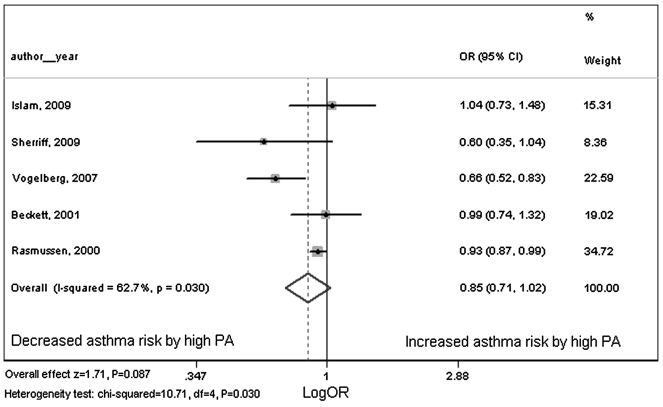

Abstract S84 Figure 1 Random effect meta-analysis of physical activity (PA) and new-onset childhood asthma.

participants n=12 889; total new-onset asthma n=912). Meta-analysis of these studies showed the following associations of high PA with new-onset asthma: Random effect model: OR (95% CI) 0.854 (0.713; 1.023) (Abstract S84 Figure 1) and fixed effect model: 0.909 (0.855; 0.967). I-squared=62.7% (both models).

Conclusion The results of this review did support some inverse association between high levels of PA and asthma development in children. However, a limited number of eligible studies were identified and considerable heterogeneity was present.

S85 THE EFFECTS OF EXPOSURE TO IL-9 ALONE OR IN COMBINATION WITH IL-13 ON THE MUCOCILIARY DIFFERENTIATION OF BRONCHIAL EPITHELIAL CELLS FROM NORMAL AND ASTHMATIC CHILDREN.

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Background IL-9 is a pleiotropic Th2 cytokine that has been implicated in the pathogenesis of asthma. IL-9 has been linked to goblet cell hyperplasia and decreased ciliogenesis in animal models and an epithelial injury model in adults. We tested the effects of IL-9 alone and in combination with IL-13, an important cytokine in allergic asthma, during differentiation of bronchial epithelial cells from both asthmatic and normal children.

Hypothesis We hypothesised that bronchial epithelial cells from normal children exposed to IL-9 would result in goblet cell hyperplasia and decreased ciliogenesis, with additional augmented response when treated with a combination of IL-9 and IL-13.

Methods We cultured bronchial epithelial cells from asthmatic and normal children at an air–liquid interface for 28 days. We enumerated the presence of goblet and ciliated cells at the end of the experimental period.

Results IL-9 stimulation alone did not alter goblet cell numbers in differentiating cultures from normal or asthmatic children. IL-9 stimulated PBECs from normal children had reduced ciliated cell numbers and increased MUC5AC secretion at the apical surface which was not seen in asthmatic cells. Combining IL-9 and IL-13 had no additional synergistic effect.

Conclusions We conclude that IL-9 alone or in combination with IL-13 did not stimulate goblet cell hyperplasia in bronchial epithelial cells cultures from normal children. We have shown that it is does lower the number of ciliated cells during differentiation of PBECs from normal children however this effect is not seen in cells from asthmatic children.

S86 EFFECTS OF EXPOSURE TO IL-13, IL-31 AND AN IL-13/31 COMBINATION ON MUCOCILIARY DIFFERENTIATION OF BRONCHIAL EPITHELIAL CELLS FROM NORMAL CHILDREN

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Background Asthma is characterised by airway remodelling which includes smooth muscle hypertrophy, goblet cell hyperplasia and subsequent mucus hyper-secretion. Th2 cytokines including IL-13 and more recently IL-31 have been implicated in the pathogenesis of asthma.

Objectives We aimed to examine the effects of IL-13 (20 ng/ml), IL-31 (20 ng/ml) and an IL-13/31 combination (20 ng/ml of both) on the in vitro mucociliary differentiation of paediatric bronchial epithelial cells (PBECs) from normal patients.

Hypothesis We hypothesised that cells from normal children exposed to IL-13, IL-31 or an IL-13/31 combination would alter their phenotype towards that of an asthmatic epithelium.

Methods Markers of differentiation, real time PCR for MUC5AC, MUC5AC ELISA and transepithelial electrical resistance (TEER) were assessed.

Results We found that well-differentiated paediatric bronchial epithelial cells highly expressed the IL-31 receptor (IL-31RA). Transepithelial electrical resistance (TEER) indicated good formation of tight junctions which was found to be similar across all treatment groups. We found that IL-13 stimulation reduced the number of ciliated cells compared with control (IL-13 stimulation: mean=4.8% (SD=2.5); Control: mean=18.1%, (SD=5.9)). We did not find that the combination of IL-13 and IL-31 had any additional effects to that of IL-13 alone (IL-13/31 combination stimulation: mean=5.1% (SD=4.6); Control: mean=18.1%, (SD=5.9)). Stimulation with IL-13, IL-31 and the IL-13/IL-31 combination did not result in any changes of goblet cell numbers.

Conclusions IL-31RA receptor is present in abundance in well-differentiated paediatric bronchial epithelial cells however IL-31 does not exhibit any detrimental effects on mucociliary differentiation or proliferation. In addition, IL-31 does not appear to have a synergistic effect when combined in culture with IL-13, in the differentiation process.

S87 RELATIONSHIP BETWEEN BRONCHIAL RETICULAR BASEMENT MEMBRANE THICKNESS (RBM) AND SMOOTH MUSCLE MASS IN CHILDHOOD SEVERE ASTHMA (SA)

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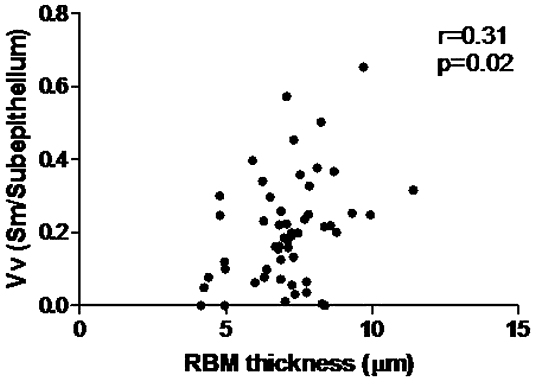
Background In asthma there is a direct relationship between tissue eosinophilic inflammation and RBM thickness. However, relationships between components of remodelling have not been explored, but may be important especially in determining disease severity. There are no reports of an association between smooth muscle mass and asthma severity in children. We hypothesised that increases in both RBM thickness and smooth muscle mass is present in children with SA, only increased RBM thickness is present in mild asthma and neither feature is present in controls.

Methods 75 children, mean age 11.8 (5.6–17.3) years, 53 with SA, 7 with mild/moderate asthma and 15 non-asthmatic controls



Abstract S87 Figure 1 Correlation between RBM and volume fraction of airway smooth muscle in asthma.

(bronchoscoped for upper airway symptoms) were included. All underwent fibreoptic bronchoscopy with endobronchial biopsies (EB). EB were processed to paraffin, and 5 µm sections were cut and stained with haematoxylin and eosin and used to quantify RBM thickness, epithelial shedding and volume fraction (Vv) of subepithelial smooth muscle indexed to submucosa.

Results Epithelial shedding was increased in atopic but not asthmatic subjects, (p=0.02 and p=0.37, respectively), and in children with asthma was correlated with exhaled nitric oxide (r=0.4, p=0.005). RBM thickness was increased in severe asthmatics compared to controls (p<0.0001), but a trend only to increased thickness was seen in mild asthmatics compared to controls (median (range) values: 6 (4.4–8.4) and 4 (3.1–7.5) µm, respectively; p=0.06). The Vv of subepithelial airway smooth muscle was only increased in severe asthmatics compared to controls (0.20 (0–0.65) and 0.09 (0–0.16), respectively; p=0.002). Interestingly, there was a positive relationship between RBM thickness and smooth muscle Vv fraction in asthmatics, but not in controls (r=0.31, p=0.02 and r=0.5, p=0.07, respectively) (Abstract S87 Figure 1).

Discussion We report for the first time a direct relationship between RBM thickness and airway smooth muscle mass in paediatric asthma. It is unknown if the relationship is causal, or both are driven by a common underlying process. Combinations of components of airway remodelling, rather than single factors, may prove to be more informative when phenotyping children with severe asthma.

S88 MAST CELL MYOSITIS IS ASSOCIATED WITH PERSISTENT AIRFLOW LIMITATION (PAL) IN CHILDHOOD SEVERE ASTHMA (SA)

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Background Studies of airway inflammation and remodelling may help us to understand the pathophysiology of SA. Adult studies have shown mast cell inflammation within smooth muscle is specific to asthma and is associated with airway hyperresponsiveness (AHR). However, this has not been studied in childhood disease.

Hypothesis Children with SA have increased submucosal eosinophils and mast cells within smooth muscle compared to age-matched mild asthmatics and non-asthmatic controls.

Methods 75 children, mean age 11.8 (5.6–17.3) years, 53 with SA, 7 with mild/moderate asthma (MA) and 15 non-asthmatic controls (bronchoscoped for upper airway symptoms) were included. All underwent spirometry and bronchodilator reversibility, fractional exhaled nitric oxide (FeNO) measurement, fibreoptic bronchoscopy with bronchoalveolar lavage (BAL) and endobronchial biopsy (EB). EB were stained for: eosinophils (congo red), neutrophils (neutrophil elastase), mast cells (mast cell tryptase); and reticular basement membrane (RBM) thickness, epithelial shedding and volume fraction (Vv) of smooth muscle.

Results **See Abstract S88 Table 1.** Children with SA had significantly increased BAL and submucosal eosinophils compared to controls. There were no significant group differences in submucosal mast cells, but the presence of mast cells within smooth muscle exhibited a non-significant trend to be increased in SA and MA. Children with mast cells within smooth muscle were more likely to have PAL (post bronchodilator, post steroid trial FEV_1<80% predicted) (p<0.05). The Vv of subepithelial tissue occupied by airway smooth muscle (ASM) was only increased in SA.

Abstract S88 Table 1 Airway inflammation and remodelling in severe, mild/moderate asthma and non asthmatic control subjects

	Severe asthma (n=53)	Mild/moderate asthma (n=7)	Control (n=15)	p
BAL eosinophils %	**2.7 (1–51)**	**0.7 (0–27.7)**	**0 (0–5.7)**	**<0.001**
BAL neutrophils %	3.3 (0.3–73.7)	1.7 (0–7.3)	2.7 (0.6–14)	NS
Mucosal eosinophils (/mm²)	**11.2 (0–209.3)**	**3.7 (0–14.5)**	**0 (0–25.1)**	**0.01**
Mucosal neutrophils (/mm²)	9.8 (0–125.6)	11.4 (0–22.2)	1.2 (0–58.3)	NS
Mucosal mast cells (/mm²)	45.7 (0–185)	63.1 (9.2–79.7)	60.5 (0–165.6)	NS
Muscle mast cells (/mm²)	12.3 (0–299)	18.3 (0–72.8)	0 (0–50)	NS
Vv (sm/subepithelium)	**0.20 (0–0.65)**	**0.06 (0–0.3)**	**0.09 (0–0.16)**	**0.002**

Values are median (range).
All highlighted p values denote difference between severe asthma and controls.
BAL, bronchoalveolarlavage; RBM, reticular basement membrane; sm, smooth muscle; Vv, volume fraction of airway smooth muscle indexed to subepithelium.

Conclusions Children with SA have increased luminal and submucosal eosinophilia. However, in contrast to reports in adults of AHR being associated with mast cell myositis, we have found severe asthmatic children with mast cell myositis were more likely to have PAL. Mast cell myositis may be a feature of severe asthma in children.

Basic mechanisms in lung cancer

S89 BIMODAL IRON OXIDE NANOPARTICLES FOR HYPERTHERMIA THERAPY AND MR IMAGING IN CANCER

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Introduction Super paramagnetic iron oxide nanoparticles (SPION) offer attractive possibilities in biomedicine. Hyperthermia treatment of cancer involves introducing SPION into tumours and applying an alternating magnetic field (AMF). The AMF causes the SPION to heat, resulting in cell death. It has been shown previously that mesenchymal stem cells (MSCs) can be labelled with SPION, with no effect on cell survival, and that they will migrate to and integrate into lung metastases in vivo, following systemic administration. Furthermore, SPION can be used to follow the fate of labelled cells in the body as they cause a marked shortening in T2* on MRI. Therefore, MSCs labelled with SPION offer a promising delivery mechanism for treating lung metastases with hyperthermia therapy. In this preliminary study, the distribution of SPION labelled MSCs and the anti-tumour effect of hyperthermia treatment was evaluated in vitro and in a subcutaneous murine tumour model.

Methods

- MSCs were obtained from Tulane University, New Orleans. Cells were incubated overnight in 0.5 mg/ml of the SPION