

The implications of epithelial activation across the upper and lower airway

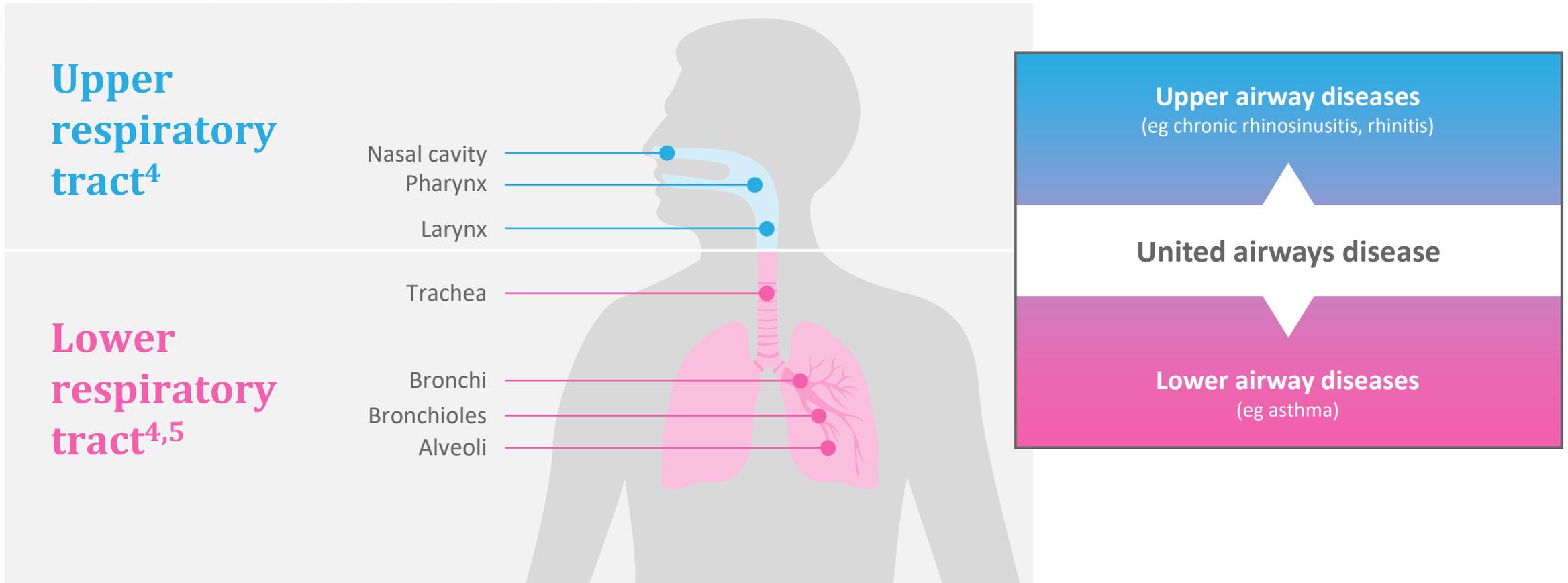
Professor Tanya Laidlaw

Brigham and Women's Hospital | Harvard Medical School, Boston, USA

ERS Congress 2025



The co-occurrence of upper and lower airway diseases is known as 'united airways disease'¹⁻³



The epithelium forms a **continuous link across the upper and lower airway**, acting as the **first line of defence** from environmental insults^{9,10}

Figure adapted from Laulajainen-Hongisto A, et al. *Front Cell Dev Biol* 2020;8:204, Adivitiya, et al. *Biology (Basel)* 2021;10:95 and Baldassi D, et al. *Adv Nanobiomed Res* 2021;1:2000111⁶⁻⁸

1. Jakwerth CA, et al. *Cells* 2022;11:1387; 2. Kicic A, et al. *J Allergy Clin Immunol* 2020;145:1562–1573; 3. Yii ACA, et al. *Allergy* 2018;73:1964–1978; 4. Ball M, et al. *Anatomy, airway*. In: StatPearls [Internet]. Treasure Island, FL, USA: StatPearls Publishing, 2023; 5. Hewitt RJ, Lloyd CM. *Nat Rev Immunol* 2021;21:347–362; 6. Laulajainen-Hongisto A, et al. *Front Cell Dev Biol* 2020;8:204; 7. Adivitiya, et al. *Biology (Basel)* 2021;10:95; 8. Baldassi D, et al. *Adv Nanobiomed Res* 2021;1:2000111; 9. Fokkens W, Reitsma S. *Otolaryngol Clin North Am* 2023;56:1–10; 10. Bartemes KR, Kita H. *Clin Immunol* 2012;143:222–235

Epithelial-driven diseases of the airway frequently co-occur

Upper airways

Patients with diagnosed CRSwNP and asthma have a **greater burden of disease** than those without asthma¹⁻³

Asthma in the presence of allergic rhinitis is **more difficult to control**⁴

CRSwNP



of patients have **asthma**^{5*}

Allergic rhinitis



of patients have **asthma**⁶

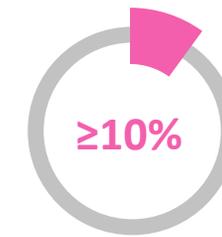
Lower airways

Asthma in the presence of nasal polyps is **more difficult to control**¹

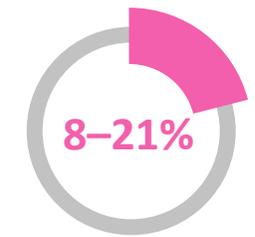
Asthma



of patients have **allergic rhinitis**⁷



of patients have **chronic sinusitis**^{7†}



of patients with severe asthma have a history of **nasal or sinus polyps**^{8,9}

Data are from independent publications and are not suitable for direct comparison

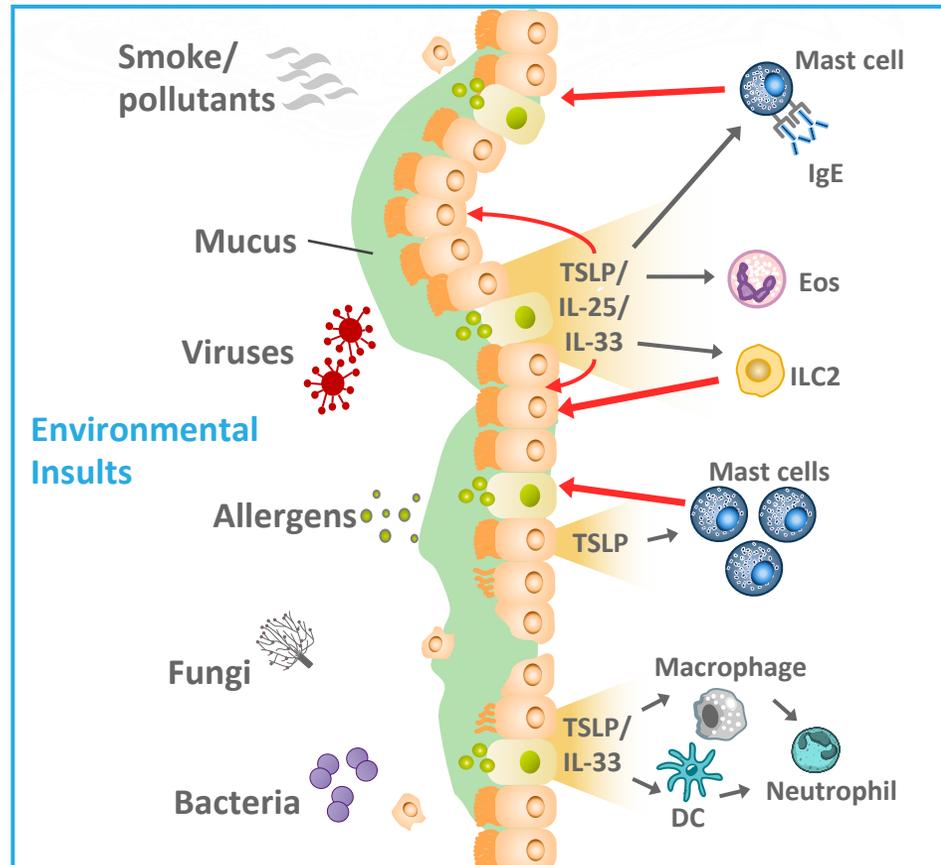
*Data were collected as part of a systemic literature review of the epidemiology and clinical burden of CRSwNP. Embase, MEDLINE and Evidence-Based Medicine Reviews databases were searched using OVID.

For epidemiology and clinical burden, 147 records and 119 records, respectively, were included;¹ †the prevalence of CRS in patients with asthma varies according to disease severity¹⁰

CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps

1. Laidlaw TM, et al. J Allergy Clin Immunol Pract 2021;9:1133-1141; 2. Bachert C, et al. J Asthma Allergy 2021;14:127-134; 3. Toppila-Salmi S, et al. Clin Transl Allergy 2022;12:e12200; 4. Al-Hadrawi Z, et al. Eur Clin Respir J 2024;11:2397174; 5. Chen S, et al. Curr Med Res Opin 2020;36:1897-1911; 6. Valero A, et al. J Investig Allergol Clin Immunol 2009;19:167-172; 7. Nunes C, et al. Asthma Res Pract 2017;3:1; 8. Reddel HK, et al. Eur Respir J 2021;58:2003927; 9. Scelo G, et al. Ann Allergy Asthma Immunol 2024;132:42-53; 10. Seccia V, et al. J Pers Med 2022;12:1096

Impaired epithelial health drives the pathology and clinical manifestations of upper airway diseases¹⁻⁹



Upper airway diseases: CRSwNP and allergic rhinitis

Disease pathology

Shared: chronic inflammation and remodelling^{2,8,10}

CRSwNP-specific: nasal polyp formation²

Clinical manifestations

Shared: nasal symptoms including rhinorrhoea and nasal blockage/congestion^{2,8}

CRSwNP-specific: exacerbations, a reduction or loss of sense of smell and need for surgery²

Allergic rhinitis-specific: red/itchy eyes and nasal itch⁸

Information presented in this image has been simplified for illustration purposes only

Figure adapted from Caminati M, et al. Allergy 2024;79:1134–1145. Licenced under CC BY-NC 4.0 from: <https://creativecommons.org/licenses/by-nc/4.0/> (Accessed 8 September 2025)

CRSwNP, chronic rhinosinusitis with nasal polyps; DC, dendritic cell; Eos, eosinophil(s); IgE, immunoglobulin E; IL, interleukin; ILC, innate lymphoid cell; TSLP, thymic stromal lymphopoietin

1. Calderon AA, et al. Eur Respir Rev 2023;32:220144; 2. Fokkens WJ, et al. Rhinology 2020;58(Suppl. S29):1–464; 3. Staudacher AG, et al. Ann Allergy Asthma Immunol 2020;124:318–325;

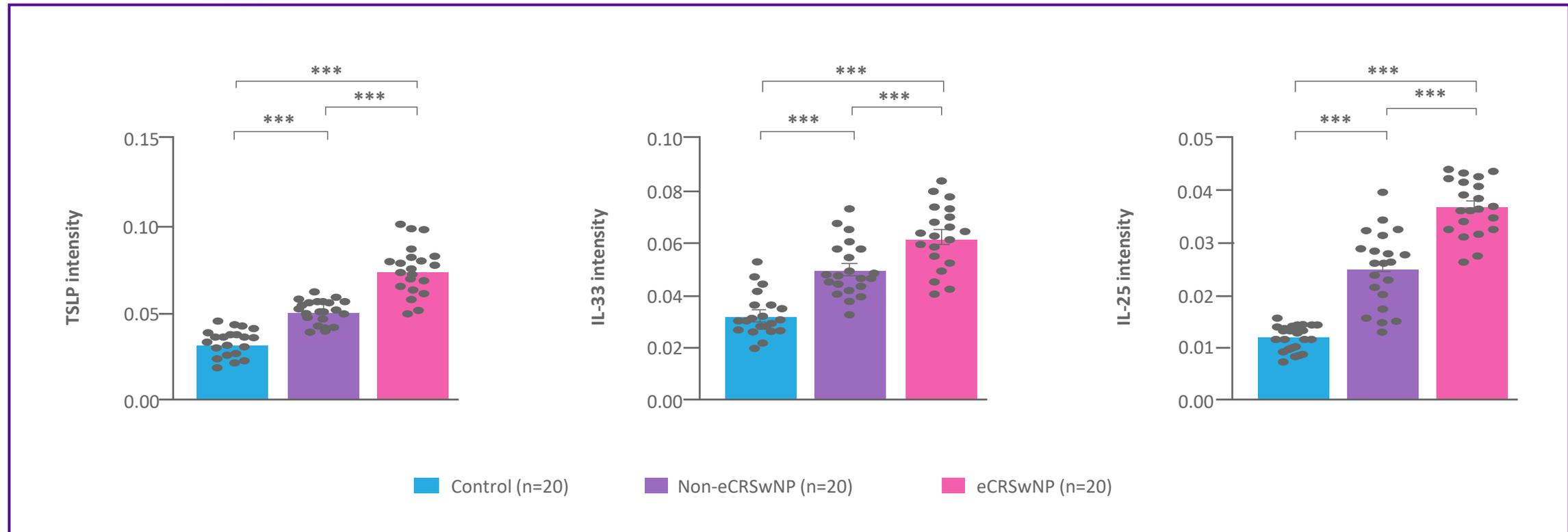
4. Caminati M, et al. Allergy 2024;79:1134–1145; 5. Yip ACA, et al. Allergy 2018;73:1964–1978; 6. Fokkens W, Reitsma S. Otolaryngol Clin North Am 2023;56:1–10;

7. Brightling C, Greening N. Eur Respir J 2019;54:1900651; 8. Bousquet J, et al. Nat Rev Dis Primers 2020;6:95; 9. Hellings PW, et al. J Allergy Clin Immunol 2020;145:1499–1509;

10. Bjermer L, et al. Allergy Asthma Clin Immunol 2019;15:24

Epithelial cytokine expression is increased in eosinophilic and non-eosinophilic CRSwNP

Nasal mucosal epithelial tissue shows an **increase in levels of TSLP, IL-25 and IL-33** in patients with non-eCRSwNP and eCRSwNP compared with controls, with the **highest levels observed in the eCRSwNP group**

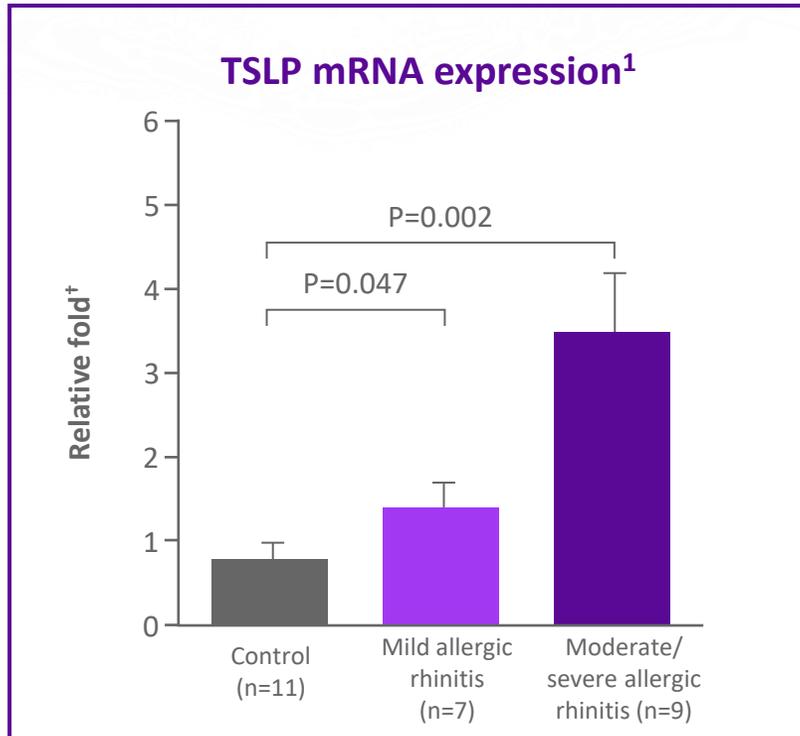


Figures adapted from Zhang M, et al. *Int Immunopharmacol* 2023;121:110559. Licenced under CC BY NC ND 4.0 from: <https://creativecommons.org/licenses/by-nc-nd/4.0/> (Accessed 8 September 2025)
Eosinophilic CRSwNP was defined as the proportion of eosinophils in the nasal polyp tissue accounting for >10% of the total number of infiltrating cells; otherwise, it was defined as non-eosinophilic CRSwNP. Values represent the mean \pm SEM; ***P<0.001

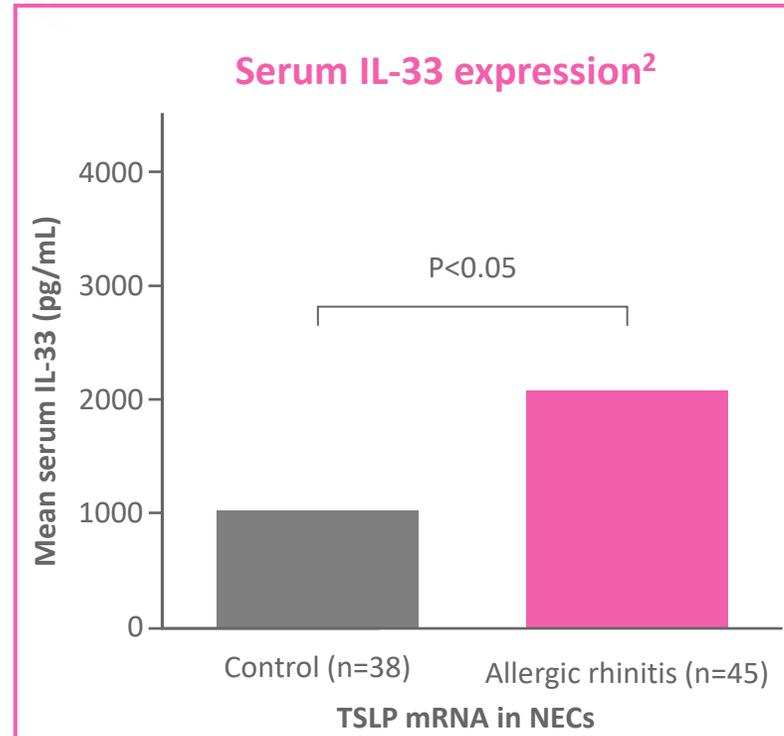
CRS, chronic rhinosinusitis; CRSwNP, CRS with nasal polyps; eCRSwNP, eosinophilic CRSwNP; IL, interleukin; SEM, standard error of the mean; TSLP, thymic stromal lymphopoietin

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

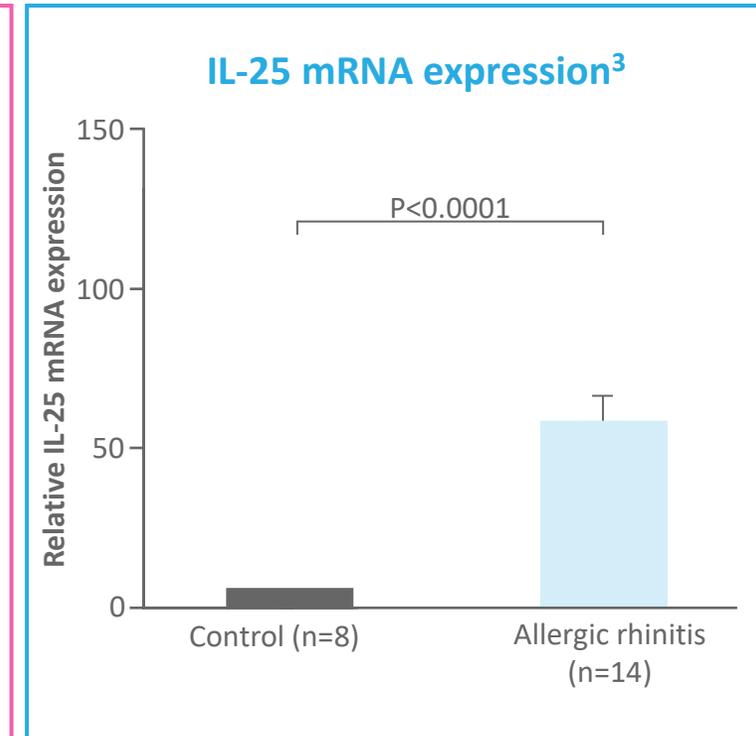
Epithelial cytokine expression is increased in allergic rhinitis



TSLP mRNA significantly increased according to disease severity in patients with allergic rhinitis^{1*}



Serum IL-33 was significantly increased in patients with allergic rhinitis compared with controls²



IL-25 mRNA expression was significantly increased in patients with allergic rhinitis³

Figure adapted from Mou Z, et al. Acta Otolaryngol 2009;129:297–301 (left), Kamekura R, et al. Clin Exp Allergy 2012;42:218–228 (middle), Kim DW, et al. Mediators Inflamm 2017;2017:3908049 (right)

Figures are from independent publications and are not suitable for direct comparison

*Severity defined using ARIA guidelines; †performed in duplicate

ARIA, Allergic Rhinitis and its Impact on Asthma; IL, interleukin; mRNA, messenger RNA; TSLP, thymic stromal lymphopoietin

1. Mou Z, et al. Acta Otolaryngol 2009;129:297–301; 2. Kamekura R, et al. Clin Exp Allergy 2012;42:218–228; 3. Kim DW, et al. Mediators Inflamm 2017;2017:3908049

Disruption of epithelial health is central to the pathogenesis of upper and lower airway diseases¹⁻⁴



The epithelium forms a **continuous link** across the upper and lower airway,⁵ **initiating** and **amplifying** inflammatory responses in epithelial-driven diseases^{6,7}



Upper and lower airways diseases have **heterogeneous and overlapping inflammatory pathways**, driven by **epithelial cytokines**^{1,5,8-13}



Epithelial cytokines are elevated in CRSwNP and allergic rhinitis¹⁴⁻¹⁸

CRSwNP, chronic rhinosinusitis with nasal polyps

1. Hellings PW, Steelant B. J Allergy Clin Immunol 2020;145:1499–1509; 2. Russell RJ, et al. Eur Respir J 2024;63:2301397; 3. Ha J-G, Cho H-J. Int J Mol Sci 2023;24:14229; 4. Porsbjerg C, et al. Lancet 2023;401:858–873; 5. Fokkens W, Reitsma S. Otolaryngol Clin North Am 2023;56:1–10; 6. Bartemes KR, Kita H. Clin Immunol 2012;143:222–235; 7. Raby KL, et al. Front Immunol 2023;14:1201658; 8. Yii ACA, et al. Allergy 2018;73:1964–1978; 9. Bousquet J, et al. Nat Rev Dis Primers 2020;6:95; 10. Fokkens WJ, et al. Rhinology 2020;58(Suppl. S29):1–464; 11. Staudacher AG, et al. Ann Allergy Asthma Immunol 2020;124:318–325; 12. Caminati M, et al. Allergy 2024;79:1134–1145; 13. Calderon AA, et al. Eur Respir Rev 2023;32:220144; 14. Zhang M, et al. Int Immunopharmacol 2023;121:110559; 15. Liao B, et al. Allergy 2015;70:1169–1180; 16. Xu G, et al. Allergy 2010;65:581–589; 17. Mou Z, et al. Acta Otolaryngol 2009;129:297–301; 18. Kamekura R, et al. Clin Exp Allergy 2012;42:218–228

Patient with asthma and comorbid upper airways disease (1/2)

32-year-old male patient



Main complaint:

- ❖ Shortness of breath and periods of wheezing during physical activity (complains that he 'cannot keep up with his young children or even walk the dog')



History of present illness:

- ❖ History of childhood allergies and frequent colds lasting for months
- ❖ Childhood asthma returned with additional symptom of wheezing in his late twenties
- ❖ Exhausted during physical activity and has sneezing, sinus pressure and rhinorrhoea
- ❖ Lost his sense of smell and has headaches during certain seasons



Medications: ICS/LABA daily + nasal saline irrigation

- ❖ ICS/LABA insufficient at reducing symptoms during physical exercise
- ❖ Nasal corticosteroids improve, but do not eliminate, sinus pressure and rhinorrhoea
- ❖ Sense of smell is still affected despite treatment

Patient with asthma and comorbid upper airways disease (1/2)

32-year-old male patient

Examination: reveals wheezing as well as presence of nasal polyps

Tests:

Spirometry (FEV₁ predicted)	62% + 18% improvement post β_2 -agonist
Blood eosinophil count	320 cells/ μ L
Total IgE	675 IU/mL
Tree pollen (skin prick test)	Positive
Grass (skin prick test)	Positive
FeNO	55 ppb
Nasal polyp score	5/8 (2 on left, 3 on right)
SNOT-22 score	56

Diagnosis:

Allergic eosinophilic asthma and comorbid CRSwNP

Not an actual patient. For illustrative purposes only

CRSwNP, chronic rhinosinusitis with nasal polyps; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; IgE, immunoglobulin E; IU, international units; ppb, parts per billion; SNOT-22, Sino-Nasal Outcome Test