The prevalence of primary chronic rhinosinusitis in young adults from a Swedish birth cohort

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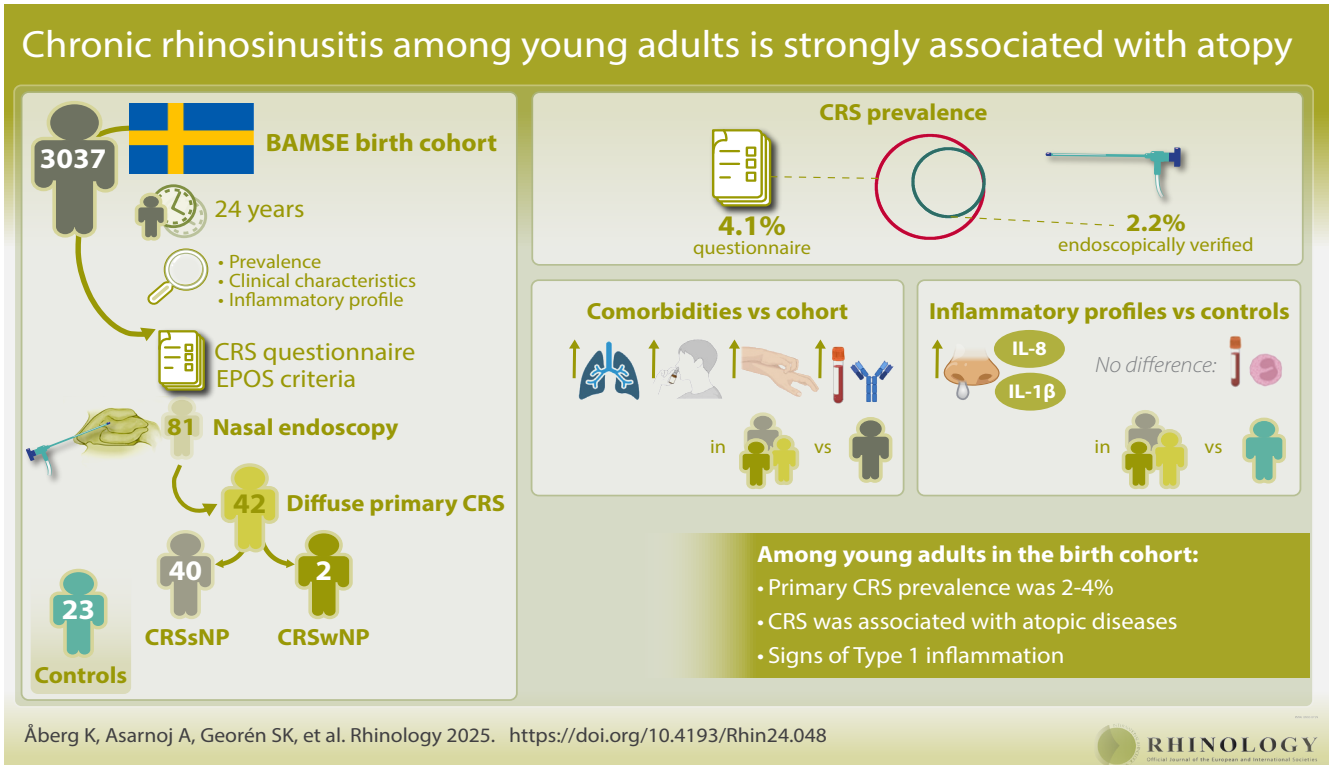

Abstract

Background: Chronic rhinosinusitis (CRS) is common worldwide but scarcely studied among young adults. The aim was to investigate prevalence, clinical features, comorbidity, and mucosal inflammatory patterns of CRS among 24-year-olds in a population-based study.

Method: 3037 subjects from the birth cohort BAMSE (Barn/children Allergy Milieu Stockholm Epidemiology) had complete questionnaire answers on CRS at the 24-year-follow-up. Subjects fulfilling the European Position Paper on Rhinosinusitis (EPOS) criteria of CRS at 16 and/or 24 years (n=141), were invited to a clinical examination. We examined 81 subjects. Sixty-eight subjects were included, of whom 40 had CRSsNP, 2 CRSwNP and 26 CRS symptoms only. Twenty-three controls without CRS from BAMSE were included. Nasal endoscopy was performed, IgE against airborne allergens and cytokine gene expression in nasal lavage (NAL) were analyzed.

Results: The questionnaire-based CRS prevalence was 4.1%, of which 2.2% was endoscopically verified. Sensitization to airborne allergens was more often seen among CRSsNP and "CRS symptoms only", compared to controls. Among CRS subjects overall, the proportion of asthma, AR, atopic eczema, and sensitization to airborne allergens was significantly higher compared to the rest of the cohort. The gene expression of IL-1β and IL-8 in NAL was elevated among CRSsNP and "CRS symptoms only" compared to controls, with a trend for TNF-α and MPO.

Conclusions: The prevalence of primary CRS was estimated to 2-4%. There was a significant association between CRS and atopic diseases in this age group. The NAL profile showed signs of type-1 inflammation.

Key words: chronic rhinosinusitis, atopy, prevalence, inflammation, birth cohort

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disease located in the nose and paranasal sinuses. The symptom criteria are at least two out of four symptoms (nasal congestion, nasal discharge, facial pain/pressure or impaired sense of smell), of which one must be nasal congestion or nasal discharge, present for more than 12 subsequent weeks [1]. The prevalence of CRS in the population is challenging to determine due to the difficulty of verifying the symptoms in population-based materials. Self-reported CRS symptoms are estimated to be around 10-12% in the adult population but with geographical differences [1,2]. The few studies on CRS verified by nasal endoscopy or CT scan give an estimate of around 3% [1].

CRS has traditionally been divided into CRS with nasal polyps (CRSwNP) or without nasal polyps (CRSsNP). Symptoms should be verified with nasal endoscopy, which is the only way to distinguish between CRSwNP and CRSsNP, or with a CT-scan. Furthermore, there are different endotypes of CRS [3,4]. As presented in the European Position Paper on Rhinosinusitis (EPOS) from 2020, CRS can be divided into primary and secondary CRS, where primary diffuse (bilateral) CRS is further divided into eosinophilic CRS (eCRS) and non-eCRS, depending on the level of eosinophils in mucosal tissue biopsy [1]. Patients with CRSsNP most often present with type 1 neutrophilic inflammation (non eCRS) in the nasal mucosa with elevated levels of IL-1β, IL-6, IL-8 and MPO, although previous research from our group point to a possible shift towards type 2 inflammation among non-asthmatics with CRSsNP [5]. In contrast, most patients with CRSwNP, present with type 2 inflammation, with cytokines associated with eosinophilic inflammation such as IL-4, IL-5 and ECP. However, in other parts of the world, for example in Asia, the inflammatory pattern may differ [6].

Asthma is common among adults with CRS, 25% have been reported to have asthma [1] and nearly 50% among patients with CRSwNP. This can be compared to a reported overall prevalence of asthma in the EU of 8.2% [7]. An association to allergic rhinitis (AR) has been suggested, but the results are conflicting [8]. CRS-affected individuals often have substantial loss of quality of life (QoL) and productivity [9-11] which equals that of other chronic diseases such as asthma and chronic heart failure [1].

Data on CRS from population-based material is scarce and above all, CRS is not well studied among young adults. The aim of this study was to investigate the prevalence and clinical features of CRS at 24 years of age, such as type and burden of symptoms, QoL and comorbidity as well as pattern of inflammation in the nasal mucosa, using a well characterized birth cohort. This is to our knowledge the first study where CRS has been characterized on the clinical as well as on the inflammatory levels in a population-based birth cohort.

Materials and methods

The BAMSE cohort

Young adults from the population-based birth cohort BAMSE (barn/children, allergy, milieu, Stockholm, epidemiology) were enrolled in the study. The cohort has previously been described in detail [12]. Briefly, the cohort consists of 4089 children included within a few months after birth. Questionnaires were repeatedly used to obtain data on allergic diseases and asthma. The 16- and 24-year questionnaires included questions on CRS according to EPOS. At 4, 8, 16 and 24 years of age clinical examinations were also performed, including blood samples for analysis of IgE to inhalant allergens.

Subgroup study and study population

All subjects fulfilling the EPOS criteria of CRS in the 24-year follow-up questionnaire (n=125) were targeted for inclusion. Telephone interviews were performed to find the subjects with ongoing symptoms of CRS. To reduce the risk of missing subjects not fulfilling the EPOS criteria at the time of the 24-year questionnaire, we also contacted subjects with CRS symptoms, verified by telephone interview at 16 years of age, which we considered at greater risk of still having CRS at 24 years, rendering an additional 16 subjects. Thus, a total number of 141 were addressed for the telephone interview.

Subjects with ongoing symptoms for at least 12 weeks, were invited to participate in a clinical follow-up, including nasal endoscopy, nasal lavage for inflammatory markers, blood samples for eosinophils and total IgE. In addition, 27 controls without CRS symptoms from the same cohort were included. They were randomly retrieved from a subgroup who had nasal lavage performed at 16 years of age, and without CRS symptoms at 24 or 16 years. For ethical reasons (radiation hygiene) no CT scan was performed on subjects or controls.

Definitions

Symptoms of CRS were based on the questionnaire and the telephone interview and defined according to EPOS criteria for chronic rhinosinusitis [1]:

≥12 weeks duration of at least two out of four symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip): ± facial pain/pressure ± reduction or loss of smell.

CRS classification was done according to EPOS2020 into CRSsNP and CRSwNP [1].

- *CRSsNP*: symptoms of CRS as above and bilateral endoscopic signs of mucopurulent discharge primarily from middle meatus and/or oedema/mucosal obstruction primarily in middle meatus.
- *CRSwNP*: Symptoms of CRS as above and endoscopic signs of bilateral nasal polyps.
- *Symptoms of CRS only*: Symptoms as above, but no endosco-

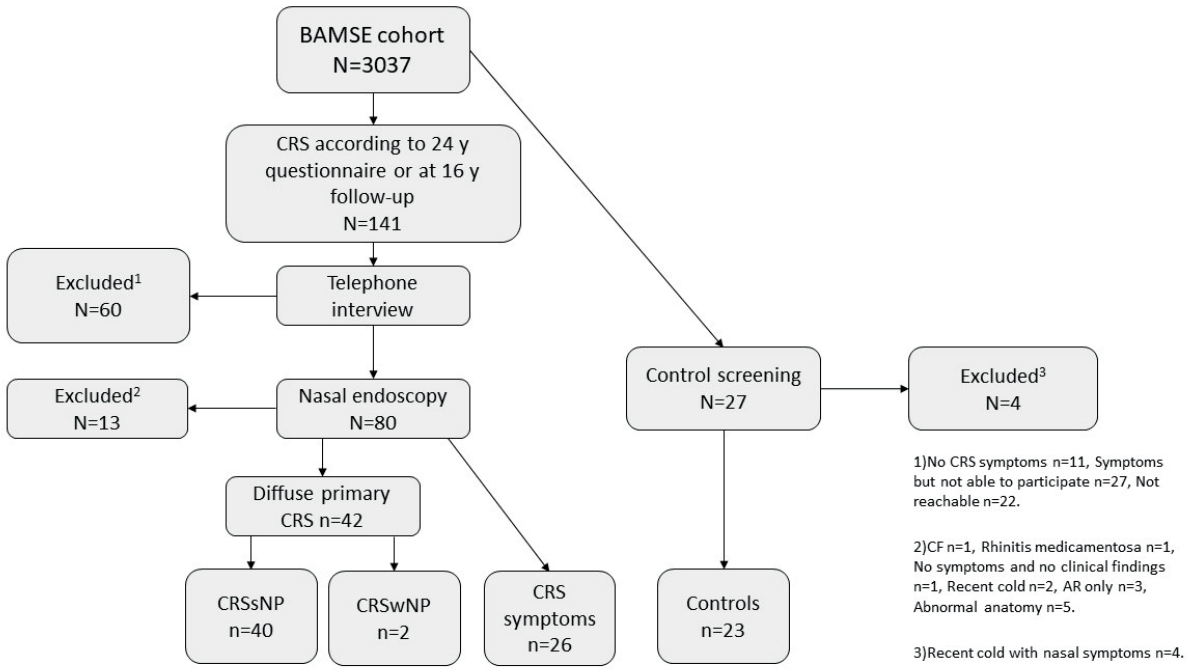

Figure 1. Flow chart of the study population.

pic findings at examination.

- *Asthma*: Doctor´s diagnosis of asthma ever AND episodes of breathing difficulties or asthma medication during the last 12 months.
- *Severe asthma*: Asthma as above, requiring ICS + LABA and/or LTRA, still not controlled (episodes of breathing difficulties, OCS, hospital visits).
- *Symptoms of allergic rhinitis (AR)*: Symptoms from nose/eyes at exposure to an inhalant allergen.
- *Atopic eczema*: Dry skin in combination with itchy rash for 2 weeks or more AND typical localization (face or arms/legs extension surfaces or arms/legs flexures or wrists/ankles flexures) up to the date of questionnaire 24 AND/OR Doctor's diagnosis of eczema up to the date of questionnaire 24 [13].

Quality-of-life

Quality-of-life (QoL) and burden of symptoms were assessed by symptoms scoring with Visual Analogue Symptom Scale (VAS) and SinoNasal Outcome Test (SNOT-22) [11,14,15]. (All rights reserved. Copyright 2006 by Washington University in St. Louis, MI, USA)

Blood samples

IgE to inhalant allergens was assessed among all participants at the BAMSE 24-year follow-up using Phadiatop® [a mixture of common inhalant allergens: birch, grass (timothy), mugwort, cat, dog, horse, mould (*Cladosporium herbarum*) and house dust mite (*Dermatophagoides pteronyssinus*), Thermo Fisher Diagnostics AB, Uppsala, Sweden]. A positive Phadiatop® test was defined as IgE ≥0.35 kUA/l. Blood samples for total serum IgE and blood eosinophils were drawn from the subjects and controls attending the CRS subgroup follow-up and analyzed at the Department of Clinical Immunology and Transfusion Medicine, and the Department of Clinical Chemistry, respectively, Karolinska University Hospital. Cut off for total IgE was set to 100 kU/L [1]. For blood eosinophils two different cut off levels were used for comparison, ≥0.15 and ≥0.25 10^9/L, respectively [16].

Nasal cytokines

Nasal epithelial cells, collected by nasal lavage (NAL), were tested for gene expression of a panel of common inflammatory cytokines (IL-1β, IL-5, IL-6, IL-8, TNF-α, MPO and ECP). For details see online supplement.

Statistical analyses

For calculations on differences of proportions between two groups (controls vs CRSsNP, CRSwNP or CRS symptoms only, respectively), χ^2 test was used and Fishers exact test when appropriate ($n < 5$).

For the distribution of the continuous variables, VAS, SNOT 22 and eosinophils, the median was calculated and for comparison between the groups the Wilcoxon/rank-sum test was used. Values of eosinophils < $0.1x10^9$/L, were put as 0.09.

Calculations on differences in distributions of inflammatory markers were made with an ANOVA test and thereafter Wilcoxon/rank-sum test if significant differences in medians were found.

Table 1. Sinonasal symptoms and QoL among subjects with CRSsNP, CRSwNP, CRS symptoms only, and 23 controls, from the BAMSE birth cohort, Stockholm, Sweden.

	Controls n=23		CRSsNP [1] n=40			CRSwNP [2] n=2			CRS symptoms only [3] n=26			
	n	%	n	%	p-value*	n	%	p-value*	n	%	p-value*	p-value[§]
Sinonasal symptoms												
Congestion	0	0.0	39	97.5	<0.001	2	100	0.003	25	96.2	<0.001	0.755
Secretions	0	0.0	31	77.5	<0.001	0	0.0	n.a.	19	73.1	<0.001	0.682
Pain/preassure	0	0.0	20	50.0	<0.001	0	0.0	n.a.	5	19.2	0.052	0.019
Reduced sense of smell	0	0.0	26	65.0	<0.001	2	100	0.003	10	38.5	0.001	0.034
Cough	0	0.0	10	25.0	0.009	0	0.0	n.a.	5	19.2	0.052	0.756
Doctor's diagnose of CRS [4]	0	0.0	4	10.0	0.288	0	0.0	n.a.	1	4.2	1.000	0.640
Treated with nasal steroids	0	0.0	22	55.0	<0.001	2	100	0.003	14	53.9	<0.001	0.927
Consider themselves completely healthy [4]	17	73.9	11	29.7	0.001	0	0.0	0.093	8	33.3	0.005	0.767
	M			M			M			M		
SNOT-22	3.0			37.5	<0.001		39.5	0.007		30	<0.001	0.097
VAS nasal	0.0			5.3	<0.001		6.8	0.007		4.8	<0.001	0.567

[1] Symptoms of CRS according to EPOS and signs of oedema or secretions in middle meatus at nasal endoscopy. [2] Symptoms of CRS according to EPOS and signs of nasal polyps at nasal endoscopy. [3] Symptoms of CRS according to EPOS but without endoscopic signs of CRS at follow up. [4] Internal missing <6%. M=median; * Compared to controls; [§] CRS symptoms only compared to CRSsNP.

P-values ≤0.05 were considered statistically significant. STATA statistical software (Version 16.1 SE StataCorp, Collage Station, TX, USA) was used for all statistical analyses except the calculations and graphical illustration of the inflammatory markers where Graph Pad Prism (GraphPad Software Inc., La Jolla, CA, USA) was used.

Ethical permission for the cohort (2016/1380-13/2), as well as for the subgroup study (2018/209-32), was obtained from the Regional Ethical Review Board at Karolinska Institutet, Stockholm, Sweden. Parents, and later the grown-up participants, gave informed consent for each follow up.

Results

At the 24-year-follow-up, the response rate was 75% from baseline. The 3037 participants who completed the questions on CRS constituted the study base from which the CRS subjects were identified. Complete answers on CRS, allergic rhinitis, asthma, and eczema were found in 3001 participants. Comparison of these two populations, respectively, to the original cohort showed a somewhat higher proportion of females and lower proportion of low socioeconomic status (Table S1).

Study population

Of the 3037 with complete questionnaire answers regarding CRS in the BAMSE cohort 24-year follow-up, 125 met the criteria for CRS. Sixteen additional subjects with CRS symptoms at the 16 year-follow-up were addressed with telephone interviews. Eleven out of a total of 141 subjects reported no symptoms at the time of the telephone interview and 27 reported symptoms but were not able/not willing to participate in the study. Twenty-two subjects were never reached. Thus, out of the 141 targeted, 81 individuals with symptoms of CRS underwent clinical examination (Figure 1). Six of these 81 subjects came from the group that claimed symptoms in the telephone interview at 16 years, but screened negative, or did not answer the questions regarding CRS, at the 24 years questionnaire. Thirteen of the 81 (16%) examined subjects were excluded due to 1) symptoms not suggestive of CRS (abnormal anatomy, n=5, intermittent allergic rhinitis, n=3, complete symptom recovery, n=1), 2) secondary CRS (CF, n=1), or 3) that the CRS diagnose could not be reliably verified (recent cold, n=2, rhinitis medicamentosa n=1). Sixty-eight subjects were included in the analyses and labeled as CRSsNP (n=40), CRSwNP (n=2) or CRS symptoms only (n=26). Five of the 42 subjects with endoscopically verified CRS came from the 16-year follow-up. Only 2 subjects with nasal polyps were found. These two subjects remained in the analyses for comparison, although interpretation must be carried out with caution due to the low number. Twenty-seven controls were examined, of which 4 were excluded from the analyses due to recent colds. In total, 23 controls were included in the analyses.

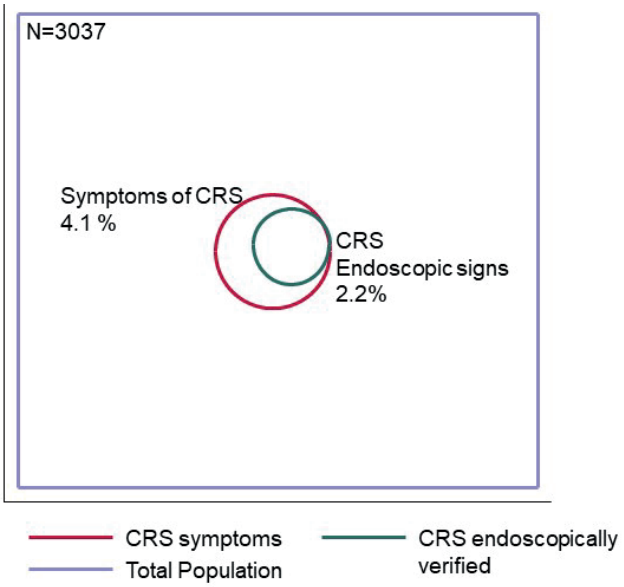

Figure 2. Estimated prevalence of chronic rhinosinusitis among 24-year-olds in the population-based BAMSE cohort, Stockholm, Sweden (N=3037).

Prevalence of CRS

The prevalence of CRS at 24 years of age according to the questionnaire was 4.1% (125/3037) (Figure 2). Forty-two of the 81 symptomatic subjects had endoscopic signs of CRS (51.9%). The estimated prevalence of endoscopically verified CRS was 2.2%, and 2.0% when excluding the 5 additional subjects from the 16-year follow-up. The calculation, also considering the subjects not examined, is presented in the Online supplement.

Symptoms and QoL

In general, subjects with CRSsNP and CRSwNP had very discrete endoscopic findings. None of them ever underwent sinus surgery. Among those with CRSsNP the most common symptom was nasal congestion (97.5% of subjects) followed by nasal secretions (77.5%) (Table 1). Similar proportions were seen among those with CRS symptoms only, i.e no endoscopic findings (96.2 % and 73.1%, respectively). Reduced sense of smell and facial pain/pressure was significantly more common among those with endoscopic findings of CRS compared to those with symptoms only (65.0% vs 38.5%, p=0.034 and 50.0 % vs 19.2 %, p=0.019, respectively). The two subjects with CRSwNP both reported nasal congestion and reduced sense of smell as only symptoms. They were previously treated with nasal steroids but none of them had a doctor's diagnosis of nasal polyposis. Median SNOT-22 scores were elevated in all groups compared to controls (CRSsNP 37.5, CRSwNP 39.5, CRS symptoms only 30.0). Among controls, 73.9% reported that they considered themselves completely healthy. The corresponding proportion for CRSsNP was 29.7%, and for CRSwNP and CRS symptoms only, 0.0% and 33.3%, respectively.

Comorbidities and characteristics

The proportion of subjects with asthma was significantly higher among those with verified CRSsNP (20%, p=0.023), CRSwNP (100%, p=0.003) and CRS symptoms only (23%, p=0.024), compared to controls (0%) (Table 2). The proportion of subjects with symptoms of AR was significantly higher in those with CRSwNP (100%, p=0.050) and "CRS symptoms only" (65.4%, p=0.001) than in the control group (17.4%). In the CRSsNP group, this proportion was also higher than in the control group, although not statistically significant (40%, p=0.092). Atopic eczema was significantly more common among those with verified CRS (CRSsNP 35%, p=0.034 and CRSwNP 100%, p=0.020) compared to controls (8.7%). Sensitization against airborne allergens was higher in all groups compared to controls, although statistical significance was not reached for CRSwNP.

Since the frequency of atopic manifestations in the control group was somewhat lower than expected in the general population, we performed an overall comparison of the CRS subjects with rest of the BAMSE cohort (Table S2). Asthma (23.5 % vs 11.1%, p=0.001), symptoms of AR (51.5% vs 30.1%, p<0.001), eczema (33.8% vs 17.4%, p<0.001) and sensitization to airborne allergens (60.7% vs 42.7%, p=0.005) were all significantly more common among CRS subjects than among individuals in the rest of the cohort (Table S2). Current smoking was notably more common among those with CRS symptoms only compared to controls (30.8% vs 8.7%, p=0.080), although not statistically significant. No significant gender differences were noted.

Inflammatory profiles

No significant differences were seen in median blood eosinophil levels, or in proportion of subjects with levels above cut off 0.15 or $0.25x10^9$/L, in any of the groups compared to controls (Table 2). The two individuals with CRSwNP both had total serum IgE > 100 kU/L (Table 2).

Using the EPOS 2020 classification of CRS for comparison [1], we analyzed what the division into type 2 and non-type 2 would look like, based on blood eosinophils alone. With a cut off 0.25x 10^9/L, 34 subjects with diffuse primary CRS were non type 2 and 8 were type 2, with 1 of the subjects with nasal polyps in each group.

In the nasal lavage there were signs of type-1 inflammation. The gene expression of IL-8 and IL-1β was significantly elevated among CRSsNP compared to controls, and for IL-8 also among "CRS symptoms only" compared to controls (Figure 3). There was a trend for TNF-α and MPO among CRSsNP and "CRS symptoms only" compared to controls. For CRSwNP a trend for elevated ECP was seen. No gene expression for IL-5 was detected in any sample.

Table 2. Sex, comorbid diseases and current smoking among subjects with CRSsNP, CRSwNP and CRS symptoms only, compared to controls.

N=91	Controls n=23		CRSsNP n=40			CRSwNP n=2			CRS symptoms only n=26		
	n	%	n	%	p-value	n	%	p-value	n	%	p-value
Males	9	39.1	18	45.0	0.793	2	100	0.183	11	42.3	1.000
Asthma [1]	0	0.0	8	20.0	**0.023**	2	100	**0.003**	6	23.1	**0.024**
Severe asthma [2]	0	0.0	2	5.0	0.529	1	50.0	0.080	1	3.9	1.000
Symptoms of AR [3]	4	17.4	16	40.0	0.092	2	100	**0.050**	17	65.4	**0.001**
AERD [4]	0	0.0	1	2.5	1.000	0	0.0	n.a.	1	3.9	1.000
Ezcema [5]	2	8.7	14	35.0	**0.034**	2	100	**0.020**	7	26.9	0.145
Current smoking	2	8.7	5	12.5	1.000	0	0.0	1.000	8	30.8	0.080
Sensitization [6]	6	26.1	24	60.0	**0.017**	2	100	0.093	18	69.2	**0.004**
Total IgE ≥100	3	13.0	11	27.5	0.223	2	100	**0.033**	7	26.9	0.299
Eosinophils ≥0.15	8	34.8	18	45.0	0.596	2	100	0.150	16	61.5	0.088
Eosinophils ≥0.25	3	13.0	7	17.5	0.734	1	50.0	0.300	3	11.5	1.000
	M	**IQR**	**M**	**IQR**		**M**	**IQR**		**M**	**IQR**	
Eosinophils	0.1	<0.1-0.2	0.1	<0.1-0.2	0.549	0.3	0.2-0.4	0.200	0.2	<0.1-0.2	0.199

[1] Doctor´s diagnosis of asthma ever AND episodes of breathing difficulties or asthma medication during the last 12 months. [2] Asthma as above, requiring ICS + LABA and/or LTRA, still not controlled (episodes of breathing difficulties, OCS, hospital visits). [3] Symptoms from nose/eyes at exposure to an inhalant allergen. [4] Aspirin Exacerbated Respiratory Disease. Reported. [5] Dry skin in combination with itchy rash for 2 weeks or more AND typical localization (face or arms/legs extension surfaces or arms/legs flexures or wrists/ ankles flexures) up to the date of questionnaire 1 AND/OR Doctor's diagnosis of eczema up to the date of questionnaire 1. [6] Phadiatop positive. M= median, IQR=inter quartile range.

Discussion

In this large population-based study of 24-year-old subjects, we found a prevalence of CRS symptoms of 4.1 % and endoscopically verified CRS of 2.0-2.2 %. A strong association with asthma was seen among those with CRSsNP, CRSwNP as well as CRS symptoms only. In addition, a significant association with AR, sensitization to airborne allergens and to atopic eczema was observed. Among those with CRS symptoms only, there was a clear overrepresentation of smokers.

We found that the prevalence of questionnaire-based symptoms of CRS (4.1%) was somewhat lower than most current population-based studies on CRS prevalence using EPOS criteria. Questionnaire-based studies from Europe, Korea and US have shown an overall prevalence of 11-12 %, China 8% and Brazil 5.5% [17-20]. Geographical differences have been noted, in Europe ranging from 6.9% to 27.1% [17] and in China from 4.8% to 9.7% [20]. In the same geographical area as the current study, GA²LEN reported a questionnaire-based prevalence of 9.6% [17]. No significant differences were seen in different age groups, but a lower prevalence at 55 years or older [17]. In the US, the prevalence was somewhat lower in the youngest age group, 18-39-year-olds, (13.2%), and peaking at 50-59 years (15.9%) [18]. In the Chinese study the prevalence at 15-34 years was 8.9% and at 35-59 years 7.6% [20]. The clinical experience of CRS is that the disease appears to increase up to middle age which seems to be in line with our results. We previously found a prevalence of 1.5% among 16-year-olds in our cohort [21], which has now increased to 4.1% among 24-year-olds.

A lower prevalence of CRS based on nasal endoscopy has also been found by others [22,23] and underlines the risk of overestimating the prevalence using symptoms only. On the other hand, using nasal endoscopy, the prevalence may also be underestimated. We have only examined the subjects once and, given the fluctuating nature of inflammatory diseases, there may be a certain degree of misclassification between "CRS symptoms only" and CRSsNP. This is also supported by the similarities in symptoms, comorbidities, HRQoL, and to some extent, the inflammatory profile between the two groups. Another way of confirming the diagnosis of CRS is radiology of the sinuses [24,25]. For ethical reasons we decided not to perform CT scan in this population-based setting. In a Dutch study based on CT/MR they found poor correlation between symptoms and objective findings [24].

An increased frequency of AR, atopic eczema, as well as sensitization to inhalant allergens, was seen for CRS symptoms only, CRSsNP and CRSwNP compared to controls. For some analyses statistical significance was not reached, which may be due to the low number of subjects. When comparing all subjects with

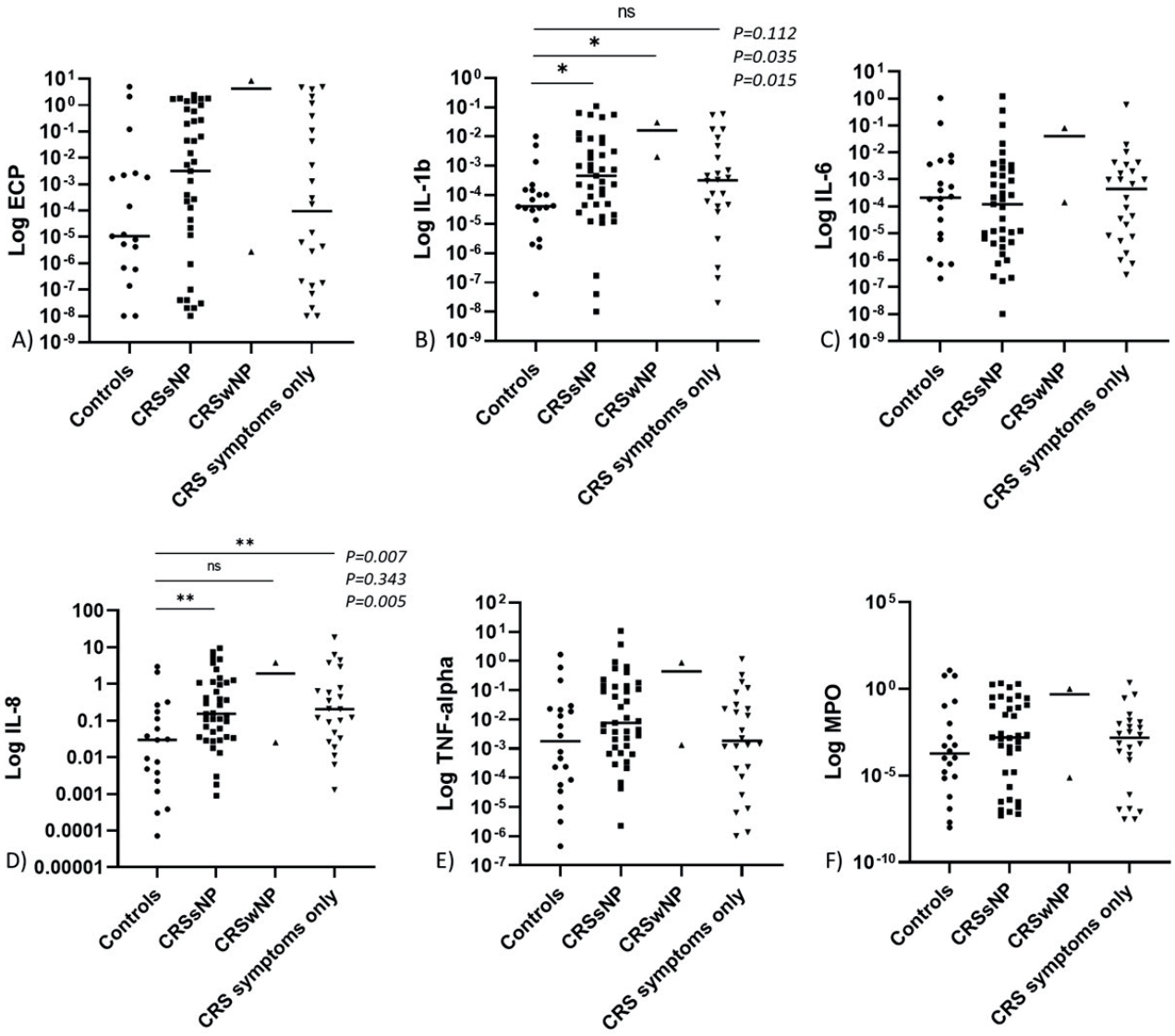

Figure 3. Gene expression from nasal cells collected by nasal lavage. Relative expression of A) ECP, B) IL-1β, C) IL-6, D) IL-8, E) TNF-α and F) MPO, respectively, compared to GAPDH + ACTB.

CRS symptoms, with or without endoscopic findings, to the rest of the cohort there was a significantly higher proportion of all the atopic manifestations in the CRS groups. A large review addressing the potential association between CRS and atopy concluded that the results are conflicting [8]. There are equal numbers of studies supporting and rejecting the importance of allergy in CRS, possibly due to differences in patient selection and age groups. Recently, a new subgroup of CRS has been proposed, central compartment atopic disease (CCAD), which is strongly associated with sensitization to airborne allergens [26,27]. The current study was not designed to evaluate CCAD, and no CT-scans were performed, why the possibility of this condition among our participants cannot be excluded.

The major differences found between the two groups CRSsNP and "CRS symptoms only" were current smoking and symptoms of AR, both being more common among those with CRS symptoms only, than those with endoscopic signs of CRS. Tobacco smoke has been shown to induce inflammation in the nasal mucosa [28,29] and previous, questionnaire-based, studies have reported an association between CRS symptoms and smoking [17,30,31]. Thus, a certain proportion of CRS symptoms in this group of young adults is most probably attributed to smoking, AR or non-allergic rhinitis. The fact that AR and atopy is overrepresented among subjects with CRS symptoms, with and without endoscopic findings, may be an explanation for the high prevalence of CRS symptoms found among adolescents and young adults in epidemiological studies [17]. Most probably AR may mimic CRS symptoms on the one hand, and on the other hand be a contributing cause of CRS among predisposed individuals in this age group. However, as mentioned above, we

cannot exclude the possibility that some of the subjects in the group of "CRS symptoms only" may have been misclassified and may represent CRS at an early or mild clinical stage.

The gene expression of IL-1β and IL-8 from nasal epithelial cells was higher among CRSsNP than controls, reflecting an inflammatory process in the nose. The inflammatory profile seemed to be skewed towards a type-1, neutrophilic, response despite the overrepresentation of atopic manifestations. Recent findings have pointed out the immunological complexity of CRS, making it clear that the concept of Th1/Th2 inflammation is not sufficient to explain the pathology. Several studies have indicated a role for neutrophiles and their mediators in allergic disease as well as in CRSwNP [32-34]. Both neutrophils and eosinophils are known to increase upon allergen exposure. Arebro et al. proposed that activated neutrophils may contribute to allergic inflammation in allergic rhinitis by priming T cells and attracting eosinophils [33].

We did not find convincing signs of type 2 inflammation in any of the groups. The median blood eosinophil levels were not significantly elevated. No gene expression of IL-5 was found in any samples, regardless of the primer used. This may be due to a lack of IL-5 expression or to the method used. However, the range of ECP expressions in nasal secretions was large. The inflammatory pattern found may have been different had we used nasal tissue samples.

Although all subjects with CRS in this study presented with mild endoscopic findings, the reported symptom burden was relatively high in all groups. Only around one third of the subjects with symptoms of CRS reported that they considered themselves healthy, compared to 73 % of the controls. The median VAS-scores for subjects with CRSsNP and CRSwNP were above 5 which is considered to represent uncontrolled disease [1]. Subjects with CRS symptoms only reported slightly lower scores. Taken together, this indicates a substantial effect of CRS symptoms on QoL, similarly noted previously among the 16-year-olds from the same cohort [21].

The major strength of this study is that it is based on a well characterized, unselected large birth cohort BAMSE, with a high participation rate, in combination with access to well validated comorbidities, clinical examination, IgE-analyzes and NAL.

There are some limitations of the study that need to be addressed. Given the study design and epidemiologic setting, misclassifications of subjects cannot be ruled out. The participants answered the questionnaire at only one time-point and there may have been CRS cases who were asymptomatic at the time of the questionnaire that we have missed. Furthermore, we have only examined the subjects once. There is a possibility that some of the subjects with "CRS symptoms only", or some of those excluded from the study, could have had endoscopic findings, if we had reexamined them after some time. This would lead to an underestimation of the prevalence. Another limitation is the relatively low number of subjects and controls (which partly is a result of the prevalence of CRS). Among all subjects with assumed CRS symptoms, we performed nasal endoscopy on 62%. We had only 23 controls and they seemed healthier than the general population. This could result in clearer differences between the groups regarding inflammatory markers. On the other hand, this could lead to an overestimation of the association with comorbid diseases, which is why we also compared the frequency of comorbid diseases with the rest of the cohort. Also, the lack of mucosal biopsies is a limitation that prevents us from using the latest classification of CRS, i.e from subtyping CRS into eCRS and non-eCRS.

More females than males attended the 24-year follow-up. A sensitivity analysis has previously been performed [35], which showed that atopic eczema, rhinitis, and IgE-sensitization, were slightly more common among those who attended the 24-year follow-up, but no differences were seen between males and females. This could overestimate the frequency of these diseases among those with CRS. The proportion of AR noted in the cohort, 30.1%, is in the upper range of what was reported among 18-39-years-olds in the general Swedish population 2015, 28-30%, (Miljöhälsorapporten©, Folkhälsomyndigheten, 2017. Artikelnummer: 02096-2016).

Conclusion

The prevalence of CRS was estimated to be 2-4% among young adults in northern Europe. A significant association between CRS and atopic manifestations in this age group was found. Furthermore, the nasal inflammatory profile showed signs of type 1 inflammation. Although endoscopic signs of CRS were mild, the impact on QoL was high.

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Authors' contributions

MW, MvH, AA, MH, LOC, SKG and KÅ were involved in planning and writing. KÅ and MW conducted the clinical examination, data collection and data analyses on the subgroup follow-up. EM, IK and AB are managing the planning, follow-ups and data collection in the cohort. All authors were involved in interpretation of data, provided critical feedback during development of the manuscript, and approved the final version of the manuscript.

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Conflicts of interest

AA has received lecture fees from Orion Pharma, Nestlé, Semper, ThermoFisher, and ALK and advisory board fees from Novartis, Sanofi, Danone, and Nestlé Health Science, all outside the submitted work. EM has received lecture and/or advisory board fees from Airsonett, ALK, AstraZeneca, Chiesi and Sanofi, all outside the submitted work. MvH has received lecture fees from Thermo Fisher Scientific and Astra Zeneca, all outside the submitted work. MW has received lecture fees from Sanofi, Orion Pharma and ALK, personal fees from Viatris and research funding from ALK, all outside the submitted work.

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SUPPLEMENTARY MATERIAL

Materials and methods

Nasal lavage (NAL) and quantitative reverse transcription polymerase chain reaction (qrt-PCR) on NAL pellets

Nasal epithelial cells, collected by nasal lavage (NAL), was tested for gene expression to a panel of common inflammatory cytokines.

NAL from study participants was collected by spraying normal saline into each nostril respectively. RNA was extracted from the cell pellets and stored in RNAlater using Qiagen's "RNeasy Plus Micro Kit". Generation and amplification of cDNA were done from 20 ng RNA using Qiagen's "QuantiTect Whole Transcriptome Kit".

Gene expression of IL-1β, IL-5, IL-6, IL-8, TNF-α, MPO and ECP was quantified on the mRNA level using quantitative reverse transcription-polymerase chain reaction (qrt-PCR) on the cDNA samples. ACTB primer pairs were used as housekeeping genes to get a relative mRNA expression for each target gene.

For the determination of expression levels of target genes, the comparative cycle threshold (Ct) method was used [(1)]. The ΔCt value was determined by subtracting the average of *GAPDH*, or the average of *GAPDH+ACTB* Ct value from the average Ct value. 6 samples were excluded due to low RNA quality, and from 3 samples the amount of RNA was not sufficient for all analyses.

Calculation of prevalence of endoscopically verified CRS

When calculating the estimated population prevalence of CRS with endoscopic signs we were taking into account the subjects never reached (n=22) and the subjects with symptoms of CRS according to the telephone interview but not examined (n=27).

The proportion of subjects with ongoing symptoms according to the telephone interview was 90.8% (108/119=0.908).

The proportion of subjects with endoscopic signs of CRS among those examined was 51.9% (42/81 = 0.519).

We assumed that the same proportion of subjects among those never reached would have symptoms of CRS, rendering an additional 20 subjects with symptoms (22 x 0.908=20).

We assumed that the same proportion among those with symptoms but not examined would have endoscopic signs of CRS (27 x 0.519) + (20 x 0.519) = 24.

42 + 24 / 3037 = 2.2%

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Table S1. Study base compared to the original cohort.

	The BAMSE Cohort N=4089		Study base N=3037			Comparison group from the cohort N=3001		
	n	%	n	%	95% CI	n	%	95% CI
Males	2065	50.5	1428	47.0	45.2-48.8	1409	47.0	45.2-48.7
Family history of atopy [1]	1746	43.2	1326	44.0	42.2-45.8	1315	44.2	42.4-46.0
Low socioeconomic status	695	17.1	461	15.2	14.0-16.6	455	15.2	14.0-16.6
Any parent born outside Scandinavia	543	16.0	417	15.6	14.2-17.0	413	15.6	14.2-17.0
Any parent smoking at time of birth	855	21.0	611	20.2	18.8-21.7	599	20.1	18.7-21.6

[1] Any parent with asthma, allergic rhinitis or eczema at time of birth.

Table S2. All subjects with CRS symptoms compared to the cohort regarding atopic manifestations.

N=3001	Cohort N=2933		CRS symptoms N=68		
	n	%	n	%	95% CI
Asthma [1]	325	11.1	16	23.5	0.001
Severe asthma [2]	23	0.78	4	5.9	<0.001
Symptoms of AR [3]	883	30.1	35	51.5	<0.001
Eczema [4]	510	17.4	23	33.8	<0.001
Sensitization [5]	911	42.7	37	60.7	0.005

[1] Doctor´s diagnosis of asthma ever AND episodes of breathing difficulties or asthma medication during the last 12 months. [2] Asthma as above, requiring ICS + LABA and/or LTRA, still not controlled (episodes of breathing difficulties, OCS, hospital visits). 3 Symptoms from nose/eyes at exposure to an inhalant allergen. 4 Dry skin in combination with itchy rash for 2 weeks or more AND typical localization (face or arms/legs extension surfaces or arms/legs flexures or wrists/ ankles flexures) up to the date of questionnaire 1 AND/OR Doctor's diagnosis of eczema up to the date of questionnaire 1.
[5] Phadiatop positive.