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ORIGINAL RESEARCH

Chronic Airflow Limitation, Lower Respiratory Symptoms, COPD and Chronic Rhinosinusitis in a Middle-Aged Population: The Swedish CArdioPulmonary bioImage Study (SCAPIS). A Link Between the Lower and Upper Airways

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Purpose: Chronic rhinosinusitis (CRS) is related to asthma and chronic obstructive pulmonary disease (COPD). However, combined data on CRS, pulmonary function, lower airway symptoms, and cigarette smoking from the general population are lacking. The current study investigates the relationships between CRS and chronic airflow limitation (CAL), lower airway symptoms and COPD in a middle-aged population of ever-smokers and never-smokers.

Patients and Methods: All subjects from the Swedish CArdioPulmonary bioImage Study (SCAPIS) were included. Subjects underwent spirometry after bronchodilation. Chronic airflow limitation was defined as FEV_1/FVC ratio <0.7. Computed tomography imaging of the thorax was performed to detect the presence of emphysema, and the subjects answered a comprehensive questionnaire on CRS, lower airway symptoms, asthma, chronic bronchitis, and cigarette smoking habits.

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Results: In total, 30,154 adult subjects in the age range of 50–64 years were included. The prevalence of CRS was 5.6%. CRS was more-prevalent among subjects in the following categories: CAL (7.6%), lower airway symptoms (15.7%), current smokers (8.2%), asthma (13.6%), never-smokers and ever-smokers with COPD (17.6% and 15.3%, respectively), emphysema (6.7%), and chronic bronchitis (24.5%). In the adjusted regression model, CRS was significantly associated with CAL (OR 1.40), lower airway symptoms (OR 4.59), chronic bronchitis (OR 6.48), asthma (OR 3.08), and COPD (OR 3.10).

Conclusion: In this national, randomly chosen population sample of more than 30,000 middle-aged men and women, CRS is associated with CAL, lower airway symptoms, chronic bronchitis, asthma, and COPD. In patients with CRS and in patients with lower airway inflammation, it is important to consider the inflammatory status of the entire airway system.

Keywords: asthma, chronic bronchitis, chronic obstructive pulmonary disease, emphysema, CRS, smoking

Introduction

Chronic rhinosinusitis (CRS) affects 11% of the European population and 8.1–9.6% of the Swedish population in the age range of 15–75 years, and is associated with asthma and chronic obstructive pulmonary disease (COPD).[1] CRS, which is a multifactorial, inflammatory disease of the respiratory mucosa of the nose and sinuses, has a pronounced negative impact on the health-related quality of life of affected persons.[2] The disease encompasses several subtypes that typically involve remodeling of the sinonasal mucosa and, in some patients, the formation of sinonasal polyps.[3] The diagnosis of CRS includes symptoms of nasal blockage, nasal discharge, facial pain and/or pressure, as well as loss of the sense of smell. Examination with flexible or rigid nasal endoscopy and/or sinus computed tomography (CT) is required for the diagnosis in cases of more-advanced or treatment-recalcitrant disease.[3] For epidemiological studies of large population samples, a symptom-based definition of CRS according to The European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS) is used.[3,4]

Both epidemiological and clinical data support the idea of an association between the upper airway inflammation in CRS and inflammatory lower airway diseases, such as asthma and COPD.[5–10] Lung function has, however, only been studied in limited cohorts of hospitalized CRS patients, and due to the exclusion of patients with lower respiratory disease and the lack of spirometry after bronchodilation, the results are inconclusive.[11] To the best of our knowledge, there are no previous studies in which CRS was specifically studied in relation to dynamic spirometry, including bronchodilation and lower airway symptoms, in such a large, random population sample.

Chronic airflow limitation (CAL) is an "umbrella term" for airway obstruction, which is defined as a spirometry ratio of FEV_1/FVC of <0.7 post-bronchodilatation.[12,13] The combination of CAL and lower airway symptoms in patients who are exposed to tobacco smoke is strongly indicative of a COPD diagnosis. The most-important lower airway symptoms are cough, wheeze, dyspnea, and sputum production. The presence of these symptoms is critical for a diagnosis of asthma, COPD or chronic bronchitis (CB).

Exposure to tobacco smoke is a common risk factor for CRS, COPD, CB and emphysema.[14,15] As tobacco smoking decreases in the Western hemisphere, the proportions of tobacco smoke-related COPD and CRS cases will decrease. However, there are 20–40% never-smokers in the cohort with COPD, and this proportion is expected to increase.[16,17] It is, therefore, important to study CRS and COPD in never-smokers.[18]

The present study investigates how CRS in the population relates to several indicators of inflammatory lower airway disease. These indicators include the presence of CAL, lower airway symptoms, asthma, COPD, CB, and emphysema, as assessed in both smokers and never-smokers. The underlying hypothesis for this study is that these symptoms and signs of inflammatory lower airway diseases are related to CRS, with the strongest correlation being between CRS and CAL.

Materials and Methods

Study Design and Study Population

This is a cross-sectional, nationwide study of randomly selected men and women, in the age range of 50–64 years, from the Swedish general population. All subjects were invited to participate in the Swedish CArdioPulmonary bioImage Study (SCAPIS), which is a prospective, multicenter study of cardiopulmonary diseases and symptoms. Data were collected during the period of 2013–2018 at all the major universities in Sweden: in Gothenburg, Stockholm, Uppsala,

Linköping, Lund and Umeå. Totally, 59,909 subjects were invited, and 30,154 subjects were included in the study with an overall participation rate of 50.3%.[19] All residents in Sweden have a personal and unique identification number. At random, the participants were invited by sending out information about to study and how to contact the study centers. The most common causes for not participating in the study were: inability to get in contact with the subject, declining participation due to lack of time, sickness or language difficulties. The full study protocol and design have been described previously and informed consent was collected from each participant as the first procedure.[20]

While the SCAPIS study involves a wide range of clinical parameters, for this study we have used data related to upper and lower airway diseases and smoking habits. All the participants performed spirometry after bronchodilation and underwent a low-dose CT scan of the thorax. They answered an extensive respiratory questionnaire, including questions on CRS, asthma, CB, and emphysema, as well as lower respiratory symptoms, ie, cough, wheeze, and dyspnea.

The study was approved by the Swedish Ethical Review Authority (Dnr. 2022–00302-01).

Definitions of CRS and CAL

CRS was defined according to the EPOS 2020 criteria as the presence of CRS cardinal symptoms for at least 12 weeks. The CRS cardinal symptoms consist of two major symptoms, ie, nasal blockage/obstruction/congestion, and nasal discharge (anterior/posterior nasal drip), and two minor symptoms, ie, facial pain/pressure and reduction or loss of the sense of smell. The diagnosis of CRS was based upon having (at least) two major symptoms or having one major and one minor symptom.[3]

CAL was defined as an FEV_1/FVC ratio of <0.7 after bronchodilation with a β2-receptor agonist.[21]

Definition of Specific Lower Airway Symptoms

Lower airway symptoms were defined as the presence of one or more of the symptoms: cough, wheeze or dyspnea.

Cough was defined as affirmative responses to both of the following questions: "Do you usually cough when you don´t have a cold?" and "Do you cough on most days for at least 3 months each year?". The subject also had to report these symptoms for at least 2 years.

Wheeze was defined as an affirmative response to the question: "Do you usually have whistling or wheezing in your chest when you breathe?"

Dyspnea was defined according to the modified Medical Research Council (mMRC) scale, using a mMRC score of ≥2.

Definitions of Asthma and Chronic Bronchitis

Asthma was defined as self-reported, physician-diagnosed asthma.[22]

Chronic bronchitis was defined as chronic cough and sputum production for at least 3 months a year for at least 2 consecutive years.[21,23]

Definitions of Cigarette Smoking and Emphysema

Cigarette smoking was classified into three categories: *never-smokers, ex-smokers*, and *current smokers*. The group of never-smokers contained those who stated that: "No, I have never smoked". The group of ex-smokers was made up of individuals who had smoked for at least 1 year in the past but who had not smoked in the last year. Current smokers answered in the affirmative to the question: "Do you smoke?" and they qualified this by choosing between "Yes, regularly" or "Yes, occasionally". The group of ever-smokers consisted of both ex-smokers and current smokers. For those with a history of smoking, the numbers of pack-years were calculated. Emphysema was diagnosed by a skilled thoracic radiologist who visually interpreted and judged the thoracic computed tomographic images as indicating the presence or absence of emphysema.[24]

Definitions of Age, Sex and BMI

Age and sex were self-reported, and height and weight were measured at enrollment.

Body mass index (BMI) was calculated as: $weight/(height)^2$.

Spirometry and Computed Tomography

Dynamic spirometry, including forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC), was conducted at least 15 minutes after the inhalation of 400 µg of salbutamol. The procedure was performed with the subject in a sitting position and wearing a nose clip. The Jaeger MasterScreen PFT (Vyaire Medical, Mettawa, IL, USA) was used for all the measurements, which were performed according to the ATS/ERS standards.[25] The Global Lung Function Initiative (GLI) equations based on age, gender and height were used to calculate predicted values.[26]

The CT scanning of the thorax was performed using the Somatom Definition Flash scanner with the Stellar detector (Siemens Healthcare, Forchheim, Germany).

Definition of COPD

COPD was defined as having the combination of CAL and lower airway symptoms. The COPD group was further stratified according to cigarette smoking status.

Never-Smokers

- $CAL_{\ symptoms-}$ CAL without any lower airway symptoms
- $CAL_{\ symptoms+}$ COPD in never-smokers

Ever-Smokers

- $CAL_{\ symptoms-}$ CAL without any lower airway symptoms
- $CAL_{\ symptoms+}$ "Classic" COPD

Statistical Analyses

Descriptive statistics are presented as frequency with the percentage and median with the interquartile range for categorical and continuous variables, respectively. Confidence intervals (CI) for prevalence ratios (PR) were calculated by the Wald method on log-transformed estimates. The Odds Ratios (ORs) for CRS were calculated using a multivariable logistic regression model, adjusted for sex, age and BMI. To avoid assumptions of linearity for the log-odds data, we included age as a 2-degree polynomial and BMI and pack-years as a restricted cubic spline with knots place at the 5^{th}, 35^{th}, 65^{th} and 95^{th} percentiles, where the distribution among ever-smokers was used for pack-years. For Figure 1, a cubic restricted spline with knots at the 5^{th}, 27.5^{th}, 50^{th}, 72.5^{th} and 95^{th} percentiles were used. All the statistical analyses were performed using the SAS ver. 9.4M7 (SAS Inc., Cary, NC, USA). Statistical significance was defined as $P < 0.05$, and 95% CI was used for all confidence intervals. All tests were two-sided.

Results

CRS in Relation to CAL, Emphysema, Lower Airway Symptoms, Asthma, CB and Cigarette Smoking

In total, 30,154 adult subjects in the age range of 50–64 years were included. The population had an equal sex distribution, the median age was 57 years, and the median BMI was 26.3 kg/m^2 (Table 1). CRS was reported by 5.6% of the study population. There was no significant difference between men and women regarding the prevalence of CRS (5.4% and 5.7%, respectively, data not shown). CRS was more-prevalent in subjects with CAL (7.6%), emphysema (6.7%), lower airway symptoms (15.7%), asthma (13.6%), CB (24.5%), and in current smokers (8.2%). In the subjects with CRS, the reported level of cigarette smoking was 10 pack-years for those with CAL, 20 pack-years for subjects with emphysema, 5 pack-years for subjects with lower airway symptoms, and 6 pack-years for those with CB.

In the multivariable logistic regression model for CRS in relation to different FEV_1/FVC ratios, adjusted for sex, age, BMI, pack-years and cigarette smoking, there was a near-linear increase of FEV_1/FVC ratios <0.75 (Figure 1).

The prevalence of CRS in the unadjusted model was increased in relation to CAL, emphysema, lower airway symptoms, asthma, CB and cigarette smoking (Table 2). Less-prominent associations to CRS were found in relation to CAL (PR 1.43) and emphysema (PR 1.25). Strong associations were found between CRS and lower airway symptoms

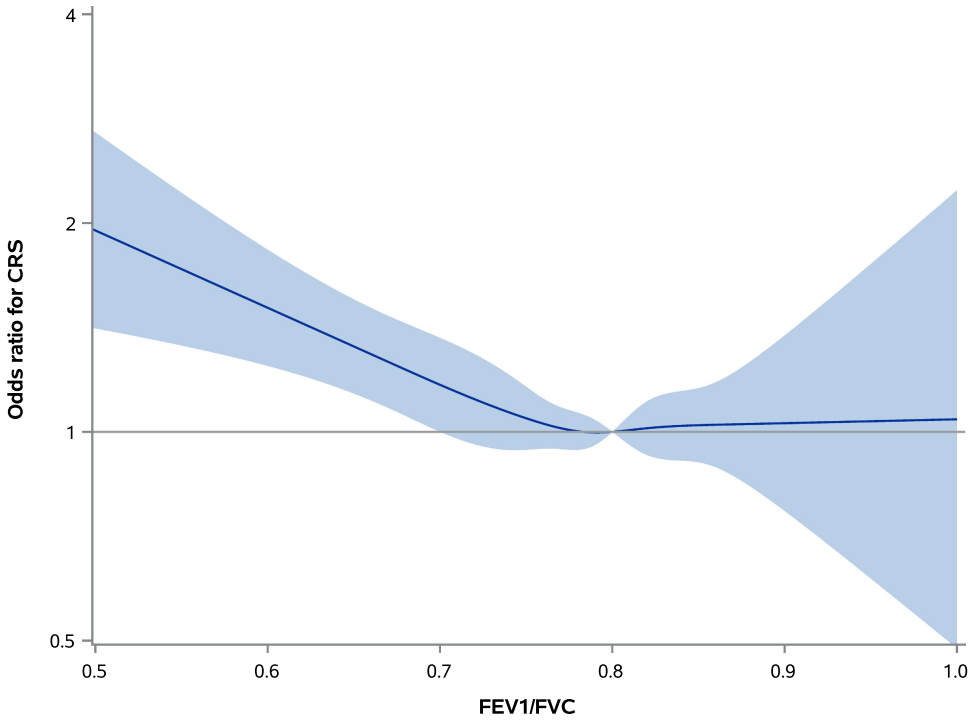

Figure 1 Odds ratio for CRS in the relation to the quota of FEV1/FVC. Adjusted Odds ratios (ORs) including 95% CI (the shaded blue area) from the multivariable logistic regression model for chronic rhinosinusitis (CRS) in relation to different ratios of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC). The model is adjusted for sex, age, BMI, pack-years and cigarette smoking. FEV1/FVC as cubic restricted spline with overall p=0.001.

(PR 4.26), asthma (PR 2.84) and chronic bronchitis (PR 5.47). Associations to CRS were also found for both current-smokers and ex-smokers (PR 1.7 and 1.18, respectively).

In the adjusted multivariable model, the OR for CRS remained significantly associated with CAL, lower airway symptoms, CB, asthma and COPD (ever-smokers and never-smokers), but not with emphysema OR 1.15 (95% CI 0.93–1.42) (Figure 2A). The very same pattern was observed when the study population was divided into men and women. However, the ORs for men with lower airway symptoms, chronic bronchitis and COPD were numerically slightly higher than for women (Figure 2B).

In a sub-analysis, the OR for CRS was analyzed in relation to the number of reported lower airway symptoms. The OR for CRS increased with the number of reported lower airway symptoms. The strongest association was seen for subjects who reported all of the lower airway symptoms (cough, wheeze and dyspnea) (Figure 3).

CRS in Relation to the CAL Subgroups

Table 3 displays the demographics of CAL in relation to the presence or absence of lower airway symptoms in never-smokers and ever-smokers. CRS was prevalent in ever-smokers with CAL and lower airway symptoms (15.3%), here defined as "classic COPD". It was, however, even further increased in never-smokers with CAL and lower airway symptoms (17.6%), defined as "COPD in never-smokers". There were higher proportions of men in the two CAL groups of never-smokers, both with and without lower airway symptoms.

In an unadjusted model, the never-smokers with CAL and lower airway symptoms showed the highest PR of 3.33 (95% CI 2.41–4.60) for CRS, in comparison with the ever-smokers with CAL and lower airway symptoms who showed a PR of 2.90 (95% CI 2.39–3.51) (Table 3 and Table 4). No difference was observed between the two groups of CAL with no lower airway symptoms, regardless of smoking status.

The results for the lower airway symptom of dyspnea defined by the mMRC scale, in relation to the OR for CRS adjusted for age, sex, BMI, asthma and cigarette smoke are shown in Figure 4. A higher mMRC score was related to an increased OR for CRS.

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Table 1 Demographics of the Study Population

		% (N)	CRS % (N)	Sex, Male % (N)	Age, Years*	BMI, kg/ m^2*	Pack- Years*	FEV_1 (L)*	FEV_1% of pred.*	FEV_1/FVC*
All		100 (30,154)	5.6 (1,598)	48.6 (14,646)	57 (54–61)	26.3 (23.9–29.4)	0 (0–12)	3.2 (2.7–3.8)	102.4 (93.4–111.2)	0.79 (0.75–0.82)
CAL	-	90.5 (26,914)	5.3 (1,361)	47.8 (12,857)	57 (54–61)	26.4 (23.9–29.4)	0 (0–11)	3.2 (2.7–3.9)	103.6 (95.2–112.1)	0.79 (0.76–0.83)
	+	9.5 (2,829)	7.6 (204)	56.8 (1,608)	59 (55–63)	25.9 (23.5–28.8)	10 (0–28)	2.8 (2.3–3.4)	88.1 (78.3–97.3)	0.67 (0.63–0.69)
Emphysema	-	94.3 (27,891)	5.4 (1,445)	48.4 (13,500)	57 (54–61)	26.4 (24–29.4)	0 (0–10)	3.2 (2.7–3.8)	102.8 (93.9–111.5)	0.79 (0.75–0.82)
	+	5.7 (1,688)	6.7 (107)	53.9 (909)	59 (55–63)	25.6 (23.1–28.5)	20 (4–33)	3 (2.4–3.6)	96.3 (84.2–106.5)	0.73 (0.67–0.79)
Lower airway	-	85 (24,232)	3.7 (881)	49 (11,878)	57 (54–61)	26 (23.7–28.9)	0 (0–10)	3.2 (2.7–3.9)	103.4 (94.9–112)	0.79 (0.75–0.82)
Symptoms†	+	15 (4,271)	15.7 (648)	45 (1,922)	58 (54–62)	28.3 (25.3–32)	5 (0–23)	2.9 (2.4–3.5)	96.2 (86–106.3)	0.77 (0.72–0.81)
Asthma	-	91.7 (26,621)	4.8 (1,241)	49.1 (13,060)	58 (54–61)	26.3 (23.9–29.3)	0 (0–12)	3.2 (2.7–3.8)	102.9 (94–111.6)	0.79 (0.75–0.82)
	+	8.3 (2,422)	13.6 (318)	39.8 (963)	57 (53–61)	27.1 (24.2–30.4)	0 (0–12)	2.9 (2.5–3.5)	97.1 (87.1–107.1)	0.76 (0.71–0.80)
Chronic	-	95 (27,358)	4.5 (1,202)	48.1 (13,168)	57 (54–61)	26.3 (23.9–29.3)	0 (0–11)	3.2 (2.7–3.8)	102.7 (93.8–111.4)	0.79 (0.75–0.82)
Bronchitis	+	5 (1,437)	24.5 (337)	53 (762)	58 (54–62)	27.3 (24.5–30.7)	6 (0–26)	3 (2.5–3.6)	97.5 (86.1–107.7)	0.77 (0.71–0.81)
Cigarette smoking										
Never-smokers		50.4 (14,707)	4.8 (697)	51 (7,500)	57 (53–61)	26.1 (23.7–29)	0 (0–0)	3.3 (2.8–3.9)	103.4 (94.7–111.7)	0.8 (0.76–0.83)
Ex-smokers		36 (10,508)	5.7 (585)	44.8 (4,706)	59 (55–62)	26.7 (24.3–29.8)	10 (4–19)	3.1 (2.7–3.7)	102.5 (93.6–111.5)	0.78 (0.74–0.82)
Current smokers		13.6 (3,977)	8.2 (303)	48.8 (1,942)	57 (54–61)	26.4 (23.9–29.4)	22 (12–34)	3 (2.5–3.6)	98.2 (87.5–107.7)	0.76 (0.71–0.81)

Notes: *Median (IQR); †cough, wheeze or dyspnea. Without and with the specified diagnosis are indicated by "-" and "+", respectively. Demographics of the study population regarding chronic rhinosinusitis (CRS), sex, age, body mass index (BMI), pack-years, FEV_1 (L), FEV_1% of pred., and the FEV_1/FVC ratio in relation to (without/with) chronic airflow limitation (CAL), emphysema, lower airway symptoms, asthma and chronic bronchitis, as well as cigarette smoking.
Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range.

Table 2 Prevalence Ratio of CRS

Variable		CRS (%)	PR (95% CI)	n Missing
All		5.6	–	
CAL	– +	5.3 7.6	(ref) 1.43 (1.24–1.64)	1,322
Emphysema	–	5.4	(ref)	1.294
	+	6.7	1.25 (1.03–1.51)	
Lower airway symptoms[†]	– +	3.7 15.7	(ref) 4.26 (3.87–4.68)	508
Asthma	–	4.8	(ref)	678
	+	13.6	2.84 (2.53–3.19)	
Chronic bronchitis	– +	4.5 24.5	(ref) 5.47 (4.91–6.10)	521
Cigarette smoking				801
Never-smokers		4.8	(ref)	
Ex-smokers		5.7	1.18 (1.06–1.31)	
Current smokers		8.2	1.70 (1.49–1.93)	

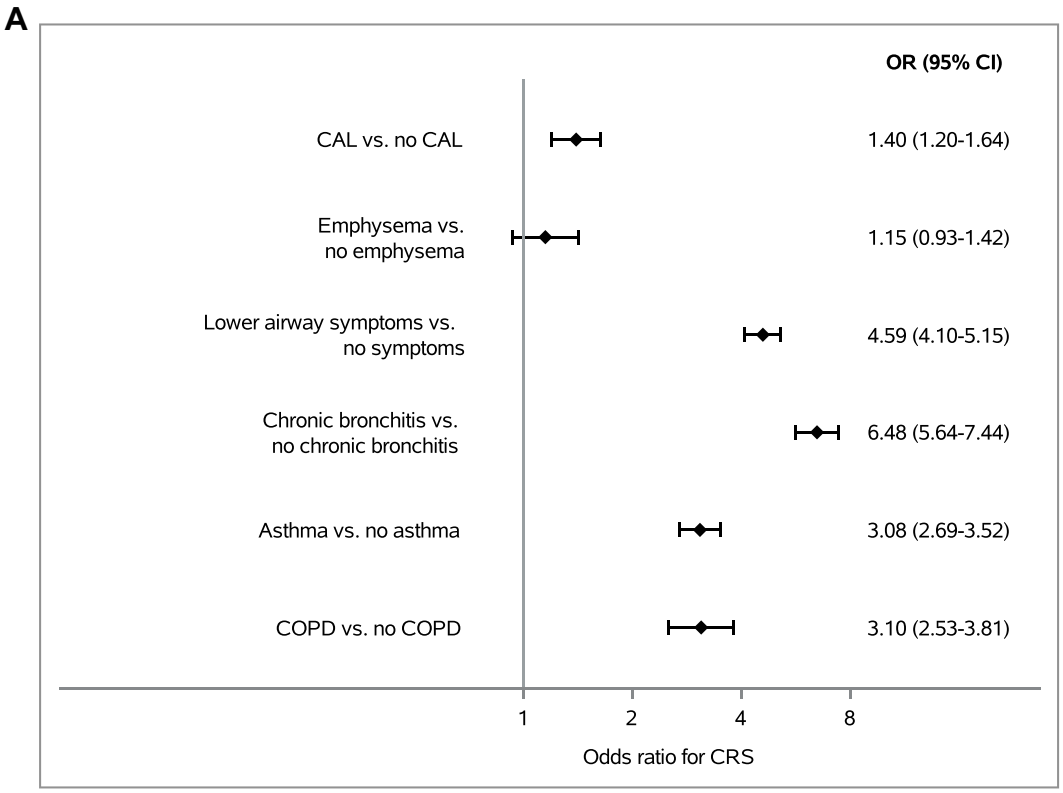
Notes: [†]Cough, wheeze or dyspnea. Without and with the specified diagnosis is indicated by "-" and "+", respectively. Unadjusted statistical model of the prevalence and prevalence ratio (PR) of chronic rhinosinusitis (CRS) in relation to chronic airflow limitation (CAL), emphysema, lower airway symptoms, asthma, chronic bronchitis and cigarette smoking.
Abbreviations: PR, prevalence risk; CI, confidence interval.

Discussion

In this large, middle-aged, randomly chosen population sample, CRS was present in 5.6% of the subjects, with no difference between men and women. CRS was four-times more prevalent in subjects with CB and almost three-times more prevalent in subjects with lower airway symptoms. In the multivariable regression model adjusted for age, sex, BMI and cigarette smoking, CAL was associated with an increased OR for having CRS. Surprisingly, lower airway symptoms displayed a higher OR than CAL even if CB was most-pronounced. In both never-smokers and ever-smokers with COPD, the observed pattern was remarkably consistent and, surprisingly, unrelated to cigarette smoking. The OR for having CRS was slightly higher in men than in women with lower airway symptoms, chronic bronchitis and COPD.

Previous studies of random population cohorts have reported a higher prevalence of CRS than was seen in the present study. In a European multicenter study, the overall prevalence was 8.1–9.6% in the Swedish centers.[1] However, in that study, the subjects had a much broader age span than in our study. Furthermore, a newly published paper from a Norwegian cohort where the subjects were aged 16–50 years, showed a prevalence of 6.6%[7] in accordance with the results from our study.

An important strength of this study is the availability of post-bronchodilatory spirometry data for more than 30,000 subjects. To the best of our knowledge, this is the largest study to date using spirometry after bronchodilation, showing that CRS is associated with a persistent narrowing of the lower airways. In two previous population-based studies, an FEV_1/FVC ratio <0.7 was significantly related to having upper airway symptoms, including CRS. However, bronchodilators were not used in those studies and, therefore, it cannot be ruled out that the subjects with asthma affected the results.[9,27] In the present study, we have used the concept of CAL, which is defined as FEV_1/FVC <0.7 after bronchodilation. One earlier clinical study from Denmark have found an association between CRS and COPD.[6] Hence, our study further strengthens the link between CRS and decreased lung function after bronchodilation. Interestingly, for the whole study population, the OR for having CRS increased with reduced FEV_1/FVC ratio, showing



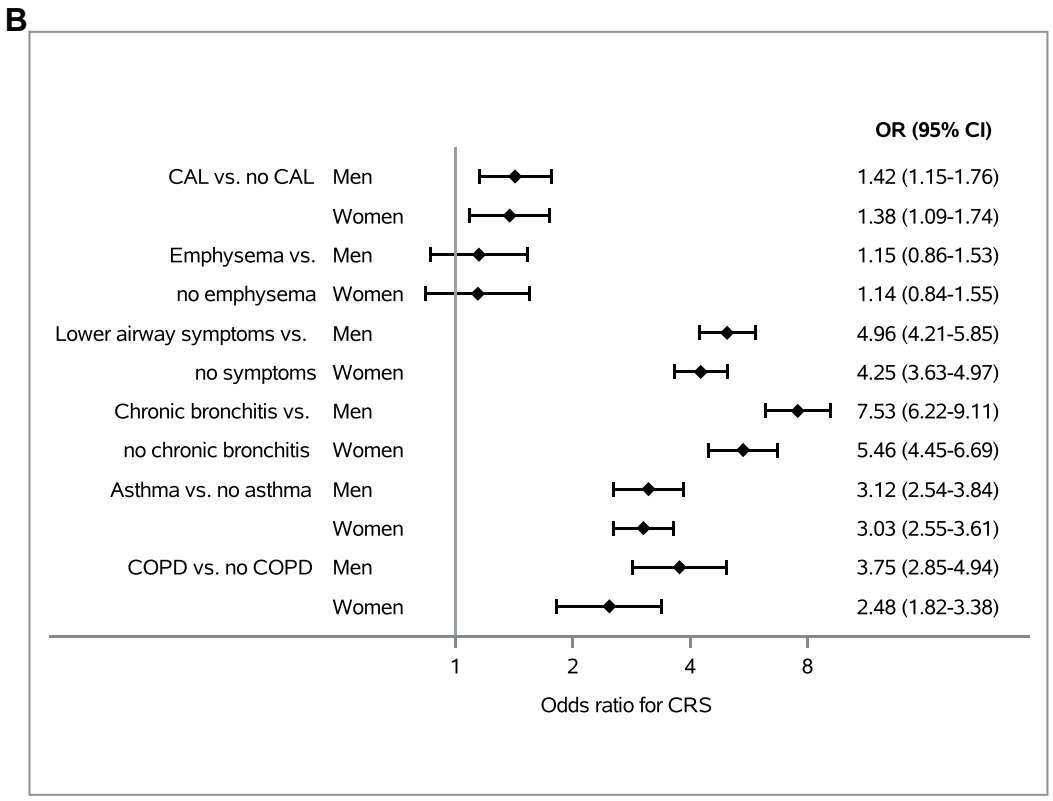


Figure 2 (**A** and **B**) Odds ratio for having CRS in relation to lower airway diseases and symptoms. Multivariable logistic regression model of Odds ratio (OR) and 95% CI for chronic rhinosinusitis (CRS) in relation to chronic airflow limitation (CAL), emphysema, lower airway symptoms (cough, wheeze or dyspnea), chronic bronchitis, asthma and COPD in six individual models adjusted for age, sex, BMI and cigarette smoking. COPD was defined as having CAL and at least one lower airway symptom, irrespective of cigarette smoking status. The whole study population is shown (**A**) and divided into men and women (**B**).

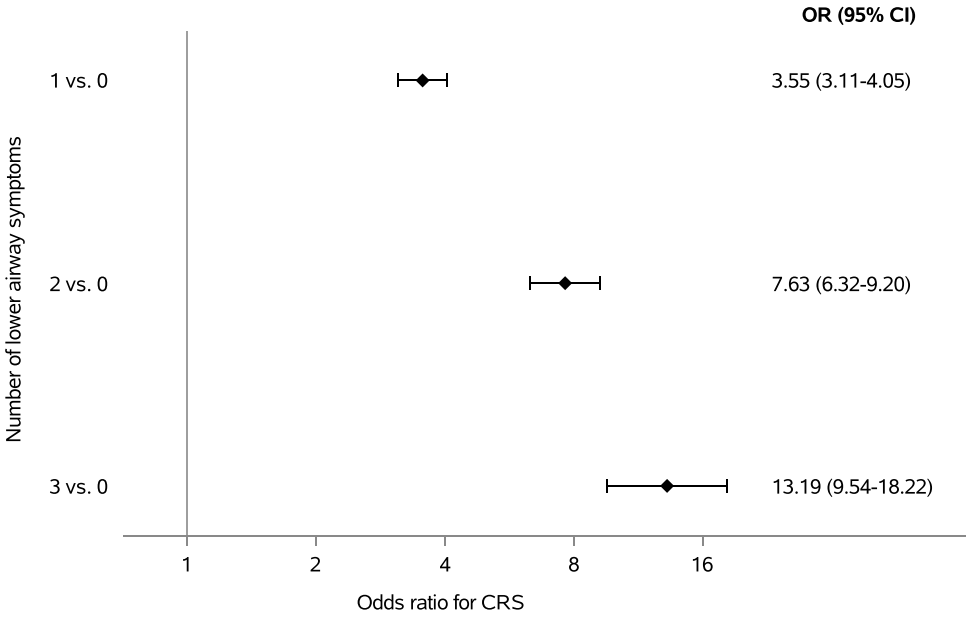


Figure 3 Number of lower airway symptoms in relation to the Odds ratio of having CRS. Logistic regression model of the Odds ratio (OR) and 95% CI for chronic rhinosinusitis (CRS) in relation to the number of reported lower airway symptoms (cough, wheeze, dyspnea = mMRC≥2), adjusted for age, sex, BMI, and cigarette smoking status.

an almost linear correlation below 0.8. When adjusting for relevant confounding factors, the effect of CAL, in relation to CRS, remained significant, albeit of small magnitude. Unexpectedly, the lower airway symptoms showed a much stronger association with CRS than with CAL. It must be borne in mind, however, that CRS is a prevalent and heterogeneous disease, and that our study design does not enable us to stratify CRS subjects into either specific clinical phenotypes or levels of disease severity. In a population-based design, many subjects who report CRS also have mild disease, as compared with hospital cohorts, and they may not even have been in contact with the healthcare system.

A major finding of this study is that there is a strongly increased prevalence ratio of having CRS in subjects with CB. Few epidemiological studies have investigated the relationship between inflammatory sinonasal disease and CB, and even fewer have explored the association between CRS and CB. An early population-based study from Sweden showed that the presence of nasal symptoms was a risk factor for developing CB.[10,28] Furthermore, in a longitudinal study of a Norwegian population cohort, CRS was associated with an increased risk of developing CB during a 5-year observation period.[7] CRS and CB are characterized by excessive production of troublesome airway secretions, which may be the key to understanding the inflammatory mechanisms that link these two diseases.

The lower airway symptoms analyzed in this study in relation to CRS are important clinical symptoms for asthma, COPD and CB. Subjects who reported one or more of these symptoms had a three-fold increase in the PR of having CRS. In the sub-analysis, we found that the number of lower airway symptoms, from one to three, increased the OR of having CRS, which indicates that CRS is associated with more-complex lower airway disease. We also studied the symptom of dyspnea, expressed on the mMRC scale, in a similar way. We found a significant relationship between increasing severity of dyspnea and the OR for having CRS, with the highest OR for the highest mMRC score observed in Category 4. Again, this could indicate that patients with more-severe lower airway disease are more likely to have CRS.

The PR for CRS in this study was higher in subjects with asthma, as expected. CRS has previously been associated with asthma, in particular certain endotypes, such as eosinophilic inflammation.[29] Thus, the results of this study confirm earlier findings. Low-dose CT images of the thorax were available for the entire study population. However, we were unable to find any relationship between CRS and emphysema in the adjusted statistical model.

In this study, we have defined patients with COPD as having both CAL and lower airway symptoms. The subjects with COPD had a significantly increased OR of having CRS in the adjusted model, irrespective of cigarette smoking. Previous population-based studies that showed such an association did not use post-bronchodilatory spirometry and did not use the EPOS

Table 3 CRS, CAL and COPD

	% (N)	CRS % (N)	PR (95% CI)	Sex, Male % (N)	Age, Years*	BMI, kg/m^2*	Pack-Years*	FEV1 (L)*	FEV1% of pred.*	FEV_1/FVC*
No CAL	91 (26,914)	5.3 (1,361)	Reference	47.8 (12,857)	57 (54–61)	26.4 (23.9–29.4)	0 (0–11)	3.2 (2.7–3.9)	103.6(95.2–112.1)	0.79 (76–82.6)
CAL										
Never-smokers										
$CAL_{symptoms\ -}$	2.3 (692)	3.7 (25)	0.69 (0.47–1.02)	67.5 (467)	58 (54–62)	25.1 (23–27.3)	0 (0–0)	3.2 (2.7–3.8)	92.5 (84–100.9)	0.68 (0.66–0.69)
$CAL_{symptoms\ +}$	0.6 (179)	17.6 (31)	3.33 (2.41–4.60)	59.8 (107)	58 (54–62)	27.5 (24.2–30.9)	0 (0–0)	2.7 (2.2–3.2)	85.1 (74.4–92.2)	0.66 (0.63–0.68)
Ever-smokers										
$CAL_{symptoms\ -}$	3.9 (1,141)	4.2 (47)	0.79 (0.60–1.05)	53.9 (615)	60 (56–63)	25.8 (23.5–28.4)	17 (8–29)	2.8 (2.4–3.4)	90.4 (80.6–98.2)	0.67 (0.64–0.69)
$CAL_{symptoms\ +}$	2.2 (643)	15.3 (96)	2.90 (2.39–3.51)	48.7 (313)	60 (56–63)	26.9 (23.9–30.8)	29 (16–39)	2.4 (1.9–3)	80.2 (69.1–89.6)	0.64 (0.59–0.68)

Notes: *Median (IQR). Demographics of the study population characterized by chronic airflow limitation (CAL), and cigarette smoking: never-smokers and ever-smokers (ex-smokers and current-smokers), as well as without or with lower airway symptoms (cough, wheeze or dyspnea) ("symptoms-" and "symptoms+", respectively). CAL + lower airway symptoms= COPD.

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Table 4 Prevalence Ratio of CRS in CAL and COPD

Variable	CRS (%)	PR (95% CI)
No CAL	5.3	Reference
CAL		
Never-smokers		
$CAL_{symptoms\ -}$	3.7	0.69 (0.47–1.02)
$CAL_{symptoms\ +}$	17.6	3.33 (2.41–4.60)
Ever-smokers		
$CAL_{symptoms\ -}$	4.2	0.79 (0.60–1.05)
$CAL_{symptoms\ +}$	15.3	2.90 (2.39–3.51)

Notes: This table is an extract from Table 3. The prevalence risk (PR) of chronic rhinosinusitis (CRS) for subjects with chronic airflow limitation (CAL), divided into the groups of cigarette smoking: never-smokers and ever-smokers (ie, ex-smokers and current smokers) and also without or with *lower airway symptoms* (cough, wheeze or dyspnea) ("symptoms-" and "symptoms+", respectively). CAL + lower airway symptoms= COPD.

definition of CRS.[9,27,30] We also analyzed the relationship between CRS and COPD in ever-smokers and never-smokers. When dividing the COPD group into "classic" COPD, which is typically related to tobacco smoke exposure, and COPD in never-smokers, the PR of having COPD in never-smokers was somewhat higher than that of having COPD in ever-smokers. This strongly suggests that lower airway symptoms in never-smokers represent an important subgroup or phenotype of patients who require a more-comprehensive investigation. To our knowledge, this is the first study showing that COPD in never-smokers as well as CAL is associated with CRS. It also implies that COPD and its relationship to CRS is more complex than the common risk factor of tobacco smoke exposure. In fact, the factors that drive this inflammation in never-smokers is largely unknown. In

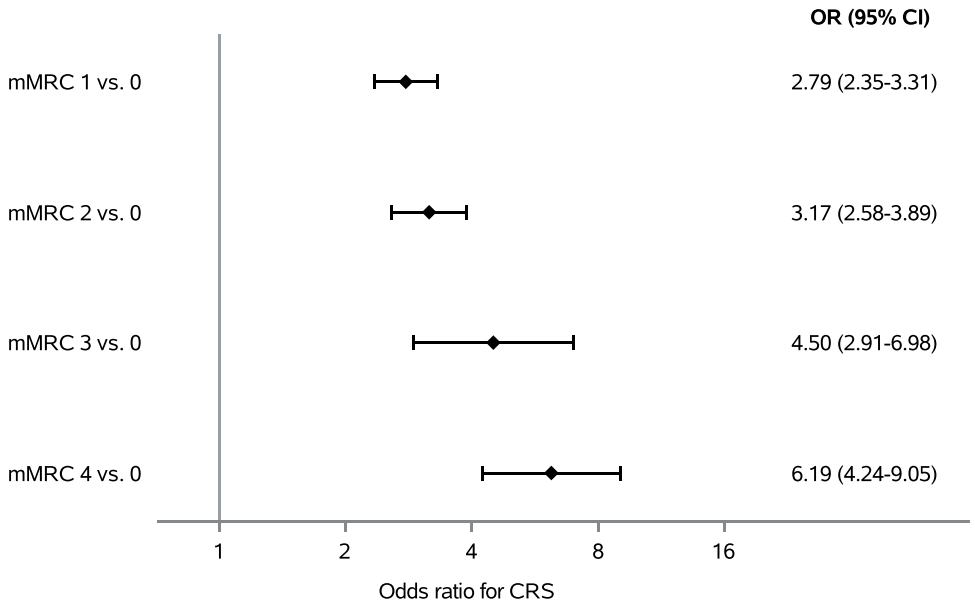

Figure 4 Level of mMRC in relation to Odds ratio of having CRS. Logistic regression model of the Odds ratio (OR) with 95% CI of chronic rhinosinusitis (CRS) in relation to the symptom dyspnea defined as mMRC 0–4. Model is adjusted for age, sex, BMI, asthma and cigarette smoking status.

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general, the data regarding never-smokers are limited, although it has been reported that the presence of respiratory symptoms among never-smokers without CAL predicts COPD exacerbations and hospitalizations for pneumonia.[31] In addition, supportive data indicate that never-smokers without CAL exhibit increased odds of respiratory symptoms.[12]

This study was performed in a large, well-defined and random population sample. For practical reasons, the nose was not examined clinically, and no sinonasal CT scans were performed. This limits the CRS diagnosis to self-reported sinonasal symptoms. In the absence of a nasal examination, it is not possible to rule out other causes of nasal obstruction, such as nasal septal deviation. Furthermore, we were not able to stratify CRS according to severity. The age span of 50–64 years is narrow, and this reduces the ability to draw general conclusions related to the whole adult population. Nevertheless, the age span is relevant when studying CRS in relation to CAL, since both CRS and CAL are prevalent conditions within this age range.[2] The participation rate in the SCAPIS study was 50.3%, which is why the risk of selection bias must also be considered.[19] Lastly, self-reporting of symptoms might be susceptible to reporting bias, in contrast to objective measures data reported by a physician. Further studies are needed to better understand, describe and investigate the phenotypes of inflammation of the upper airways in patients with CRS and its relationship to concomitant lower respiratory tract disease. The ultimate goal is to gain an understanding that can facilitate and improve diagnosis and treatments for these patients with combined diseases of the upper and lower airways.

Conclusions

In this random, population-based national cohort of 30,154 adult subjects, chronic rhinosinusitis is associated with chronic bronchitis, lower airway symptoms, chronic airflow limitation, asthma, and both ever-smokers and never-smokers with COPD. Clinicians should be aware of the association with lower airway disease in patients with CRS. This study also highlights the importance of obtaining a medical history that includes respiratory symptoms linked to both the upper and lower airways.

Abbreviations

BMI, body mass index; CAL, chronic airflow limitation; CB, chronic bronchitis; CI, confidence intervals; CRS, chronic rhinosinusitis; COPD, chronic obstructive pulmonary disease; CT, computed tomography; EPOS, The European Position Paper on Rhinosinusitis and Nasal Polyps; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GLI, Global Lung Function Initiative; IQR, interquartile range; OR, Odds ratio; PR, prevalence ratio; SCAPIS, Swedish CArdioPulmonary bioImage Study.

Data Sharing Statement

The datasets analysed are not publicly available because they were used under licence for the current study. They are available upon reasonable request, please contact the corresponding author.

Ethics Approval and Informed Consent

The SCAPIS multicenter study was approved by the ethics committee at Umeå University, Sweden (Dnr 2010-228-31 M) and adheres to the Declaration of Helsinki. Written informed consent was obtained from all participants. The current study was approved by the Swedish Ethical Review Authority (Dnr. 2022-00302-01).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Dr Anders Andersson reports personal fees from Astra-Zeneca, Chiesi, and TEVA, outside the submitted work. Dr Apostolos Bossios reports grants paid to institution from AstraZeneca, Chiesi, and GSK, outside the submitted work; and Head of Assembly 5 (Airway diseases, asthma, COPD, and chronic cough), European Respiratory Society; co-chair of the Nordic severe asthma network; member of the steering committee of SHARP, ERS severe asthma Clinical Research Collaboration; member of the steering committee of the Swedish National Airway Register. Professor Magnus Sköld reports grants from Pharmaceutical companies paid to his institution for consultancy, outside the submitted work. The authors declare that they have no other competing interests in this work.

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