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Self-reported nasal hyperreactivity is common in all chronic upper airway inflammatory phenotypes and not related to general well-being

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To the editor

Chronic upper airway inflammatory diseases like allergic rhinitis (AR), non-allergic rhinitis (NAR), and chronic rhinosinusitis (CRS) are prevalent and relate to higher stress, anxiety, and depression, impacting life quality and raising a large economic burden.¹⁻³

Nasal hyperreactivity (NHR) – defined as worsening of upper airway symptoms upon exposure to environmental triggers such as temperature/humidity changes – can be diagnosed objectively by a cold, dry air (CDA) provocation test.⁴ However, most studies are questionnaire-based with varying definitions of NHR poorly discriminating between physiologic and pathologic responses to environmental triggers. Moreover, no studies investigated NHR in various phenotypes simultaneously.

We investigated the prevalence and triggers of clearly-defined NHR, its' relationship with disease severity and general well-being in well-characterized patients with chronic upper airway inflammation.

To swiftly gain a general overview of the prevalence of NHR in chronic upper airway inflammation, we performed a questionnaire-based study in 605 otorhinolaryngologist-diagnosed patients with various phenotypes and 151 healthy controls (HC) (Table S1). Diagnosis of the specific chronic upper airway inflammatory phenotype was based on patient history, nasal endoscopy, skin prick test, and CT-scanning when necessary. Self-reported NHR (sNHR) was defined by a positive answer to the questions “Are your

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nasal complaints triggered or exacerbated by any of the following triggers: (...)?" and "If so, do they last longer than 10 minutes?". Visual Analogue Scales (VAS) assessed symptom severity and improvement with medication. Stress, anxiety, depression, and somatic symptom severity were assessed using the questionnaires Perceived Stress Scale (PSS), General Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire-9 (PHQ-9), and Patient Health Questionnaire-15 (PHQ-15) respectively. Methods are elaborated in the Supplement.

Prevalence of sNHR in upper airway inflammatory phenotypes was between 40.5 and 52.1%, without differences between groups ($p=0.33$) (Figure 1A/S2). Other studies reported higher prevalences of sNHR in AR (55.1-63.4%^{4,5}), NAR (60.9-66.9%^{4,5}), and CRS (64.8%⁶), supposedly related to variations in patient-characterization or, chiefly, to differences in NHR-definitions. To diagnose sNHR we required symptoms to last at least 10 minutes to discard normal physiological reactions to, e.g., cold. Interestingly, 8.6% of HC-subjects reported NHR. These participants might suffer mild/undiagnosed NAR.

VAS scores for total nasal symptoms were higher in sNHR-positive NAR-subjects, but not in other subgroups (Figure 1B/S1). This discrepancy is probably related to the complexity of underlying mechanisms. In NAR, symptoms are presumably mainly neurogenically mediated whereas other phenotypes exhibit also type 1 or 2 inflammatory mechanisms and barrier defects. NHR, but also for example sneezing and itch, are mainly neurogenically mediated and respond poorly to available treatments (Figure 1C/D, Table S2).

sNHR-positive patients mainly reported temperature/humidity changes and air-conditioning as triggers (Figure 1E, Table S3), supporting use of CDA provocation for objectification. In a CDA provocation test, objective diagnosis of NHR is purely based on decreased peak nasal inspiratory flow reflecting nasal obstruction. However, also rhinorrhea is triggered in patients with sNHR (Figure 1F). Consequently, we propose extending the diagnostic criteria of a CDA provocation test with rhinorrhea measurements.

Generalized anxiety disorder and major depression were observed in 11.3 and 7.3% (HC), 24.4 and 16.6% (AR), 19.8 and 13.5% (NAR), 10.8 and 10.9% CRS with nasal polyps (CRSwNP), and 20.7 and 23.0% CRS without nasal polyps (CRSSNP) respectively (Figure 2). PSS, GAD-7, PHQ-9, and PHQ-15 scores were similar in patients with and without sNHR. Since mental well-being was previously shown to correlate with subjective sinonasal symptom severity but not with objective measurements of disease severity, increased prevalence of sNHR in patients cannot be explained by impaired mental well-being.³

This study's strength is the excellent otorhinolaryngologist-based patient-characterization and solid definition of sNHR discriminating physiological from pathological responses to environmental triggers.

Questionnaires remain limited by their subjective nature, although sNHR is previously shown to be well correlated with objectively diagnosed NHR in patients with AR or NAR.⁴

We conclude that sNHR is prevalent in all phenotypes of chronic upper airway inflammation (AR, NAR, CRSwNP, CRSsNP, and mixed phenotype) regardless of disease severity, medication use, and general well-being.

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Short title

sNHR in chronic upper airway inflammation

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Author contributions

WB, PH, LVG: study design and conception, data collection, drafting the article, and revising the article for important intellectual content.

BS, KT, LVO: drafting the article and revising the article for important intellectual content.

MJ: data collection and revising the article for important intellectual content.

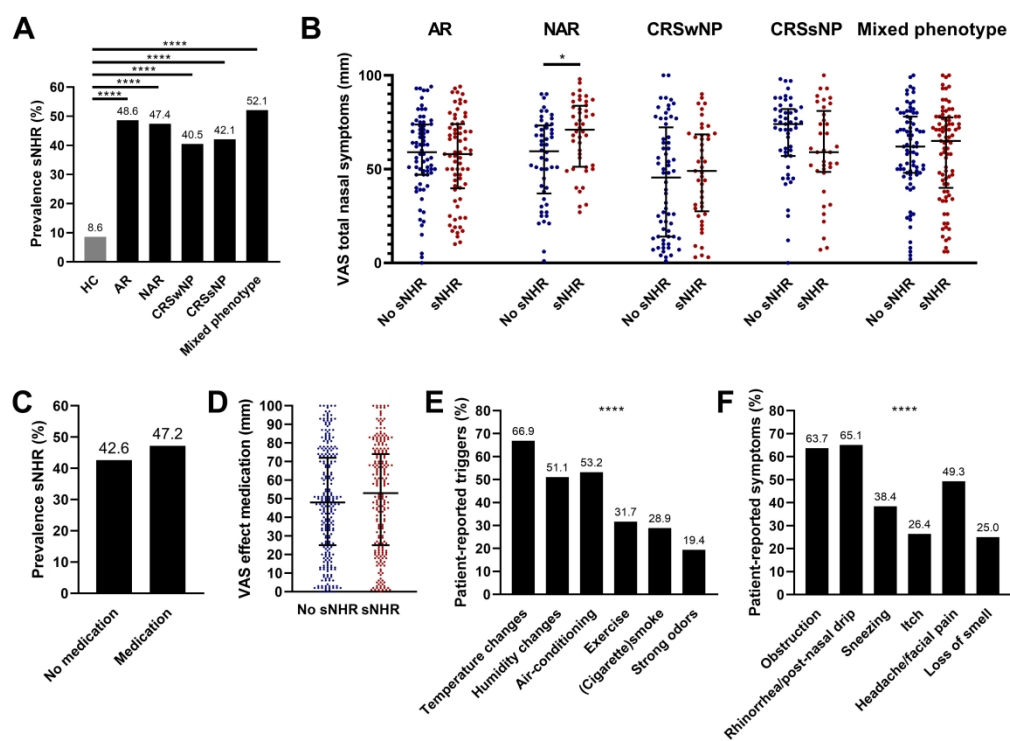
Conflicts of interest

The authors declare no conflicts of interest.

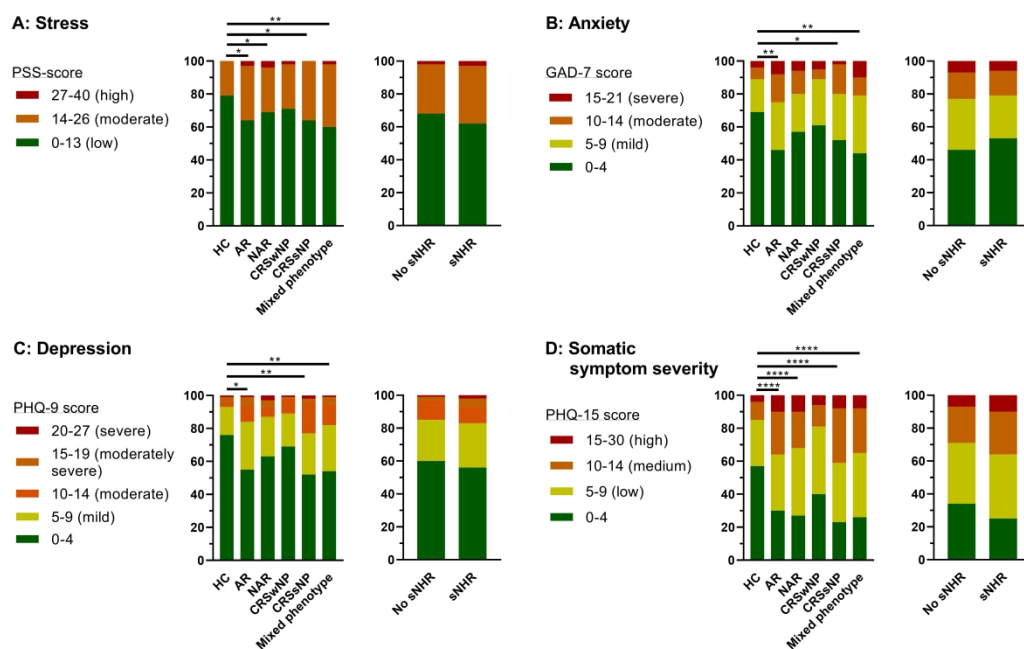
Figure legends

Figure 1: A) Prevalence of self-reported nasal hyperreactivity (sNHR) in healthy controls (HC) and various phenotypes of chronic upper airway inflammation. **B)** Visual analogue scale (VAS) score of total nasal symptoms of patients with and without sNHR in the phenotypic subgroups. **C)** Prevalence of sNHR in patients under medication for their (sino)nasal symptoms and patients not under medication for their (sino)nasal symptoms. **D)** VAS scores of the effect of medication in patients with and without sNHR. **E)** Percentage of patients with sNHR reacting to each trigger. **F)** Percentage of patients with sNHR reporting each symptom to be triggered. (A and C: Two-tailed Fisher's exact test with Holm-Sidak correction for multiple testing, **** $p < 0.0001$. B and D: Data presented as median and interquartile range, Mann-Whitney test with Holm-Sidak correction for multiple testing, * $p < 0.05$. E and F: Chi-square test, **** $p < 0.0001$.) AR: allergic rhinitis; NAR: non-allergic rhinitis, CRSwNP: chronic rhinosinusitis with nasal polyps, CRSsNP: chronic rhinosinusitis without nasal polyps.

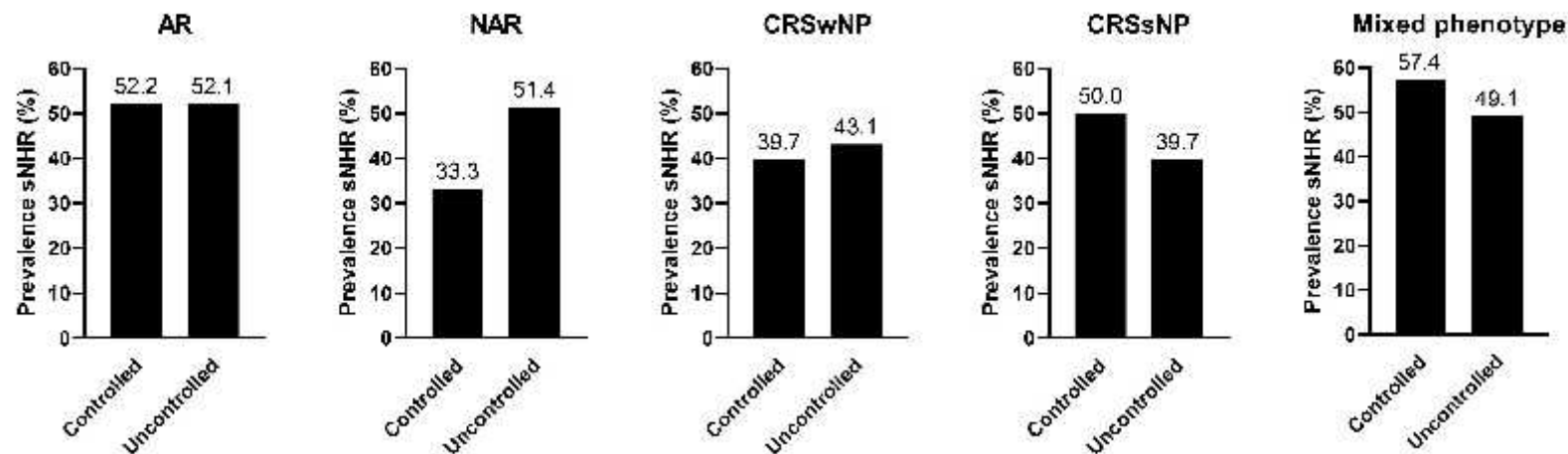
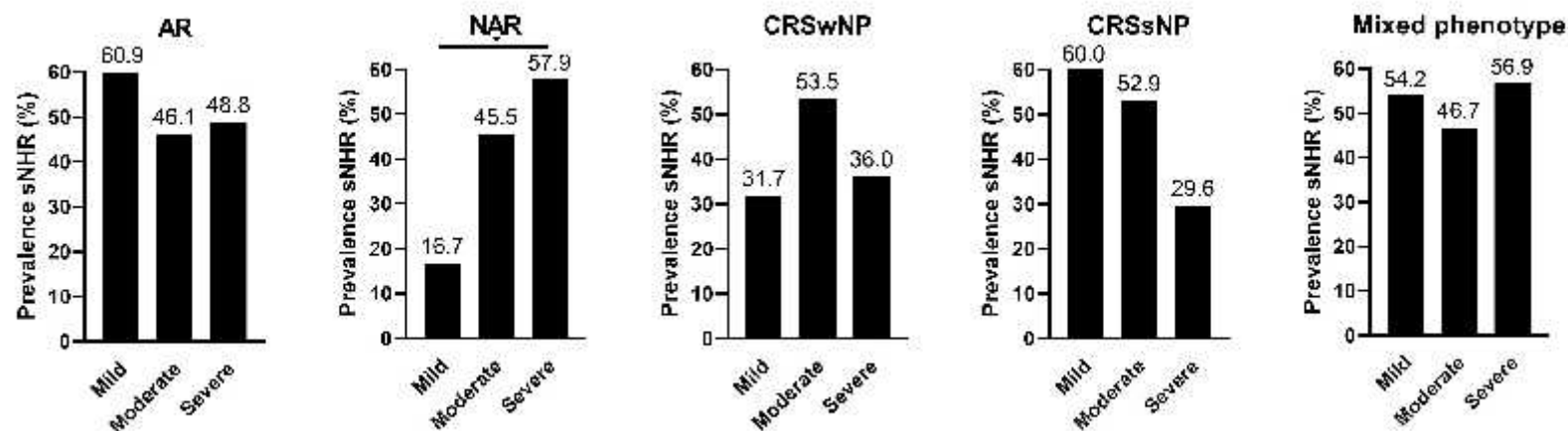
Figure 2: Evaluation of stress levels (A), anxiety levels (B), depressive symptoms (C) and somatic symptom severity (D) in various phenotypes of chronic upper airway inflammation and in patients with and without self-reported nasal hyperreactivity (sNHR). (Chi-square test with Holm-Sidak correction for multiple testing, * $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$.) PSS: perceived stress scale, GAD-7: general anxiety disorder 7, PHQ-9: patient health questionnaire 9, PHQ-15: patient health questionnaire 15, HC: healthy control, AR: allergic rhinitis; NAR: non-allergic rhinitis, CRSwNP: chronic rhinosinusitis with nasal polyps, CRSsNP: chronic rhinosinusitis without nasal polyps.

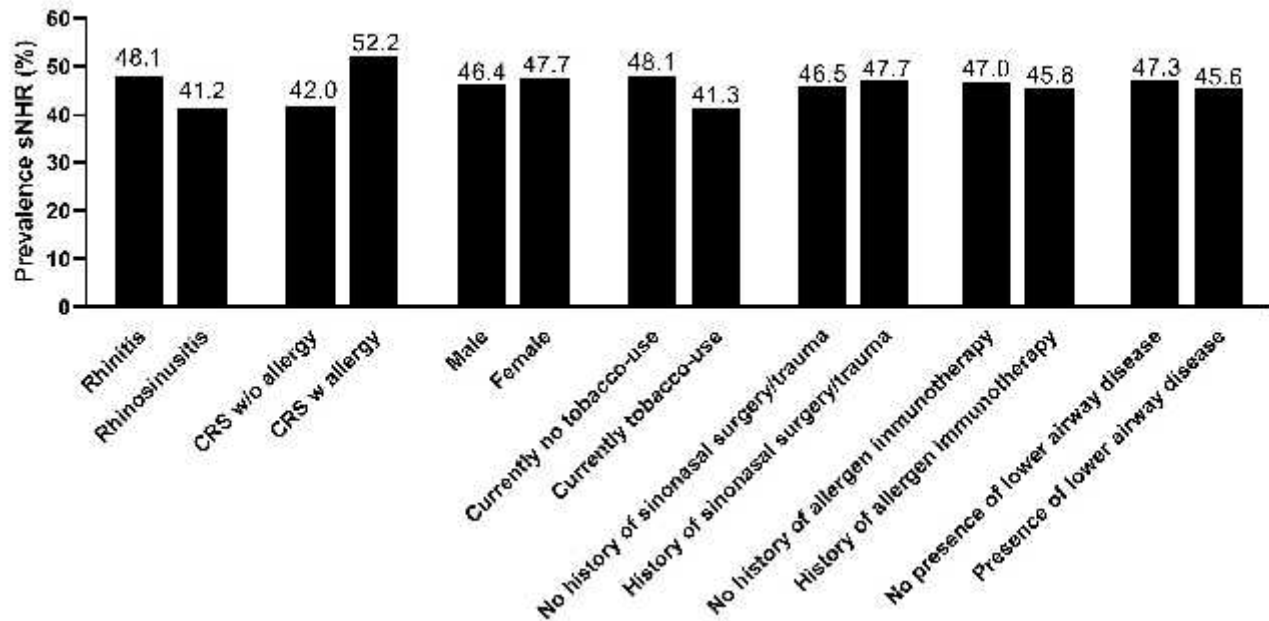


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A**B**



Self-reported nasal hyperreactivity is common in all chronic upper airway inflammatory phenotypes and not related to general well-being

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Supplement

Supplementary methods

Study design

From January 2019 until September 2020, patients and healthy volunteers (patients' companions) were recruited from the outpatient clinic of the Department for Otorhinolaryngology of University Hospitals Leuven (Leuven, Belgium) and asked to fill out a questionnaire. General mental and physical well-being were assessed using the Perceived Stress Scale (PSS) for stress¹, General Anxiety Disorder-7 (GAD-7)² for anxiety, Patient Health Questionnaire-9 (PHQ-9)³ for depression, and Patient Health Questionnaire-15 (PHQ-15)⁴ for somatic symptom severity. The study was approved by the Ethical Committee Research of University Hospitals Leuven (S62213) and registered on clinicaltrials.gov (NCT03893227).

Study participants

All participants were aged 18-65 years old at the moment of inclusion and were Dutch-speaking. Participants were excluded in case of relevant nasal structural abnormalities, such as major septal

deviation, and in case of ear-/nose-/throat-surgery or intranasal capsaicin therapy in the past three months. All participants gave written informed consent.

Participants were included as patients in case of physician-diagnosed chronic upper airway inflammation. This could be either AR, NAR, CRS without nasal polyps (CRSsNP), CRS with nasal polyps (CRSwNP), or a mixed phenotype.

The AR group consists of patients with a positive skin prick test to any of the most frequent aero-allergens in Belgium (*i.e.* house dust mite, timothy grass, English ryegrass, rye, stinging nettle, plantago, ragweed, mugwort, alder, birch, hazel, horse, cat, dog, rabbit, *Alternaria*, *Aspergillus*, *Cladosporium*) and a pattern of nasal symptoms compatible with the atopic sensitizations identified.

30The NAR group consist of patients with persistent symptoms of upper airway inflammation (*i.e.* rhinorrhea/postnasal drip, nasal obstruction, sneezing, itch) where inflammation was limited to the nasal cavity as seen on nasal endoscopy and/or CT scan and with negative skin prick tests.

CRS patients were defined according to the EPOS-guidelines⁵: inflammation of the nose and paranasal sinuses characterized by two or more symptoms of which at least one is nasal obstruction 35or rhinorrhea, with or without facial pain or loss of smell, together with endoscopic signs of sinonasal inflammation and/or mucosal changes within the ostiomeatal complex or sinuses. If nasal polyps could be observed on nasal endoscopy, patients were included in the CRSwNP group; if not, they were included in the CRSsNP group.

Lastly, patients with two or more of the abovementioned phenotypes were defined as patients 40having a mixed phenotype (*e.g.* patients with presence of both nasal polyps and house dust mite allergy).

Healthy control subjects had no known sinonasal symptoms nor (history of) sinonasal pathology, no proven nor suspected allergy, and a mean Visual Analogue Scale (VAS) score for nasal obstruction, postnasal drip, rhinorrhea, itch, sneezing, facial pain, and loss of smell of 20 mm or less.

45 *Outcome parameters*

The primary outcome parameter was the prevalence of sNHR, defined as mentioned in the text. Participants could tick multiple of the following triggers: temperature changes, humidity changes, physical exercise or sports, (cigarette) smoke, air conditioning, strong odors, or others. For the VAS scores, participants indicated symptom severity and improvement with medication on a 100 mm long 50line.

For stress, a PSS-score of 0-13, 14-26, and 27-40 correlate with low, moderate and high stress levels respectively.¹ For anxiety, cutoff values were 5, 10, and 15 for mild, moderate and severe anxiety. A cutoff value of 10 is used for screening purposes for generalized anxiety disorder with a sensitivity of 89% and specificity of 82%.² For depression, cutoff values were 5, 10, 15, and 20 for mild, moderate, 55moderately severe, and severe depression respectively. Patients scoring 10 or higher screen positive for major depression with a sensitivity and specificity of 88%.³ Lastly, somatic symptom severity could be considered to be negligible (PHQ-15 score of 0-4), low (PHQ-15 score of 5-9), medium (PHQ-15 score of 10-14), or high (PHQ-15 score of 15-30).⁴

Statistical methods

60Data were analyzed using GraphPad Prism 8 (GraphPad Software, San Diego, Calif, USA). For comparison of proportions, chi-square or Fisher's exact test was used. For continuous variables, normality was tested with Shapiro-Wilk test. Differences were analyzed using two-tailed unpaired t-test or Mann-Whitney test, depending on normality, and Holm-Sidak correction for multiple testing was applied when multiple outcomes were being compared between groups. Data are presented as 65mean $\pm$ SD in case of normally distributed data, or median and interquartile range in case of non-normally distributed data. Values were considered significantly different when $p < 0.05$.

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Supplementary tables

	Controls (N=151)	AR (N=144)	NAR (N=97)	CRSwNP (N=111)	CRSsNP (N=88)	Mixed phenotype (N=165)	Total patients (N=605)	P-value (controls vs patients)
Mean age (years ± SD)	44 ± 14	36 ± 12	43 ± 14	51 ± 12	44 ± 14	43 ± 13	43 ± 14	NS [†]
Male/female	74/77	77/67	44/53	82/27	50/38	94/71	347/258	NS [‡]
Current smokers (%)	14.7	15.3	16.1	17.3	18.2	12.8	15.3	NS [‡]
Previous rhinological surgery/trauma (%)	10.6	23.6	38.1	80.2	55.7	60.0	50.9	<0.0001 [‡]
Asthma or COPD (%)	4.0	12.6	10.3	19.1	9.1	28.0	17.1	<0.0001 [‡]
Cystic fibrosis (%)	0.0	0.7	0.0	6.4	1.1	3.0	2.3	NS [‡]

Table S1: Demographic data. AR: allergic rhinitis; NAR: non-allergic rhinitis, CRSwNP: chronic

rhinosinusitis with nasal polyps, CRSsNP: chronic rhinosinusitis without nasal polyps. (†Mann-

85Whitney test, ‡ Fisher's exact test.)

Correlation with VAS effect of medication

	r	Significance	p
VAS total nasal symptoms	-0.2517	****	<0.0001
VAS nasal obstruction	-0.1796	****	<0.0001
VAS postnasal drip	-0.1673	****	<0.0001
VAS rhinorrhea	-0.1163	***	0.0069
VAS nasal itch	-0.09361	*	0.0302
VAS sneezing	-0.07919	NS	0.0677
VAS headache/facial pain	-0.1937	****	<0.0001
VAS loss of smell	-0.1637	****	<0.0001
VAS ocular itch	-0.02118	NS	0.6234

Table S2: Correlation between the visual analogue scale (VAS) scores on the effect of medication

and VAS-scores of various (sino)nasal symptoms. (Spearman r test.)

Correlation with number of triggers

	r	Significance	p
VAS total nasal symptoms	0.05480	NS	0.3601
VAS nasal obstruction	-0.01943	NS	0.7458
VAS postnasal drip	0.1485	*	0.0124
VAS rhinorrhea	0.1604	**	0.0069
VAS nasal itch	0.2676	****	<0.0001
VAS sneezing	0.2179	***	0.0003
VAS headache/facial pain	0.1487	*	0.0126
VAS loss of smell	0.1457	*	0.0143
VAS ocular itch	0.1697	**	0.0042

90Table S3: Correlation between the number of triggers of symptoms in patients with self-reported nasal hyperreactivity and visual analogue scale (VAS) scores of various (sino)nasal symptoms.

There is a correlation between the number of triggers and many (sino)nasal symptoms, most significantly with the neurogenically mediated symptoms nasal/ocular itch and sneezing. (Spearman r test.)

Supplementary figure legends

Figure S1: Relationship between the prevalence of self-reported nasal hyperreactivity (sNHR) and

disease severity. A) Prevalence of self-reported NHR in controlled (visual analogue scale (VAS) total

nasal symptoms <50 mm) and uncontrolled (VAS total nasal symptoms ≥50 mm) patients.⁵ **B)**

100Prevalence of self-reported NHR in patients with mild (VAS total nasal symptoms 0-30 mm),

moderate (VAS total nasal symptoms 31-70 mm) and severe (VAS total nasal symptoms 71-100 mm)

disease.⁵ (A: two-tailed Fisher's exact test with Holm-Sidak correction for multiple testing, not

significant; B: chi-square test with Holm-Sidak correction for multiple testing, * $p < 0.05$.) AR: allergic

rhinitis; NAR: non-allergic rhinitis, CRSwNP: chronic rhinosinusitis with nasal polyps, CRSsNP: chronic

105rhinosinusitis without nasal polyps.

Figure S2: Prevalence of self-reported nasal hyperreactivity (sNHR) in specific subgroups.

Prevalence of sNHR did not differ when comparing patient groups based on sinus involvement, presence of concomitant allergy in CRS patients, gender, current tobacco-use, history of rhinological surgery or severe nasal trauma, history of allergen immunotherapy, or presence of lower airway disease. (Fisher's exact test, not significant.) CRS: chronic rhinosinusitis.