pii: jc-18-00575 https://dx.doi.org/10.5664/jcsm.7846

JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Incident Chronic Rhinosinusitis Is Associated With Impaired Sleep Quality: Results of the RHINE Study

Caroline Bengtsson, MD[1]; Lars Jonsson, MD, PhD[1]; Mats Holmström, MD, PhD[2]; Johan Hellgren, MD, PhD[3]; Karl Franklin, MD, PhD[4]; Tórarinn Gíslason, MD, PhD[5]; Mathias Holm, MD, PhD[6]; Ane Johannessen, PhD[7,8]; Rain Jõgi, MD, PhD[9]; Vivi Schlünssen, MD, PhD[10]; Christer Janson, MD, PhD[11]; Eva Lindberg, MD, PhD[11]

[1]Department of Surgical Sciences, Otorhinolaryngology, Head and Neck Surgery, Uppsala University, Uppsala, Sweden; [2]Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and Technology, Karolinska University Hospital, Huddinge, Sweden; [3]Department of Otorhinolaryngology, Head and Neck Surgery, Sahlgrenska Academy, Gothenburg, Institute of Clinical Science, University of Gothenburg, Sweden; [4]Department of Surgical and Perioperative Sciences, Surgery, Umeå University, Umeå, Sweden; [5]Department of Respiratory Medicine and Sleep, University of Iceland, Reykjavik, Iceland; [6]Department of Occupational and Environmental Medicine, University of Gothenburg, Gothenburg, Sweden; [7]Department of Global Public Health and Primary Care, Centre for International Health, University of Bergen, Bergen, Norway; [8]Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway; [9]Department of Pulmonology, Tartu University Hospital, Tartu, Estonia; [10]Department of Public Health, Aarhus University, Aarhus, Denmark, National Research Centre for the Working Environment, Copenhagen, Denmark; [11]Department of Medical Sciences, Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden

Study Objectives: Chronic rhinosinusitis (CRS) is a common inflammatory disease of the nasal cavity and paranasal sinuses. Associations between CRS and poor sleep quality have been reported. This 10-year follow-up study investigates possible associations between incident CRS and sleep quality.
Methods: A questionnaire was sent to 16,500 individuals in Sweden, Norway, Denmark, Iceland and Estonia in 2000. It included questions on airway diseases, age, sex, body mass index, smoking habits, comorbidities, education and sleep quality. In 2010, a second questionnaire was sent to the same individuals, with a response rate of 53%. A subgroup of 5,145 individuals without nasal symptoms in 2000 was studied. Multiple logistic regression was performed to examine associations between CRS (defined according to the European position paper on rhinosinusitis and nasal polyps epidemiological criteria) at follow-up and sleep quality, with adjustment for potential confounders. Individuals with the respective sleep problem at baseline were excluded.
Results: Over 10 years, 141 (2.7%) of the individuals without nasal symptoms in 2000 had developed CRS. CRS was associated with difficulties inducing sleep (adjusted odds ratio 2.81 [95% CI 1.67–4.70]), difficulties maintaining sleep (2.07 [1.35–3.18]), early morning awakening (3.03 [1.91–4.81]), insomnia (2.21 [1.46–3.35]), excessive daytime sleepiness (2.85 [1.79–4.55]), and snoring (3.31 [2.07–5.31]). Three insomnia symptoms at baseline increased the risk of CRS at follow-up by 5.00 (1.93–12.99).
Conclusions: Incident CRS is associated with impaired sleep quality and excessive daytime sleepiness. Insomnia symptoms may be a risk factor for the development of CRS.

Keywords: chronic rhinosinusitis, CRS, epidemiology, insomnia, sleep quality
Citation: Bengtsson C, Jonsson L, Holmström M, Hellgren J, Franklin K, Gíslason T, Holm M, Johannessen A, Jõgi R, Schlünssen V, Janson C, Lindberg E. Incident chronic rhinosinusitis is associated with impaired sleep quality: results of the RHINE study. *J Clin Sleep Med.* 2019;15(6):899–905.

BRIEF SUMMARY
Current Knowledge/Study Rationale: Chronic rhinosinusitis affects the quality of life of millions of people worldwide. The knowledge of sleep quality in chronic rhinosinusitis is limited, however. There is a need for large scale epidemiological studies to estimate the prevalence and incidence of chronic rhinosinusitis and its impact on sleep quality.
Study Impact: This 10-year follow-up study contributes to the understanding of how the development of chronic rhinosinusitis affects self-reported sleep quality. It also illuminates a possible link between insomnia symptoms and the later development of an inflammatory disorder of the respiratory airway.

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common inflammatory disease of the paranasal sinuses and nasal cavity affecting 5% to 15% of the general population in Europe and the United States. The socioeconomic consequences of the disease for the individual and society are vast.[1] CRS also has a substantial negative effect on quality of life, including disturbed sleep.[2] Recent epidemiological and clinical research presents strong associations between CRS and poor sleep quality.[3,4] In spite of this, there are no epidemiological studies investigating the association between incident CRS and sleep quality.

Insomnia symptoms may be a risk factor for the development of inflammatory disorders in the respiratory airway. In a recent prospective study of asthma and sleep quality, insomnia symptoms were associated with an increased risk of developing asthma.[5] One mechanism for this association may be the pro-inflammatory effects of cytokine changes induced by

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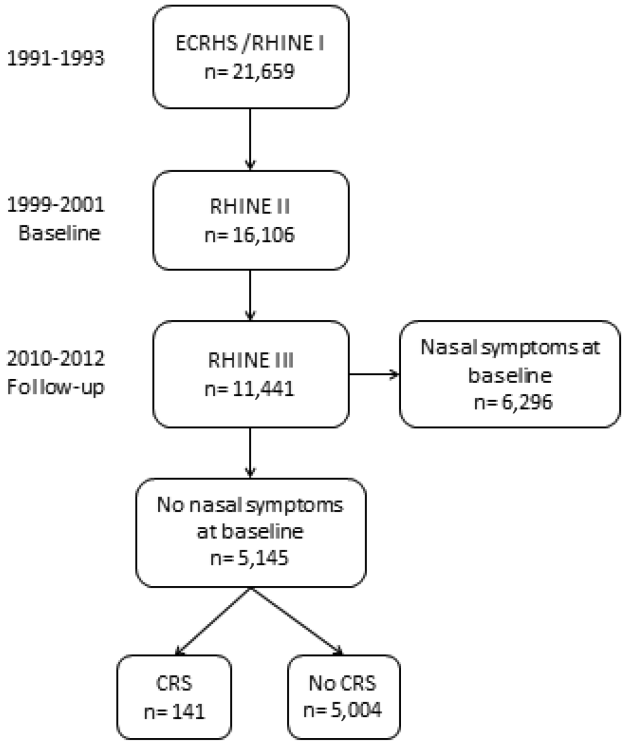
Figure 1—Flow chart of the study population.



CRS = chronic rhinosinusitis, ECRHS = European Community Respiratory Health Survey, RHINE = Respiratory Health in Northern Europe.

insomnia symptoms.[6–8] The increased secretion of the stress hormones adrenocorticotropin and cortisol found in insomniacs is another possible mechanism for an elevated risk of developing inflammatory disorders.[9,10] Since CRS is an inflammatory disorder of the respiratory airway, just like asthma, it is of interest to explore whether insomnia symptoms increase the risk of developing CRS. No such studies have previously been performed.

The population-based Respiratory Health in Northern Europe (RHINE) 10-year follow-up study included questions on both CRS and sleep. Using data drawn from this unique, large epidemiological study, our aim was to investigate whether the development of CRS is associated with impairments of self-reported sleep quality. To improve the possibility to interpret causal relationships incident CRS was studied. Another aim was to study whether insomnia symptoms constitute an increased risk for the development of CRS.

METHODS

The Study Population

The population-based RHINE study has been conducted in five Northern European countries during a 20-year period.[11] The study centers were situated in Umeå, Uppsala and Gothenburg in Sweden, Aarhus in Denmark, Bergen in Norway, Reykjavik in Iceland and Tartu in Estonia. The first stage of the study, RHINE I, was conducted in 1991–1993 and it was also part of the European Community Respiratory Health Survey Stage I. The present study is based on data from the two follow-up stages, RHINE II and RHINE III, which were conducted in 1999–2001 and 2010–2012 respectively (**Figure 1**). Randomly selected men and women born in 1945–1973 were sent almost identical postal questionnaires to collect baseline (RHINE II) and follow-up data (RHINE III). The questionnaires included questions on upper and lower respiratory disease, age, sex, body mass index (BMI), smoking habits, comorbidities, environmental and workplace exposure, education and insomnia symptoms, snoring and daytime sleepiness. After two reminders, the response rate to RHINE II was 75%, equivalent to 16,106 individuals, and to RHINE III 53%, equivalent to 11,441 individuals. To be able to analyze those who developed CRS, a subgroup of 5,145 individuals was identified among those who had responded to both questionnaires. These individuals had no nasal symptoms at baseline. They confirmed the absence of hay fever and any other kind of nasal allergy and denied having symptoms of nasal obstruction, nasal secretion and/or sneezing attacks without having a cold. The data on this subgroup were analyzed at baseline and follow-up (**Figure 1**).

The study was approved by the regional medical ethics committees at each study center. Written consent was obtained from the study participants at each stage of the study.

Definitions

Chronic Rhinosinusitis

CRS was defined according to the epidemiological criteria in the European position paper on rhinosinusitis and nasal polyps (EPOS).[1] The participants had to confirm the presence of two or more of the following symptoms during the last 12 months: (1) nasal blockage/obstruction/congestion, (2) nasal discharge (anterior/posterior nasal drip), (3) facial pain or pressure and (4) reduction in or loss of smell. At least one symptom had to be nasal blockage or nasal discharge and all symptoms needed to have a minimum symptom duration of ≥ 12 weeks.

Current Asthma

Current asthma was defined as a positive answer to either or both of the two questions "Have you had an attack of asthma in the last 12 months?" and "Are you currently taking any medicine (including inhalers, aerosols or tablets) for asthma?"

Smoking

Smoking was defined by a positive answer to the questions "Are you a smoker (this applies even if you only smoke the odd cigarette/cigar or pipe every week)?" at baseline and "Do you smoke? (this applies even if you only smoke the odd cigarette/cigar or pipe every week)" at follow-up.

Insomnia

Insomnia symptoms analyzed were: difficulties inducing sleep (DIS), difficulties maintaining sleep (DMS), and early morning awakening (EMA) for at least 3 to 5 nights/wk according to the

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Table 1—Baseline characteristics of the total population and for those who did and did not develop CRS at follow-up.

	Total Population (n = 5,145)	No CRS at Follow-Up (n = 5,004)	CRS at Follow-Up (n = 141)	*P*
Age	31.6 ± 7.3	31.7 ± 7.3	30.1 ± 7.0	.011
Sex, female	2,702 (52.5)	2,629 (52.5)	73 (51.8)	.858
BMI	24.6 ± 4.0	24.6 ± 4.0	24.9 ± 4.1	.385
Delta BMI	1.2 ± 2.9	1.2 ± 2.9	1.8 ± 3.0	.015
Smoking	1,285 (25.2)	1,231 (24.8)	54 (38.6)	< .001
Smoking (follow-up)	818 (16.0)	782 (15.7)	36 (25.5)	.002
Asthma	88 (1.7)	82 (1.6)	6 (4.3)	.018
Asthma (follow-up)	182 (3.6)	159 (3.2)	23 (17.0)	< .001
nGER	101 (2.0)	93 (1.9)	8 (5.9)	.001
Cardiometabolic disease				
Diabetes	75 (1.5)	72 (1.5)	3 (2.1)	.501
Heart disease	67 (1.3)	65 (1.3)	2 (1.4)	.899
Hypertension	312 (6.2)	302 (6.1)	10 (7.3)	.588
Education				
Compulsory school	595 (11.6)	579 (11.6)	16 (11.4)	.870
High school	2,141 (41.8)	2,079 (41.8)	62 (44.0)	
Academic degree	2,383 (46.6)	2,320 (46.6)	63 (44.7)	

Follow-up data are presented for smoking and asthma. The results are presented as n (%) or mean ± standard deviation. BMI = body mass index, CRS = chronic rhinosinusitis, nGER = gastroesophageal reflux at night.

Basic Nordic Sleep Questionnaire.[12] Insomnia was defined as either of the symptoms for at least 3 to 5 nights/wk.

Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS) was defined by the Basic Nordic Sleep Questionnaire[12] and occurred at least 3 to 5 d/wk.

Snoring

Snoring was defined as having loud and disturbing snoring at least 3 to 5 nights/wk.[13]

Gastroesophageal Reflux at Night

Gastroesophageal reflux at night (nGER) was defined by the question "How often in the last few months have you had heartburn or belching when you have gone to bed?" The responses "at least 3 to 5 nights/days a week" and "almost every day or night" were considered positive answers.[14]

Body Mass Index

BMI was calculated as self-reported body weight (kg) divided by height (m) squared (kg/m^2). Delta BMI was calculated as the difference between BMI at follow-up and BMI at baseline.

Educational Level

Educational level was categorized as 9-year compulsory school, high-school graduation and academic degree. Information on educational level was only provided at follow-up.

Cardiometabolic Disease at Baseline

Cardiometabolic disease at baseline was defined as positive answers to any of the three questions "Do you have high blood pressure?"; "Do you have any cardiac disease?"; and "Has any doctor ever told you that you have diabetes?"

Cardiometabolic Disease at Follow-Up

Cardiometabolic disease at follow-up was defined as positive answers to any of the three questions "Have you ever had hypertension (high blood pressure) diagnosed by a doctor?"; "Have you ever been treated in hospital because of heart infarction or angina pectoris?"; and "Have you ever had diabetes diagnosed by a doctor?"

Statistical Analyses

Stata 12.1 (Stata Corp, Texas, United States) was used in all the statistical analyses. The unpaired *t* test and χ^2 test were used to perform univariate analyses (**Table 1**, **Figure 2**). The results were presented as n (%) and mean ± standard deviation.

Multiple logistic regression analyses were performed to analyze possible associations between individuals with CRS and sleep problems and EDS at follow-up, adjusting for possible confounders. Calculations excluded those with the respective sleep problem and EDS at baseline (**Table 2**).

Multiple logistic regression analyses were also used to analyze possible associations between the individual sleep problems and EDS at baseline and CRS at follow-up (**Table 3**). Equivalent calculations were made analyzing the number of insomnia symptoms at baseline and CRS at follow-up (**Table 4**). The data in **Table 3** and **Table 4** were also calculated by excluding those with CRS who also developed asthma (data not shown).

The results were presented as odds ratios and 95% confidence intervals. The null hypothesis was rejected at a level of $P < .05$.

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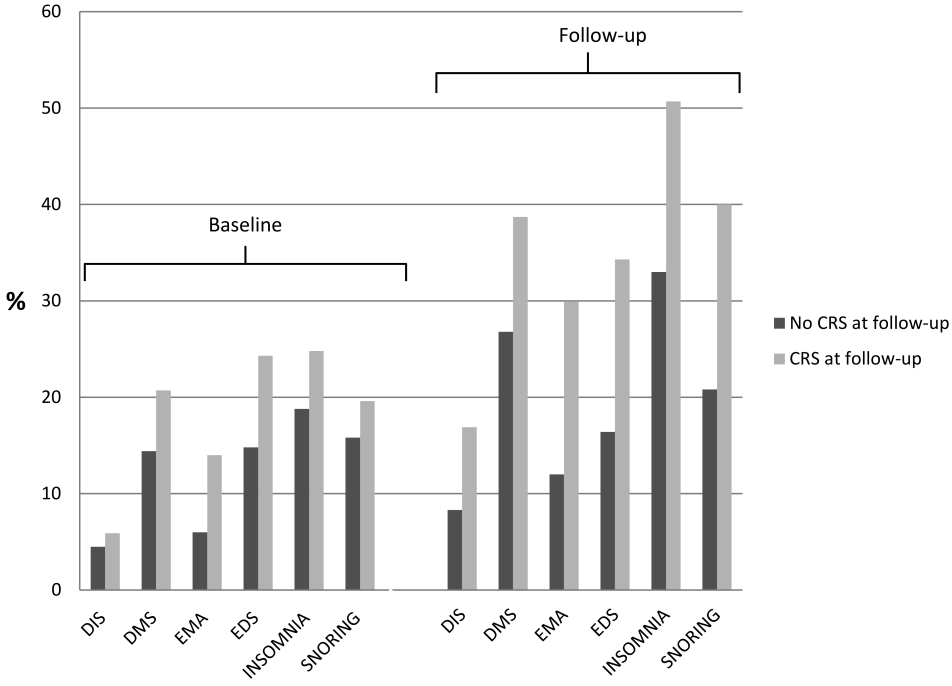
Figure 2—Prevalence of sleep problems and EDS at baseline and follow-up in those with and without incident CRS during the 10-year study period.



CRS = chronic rhinosinusitis, DIS = difficulties inducing sleep, DMS = difficulties maintaining sleep, EDS = excessive daytime sleepiness, EMA = early morning awakening, insomnia = DIS or DMS or EMA.

Table 2—Cross-sectional analysis of the risk of sleep problems and EDS at follow-up among those with CRS at follow-up.

	DIS	DMS	EMA	Insomnia	Snoring	EDS
CRS	2.81 (1.67–4.70)	2.07 (1.35–3.18)	3.03 (1.91–4.81)	2.21 (1.46–3.35)	3.31 (2.07–5.31)	2.85 (1.79–4.55)
Age	1.03 (1.01–1.05)	1.03 (1.02–1.04)	1.02 (1.01–1.03)	1.03 (1.02–1.04)	1.02 (1.01–1.04)	0.97 (0.96–0.99)
Sex (female)	1.96 (1.52–2.53)	1.43 (1.22–1.67)	1.29 (1.05–1.58)	1.41 (1.22–1.64)	0.55 (0.45–0.67)	1.09 (0.89–1.32)
BMI	1.01 (0.98–1.05)	1.00 (0.98–1.02)	1.00 (0.97–1.02)	1.00 (0.98–1.03)	1.13 (1.10–1.16)	1.05 (1.02–1.08)
Delta BMI	1.04 (0.99- 1.08)	1.03 (1.00–1.06)	1.00 (0.96–1.04)	1.04 (1.01–1.07)	1.19 (1.15–1.24)	1.06 (1.02–1.09)
Smoking	1.58 (1.22–2.04)	0.94 (0.79–1.13)	0.96 (0.76–1.22)	1.03 (0.87–1.23)	1.42 (1.13–1.77)	1.21 (0.97–1.51)
Asthma	1.16 (0.52–2.60)	1.61 (0.93–2.80)	1.54 (0.79–3.01)	1.32 (0.74–2.35)	0.58 (0.24–1.42)	1.55 (0.79–3.06)
nGER	2.29 (1.21–4.33)	1.58 (0.89–2.79)	1.83 (0.96–3.46)	1.92 (1.03–3.58)	1.82 (0.94–3.52)	1.17 (0.54–2.54)
Cardiometabolic Disease	0.68 (0.41–1.12)	1.40 (1.07–1.84)	1.50 (1.11–2.15)	1.43 (1.09–1.86)	0.96 (0.67–1.38)	0.84 (0.57–1.24)

The results are presented as odds ratios (95% confidence intervals), after adjusting for all variables in the table, center and educational level. The calculations exclude those with the respective sleep problem at baseline. BMI = body mass index, cardiometabolic disease = diabetes and/or hypertension and/or heart disease, CRS = chronic rhinosinusitis, DIS = difficulties inducing sleep, DMS = difficulties maintaining sleep, EDS = excessive daytime sleepiness, EMA = early morning awakening, insomnia = DIS or DMS or EMA, nGER = gastroesophageal reflux at night.

RESULTS

The total study population consisted of 5,145 individuals who did not report nasal symptoms at baseline. At the follow-up 10 years later, 141 (2.7%) had developed CRS. The prevalence rates of the individual CRS symptoms at follow-up among those with and without CRS were: nasal obstruction 82.3% versus 2.0%, nasal discharge 72.3% versus 1.4%, facial pain/pressure 62.4% versus 1.7% and reduction/loss of smell 48.2% versus 1.7%. The prevalence of CRS in the total study population (n = 11,441) was 6.8% at follow-up. The population characteristics are presented in **Table 1**. Individuals who developed CRS were slightly younger at baseline than those who did not develop CRS. They also had a larger weight gain at follow-up, but their BMI at follow-up did not differ compared with those who did not develop CRS. Current smoking was substantially more common among those with CRS, as were asthma and nGER. Current smoking and asthma had declined in both groups at follow-up. Neither hypertension, diabetes or heart disease differed with respect to the CRS definition, nor did educational level or sex.

All the analyzed sleep problems (DIS, DMS, EMA, snoring) and EDS were more prevalent at baseline among those who developed CRS compared with those who did not, **Figure 2**. At

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Table 3—Odds ratios for CRS at follow-up depending on the presence of sleep problems at baseline.

	Univariate	Adjusted Model
DIS baseline	1.34 (0.65–2.78)	1.40 (0.68–2.91)
DMS baseline	1.55 (1.02–2.37)	1.54 (0.99–2.37)
EMA baseline	2.55 (1.55–4.20)	3.06 (1.83–5.11)
Insomnia baseline	1.43 (0.96–2.12)	1.45 (0.97–2.16)
Snoring baseline	1.29 (0.84–2.00)	1.38 (0.87–2.18)
EDS baseline	1.85 (1.24–2.76)	1.79 (1.19–2.68)

The adjusted model is adjusted for age, sex, and body mass index. Data are presented as odds ratios (95% confidence intervals). CRS = chronic rhinosinusitis, DIS = difficulties inducing sleep, DMS = difficulties maintaining sleep, EDS = excessive daytime sleepiness, EMA = early morning awakening, insomnia = DIS or DMS or EMA.

Table 4—Odds ratios for CRS at follow-up depending on the number of insomnia symptoms at baseline.

Insomnia Symptoms at Baseline	Univariate	Adjusted Model
0	1.00	1.00
1	0.89 (0.52–1.55)	0.85 (0.48–1.50)
2	2.11 (1.12–4.00)	2.37 (1.24–4.51)
3	4.30 (1.68–11.06)	5.00 (1.93–12.99)

The adjusted model is adjusted for age, sex, and body mass index. Data are presented as odds ratios (95% confidence intervals). Insomnia symptoms include difficulties inducing sleep, difficulties maintaining sleep, and early morning awakening. CRS = chronic rhinosinusitis.

follow-up, those with CRS and without CRS had a higher prevalence of sleep problems and EDS compared with baseline, but the increase in prevalence was much larger among those with CRS. DIS, EMA and EDS were more than twice as common among those who had developed CRS at follow-up and snoring had a prevalence of 40% among those with CRS compared with 20.8% among those without. DMS was also more prevalent among those with CRS at follow-up, 38.7% compared with 26.8%.

CRS was significantly associated with all the analyzed sleep problems and EDS at follow-up. Other significant associations were female sex, smoking, nGER and analyzed comorbidities (**Table 2**).

Both EMA and EDS were found to be risk factors for CRS in the adjusted model (**Table 3**). Two and three insomnia symptoms at baseline were associated with CRS at follow-up in the adjusted model (**Table 4**). Models including further adjustment for age, sex, BMI, delta BMI, asthma at baseline, smoking at baseline, gastroesophageal reflux at baseline, cardiometabolic disease at baseline, center and educational level at follow-up, did not substantially change the results of **Table 3** and **Table 4**, (data not shown). In addition, calculations excluding those with asthma did not differ compared with the analyses including those with asthma (**Table 3** and **Table 4**).

DISCUSSION

The main finding in the present study was the strong associations between incident CRS and all sleep problems (DIS, DMS, EMA, snoring, insomnia) and EDS at the 10-year follow-up. It is suggestive of a causal relationship which is strengthened by the fact that those with the respective sleep problem or EDS at baseline were excluded in our analysis. This result is also in accordance with a recently reported study from our group, in which CRS was strongly associated with impaired sleep quality.[4] The high prevalence of sleep problems and EDS among those with CRS found at follow-up is also in line with our previous study, in which sleep problems and EDS were 50% to 90% more common among those with CRS compared with those without. Other studies report that > 70% of patients with CRS have poor sleep quality.[3,15]

Another finding was a higher prevalence of all sleep problems and EDS at baseline among those who developed CRS, compared with those who did not. Furthermore, EMA and EDS at baseline were associated with an increased risk of subsequent CRS. In addition, three insomnia symptoms at baseline were associated with a 5-fold increase in the risk of CRS. It is difficult to discern why EMA and EDS are risk factors for CRS and not the other closely related sleep disturbances. They may represent symptoms of early stages of insomnia or another sleep disorder, which would explain the increase in prevalence of all sleep problems 10 years later. That in turn, would support the theory of insomnia as a cause for CRS. Similar results for insomnia and asthma were recently published by Brumpton et al.[5] As mentioned initially, there are plausible causal links to explain the observed association between insomnia symptoms and subsequent inflammatory disease. The underlying biological mechanisms are complex, however, and require further investigation.

The effects of pro-inflammatory cytokines may account for the poor sleep quality reported by those with CRS in this study. Elevated levels of sleep-inducing pro-inflammatory cytokines (tumour necrosis factor-α and interleukin-1) and their antagonists (interleukin-4 and -13 and tumour growth factor-β) have been found in tissue samples from patients with CRS.[16,17] Alt et al. reported that the increased expression of interleukin-4 and tumour growth factor-β (both sleep-reducing cytokines) in the nasal mucosa was associated with a reduction in self-reported sleep quality in patients with CRS, suggesting a link between CRS and sleep dysfunction.[17]

Nasal obstruction is another possible explanation for the widespread sleep disturbances among affected individuals in the present study. It was the most common symptom, with a prevalence of 82.3%, and is a known risk factor for impaired sleep quality.[18,19] In previous work by our group, nasal obstruction had a high prevalence of 89.1% among those with CRS and associations were found with self-reported sleep problems and daytime sleepiness.[4] In another study by our group, self-reported nasal obstruction at night in women was associated with poor self-reported sleep quality and a negative impact on daytime symptoms.[20] These results highlight the role of nasal obstruction as an important symptom in sleep medicine. In the study by Thomas et al., however, the association of nasal obstruction and sleep quality was limited when investigating 28

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patients with CRS.[21] In recent work by Ando et al., all four CRS symptoms, together with a cough, were predictors of an increased risk of sleep impairment in CRS.[22] This result supports our previous study in which the disease severity of CRS, defined as the number of symptoms, was correlated to an increased prevalence of self-reported sleep problems and daytime sleepiness.[4]

Cigarette smoking is associated with CRS, according to several previous studies.[4,23,24] It may cause inflammatory changes and disturb the function of the nasal mucosa, as well as causing self-reported nasal obstruction, which may explain this association.[25–27] Furthermore, studies of smoking and nicotine on polysomnographic recordings reveal a negative effect on sleep quality.[28,29] Undoubtedly, cigarette smoking is an important confounder in the present study, considering that the prevalence of smoking among those with CRS was 38.6% at baseline and decreased to 25.5% at follow-up. Strong associations remained, however, between CRS and sleep problems and EDS after adjustment for smoking.

Asthma is also associated with CRS[24,30] and poor sleep quality.[13] In the present study, the prevalence of asthma increased from 4.3% to 17% among those who developed CRS during the study time frame, which may have influenced the reported sleep problems. Calculations excluding those with asthma did not change the results. Another possible confounder that we adjusted for in our analyses was nGER. We found that nGER was more prevalent among those with CRS and was associated with insomnia symptoms, results in line with previous studies.[31–33] A causal link between nGER and CRS has been suggested, but it has yet to be proven.

The main strength of the present study was the 10-year study time frame and the large population-based material on which it was based. As opposed to cross-sectional studies this prospective study offered the possibility to study causal relationships. It included young and middle-aged men and women from urban environments in five different Nordic countries, taking geographical, cultural and environmental aspects into account. Furthermore, the validated EPOS epidemiological symptom criteria were used to define CRS and the Basic Nordic Sleep questionnaire was used to analyze sleep.

One limitation of the present study was that no clinical examination of the nose or radiological investigations of the nasal cavity and sinuses were performed. Another limitation was that the questionnaire did not include information on depression, which is closely associated with CRS, sleep disturbances, daytime sleepiness and fatigue.[34–36] The questions on cardiometabolic diseases were not identically formulated in the two questionnaires, which may have influenced the responses. There were no associations between CRS and cardiometabolic diseases at baseline, however (data not shown). A further drawback was the lack of objective assessments of other sleep disorders. Obstructive sleep apnea (OSA) was, however, diagnosed by a doctor among 4.4% of those with CRS at follow-up. Calculations excluding those with CRS and doctor-diagnosed OSA did not change our results (data not shown).

RHINE data was found to have high validity by Johannessen et al.[11] The baseline prevalence of several respiratory symptoms was found to be lower among long-term participants compared to all baseline participants. Exposure-outcome associations were mainly unchanged by loss to follow-up, however. Consequently, the prevalence rates of respiratory symptoms in the present study may therefore be underestimated. The exclusion of those with nasal symptoms at baseline may have rendered a somewhat healthier cohort. This may have contributed to lower prevalence rates of incident CRS and the related sleep problems and EDS and restricts the generalizability of the results to some extent.

This is the first epidemiological study of incident CRS, as defined by the EPOS epidemiological criteria, and sleep quality. We found strong associations between the development of CRS and increased self-reported sleep problems and EDS, suggestive of a causal relationship. Our results also indicate that insomnia symptoms may be a risk factor for the development of CRS. Clinicians should consider the possibility of poor sleep quality in patients with CRS and offer appropriate treatment, not only to improve self-reported sleep quality but also to prevent further possible inflammation.

ABBREVIATIONS

BMI, body mass index
CRS, chronic rhinosinusitis
DIS, difficulties inducing sleep
DMS, difficulties maintaining sleep
EDS, excessive daytime sleepiness
EMA, early morning awakening
EPOS, European position paper on rhinosinusitis and nasal polyps
nGER, gastroesophageal reflux at night
OSA, obstructive sleep apnea
RHINE, Respiratory Health in Northern Europe

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication September 26, 2018
Submitted in final revised form December 30, 2018
Accepted for publication February 18, 2019
Address correspondence to: Caroline Bengtsson, Department of Surgical Sciences, Otorhinolaryngology, Akademiska sjukhuset, SE-751 85 Uppsala, Sweden; Tel: +46 70 579 16 76; Email: caroline.bengtsson@surgsci.uu.se

DISCLOSURE STATEMENT

The work was performed at the Department of Surgical Sciences and at the Department of Medical Sciences, Uppsala University, Uppsala, Sweden
All of the authors have seen and approved this manuscript. Dr. Bengtsson, Dr. Jonsson, Dr. Holmström, Dr. Hellgren, Dr. Franklin, Dr. Gislason, Dr. Holm, Dr. Johannessen, Dr. Janson, Dr. Lindberg have nothing to disclose. Dr. Schlünssen reports grants from the Wood Dust Foundation (Project no. 444508795), during the conduct of the study. Dr. Jõgi reports grants from the Estonian Research Council Personal Research Grant no 562, during the conduct of the study and personal fees from consultancy, grants from grants/grants pending, personal fees from payment for lectures, personal fees from travel/accommodations/meeting expenses, outside the submitted work. The study was funded by the Swedish Heart and Lung Foundation, the Swedish Association Against Asthma and Allergy, the Swedish Association against Heart and Lung Disease, the Swedish Council for Working Life and Social Research, the Bror Hjerpstedt Foundation, ACTA Otolaryngologica, Uppsala University, ALF funding, The Faculty of Health, Aarhus University, Denmark (Project No. 240008), The Wood Dust Foundation (Project No. 444508795), The Danish Lung Association, The Norwegian Research Council project 135773/330, The Norwegian Asthma and Allergy Association, The Icelandic Research Council and the Estonian Science Foundation (Grant No. 4350). Vivi Schlünssen and Thorarinn Gislason are members of the COST BM1201 network. The authors report no conflicts of interest.

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