

The Bronchodilator Response in Preschool Children: A Systematic Review

Emma Raywood, MSc,¹ Sooky Lum, PhD,¹ Paul Aurora, PhD,^{1,2} and Katharine Pike, PhD^{1,2*}

Summary. Background: The bronchodilator response (BDR) is frequently used to support diagnostic and therapeutic decision-making for children who wheeze. However, there is little evidence-based guidance describing the role of BDR testing in preschool children and it is unclear whether published cut-off values, which are derived from adult data, can be applied to this population. Methods: We searched MEDLINE, EMBASE, Web of Science, and Cochrane databases (inception–September 2015) for studies reporting response to a bronchodilator in healthy preschool children, response following placebo inhalation, and the diagnostic efficacy of BDR compared with a clinical diagnosis of asthma/recurrent wheezing. Findings: We included 14 studies. Thirteen studies provided BDR data from healthy preschool children. Two studies reported response to placebo in preschool children with asthma/recurrent wheezing. Twelve studies compared BDR measurements from preschool children with asthma/recurrent wheeze to those from healthy children and seven of these studies reported diagnostic efficacy. Significant differences between the BDR measured in healthy preschool children compared with that in children with asthma/recurrent wheeze were demonstrated in some, but not all studies. Techniques such as interrupter resistance, oscillometry, and plethysmography were more consistently successfully completed than spirometry. Between study heterogeneity precluded determination of an optimum technique. Interpretation: There is little evidence to suggest spirometry-based BDR can be used in the clinical assessment of preschool children who wheeze. Further evaluation of simple alternative techniques is required. Future studies should recruit children in whom airways disease is suspected and should evaluate the ability of BDR testing to predict treatment response. *Pediatr Pulmonol.* 2016;51:1242–1250. © 2016 Wiley Periodicals, Inc.

Key words: pulmonary function testing (PFT); asthma and early wheeze; bronchodilator response; spirometry; preschool child.

INTRODUCTION

In school-aged children and adults asthma is diagnosed clinically using patient history and objective investigations which include respiratory function testing.¹ In adults and older children the bronchodilator response (BDR) can be used to quantify reversible airways obstruction and to support diagnostic and therapeutic decision-making. ERS guidelines for adult patients recommend that an increase in forced expiratory volume in the first second of expiration (FEV₁) of 200 ml and 12% of the baseline value represents a positive BDR test.¹ More recently, a guideline for asthma diagnosis and management has been proposed; this endorsed these cut-offs but found no evidence against which to assess their use in children.² No guidance at all was provided relating

¹Respiratory, Critical Care and Anaesthesia Section, University College London Institute of Child Health, 30 Guilford Street, London WC1N 1EH, United Kingdom.

²Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom.

*Correspondence to: Katharine Pike, PhD, Respiratory, Critical Care and Anaesthesia Section, University College London Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK. E-mail: k.pike@ucl.ac.uk

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to objective testing of preschool-aged children, (normally 2–5 years of age inclusive).

It is unlikely that adult guidelines can be applied to preschool-aged children. A cut-off based upon absolute increase in FEV₁ does not account for changes in lung size with growth. Similarly, while expressing the increase as a percentage of baseline might adjust for lung size,^{1,2} it remains unclear whether percentage cut-offs derived from adult data can be applied to preschool children. Finally, difficulties associated with technique and cooperation are likely to limit the accuracy and repeatability of spirometry-based BDR testing in young children.³ Alternative techniques have been developed and the American and European Respiratory Societies have published a position statement on preschool lung function testing.⁴ This was based upon literature published before 2007, it offered little guidance on the best method to measure and express BDR in preschool children and did not present definitive cut-off values.

This review sought to systematically assess studies relating to BDR determination in preschool children, including those published since the ATS/ERS statement. First, to determine a clinically meaningful and significant response to bronchodilator we reviewed studies describing the magnitude of BDR in healthy preschool children or change in lung function following placebo inhalation in preschool children with wheezing disorders. Second, we reviewed studies assessing the ability of the BDR to discriminate healthy preschool children from those with asthma or recurrent wheezing. Finally, we considered the optimal means of measuring and expressing BDR in preschool children.

METHODS

This review was conducted according to a prospectively designed protocol (online supplementary material).

Search Strategy

Potentially eligible studies were identified from MEDLINE, EMBASE, Web of Science, and the Cochrane Database. Searches were built to identify all English language studies referencing bronchodilator response or a variant or abbreviation of this in the title or abstract. Studies were limited to those conducted in humans and preschool-aged participants. Searches were run from the inception of each database until September 25, 2015. Additional studies were identified by manually checking the citations of each study selected for inclusion.

Study Selection

Studies of preschool children were included if they presented numerical data describing either BDR in healthy children alone or comparing this with BDR

in children with asthma or recurrent wheeze. Eligible studies included those measuring either response to bronchodilator in healthy control children, or change in lung function following placebo inhalation in children with asthma or recurrent wheeze. Where possible the clinically significant or meaningful bronchodilator response cut-off was calculated. The method of Sourk and Nugent was used to calculate a cut-off which included only the greatest 5% of responses found in healthy preschool children.⁵ To assess diagnostic efficacy, studies comparing the response to bronchodilator in preschool children with asthma or recurrent wheeze to that in those without were identified. All methods of measuring and expressing the bronchodilator response were permitted. Piloting the inclusion criteria revealed that many studies were not strictly limited to children conventionally considered of preschool age. Studies were included if no participant was aged 7 years or older and at least two thirds of the participants were 2 years of age or older but younger than 6 years. Studies displaying data from preschool-aged children separately from data from older individuals were also eligible for inclusion. To reduce the influence of outliers upon BDR cut-off, studies were also excluded if the number of participants per group was low (<20). Modified QUADAS-2 criteria were used to assess study quality⁶ (Table S1). Following current recommendations, formal scores were not assigned but a subjective assessment made and summarized.⁷

Data Synthesis

Considerable heterogeneity was expected with respect to participants' diagnoses and included studies' choice of physiological parameters, BDR protocol and method of BDR expression. For this reason, no meta-analyses were planned. However, where possible the results of studies of comparable physiological parameters were compared. For simplicity, where multiple means of expression were employed, comparisons were made using BDR expressed as percentage change in lung function relative to baseline since this mode of expression is recommended in ERS guidelines and we wished to assess the applicability of this guideline to the preschool population.¹

RESULTS

Study Selection and Quality

After excluding duplicates, 254 studies were screened, 22 full papers assessed and fourteen selected for inclusion (Fig. 1 and Table 1). One study measured BDR in healthy preschool children only,⁸ 12 provided BDR data from healthy children alongside measurements from children with asthma or recurrent wheeze, 12 compared BDR in preschool children with asthma or recurrent wheeze to

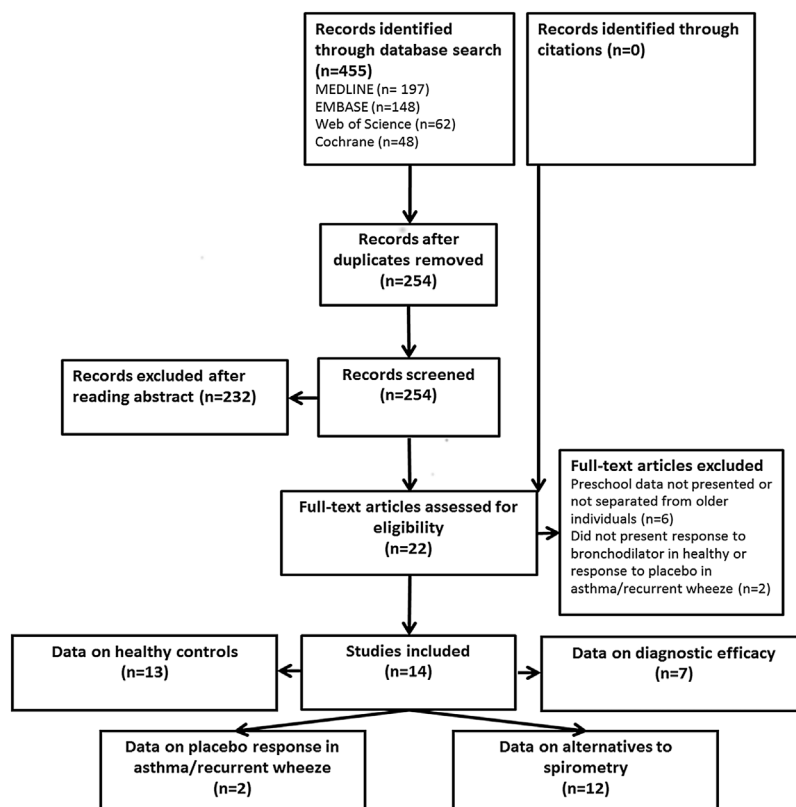


Fig. 1. PRISMA flow diagram.

that in those without, and seven reported diagnostic sensitivity and specificity. Two studies measured change in lung function following placebo inhalation in children with asthma or recurrent wheeze^{9,10} (Table 1). Using modified QUADAS-2 criteria study quality was moderate (Table S2). However, few studies stated whether the BDR test was applied independently of the reference standard, not all studies followed the ERS protocol completely, and many selected a threshold to maximize sensitivity and specificity in the study population.^{11–14} BDR was not tested in every participant in every study, younger and healthy children were less likely to complete testing.⁸ Most studies reporting diagnostic efficacy, rather than apply the BDR test to individuals under investigation for wheezing disorders, used a case-control design, comparing the BDR measured in preschool children with asthma or recurrent wheeze to that in healthy children.

Spirometry BDR in Healthy Preschool Children

The largest study of BDR in preschool children without asthma presented data from 42 children. These children although currently healthy were at high risk of asthma due to previous wheeze.¹⁵ Three smaller studies included 30 children or fewer (Table 2).^{9,11,14} In one only seven of the 30 participants achieved an expiratory time greater than 1 sec.¹¹ Shin et al. selected children for testing based upon

ability to complete the testing protocol.¹⁴ In the remaining studies success ranged from 23% to 95%,^{9,11,15} and within studies success rates increased with age.⁹ No study reported an upper 95% confidence limit for healthy preschool children. This could be calculated as 19% and 13%, respectively from Borrego et al. and Shin et al. data (Table 2). Two studies reported change in $FEF_{0.75}$ following bronchodilator (calculated upper 95% confidence limits both 15%)^{9,14} and two reported change in $FEV_{0.5}$ (calculated upper 95% confidence limits 22% and 20%).^{11,14}

Spirometry Response After Placebo Inhalation in Preschool Children With Asthma

Borrego et al. reported percentage change relative to baseline following placebo inhalation for 43 preschool children with mild-moderate doctor-diagnosed asthma.⁹ The mean (SD) reported changes for FEV_1 and $FEV_{0.75}$ were 2.6% (7.5%) and 2.1% (5.2%), equating to upper 95% confidence limit cut-offs of 18% and 13%, respectively (Table 2).

Ability of Spirometry BDR to Identify Children With Asthma or Recurrent Wheeze

Four studies reported spirometry BDR data from both healthy preschool children and those with asthma or

TABLE 1—Summary of Included Studies

Publication	Population: control	Population: asthma/recurrent wheeze	Lung function technique and BDR protocol	Reported data on			
				Healthy BDR	Placebo response	Diagnostic efficacy	Alternatives to spirometry
Hellinckx et al. ²⁰ ; Belgium	228 kindergarten pupils mean (range) 4.5 (2.7–6.6) years: questionnaire screened no asthma (based on symptom and previous diagnosis)	25 kindergarten pupils 2.7–6.6 years: questionnaire determined asthma (mild)	IOS before and 20 min after 200 µcg salbutamol MDI + spacer	✓			✓
McKenzie et al. ¹² ; UK	48 outpatients 3.8 ± 0.72 years: no history of wheeze or cough	82 outpatients 3.6 ± 0.86 years: doctor-diagnosed past wheeze no symptoms in last month or asthma therapy ever	Interrupter resistance before and after 400 µcg salbutamol MDI + spacer	✓		✓	✓
Nielsen et al. ¹³ ; Denmark	37 children recruited by postal health questionnaire 3.8 ± 1.0 years: no lung illness, tobacco smoke exposure or family atopy	55 outpatients 4.6 ± 1.0 years: doctor-diagnosed asthma no current symptoms	Plethysmography Interrupter resistance and IOS before and 20 min after 500 µcg terbutaline MDI + spacer	✓		✓	✓
Marotta et al. ¹⁵ ; US	45 cohort participants mean (range) 4 (4.1–5) years: questionnaire screened without asthma but high asthma risk due to previous wheeze no preterms	28 cohort participants mean (range) 4 (4.1–5) years: with asthma no preterms questionnaire determined asthma	IOS and spirometry before and 15 min after 2.5 mg salbutamol nebuliser	✓		✓	✓
Olaguibel et al. ¹⁰ ; Spain		33 outpatients median (IQR) 5, (3–6) years: doctor-diagnosed asthma	IOS before and 15 min after placebo and Spirometry, IOS and plethysmography 15 min after 400 µcg salbutamol MDI + spacer		✓		✓
Thamrin et al. ¹⁷ ; Australia	78 healthy children from previous research protocols median (10th, 90th percentiles) 5 (4.2–5.2) years: no asthma or wheeze	56 children under clinical follow-up (10th, 90th percentiles) 5.1 (3.9–6.7) years: doctor-diagnosed asthma	FOT before and 15 min after 600 µcg salbutamol MDI + spacer	✓			✓
Song et al. ²¹ ; Korea	55 outpatients 4.9 ± 0.1 years: no allergic or inflammatory disease	77 outpatients 5.1 ± 0.1 years: doctor-diagnosed asthma	IOS and spirometry (Raw spirometry data not presented) before and 15 min after 200 µcg salbutamol MDI + spacer (spirometry conducted data not reported)	✓			✓
Calogero et al. ⁸ ; Italy	154 kindergarten pupils median (range) 4.8 (2.9–6.1) years: no preterms, asthma, recent or recurrent wheeze		FOT before and 15 min after 200 µcg salbutamol MDI + spacer	✓			✓
Mele et al. ¹⁶ ; Italy	60 children 5.4 ± 1.0 years: from kindergartens or surgical outpatients no recent or recurrent wheeze	60 children 4.4 ± 0.7 years: recent recurrent wheeze currently symptomatic	Interrupter resistance before and 15 min after 200 µcg salbutamol MDI + spacer	✓		✓	✓
Oostveen et al. ¹⁹ ; Belgium	144 cohort study participants 4.4 ± 0.2 years: questionnaire screened never wheeze	54 cohort study participants 4.4 ± 0.2 years: questionnaire identified recurrent wheeze	FOT before and 15 min after 200 µcg salbutamol MDI + spacer	✓		✓	✓
Shin et al. ¹⁴ ; Korea	29 kindergarten pupils 4.6 ± 0.3 years: ISAAC questionnaire screened no asthma, atopy or wheeze	30 outpatients 4.6 ± 0.4 years: doctor-diagnosed asthma	Spirometry and IOS before and 15 min after 400 µcg salbutamol MDI + spacer	✓		✓	✓
Simpson et al. ¹⁸ ; Australia	78 children from previous research protocols mean (95%CI) 4.9 (4.8–5.0) years: no asthma or wheeze	56 children under clinical follow-up mean (95%CI) 5.3 (5.0–5.6) years: doctor-diagnosed asthma	FOT before and 15 min after 600 µcg salbutamol MDI + spacer	✓			✓

Continued

TABLE 1—(Continued)

Publication	Population: control	Population: asthma/recurrent wheeze	Lung function technique and BDR protocol	Reported data on			
				Healthy BDR	Placebo response	Diagnostic efficacy	Alternatives to spirometry
Borrego et al. ⁹ ; Portugal	22 children from local health clinics 5.1 ± 0.9 years: no preterms, IUGR, wheeze, lower respiratory illness, allergic disorder or parental asthma	43 outpatients 5.1 ± 0.8 years: doctor-diagnosed asthma (mild-mod)	Spirometry before and 20 min after 400 µcg salbutamol/placebo MDI + spacer	✓	✓		
Passerini et al. ¹¹ ; Chile	30 children selected randomly from day care centres mean (range) 4.1 (3.0–5.6) years: questionnaire screened no asthma (matched to asthma participants)	61 children mean (range) 4 (3.0–5.9) years: moderate/severe doctor-diagnosed persistent asthma	Spirometry before and after 200 µcg salbutamol MDI + spacer (FEV ₁ data from 7 children only)	✓		✓	

FOT, forced oscillation technique; IOS, impulse oscillometry system; IUGR, intrauterine growth retardation; MDI, metered dose inhaler. Ages mean ± SD unless otherwise stated.

recurrent wheeze,^{9,11,14,15} although one included only seven healthy children with successful FEV₁ measurements¹¹ (Table S4). BDR protocol, diagnostic criteria, asthma severity, and treatment level varied between studies. No study measured diagnostic sensitivity and

specificity for spirometry-based BDR in preschool children with respiratory symptoms potentially attributable to asthma. However Marotta et al. measured BDR in children at high risk of asthma due to previous wheeze. No significant difference between those with and without

TABLE 2—Cut-Off Values for Meaningful FEV₁ BDR^a

Publication	Population	BDR protocol	Reported BDR	95% upper confidence limit
Cut-off calculated from response to bronchodilator in healthy preschool children				
Shin et al. ¹⁴ ; Korea	29 kindergarten pupils 4.6 ± 0.3 years ISAAC questionnaire screened no asthma, atopy or wheeze	Measures before and 15 min after 400 µcg salbutamol MDI + spacer	Mean (95%CI) 2.45% (0.66–4.25%)	13% ^b
Borrego et al. ⁹ ; Portugal	22 children from local health clinics 5.1 ± 0.9 years no preterms, IUGR, wheeze, lower respiratory illness, allergic disorder or parental asthma	Measures before and 20 min after 400 µcg salbutamol MDI + spacer	Mean (SD) 4.7% (6.8)%	19% ^b
Marotta et al. ¹⁵ ; US	42 cohort participants mean (range) 4 (4.1–5) years questionnaire screened without asthma but high asthma risk due to previous wheeze no preterms	Measures before and 15 min after 2.5 mg salbutamol nebuliser	Median (IQR) 6.5% (–1% to 18%)	Could not be calculated non-normally distributed data
Cut-off calculated from response to placebo in preschool children with recurrent wheeze or asthma				
Borrego et al. ⁹ ; Portugal	43 outpatients 5.1 ± 0.9 years doctor-diagnosed asthma (mild-moderate)	Before and 20 min after placebo MDI + spacer	Mean (SD) 2.6% (7.5)%	18% ^b

MDI, metered dose inhaler.

BDR upper 95% confidence interval expressed as change in FEV₁ as a percentage of baseline.

^aA further study by Linares Passerini et al. assessed spirometry BDR but is not included in this table as the criteria of FEV₁ measurements from at least 20 healthy children was not met.

^bCut-off calculated from data presented in original paper.

asthma was found in this study.¹⁵ By contrast, three case-control studies comparing healthy preschool children to those with doctor-diagnosed asthma found significant between-group differences in BDR^{9,11,14} (Table S4). Using cut-offs optimized to the population tested Shin et al. reported 80% sensitivity and 72% specificity associated with a 5.3% FEV₁ increase relative to baseline,¹⁴ while Linares Paserini et al. reported 30% sensitivity and 90% specificity using an 11% FEV_{0.5} increase relative to baseline.¹¹ Borrego et al. reported that 15% of healthy preschool children had a greater than 12% increase relative to baseline,⁹ no study presented both sensitivity and specificity of a 12% cut-off.

Alternatives to Spirometry

Interrupter Resistance

Three case-control interrupter resistance (Rint) studies compared data from healthy preschool children with those with asthma or recurrent wheeze^{12,13,16} (Table S5). The only reported test failures were 4 of the 41 healthy children studied by Nielsen et al. who did not tolerate wearing a facemask. These studies contained between 37 and 82 children in each group. Two studies reported mean percentage changes in Rint relative to baseline of -8% ¹⁶ to -9.7% ,¹³ respectively; corresponding 5th percentiles in healthy children were -32% and -25% . Mele et al. used the 5th percentile from healthy children to identify children who not only had a history of recurrent wheeze but were also currently symptomatic; 35% sensitivity and 93% specificity were found.¹⁶ Two studies proposed cut-offs based upon optimizing sensitivity and specificity within their population. In one, a 20% cut-off relative to baseline was associated with 76% sensitivity and 80% specificity¹² while the other found 58% sensitivity and 70% specificity using a cut-off of 2.5 intra-subject standard deviations of baseline Rint.¹³

Forced Oscillometry

A study recruiting 154 healthy preschool children⁸ reported a 5th percentile value for change in respiratory system resistance at 8 Hz (Rrs₈) relative to baseline of -34% and a 95th percentile for change in respiratory system reactance at 8 Hz (Xrs₈) of 61% (Table S5). There were three case-control FOT studies. One reported an unexpected greater decrease in Rrs₈ relative to baseline following bronchodilator in healthy children than in those with asthma; (median [10th, 90th percentiles] -18.7% [-35.0 , -4.4%] vs. -16.0% [-33.1 , 9.7%]).¹⁷ Unsurprisingly, using the 5th percentile for healthy children (-37% of baseline) as a cut-off yielded low sensitivity (2%). Relative changes in respiratory admittance data from this cohort also failed to demonstrate significant differences between healthy children and those with asthma.¹⁸ Oostveen et al. found absolute change in Rrs₄

and percentage change in area under the reactance curve relative to baseline to be most discriminative for identifying persistent wheezing¹⁹; 5th percentile values for -5.5 and -31 hPaL⁻¹ were associated with 13% and 23% sensitivity, respectively with 96% specificity in both cases. Overall success rates were 85–95% increasing with age up to 100% in children aged 4 years or older.

Impulse Oscillometry

An early Impulse Oscillometry (IOS) study by Hellinckx et al. measured BDR in 228 healthy children and in those with mild asthma; BDR did not differ significantly between the two groups²⁰ so results were combined, the 95th percentile for Rrs₅ was -41.4% . Four further studies reported measures of respiratory resistance in healthy children alongside measurements made in children largely recruited from outpatient clinics with potentially more severe asthma or wheeze.^{13–15,21} Successful tests were completed in 80–90% of participants. Where reported, the mean change relative to baseline in Rrs₅ for healthy children ranged from -9.5% to -17% . The only study to report the 5th percentile in healthy children reported a value of -29% .¹³ Only one study compared BDR measured in children with and without asthma within a high risk population.¹⁵ Median (IQR) percentage change Rrs₅ relative to baseline values for 28 children with asthma were -17.0% (-32.8% to -9.9%) and -26.9% (-39.2% to -17.1%) for 45 children without asthma but at high risk due to previous wheeze. The difference in median BDR between those with and without asthma was greater still for atopic children. Two studies used receiver operator characteristic (ROC) curves to optimize diagnostic efficacy. Nielsen et al. reported 76% sensitivity and 65% specificity using a cut-off of one within subject SD in pre-bronchodilator Rrs₅.¹³ Shin et al. reported 87% sensitivity and 62% in using an Rrs₅ cut-off of -15.6% relative to baseline.¹⁴

Plethysmography

One study measured change in specific airways resistance (sRaw) relative to baseline using plethysmography.¹³ Mean BDR was -16.3% in 37 healthy preschool children and the 95th percentile was -32% , optimal sensitivity (66%), and specificity (81%) were associated with a cut-off of three within individual standard deviations (difference between two baseline measurements/ $\sqrt{2}$). Measurement failed due to facemask intolerance in 10% of children.

Comparison of Spirometry and Alternative Measures of Lung Function

Few studies compared multiple techniques and comparisons between studies were limited by methodological differences. Success rates varied most between studies for spirometry but overall spirometry generally

had lower success than other techniques. Three studies compared the discriminative ability of impulse oscillometry with that of spirometry. Two studies found the IOS technique but not spirometry BDR significantly different between healthy preschool children and those with asthma or wheeze,^{15,21} while another study considered spirometry superior based upon area under a ROC curve.¹⁴ Also using ROC analysis Nielsen and Bisgaard found plethysmographic sRaw more discriminative than Rint or FOT measures.¹³

Comparison of Methods of Expressing the BDR

Mele et al. reported that absolute changes in Rint in their study were not associated with baseline values and that absolute or z-score change in Rint were associated with greater sensitivity and specificity than either change in percentage of baseline or predicted values.¹⁶ Similarly, Oostveen et al. found BDR based upon absolute FOT values more frequently distinguished children with persistent wheeze from those without than did BDR based upon relative change.¹⁹ In contrast, Calogero et al. found absolute BDR values to be associated with height and recommended expression in terms of change as a percentage of predicted value or as change in z-score to avoid this issue.⁸ Simpson et al. found a significant difference in percentage change in Rrs₈ relative to baseline between children with asthma and those without, but no difference using absolute BDR values.¹⁸

DISCUSSION

This review found evidence that spirometry-based BDR can be performed in preschool children but success rates vary and are generally low likely reflecting the experience of the laboratory. Furthermore, the ability to distinguish healthy children from those with asthma or recurrent wheeze is limited by both variability associated with repeated measures and by the overlap between BDR measurements made in these groups. There is also evidence that BDR can be measured in preschool-aged children using a number of alternative techniques, including interrupter resistance, oscillometry, and plethysmography. While many of these alternative techniques require specialist expertise to conduct, interpret or both, BDR measured using these techniques has been demonstrated to differ significantly between healthy children and those with asthma or recurrent wheeze. Unfortunately, few studies have directly compared these techniques and there is insufficient evidence that any technique is superior.

Recently, attention has focused upon the contribution of objective testing to asthma diagnosis. The NICE guideline for “diagnosing and monitoring asthma in adults, children and young people” recommends spirometry BDR testing should be offered to adults and children

>5 years of age with a FEV₁/FVC ratio < 70%.² However, no preschool study supported the use of a 200 ml absolute increase in FEV₁ in association with a 12% increase relative to baseline in this population. An absolute cut-off based upon adult data is unlikely to be valid in children due to differences in lung size. Moreover, the between occasion variability demonstrated in placebo studies suggests that poor technique may limit the repeatability of spirometry measurements in preschool-aged children, potentially increasing the relative change necessary to exceed spontaneous variability.^{9,10}

Ultimately the low success rates associated with spirometry in preschool children unless assessed in a specialist laboratory limit its usefulness in this population. Unfortunately, while numerous alternative techniques have been used in both healthy children and those with wheezing disorders,^{11–19,21} there is insufficient evidence to identify the optimal means of measuring BDR in children who wheeze. We note, however, that some techniques have been demonstrated to be superior to spirometry for quantifying other lung diseases in this age group, for example, multiple breath wash out in cystic fibrosis.²² Similarly the optimal means of expressing BDR requires further investigation. Since changes in lung function occur with both growth and disease, a measure of BDR should be independent of both height and baseline lung function. While this has led to proposals that BDR should be expressed either as a z-score change^{8,23} or as a percentage of predicted,¹³ both approaches need testing in well powered studies.

In this review, we used broad search terms within a comprehensive literature search to systematically review data relating to BDR determination in preschool children. We were able to identify studies describing a clinically significant BDR and diagnostic efficacy in preschool children using spirometry and alternative techniques. Our conclusions are constrained by the quality and variability of identified studies. Many studies recruited very small numbers of children and few, if any, recruited adequate numbers to be considered reliable reference data.²⁴ Potential sources of bias include the low number of studies assessing diagnostic efficacy in a clinically relevant population of individuals, and the high number of studies using a case-control design or selecting a threshold to maximize sensitivity and specificity. A further problem was incomplete and inconsistent reporting of results and methodology. Heterogeneity precluded meta-analysis and limited the comparisons that could be made between studies.

Given the predominance of case-control designs, it is difficult to assess the diagnostic efficacy of BDR within a clinical population of children with symptoms potentially attributable to asthma. A cut-off which theoretically best discriminates health from disease can be calculated from receiver operator characteristic curves. However, where

significant overlap exists between healthy individuals and those potentially requiring treatment clinical factors should be considered before deciding a threshold. The relative weight placed upon sensitivity and specificity may differ according to age. For example, lower cut-offs increase sensitivity but may increase the risk of over-treatment with inhaled steroids leading to undesirable effects upon young children's growth.²⁵ An important criterion by which to judge a diagnostic test is the test's ability to predict response to treatment; this is particularly the case for conditions such as asthma where there is no gold-standard test beyond clinical diagnosis. Pertinent to this issue are observations in both children and adults that greater bronchodilator responses were measured in individuals responding to inhaled steroids^{26,27}; and some evidence that BDR can predict treatment response in preschool children with wheeze.²⁸

Current guidelines recommend measuring spirometry BDR as a component in the diagnostic pathway for asthma but are not based on evidence relevant to children and no recommendations are made for preschool-aged children. Clear evidence-based guidelines are needed to ensure the correct patients receive trials of asthma treatments. Our findings have implications for practice in terms of serving as a reminder that healthy children demonstrate considerable BDR which overlaps with that seen in children with asthma or other wheezing disorders. Based upon available evidence spirometry does not appear fit for this purpose in preschool-aged children, although other techniques may be better and merit further evaluation. The relative lack of high quality published data to inform clinical decision making suggests further studies are required. Recommendations for further research include studies of 1) BDR in children suspected of having a chronic wheezing disorder, 2) the ability of BDR to predict treatment response, and 3) new techniques which can be reliably conducted outside of a specialist lung function laboratory.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Bronchodilator response determination in preschool children: systematic review protocol

Background:

The bronchodilator response (BDR) can be used to quantify reversible obstructive airways disease. As with all diagnostic tests, the utility of the BDR is dependent upon the efficacy with which it discriminates health from disease. This, in turn, reflects the relative magnitude of BDR in those with the disease under test compared to those without, the variability of BDR within both groups, and the precision with which the BDR can be measured.

Reference values are needed to interpret individual test results. Based upon measurements made following placebo administration to adults referred for spirometry testing¹, and later reinforced by measures of response in populations², ERS guidelines state that an increase in FEV₁ greater than 200 ml and greater 12% from baseline represents a positive bronchodilator response³. Since reference values reflect the characteristics of the population from which they are calculated it is not necessarily appropriate to apply reference cut-offs based upon adult data to paediatric patients. In children, particularly young children of preschool age, developmental limitations upon cooperation impact upon respiratory function testing. Moreover, changes in lung size and function with age are likely to influence the optimal means of measuring and expressing the BDR.

Wheezing is a prevalent symptom in the preschool period where it constitutes a management dilemma. It is difficult to distinguish those children likely to benefit from inhaled steroid treatment from those who will not. Given the difficulties associated with obtaining repeatable measures of lung function from young children, BDR testing is not generally performed as part of the clinical assessment of preschool wheeze. Recent guidelines for the diagnosis and management of asthma have argued for greater objective testing in older children and adults but made no recommendations for preschool children⁴. It is not clear whether BDR testing is a useful means of identifying preschool children with asthma or recurrent wheeze. The purpose of this review is to systematically assess published data relating to BDR determination.

Aims:

To consider the evidence for diagnostic cut-off values appropriate for use in the preschool population by reviewing data which describes:

1. The magnitude of the BDR in healthy children
2. The magnitude of the response to placebo in children with obstructive airways disease
3. Discrimination of healthy children from those with asthma or recurrent wheeze by BDR

Review questions structure:

Question 1. (aim to determine clinically relevant response)

Population: healthy preschool children aged 2 to 5 years

Intervention: BDR testing using ERS protocol (lung function measurements before and 15 minutes after 400 mcg salbutamol MDI plus spacer)

Outcome: Normal range of BDR in healthy children

Question 2. (aim to determine meaningful response)

Population: preschool children aged 2 to 5 years with asthma or recurrent wheeze

Intervention: Lung function measurements before and 15 minutes after placebo inhalation

Outcome: Repeatability of measurement in target population

Question 3. (aim to determine clinical efficacy)

Population: preschool children aged 2 to 5 years

Intervention: BDR testing to using ERS protocol (lung function measurements before and 15 minutes after 400 mcg salbutamol MDI plus spacer)

Comparator: clinical or validated questionnaire diagnosis of asthma or recurrent wheeze

Outcome: accurate diagnosis

Search strategy:

An electronic database search will be conducted within MEDLINE, EMBASE, Web of Science and the Cochrane databases and citations of selected manuscripts will be searched.

Searches built for each database will identify all studies referencing bronchodilator response or a variant or abbreviation of this in the title or abstract. Studies will be limited to those conducted in humans and reported in English. Database specific limits will be set to identify studies restricted to child participants. Searches will be run from the inception of each database until 25th September 2015.

OVID search strategy (used for MEDLINE & EMBASE)

1. bronchoreversibility.mp.
2. ((bronchodilator* or bronchial dilat* or broncholytic*) adj3 (test* or revers* or respons* or respond*)).ab,ti.
3. "BDR".ab,ti.
4. 1 or 2 or 3
5. limit 4 to (English language and humans and "preschool child (2 to 5 years)" and journal article)

For EMBASE the search was restricted to children using the above search combined with 'and'

6. preschool child (1 to 6 years)

Web of Science search strategy

1. TS =(bronchoreversibility OR "BDR") OR TI=(bronchoreversibility OR "BDR")
2. TI =((bronchodilator* OR bronchial dilat* OR broncholytic*) AND (test* OR revers* OR respons* OR respond*))
3. TS=(preschool child)

4. #2 OR #1
5. LA=(English)
6. #3 AND #4 AND #5
7. Refine #6 article

Cochrane search strategy

((bronchodilator* or bronchial dilat* or broncholytic*) near/3 (test* or revers* or respons* or respond*)) or (bronchoreversibility or BDR)) and (preschool child) in Title, Abstract, Keywords (including word variations)

Inclusion/Exclusion criteria

Studies of preschool children will be included if they present numerical data describing either BDR in healthy children alone or comparing this with BDR in children with asthma or recurrent wheeze. Eligible studies will include: 1) those measuring the magnitude and range of responses to a bronchodilator in a healthy preschool population, 2) those measuring the magnitude and range of responses to a placebo inhalation in preschool children with clearly defined asthma or recurrent wheeze or 3) those comparing the response to bronchodilator in healthy preschool children to that measured in preschool children with asthma or recurrent wheeze. Where possible the clinically significant or meaningful bronchodilator response cut-off will be calculated. The method of Sourk and Nugent will be used to calculate a cut-off which includes only the greatest 5% of responses found in healthy preschool children.

Studies will be considered relevant to preschool children if no participant is aged 7 years or older and at least two thirds of the study participants are 2 years of age or older but younger than 6 years. Studies which display data from children meeting these age criteria separately from data collected from older individuals will also be eligible for inclusion.

To reduce the influence of outlier values upon the BDR estimate, studies will also be excluded if the number of participants per group is very low (less than 20).

Reviews, editorials, letters and conference abstracts will be excluded.

Selection of studies

- Initial screening – studies will be screened by a single author [KCP] for potential relevance to paediatric BDR cut-off determination
- Secondary screening – full papers will be screened by two authors [KCP and ER] against inclusion criteria and disagreements resolved by consensus

Assessment of quality:

Modified QUADAS-2 criteria will be used⁵. Following current recommendations, formal scores will not be assigned⁶. Since there is no reference group in study designs 1) or 2) studies following these designs will not be assessed according to quality criteria relating to the reference standard. In the absence of a gold-standard diagnostic test for asthma or other childhood wheezing disorders a clinical diagnosis based upon questionnaire data, clinical history or assessment by a doctor will be considered the reference test and patients under investigation for a diagnosis of asthma/recurrent wheeze the most appropriate patient group for study design 3).

Study quality will be assessed according to:

Table S1 QUADAS-2 criteria

Domain	Signalling question	Study design	
		1/2*	3
Patient selection	Was a consecutive or random sample of patients enrolled?	✓	✓
	Was a case-control design avoided?	N/A	✓
	Were inappropriate exclusions avoided?	✓	✓
	Are there concerns that the included participants do not match the review question?	✓	✓
Index test	Were BDR results interpreted without knowledge of disease group?	N/A	✓
	If a threshold was used was it pre-specified?	N/A	✓
	Are there concerns that the BDR test, its conduct, or its interpretation differ from the review question?	✓	✓
Reference standard	Is the disease grouping likely to correctly classify the participants according to asthma/recurrent wheeze?	N/A	✓
	Were the disease groups assigned without knowledge of the BDR results?	N/A	✓
	Are there concerns that the disease groups did not reflect the review question?	N/A	✓
Flow and timing	Was there an appropriate interval between determining BDR and disease grouping?	N/A	✓
	Were all participants assigned a disease group?	N/A	✓
	Were all participants assigned a disease group in the same way?	N/A	✓
	Were all participants included in the analysis?	✓	✓

*In study design 2) the index test will be administration of placebo rather than bronchodilator

Data synthesis:

The studies identified for inclusion are likely to demonstrate significant heterogeneity with respect to age and diagnosis of participants, and also with respect to bronchodilator administration protocol, physiological parameters measured and expression of the bronchodilator response. For this reason no meta-analyses are planned, however, where possible the results of studies of comparable physiological parameters will be compared. Where multiple means of expressing BDR cut-offs are presented, cut-offs from different studies will be compared using the percentage change in parameter following bronchodilator administration relative to the baseline value of the parameter since this is the mode of expression favoured in international guidelines.(3)

Table S2. QUADAS-2 Quality assessment of included studies assessing normal range of BDR in healthy children or response to placebo in those with asthma or recurrent wheeze

Study	Bias			Applicability	
	Patient selection		flow and timing	Patient selection	Index test
	Consecutive	Avoid inappropriate exclusion	all included		
Studies designed to asses BDR in healthy PS children					
Calogero 2010					
Case control studies presenting BDR data from Healthy preschool children					
Hellinckx 1998	?				
McKenzie 2000					?
Nielsen 2001					
Marotta 2003					
Thamrin 2007	?				
Song 2008		?	?	?	
Mele 2010					
Oostveen 2010					
Shin 2012					
Simpson 2012	?				
Borrego 2013					
Linares Passerini 2014					
Studies reporting change in lung function following placebo in preschool children with asthma/recurrent wheeze					
Olaguibel 2005					
Borrego 2013					

 low risk bias;  high risk bias; ? = cannot be sure of risk of bias from information presented

Table S3. QUADAS-2 Quality assessment of included studies comparing BDR measured in healthy preschool children and in those with asthma or recurrent wheeze

Study	Bias											Applicability		
	Patient selection			Index		Reference		Flow and Timing				Patient selection	Index test	Reference standard
	Consecutive	Avoid case control	Avoid inappropriate exclusions	Blind to reference	Avoid pre-specified cut off	Reference likely correct	Blind to index	Interval	All categorised	Same reference	All included			
Studies comparing BDR data from healthy preschool children with and without asthma/recurrent wheeze														
Hellinckx 1998	?	⊗	⊙	⊗	n/a	⊙	⊙	⊙	⊙	⊙	⊗	⊗	⊗	⊙
McKenzie 2000	⊙	⊗	⊗	⊗	⊗	⊙	⊙	⊙	⊙	⊙	⊙	⊗	?	⊙
Nielsen 2001	⊙	⊗	⊙	⊗	⊗	⊙	⊙	⊙	⊙	⊗	⊗	⊗	⊗	⊙
Marotta 2003	⊙	⊗	⊙	⊗	n/a	⊙	⊙	⊙	⊙	⊙	⊗	⊙	⊗	⊙
Thamrin 2007	?	⊗	⊙	⊗	n/a	⊙	⊙	⊙	⊙	⊙	⊙	⊗	⊗	⊙
Song 2008	⊙	⊗	?	⊗	n/a	⊙	⊙	⊙	⊙	⊙	?	⊗	⊗	⊙
Mele 2010	⊙	⊗	⊙	⊗	⊙	⊙	⊙	⊙	⊙	⊙	⊙	⊗	⊗	⊗
Oostveen 2010	⊙	⊗	⊙	⊗	⊙	⊙	⊙	⊙	⊗	⊙	⊗	⊗	⊗	⊙
Shin 2012	⊙	⊗	⊗	⊗	⊗	⊙	⊙	⊙	⊗	⊗	⊗	⊗	⊙	⊙
Simpson 2012	?	⊗	⊙	⊗	n/a	⊙	⊙	⊙	⊙	⊙	⊗	⊗	⊗	⊙
Borrego 2013	⊙	⊗	⊙	⊗	⊙	⊙	⊙	⊙	⊙	⊙	⊗	⊗	⊗	⊙
Linares Passerini 2014	⊙	⊗	⊗	⊗	⊗	⊙	⊙	⊙	⊙	⊙	⊗	⊗	⊗	⊙

⊙ low risk bias; ⊗ high risk bias; ? = cannot be sure of risk of bias from information presented

Table S4 Comparison of BDR values based upon change in FEV₁ after bronchodilator in healthy preschool children and those with asthma/recurrent wheeze^a

Publication	Population: Control	Population: Asthma/recurrent wheeze	FEV ₁ measured	Healthy BDR	Asthma/wheeze BDR	p-value
Marotta, A 2003¹⁵ US	42 cohort participants mean (range) 4 (4.1-5) years questionnaire screened without asthma but high asthma risk due to previous wheeze no preterms	27 cohort participants mean (range) 4 (4.1-5) years with asthma no preterms questionnaire determined asthma	before and 15 minutes after 2.5 mg salbutamol nebuliser	mean (IQR) ^b 6.5 (-1.0 to 18.0)	Mean (IQR) ^b 4.0 (-7.0 to 18.0)	0.28
Shin, YH 2012¹⁴ Korea	29 kindergarten pupils 4.6 ± 0.3 years questionnaire screened no asthma, atopy or wheeze	30 children 4.6 ± 0.4 years doctor-diagnosed asthma	before and 15 minutes after 400 µcg salbutamol MDI + spacer	Mean (95% CI) ^c 2.45 (0.66 to 4.25)	Mean (95% CI) ^c 11.63 (8.01 to 15.25)	<0.001
Borrego, LM 2013⁹ portugal	22 children from local health clinics 5.1 ± 0.9 years no preterms, IUGR, wheeze, lower respiratory illness, allergic disorder or parental asthma	43 outpatients 5.1 ± 0.8 years Doctor- diagnosed asthma (mild-mod)	before and 20 minutes after 400 µcg salbutamol MDI + spacer	mean (SD) ^c 4.7 (6.8)	mean (SD) ^c 10.7 (69.9)	<0.05

^aA further study by Linares Passerini *et al* assessed spirometry BDR but is not included in this table as the criteria of FEV₁ measurements from at least 20 healthy children was not met: ^bBDR expressed as change in FEV₁ as a percentage of predicted; ^cBDR expressed as change in FEV₁ as a percentage of baseline

Table S5. Summary of studies measuring BDR in preschool children using techniques other than spirometry

Publication	Population: Control	Population: Asthma/recurrent wheeze	BDR protocol (time interval bronchodilator)	Reported results in Healthy subjects	Reported results in Asthma/recurrent wheeze	Suggested cut-off	
						Sensitivity	Specificity
McKenzie, SA 2000 ¹² UK	48 outpatients 2-5 years no history of wheeze or cough	82 outpatients 2-5 years doctor-diagnosed past wheeze no current symptoms or therapy	time unspecified 400 µcg salbutamol MDI + spacer	Δ%pre Rint median (IQR) -7% (-17% to -3%)	Δ%pre Rint median (IQR) -40% (-60% to -22%)	Δ%pre Rint -22% ^b 76%	80%
Nielsen, KG 2001 ¹³ Denmark	37 healthy children 2.5-5.9 years no tobacco smoke exposure or family atopy	55 children 2.3-5.9 years doctor-diagnosed asthma no current symptoms	20 minutes 500 µcg terbutaline MDI + spacer	Δ%pre Rint mean 5 th percentile -9.7%, -25%	Δ%pre Rint mean (90% range) -18.8% (-44% to 10%)	Δ%pre Rint 5 th percentile -25% ^c ΔSDw Rint ^b intrasubject SD -2.5 58%	70%
Mele, L 2010 ¹⁶ Italy	60 children 2.7-6.4 years from kindergartens or surgical outpatients no recent or recurrent wheeze	60 children 2.9-6.1 years recent recurrent wheeze currently symptomatic	15 minutes 200 µcg salbutamol MDI + spacer	Δ%pre Rint mean (SD) -8.0% (14.6%)	Not reported	5 th percentile Δ%pre Rint -32% ^c 35% Δabs Rint 0.26 kPaL ⁻¹ s 80% ΔZ Rint 1.25 Z-scores 80%	93% 82%
Forced oscillometry							
Thamrin, C 2007 ¹⁷ Australia ^a	78 children 4-5 years: no asthma or wheeze	56 children 4-6.7 years: doctor-diagnosed	15 minutes 600 µcg salbutamol	Δ%pre mean (10 th to 90 th)	Δ%pre mean (10 th to 90 th percentile)	Δ%pre Xrs ₈ 95 th percentile 67.0% ^c 4%	95%

		asthma 66 wheeze in last 6 months	MDI + spacer	percentile) Xrs ₈ 30.9% (-1.6% to 62.6%) Rrs ₈ -18.7% (-35% to - 4.4%)	Xrs ₈ 30.3% (-7.8% to 58.9%) Rrs ₈ -16.0% (-33.1% to 9.7%)	Δ%pre Rrs ₈ 5 th percentile-37.0% ^c 2% 96%
Calogero, C 2010 ⁸ Italy	154 kindergarten children 2.9-6.1 years no preterms, asthma, recent or recurrent wheeze		15 minutes 200 μcg salbutamol MDI + spacer	Δabs mean Rrs8 -1.09 hPa s L ⁻¹ Xrs8 -0.71 hPa s L ⁻¹	no disease group	Δ%pre Rrs ₈ 5 th percentile -34% ^c Δ%pre Xrs ₈ 95 th percentile 61% ^c (sensitivity/specificity could not be calculated since no disease group)
Oostveen, E 2010 ¹⁹ Belgium	144 cohort study participants 4 years questionnaire screened never wheeze	54 cohort study participants 4 years persistent wheeze	15 minutes 200 μcg salbutamol MDI + spacer	Δabs [†] mean (95% CI) AX hPaL ⁻¹ -9.8 (-11.6 to -8.1) R4 hPaL ⁻¹ s -2.3 (-2.6 to -2.0)	Δabs [†] mean (95% CI) AX hPaL ⁻¹ -21.2 (-27.4 to -15.1) R4 hPaL ⁻¹ s -3.4 (-4.1 to -2.7)	Δabs [†] AX 5 th percentile -31 hPaL ⁻¹ 23% 96% Δabs ^c R4 5 th percentile -5.5 hPaL ⁻¹ 13% 96%

Impulse oscillometry

Hellinckx, J 1998 ²⁰ Belgium	228 kindergarten pupils 2.7-6.6 years questionnaire screened no asthma	25 kindergarten pupils 2.7-6.6 years asthma (mild) identified by questionnaire	20 minutes 200 μcg salbutamol MDI + spacer	Δ%pre mean (SD) (for whole group) Rrs ₅ -11.9% (18.0%) Xrs ₅ -6.5% (44.1%)		(could not be calculated due to absence of significant difference between groups)
Nielsen, KG 2001 ¹³ Denmark	37 healthy children 2.5-5.9 years no tobacco smoke	55 children 2.3-5.9 years doctor-diagnosed	20 minutes 500 μcg terbutaline	Δ%pre mean 5 th , percentile Rrs ₅ -9.5%, -29%	Δ%pre mean, 5 th percentile Rrs ₅ -17.7%, -37%	ΔSDw Rrs ₅ ^b -1 intrasubject SD 76% 65%

	exposure or family atopy	asthma no current symptoms	MDI + spacer	mean, 95 th percentile Xrs ₅ 10%, 42%	Mean, 95 th percentile Xrs ₅ 22.8%, 63%	ΔSDw Xrs ₅ ^b 1.5 intrasubject SD 33% 89%
Marotta, A 2003 ¹⁵ US	45 cohort study participants 4 years high asthma risk due to previous wheeze but no asthma, no preterms	28 participants from the same cohort study 4 years asthma no preterms	15 minutes 2.5 mg salbutamol nebuliser	Δ%pre mean (IQR) Rrs ₅ -17.0% (-32.8%to -9.9%) Rrs ₁₀ -15.6% (-25.4%to-9.7%) Xrs ₅ 27.8% (6.1% to 38.7%)	Δ%pre mean (IQR) Rrs ₅ -26.9% (-39.2% to -17.1%) Rrs ₁₀ -23.6% (-31.1% to-15.0%) Xrs ₅ 35.8% (21.7% to 48.3%)	Δ%pre Rrs ₅ -20 to -25% ^c Δ%pre Rrs ₁₀ -15 to -20% ^c sensitivity/specificity not calculated
Song, TW 2008 ²¹ Korea	55 outpatients 3-6 years no allergic or inflammatory disease	77 outpatients 3-6 years doctor-diagnosed asthma	15 minutes 200 µcg salbutamol MDI + spacer	Δ%pre mean (95% CI) Rrs ₅ -13.1% (-18.4% to -7.8%) Xrs ₅ 40.7% (-91.8% to 173%)	Δ%pre mean (95% CI) Rrs ₅ -27.4% (-33.7% to -21.0%) Xrs ₅ -22.9% (-93.9% to 48.2%)	Δ%pre Rrs ₅ -20% ^c Based on 95% CI not calculated
Shin, YH 2012 ¹⁴ Korea	29 kindergarten pupils 2-6 years questionnaire screened no asthma, atopy or wheeze	30 outpatients 2-6 years doctor-diagnosed asthma	15 minutes 400 µcg salbutamol MDI + spacer	Δ%pre mean (95% CI) Rrs ₅ -15.6% (-19.0% to -12.1%) Xrs ₅ 15.2%% (5.8% to 24.7%)	Δ%pre (95% CI) Rrs ₅ -24.1% (-27.6% to -20.6%) Xrs ₅ 52.9% (18.1% to 87.7%)	Δ%pre Rrs ₅ -15.6% ^b 87% 62%
Plethysmography						
Nielsen, KG 2001 ¹³ Denmark	37 healthy children 2.5-5.9 years no tobacco smoke exposure or family atopy	55 children 2.3-5.9 years doctor-diagnosed asthma no current symptoms	20 minutes 500 µcg terbutaline MDI + spacer	Δ%pre mean 5 th percentile sRaw -16.3%, -32%	Δ%pre mean 5 th percentile sRaw -24.8%, -44%	SDw sRaw -3 intrasubject SD ^b 66% 81%

^a(data also presented in Simpson, SJ 2012)

Cut-offs presented are those recommended by the authors of contributing papers and $\Delta\%$ pred where available. ^bcut-off calculated by optimising sensitivity and specificity ^ccut-off calculated from healthy control data

MDI metered dose inhaler, Δ abs absolute change in value, $\Delta\%$ pre percentage change in parameter relative to baseline value, $\Delta\%$ pred percentage change in parameter relative to predicted value, Δ SDw change expressed per intrasubject SD in baseline value, Δ Z change expressed in z-scores, AX area of reactance, Rrs respiratory system resistance, Xrs respiratory system reactance, Rint airway resistance measured with interrupter resistance technique, sRaw specific airways resistance

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