Chronic rhinosinusitis, what do patient-reported outcome measures measure?

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Chronic Rhinosinusitis, What do Patient-Reported Outcome Measures measure?

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CHAPTER 1

GENERAL INTRODUCTION

CHRONIC RHINOSINUSITIS

Chronic rhinosinusitis (CRS) is a multifactorial chronic inflammatory disease of the nose and paranasal sinuses and is one of the most common chronic health conditions in the world. According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) CRS (with or without nasal polyps) in adults is defined as inflammation of the nose and the paranasal sinuses for more than 12 weeks, clinically characterised by the presence of two or more symptoms, one of which should be either nasal blockage / obstruction / congestion or nasal discharge (anterior / posterior). Further symptoms include facial pain or pressure, and reduction or loss of smell. EPOS provides two definitions of CRS; a clinical diagnosis based on these symptoms, supported by signs of mucosal inflammation found on imaging or with nasal endoscopy, and a symptom-based definition to be used in epidemiologic research (mostly questionnaire-based), without radiologic imaging or endoscopic examination [1].

CRS has a major impact on the quality of life and places a large financial burden on society mainly due productivity loss or presenteeism [2]. This means that many patients with partially controlled or uncontrolled CRS continue working, but (far) less productively. This implies that optimised treatment and, hence, better control of symptoms would generate an enormous save on societal costs.

The perception of patients with CRS is increasingly recognised as an important modulator of the CRS disease burden, affecting tolerance of symptoms and QoL impact felt by patients [3-5]. Identification of symptoms most noticeable and most bothersome to these patients may provide focused therapeutic targets and strategies in the treatment of CRS.

As a clinician, to get a view on a patient's burden of disease and quality of life, well-designed and validated questionnaires are indispensable. Furthermore, the clinician should be aware of the value – and limitations – of the available clinical measurements, like nasal endoscopy, and imaging.

SYMPTOM MEASUREMENTS

The burden and relief of symptoms as perceived by the patient should play an essential role in the choice and evaluation of treatment by the clinician in treating disease, especially chronic disease. There are many possible ways to assess the burden of disease or to evaluate the success of initiated treatment, e.g. clinical measures, such as imaging, medication use, provocation tests or the degree of symptoms [6].

In rhinology, it is well known that there is poor correlation between clinical measures like imaging, endoscopy and symptoms, like in asthma [7-9]. This might probably be caused by an underlying variation of endotypes, leading to a common phenotype [10]. Several publications have demonstrated the lack of correlation between patient-derived measures of symptom severity in CRS and clinical measures, such as the radiological Lund-Mackay scoring or nasal endoscopy [11-13]. Similarly, no correlation was demonstrated in a systematic review on sensation of nasal obstruction and measurements of cross-sectional airflow using rhinometry [14]. The absence of correlation does not suggest that either patient-related or clinical measures are invalid, but rather they are measuring different aspects of the disease process, and therefore are useful adjuncts in outcome measurement.

Quality of life (QoL) measurements are the best approximation of the burden of disease for the patient. In rhinology, questionnaires are widely used both in clinical practice and in research, to assess the health-related quality of life (HRQoL). The burden of disease is defined by more than only nasal symptoms, for example troubled sleep, bothered daily activities or the emotional consequences of the disease. It must be emphasized that there is a major difference between symptom scores on one hand, and HRQoL instruments on the other hand, as the latter aim to provide a comprehensive physical, functional and psychosocial quality of life assessment.

The last decades there has been a lot of research on mapping symptoms and on constructing, validating and refining disease specific HRQoL instruments. The awareness of HRQoL started in the '80s, but still took until 1995 for the first health-related QoL instrument to be constructed and validated [15, 16]. Since then multiple instruments were constructed, validated, translated and adapted in multiple cultures and languages [17-19].

Characteristics of the 22-item SinoNasal Outcome Test (SNOT-22)

The SNOT-22 is probably the most widely applied HRQoL instrument in rhinology. The SNOT-22 questionnaire is a patient-reported measure of outcome developed for use in CRS with or without nasal polyposis [18]. The questionnaire is a modification of the SNOT-20, which again was a psychometric and clinimetric optimisation of the original 31-question Rhinosinusitis Outcome Measure (RSOM-31) [15, 17]. In the RSOM-31 the CRS-related items were obtained from interviews with patients, discussion with physicians and a review of published literature. Interpretation of the original RSOM-31 was quite complex; the instrument contained 31 items, had a symptom severity scale of 0-5 (the *Magnitude scale*) and additionally had an importance rating (*Importance scale*). The product of the Magnitude and Importance score created the *Symptom-Impact score*. Based on patient and physician focus group discussion and on psychometric evaluation, the number of items was reduced to a more compact version of 20 items. However, SNOT-20 missed two major items contributing to content validity: 'nasal blockage' and 'loss of sense of taste and smell' and were again added in the SNOT-22. Furthermore, the questionnaire was simplified by removing the importance rating. The SNOT-22 is composed of CRS-related items, which evaluate the severity of complaints that the patient has been experiencing over the past two weeks. Patients score their symptoms on a 6-item scale (0-5; *0) Not present/ no problem, 1) Very mild problem, 2) Mild or slight problem, 3) Moderate problem, 4) Severe problem, 5) Problem is "as bad as it can be").* The sum of each item results in a minimum score of 0 and a maximum score of 110, with higher total SNOT-22 scores indicating worse symptoms. The SNOT-22 covers 4 domains potentially affected by CRS; nasal, sleep, otologic/facial pain, and emotional symptoms [20]. Domain scores are mean scores of the related symptom scores and all symptoms contribute equally. Good psychometric properties have been reported for the original SNOT-22 total score [18]. For participants without CRS a median SNOT-22 total score of 7 was previously reported [21].

Repeated measures map the individual patient's well-being, and allow improvements or exacerbations to be readily identified. It also helps to identify, together with the patient, what the present aims of the treatment will be. Often, over time, the symptoms and therefore

the desire for symptom relief change, and identifying these shifts is made easy with the use of a structured questionnaire.

In research, the use of validated questionnaires is crucial for reliable interpretation of results, and can be used as primary outcome of clinical trials [22]. PROMs can be used to assess the effect of a (new) treatment, or to compare the effects of different treatments on the issues most important to the patient. However, it is important the proper PROMs are used in the proper population. The first important question is whether the questionnaire has been validated in a population comparable to the research population. This concerns not only diagnosis but also patient characteristics and baseline HRQoL measurements. To interpret the burden of initial disease, one has to know what score is 'normal' in a healthy population. Hopkins recruited healthy individuals from hospital staff and the local tennis club and found an average SNOT-22 score of 9.3 in healthy individuals, compared to a SNOT-22 of 42.0 in the pre-operative CRS population (theoretical range SNOT-22 0-110) [18]. The importance of knowing the symptom scores in a non-affected population is evident; clinicians treating patients with near-normal scores can expect little patient satisfaction and might need to revise their diagnosis. To interpret the effect of treatment, the minimally clinical important difference (MCID) should be available for the instrument [23]. This defines the difference in score that is large enough to have an implication for the patient's treatment or care. Various methodologies have been developed for the calculation of the MCID, and on top, the MCID is dependent on patient expectations in relation to the treatment that is being given. This means that the reported MCID for the SNOT-22 in endoscopic sinus surgery (ESS) is 9.0 vs. 12 in medical management [24, 25].

CLINICAL MEASUREMENTS

Rhinologic radiologic evaluation is best done by means of computerized tomography (CT) [26]. CT imaging can be used in gathering signs of mucosal inflammation in diagnosing CRS. In CRS, otorhinolaryngologists will use nasal endoscopy to evaluate the extent of mucosal inflammation, and will use CT imaging mainly for pre-operative assessment. Other imaging modalities include conventional X-ray, cone beam CT and magnetic resonance imaging (MRI), but overall CT remains the gold standard [26, 27]. There is only a modest correlation between symptom scores and findings on imaging [28]. An example of this is the high prevalence of CT abnormalities found in symptom-negative populations, and also common cold has been shown to give sinus abnormalities on imaging in otherwise healthy subjects, usually dissolving in a few weeks [29-32]. Furthermore, there is a moderate agreement between nasal endoscopy and radiological data [33-36].

A widely used staging system in imaging is the Lund-Mackay score (LMS) as described initially in 1993 [37]. The aim of this instrument is to provide a user-friendly and as-simple-as-possible staging system. The authors describe that the simplicity of the application will be its main strength. Each sinus group (Maxillary, Anterior ethmoids, Posterior ethmoids, Sphenoid and Frontal) is graded between 0 and 2 (0: no abnormality; 1: partial opacification; 2: total opacification). The ostiomeatal complex is scored as "0" (not obstructed) or "2" (obstructed). A total score of 0-24 is possible, and each side can be considered separately (0-12). In a non-sinusitis population a LMS from 0-5 has been described [38].

Epidemiologic studies in CRS

Knowledge of CRS epidemiology may directly impact patient care; aiding patient identification and establishing accurate diagnosis as well as informing treatment decisions. There are several methods of determining prevalence, resulting in a variation in prevalence of CRS in epidemiologic research. Prevalence measured based on symptoms alone (5-12%) [39-43], or combined with nasal endoscopy (2.6-5.8%) [12, 44] all differ. Using relevant International Classification of Diseases (ICD) codes from health care administrative databases has the advantage that the numbers are widely available. Disadvantage is that different code-based definitions of CRS may be used, as well as the understanding that much of CRS coding is performed by non-specialists who are less likely to follow clinical consensus diagnostic definitions [45-47].

Alternatively, the Global Allergy and Asthma Network of Excellence (GA2LEN) conducted a postal survey using a consensus criteria-based diagnosis of CRS, using the symptom-only epidemiologic criteria from the EPOS guidelines [43]. A disadvantage of this method is that there might be an overestimation due to considerable overlap of symptoms between CRS, Acute rhinosinusitis (ARS) and (Non-)Allergic Rhinitis (NAR / AR); up to 10% of responders had symptoms of all three diagnoses [12, 48].

When both symptom criteria and physician-reported evidence of mucosal inflammation are used, the estimated prevalence of CRS is significantly reduced with roughly 2/3rd using nasal endoscopy [12] or imaging [49]. The challenge of validating the epidemiologic prevalence of CRS; is that all, mainly non-affected, subjects need to undergo either nasal endoscopy (invasive) or imaging (radiation exposure in CT imaging or expensive in MRI imaging).

CURRENT MANAGEMENT OF CRS

The goal of CRS treatment is to achieve and maintain clinical control so that patients do not have symptoms at all, or that the symptoms are not bothersome. If possible, this should be combined with a healthy or almost healthy mucosa. The EPOS evidence-based guidelines summarised the management in a management scheme or care pathway. Basics of treatment of Appropriate Medical Therapy (AMT), consisting of nasal saline irrigation [50, 51], topical or systemic steroids and evaluation of rinsing technique and compliance [1, 52-57]. In cases of insufficient control, endoscopic sinus surgery (ESS) [22, 58, 59] and application of biologicals (monoclonal antibodies) in selected cases suspected for Type 2 endotype [60-64] can be considered. Patients and clinicians should discuss the balance between getting as much grip on their disease on one hand, and on the other hand, have a tolerable medication regime. In other words; what's worth the extra efforts by means of alleviation of symptoms?

Assessment of current clinical control is based on the severity of several symptoms as perceived by the patient in the last month, combined with findings on nasal endoscopy and need for rescue treatment in the last 6 months. Symptoms include 'Nasal blockage', 'Rhinorrhoea / Postnasal drip', 'Facial pain / Pressure', 'Smell' and 'Sleep disturbance or fatigue' [1]. *Controlled disease* means absent, or not-bothersome symptoms, healthy of almost healthy mucosa on endoscopy and no need for rescue treatment in the last 6 months. In *partially controlled* disease, 1 or 2 symptoms or items are

EPOS 2020: Assessment of current clinical control of CRS (in the last month)

	Controlled (all of the following)	**Partly controlled** (**at least 1** present)	**Uncontrolled** (**3 or more** present)
Nasal blockage[1]	Not present or not bothersome[2]	Present on most days of the week[3]	Present on most days of the week[3]
Rhinorrhoea / Postnasal drip[1]	Little and mucous[2]	Mucopurulent on most days of the week[3]	Mucopurulent on most days of the week[3]
Facial pain / Pressure[1]	Not present or not bothersome[2]	Present on most days of the week[3]	Present on most days of the week[3]
Smell[1]	Normal or only slightly impaired[2]	Impaired[3]	Impaired[3]
Sleep disturbance or fatigue[1]	Not present[2]	Present[3]	Present[3]
Nasal endoscopy (if available)	Healthy or almost healthy mucosa	Diseased mucosa[4]	Diseased mucosa[4]
Rescue treatment (in last 6 months)	Not needed	Need of 1 course of rescue treatment	Symptoms (as above) persist despite rescue treatment(s)

[1] Symptoms of CRS; [2] For research VAS ≤ 5; [3] For research VAS > 5; [4] Showing nasal polyps, mucopurulent secretions or inflamed mucosa

Physicians treating CRS patients should be aware of treatable traits. A few should be actively assessed, such as smoking and occupational exposure [65, 66].

present and/or there was 1 course of rescue treatment needed. In *uncontrolled CRS* 3 or more items are present and/or symptoms persist despite rescue treatment. Unfortunately, there still remains a need for a gold standard to assess disease control in CRS.

Occupational exposure

It is estimated that currently at least 40% of CRS patients remain uncontrolled despite treatment [67]. These difficult-to-treat CRS-patients should be analysed for several factors that can cause lack of control; these can be related to either the disease, diagnosis, therapy, or specific patient. One of these factors might be an (unrecognised) occupational exposure [68].

The airways are the primary contact site for a variety of work-related dusts, gases, fumes and vapours. Depending on the amount inhaled and their physical-chemical properties, these agents can cause irritation, corrosive changes, and/or sensitization of the respiratory mucosa [69-71], not only posing as a risk factor for malignancies in specific cases, but more generally contributing to occupational airway disease, like rhinitis, rhinosinusitis and asthma [48, 72, 73].

A well-studied example is the increased prevalence of CRS in firefighters that had been exposed in the 9/11 World Trade Centre collapse in 2001. In this cohort a higher prevalence of non-resolving upper airway inflammation responding poorly to medical management was found, ultimately treated with surgery even years later. In the whole cohort of rescue and recovery workers a continued increasing cumulative incidence of 'asthma' and 'sinusitis' was found up to 9 years after exposure, compared to pre-exposure [74, 75].

Occupational agents can be classified as high molecular weight (HMW) compounds (>5kDa) — such as flour or animal antigens— or low molecular weight (LMW) compounds (<5kDa). The LMW

compounds are again subdivided into two groups, depending on their sensitization capacity; LMW sensitizers, such as isocyanates, persulphate salts and acid anhydrides, lead to airway inflammation after the latency phase of immunologic sensitization, whereas LMW irritants, such as chlorine, ammonia or ozone, cause an immediate airway injury and inflammation through nonallergic pathways [76].

The close link between the upper and lower airways has been known for decades, and inflammation in one part of the airway influences the homeostasis of the other, a phenomenon that is referred to as 'global airway disease' [77]. It is known that over 90% of individuals with asthma suffer from rhinitis and one-third of patients with allergic rhinitis suffer from asthma [78]. CRS has also been associated with adult-onset asthma [79]. Available epidemiological data suggests that this is not different in the occupational airway disease field; upper airway symptoms are present in up to 92% of subjects with occupational asthma, and they seem to precede lower airway symptoms in 58% of asthma induced by HMW-agents 25% of LMW-agents [80, 81].

An earlier study on the impact of occupational exposure, suggested a linear correlation between the reporting of occupational exposure and number of Endoscopic Sinus Surgery (ESS) procedures in patients with CRS needed to control disease. This suggests that occupational exposure can be considered a risk factor for the occurrence of rhinosinusitis and its recurrence after surgery [72]. This emphasises the importance for the clinician to enquire on possible contribution of occupational exposure in patients with uncontrolled symptoms, despite maximal conservative therapy.

In occupational airway disease, the initial step in management is prevention of its development by appropriate occupational hygiene including observance of exposure standards and surveillance of employees in high-risk environments. Early symptoms or sensitizations can be picked up by means of questionnaires, skin prick tests and increased awareness for onset of nasal symptoms with referral if needed [82]. When an occupational agent has been identified, avoidance or reduction in exposure to the suspected causal agent is the key feature of the treatment strategy, for example exposure in latex or biological enzymes [83, 84]. Reduced exposure can be achieved by improving ventilation systems, wearing appropriate protective clothing and masks, and, if possible, relocation of the patient to another job without exposure, because it is clear that patients suffering from occupational upper airway disease are at higher risk of developing occupational asthma [73].

AIM AND OUTLINE OF THE THESIS

The general aim of this thesis is to analyse and thereby optimise the use of patient-reported outcome measurements (PROMs) in CRS.

As a main concept, the burden and relief of symptoms as perceived by the patient should play an essential role in the choice and evaluation of treatment by the clinician in treating chronic disease like CRS. To be able to get a view on this burden; the clinician needs measurements which estimate this health-related quality of life (HRQoL). HRQoL questionnaires not only give insight in nasal symptoms, but also in other domains affected by the disease. In the last decades several instruments were developed and evolved through fine-tuning psychometric qualities. In **chapter 2** we provide an overview and quality assessment of PROMs used in rhinitis and rhinosinusitis.

We describe what instruments are suitable for what disease and which instruments score best on quality assessment. Furthermore, we describe the use of PROMs in daily clinical practice and in research. Already widely used, but surprisingly not validated in the Netherlands yet, we describe the Dutch translation and validation of the widely used SNOT-22 in **chapter 3**. This HRQoL instrument is an essential instrument in treating CRS patients and reliably comparing outcomes in clinical practice or research.

It is the clinical impression of otorhinolaryngologists that patients with CRSwNP more often complain of nasal obstruction and loss of smell, and that patients with CRSsNP mainly complain of facial pain and rhinorrhoea. As HRQoL instruments fulfil a substantial role in the diagnosis and evaluation of treatment of CRS, in **chapter 4** we describe the difference in symptoms between patients with CRSwNP and patients with CRSsNP according to EPOS criteria. Additionally, we analysed whether it is possible to make a distinction between patients with CRSwNP and patients with CRSsNP based on Rhinosinusitis Outcome Measure 31 (RSOM-31) symptom scores.

in **chapter 5** we describe the prevalence of epidemiologically (symptom-) based versus the prevalence of clinically (imaging-) based CRS in a non-rhinologic population, to gain more insight in the reliability of epidemiologically defined CRS in population studies. Furthermore, we analyse the alignment of imaging abnormalities with the symptom scores to test the feasibility of the imaging-based CRS diagnosis as a solid construct. The influence of other factors on imaging abnormalities is also considered (e.g., patient demographics and comorbidities such as asthma). Moreover, we investigate whether it would make any difference if we used the definition of CRS (containing 3 months of symptoms in the last year) or current symptoms of CRS (defined as CRS in the last three months) as it might reflect a difference in LMS at the time of imaging. Furthermore, we investigate what symptoms and findings are associated with the outcome of clinically relevant opacification on imaging and whether we were able to predict no abnormalities at CT scan (LMS=0).

Management of CRS is focused on achieving and maintaining clinical control of symptoms, which can be defined as a disease state in which a patient has no symptoms, or they do not affect QoL. In **chapter 6** we further focus on the measurements of control of disease. We analyse the correlations between individual SNOT-22 items and symptom-specific questions measured in VAS. EPOS2020 suggests to use several symptom-specific VAS scores to determine disease control; we analysed that individual SNOT-22 items can be used with a cut off at ≥3 instead of VAS as well. Unrecognised occupational exposure can be a factor contributing to lack of control. Undergoing (multiple) ESS can be assumed a reflection of uncontrolled CRS. In **chapter 7** we test the hypothesis that work-related exposures are related to the risk of undergoing ESS.

1

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CHAPTER 2

DISEASE SPECIFIC QUALITY-OF-LIFE QUESTIONNAIRES IN RHINITIS AND RHINOSINUSITIS: REVIEW AND EVALUATION

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ABSTRACT

Quality of Life (QoL) measurements are the best approximation of the burden of disease for the patient. Patient Reported Outcome Measurements (PROMs) estimate HRQoL. PROMs can be generic or disease specific. Generic PROMs allow comparisons between different diseases but can be relatively insensitive to measure changes within a disease. Recommended QoL questionnaires in Allergic Rhinitis and Rhinoconjunctivitis are the RQLQ (or adapted versions), in CRS the SNOT-22 or RSOM-31 and in ARS the modified SNOT-16. PROMs can be used both for daily clinical work and for research. In daily practice a quick evaluation of the questionnaire directly indicates how the patient is doing. It makes sure that symptoms important for the patient are not overlooked and during the consultation, the physician can elaborate on specific aspects of the symptomatology. It is important, especially in research, to realize that disease specific questionnaires are only validated for specific diseases and are not automatically valid in other diseases.

INTRODUCTION

The burden and relief of symptoms as perceived by the patient, should play an essential role in the choice and evaluation of treatment by the clinician in treating disease, especially chronic disease.

There are many possible ways to assess the burden of disease or to evaluate the success of initiated treatment, e.g. objective measures, such as imaging, medication use, provocation tests or the degree of symptoms[1]. In Rhinology, it is well known that the correlation between imaging and endoscopy and symptoms is limited[2, 3]. Also, the use of medication does not provide complete insight into the patients' troubles, as is the case when measuring the degree of symptoms only. Recently also in rhinitis and rhinosinusitis the concept of control as an important way to describe effectiveness of treatment on disease has been proposed[4, 5]. Quality of Life (QoL) measurements are the best approximation of the burden of disease for the patient. In Rhinology, questionnaires are widely used both in clinical practice and in research, to assess the Health Related Quality of Life (HRQoL). The burden of disease is defined by more than nasal symptoms only and HRQoL questionnaires also give insight into issues like sleep, daily activities or the emotional consequences from the disease. It must be emphasized that there is a major difference between symptom scores and HRQoL instruments, as the latter aim to provide a comprehensive physical, functional and psychosocial quality of life assessment.

PROMS

Patient Reported Outcome Measurements (PROMs) estimate HRQoL. These questionnaires have been developed to provide a standardized, quantified and summarized version of the patients' physical symptoms and the functional and psychosocial consequences of the disease and treatment. PROMs differ from symptom-scores in such way that HRQoL instruments translate symptoms into broader concerns that are important to patients.

GENERIC VS. DISEASE SPECIFIC PROMS

Generic PROMs measure overall QoL. The most widely tested and used instrument for general health assessment is the Medical Outcomes Study Short-Form 36-Item Health Survey (SF-36). This instrument is translated and validated in many languages.

Generic PROMs allow comparisons between conditions or treatments, and therefore can be used to determine not only the impact of different diseases on patient groups, but also the relative cost-utility of different interventions and to inform commissioning decisions. However, generic instruments may be unresponsive to small, but important to the patient changes in HRQoL. This makes generic instruments less suitable for measuring individual clinical outcomes.

Disease specific QoL questionnaires for allergic rhinitis where first developed by Juniper in 1991[6], and for rhinosinusitis in 1995 by Piccirillo[7]. In the following decade, many other questionnaires were designed for clinical and research use, each with its specific purpose[8-11]. With the development of rhinitis and rhinosinusitis specific HRQoL instruments, quality criteria were postulated regarding the psychometric properties of these questionnaires. Van Oene et al. [12] assessed the construction,

description, feasibility, validation study and the psychometric performance of QoL questionnaires concerning rhinitis and rhinosinusitis for adults (Table 1 – copy of van Oene with permission).

In this review, an update is provided on the quality assessment of the disease-specific QoL questionnaires for rhinitis and rhinosinusitis, including those developed since the publication by van Oene et al[12].

SPECIFIC PROM IN WHICH DISEASE?

In a well-designed instrument the generation of items is based on 1) research of literature, 2) input of experienced clinicians and 3) input of patients. This instrument is then validated for this specific patient group. Therefore, HRQoL instruments cannot be used interchangeably between rhinitis, acute and chronic rhinosinusitis.

In patients with allergic rhinitis and rhinoconjunctivitis the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)[6, 10] is considered the gold standard in assessment of HRQoL. This instrument has been adapted in several forms: the standardized form of RQLQ, Nocturnal RQLQ (NRQLQ) for measurement of nocturnal rhinitis, and the mini-RQLQ, using only half of the 28 questions. Although Juniper developed a questionnaire measuring perennial rhinitis in patients with allergic and non-allergic rhinitis [13], for pure non-allergic rhinitis (NAR), to date, there are no validated questionnaires available.

To measure the burden of nasal obstruction, the Nasal obstruction symptom evaluation (NOSE) scale was developed by Stewart in 2004[14]. However, this instrument is validated on septoplasty patients, and therefore not to be used in rhinosinusitis patients.

The recent EPOS 2012 document[4] has made recommendations for the use of specific instruments in rhinosinusitis. The assessment was based on several factors: 1) Availability of a published psychometric validation, 2) Time to complete an instrument for the patient and, 3) the number of studies utilising each instrument (validation studies excluded).

OVERVIEW OF VALIDATED HRQOL INSTRUMENTS

Based on the systematic review by van Oene[12], we give an overview of instruments that have high quality psychometric properties. Instruments validated after the publication by van Oene were graded by the authors, as proposed by van Oene.

Allergic rhinitis

Rhinoconjunctivitis quality of life questionnaire (RQLQ)

The RQLQ was developed to measure QoL in rhinoconjunctivitis as a result of nose and eye symptoms[6]. It has 28 questions in seven domains (activity limitations, sleep problems, non-nose/eye symptoms, practical problems). This instrument has been translated into 16 languages and is used extensively throughout the world in both clinical studies and clinical practice.

Table 1 Characteristics and criteria for quality-assessment (van Oene et al, 2007, with permission)

Property	Part	Criterion	Points
A. Construction			
Measurement	Targeted patient population	If provided	1
Goals	Purpose:	If provided	1
	discrimination and/or evaluation		
	For use in:	Used for level of reliability	-
	(clinical) trial or clinical practice		
Item generation	Sources:	If all 3 sources are used	1
	literature (incl. questionnaires)		
	clinician patients		
Item reduction	Approach: conceptual patient feedback statistical analysis	If all 3 methods are used	1
	Scale construction:	If all 3 methods are used	1
	conceptual patient feedback statistical analysis		
B. Description			
	Items, domains, response, score	If all 4 are provided	1
	Timeframe	If provided	1
C. Feasibility			
	Feedback of patients	If obtained	1
	Completion time	If provided	1
D. Validation Study			
	Kind of patients	If representative of target patient population	1
	Number of patients	If ≥ 100	1
E. Psychometric properties			
Reliability	Internal reliability	At group level: Cronbach's α ≥ 0.7 or	1
		At individual level: Cronbach's α ≥ 0.9	
	Test-retest	(significant T-test and Pearson/Spearman) or (ICC):	1
		At group level: correlation ≥ 0.7 or	
		At individual level: correlation ≥ 0.9	
Validity	Content validity	If confirmed (qualitative)	1
	Convergent validity	If correlation is between 0.4 – 0.8	1
	Discriminant validity	If the purpose is:	
		evaluation: this item is NA	NA
		discrimination: *p*-value < 0.05	1
Responsiveness		If the purpose is:	
		evaluation: *p*-value < 0.05 or responsiveness statistic is ≥ 0.5	1
		discrimination: this item is NA	NA
Clinically significant change		If the purpose is:	
		evaluation: used method and outcome provided	1
		discrimination: this item is NA	NA

Table 2 Recommended outcome tools based on current literature

Adult Allergic Rhinitis and Rhinoconjunctivitis – RQLQ (or adapted versions)[6, 10, 11]
Adult ARS – Modified SNOT-16[15]
Adult CRS – SNOT 22[9] or RSOM-31[7]

RQLQ – rhinoconjunctivitis quality of life questionnaire; ARS – acute rhinosinusitis; SNOT – sinonasal outcome test; CRS – chronic rhinosinusitis; RSOM – rhinosinusitis outcome measure; Based on: EPOS 2012[4] and van Oene[12]

Standardized version of the RQLQ (RQLQ(S))

In the RQLQ, the patient can choose 3 activities that are bothered by his/her complaints, in the RQLQ(S), these 3 freely chosen activities have been replaced by generic activities (regular activities at home and at work, recreational activities and sleep), to create a more suitable instrument for large clinical trials and cross-sectional surveys[10].

MiniRQLQ

In order to create an instrument more suitable for large clinical trials, Juniper developed the MiniRQLQ containing only 14 questions[11].

Nocturnal rhinoconjunctivitis quality of life questionnaire (NRQLQ)

The NRQLQ was designed to measure the functional problems that are most troublesome to patients with nocturnal allergic rhinitis. The instrument consists of 16 items over 4 domains (sleep problems, symptoms during sleep time, symptoms on waking and practical problems) [16].

Nasal Obstruction Symptom Evaluation (NOSE)

The NOSE scale is an instrument used in patients with nasal obstruction. The instrument consists of 5 questions asking to rate the burden of nasal obstruction during the past month. Strictly it is not a disease specific QOL questionnaire because it only evaluates one symptom. It is well validated and easy to use in epidemiologic studies[14].

RHINOSINUSITIS

RhinoSinusitis Outcome Measure-31 *(RSOM-31)*

The RSOM-31 contains 31 items divided into seven domains (nasal, eye, ear, sleep, general, functional and emotional problems). For each symptom there are two response scales: severity and importance. The product of the magnitude and importance scores creates the symptom-impact score. The instrument is well validated and is widely used, however, the severity and importance scales make it somewhat difficult for the patient to fill the questionnaire[7]. For this reason it is often used as the SNOT questionnaire with only the severity scales[9, 17].

SinoNasal Outcome Test *(SNOT-20)*

The SNOT-20 is a modification of the 31-item RSOM, containing 20 nose, sinus and general items. The importance scale was removed to make scoring easier. The SNOT-20 provides two main scores: 1) Total score, which is the mean score for all 20 items, and 2) importance score, which is the mean score for the five items identified as important[17]. A limitation of this questionnaire is that two critical questions are not included, 'nasal obstruction' and 'loss of smell'.

SinoNasal Outcome Test *(SNOT-22)*

The SNOT-20 questionnaire, based on the RSOM-31, missed two critical questions: nasal obstruction and loss of smell. These were again included in the SNOT-22 questionnaire. In addition, the magnitude level was changed back to a five-category scale. In 2009, Hopkins et al. validated this instrument, which appeared to be a valid and reliable questionnaire that is easy to use[9].

SinoNasal Outcome Test *modified for acute rhinosinusitis (SNOT-16-ARS)*

The SNOT-16 was modified to an easy to use tool in primary care patients with clinically diagnosed acute rhinosinusitis. The instrument uses a 4-item response scale and patients select maximum of 5 items that they felt were most important from the list. The validation study is well described and the modified SNOT-16 is a valid and reliable instrument for primary care patients with ARS[15].

Rhinosinusitis quality of life survey (RhinoQoL)

The RhinoQoL is a 17-item instrument, which measures symptom frequency, bothersomeness and impact scales in patients with acute and chronic sinusitis[18].

Impact of rhinitis on QoL

Adults and children with allergic and non-allergic rhinitis are bothered both by the nasal symptoms themselves and by associated symptoms such as headache and fatigue. The combination can produce quite severe impairment of day-to-day physical, emotional, occupational, and social functioning and can cause emotional distress[19]. The importance is demonstrated by the WHO ARIA guidelines: rhinitis severity is now based on the impact of disease on QOL [20]. There is also ample evidence that AR and NAR are associated with an incremental adverse impact on the disease-specific QOL of patients with asthma and the level of asthma control[20, 21]. One of the aims of treating patients with rhinitis should be that all individual patient problems are recognized and treated appropriately.

Impact of ARS on QoL

ARS is thought to have a substantial impact on patients' HRQoL and daily functioning, but this has not been well documented. The EPOS 2012 document recommends assessing the severity of symptoms with the use of a 10 cm visual analogue scale (VAS), or at least asking the patient to rate their symptoms as absent, mild, moderate or severe. It is advised to record the severity of symptoms in a fashion that is clinically meaningful.

Generic measures of QoL in ARS

Rechtweg et al. [22] used SF-36 questionnaires to measure possible difference in QoL outcomes in ARS patients treated with either Clarithromycin or Amoxicillin/Clavulanate. Regrettably, they only provide the p-values of these differences and no SF-36 scores for comparison with other diseases.

Impact of CRS on QoL

Generic measures of QoL in CRS

Van Agthoven measured SF-36 scores in patients with refractory CRS. All subscales were scored below the general population, and even lower than patients with hypertension, diabetes or angina[23]. Bhattacharyya has outlined the costs of CRS in the US in several studies[24-26]. Health care spending was significantly greater for sinusitis than for other chronic diseases, e.g. peptic ulcer disease, acute asthma and hay fever.

Disease specific measures of QoL in CRS

Measuring disease specific quality of life, means asking patients a fixed set of questions regarding possibly suffered symptoms, and to rate these according to the perceived burden. The RSOM-31, SNOT-22 and RhinoQoL cover not only the nasal symptoms, but also symptoms of the ears or eyes. Furthermore the instruments try to capture the disturbed sleeping or excessive tiredness. Emotional problems as irritability, frustration or depression are also addressed.

Nasal obstruction is one of the most commonly reported symptoms of CRS. Comparing patients with CRSwNP and CRSsNP using the RSOM-31, the former more often score higher on nasal symptoms, such as decreased sense of taste/smell or rhinorrhoea, while the latter score higher on facial pain and ear pain[27].

WHEN DO YOU USE PROMS IN CLINIC AND RESEARCH

PROMs can be used both for daily clinical work and for research. It seems intuitive that physicians would wish to measure whether they are successful in achieving their treatment aims.

For centuries, assessment of outcomes has involved simple dichotomous measurements, usually decided by the surgeons themselves, e.g. dead or alive, cure or residual disease, sometimes with some subtleties, e.g. better or worse. There has been a growing demand for greater transparency and publication of outcome data following treatment. Moreover, increasing emphasis has been placed on the patients' own evaluation of their HRQoL before and following medical or surgical interventions. Coupled with the explosion of Evidence Based Medicine, this has led to a significant refinement in the measurement of outcomes. The use of validated outcome measures helps physicians to evaluate their practice and improve management schemes. In many healthcare systems measurements of outcomes have become an important assessment tool for the quality of patient care.

THE USE OF PROMS IN THE DAILY PRACTICE

In the daily practice, measurements of patients symptoms is performed with validated questionnaires. The patient fills in the questionnaire at home before the visit to the clinic or when sitting in the waiting room. Questionnaires for rhinitis (RQLQ), rhinosinusitis (RSOM-31) and asthma (asthma control test (ACT)) are routinely used.

When the patient enters the consultation room, a quick evaluation of the questionnaire directly indicates how the patient is doing. Apart from the questions about nasal symptoms, these disease specific questionnaires contain questions on the eye, sleep, ear and general symptom domains. During the consultation, the physician can elaborate on specific aspects of the symptomatology and in a very efficient semi-structured way perform the consultation. This way of working is time saving and ensures that symptoms important for the patient are not overlooked. It also directly points to patients that will be difficult to treat, e.g. because of very many symptoms not directly related to the disease or to another diagnosis than originally considered: facial pain/headache without relevant nasal symptoms and not caused by a sinus problem. One has to realize, however, that standardised questionnaires derived from the population as a whole may restrict a patient's choice of symptoms to report, and may fail to capture those of importance to the individual. It is therefore important to always ask the patient whether other symptoms not in the questionnaire bother him or her. Finally the questionnaire makes sure that other important aspects like the lower airways or smoking are never forgotten.

Several publications have demonstrated the lack of correlation between patient rated measures of symptom severity in chronic rhinosinusitis and objective measures, such as the radiological Lund-Mackay scoring[2]. Similarly a recent systematic review has demonstrated no correlation between sensation of nasal obstruction and measurements of cross-sectional airflow using rhinometry[28]. The absence of correlation does not suggest that either patient rated or objective scores are invalid, but that they are measuring different aspects of the disease process, and therefore are useful adjuncts in outcome measurement.

For the majority of rhinological symptoms where reducing the impact of symptoms on the quality of life of the patient is the primary aim of treatment, patient-rated measures are usually more useful in guiding treatment and measuring the resulting outcome. Clinician-rated measures may however provide more useful feedback to give an indication whether the aimed reduction in symptoms is feasible. When there are a lot of symptoms in absence of significant disease as rated by the doctor the chance of a favourable outcome is smaller.

In the clinical setting, repeated measures map the individual patient's well-being, and allow improvements or exacerbations to be readily identified. It also helps to identify together with the patient what the present aims of the treatment will be. Often over time the symptoms and therefore the desire for symptom relief change, and identifying these shifts is made easy by the structured questionnaire.

If used in other diseases, it is unclear whether they will reliably measure improvements or exacerbations. The amount of information derived from the questionnaire has to be balanced against the effort of the patient. For many practices, short questionnaires like the mini RQLQ for

rhinitis (14 questions), the Nasal Obstruction Symptom Evaluation (NOSE) questionnaire for nasal obstruction (5 questions), the SNOT-22 for CRS (22 questions) and the asthma control test in patients with asthma (5 questions) are useful and easy to use.

THE USE OF PROMS IN RESEARCH

In research, the use of validated questionnaires is crucial for reliable interpretation of results and some guidelines even recommended to be the primary outcome of clinical trials [29]. Not for all diseases and interventions PROMs have been developed and in that case often QOL questionnaires are used that are not validated for the disease [22, 30]. The results of these studies should always be interpreted with some care.

Most importantly, PROMs can be used to assess the effect of a (new) treatment, or to compare the effects of two different treatments on the issues most important to the patient. However it is important the proper PROMs are used in the proper population.

The first important question is whether the questionnaire has been validated in a population comparable to the research population. This concerns not only diagnosis, but also patient characteristics and baseline HRQoL measurements.

To interpret the burden of initial disease, one has to know what score is 'normal'. This can be done by comparing the score of the affected population to a not-affected population. Picirillo[7] described RSOM-31 mean symptom impact score of 1.85 (theoretical range RSOM-31: 0-20) in audiology patients, compared to a score of 5.81 in a pre-treatment CRS population. Atlas[18] described a symptom impact score of 97.8 in a group of control patients, compared to a symptom impact score of 47.6 in ARS and 55.3 in CRS patients, where lower scores indicate more severe symptoms (theoretical range RhinoQoL: 0-100). Hopkins[9] recruited healthy individuals from hospital staff and the local tennis club and found an average SNOT-22 score of 9.3 (mean: 0.42) in healthy individuals, compared to a SNOT-22 score of 42.0 (mean: 1.91) in the pre-operative CRS population (theoretical range SNOT-22: 0-110). Due to the importance scale used by Picirillo, the RSOM-31 and SNOT-22 cannot directly be compared with each other. The importance to know the symptom scores in a normal population is evident; clinicians treating patients with near-normal scores can expect little patient satisfaction and might need to revise their diagnosis.

To interpret the effect of treatment, the minimally important difference (MID) should be available for the instrument[31]. This defines a difference in score that is *clinically* significant, as opposed to *statistically* significant, which is more commonly reported. For example, the MID in the RQLQ is approximately 0.5, in the MiniRQLQ 0.70, in the RSOM-31 a 30% change in total score, in the SNOT-16 (for ARS) 0.5 and in the SNOT-22 8.9 (mean approximately 0.5)[7, 9, 11, 15].

Which instrument to choose based on quality?

Based on a thorough and valid assessment of the clinimetric quality, one can decide which instrument is most suitable for the specific research population. Also, the findings of a generic and a disease specific instrument can be combined.

For allergic rhinitis, the MiniRQLQ and the standardized RQLQ score well on the quality assessment.

For CRS, both the RSOM-31 and its product SNOT-22 score very well in the quality assessment, together with the RhinoQoL. The SNOT-22 score is easier to calculate and interpret than the RSOM-31 score.

For ARS, only the RhinoQoL and the modified SNOT-16 have been validated. In both instruments the validation process was well documented. The SNOT-16 might be somewhat easier for the patient to fill in, and the calculation of the score is less complicated.

When measuring HRQoL in Rhinology patients, the Asthma control test (ACT) or the RhinAsthma Patient Perspective (RAPP) are helpful to identify patients with poorly controlled asthma[32, 33]. The RAPP is a simple eight-question questionnaire with good measurement properties and sensitivity to health changes, which will provide a valid, reliable and standardized HRQoL measurement in patients with asthma and comorbid allergic rhinitis in clinical practice.

PATIENT-REPORTED OUTCOME MEASURES IN THE LOWER AIRWAYS

Also in asthma there is a strong body of evidence about the relationship between HRQoL evaluated by PROMs and objective measures of lung function[34, 35].

Asthma appears to be a close lower airways correlate to the reactive diseases of the nose. Currently, several outcome measures are considered important in asthma: FEV_1, bronchial hyperreactivity, symptom scores, emergency department visits and hospitalizations, exhaled nitric oxide or other exhaled gases, beta-agonist use, exacerbations, and quality of life (QoL) [36]. However, the burden of the disease and the HRQoL are of primary concern for physicians.

Many of the asthma outcome measures do not correlate well with one another. Specifically, comparisons between lung function and daytime symptom scores or beta-agonist use reveal a poor correlation[35]. In a study of patients with persistent asthma treated with triamcinolone or switching to salmeterol, lung function was shown not to correlate with asthma exacerbations[37]. As there is no one parameter that can exclusively serve as a marker of asthma control, patient-derived information becomes critical in evaluating this disease.

Similar observations can be made in chronic obstructive pulmonary disease (COPD). Tsiligianni et al. performed a meta-analysis of factors influencing disease-specific QoL in COPD patients[34]. Most studies showed a non-significant or weak association between FEV_1 and health status, while others revealed a moderate association. Highest correlations (in modest range, 0.4-0.6) were found for 3 questionnaires (Quality of Well Being Scale, Chronic Respiratory Questionnaire dyspnoea and COPD Control Questionnaire) used only in 6 studies. The other health status measures, including the most frequently used St George's Respiratory Questionnaire, correlated weakly with FEV_1.

GENERAL THOUGHTS ON THE PHILOSOPHY OF USING PROMS

The patient's perspective on the disease, which the PROMs try to capture, is neither the defining feature of disease, nor second to the objective findings. In 1995, Wilson and Cleary proposed

a conceptual model of patient outcomes[38]. They are to be considered in the perspective of objective findings (biological and physiological variables, e.g. radiographic or endoscopic measures of sinusitis) in combination with characteristics of the individual (symptom amplification, personal motivation, values and preferences) and the environment (psychological, social and economic supports). These variables contribute to the formation of five levels of outcomes, moving from the cellular to individual to societal levels: *biological and physiological*, *symptom status*, *functional status*, *general health perceptions* and *overall quality of life*. Even though HRQoL measures in rhinitis and rhinosinusitis combine, to a variety of degrees, measures from all five levels of this model, it is necessary to remind that frequently physicians focus on the level close to their understanding of disease (e.g. questions on nasal symptoms in case of rhinosinusitis). Specialists are more prone to treating the specific aspects of disease (*biological and physiological* and *symptom status* levels), while general practitioners are more inclined to address the overall health of the individual as well (*functional* and *general health perceptions* levels).

What makes continuous need for utilization of PROMs in health care critical is the fact that they capture aspects of the disease that are not easily recorded by static quantifiable parameters. They provide an opportunity to measure these variables not captured on the biological level. In addition, they allow for continuous measurement of the overall perception of health by the patient. Ultimately, it is the patient that we treat, and their symptoms are what brings them to our care.

CONCLUSION

PROMs measuring QOL are an essential part of instruments of the clinician interested in his patients and the researcher needing validated and reliable tools.

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CHAPTER 3

VALIDATION OF THE DUTCH VERSION OF THE 22-ITEM SINO-NASAL OUTCOME TEST (SNOT-22)

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ABSTRACT

Background

The 22-item Sino-Nasal Outcome Test (SNOT-22) is a widely used questionnaire to measure disease-specific health-related quality of life in patients with chronic rhinosinusitis (CRS).

Aim

To validate the Dutch version of the SNOT-22

Methods

The SNOT-22 was translated through a forward-backward translation technique and validated by a test-retest protocol in CRS patients, a responsiveness analysis in CRS patients treated with dupilumab, using healthy individuals as controls.

Results

The Dutch SNOT-22 showed excellent test-retest properties, good responsiveness to treatment with dupilumab, and a clear distinction between outcomes of CRS patients and healthy controls.

Conclusion

The Dutch version of the SNOT-22 is a valid outcome measure in CRS patients.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a relatively common chronic disease affecting between 4-11% of Western populations [1, 2]. The diagnostic construct is based on a combination of specific symptoms (nasal obstruction and/or rhinorrhoea, combined with loss of smell and/or facial pressure/fullness) and abnormalities upon nasal endoscopy and/or imaging [3]. CRS has a marked influence on health-related quality of life, and results in major health care costs [4, 5].

Currently, there is no cure for CRS and, as such, treatment should be aimed at attaining (some level) of disease control. Especially in this respect, the patient perspective on CRS is pivotal in determining treatment success. Over the past decades, several patient-reported outcome measures (PROMs) have been developed in the field of CRS. The 22-item SinoNasal Outcome Test (SNOT-22) is a widely accepted tool to measure disease-specific health-related quality of life (HRQoL) [6]. It is suggested as part of the Core Outcome Set for CRS research [7], and is used in large clinical trials as primary outcome measure [8].

The SNOT-22 was originally developed in 2009 as a modification of a 20-item questionnaire (SNOT-20), which in turn was derived from the 31-item Rhinosinusitis Outcome Measure (RSOM-31)[6]. Since then, the SNOT-22 has been translated and validated in many languages [9-26]. In-depth analyses of SNOT-22 metrics, such as the minimal clinically important di fference have been performed as well [27].

The items in the SNOT-22 are not limited to nasal complaints only; the different domains also cover emotional complaints, and other physical areas, such as otologic symptoms. It is therefore not surprising that conditions or treatments affecting these domains, can influence SNOT-22 scores [28, 29]

With the recent advent of biological therapy for CRS with nasal polyps, a new emphasis is placed on PROMs such as the SNOT-22. On the one hand as one of the indication criteria to start biological therapy, on the other hand as a measure of treatment success [3]. Given the high costs of biological therapy, the debate of benefit over costs will require patient-reported input, and it is very likely the SNOT-22 will play a pivotal role in this discussion. Post-hoc analyses and real-life studies [30-35] already confirm the effectiveness of the three currently registered biologicals for CRS with nasal polyps (mepolizumab [36], dupilumab [37], and omalizumab [38]). Still, the patient perspective in these analyses and their effect on treatment algorithms is essential [39].

Although commonly used in many clinics in the Netherlands, the Dutch version of the SNOT-22 has not been validated yet. The aim of this study was to translate and validate the SNOT-22 for Dutch-speaking patients. We assessed the reliability, validity and responsiveness of the translated SNOT-22 questionnaire.

METHODS

SNOT-22

The SNOT-22 consists of 22 questions, 12 of which are relating to symptoms, (rhinologic, ear and facial symptoms), and 10 of which concern general health questions (sleep function and psychological issues). Per item, symptom severity is graded from 0 to 5: no problem (0), very mild problem (1), mild or slight problem (2), moderate problem (3), severe problem (4) and problem as bad as it can

be (5). The total sum of item-scores can thus range from zero to 110 with higher scores indicating more severe disease.

Forward and backward translation

A professional translator translated the questionnaire from English into Dutch. The study group then evaluated that the meaning of the wording preserved that of the original English version. Next, the backward translation was again performed by a professional translator. Any deviations from the original English SNOT-22 were studied, and none were deemed relevant.

Study population

This study was approved by the Ethics Committee of the Amsterdam University Medical Centres, location AMC (W21_195 # 21.212). Three groups were defined. *Group A* consisted of adult patients (18 years or older) with CRS (based on EPOS criteria) visiting the outpatient clinic of the AMC. They were asked to fill in the Dutch SNOT-22 as part of their regular care, irrespective of their current disease control (baseline measurement). If patients agreed to participate, they were given a blank SNOT-22, and a small questionnaire for identification and to indicate whether their health status had changed over the past weeks. Patients were given a return envelope, and asked to return these questionnaires after 2-4 weeks (follow-up measurement). Only patients returning a complete SNOT-22 within 4 weeks, and indicating no change in health status were included in the analysis (n=22).

Group B consisted of 23 adult CRS patients starting on biological therapy (dupilumab). This group was formed to assess the responsiveness of the Dutch SNOT-22. Patients filled in a Dutch SNOT-22 as part of their regular care at the start of treatment (baseline measurement) and after 4 weeks (follow-up measurement; i.e. after two gifts of 300 mg dupilumab s.c.).

Group C consisted of adult healthy native Dutch volunteers that were recruited from the close circle of the study team members: a local padel club, a local tennis club, non-direct neighbours and family members from medical staff. Participation was voluntary. Information on the aim of the study was provided. The volunteers were asked to fill in the Dutch SNOT-22, along with a small questionnaire regarding baseline characteristics (age, gender, smoking), and whether they had ever been diagnosed with, or treated for (non-)allergic rhinitis, CRS, or asthma. Those confirming such a medical history were excluded from this group. This way, 75 subjects could be included in group C.

Statistical analysis

Data were analysed in SPSS (IBM SPSS Statistics, version 26). Data are presented as mean ± standard deviation, unless otherwise specified. In group A, a Pearson correlation test was used. In group B, a paired-samples t-test was used; differences between group B and C were tested with an uncorrected independent-samples t-test. Internal consistency was tested using Cronbach's alpha, both for the full SNOT-22, as by item-wise determination when leaving out a single question. A p-value <0.05 was considered significant.

RESULTS

The baseline characteristics for the three groups are given in Table 1. For group A, the left panel of Figure 1 shows the baseline and retest measurements, with a Pearson correlation coefficient of 0.968, indicating excellent correlation (p<0.0001).

The right panel of Figure 1 shows the data from the dupilumab treated patients, starting at a mean SNOT-22 score of 57.4 ± 16.6. After four weeks of dupilumab treatment, this decreased to 29.6 ±16.7 (p<0.0001). The data from group C are also summarized in this panel. The mean SNOT-22 score for healthy controls was 11.8 ± 8.5 (p<0.0001 versus group B baseline and after 4 weeks of dupilumab). In this group, no effect on the SNOT-22 score was found for age, gender, or smoking (not shown).

Cronbach's alpha was 0.958 in group A for the baseline measurement, and 0.960 for the retest; in group B it was 0.901 at baseline, and 0.928 after 4 weeks of treatment with dupilumab. Item-wise

Table 1 Baseline characteristics of the study groups

Group	A: test – retest	B: dupilumab treatment	C: healthy controls
N	22	23	75
Age	56.1 ± 11.0	50.7 ± 10.2	46.2 ± 13.2
Gender (n (%) female)	9 (40.9%)	7 (30.4%)	36 (48.0%)
Smoking			
Never	14 (63.6%)	12 (52.2%)	65 (86.7%)
Former	7 (31.8%)	11 (47.8%)	5 (6.7%)
Current	1 (4.5%)	0 (0%)^	5 (6.7%)

^Smoking is a contra-indication for biological treatment in the Netherlands.

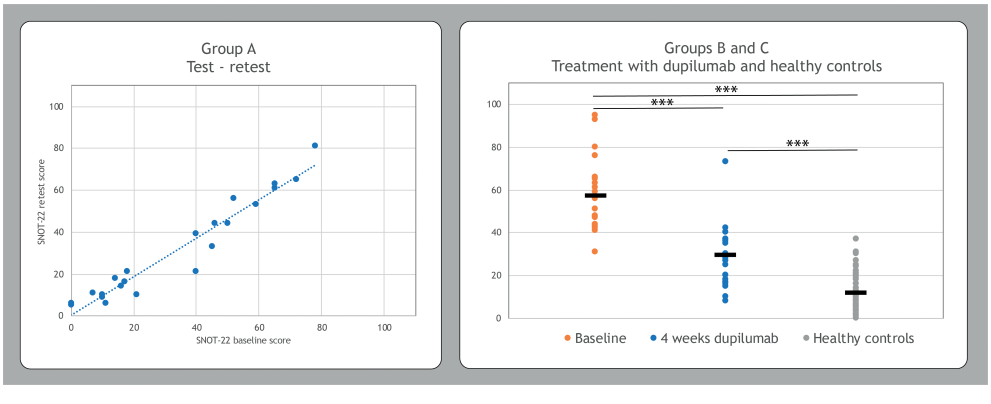

Figure 1 Left panel: outcomes for group A (test-retest): the x-axis shows the SNOT-22 scores at the baseline test; the y-axis shows those after 2-4 weeks. Dots indicate single patient outcomes. There is an excellent correlation between the two (dotted line). Right panel: SNOT-22 scores for group B before (orange dots) and after (blue dots) 4 weeks of dupilumab, and for group C (healthy controls; grey dots). Horizontal bars indicate the group mean SNOT-22 score. *** p<0.0001

analysis of Cronbach's alpha when deleting a single question showed a value of ≥0.893 in these groups.

DISCUSSION

The current study shows that the Dutch version of the SNOT-22 is robust, valid, responsive, and has a good to excellent internal consistency. This is in line with the other studies describing its translation and validation in other languages. It validates the already common use of the SNOT-22 in Dutch clinics.

The limitations of the study include a relatively small sample size in groups A and B. Given the fact that group A covers a large range of SNOT-22 scores, we would not expect a large sample to give significantly different results. For group B the effects are already quite drastic and in line with a larger cohort using dupilumab [35]; therefore, we would not expect relevant changes from expanding this group either.

Another limitation is the recruitment of patients from a tertiary clinic, possibly leading to selection bias of more severe patients. The distribution of the SNOT-22 scores in group A suggests that this bias is limited.

Finally, strictly speaking it would be necessary to revalidate the Dutch SNOT-22 in other Dutch speaking areas such as parts of Belgium, or the former Dutch colonies, although it is very likely the current Dutch version can be used reliably in these patient / demographic groups as well.

CONCLUSIONS

The presented Dutch version of the SNOT-22 is valid and reliable and can be used to measure HRQoL in Dutch CRS patients.

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SUPPLEMENTARY DATA

SNOT-22

Uitkomstmeting (neus)bijholteontsteking

Hieronder vindt u een lijst met de symptomen, functionele beperkingen en emotionele gevolgen van uw (neus)bijholteklachten. We willen graag meer weten over deze klachten en zouden het op prijs stellen als u de volgende vragen zo goed mogelijk zou willen beantwoorden. Er zijn geen 'goede' of 'foute' antwoorden en alleen u kunt ons aan deze informatie helpen. Beoordeel uw problemen zoals deze de afgelopen twee weken zijn geweest. Aarzel niet om de onderzoeksassistent of een van de medewerkers om hulp te vragen. Bedankt voor uw medewerking!

Mate van Ernst

Bekijk hoe ernstig het probleem is, als het zich manifesteert en hoe vaak het zich voordoet.

Geef voor elke vraag aan hoe 'slecht' het gesteld is. Gebruik daarbij de onderstaande schaalverdeling:

0 = Niet aanwezig / geen probleem

1 = Minimaal probleem

2 = Matig / klein probleem

3 = Gemiddeld probleem

4 = Ernstig probleem

5 = Probleem 'is zo erg als het maar zijn kan'

Neusklachten						
	Ernst					
1. Verstopte neus	0	1	2	3	4	5
2. Loopneus	0	1	2	3	4	5
3. Niezen	0	1	2	3	4	5
4. Verminderde reuk of smaak	0	1	2	3	4	5
5. Slijm dat van achteruit de neus in de keel loopt (postnasale drip)	0	1	2	3	4	5
6. Taai snot	0	1	2	3	4	5
Slaapproblemen						
	Ernst					
7. Moeite om in slaap te komen	0	1	2	3	4	5
8. Midden in de nacht wakker worden	0	1	2	3	4	5
9. Gebrek aan een goede nachtrust	0	1	2	3	4	5
10. Vermoeid wakker worden	0	1	2	3	4	5
Oorklachten						
	Ernst					
11. Dichte oren	0	1	2	3	4	5
12. Duizeligheid	0	1	2	3	4	5
13. Oorpijn	0	1	2	3	4	5
Algemene klachten						
	Ernst					
14. Moeheid / uitgeput gevoel	0	1	2	3	4	5
15. Verminderde productiviteit	0	1	2	3	4	5
16. Slechte concentratie	0	1	2	3	4	5
17. Aangezichtspijn of drukkend gevoel	0	1	2	3	4	5
18. Hoesten	0	1	2	3	4	5
Praktische problemen						
	Ernst					
19. Behoefte om herhaaldelijk de neus te snuiten	0	1	2	3	4	5
Emotionele gevolgen						
	Ernst					
20. Gefrustreerd, ongeduldig of geïrriteerd	0	1	2	3	4	5
21. Somber gevoel	0	1	2	3	4	5
22. Opgelaten door uw symptomen	0	1	2	3	4	5
Bedankt voor uw medewerking!						

CHAPTER 4

SYMPTOMS IN CHRONIC RHINOSINUSITIS WITH AND WITHOUT NASAL POLYPS

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SUMMARY

Objective

In this study we analyse differences in symptoms scored between chronic rhinosinusitis patients with (CRSwNP) and without nasal polyps (CRSsNP). According to EPOS, chronic rhinosinusitis with and without nasal polyps diagnoses are defined by clinical criteria, supported with endoscopy. We want to know if it is possible to make an accurate distinction between patients with and without nasal polyps based on clinical impression.

Study design

Retrospective case-control study.

Methods

We collected RSOM-31 questionnaires from CRS patients with and without nasal polyps and compared mean total RSOM-31 scores, mean domain scores, mean symptoms scores, and percentages of patients reporting symptoms per diagnosis based on endoscopy and CT scan.

Results

RSOM-31 Questionnaires were collected from 234 patients. Although total RSOM-31 score was similar and symptomatology considerably overlapping, patients with CRSwNP scored significantly higher and more often on nasal symptoms as 'Rhinorrhoea' and 'Decreased sense of taste or smell'. Patients with CRSsNP significantly scored more often and higher on 'facial pain' and 'ear pain'.

Conclusion

Although there are significant differences scored on several symptoms, there is considerable overlap of many symptoms and it remains difficult to distinguish between CRSwNP and CRSsNP based on clinical impression alone.

INTRODUCTION

In the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS)[1, 2] chronic rhinosinusitis (CRS) is defined as an inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, during more than 12 weeks, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) supplemented with facial pain/pressure and/or reduction or loss of smell and either endoscopic signs of disease and/or CT changes.

In recent years it has been shown that in the western world, CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) have a different inflammatory pattern[3]. CRSwNP is characterized by higher eosinophilia, IgE and IL-5 compared to CRSsNP and patients with CRSwNP more often have asthma than patients with CRSsNP[4]. Also in the response to treatment there seem to be differences. Patients with CRSwNP tend to react better to nasal and systemic corticosteroids,[5, 6] the effect of local corticosteroids in CRSsNP is less prominent[7]; there are some indications that in CRSsNP, especially in patients with low IgE, long term therapy with macrolides is effective[8].

It is the clinical impression of otorhinolaryngologists that patients with CRSwNP more often complain of nasal obstruction and loss of smell and that patients with CRSsNP mainly complain of facial pain and rhinorrhoea[9, 10]. As health-related quality of life questionnaires fulfil a substantial role in the diagnosis and evaluation of treatment of chronic rhinosinusitis, we want to analyse the difference in symptoms between patients with CRSwNP and patients with CRSsNP, according to EPOS criteria. Additionally we analyse if it is possible to make a distinction between patients with CRSwNP and patients with CRSsNP based on RSOM-31 symptom scores.

MATERIALS AND METHODS

Patients visiting our tertiary referral outpatient clinic are asked to fill in a standard set of questionnaires, including the RSOM-31. Additional presence of asthma, based on doctors diagnosis and aeroallergen sensitisation, based on IgE or skin prick test is recorded. In this study we analysed patients who visited our clinic for the first time with the diagnosis CRS with or without nasal polyps, according to EPOS criteria. Presence of nasal polyps is defined as bilateral endoscopically visualised grape-like pedunculated lesions the middle meatus. Patients suffering from cystic fibrosis (CF), vasculitis, granulomatous disorders, immotile cilia dysfunction syndrome, neoplasia and cocaine abuse were excluded.

The patients with chronic rhinosinusitis were divided into two groups based on endoscopy: CRSwNP and CRSsNP. In case the diagnosis CRS was doubted, diagnose was based on consensus by the AMC rhinologists, all of whom are experts in the field of sinonasal disease, based on endoscopy and CT scan. All patients included had abnormalities on CT scan and endoscopy, fulfilling the EPOS criteria for CRS.

Paranasal CT-scans were scored according to the Lund-McKay scoring system (0-24).

Other investigations

Inhalation allergy was determined based on either a positive skin prick test or detection of specific IgE in the blood, unless the referring specialist provided us with recent investigations on

sensitisation. Asthma diagnosis was based on doctor-diagnosed asthma. In case the patient was suspected of asthma and not known with the diagnosis the patient was send to the pulmonologist for confirmation of the diagnosis asthma.

The RSOM-31 is a 31- item rhinosinusitis-specific questionnaire which contains 7 subscales: nasal, eye, sleep, ear, general, practical and emotional. Patients score their symptoms on a 6-item scale (0-5; *0) Not present/ no problem, 1) Very mild problem, 2) Mild or slight problem, 3) Moderate problem, 4) Severe problem, 5) Problem is "as bad as it can be")*. Maximum RSOM-31 score can be 155, domain scores are mean scores of the related symptom scores and all symptoms contribute equally.

The items in the questionnaire reflect the full spectrum of physical problems, functional limitations, and emotional consequences of rhinosinusitis[11]. The RSOM-31 has been found to be one of the best Quality of Life (QoL) questionnaires in CRS based on the measurement goals, the discriminant validity, responsiveness and the points obtained in the quality assessment[12].

Only fully completed questionnaires were included.

Statistical analysis

Data were analysed using Statistical package for social sciences (SPSS) version 18.0.

Means, standard deviations (SD), mean differences and 95% confidence intervals (95% CI) of the total RSOM-31 scores, the domain scores and the individual RSOM-31 symptom scores for both groups were calculated and compared with t-tests. Apart from analysing the mean differences per item score, we dichotomized the answers into no/yes, based on a symptom score ≥ 2 (i.e., mild or slight problem, and worse). Percentage of positive outcomes of the separate symptom scores in the two groups were compared using chi-square test, with the corresponding odds ratio (OR) and 95% confidence interval (95% CI).

A *p*-value <0.05 was considered statistically significant. A Bonferroni correction was applied to correct for multiple testing, resulting in a *p*-value considered statistically significant of (0.05 / 31=) 0.0016.

Additionally we conducted a multivariable regression analysis to determine the best set of independent predictors for CRSwNP.

Because there is no linear association between symptom severity and risk for CRSwNP, we dichotomised the RSOM-31 scores based on a symptom score ≥ 2 (i.e., *'mild or slight problem'* and worse).

First we made a pre-selection of possible predictors by univariate regression analysis.

Based on the total number of patients with nasal polyps (n=137), we could examine about 13 possible predictors. Possible predictors with a *Wald-p* value <0.10 were included in a multivariable logistic regression analysis.

To obtain a model for predicting individual risk for nasal polyps that can be used in daily practice, we applied a backward selection (significance level to stay in the model: $p \leq 0.05$ and based on likelihood-ratio test ($p \leq 0.10$) and Nagelkerke R^2) to reduce the number of predictors.

The last remaining variables were double-checked for association with nasal polyps, based on the univariate Ln-odds, and on *Wald-p* value when running the model separately with every variable one-by-one.

RESULTS

In total 234 patients (Mean age: 44 yrs (SD 15), 60% male) fulfilling the EPOS criteria for CRS were included, with 137 patients with CRSwNP. Characteristics are shown in table 1. Prevalence of asthma is more common in patients with CRSwNP (51%) than in patients with CRSsNP (31%), as is sensitisation to aeroallergens: 47% in patients with CRSwNP and 26% in patients with CRSsNP.

Total RSOM-31 and domain scores

When comparing total RSOM-31 scores, there is no significant difference between patients with CRSwNP (mean: 66 (SD 26.8)) and patients with CRSsNP (mean: 67 (SD 25.5)).

As showed in table 2, there are differences in domain scores. The nasal domain scores are higher in patients with CRSwNP versus patients with CRSsNP (mean 3.0 (SD 0.9) vs. mean 2.5 (SD 0.8),

Table 1 Patient characteristics

	CRSwNP n = 137	**CRSsNP n = 97**
Age, mean (SD)	44.8 y (15)	42.9 (15)
Male %	69	47
Smoking %		
Current	15	24
Stopped	35	32
Never	50	43
Asthma %	51	31
Patients tested for allergy %	91	89
Aeroallergen sensitisation %	47	26
Patients with CT scan %	100	99
Median LM-score[a] (range)	18 (12-22)	5 (2-10)

[a]: Lund-Mackay score (0-24)

Table 2 Domain scores

RSOM-31 Domain score	**CRSwNP Mean symptom score**	**CRSsNP Mean symptom score**	**Mean difference**	**95% CI**
Nasal	3.0	2.5	0.41[a]	0.20 – 0.63
Eye	1.3	1.5	-0.19	-0.55 – 0.18
Sleep	2.0	2.2	-0.21	-0.56 – 0.14
Ear	1.4	1.5	-0.17	-0.50 – 0.15
General	2.3	2.6	-0.33[b]	-0.63 - -0.03
Practical	2.2	1.9	0.32[c]	-0.0004 – 0.65
Emotional	2.1	2.3	-0.12	-0.50 – 0.26
Total RSOM-31 score	66.2	67.1	-0.99	-7.85 – 5.87

[a]: $p<0.001$, [b]:$p=0.033$, [c]: $p=0.050$

p<0.001). There is a trend for the practical domain scores in patients with CRSwNP versus CRSsNP (mean 2.2 (SD 1.2) vs. mean 1.9 (SD 1.3), p=0.05). The general domain scores tend to be higher in patients with CRSsNP versus CRSwNP (mean 2.6 (SD 1.1) vs. mean 2.3 (SD 1.2), p=0.033).

Symptom scores

Table 3 shows that there is a considerable overlap of the majority of symptom scores between patients with and without NP. Patients with CRSwNP score higher on nasal symptoms. Patients with CRSsNP score higher on 'headache'.

Table 3 Mean symptom score

	CRSwNP Mean symptom score	**CRSsNP Mean symptom score**	***p*-value**	**95% CI**
1. Blockage / congestion of nose	3.5	3.2	0.047	0.004 – 0.6
2. Rhinorrhoea	2.6	1.7	<0.001*	0.44 – 1.19
3. Sneezing	1.8	1.7		-0.20 – 0.48
4. Sense of taste/smell	3.9	2.8	<0.001*	0.75 – 1.54
5. Postnasal drip	3.0	3.0		-0.44 – 0.40
6. Thick nasal discharge	3.0	2.9		-0.30 – 0.51
7. Itchy eyes	1.6	1.6		-0.41 – 0.43
8. Swollen eyes	1.1	1.4		-0.80 – 0.03
9. Difficulty falling asleep	1.4	1.6		-0.61 – 0.21
10. Waking up at night	2.1	2.2		-0.59 – 0.25
11. Lack of good night's sleep	2.0	2.2		-0.59 – 0.29
12. Waking up tired	2.4	2.8		-0.76 – 0.09
13. Ear fullness	1.8	1.9		-0.58 – 0.33
14. Ringing	1.3	1.7		-0.85 – 0.08
15. Dizziness	1.1	1.3		-0.53 – 0.22
16. Ear pain	0.9	1.2		-0.63 – 0.08
17. Decreased hearing	1.8	1.7		-0.39 – 0.50
18. Fatigue	2.6	3.1	0.026	-0.89 - -0.06
19. Reduced productivity	2.3	2.6		-0.67 – 0.71
20. Reduced concentration	2.2	2.4		-0.69 – 0.13
21. Headache	2.0	2.9	0.001*	-1.27 - -0.36
22. Facial pain/pressure	2.2	2.9	0.003	-1.15 - -0.24
23. Cough	2.1	2.0		-0.32 – 0.54
24. Short of breath	2.5	2.4		-0.32 – 0.53
25. Inconvenience of having to carry tissues	2.2	1.4	0.002	0.29 – 1.22
26. Need to rub nose/eyes	2.1	2.0		-0.29 – 0.53
27. Need to blow nose	3.0	2.3	0.002	0.26 – 1.12
28. Bad breath	1.5	1.8		-0.69 – 0.17
29. Frustrated/restless/irritable	2.4	2.5		-0.55 – 0.31
30. Sad	1.9	2.0		-0.52 – 0.35
31. Embarrassed	2.1	2.2		-0.60 – 0.31
	N= 137	N=97		

*: *p*<0.0016 (Bonferroni correction)

Table 4 displays the frequency of symptoms scored in each group. Patients with CRSwNP scored nasal symptoms 'rhinorrhoea' and 'decreased sense of taste or smell', with its associated symptoms 'inconvenience of having to carry tissues' and 'need to blow nose' significantly more often than patients with CRSsNP.

Table 4 Symptom frequency

Symptom score ≥ 2	CRSwNP Symptom frequency	CRSsNP Symptom frequency	*p*-value (Fisher exact)	Odds Ratio	95% CI
1. Blockage / congestion of nose	93	91			
2. Rhinorrhoea	75	55	0.001*	2.52	1.44 - 4.39
3. Sneezing	57	55			
4. Sense of taste/smell	91	73	<0.001*	3.49	1.69 – 7.23
5. Postnasal drip	81	78			
6. Thick nasal discharge	80	80			
7. Itchy eyes	45	44			
8. Swollen eyes	31	37			
9. Difficulty falling asleep	38	46			
10. Waking up at night	60	63			
11. Lack of good night's sleep	58	61			
12. Waking up tired	65	75			
13. Ear fullness	47	54			
14. Ringing	34	41			
15. Dizziness	32	40			
16. Ear pain	26	38	0.028	0.56	0.32 – 0.98
17. Decreased hearing	49	45			
18. Fatigue	74	81			
19. Reduced productivity	68	73			
20. Reduced concentration	66	69			
21. Headache	59	71	0.040	0.59	0.34 – 1.02
22. Facial pain/pressure	62	73	0.050	0.60	0.34 – 1.06
23. Cough	58	59			
24. Short of breath	69	65			
25. Inconvenience of having to carry tissues	56	34	0.001*	2.49	1.45 – 4.27
26. Need to rub nose/eyes	59	57			
27. Need to blow nose	79	59	0.001*	2.61	1.47 – 4.65
28. Bad breath	39	45			
29. Frustrated/restless/irritable	69	68			
30. Sad	55	54			
31. Embarrassed	58	58			
	n=137	n=97			

*: $p<0.0016$ (Bonferroni correction)

CRSwNP: chronic rhinosinusitis with nasal polyps; CRSsNP: chronic rhinosinusitis without nasal polyps; CI: confidence interval

Sub analyses of patients with asthma and aeroallergen sensitisation

For the whole group of patients, patients with asthma were comparable to patients without asthma but for shortness of breath ($p < 0.001$). The domain 'general health' showed a trend of being worse in the patients with asthma as did the symptoms 'dizziness' and 'cough' (see table 5).

When sub analyses were performed separately for patients with CRSwNP and CRSsNP the same pattern was seen, although patients with CRSwNP with asthma score significantly higher symptom scores on the 'general domain' (mean 2.5 (SD 1.20) versus without asthma: mean 2.0(SD 1.10) p=0.019), mainly due to the significant difference in symptom score on the item 'short of breath' (mean 3.04 (SD 1.56) vs. without asthma: mean 1.86(SD 1.44), p<0.0001).

Patients sensitised to aeroallergens had significantly less often hearing problems (1.30 (SD 1.53) versus not sensitised patients 2.13 (SD 1.79), p<0.0001) and tended to have a lower score on the 'domain ear' (1.22 (SD 1.23) versus 1.65 (SD 1.28), p= 0.015) and the item 'ear fullness'.

Multivariable regression analysis

Several potential prognostic factors were significantly associated with CRSwNP in the univariate analysis as shown in table 6.

However, in the multivariable model, 'rhinorrhoea', 'decreased sense of taste or smell', 'ear pain', 'facial pain' and 'the inconvenience of having to carry tissues' were significantly associated with nasal polyps. Table 7 shows symptoms with its corresponding odd's ratio for having nasal polyps.

Table 5 Mean symptoms scores with and without Asthma

Asthma	Yes Mean symptom score	No Mean symptom score	*p*-value	95% CI
Total RSOM-31 score	69.56	64.26		-1.60 – 12.20
Domain Nose	2.85	2.74		-0.13 – 0.32
Domain Eye	1.45	1.37		-0.29 – 0.45
Domain Sleep	2.17	1.89		-0.17 – 0.55
Domain Ear	1.61	1.30		-0.02 – 0.63
Domain General	2.59	2.24	0.026	0.04 – 0.65
Domain Practical	2.00	2.11		-0.44 – 0.22
Domain emotional	2.25	2.15		-0.28 – 0.48
1. Blockage / congestion of nose	3.29	3.46		-0.47 – 0.14
2. Rhinorrhoea	2.24	2.19		-0.35 – 0.45
3. Sneezing	1.90	1.66		-0.10 – 0.58
4. Sense of taste/smell	3.64	3.31		-0.09 – 0.74
5. Postnasal drip	3.02	2.96		-0.37 – 0.48
6. Thick nasal discharge	2.89	2.90		-0.32 – 0.49
23. Cough	2.31	1.83	0.032	0.04 – 0.91
24. Short of breath	2.99	1.97	<0.001*	0.60 – 1.44
	n=100	n=127		

*: p<0.0016 (Bonferroni correction)

CI: confidence interval; RSOM-31: Rhinosinusitis Outcome Measure-31 questionnaire

Table 6 Independent risk factors for CRSwNP in univariate model

Characteristics	OR[a]	95% CI[b]
2. Rhinorrhoea	2.40	1.26 – 4.57
4. Decreased sense of smell/taste	3.72	1.72 – 8.04
16. Ear pain	0.44	0.24 – 0.82
22. Facial pain	0.55	0.29 – 1.03
25. Inconvenience of having to carry tissues	1.98	1.08 – 9.63

[a] : Odd's Ratio, [b] : 95% confidence interval

Table 7 Risk factors for CRSwNP in multivariable model.

Characteristics	OR[a]	95% CI[b]
2. Rhinorrhoea	2.52	1.44 – 4.39
4. Decreased sense of smell/taste	3.49	1.69 – 7.23
12. Wake up tired	0.61	0.34 – 1.089
16. Ear pain	0.56	0.32 – 0.98
21. Headache	0.59	0.34 – 1.02
22. Facial pain	0.60	0.34 – 1.06
25. Inconvenience of having to carry tissues	2.49	1.45 – 4.27
27. Need to blow nose	2.61	1.47 – 4.65

[a] : Odd's Ratio, [b] : 95% confidence interval

Please note that 'facial pain' appears not to be a significant predictor of nasal polyps. However, when it is excluded from the model there is a significant change in the -2 log likelihood test ($p < 0.10$). This can be interpreted that 'facial pain' is a relevant variable in the model.

DISCUSSION

Otorhinolaryngologists often tend to assign typical signs of disease to patients with or without NP. Previous literature is not always applicable to our own population, when we want to analyse if we can make a distinction based on symptom scores between patients with CRSwNP and patients with CRSsNP, based on EPOS criteria.

Eccles[13], in his review describes primary and secondary symptoms of rhinosinusitis, but he provides no specific numbers or comparison. Deal[14], in his evaluation for the need for revision surgery between patients with CRSwNP and patients with CRSsNP describes the difference in total SNOT-20 but gives no further analysis on domain or individual item scores.

Banerji, in her prospective analysis on the burden of illness in a population of 126 patients with CRS describes similar findings using SNOT-20+1 questionnaires; patients with CRSsNP more often suffer from facial pain/ pressure/ headache, and patients with CRSwNP score higher on nasal obstruction and hyposmia[15]. However, to analyse 17 different variables in such an analysis, at least 170 patients with CRSwNP are needed[16].

Bhattacharyya[17], in his study on the additional disease burden of nasal polyps in CRS with 462 patients, also finds higher scores on nasal symptom severity in patients with CRSwNP and higher scores on facial symptom severity in patients with CRSsNP. However, he used the Rhinosinusitis Symptom Inventory, with no analysis in further detail.

Ragab[18], in his prospective randomized controlled trial, evaluating and comparing the effect of medical and surgical treatment of chronic rhinosinusitis mentions that the mean SNOT-20 in the medical group before treatment was 2.3 (SD 0.9) for the patients with CRSsNP and 2.0 (SD 1.0) in the group with CRSwNP. For the surgical group these data were 2.1. (SD 1.0) for the patients with CRSsNP and 1.6 (SD 0.6) in the group with CRSwNP. Data for the whole group are not given, nor statistical analysis of these differences. Sahlstrand[19] compares SNOT-22 in patients with recurrent acute rhinosinusitis, CRSsNP and CRSwNP. She finds no difference in the mean SNOT-22 between these groups. However differences between the three groups were found for the items 'runny nose', 'loss of sense of taste/smell', 'cough', 'dizziness', 'ear pain', 'facial pain/pressure', 'fatigue', 'reduced productivity' and 'sad'. Unfortunately no statistical analysis was made between patients with CRSsNP and CRSwNP but judging from the data 'loss of sense of taste/smell', 'cough', and 'facial pain/pressure' were different between these groups where 'loss of sense of taste/smell' was worse in the CRSwNP and the other two items worse in the CRSsNP. The latter data are in concordance with the data found in our study.

Furthermore, Agius[10] found in his CRS cohort in Malta that 'postnasal drip', 'nasal obstruction' and 'hyposmia' significantly associated with positive CT findings, whereas 'facial pain' was significantly associated with negative CT findings. Also, he underlines the challenge of facial pain in CRS patients, where in the majority the diagnosis cannot be supported by CT or endoscopy findings[9].

Although we found some symptoms to be more prevalent in patients with CRSwNP than CRSsNP the overlap is considerable. For example, 'loss of taste/smell' would seem a 'typical' CRSwNP item, however, 63% of CRSsNP score this symptom present. On the contrary, 'facial pain' would seem a 'typical' CRSsNP symptom, but almost half of CRSwNP scores this item present.

Despite some indications for pathophysiological differences between CRSwNP and CRSsNP, at this moment it does not seem to be possible to differentiate based on symptoms. However also in the pathophysiology there seems to be a considerable overlap and also no correlation between endoscopic appearance and inflammatory pattern[20, 21]. Chinese and European polyps cannot be discriminated based on endoscopy but show a very different inflammatory pattern. The same holds true for polyps in patients with CF compared to non-CF polyps [22, 23].

We dichotomised the data to account for the symptom frequency based on a symptom score of ≥2. This means, patients grade their symptom as *'a mild or slight problem'* or worse. Keeping in mind that the most important findings of this study are the mean symptom scores, we found it illustrative to add a symptom frequency table and a multivariable regression model to our analysis. A linear regression model was not possible, because we found no linear association between symptom scores and outcome (CRSwNP); therefore we had to dichotomise our data for a multivariable logistic regression model.

The cut off at a symptom score of ≥2 was chosen, because we felt we had to count at least present symptoms, rated as *'mild or slight'*. We also made sub analyses of other limits. A cut off at ≥1 would

count too many irrelevant complaints and a cut off at ≥4 would give to many false negative findings. A cut off at ≥3 gave comparable results.

In agreement with others we find a higher portion of asthmatics in the CRSwNP group[4, 24-28]. Interestingly the patients in the CRSwNP group do not complain significantly more often about cough and shortness of breath compared to the patients with CRSsNP. In the Sahlstrand[19] study cough was even found more in the CRSsNP group. Unfortunately prevalence of asthma is not given for the subgroups in this study.

We found a higher prevalence of aeroallergen sensitisation in patients with CRSwNP, contrary to Collin's findings[29]. Emanuel and Shah describe a higher prevalence of aeroallergen sensitisation in patients with grade 2 (88%) and grade 3 (88%) CT classification, according to Glicklich[30]. Unfortunately, abnormalities on CT scan were not described in further detail, or was the reader provided with more detailed clinical information. A sub-analysis in our study shows no significant influence of aeroallergen sensitisation on the symptom scores.

Also we found 'ear pain' as a significant predictor of CRSwNP in the multivariable regression analysis. This association is previously described by Stoikes and Dutton, and might be related to Eustachian tube dysfunction[31].

A potential weakness of this study is that it is performed in a tertiary referral rhinosinus specialized outpatient clinic with a selected population. All patients have undergone previous treatment usually also surgery, and visit our centre with persisting symptoms. However, all selected patients fulfil the EPOS diagnosis 'Chronic rhinosinusitis' with or without nasal polyps based on symptomatology and endoscopy and/or CT scan[1]. It is not very likely that the subject of this study: the difference in symptomatology between patients with and without nasal polyps will be very different but e.g. difference in total mean RSOM score could be different in a primary population: only patients with persistent symptoms are referred to us.

Interesting for further research would be how symptom scores differ between CRSwNP and CRSsNP in patients without any previous treatment or surgery.

The 'golden standard' for the diagnosis nasal polyps will remain nasal endoscopy, with grading of the nasal mucosa for polyps, oedema, discharge scarring and crusting[32] however, pulmonologists, general practitioners and many other medical professionals dealing with CRS patients, do not have an endoscope at hand like standard ENT practice.

This analysis does not provide a diagnostic tool, but gives scientific support for evidence based discussions on differences between patients with chronic rhinosinusitis with and without nasal polyps.

CONCLUSION

This study shows that there is a considerable overlap in CRS symptoms in patients with and without nasal polyps. Nasal symptoms, as decreased sense of taste/smell and rhinorrhoea are often seen and more bothersome in patients CRSwNP. Patients with CRSsNP more often score on facial pain and ear pain.

Unfortunately, the clinical impression that distinction between patients with CRSwNP and patients with CRSsNP only based on 'typical' symptoms is not very accurate due to considerable overlap of symptom scores.

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CHAPTER 5

PREVALENCE OF CHRONIC RHINOSINUSITIS IN THE GENERAL POPULATION BASED ON SINUS RADIOLOGY AND SYMPTOMATOLOGY

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ABSTRACT

Background

The prevalence of Chronic Rhinosinusitis (CRS) measured in epidemiological studies is 5-12%. This might be an overestimation because of overlap with other diseases like allergic rhinitis.

Objective

We aimed to calculate the prevalence of CRS using a combination of epidemiologically based CRS according to EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) together with sinonasal opacification on imaging.

Methods

Subjects who underwent a computed tomographic or magnetic resonance imaging scan of the head for any nonrhinologic indication were asked to fill in the Global Allergy and Asthma European Network survey containing the EPOS symptom criteria. The scans were evaluated according to the Lund-Mackay (LM) scoring system. Epidemiologically based CRS is based on nasal symptoms according to EPOS, clinically based CRS also encompasses endoscopy and/or CT scanning.

Results

Eight hundred thirty-four subjects were included. One hundred seven (12.8%) had epidemiologically based CRS according to EPOS. Of these subjects ,50% had an LM score of 0; 26% had an LM score of 1 to 3, and 23% had an LM score of 4 or greater. Twenty-five (3.0%) subjects had clinically based CRS (based on LM score ≥4) and 53 (6.4%) subjects had clinically based CRS (based on LM score >0). Allergic rhinitis was reported by 167 (20%) subjects. In subjects that did not report upper airway symptoms, 57% had an LM score of 0, 30% had an LM score of 4 or greater.

Conclusion: We found a prevalence of 3.0 to 6.4% of clinically based CRS (depending on an LM cutoff point; ie, LM ≥ 4 or LM > 0, respectively) in a relatively randomly selected group of subjects.

LIST OF ABBREVIATIONS

AR Allergic Rhinitis
ARS Acute Rhinosinusitis
CRS Chronic Rhinosinusitis
CT Computed Tomography
ECR Expected Count Ratio
EPOS European Position Paper on Rhinosinusitis and Nasal Polyps
GA2LEN Global Allergy and Asthma European Network
LM Lund-Mackay
MRI Magnetic Resonance Imaging
OR Odds ratio

INTRODUCTION

Chronic rhinosinusitis (CRS) is a significant health problem and affects 5-12% of the general population.[1] CRS is characterized by at least nasal blockage/obstruction/congestion or nasal discharge with facial pain and/or reduction of smell. Reliable epidemiologic research is extremely important in addressing this major social healthcare issue to get a clear understanding of the quantitative impact of the disease.

The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) provides 2 definitions of CRS: a clinical diagnosis based on symptoms, supported by signs of mucosal inflammation found on imaging or with nasal endoscopy, and a symptom-based definition to be used in epidemiologic research, without radiologic imaging or endoscopic examination. [1]

CRS is a clinically challenging disease, as in asthmatic patients, symptoms lack good correlation with objective measurements, because of the lack of a gold standard.[2, 3] This might be caused by an underlying variation of endotypes leading to a common phenotype[4] and results in a discrepancy of estimates of prevalence based on either symptoms or objective measures.[5]Current data on prevalence of CRS based on the EPOS symptom-based definition show a prevalence of 5,5% in Brazil[6], 8% in China[7], 11% in Europe [8] and Korea [9] and 12% in the USA[10]. These numbers might be an overestimation because of the overlap of symptoms between CRS, acute rhinosinusitis (ARS) and (non-)allergic rhinitis (AR); up to 10% of responders had symptoms of all three diagnoses. [11, 12]

Earlier, we evaluated the value of nasal endoscopy in the epidemiologically based diagnosis of CRS.[12] In this Global Allergy and Asthma European Network (GA2LEN) follow-up study, subjects with CRS, asthma, asthma and CRS, and no asthma or CRS were invited to undergo nasal endoscopy, blinded for symptom status and found to have a sensitivity of nasal endoscopy of 62% in a population with symptom-based CRS. This might imply a one-third overestimation of "true" or "clinical" CRS in patients when using a symptom-based diagnosis of CRS.

To gain more insight in the prevalence of clinically based prevalence of CRS based on imaging, we would ideally scan a selection of the prior named GA2LEN study population with known sinonasal symptoms; however, this is both ethically unacceptable because of radiation exposure and too expensive because of the need for hundreds of magnetic resonance imaging (MRI) scans.

Previous epidemiologic studies found 20 to 40% computed tomography (CT) scan abnormalities in symptom negative populations.[13-15] Also common cold has been shown to show sinus abnormalities on imaging in a majority of otherwise healthy subjects, usually clearing in a few weeks.[16] In patients with AR, opacification of the sinuses is infrequent and only minimal during natural seasonal exposure, [17] with an average Lund-Mackay (LM) score comparable with that in of a normal population. [18] In a population without sinusitis, an LM score of 0 to 5 has been described. [19]

In this study, we primarily describe the prevalence of epidemiologically (symptom-) based versus clinically (imaging-) based CRS in a population with nonrhinologic indications. Furthermore, we analyse the alignment of imaging abnormalities with symptom scores to test the feasibility of the imaging-based CRS diagnosis as a solid construct. The influence of other factors on imaging abnormalities is also considered (eg, patient demographics and comorbidities such as asthma). Moreover, we investigate whether it would make any difference if we used the definition of CRS

(containing 3 months of symptoms in the last year) or current symptoms of CRS (defined as CRS in the last three months) because it might reflect a difference in LM scores at the time of imaging. Furthermore, we investigate what symptoms and findings are associated with the outcome of clinically relevant opacification on imaging and whether we were able to predict no abnormalities at the time of CT scan (LM score = 0).

METHODS

Study design

We conducted a cross-sectional survey of consecutive subjects referred to our radiology department for imaging of the head for nonrhinologic indications. All consecutive subjects that underwent CT or MRI of the head (patients undergoing sinus CT were excluded) were asked to fill in the GA2LEN questionnaire on upper and lower airway symptoms [supplementary table 1]. The questionnaire was sent 1 week before the radiology appointment, and patients were asked to fill in the questionnaire during their imaging appointment.

Indications for imaging included stroke, seizures, head injury, or suspected skull-base, intracranial, or intra-orbital pathology.

Exclusion criteria were inability to fill in the questionnaire because of confusion, aphasia, or severe illness; incomplete imaging or artifacts of the nasal sinus prohibiting complete LM scoring; or a history of transsphenoidal pituitary surgery or radiotherapy in sinonasal area. Patients were also excluded if the interval between imaging and completion of the questionnaire exceeded 3 months. All dedicated sinus sequences were also excluded from this study.

Data were obtained between January 2012 and December 2013. The study was approved by the medical ethical committee of the Academic Medical Centre Amsterdam.

Measurements

The GA2LEN survey was developed by GA2LEN and funded by the European Union and was based on validated questions from the European Community Respiratory Health Survey [20-22] and EPOS. [12, 23] The GA2LEN questionnaire was previously used in epidemiologic research on the prevalence of allergy, asthma, and upper airway symptoms [8, 24]. Subjects were asked for symptoms of CRS, ARS, asthma, and AR in the last 3 months and in the last year. For the full survey, see supplementary table 1.

Imaging was scored by a radiologist specialized in otolaryngology and skull-base imaging (N.J.M.F.) according to LM scoring system [25]. Opacification on imaging was classified into the following groups: LM score of 0, LM score of 1 to 3, LM score of 1 and greater, and LM score of 4 and greater. For the full scoring system, see supplementary table 2.

Definitions used

Epidemiologically based CRS was defined as the continuous presence of 2 or more nasal symptoms, including blocked nose; pain or pressure around the forehead, nose or eyes; nasal

Table 1 Subjects' Characteristics

	n/total n[a]	% or mean (SD)
Age (years)	834/834	53 (16)[b]
Female sex	525/834	62.9%
CRS (EPOS, 12mo)	107/828	12.9 %
Current CRS	67/747	9.0 %
Asthma	83/829	10.0%
AR	167/830	20.1%
CRS and AR	57/824	6.9%
No CRS, no AR	612/824	74.3%
Current AR	50/761	6.6%
No symptoms	508/826	61.5%
Smoke		
Never	410/833	49%
Ever	423/833	51%
Current	167/418[c]	40%
Former	251/418[c]	60%
Pack-years smoking		
Ever	204 /423	17.4
Current	16/167	11.2
Former	185/251	17.7
Self-reported doctor-diagnosed CRS	38/834	4.6%
Ethnicity		
White	748/834	89.7%
African	28/834	3.4%
Asian	20/834	2.4%
Mediterranean	17/834	2.0%
Other	21/834	2.5%

AR: Allergic Rhinitis (self-reported hay fever), Current AR: Allergic Rhinitis (self-reported hay fever) with current nasal obstruction, rhinorrhoea, or both Current CRS: Chronic rhinosinusitis in the past three months, Asthma: Self-reported Asthma, Pack-years: number of packs of cigarettes smoked per day x the number of years the subject has smoked.

[a] Total number of subjects is maximal 834 but sometimes less because some data were missing.

[b] Median age: 54 years; inter quartile range: 42 to 64 years, range: 8-89 years.

[c] Five participants who stated they had smoked for at least a year, did not answer whether they had smoked the last month.

discharge or postnasal drip; and reduced smell for more than 12 weeks during the last year (see supplementary table 3).

Epidemiologically based current CRS was defined as the continuous presence of 2 or more nasal symptoms, including blocked nose; pain or pressure around the forehead, nose or eyes; nasal discharge or postnasal drip; and reduced smell in the last 3 months.

Clinically based CRS was defined as the continuous presence of 2 or more nasal symptoms, including blocked nose; pain or pressure around the forehead, nose or eyes; nasal discharge or postnasal drip; and reduced smell for more than 12 weeks during the last year together with an LM score of greater than 0 or 4 or greater.

Clinically based current CRS was defined as the continuous presence of 2 or more nasal symptoms, including blocked nose; pain or pressure around the forehead, nose or eyes; nasal discharge or postnasal drip; and reduced smell for the last 12 weeks together with an LM score of 4 or greater.

ARS was defined as the presence of an acute episode of blocked nose, colored nasal discharge and facial pressure or pain during at least at least 10 days.

Allergic rhinitis was defined as a positive answer to the following question: "Do you have nasal allergies including hay fever?".

Current AR was defined as AR(self-reported hay fever) with current nasal obstruction, rhinorrhoea, or both.

No nasal symptoms was defined as a negative response to questions on any nasal symptom and on the questions for hay fever symptoms in the last year and doctor-diagnosed CRS.

Asthma was defined as a positive answer to the following question "Do you have asthma?".

History of smoking was defined as a positive answer to the following question "Have you ever smoked during at least a year?".

Current smoker was defined as a positive answer to the question "Have you ever smoked during at least a year?" in combination with a positive answer to the question "Have you smoked in the last month?".

Former smoker was defined as a positive answer to the question "Have you ever smoked during at least a year?" in combination with a negative answer to the question "Have you smoked the last month?".

Statistical analysis

Data were collected in a predesigned Microsoft Access 2010 database. Analysis of data was performed using IBM SPSS Statistics 24 (Armonk, New York, US).

The primary question (ie, "What is the prevalence of clinically based CRS?") was answered by describing the prevalence of epidemiologically based CRS and clinically based CRS, both using cutoff points of an LM score of greater than 0 and LM scores of 4 or greater and calculating prevalence of current CRS. Similarly, the prevalence of current CRS (both epidemiologically and clinically based) was determined as was its overlap with (epidemiologically and clinically based) CRS and AR.

We constructed a contingency table of the five main categories of indications for imaging (neurovascular, cerebral tumors, orbital, mastoid, and other) and the epidemiologic CRS diagnosis and tested whether both variables were independent (Pearson's χ^2 test of independence).

Variables associated with opacification on imaging

The secondary research question (ie, "What symptoms and findings are associated with opacification on imaging?") was analysed in 3 ways: (1) by analysing predictors of having a LM score of 4 or greater, which is the characteristic that bridges the epidemiologic and clinical diagnosis of CRS; (2) by analysing predictors of total LM score; and (3) by analysing predictors of having a LM score of 0.

Table 2 Indications for imaging (n=834)

		n	%	Prevalence of epidemiological CRS (%)
Neurovascular	Stroke/CVA/Aneurysm	322	38.6	36/321 (11.2%)
Cerebral Tumor	Endocranial / metastasis	109	13.1	30/219 (13.7%)
	Pituitary	46	5.5	
	Meningeoma	65	7.8	
Orbital	Graves	37	4.4	19/104 (18.3%)
	Tumor	53	6.4	
	Trauma / visual loss	14	1.7	
Mastoid	Cholesteatoma	18	2.2	9/89 (10.1%)
	Pre-CI / Vertigo	8	1.0	
	Vestibular schwannoma	66	7.9	
Other	Headache	46	5.5	13/95 (13.7%)
	Parkinson	21	2.5	
	Psychiatry	15	1.8	
	Pre-deep brain stimulation	5	0.6	
	Salivary glands / facial tumors	9	1.1	
Total		**834**	**100**	**107/828 (12.9%)**

CVA: cerebrovascular accident, Pre-CI: pre-Cochlear implant.

Table 3 Findings on imaging in CRS and AR

	LM score = 0	LM score = 1-3	LM score ≥ 4
Total (n=834)	464 (56%)	251 (30%)	119 (14%)
CRS (n=107)	54 (50%)	28 (26%)	25 (23%)
Current CRS (n=67)	37 (55%)	19 (28%)	11 (16%)
AR (n=167)	76 (46%)	58 (35%)	33 (20%)
Current AR (n=50)	25 (50%)	16 (32%)	9 (18%)
CRS and AR (n=57)	24 (42%)	19 (33%)	14 (25%)
No symptoms (n=508)	292 (57%)	154 (30%)	62 (12%)

AR: Allergic Rhinitis (self-reported hay fever); Current AR: AR (self-reported hay fever) with current nasal obstruction, rhinorrhoea, or both; Current CRS: Chronic rhinosinusitis in the past three months; LM score = 0: No opacifications on imaging, No symptoms, no nasal symptoms.

With around 850 included subjects, and a prevalence of 12 to 14% (based on epidemiologic data available), the smallest group would be around 100 to 120 respondents. This provided room for multivariate analyses with around 10 to 12 factors.[8, 10]

Variables associated with a positive LM score (LM ≥ 4)

Univariate logistic regression models were used for models to study the association of a selection of relevant symptoms and descriptive factors (see Table 4) and the outcome variable. Odds ratios

Table 4 Univariate Logistic regression – Odds ratio on LM scores of 4 or greater

Variable	OR	*p*-value	95% CI
Obstruction	2.10	.002	1.31 – 3.36
Facial pain/pressure	1.24	.37	0.78 – 1.94
Rhinorrhoea/PND	1.84	.031	1.06 – 3.19
Loss of smell	1.75	.034	1.04 – 2.94
Female sex	0.55	.002	0.37 - 0.81
Smoking	1.79	.004	1.20 – 2.68
AR	1.65	.026	1.06 – 2.57
Woke up short of breath in last 12 mo	1.72	.048	1.01 – 2.94
Wheezing in last 12 mo	1.20	.53	0.68 – 2.14
Woke up with chest tightness	1.37	.25	0.80 – 2.35
Woke up coughing	0.92	.73	0.59 – 1.45
Coughing up sputum on most days >3mo/y	0.84	.60	0.44 – 1.59
Ever asthma	1.49	.18	0.83 – 2.67
Admitted to hospital because of asthma	0.99	.99	0.22 – 4.50
Exacerbation of asthma in last 3 mo	1.61	.40	0.53 – 4.94
Current asthma medication	1.39	.42	0.63 – 3.08
Episode of ARS in last year	1.33	.23	0.83 – 2.13
Itchy rashes	1.07	.80	0.64 – 1.78
Eczema	0.83	.38	0.54 – 1.27
NSAID-intolerance	2.02	.23	0.64 – 6.36
Current smoker	1.16	.52	0.73 – 1.85
Occupation in health care	0.93	.88	0.35 – 2.43
Occupation in cleaning	0.59	.48	0.14 – 2.55

AR, positive answer to question on hay fever; NSAID, nonsteroidal anti-inflammatory drug; PND, Postnasal drip, Smoking: History of smoking.

(ORs), 95% CIs and P values of all univariate test were reported. Additionally, multivariable regression analysis was conducted.

The goal of the first model was to determine which predictors were of additional predictive value for an LM of 4 or greater compared with the 4 EPOS symptoms alone. Based on the total number of subjects with LM scores of 4 or greater (n =119), we could include approximately 12 variables in a multivariable logistic regression analysis. The multivariable model for an LM score of 4 or greater was built in two steps. In the first step, all 4 EPOS symptoms (nasal obstruction, rhinorrhoea / postnasal drip, loss of smell and facial pain or pressure) were included. In the second step, other potentially relevant factors (operationalized as factors with *P* levels of less than .10) from the univariate analysis were included. We applied a backward selection (significance level to stay in the model: $P \leq .05$, based on a likelihood ratio test [$P \leq .05$]) on the predictors that were added in the second step. After both steps, ORs, 95% CIs, *P* values, the Nagelkerke R^2 values and the area under the curve were reported.

Table 5 Multivariable Logistic regression – Prediction model for EPOS symptoms with an LM score of 4 or greater (Nagelkerke R^2 value = .023)

EPOS symptoms	OR	*p*-value	95% CI
Obstruction	1.91	.026	1.08 - 3.39
Facial pain/pressure	0.84	.52	0.49 - 1.44
Rhinorrhoea/PND	1.26	.49	0.65 - 2.45
Loss of smell	1.35	.31	0.76 - 2.40

PND: Postnasal drip. (>12 weeks in the last 12 months)

Variables associated with total LM score

To identify variables that are significantly associated with the total LM score (model 2), we conducted negative binominal regression analyses with a log link. The distribution of the LM score in this specific sample was very much like a count score (heavily left-skewed and bound at zero), which allowed us to model the actual LM score also in a negative binomial regression model rather than dichotomizing the LM score, as we did with models 1 and 3. The same procedures were conducted as for the dichotomous variable of an LM score of 4 or greater: run univariate models, run a multivariable model with EPOS symptoms only, and run a series of multivariable models that included EPOS symptoms and other factors. Effects (the natural logs of regression coefficients B) are quantified as expected count ratios (ECRs), which display the multiplicative effect of a variable or the presence of a symptom on the LM score. Predictive count ratios with 95% CIs and *P* values of all univariate tests and the final multivariable model were reported.

Variables associated with having no opacification (LM score = 0)

The goal of model 3, predicting a LM score of 0, was to determine which factors could help to rule out any opacification. We used the same variables as for model 1 for univariate logistic regressions. The multivariable model for an LM score of 0 was built by applying backward selection ($P \leq .05$) on the variables that had *P* values of less than .1 in the univariate regressions. The final model after the backward selection procedure was rerun to include subjects with missing data on any of the deselected variables. ORs, 95% CIs, *P* values, Nagelkerke R^2 and the area under the curve were reported.

Analysis of seasonal influence

We performed Mann-Witney *U* tests to analyse the influence of seasons on the LM scores. We used 2 distinctions: May to July compared with the rest of the year ("pollen1"), and June to September ("pollen2") compared with the rest of the year. Additionally, we checked how many participants who reported to have loss of smell also had an epidemiological CRS diagnosis.

Table 6 Multivariable Logistic regression: Prediction model for an LM score of 4 or greater (Nagelkerke R^2 value = .061)

Variable	OR	*p*-value	95% CI
Obstruction	2.08	.014	1.16-3.70
Facial pain/pressure	0.84	.53	0.48-1.46
Rhinorrhoea/PND	1.35	.38	0.69-2.65
Loss of smell	1.31	.38	0.72-2.37
Female sex	0.57	.005	0.38-0.85
Smoking (ever)	1.69	.029	1.13-2.55

PND: Postnasal drip

Table 7 Univariate Generalized Linear Model Analysis: Effect of variable on increase of LM score

Variable	ECR	*p*-value	95% CI
Obstruction	2.01	.000	1.46 – 2.78
Facial pain/pressure	1.21	.24	.88 – 1.67
Rhinorrhoea/PND	1.81	.002	1.24 – 2.66
Loss of smell	1.75	.002	1.22 – 2.49
$Sex_{(female = 1)}$	.63	.000	.49 - .80
Smoking	1.39	.01	1.08 – 1.78
Asthma	1.50	.05	.99 – 2.25
AR	1.46	.007	1.11 – 1.93
AR in last 12 mo	1.34	.06	.99 – 1.81
Episode of ARS in last year	1.46	.01	1.05 – 1.97
Itchy rashes	.73	.06	.52 – 1.01
Occupation in cleaning	.48	.06	.23 – 1.03
ARS	1.46	.01	1.05 – 1.97
Current asthma medication	1.60	.09	.93 – 2.75
Age	1.00	.36	.99 – 1.00
Wheezing in last 12 mo	1.08	.68	.75 – 1.56
Woke up with chest tightness	1.08	.64	.78 – 1.50
Woke up short of breath	1.25	.19	.90 – 1.75
Woke up coughing	.89	.44	.67 – 1.19
Coughing up sputum on most days >3 months/yr	.80	.21	.56 – 1.14
Admitted to hospital due to asthma	.73	.56	.25 – 2.14
Exacerbation of asthma last 3 months	1.69	.16	.81 – 3.50
Eczema	.89	.38	.67 – 1.16
NSAID-intolerance	1.49	.27	.74 – 3.03
Current smoker	1.19	.26	.88 – 1.60
Occupation in healthcare	1.17	.68	.57 – 2.41

The expected count ratio (exp(B)) means that the expected number of opacified sinus (LM-score) is multiplied by a factor of, for example, 2.014 when a certain symptom is present or the independent variable increases by one unit.

AR: Positive answer on question about hay fever; Itchy rashes: itching skin in the last 12 months; NSAID, nonsteroidal anti-inflammatory drug; PND: Postnasal drip; Smoking: History of more than one year of smoking.

RESULTS

Participants

In total, 2051 subjects were invited to participate, 1003 of whom responded. Of these, 169 subjects refused participation or had incomplete imaging. One thousand forty-eight subjects did not respond at all. Age and sex of the responders and non-responders were comparable, but the subjects who did not respond or actively refused more often had brain damage, very serious disease, or both, rendering them unable to answer or probably too ill to care.

In total, 834 subjects were included, with a mean age of 53 years (SD: 16; range 8-89 years). Sixty-three percent were female, and 37% were male. The subjects' characteristics are specified in Table 1.

Subjects had imaging for a number of neurological (eg, neurovascular or aneurysm evaluation and evaluation of intracranial tumors, including pituitary tumors), ophthalmological (eg, intra-orbital tumors, graves, and trauma), and otological (eg, evaluation of cholesteatoma and internal auditory canal) reasons. For details see Table 2.

No association was found between the type of indication and having an epidemiologic CRS diagnosis ($\chi^2[4] = 4.27$, $P = 0.37$).

Prevalence of CRS

One hundred and seven (12.8%) subjects had epidemiologically based CRS. Of these subjects, 50% had an LM score of greater than 0 and 23% had an LM score of 4 or greater (Table 3). The prevalence of clinically based CRS in this study was 3.0% or 6.4%, depending on which cutoff point is used (LM score of 4 or greater or greater than 0). In subjects with abnormalities on imaging (LM score ≥ 4), only 21% had epidemiologically based CRS. In subjects who denied nasal symptoms, 57% had an LM score of 0, and 12% had an LM score of 4 or greater.

Of 107 participants who reported loss of smell in the last 12 months, 56 satisfy the epidemiological criteria for CRS.

Prevalence of current CRS

We asked ourselves whether it would make any difference whether we used the definition of CRS (containing 3 months of symptoms in the last year) or current symptoms of CRS (defined as CRS in the last three months). It did not make any difference; 67 (7.7%) subjects reported current CRS. Of these subjects, 45% had an LM score of greater than 0, and 17% had an LM score of 4 or greater (see Table 3).

LM score in other groups

Furthermore, we investigated whether having AR would influence LM scores in subjects with CRS. AR was reported by 167 (20%) subjects, 54% of whom had LM scores of greater than 0 and 20% of whom had LM scores of 4 or greater. Fifty-seven (6.9%) subjects had epidemiologically based CRS and AR, 58% of whom had LM scores of greater than 0 and 25% of whom had LM scores of 4 or greater.

Table 8 Multivariate Generalized Linear Model Analysis: Effect of EPOS symptoms on increase in LM score

Variable	ECR	*p*-value	95% CI
Obstruction	1.53	.03	1.04 – 2.39
Rhinorrhoea/PND	1.23	.36	.79 – 1.91
Loss of smell	1.20	.39	.79 – 1.82
Facial pain/pressure	.83	.30	.58 – 1.18

PND: Postnasal drip

We also analysed to what extent season influenced opacification, using two definitions. When comparing the LM scores of scans made in May to July (the grass pollen season in The Netherlands) with those that were made in the rest of the year, no difference was found ($N_{pollen1}$ = 22, N_{other1} = 812, U = 9,139.5, *P* =.84). When shifting this period to June to September to account for time of AR to induce CRS symptoms (arbitrarily taken as 1 month) and for symptoms to cure/heal, a very small difference in the opposite direction of what was expected was seen: the scans made in this period had slightly lower LM scores compared with those made in the rest of the year. Medians were zero in both groups; mean LM scores were 1.1 and 1.4 respectively ($N_{pollen2}$ = 99, N_{other2} = 735, U = 32,241.5, *P* = .04).

Variables associated with positive LM scores (LM ≥ 4)

To investigate which symptoms were associated with an LM score of 4 or greater, we conducted univariate logistic regression. Table 4 shows that male sex (OR = .55, *P* =.002), history of smoking (OR = 1.79, *P* =.004), AR (OR = 1.65, *P* =.026), waking up short of breath in the last 12 months (OR = 1.72, *P* =.048), nasal obstruction (OR = 2.10, *P* =.002), rhinorrhoea/postnasal drip (OR = 1.84, *P* =.031) and loss of smell (OR = 1.75, *P* =.034) were associated with increased odds of having an LM score of 4 or greater. Table 5 shows the association of the EPOS symptoms with LM scores of 4 or greater, this model has a Nagelkerke R^2 value of .023. The area under the curve was .579, which indicated that EPOS symptoms are incapable of predicting LM scores of 4 or greater. Several prognostic factors were significantly associated with LM scores of 4 or greater (Table 6) in a multivariable regression model that also included all 4 EPOS symptoms: male sex and history of smoking were associated with increased odds for having an LM score of 4 or greater. The model had a R^2 value of 0.061. The area under the curve was 0.625.

Variables associated with total LM score

To avoid dichitomisation of the LM score, we also investigated the association of the symptoms and descriptive factors with the total LM score by conducting negative binomial logistic regression (Table 7). From the EPOS symptoms, nasal obstruction (ECR = 2.01; *P* < .001), rhinorrhoea (ECR = 1.81; *P* =.002) and loss of smell (ECR = 1.75; *P* =.002) were associated with higher LM scores. Additionally, male sex, history of smoking, asthma, AR, ARS, itchy rashes, and occupation in cleaning were associated with higher LM scores. Table 8 shows the model with EPOS symptoms only. In a model

that includes all 4 EPOS symptoms, male sex, history of smoking, itchy rashes and occupation in cleaning are significantly associated with greater LM scores (Table 9).

Variables associated with LM scores of 0

To investigate whether it was possible to predict an LM score of zero, we conducted logistic regression. It was again not possible to produce a model that reliably predicted LM scores of 0 (Table 10 and 11).

DISCUSSION

We set out to find the prevalence of clinically based CRS based on CT scans in a (rather) healthy population, which was 3.0% or 6.4%, depending on which cut offpoint was used (LM scores of 4 or greater or greater than 0). This value is in the same range as studies using nasal endoscopy (1.2-5.7)[12] and percentages found in the Korean National Health and Nutrition Examination Survey (KNHANES) (CRS with nasal polyps, 2.6%; CRS without nasal polyps, 5.8%)[26] but greater than those in the earlier version of the Korean National Health and Nutrition Examination Survey (KNHANES) (1.2%) found by Kim et al.[9]in South Korea. The prevalence of epidemiologically based CRS found in this study (12%) compares well with these studies (both ±11%), with our previous studies using the GA2LEN questionnaire (14% to16%),[8, 24], and to other existing literature where it is found to be 5% to 12 %, with significant variation between countries. [6, 7, 10, 27]

Although the role of allergy in CRS with and without nasal polyps continues to be controversial, AR might be a potential relevant factor influencing LM scores in the current population.[28] Seasonal variation has been described with a paradoxical improvement in LM scores in season.[18] In the current data an improvement (although very slight and based on small numbers) in LM scores was seen but only when the period July through September was analyzed. From the current data, we cannot find a good explanation for this phenomenon.

For CRS *per se*, no seasonal influence is to be expected. Moreover, the time between complaints and imaging does not explain the poor alignment because the subjects with current CRS (complaints in the past 3 months) show the exact same distribution as those with epidemiologic CRS (complaints for 3 months somewhere in the past year; Table 3). The CRS symptom most strongly associated

Table 9 Multivariate Generalized Linear Model Analysis: Effect of variable on increase in LM score

Variable	ECR	*p*-value	95% CI
Obstruction	1.53	.03	1.04 – 2.39
Rhinorrhoea/PND	1.23	.36	.79 – 1.91
Loss of smell	1.20	.39	.79 – 1.82
Facial pain/pressure	.83	.30	.58 – 1.18
Sex	.67	.002	.52 - .86
Smoking	1.37	.02	1.06 – 1.79
Itchy rashes	.67	.01	.49 - .92

PND: Postnasal drip, Smoking: History of more than one year of smoking. Sex: Female = 1

Table 10 Univariate logistic regression – OR on LM scores of 0

Variable	OR	*p*-value	95% CI
Obstruction	0.86	.43	0.59 – 1.26
Facial pain/pressure	1.11	.56	0.79 – 1.56
Rhinorrhoea/PND	0.78	.27	0.50 – 1.21
Loss of smell	0.71	.10	0.47 – 1.07
Female sex	1.87	< .001	1.40 – 2.48
Smoking	0.76	.05	0.58 – 1.00
AR in last 12 mo	0.60	.006	0.41 – 0.86
Woke up short of breath in last 12 mo	0.76	.21	0.50 – 1.17
Wheezing in last 12 mo	1.09	.68	0.72 – 1.67
Woke up with chest tightness in last 12 mo	0.96	.85	0.64 – 1.45
Woke up coughing in last 12 mo	1.03	.85	0.75 – 1.41
Coughing up sputum on most days >3months/yr	1.08	.72	0.70 – 1.66
Asthma ever	0.58	.02	0.37 – 0.92
Admitted to hospital because of asthma	1.45	.51	0.48 – 4.37
Exacerbation of asthma in last 12 mo	0.72	.47	0.29 – 1.78
Current asthma medication	0.51	.03	0.27 – 0.95
Episode of ARS in last year	0.91	.58	0.64 – 1.29
Itchy rashes	1.16	.44	0.80 – 1.70
Eczema	1.06	.68	0.79 – 1.43
NSAID intolerance	0.62	.34	0.23 – 1.67
Current smoker	0.72	.07	0.51 – 1.02
Occupation in healthcare	1.06	.86	0.55 – 2.06
Occupation in cleaning	1.75	.23	0.71 – 4.33

PND: Postnasal drip, Smoke: History of smoking, AR: Positive answer on 'hay fever', 12mo: in the last 12 months. Note: Odds ratios below 1 reflect increased odds for having opacifications.

Table 11 Multivariable logistic regression – OR on LM score of 0

Variable	OR	*p*-value	95% CI
Female sex	2.06	<.001	1.49 – 2.85
AR in last 12 mo	0.58	.004	0.40 – 0.84

Note: Results after backward selection (P_{out} = .05) of a multivariable model that included 7 predictors: loss of smell, sex, AR in the last 12 months, asthma (ever), current medication for asthma, ever smoked, and current smoker. We reran this model to also include cases with missing values of the deselected variables. This model predicted 118 (57%) false-positive results, and therefore 118 of 326 patients for whom an LM score of 0 was predicted in fact had an LM score of greater than 0. Area under the curve =.607.
AR in last 12 mo: Positive answer on hay fever and on the question Have you been troubled by nasal allergies in the last 12 months?.

with CT abnormalities in the paranasal sinuses is nasal obstruction. Other symptoms that constitute epidemiologic CRS have a smaller influence in the models; facial pain or pressure did not reach significance in any of them. This might be due to the study population in which headache (usually without sinonasal disease) is slightly overrepresented (5.5%).

In the end, the key question remains how CRS can be diagnosed correctly and reliably. Although this study was not primarily set up to answer this question, some interesting points can be made from the current data. Having nasal symptoms is a common finding; 58% of the subjects reported any form of nasal complaint, and 12% fulfil the EPOS criteria for CRS. Conversely, having abnormalities on imaging is also a common finding: 44% of the subjects had an LM score of greater than 0, of whom roughly one third had a score of 4 or greater. Combining both modalities will lead to reduction of the prevalence (eliminate false-positive results), while at the same time inducing false-negative results. For example, the prevalence of clinically based CRS is found to be 3.0% when taking an LM score of 4 or greater (a cutoff that is well in line with other studies).[19, 29-32] This eliminates three quarters of the patients with epidemiologically based CRS, half of whom had no CT abnormalities and a quarter of whom had LM scores of between 1 and 3. Other studies have shown that the same tradeoff is true when combining the epidemiologic diagnosis with findings on nasal endoscopy.[9, 12] To make matters worse, there is only moderate agreement between nasal endoscopy and radiologic data. [33-36] We wondered whether it was possible to exclude the diagnosis of clinically based CRS with these questions. Unfortunately, just like it was not possible to predict CRS, it was also not possible to exclude (data not shown).

In the end, the multivariate models we demonstrate here, based largely on the epidemiologic CRS symptoms, have poor model fits. Using other techniques for variable selection (such as the lasso technique) did not improve this (data not shown). As such, predicting clinically based CRS from questionnaires remains difficult. In other words, the construct for the diagnosis of CRS requires careful further consideration because there is room for improvement to align the data from history with objective outcomes (imaging/nasal endoscopy). An interesting recent development in this field is the identification of symptom clustering within factors (eg, nasal obstruction and discharge) depending on the severity and frequency of these symptoms.[37]

This study had several limitations. Because the study population underwent imaging of the head mainly for neurological evaluation (Table 2), the mean age (53 years) was greater than that in the general population in The Netherlands (39 years).[38, 39] Because the prevalence of CRS is lower in the elderly, we performed a subanalysis excluding all subjects older than 70 years. This did not lead to any remarkable change in the overall epidemiologically based CRS prevalence or in the distribution of the LM scores (data not shown). Therefore there are no clear indications that the current study population should differ significantly from the general population.

Our choice to exclude all dedicated sinus sequences (CT sinus) from the study might also have induced bias. Because we have a large national tertiary center treating many patients with CRS, including the dedicated sinus sequences would probably have increased the prevalence of CRS disproportionally. On the other hand, excluding all of them might decrease the prevalence.

Finally, the number of questions in the GA2LEN questionnaire about CRS and AR are limited, and we did not perform skin prick tests. Ideally, we could have used more extensive questionnaires like the Sino-Nasal Outcome Test-22.[40, 41] However, these more extensive quality-of-life questionnaires have not been shown to be correlated with CT scan abnormalities in otorhinolaryngologic patients.[40]

In conclusion, the clinically based prevalence of CRS in the Dutch population based on radiological examination is 3.0%. There is a poor alignment of reported symptoms and objective findings, which urges us to reconsider the construction of a CRS diagnosis.

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SUPPLEMENTARY DATA

Supplementary table 1 the GA2LEN survey

Number	Question	Answering options
1	Have you had wheezing or whistling in your chest at any time in the last 12 months?	Yes/No If no, go to 2
1.1	Have you been at all breathless when the wheezing noise was present?	Yes/No
1.2	Have you had this wheezing or whistling when you did not have a cold?	Yes/No
2	Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?	Yes/No
3	Have you been woken by an attack of shortness of breath at any time in the last 12 months?	Yes/No
4	Have you been woken by an attack of coughing at any time in the last 12 months?	Yes/No
5	Do you bring up phlegm from your chest on most days for as much as three months each year?	Yes/No
6	Have you ever had asthma?	Yes/No If no, go to 7
6.1	How old were you when you had your first attack of asthma? (If unsure, give your best guess!)	Number
6.2	Have you ever been hospitalised with asthma?	Yes/No
6.3	Have you had an attack of asthma in the last 12 months?	Yes/No
6.4	Are you currently taking any medicine (including inhalers, aerosols or tablets) for asthma?	Yes/No
7	Do you have any nasal allergies including hay fever?	Yes/No If no, go to 8
7.1	Have you been troubled by nasal allergies in the last 12 months?	Yes/No
7.2	Have you ever been troubled by nasal allergies for more than 4 days in any one week?	Yes/No
7.3	If yes did this happen for more than 4 weeks continuously?	Yes/No
8	Has your nose been blocked for more than 12 weeks during the last 12 months?	Yes/No
9	Have you had pain or pressure around the forehead, nose or eyes for more than 12 weeks during the last 12 months?	Yes/No
10	Have you had discoloured nasal discharge (snot) or discoloured mucus in the throat for more than 12 weeks during the last 12 months?	Yes/No
11	Has your sense of smell been reduced or absent for more than 12 weeks during the last 12 months?	Yes/No
12	Has a doctor ever told you that you have chronic sinusitis?	Yes/No
12A	In the past 12 months, have you had at least one episode of at least ten days where you had a blocked nose, discoloured nasal discharge (snot) and pain or pressure over the sinuses?	Yes/No If no, go to 13
12A.1	How many of these episodes of at least 10 days where you had a blocked nose, discoloured nasal discharge (snot) and pain or pressure over the sinuses did you have in the past 12 months?	1, 2, 3, 4, >4
12A.2	Have you visited a doctor for one of these episodes?	Yes/No
12A.3	Have you received antibiotics for one of these episodes?	Yes/No

Supplementary table 1 (continued)

Number	Question	Answering options
12A.4	Have you received a corticosteroid nose spray for one of these episodes?	Yes/No
13	Have you ever had an itchy rash that was coming and going for at least 6 months?	Yes/No If no, go to 14
13.1	Have you had this itchy rash in the last 12 months?	Yes/No
13.2	Does this affect only your hands?	Yes/No
14	Have you ever had eczema or any kind of skin allergy?	Yes/No
15	Have you ever had any difficulty with your breathing within 3 hours after taking a pain killer?	Yes/No If no, go to 16
15.1	Please write the name of the tablet?	Open
16	Have you ever smoked for as long as a year?	Yes/No If no, go to 17
16.1	How old were you when you started smoking?	Number
16.2	Have you smoked at all in the last month?	Yes/No If yes, go to 16.3
16.2.1	How old were you when you stopped smoking?	Number
16.3	On average how much do you (or did you) smoke?	Number
17	Are you currently: a. employed b. self-employed c. unemployed d. not working because of poor health e. full-time house person f. full-time student g. retired h. other	Select one option
18A	Are you currently working as a health care worker (e.g. as a nurse, medical technician, doctor, paramedic or similar)?	Yes/No
18B	Are you currently working in a job that is mainly involved with any sort of cleaning?	Yes/No
19.1	Do you understand the language in which this questionnaire is composed?	Yes/No
19.2	Which language do you speak most when you're at home?	Open
19.3	Which language do you speak most when you're away from home?	Open
20.1	In which country were you born?	Open
20.2	In which country was your father born?	Open
20.3	In which country was your mother born?	Open
20.4	What is your ethnicity? a. Caucasian/white b. Asian c. African/Creole d. Latin-American e. Hindustani f. Mediterranean g. Other (please specify):	Select one option

Supplementary table 1 (continued)

Number	Question	Answering options
20.5	How many years have you been living in the Netherlands	Number
21	What is your date of birth?	Date
22	What is today's date?	Date
23	Are you male or female?	Male/Female
24	What is your postal code?	Postal code

Supplementary table 2 the Lund-Mackay score

Sinus / location	Score left side	Score right side
Frontal	0 / 1 / 2	0 / 1 / 2
Anterior ethmoid	0 / 1 / 2	0 / 1 / 2
Posterior ethmoid	0 / 1 / 2	0 / 1 / 2
Sphenoid	0 / 1 / 2	0 / 1 / 2
Ostiomeatal complex	0 / 2	0 / 2
Maxillary	0 / 1 / 2	0 / 1 / 2

0 = no abnormality / 1 = partially opacification / 2 = complete opacification

The ostiomeatal complex is assigned a score of either 0 (not obstructed) or 2 (obstructed).

The maximum score is 24.

Supplementary table 3 EPOS symptoms defining chronic rhinosinusitis

Primary symptoms	Secondary symptoms	Objective findings	Duration
Nasal obstruction	Loss of smell	Nasal endoscopy	<12 weeks
Rhinorrhoea (anterior or posterior)	Pressure over the sinuses	Radiology	³12 weeks

Epidemiologically based chronic rhinosinusitis is defined as two or more nasal symptoms, at least one of them from the 'primary symptoms', and a duration of 12 weeks or more. Clinically based chronic rhinosinusitis is defined in the same way, but also requires abnormalities on endoscopic or radiologic examination.

CHAPTER 6

MEASURING CONTROL OF DISEASE IN CHRONIC RHINOSINUSITIS; ASSESSING THE CORRELATION BETWEEN SINONASAL OUTCOME TEST-22 AND VISUAL ANALOGUE SCALE ITEM SCORES

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ABSTRACT

Background

In chronic rhinosinusitis (CRS), aim of treatment is control of disease. EPOS2020 suggests the use of visual analogue scale (VAS) measurements on several symptoms. We aim to determine if individual VAS items can be replaced by widely used SinoNasal Outcome Test-22 (SNOT-22) items when determining control of disease, to avoid using double measurements and to stimulate its use in clinical practice.

Methods

Analyses were made on correlations between individual SNOT-22 scores and symptom-specific questions from consecutive patients with CRS visiting our tertiary referral rhinologic clinic for the first time.

Results

157 CRS patients were included. Correlations of individual items were strong (r>0.8). Best parity in sensitivity, specificity, positive predicting value, negative predicting value, odds ratio and Receiver Operating Characteristic curves were found in individual item score of VAS>5 and SNOT item-score ≥3. This cut off is valid for measuring control of disease, combining several nasal, facial pain and sleep symptoms (controlled, partially controlled and uncontrolled).

Conclusion

There is strong correlation between individual items measured as SNOT or VAS. For the definition of CRS disease control, as proposed in EPOS2020, the use of symptoms specific SNOT ≥3 is predictive of VAS>5.

INTRODUCTION

In chronic rhinosinusitis (CRS), treatment is aimed at attaining control of disease. This is a state where complaints are absent, or at least not bothersome, without the need for rescue medication on top of topical steroids and/or saline rinses[1]. From a patient perspective, control of disease translates to alleviation of symptoms and is an important motivation for treatment adherence. In a controlled state, the impact of the disease on quality of life (QoL) is limited. In general, the concept of disease control is based on a combination of symptom severity and medication needed.

To estimate the current severity of the disease and its impact on QoL, several tools can be used. For CRS, the 22-item SinoNasal Outcome Test (SNOT-22) has become one of the most widely applied questionnaires to investigate disease-specific QoL in CRS[2]. Several studies have shown its applicability in CRS and its responsiveness to treatment[3, 4]. Also, shorter questionnaires on certain separate symptoms measured with a visual analogue scale (VAS) are often used instead, especially in digital solutions that monitor disease control, such as health diary apps[5]. Previous studies in conditions as allergic rhinitis have shown that a VAS can be used for this purpose[6]. For CRS, a study in 180 subjects showed a moderate correlation between an overall VAS and the SNOT-22 score, debatably claiming such a simple VAS can be used to '*assess disease severity, monitoring of the course of the disease, and (...) for treatment decisions and disease burden*'[7]. When asking patients to rate their disease severity as mild, moderate or severe, by a VAS scale and by stating whether they felt their QoL was affected, Lim at al. could define three levels of VAS scores (0-10 cm) in 116 CRS cases: 0-3 mild disease, >3-7 moderate, >7-10 severe[8]. Moreover, these three levels of self-reported disease severity have been shown to overlap well with SNOT-22 scores (0-20 mild, >20-50 moderate, >50-110 severe) in a small study with 65 CRS patients[9]. Similarly, in a study with 300 CRS patients, a SNOT-22 score of ≤25 was associated with self-reported well-controlled CRS[10]. In a more recent study of 309 CRS subjects, Philips et al. stepwise determined disease control, based on EPOS 2012 criteria, VAS, SNOT-22 and specifically asking subjects whether they rated their disease as 'controlled', 'partially controlled' or 'uncontrolled'. In their thorough analysis they describe a cut-off at VAS >3.5 corresponding with 'poorly controlled' symptom criteria on the EPOS 2012 descriptive scale[11].

Additionally, other studies have shown that the influence of extranasal symptom domains in the SNOT-22 (such as the ear and sleep domains) have a large impact on an overall VAS score[12-15].

The 2020 edition of the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS2020) describes the use of a VAS in individual symptoms (i.e., 'Nasal blockage', 'Rhinorrhoea / Postnasal drip', Facial pain / Pressure', 'Smell', 'Sleep disturbance or fatigue') to determine whether these symptoms are deemed bothersome or not; for research purposes a VAS of 5 or less may be interpreted as 'not bothersome'[1]. To our knowledge, there is hardly any data supporting the use of a VAS per symptom and how this would relate to the specific symptom-based questions in the SNOT-22 and/or the total SNOT-22 score. Not surprisingly, one of the research needs identified in EPOS2020 is *'Real life studies evaluating and validating cut off levels for visual analogue scale (VAS) or other measurements of control.'* In the current study, we set out to determine the correlations between SNOT-22 individual items and symptom-specific questions (VAS) in a large CRS population, in order

to explore on the EPOS2020 suggestion to use symptom-specific VAS scores or individual SNOT-22 items to determine disease control. The results of this study may directly impact clinical practice, as a clinician using SNOT-22 questionnaires in his or her practice, can now also reliably interpret degree of control based on the SNOT-22 items, instead of using multiple instruments (i.e. SNOT-22 and VAS measurements).

MATERIALS AND METHODS

Participants

Patients visiting our tertiary referral outpatient clinic were asked to fill in a set of questionnaires, including the SNOT-22 and several disease-specific symptoms measured as VAS. Additional presence of physician-diagnosed asthma, NSAID-exacerbated respiratory disease (N-ERD), and IgE or skin prick test confirmed aeroallergen sensitisation was recorded. In this study we included a consecutive series of adult patients who visited our clinic for the first time and were diagnosed with CRS with or without nasal polyps, according to EPOS criteria[1]. They were divided into two groups based on endoscopic findings: patients with nasal polyps (CRSwNP) and patients without nasal polyps (CRSsNP). No further CRS classification was applied.

Measurements

SNOT-22

The SNOT-22 is a widely used 22-item rhinosinusitis-specific questionnaire originally derived from the RSOM-31[2, 16]. The SNOT-22 covers 4 subdomains potentially affected by CRS; nasal, sleep, otologic/facial pain, and emotional symptoms[17]. Patients score their symptoms from the last two weeks on a 6-item scale (0-5; *0) Not present/ no problem, 1) Very mild problem, 2) Mild or slight problem, 3) Moderate problem, 4) Severe problem, 5) Problem is "as bad as it can be").*

The SNOT-22 has been found to be one of the best disease-specific Quality of Life (QoL) questionnaires in CRS based on the measurement goals, the discriminant validity, responsiveness and the points obtained in the quality assessment[3, 4].

VAS

The visual analogue scale uses a 10-centimetre continuous line to indicate current symptom severity. Patients were asked to score the items 'Nasal blockage', 'Rhinorrhoea', 'Posterior nasal discharge', 'Facial pain (forehead, around the eyes, cheek), 'Reduced smell', 'Trouble sleeping' and 'Fatigue'. Scores range from no symptoms to worst symptoms possible (0-10). To explore the EPOS2020 suggestion for the use of symptom-specific VAS scores, patients scored these VAS items for several individual nasal symptoms comparable to the nasal SNOT-22 items.

Data analysis

Fully completed SNOT-22 questionnaires and fully completed individual VAS items were used for the analysis, to avoid calculating with imputed scores on the domain scores or extranasal symptoms.

The SNOT-22 scores were normally distributed, but the distribution of VAS symptoms scores was skewed to the left (i.e. the 'tail' in the distribution figure is on the left, and the mass of the distribution is on the right of the figure), therefore Spearman's rank correlation coefficient (r) was used to measure the association between SNOT-22 and VAS questions. The Spearman's rank correlation coefficient (range -1 to +1) is a standardized measure of the strength of relationship between two variables, where a score, whether it is positive or negative, of 0-0.5 indicates a weak, 0.5-0.8 a moderate and 0.8-1 a strong correlation[18].

To assess the best alternative symptom-specific SNOT-22 item score for the symptom-specific VAS items used for determining control of disease, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for several cut-off points in SNOT-22 and VAS symptoms. Due to the difference in distribution of SNOT-22 scores (normally) and VAS scores (skewed to the left) we hypothesised that we might find the best parity in the upper range of the VAS scores (i.e. 5, 6 or 7) and we chose to explore several arbitrary cut-off points in the upper half of the scales; SNOT ≥3 and SNOT>3 with VAS >5, VAS>6 and VAS>7. Corresponding odds ratios (OR) with 95% confidence intervals (95%CI) were calculated from the chi-squared test. Additionally, predictive ability was calculated using Receiver Operating Characteristic (ROC) curve analysis. Furthermore, Area Under the Curve (AUC) with sensitivity and 1-specificity were calculated. Best matching symptom specific SNOT-22 and VAS cut-off was chosen based on best on the highest AUC.

Clinical control of CRS as per EPOS2020

To assess SNOT-22 equivalent 'controlled', 'partially controlled' and 'uncontrolled' as described in EPOS2020, we divided patients accordingly in three groups, based on the individual SNOT-22 score on items 'Nasal obstruction', 'Rhinorrhoea' and 'Postnasal drip', 'Facial pain', 'Reduced smell', 'Trouble sleeping' and 'Fatigue'. In EPOS2020 two combined items are used: 'Rhinorrhoea / Postnasal drip' and 'Trouble sleeping and Fatigue', which were separate items in the SNOT-22 and VAS questionnaires. To determine the degree of control, we wanted to analyse the most bothering symptom, which would most likely affect the degree of control, so the highest score from either of the individual two items was used.

Symptoms were named the same in the Dutch SNOT-22 and VAS questionnaires, except for the sleeping items; SNOT-22-item 'Lack of a good night's sleep' was used as a surrogate for VAS item 'Sleeping problems'. 'Controlled' CRS was defined as all symptoms scored SNOT≤2. 'Partially controlled' disease was defined as at least one (but maximum two) of the symptoms present (i.e. SNOT-22 score ≥3). 'Uncontrolled' CRS was defined as 3 or more symptoms scored ≥3. As such, only the symptom severity portion of disease control was measured in this study; use of (rescue) medication or endoscopic appearance were not added as parameters. Mean SNOT-22 scores with standard deviation were calculated per group.

Statistical analyses were performed with IBM SPSS Statistics 26. Differences in characteristics were calculated through χ^2 test, One-way ANOVA test or Independent-samples Kruskal-Wallis Test, depending on whether categorical or numerical data were tested.

A *p*-value below 0.05 was regarded statistically significant.

RESULTS

During the 7-year study period we included 554 first-visits of patients with CRSwNP and patients with CRSsNP. In total 157 questionnaires from patients (mean age: 47 years (SD 14), 57% male) fulfilling the EPOS criteria for CRS were evaluated, of whom 85 (54%) patients with CRSwNP (table 1). We found statistically significant more female patients with CRSsNP (54%) compared to female patients with CRSwNP (33%; χ^2=7.18, *p*:.007).

Allergy to common aeroallergens was statistically significant more prevalent in patients with CRSwNP (49%) than in patients with CRSsNP (22%; χ^2=12.0, *p*: .001), as was asthma: 51% in patients with CRSwNP and 28% in patients with CRSsNP (χ^2=7.7, *p*: .005), and N-ERD: 18% in patients with CRSwNP and none in patients with CRSsNP (χ^2=8.7, *p*: .003).

Correlation in individual items

Correlation in individual items from SNOT-22 and VAS are strong (table 2; all correlations r>0.8). For the items required for the EPOS control scheme, the scatterplots of individual VAS and individual SNOT scores are depicted in Figures 1a-e.

Cut-off points for individual SNOT-22 and VAS items

Best parity between SNOT-22 and VAS individual items was found with a cut-off point of SNOT ≥3 and VAS >5, as shown in Table 3. Per symptom, the sensitivity and specificity: 'Nasal obstruction': sens: 86%, spec: 93%; 'Rhinorrhoea or PND': sens: 76%, spec: 95%; 'Facial pain': sens: 88%, spec: 86%;

Table 1 Patient characteristics

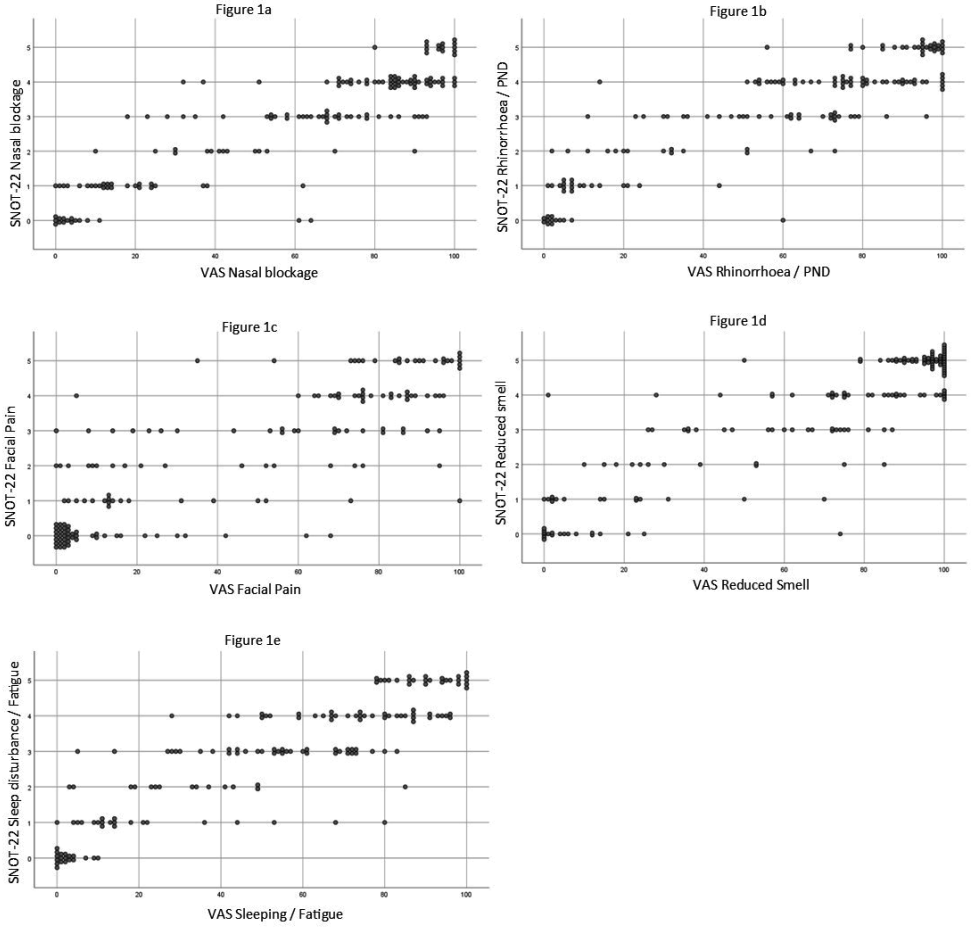
	Total n=157	**CRSwNP n=85**	**CRSsNP n=72**	***p*-value**
Age (SD)	47 (14)	47 (13)	46 (14)	-
Gender (male) (n)	90	57	33	
%	57	67	46	.007
Smoking – Never (n)	66	38	28	.240
%	42	45	39	
Current (n)	28	11	17	
%	17	13	24	
Former (n)	59	33	26	
%	38	39	36	
Allergy (n)	58	42	16	.001
%	37	49	22	
Asthma (n)	63	43	20	.005
%	40	51	28	
N-ERD (n)	15	15	0	.003
%	9.6	18	0	

CRSwNP: Chronic rhinosinusitis with nasal polyps; CRSsNP: Chronic rhinosinusitis without nasal polyps; *p*-value : *p*-value in chi-square test, compared between CRSwNP and CRSsNP; Allergy: Allergy to common aeroallergens; N-ERD: NSAID-Exacerbated Respiratory Disease.

Table 2 Correlation of SNOT-22 and VAS items

Individual items from SNOT-22 and specific VAS	Spearman's rho*
Nasal blockage	.866
Rhinorrhoea / Postnasal drip	.849
Facial pain / pressure	.802
Sense of smell	.857
Sleeping problems / Fatigue	.866

*all p<.001; VAS: Visual Analogue Scale; SNOT-22: SinoNasal Outcome Test. n=157



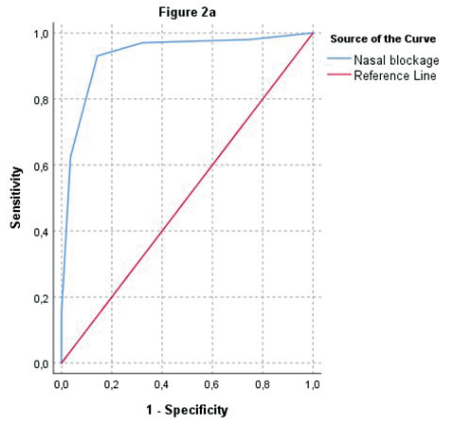
Figures 1a-e Correlation of individual SNOT-22 and VAS items

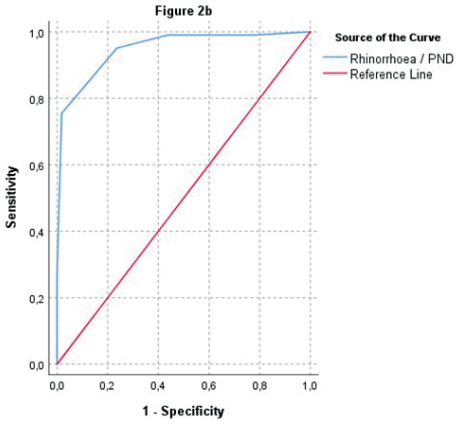
'Reduced smell': sens: 77%, spec: 94%; 'Sleeping problems or fatigue': sens: 71%, spec: 95%. The AUC at VAS cut-off >5 was slightly better, compared to cut-off >7, although 95% confidence intervals were overlapping, this means there is no significant difference (Table 4). The Receiver Operating

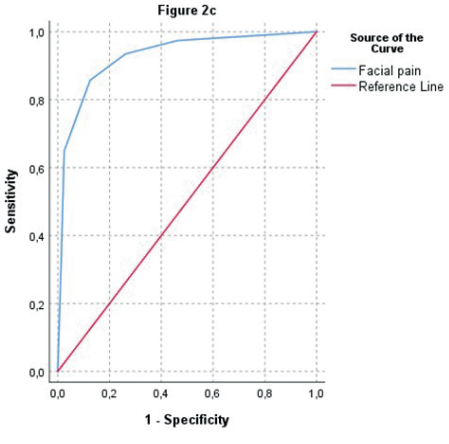
Tables 3 Sensitivity, specificity, positive predictive value and negative predictive value per symptom. Cut-off: SNOT at ≥3 and VAS at >5

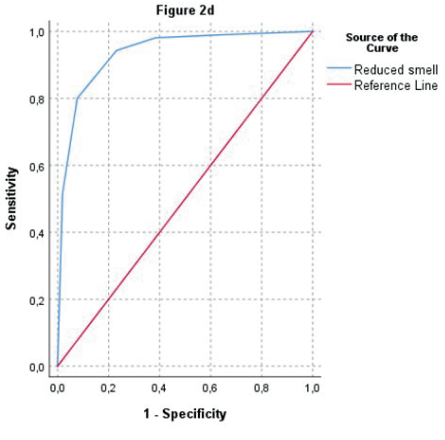
Nasal obstruction	**VAS**		
SNOT-22	≤5	>5	
<3	48	7	55
≥3	8	94	102
	56	101	157
Sens	86	PPV	87
Spec	93	NPV	92
OR (95%CI)	80.57	27.6	235.4
Rhinorrhoea/PND	**VAS**		
SNOT-22	≤5	>5	
<3	42	5	47
≥3	13	97	110
	55	102	157
Sens	76	PPV	89
Spec	95	NPV	88
OR (95%CI)	62.68	21.01	187.00
Facial pain	**VAS**		
SNOT-22	≤5	>5	
<3	70	11	81
≥3	10	66	76
	80	77	157
Sens	88	PPV	86
Spec	86	NPV	87
OR (95%CI)	42.00	16.74	105.39
Smell	**VAS**		
SNOT-22	≤5	>5	
<3	40	6	46
≥3	12	99	111
	52	105	157
Sens	77	PPV	87
Spec	94	NPV	85
OR (95%CI)	55.00	19.31	156.63
Sleep/Fatigue	**VAS**		
SNOT-22	≤5	>5	
<3	51	4	55
≥3	20	82	102
	71	86	157
Sens	71	PPV	93
Spec	95	NPV	80
OR (95%CI)	52.28	16.90	161.66

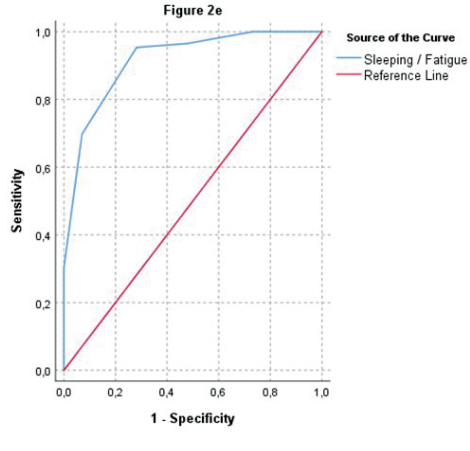
Characteristic (ROC) curve analysis and Area Under the Curve (AUC) with sensitivity and 1-specificity were calculated for VAS >5 (figures 2a-e). Additionally, in table 6, sensitivity, specificity, PPV, NPV, and OR are shown more extensively for several cut-off points. *(Table 6, online supplementary)*.











Figures 2a-e Receiver Operating Characteristic Curve for SNOT -22 and VAS>5 individual items

Table 4 Area Under the Curve (AUC) with VAS >5 and VAS>7

VAS>5	AUC	95% CI lower	95% CI upper
Blockage	.932	.889	.975
Rhinorrhoea / PND	**.949**	.916	.981
Facial Pain	**.928**	.886	.970
Smell	.935	.893	.977
Sleeping / Fatigue	**.915**	.837	.958
VAS>7	**AUC**	**95% CI lower**	**95% CI upper**
Blockage	**.944**	.911	.978
Rhinorrhoea / PND	.891	.843	.940
Facial Pain	.914	.871	.958
Smell	**.938**	.900	.976
Sleeping / Fatigue	.905	.859	.951

VAS: Visual Analogue Scale; AUC: Area Under the Curve; CI: confidence interval; PND: Postnasal drip

Analysis on control of disease

Based on the EPOS2020 definition on current control of disease, based on scores of individual items ('Nasal blockage', 'Rhinorrhoea / Postnasal drip', 'Facial pain / Pressure', 'Smell' and 'Sleep disturbance or fatigue'), measured in VAS, patients were classified as 'controlled' (n=16, 10%, mean SNOT-22: 12.9), 'partially controlled' (n=40, 25%, mean SNOT-22: 30.1) or 'uncontrolled' (n=101, 64%, mean SNOT-22: 57.8). Measuring control of disease based on individual SNOT-22 items gives similar results: 'controlled' (n=16, 10%), 'partially controlled' (n=41, 26%) or 'uncontrolled' (n=100, 64%), with respective mean SNOT-22 scores 10.6, 29.8 and 58.6. (Tables 5a and b). There were no significant differences for CRSwNP or CRSsNP.

DISCUSSION

The aim of this study was to analyse the current EPOS2020 control guidelines. We set out to make a quantitative analysis on several cut-off points and also to analyse if an item-specific SNOT-22 score could be used instead of a VAS item. To our knowledge, this study represents the first quantitative analysis on the correlation of SNOT-22 and VAS items in measuring control of disease.

Table 2 and Figures 1a-e show that the correlation for individual items/symptoms is strong between SNOT-22 and VAS, at least for the items required for the EPOS control scheme.

In search for an optimum cut-off and best parity between individual symptoms; we analysed several different possible combinations of SNOT-22 and VAS. We found best parity in sensitivity, specificity, positive predicting value, negative predicting value and odds ratio in VAS>5 and SNOT ≥3.

When observing the three patient groups, controlled, partially controlled and uncontrolled, that are thus obtained, the total SNOT-22 scores show a good overlap with those reported in literature for mild/moderate/severe CRS (Table 5). It is important to realise, however, that this only represents the symptom-derived part of disease control. The EPOS2020 definitions also entail nasal endoscopy and the need for rescue treatment. It is possible that in the current study, levels

Table 5a and 5b Controlled – partially controlled – uncontrolled CRS based on VAS and SNOT-22 items

Controlled CRS (all items ≤5)			
VAS	**CRS**	**wNP**	**sNP**
n=	16 (10%)	8	8
Mean SNOT-22	12.9	13.5	12.4
SD	6.2	7.4	5.3
Partially controlled CRS (1 or 2 items >5)			
VAS	**CRS**	**wNP**	**sNP**
n=	40 (25%)	21	19
Mean SNOT-22	30.1	23.6	37.2
SD	16.6	13.4	17.1
Uncontrolled CRS (≥3 items >5)			
VAS	**CRS**	**wNP**	**sNP**
n=	101 (64%)	56	45
Mean SNOT-22	57.8	58.1	57.4
SD	18	19.1	17.1
Table 5b			
Controlled CRS (all items <3)			
SNOT-22	**CRS**	**wNP**	**sNP**
n=	16 (10%)	8	8
Mean SNOT-22	10.6	10.1	11.1
SD	5.8	3.5	7.6
Partially controlled CRS (1 or 2 items ≥3)			
SNOT-22	**CRS**	**wNP**	**sNP**
n=	41 (26%)	23	18
Mean SNOT-22	29.8	24	37.1
SD	13.1	10.1	12.8
Uncontrolled CRS (≥3 items ≥3)			
SNOT-22	**CRS**	**wNP**	**sNP**
n=	100 (64%)	54	46
Mean SNOT-22	58.6	59.7	57.2
SD	18	18	18.1

n=157

CRS: Chronic rhinosinusitis; VAS: Visual Analogue Scale; SNOT-22: SinoNasal Outcome Test-22; SD: Standard deviation; wNP: Chronic rhinosinusitis with nasal polyps; sNP: Chronic rhinosinusitis without nasal polyps.

of control were overestimated (more patients 'controlled' or 'partially controlled') as these two factors were not accounted for. From a research point of view, it will be interesting to have future studies using symptom-specific scores and the need for rescue treatment, using SNOT ≥3 as cut-off, parallel with the clinical vs. epidemiological definition of CRS, which is based on symptoms, without nasal endoscopy or imaging.

Limitations

A major limitation of the current study is its base population, namely CRS patients referred to our tertiary care hospital. This might reflect a more severe population, which is indeed suggested by the relatively high number of 'uncontrolled' patients (Table 5). We feel confident that the numbers are large enough to also represent milder cases sufficiently, but it cannot be excluded that results would be different in a more general population, or at the level of secondary care.

Another important limitation of this study is the lack of a golden standard for disease severity and/or symptom severity. We can only point to the internal consistency of our data, and to the large amount of overlap with the data already published from other studies[5, 7-9, 13-15]. This internal and external consistency suggests that the already defined cut-offs for mild/moderate/severe CRS for SNOT-22 scores are valid.

CONCLUSION

There is strong correlation between individual items measured as SNOT-22 or VAS. For the definition of CRS disease control, as proposed in EPOS2020, the use of symptoms specific SNOT ≥3 (as 'moderate problem' or worse) is predictive of VAS>5.

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Tables 6 Sensitivity, specificity, positive predictive value and negative predictive value per symptom. Cut-off: SNOT-22 at 3 and VAS at 5

Nasal obstruction	**VAS**		
SNOT-22	**<=5**	**>5**	
≤3	54	38	79
>3	2	63	78
	56	101	157
Sens	96	PPV	59
Spec	62	NPV	97
OR (95%CI)	44.76	10.32	194.22
Rhinorrhoea/PND	**VAS**		
SNOT-22	**<=5**	**>5**	
≤3	54	25	79
>3	1	77	78
	55	102	157
Sens	98	PPV	68
Spec	75	NPV	99
OR (95%CI)	166.32	21.87	1264.9
Facial pain	**VAS**		
SNOT-22	**<=5**	**>5**	
≤3	78	27	105
>3	2	50	52
	80	77	157
Sens	98	**PPV**	72
Spec	65	**NPV**	96
OR (95%CI)	72.22	16.45	317.13
Smell	**VAS**		
SNOT	**<=5**	**>5**	
≤3	48	21	69
>3	4	84	88
	52	105	157
Sens	92	**PPV**	70
Spec	80	**NPV**	95
OR (95%CI)	48	15.56	148.08
Sleep/Fatigue	**VAS**		
SNOT-22	**<=5**	**>5**	
≤3	66	26	92
>3	5	60	65
	71	86	157
Sens	93	**PPV**	72
Spec	70	**NPV**	92
OR (95%CI)	30.46	11	84.39

Tables 6 (continued)

Cut-off: SNOT-22 at 3 and VAS at 7			
Nasal obstruction	**VAS**		
SNOT-22	<=7	>7	
≤3	77	15	92
>3	4	61	65
	81	76	157
Sens	95	**PPV**	84
Spec	80	**NPV**	94
OR (95%CI)	78.28	24.71	247.97
Rhinorrhoea/PND	**VAS**		
SNOT-22	**<=7**	**>7**	
≤3	67	12	79
>3	17	61	78
	84	73	157
Sens	80	**PPV**	85
Spec	84	**NPV**	78
OR (95%CI)	20.03	8.86	45.32
Facial Pain	**VAS**		
SNOT-22	**<=7**	**>7**	
<=3	92	13	105
>3	10	42	52
	102	55	157
Sens	90	**PPV**	88
Spec	76	**NPV**	81
OR (95%CI)	29.72	12.07	73.22
Smell	**VAS**		
SNOT-22	**<=7**	**>7**	
≤3	57	12	69
>3	7	81	88
	64	93	157
Sens	89	**PPV**	83
Spec	87	**NPV**	92
OR (95%CI)	54.96	20.39	148.19
Sleep/Fatigue	**VAS**		
SNOT-22	**<=7**	**>7**	
≤3	81	11	92
>3	15	50	65
	96	61	157
Sens	84	**PPV**	88
Spec	82	**NPV**	77
OR (95%CI)	24.55	10.45	57.67

Tables 6 (continued)

Cut-off: SNOT at 2 and VAS at 5			
Nasal obstruction	**VAS**		
SNOT-22	**<=5**	**>5**	
≤2	48	7	55
>2	8	94	102
	56	101	157
Sens	86	PPV	87
Spec	93	NPV	92
OR (95%CI)	80.57	27.6	235.4
Rhinorrhoea	**VAS**		
SNOT-22	**<=5**	**>5**	
≤2	42	5	47
>2	13	97	110
	55	102	157
Sens	76	PPV	89
Spec	95	NPV	88
OR (95%CI)	62.68	21.01	187
Facial pain	**VAS**		
SNOT-22	**<=5**	**>5**	
≤2	70	11	81
>2	10	66	76
	80	77	157
Sens	88	PPV	86
Spec	86	NPV	87
OR (95%CI)	42	16.74	105.39
Smell	**VAS**		
SNOT-22	**<=5**	**>5**	
≤2	40	6	46
>2	12	99	111
	52	105	157
Sens	77	PPV	87
Spec	94	NPV	85
OR (95%CI)	55	19.31	156.63
Sleep/Fatigue	**VAS**		
SNOT-22	**<=5**	**>5**	
≤2	51	4	55
>2	20	82	102
	71	86	157
Sens	71	PPV	93
Spec	95	NPV	80
OR (95%CI)	52.28	16.9	161.66

Tables 6 (continued)

Cut-off: SNOT at 2 and VAS at 6			
Nasal obstruction	**VAS**		
SNOT-22	**<=6**	**>6**	
≤2	50	5	55
>2	15	87	102
	65	92	157
Sens	77	PPV	91
Spec	95	NPV	85
OR (95%CI)	59	19.89	169.13
Rhinorrhoea	**VAS**		
SNOT-22	**<=6**	**>6**	
≤2	45	2	47
>2	27	83	110
	72	85	157
Sens	63	PPV	96
Spec	98	NPV	75
OR (95%CI)	69.17	15.72	304.28
AUC (sens/1-spec)	0.801	0.976	0.375
Facial Pain	**VAS**		
SNOT-22	**<=6**	**>6**	
≤2	73	8	81
>2	17	59	76
	90	67	157
Sens	81	PPV	81
Spec	88	NPV	78
OR (95%CI)	31.67	12.78	78.49
Smell	**VAS**		
SNOT-22	**<=6**	**>6**	
≤2	42	4	46
>2	17	94	111
	59	98	157
Sens	71	PPV	91
Spec	96	NPV	85
OR (95%CI)	58.06	18.41	183.06

Tables 6 (continued)

Cut-off: SNOT-22at 2 and VAS at 7			
Nasal obstruction	**VAS**		
SNOT-22	**<=7**	**>7**	
≤2	54	1	55
>2	27	75	102
	81	76	157
Sens	67	PPV	98
Spec	99	NPV	74
OR (95%CI)	150	19.77	1137.95
Rhinorrhoea	**VAS**		
SNOT-22	**<=7**	**>7**	
≤2	46	1	47
>2	38	72	110
	84	73	157
Sens	55	PPV	98
Spec	99	NPV	65
OR (95%CI)	87.16	11.57	656.86
Facial Pain	**VAS**		
SNOT-22	**<=7**	**>7**	
≤2	76	5	81
>2	26	50	76
	102	55	157
Sens	75	PPV	94
Spec	91	NPV	66
OR (95%CI)	29.23	10.53	81.18
Smell	**VAS**		
SNOT-22	**<=7**	**>7**	
≤2	43	3	46
>2	21	90	111
	64	93	157
Sens	67	PPV	93
Spec	97	NPV	81
OR (95%CI)	61.43	17.37	217.24
Sleep	**VAS**		
SNOT-22	**<=7**	**>7**	
≤2	53	2	55
>2	43	59	102
	96	61	157
Sens	55	PPV	96
Spec	97	NPV	58
OR (95%CI)	36.36	8.4	157.43

Tables 6 (continued)

Cut-off: SNOT-22at 3 and VAS at 6			
Nasal obstruction	**VAS**		
SNOT-22	**<=6**	**>6**	
≤3	62	30	92
>3	3	62	65
	65	92	157
Sens	95	PPV	67
Spec	67	NPV	95
OR (95%CI)	42.71	12.39	147.29
Rhinorrhoea	**VAS**		
SNOT-22	**<=6**	**>6**	
≤3	60	19	79
>3	12	66	78
	72	85	157
Sens	83	PPV	76
Spec	78	NPV	85
OR (95%CI)	17.39	7.78	38.76
Facial pain	**VAS**		
SNOT-22	**<=6**	**>6**	
≤3	86	19	105
>3	4	48	52
	90	67	157
Sens	96	PPV	82
Spec	71	NPV	92
OR (95%CI)	54.32	17.47	167.91
Smell	**VAS**		
SNOT-22	**<=6**	**>6**	
≤3	53	16	69
>3	6	82	88
	59	98	157
Sens	90	PPV	77
Spec	84	NPV	93
OR (95%CI)	45.27	16.66	123.04
Sleep	VAS		
SNOT-22	<=6	>6	
≤3	75	17	92
>3	9	56	65
	84	73	157
Sens	89	PPV	82
Spec	77	NPV	86
OR (95%CI)	27.45	11.4	66.11

CHAPTER 7

OCCUPATIONAL EXPOSURE INFLUENCES CONTROL OF DISEASE IN PATIENTS WITH CHRONIC RHINOSINUSITIS

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SUMMARY

Background

Chronic rhinosinusitis (CRS) is a frequent condition that is treated by endoscopic sinus surgery (ESS) when medical treatment fails. Irritating or sensitizing airborne agents can contribute to uncontrolled CRS. A prior study showed a linear correlation between occupational exposure and the number of ESS.

Methods

In this cross-sectional study we tested the hypothesis that occupational exposure is a risk for undergoing ESS. We sent questionnaires enquiring occupational exposure in patients with CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP). An expert assessed blindly the reported work exposures to inhaled agents. The relationship between occupational exposure on undergoing ESS was analysed.

Results

Among all patients who underwent ESS (n=343), 30% reported a relevant occupational exposure, which is significantly higher than the 4.8% found among CRS patients that underwent no prior sinus surgery (n=21) (χ^2=6.30, p=0.04). Besides occupational exposure (OR: 8.7; 95% CI: 1.15 – 65.71), self-reported doctor-diagnosed asthma (OR: 2; 95% CI: 0.93 – 5.70) were independent variables contributing to the chance of undergoing ESS.

Conclusion

In our study we confirm occupational exposure as a risk factor for uncontrolled CRS, if defined by undergoing ESS. In CRS patients with uncontrolled symptoms, despite maximal conservative therapy, the clinician should explore the possible contribution of occupational exposure.

INTRODUCTION

At the entry of the airway, the nasal mucosa is continuously exposed to a variety of airborne substances. These include the common aeroallergens that cause allergic rhinitis in atopic individuals, but also airborne pollutants and irritants and all of these can be encountered at the work floor as occupational exposures. The airways are the primary contact site for a variety of work-related dusts, gases, fumes and vapours. Depending on the amount inhaled and their physical-chemical properties, these agents can cause irritation, corrosive changes, and/or sensitization of the respiratory mucosa[1-3], not only posing as a risk factor for malignancies in specific cases, but more generally contributing to occupational airway disease, like rhinitis, rhinosinusitis and asthma[4, 5].

Chronic rhinosinusitis (CRS) is defined as an inflammation of the mucosa of the nose and the paranasal sinuses characterised by two or more symptoms, lasting more than 12 weeks, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) supplemented with facial pain/pressure and/or reduction or loss of smell. The symptoms need to be confirmed by either endoscopic abnormalities and/or computed tomography (CT) changes[6]. Management of CRS is focused on achieving and maintaining clinical control of symptoms, which can be defined as a disease state in which a patient has no symptoms, or they do not affect quality of life (QoL)[6]. Ideally, prophylactic measures would exist to prevent a chronic disorder like CRS[7]. Precision medicine aims to tailor prevention and management of disease in the individual patient in order to optimise outcomes and minimise costs[8-11]. It is estimated that currently at least 40% of CRS patients remain uncontrolled despite treatment[12]. These difficult-to-treat CRS-patients should be analysed for several factors that can cause lack of control; these can be related to either the disease, diagnosis, therapy, or patient. One of these factors, might be an (unrecognised) occupational exposure[13]. A well-known example is the increased prevalence of CRS in firefighters that had been exposed in the 9/11 World Trade Centre collapse in 2001. In this cohort a higher prevalence of non-resolving upper airway inflammation responding poorly to medical management was found, ultimately treated with surgery even years later. In the whole cohort of rescue and recovery workers a continued increasing cumulative incidence of 'asthma' and 'sinusitis' was found up to 9 years after exposure, compared to pre-exposure[14, 15].

Occupational agents can be classified as high molecular weight (HMW) compounds (>5kDa) — such as flour or animal antigens— or low molecular weight (LMW) compounds (<5kDa). The LMW compounds are again subdivided into two groups, depending on their sensitization capacity; LMW sensitizers, such as isocyanates, persulphate salts and acid anhydrides, lead to airway inflammation after the latency phase of immunologic sensitization, whereas LMW irritants, such as chlorine, ammonia or ozone, cause an immediate airway injury and inflammation through nonallergic pathways[16].

An earlier study on the impact of occupational exposure, suggested a linear correlation between the reporting of occupational exposure and number of Endoscopic Sinus Surgery (ESS) procedures in patients with CRS needed to control disease. This suggests that occupational exposure can be considered a risk factor for the occurrence of rhinosinusitis and its recurrence after surgery[5]. This

means ESS, or multiple ESS, reflects uncontrolled CRS. The aim of this study is to confirm these findings in a second population and to test the hypothesis that work-related exposures are related to the risk of undergoing ESS.

MATERIALS AND METHODS

Study population

In this cross-sectional study we selected patients who had visited our tertiary referral rhinologic clinic, initially diagnosed with CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP), according to EPOS[6]. Patients were excluded if they were younger than 18 years or diagnosed with localized disease such as sinusitis from dental origin, fungal balls, and benign and malignant neoplasms, or those with underlying pathology such as primary ciliary dyskinesia, cystic fibrosis or immune deficiencies. We collected data on previous ESS, allergy to common aeroallergens, asthma and NSAIDs-exacerbated respiratory disease (N-ERD)[17] from medical files.

The study was approved by the local ethics committee of the Amsterdam University Medical Centers, location AMC (W13_152 # 13.17.0195).

Questionnaires

An extensive questionnaire (based on and modified from 'the occupational history form' proposed by Bernstein and also used by Hox et al) was sent by mail to the screened patient population[5, 18]. This questionnaire enquires about rhinologic, pulmonary and general medical history, smoking, and current occupation, including specification of tasks.

Questions included occupational and recreational exposures, duration of exposures, type of agents (including an extensive list to choose from), and sinonasal symptoms.

Furthermore, subjects filled out the RSOM-31 to measure current rhinologic symptoms[19]. The RSOM-31 is a 31- item rhinosinusitis-specific questionnaire which contains 7 subscales: nasal, eye, sleep, ear, general, practical and emotional. Patients score their symptoms on a 6-item scale (0-5; *0) Not present/ no problem, 1) Very mild problem, 2) Mild or slight problem, 3) Moderate problem, 4) Severe problem, 5) Problem is "as bad as it can be"*, with a score ranging from 0 to 155. This questionnaire is the precursor of the widely used SNOT-22[20]. We included RSOM-31 scores of patients that answered at least 50% of the items (≥16 items), to reliably calculate a mean score[20].

Analysis of questionnaire responses

All returned questionnaires were analysed for relevant occupational exposure, independently and blindly by a physician specialised in occupational medicine (SRo). Occupational agents were categorized as being HMW sensitizers, LMW sensitizers or LMW irritants.

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 26. Differences in characteristics were calculated through χ^2 test, One-way ANOVA test or Independent-samples Kruskal-Wallis

Table 1 Patient characteristics

			nESS					
		Total	**0**	**1**	**2**	**3**	**≥4**	***p*-value**
	n	**364**	21	80	74	64	125	
	%	**100**	5,8	22	20	18	34	
Diagnosis (CRSwNP)	n	**225**	11	46	43	49	76	0,1
	%	**62**	52	58	58	77	61	
Age	Median	**56**	63	57	57	51	57	0,1
	IQR	**19**	20	17	17	23	16	
Gender (male)	n	**205**	12	41	40	35	77	0,7
	%	**55**	57	51	54	55	62	
Smoking	Yes (n)	**36**	3	10	7	2	14	0,3
	%	**9,9**	14	13	9,5	3,1	11	
	No (n)	**203**	10	46	44	43	60	
	%	**56**	48	58	60	67	48	
	Former (n)	**125**	8	24	23	19	51	
	%	**34**	38	30	31	30	41	
Allergy to common aeroallergens	n	**128**	7	28	24	27	42	0,7
	%	**35**	33	35	32	43	34	
Asthma	n	**176**	8	32	36	35	65	0,3
	%	**49**	38	40	49	56	52	
N-ERD	n	**61**	2	8	9	16	26	0,05
	%	**17**	10	10	13	26	21	
RSOM-31	μ (0-5)	**346**	1,13	1,55	1,57	1,80	1,83	0,05
	SD		0,90	1,08	1,14	1,04	1,09	

Total = Total study population; nESS = number of previous ESS; CRSwNP = Chronic rhinosinusitis with nasal polyps; IQR = Inter quartile range; N-ERD – NSAIDs Exacerbated Respiratory Disease; RSOM-31 = RhinoSinusitis Outcome Measurement; μ = mean; SD = Standard deviation.

Test, depending on whether categorical or numerical data were tested. A *p*-value below 0.05 was regarded statistically significant.

Additionally, we conducted a multivariate regression analysis to determine the best set of independent predictors for undergoing ESS.

First, we made a pre-selection of possible predictors by univariate regression analysis.

Based on the total number of patients with no surgery (n=21), we could report on only 2 possible predictors. Possible predictors with a *Wald-p* value <0.10 were included in a multivariate logistic regression analysis.

To obtain a model for predicting individual risk for ESS in a CRS population that can be used in daily practice, we applied a backward selection (significance level to stay in the model: $p \leq 0.05$ and based on likelihood-ratio test ($p \leq 0.10$) and Nagelkerke R^2) to reduce the number of predictors.

RESULTS

Patient characteristics

Of the invited 877 patients with chronic rhinosinusitis with and without nasal polyps, 410 responded (46% response rate). 38 patients returned the questionnaire empty and 8 were excluded because they met exclusion criteria.

Of the patients that responded, 62% (n=225) were diagnosed with CRSwNP. 5.8% had undergone no surgery (n=21), 22% had undergone one surgery (n=80), 20% (n=74) two surgeries, 18% (n=64) three surgeries and 34% (n=125) four or more sinus surgeries. General patient characteristics are listed in Table 1. Patients that had undergone ESS only showed a trend of higher prevalence of N-ERD (p=0.05) and a higher RSOM-31 score (p=0.05).

There were no significant differences between responders and non-responders for diagnosis or items like age, gender, smoking, allergy, asthma or N-ERD.

Occupational exposure

Among all patients who underwent ESS (n=343), 30% reported a relevant occupational exposure, which is significantly higher than the 4.8% found among CRS patients that underwent no prior sinus surgery (n=21)(χ^2=6.30, p=0.04) (Figure 1). No significant difference were seen between patient groups with regards to exposures related to leisure activities (9.9% in ESS group vs. 14% in non-surgical group), including swimming in chlorinated pools (12% in ESS group vs. 14% in non-surgical group). The most frequently reported occupational agents are listed in table 2.

Table 2 Most frequently reported occupational agents

Substance	Occupation	Frequency reported
Solvents (e.g., thinner, acetone, white spirit)	Painters, engineers, mechanics, ...	35
Cleaning products and disinfectants (incl. bleach)	Cleaners, caretakers, housewives, nurses, ...	34
Reactive chemicals (e.g., di-isocyanates, acrylates, epoxy resins)	(Spray) painters, car body repair, dentists, insulation worker	31
Welding fumes and metal dust	Mechanic, motor/car maintenance, metal workers, ...	14
Combustion engine exhaust	Motor/car maintenance, drivers, ...	13
Medication	Health care / pharmacy	12
Ammonia	Carpenters, mechanics, ...	10
Flour	Baker, Farmer, ...	9
Flowers	Floriculture, flower shop, ...	9
Inorganic dust	Builders, warehousemen, ...	8
Latex	Health care, dentist, nurse, ...	6
Animals	Farmer, laboratory, ...	4
Cement	Builders	4

70% of patients that had a relevant occupational exposure, were exposed to irritants, 37% to LMW sensitizers and 23% exposure to HMW sensitizers. Prevalence of exposure to irritants, LMW sensitizers and HMW sensitizers are shown in figure 2; we found a higher prevalence in patients that underwent ESS (irritants χ^2= 5.51, *p*=0.018; LMW sensitizers χ^2= 2.67, *p*=0.102, HWM sensitizers χ^2= 0.12, *p*=0.728).

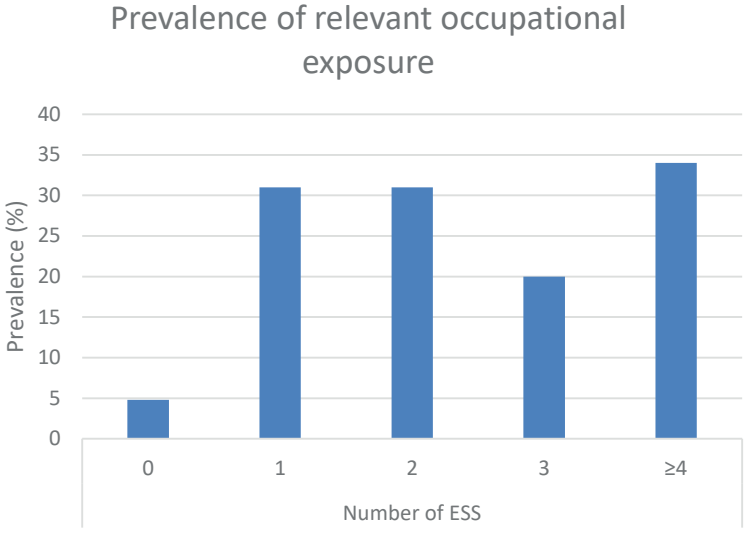

Figure 1 Prevalence of relevant occupational exposure. Prevalence: nESS=0: 4,8% (n=1), nESS=1: 31% (n=25), nESS=2: 31% (n=23), nESS=3: 20% (n=13), nESS≥4: 34% (n=43)

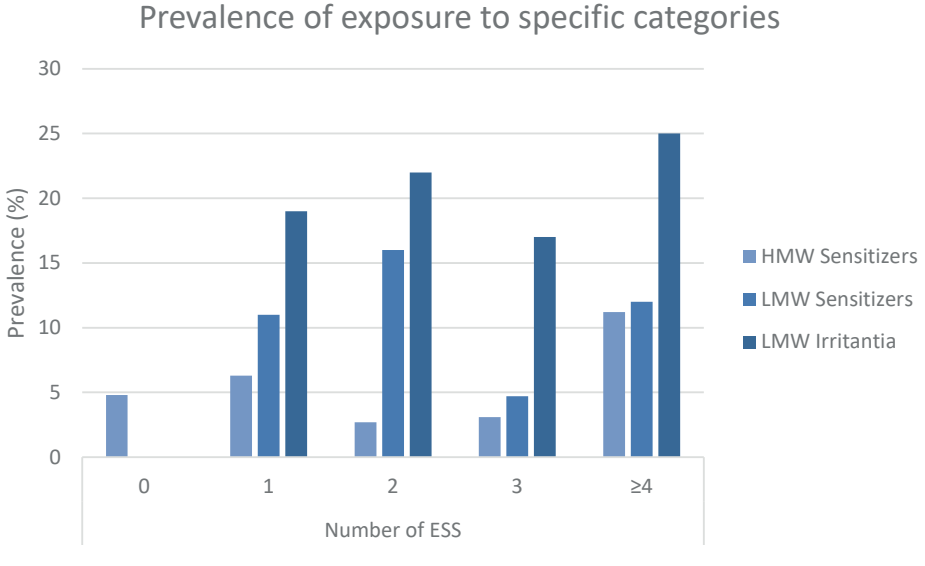

Figure 2 Prevalence of exposure to specific categories of occupational agents.

Table 3 Prediction model (multivariable regression model) on having had at least one ESS

							95% C.I.for EXP(B)	
	B	**S.E.**	**Wald**	**df**	**Sig.**	**Exp(B)**	**Lower**	**Upper**
Self-reported doctor diagnosed Asthma	,809	,466	3,009	1	,083	2,246	,900	5,602
Occupational exposure	2,145	1,032	4,315	1	,038	8,541	1,129	64,617
Constant	2,093	,298	49,389	1	,000	8,111		

Note: R^2=0,31 (Cox-Snell), 0,87 (Nagelkerke). Model $\chi(2)$=11,5

Several potential prognostic factors were significantly associated with having at least one ESS, in the univariate analysis.

» Self-reported doctor-diagnosed asthma (OR: 2; 95% CI: 0.93 – 5.70)

» Occupational exposure (OR: 8.7; 95% CI: 1.15 – 65.71)

This was also the case in the prediction model; the multivariable regression analysis on having had at least one ESS.

In this prediction model, variables like 'age', 'CRSwNP', 'allergy to common aeroallergens', 'smoking' or 'N-ERD' did not have a significant additional contribution to the chance of having had at least one ESS.

Current rhinologic symptoms

RSOM-31

Of the 364 patients analysed for occupational exposure, 95% (n=346) had answered at least 16 items on the RSOM-31 questionnaire. Mean scores (0-5) for RSOM-31 were 1,13 in patients that never underwent ESS, ascending from 1,55 (1 ESS), to 1,57 (2 ESS), to 1,80 (3 ESS) to 1,83 (≥4 ESS), suggesting that more uncontrolled disease was found in the group with more prior ESS. However, the one-way ANOVA test was not significant (p=0.05).

DISCUSSION

The aim of this study was to confirm the previously suggested relationship between occupational exposure and the difficulty to control CRS, as measured by need and number of sinus surgeries. In this retrospective questionnaire-based study in a single tertiary centre CRS population, we confirmed that occupational exposure is a risk factor for ESS. In addition to self-reported occupational exposure, only self-reported doctor-diagnosed asthma was detected as a second independent variable contributing to the chance of undergoing ESS.

Previously Hox et al. also reported an increasing prevalence of occupational exposure, in groups with increasing number of ESS[5], we could not confirm this finding. This different finding might be explained by the remarkable characteristics of the subjects with nESS=3. In these patients we found a relatively higher prevalence of CRSwNP, a lower age, less smokers, a higher prevalence of allergy

to common aeroallergens, asthma and N-ERD, but a lower prevalence of occupational exposure, compared to the nESS=2 and nESS≥4 patients.

The difference in patient populations, as we serve as a tertiary referral rhinosinusitis clinic and in general see patients that were treated by other otorhinolaryngologists before, might cause selection bias, with relatively more patients with uncontrolled CRS, or possibly more risk factors contributing to uncontrolled CRS. This also means that the indications for previous surgery were set by other otorhinolaryngologists which could have led to a overrepresentation of the number of ESS procedures, and, therefore an overrepresentation of patients with uncontrolled CRS. Hox et al. included CRS patients planned for ESS, investigating a population sample with uncontrolled symptoms at inclusion. In our cross-sectional study we also included patients with controlled and partially controlled symptoms. Hox et al. also included patients with recurrent acute rhinosinusitis (ARS), we cannot compare this part of the study population. Also Hox et al. included a control group of patients undergoing vocal cord surgery, where they found a prevalence of 12% of occupational exposure. We did not include a non-CRS control group, so we cannot compare. We included 21 patients that did not have prior ESS at the time they were included in our study. This small non-ESS part of the population might give an unbalanced view on prevalence of occupational exposure in CRS patients that were not treated with ESS before. Main reasons for not having undergone prior surgery were: successful medical therapy, indication for primary ESS at our first consultation, or a relative contra-indication for ESS; underlying disease or medication unfavourable for ESS (e.g. anticoagulants and heart failure).

Furthermore, the results from our tertiary referral centre study population might not be translated 1:1 to primary or secondary care CRS patients. However, lessons learnt in tertiary care might be applicable to any uncontrolled CRS patient; awareness of occupational exposure is relevant throughout the entire care system.

We used the same questionnaire as modified from Bernstein[18], so as to have the same occupational agents identified and have a similar scoring on possible relevant exposure. In our study we had one assessor of the occupational exposure (SRo), who was trained in the same clinic by the experts that scored the occupational exposure in the study by Hox, so we assumed a reliable comparable assessment of possible relevant occupational agents. Nevertheless, exposure misclassification is possible when using exposure assessments by experts.

For inclusion we set no maximum age of 65 years, risking recall bias for retired patients. Evaluation of relevant exposure is based on occupation and an extensive list of possible agents to choose from. We argued that retired patients could still recall their type of job and possible agents they were exposed to and the possible effects on CRS probably do not have an age limit. A similar analysis on our data with only patients between 18 and 65 years still has 'relevant occupational exposure' as a significant risk factor for undergoing ESS (data not shown). However, it should be noted that self-reported exposure may both over- and underestimate the actual exposure, especially if there has been a long delay between the exposure and the self-report. Patients who have developed symptoms may also be more prone to report exposure; this remains a limitation in self-reporting occupational exposure.

In our cross-sectional design, we sent a postal questionnaire to a selected set of CRS patients that had visited our rhinology practice. Due to the fact that we included patients from visits spread over several years, we did not attempt another postal or telephone reminder. We had a 46% response rate, which is a common response rate in mail surveys.

To evaluate current symptoms in our study population, we added the RSOM-31 to the occupational exposure questionnaire. The mean scores between 1.14 and 1.83 might imply that these patients still suffer from partially controlled CRS[12] as proposed by van der Veen in a Real-life study on uncontrolled CRS. For this comparison we transformed the RSOM-31 items to the SNOT-22 items, patients score 1.18 – 1.90 mean SNOT-22 score.

The cornerstone in managing occupational airway disease is prevention of its development by appropriate occupational hygiene. Early symptoms or sensitizations can be picked up by means of questionnaires, skin prick tests for specific agents, and increased awareness for onset of nasal symptoms[21]. Once occupational work-related upper airway symptoms are established, avoidance of or reduction in exposure to the suspected causal agent is the key feature of the treatment strategy, with in ultimo relocation of the patient to another job without exposure. When adequate reduction in exposure is impossible or insufficient, rhinitis or rhinosinusitis should be treated according to the guidelines for non-occupational upper airway disease, including topical steroids and nasal rinsing and subsequent clinical evaluation of therapy compliance[6, 22]. This should include asking how patients rinse their nose (type of device, technique, medication, frequency etc.).

Other studies on occupational exposure and CRS are mainly large-population epidemiologic studies, missing otorhinolaryngologists-based diagnosis of CRS[23-27]. They use questionnaire-based diagnosis of CRS in large population samples and mainly support the relationship between CRS and occupational exposure on a macro level. These results can be very useful in macro-economic and social policy making, however there is increased uncertainty on the actual CRS diagnosis.

The cross-sectional design of our study is well suited for investigating prevalences, however, we experienced several limitations. Our tertiary-care referral CRS population would be eminently suitable for investigating factors contributing to uncontrolled CRS. On the other hand, in several variables we measured unexpected prevalences; for example lower prevalence of CRSwNP in nESS≥4 compared to nESS=3 (61% and 77% resp.), non-significant increase of prevalence of N-ERD with increased number of ESS and no relation with smoking, which is not in line with literature.

Despite the fact that our study cannot show a significant linear correlation between prevalence of occupational exposure and increased number of ESS, this study does confirm occupational exposure as a risk factor for CRS. For the clinician this yields a potential preventable factor in the complex aetiology of CRS and asthma. Recent papers by Feary et al. and Tarlo et al. on occupational exposures in asthma highlighted the importance of identifying occupational exposure by (primary) health care practitioners, to minimize the risk of long-term impairment from occupational asthma[28, 29].

CONCLUSION

In our study we confirm occupational exposure as a risk factor for uncontrolled CRS, defined by the need for ESS. In CRS patients with uncontrolled symptoms, despite maximal conservative therapy, the clinician should explore the possible contribution of occupational exposure.

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CHAPTER 8

GENERAL DISCUSSION

Chronic rhinosinusitis (CRS) is based on a diagnostic construct. According to EPOS[1], it requires

1. patient-reported outcomes (symptoms such as rhinorrhoea, nasal obstruction, loss of smell and/or facial fullness);
2. physician-reported outcomes (abnormalities upon imaging or nasal endoscopy); and
3. a duration of at least 12 weeks.

Although this is a very clear definition, it also implies various challenges. From a patient perspective, there is a lot more to say about the impact of CRS in daily life than the four 'major' symptoms can predict. No wonder that patient-reported outcome measures (PROMs) or disease-specific health related quality of life instruments, cover a number of domains and have more than just four questions on symptoms. On the other hand, various other diseases than CRS would give positive scores on these PROMs. It is known, for example, that patients suffering from e.g. migraine or obstructive sleep apnoea have higher SNOT-22 scores than healthy subjects[2, 3] and that otologic/facial pain and sleep-related symptoms – and thus their underlying pathophysiologic mechanisms – may affect impact on the general health-related QoL[4]. As such, it makes sense to include a physician-reported parameter to diagnose CRS. Interestingly, these give the same challenges. Nasal endoscopy has been shown to roughly reduce the prevalence of CRS to 2/3rd in the population when compared to patient-reported outcomes[5, 6]. The same can be seen when applying CT-scan scores as the physician-reported parameter, as it also reduces the prevalence of CRS to half[7]. It remains to be seen whether these two 'halves' represent the same parts of the population. In a predefined CRS patient group, the correlation between nasal endoscopy and imaging has been shown to be moderate to strong[8]. However, it is at this stage unclear how these two modalities would overlap in a general population. Based on our own data in Chapter 5, we can conclude that the physician-reported outcome of CT imaging per se is not a good discriminator of CRS patients and healthy controls. Many controls without symptoms of CRS have abnormalities in a CT scan and vice versa, patients that fulfil the epidemiological criteria for CRS regularly do not show abnormalities on a CT scan, which are familiar incidental findings or might be caused after viral upper respiratory tract infections[9, 10]. It would therefore be very interesting to conduct a study in the general population combining patient-reported outcomes with both nasal endoscopy and imaging.

In this thesis we used various PROMs to diagnose CRS. However, PROMs are not designed as a diagnostic tool, but to measure the impact of disease on quality of life. In chapter 5 we used a non-validated PROM based on the EPOS construct (GA2LEN questionnaire) to investigate the prevalence of CRS in the general population. Using this questionnaire, a prevalence of 11% (6.9 – 27.1 %) was found in the general population[11]. Adding imaging as criterium for the diagnosis CRS, reduces this prevalence to ~6% as discussed above. The advantage of the GA2LEN questionnaire is the limited number of items compared to e.g. the SNOT-22. However, it is unknown how well this questionnaire discriminates CRS patients from healthy subjects or from those with other diseases (e.g. (non-) allergic rhinitis). Moreover, it is also unknown whether adding more items would increase the discriminative value of such a questionnaire. The widely-used SNOT-22 is also not validated in this respect as a diagnostic tool. The ideal questionnaire would have a perfect discrimination with

a limited number of questions. For (allergic) rhinitis a questionnaire with 7 questions has shown to have a PPV of 98% and a NPV of 86%[12]. Whether a similar questionnaire – without the need for a physician-reported parameter - could be developed for the diagnosis of CRS is unclear.

In chapter 4, we have shown the difference in PROMs between CRS patients with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP). To some extent, this would enable a more precise diagnosis (phenotype) based on questionnaires. Although differences exist on a group level between CRSwNP and CRSsNP, prediction of these phenotypes based on specific items is not very accurate. Psychometric analyses can optimise questionnaires, as was the case with the evolution of RSOM-31 to SNOT-22, through SNOT-16 and SNOT-20[13-16]. Gaining insight in the contribution of the items in a questionnaire facilitates improved interpretation of the scores.

It would be very interesting to know whether a PROM, apart from additional clinical characteristics[17], could be used to predict the underlying inflammatory endotype. Better identification of endotypes might permit individualization of therapy that can be targeted against the pathophysiologic processes of a patient's endotype, with potential for more effective treatment and better patient outcomes. Literature suggests that this is possible to some extent; smell loss (OR 2.80, 95%CI [1.45-5.51]) was associated with type-2 endotype and intra-operative pus was associated with type-3 endotype (OR 5.42, 95%CI [2.23-13.61]). In another study on 7 major clinical symptoms and inflammatory endotypes, 'headache/facial' pain was positively associated with type-1 endotype (OR 1.18, 95% CI [1.01-1.38]); 'loss of smell' was positively associated with type-2 endotype (OR 1.22, 95%CI 1.03-1.45]) and purulent rhinorrhoea was positively associated with type-3 endotype (OR 1.29, 95%CI [1.10-1.50])[18, 19]. For the SNOT-22 a relevant question would be whether adding the item: *"Which are your most bothering symptoms?"* would improve the discrimination.

In this thesis we have made use of the RSOM-31[13]. Strictly speaking, this questionnaire consists of two scales; a magnitude scale (0-5) on how bad the problem is, and an importance scale (0-4) on how important it is to the subject. These numbers were supposed to be multiplied to give a total symptom impact score. In real life, patients struggle with the difference between severity (magnitude) and importance of symptoms. Based on this struggle, and a number of methodological issues, it was proposed to only use the magnitude grading[15]. The importance scale greatly complicated the instrument scoring and did not greatly contribute to the overall score. Over the period in which this thesis was developed, the RSOM-31 has mostly been abandoned and replaced by its derivative, the SNOT-22, only using the magnitude grading. This is why we have adopted the SNOT-22 over the course of the chapters in this thesis[16]. When changing to a different questionnaire, one should be aware of its validation for the specific patient group and goal of research. This is exactly why we have validated the SNOT-22 in a Dutch population in chapter 3.

Just as patients struggle with the difference between severity and importance, physicians often struggle to discriminate disease severity from disease control. Disease control can be broadly defined as the extent to which manifestations of CRS are within acceptable limits. In case disease control is the goal of treatment (and for CRS, it is), then the treatment needed to achieve this degree of control is of interest as well. Therefore, three major components are involved in the concept of disease control:

1. The level of manifestations of disease (or disease burden, severity etc.)
2. The extent to which these manifestations are within acceptable limits (mild, not bothersome etc.)
3. The needed treatment to achieve current level of control (e.g. topical steroids or regular courses of systemic corticosteroids)

Although the concept of CRS control is clear, the actual clinical translation is still a matter of debate. This mostly concerns what manifestations are important, how to measure them, and how to determine what 'acceptable limits' are. Like in asthma, the EPOS2012 guidelines have proposed a definition of CRS control based on a combination of symptoms, findings at physical examination and the need for rescue treatment, that still needs validation[20, 21].

When patients with CRS are asked what components constitute control, they point to their daily symptoms, the severity and frequency of CRS exacerbations, the impact on quality of life, as well as the exacerbation of comorbid disease (such as asthma)[22]. If simply asked to rate their control on a 5-point scale, patients responses correlate strongly to disease burden (as measured with SNOT-22 or an overall VAS score)[23]. It appears that EPOS guidelines regularly assess worse CRS control than assessed by patients, possibly caused by the contribution of nasal endoscopy findings; in many studies the polyp size only has a weak or moderate correlation with the QoL measurement[24]. Replacement of this physician based outcome with a measure of patient-reported CRS disease control better aligns EPOS CRS disease control with patients' perspectives[25].

For example both in the Sinus Control test and Asthma Control test, there is an item that asks patients to assess the impact of disease on everyday functioning at home, school or work, that significantly contributes to the reliability of assessing control of disease[26, 27].

The agreement of a rhinologists' assessment of CRS control with EPOS guidelines is remarkably accurate. Moreover, the agreement with patient-reported CRS control is significantly greater when given patient-reported CRS control (χ=0.736) vs. when not given patient-reported CRS control (χ=0.554), p<0.001 *(personal communication CEORL-HNS Milan 2022, A.R. Sedaghat – soon to be published)*. This means that including patient-reported CRS control is of importance in determining the degree of control, and may even be more contributing than nasal endoscopy findings.

The loss of smell is often regarded as a major symptom influencing the quality of life, and is therefore deemed important in the establishment of CRS control, especially in CRSwNP. Interestingly, studies show that isolated loss of sense of smell (i.e. without nasal obstruction or rhinorrhoea) is rare and that assessing olfactory dysfunction might not necessarily be needed in assessment of disease control in CRS[28]. On the other hand, it is conceivable that different phenotypes of CRS, and even different gender, have a different pattern of complaints (as discussed above) and would therefore require a (slightly) different approach to the establishment of disease control[29].

EPOS2020 suggested the use of a VAS>50 for single CRS control items to be relevant in a research context. From our own data in chapter 6, we know that there is a strong correlation between single VAS item scores and their respective scores in the SNOT-22 questionnaire; the VAS>50 criterion can reliably be replaced by a SNOT-22 item score of ≥3. This enables easy input for the determination

of CRS control, especially in retrospective studies when patients filled in a SNOT-22 but no item-specific VAS scores. This might aid tremendously in the validation or correction of the EPOS2020 suggested CRS control scheme.

Regarding the use of the SNOT-22 in research, the American Food and Drug Administration (FDA) recently published a guidance document on developing drugs or monoclonal antibodies for treatment of CRSwNP[30]. In this document they confirm that patients have impaired QoL scores and that treatment goals include reduction of symptoms and systemic corticosteroid use and avoidance of surgery, as well as improved quality of life. On the other hand, they advise on two main endpoints of studies, being *an endoscopic nasal polyp score* and *evaluation of nasal congestion*. As secondary endpoints, the FDA advises to evaluate 'smell', 'Patient-reported symptom scores', 'surgery and oral corticosteroid use' and 'imaging'. Even more remarkable:

» *"We do not recommend use of sino-nasal outcome test (SNOT-22, or other versions of SNOT) to derive key study endpoints to support regulatory decision-making because of interpretability concerns inherent to the design of this PRO instrument (e.g. inclusion of items that either lack relevance or are not well understood by patients with CRSwNP), as well as redundancy of some of the SNOT-22 items with the individual symptom items used to derive other study endpoints (e.g., the primary efficacy endpoint)."*[30]

With this statement, the FDA completely misses the mark of clinical outcome evaluation. Why are a physician-reported parameter and a single symptom the main endpoints for a disease that affects a patient on multiple health domains? In this thesis, we already mentioned the lack of correlation between physician-reported outcomes and patient-reported outcomes and the role of the SNOT-22 items in measuring control of disease. We emphasise the importance of involving patient-reported outcome measures in any clinical study in CRS.

If disease control is the goal of treatment, then this implies that lack of control (e.g. partially controlled or uncontrolled disease) is cue to intensify treatment. To turn this around; one could argue that an upscaling of treatment (e.g. the indication to perform sinus surgery) is a measure of uncontrolled disease. Oftentimes, CRS patients undergo a repetition of treatments without longstanding effects on disease control. It is imperative for otorhinolaryngologists to consider treatable traits in these patients. The obvious traits include smoking, allergic rhinitis, and asthma. Based on our current work as described in chapter 7, occupational exposure to antigens, irritants and sensitizers, should also be considered in uncontrolled disease.

Another issue to consider is the effect of repetitive measurements on the outcome scores. With the arrival of biologicals in the treatment of CRS, clinicians and moreover patients, may notice a rapid relief of symptoms, in a majority already within two weeks after start of treatment[31]. With emergence of relying on PROMs, clinicians should be aware of the possible influence of *response shift*, which is well identified in oncology, coronary artery disease and severe fatigue[32-35]. This is defined as *a change in the meaning of one's self-evaluation, as a result of changes in internal standards, values, and/or conceptualization of the patient-reported outcome (PRO)*[36].

This phenomenon should be taken into account both on individual patient level, as well as at the healthcare policy level; e.g. a first-visit patient exaggerating symptoms to fulfil criteria to receive

expensive biological treatment or the effect on longitudinal follow-up of a biological-patient where several prior 'minor' rest-symptoms amplify the SNOT-22 score during the course of the treatment, when these symptoms are 'the only' symptoms the patient is bothered about. On healthcare policy level response shift should be kept in mind in comparing a more invasive procedure with longer recovery time (e.g. surgery) with a less invasive method with few side-effects (e.g. biologicals). The more invasive procedure might cause adaptation, and thus at follow-up a higher level of HRQoL than the less invasive treatment. The result might be that a guideline might advise for invasive surgery with several risks and underestimate the net effect of the less invasive treatment[37].

This thesis focused on the discrepancy of patient-reported outcomes vs. physician-reported outcomes in clinical practice and in epidemiologic research. In the last decades there is a clear evolution in the concept of determining burden and control of disease; historically mainly from a physician-centred perspective, but currently more and more from a patient-centred perspective. PROMs provide an opportunity to measure variables that are not captured on the biological level. Overall, they allow for continuous measurement of the overall perception of health by the patient. Ultimately, it is the patient that we treat and their symptoms are what brings them to our care.

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APPENDIX

&

SUMMARY

SAMENVATTING

PORTFOLIO

AUTHORS AND AFFILIATIONS

OVER DE AUTEUR

DANKWOORD

SUMMARY

Chronic rhinosinusitis (CRS) is a multifactorial chronic mucosal inflammatory disease of the nose and paranasal sinuses. The definition of CRS is based on patient-reported outcomes, physician-reported outcomes and a duration of at least 12 weeks. This seems a clear way of defining disease, however, there are discrepancies between these different perspectives. To determine the level of control of disease in the course of treatment, it is essential to use an instrument that is validated for that specific use, and to know about the strengths, possible weaknesses and limitations of Patient-reported outcome measurements (PROMs).

In the future there will be an increasing role for the use of PROMs in managing CRS. Thorough knowledge on PROMs is indispensable to give opportunities for these future evolutions.

This thesis focused on gaining insight on the use of PROMs, in particular 22-item SinoNasal Outcome Test (SNOT-22), applied during diagnosis, evaluation of treatment and in research.

In **Chapter 2** we make a comprehensive review on the use of questionnaires in CRS and allergic rhinitis (AR). We explain on the fact that PROMs measure Health-Related Quality of Life (HRQoL), which is different from general Quality of Life. PROMs provide a standardised, quantified and summarised version of the patients' physical symptoms and functional and psychosocial consequences of the disease. We conducted a thorough quality assessment on the characteristics of several HRQoL instruments often used in AR and CRS, in which we assessed the instruments on the construction, description, feasibility, validation study and psychometric properties. This chapter serves as introduction on the quality aspects PROMs should meet and when to properly use what instrument for AR and CRS in clinical practice and research.

In **Chapter 3** we describe the validation of the NL-SNOT-22. The SNOT-22 is considered the reference questionnaire to assess CRS-symptoms, HRQoL and treatment response in CRS patients. Assuming a prevalence of CRS between 5-12% in the general population, there are 0.9 – 2.1 million CRS patients in the Netherlands, there was a need for a psychometric validation of the Dutch version of the SNOT-22. The NL-SNOT-22 shares comparable psychometric characteristics and reliability, compared to the original SNOT-22 and its many translations and cross-cultural adaptations. It therefore is a robust, reliable, valid, responsive instrument for use in daily clinical rhinology practice.

In **Chapter 4** we analyse whether symptoms can differentiate between patients with CRS with nasal polyps (CRSwNP) and patients with CRS without nasal polyps (CRSsNP). Typically in clinical practice, patients with CRSwNP complain of decreased sense of smell and of rhinorrhoea, and patients with CRSsNP complain of facial pain. In this study patients with CRSwNP score higher on nasal symptoms like 'rhinorrhoea' and 'decreased smell' and associated symptoms like 'the inconvenience of having to carry tissues' and 'need to blow nose'. Patients with CRSsNP score higher on 'headache'. Total RhinoSinusitis Outcome Measurement-31 (RSOM-31) scores show no significant difference. We conclude that there are significant differences in scores on several symptoms, but there is considerable overlap of many symptoms and it remains difficult to distinguish between CRSwNP and CRSsNP based on clinical impression alone.

In **Chapter 5**, we enquire on the value of imaging, a physician-reported parameter in diagnosing CRS. From clinician's perspective it is desirable to have some form of confirmation of mucosal inflammation. Apart from the presence and duration of symptoms, involvement of sinonasal cavities distinguishes between CRS and other nasal (like) diseases like (non-)allergic rhinitis, acute rhinosinusitis and some forms of migraines or facial pain syndromes. Especially in epidemiologic research it is difficult to make this distinction, due to the fact that the epidemiologic definition of CRS is based on symptoms only. We were the first to evaluate the clinically based prevalence of CRS using imaging, in a (rather) normal population, which was 3.0 or 6.4%, depending on which cut off point is used (Lund Mackay (LM) ≥4 or LM≥0). The prevalence of epidemiological based CRS found in our study (12%) compares well to previous studies using the GA2LEN questionnaire (11-16%). This drop in prevalence is also seen in studies using nasal endoscopy (1.2 – 5.7%), but it remains unclear whether these different numbers correspond with the same subjects.

Current control of disease is measured in VAS items according to EPOS. In practice, most clinicians will apply the SNOT-22. Therefore, in **Chapter 6** we analyse correlation of individual SNOT-22 and VAS items; which was good (all ✗0.8). Thereafter we searched the best parity and cut-off point for individual SNOT-22 and VAS items, calculating sensitivity, specificity, positive predicting value, negative predicting value, a Receiver Operating Characteristic (ROC) curve and Area Under the Curve (AUC). Our major findings are a cut-off of SNOT≥3 (describing a 'moderate problem' or worse) and VAS>50. This means that in clinical practice or research, we can apply the SNOT-22 items in evaluating the degree of disease control in CRS, instead of using multiple instruments.

In **Chapter 7** we analysed the role of occupational exposure in CRS. Assuming that the need for undergoing endoscopic sinus surgery (ESS), or multiple ESS, reflects uncontrolled CRS; we confirmed occupational exposure as a risk factor, together with self-reported doctor-diagnosed asthma. Most frequently reported occupational agents were solvents (e.g. thinner, acetone, white spirit), cleaning products and disinfectants (incl. bleach), reactive chemicals (e.g. di-isocyanates, acrylates, epoxy resins), often used by painters, engineers, mechanics, cleaners, caretakers, housewives, nurses, car technicians, dentists and insulation workers. For the clinician this yields a potential preventable factor in the complex aetiology of CRS and asthma.

Chapter 8 comprises the general discussion, overall conclusions and future perspective of the use of PROMs in CRS.

SAMENVATTING

Chronische rhinosinusitis (CRS) is een multifactoriële chronische aandoening van inflammatie van slijmvliezen van de neus- en bijholten. De definitie van CRS is gebaseerd op patiënt-gebaseerde uitkomsten, arts-gebaseerde uitkomsten en op een minimale duur van 12 weken. In eerste instantie lijkt dit een duidelijke manier om de aandoening te definiëren, echter, schuilen er toch afwijkingen in deze verschillende perspectieven. Om in het verloop van de behandeling de mate van ziektecontrole te bepalen, is het essentieel om een instrument te gebruiken dat daadwerkelijk gevalideerd is voor de beoogde toepassing. Hiervoor is onder andere nodig dat men zich op de hoogte stelt van de sterke en zwakke kanten en de beperkingen van patiënt-gerapporteerde uitkomstmaten (PROMs).

In de toekomst zal er een toenemende mate gebruik gemaakt worden van het PROMs in de behandeling van CRS.

Dit proefschrift is erop gericht om meer inzicht te verkrijgen in de toepassing van PROMs, in het bijzonder de 22-item SinoNasal Outcome Test (SNOT-22), tijdens diagnose, evaluatie van behandeling en onderzoek.

In **Hoofdstuk 2** beschrijven we een uitgebreide beoordeling over het gebruik van vragenlijsten bij CRS en allergische rhinitis (AR). We leggen uit dat PROMs ziekte-specifieke kwaliteit van leven meten, wat anders is dan algemene kwaliteit van leven. PROMs leveren een gestandaardiseerde, gekwantificeerde en bondige samenvatting van de fysieke symptomen en functionele en psychosociale consequenties van de ziekte, voor de patiënt. We hebben een uitgebreide kwalitatieve beoordeling verricht van verschillende kenmerken van de veelgebruikte ziekte-specifieke kwaliteit van leven instrumenten bij CRS en AR. Hierbij beoordeelden we de instrumenten op het ontwerp, de beschrijving, geschiktheid, aanwezigheid van een validatie studie en de psychometrische kenmerken. Dit hoofdstuk kan beschouwd worden als een introductie op de kwalitatieve aspecten waar PROMs aan zouden moeten voldoen voor adequate toepassing in de klinische praktijk en bij onderzoek van CRS en AR.

In **Hoofdstuk 3** beschrijven we de validatie studie van de NL-SNOT-22. De SNOT-22 wordt beschouwd als de standaard vragenlijst in de beoordeling van de symptomen bij CRS, de beoordeling van ziekte-specifieke kwaliteit van leven en bij de evaluatie van behandeling bij CRS patiënten. Aannemende dat de prevalentie van CRS tussen 5 - 12% is, er dus in Nederland 0.9 – 2.1 miljoen patiënten met CRS zijn, blijkt er een belang van de psychometrische validatie van de Nederlandse versie van de SNOT-22. De NL-SNOT-22 heeft vergelijkbaar betrouwbare psychometrische eigenschappen met de originele SNOT-22 en haar vele vertalingen en culturele adaptaties. Het blijkt een robuust, betrouwbaar, geldig en responsief instrument voor gebruik in de dagelijkse klinische rhinologie praktijk.

In **Hoofdstuk 4** analyseren we of het mogelijk is om op basis van symptomen patiënten met CRS met polyposis (CRSwNP) te onderscheiden van patiënten met CRS zonder polyposis (CRSsNP). In de klinische praktijk zal de doorsnee patiënt met CRSwNP klagen over verminderd reukvermogen en een loopneus en de doorsnee patiënt met CRSsNP klagen over aangezichtspijn. In deze studie scoren patiënten met CRSwNP hoger op nasale symptomen als ‘loopneus’ en ‘verminderd

reukvermogen' en verwante symptomen zoals 'lastig om altijd tissues of een zakdoek te moeten meenemen' en 'de behoefte om herhaaldelijk de neus te snuiten'. Patiënten met CRSsNP scoren hoger op 'hoofdpijn'. Uiteindelijk is er geen significant verschil tussen de totale RhinoSinusitis Outcome Measurement-31 (RSOM-31) scores. We concluderen dat er significante verschillen zijn in scores op een aantal symptomen, maar dat er aanzienlijk overlappende symptomen zijn en het daardoor moeilijk blijft om op basis van alléén de klinische indruk onderscheid te maken tussen CRSwNP en CRSsNP.

In **Hoofdstuk 5** onderzoeken we de waarde van beeldvorming; een arts-gebaseerde parameter in de diagnose CRS. Vanuit het perspectief van de clinicus is het wenselijk om een bepaalde mate van bevestiging van mucosale inflammatie te krijgen. Naast de aanwezigheid en duur van symptomen maakt de betrokkenheid van mucosale inflammatie in de neusbijholten het onderscheid tussen andere nasale ziekten, zoals (niet-)allergische rhinitis, acute rhinosinusitis en ook sommige varianten van migraines of aangezichtspijn syndromen. Het onderscheid blijkt vooral moeilijk bij epidemiologisch onderzoek omdat de epidemiologische definitie van CRS is gebaseerd op uitsluitend symptomen. Wij waren de eersten die de klinisch gebaseerde prevalentie van CRS met behulp van beeldvorming in een (redelijk) normale populatie te bepaalden, te weten 3.0 of 6.4%, afhankelijks welke afkapwaarde werd toegepast (Lund Mackay (LM) ≥4 of LM≥0). Daarnaast vinden we een met andere onderzoeken vergelijkbare epidemiologisch-gebaseerde prevalentie van CRS (12%) die ook de GA2LEN vragenlijst gebruiken (11-16%). Deze daling in prevalentie wordt ook in andere studies waargenomen waar nasendoscopie wordt toegepast (1.2 – 5.7%), maar het blijft nog onduidelijk of deze aantallen corresponderen met dezelfde deelnemers binnen die populatie.

Volgens EPOS wordt de huidige mate van ziektecontrole gemeten aan de hand van VAS vragen. De meeste clinici zullen gebruik maken van de SNOT-22. Daarom analyseren we in **Hoofdstuk 6** de correlatie van individuele SNOT-22 en VAS vragen; welke goed was (allen ✗0.8). Vervolgens gingen we op zoek naar de beste pariteit en afkapwaarden voor individuele SNOT-22 en VAS vragen, door de sensitiviteit, specificiteit, positief voorspellende waarde, negatief voorspellende waarde, een Receiver Operating Characteristic (ROC) curve en Area Under the Curve (AUC) te berekenen. De meest belangrijke uitkomst was de overeenkomstige afkapwaarden van SNOT≥3 (dit beschrijft een 'gemiddeld probleem' of heviger) en een VAS>50. Dit betekent dat zowel in de klinische praktijk als in onderzoek, de SNOT-22 vragen toegepast kunnen worden om de mate van ziektecontrole van CRS te bepalen, in plaats van het moeten toepassen van meerdere instrumenten.

In **Hoofdstuk 7** analyseren we de rol van beroepsgebonden blootstelling aan bepaalde stoffen in CRS, als risicofactor voor ongecontroleerde ziekte. Als we kunnen aannemen dat het ondergaan van bijholte chirurgie (ESS), of meerdere ESS, een weerspiegeling is van ongecontroleerde CRS, dan is 'beroepsexpositie' een significante risicofactor, tezamen met 'zelf-gerapporteerde dokter-gediagnosticeerd astma'. De vaakst gerapporteerde stoffen waren oplosmiddelen (zoals thinner, aceton en spiritus), schoonmaakmiddelen en desinfectantia (inclusief bleekmiddel), reactieve chemicaliën (bv. Di-isocyanaten, acrylaten, epoxy harsen), die vaak worden toegepast door schilders, monteurs, schoonmakers, verzorgenden, huisvrouwen, verpleegkundigen,

automonteurs, tandartsen en monteurs van isolatiemateriaal. De clinicus heeft met deze kennis weer extra gereedschap in handen wat kan bijdragen in het mogelijk voorkomen van CRS of astma.

Hoofdstuk 8 bevat de algemene discussie, de belangrijkste conclusies en de perspectieven voor toekomstig gebruik van PROMs in CRS.

PORTFOLIO

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Courses

2022	Diving medicine level 1, Medical Examiner of Divers, Nederlandse Vereniging van Duikgeneeskunde (ECTS 0.5)
2022	International Course in Advanced Rhinoplasty Techniques, UMC Utrecht (ECTS 0.75)
2020	Teach the teacher I, Isala Academie, Zwolle (ECTS 0.25)
2019	Training Medisch Leiderschap, 'de klas van', Isala Zwolle (ECTS 0.25)
2019	European Board Exam of Facial Plastic and Reconstructive Surgery (ECTS 10)
2019	International Course on Reconstructive and Aesthetic Surgery of the Nose and Face, RadboudUMC, Nijmegen (ECTS 0.75)
2018	Speerpuntencursus XXI, Garderen (ECTS 0.5)
2018	International Course in Advanced Rhinoplasty Techniques, UMC Utrecht (ECTS 0.75)
2018	International Course on Reconstructive and Aesthetic Surgery of the Nose and Face, RadboudUMC, Nijmegen (ECTS 0.75)
2017	Basiscursus Duikgeneeskunde II, Scott Haldane Foundation (ECTS 0.25)
2016	Basiscursus Regelgeving & Organisatie (BROK) ECTS 1.0)
2016	European Head and Neck course, VUmc, Amsterdam (ECTS 0.5)
2016	Endoscopic Skull Base masterclass, Symposium and dissection, LUMC (ECTS 0.25)
2016	Mondpathologie cursus, VUmc, Amsterdam (ECTS 0.5)
2015	Mini-Around the nose, RadboudUMC, Nijmegen (ECTS 0.5)
2015	Medical Business Masterclass (ECTS 0.25)
2015	Mini-Oren cursus, RadboudUMC, Nijmegen (ECTS 0.5)
2014	KNO-Radiologie 'KNOR' cursus, Zaandam (ECTS 0.5)
2014	Mini-FESS cursus, AMC, Amsterdam (ECTS 0.5)
2013	Basiscursus Duikgeneeskunde I (ECTS 0.25)
2012	Coach de co (ECTS 0.25)
2012	Mini-Endoscopie cursus, UMCG, Groningen (ECTS 0.5)
2012	Practical Biostatistics (ECTS 1.5)
2012	Clinical Epidemiology (ECTS 1.0)
2012	Evidence Based Medicine in KNO, SKG (ECTS 0.5)
2011	Basiscursus Regelgeving & Organisatie voor Klinisch onderzoek (BROK) (ECTS 1.0)

Presentations

2021	Occupational exposure influences control of disease in chronic rhinosinusitis. *Oral presentation, European Rhinologic Society congress*, September 2021, Thessaloniki, Greece (ECTS 0.5)
2021	Control of disease in CRS – Assessing the correlation between SNOT-22 and VAS. *Oral presentation, European Rhinologic Society congress*, September 2021, Thessaloniki, Greece (ECTS 0.5)
2016	CRS epidemiologic research and imaging. *Oral presentation, European Rhinologic Society congress*, July 2016, Stockholm, Sweden (ECTS 0.5)

Portfolio (continued)

2016 CRS epidemiologisch onderzoek en beeldvorming. *Oral presentation,* KNO vergadering, april 2016, Nieuwegein, the Netherlands (ECTS 0.5)

2015 Correlation RSOM-31 and VAS. *Poster presentation, SERIN congress*, March 2015, Stockholm, Sweden (ECTS 0.5)

2014 Correlatie RSOM-31 en VAS. *Oral presentation,* KNO vergadering, april 2014, Nieuwegein, the Netherlands (ECTS 0.5)

2014 CRS and Quality of Life: correlation between RSOM-31 and VAS, *Poster presentation, European Rhinologic Society Congress*, June 2014, Amsterdam, the Netherlands (ECTS 0.5)

2014 Symptoms in CRS with and without nasal polyps. *Poster presentation, European Rhinologic Society Congress*, June 2014, Amsterdam, the Netherlands (ECTS 0.5)

2013 Difference in symptoms in chronic rhinosinusitis with and without nasal polyps. *Oral presentation, SERIN congress*, March 2013, Leuven, Belgium (ECTS 0.5)

2013 Intracraniële complicaties vanuit het KNO gebied, *Oral presentation, Jonkees Lecture AMC*, March 2013, Amsterdam, the Netherlands (ECTS 0.5)

2012 Verschil in symptomen tussen CRS met en zonder polyposis. *Oral presentation,* KNO vergadering, oktober 2012, Nieuwegein, the Netherlands (ECTS 0.5)

National and international conferences

2022 Congress of European Otorhinolaryngology – Head & Neck Surgery, Milano, Italy (ECTS 0.75)

2021 Congress of the European Rhinologic Society, Thessaloniki, Greece (ECTS 0.75)

2020 Congress of the European Academy of Facial Plastic and Reconstructive Surgery, virtual meeting (ECTS 0.5)

2019 Congress of the European Academy of Facial Plastic and Reconstructive Surgery, Amsterdam, the Netherlands (ECTS 0.75)

2017 Congress of European Otorhinolaryngology and Head and Neck Surgery, Barcelona, Spain (ECTS 0.75)

2016 Congress of the European Rhinologic Society, Stockholm, Sweden (ECTS 0.75)

2015 Symposium on Experiment al Rhinology and Immunology of the Nose, Stockholm, Sweden (ECTS 0.5)

2014 Congress of the European Rhinologic Society, Amsterdam, the Netherlands (ECTS 0.75)

2013 Symposium on Experiment al Rhinology and Immunology of the Nose, Leuven, Belgium (ECTS 0.5)

List of publications

2023 Dietz de Loos DAE, Cornet ME, Hopkins C, Fokkens WJ, Reitsma S. Measuring control of disease in Chronic Rhinosinusitis; assessing the correlation between SinoNasal Outcome Test-22 and Visual Analogue Scale item scores. *Rhinology* 2023 Feb 1;61(1):39-46.

2022 Dietz de Loos DAE, Cornet ME, Fokkens WJ, Reitsma S. Validation of the Dutch version of the 22-item Sino-Nasal Outcome Test (SNOT-22). *Rhinology Online*, 2022 Vol 5: 128 – 132.

2021 Dietz de Loos DAE, Ronsmans S, Cornet ME, Hellings PW, Hox V, Fokkens WJ, Reitsma S, Occupational exposure influences control of disease in patients with chronic rhinosinusitis: *Rhinology* 2021 Aug 1;59(4):380-386.

2019 Dietz de Loos DAE, Lourijsen ES, Wildeman MAM, Wolvers MDJ, Reitsma S, Fokkens WJ, Prevalence of chronic rhinosinusitis in the general population based on sinus radiology and symptomatology: *J Allergy Clin Immunol* 2019 Mar:143(3):1207-1214.

2017 Van der Poel NA, van Spronsen E, Dietz de Loos DAE, Ebbens FA, Early signs and symptoms of intracranial complications of otitis media in pediatric and adult patients - a different presentation? *Int J Pediatr Otorhinolaryngol*; 102 (2017): 56-60.

Portfolio (continued)

2013	Dietz de Loos DAE, Segboer CL, Gevorgyan A, Fokkens WJ, Disease specific quality of life questionnaires in rhinitis and rhinosinusitis: Review and evaluation. *Curr Allergy Asthma Rep* 2013; 13(2): 162-70.
2013	Dietz de Loos DAE, Hopkins C, Fokkens WJ. Symptoms in chronic rhinosinusitis with and without nasal polyps. *The Laryngoscope* 2013; 123(1):57-63.
2012	Hellings PW, Fokkens WJ, Akdis C, Bachert C, Cingi C, Dietz de Loos D, Gevaert P, Hox V, Kalogjera L, Lund V, Mullol J, Papadopoulos NG, Passalacqua G, Rondón C, Scadding G, Timmermans M, Toskala E, Zhang N, Bousquet J. Uncontrolled allergic rhinitis and chronic rhinosinusitis: where do we stand today? *Allergy* 2012; 68(1):1-7.
2010	Dietz de Loos DAE, Mesman JAJM, Zwart JJ, Roosmalen J van. Risicoselectie en substandaardzorg factoren bij ernstige fluxus post partum na thuispartus: LEMMoN audit. *Ned Tijdschr Obstet Gynaecol* 2010; 123:11-15
2009	Dietz de Loos DAE, Mesman JAJM, Zwart JJ, Roosmalen J van. Risicoselectie en substandaardzorg factoren bij eclampsie en HELLP in de eerste lijn: LEMMoN audit. *Ned Tijdschr Obstet Gynaecol* 2009; 122:330-34

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OVER DE AUTEUR

Dirk Albert Elisa Dietz de Loos werd geboren op 3 september 1985 in Den Haag. Hij groeide op in Wassenaar, waar hij zijn VWO-diploma behaalde aan het Rijnlands Lyceum in 2003. Aansluitend startte hij de opleiding Geneeskunde aan de Universiteit Leiden en was tijdens de studie actief lid van studentenvereniging 'Minerva'. In 2009 volgde hij zijn coschappen in zowel het Leids Universitair Medisch Centrum (LUMC) als Westeinde ziekenhuis, Bronovo ziekenhuis, Haga ziekenhuis in Den Haag en Sint Vincentius Ziekenhuis in Paramaribo, Suriname. Zijn wetenschappelijke stage volgde hij bij prof. dr. J. van Roosmalen, gynaecoloog, perinatoloog in het LUMC. Tijdens de coschappen werd zijn interesse voor het praktische en gevarieerde vak Keel- Neus- Oorheelkunde gewekt. In maart 2011 behaalde hij zijn artsendiploma en werd hij aansluitend aangenomen voor een onderzoeks- en opleidingsplek in het Academisch Medisch Centrum in Amsterdam, bij prof. dr. W.J. Fokkens en prof. dr. S. van der Baan. In februari 2018 rondde hij zijn opleiding tot kno arts af onder prof. dr. F.G. Dikkers, na perifere stages in het VU Medisch Centrum in Amsterdam, Kennemer Gasthuis in Haarlem en OLVG in Amsterdam. Aansluitend volgde hij het fellowship 'plastische en reconstructieve aangezichtschirurgie' onder leiding van dr. K.I. Ingels in het RadboudUMC, Nijmegen en bij dr. W.M. Boek in het ziekenhuis Gelderse Vallei, Ede, waarna hij in december 2021 de International Board certificering behaalde (IBCFPRS). Inmiddels werkt hij als kno arts in de Isala Klinieken te Zwolle en is duikerarts (MED-1 en expertgroep duikgeneeskunde). Dirk is in 2014 getrouwd met Arjenne en samen hebben zij vier kinderen, Emma (2015), Gijs (2016), Merel (2018) en Daan (2020).

&

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