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Acute and chronic rhinosinusitis and allergic rhinitis in relation to comorbidity, ethnicity and environment

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Data Availability Statement: The database contains personal information of participants like postal code, date of birth and place of residence. Participants did not consent to have their personal information made publicly available. Data without this personal information of the participants are available in the supporting information files. Questions regarding the data can be sent to corresponding author at r.hoffmans@amc.nl or our ethics comittee at mecamc@amc.nl.

Abstract

Background

This study was conducted to assess the effect of comorbidity, ethnicity, occupation, smoking and place of residence on allergic rhinitis (AR), acute rhinosinusitis (ARS) and chronic rhinosinusitis (CRS).

Methods

A GA^{2}LEN (The Global Allergy and Asthma European Network) screening questionnaire was sent to a random sample of the Dutch population (n = 16700) in three different areas of the Netherlands.

Results

Fifty percent (8347) of the questionnaires sent were returned. A total of 29% respondents (27–31% in different areas) met the criteria for AR, 18% (17–21%) for ARS and 16% (13–18%) for CRS. Risk factors for AR were itchy rash, eczema, adverse response after taking a painkiller, asthma, CRS and ARS. Moreover, the risk of AR was twice as low for full-time housewives/househusbands than for people with jobs. The risk of ARS or CRS was significantly higher in respondents with a doctor's diagnosis of CRS, AR, itchy rash or smoking. The risk of CRS was also significantly higher in respondents with an adverse response after taking painkillers, active smoking or asthma. Caucasians are generally less likely to have AR or CRS than Latin-Americans, Hindustani and African-Creoles, and more likely to have ARS than Asian, Hindustani, Mediterranean and African-Creoles.

Conclusions

This study found shared and distinct risk factors for AR, ARS and CRS and therefore provides support for the belief that they have shared symptoms but are different diseases with different aetiologies.

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Abbreviations: AERD, aspirin-exacerbated respiratory disease; ANOVA, analysis of variance; AR, allergic rhinitis; ARS, acute rhinosinusitis; CRS, chronic rhinosinusitis; CI, confidence interval; CT, computed tomography; EPOS, European position paper on rhinosinusitis and nasal polyps; FESS, functional endoscopic sinus surgery; GA^{2}LEN, The Global Allergy and Asthma European Network; OR, odds ratio; SPSS, Statistical Package for the Social Sciences.

Introduction

Allergic rhinitis (AR), acute rhinosinusitis (ARS) and chronic rhinosinusitis (CRS) are common upper airway diseases. [1–4] According to the European position paper on rhinosinusitis and nasal polyps (EPOS), rhinosinusitis is clinically defined as inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) and/or facial pain/pressure and reduction or loss of smell, combined with objective signs of disease identified by endoscope or CT scan. The definition without objective signs is used in epidemiological studies. When the onset of these symptoms is acute and when they are present for less than twelve weeks, the diagnosis is ARS. When they persist for more than twelve weeks, the diagnosis is CRS. [2]

AR is clinically defined as a symptomatic disorder of the nose induced after allergen exposure by an IgE-mediated inflammation of the nasal membranes. The symptoms include rhinorrhoea (anterior or posterior), nasal congestion, nasal itching, and sneezing. [5] There is no uniform definition for epidemiological studies. Different definitions have been used in questionnaires in previous studies. [5, 6]

There is a lot of data about the effect of comorbidity (eczema, urticaria and asthma, for example), ethnicity, occupation, smoking and place of residence on the incidence of AR [5], but less is known about the effect of these factors on CRS [2] and little is known about ARS.

The GA^{2}LEN survey was conducted under the auspices of The Global Allergy and Asthma European Network (GA^{2}LEN). The associated questionnaire was designed to focus specifically on upper airway symptoms and particularly upper airway disease like rhinitis and rhinosinusitis, but also on some gaps in our scientific understanding of allergic disease and some risk factors such as adverse response to painkillers, occupation, ethnicity, smoking exposure, age and gender.

There are theories about the association between AR and ARS and CRS. One theory is that allergy causes swelling of the mucosa, which obstructs the ostium of the sinuses and impairs mucocilliary transport, and possibly induces rhinosinusitis. [2] Another theory argues that there is significantly more inflammation (eosinophils) in the maxillary sinus of allergic patients during the season than out of season. [7, 8] Pathophysiological processes that involve the upper airway generally affect lower airway disease. Mucosa in the ear, nose, sinus and lower airways is often inflamed at the same time. The majority of patients with asthma also have allergic rhinitis. Support for the unified airway theory is found in epidemiological studies, in shared pathophysiological mechanisms, and in interactive treatment effects. [5, 9–11]

We wanted to look at whether different areas (with different levels of air pollution) in the Netherlands (Amsterdam and the east of the Netherlands) and/or ethnicity could play a role in the prevalence and severity of ARS, CRS and AR. This study was conducted to assess the relationships between AR, ARS and CRS and comorbidity, ethnicity, occupation, smoking and place of residence.

Methods

Study design

Most of the data for the present study were obtained using the GA^{2}LEN questionnaire, which consists of 22 questions. The questionnaire was sent to a random sample of the Dutch population in three different areas of the Netherlands (Fig 1) with different geographic locations, housing, population densities, ethnic profiles:

1. Ouderkerk aan de Amstel, a suburban village close to Amsterdam (545 inhabitants/km^2): 5000 questionnaires

Fig 1. Map of the Netherlands with the three different areas.

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2. Amsterdam South East (urban area with many different ethnicities, 4704 inhabitants/km^2): 6700 questionnaires
3. Almelo, a city in a more rural area in the east of the Netherlands (1077 inhabitants/km^2): 5000 questionnaires

In the surveys in Amsterdam and Almelo (sent in 2009), we included extra questions about acute rhinosinusitis (ARS) and ethnicity alongside the questions about chronic rhinosinusitis (CRS) and allergic rhinitis (AR).

The questionnaire can be found in the supporting files (S1 Appendix). We sent it up to three times if there was no response.

Relevant definitions based on the questions in the questionnaire

AR: A positive answer to the question: Do you have any nasal allergies including hay fever?

ARS: A positive answer to the question: In the past twelve months, did you have at least one episode of at least ten days with a blocked nose, discoloured nasal discharge and pain or pressure in the sinuses?

CRS: A combination of two positive answers to the next questions (with at least a positive answer to either A or B):

a. Has your nose been blocked for more than twelve weeks in the last twelve months?
b. Have you had discoloured nasal discharge (snot) or discoloured mucus in the throat for more than twelve weeks in the last twelve months?
c. Have you had pain or pressure around the forehead, nose or eyes for more than twelve weeks in the last twelve months?
d. Has your sense of smell been reduced or absent for more than twelve weeks in the last twelve months?

A doctor's diagnosis of CRS: A positive answer to the question: Has a doctor ever told you that you have chronic sinusitis?

Itchy rash: A positive answer to the question: Have you ever had an itchy rash that came and went for at least six months?

Eczema: A positive answer to the question: Have you ever had eczema or any kind of skin allergy?

Adverse response after taking painkillers: A positive answer to the question: Have you ever had any difficulty with your breathing within three hours after taking a painkiller?

Active smoking: A positive answer to the questions: Have you ever smoked for as long as a year? AND Have you smoked at all in the last month?

Asthma: A positive answer to the question: Have you ever had asthma? AND one of the following:

- Have you had wheezing or whistling in your chest at any time in the last twelve months?
- Have you woken up with a feeling of tightness in your chest at any time in the last twelve months?
- Have you been woken by an attack of shortness of breath at any time in the last twelve months?
- Have you been woken by an attack of coughing at any time in the last twelve months?

Ethics statement

Our institutional review board (ethics committee) decided that their approval was not needed to start this study because participants were not subject to any intervention.

Statistical analysis

Statistical analyses were conducted with SPSS 21.0 statistical software.

Univariate statistical analyses for all the different variables in each area were completed. The percentages were calculated using the frequencies and total available data for each area and variable (without missing values). Significant differences between the areas were calculated using Chi-square or ANOVA (Analysis of variance) for each variable.

Univariate analysis was then conducted for the three outcome variables ARS, CRS and AR using Pearson chi-square or t-test depending on binary or continuous data for each variable. The independent variables with a p-value of less than 0.20 in the univariate analysis were selected for multivariate analysis. Multivariate logistic regressions were fitted by using the backward elimination technique based on likelihood ratio to identify factors that affect ARS, CRS and AR separately. The association between independent variables was assessed using odds ratio (OR) and a 95% confidence interval (CI). Correlations were considered to be significant if the p-value was less than 0.05.

Results

Fifty percent (8347) of the 16700 questionnaires sent were returned (Table 1).

The mean age of the respondents was 46 years (range 6–90); 45% were male.

Univariate analysis

Table 2 summarises the results of the univariate analysis.

A total of 2274 respondents met the criteria for ARS, of whom 841 also met the criteria for CRS. Those 841 patients were excluded from the ARS group since they will have answered 'yes' to this question given their CRS. The prevalence of ARS is therefore 18% (1433/8170). The prevalence of CRS was 16% (1281/8227). In total, 29% (2259/7804) of the respondents met the criteria for AR.

All variables were compared for the different areas. AR, ARS, itchy rash, adverse response to painkillers, smoking (active and at least one year), occupation, ethnicity, CRS, asthma and age differed significantly between the areas.

Multivariate analysis

ARS. The risk of ARS was significantly higher in respondents with a doctor's diagnosis of CRS (OR 2.14), AR (OR 1.70), itchy rash (OR 1.28) and eczema (OR 1.33), in female respondents (OR 1.39) or those with a history of smoking for at least one year (OR 1.22). Caucasians have a significantly higher risk of ARS than people of most other ethnicities in our survey.

Table 1. Respondents.

Area	Sent	Respondents	Percentage
Ouderkerk a/d Amstel	5000	3192	64
Amsterdam SE	6700	2586	39
Almelo	5000	2569	51
Total	16700	8347	50

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Table 2. Summary of results (univariate).

	Amsterdam SE N (%)	Almelo N (%)	Ouderkerk N (%)	Total N (%)	P
Allergic rhinitis	750 (31) [$]	699 (29)	810 (27)	2259 (29)	0.005
Doctor's diagnosis CRS	104 (4)	94 (4)	108 (3)	306 (4)	0.366
ARS	368 (17) [#,$]	469 (21)	596 (20)	1433 (18)	0.000
Itchy rash	622 (25) [$]	601 (24) [&]	612 (20)	1835 (23)	0.000
Eczema	1095 (45)	1108 (45)	1283 (43)	3486 (44)	0.245
Adverse response painkiller	56 (2) [$]	54 (2) [&]	36 (1)	146 (2)	0.002
Smoking (1 year)	1164 (47) [#,$]	1319 (52) [&]	1563 (50)	4046 (50)	0.000
Smoking (active)	595 (43) [$]	630 (44) [&]	695 (32)	1920 (39)	0.000
Occupation					0.000
Employed	1389 (56) [#,$]	1283 (52)	1672 (53)	4344 (54)	0.023
Self-employed	117 (5) [#,$]	153 (6) [&]	360 (11)	630 (8)	0.000
Unemployed	94 (4) [#,$]	55 (2) [&]	40 (1)	189 (2)	0.000
Not working because of poor health	128 (5) [$]	101 (4) [&]	67 (2)	296 (4)	0.000
Full time house person	101 (4) [#,$]	207 (8) [&]	201 (6)	509 (6)	0.000
Full time student	215 (9) [$]	193 (8)	230 (7)	638 (8)	0.276
Retired	312 (13) [#,$]	393 (16)	481 (15)	1186 (15)	0.001
Other	111 (5)	97 (4)	119 (4)	327 (4)	0.495
Ethnicity					0.000
Caucasian	1293 (56) [#]	1799 (86)		3092 (70)	0.000
Asian	141 (6)	104 (5)		245 (6)	0.108
African-Creole	354 (15) [#]	12 (1)		366 (8)	0.000
Latin-American	59 (3) [#]	4 (0,2)		63 (1)	0.000
Hindustani	206 (9) [#]	7 (0,3)		213 (5)	0.000
Mediterranean	45 (2)	53 (3)		98 (2)	0.182
Other	225 (10) [#]	117 (6)		342 (8)	0.000
Gender (female)	1453 (57) [#]	1361 (53)	1748 (55)	4562 (55)	0.058
CRS	450 (18) [$]	420 (17) [&]	411 (13)	1281 (16)	0.000
Asthma	185 (8) [$]	208 (9) [&]	185 (94)	578 (7)	0.000
Age (mean)	45.4 [$]	46.5 [&]	47.0		0.000

significant difference between Amsterdam Southeast and Almelo

$ significant difference between Amsterdam Southeast and Ouderkerk aan de Amstel

& significant difference between Almelo and Ouderkerk aan de Amstel

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Getting older reduces the risk of ARS by an OR of 0.99 per year. Table 3 shows all variables significantly related to ARS. No significant relation with work/occupation or place of residence was found.

CRS. The risk of CRS is significantly higher in respondents with a doctor's diagnosis of CRS (OR 6.83), AR (OR 2.87), asthma (OR 2,36), an adverse response after taking painkillers (OR 2.34), itchy rash (OR 1.71), or active smoking (OR 1.45). Caucasians were less likely to meet the criteria for CRS than people with some other ethnicities (African-Creole, Latin-American, Hindustani). CRS is also less likely in older patients. No significant relation was found with work/occupation, place of residence or gender.

Table 4 shows the variables significantly associated with CRS.

AR. The risk of AR was significantly higher in respondents with an adverse response after taking a painkiller (OR 4.12), asthma (OR 3.24), CRS (OR 2.24) or a doctor's diagnosis of CRS (OR 2.29), ARS (OR 1.74), eczema (OR 1.60), or itchy rash (OR 1.43). Active smokers were

Table 3. Variables related to ARS (multivariate).

Variable	p	OR	95% CI-	95% CI
Doctor's diagnosis CRS	0.01	2.14	1.17	3.91
AR	0.00	1.70	1.38	2.10
Gender (ref: male)	0.00	1.39	1.14	1.69
Eczema	0.01	1.33	1.08	1.65
Itchy rash	0.04	1.28	1.01	1.62
Smoking (1 year)	0.05	1.22	1.00	1.50
Age (per year)	0.05	0.99	0.99	1.00
Ethnicity (ref: Caucasian)	0.00			
Other	0.10	0.74	0.52	1.06
Latin-American	0.26	0.54	0.18	1.59
Asian	0.00	0.45	0.26	0.76
Hindustani	0.00	0.40	0.22	0.74
Mediterranean	0.04	0.40	0.17	0.95
African-Creole	0.00	0.35	0.21	0.59

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less likely to have AR (OR 0.74). Full-time housewives/househusbands were significantly less likely to have AR than respondents in employment (OR 0.46). Caucasians generally were less likely to have AR than African-Creoles, Latin-Americans and Hindustanis. Once again, the risk of AR declined with increasing age and no significant relation was found with gender or place of residence. Table 5 lists the variables related to AR.

Discussion

We evaluated the risk factors for AR, ARS and CRS in an epidemiological study looking at three different locations in the Netherlands.

Most studies in the past have asked subjects whether they had 'sinusitis' (diagnosed by a doctor), often without distinguishing between ARS and CRS. [12–14] The present study used the GA^{2}LEN questionnaire and so we were able to distinguish between ARS and CRS on the basis of symptoms reported by the patients and a possible doctor's diagnosis of CRS.

Table 4. Variables related to CRS (multivariate).

Variable	p	OR	95% CI-	95% CI
Doctor's diagnosis CRS	0.00	6.83	3.91	11.94
AR	0.00	2.87	2.11	3.81
Adverse response painkiller	0.01	2.34	1.20	4.54
Asthma	0.00	2.36	1.52	3.66
Itchy rash	0.00	1.71	1.26	2.31
Smoking (active)	0.01	1.45	1.08	1.95
Age (per year)	0.02	0.99	0.98	1.00
Ethnicity (ref: Caucasian)	0.00			
Latin-American	0.05	3.56	1.01	12.51
African-Creole	0.00	2.53	1.52	4.20
Hindustani	0.04	2.04	1.04	4.01
Mediterranean	0.20	1.77	0.74	4.26
Asian	0.10	1.74	0.90	3.37
Other	0.35	0.75	0.42	1.36

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Table 5. Variables related to AR (multivariate).

Variable	p	OR	95% CI -	95% CI
Adverse response painkiller	0.00	4.12	1.71	9.93
Asthma	0.00	3.24	1.98	5.31
Doctor's diagnosis CRS	0.04	2.29	1.04	5.04
CRS	0.00	2.24	1.34	3.73
ARS	0.00	1.74	1.29	2.35
Eczema	0.00	1.60	1.20	2.13
Itchy rash	0.02	1.43	1.05	1.96
Age (per year)	0.00	0.98	0.97	0.99
Smoking (active)	0.03	0.74	0.56	0.97
Ethnicity (ref: Caucasian)	0.01			
Latin-American	0.03	5.13	1.16	22.70
Hindustani	0.02	2.35	1.15	4.80
African-Creole	0.01	1.97	1.14	3.37
Mediterranean	0.29	1.60	0.67	3.83
Other	0.12	1.45	0.90	2.33
Asian	0.73	1.13	0.57	2.23
Occupation (ref: employed)	0.08			
Unemployed	0.20	1.58	0.78	3.21
Retired	0.66	1.12	0.68	1.83
Not working because of poor health	0.82	1.07	0.59	1.97
Self-employed	0.71	0.90	0.53	1.55
Full-time student	0.10	0.57	0.29	1.12
Other	0.14	0.55	0.25	1.22
Full-time housewife/husband	0.02	0.46	0.24	0.87

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A doctor's diagnosis of CRS and the diagnosis CRS based on symptoms are obviously related (OR 2,29). But not all participants with symptom based CRS have a doctor's diagnosis. They may be less care seeking or they may have less severe complaints. Also in the Dutch healthcare system, general practitioners are not always aware of the difference between acute and chronic rhinosinusitis.[15, 16] Therefore the participants that did go to their general practitioner did probably only hear a diagnosis of "sinusitis" and not "chronic rhinosinusitis".

The strength of symptom based diagnosis of CRS is that participants that are not aware of their diagnosis can be found. We realise that we are not always able to distinguish perfectly between the different diseases: persistent AR and CRS, for example, are not always easy to separate on the basis of symptoms alone.[17] However, using the same GA^{2}LEN questionnaire, Tomassen et al. found that 62% of the subjects reporting CRS on the basis of symptoms also had objective abnormalities at endoscopy. [18] A Korean study correlated all the different combinations of CRS symptoms with the findings of nasal endoscopy and found that all combinations with a reduction or loss of smell had the highest OR for a positive endoscopy. [19].

The strength of doctor's diagnosed CRS is that a professional has combined symptoms and objective findings to make a diagnosis. However part of the patients will not visit their doctor and some doctors will not recognize CRS, leading to an underestimation of the prevalence of CRS.

We have to keep in mind that there may be a participation bias. Individuals with nasal and sinus symptoms are more likely to respond to a questionnaire about these symptoms than individuals without these symptoms. Therefore the prevalence may be overestimated. The

prevalence found in this study was slightly higher than reported for the Netherlands on the basis of the Ouderkerk data only (CRS 14.3%) and also confirms the relatively high prevalence of CRS in the Netherlands by comparison with the average in Europe (11%) [20] and the US (12%). [21]

We also realise that some of the subjects reporting allergies tested negative in skin-prick testing and that others were not aware of the allergic basis for their complaints. In an Italian study, 79% of the participants reporting AR had either a positive skin prick test or at least one specific IgE measurement $\geq$ 0.35 kU/l. [22] Twenty-eight percent of the participants in a Turkish study who answered 'yes' to the question 'Do you have or have you ever had any nasal allergies, including hay fever?' had a positive skin prick test. [23]

The associations found between AR, ARS, CRS and asthma and eczema concur with other studies evaluating the comorbidities of AR. [24, 25]

We found that Caucasians were less likely to have AR than most other ethnicities. In an English study in general practice, significantly fewer Southern Irish participants and significantly more West Indian women consulted a general practitioner for AR than the native British population. [26] By contrast, Salo et al. found that non-Hispanic whites reported more hay fever than non-Hispanic blacks, Mexican Americans and other ethnicities. [27]

Interestingly, we found that full-time housewives/househusbands were significantly less likely to have AR than respondents with jobs. This is a new finding that could possibly be explained by occupational AR in the latter group. It is known that occupational exposure is related to upper airway disease.[28] Occupational AR may result from a wide variety of high-molecular-weight agents and some low-molecular-weight agents. Examples of occupations at increased risk are furriers, bakers, livestock breeders, food-processing workers, veterinarians, farmers, electronic/electrical products assemblers and boat builders. [29–31] Furthermore, AR has been found be more prevalent in medical professionals than in office workers and in cleaners [32, 33].

Occupational status might reflect socioeconomic status and may be of influence on the prevalence of ARS, CRS and AR. In a recent study by Philpott factors such as occupation, highest academic qualification, rural/urban location, duration of residency, proximity to crops, postcode, annual income, ethnicity, household occupancy and social class were studied in relation to CRS. No significant differences were found after adjusting for age and sex.[34]

Hirsch used the history of receiving Medical Assistance as surrogate for socioeconomic status and found that this was associated with CRS.[21]

Kilty found that participants with an educational level of high school of less report higher sinus symptom scores than participants with post-secondary education. Their Lund MacKay score on CT however is not significantly different.[35] This indicates that socioeconomic factors may be of influence on reporting of (severity) of symptoms. Unfortunately, we do not have information about the socioeconomic status of our participants.

Conflicting results have been found in previous studies about the effect of smoking on AR. [5, 27, 36–39] In our study, we found a negative association between smoking and AR. The healthy smoker phenomenon could explain why our study and some other studies have shown that smokers are less likely to have AR than non-smokers. [5, 36–38] It is possible that allergy subjects are less likely to start smoking and more likely to quit smoking. Smoking may have an immunosuppressive effect and reduce the number of IgE sensitizations. [27, 39]

In our multivariate analysis, we did not find any association between place of residence and AR. However, several studies have found a link between living environment and nasal symptoms/AR. People living close to heavy traffic and in cities reported nasal symptoms more often. [40–42] It is very probable that the wide range of living conditions in the three locations was such that these differences could not be found.

The present survey confirmed the findings in the literature indicating a significant correlation between asthma and CRS and AR, but not between asthma and ARS. [43–46] This could be explained by the fact that CRS and AR are chronic diseases, as is asthma. The finding supports the unified airway theory and the conclusion that ARS and CRS are two different diseases.

The relation of an adverse response to painkillers and CRS (with nasal polyps) is not surprising because they often occur together with asthma as part of AERD (aspirin-exacerbated respiratory disease).[2]Itchy rash as defined in our study might fit the diagnosis of urticaria.

When we look at the relation of urticaria with ARS and CRS in other studies, we found that chronic urticaria are often related to infections (in general) in several studies.[47–50] Positive nasal swabs were more often found in patients with urticaria than in controls.[48]

In this study, Caucasians tended to have a higher prevalence of ARS and a lower prevalence of chronic respiratory conditions as CRS and AR by comparison with other ethnicities. It is difficult to compare these data with previous studies because of differences in the definitions of race/ethnicity and rhinosinusitis (ARS and CRS were not studied separately elsewhere). Our data confirm an earlier study by Tan, in which the local population of Singapore had more CRS than the Caucasian population. The local population of Singapore consisted of Chinese (71,2%), Malay (8,9%), Indian (13,5%) and other ethnicities (6,6%). [51] A survey from the US found associations between the prevalence of rhinosinusitis (defined as a positive response to the question: 'During the past twelve months, have you had sinusitis or sinus problems?') and female gender, non-Hispanic white or black race, higher income status and higher educational level. [12] Contrary to our data, Hirsch et al. found that non-whites had a lower risk of meeting the EPOS CRS criteria than whites in the United States (OR 0.53). [21]

We found that women were more likely to have ARS, but not CRS. This concurs with the study by Hirsch. [21] Almost 15% of the respondents from the 2002–2005 National Health Interview Survey of the United States had been diagnosed with rhinosinusitis in the previous year (doctor's diagnosis, no differentiation between ARS and CRS). This prevalence was lower in the Asian (7%) and Hispanic populations (8.6–8.8%) than in the black population (13.3–14.4%) and the white population (13.0–16.0%). [13, 14] In a retrospective study in children it was found that there were more white children in the CRS group (77%) than in the group without CRS (47%). (CRS group: 77% white, 10% black, 13% other; control group: 47% white, 33% black, 20% other). [52] Different study types with different populations and different definitions of ethnicities and rhinosinusitis may explain the conflicting findings on this subject. It may be a genetical issue, but habits/environment may also play a role. Further research is needed to elucidate the findings regarding ethnicity in our study.We did not find any significant association between CRS and work/occupation. Earlier, Thilsing et al. did find an increased prevalence of CRS in subjects working in a cleaning job. [53] A correlation has also been found between occupational exposure to low- and high-molecular-weight irritants and the number of FESS (functional endoscopic sinus surgery) procedures in patients with CRS. [54] However, a recent review by Sundaresan evaluating 41 articles that discussed occupational and environmental influences on CRS stated that the literature at present allows us to draw very few conclusions about the role of hazardous occupational or environmental exposures in CRS, leaving a critical knowledge gap regarding potentially modifiable risk factors for disease onset and progression. [55] More research is definitely needed to elucidate the effect of occupational exposure on CRS.

We found a positive link between smoking and CRS and ARS, confirming other studies. [3, 12, 21, 53, 54]

In conclusion, this study found new associations between different upper airway diseases and relevant factors. It is again clear that chronic upper airway diseases like AR and CRS are associated with other factors than acute diseases like ARS.

More studies are required evaluating sensitisation and other objective signs of disease to further unravel these observations.

Supporting information

S1 Appendix.
(PDF)

S1 Dataset.
(SAV)

Author Contributions

Conceptualization: Ruth Hoffmans, Alex Wagemakers, Cornelis van Drunen, Wytske Fokkens.

Data curation: Ruth Hoffmans.

Formal analysis: Ruth Hoffmans.

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GA2LEN SURVEY QUESTIONNAIRE

TIP

TO ANSWER THE QUESTIONS PLEASE TICK THE APPROPRIATE BOX

IF YOU ARE UNSURE OF THE ANSWER PLEASE CHOOSE 'NO'

	NO	YES
	☐	☑

	NO	YES
1. Have you had wheezing or whistling in your chest at any time **in the last 12 months**?	☐	☐

IF 'NO' GO TO QUESTION 2 *IF 'YES' GO TO QUESTION 1.1*

	NO	YES
1.1 Have you been at all breathless when the wheezing noise was present?	☐	☐
1.2 Have you had this wheezing or whistling when you did not have a cold?	☐	☐
2. Have you woken up with a feeling of tightness in your chest at any time **in the last 12 months**?	☐	☐
3. Have you been woken by an attack of shortness of breath at any time **in the last 12 months**?	☐	☐
4. Have you been woken by an attack of coughing at any time **in the last 12 months?**	☐	☐
5. Do you bring up phlegm from your chest on most days for as much as three months each year?	☐	☐
6. Have you **ever** had asthma?	☐	☐

IF 'NO' GO TO QUESTION 7 *IF 'YES' GO TO QUESTION 6.1*

	YEARS
6.1 How old were you when you had your first attack of asthma? (If unsure, give your best guess!)	☐☐

	NO	YES
6.2 Have you **ever** been hospitalised with asthma?	☐	☐
6.3 Have you had an attack of asthma **in the last 12 months?**	☐	☐
6.4 Are you **currently** taking any medicine (including inhalers, aerosols or tablets) for **asthma?**	☐	☐

	NO	YES
7. Do you have any nasal allergies including hay fever?	☐	☐

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IF 'NO' GO TO QUESTION 8 *IF 'YES' GO TO QUESTION 7.1*

7.1 Have you been troubled by nasal allergies **in the last 12 months?** NO ☐ YES ☐

7.2 Have you ever been troubled by nasal allergies for **more than 4 days in any one week**? NO ☐ YES ☐

7.3 If yes did this happen for **more than 4 weeks continuously?** NO ☐ YES ☐

8. Has your nose been blocked **for more than 12 weeks during the last 12 months?** NO ☐ YES ☐

9. Have you had pain or pressure around the forehead, nose or eyes **for more than 12 weeks during the last 12 months?** NO ☐ YES ☐

10. Have you had discoloured nasal discharge (snot) or discoloured mucus in the throat **for more than 12 weeks during the last 12 months?** NO ☐ YES ☐

11. Has your sense of smell been reduced or absent **for more than 12 weeks during the last 12 months?** NO ☐ YES ☐

12. Has a doctor **ever** told you that you have **chronic** sinusitis? NO ☐ YES ☐

12. A In the past 12 months, have you had at least one episode of at least ten days where you had a blocked nose, discoloured nasal discharge (snot) **and** pain or pressure over the sinuses? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 13 *IF 'YES' GO TO QUESTION 12.A.1.*

12.A.1. How many of these episodes of at least 10 days where you had a blocked nose, discoloured nasal discharge (snot) **and** pain or pressure over the sinuses did you have **in the past 12 months**?

1 2 3 4 >4

12.A.2. Have you visited a doctor for one of these episodes? NO ☐ YES ☐

12.A.3. Have you received antibiotics for one of these episodes? NO ☐ YES ☐

12.A.4. Have you received a corticosteroid nose spray for one of these episodes? NO ☐ YES ☐

13. Have you ever had an itchy rash that was coming and going **for at least 6 months?** NO ☐ YES ☐

IF 'NO', GO TO QUESTION 1 *IF 'YES' GO TO QUESTION 13.1*

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13.1 Have you had this itchy rash **<u>in the last 12 months</u>**? NO ☐ YES ☐

13.2 Does this affect **<u>only</u>** your hands? NO ☐ YES ☐

14. Have you ever had eczema or any kind of skin allergy? NO ☐ YES ☐

15. Have you ever had any difficulty with your breathing within 3 hours after taking a pain killer? NO ☐ YES ☐

IF 'NO' GO TO QUESTION 16 ***IF 'YES' GO TO QUESTION 15.1***

15.1 Please write the name of the tablet? …….....

16. Have you ever smoked for as long as a year? NO ☐ YES ☐

['YES' means at least one cigarette per day or one cigar per week for one year]

IF 'NO' GO TO QUESTION 17 ***IF 'YES' GO TO QUESTION 16.1***

16.1 How old were you when you started smoking? YEARS ☐☐

16.2 Have you smoked at all in the **last month**? NO ☐ YES ☐

IF 'YES' GO TO QUESTION 16.3 ***IF 'NO' GO TO 16.2.1***

16.2.1 How old were you when you stopped smoking? YEARS ☐☐

16.3 **<u>On average</u>** how much do you (or did you) smoke? Cigarettes per day ☐☐

17. Are you currently: ***Tick one box only!***

a. employed	☐	1.
b. self-employed	☐	2.
c. unemployed	☐	3.
d. not working because of poor health	☐	4.
e. full-time house person	☐	5.
f. full-time student	☐	6.
g. retired	☐	7.
h. other	☐	8.

18. Are you currently working:

a. As a health care worker (e.g. as a nurse, medical technician, NO ☐ YES ☐

«

doctor, paramedic or similar)?

b. In a job that is mainly involved with any sort of cleaning? NO ☐ YES ☐

19.1 Do you understand the language in which this questionnaire is composed? NO ☐ YES ☐

19.2 Which language do you speak most when you're at home? ☐

19.3 Which language do you speak most when you're away from home? ☐

20.1 In which country were you born? ☐

20.2 In which country was your father born? ☐

20.3 In which country was your mother born? ☐

Tick one box only!

20.4 What is your ethnicity?

- **a.** Caucasian/white ☐ 1.
- **b.** Asian ☐ 2.
- **c.** African/Creole ☐ 3.
- **d.** Latin-American ☐ 4.
- **e.** Hindustani ☐ 5.
- **f.** Mediterranean ☐ 6.
- **g.** Other (please specify): ☐

20.5 How many years have you been living in The Netherlands? YEARS ☐

21. What is your date of birth? DAY ☐☐ MONTH ☐☐ **19** YEAR ☐☐

22. What is today's date? DAY ☐☐ MONTH ☐☐ **20** YEAR ☐☐

23. Are you male or female? MALE ☐ FEMALE ☐

24. What is your postal code? ☐☐☐☐ ☐☐

May we contact you again for further scientific research? NO ☐ YES ☐

Thanks for your help!

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