

The relationship between inflammation and remodeling in childhood asthma: A systematic review

Jose A. Castro-Rodriguez MD, PhD¹  | Sejal Saglani MD^{2,3} |
Carlos E. Rodriguez-Martinez MD, MSc^{4,5} | Maria A. Oyarzun MD¹ |
Louis Fleming MD^{2,3} | Andrew Bush MD^{2,3}

¹ Division of Pediatrics, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

² National Heart and Lung Institute, Imperial College London, London, UK

³ Respiratory Paediatrics, Royal Brompton Hospital, London, UK

⁴ Department of Pediatrics, School of Medicine, Universidad Nacional de Colombia, Bogotá, Colombia

⁵ Department of Pediatric Pulmonology and Pediatric Critical Care Medicine, School of Medicine, Universidad El Bosque, Bogotá, Colombia

Correspondence

Jose A. Castro Rodriguez, MD, PhD, Division of Pediatrics, School of Medicine, Pontificia Universidad Católica de Chile, Lira 44, 1er Piso, Casilla 114-D, Santiago, Chile.
Email: jacastro17@hotmail.com

Funding information

Asthma UK Centre in the Allergic Mechanisms of Asthma; National Institute for Health Research

Objectives: We aimed to perform a systematic review of all studies with direct measurements of both airway inflammation and remodeling in the subgroup of children with repeated wheezing and/or persistent asthma severe enough to warrant bronchoscopy, to address whether airway inflammation precedes remodeling or is a parallel process, and also to assess the impact of remodeling on lung function.

Methods: Four databases were searched up to June 2017. Two independent reviewers screened the literature and extracted relevant data.

Results: We found 526 references, and 39 studies (2390 children under 18 years old) were included. Airway inflammation (eosinophilic/neutrophilic) and remodeling were not present in wheezers at a mean age of 12 months, but in older pre-school children (mean 2.5 years), remodeling (mainly increased reticular basement membrane [RBM] thickness and increased area of airway smooth muscle) and also airway eosinophilia was reported. This was worse in school-age children. RBM thickness was similar in atopic and non-atopic preschool wheezers. Airway remodeling was correlated with lung function in seven studies, with FeNO in three, and with HRCT-scan in one. Eosinophilic inflammation was not seen in patients without remodeling. There were no invasive longitudinal or intervention studies.

Conclusion: The relationship between inflammation and remodeling in children cannot be determined. Failure to demonstrate eosinophilic inflammation in the absence of remodeling is contrary to the hypothesis that inflammation causes these changes. We need reliable, non-invasive markers of remodeling in particular if this is to be addressed.

KEYWORDS

airway biopsy, airway inflammation, airway remodeling, asthma, bronchial biopsy, bronchoalveolar lavage, children, infants, wheezing

1 | INTRODUCTION

Data from worldwide birth-cohort studies show that lung function is reduced in the early preschool years in children who develop asthma, and that the loss in lung function by the age of 5 years tracks into adulthood without recovering.¹ Antenatal causes of decline in lung

function include maternal cigarette smoking and environmental pollution. It is estimated that 40% of asthmatic airflow obstruction is present at birth in high risk infants, before the onset of inflammation or infection, and 60% is postnatal.² Postnatal pathological structural airway changes are related to airway remodeling, including epithelial injury, increased thickness of the sub-epithelial reticular basement

membrane (RBM), goblet cell hyperplasia, airway smooth muscle (ASM) hypertrophy and hyperplasia, and angiogenesis.³

The relationship between airway inflammation and airway remodeling is controversial.⁴ It should be noted that remodeling is not one entity but multifaceted (above). Potential hypotheses (and different hypotheses may apply to the different components of remodeling) are (1) repeated cycles of acute and acute on chronic airway inflammation are the early events that lead eventually to airway remodeling; (2) airway inflammation and remodeling are parallel processes triggered by the same underlying problem but progress independently; (3) the primary disorder is airway repair and inflammation is secondary to abnormal repair processes; and (4) although remodeling is thought to be damaging, there is at least some evidence that it may be a protective response, for example limiting bronchoconstriction,⁵ and possibly also limiting systemic absorption of inflammatory mediators from the airway lumen. The clinical importance of confirming or refuting these hypotheses is that if elements of remodeling are protective, treatment strategies should be aimed at augmenting them, whereas if harmful, the contrary strategy, namely trying to ameliorate the changes, is appropriate.

Since today there is not an indirect measure for inflammation available, here we report a systematic review, using only those published papers where direct measurements of both airway inflammation and/or remodeling (eg, by bronchial alveolar lavage and bronchial biopsy), were made in the subgroup of children with repeated wheezing and/or persistent asthma sufficiently severe to merit bronchoscopy, to try to differentiate between these fundamentally different hypotheses.

2 | METHODS

We identified published studies in MEDLINE, EMBASE, CINAHL, and SCOPUS (up to June 2017) database, using the terms: “((bronchoalveolar lavage) OR (airway biopsy) OR (bronchial biopsy)) AND ((wheeze) OR (asthma)) AND ((airway inflammation or airway remodeling))” restricted to child (birth to 18 years old), without language restriction. Studies published solely in abstract form were excluded because the methods and results could not be fully analyzed.

To be included, studies had to meet all of the following criteria: (1) cross-sectional or cohort studies of airway inflammation and/or remodeling measured directly by bronchoalveolar lavage and/or biopsy in children with asthma or recurrent wheezing; (2) inclusion of children (1-18 years) or in a mixed population (adults and children) only when children were analyzed separately; (3) experimental or intervention studies. Those studies in which markers of inflammation and remodeling were only measured in blood, urine, saliva or sputum, exhaled breath condensate, lung function or imaging were excluded unless a concomitant bronchoalveolar lavage or endo-bronchial biopsy were performed for comparison. Autopsy studies, reviews and letters to the editor (without data reports) were also excluded.

2.1 | Data extraction and assessment of risk of bias

Titles, abstracts, and citations were independently analyzed by two authors (A.O. and C. R-M). Based on the full text form, all the studies were evaluated for inclusion criteria, type of intervention, population included, study design, and outcomes. After obtaining full reports about potentially relevant studies, eligibility was assessed. Disagreements were discussed and resolved by consensus, and when necessary advice was sought from the third reviewer (J.C-R.). A prespecified data analysis included year, country, type of study, number of participants, age, type of asthma/wheezing and severity, age of diagnosis, atopic status, type of cellular inflammation and, result of airway biopsy, all of which were recorded. Additionally, we recorded any other tests of inflammation, that is, in blood, urine, breath condensate, fraction exhaled nitric oxide (FeNO), high resolution CT-scan (HRCT-scan), and lung function.

3 | RESULTS

Five hundred and twenty-six studies were retrieved from the databases, of which 39 were eligible for inclusion (Figure 1). Most ($n = 33$) came from Europe (UK = 16, France = 8, Italy = 3, UK and Czech Republic = 1, UK and Finland = 1, Czech Republic = 1, the Netherlands = 1, Turkey = 1, and Ireland = 1); there were three studies from United States, two from Australia, and one from Korea. Most studies were case-control ($n = 11$), cross-sectional ($n = 12$), and prospective cohort ($n = 11$); others were case series ($n = 3$) and retrospective cohorts ($n = 2$). See Table 1.

There were 2390 children included in the 39 studies. In 14 studies^{6-18,20} ($n = 637$) the population was school age children with a clinical diagnosis of asthma (mainly “difficult to treat” or “severe asthma”), nine studies²²⁻³⁰ were exclusively in infants or pre-schoolers under the age of 5 years with severe recurrent wheezing ($n = 409$). Fourteen studies³¹⁻⁴⁴ combined pre-schoolers and school-aged children ($n = 1252$). Two studies^{45,46} combined asthmatic children and adults, for this review we only included data from the children ($n = 92$). Only 11 studies^{13-18,20,23,28,41,43} recorded the age of onset of asthma, which varied from 5 months to 11 years.

Thirty-two studies evaluated atopy in their patients. In 27 studies^{6-9,10-18,20,23,24,28,31,32,34-36,38-40,44-46} this was by skin prick test, or specific IgE or total IgE; while in seven studies^{22,26,27,37,41-43} atopy was evaluated by total IgE or clinically; and in three studies only on clinical criteria.^{25,29,30} Sixteen studies^{9,12-16,18,23-27,29,31,45} recorded the presence of previous asthma attacks. Twenty-nine studies recorded current asthma medications.^{3,6-16,18,20,24-27,29-31,33-35,37,38,41,43-45}

Fourteen studies^{9,25,28,30,34-36,38,39,42-44} had a control group defined as non-asthmatic/wheezing children (two also included adults^{45,46}); in 11 studies^{11,13,15,16,20,24,31,32,37,40,41} there was no control group; in six studies^{6,8,10,23,26,27} the control group was defined as upper airways symptoms; in six studies^{12,14,17,18,29,33} the control group was defined as lower respiratory problems but non-asthma; and one study²² compared children that in the future

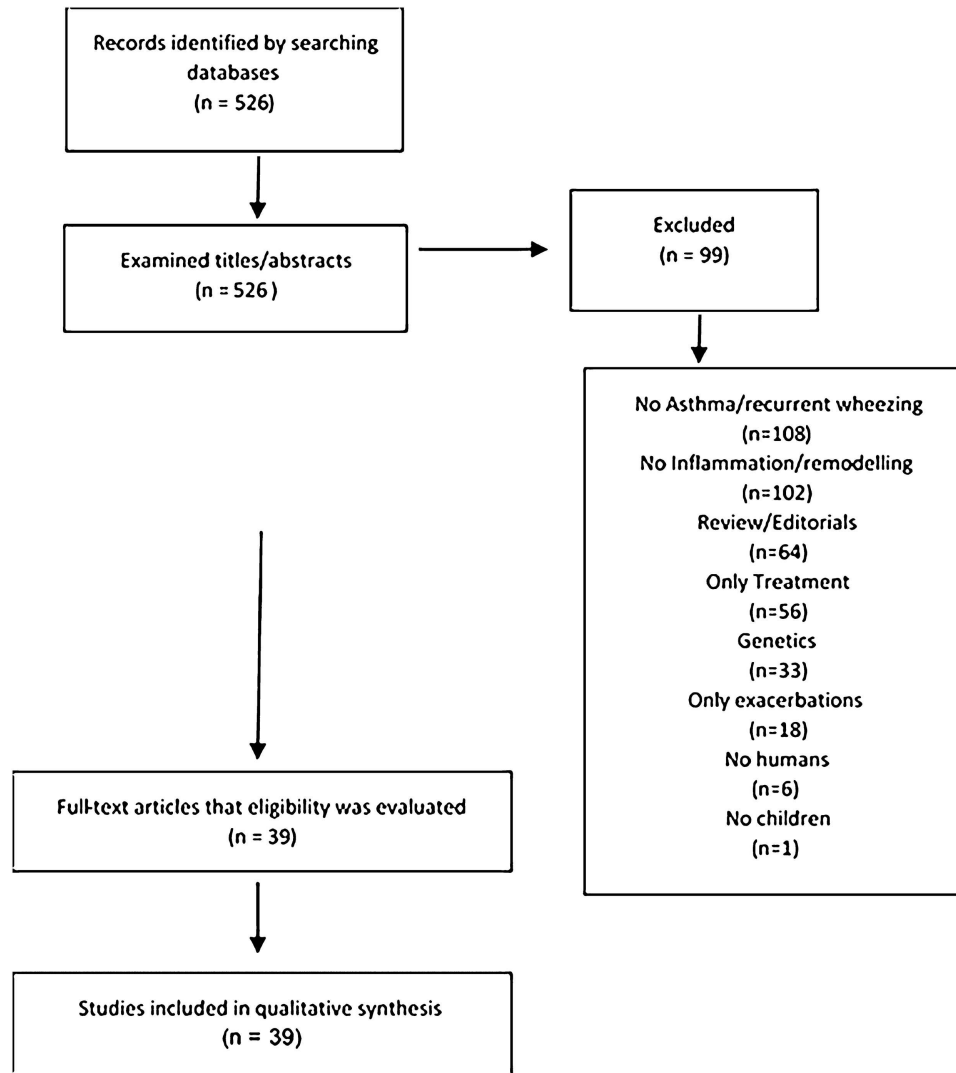


FIGURE 1 Process of study selection

developed asthma (positive vs negative asthma predictive index [API]⁴⁷) (Table 1).

3.1 | Airway inflammation

Airway inflammation was determined in 20 studies.^{6,8,15,16,23,25,26,29,30–33,37–40,42,43,45} Significant airway eosinophilia was reported in seven studies (in BAL alone,^{25,30,42} in biopsy alone,¹² and in both^{6,8,9}); while eosinophilic cationic protein (ECP) in BAL was elevated in three studies,^{13,38,44} but not in one.⁴³ In contrast, only one study (median aged 14.5 months)³⁷ reported more BAL neutrophilic inflammation than controls. Mixed eosinophilic and neutrophilic inflammation was reported in BAL in four studies,^{6,9,30,45} and also in the submucosa or intraepithelial in three.^{6,9,16} One study reported significantly more BAL neutrophilic inflammation in pre-schoolers with severe recurrent wheezing compared with more eosinophilic inflammation in school-age severe asthmatics.³¹ One study showed that eosinophilic inflammation and

remodeling were still present in children who had apparently outgrown asthma.⁴² See Table 1.

3.2 | Airway remodeling

Airway remodeling was directly assessed from endobronchial biopsy in 27 studies.^{6–18,22–24,27,28,32–36,40,41,46} The main finding was increased thickness of the RBM in asthmatics compared to controls^{5,12,14,17,18,27,33}, but with normal ultrastructure (ratio of fibril to matrix).⁴⁶ The RBM was thicker and ASM area greater in school children with severe asthma compared with controls¹⁰ and with pre-schoolers,³² and vascularity was higher in younger preschoolers than in older.³² The only study which compared adults and children¹⁸ reported that the RBM thickness of school-age children with difficult asthma was similar to that seen in adults with either mild intermittent or acute life-threatening asthma. In one study, children (median age 13.5 months)²² who later developed asthma (by a positive API⁴⁷) already had increased RBM thickening, but not tenascin deposition, than those with negative API; however, no data on inflammatory cells were

TABLE 1 Characteristics of included studies

Ref	Author/year	Country	Study type	N	Age: months or year; x ± SD or median [range]	Controls defined	BAL significant findings	Biopsy significant findings
Studies with both inflammation and remodeling simultaneously data								
6	Andersson (2017)	UK	CC	66	STRA: 12.6 y [6-16.3] C: 4.8 y [1.6-10]	Upper airway symptoms	Eosinophils higher in STRA vs C	Intraepithelial neutrophils increased in STRA vs C. More IL-17RA-positive cells in the submucosal & epithelium in STRA vs C.
32	Lezmi (2015)	France	PC	70	Psch1: 27.2 m [24.5-30.3] Psch2: 44.5 m [41-54.6] Sch: 117.7 m [102.4-124.3]	None	No difference in cytology	RBM thickness higher in Sch vs PSch. RBM thickness higher in PSch 2 vs PSch1. ASM area higher in Sch vs PSch1. More vessel number in PSch1 vs Sch. More submucosal eosinophils in PSch2 vs PSch1.
33	Van Mastrigt (2015)	The Netherlands	RC	152	SA: 11.0 ± 4.5 y; MA: 9.7 ± 4.6; C: 8.9 ± 4.6 y	Other LRTs non-A/Wh	No difference in eosinophils and neutrophils between SA, MA and C.	RBM thickness between SA vs C, and between SA vs MA. Not between MA vs C. RBM thickness correlated with FeNO ($r = 0.45$), FEV1 ($r = -0.18$) and FVC ($r = -0.23$).
8	Bossley (2012)	UK	CC	69	STRA: 11.97 y [9.97-14.4] C: 10.65 y [7.54-12.96]	Upper airway symptoms	Eosinophils higher in STRA than C	Increased RBM thickness, ASM/vv, and ASM/vf in STRA vs C. Increased sub epithelial mucosal eosinophils in STRA vs C. Atopic STRA increases ASM mass vs atopic C. Negative association ASM and OCS.
40	Lex (2006)	UK	PC	29	MA: 10.2 y [4-15]	None	EBC cysLTs were lower in MA who were on MTK vs without MTK.	No difference in RBM thickness and MTK or ICS or OC therapy
15	Mahut (2004)	France	PC	28	11 y [9.8-13.7]	None	FANO correlated with ECP ($r = 0.67$) and with IFN- γ /IL-4 ($r = -0.40$). Both FANO ($r = 0.42$) and QMAX,CA ($r = 0.41$) correlated with TGF- β 1. QMAX, CA correlated with TIMP-1/MMP-9 ($r = 0.43$).	QMAX,CA correlated with subepithelial eosinophilic infiltration ($r = 0.40$). QMAX, CA correlated with RBM thickness ($r = 0.61$).
16	de Blic (2004)	France	CS	28	Symptomatic A: 10.4 y [9.6-12.5], Paucysymptomatic A: 13.3 y [10-15]	None	Higher neutrophils in the symptomatic A. Higher lymphocytes, IFN γ and IFN γ /IL-4 in the paucysymptomatic A.	Within the epithelium, eosinophil and neutrophil higher in symptomatic group. RBM was similar between groups.
Studies with only inflammation data								
31	Guiddir (2017)	France	CS	350	PSch STRW: 33.9 ± 21.9 m Sch STRA: 138 ± 22.5 m	None	More neutrophils and lower eosinophils in PSch vs Sch	Not performed.
25	Thavagnanam (2010)	Ireland	PC	65	<5 y	No wheeze	No bronchoscopy BAL: Higher eosinophils in LOCW vs NW.	Not performed

(Continues)

TABLE 1 (Continued)

Ref	Author/year	Country	Study type	N	Age: months or year; x ± SD or median [range]	Controls defined	BAL significant findings	Biopsy significant findings
45	Fitzpatrick (2010)	US	CC	53	C: 38 ± 10 y SA: 11 ± 8 y MA: 10 ± 4 y	Non-A/Wh	Neutrophils higher in SA vs C and in MA vs C. Eosinophils higher in SA vs C and in SA vs MA. IL-13 and IL-6 higher in SA vs C and in MA vs C.	Not performed
37	Hauk (2008)	US	CS	18	SA: 14.5 m [6-156]	None	Neutrophilic associated with increased IL-8, MMP-9, TIMP-1, and MMP-9/TIMP-1. Correlation between LPS and neutrophils in a subgroup who had increased MMP-9 and TIMP-1.	Not performed
26	Erlewyn-Lajeunesse (2008)	UK	CC	66	C: 1.7 y [0.2-5.1], W: 1.1 y [0.5-3.8]	Upper airway symptoms	MMP-9/TIMP-1 higher in W vs C, and showed an excess of TIMP-1. TIMP-1 raised in PW. Absolute concentration TIMP-1 associated PW	Not performed
38	von Ungern-Sternberg (2006)	Australia	CC	42	C: 73.8 ± 31.4 m A: 82.5 ± 29.5 m	Non-A/Wh	ECP more in A vs C, and with higher levels. Tryptase more in A. Respiratory resistance was higher in A with detectable ECP than in those with undetectable ECP levels (P = 0.019).	Not performed
39	MacLennan (2006)	Australia	CC	42	Infrequent non-atopic EW: 5 y [3-8.6] C: 5 y [2.3-7.5]	Non-A/Wh	No difference in cells. No difference in T-cell expression of HLA-DR and CD25, or in PMA-induced IFN-γ. IL-2, IL-4, IL-5, and IL-10	Not performed
42	Warke (2002)	UK	RC	70	AA outgrown: 7.3 y [5.7-9.9]; viral wheeze outgrown: 6.6 y [3.3-7.3]; C: 7.3 y [4.8-9.8]	Non-A/Wh	Eosinophils raised in non-broncoscopic BAL in AA who had apparently outgrown asthma.	Not performed
29	Arnoux (2001)	France	CS	28	W: 15.4 m [7-49]; C: 24.1 m [8-36]	Other LRTs non-A/Wh	Increase in CD8+ in W vs C. Decreased expression of HLA-DR in macrophage of W vs C.	Not performed
43	Marguet (2001)	France	CS	56	A: 90 m [49-180]; RW: 25 m [5-46]; C: 97.8 m [17-190]	Non-A/Wh	In A: correlation between ECP and eosinophil (r = 0.618), and between neutrophil and IL-8 (r = 0.747); and increasing IL-8 Levels with symptom score. In RW: IL-8 significantly increased when neutrophils were >10%; ECP correlated to neutrophil % (R = 0.832); and a threshold of ECP > 20 ng/mL associated with persistent symptoms.	Not performed

(Continues)

TABLE 1 (Continued)

Ref	Author/year	Country	Study type	N	Age: months or year; x $\pm$ SD or median [range]	Controls defined	BAL significant findings	Biopsy significant findings
30	Krawiec (2001)	US	CC	26	PW: 14.9 $\pm$ 2.5 m; C: 23.3 $\pm$ 3.4 m	Non-A/Wh	Total BAL cells, eosinophils, PMN, lymphocytes, macrophages/monocytes, epithelial cells, LTE4, LTB4 ($P = 0.05$), PGE2, 15-HETE were more in PW vs C.	Not performed
44	Ennis (1999)	UK	CS	161	AA: 8.09 y [1.08-15.3] VAW: 3.6 y [1-13]; Atopic non-A: 7.58 y [1.7-13.6]; C: 7.23 y [0.42-14.5]	Non-A/Wh	ECP: AA higher than C ($P < 0.01$). Histamine: higher in AA and VAW vs C ($P < 0.02$), higher in AA vs atopics non-A ($P < 0.03$).	Not performed
Studies with only airway remodeling data								
22	Berankova (2014)	Czech Rep	Serie	30	+API: 19.5 [4-44] -API: 11 [3-38]	None	Not performed	RBM thickness higher in +API vs -API. Laminin layer higher in +API vs -API. Collagen IV lower in +API vs -API.
7	Saglani (2013)	UK	Serie	69	STRA: 11.9 y [9-14] C: 10.7 [7.5-12.9]	Mild-moderate A	Not performed	IL33 increased in submucosa in STRA vs C. Mucosal IL33 expression correlated with RBM in STRA. IL33 promoted increased RBM thickness by collagen secretion of fibroblasts.
23	O'Reilly (2013)	UK	PC	51	SRW: 28 m (3-57), C: 17 m (3-55)	Upper airway symptoms	Not performed	Children with SRW at preschool age had increased RBM thickness and subepithelial eosinophil numbers compared with nonwheezing control at preschool age. However, preschool RBM thickness and subepithelial eosinophil density were similar in children who did or did not have asthma by school-age
9	Gupta (2011)	UK	PC	86	STRA: 11.5 y [9.5-14] MA: 12.5 y [11-13]	Non-A/Wh	Not performed	ASM mass correlated with 25(OH) D3 ($r = -0.6$). ASM v ℓ correlated with BDR ($r = 0.6$), and ACT ($r = -0.7$).
34	Sonnappa (2011)	UK	CS	100	SW: 5 y [4.4-5.9], C: 5.5 y [5.1-6.2],	Non-A/Wh	Not performed	RBM thickness and EG2+ greater in MTW vs VAW. RBM thickness and EG2+ correlated with FeNO ($r = 0.47$) and ($r = 0.55$)
35	Baraldo (2011)	Italy	CC	80	ANE: 7.2 $\pm$ 0.5 y, AE: 5.0 $\pm$ 0.5 y, C: 4.9 $\pm$ 0.5 y	Non-A/Wh	Not performed	Eosinophils higher in AE vs NE, and in ANE vs C. Epithelial loss higher in AE vs C. RBM thickness higher in AE and in ANE vs C. Vessels higher in AE and in ANE vs C. IL4+ higher in AE and in ANE vs C.
24	Malmström (2011)	UK	PC	50	RW: 2.3 y [1.1-2.9]	None	Not performed	RBM thickness correlated with ICS ($r = 0.406$) Mast cells correlated with ICS ($r = 0.378$)

(Continues)

TABLE 1 (Continued)

Ref	Author/year	Country	Study type	N	Age: months or year; x $\pm$ SD or median [range]	Controls defined	BAL significant findings	Biopsy significant findings
10	Regamey (2008)	UK	CC	78	A: 12.5 y [6.7-15.8], C: 11.8 y [5.9-16.4]	Upper airway symptoms	Not performed	ASM (number and size) increased in A vs C. ASM content correlated with BD responsiveness ($r = 0.66$)
36	Turato (2008)	Italy	CC	55	MTW non atopic: [2-10] y; MTW [2-15] y; C: [2-14] y	Non-A/Wh	Not performed	Compared with C, both nonatopic and atopic MTW had increased epithelial loss, thickened RBM, and increased number of vessels and eosinophils. Moreover, they had increased IL-4 and IL-5.
11	Tillie-Leblond (2008)	France	CS	25	Obstructive A: 10.9 y [6-14], Non-obstructive A: 8.9 y [5-13]	None	Not performed	Surface area ASM, MLCK expression, and number vessels were increased in Obstructive A vs Non-obstructive A. Distance RBM-ASM shorter in Obstructive A. FEV1 correlated with ASM area ($r = -0.6$), MLCK expression ($r = -0.45$) and CD31 expression ($r = -0.7$), and with distance of RBM-ASM ($r = 0.5$).
27	Saglani (2007)	UK	CC	40	CW: 29 m [7-57] RW: 17 m [8-58] C: 19.5 m [5-42]	Upper airway symptoms	Not performed	RBM thicker in CW vs C. Subepithelial eosinophilic density greater in CW vs C.
12	Kim (2007)	Korea	CC	42	A: 13 ± 1 y; C: 12 ± 3 y	Other LRTs non-A/Wh	Not performed	RBM thickness greater in A vs C. Sex, FEV1/FVC, total IgE, and atopy (IgE for D. pteronyssinus) were predictive factors for RBM thickness.
46	Saglani (2006)	UK	CS	39	SA: 10 y [6-16] SRW: 12 m [4-24]	Non-A for Sch. RW normal LF for PreSch	Not performed	Fibrils in the RBM were thinner and fewer fibrils were banded than in the interstitial collagen. Ratio of fibrils to matrix in the thickened RBM of SA or SRW similar to C.
13	de Blic (2005)	France	PC	37	10.4 y [9-13]	None	Not performed	BWT score correlated with RBM ($r = 0.34$), with NO production by the airway wall ($r = 0.45$) and with ECP ($r = 0.40$).
28	Saglani (2005)	UK, Finland	CS	53	RW with BD reversibility: 12 m [3.4-26] m. RW with BD w/reversibility: 12.4 m [5.1-25.9]. RW normal LF: 11.5 m [3.4-24.3]. SA: 10.3 y [6-16]. C: 10 y [6-16]. C adults: 27 y [21-42]	Non-A/Wh	Not performed	RBM thickening and eosinophilic inflammation in Sch and adults, but not present in RW infants with reversible airflow obstruction, even if atopic.

(Continues)

TABLE 1 (Continued)

Ref	Author/year	Country	Study type	N	Age: months or year; x ± SD or median [range]	Controls defined	BAL significant findings	Biopsy significant findings
41	Pohunek (2005)	Czech Rep, UK	PC	27	SA: 8.7 y [1.2-11.7]	None	Not performed	More eosinophils in lamina propria and greater thickness of subepithelial lamina reticularis in children with A diagnosis at follow-up vs who did not progress to A.
14	Payne (2004)	UK	PC	47	SA: 13 y [6-16]; C: 10 y [7-16]	Other LRTs non-A/Wh	Not performed	RBM thickness greater in SA vs C. CD4+ T lymphocyte density higher in SA with persistent airflow limitation vs without. In SA, a correlation between CD4+ T lymphocytes and both pre-BD FEV1 ($r = -20.6$) and post-BD FEV1 ($r = -20.6$).
17	Barbato (2003)	Italy	CS	23	MildA: 8 ± 1 y; Atopy nonA: 7 ± 1 y; C: 7 ± 1 y	Other LTRs non-A/Wh	Not performed	Increase RBM thickness and eosinophils in A vs C, but not with atopy. Increase RBM thickness in atopy nonA vs C ($P = 0.05$). Decreased expression of TGFβ-RII in A compared with both those with atopy and C. In A, eosinophils correlated with TGFβ-RII ($r = -0.86$) and with symptom duration ($r = 0.79$).
18	Payne (2003)	UK	CS	29	Difficult A: 13 y [6-16]; C: 10.5 y [7-16]	Other LRTs non-A/Wh	Not performed	RBM thickness in children difficult A similar to adults with either mild or SA. RBM thickness in children A paediatric greater than both the adults C and children C. In children with A no correlation between RBM thickness and age, duration of A, or both pre-/post-BD.
20	Cokugras (2001)	Turkey	Serie	10	9.3 ± 3.8 y	None	Not performed	Thickening & hyalinisation of the RBM in nine patients. The ciliated epithelial cells showed loss of cilia in some cases. Overactive fibroblasts were consistently found. Six patients had degranulating mast cells and lymphocyte infiltration in the submucosa. Eosinophils were seen in only one biopsy sample.

A, asthma; AA, atopic asthma; BWT, bronchial wall thickening; CC, case-control; C, controls; CS, cross sectional; CW, confirmed wheezing; EA, eosinophilic asthma; ECP, eosinophilic cationic protein; EBC, exhaled breath component; EPC, eosinophils protein cationic; EW, episodic asthma; FANO, Alveolar NO concentrations; ICS, inhaled corticosteroids; LOCW, late onset childhood wheezing; MA, moderate asthma; MTK, montelukast; MMP, metalloproteinase; MW nonatopic, multitrigger wheeze non atopic; Mwatopic, multitrigger wheeze atopic; NEA, non-eosinophilic asthma; NW, never wheezing; non-A/Wh, non-asthma/wheeze; OCS, oral steroids; other RTs non-A/Wh, other respiratory tract problems non-asthma/wheeze; PC, prospective cohort; PSch, preschooler; PW, persistent wheezing; QMAX, CA, maximal NO output from the conducting airways; RC, retrospective cohort; RW, reported wheezing; TIMP, tissue inhibitor of metalloproteinase; SA, severe asthma; STRA, severe treatment-resistant asthma; SRW, severe recurrent wheezing; SC, schoolchildren; VAW, viral associated wheezing; W, wheezers.

reported. One study²³ reported that increased preschool ASM area—but not RBM thickness, mucosal eosinophils, or ASM mast cells—was seen in children who had asthma at school age. Preschool ASM biopsy proportion of greater than 10% had similar negative predictive value but improved positive predictive value of future asthma compared to a positive API.⁴⁷ Finally, increased epithelial shedding in asthmatic children compared to controls was reported in one study,³⁶ but not in two others.^{8,9} See Table 1.

In only seven studies^{6,8,15,16,32,33,40} were both airway inflammation and remodeling measured simultaneously. In terms of inflammatory cells, one study⁸ demonstrated eosinophilic inflammation in association with remodeling; one study³² reported no differences in BAL cytology compared with controls, but more submucosal eosinophils in the biopsies; and in another study⁶ there was BAL eosinophilia while intraepithelial neutrophils were present in the bronchial biopsies. However, in all studies in which airway remodeling and inflammation were simultaneously reported, inflammation (mainly eosinophilic) co-existed with remodeling.

3.3 | Subgroup analysis by age and control groups

Paediatric studies that have made direct assessments of airway pathology in wheeze/asthma can be divided into three groups. (1) Studies exclusively in school-age asthmatics compared with controls (defined by the presence of upper airway symptoms) which have shown significantly more BAL eosinophils,²³ EPC and tryptase,³⁸ subepithelial eosinophils,¹⁷ mucosal eosinophils,⁶ intraepithelial neutrophils,⁶ and submucosal and epithelial IL-17RA-positive cells.⁶ There were also studies that reported significantly increased RBM thickness,^{8,17,33} hypertrophy and hyperplasia of ASM,^{8,10} but not epithelial shedding,⁸ and decreased expression of TGF β -RII,¹⁷ in asthmatic. (2) Studies exclusively in school-age asthmatics compared with controls (defined by the presence of lower respiratory symptoms, but not asthma) have reported more mucosal eosinophils,⁴¹ and significantly increased RBM thickness,^{12,14,41} in asthmatic. (3) Studies exclusively in preschoolers have reported higher BAL eosinophils,²⁵ neutrophils,³⁰ in wheezers compared to non-wheezers. There were higher BAL MMP-9/TIMP-1 ratio in wheezers than controls,²⁶ a significant increase in the BAL CD8+ lymphocyte population and decreased expression of HLA-DR in the macrophage population in wheezers as compared to non-wheezers,²⁹ and significantly higher BAL eosinophils, neutrophils, lymphocytes, epithelial cells, LTE4, LTB4, PGE2, 15-HETE in persistent wheezers compared to controls.³⁰ Those with confirmed wheezing had greater RBM thickness²⁷ and eosinophil density²⁷ than controls. RBM thickness and eosinophilic inflammation, characteristics of asthma in older children and adults, were not present in symptomatic infants (mean age 1 year) with reversible airflow obstruction, even in the presence of atopy.²⁸

3.4 | Subgroup analysis by atopy

No difference in RBM thickness was reported between atopic and non-atopic severe pre-school wheezers.^{27,34} However, in school age children

with severe therapy resistant asthma, RBM thickness was significantly higher in atopic compared to non-atopic patients.⁸ ASM area was larger in atopic compared to non-atopic preschool wheezers.³² Epithelial shedding, RBM thickness, angiogenesis, eosinophilia, and expression of IL-4 and IL-5 were also present to a similar degree in non-atopic and atopic children with multitrigger wheeze.³⁶ Subepithelial eosinophilic inflammation was similar in atopic and nonatopic confirmed preschool wheezers.²⁷ No differences in BAL ECP levels was found between atopic and non-atopic asthmatic children.⁴³ MMP-9 was increased in both atopic and nonatopic preschool wheezers.²⁶ However, significantly more mast cell tryptase positive cells were present in the lamina propria in atopic compared to non-atopic asthmatics.⁴¹

3.5 | Correlation with other biomarkers

We looked for correlations between airway inflammation and remodeling with other biomarkers, including radiological imaging. FeNO was measured in eleven studies,^{6,8-10,13-15,18,23,45} but only had a direct correlation with RBM thickness in three ($r = 0.474$,⁹ $r = 0.61$,¹⁵ $r = 0.45$ ³³). There was no association between FeNO and airway inflammation,¹⁴ presumably related to the high levels of treatment prescribed for patients undergoing clinically indicated bronchoscopy.¹⁹ Exhaled breath condensate cysteinyl leukotrienes were measured in one study and significantly correlated with RBM thickness ($r = 0.75$).⁴⁰ The value of HRCT-scanning was evaluated in only one study,¹³ reporting a significant correlation between CT measures of airway wall and direct measurement of RBM thickness ($r = 0.34$). Lung function, mainly spirometry, was measured in 23 studies,^{8-18,20,23,24,28,33-35,38,40,41,45,46} but was significantly correlated in only seven^{6,10-12,14,33,38}; for example, an inverse correlation was reported between FEV1 and ASM (FEV1 $r = -0.60$),¹¹ FEV1/FVC and RBM thickness ($r = -0.54$),¹² FEV1 and RBM thickness ($r = -0.18$),³³ FVC and RBM thickness ($r = -0.23$),³³ pre- and postbronchodilator FEV1 and biopsy CD4 cell counts ($r = -0.57$ and $r = -0.61$, respectively),¹⁴ and between bronchodilator reversibility and ASM ($r = 0.66$).¹⁰ Respiratory system resistance was higher in asthmatics with detectable BAL ECP.³⁸ A direct correlation was found between intraepithelial neutrophils and FEV1 % predicted ($r = 0.43$).⁶ There were no reports comparing sputum or urinary biomarkers with BAL or airway biopsy.

4 | DISCUSSION

In this systematic review of 39 studies ($n = 2390$ children) on airway inflammation and remodeling in asthmatic children under 18 years of age, we found that airway inflammation and remodeling was not present at a mean of 12 months of age, but in older pre-school children (mean 2.5 years), remodeling (mainly increased RBM thickness) and airway eosinophilia was reported, especially in the oldest children. However, most of the children studied had been prescribed anti-inflammatory medications, usually inhaled corticosteroids (ICS), and it is likely that, had it been ethical to stop their treatment, inflammation would have been more prominent.

However, some studies found no differences in RBM,²⁷ ASM,¹⁰ or BAL cellularity^{10,30} when comparing asthmatics who were and were not prescribed ICS. There is no study reporting eosinophilic inflammation without remodeling being present; conversely, the presence of remodeling with no eosinophilic inflammation most likely reflects the anti-inflammatory effects of ICS, and cannot be taken as evidence that remodeling precedes inflammation.

The ideal study to determine the relationship between the onset of symptoms and the progression of airway inflammation and remodeling would be to undertake bronchoscopy with BAL and airway biopsy in high risk children (eg, parental history of asthma/atopy or positive API) before the onset of symptoms, repeating this test frequently over time. For obvious ethical reasons this is not possible, and we have to draw inferences from inevitably suboptimal studies. We know that symptoms precede inflammation and remodeling²⁸; and we know that remodeling and eosinophilic inflammation may be present with no symptoms in young people who may have outgrown asthma.²¹ Only one study²² demonstrated that remodeling is present before a diagnosis of asthma was made, but these children had significant symptoms at the time of bronchoscopy, and it could be argued that with retrospect, asthma should have been diagnosed much earlier. Taken together, the literature supports the view that at the inception of respiratory symptoms the airway is normal; from age 1 year to school age, remodeling and inflammation develop in parallel; from school age, remodeling is stable, whereas inflammation continues unabated; and inflammation and remodeling persist even in those whose symptoms have resolved.

In the present review, failure to demonstrate eosinophilic inflammation in the setting of a non-remodeled airway would not support the hypothesis that eosinophilic inflammation causes remodeling. Indeed, airway inflammation is ongoing into adult life, whereas at least some aspects of remodeling, such as RBM thickness, are non-progressive,¹⁸ although in the first years of life, the processes seem to go in parallel.^{27,28}

There are some data from adult studies which are informative. In an experimental study performed in adults with mild asthma, repeated methacholine-induced bronchoconstriction can cause remodeling (increased sub-epithelial collagen deposition, increased periodicacid Schiff staining) without inducing airway inflammation.⁴⁸ In this context, it is interesting to note the three paediatric studies which have measured AHR shortly after birth, before the onset of infection or inflammation.^{49–51} AHR, presumably as a result of anatomical changes,⁵² is associated with long-term adverse respiratory outcomes^{50,53–55}; although the pathological correlates of this are unknown, and hence whether in reality in infants, AHR drives remodeling. Segmental allergen challenge in adults is also associated with upregulation of expression of mediators associated with remodeling⁵⁶; however, this effect appeared to be independent of an airway eosinophilic response⁵⁷ and in any case the relevance of acute changes to chronic remodeling is difficult to determine.

Hence we cannot confirm or refute any of the three hypotheses as to the relationship between inflammation and remodeling, but the balance of evidence (at least in pre-clinical models) is that airway

inflammation and remodeling are parallel processes, as was demonstrated in a murine model.⁵⁸ In that study using a neonatal murine model with intranasal house dust mite challenge, airway responsiveness, airway remodeling and eosinophilic inflammation developed in parallel.⁵⁸ Interestingly, among those seven studies where airway inflammation and remodeling were simultaneously measured, there was no single study where remodeling was present in absence of inflammation. Currently, no studies in patient with asthma have been able to determine whether some aspects of airway remodeling may be protective or deleterious.

We could find two autopsy studies in the literature. Similarly to our findings, in a recent study⁵⁹ airways of 12 fatal cases of childhood (mean age of death of 3.1 years) and adolescent asthma were compared with eight controls showed significantly thickened RBM and eosinophil inflammation than controls; but ASM% was increased only in one-third of fatal asthma cases, exclusively in large airways. Large airway ASM% increased with age and correlated with RBM and duration of asthma. A much older study⁶⁰ reported results from four children, two lung biopsies and two autopsies, with similar findings. Lung tissue showed eosinophilic inflammation and reticular basement membrane thickening.

The obvious weakness of this systematic review is the absence of the definitive study in the literature (above). Another problem is that, whereas there are numerous surrogates for airway inflammation, including induced sputum, FeNO and peripheral blood eosinophil count, there are no real non-invasive surrogates for remodeling. Urinary desmosine has been proposed, but changes are not closely related to airway remodeling, and CT measurements of airway wall thickness in children were disappointing.⁶¹ Possibly newer imaging techniques, for example, magnetic resonance imaging with inhalation of hyperpolarized gas, molecular oxygen, and fluorinated gas will be of more use.⁶² A pilot study suggested exhaled breath condensate cystenyl leukotriene and RBM thickness has a significant relationship in the subgroup of children who were not treated with montelukasts⁴⁰ but this has not been confirmed. Non-invasive measures of airway remodeling are a current research priority. Finally, most if not all studies are confounded by treatment effects. It is rarely if ever justified to bronchoscope a treatment naïve wheezing child. So the effects of ICS in particular on inflammation and remodeling cannot be quantified.

Another weakness is the lack of standardization of morphometric techniques. A joint task force of the American Thoracic Society and European Respiratory Society critically reviewed the state-of-the-art stereological methods in lung morphometry and defined standards to promote comparability of morphometric studies in pulmonary research.⁶³ Most of the studies (25/40) reported in the present systematic review were performed before this statement was published, and there are methodological inconsistencies between them. Future collaborative studies with common protocols following the Task Force recommendations are crucial for a better understanding of the relationship between airway inflammation and remodeling in children with asthma.

Another weakness is the paucity of studies which analyzed more parameters of airway remodeling than RBM thickness or ASM volume.

Airway remodeling is an umbrella term comprising many components which may have different pathways, and conclusions may be different for different parameters. Also, the subgroup analysis in age less than 1-2 years of age relies on a single study. Furthermore, children with only mild and moderate wheezing syndromes are unlikely to come to bronchoscopy, and our conclusions are only applicable to the subgroup with really severe symptoms.

It is unclear whether epithelial desquamation in endobronchial biopsies in asthmatic children is an artefact of tissue sampling or a true pathologic feature of asthma. In small biopsies in particular mechanical force may affect the tissues during collection and processing.⁶³ We found only three studies,^{8,9,36} reporting epithelial shedding, and in one increased epithelial shedding was found in asthmatics compared to controls.³⁶

In summary, this systematic review has failed to identify data to elucidate the relationship between inflammation and remodeling in children with wheezing/asthma. If the relationship between inflammation and remodeling is to be resolved, a key research priority is to identify reliable non-invasive measurements of inflammation and remodeling that can be used at all ages, including infants and preschool children. This would allow longitudinal assessments and enable us to determine which if any aspects of remodeling are protective and should be augmented, and which worsen airflow obstruction and should be treated.

ACKNOWLEDGMENTS

This study was supported by Asthma UK Centre in the Allergic Mechanisms of Asthma. AB is an NIHR Senior Investigator. SS is an NIHR Career Development Fellow.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ORCID

Jose A. Castro-Rodriguez  <http://orcid.org/0000-0002-0708-4281>

REFERENCES

1. Saglani S, Bush A. Onset of structural airway changes in preschool wheezers. A window and target for secondary asthma prevention? *Am J Respir Crit Care Med*. 2015;192:121–122.
2. Bisgaard H, Jensen SM, Bønnelykke K. Interaction between asthma and lung function growth in early life. *Am J Respir Crit Care Med*. 2012;185:1183–1189.
3. Fehrenbach H, Wagner C, Wegmann M. Airway remodeling in asthma: what really matters. *Cell Tissue Res*. 2017;367:551–569.
4. Saglani S, Lloyd CM. Novel concepts in airway inflammation and remodelling in asthma. *Eur Respir J*. 2015;46:1796–1804.
5. Milanese M, Scordamaglia A, Riccio A, Pellegrino R, Canonica GW, Brusasco V. On the functional consequences of bronchial basement membrane thickening. *J Appl Physiol* (1985). 2001;91:1035–1040.
6. Andersson CK, Adams A, Nagakumar P, et al. Intraepithelial neutrophils in pediatric severe asthma are associated with better lung function. *J Allergy Clin Immunol*. 2017;139:1819–1829.e11.
7. Saglani S, Lui S, Ullmann N, et al. IL-33 promotes airway remodeling in pediatric patients with severe steroid-resistant asthma. *J Allergy Clin Immunol*. 2013;132:676–685.e13.
8. Bossley CJ, Fleming L, Gupta A, et al. Pediatric severe asthma is characterized by eosinophilia and remodeling without T(H)2 cytokines. *J Allergy Clin Immunol*. 2012;129:974–982. e13.
9. Gupta A, Sjoukes A, Richards D, et al. Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. *Am J Respir Crit Care Med*. 2011;184:1342–1349.
10. Regamey N, Ochs M, Hilliard TN, et al. Increased airway smooth muscle mass in children with asthma, cystic fibrosis, and non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med*. 2008;177:837–843.
11. Tillie-Leblond I, de Blic J, Jaubert F, Wallaert B, Scheinmann P, Gosset P. Airway remodeling is correlated with obstruction in children with severe asthma. *Allergy*. 2008;63:533–541.
12. Kim ES, Kim SH, Kim KW, et al. Basement membrane thickening and clinical features of children with asthma. *Allergy*. 2007;62:635–640.
13. de Blic J, Tillie-Leblond I, Emond S, Mahut B, Dang Duy TL, Scheinmann P. High-resolution computed tomography scan and airway remodeling in children with severe asthma. *J Allergy Clin Immunol*. 2005;116:750–754.
14. Payne DN, Qiu Y, Zhu J, et al. Airway inflammation in children with difficult asthma: relationships with airflow limitation and persistent symptoms. *Thorax*. 2004;59:862–869.
15. Mahut B, Delclaux C, Tillie-Leblond I, et al. Both inflammation and remodeling influence nitric oxide output in children with refractory asthma. *J Allergy Clin Immunol*. 2004;113:252–256.
16. de Blic J, Tillie-Leblond I, Tonnel AB, Jaubert F, Scheinmann P, Gosset P. Difficult asthma in children: an analysis of airway inflammation. *J Allergy Clin Immunol*. 2004;113:94–100.
17. Barbato A, Turato G, Baraldo S, et al. Airway inflammation in childhood asthma. *Am J Respir Crit Care Med*. 2003;168:798–803.
18. Payne DN, Rogers AV, Adelroth E, et al. Early thickening of the reticular basement membrane in children with difficult asthma. *Am J Respir Crit Care Med*. 2003;167:78–82.
19. Piacentini GL, Bodini A, Costella S, et al. Exhaled nitric oxide and sputum eosinophil markers of inflammation in asthmatic children. *Eur Respir J*. 1999;13:1386–1390.
20. Cokugras H, Akçakaya N, Seçkin, Camcioglu Y, Sarimurat N, Aksoy F. Ultrastructural examination of bronchial biopsy specimens from children with moderate asthma. *Thorax*. 2001;56:25–29.
21. van den Toorn LM, Overbeek SE, de Jongste JC, Leman K, Hoogsteden HC, Prins JB. Airway inflammation is present during clinical remission of atopic asthma. *Am J Respir Crit Care Med*. 2001;164:2107–2113.
22. Berankova K, Uhlik J, Honkova L, Pohunek P. Structural changes in the bronchial mucosa of young children at risk of developing asthma. *Pediatr Allergy Immunol*. 2014;25:136–142.
23. O'Reilly R, Ullmann N, Irving S, et al. Increased airway smooth muscle in preschool wheezers who have asthma at school age. *J Allergy Clin Immunol*. 2013;131:1024–1032. e1.
24. Malmström K, Pelkonen AS, Malmberg LP, et al. Lung function, airway remodelling and inflammation in symptomatic infants: outcome at 3 years. *Thorax*. 2011;66:157–162.
25. Thavagnanam S, Williamson G, Ennis M, Heaney LG, Shields MD. Does airway allergic inflammation pre-exist before late onset wheeze in children? *Pediatr Allergy Immunol*. 2010;21:1002–1007.
26. Erlewyn-Lajeunesse MD, Hunt LP, Pohunek P, et al. Bronchoalveolar lavage MMP-9 and TIMP-1 in preschool wheezers and their relationship to persistent wheeze. *Pediatr Res*. 2008;64:194–199.
27. Saglani S, Payne DN, Zhu J, et al. Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. *Am J Respir Crit Care Med*. 2007;176:858–864.

28. Saglani S, Malmström K, Pelkonen AS, et al. Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction. *Am J Respir Crit Care Med*. 2005;171:722–727.
29. Arnoux B, Bousquet J, Rongier M, Scheinmann P, de Blic J. Increased bronchoalveolar lavage CD8 lymphocyte subset population in wheezy infants. *Pediatr Allergy Immunol*. 2001;12:194–200.
30. Krawiec ME, Westcott JY, Chu HW, et al. Persistent wheezing in very young children is associated with lower respiratory inflammation. *Am J Respir Crit Care Med*. 2001;163:1338–1343.
31. Guiddir T, Saint-Pierre P, Purenne-Denis E, et al. Neutrophilic steroid-refractory recurrent wheeze and eosinophilic steroid-refractory asthma in children. *J Allergy Clin Immunol Pract*. 2017;S2213–S2198.
32. Lezmi G, Gosset P, Deschildre A, et al. Airway remodeling in preschool children with severe recurrent wheeze. *Am J Respir Crit Care Med*. 2015;192:164–171.
33. van Mastrigt E, Vanlaeken L, Heida F, et al. The clinical utility of reticular basementmembrane thickness measurements in asthmatic children. *J Asthma*. 2015;52:926–930.
34. Sonnappa S, Bastardo CM, Saglani S, Bush A, Aurora P. Relationship between past airway pathology and current lung function in preschool wheezers. *Eur Respir J*. 2011;38:1431–1436.
35. Baraldo S, Turato G, Bazzan E, et al. Noneosinophilic asthma in children: relation with airway remodelling. *Eur Respir J*. 2011;38:575–583.
36. Turato G, Barbato A, Baraldo S, et al. Nonatopic children with multitrigger wheezing have airway pathology comparable to atopic asthma. *Am J Respir Crit Care Med*. 2008;178:476–482.
37. Hauk PJ, Krawiec M, Murphy J, et al. Neutrophilic airway inflammation and association with bacterial lipopolysaccharide in children with asthma and wheezing. *Pediatr Pulmonol*. 2008;43:916–923.
38. von Ungern-Sternberg BS, Sly PD, Loh RK, Isidoro A, Habre W. Value of eosinophil cationic protein and tryptase levels in bronchoalveolar lavage fluid for predicting lung function impairment in anaesthetised, asthmatic children. *Anaesthesia*. 2006;61:1149–1154.
39. MacLennan C, Hutchinson P, Holdsworth S, Bardin PG, Freezer NJ. Airway inflammation in asymptomatic children with episodic wheeze. *Pediatr Pulmonol*. 2006;41:577–583.
40. Lex C, Zacharasiewicz A, Payne DN, et al. Exhaled breath condensate cysteinyl leukotrienes and airway remodeling in childhood asthma: a pilot study. *Respir Res*. 2006;7:63.
41. Pohunek P, Warner JO, Turziková J, Kudrmann J, Roche WR. Markers of eosinophilic inflammation and tissue re-modelling in children before clinically diagnosed bronchial asthma. *Pediatr Allergy Immunol*. 2005;16:43–51.
42. Warke TJ, Fitch PS, Brown V, et al. Outgrown asthma does not mean no airways inflammation. *Eur Respir J*. 2002;19:284–287.
43. Marguet C, Dean TP, Basuyau JP, Warner JO. Eosinophil cationic protein and interleukin-8 levels in bronchial lavage fluid from children with asthma and infantile wheeze. *Pediatr Allergy Immunol*. 2001;12:27–33.
44. Ennis M, Turner G, Schock BC, et al. Inflammatory mediators in bronchoalveolar lavage samples from children with and without asthma. *Clin Exp Allergy*. 1999;29:362–366.
45. Fitzpatrick AM, Higgins M, Holguin F, Brown LA, Teague WG. The molecular phenotype of severe asthma in children. *J Allergy Clin Immunol*. 2010;125:851–857. e18.
46. Saglani S, Molyneux C, Gong H, et al. Ultrastructure of the reticular basement membrane in asthmatic adults, children and infants. *Eur Respir J*. 2006;28:505–512.
47. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med*. 2000;162:1403–1406.
48. Grainge CL, Lau LC, Ward JA, et al. Effect of bronchoconstriction on airway remodeling in asthma. *N Engl J Med*. 2011;364:2006–2015.
49. Lesouëf PN, Geelhoed GC, Turner DJ, Morgan SE, Landau LI. Response of normal infants to inhaled histamine. *Am Rev Respir Dis*. 1989;139:62–66.
50. Clarke JR, Salmon B, Silverman M. Bronchial responsiveness in the neonatal period as a risk factor for wheezing in infancy. *Am J Respir Crit Care Med*. 1995;151:1434–1440.
51. Bisgaard H, Jensen SM, Bønnelykke K. Interaction between asthma and lung function growth in early life. *Am J Respir Crit Care Med*. 2012;185:1183–1189.
52. Wongtrakool C, Wang N, Hyde DM, Roman J, Spindel ER. Prenatal nicotine exposure alters lung function and airway geometry through $\alpha 7$ nicotinic receptors. *Am J Respir Cell Mol Biol*. 2012;46:695–702.
53. Grol MH, Gerritsen J, Vonk JM, et al. Risk factors for growth and decline of lung function in asthmatic individuals up to age 42 years. A 30-year follow-up study. *Am J Respir Crit Care Med*. 1999;160:1830–1837.
54. Bisgaard H, Jensen SM, Bønnelykke K. Interaction between asthma and lung function growth in early life. *Am J Respir Crit Care Med*. 2012;185:1183–1189.
55. Cox DW, Mullane D, Zhang GC, et al. Longitudinal assessment of airway responsiveness from 1 month to 18 years in the PIAF birth cohort. *Eur Respir J*. 2015;46:1654–1661.
56. Kelly EA, Busse WW, Jarjour NN. Increased matrix metalloproteinase-9 in the airway after allergen challenge. *Am J Respir Crit Care Med*. 2000;162:1157–1161.
57. Hastie AT, Kraft WK, Nyce KB, et al. Asthmatic epithelial cell proliferation and stimulation of collagen production: human asthmatic epithelial cells stimulate collagen type III production by human lung myofibroblasts after segmental allergen challenge. *Am J Respir Crit Care Med*. 2002;165:266–272.
58. Saglani S, Mathie SA, Gregory LG, Bell MJ, Bush A, Lloyd CM. Pathophysiological features of asthma develop in parallel in house dust mite-exposed neonatal mice. *Am J Respir Cell Mol Biol*. 2009;41:281–289.
59. Malmström K, Lohi J, Sajantila A, et al. Immunohistology and remodeling in fatal pediatric and adolescent asthma. *Respir Res*. 2017;18:94.
60. Cutz E, Levison H, Cooper DM. Ultrastructure of airways in children with asthma. *Histopathology*. 1978;2:407–421.
61. Saglani S, Papaioannou G, Khoo L, et al. Can HRCT be used as a marker of airway remodelling in children with difficult asthma? *Respir Res*. 2006;7:46.
62. Kruger SJ, Nagle SK, Couch MJ, Ohno Y, Albert M, Fain SB. Functional imaging of the lung with gas agents. *J Magn Reson Imaging*. 2016;43:295–315.
63. Hsia CC, Hyde DM, Ochs M, Weibel ER, ATS/ERS Joint Task Force on Quantitative Assessment of Lung Structure. An official research policy statement of the American Thoracic Society/European Respiratory Society: standards for quantitative assessment of lung structure. *Am J Respir Crit Care Med*. 2010;181:394–418.

How to cite this article: Castro-Rodríguez JA, Saglani S, Rodríguez-Martínez CE, Oyarzun MA, Fleming L, Bush A. The relationship between inflammation and remodeling in childhood asthma: A systematic review. *Pediatric Pulmonology*. 2018;1–12.

<https://doi.org/10.1002/ppul.23968>