer to these two Figures in the main paper and add a sentence or two on how these plots are interpreted.</p> <p>Supplementary information files 1-4: Please refer to these Supplementary files in the appropriate sections of the main paper.</p>
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VERSION 1 – AUTHOR RESPONSE

Response to Reviewers

Reviewer #1: General comments

Hypothesis about the relationship between BPD and CP are well known, so I think that conclusions of this paper don't give new information or prospective.

Major suggestions are as follows:

Questions 1: *Among prematurity we know that the etiology of neurological damage in case of*

premature spontaneous birth and iatrogenic preterm birth is really different, this difference is not clear explained.

Response: We appreciate the reviewer's valuable suggestion. We have explained the difference in the etiology of neurological damage between premature spontaneous birth and iatrogenic preterm birth in the revised manuscript (Page 12, line 16-20, colored blue)

Question 2: *The clear and univocal definition of BPD, in my opinion, has to be considered to evaluate the relationship with neurological outcome.*

Response: We appreciate the reviewer's suggestion. We have considered the definition of BPD to be related to CP (Page 13, line 3-4, colored blue).

Reviewer #2 General comments

I have elaborated any NO answer of the checklist, and also made other suggestions highlighted on the file attached (manuscript)

Response: We appreciate your thoughtful comments. We revised the manuscript according to the highlighted suggestions in the file attached (manuscript) (Page 2-13, colored blue)

Question 1: *Abstract (as the paper) needs an idiomatic review. Objective on abstract and manuscript should be alike; they are not: "to identify the factors that may explain these differences" does not appear in the manuscript's objective.*

Response: We appreciate the reviewer's suggestion. We have revised the objective in the revised manuscript (Page 2, line 3-4, colored blue).

Question 2: *Meta analysis does not necessarily need previous ethical approval by any Review Board, as these 3 cites: Cochrane Database 2016, Issue 6. Art. No.: CD00124 3 ; BMJ 2013;347:f5980; Cochrane Database of Systematic Reviews 2003, Issue 2. Art. No.: CD000143. However a statement like this could help: °Ethical approval: Not required"*

Response: We appreciate the reviewer's suggestion. We have not required the ethical approval (Page 14, line 8-9, colored blue).

Question 3: *Main outcomes and measures are only stated neither in the abstract nor in the manuscript. Besides, on the abstract appears as this: neurodevelopment outcomes specially CP, but last one is the only one assessed. Definitely outcomes, as other variables studied, were not clearly defined.*

Response: Thanks for your suggestions. We have clearly defined the outcomes in the revised manuscript (Page 2, line 13, Page 6, line 18-20, colored blue).

Question 4: *For example 1st reference is inappropriate. It is better elaborated on the file attached. Many sentences in the manuscript are not accurately referenced*

Answer: We appreciate the reviewer's suggestion. We have accurately referenced in the revised manuscript (Page 4, line 3, line 22, Page 7, line 16, Page 11, line 25, Page 12, line 9, colored blue).

Question 5: *Despite English is not my native language, I have noticed several mistakes so a critical idiomatic review must be performed.*

Response: Thank you for your thoughtful comments. We have revised the manuscript to reflect your criticisms (Page 2-13, line, colored blue).

Reviewer #3 General comments

With regard to the statistical analysis, the methods are appropriate, sound and generally well described. Otherwise, the analysis section is thorough and well reported.

Question 1: On page 6, spell out ORs, RRs and CIs on line 24/25 as this is the first time they are used.

Response: Thanks for your suggestions. We have spelled out ORs, RRs and CIs as the first time they are used (Page 6, line 20-22).

Question 2: On line 26/27, “the ORs and RRs were directly considered as ORs” whilst this is fine, I would provide a justification for doing this and/or provide a reference to support this.

Response: Thanks very much for your comments and we provide a reference to support this (Page 7, line 14, colored blue).

Reviewer #4 General comments

I have provided a statistical review of the manuscript “The association between bronchopulmonary dysplasia and cerebral palsy in children: A meta-analysis.”

The authors have performed a mostly well conducted meta-analysis with difficult sources of evidence and results are interpreted appropriately. I have a few minor comments for the attention of the authors.

Minor comments

Question 1: Page 4, line 31: “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.”

Perhaps I am missing something here as I am not a clinical expert but leading on from the previous paragraphs, I do not understand oxygen dependency relates to BPD?

Response: Thanks for your suggestion. BPD is a chronic lung disease developed after mechanical ventilation or oxygen inhalation usually occurring in certain premature neonates with respiratory distress syndrome (Page 4, line 15-17, colored blue).

Question 2: Page 4, line 42-52: “A number of studies have ... any other studies showed a significant association between BPD and CP.”

I'm not following this paragraph - does this mean that individual studies have shown different results and used different definitions?

Response: We have revised it. The association between BPD and CP was inconsistent. Some of the studies have significant association, while other studies have insignificant association (Page 4, line 24-26, Page 5, line 1-3, colored blue).

Question 3: Page 5, Inclusion/Exclusion Criteria: Criteria 4 – were studies also included if data were 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)?

Response: Thanks for your suggestion and the data was reported directly by ORs/RRs and 95%CI (Page 6, line 17-25, Page 7, line 1-2, colored blue).

Question 4: Related comment on Figure 1 – 14 studies were excluded for ‘unusable data,’ could the authors expand on this? Which data were published which were unusable?

Response: Thank you for your thoughtful comments. The data was directly reported by ORs/RRs and 95%CI, and the data that reported with that (e.g. number of cases of BPD events and total number of children with CP) was excluded (Page 6, line 17-25, Page 7, line 1-2, colored blue).

Question 5: Page 6, Data extraction: Please clarify that 'Primary outcome' here refers to the 'primary' outcome of this meta-analysis (i.e. the association between BPD and risk of CP), which I assume may not have been the specified primary outcome of the original study? Also I note that no outcomes are explicitly defined for this meta-analysis. I suggest adding a brief section on this to the methods for complete clarity.

Response: Thanks for your suggestion and we have defined the outcomes of the meta-analysis (Page 6, line 18-20, Page 7, line 6-7, colored blue)

Question 6: Page 6, Statistical Analysis: "We performed sensitivity analyses by omitting one study at a time."

I do not recommend this type of sensitivity analysis. Such an analysis is highly selective and will penalize studies of large sample sizes. Any exclusions should be made for clearly justified reasons (e.g. studies are of low quality or have a lot of missing data) to examine whether any problems with included studies could have influenced the overall meta-analysis results. I suggest removing all references to this sensitivity analysis (I note that results were consistent anyway).

Response: Thanks for your suggestion and we have removed the sensitivity analysis.

Question 7: Page 7-8, Results: Please also make reference to the high levels of heterogeneity present within the analyses in the main text and the OR quoted in the abstract to aid interpretations (e.g. quote I-squared statistics after odds ratios).

Response: Thank you for your suggestion. We have added the I-squared statistics after ORs (Page 9, line 19-22, Page 10, line 1-5, colored blue).

Question 8: Page 8: "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").

Response: Thanks for your valuable suggestion and we have revised it (Page 10, line 11-13, colored blue).

Question 9: Please note that the stratified analyses presented here are not testing differences in the subgroups. In other words, these results show a significant OR from adjusted estimates and a significant OR from unadjusted estimates but the information presented does not show whether the unadjusted estimates are significantly smaller (or larger) than the adjusted estimates. Please either reword this or consider performing a 'test of subgroups' to determine whether there are any significantly different results across the subgroups considered.

Response: Thank you for your suggestion. We have performed stratified analysis to determine whether there are any significantly different results across the subgroups considered in our revised manuscript (Page 9, line 17-19, colored blue).

Question 10: Page 10, line 40: "Second, the study used stratified analysis to explore the heterogeneity source, yet, we failed to identify the source of heterogeneity."

I think the authors are being harsh on themselves here. I'm not entirely sure what the authors mean by 'failing' to find the source – looking at Table 2 and Figure 2 I'd certainly say that the Definition of BPD seems to be a major source of heterogeneity and within some of these sub-categories the results seem more consistent. As the authors state in the previous paragraph, there is inherent bias and likely heterogeneity (including unknown sources of heterogeneity) associated with observational studies so I think the authors have done all they can and interpreted their results appropriately – i.e. that there appears to be an association but the size of the association is unknown due to the heterogeneity. No 'failure' here in my view.

Response: Thank you for your suggestion and we have replaced it with the sentence “the different definition of BPD may contribute to the source of heterogeneity” (Page 13, line 3, colored blue).

Question 11: *Figure 3 and Figure 4: Please refer to these two Figures in the main paper and add a sentence or two on how these plots are interpreted.*

Response: Thanks for your valuable suggestion and we have interpreted Figure 3 and Figure 4 in the revised manuscript (Page 10, line 15, colored blue).

Question 12: *Supplementary information files 1-4: Please refer to these Supplementary files in the appropriate sections of the main paper.*

Response: Thanks for your valuable suggestion and we have refer to these Supplementary files in the appropriate sections of the main paper (Page 6, line 10-11, Page 9, line 12-13, Page 10, line 16, colored blue).

VERSION 2 – REVIEW

REVIEWER	Rebecca Wilson Research Associate King's College London, UK
REVIEW RETURNED	18-Apr-2018

GENERAL COMMENTS	The authors have thoughtfully and thoroughly addressed all comments and suggestions and I recommend this manuscript for publication.
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REVIEWER	Sarah Nevitt University of Liverpool United Kingdom
REVIEW RETURNED	18-Apr-2018

GENERAL COMMENTS	<p>Thank you to the authors for their efforts in addressing my statistical comments. I believe that the authors may have misunderstood a couple of my comments, I would like to clarify.</p> <p>1) Original comments questions 3 and 4</p> <p>Original comment, Question 3: Page 5, Inclusion/Exclusion Criteria: Criteria 4 – were studies also included if data were 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)? Author Response: Thanks for your suggestion and the data was reported directly by ORs/RRs and 95%CI (Page 6, line 17-25, Page 7, line 1-2, colored blue).</p> <p>Original comment, Question 4: Related comment on Figure 1 – 14 studies were excluded for ‘unusable data,’ could the authors expand on this? Which data were published which were unusable? Response: Thank you for your thoughtful comments. The data was directly reported by ORs/RRs and 95%CI, and the data that reported with that (e.g. number of cases of BPD events and total number of children with CP) was excluded (Page 6, line 17-25, Page 7, line 1-2, colored blue).</p> <p>Additional comment: I note that if the number of cases of BPD</p>
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	<p>events and the number of children with CP were published within the paper then this would mean that RR and OR could be calculated, so this data would not be 'unusable.' Did the authors exclude any data that could have been used?</p> <p>2) Original comment, Question 9: Please note that the stratified analyses presented here are not testing differences in the subgroups. In other words, these results show a significant OR from adjusted estimates and a significant OR from unadjusted estimates but the information presented does not show whether the unadjusted estimates are significantly smaller (or larger) than the adjusted estimates. Please either reword this or consider performing a 'test of subgroups' to determine whether there are any significantly different results across the subgroups considered.</p> <p>Response: Thank you for your suggestion. We have performed stratified analysis to determine whether there are any significantly different results across the subgroups considered in our revised manuscript (Page 9, line 17-19, colored blue).</p> <p>Additional comment: The authors have misunderstood here – determining whether there are any significant differences across subgroups is what you have NOT done. Currently the analysis determines whether each subgroup individually shows a significant result, but no analysis has been conducted which informs whether any subgroup is significantly different from another. It is possible to perform a 'Test of Subgroup differences' in software such as Review Manager (Cochrane) and any statistical software that allows meta-analysis.</p>
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VERSION 2 – AUTHOR RESPONSE

Response to Reviewers

Reviewer #3 General comments

The authors have thoughtfully and thoroughly addressed all comments and suggestions and I recommend this manuscript for publication. Response: Thanks for your suggestions.

Reviewer #4 General comments

Thank you to the authors for their efforts in addressing my statistical comments.

I believe that the authors may have misunderstood a couple of my comments, I would like to clarify.

Minor comments

Question 1: I note that if the number of cases of BPD events and the number of children with CP were published within the paper then this would mean that the RR and OR could be calculated, so this data would not be "unusable". Did the authors exclude any data that could have been used?

Original comment, Question 3: Page 5, Inclusion/Exclusion Criteria: Criteria 4 – were studies also included if data were 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)?

Response: Thanks for your suggestion. We have allowed RRs/ORs to be calculated. We checked the excluded studies carefully, and there were no data 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). (Page 7 line 22-26, underlined)

Original comment, Question 4: Related comment on Figure 1 – 14 studies were excluded for ‘unusable data,’ could the authors expand on this? Which data were published which were unusable?

Response: Thank you for your thoughtful comments. The data that 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. (Page 8 line 3-10, underlined)

Question 2: The authors have misunderstood here-determining whether there are any significantly different results across the subgroups is what you have not done. Currently the analysis determines whether each subgroup individually shows a significant result, but no analysis has been conducted which informs whether any subgroup is significantly different from another.

It is possible to perform a “Test of Subgroup differences” in software such as Review Manager (Cochrane) and any statistical software that allows meta-analysis.

Original comment, Question 9: Please note that the stratified analyses presented here are not testing differences in the subgroups. In other words, these results show a significant OR from adjusted estimates and a significant OR from unadjusted estimates but the information presented does not show whether the unadjusted estimates are significantly smaller (or larger) than the adjusted estimates. Please either reword this or consider performing a ‘test of subgroups’ to determine whether there are any significantly different results across the subgroups considered.

Response: Thank you for your suggestion. We have performed a “Test of Subgroup differences” in software such as Review Manager (Cochrane) in our revised manuscript. (Page 9 line 7-10, underlined; Page 10 line 22-25, underlined; Page 11 line 8-20, underlined; Table 2)