Author Response

Reviewer 1

General Comments: The authors present a comprehensive review on the topic of Bronchopulmonary dysplasia – what are its links to COPD? It represents a narrative review. There is no particular comment made on the choice of citations. Obviously, they have prioritized the most recent citations. The review is very well written, and gives a good overview on the topic by taking into consideration various important aspects. The following comments are merely suggestions, to put more focus on the link between the two diseases BPD and COPD.

Comment 1: The review does not mention the characteristics of COPD such as airflow limitation and the contributing conditions of emphysema and chronic bronchitis. By pointing out the similarities of the pathophysiologic and histopathologic picture of the two diseases, it makes it easier to understand the contribution of BPD to the development of COPD and possible common pathways.

Response 1: We agree with the above reviewer and have added additional text to the section of respiratory health trajectories:

Comment 2: In the section of respiratory health trajectories, the authors could explain normal lung growth a bit more detailed. It would help to visualize possible changes of lung function trajectories after premature birth and additional influencing factors, which might lead to a critical threshold of lung disease with age (Stocks J et al, Lancet Respir Med 2013; 1: 728-42. Burrows B et al, Am Rev Respir Dis 1977; 115: 751-60.). The concept of “fetal programming” could be mentioned (Barker D et al, BMJ 1991 303: 671-675).

Response 2: We appreciate the reviewer 1’s comments and have added these recommendations to the section on respiratory health trajectories.

Comment 3: At the end of the section pathophysiology of BPD, I would expect a short introduction of the following sections in order to realize that they are part of the pathophysiology section. Otherwise, the pathophysiology section seems much too brief.

Disruption of angiogenesis and subsequently of pulmonary vasculature as part of the pathophysiology of BPD could be stressed more which is directly linked to disrupted lung development.

What is known about the influence of preterm birth on airway microbiome and of links to COPD?

Response 3: This has been addressed

Comment 4: Genetic factors in BPD and COPD. The authors could think about giving one concrete example of how alteration in early lung growth regulating pathway influences COPD susceptibility (e.g.: Van Dume YM et al. Eur Respir J 2010;36:89-95). This gives a better idea of possible linking mechanism from a genetic point of view.

Response 4: Thank you for the helpful example; we have added it to the manuscript.

Comment 5: Link between BPD and COPD. Table 1 nicely outlines the influencing factors according to developmental stages on adult lung function. It could be even more informative if the authors fill in the blanks either by estimating the strength of evidence for the respective factor or by briefly mentioning how the respective factor influences the lung, and refer to literature.

Response 5: For Table 1, we have added supplementary references that support links between developmental stages and conditional that may influence adult lung function. Unfortunately, a systematic review of the literature to provide formal estimate of strengths of evidence is beyond the scope of this invited review.

Comment 6: Conclusions. The authors should highlight the remaining gaps of knowledge more clearly, its implications for future research and possible strategies for therapeutic advances.

The so-called “critical period” of postnatal lung development represents at the same time a window of opportunity for new therapies that might enhance the process of ongoing lung-development and late alveolarization. Better understanding of the pathogenesis and the links of both diseases, will allow to develop new therapeutic advances. I miss a summary of existing, experimental therapies (e.g. stem cell transplantation) and an outlook on new therapeutic strategies (Naeem A et al, Eur Med J, 2019;4:20-29).

Response 6: We have highlighted gaps in knowledge under the conclusion section of the review and have added a summary of the existing experimental therapies under the pathophysiology section

Comment 7: Figure 1: Please add z-score for lung function values, instead of % predicted.

Response 7: Addition made as requested.

Comment 8: It would be illustrative to add another figure next to figure 1 with the lung function and chest CT from an adult COPD patient. This would show the similarities of functional and structural lung changes in both disease entities, highlighting their possible common pathways.

Response 8: We agree with reviewer one and have added a figure from an adult COPD patient.

Reviewer 2

General Comments: In this review, authors described the clinical manifestations of BPD, the pathophysiology of this disease and the arguments in favor of the role of BPD in further development of COPD in adults. This review summarizes the current knowledge on the subject.

Comment 1: Page 5 line 14-16 : I agree that BPD may be associated to pulmonary hypertension but it is important to detail that most of the time this is due to chronic hypoxemia leading to pulmonary vessels vasoconstriction in combination with a real vascular disease in the more preterm babies, and with a potential aggravating role of persistent ductus arteriosus that may add an overflow in pulmonary arteries. Nevertheless, I do not understand why the authors evoke the role of LV dysfunction, intracardiac shunts or pulmonary venous stenosis especially in this setting of preterm birth and BPD.

Response 1: We have clarified this sentence to reflect that vascular disease is the most common etiology, and note that other etiologies may contribute.

Comment 2: Page 5 line 30 : I would precise “the majority of infants on supplemental oxygen when discharged home are weaned to room air by 12 months of age and the median age of being weaned from home mechanical ventilation is 25 months.” If not, there is a risk for the reader to assume that this data relate to all preterm babies that develop BPD.

Response 2: We have clarified this sentence.

Comment 3: Page 6, line 50-53: “In general, it is not known whether any specific asthma or COPD risk genes are more likely to be present in children with BPD, particularly severe BPD”. The authors should replace “genes” by “genes variants” because all individuals have the same genes but with different possible variations.

Response 3: Edit made.

Comment 4: Page 7 line 12-17: “Identification of SNPs in BPD will help to identify risk genes and provide mechanistic insights into disease severity and progression in BPD, and potentially have relevance for COPD.” Again gene is not the proper word and should be replace by “alleles” here.

Response 4: Edit made.