

ORIGINAL ARTICLE

Airways Disease

Bronchial hyper-responsiveness in preterm-born subjects: A systematic review and meta-analysis

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Edited by: Ömer Kalayci

Abstract

Background: Preterm-born survivors have increased respiratory symptoms and decreased lung function, but the nature of bronchial hyper-responsiveness (BHR) is unclear. We conducted a systematic review and meta-analysis for BHR in preterm-born survivors including those with and without chronic lung disease in infancy (CLD) comparing results to term-born subjects.

Methods: We searched eight databases up to December 2016. Included articles compared BHR in preterm-born and term-born subjects. Studies reporting BHR as decreases in forced expiratory volume in 1 second (FEV₁) after provocation stimuli were included. The analysis used Review Manager V5.3.

Results: From 10 638 titles, 265 full articles were screened, and 28 included in a descriptive analysis. Eighteen articles were included in a meta-analysis as they reported the proportion of subjects who had BHR. Pooled odds ratio (OR) estimates (95% confidence interval) for BHR comparing the preterm and term-born groups was 1.88 (1.32, 2.66). The majority of the studies reported BHR after a methacholine challenge or an exercise test. Odds ratio was 1.89 (1.12, 3.19) after methacholine challenge and 2.59 (1.50, 4.50) after an exercise test. Nine of fifteen articles reporting BHR in CLD subjects were included in a meta-analysis. Differences for BHR including for methacholine (OR 4.35; 2.36, 8.03) and exercise (OR 5.13; 1.82, 14.47) were greater in the CLD group compared to the term group.

Conclusions: Preterm-born subjects especially those who had CLD had increased rates of BHR to direct (methacholine) and indirect (exercise) stimuli compared to term-born subjects suggesting subgroups might benefit from anti-inflammatory or bronchodilator therapies.

KEYWORDS

asthma, bronchial hyper-responsiveness, bronchopulmonary dysplasia, chronic lung disease of prematurity, exercise, methacholine, prematurity

1 | INTRODUCTION

Preterm birth is associated with increased respiratory symptoms^{1,2} and decreased lung function.³ However, whilst it is often stated that

these adverse events result from birth at an early stage of lung development⁴ and interventions such as mechanical ventilation, the underlying mechanisms for the respiratory deficits continuing into childhood and beyond remain uncertain. These deficits may be due to

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long-standing structural consequences of preterm birth, as evidenced by smooth muscle extension into the smaller airways well beyond that observed in term-born infants, especially where the infant has been diagnosed with chronic lung disease of prematurity (chronic lung disease [CLD], also called bronchopulmonary dysplasia, BPD).^{5,6} Alternatively, there are limited data suggesting that an active pro-inflammatory neutrophilic status⁷ and oxidant process may be continuing.⁸

The nature of the airway narrowing observed in preterm-born children can be tested using pharmacological stimuli, for example directly acting on smooth muscle cells' receptors or indirectly via the release of mediators by pro-inflammatory airway cells.⁹ This process of assessment of bronchial hyper-responsiveness (BHR) has been extensively used in asthma, although it is not as discriminatory as expected as many asymptomatic subjects may have increased BHR and those with the disease may not.¹⁰ Nevertheless, BHR by both direct (eg histamine, methacholine) and indirect (eg exercise, mannitol) means has been used in preterm-born survivors to try to elucidate the potential mechanisms underlying the airway obstruction observed. The current data do not conclusively confirm that BHR is increased in preterm survivors; furthermore, it is even less clear if direct agents have greater or similar effects to indirect agents. Thus, we conducted a systematic review and meta-analysis to identify if:

1. BHR was increased after preterm birth when compared to term-born controls.
2. BHR was increased in preterm-born subjects who had CLD compared to term-born subject
3. Any increase in BHR was due to responses to (a) direct or (b) indirect stimuli.

2 | METHODS

We used methodologies and data from our three previous systematic reviews.^{3,11,12} As data for BHR are often not reported in titles or abstracts, we combined several approaches. We (a) re-ran the initial searches for articles reporting FEV₁ in preterm-born subjects³; (b) adapted the initial search strategies to include additional keywords relating to BHR and ran them in eight databases; and (c) searched references in the included articles to identify additional papers reporting BHR in preterm-born subjects compared to term-born subjects (see Data S1 for protocol, search strategy, and data collection form). Eight databases were searched: EMBASE, Health Management Information Consortium (HMIC), MEDLINE, Medline in Process, Scopus, OpenSIGLE, CINAHL and Web of Science. Ethical approval was not required.

2.1 | Eligibility criteria

Studies on BHR in preterm-born subjects of any age, (adults and children), with or without CLD, and of any gender were included. Randomized and nonrandomized intervention studies, prospective and retrospective case-control studies, and prospective and retrospective

cohort studies were included. Preterm defined as birth <37 weeks' gestation and term as birth ≥37 weeks' gestation. Studies which recruited on the basis of birthweight were included if they reported gestational age and all subjects in the study group were preterm and the control group were term-born, or the birthweight cut-off for the preterm group was <1501 g. Authors' definitions of CLD and what constituted BHR, and all methods of assessing BHR were accepted. However, only studies reporting a change in FEV₁ after a challenge were included. Studies in all languages from all countries were considered.

2.2 | Study selection

Searches were conducted in December 2016 and January 2017. Two reviewers (SJK and HC) independently screened each reference title and available abstracts, using the inclusion criteria. Complete manuscripts were obtained for those that met the inclusion criteria as judged by either reviewer. The two reviewers then screened the full manuscripts against the inclusion criteria. Where there was disagreement, a third reviewer (SK) made the final decision.

2.3 | Data collection process

SJK data extracted included articles. Authors of articles were contacted, where possible, for further details if the information was not in a format which enabled data extraction for inclusion in the systematic review. Multiple articles from the same cohort were reviewed by SK and SJK, and the article reporting the most complete data was included.

2.4 | Assessment of study quality and risk of bias

Study quality was assessed based on criteria from the Newcastle Ottawa criteria and the Cochrane risk of bias tool. The quality assessment sheet is shown in the Data S1. Each study was scored for representativeness of the cohort, appropriate selection of the non-exposed group, exposure ascertainment and demonstration that the outcome of interest was not present at the start of the study, outcome assessment and adequacy of follow-up by SJK. Minimum score was six and maximum score was 20.

2.5 | Outcome measures

Number of subjects with BHR (given by a defined change in FEV₁ after BHR challenge) in the premature group and in the premature CLD subgroup, compared with a term control group.

2.6 | Analysis of results

A formal meta-analysis was conducted for the studies which reported the number of subjects in the (a) preterm (with and without CLD) and control groups, and (b) preterm group with CLD and a term control group who had a positive BHR result as defined by the authors of each manuscript. Both meta-analyses were further analysed by dividing the

subjects into the different methods of testing for BHR to separate out the effects of direct and indirect challenges. The results of all studies including those not in the meta-analyses are also presented descriptively. A sensitivity analysis was performed to investigate the effect of year of birth of the preterm-born subjects on BHR by dividing the preterm-born subjects into two groups (a) born on or after 1990 and (b) born before 1990. Where the subjects were born over a range of years, a mid-point was used.

2.7 | Statistical analysis

Statistical analyses were performed using Review Manager (RevMan) version 5.3.¹³ After initial exploration of the data, we used random-effects meta-analyses to allow for heterogeneity. Heterogeneity was

assessed using the I^2 statistic produced by RevMan. The following were used as a rough guide I^2 "0%-40% might not be important; 30%-60%: may represent moderate heterogeneity; 50%-90%: may represent substantial heterogeneity; 75%-100%: considerable heterogeneity".¹⁴ There was large heterogeneity between the articles, due to a range of methods to assess BHR, variable outcomes measures and range of ages and gestations studied over a number of years.

3 | RESULTS

3.1 | Studies selected and their characteristics

A total of 10 638 article titles were identified of which 265 full articles were screened for inclusion. Twenty-eight¹⁵⁻⁴² met the inclusion

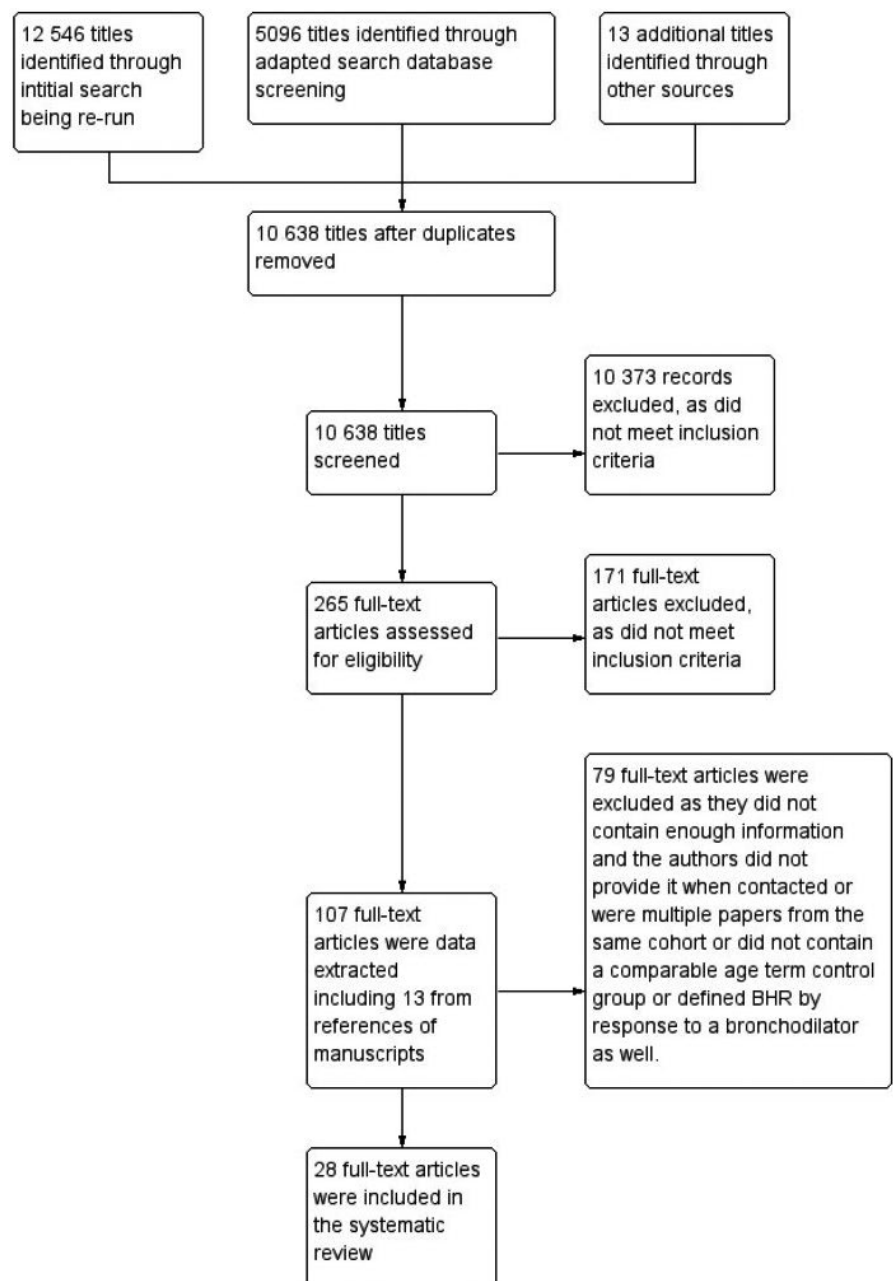


FIGURE 1 Study selection results

criteria (Figure 1). For the two studies that overlapped^{24,26} the one reporting BHR as a proportion of responders²⁶ was included in the meta-analyses. Detailed demographics of included articles are shown in Table E1 (Data S1), and a summary of the demographics for the direct and indirect methods of assessing BHR is shown in Table 1a and b, respectively.

Of the 28 articles reporting BHR:

1. 14 performed a methacholine challenge
2. 12 performed an exercise test
3. 1 performed a cold air challenge
4. 1 performed testing with hypertonic saline

Many of the articles studied preterm-born subjects where prematurity was defined as being born at a gestation of <37 weeks,^{15,18-21,23,29,34,37,39,40,42} but there was heterogeneity in the groups as articles also sometimes only included extremely (<28 weeks' gestation) or very (≤ 32 weeks' gestation)^{17,24-28,31-33,35,36,41} or late (33-36 weeks' gestation) preterm-born subjects.³⁸ Although the majority of studies studied randomly selected preterm subjects or studied cohorts, one study included preterm infants with congenital diaphragmatic hernia (CDH), but the authors provided data to us to only include the preterm and term control infants excluding CDH.²² Sensitivity analyses removing that study from all analyses marginally increased the odds ratios in favour of the preterm groups. In most of the included studies, BHR was tested as part of wider ranges of lung function assessments.

3.2 | Risk of bias across studies

The quality scores ranged from 9 to 18 (median 14). The studies not included in the meta-analyses had similar quality scores to those included in the meta-analyses. Included studies range from 11 to 16 (median 14) and not-included studies range from 9 to 18 (median 14.5).

3.3 | Study outcomes

3.3.1 | BHR in preterm group compared to term control group

Eighteen of the 28 included articles were included in a meta-analysis.

The results of the meta-analysis of the 18 articles are shown in Figure 2A; demographics are described in the Data S1 (Table E1). The pooled estimates of OR (95% CI) for BHR in the preterm group was 1.88 (1.32, 2.66) $P = 0.01$.

The results for subjects who had a methacholine (direct) challenge or who had an exercise test (indirect challenge) are reported in Figure 2B and C, respectively, and demographics are shown in Table E1 (Data S1). The pooled estimates of OR (95% CI) for BHR in the preterm group was 1.89 (1.12, 3.19) $P = 0.009$ for the eight articles reporting results after a methacholine challenge and 2.59 (1.50, 4.50) $P = 0.0007$ for the eight articles reporting results after an exercise test.

OR were greater for studies where the preterm-born subjects were born on or after 1990 than studies where the preterm-born subjects were born before 1990.

3.3.2 | BHR in preterm group who had CLD in infancy compared to term control group

Fifteen of the 18 articles also compared BHR in preterm-born subjects who had CLD with term controls,^{17,18,21,24-27,29,31,33-37,41} see Data S1 for demographics (Table E1). We performed a meta-analysis for nine of the 15 articles although the total number studied was small (Figure 3A). The definitions of CLD used by the authors' of the nine articles are reported in Table E2 (Data S1). The pooled estimates of OR (95% CI) for BHR in the preterm group who had CLD was 4.54 (2.68, 7.69), $P < 0.00001$. The results for the subjects who had a methacholine challenge or who had an exercise test are reported in Figure 3B and C, respectively. The pooled estimates of OR (95% CI) for BHR in the preterm group who had CLD was 4.35 (2.36, 8.03), $P < 0.00001$ for the four articles reporting results after a methacholine challenge and 5.13 (1.82, 14.47), $P = 0.002$ for the five articles reporting results after an exercise test. It should be noted that one study used different definitions for the preterm ($PC_{20} < 4$ mg/mL) and CLD ($PC_{20} < 1$ mg/mL) groups to define a positive BHR response.²⁷

3.3.3 | Description of studies not included in the meta-analyses

Ten articles were not included in the meta-analysis.^{17,19,23-26,29,33,36,39,40} Six articles reported BHR after a methacholine challenge,^{17,19,23-26,39} and four articles reported after an exercise test.^{29,33,36,40} The studies are described in detail in the Data S1 (Table E1). In general, all studies for both methacholine and exercise reported increases in BHR but the results were not always significantly different from included term-born controls. However, comparisons between articles were difficult due to heterogeneity.

4 | DISCUSSION

The results of our systematic review and meta-analyses suggest preterm-born subjects have greater BHR compared to term-born subjects, and differences are greatest for subjects who had CLD. Furthermore, the commonest used direct agent, methacholine, and indirect method, exercise testing, both resulted in greater BHR in preterm-born survivors with and without CLD and preterm-born subjects with CLD compared to term controls. Of note was the variety of different stimuli and outcome measures used, making comparisons difficult between studies.

Respiratory symptoms in school-age preterm-born children are often inappropriately labelled as asthma; however, the underlying mechanisms are likely to be different to those in asthma. Previous studies⁴³ have suggested that studying BHR by both direct and

TABLE 1 (a) Characteristics of the studies using direct bronchial provocation tests; (b) Characteristics of the studies using indirect bronchial provocation tests

(a) Study	Year of publication	Type of study	Prematurity	Age range	Sample size	Method used	Effect of intervention	Quality score
Todisco ³⁸	1993	Unselected population Retrospective	34–36 wk	8–15 y	34 preterms 34 terms	Methacholine	BHR (bronchial hyper-responsiveness) preterms 4/34 BHR terms 2/34	14
Schraeder ¹⁶	1998	Prospective longitudinal study of development	Birthweight ≤1500 g	10–11 y	28 VLBW 42 NBW	Methacholine	BHR VLBW 17/28 BHR NBW 23/42	15
Rona ³⁹	2005	Nonconcurrent prospective study	Not stated <37 wk	Not stated	1232 subjects in total approx. 10% <37 wk	Methacholine	Increased OR of a positive BHR response with a gestation of <37 wk, not statistically significantly	15
Lum ¹⁷	2011	Population-based study Prospective	≤25 wk +6	11 y	49 preterms 52 terms	Methacholine	Airway hyper-responsiveness abnormalities were most marked in EP with BPD	17
Korhonen ¹⁸	2004	Cohort Prospective	23–35 wk	7–8 y	54 preterms 30 terms	Methacholine	BHR preterms 43/54 BHR terms 14/30	16
Galdes-Sebaldt ¹⁹	1989	Cross-sectional Retrospective	26–32 wk mixed group <39 wk	10–13 y	41 preterms 22 terms	Methacholine	VLBW preterm subjects had significantly higher rates of BHR than terms	12
Kotecha ²⁰	2011	Population-based cohort Prospective	25–36 wk	8–9 y	238 preterms 4123 terms	Methacholine	BHR preterms 40/238 BHR terms 646/4123	15
Landry ²¹	2016	Cross-sectional study Retrospective	<37 wk	21–22 y	76 preterms 33 terms	Methacholine	BHR preterms 51/76 BHR terms 15/33	13
Ijsselstijn ²²	1997	Matched study Retrospective	29–36 wk	7–18 y	18 preterms 38 terms	Methacholine	BHR preterms 5/18 BHR terms 17/38	13
Pike ²³	2014	Human mother-child cohort Prospective	<37 wk	6–7 y	246 children in total	Methacholine	Term-born children with lower abdominal growth had a significantly higher rate of BHR but preterm-born children did not.	14
Halvorsen ²⁴	2005	Population-based cohort Prospective	≤28 wk or birthweight ≤1000 g	First cohort mean 17.7 SD 1.2 y Second cohort mean 10.6 SD 0.4 y	74 preterms 79 terms	Methacholine	Airway hyper-responsiveness was substantially increased in the preterms compared to the terms.	15
Vollsaeter ²⁵	2015	Population-based cohort Prospective	<28 wk or birthweight <1000 g	Preterms mean 11.4 SD 0.6	57 preterms 54 terms	Methacholine	Preterms had more BHR than terms	15
Halvorsen ²⁶	2004	Population-based cohort Prospective	≤28 wk or birthweight ≤1000 g	Mean 17.7 y SD 1.2	41 preterms 46 preterms	Methacholine	BHR preterms 23/41 BHR terms 12/46	15

(Continues)

TABLE 1 (Continued)

(a) Study	Year of publication	Type of study	Prematurity	Age range	Sample size	Method used	Effect of intervention	Quality score
Kaplan ²⁷	2012	Cohort Retrospective	≤28 wk	Mean age 9-10 y	43 preterms 23 terms	Methacholine	BHR preterms 21/43 BHR terms 5/23	14
(b) Study								
Ronkainen ²⁸	2015	Prospective birth cohort	<32 wk	6-14 y	87 preterms 88 terms	Exercise	BHR preterms 2/87 BHR terms 3/88	15
Mitchell ²⁹	1998	Cross-sectional Retrospective	BPD mean 30 SD 5 Non-BPD mean 31 SD 3	6-9 y	20 preterms 10 terms	Exercise	Exercise induced bronchospasm though statistically significant was mild for preterms.	11
McLeod ³⁰	1996	Population-based cohort Prospective	VLBW <1500 g	8-9 y	300 VLBW 590 terms	Exercise	BHR VLBW 30/300 BHR terms 31/590	15
Kriemler ³¹	2005	Cohort Prospective	24-30 wk	5-7 y	28 preterms 23 terms	Exercise	BHR preterms 14/28 BHR terms 5/23	13
Hamon ³²	2013	Cohort Prospective	<32 wk	7 y	42 preterms 27 terms	Exercise	BHR preterms 10/42 BHR terms 0/27	15
Gross ³³	1998	Cohort Prospective	<32 wk	7 y	96 preterms 108 terms	Exercise	After exercise FEV ₁ was abnormal more often in the preterms compared to terms.	18
Barker ³⁴	2003	Cross-sectional cohort Retrospective	28-36 wk	8-14 y	26 preterms 13 terms	Exercise	BHR preterms 4/26 BHR terms 0/13	16
Bader ³⁵	1987	Cohort Retrospective	26-32 wk	7-12 y	10 preterms 8 terms	Exercise	BHR preterms 5/10 BHR terms 0/8	12
Joshi ³⁶	2014	Cross-sectional Retrospective	≤32 wk	8-12 y	49 preterms 26 terms	Exercise	CLD (chronic lung disease) group had significant EIB	9
Abreu ³⁷	2007	Cohort Retrospective	28-36 wk	7-10 y	23 preterms 17 terms	Exercise	BHR preterms 3/23 BHR terms 0/17	14
Siltanen ⁴⁰	2004	Cohort Retrospective	23-33 wk	9-10 y	72 preterms 65 terms	Exercise	Changes in lung function after exercise were not significantly different.	13
Santuz ⁴¹	1995	Control study Retrospective	27-32 wk	6-12 y	12 preterms 16 terms	Exercise	BHR preterms 2/12 BHR terms 0/16	11
Mai ⁴²	2003	Cohort Prospective	25-36 wk	12 years	68 preterms 59 terms	Hypertonic saline provocation test	BHR preterms 22/68 BHR terms 18/59	13
Von Mutius ¹⁵	1993	Population study Retrospective	Not stated <37 wk	9-11 y	118 preterms 2113 terms	Cold air challenge	BHR preterms 7/118 BHR terms 133/2113	12

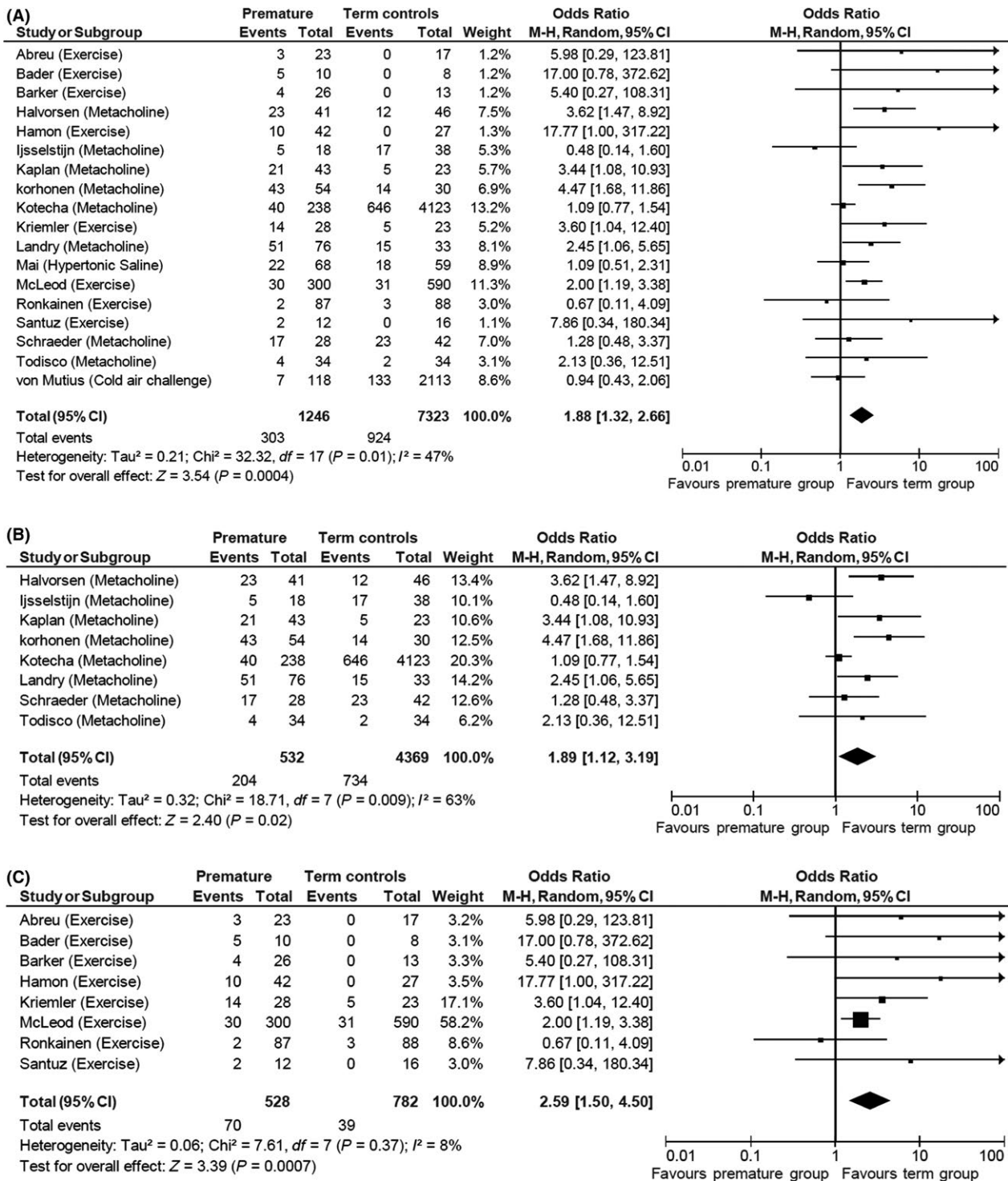


FIGURE 2 A, Number of subjects with bronchial hyper-responsiveness (BHR) in the premature group compared with term control group. B, Number of subjects with BHR after a methacholine challenge in the premature group compared with term control group. C, Number of subjects with BHR after an exercise test in the premature group compared with term control group

indirect means may help elucidate the underlying mechanisms and aid targeted therapy, for example anti-inflammatory or smooth muscle relaxants. However, despite the various methods used in the meta-analyses and descriptive analyses, the collated results strongly suggest that BHR is more prevalent in preterm-born group

compared to term-born subjects, especially in those who had CLD—a finding similar to those with asthma.

As different mechanisms may potentially be identified using direct (assessing smooth muscle phenotypes and responses) and indirect methods (pathways of inflammatory mediators), to assess

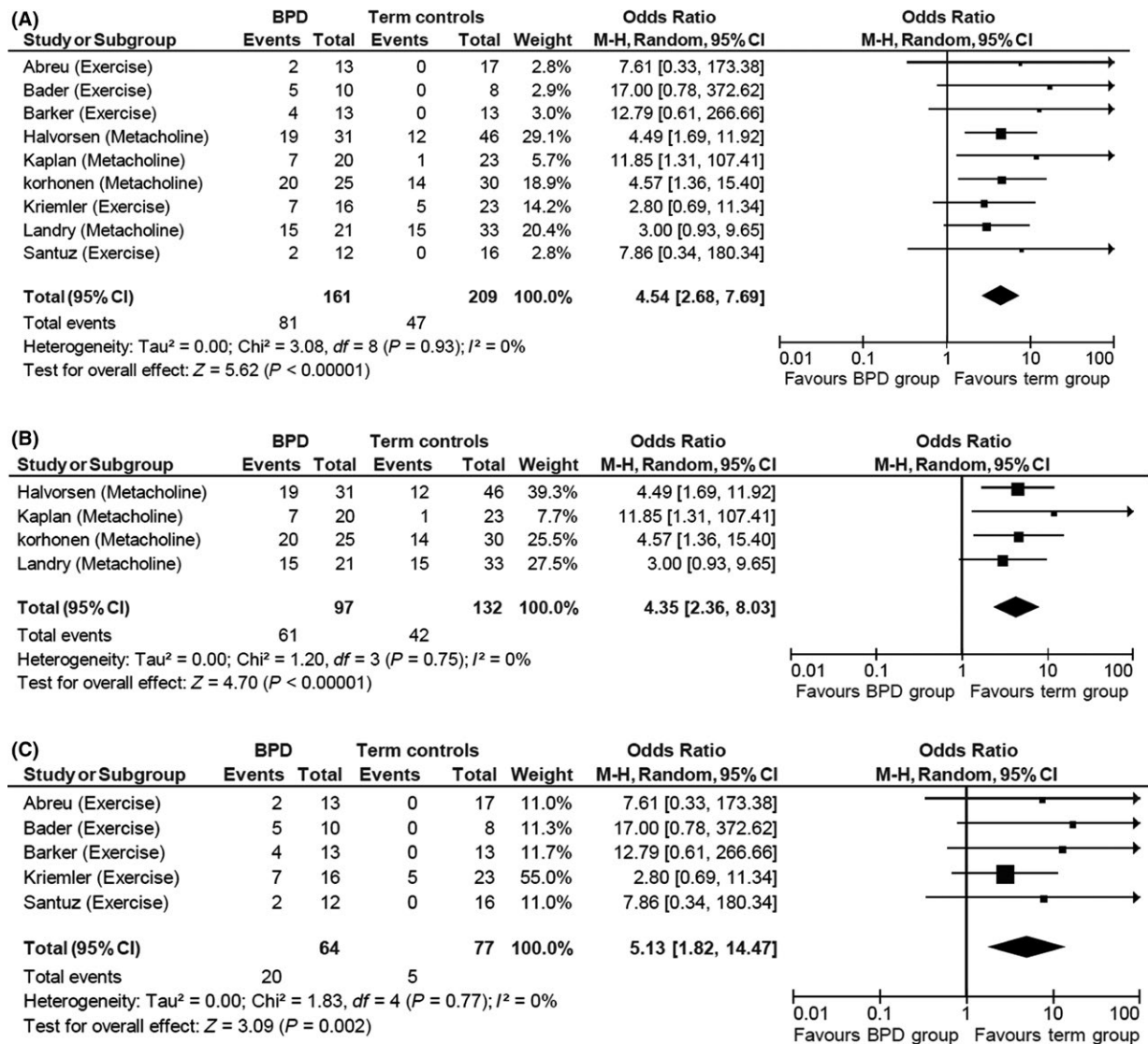


FIGURE 3 A, Number of subjects with bronchial hyper-responsiveness (BHR) in the premature group who had chronic lung disease (CLD) in infancy compared with term control group. B, Number of subjects with BHR after a methacholine challenge in the premature group who had CLD in infancy compared with term control group. C, Number of subjects with BHR after an exercise test in the premature group who had CLD in infancy compared with term control group

BHR,⁹ we classified the studies using direct and indirect means to assess BHR. This is an important distinction to make as there is a suggestion that BHR responses may be different in asthma and in lung disease of preterm-born children: Kim et al⁴³ reported children with asthma responded to both methacholine and adenosine 5'-monophosphate but children with CLD only responded to the methacholine suggesting that continuing inflammation may not be a factor in preterm-born subjects. Methacholine is a direct method of assessing BHR by assessing bronchial smooth muscle response, and adenosine 5'-monophosphate is an indirect method of assessing BHR by pathways of inflammatory mediator release from airway mast cells. Therefore, as children with CLD only responded to the direct method, not indirect methods, it is possible inflammation may not be a factor in BHR of the CLD subjects in the study by Kim et al. This is clearly contradictory to two studies

which reported increased neutrophilic inflammation in induced sputum and increased oxidant activity in exhaled breath condensate from children with CLD.^{7,8} The results, however, are in agreement with reports of low exhaled nitric oxide in children with CLD.⁴⁴

Interestingly, separating the data on whether a direct or indirect method was used showed that both methods resulted in increased BHR in preterm-born subjects including the CLD group despite smaller numbers available for inclusion. Historically, it has been shown at autopsy that airway smooth muscle is both thicker and extends further down the airways in preterm subjects especially those dying from CLD when compared to matched term controls.^{5,6} However, what happens in the current cohorts of survivors can only be speculative. Our data suggest that preterm-born subjects have increased responses to direct stimuli suggesting that treatment with

bronchodilators may be successful. Our previous systematic review confirmed responses to single doses of bronchodilators but longer term studies of bronchodilators in this group are lacking.¹¹ Currently, treatment is variable with individual clinicians forming their own opinions based on limited data. The situation is further complicated as the smooth muscle phenotype may initially respond to bronchodilators but there is speculation that these cells may develop a more fixed unresponsive myofibroblast phenotype which may not respond to bronchodilator treatment.⁴⁵

Our data also showed that exercise also resulted in convincing differences between the preterm groups when compared to term controls. Two small studies show that (neutrophilic) airway inflammation and oxidant injury may be continuing in childhood in preterm airway disease but replication of these studies in larger numbers is required.^{7,8} The evidence for the efficacy of inhaled corticosteroids in lung disease of preterm-born survivors is also limited, although, taken together with our data, there is a suggestion that subgroups of preterm-born subjects may benefit from inhaled corticosteroids, although they may not be effective if neutrophilic inflammation is confirmed. Role of targeting the leukotriene pathway is also poorly studied in preterm-born children with lung disease. Appropriate studies to evaluate the efficacy of both bronchodilators and inhaled corticosteroids are urgently required.

The preterm group with and without CLD has increased BHR to both direct and indirect but we were not able to assess if both were present in the same individuals. Besides the study by Kim et al⁴³ (who assessed BHR by auscultation and oximetry), the study by Nikolajev and colleagues of moderately preterm-born children (mean gestation of 35 weeks) reported overlap between exercise, methacholine and cold air challenges as well as with responses to bronchodilators.⁴⁶ It is likely that preterm-born subjects have either structural abnormalities or airway inflammation or both, but the relevant studies to confirm or refute either are currently lacking.

5 | LIMITATIONS

As with all systematic reviews, we were limited by the data in included articles. The majority of articles examined BHR as part of a wider range of lung function tests, and there was disparity in the articles. Interpreting the results was complex as the articles reported a range of methods used to test BHR. Variable inclusion criteria and agents—both pharmacological and physiological—were used to assess and report BHR outcomes which included induction of wheeze, changes in spirometry and changes in oxygen saturation. Even when a change in FEV₁ was used, the definitions of a positive response varied. A number of articles were excluded as they not only defined BHR after testing with a provocative agent/test, but they also included data on subjects with a low FEV₁ who had responded to an inhaled bronchodilator. In addition, articles reporting BHR in preterm-born subjects without a term-born control group and articles with preterm and term-born subjects combined in the results were excluded. Variable criteria were used to define

CLD in articles included in the meta-analyses. We ideally would have liked to further analysis the CLD group by dividing the group into two: (a) CLD defined as a requirement for supplemental oxygen at ≥ 28 postnatal days and (b) CLD defined as a requirement for supplemental oxygen at ≥ 36 weeks postmenstrual age. However, the small number of subjects in the articles with the later definition meant this was not possible. Additionally, the subjects were born at a wide range of gestational ages over a number of decades when medical management has progressed—whether BHR is affected by the survival of the extremely preterm babies is unclear.

6 | CONCLUSIONS

This is the first comprehensive systematic review and meta-analysis which collated and reported the effect of preterm birth on later BHR. Suggesting an increased rate of BHR in preterm-born subjects compared to term-born subjects, differences were greatest for subjects who had CLD. Both direct (methacholine challenge) and indirect (exercise) challenges resulted in increased BHR suggesting that subgroups of preterm-born subjects could potentially benefit from anti-inflammatory and/or bronchodilator therapies.

ACKNOWLEDGMENTS

We are very grateful to all the authors who supplied additional data.

CONFLICT OF INTEREST

TH, HHC and SJK report no conflict of interest. SK reports funding from MRC (MR/M022552/1) for this submitted work; and grants from NIHR (16/111/106), Welsh Government, and EU FP7 outside of this submitted work.

AUTHOR CONTRIBUTION

SJK, SK, HC and TH substantially contributed to the conception, design of the work, and the acquisition, analysis and interpretation of data. SJK and SK wrote the first draft of the manuscript which all the authors revised critically for important intellectual content. All authors approved the final version and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Kotecha S, Clemm H, Halvorsen T, Kotecha SJ. Bronchial hyper-responsiveness in preterm-born subjects: A systematic review and meta-analysis. *Pediatr Allergy Immunol*. 2018;29:715-725.
<https://doi.org/10.1111/pai.12957>