Epithelial science congress highlights: The European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress

1–3 July 2022 | Prague, Czech Republic

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EpiCentral
UNDERSTANDING THE CENTRAL ROLE OF THE EPITHELIUM IN SEVERE ASTHMA AND BEYOND

Contents

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Aims

- These slides cover **congress highlights** from abstracts that were presented at EAACI 2022
- The abstracts were carefully selected to include data that further the understanding of **epithelial science**; this is not an exhaustive list of all abstracts

Permissions

- Authors of each abstract were notified that their data will be included in this report
- Please note that **the key takeaways** are not corroborated by these authors, but **were developed** based on the data presented within the abstracts **for the purposes of this report**

Conference details

- Please note that this report was **developed specifically for EpiCentral** and is independent of the congress
- The EAACI Hybrid Congress was held on 1–3 July 2022 in Prague, Czech Republic

Report sections

EAACI, European Academy of Allergy and Clinical Immunology

Key takeaways

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- Differences in characteristics and biomarkers between patients and over time demonstrated the variability of asthma phenotypes and underlying inflammatory pathways[1–4]. Patients who have a dynamic phenotype may experience worse outcomes than those with a stable phenotype[3]
- Exposure of the airway epithelium to environmental insults can trigger inflammatory processes[5,6]. In patients with allergic asthma, pollen glycolipids were shown to activate NKT cells, induce cytokine production and promote airway inflammation; however, this environmental insult was not associated with AHR[6]
- In adults, the presence of eosinophilia was associated with exacerbations leading to hospitalisation[7], while eosinophilic activation (as measured by EDN) may be a prognostic biomarker in children with asthma, as shown by increased blood EDN that correlated with hospital stay[8]
- Exposure to RV and MPV may promote the development of allergic asthma in children and these viral insults were associated with increased AHR as measured by methacholine[9]

AHR, airway hyperresponsiveness; EDN, eosinophil-derived neurotoxin; MPV, metapneumovirus; NKT, natural killer T; RV, rhinovirus

1. Delgado-Dolset M, et al. Poster 001865 presented at EAACI 2022; 2. Li X, et al. Poster 000315 presented at EAACI 2022; 3. Emelyanov A, et al. Poster 000308 presented at EAACI 2022; 4. De Boer GM, et al. Poster 001628 presented at EAACI 2022; 5. Fatkhutdinova LM, et al. Poster 001042 presented at EAACI 2022; 6. González Roldán N, et al. Oral presentation 000971 presented at EAACI 2022; 7. dos Santos FR, Silva BS. Poster 000224 presented at EAACI 2022; 8. Kim HS, et al. Poster 000078 presented at EAACI 2022; 9. Myklebust Å, et al. Poster 100056 presented at EAACI 2022

Complexity of severe asthma

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Role of allergy in the pathogenesis of severe uncontrolled asthma

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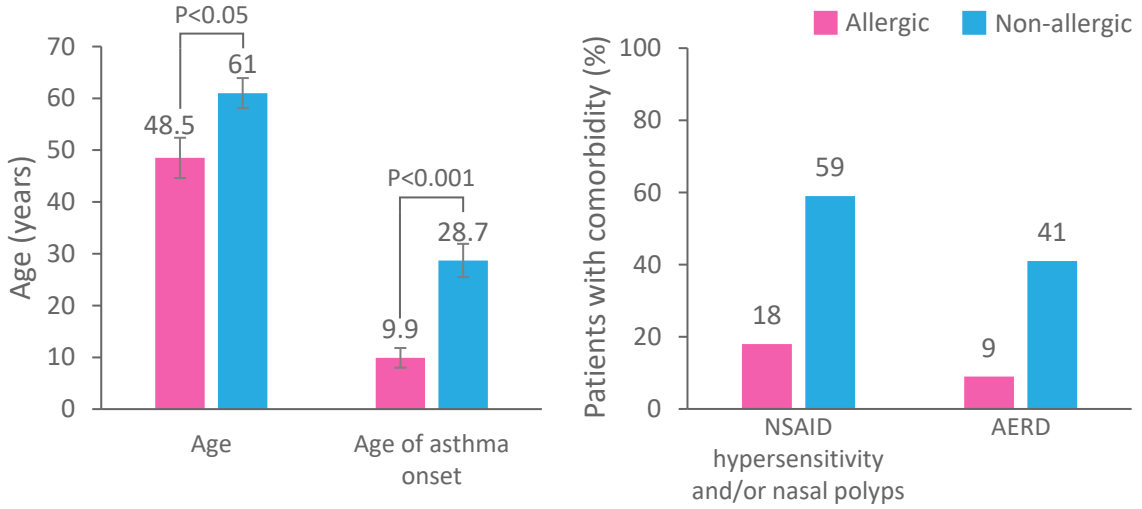
- Baseline characteristics for patients with uncontrolled house dust mite-allergic asthma (n=11) and uncontrolled, non-allergic asthma (n=17) were compared
- Metabolomic analysis of serum samples by LC-MS with hierarchical clustering analysis was used to determine signals that were significantly different between the two groups

Delgado-Dolset M.
Universidad San Pablo CEU, Madrid, Spain

- Baseline characteristics were different between allergic and non-allergic patients; those in the non-allergic group were typically older, with a higher age of asthma onset, and were more likely to have NSAID hypersensitivity, nasal polyps or AERD

Baseline characteristics for allergic and non-allergic patients



- Overall, 52 signals were significantly (P<0.05) different between the allergic and non-allergic groups
  - Of which, 51 were increased in the allergic group with one (deoxycholic acid) being decreased
- Relevant metabolites significantly (P<0.05) elevated in the allergic group included LPC 22:5, LPC 18:2, LPC 20:4 and LPC 18:3

Key takeaways: *Patients with allergic and non-allergic asthma differ in baseline characteristics and metabolic profiles, suggesting differences in inflammatory status and disease mechanism*

AERD, aspirin-exacerbated respiratory disease; LC-MS, liquid chromatography coupled to mass spectrometry; LPC, lysophosphatidylcholine; NSAID, non-steroidal anti-inflammatory drug
Delgado-Dolset M, et al. Poster 001865 presented at EAACI 2022

Phenotypic and genetic analyses of non-atopic asthma, atopic asthma with fungal or non-fungal sensitization identify shared and distinct characteristics in children and adults

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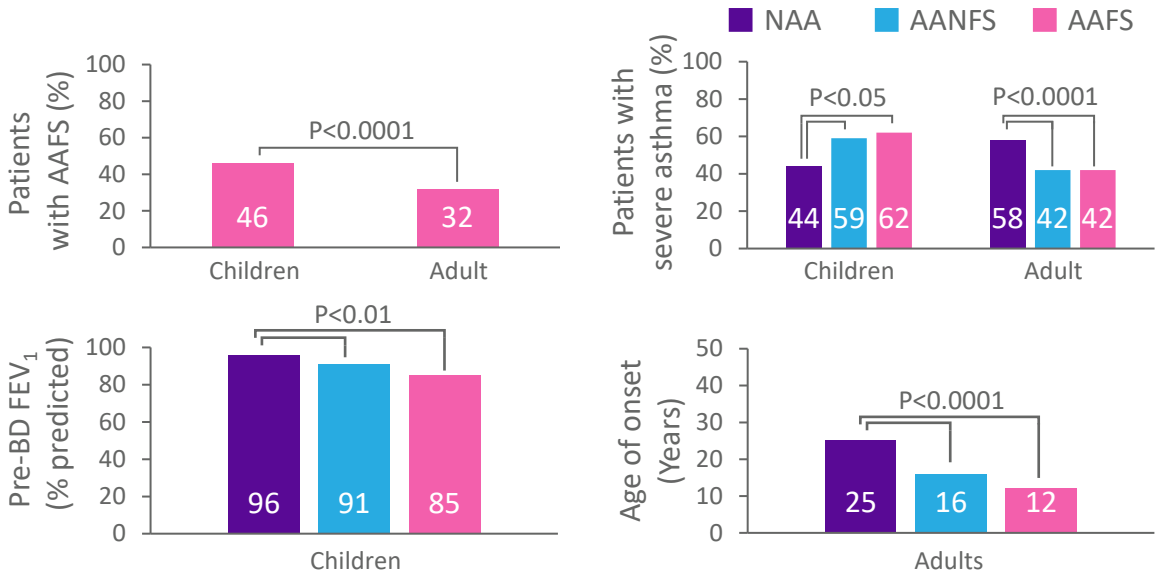
- Characteristics of adults and children (6–18 years) with non-atopic asthma (NAA) (n=225 and n=41 for adults and children, respectively), atopic asthma with fungal sensitisation (AAFS) (n=436 and n=149) or atopic asthma with non-fungal sensitisation (AANFS) (n=692 and n=135) were compared

Li X.
University of Arizona, Tucson, USA

- AHR and total IgE levels increased from NAA to AANFS and to AAFS
- In children, T2 biomarkers (IgE, FeNO, blood Eos and sputum Eos) increased from NAA to AANFS and to AAFS, and AAFS and AANFS were associated with severe asthma*, reduced lung function and greater OCS use
- In adults, non-T2 biomarkers (blood neutrophils and serum IL-6) and age of asthma onset decreased from NAA to AANFS and to AAFS, and NAA was associated with severe asthma, comorbidities, corticosteroid use and healthcare utilisation
- SNPs within *HLA-DRA* and *GSDMB* genes were found to be associated with fungal sensitivity (P<0.05 and P<0.01, respectively); the latter was also associated with earlier age of onset and severe asthma

Characteristics of patients with AAFS, AANFS or NAA



Key takeaways: *Asthma phenotypes may involve different inflammatory processes. Genetics may play an underlying role in fungal sensitivity; however, it is likely that environmental factors are also important*

*According to ATS-ERS definition

AAFS, atopic asthma with fungal sensitisation; AANFS, atopic asthma with non-fungal sensitisation; AHR, airway hyperresponsiveness; ATS-ERS, American Thoracic Society-European Respiratory Society; BD, bronchodilator; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; IL, interleukin; NAA, non-atopic asthma; OCS, oral corticosteroid(s); SNP, single nucleotide polymorphism; T2, type 2

Li X, et al. Poster 000315 presented at EAACI 2022

Stability of allergen-driven severe asthma: a real life 5-year follow-up study

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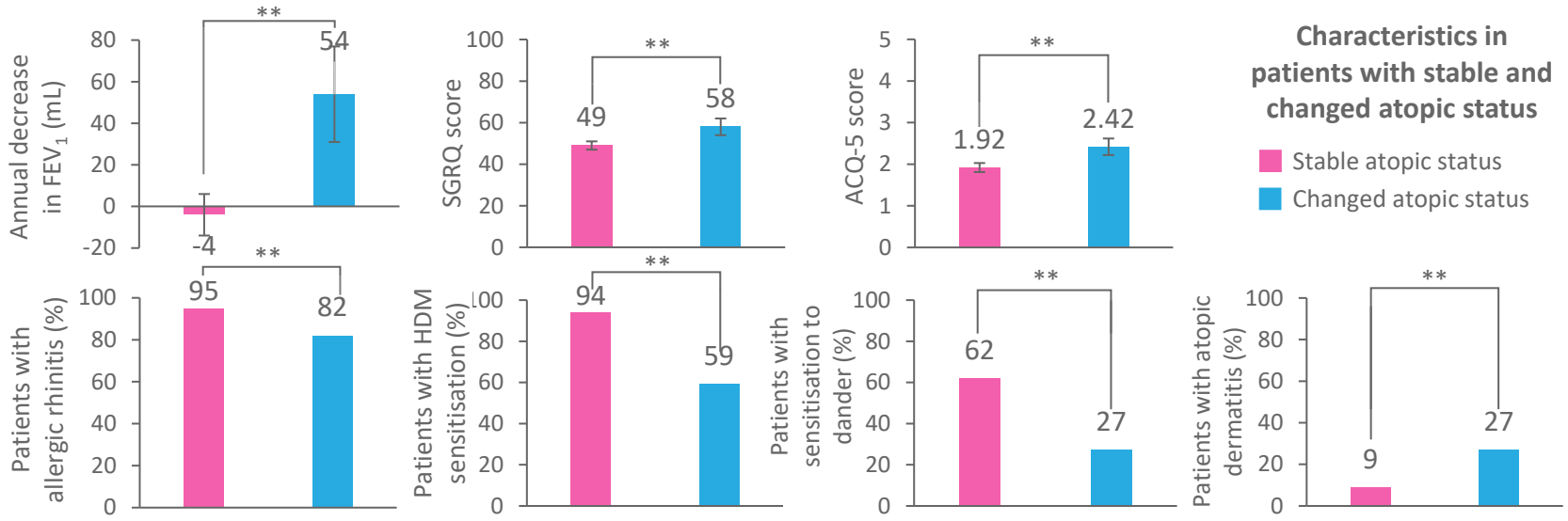
- The stability of allergen-driven* severe asthma† was investigated in 117 adult patients over a 5-year period
- Biomarkers and clinically important outcomes, including number of exacerbations, SGRQ, ACQ-5, FEV_1 and total IgE, were recorded at baseline and after 5 years; patients who reported the absence of allergen-driven symptoms (n=48) during the study had their atopic status re-assessed

Emelyanov A.
North-Western State Medical University named after I.I. Mechnikov, St Petersburg, Russia

- After 5 years, 19% of patients changed atopic status from positive to negative
- Change in atopic status was associated with a decrease in lung function and asthma control and a worse quality of life
- Patients who changed atopic status were less likely to have allergic rhinitis, sensitisation to HDM or animal dander, but more likely to have atopic dermatitis



Key takeaways: *Mechanisms driving a patient's asthma can change over time; patients who have a dynamic phenotype may experience worse outcomes than those with a stable phenotype*

*Confirmed by either a positive skin-prick test or serum-specific IgE to common inhalant allergens; †according to ATS-ERS definition; **P<0.05
ACQ-5, Asthma Control Questionnaire-5; ATS-ERS, American Thoracic Society-European Respiratory Society; FEV_1, forced expiratory volume in 1 second; HDM, house dust mite; IgE, immunoglobulin E; SGRQ, St George's Respiratory Questionnaire
Emelyanov A, et al. Poster 000308 presented at EAACI 2022

Variability of type 2 inflammatory biomarkers in severe asthma: 18 months follow-up

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- The variability of inflammatory endotypes was assessed in patients (n=70) with severe asthma (GINA Step 4) and recurrent asthma exacerbations
- Asthma endotypes were analysed over time and the relationship between T2 inflammatory mediators with seasons and asthma exacerbations was investigated

De Boer GM.
Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands

- In total, 27% of patients demonstrated a variable T2 endotype*; variability in T2 classification was not influenced by seasonal changes or frequency of asthma exacerbations
- Over 18 months:

Across all patients (n=70)	↓ Blood Eos decreased (P=0.032)	↔ FeNO remained stable	
In a subgroup of patients with T2 asthma (n=41)	↑ Blood Eos increased (P=0.040)	↑ IL-4-producing $CD45RA^-CD4^+$ T cells increased with a seasonal change in spring	↑ $Foxp3^+CD45RA^+CD4^+$ T cells increased with a seasonal change in spring

- During exacerbations, circulating IL-4-, IL-5- and IL-9-producing $CD45RA^-CD4^+$ T cells increased (P= 0.02, 0.07 and 0.02, respectively) and returned to baseline afterwards

Key takeaways: *T2 asthma is dynamic, with inflammatory biomarkers changing over time*

*T2 endotype defined as blood Eos ≥150 cells/µL or FeNO ≥20 ppb
Eos, eosinophils; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; IL, interleukin; ppb, parts per billion; T2, Type 2
De Boer GM, et al. Poster 001628 presented at EAACI 2022

Epithelial cytokines and the inflammatory cascade

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Biomarkers of allergic and non-allergic phenotypes of the T2 endotype of bronchial asthma under exposure to fine particles in the ambient air

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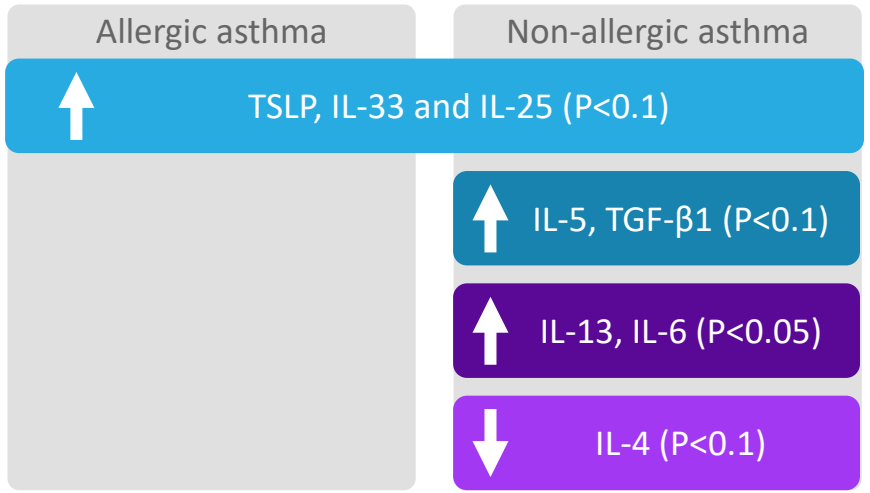
- The effect of fine particles (PM2.5–PM10.0) on patients with allergic T2 (n=40) or non-allergic T2 asthma (n=42), or on health controls (n=48) was investigated
- Serum concentrations of key inflammatory biomarkers* and expression of *IL-4*, *TGF-β1* and *IL-17A* genes in blood were measured and correlated with particle exposure†

Fatkhutdinova LM.
Kazan State Medical University, Kazan, Russia

- The T2-response level depended on the dose of deposited particles for allergic patients; for non-allergic patients, both T2 and T17 responses were dose dependent
- Increased secretion of epithelial cytokines (TSLP, IL-33 and IL-25) in correlation with particle exposure was found for both asthma subgroups
- In patients with non-allergic asthma, particle exposure correlated with expression of *TGF-β1*, levels of IL-5, IL-6 and IL-13 (dependent on deposited thoracic dose), and negatively correlated with IL-4 levels
- Bacterial endotoxin levels in air samples‡ associated with increased expression of *IL-4* (P<0.1) and decreased epithelial cytokines and IL-17A (P<0.05)

Biomarker changes correlating with dose of deposited particles



Key takeaways: *In patients with T2 asthma, cytokines, and in particular epithelial cytokines, play a key role in the response to environmental insults, but downstream inflammatory mediators play different roles in different asthma endotypes*

*Measured via multiplex immunoassay; †estimated using averaged annual concentrations of PM in a geospatial approach and calculation of mass doses deposited in lung regions using multiple-path particle dosimetry code; ‡measured by LAL analysis
IL, interleukin; LAL, limulus amebocyte lysate; PM, particulate matter; T2, type 2; TGF-β1, transforming growth factor β1; TSLP, thymic stromal lymphopoietin
Fatkhutdinova LM, et al. Poster 001042 presented at EAACI 2022

Diacylgalactosyldiacylglicerols from grass pollen prime the development of allergic airway inflammation

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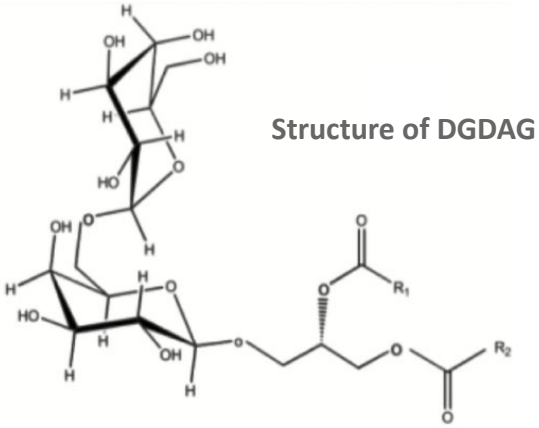
González Roldán N.
Research Center Borstel, Borstel, Germany

- Previous research into pollen allergies has focused on pollen proteins as allergens; however, the pollen coat contains a large range of lipids in addition to proteins
  - There is presently limited research into the detailed structure-activity relationship between lipid classes and reactive immune cells in allergic inflammation
- This study aimed to isolate and characterise the chemical structure of glycolipids present in Timothy grass (*Phleum pratense*) pollen and to determine their role in allergic airway inflammation

- Total extracted and fractionated glycolipids from *P. pratense* pollen-induced upregulation of CD69 in human NKT cells in blood and proliferation of murine NKT cells
- Structural determination* showed three diacylgalactosyldiacylglycerols (DGDAGs) to be responsible for biological activity
- Synthetic DGDAGs induced murine NKT proliferation *ex vivo* and IL-13 expression
- In an *in vivo* murine model, DGDAGs induced airway inflammation and eosinophilia, but did not lead to development of AHR



Structure of DGDAG

Key takeaways: *Pollen glycolipids can activate NKT cells, induce cytokine production and promote airway inflammation*

*Via GC-MS, ESI-MS and NMR analyses, and structure-function analyses using synthetic DGDAGs

AHR, airway hyperresponsiveness; ESI-MS, electrospray ionisation mass spectrometry; GC-MS, gas chromatography coupled to mass spectrometry; IL, interleukin; NKT, natural killer T; NMR, nuclear magnetic resonance

González Roldán N, et al. Oral presentation 000971 presented at EAACI 2022

Role of eosinophil and neutrophils on lung function and prognosis in children with acute asthma exacerbation

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- The relationship of lung function and prognosis with activity of eosinophils and neutrophils, represented by the biomarkers EDN and MPO, respectively, was investigated in children admitted to hospital for asthma exacerbations (5–18 years; n=82)
- Upon hospital admission and discharge, lung-function tests and blood analyses (WBC, MPO, eosinophil fraction, EDN, CRP, IL-4, IL-5 and IL-10) were performed

Kim HS.
The Catholic University of Korea, Seoul, South Korea

- Between admission and discharge, there were:
  - ↑ Significant improvements in lung function (FEV_1, FVC, FEV_1/FVC and MMEF)
  - ↓ Significant reductions in blood MPO, EDN and IL-4
- Blood EDN concentration was found to correlate with FEV_1 and duration of hospital stay (r=0.221, P<0.001)

Key takeaways: *Eos activation, measured by blood EDN, may act as a prognostic biomarker in children with asthma exacerbations*

CRP, C-reactive protein; EDN, eosinophil-derived neurotoxin; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IL, interleukin; MMEF, maximal mid-expiratory flow; MPO, myeloperoxidase; WBC, white blood cell

Kim HS, et al. Poster 000078 presented at EAACI 2022

Eosinophilia in hospitalized patients with acute asthma exacerbation

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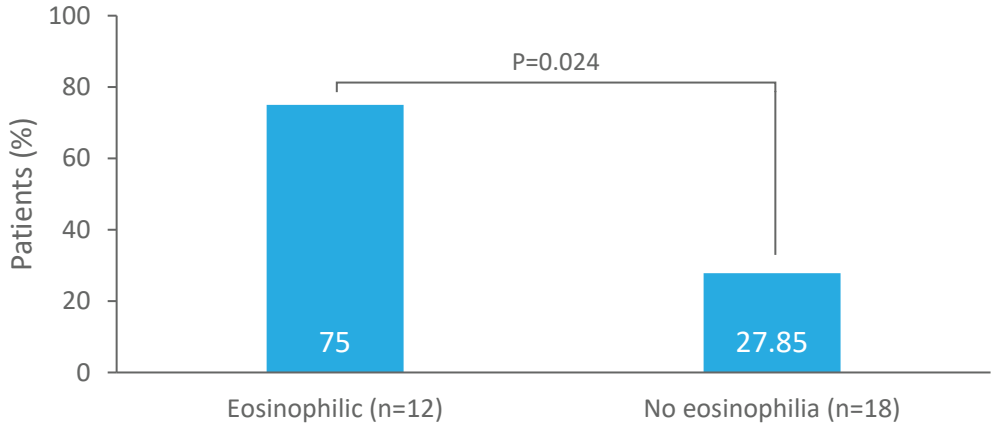
- The study aimed to describe the prevalence of eosinophilia* in adult patients (20–91 years) hospitalised with acute asthma exacerbations and its influencing factors (n=30)

dos Santos FR.
Centro Hospitalar Universitário do Porto, Porto, Portugal

- 40% of patients hospitalised for an asthma exacerbation had eosinophilia
- Eosinophilia was associated with asthma exacerbations in the previous 12 months requiring hospital admission (P=0.024)
- There was no significant relationship between eosinophilia and age (P=0.871), sex (P=1.000), early hospital readmission (P=0.334), respiratory infection (P=0.139), smoking (P=0.052), FEV_1 (P=0.249), poor treatment adherence (P=0.710) or maintenance systemic steroid use (P=0.500)

Proportion of patients admitted to hospital during the previous 12 months, by eosinophilic status



Key takeaways: *Elevated blood Eos levels are associated with repeat hospitalisations for asthma exacerbations*

*Defined as blood Eos >300 cells/µL
Eos, eosinophils; FEV_1, forced expiratory volume in 1 second
dos Santos FR, Silva BS. Poster 000224 presented at EAACI 2022

Airway hyperresponsiveness

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Airway hyperresponsiveness and lung function in fungal asthma with and without IgE sensitization to *Aspergillus fumigatus*

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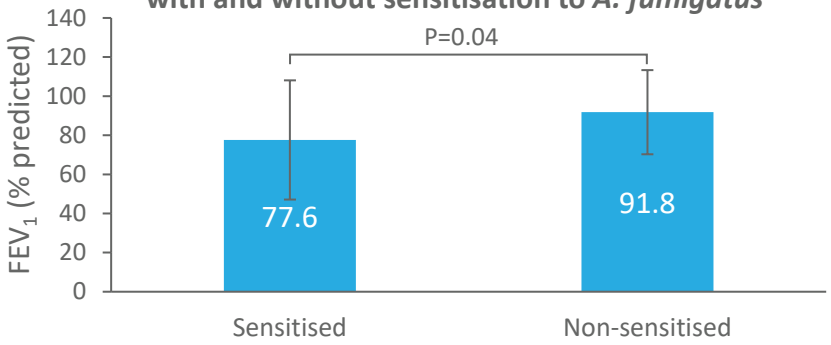
- Differences in AHR* and lung function were investigated in adult, steroid-naïve patients with fungal asthma who had IgE sensitisation to *Aspergillus fumigatus* (n=24) and those who had sensitisation to other fungi (n=36; 89% were sensitised to *Candida*)

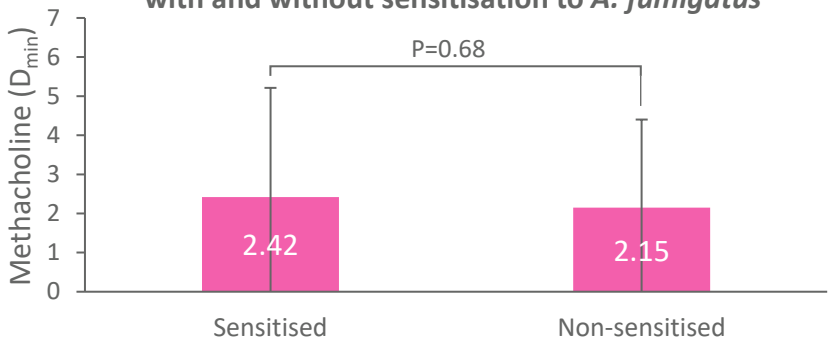
Imaoka M.
Matsuyama Kinen Hospital, Matsuyama, Japan

- There were no significant differences in demographic or biomarker levels (blood Eos, total IgE or FeNO) between patients who had sensitisation to *A. fumigatus* and those who did not
- Lung function was significantly lower in patients with sensitisation to *A. fumigatus* compared with those who did not (P=0.04), while there was no significant difference in AHR between the groups (P=0.68)

Lung function in patients with fungal asthma, with and without sensitisation to *A. fumigatus*



AHR in patients with fungal asthma, with and without sensitisation to *A. fumigatus*



Key takeaways: *Further research is required to understand the mechanisms underlying AHR in fungal asthma and to elucidate how differing IgE sensitisation impacts lung function*

*Measured via methacholine challenge using Astograph method

AHR, airway hyperresponsiveness; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiration volume in one second; IgE, immunoglobulin E

Imaoka M. Poster 001455 presented at EAACI 2022

Asthma and bronchial hyperresponsiveness in school-aged children after human metapneumovirus infection in early childhood – a risk factor comparable to RV bronchiolitis?

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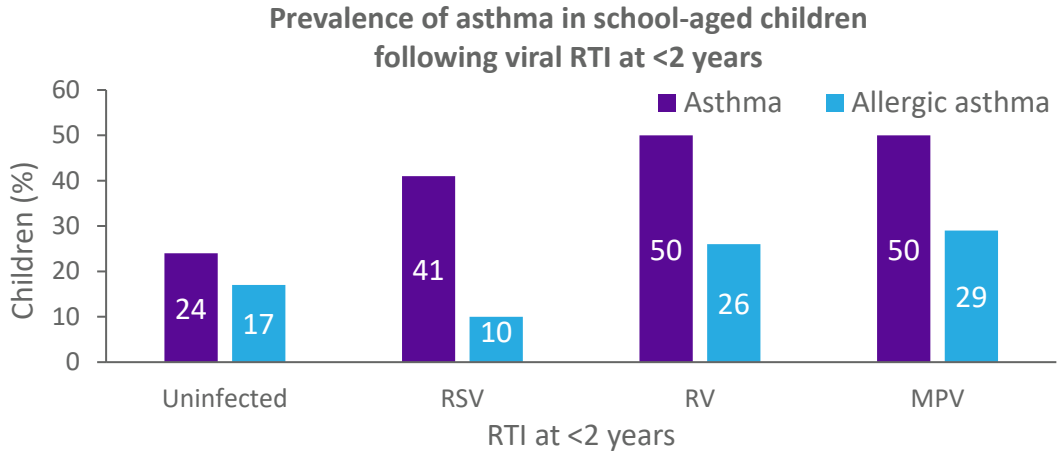
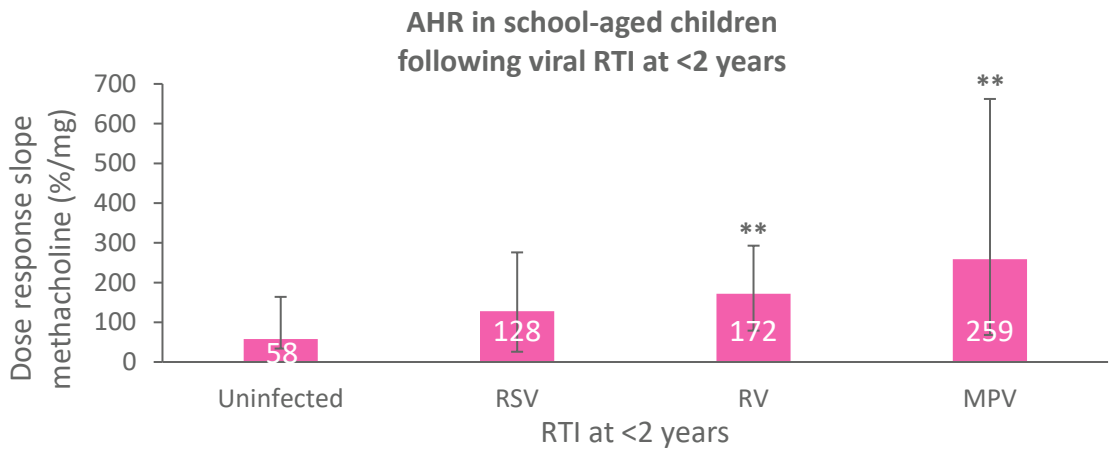
- The prevalence of asthma and AHR* was investigated in school-aged children (6–13 years) who had been infected with MPV (n=16), RSV (n=51) or RV (n=34) at <2 years, and compared with those in uninfected children (n=21)

Myklebust Å.
St Olavs Hospital, Trondheim, Norway

- Children previously hospitalised with viral RTI showed a numerically higher prevalence of asthma and allergic asthma compared with uninfected children (P=0.07)



- AHR was significantly greater in the MPV group (P=0.015) and RV group (P=0.049) compared with uninfected children; no significant difference was observed in the RSV group (P=0.817)



Bars represent median values and error bars represent IQR

Key takeaways: *RV or MPV infection during infancy are associated with AHR and increased likelihood for development of asthma and allergic asthma*

*Measured by methacholine challenge; **statistically significant (P<0.05) compared to uninfected controls in Mann-Whitney U test
AHR, airway hyperresponsiveness; IQR, interquartile range; MPV, metapneumovirus; RSV, respiratory syncytial virus; RTI, respiratory tract infection; RV, rhinovirus
Myklebust Å, et al. Poster 100056 presented at EAACI 2022