Uncovering the hidden burden: Understanding loss of smell in CRSwNP

Disclaimer: This document has been reviewed by Professor Peter Hellings, University of Leuven, Belgium

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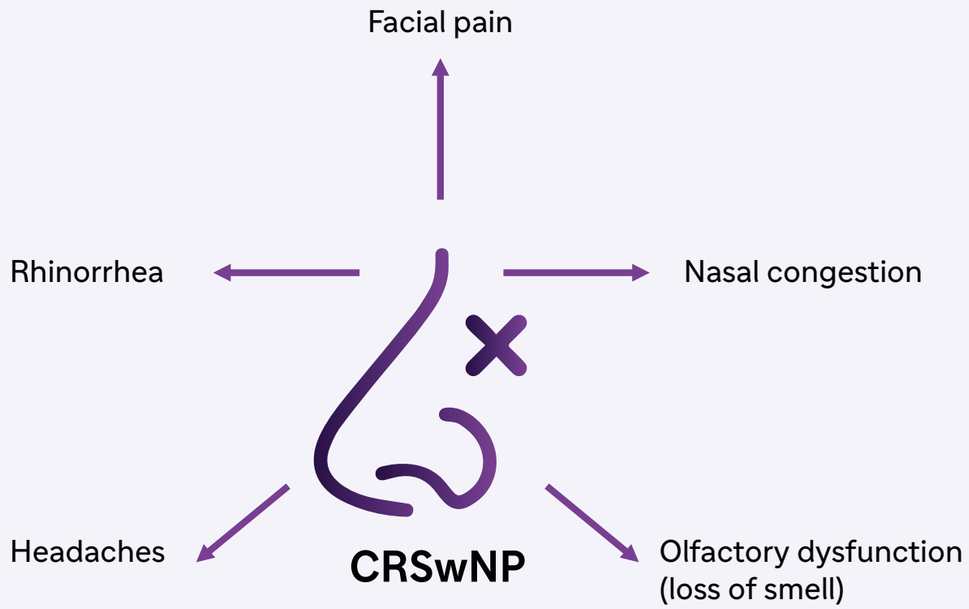
Overview of CRSwNP and its disease burden

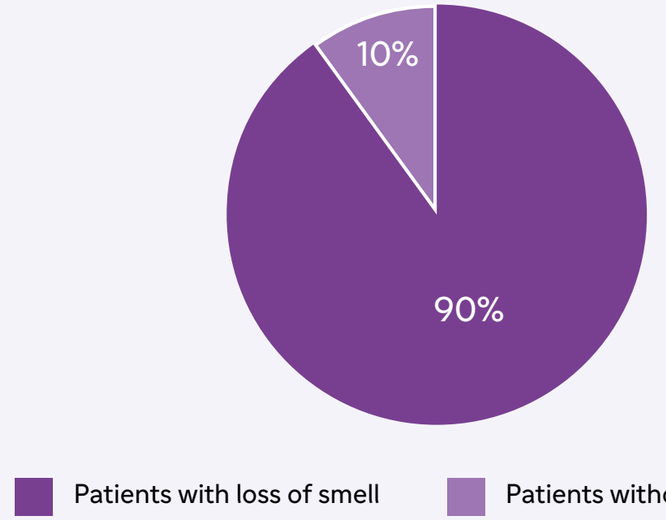
Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic disease of the nasal mucosa and paranasal sinuses predominantly mediated by Type 2 inflammation.[1, 2]

- CRSwNP affects approximately 1–2% of the European population[3]
- The average age range of onset is 40–60 years and many patients with CRSwNP also have comorbid asthma and/or nonsteroidal anti-inflammatory drug-exacerbated respiratory disease[1, 2]
- CRSwNP is more common in men than women, except for in the presence of aspirin-exacerbated respiratory disease[4, 5]

Main symptoms of CRSwNP[1, 2]



High prevalence of loss of smell in patients with CRSwNP (%)[2]



The hidden impact: How loss of smell affects patients' quality of life

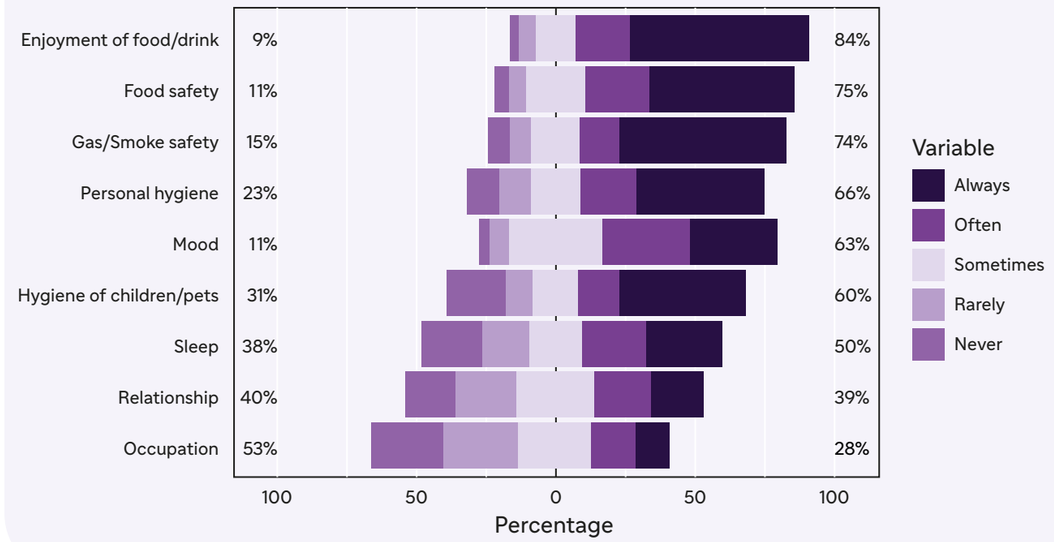
Patient quotes:[6]

> **Living with no sense of taste and smell is like watching TV in black and white in the 21st century. […] You miss a lot of impressions of the surroundings, you don't get any input.**

> **When I go to friends for dinner, I often don't taste the food. I don't dare to say this then, because the problem is so difficult to explain and no one understands it.**

- Results from an anonymised survey demonstrated that olfactory dysfunction was the most impactful symptom on patients' quality of life (QoL), with 71% of patients with CRSwNP describing their loss of smell as their most debilitating symptom and being 'as bad as it can be'[7]
- Poor QoL associated with loss of smell in CRSwNP is a result of multiple physical and psychological factors, including the inability to smell environmental dangers, personal hygiene, enjoyment of food/drink, anxiety and depression[1,7]
- The presence of nasal polyps is a strong predictor of olfactory loss[8]
- CRSwNP can often be managed by surgical and medical interventions; however, some patients experience recurrent disease despite treatment[9]
- The use of oral corticosteroids can provide improvement to patients' sense of smell, however these benefits are frequently temporary and only last for the duration of the treatment course[10]
- Loss of smell is also associated with a subjective loss of taste in many patients[11]

Impact of reduced/loss of smell and taste on various aspects of life[7]



Percentage on each end shows the percentage of responses above and below 'Sometimes'.
Results from a cross-sectional, anonymised online survey of patients with CRSwNP (N=107).
Adapted from: Luke L, et al. *J Clin Med*. 2023;12(16)5367.
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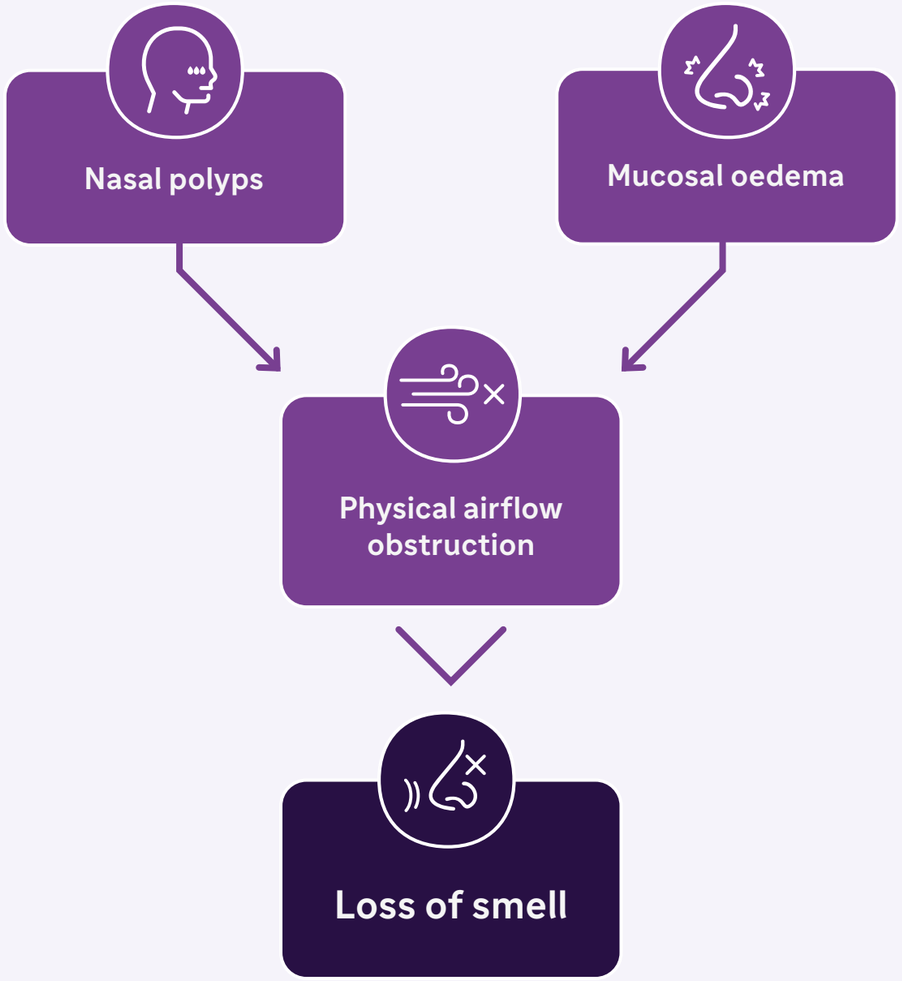
Understanding olfactory dysfunction in CRSwNP

Mechanisms of olfactory dysfunction

Olfactory dysfunction in patients with CRSwNP can result from conductive and **sensorineural** impairment.[12]

Conductive olfactory dysfunction

In conductive disease, physical airflow obstructions prevent odorants from reaching the olfactory epithelium in the nasal cavity.[13–15]



Sensorineural loss of smell

In sensorineural disease, olfactory receptor signalling to the brain is impaired.[13]

- **Loss of olfactory receptors**
  - Evidence suggests that Type 2 inflammation at the level of the olfactory epithelium contributes to the loss of millions of olfactory receptor neurons, which exacerbates the reduction or loss of smell in patients with CRSwNP[13,15,16]

- **Nerve damage**
  - Neurogenic inflammation, caused by substances that nerves release in the nasal passages, is believed to be implicated in CRSwNP pathophysiology. Inflammatory mediators interact with nasal epithelial nerves, while neural and immune cells produce neurotransmitters and neuropeptides resulting in exacerbation of neurogenic inflammation during the CRSwNP disease state[17]
  - The autonomic nervous system, including the vagus nerve, regulates many functions in the nasal mucosa, including olfactory processing, and evidence suggests that disruption of the autonomic nervous system may be linked to the pathophysiology of CRSwNP via changes in the local immune response and increased inflammation[1, 17, 18]

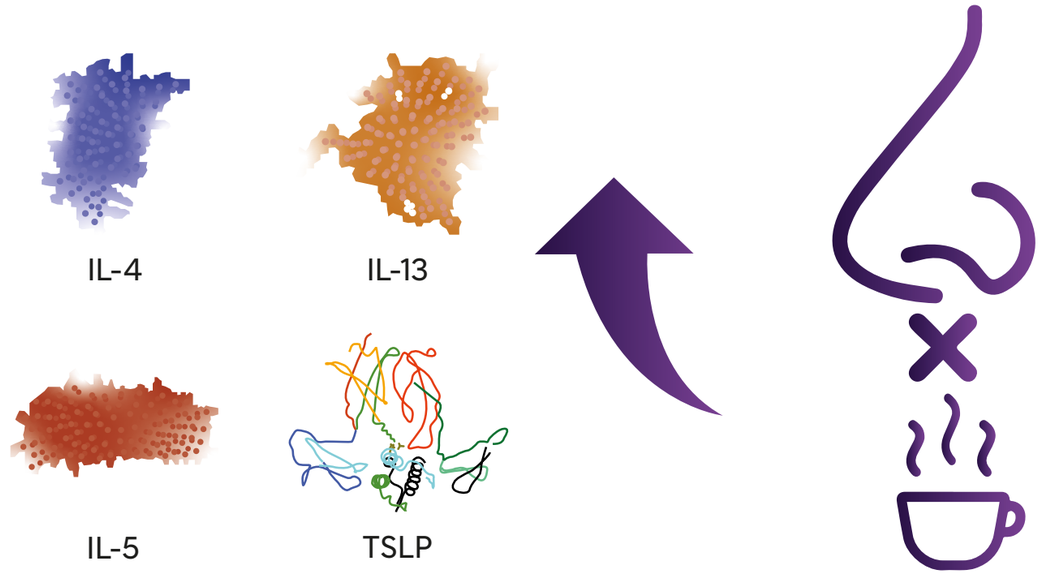
- **Mucosal cytokine imbalance and Type 2 inflammation**
  - There are three types of inflammatory endotypes associated with CRSwNP:
    - → The type 2 (T2) endotype is characterised by a Type 2 inflammatory response, with approximately 80% of patients with CRSwNP in Western countries presenting with this robust T helper type 2 (Th2)-mediated inflammatory profile.[5] Increases in Th2 cytokine release, including interleukin-4 (IL-4), IL-5 and IL-13, along with high levels of immunoglobulin E (IgE) and eosinophilic dominant infiltration in nasal polyps are distinguishing features of the T2 endotype[19]
    - → The T1 and T3 endotypes are associated with IL-17A and interferon gamma expression by Th1 and Th17 cells and the infiltration of neutrophils.[19] The T3 endotype is associated with clinical features, such as pus[20]
    - → Mixed eosinophilic-neutrophilic inflammation is associated with a severe Type 2 response and involves varying proportions of eosinophils and neutrophils[20]
  - Type 2 inflammation, as characterised by high levels of eosinophils, is a strong predictor of disease recurrence and loss of smell in CRSwNP[14, 20–22]
  - Inflammation can also contribute to structural changes to the olfactory epithelium, disrupting signal propagation to the olfactory bulb and cortex[23]

The role of cytokines in CRSwNP pathophysiology

In the olfactory epithelium, increased levels of IL-4, IL-5 and IL-13, as well as mast cells and eosinophils that infiltrate the olfactory mucosa have been observed in CRSwNP.[24] In addition, elevated levels of Type 2 inflammatory cytokines, IL-4, IL-13, IL-5, thymic stromal lymphopoietin (TSLP), eoxatin-3 and periostin have been correlated with a decline in olfactory function.[21, 25–28]

Cytokines involved in Type 2 inflammation

- **IL-4** is a cytokine produced by Th2 cells contributing to several processes central to a Type 2 inflammatory response, including IgE production and innate cell recruitment, which underpin the pathophysiology of CRSwNP.[28, 29] Additionally, IL-4 is involved in CRSwNP nasal epithelial barrier dysfunction and nasal polyp formation.[30–32] In murine models, IL-4 activation has been linked to olfactory dysfunction by acting on calcium uptake of olfactory sensory neurons, highlighting its complex role in sensory perception beyond its classical immune functions.[25, 26] Further research aims to reveal the precise mechanisms through which IL-4 impacts olfactory pathways, offering insights into potential therapeutic strategies for olfactory disorders
- **IL-13** has also been implicated in CRSwNP pathophysiology as it impairs mucociliary function and causes mucus hypersecretion which can lead to nasal blockage and discharge.[33–35] IL-13 overexpression in murine models has been shown to drive inflammatory processes that contribute to the development of nasal polyps, with evidence suggesting that IL-13 induces goblet cell hyperplasia and ciliated cell loss in human bronchial epithelial cells.[36, 37] IL-13 has also been demonstrated to be involved in nasal epithelial barrier impairment, and promotes neuron loss in the olfactory epithelium.[30, 36] IL-13 causes subepithelial airway fibrosis and extracellular matrix deposition by stimulating M2 macrophages that inhibit fibrin degradation, aiding nasal polyp formation.[31, 32, 37] These structural and functional changes facilitated by IL-13 can contribute to obstruction in the nasal environment that can severely impact olfactory function and contribute to symptoms of CRSwNP
- **IL-5** is an important regulator of eosinophil development and maturation, and elevated IL-5 levels are linked to eosinophilic tissue infiltration as part of Type 2 inflammation. IL-5 is partly regulated by IL-4, and its expression correlates with the severity of nasal polyps and is a strong predictor of poor olfactory outcomes after surgery for nasal polyposis.[21, 38, 39] IL-5 also has a down-regulatory effect on cell adhesion molecules in human epithelial cells, suggesting that IL-5 may compromise the integrity of the epithelial barrier, although further research to substantiate the role of IL-5 in CRSwNP is required[39]
- **TSLP** is an alarmin that is expressed by epithelial cells and drives dendritic cell activation and Th2 cytokine production, playing a key role in Type 2 inflammation in CRSwNP.[40] TSLP has been shown to be elevated in the tissue of nasal polyps of patients with CRSwNP compared with controls, and inhibition of TSLP may ameliorate nasal epithelial barrier dysfunction, highlighting its potential role in CRSwNP pathophysiology.[28, 30] Increases of TSLP-positive nasal epithelial cells correlates with levels of eosinophils and IgE in nasal polyp tissue, and DNA methylation of the TSLP locus is thought to contribute to CRSwNP pathophysiology[41, 42]



Therapies that target IL-4, IL-5 and IL-13 signalling have provided significant improvements to the sense of smell, and reductions in nasal polyps and nasal congestion in Phase 3 trials, highlighting the importance of Type-2 inflammatory cytokines as valuable targets for improving the symptom burden of patients with CRSwNP.[1, 43, 44] Studies investigating therapies which inhibit TSLP in CRSwNP are currently ongoing.[30, 45]

Assessment tools for olfactory dysfunction

Sniffin' Sticks Test

The Sniffin' Sticks Test is a non-invasive, quick to administer, standardised and cheap method used to evaluate olfactory function through pen-like devices containing various scents. It assesses three key aspects of smell: odour identification, where participants identify different scents from multiple-choice options; odour discrimination, where participants distinguish the different scent among sets of three; and olfactory threshold, which determines the faintest detectable smell by gradually increasing odour concentration.[46] The Sniffin' Sticks test is often used in academic research and clinical studies (e.g. rhinology centres involved in registries), as well as for clinical use.[47]

University of Pennsylvania Smell Identification Test (UPSIT)

The UPSIT is widely used as a standardised test in clinical trials and is designed to assess olfactory function and assist in diagnosis of olfactory disorders. The test comprises a booklet with 40 scratch-and-sniff odorant strips, each releasing a specific scent. Participants are asked to identify each scent from four multiple-choice options provided for each strip, their ultimate score being based on the number of correct identifications out of 40, with higher scores indicating better olfactory function.[48] Some of the odours used in this test might not be recognised by European patients.[49]

Visual Analogue Scale (VAS) smell test[50]

The VAS smell test is a subjective method for assessing olfactory function, involving a 10 cm straight line labelled 0 to 10, where 0 indicates normal smell and 10 corresponds to total loss of smell. Participants sniff a specific odorant and mark on the line where they perceive the smell's intensity, which is measured to provide a quantifiable score of their olfactory perception.

There are several other additional smell tests commonly used in clinical and research settings. The Connecticut Olfactory Test evaluates odour identification and discrimination using serial standards of odorants, whereas the Smell Diskettes method includes capsules containing specific scents for participants to identify. The Barcelona Smell Test assesses olfactory function through 24 odours captured in semi-solid gels and evaluates detection and identification. Olfactory Threshold Testing is a method by which a patient's olfactory sensitivity is measured by determining the lowest concentration of a diluted odorant that the patient can smell, and the Universal Smell Test includes 12 odours in felt-tip pens and descriptors presented in images and writing. Objective tests such as functional magnetic resonance imaging or olfactory event-related potentials are available but usually expensive, and their use is reserved for experimental research in specialised centres.[50, 51]

Role of olfactory assessment in diagnosis and monitoring disease progression and treatment response

Just as a hearing test would be required to assess hearing loss, conducting a smell test for evaluating smell loss (olfactory impairment) should be common practise.[52] Assessment tools for olfactory dysfunction, such as the Sniffin' Sticks Test, UPSIT and the VAS smell tests, can be used to diagnose olfactory disfunction in CRSwNP, monitor loss of smell and guide treatment decisions.[3, 50, 53–55]

Diagnosis

- Smell impairment is one of the four main symptoms of CRSwNP and is used for clinical diagnosis in both the American and the European rhinosinusitis guidelines[3, 50, 56]
  - Extent of loss of smell is a marker of disease severity and correlates with other CRSwNP outcomes such as nasal endoscopy and QoL[50]

Monitoring disease progression

- Smell assessments have been shown to be a useful tool in disease characterisation. The extent of olfactory impairment can be associated with inflammatory status and correlates with disease recurrence in CRSwNP[53, 54]

Treatment response

- Olfactory function is included in expert consensus criteria from the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) and the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) to determine therapeutic response in patients and can also be indicative of disease control[3, 56]
  - Symptom severity and disease recurrence are generally used to guide a step-wise treatment approach of topical, systemic or surgical interventions for patients with CRSwNP[3, 55]

> **Olfactory function is an important indicator of QoL and underlying patient pathophysiology in CRSwNP and improvements in smell represent a valuable therapeutic goal[53]**

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