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Dirk Dietz de Loos, MD, Evelijn S. Lourijsen, MD, Maarten A.M. Wildeman, MD PhD, Nicole .J.M. Freling, MD PhD, Marije D.J. Wolvers, PhD, Sietze Reitsma, Wytse J. Fokkens, MD PhD



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Prevalence of chronic rhinosinusitis in the general population based on sinus radiology and symptomatology.

Dirk Dietz de Loos MD¹, Evelijn S. Lourijzen MD¹, Maarten A.M. Wildeman MD PhD¹, Nicole .J.M. Freling MD PhD², Marije D.J. Wolvers PhD¹, Sietze Reitsma¹, Wytke J. Fokkens MD PhD¹

1. Department of Otorhinolaryngology, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands

2. Department of Radiology, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands

Corresponding author:

W.J. Fokkens

Department of Otorhinolaryngology

Room A2-230

Amsterdam UMC,

University of Amsterdam,

Meibergdreef 9

1105 AZ Amsterdam

The Netherlands

w.j.fokkens@amc.nl

Fax: +31205669573

Tel: +31205663789

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Clinical implications

There is a poor alignment of reported symptoms and objective findings in CRS, which urges us to reconsider the construct of CRS diagnosis.

Capsule summary

We found a prevalence of 2.9% or 6.1% ‘Clinically based CRS’, for cut-offs of $LM \geq 4$ or $LM > 0$ respectively, in a ‘normal’ (non-rhinologic imaging of the head) population, based on nasal symptoms and imaging abnormalities.

Keywords

Chronic rhinosinusitis, epidemiology, imaging, population,

List of abbreviations

AR Allergic Rhinitis

ARS Acute Rhinosinusitis

CRS Chronic Rhinosinusitis

CT Computed Tomography

ECR Expected Count Ratio

ECRHS European Community Respiratory Health Survey

EPOS European Position Paper on Rhinosinusitis and Nasal Polyps

GA2LEN Global Allergy and Asthma European Network

LM Lund - Mackay

MRI Magnetic Resonance Imaging

NAR Non-Allergic Rhinitis

NSAID Non-steroidal anti-inflammatory drugs

OR Odds ratio

PND Postnasal drip

RSI Rhinosinusitis symptom inventory

SD Standard deviation

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 sino-nasal opacification on imaging.

Methods: Subjects who underwent a CT or MRI scan of the head for any non-rhinologic indication were asked to fill in the GA2LEN 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 scan.

Results: 834 subjects were included. 107 subjects (12,8%) had epidemiologically based CRS according to EPOS. Of these subjects 50 % had a LM score of 0; 26% had a LM score of 1-3 and 23% had a LM score of ≥ 4 . Twenty-five subjects (3.0%) had clinically based CRS (based on LM ≥ 4) and 53 subjects (6.4%) had clinically based CRS (based on LM > 0). AR was reported by 167 subjects (20%). In subjects that did not report upper airway symptoms: 57% had a LM 0; 30% had a LM 1-3 and 12% had a LM ≥ 4 .

Conclusion: We found a prevalence of 3.0 – 6.4% of clinically based CRS (depending on LM cut-off point, LM ≥ 4 or LM > 0 respectively) in a relatively randomly selected group of subjects.

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.

EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) provides two 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, like in asthma, symptoms lack good correlation with objective measurements, due to a lack of gold standard.(2, 3) This might probably 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 due to the 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. (11, 12)

Earlier, we evaluated the value of nasal endoscopy in the epidemiologically based diagnosis of CRS.(12) In this GA2LEN Follow Up study, a sample of subjects with CRS, asthma, asthma and CRS, and 'no asthma nor CRS' was invited to undergo nasal endoscopy, blinded for symptom status and found a sensitivity of nasal endoscopy of 62% in a population with symptom-based CRS. This might imply a 1/3 overestimation of 'true' or 'clinical' CRS in patients when employing 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 due to radiation exposure and too expensive to undertake hundreds of Magnetic Resonance Imaging (MRI)-scans.

Previous epidemiological studies found 20-40% Computed Tomography (CT)- scan abnormalities in symptom negative populations.(13-15) Also common cold has been shown to give sinus abnormalities on imaging in a majority of otherwise healthy subjects, usually dissolving in a few weeks.(16) In allergic rhinitis, opacification of the sinuses is infrequent

and only minimal during natural seasonal exposure (17) with an average LM score comparable to a normal population. (18)

In a non-sinusitis population a Lund-Mackay score from 0-5 has been described. (19)

In this study, we primarily describe the prevalence of epidemiologically (symptom-) based versus the prevalence of clinically (imaging-) based CRS in a non-rhinologic population. 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 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 CT scan (LM=0).

Methods

Study design

We conducted a cross-sectional survey of consecutive subjects referred to our radiology department for imaging of the head for non-rhinologic indications. All consecutive subjects that underwent Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of the head (patients undergoing CT-sinus were excluded) were asked to fill in the GA2LEN questionnaire on upper and lower airway symptoms [supplementary table 1]. The questionnaire was sent one 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 i.e. due to confusion, aphasia or severe illness, incomplete imaging or artefacts of the nasal sinus prohibiting complete Lund-Mackay scoring, history of trans-sphenoidal pituitary surgery, history of radiotherapy in sinonasal area or 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 is a survey developed by the The Global Allergy and Asthma Network of Excellence (GA2LEN) funded by the EU and was based on validated questions from the European Community Respiratory Health Survey (ECRHS) (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, acute rhinosinusitis (ARS), asthma and allergic rhinitis (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 (NF) according to Lund-Mackay scoring system (25). Opacification on imaging was classified into: LM score of 0 (LM0), LM of 1-3 (LM1-3), LM1 and up (LM>0) and LM of 4 and up (LM≥4). For the full scoring system, see supplementary table 2.

Definitions used:

Epidemiologically based CRS: Continuous presence of two 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 twelve weeks during the last year (see supplementary table 3).

Epidemiologically based current CRS: Continuous presence of two 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 three months.

Clinically based CRS: Continuous presence of two 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 twelve weeks during the last year, together with a Lund-Mackay score >0 or ≥ 4 ($LM>0$ or $LM\geq 4$).

Clinically based current CRS: Continuous presence of two 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 twelve weeks, together with a Lund-Mackay score ≥ 4 .

Acute Rhinosinusitis (ARS): Presence of an acute episode of 'blocked nose', 'coloured nasal discharge' and 'facial pressure or pain' during at least at least 10 days.

Allergic rhinitis (AR): Positive answer to 'Do you have nasal allergies including hay fever?'.
Current AR: Allergic Rhinitis (self-reported hay fever) with current nasal obstruction and/or rhinorrhoea.

No nasal symptoms: A negative answer on any nasal symptom and on the questions for hay fever symptoms in the last year, and doctor-diagnosed CRS.

Asthma: Positive answer to 'Do you have asthma?'.

History of smoking: Positive answer to 'Have you ever smoked during at least a year?'.

Current smoker: Positive answer to 'Have you ever smoked during at least a year?' in combination with a positive answer on 'Have you smoked the last month?'.

Former smoker: Positive answer to 'Have you ever smoked during at least a year?' in combination with a negative answer on '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, what is the prevalence of clinically based CRS, was answered by describing the prevalence of epidemiologically based CRS and clinically based CRS, both using a cut-off point of $LM > 0$ and $LM \geq 4$ and calculating prevalence of current CRS.

Similarly, the prevalence of current CRS (both epidemiologically and clinically based) was determined and its overlap with (epidemiologically and clinically based) CRS and AR.

We constructed a contingency table of the five main categories of indication for imaging (neurovascular, cerebral tumors, orbital, mastoid, and other) and the epidemiological CRS diagnosis, and tested whether both variables were independent (Pearson's chi-square-test of independence).

Variables associated with opacification on imaging

The secondary research question, what symptoms and findings are associated with opacification on imaging, was analysed in three ways: by analysing predictors of having a Lund-Mackay score of 4 or higher ($LM \geq 4$), which is the characteristic that bridges the epidemiological and the clinical diagnosis of CRS (1), by analysing predictors of the total LM score (2), and by analysing having a Lund-Mackay score of 0 ($LM = 0$) (3).

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

Variables associated with a positive LM score ($LM \geq 4$)

Univariate logistic regression models were used for models (1), to study the association of a selection of relevant symptoms and descriptive factors (see Table 4a), and the outcome variable. Odds ratios, 95% confidence intervals 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 of $LM \geq 4$, compared with the 4 EPOS symptoms alone. Based on the total number of subjects with a $LM \geq 4$ ($n = 119$) we could include approximately 12 variables in a multivariable logistic regression analysis. The multivariable model for $LM \geq 4$ was built in two steps: in the first step, all 4 EPOS symptoms ('nasal obstruction', 'rhinorrhoea / PND (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 below .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, odds ratios, 95% confidence intervals, p -values, the Nagelkerke R^2 and the area under the curve were reported.

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 Lund-Mackay score in this specific sample was very much like a count score (heavily left-skewed, 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, like we did models 1 and 3. The same procedures were conducted as for the dichotomous variable $LM \geq 4$: run univariate models, run a multivariable model with EPOS symptoms only, and run a series of multivariable model that included EPOS symptoms as well as other factors. Effects (the natural logs of regression coefficients B) are quantified as ‘expected count ratios’ (ECR), which displays the multiplicative effect of a variable, or the presence of a symptom, on the LM-score. Predictive count ratios with 95% confidence intervals and p -values of all univariate tests and the final multivariable model were reported.

Variables associated with having no opacification ($LM = 0$).

The goal of model 3, predicting a Lund-Mackay 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 $LM=0$ was built by applying backward selection ($p \leq .05$) on the variables that had $p < .1$ 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. Odds ratios, 95% confidence intervals, p -values, the Nagelkerke R^2 and the area under the curve were reported.

Analysis of season influence

We performed Mann-Witney U tests to analyse the influence of seasons on the LM-scores. We used two distinctions: May to July compared to the rest of the year (“pollen1”), and June to September (“pollen2”) compared to the rest of the year.

Additionally, we checked how many participants who reported to have ‘loss of smell’ also had an epidemiological CRS diagnosis.

Results

Participants

In total 2051 subjects were invited to participate of which 1003 responded. Of these, 169 subjects refused participation or had incomplete imaging. 1048 subjects did not respond at all. Age and gender of the responders and non-responders were comparable, but the subjects who did not respond or actively refused more often had brain damage and/or very serious disease, rendering them unable to answer or probably too ill to care. Finally, 834 subjects were included, with a mean age of 53 years (SD: 16, range 8-89). 63% were female and 37% were male. The subject characteristics are specified in Table 1.

Subjects had imaging for a number of neurological (e.g. neurovascular or aneurysm evaluation, evaluation of intracranial tumours, including pituitary), ophthalmological (e.g. intra-orbital tumours, graves and trauma) and otological (e.g. 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 epidemiological CRS diagnosis ($X^2(4) = 4.27$, $p = 0.37$).

Prevalence of CRS

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

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 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). It did not make any difference 67 (7.7%) subjects reported

current CRS. Of these subjects 45% had a LM score >0 ; 17% had a LM score ≥ 4 (see Table 3).

LM score in other groups

Furthermore, we investigated whether having AR would influence the LM scores in subjects with CRS. AR was reported by 167 (20%) subjects, of which 54% had LM scores > 0 and 20% had LM scores ≥ 4 . Fifty-seven subjects (6.9%) had epidemiologically based CRS and AR of which 58% had LM score > 0 and 25% had a LM score ≥ 4 .

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 ($N_{\text{pollen1}} = 22$, $N_{\text{other1}} = 812$, $U = 9,139.5$, $p = .84$). When shifting this period to June to September to account for time of AR to induce CRS symptoms (arbitrarily taken as one 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 to scans that were made in the rest of the year. The medians were zero in both groups; the mean LM scores were 1.1 and 1.4 respectively ($N_{\text{pollen2}} = 99$, $N_{\text{other2}} = 735$, $U = 32,241.5$, $p = .04$).

Variables associated with positive LM score ($LM \geq 4$)

To investigate which symptoms were associated with a $LM \geq 4$, we conducted univariate logistic regression. Table 4a shows that ‘male gender’ ($OR = .55$, $p = .002$), ‘history of smoking’ ($OR = 1.79$, $p = .004$), ‘allergic rhinitis’ ($OR = 1.65$, $p = .026$), ‘woke-up short of breath in the last 12 months’ ($OR = 1.72$, $p = .048$), ‘nasal obstruction’ ($OR = 2.10$, $p = .002$), ‘rhinorrhoea/PND’ ($OR = 1.84$, $p = .031$) and ‘loss of smell’ ($OR = 1.75$, $p = .034$) were associated with increased odds of having a $LM \geq 4$. Table 4b shows association of the EPOS symptoms with $LM \geq 4$, this model has a Nagelkerke R^2 of .023. The area under the curve was .579, which indicated that EPOS symptoms are incapable of predicting $LM \geq 4$. Several prognostic factors were significantly associated with $LM \geq 4$ (Table 4c) in a multivariable regression model that also included all 4 EPOS symptoms: ‘male gender’ and ‘history of smoking’ were associated with increased odds for having a $LM \geq 4$. The model had a R^2 of .061. The area under the curve was 0.625.

Variables associated with total LM score

To avoid dichotomisation 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 5a). 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 gender', 'history of smoking', 'asthma', 'allergic rhinitis', 'acute rhinosinusitis', 'itchy rashes', and 'occupation in cleaning' were associated with higher LM scores. Table 5b shows the model with EPOS symptoms only. In a model that includes all 4 EPOS symptoms, 'male gender', 'history of smoking', 'itchy rashes' and 'occupation in cleaning' are significantly associated with higher LM scores (Table 5c).

Variables associated with LM score = 0

To investigate also whether it was possible to predict a LM score of zero, we conducted logistic regression. It was again not possible to produce a model that reliably predicted LM0 (Table 6a and 6b).

Discussion

We set out to find the prevalence of clinically based CRS based in CT scan in a (rather) normal population, which was 3.0% or 6.4%, depending on which cut off point is used ($LM \geq 4$ or $LM > 0$). 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) (CRSwNP 2.6%; CRSsNP 5.8%), (26) but higher than the earlier version of the (KNHANES) (1.2%) found by Kim et al. in South Korea. (9) The prevalence of epidemiological based CRS found in this study (12%) compares well to these studies (both $\pm 11\%$), to our previous studies using the GA2LEN questionnaire (14-16%), (8, 24), and to other existing literature where it is found to be 5 – 12 % with significant variation between countries. (6, 7, 10, 27).

Although the role of allergy in CRSwNP and CRSsNP continues to be controversial, allergic rhinitis might be a potential relevant factor influencing the LM scores in the current population. (28) Seasonal variation has been described with a paradoxical improvement of LM scores in-season. (18) In the current data, also an improvement (although very slight, and based on small numbers) of LM scores was seen, but only when the period July-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 their poor alignment, as the subjects with current CRS (complaints in the past three months) show the exact same distribution as the ones with epidemiological CRS (complaints for 3 months somewhere in the past year; Table 3). The CRS symptom most strongly associated with CT abnormalities in the paranasal sinuses is nasal obstruction. Other symptoms that constitute epidemiological 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% fulfils the EPOS criteria for CRS. Conversely, having abnormalities on imaging is also a common finding: 44% of the subjects

had a LM score >0 , of whom roughly one third had a score ≥ 4 . Combining both modalities will lead to reduction of the prevalence (eliminate false-positives), while at the same time inducing false-negatives. For example: the prevalence of clinically based CRS is found to be 2.9% when taking a LM score of ≥ 4 (a cut-off that is well in line with other studies). (19, 29-32) This eliminates three-quarters of the epidemiological based CRS, half of whom had no CT abnormalities, and a quarter of whom did have LM-scores between 1 and 3. Other studies have shown that the same trade-off is true when combining the epidemiological diagnosis with findings on nasal endoscopy.(9, 12). To make matters worse, there is only moderate agreement between nasal endoscopy and radiological data. (33-36) We wondered whether it was possible to exclude the diagnosis 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 epidemiological CRS symptoms, have poor model fits. Using other techniques for variable selection (such as the LASSO technique) did not improve this (not shown). As such, predicting clinically based CRS from questionnaires remains hard. In other words, the construct for the diagnosis of CRS needs careful further consideration as 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 (such as nasal obstruction and discharge) depending on severity and frequency of these symptoms.(37) This study knows several limitations. As the study population underwent imaging of the head mainly for neurological evaluation (Table 2), the mean age (53 years) was above that in the general population in the Netherlands (39 years). (38, 39) As the prevalence of CRS is lower in the elderly, we performed a sub-analysis excluding all subjects over 70 years old. This did not lead to any remarkable change in the overall epidemiological based CRS prevalence, nor 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. Since 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 lower the prevalence. Finally, the number of questions in the QA2LEN questionnaire about CRS and AR are limited, nor did we do skin prick testing. Ideally, we could have used more extensive

questionnaires like the SNOT-22. (40, 41). However, also these more extensive QOL questionnaires have not shown to be correlated to CT-scan abnormalities in otorhinolaryngologic patients. (40)

Conclusions

The clinically based prevalence of CRS in the Dutch population based on radiological examination is 2.9%. There is a poor alignment of reported symptoms and objective findings, which urges us to reconsider the construct of CRS diagnosis.

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Table 1 – Subject Characteristics

	n/total n ^a	% or mean (SD)
Age (years)	834/834	53 (16) ^b
Gender (female)	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		
Caucasian	748/834	89.7%
African	28/834	3.4%
Asian	20/834	2.4%
Mediterranean	17/834	2.0%
Other	21/834	2.5%

CRS: Chronic Rhinosinusitis, **Current CRS:** Chronic rhinosinusitis in the past three months, **Asthma:** Self-reported Asthma, **AR:** Allergic Rhinitis (self-reported hay fever), **Current AR:** Allergic Rhinitis (self-reported hay fever) with current nasal obstruction and/or rhinorrhoea, **Pack-years:** number of packs of cigarettes smoked per day * 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: 42-64 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. 720 participants filled in both questions.

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=0	LM 1-3	LM$\geq$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%)

CRS: Chronic Rhinosinusitis, **Current CRS:** Chronic rhinosinusitis in the past three months,

Current CRS: Chronic rhinosinusitis in the past three months, **AR:** Allergic Rhinitis (self-reported hay fever),

Current AR: Allergic Rhinitis (self-reported hay fever) with current nasal obstruction and/or rhinorrhoea, **No symptoms:** no nasal symptoms, **LM=0:** No opacifications on imaging,

LM $\geq$ 4: Lund-Mackay score $\geq$ 4.

Table 4a – Univariate Logistic regression – Odds ratio on LM≥4

Variable	Odds ratio	p-value	95% Confidence Interval
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
Gender (female)	0.55	.002	0.37 – 0.81
Smoke	1.79	.004	1.20 – 2.68
AR	1.65	.026	1.06 – 2.57
Woke up short of breath 12mo	1.72	.048	1.01 – 2.94
Wheezing 12mo	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 >3months/yr	0.84	.60	0.44 – 1.59
Did you ever have asthma	1.49	.18	0.83 – 2.67
Admitted to hospital due to asthma	0.99	.99	0.22 – 4.50
Exacerbation of asthma last 3 months	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 healthcare	0.93	.88	0.35 – 2.43
Occupation in cleaning	0.59	.48	0.14 – 2.55

PND: Postnasal drip, Smoke: History of smoking, AR: Positive answer on 'hay fever', 12mo: in the last 12 months.

Table 4b – Multivariable Logistic regression – Prediction model for LM≥4 EPOS symptoms
Nagelkerke R²: .023

EPOS symptoms	Odds ratio	p-value	95% Confidence Interval
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)

Table 4c – Multivariable Logistic regression – Prediction model for LM $\geq$ 4
Nagelkerke R²: .061

Variable	Odds ratio	p-value	95% Confidence Interval
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
Gender (female)	0.57	.005	0.38-0.85
Smoke (ever)	1.69	.029	1.13-2.55

PND: Postnasal drip, Smoke: History of smoking.

Table 5a – Univariate Generalized Linear Model Analysis – Effect of variable on increase of LM-score.

Variable	Expected count ratio	p-value	95% Confidence Interval
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
Gender (female = 1)	.63	.000	.49 – .80
Smoke	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 months	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 months	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

PND: Postnasal drip, AR: Positive answer on 'hay fever', Smoke: History of more than one year of smoking, Itchy rashes: itching skin in the last 12 months, ARS: Acute Rhinosinusitis. 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.

Table 5b – Multivariate Generalized Linear Model Analysis –

Effect of EPOS symptoms on increase of LM-score.

Variable	Expected count ratio	p-value	95% Confidence Interval
Obstruction	1.53	.03	1.04 – 2.23
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

Table 5c – Multivariate Generalized Linear Model Analysis – Effect of variable on increase of LM-score.

Variable	Expected count ratio	p-value	95% Confidence Interval
Obstruction	1.53	.03	1.04 – 2.23
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
Gender [†] (female = 1)	.67	.002	.52 – .86
Smoke	1.37	.02	1.06 – 1.78
Itchy rashes	.67	.01	.49 – .92

PND: Postnasal drip,
Smoke: History of

more than one year of smoking.

Table 6a – Univariate logistic regression – Odds ratio on LM=0

Variable	Odds ratio	p-value	95% Confidence Interval
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
Gender (female)	1.87	< .001	1.40 – 2.48
Smoke	0.76	.05	0.58 – 1.00
AR 12mo	0.60	.006	0.41 – 0.86
Woke up short of breath 12mo	0.76	.21	0.50 – 1.17
Wheezing 12mo	1.09	.68	0.72 – 1.67
Woke up with chest tightness 12mo	0.96	.85	0.64 – 1.45
Woke up coughing 12mo	1.03	.85	0.75 – 1.41
Coughing up sputum on most days >3months/yr	1.08	.72	0.70 – 1.66
Did you ever have asthma	0.58	.02	0.37 – 0.92
Admitted to hospital due to asthma	1.45	.51	0.48 – 4.37
Exacerbation of asthma 12mo	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 6b – Multivariable logistic regression – Odds ratio on LM=0

Variable	Odds ratio	p-value	95% Confidence Interval
Gender (female)	2.06	<.001	1.49 – 2.85
AR 12mo	0.58	.004	0.40 – 0.84

AR 12mo: Positive answer on 'hay fever' and on the question 'Have you been troubled by nasal allergies in the last 12 months?'. Note: results after backward selection ($p_{out} = .05$) of a multivariable model that included 7 predictors: loss of smell, gender, 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 positives, so 118 out of 326 patients for whom LM = 0 was predicted, in fact had a LM > 0. Area under the curve = .607.

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
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	Select one option

	d. Latin-American e. Hindustani f. Mediterranean g. Other (please specify):	
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	≥12 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.