Dose-dependent relationship between nocturnal gastroesophageal reflux and chronic rhinosinusitis in a middle-aged population: results from the SCAPIS pilot*

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Abstract

Background: Gastroesophageal reflux (GER) has been associated with several upper- and lower-airway diseases. It would be plausible if nightly occurring reflux via laryngopharyngeal reflux (LPR) might affect the upper airways. Still, the role of nocturnal gastroesophageal reflux (nGER) in chronic rhinosinusitis (CRS) is not fully established. The aim of this population-based study was to investigate the association between nGER and CRS.

Methodology: This cross-sectional population-based study comprises 1,111 randomly selected subjects from Gothenburg, Sweden, aged 50-64 years. The study is based on self-reported validated questionnaires. CRS was defined according to EPOS criteria. nGER was reported in relation to frequency.

Results: CRS was more common among subjects with nGER than in those without (13 vs. 4.8%). There was a dose-response association between the frequency of nGER episodes and the risk of having CRS. In the logistic regression adjusted for (age, sex, BMI, educational level, smoking, and asthma). CRS was associated with nGER, OR 1.43 and the odds ratio increased if episodes were reported "almost every night", OR 4.6.

Conclusions: The study shows an association between nocturnal GER and CRS in a middle-aged population. The revealed dose dependency supports, though does not prove causality.

Key words: chronic rhinosinusitis, gastroesophageal reflux, epidemiology, laryngopharyngeal reflux, rhinology

Introduction

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease affecting the mucosa of the nose and paranasal sinuses. The overall prevalence of self-reported CRS according to the European Position paper on rhinosinusitis and nasal polyps (EPOS) criteria varies between 5.5-28% worldwide and is approximately 10% in Europe including Sweden [(1)]. CRS has a prevalence peak at 50-59 years of age and is a multifactorial disease, associated with lower-airway inflammation, such as asthma and chronic obstructive pulmonary disease [(1-4)]. The clinical presentation is typical nasal obstruction and discharge, loss of smell, facial pain, and malaise resulting in sleep impairment and poor quality of life [(5)].

Gastroesophageal reflux (GER) is common in the adult population and is also referred to as acid reflux, heartburn, or simply

Major symptom

- Have you had a blocked nose for more than 12 weeks in the last 12 month?
- Have you experienced discolored nasal secretions or discolored mucus in your throat for more than 12 weeks in the last 12 month

Minor symptoms

- Have you experienced pain or pressure around your forehead, nose, or eyes for more than 12 weeks in the last 12 month
- Has your sense of smell been reduced or absent for more than 12 weeks in the last 12 month

Figure 1. Definition of chronic rhinosinusitis according to EPOS. Subjects are defined as having CRS when having at least two symptoms where one must be a major symptom.

Question: How often do you have heartburn or acid reflux after going to bed?

1. Never
2. Less than once a week
3. 1-2 times a week
4. 3-6 times a week
5. Almost every night

Figure 2. Assessment of nocturnal gastroesophageal reflux (nGER).

reflux. Gastroesophageal reflux disease (GERD) is defined as gastroesophageal reflux causing chronic irritating, long-lasting inflammatory symptoms, such as chest pain and painful swallowing [6]. Data on the prevalence of GERD in the general population vary. In Europe, it is estimated at 8.8-25.9%, but East Asian studies report a prevalence of less than 10% [7]. In a study from the US, 35% of the population reported "GERD symptoms within the last week" at the age of 50-59 [8]. GERD has been associated with the pathogenesis of several diseases, including chronic cough, laryngitis, asthma, COPD, and dental erosions [9-13]. In a Scandinavian study, patients with persistent nocturnal gastroesophageal reflux (nGER) had significantly more signs of laryngopharyngeal reflux (LPR) than those without nGER, and pepsin in exhaled air was more common among individuals with nGER [14]. Still, the role of GER in the pathogenesis of CRS is unclear, although supported by several clinical studies of limited patient cohorts [6,15]. Katle et al. [16,17] showed that patients with GERD had reduced scores on a sino-nasal outcome test (SNOT-20), indicating poorer CRS-related quality of life and that GERD evaluated by 24-hour esophageal impedance-pH monitoring was significantly more prevalent in CRS patients compared with healthy controls. The relationship between CRS and GERD is believed to be complex and EPOS 2020 concludes that the relationship between GERD and CRS remains indeterminate [1]. Leason et al. have, however, suggested that there is a significant body of evidence showing an association between GERD and CRS [18]. In spite of this, the mechanisms related to the way these two diseases interact are not fully understood and there is a need for data from large population-based studies to obtain a better understanding.

We have previously studied gastroesophageal reflux and upper-airway inflammation in two large, prospective, adult random population samples. We found an increased risk of developing non-infectious rhinitis during a five-year observation period in 3,307 subjects and again during a 10-year period in 5,417 subjects with nocturnal GERD at baseline [19,20]. nGER is often regarded as a more severe form of the disease with more symptoms, complications such as esophageal erosions and ulcerations, respiratory symptoms, and a risk of esophageal adenocarcinoma [21]. nGER is also associated with a greater impact on health-related quality of life [22].

In this population-based study, we aim to investigate symptoms of nGER and its association with CRS. To our knowledge, there are no previous population-based studies investigating the relationship between nGER and CRS. The present study is based on a unique and well-defined random middle-aged sample from Gothenburg, called the Swedish CArdioPulmonary bioImage Study (SCAPIS) Pilot study.

Materials and methods

Study population

The study population originated from the Swedish CArdioPulmonary bioImage Study (SCAPIS) pilot trial, which is a multi-centre, national prospective, observational study of the mechanisms involved in the development of cardiopulmonary disease in 1,111 randomly selected men and women, aged 50 to 64 years, from the city of Gothenburg in Sweden [23]. The study data include advanced imaging methods such as pulmonary CT scans and comprehensive questionnaires on pulmonary and cardiac disease and risk factors. The data collection was completed at Sahlgrenska University Hospital in 2012.

Study design

In this cross-sectional study, CRS was analysed in relation to nGER, age, sex, body mass index (BMI), educational level, smoking, and asthma. During a clinical visit to Sahlgrenska University Hospital, all the subjects completed a questionnaire comprising 140 questions regarding cardiopulmonary health, including CRS and nGER.

Table 1. Description of the study population regarding age, Body Mass Index (BMI), sex, smoking, educational level, chronic rhinosinusitis (CRS) and asthma. Nocturnal GER (nGER) is defined as having symptoms at least once a week.

	no nGER* (n=962)	nGER‡ (n=109)	All[a] (n=1,111)	Missing n
Age, years, (median (IQR))	57 (54-61)	59 (55-62)	58 (54-62)	-
BMI kg/m² (median (IQR))	26.5 (24.2-29.3)	27.9 (25.2-30.7)	26.6 (24.3-29.5)	-
Sex, n (%)				-
Male	490 (50.9)	41 (37.6)	555 (50.0%)	-
Female	472 (49.1)	68 (62.4)	556 (50.0%)	-
Smoking[b], n (%)				14
Current	166 (17.3)	23 (21.7)	197 (17.9)	
Past	388 (40.4)	36 (34)	433 (39.5)	
Never	407 (42.3)	47 (44.3)	467 (42.6)	
Educational level, n (%)				34
No basic education	24 (2.5)	5 (4.7)	30 (2.7)	
Primary	1567 (16.2)	17 (15.9)	185 (16.8)	
Secondary	404 (42.0)	59 (55.1)	480 (43.5)	
University or higher	378 (39.3)	26 (24.3)	408 (37.0)	
CRS, n (%)				73
Yes	44 (4.8)	13 (13)	58 (5.6)	
No	879 (95.2)	87 (87)	980 (94.4)	
Asthma, n (%)				15
Yes	76 (7.9)	19 (17.4)	100 (9.1)	
No	884 (92.1)	90 (82.6)	996 (90.9)	

* Symptoms of nocturnal GER reported less than once a week; ‡ Symptoms of nocturnal GER at least once a week; [a] including n=40 with missing on nGER question; [b] Occasional smokers is included in the definition as current.

Outcomes and predictors

Chronic rhinosinusitis (CRS) was defined as self-reported specific sino-nasal symptoms with a duration of more than 12 weeks according to the EPOS criteria for epidemiological questionnaire-based studies, Figure 1 [5]. nGER was assessed with the question shown in Figure 2. To be defined as nGER, the subject had to report symptoms of nGER at least once a week. Asthma was defined by an affirmative answer to the question: "Have doctors ever told you that you have asthma?".

Educational level was divided into four categories: 1) no basic education, 2) completed primary school, 3) completed secondary school and, 4) university degree of higher. Smoking status was defined based on the question: "Do you smoke?" and the subject was defined as a current smoker if answering "yes, regularly" or "yes, occasionally". Past- and never-smoker was defined as answering "no, stopped smoking" and "no, have never smoked" accordingly.

Participants had to understand written and spoken Swedish to be included in the study. The study was approved by the Swedish ethical review authority DNR 2020-07164.

Statistical analyses

Analyses were performed with the SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA). Univariate analyses included using t-tests and chi-square tests (Cochran-Armitage trend test) for continuous and categorical variables respectively. A multivariate logistic regression model was used to calculate odds ratios and 95% confidence intervals. P-values of ≤ 0.05 were considered statistically significant.

Results

The prevalence of nGER in the study population was 10.2%, while the prevalence of CRS was 5.6% (Table 1). CRS and asthma were significantly more common in subjects reporting nGER compared with subjects who did not (Table 1). There was a significant positive dose-response relationship between an increased frequency of nocturnal reflux episodes per week and having CRS (Figure 3). In the regression analysis, CRS was associated with nGER, OR 1.43 (95% CI [1.1-1.83]) adjusted for age, sex, BMI, educational level, smoking, and asthma. The odds ratio for having CRS in subjects with nGER almost every night was OR 4.6 (95% CI [1.2-17.1]) (Figure 4).

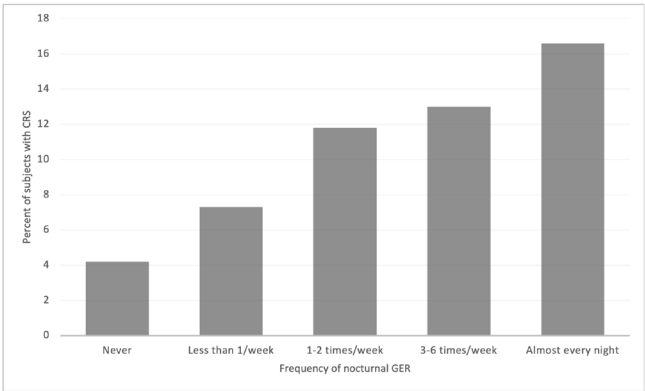

Figure 3. Frequency of nGER episodes in relation to the percentage of subjects reporting CRS. Cochran-Armitage trend test p<0.01.

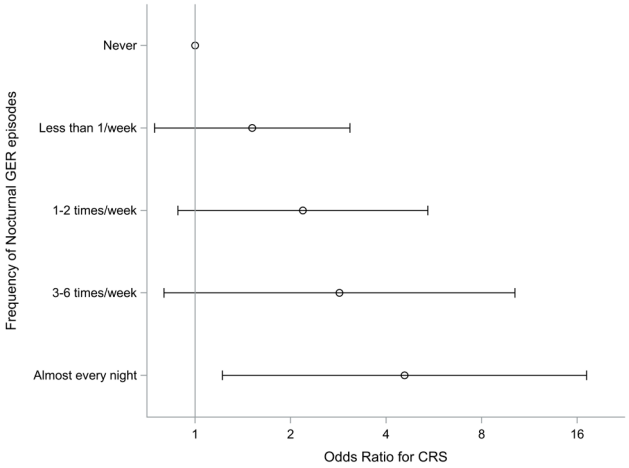

Figure 4. Logistic regression analysis of the odds ratio and 95% confidence intervals for having CRS in relation to the frequency of nocturnal GER episodes adjusted for age, sex, BMI, smoking, educational level, and asthma. Note: never-smoker was used as a reference category among the smoking categories. Abbreviations: CRS, chronic rhinosinusitis; GER, gastroesophageal reflux.

Discussion

The most important finding in this population-based, cross-sectional study from a well-defined, middle-aged random population was that nGER was significantly more common among subjects reporting CRS compared with those who did not. Moreover, there was a dose-dependent relationship between CRS and an increasing frequency of nocturnal reflux episodes. In the regression analysis, CRS was associated with nGER adjusted for age, sex, BMI, educational status, smoking, and asthma.

To our knowledge, this is the first population-based study presenting evidence of CRS defined according to the EPOS criteria and its association with nGER. The result is in line with earlier studies where an increased risk of non-infectious rhinitis has been reported by several authors, including us, in subjects with nGER [18,19]. However, CRS specifically defines chronic sino-nasal inflammation and is thus a smaller and potentially more severe sub-group of upper-airway inflammation among patients with the wider definition of non-infections rhinitis. Even though the treatment of CRS is primarily medical, involving nasal steroids and recently biologicals in selected patients, repeated functional endoscopic sinus surgery (FESS) is also a common surgical procedure in CRS. Finding the aetiology of CRS and directing causal therapy rather than symptom reduction is therefore important and nGER could be one factor to assess in the clinical evaluation of CRS. It has been suggested that several pathophysiological mechanisms explain how GER might contribute to inflammatory airway disease. One theory proposes that there is a direct cytotoxic effect of refluxate including pepsin in nasal secretion, gastric acid, and a local eosinophilic infiltration of the respiratory mucosa in the upper airways resulting in diffuse oedema and barrier breakdown. Emilsson et al. reported significantly more signs of laryngopharyngeal reflux (LPR) and pepsin in exhaled air among subjects with nGER [14,24]. A second theory suggests that the intranasal presence of *Helicobacter pylori* is responsible for the pathogenicity in the nasal cavity [25]. A third hypothesis suggests an indirect mechanism involving a neural reflex from the esophagus to the upper airways via the autonomic nervous system [26,27]. However, the present study was not designed to address the pathophysiological mechanism between nGER and CRS.

It is proposed that asthma can be triggered by the repeated flow of acidic reflux into the lungs, causing inflammation. Vagal activity induced by acidic reflux can lead to bronchoconstriction and, in some individuals, asthma. Asthma, on the other hand, can in itself also aggravate the symptoms of GER, for example, by causing negative intra-thoracic pleural pressure, which can lead to the regurgitation of reflux acid through the lower esophageal sphincter [28]. Our study confirms that asthma was a comorbidity for nGER [29]. Future RCT- or experimental studies in animal models, investigating a causal relationship how nGER can affect the airways is warranted.

One major strength of the present study is the population-based design, including a well-defined cohort with an age interval between 50-65, where both GERD and CRS are common diseases [3,28]. The random population sample is based on the unique Swedish personal identity number, where the only exclusion criterion was not being able to understand spoken and written Swedish language. The most common reason for not participating in the study was that the person could not be contacted, despite three separate telephone calls. The SCAPIS pilot cohort has previously been well described [23]. Bergstrom et al. reported that risk factor patterns were as expected in the pilot SCAPIS population in comparison to the background population and were thus representative [30]. Furthermore, CRS is defined by the EPOS criteria. The questions regarding nGER are formulated in

the present time: "now", which minimises the risk of recall bias, and the questionnaires were answered during a clinical visit to the study site and not as postal questionnaires.

This study has several weaknesses. First, it is a cross-sectional study in contrast to our previous studies of GERD and non-infectious rhinitis that were prospective. The dose-dependent relationship between the frequency of nocturnal reflux episodes and the occurrence of CRS, however, adds strong support to an association between CRS and nGER. One obvious weakness of this questionnaire-based study is that the participants' upper airways were not examined, and the reported CRS was therefore based solely on symptoms. The EPOS criteria for questionnaire-based studies of CRS were followed and, even though both CRS and nGER could have been overestimated in the absence of a clinical examination, the dose-response pattern indicates a true relationship.

There is no standardised clinical definition of nGER and the definition in this study relies on reported symptoms and lacks support from objective data as for instance 24-hour pH-metry. Such data, preferably obtained even from the larynx, would have contributed to assess the etiological influence of LPR. However, the occurrence of nocturnal heartburn has previously been significantly associated with pathological 24-hour pH-metry, which adds support for the nGER definition used in this paper [31]. In epidemiological studies, several definitions have previously been described [24,32-36]. Regarding the frequency of the symptom of heartburn after going to bed, most authors define nGER as reporting symptoms at least once a week, as used in the present study [32,33,35]. It would have been advantageous to report data on reflux symptom index, however, such data were not available for this study. The prevalence of CRS when having nGER in this study is comparable with a recent clinical trial from Denmark [37] and we are therefore confident that the population and symptoms are representative.

Conclusion

In this cross-sectional study of a representative middle-aged random population of men and women, there was a significant association between CRS and nGER. This association is also shown to have a clear dose-dependent relationship, where the occurrence of CRS is increased with the frequency of nocturnal reflux episodes. As expected, asthma was also more common in subjects with nGER. Nocturnal gastroesophageal reflux should be considered in the clinical evaluation of patients with chronic rhinosinusitis.

Authorship contribution

Conceptualisation and methodology: JB, MB, AA, LS and JH. Supervision: JH. Data curation, formal analysis, writing – original draft: JB, MB, AA, LS and JH.

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Conflict of interest

JB, AA, LS, MB and JH: no financial or intellectual conflicts of interest

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