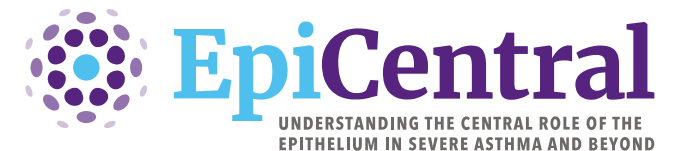




Reframing airway disease: The role of the epithelium as a key immune-functioning organ

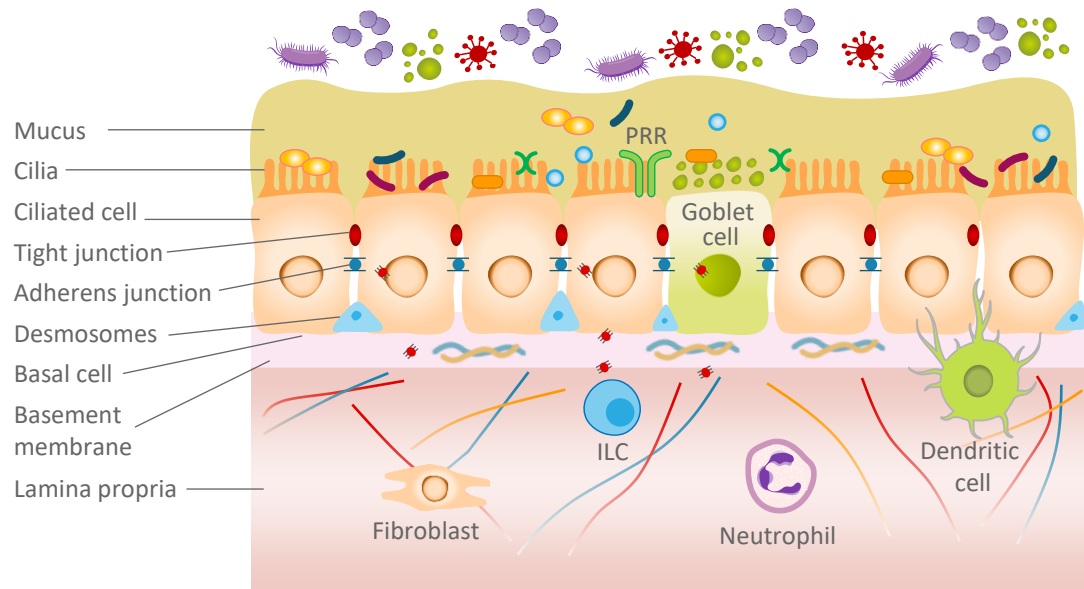
Professor Anju Peters
Northwestern University, US



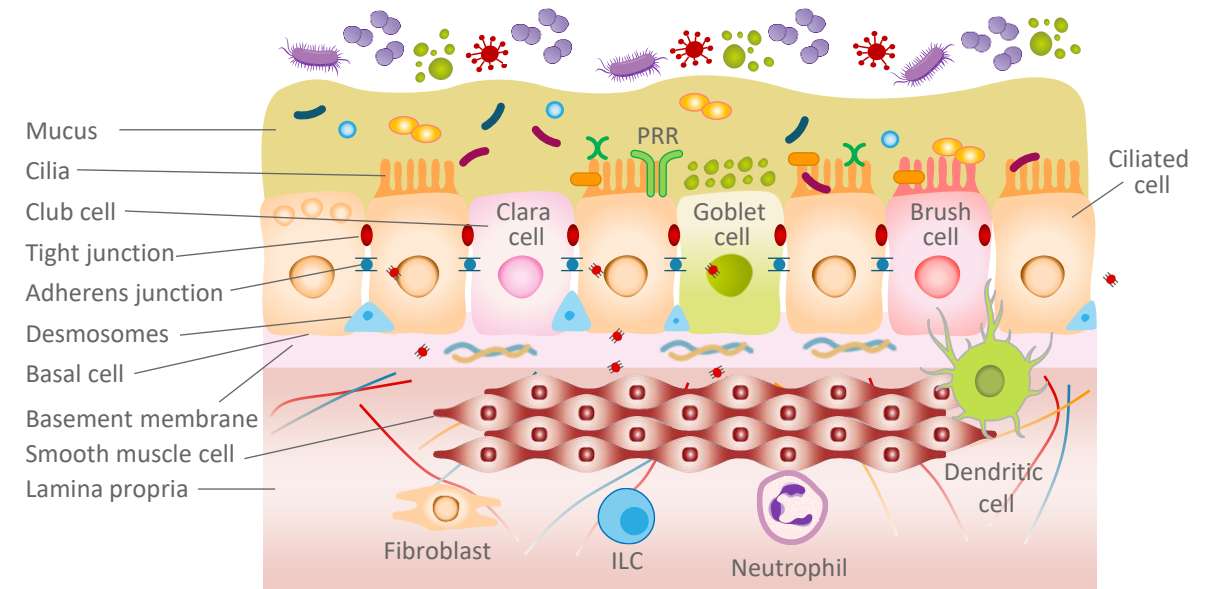
Understanding epithelial health provides a lens to explore upper and lower airways disease¹

The epithelium is central across upper and lower airways disease¹

Upper airway



Lower airway



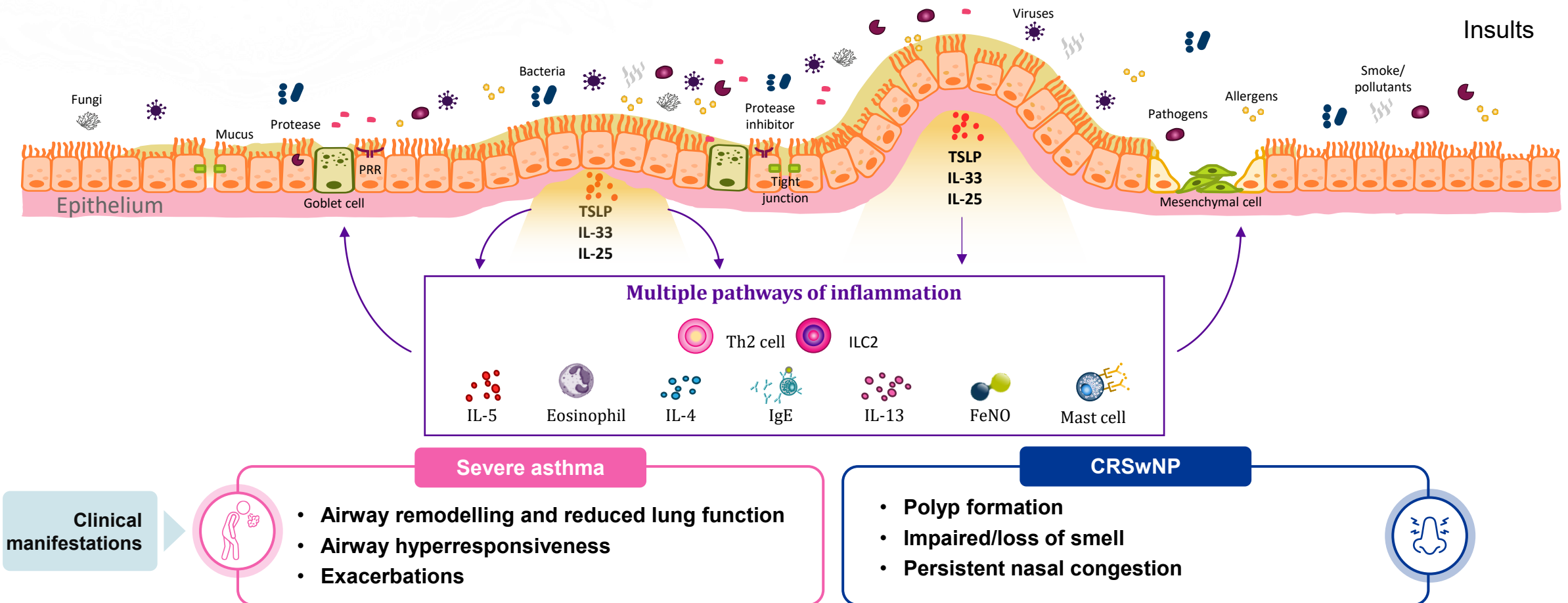
Disruption to the epithelium is a shared hallmark across the spectrum of upper and lower airways disease¹

Refer to Laulajainen-Hongisto A, et al. *Front Cell Dev Biol.* 2020;8:204.

ILC, innate lymphoid cell; PRR, pattern recognition receptor.

1. Laulajainen-Hongisto A, et al. *Front Cell Dev Biol.* 2020;8:204.

Epithelial cytokines initiate multiple pathways of inflammation in response to environmental triggers and exposures¹⁻¹⁶



The information presented in this image has been simplified for illustration purposes.

Refer to Caminati M et al. *Allergy*. 2024;79(5):1134-1145. Licenced under CC BY-NC 4.0 from: <https://creativecommons.org/licenses/by-nc/4.0/>. Accessed September 2026.

CRSwNP, chronic rhinosinusitis with nasal polyps; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; ILC2, type 2 innate lymphoid cell; PRR, pattern recognition receptor; Th2, type 2 helper T cells; TSLP, thymic stromal lymphopoietin.

1. Ha J-G, et al. *Int J Mol Sci*. 2023;24(18):14229; 2. Kato A, et al. *J Allergy Clin Immunol*. 2022;149(5):1491-503; 3. Laidlaw TM, et al. *J Allergy Clin Immunol Pract*. 2021;9(3):1133-41; 4. Stevens WW, et al. *J Allergy Clin Immunol Pract*. 2016;4(4):565-72; 5. Ordovas-Montanes J, et al. *Nature*. 2018;560(7720):649-54; 6. Takabayashi T, et al. *J Allergy Clin Immunol*. 2020;145(3):740-50; 7. Kohanski MA, et al. *J Allergy Clin Immunol*. 2021;148(5):1161-4; 8. Siddiqui S, et al. *J Allergy Clin Immunol*. 2023;152(4):841-57; 9. Chiarella E, et al. *Int J Mol Sci*. 2020;21(18):6878; 10. Qin D, et al. *Front Immunol*. 2022;13:941608; 11. De Corso E, et al. *Curr Allergy Asthma Rep* 2024;25(1):7; 12. Calvén J, et al. *Int J Mol Sci*. 2020;21(23):8907; 13. Bachert C, et al. *J Allergy Clin Immunol*. 2020;145(3):725-39; 14. Menzies-Gow A, et al. *Respir Res*. 2020;21(1):266; 15. Dekeyser A, et al. *Int J Mol Sci*. 2024;25(8):4460; 16. Porsbjerg CM, et al. *Eur Respir J*. 2020;56(5):2000260.

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Inflammation in Severe Asthma and CRSwNP is heterogeneous and more complex than T2 inflammation alone¹⁻³

Nearly 3 out of 5 patients (59%) with severe asthma have multiple elevated inflammatory biomarkers (N=1,175)¹

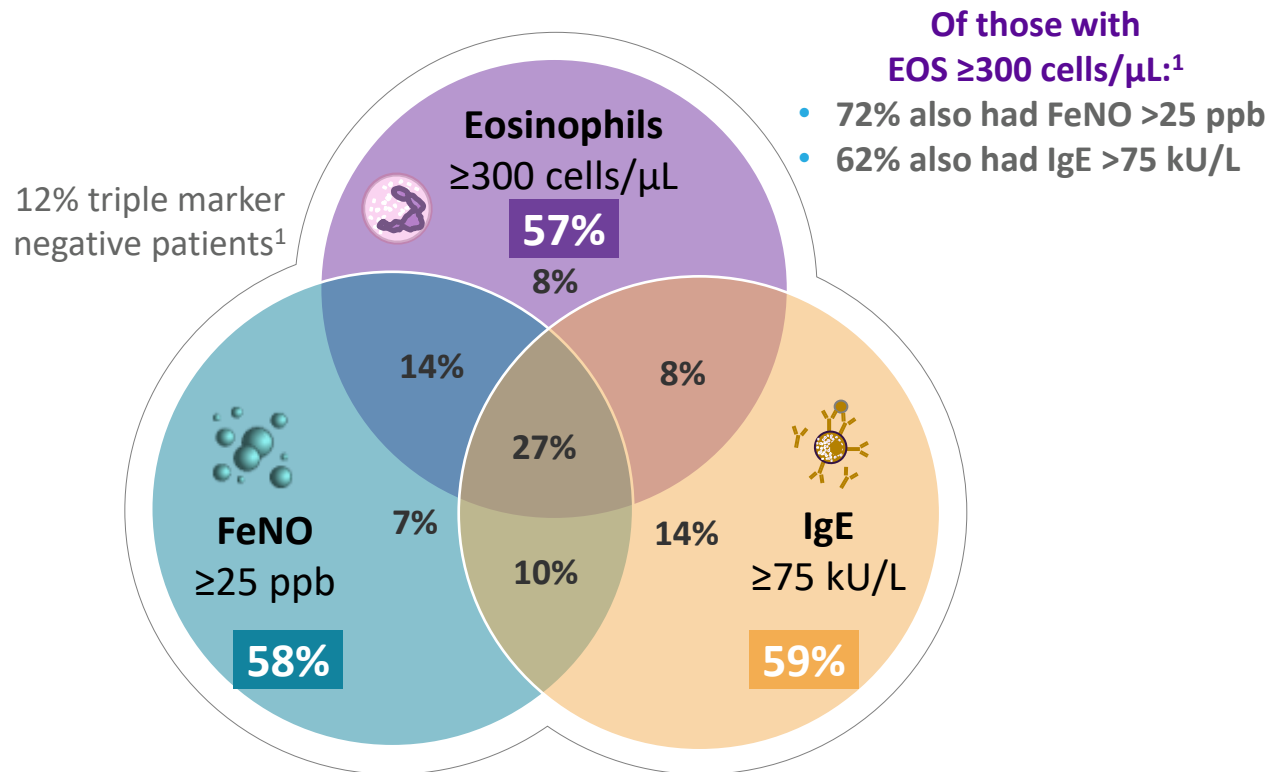
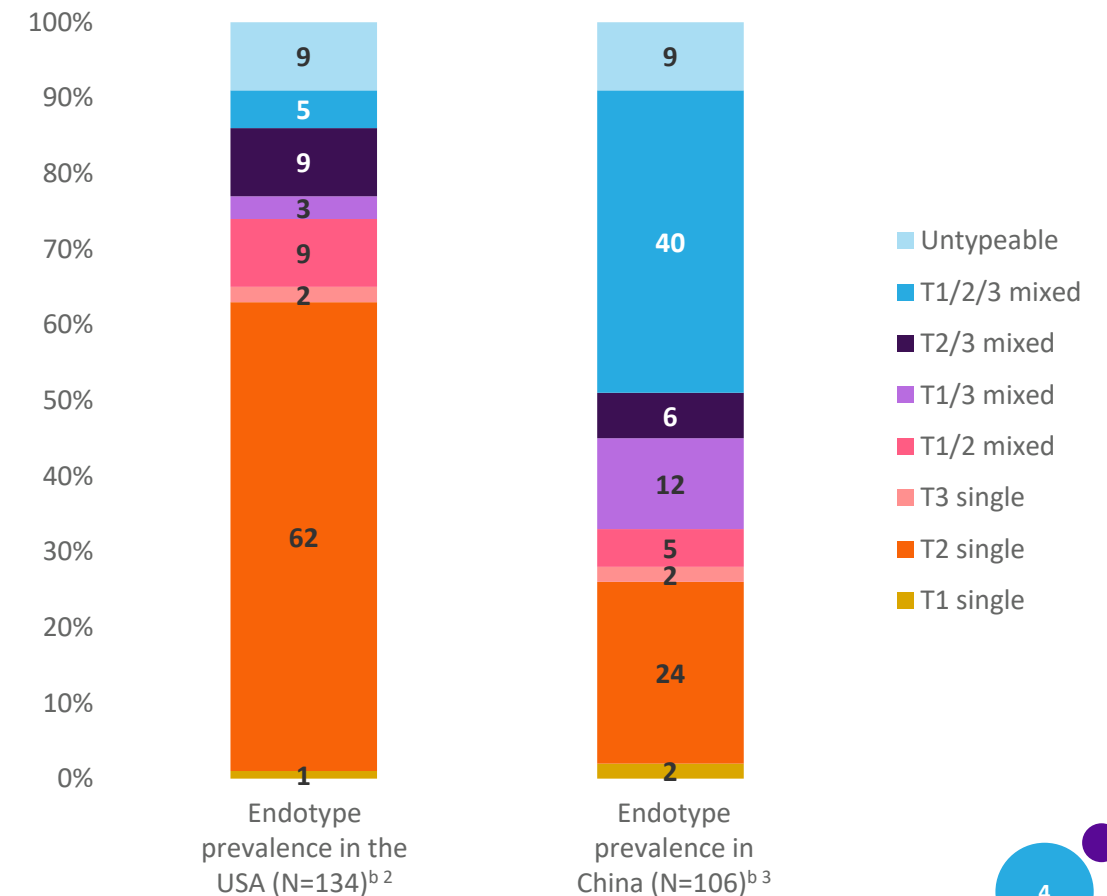


Figure on the left, refer to Denton E, et al. *J Allergy Clin Immunol Pract.* 2021;9(7):2680–88.

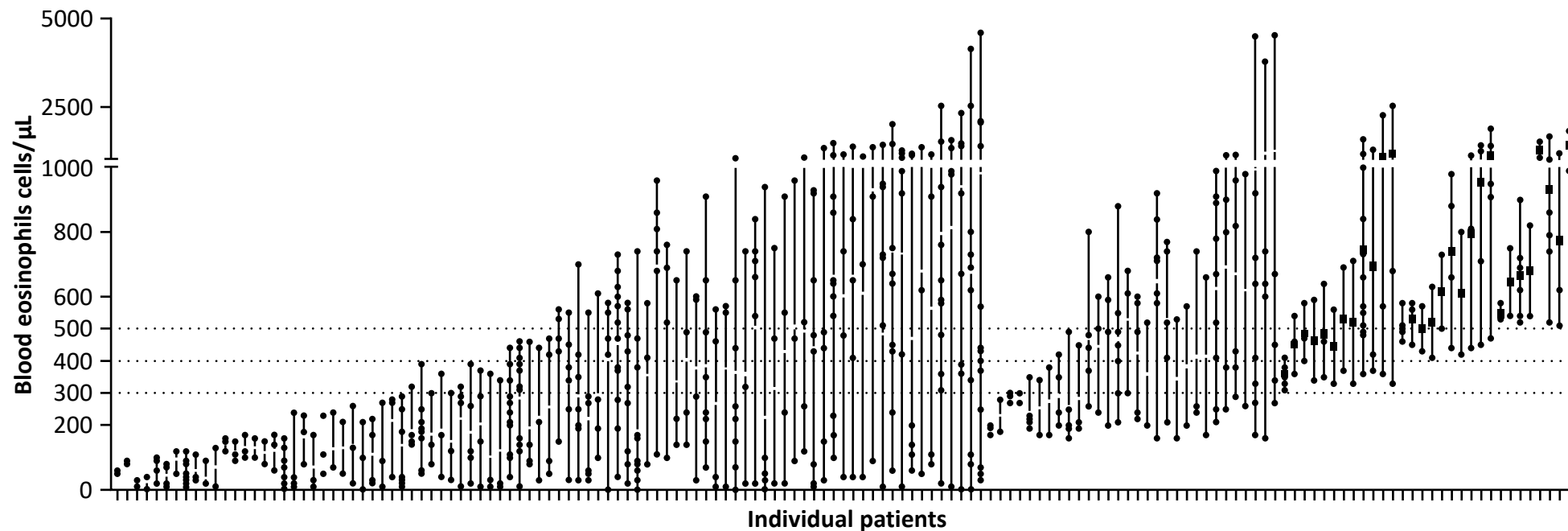
^aPatients without a clear endotype are defined as those expressing biomarkers below detection thresholds;² ^bBased on the results of a single-center trial.² CRSwNP, chronic rhinosinusitis with nasal polyps; EOS, eosinophils; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IU, international unit; ppb, parts per billion; T, type. 1. Denton E, et al. *J Allergy Clin Immunol Pract.* 2021;9(7):2680–88; 2. Stevens WW, et al. *J Allergy Clin Immunol Pract.* 2019;7(8):2812–20.e3; 3. Hao D, et al. *J Inflamm Res.* 2022;15:5557–65.

26–63% of patients^a with CRSwNP show mixed inflammatory endotypes involving T1, T2 and/or T3 pathways^{2,3}



Airways inflammation is dynamic and can vary within individual patients^{1,2}

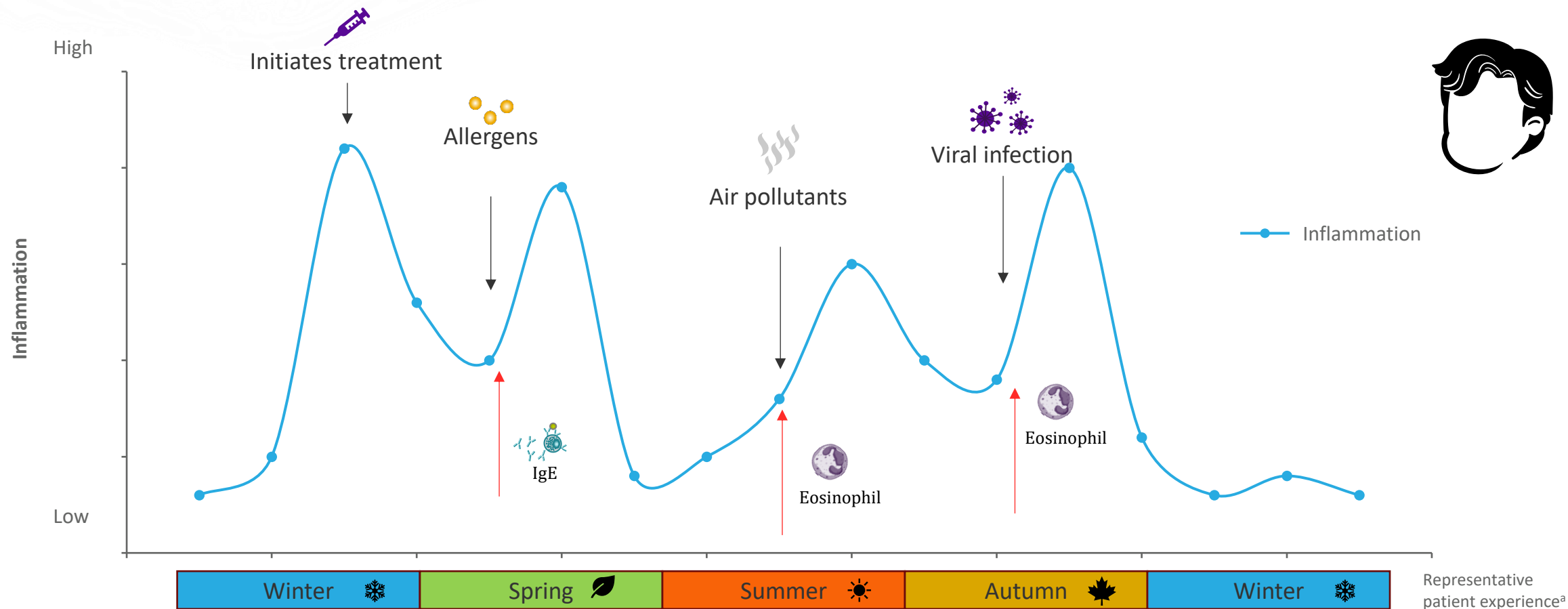
Scatter plot of blood eosinophils for individual patients with severe asthma¹



Refer to Li H, et al. *World Allergy Organ J.* 2021;14(9):100547.

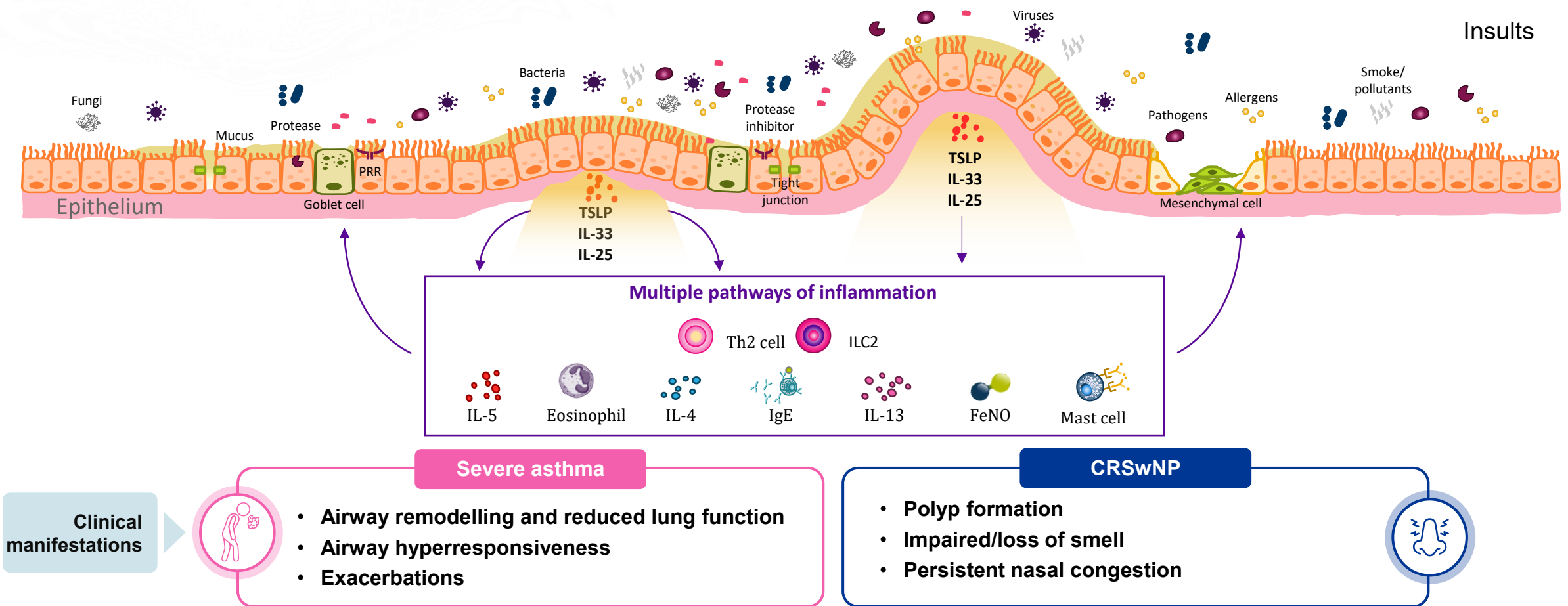
1. Li H, et al. *World Allergy Organ J.* 2021;14(9):100547; 2. Abe Y, et al. *Allergology International.* 2023;72(3):402–10.

Variable environmental triggers and exposures can activate different pathways within the inflammatory cascade¹⁻⁷



^aSeasonal patterns are illustrative and may vary by geography, sensitisation profile, climate, exposure intensity and comorbid airway disease.
IgE, immunoglobulin E; T2, type 2.
1. McDowell P, et al. *J Allergy Clin Immunol.* 2025;156(4):911–22; 2. Morris J, et al. *Int Forum Allergy Rhinol.* 2022;12(10):1313–16; 3. Jackson DJ, et al. *Lancet.* 2022; 400(10351):502–11; 4. Porsbjerg CM, et al. *Eur Respir J.* 2020;56(5):2000260; 5. Caminati M, et al. *Allergy.* 2024;79(5):1134–45; 6. Fokkens WJ, et al. *Rhinol.* 2020;58(Suppl. S29):1–464; 7. Walsh GM. *Antibodies (Basel).* 2025;14(4):101.

Despite airway inflammation heterogeneity and complexity, epithelial cytokines remain the consistent initiator across upper and lower airways¹⁻⁸



The information presented in this image has been simplified for illustration purposes.

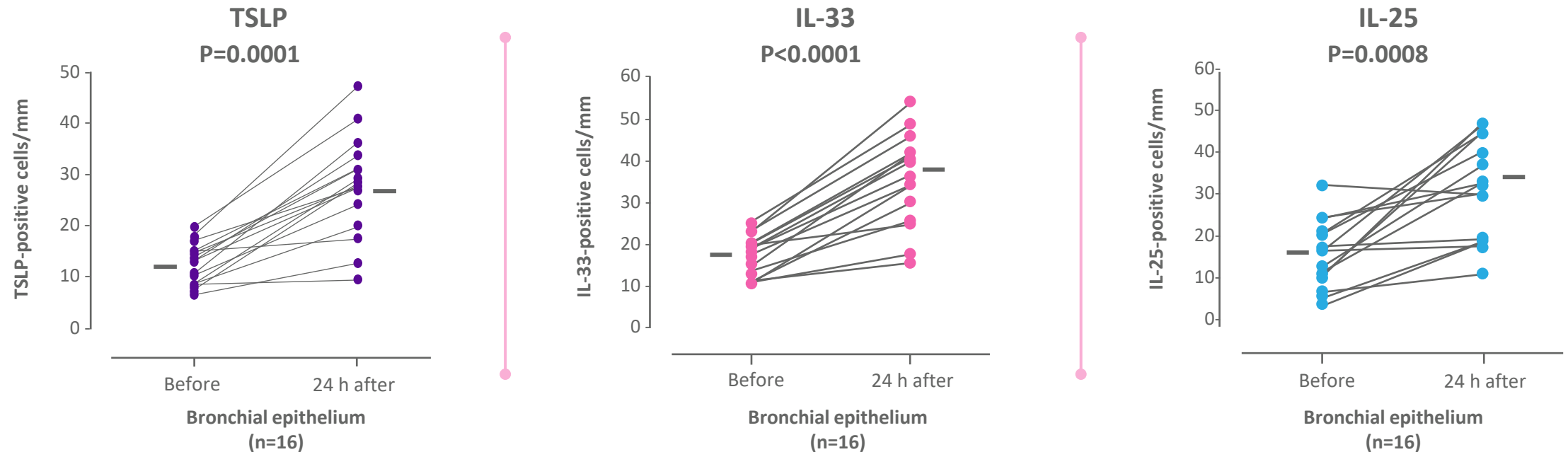
Refer to Caminati M et al. *Allergy*. 2024;79(5):1134-1145. Licenced under CC BY-NC 4.0 from: <https://creativecommons.org/licenses/by-nc/4.0/>. Accessed September 2026.

FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; ILC2, type 2 innate lymphoid cell; PRR, pattern recognition receptor; Th2, type 2 helper T cells; TSLP, thymic stromal lymphopoietin.

1. Lambrecht B, et al. *Immunity*. 2019;50(4): 975–91; 2. Howell I, et al. *J Exp Med*. 2023;220(7):e20221212; 3. Ha J-G, et al. *Int J Mol Sci*. 2023;24(18):14229; 4. Kato A, et al. *J Allergy Clin Immunol*. 2022;149(5):1491–503; 5. Qin D, et al. *Front Immunol*. 2022;13:941608; 6. De Corso E, et al. *Curr Allergy Asthma Rep* 2024;25(1):7; 7. Porsbjerg CM, et al. *Eur Respir J*. 2020;56(5):2000260; 8. McDowell P, et al. *J Allergy Clin Immunol*. 2025;156(4):911–22.

Epithelial cytokines expression increases in the epithelium 24 hours following bronchial allergen challenge¹

- ❖ In the bronchial epithelium and submucosa of sensitised patients, the median number of cells expressing epithelial cytokines increased 24 hours post allergen exposure^{a,b 1}



Total TSLP-, IL-33- and IL-25-reactive cells were inversely correlated with FEV_1 ($p \leq 0.05$)^c following allergen challenge¹

Refer to Wang W, et al. *J Immunol* 2018;201:2221–2231.

— Median number of cells

^aThis study assessed the numbers and phenotypes of IL-25-, IL-33-, and TSLP-immunoreactive cells in sections of bronchial biopsies from patients with mild atopic asthma ($n = 16$) before and 24 h after allergen inhalational challenge using single and sequential double immunohistochemistry; ^bBronchial biopsies were obtained before and after allergen challenge, which was conducted with an allergen that the patient was clinically sensitized to; ^cTSLP and IL-33 immunoreactive cells were inversely correlated with lung function both at baseline and after challenge.

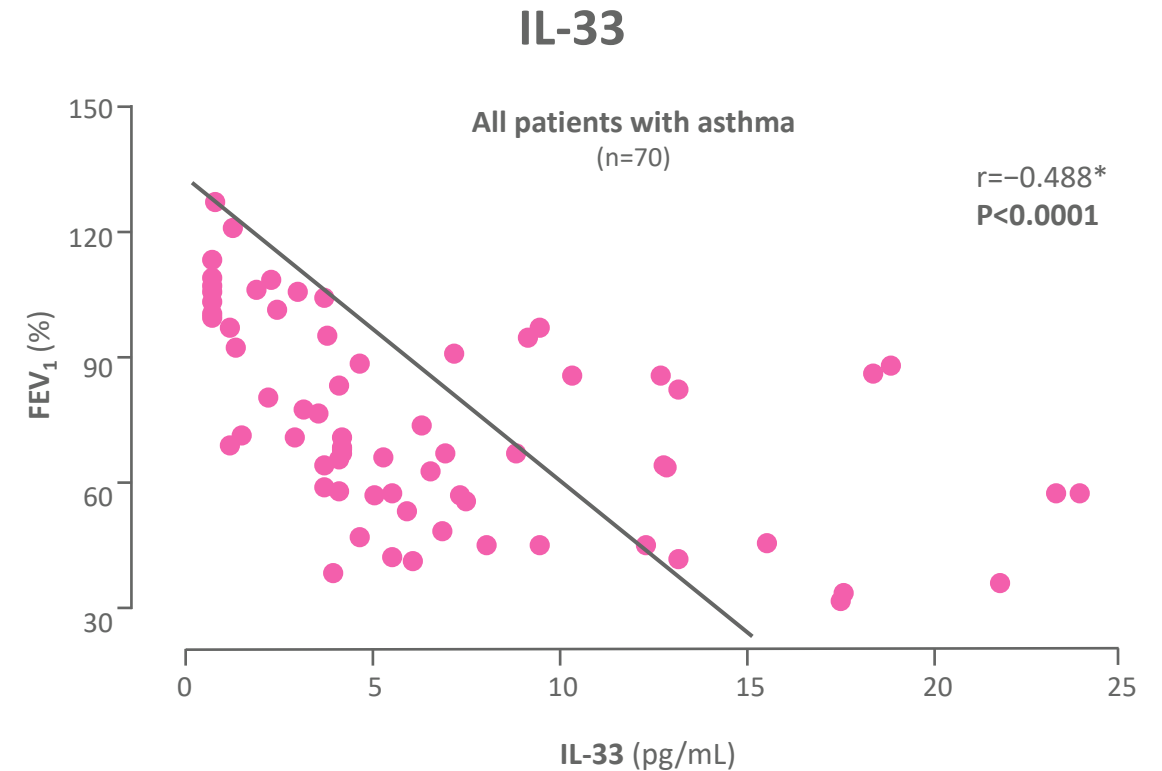
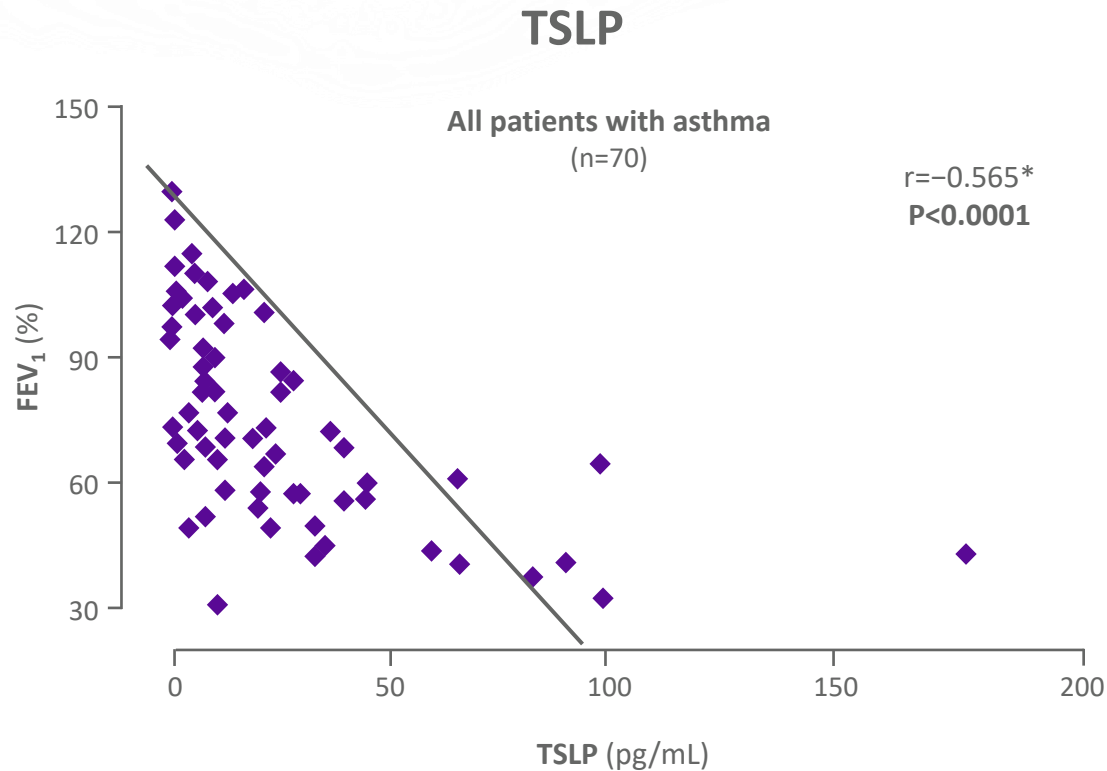
FEV_1 , forced expiratory volume in 1 second; h, hour; IL, interleukin; TSLP, thymic stromal lymphopoietin.

1. Wang W, et al. *J Immunol*. 2018;201(8):2221–2231.

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Increased epithelial cytokine concentration in BALF correlates with reduced lung function in patients with asthma¹



❁ BALF IL-25 concentrations were not elevated in patients with asthma, and did not correlate inversely with reduced lung function¹

Refer to Li Y, et al. *J Immunol* 2018;200:2253–2262.

This study compared airway concentrations of TSLP, IL-33 and IL-25 with lung function in a large group of patients with asthma (n = 70) and control subjects (n = 30) using bronchoalveolar lavage fluid (BALF).

*Spearman rank-order correlation coefficient

BALF, bronchoalveolar lavage fluid; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid(s); IL, interleukin; OCS, oral corticosteroid(s); TSLP, thymic stromal lymphopoietin

1. Li Y, et al. *J Immunol*. 2018;200(7):2253–2262.

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Epithelial cytokines contribute to exacerbation risk and airway remodelling in patients with asthma¹⁻⁴

In patients with severe asthma, higher TSLP expression was associated with a significantly greater probability of asthma exacerbation¹

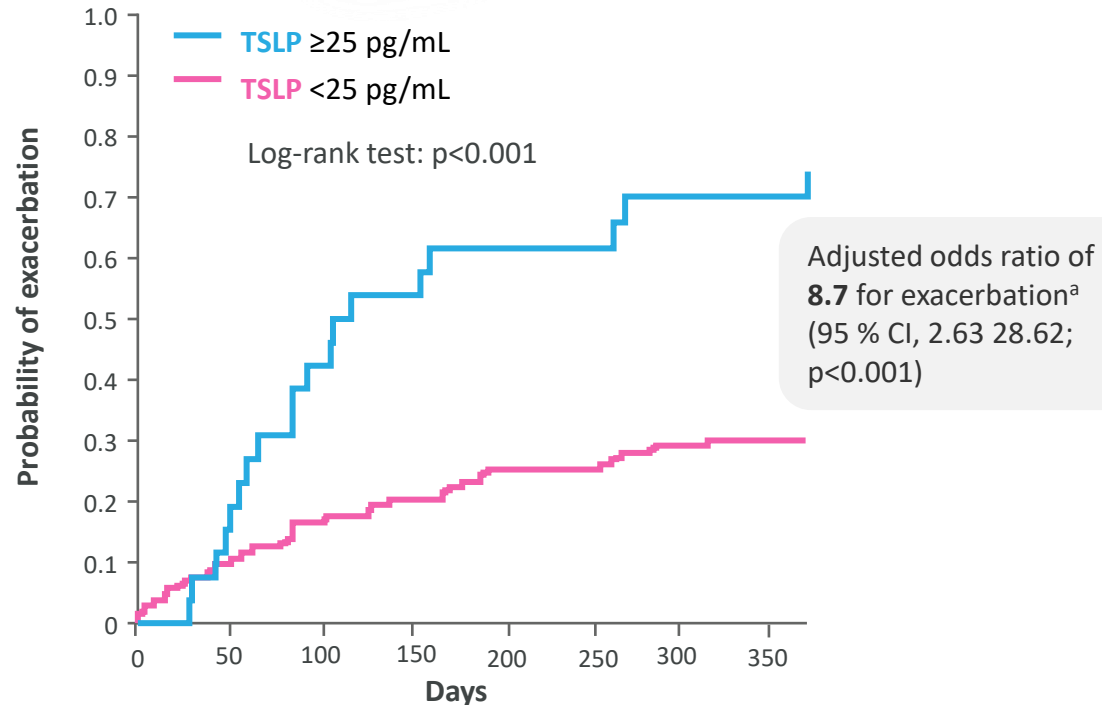


Figure on the left, refer to Ko HK et al. *Sci Rep.* 2021;11(1):8425. Kaplan–Meier curves of cumulative exacerbation probability during the 1-year follow-up in a multicenter prospective observational study conducted in Taiwan in 132 adults (20–75 years) with severe asthma, stratified by baseline serum TSLP levels. Figure on the right, refer to Cao L et al. *Exp Lung Res.* 2018;44(6):288–301, presenting findings from an *in vitro* study using human lung fibroblasts (HLF-1) stimulated with recombinant human TSLP. TSLP levels were assessed by Western blotting. IL-33 findings from Guo Z et al. *J Asthma.* 2014;51(8):863–69 were derived from *in vitro* HLF-1 fibroblast experiments and IL-25 findings from Cheng D et al. *Am J Respir Crit Care Med.* 2014;190(6):639–48 were obtained from patient bronchial biopsy analyses.

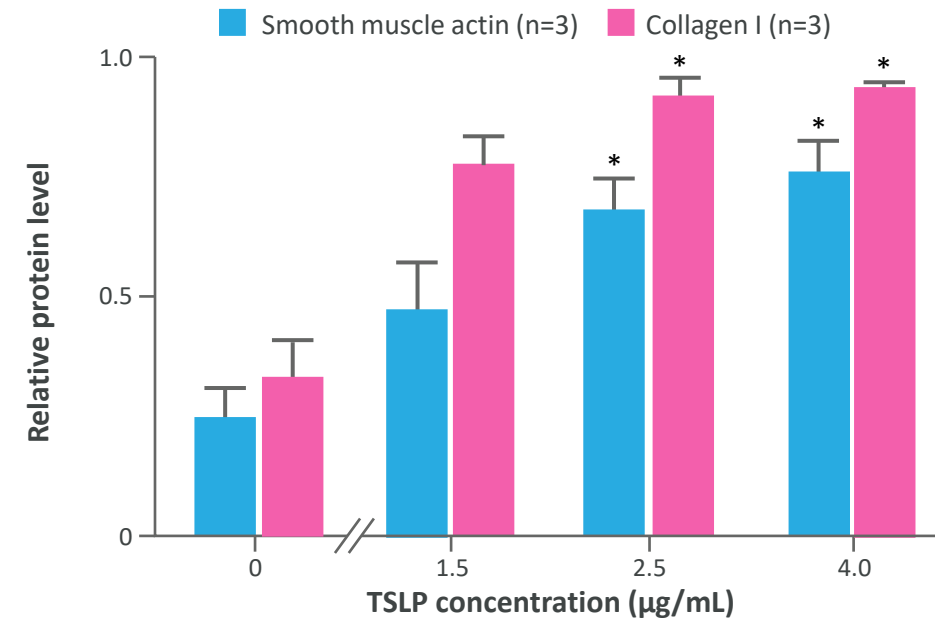
GAPDH, glyceraldehyde-3-phosphate dehydrogenase; H&E, haematoxylin and eosin; TSLP, thymic stromal lymphopoietin.

1. Ko HK et al. *Sci Rep.* 2021;11(1):8425; 2. Cao L et al. *Exp Lung Res.* 2018;44(6):288–301; 3. Guo Z et al. *J Asthma.* 2014;51(8):863–69;

4. Cheng D et al. *Am J Respir Crit Care Med.* 2014;190(6):639–48.

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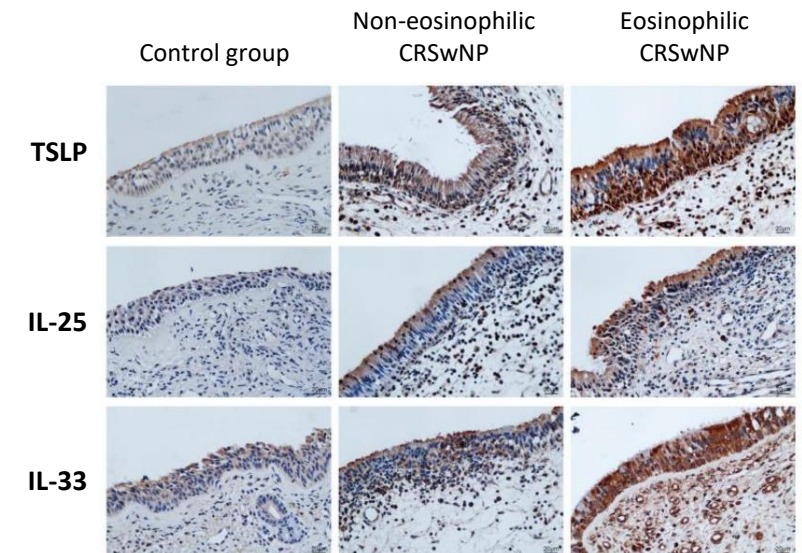
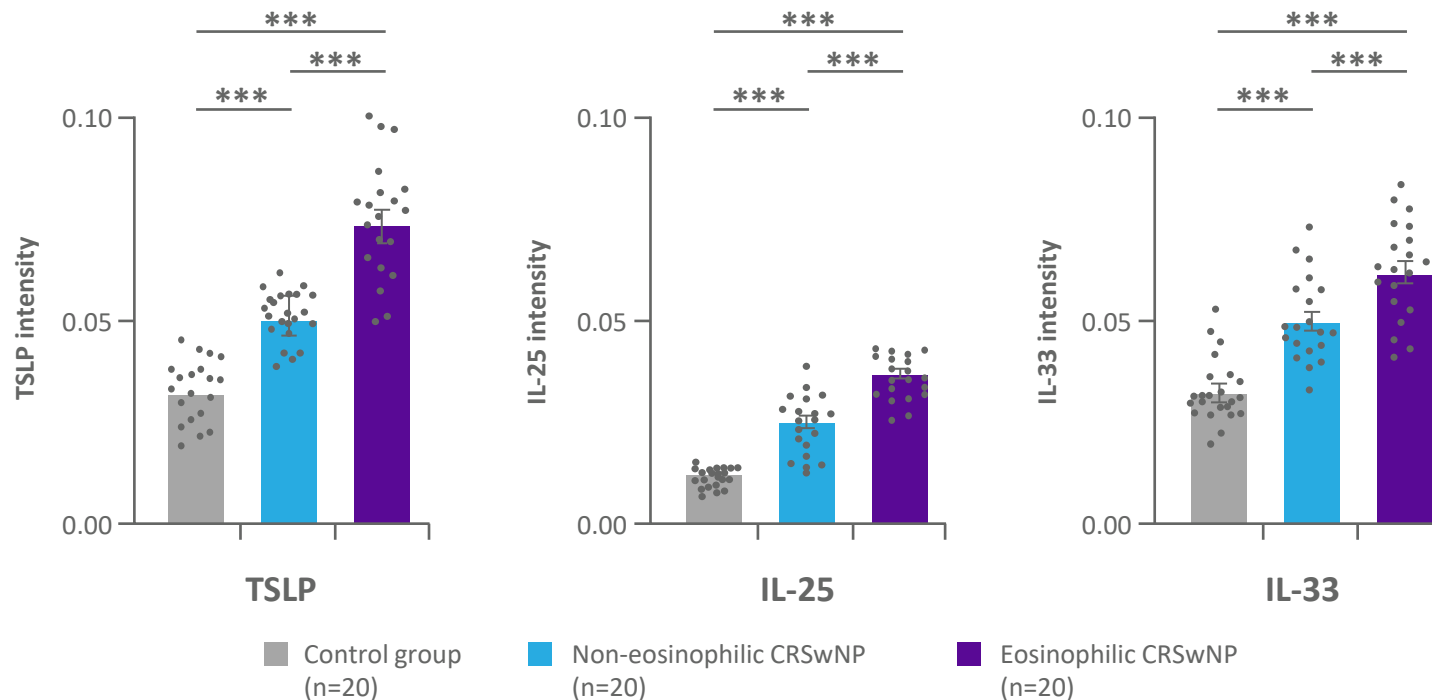
In human lung fibroblasts, TSLP stimulation was associated with increased collagen I and smooth muscle actin expression in a concentration-dependent manner ($p < 0.05$)^{a 2}



Similar trends have also been observed with IL-33 and IL-25. IL-33 expression has been associated with increased collagen and fibronectin production, while IL-25 expression has been associated with increased basement membrane thickness.^{3,4}

In CRSwNP, epithelial cytokine expression is increased across eosinophilic and non-eosinophilic disease^{1,2}

Nasal mucosal epithelial tissue shows an **increase in levels of TSLP, IL-25 and IL-33** in patients with eosinophilic CRSwNP and non-eosinophilic CRSwNP compared with the control group¹



Cells expressing labelled cytokines stain brown

Refer to Zhang M, et al. *Int Immunopharmacol.* 2023;121:110559.

***p<0.001. Eosinophilic CRSwNP was defined as the proportion of eosinophils in the nasal polyp tissue accounting for >10% of the total number of infiltrating cells; otherwise, disease was defined as non-eosinophilic CRSwNP.

CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin; TSLP, thymic stromal lymphopoietin.

1. Zhang M, et al. *Int Immunopharmacol.* 2023;121:110559; 2. Liao B, et al. *Allergy.* 2015;70(9):1169–80.

In CRSwNP, increased epithelial cytokines are associated with increased tissue inflammation and disease severity^{1,2}

Patients with nasal pathology ^a	Whole tissue (n=45)		
	TSLP	TSLP receptor	IL-33 receptor
IL-5, r (95% CI)	0.436** (0.138, 0.667)	0.494** (0.189, 0.721)	0.461** (0.170, 0.729)
IL-13, r (95% CI)	0.328* (0.018, 0.593)	0.403** (0.068, 0.679)	0.354* (0.010, 0.601)
Eos, r (95% CI)	0.625** (0.378, 0.819)	0.453** (0.158, 0.677)	0.397* (0.020, 0.615)
Patients with eosinophilic CRSwNP ^b	Whole tissue (n=28)		
	TSLP	TSLP receptor	IL-33 receptor
Total VAS score, r (95% CI)	0.598** (0.271, 0.836)	0.623** (0.323, 0.836)	0.498** (0.136, 0.774)
Total CT score, r (95% CI)	0.487** (0.075, 0.743)	0.461** (0.092, 0.720)	0.601** (0.297, 0.813)

Increased inflammation
in local tissue



Increased disease
severity



Similar results were observed in nasal epithelial cells.

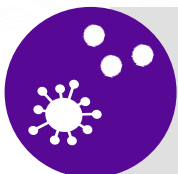
*p<0.05; **p<0.01.

^aPatients with eosinophilic or non-eosinophilic CRSwNP or patients with sinus cyst, nasal tumour or maxillofacial trauma without rhinitis or sinusitis;¹ ^bSubjective symptoms were scored on a VAS of 0 to 10; CT scans were graded using the Lund-Mackay CT scoring system.¹

CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; Eos, eosinophils; IL, interleukin; mRNA, messenger RNA; r, Spearman rank-order correlation coefficient; TSLP, thymic stromal lymphopoietin; VAS, visual analogue scale.

1. Liao B, et al. *Allergy*. 2015;70(9):1169–80; 2. Liao B, et al. Supplemental content. *Allergy*. 2015;70(9):1169–80.

Section summary



Epithelial cytokines released in response to environmental triggers and exposures drive multiple pathways of inflammation in airway diseases^{1,2}



Inflammation in severe asthma and CRSwNP is heterogeneous and dynamic, complicating diagnosis, endotype identification and treatment decisions^{3–5}



Despite heterogeneity in downstream inflammation, epithelial cytokines remain consistent drivers across airway diseases^{1,2,6}



Enhanced epithelial cytokine expression is associated with T2 inflammation, greater symptom burden and increased severity in asthma and CRSwNP^{7–9}

CRSwNP, chronic rhinosinusitis with nasal polyps; T2, type 2.

1. Ha J-G, et al. *Int J Mol Sci.* 2023;24(18):14229; 2. Howell I, et al. *J Exp Med.* 2023;220(7):e20221212; 3. Denton E, et al. *J Allergy Clin Immunol Pract.* 2021;9:2680–88; 4. Stevens WW, et al. *J Allergy Clin Immunol Pract.* 2019;7:2812–29.e3; 5. Hao D, et al. *J Inflamm Res.* 2022;15:5557–65; 6. Lambrecht B, et al. *Immunity.* 2019;50(4):975–91; 7. Zhang M, et al. *Int Immunopharmacol.* 2023;121:110559; 8. Liao B, et al. *Allergy.* 2015;70(9):1169–80; 9. Liao B et al. Supplemental content. *Allergy.* 2015;70(9):1169–1180.