INTRODUCTION

Preterm birth is associated with increased respiratory symptoms and decreased lung function. However, whilst it is often stated that these adverse events result from birth at an early stage of lung development 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
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). Alternatively, there are limited data suggesting that an active pro-inflammatory neutrophilic status and oxidant process may be continuing.

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. 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. 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. 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 subjects; (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. 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. 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-eight met the inclusion criteria.
criteria (Figure 1). For the two studies that overlapped\textsuperscript{24,26} the one reporting BHR as a proportion of responders\textsuperscript{26} 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,\textsuperscript{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) preterm- born subjects.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsubscript{20}<4 mg/mL) and CLD (PC\textsubscript{20}<1 mg/mL) groups to define a positive BHR response.\textsuperscript{27}

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

Ten articles were not included in the meta-analysis.\textsuperscript{17,19,23-26,29,33,36,39,40} Six articles reported BHR after a methacholine challenge.\textsuperscript{17,19,23-26,39} and four articles reported after an exercise test.\textsuperscript{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 studies\textsuperscript{43} have suggested that studying BHR by both direct and
| Study             | Year of publication | Type of study | Prematurity        | Age range | Sample size | Method used | Effect of intervention                                                                 | Quality score |
|-------------------|---------------------|---------------|--------------------|-----------|-------------|------------|---------------------------------------------------------------------------------------|--------------|
| Todisco          | 1993                | Unselected population Prospective | 34-36 wk           | 8-15 y    | 34 preterms 34 terms | Methacholine | BHR (bronchial hyper-responsiveness) preterms 4/34 BHR terms 2/34                    | 14           |
| Schraeder        | 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             | 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              | 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         | 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   | 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          | 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           | 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      | 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             | 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        | 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       | 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        | 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)
| Study | Year of publication | Type of study | Prematurity | Age range | Sample size | Method used | Effect of intervention | Quality score |
|-------|---------------------|---------------|-------------|-----------|-------------|-------------|------------------------|---------------|
| (a)   |                     |               |             |           |             |             |                        |               |
| Kaplan | 2012               | Cohort Retrospective | ≤28 wk     | Mean age 9-10 y | 43 preterms 23 terms | Methacholine | BHR preterms 21/43 BHR terms 5/23 | 14            |
| Ronkainen | 2015             | Prospective birth cohort | <32 wk     | 6-14 y | 87 preterms 88 terms | Exercise | BHR preterms 2/87 BHR terms 3/88 | 15            |
| Mitchell | 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 | 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 | 2005            | Cohort Prospective | 24-30 wk | 5-7 y | 28 preterms 23 terms | Exercise | BHR preterms 14/28 BHR terms 5/23 | 13            |
| Hamon | 2013              | Cohort Prospective | <32 wk     | 7 y     | 42 preterms 27 terms | Exercise | BHR preterms 10/42 BHR terms 0/27 | 15            |
| Gross | 1998              | Cohort Prospective | <32 wk     | 7 y     | 96 preterms 108 terms | Exercise | After exercise FEV1 was abnormal more often in the preterms compared to terms. | 18            |
| Barker | 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 | 1987              | Cohort Retrospective | 26-32 wk | 7-12 y | 10 preterms 8 terms | Exercise | BHR preterms 5/10 BHR terms 0/8 | 12            |
| Joshi | 2014              | Cross-sectional Retrospective | ≤32 wk     | 8-12 y | 49 preterms 26 terms | Exercise | CLD (chronic lung disease) group had significant EIB | 9             |
| Abreu | 2007              | Cohort Retrospective | 28-36 wk | 7-10 y | 23 preterms 17 terms | Exercise | BHR preterms 3/23 BHR terms 0/17 | 14            |
| Siltanen | 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 | 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 | 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 | 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            |
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 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.
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 al. 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. The results, however, are in agreement with reports of low exhaled nitric oxide in children with CLD.

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. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 al\textsuperscript{23} (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.\textsuperscript{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 FEV\textsubscript{1} of wheeze, changes in spirometry and changes in oxygen saturation were used to assess and report BHR outcomes which included induction of wheeze, changes in spirometry and changes in oxygen saturation are 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.

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CONFLICT OF INTEREST

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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.

ORCID

Sarah J. Kotecha http://orcid.org/0000-0001-5640-0300

REFERENCES

1. Edwards MO, Kotecha SJ, Lowe J, Richards L, Watkins WJ, Kotecha S. Management of prematurity-associated wheeze and its association with atopy. PloS One. 2016;11:e0155695.
2. Been JV, Lugtenberg MJ, Smets E, et al. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. *Pediatrics*. 2014;134(5):e1001596.

3. Kotecha SJ, Edwards MO, Watkins WJ, et al. Effect of preterm birth on later FEV1: a systematic review and meta-analysis. *Thorax*. 2013;68:760-766.

4. Joshi S, Kotecha S. Lung growth and development. *Early Hum Dev*. 2007;83:789-794.

5. Tiddens HA, Hofhuis W, Casotti V, Hop WC, Hulsmann AR, et al. Changes in pulmonary circulation in severe bronchopulmonary dysplasia. *Arch Dis Child*. 1990;65:739-745.

6. Teig N, Allali M, Rieger C, Hamelmann E. Inflammatory markers in induced spum of school children born before 32 completed weeks of gestation. *J Pediatr*. 2012;161:1085-1090.

7. Filippone M, Bonetto G, Corradi M, Frigo AC, Baraldi E. Evidence of unexpected oxidative stress in airways of adolescents born very preterm. *Eur Respir J*. 2012;40:1253-1259.

8. Clemm HH, Engeseth M, Vollsaeter M, Kotecha S. Bronchial hyper-responsiveness after preterm birth. *Paediatr Respir Rev*. 2016;26:34-40.

9. Lien JI, Kozyrskyj AL, Cockroft DW, Becker AB. Diagnosing asthma in children: what is the role for methacholine bronchoprovocation testing? *Pediatr Pulmonol*. 2008;43:481-489.

10. Kotecha SJ, Edwards MO, Watkins WJ, Lowe J, Henderson AJ, Kotecha S. Effect of bronchodilators on forced expiratory volume. *J Pediatr Pulmonol*. 2018;50:293-301.

11. Zysman-Colman Z, Tremblay GM, Bandeali S, Landry JS. Bronchopulmonary dystasia - trends over three decades. *Paediatr Child Health*. 2013;18:86-90.

12. Bolton CE, Bush A, Hurst JR, et al. Are early life factors considered when managing respiratory disease? a British Thoracic Society survey of current practice. *Thorax*. 2012;67:1110.

13. Korhonen P, Laitinen J, Hyodynnmaa E, Tammela O. Respiratory outcome in school-aged, very-low-birth-weight survivors of very-low-birth-weight. *Clin Pediatr*. 1998;37:237-245.

14. Lum S, Kirkby J, Welsh L, Marlow N, Hennessy E, Stocks J. Nature and severity of lung function abnormalities in extremely preterm children at 11 years of age. *Eur Respir J*. 2011;37:1199-1207.

15. Kotecha SJ, Watkins WJ, Paranjothy S, Dunstan FD, Henderson AJ, Kotecha S. Effect of late preterm birth on longitudinal lung spirometry in school age children and adolescents. *Thorax*. 2012;67:54-61.

16. Landry JS, Tremblay GM, Li PZ, Wong C, Benedetti A, Taivassalo T. Lung function and bronchial hyperresponsiveness in adults born prematurely. A cohort study. *Ann Am Thorac Soc*. 2016;13:17-24.

17. Illeslétin H, Tiboold D, Hop WJC, Molenaar JC, de Jongste JC. Long-term pulmonary sequelae in children with congenital diaphragmatic hernia. *Am J Respir Crit Care Med*. 1997;155:174-180.
43. Kim DK, Choi SH, Yu J, Yoo Y, Kim B, Koh YY. Bronchial responsiveness to methacholine and adenosine 5′-monophosphate in preschool children with bronchopulmonary dysplasia. Pediatr Pulmonol. 2006;41:538-543.

44. Baraldi E, Bonetto G, Zacchello F, Filippone M. Low exhaled nitric oxide in school-age children with bronchopulmonary dysplasia and airflow limitation. Am J Respir Crit Care Med. 2005;171:68-72.

45. Pandya HC, Kotecha S. Chronic lung disease of prematurity: clinical and pathophysiological correlates. Monaldi Arch Chest Dis. 2001;56:270-275.

46. Nikolajev K, Korppi M, Koskela H, et al. Methacholine, cold air and exercise challenge tests in the diagnosis of bronchial responsiveness at school age: a follow-up study from birth to school age. Allergol Int. 2002;51:131-138.

SUPPORTING INFORMATION

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

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