Chronic rhinosinusitis related to occupational exposure – the Telemark population study

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31 **Running title:** Chronic rhinosinusitis and occupational exposure

32 **Abstract**

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34 Objective: To investigate the association between occupational exposure and chronic
35 rhinosinusitis

36 Methods: A random population from the region of Telemark, aged 16-50, answered a
37 respiratory questionnaire including questions on chronic rhinosinusitis and exposure in the
38 occupational environment.

39 Results: A total of 16,099/48,142 subjects responded. The prevalence of chronic rhinosinusitis
40 was 9%. Exposure associated with chronic rhinosinusitis comprised paper dust (OR 1.3, 95%
41 CI 1.1, 1.5), cleaning agents (OR 1.2, CI 1.0, 1.3), metal dust (OR 1.3, CI 1.1, 1.6), animals
42 (OR 1.2, CI 1.0, 1.5), moisture/mould/mildew (OR 1.3, CI 1.1, 1.5) and physically strenuous
43 work (OR 1.4, CI 1.2, 1.7).

44 Conclusions: Occupational exposure to paper dust, cleaning agents, metal dust, animals,
45 moisture/mould/mildew and physically strenuous work was independently related to having
46 chronic rhinosinusitis. An occupational history should be reviewed when assessing patients
47 with chronic rhinosinusitis.

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49 Key words: chronic rhinosinusitis, occupational exposure, paper dust, metal dust, cleaning
50 agents, asthma

Introduction

Chronic rhinosinusitis (CRS) is characterised by a chronic inflammation of the respiratory mucosa in the nose and sinuses. CRS is also associated with asthma (1, 2). CRS is a severe form of upper airway inflammation and has a substantial negative impact on the patients' health-related quality of life (3), including depression, anxiety, sleep disturbances, sexual dysfunction and fatigue. CRS is defined as either nasal blockage or nasal discharge for more than 12 weeks. Additional symptoms, such as facial pain or a reduction in or the loss of the sense of smell, may also be present (4). CRS is stratified into CRS *with* or *without* nasal polyposis (4), but in questionnaire-based studies of CRS, without a clinical assessment, it is not possible to differentiate between CRS with or without nasal polyposis. The prevalence of CRS based on self-reported symptoms has been estimated at 10.9% in a European multicentre study (5), 8.2% in a cross-sectional survey in China (6) and 5.5% in Brazil, South America (7).

CRS is associated with both allergic and non-allergic disease (8). The causal relationship for the majority of all CRS, however, remains unknown. Occupational exposure to airborne allergens and sensitisers, such as organic dusts, spray paint, hardeners, welding fumes and working as a cleaner, has previously been associated with the development of rhinitis (9, 10). This has not as yet been thoroughly studied in CRS patients, even though CRS represents a subgroup of patients with more severe disease. In one recent study by Gao et al., based on interviews with 10,633 subjects, occupational exposure to dust and exposure to mould or damp environments was significantly associated with having CRS (11). In a case-control study, it was found that patients with CRS in need of surgery (functional endoscopic sinus surgery, FESS), in particular patients in need of repeated surgeries, are more likely to have been exposed to inhaled noxious agents at work than controls (12).

The relationship between occupational exposure and the development of CRS still remains unclear and we are aware of no previous large population-based studies addressing CRS in relation to occupational exposure. The present study is based on a random working population from Norway and is designed to study the relationship between several types of exposure in the occupational environment and chronic rhinosinusitis.

Materials and methods

Study population and design

This is a cross-sectional study of a random adult population from the County of Telemark, Norway, called the “Telemark Study”. The study has previously been extensively described in detail (13). The County of Telemark is a highly industrialised part of Norway and has a population of approximately 170,000 inhabitants. A random sample of 50,000 adult subjects of working age, 16-50, was drawn from the population registry based on the individual identity number that all Norwegian citizens have.

Health outcomes

A questionnaire asking for symptoms of CRS, asthma, smoking and atopy, as well as self-reported exposure to several airborne irritants and sensitisers in the occupational environment, was sent out. The letter included an invitation to participate in the study and an informed consent, as well as a pre-paid envelope to return the questionnaire. Two reminders were sent after 1½ months and three months. The study was also advertised in local and national media at the time the questionnaire was distributed and a lottery with a financial incentive was conducted in order to encourage participation.

CRS was defined according to the European position paper on rhinosinusitis and nasal polyposis (EPOS) criteria as the presence of two or more symptoms of which one should be

101 either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip),
 102 called “major symptoms”, and facial pain/pressure and/or a reduction in or the loss of smell,
 103 called “minor symptoms”, for ≥ 12 weeks (Table I) (4). Atopy was defined as a positive
 104 answer to the question; ‘Do you have an allergy that affects your nose, including hay
 105 fever?’ (14). Asthma was defined as a positive answer to the question; ‘Has a physician ever
 106 diagnosed you with asthma?’ (15). Smoking habits were defined by three questions; 1. ‘Do you
 107 smoke every day?’, 2. ‘Do you only smoke occasionally?’ and 3. ‘Did you use to smoke?’ (16,
 108 17).

109 Exposure

110 Self-reported occupational exposure to airborne irritants and sensitisers was assessed by
 111 several questions. Having ever been exposed at work to cooking fumes, car/engine exhaust,
 112 strong acids, stone dust, flour/grain dust, wood dust, paper dust, metal dust was inquired
 113 about using the question: “At work, have you ever been exposed to...?”
 114 Exposure to cleaning agents, superglue, painting/varnishing, welding/metal smoke, sewage,
 115 hair-care products and animals was inquired about using the question: “Have you ever worked
 116 with...?”.

117 Several types of exposure were defined according to an affirmative answer to the following
 118 questions:

- 119 - moisture/mould/mildew: “Have you worked in premises with visible moisture
 120 damage?” and “Have you ever worked in premises with visible mould, have you
 121 ever worked in premises with a smell of mildew?”
- 122 - cold work: “Have you worked in premises with cold temperatures (in cold-storage
 123 rooms or outside in the winter)?”
- 124 - physically strenuous work: “Have you had a physically strenuous job (so that you
 125 have been out of breath and sweaty)?”.

The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (REC 2012/1665).

Statistical analyses

From the original random sample, the subjects who reported that they had never been employed were excluded from the analyses. Missing answers were handled as not having the complaint or not having been exposed. Chi-square and Fisher's exact tests were used to compare the CRS and non-CRS group. To estimate the effects of smoking, asthma, atopy and occupational exposure, odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were computed by logistic regression. Both unadjusted and adjusted estimates were calculated. The estimates were adjusted for age, gender, smoking, asthma, atopy and the other types of occupational exposure. The statistical significance level was set at $p < 0.05$ and results reaching significance are marked in bold in the tables. Statistical analysis was performed with IBM SPSS Statistics for Windows (Version 23, IBM SPSS, Armonk, NY, USA).

Results

Of the 48,142 eligible participants, a total of 16,099 answered the questionnaire, resulting in a response rate of 33%, Figure 1. Baseline characteristics are shown in Table II. The overall prevalence of CRS in the population was 9%. The prevalence of CRS was higher in current and past smokers compared with non-smokers. Asthma was more common in the CRS population compared with the non-CRS population (28% and 10% respectively).

In the univariate analyses, CRS was significantly more common among subjects ever exposed to all the assessed types of occupational exposure than among the unexposed controls. In the multiple regression model adjusted for age, gender, smoking habits, asthma and atopy, exposure to paper dust, cleaning agents, metal dust, animals, moisture/mould/mildew and physically strenuous work remained independently associated with CRS, Table III. When the

data were stratified for smoking, only exposure to paper dust, animals and physically strenuous work remained independently related to CRS in never-smokers. In past smokers, only physically strenuous work remained independently related to CRS. In current smokers, cleaning agents, moisture/mould/mildew and physically strenuous work were significantly associated with CRS. When excluding persons with asthma and atopy respectively, only exposure to metal dust, moisture/mould/mildew and physically strenuous work was associated with CRS.

The prevalence of the different component symptoms of CRS and combinations of CRS symptoms is shown in Table IV. A blocked nose was the most common symptom (88%), followed by facial pain (60%), discoloured secretion (56%) and reduced sense of smell (55%).

Discussion

In this study of a large random population, CRS was significantly associated with exposure to several airborne irritants and sensitisers in the occupational environment. The most consistent finding was that CRS was significantly more common in subjects exposed to paper dust, cleaning agents, metal dust, animals, moisture/mould/mildew and physically strenuous work. The results show that occupational exposure should be taken into account when evaluating patients with CRS and that avoidance of exposure should always be considered.

A recent systematic review of the evidence linking hazardous exposure in the occupational environment to CRS concluded that there is a lack of knowledge in the field and that further studies are warranted (18). To our knowledge, the present study is the first to assess the association between airborne irritants and sensitisers and CRS in the occupational environment in a large unselected general population. The advantage of this design is that subjects who have been exposed, but who for some reason have left the exposed environment, are included in the study. This reduces the risk of the “healthy worker effect” that can be a problem in workplace-based studies, as exposed individuals who have developed symptoms

may have left the exposed environment and are thus not included. The effect of the exposure is then underestimated.

Exposure to paper dust was significantly associated with CRS in this study and female subjects were more at risk. This association was also previously found with non-infectious rhinitis in a study with a similar design (9). The results are also in line with findings from a clinical study of workers exposed to soft paper dust, where the exposed workers had increased symptoms of nasal blockage and nasal crusting compared with unexposed controls (19). Paper dust is likely to absorb moisture from the nasal mucosa and thereby affect the mucociliary transport rate. This could reduce nasal clearance and promote nasal inflammation. Paper dust can also contain substances such as chalk, lime and resins that can cause local irritation and elicit an inflammatory response in the respiratory mucosa.

Occupational cleaning was particularly associated with CRS in male subjects. This association was also previously found for non-infectious rhinitis and the present results further link occupational cleaning to nasal inflammation (9). Exposure to cleaning agents has been associated with occupational asthma, confirming its potential role as an occupational hazard for the respiratory mucosa (20). Our data do not enable us to identify specific cleaning agents, but they confirm the findings from similar studies (21).

Occupational exposure to metal dust was associated with CRS in male workers. To our knowledge, occupational exposure to metal dust has not previously been linked to CRS. Rehfisch et al. studied lung function and airway symptoms in workers exposed to cobalt dust at a hard metal plant. They found that even low levels of cobalt exposure appear to hamper lung function in both smokers and non-smokers, but the difference was not statistically significant (22).

Exposure to moisture/mould/mildew was significantly associated with CRS. In the study by Gao et al., occupational exposure to mouldy and damp environments was also related to CRS

(11). They found a dose-response relationship between the risk of having CRS and the frequency of exposure to a mouldy or damp environment. The pathophysiological mechanisms for this effect remain unclear. It is, however, known that exposure to certain fungi can cause disease and it has been suggested that mould can cause disease by three different mechanisms: the generation of a harmful immune response, direct infection by the organism and toxic-irritant effects from mould by-products (23).

In our study, CRS was significantly associated with exposure to animals at work. Exposure to laboratory animals has previously shown a strong association with allergic sensitisation and rhinitis (24). Studies of workplace animal exposure and CRS are scarce. Gao et al. found no significant association between having a pet at home and CRS, after adjusting for age, gender and smoking habits (11).

In this random population, we found that smoking was associated with CRS, which has also previously been reported (25). According to Statistics Norway (Statistisk sentralbyrå), 15% of males and 14% of females respectively smoked every day in the general population in Norway in 2013. Nine per cent were occasional smokers (26). In the whole Telemark Study cohort (n=16,009), 14% were daily smokers. This is in accordance with the general Norwegian population. In our data, we have included both daily smokers and occasional smokers in the term “current smokers”, which accounts for the higher percentage (24%) of current smokers. As smoking is a risk factor for CRS, smoking cessation should always be advocated in order to reduce the risk of CRS in the occupational environment as well.

As expected, the prevalence of CRS was significantly higher in subjects reporting asthma (22%) (27). Previous studies have shown that up to 50% of patients with CRS have clinical asthma (4). Asthma is strongly associated with rhinitis and with nasal polyps and asthma should therefore always be assessed in patients with CRS.

225 The prevalence of 9% CRS in this study is in accordance with previous studies based on the
226 EPOS criteria (5-7). In the Telemark population, the distribution of CRS was similar among
227 males and females. Previous studies have reported a higher prevalence of CRS among
228 females. We found that CRS increased with age, which is in accordance with previous data
229 (4). The different phenotypes of CRS with regard to symptom expression have not previously
230 been extensively reported on. As expected, nasal obstruction was the most common
231 complaint, reported by 88% of the subjects with CRS, followed by facial pressure and pain.
232 The loss of the sense of smell is also common in these patients, especially in patients with
233 nasal polyposis. Symptom combinations which did not include nasal obstruction were the
234 least common.

235 We can only speculate on the mechanisms by which the occupational exposure we have
236 studied relates to CRS development. The studied exposure types are classified into high
237 molecular weight (HMW) agents and low molecular weight (LMW) agents. HMW agents,
238 such as moulds and animal dander, are often organic and may cause an allergic sensitisation.
239 It is most common for sensitisation to occur to a single agent, but cases in which dual
240 sensitisation occurs have been reported (28). LMW agents are often inorganic substances,
241 such as metals. Both HMW agents (paper dust, metal dust, animals, moisture/mould/mildew)
242 and LMW agents (cleaning agents) were associated with an increased risk of CRS in this
243 study. In overall terms, laboratory animal dander is one of the most common causal agents
244 associated with occupational rhinitis and this was also seen in this study with CRS (29).

245 This study has limitations that should be considered. The Telemark Study had a
246 comparatively low response rate. The non-responders have, however, been thoroughly
247 described in a separate study, showing a prevalence of respiratory symptoms similar to that of
248 the responders. Responders had a somewhat higher prevalence of a chronic cough and the use
249 of asthma medication (13), but these outcomes are not assessed in our study. The exposure

data used in this study were self-reported and may thus be subject to recall bias in terms of timing and level of exposure. There is a potential risk that subjects with CRS symptoms recall their exposure better than controls and the prevalence of CRS will therefore be overestimated. Another weakness in a questionnaire-based study of CRS is the lack of a clinical validation of the nasal status performed through nasal endoscopy and/or with the help of a computed tomography of the sinuses (CT). When using only self-reported symptoms, there is a risk of overestimating the prevalence of CRS. The questions used to identify CRS have been validated by Bhattacharyya et al. in a study of 202 subjects using symptoms compared with CT. They found a sensitivity of 88.7% and a specificity of 12.3%, with a positive predictive value of 39.9 and a negative predictive value of 62.5 (30). Self-reported symptoms of CRS have also been validated in a pilot study from South America comprising 40 patients and 40 controls, using nasal endoscopy and/or a CT scan, showing good agreement between the symptom-based diagnosis and the clinical diagnosis by a trained otorhinolaryngologist (7). CRS develops over time and, in a cross-sectional study, it is not possible to study the relationship between time of exposure, cumulative exposure and the onset of CRS. The Telemark cohort will be followed up in 2019, giving an opportunity to study occupational exposure and the development of CRS over time.

Conclusion

In this population-based study, the overall prevalence of CRS was 9%. Occupational exposure to paper dust, cleaning agents, metal dust, animals, moisture/mould/mildew, physically strenuous work, smoking and asthma was independently related to CRS in this adult population. The results show that occupational exposure should to be taken into account when evaluating patients with CRS and when planning occupational safety.

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Excluded

Figure I. Flow chart of the study population.

Table I. Definition of CRS according to EPOS (4)

Symptom	Question
Major symptom	Have you had a blocked nose for more than 12 weeks in the last 12 months?
	Have you experienced discoloured nasal secretions (mucus) or discoloured mucus in your throat for more than 12 weeks in the last 12 months?
Minor symptom	Have you experienced pain or pressure around your forehead, nose or eyes for more than 12 weeks in the last 12 months?
	Has your sense of smell been reduced or absent for more than 12 weeks in the last 12 months?
and/either*	
endoscopic signs of:	
nasal polyps and/or	
mucopurulent discharge primarily from middle meatus and/or	
oedema/mucosal obstruction primarily in middle meatus	
and/or	
CT changes:	
Mucosal changes within the osteomeatal complex and/or sinuses	

* According to the EPOS definition not applicable in questionnaire based studies of CRS

410 Table II. Description of study population (n=16,099) with regard to age, gender, smoking
 411 habits, asthma and atopy.

	CRS (n=1326)	Non-CRS (n=13580)	Total	p-value
Age				0.006
16-30 years, n (%)	343 (8)	3911 (92)	4254	
31-40 years, n (%)	349 (9)	3687 (91)	4036	
41-50 years, n (%)	634 (10)	5982 (90)	6616	
Gender				0.602 NS
Female gender, n (%)	731 (9)	7591 (91)	8322	
Male gender, n (%)	595 (9)	5989 (91)	6584	
Smoking				< 0.001
Never, n (%)	578 (7)	7370 (93)	7948	
Past, n (%)	309 (10)	2925 (90)	3234	
Current, n (%)	435 (12)	3197 (88)	3632	
Missing, n (%)	4 (4)	88 (96)	92	
Asthma				< 0.001
No, n (%)	953 (7)	12233 (93)	13186	
Yes, n (%)	373 (22)	1347 (78)	1720	
Atopy				< 0.001
No, n (%)	562 (5)	9808 (95)	10370	
Yes, n (%)	764 (17)	3772 (83)	4536	

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Table III. OR_{adj} (multiple regression analysis of CRS and different types of occupational exposure, adjusted for age, gender, smoking, asthma, atopy) and stratified by gender. Statistically significant results are highlighted.

Exposure	Only ever employed (n=14,906) OR _{adj} (95% CI)	Female (n=8,322) OR _{adj} (95% CI)	Male (n=6,584) OR _{adj} (95% CI)
Past smoker	1.2 (1.0, 1.4)	1.2 (0.97, 1.5)	1.2 (1.0, 1.6)
Current smoker	1.6 (1.4, 1.8)	1.5 (1.3, 1.8)	1.7 (1.4, 2.0)
Asthma	2.3 (2.0, 2.7)	2.4 (2.0, 2.9)	2.2 (1.7, 2.7)
Atopy	2.8 (2.5, 3.2)	2.8 (2.4, 3.3)	2.9 (2.4, 3.5)
Cooking fumes	1.1 (0.97, 1.3)	1.2 (0.98, 1.5)	1.0 (0.75, 1.4)
Car/engine exhaust	0.95 (0.80, 1.1)	0.96 (0.70, 1.3)	0.96 (0.77, 1.2)
Strong acids	1.0 (0.85, 1.2)	0.98 (0.75, 1.3)	1.0 (0.82, 1.3)
Stone dust	1.0 (0.86, 1.3)	1.1 (0.78, 1.6)	1.1 (0.85, 1.3)
Flour/grain dust	1.0 (0.82, 1.3)	0.91 (0.68, 1.2)	1.2 (0.85, 1.7)
Wood dust	1.1 (0.89, 1.3)	1.4 (0.98, 1.9)	1.0 (0.82, 1.3)
Paper dust	1.3 (1.1, 1.5)	1.4 (1.1, 1.7)	1.2 (0.87, 1.5)
Metal dust	1.3 (1.1, 1.6)	0.85 (0.54, 1.3)	1.5 (1.2, 1.9)
Cleaning agents	1.2 (1.0, 1.3)	1.1 (0.92, 1.3)	1.2 (0.98, 1.5)
Superglue	1.1 (0.90, 1.3)	0.96 (0.67, 1.4)	1.2 (0.92, 1.4)
Painting/varnishing	0.95 (0.78, 1.2)	0.97 (0.67, 1.4)	0.95 (0.75, 1.2)
Welding/metal smoke	0.98 (0.78, 1.2)	1.5 (0.87, 2.4)	0.90 (0.70, 1.2)
Sewage	1.0 (0.80, 1.3)	0.75 (0.41, 1.4)	1.1 (0.84, 1.4)
Hair care products	1.1 (0.82, 1.4)	1.2 (0.87, 1.6)	0.84 (0.41, 1.7)
Animals	1.2 (1.0, 1.5)	1.3 (0.99, 1.7)	1.1 (0.80, 1.4)
Moisture/mould/mildew	1.3 (1.1, 1.5)	1.3 (1.0, 1.5)	1.3 (1.1, 1.6)
Cold (in cold-storage rooms or outside in winter)	1.0 (0.87, 1.2)	1.2 (0.97, 1.5)	0.83 (0.67, 1.0)
Physically strenuous work	1.4 (1.2, 1.7)	1.4 (1.2, 1.7)	1.4 (1.1, 1.8)

433 Table IV. Prevalence of CRS symptoms (>12 weeks) and combinations of symptoms (>12
 434 weeks) fulfilling the EPOS criteria (n=1,326)

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CRS symptoms	N (%)
Prevalence of CRS symptom	
Stuffy nose, n (%)	1167 (88)
Facial pain/pressure, n (%)	793 (60)
Discoloured secretion, n (%)	746 (56)
Reduced sense of smell, n (%)	726 (55)
Prevalence of combination of symptoms	
Stuffy nose, facial pain	245 (18)
Stuffy nose, reduced smell	233 (18)
Stuffy nose, discoloured mucus, facial pain, reduced smell	201 (15)
Stuffy nose, discoloured mucus, facial pain	142 (11)
Stuffy nose, discoloured mucus	136 (10)
Stuffy nose, discoloured mucus, reduced smell	108 (8)
Stuffy nose, facial pain, reduced smell	102 (8)
Discoloured mucus, facial pain	77 (6)
Discoloured mucus, reduced smell	56 (4)
Discoloured mucus, facial pain, reduced smell	26 (2)

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