

Alcohol hyper-responsiveness in chronic rhinosinusitis with nasal polyps

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Summary

Background An important percentage of subjects diagnosed with chronic upper airway disease report alcohol-induced worsening of their symptoms. The prevalence and characteristics of respiratory reactions provoked by alcohol-containing drinks have not been fully investigated yet.

Objective The aim of this study was to estimate the prevalence and characteristics of alcohol hyper-responsiveness in patients with chronic airway disease and healthy controls. Furthermore, nasal inflammation was evaluated in nasal polyp patients with and without hyper-responsiveness.

Methods We evaluated the prevalence and characteristics of alcohol-induced respiratory complaints in 1281 subjects. Chronic rhinosinusitis with nasal polyps (CRSwNP) patients with and without NSAID exacerbated respiratory disease (NERD), chronic rhinosinusitis patients without nasal polyps (CRSsNP), allergic rhinitis (AR) patients and healthy controls were approached by means of a questionnaire. Inflammatory markers (eosinophilic cationic protein (ECP), IL-5, IgE, SAE-specific IgE, IL-17, TNF α and IFN γ) in tissue were then compared between alcohol hyper-responsive and non-hyper-responsive CRSwNP patients. **Results** The highest prevalence of nasal and bronchial alcohol hyper-responsiveness was observed in patients with NERD, followed by CRSwNP, and less frequent in CRSsNP, AR and healthy controls. Alcohol hyper-responsiveness is significantly more prevalent in CRSwNP patients suffering from recurrent disease and in patients with severe symptomatology. In nasal tissue of the hyper-responsive CRSwNP group, we observed significantly higher nasal levels of the eosinophilic biomarker ECP.

Conclusion and Clinical Relevance Nasal hyper-responsiveness to alcohol is significantly more prevalent in severe eosinophilic upper airway disease.

Keywords airway hyper-responsiveness, alcohol, allergic rhinitis, chronic rhinosinusitis patients without nasal polyps, chronic rhinosinusitis with nasal polyps, NSAID exacerbated respiratory disease

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Introduction

The main symptoms of chronic rhinosinusitis with nasal polyps (CRSwNP) are olfactory dysfunction, nose obstruction and nasal secretions, but patients may also complain of postnasal drip, facial pain or headache. Symptoms are not easily controlled and impair quality of life. Nasal polyps (NP) are frequently associated with

asthma and non-steroidal anti-inflammatory drug (NSAID) hypersensitivity. Inflammation in patients with CRSwNP and NSAID exacerbated respiratory disease (NERD) is most severe, and recurrence rate of nasal polyps is high [1, 2].

A significant portion of patients diagnosed with chronic inflammatory airway diseases report aggravation of airway symptoms after drinking alcohol-

containing beverages [3], and a few clinical studies have demonstrated that alcohol is able to induce asthma exacerbations [4, 5]. The epidemiology and characteristics of alcohol hyper-responsiveness have been explored mostly by questionnaires, focused in the general population and the asthmatic population [3, 6, 7]. In daily clinics, patients with CRSwNP often report increased symptoms upon intake of alcohol. Nevertheless, only few studies previously reported alcohol hyper-responsiveness in CRSwNP [3, 8] and little is known about inflammatory characteristics of this group.

In the general population, alcohol-induced nasal symptoms vary between 3.4% and 7.4% [3, 6]. In the asthmatic population, alcohol-induced upper and lower airway symptoms are more frequent and occur in 42.6–43% [7, 8]. Percentages are similar in the case of CRSwNP (43%) and are highest in the NERD population (83%) [8]. These reactions are generally not specific to one type of alcoholic beverage and often occur after ingestion of small amounts of alcohol [8].

The mechanisms underlying the alcohol-induced aggravation of airway symptoms are largely unknown. A common pathway of NERD and alcohol hyper-responsiveness has been suggested [7, 8]. Furthermore, it is not clear whether alcohol itself is responsible or non-alcoholic additives are the main cause of these reactions. Generally, it is assumed that in the majority of patients, the non-alcoholic components, such as histamines or sulphites, are the main causes [7].

In order to assess epidemiology of alcohol hyper-responsiveness in chronic upper airway diseases and to explore characteristics of these reactions, we designed a questionnaire that assesses the alcohol hyper-responsiveness in detail in CRSwNP patients. Characteristics of the nasal polyp population and their disease were collected; and the presence of other sensitivities, including food components and environmental irritants, was investigated. Control groups consisted of chronic rhinosinusitis patients without nasal polyps (CRSsNP), allergic rhinitis (AR) patients and healthy subjects. In a second part of the study, inflammatory markers in nasal tissue were compared between CRSwNP patients with and without nasal alcohol hyper-responsiveness (HR).

Methods

Subjects

We included 534 CRSwNP and for control purposes patients with CRSsNP ($n = 198$), AR ($n = 369$), and healthy volunteers ($n = 180$). Although the true prevalence of CRSwNP is lower than CRSsNP, we intentionally weighed the survey population towards CRSwNP. CRSwNP, CRSsNP and AR patients were specialist-

diagnosed according to the EPOS guidelines [9] and ARIA guidelines [10]. These well-characterized patients were recruited from databases available in the University Hospitals in Ghent and Leuven, Belgium. Healthy volunteers were randomly selected in the general population. Exclusion criteria for healthy volunteers were the presence of nasal or lung symptoms and the diagnosis of CRSwNP, CRSsNP or AR. Questionnaires with missing answers to essential questions, subjects who did not confirm their diagnosis and patients with interfering nasal anomalies, such as cystic fibrosis, systemic/autoimmune diseases or anatomical deviations, were excluded from the study. Written informed consents were obtained from all subjects.

Study design

Questionnaire. The questionnaire comprised all relevant patient characteristics, including confirmation of diagnosis and assessment of comorbidities, such as asthma, allergy, NSAID hypersensitivity and food allergy or hypersensitivity to common food allergens (including milk, peanuts, eggs, tree nuts, gluten, soy, mustard, lupine and celery). Next to disease phenotyping, disease severity was determined based on recurrence of nasal polyps, the need for repetitive treatments with oral steroids and antibiotics and symptom control under their current treatment as evaluated by means of visual analogue scales (VAS). Recurrent CRSwNP was defined starting from at least two functional endoscopic sinus surgeries. A VAS score of more than 5 on a scale of 10 was considered as uncontrolled disease [11]. Smoking and drinking habits were assessed. Airway hyper-responsiveness of upper and lower airways to alcohol and environmental or occupational irritants was documented. A list of symptoms was given to determine which symptoms occur after exposure: nasal HR was defined as either nasal blockage and/or rhinorrhea with or without bronchial symptoms. Bronchial symptoms comprised cough, wheezing, dyspnea and exacerbation of asthmatic symptoms. Again, bronchial alcohol HR was defined as at least one of the bronchial symptoms with or without nasal symptoms. Itching, facial swelling and allergic symptoms (skin rash, conjunctivitis...) were defined as 'other symptoms'. Flushing was considered a physiologic phenomenon and is not represented as a hyper-responsive symptom. Respiratory alcohol HR was defined as either nasal alcohol HR or bronchial alcohol HR, or both. Characteristics of the nasal alcohol HR reaction were assessed, including type of causal beverage, quantity necessary to elicit symptoms, duration of symptoms and latency. Quantity was defined as 'units' of alcoholic drinks, as volumes depend on the type of beverage.

Six weeks after the initial questionnaire was sent, a reminder questionnaire was sent to the non-responders

to increase response rate. The ethical committee of the Ghent University Hospital, Ghent, Belgium, approved the study (2014/0619).

Correlation with inflammatory markers. Nasal tissue collected during functional endoscopic sinus surgery in the Ghent University Hospital is routinely preserved when the patient consents. Therefore, it was possible to retrospectively collect data on inflammatory markers, including eosinophilic cationic protein (ECP), IL-5, IgE, *Staphylococcus aureus* enterotoxin-specific IgE, IL-17, TNF α and IFN γ in 138 responders with nasal polyps.

Study endpoints. The primary endpoint of this study comprised the prevalence of alcohol hyper-responsiveness in CRSwNP subgroups and for control purposes in the allergic rhinitis, CRSsNP and healthy population.

As secondary endpoints, we aimed to determine the most reported symptoms and triggering alcoholic drinks and the characteristics of the nasal hyper-responsiveness reaction (duration, latency...). Furthermore, we aimed to evaluate inflammatory markers in CRSwNP with and without nasal alcohol HR.

Statistical analysis

A two-tailed Fisher exact test was used to examine categorical data. The Mann–Whitney *U*-test was used for continuous variables. The Kruskal–Wallis test was used to compare continuous variables between multiple groups. In addition, a multiple logistic regression test with age and gender as covariates was performed. A two-sided *P* value of <0.05 was regarded as significant for all tests. The computer-based analysis program SPSS (IBM SPSS Statistics for Macintosh, Version 21, Chicago) was used for calculations.

Results

Demographics and characteristics of all respondents

Questionnaires were sent to a total of 1281 subjects. A response rate of 65% was reached after the reminder. Only three questionnaires were excluded from analysis, as they were incomplete. More information can be found in Fig. 1, and demographic characteristics of all respondents are detailed in Table 1.

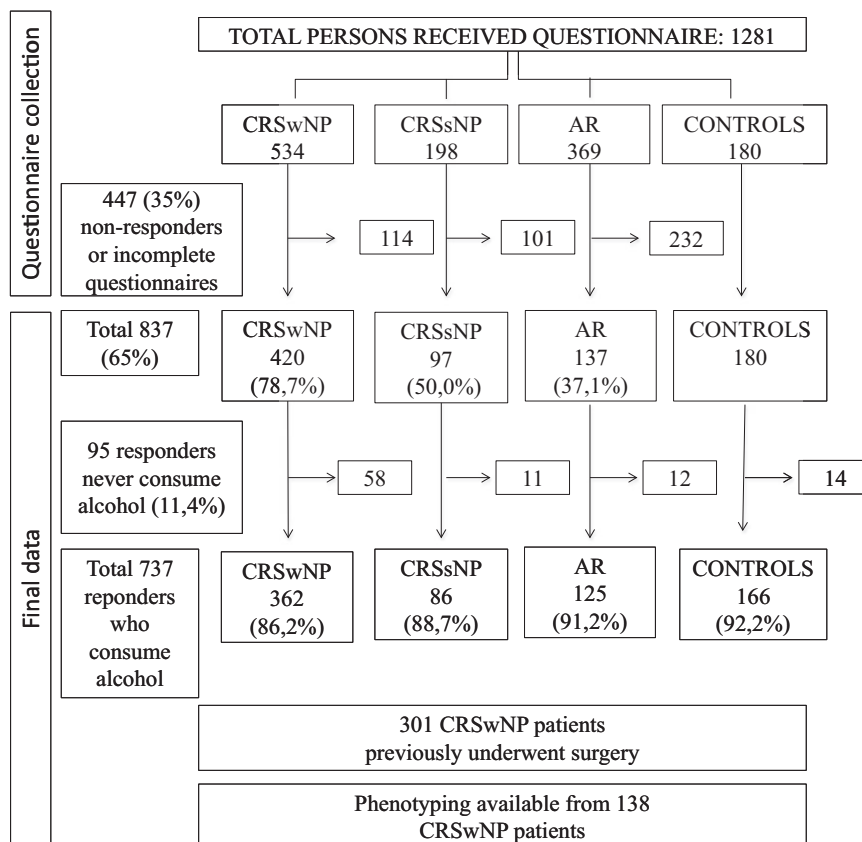


Fig. 1. The data collection and selection of questionnaires for analysis. Characteristics including drinking habits were assessed for all 837 responders. Analysis of alcohol hyper-responsiveness was performed in 737 responders who consume alcohol. Of these 369 patients previously underwent functional endoscopic sinus surgery (FESS) and data on inflammatory markers in nasal tissue was available in 165 patients.

Table 1. Demographics and characteristics of respondents

	CRSwNP	CRSsNP	Allergic rhinitis	Control
Number, n	420	97	137	180
Gender, female/male	34/66	44/56	61/39	48/52
Age, Median (IQR)	57 (46–65)	52 (41–62)	37 (28–52)	51 (33–63)
Allergy, n (%)	198 (47.6)	33 (34)	137 (100)	0 (0)
Asthma, n (%)	178 (42.4)	14 (14.6)	30 (22.1)	0 (0)
NERD, n (%)	77 (18.3)	6 (6.3)	4 (2.9)	4 (2.2)
Food allergy or hypersensitivity, n (%)	77 (18.4)	21 (22.1)	34 (24.8)	13 (7.3)
Previous FESS, n (%)	337 (83.6)	77 (88.5)	11 (8.7)	0 (0)
Recurrence, n (%)	155 (43.1)	NA	NA	NA
Smoker, n (%)	44 (10.5)	8 (8.2)	16 (11.7)	23 (12.8)
Alcohol abstainer, n (%)	58 (13.8)	11 (11.3)	12 (8.8)	14 (7.8)

Table 1 depicts the demographics and characteristics of all respondents in the different groups. Patients with chronic rhinosinusitis with nasal polyps (CRSwNP) are oldest and predominantly male. Asthma and NSAID hypersensitivity are more prevalent in CRSwNP. Self-reported food allergy or hypersensitivity is more prevalent in chronic airway diseases as compared to healthy controls. CRSwNP, chronic rhinosinusitis with nasal polyps; CRSsNP, chronic rhinosinusitis patients without nasal polyps; NERD, NSAID exacerbated respiratory disease.

Table 2. Drinking habits of respondents

	CRSwNP with NERD	CRSwNP with asthma	CRSwNP alone	CRSsNP	AR	Control
Alcohol abstainer, n (%)	11 (23.7%)	20 (14.3%)	27 (11.2)	11 (11.3%)	12 (8.8%)	14 (7.8%)
Units of alcohol/week, Median (IQR)	4 (0.5–10)	5 (2–10.75)	4 (1–10)	5 (2–10)	4 (2–7)	5 (2–10)

Table 2 demonstrates the drinking habits in the different groups. The highest percentage of alcohol abstainers is situated in the nasal polyp group. Particularly in the case of NERD, 23.7% ($n = 11$) of patients never consumes alcohol. AR, Allergic rhinitis; CRSwNP, chronic rhinosinusitis with nasal polyps; CRSsNP, chronic rhinosinusitis patients without nasal polyps; NERD, NSAID exacerbated respiratory disease.

As compared to controls, patients with CRSwNP were older ($P < 0.001$) and predominantly male ($P = 0.001$). Asthma and NSAID hypersensitivity were far more reported by the nasal polyp group as compared to the CRSsNP, allergic rhinitis and healthy groups ($P < 0.001$). Self-reported food allergy or hypersensitivity was more prevalent in chronic airway diseases as compared to healthy controls ($P < 0.001$). Smoking habits were similar between groups. We found that 11.4% of all responders never consumed alcohol or quit consuming alcohol. Interestingly, up to 23.7% of patients suffering from NERD do not consume alcohol (see Table 2), which was significantly more than the control group ($P = 0.005$). Except for smoking habits, there were no significant differences in demographic characteristics between subjects who consume alcohol and alcohol abstainers. In the population with CRSwNP and AR, significantly more subjects smoke in the alcohol-consuming group as compared to the abstainer group (resp. $P < 0.001$ and $P = 0.023$). Alcohol abstainers were excluded from further analysis.

The prevalence of alcohol-elicited respiratory reactions

All chronic airway disease groups reported significantly more respiratory alcohol HR ($P < 0.0001$), and nasal

alcohol HR ($P < 0.0001$) as compared to control patients. Bronchial reactions were significantly correlated with the presence of concomitant asthma ($P < 0.0001$). We found no significant difference in respiratory alcohol HR between patients with NERD and nasal polyp patients with concomitant asthma. However, NERD patients reported significantly more alcohol HR as compared to all the other groups, namely CRSwNP without concomitant asthma or NSAID hypersensitivity, CRSsNP, AR and the control group (Fig. 2). There was no significant difference in respiratory or nasal hyper-responsiveness between CRSwNP patients without concomitant asthma and CRSsNP and allergic rhinitis patients. Neither was there a significant difference between CRSsNP and AR patients.

The prevalence and type of respiratory reactions induced by alcohol in each group is summarized in Fig. 2. Respiratory alcohol hyper-responsiveness was reported by 62.9% of respondents with NERD, 45.9% CRSwNP patients and concomitant asthma, 31.6% of CRSwNP patients without asthma, 26.2% of respondents with CRSsNP, 25.8% of respondents with allergic rhinitis and 3.7% of healthy responders. Alcohol ingestion was more associated with the induction of nasal than bronchial complaints ($P < 0.0001$) (Fig. 2). Nasal blockage was the symptom most commonly associated with

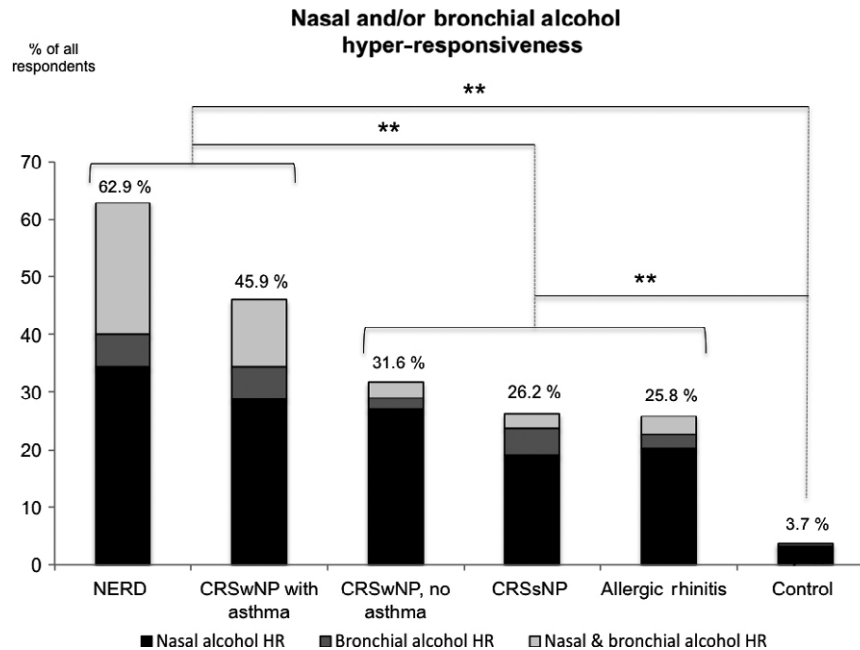


Fig. 2. The prevalence of alcohol hyper-responsiveness in different groups by means of histograms. Alcohol hyper-responsiveness (HR) is significantly higher in all groups marked with * ($P < 0.05$) or ** ($P < 0.001$). Alcohol HR is not significantly different between NSAID exacerbated respiratory disease (NERD) and chronic rhinosinusitis with nasal polyps (CRSwNP) and asthma ($P = 0.083$); between CRSwNP without asthma and chronic rhinosinusitis patients without nasal polyps (CRSsNP) ($P = 0.40$) or allergic rhinitis (AR) ($P = 0.27$); and between CRSsNP and AR ($P = 1.00$). The Fisher exact test was used to calculate statistics. In all groups, nasal symptoms are most reported.

the consumption of alcoholic drinks followed by rhinorrhea (data not shown).

As population characteristics regarding age and gender differ among upper respiratory diseases [12], we performed a multiple logistic regression test with age and gender as covariates. The odds of alcohol HR remained significantly higher in CRSwNP as compared to controls, CRSsNP and AR and were not influenced by gender ($P = 0.082$), although the odds of having AHR decreased with age ($P = 0.002$).

Within the nasal polyp population, the prevalence of nasal alcohol HR was significantly higher in subgroups with a more severe and symptomatic disease, as concluded from recurrence of nasal polyps ($P = 0.008$), a VAS score of more than 5 ($P < 0.001$), the need for repetitive treatments with oral steroids ($P = 0.041$) and antibiotics ($P = 0.002$), and the presence of concomitant asthma ($P = 0.005$) and NSAID hypersensitivity ($P = 0.010$) (Fig. 3).

Characteristics of nasal alcohol hyper-responsiveness

Nasal alcohol HR was not limited to one type of beverage but most alcohol-containing drinks appeared to cause symptoms, except for CRSwNP without asthma and CRSsNP subjects who reported, respectively, red and white wine as most forceful trigger (Figure S1). Patients with chronic airway disease reported to

experience nasal complaints in only in half of the times subsequent to drinking alcohol (Figure S2). Symptoms develop within an hour in 50.5% of CRSwNP, 41.2% of CRSsNP and 44.4% of AR patients. The remaining patients and the control group indicated it takes more than 1 h but <1 day for nasal symptoms to develop (Figure S3). Symptoms endure more than 1 h, but <1 day in the majority of patients in the inflammatory groups, although in half of the control patients, symptoms persist longer than a day (Figure S4). The quantity necessary to develop nasal alcohol HR in chronic upper airway diseases varies from 1 to more than 3 units. In contrast, 1 unit appeared not sufficient to induce symptoms in control patients (Figure S5). The quantity of units before symptoms develop was significantly correlated with the time of onset of symptoms in CRSwNP ($P < 0.001$), AR ($P < 0.001$) and CRSsNP ($P = 0.048$). The group of controls with nasal alcohol HR ($n = 6$ of 166) was underpowered for statistics. The quantity necessary, time of onset and duration of nasal alcohol HR could not be correlated with any other factor in any group, except for the AR where the onset of symptoms was significantly later in younger patients ($P = 0.015$). All patient groups reported more severe alcohol-induced upper airway symptoms as compared to healthy controls (Figure S6).

Patients with CRSwNP or AR experienced nasal alcohol HR before their diagnosis was set. In the case of

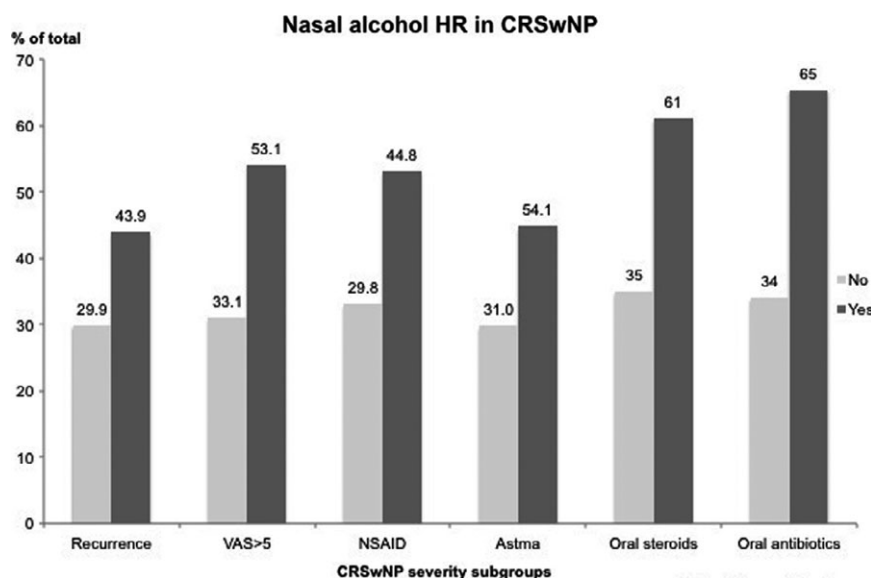


Fig. 3. The prevalence of nasal alcohol hyper-responsiveness (HR) (% of total) in respect to the severity of nasal polyp disease. Nasal alcohol HR is significantly more prevalent in recurrent disease ($P = 0.008$), in chronic rhinosinusitis with nasal polyps (CRSwNP) with uncontrolled symptoms ($P < 0.001$), in nasal polyp patients necessitating oral steroids ($P = 0.041$) and antibiotics ($P = 0.002$) and when case of concomitant asthma ($P = 0.005$) or NSAID hypersensitivity ($P = 0.010$).

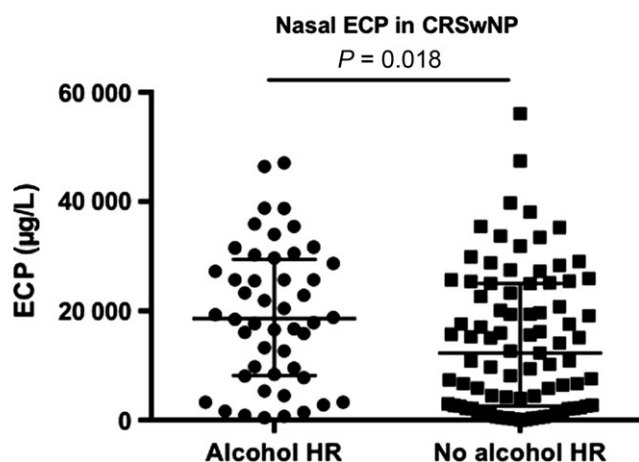


Fig. 4. Eosinophilic cationic protein (ECP) levels in chronic rhinosinusitis with nasal polyps (CRSwNP) with and without nasal alcohol hyper-responsiveness (HR) by means of a scatterplot with median and interquartile range. Levels are significantly higher in CRSwNP and alcohol HR ($P = 0.018$).

CRSwNP, nasal alcohol HR developed after diagnosis (Figure S7).

Inflammatory markers in nasal polyps from patients with alcohol hyper-responsiveness

Tissue of 138 CRSwNP patients was phenotyped by measurement of ECP, IL-5, IgE, SAE-specific IgE, IL-17, TNF α and IFN γ . ECP levels in nasal tissue were significantly higher in CRSwNP patients with nasal alcohol

HR ($P = 0.018$) (see Fig. 4). Tissue levels of IL-5, IgE, SAE-specific IgE, IL-17, TNF α and IFN γ did not differ significantly between patients with or without nasal alcohol HR.

Discussion

The prevalence of alcohol hyper-responsiveness in patients with chronic airway disease and healthy controls was assessed; and subsequently, responders with CRSwNP were phenotyped when possible. We found that the prevalence of alcohol HR and alcohol abstinence parallels the severity of the chronic upper airway pathology. Furthermore, nasal alcohol HR is significantly more frequent in CRSwNP patients with uncontrolled symptoms and recurrent disease. Nasal tissue ECP expression is significantly higher in CRSwNP with nasal alcohol HR as compared to non-HR patients.

In line with the literature, we found that upper respiratory reactions to alcoholic beverages are more prevalent than lower respiratory reactions [8]. Next to the possibility that the nasal mucosa could be more prone to the alcohol trigger, the preponderance of nasal symptoms could also be influenced by our patient selection as we focussed on chronic upper respiratory diseases. Furthermore, it has been reported that alcohol-elicited lung symptoms are most frequently reported in the asthmatic population [7]. Indeed, our results show that bronchial reactions are significantly correlated with the presence of concomitant asthma ($P < 0.0001$).

Although it has been reported that respiratory reactions to alcohol are not determined by the severity of pulmonary disease in the NERD population [8], we found that nasal alcohol HR is related to severity of upper respiratory inflammation. The prevalence of alcohol hyper-responsiveness is as high as 57.1% in the NERD subgroup, the most severe end of nasal polyp disease spectrum. Furthermore, nasal alcohol HR is significantly more prevalent in patients with a more severe and symptomatic form of nasal polyp disease.

We chose to use the term 'alcohol hyper-responsiveness', as we believe that symptoms in response to ingestion of alcohol are not a consequence of 'hypersensitivity' or 'allergy' to alcohol, but rather a symptom of severe inflammation.

We found a recurrence rate of 43.1% in the CRSwNP population, which is slightly more than the 36% that we found in the 12-year follow-up study (forthcoming). This could be explained as patients with more severe disease appear to experience more nasal alcohol HR, and these patients are thus more likely to respond to the questionnaire.

Interestingly, nasal symptoms do not always occur after alcohol consumption. Hyper-responsiveness might depend on simultaneous intake of food and on disease control. For example, patients suffering from seasonal allergy may experience more nasal alcohol HR during the pollen season and nasal alcohol HR in nasal polyp patients may improve during treatment with oral steroids or shortly after surgery or conversely worsen during exacerbations.

The quantity necessary to induce nasal alcohol HR is very variable in patients with CRSwNP. An important percentage of these patients develop symptoms rapidly, which could explain that fewer units are consumed before symptoms develop. For controls, nasal symptoms occur after at least 1 unit, and in general, they experience symptoms later and longer as compared to the subjects with respiratory inflammation.

In future, an interventional study challenging patients with pure diluted alcohol and other beverages (wines or beers) is needed to investigate the mechanism of alcohol hyper-responsiveness.

Several questions have to be addressed. First alcohol may influence immunology, or conversely the altered immunology in chronic airway diseases may cause the respiratory reactions upon exposure to alcohol. Several studies propose alcohol could cause eosinophilic inflammation [13] or induce IgE [14] supporting the first possibility [15]. The latter hypothesis is analogous to reports in NERD, suggesting respiratory mucosal inflammatory disease could be the underlying mechanism in aspirin hypersensitivity [16, 17]. Our results show that many CRSwNP experienced alcohol HR before the diagnosis of CRSwNP was made. However,

diagnosis is often delayed as polyps can only be visualized by endoscopy, so nasal polyps could already be present before or at the same time that the nasal alcohol HR developed.

The role of additives is another question when considering the mechanisms of alcohol-elicited reactions. Additives could contribute to the exacerbation of upper and/or lower airway symptoms [18–21]. Sulphites [19], salicylates [8] and histamine [22, 23] are well-known additives to alcoholic beverages [21]. Analogous to data published by Cardet and Nihlen [3, 8], our data confirmed that all types of alcohol-containing beverages elicit hyper-responsiveness, suggesting that substances common to all beverages cause respiratory reactions. In contrast to additives, alcohol is certainly a common ingredient. Furthermore, subjects reporting respiratory symptoms to alcohol did not indicate hyper-responsiveness to sulphite-containing foods (e.g. dried fruit) or histamine-rich foods (e.g. aged cheeses). In addition, it has been reported that sulphite hypersensitivity is very rare in the non-asthmatic population [24] and that treatment with loratadine has an effect on red wine-induced rhinorrhea, but not on the dominating symptom: nasal obstruction [25]. Taken together, sulphite or histamine hypersensitivity cannot completely explain alcohol hyper-responsiveness in our population.

In contrast, we found that allergy or hypersensitivity to common food allergens (milk, peanuts, eggs, tree nuts, gluten, soy, mustard, lupine, celery...) is more prevalent in the alcohol hyper-responsive population. There is a strong link between food allergy and asthma [26], and as there are significantly more asthma patients in the nasal AHR group, this could represent a possible explanation.

Finally, nasal symptoms upon alcohol consumption could be caused by non-specific mechanisms, including vasodilatation [27]. However, alcohol hyper-responsiveness is uncommon in controls rendering non-specific mechanisms less likely.

Clinical implications of this study include patient education, as alcohol can be avoided to reach better symptom control. Furthermore, the higher prevalence of polyp recurrence in the group with nasal alcohol HR is important for both the patient and the surgeon. Secondly, we suggest avoidance of topical medication with alcohol-based carrier in clinical practice or in clinical trials as the nasal mucosa might react to direct application. Thirdly, our findings help to further unravel mechanisms in CRSwNP pathogenesis. It has been suggested that alcohol hyper-responsiveness and aspirin hypersensitivity share a common pathogenesis [8]. We agree that both phenomena are a consequence of the altered microenvironment in chronic inflammatory airway diseases.

Limitations in this study are inherent to data collection by means of a questionnaire. Disease severity in the

patient groups was self-reported, as is the absence of any nasal or lung disease in healthy volunteers or the presence of aspirin exacerbated respiratory disease. The latter could explain that the hyper-responsive rate in NERD (62.9%) was lower than reported by Cardet *et al.* (80%).

Furthermore, it should be considered to what extent response bias could have influenced results. It cannot be excluded that prevalence might be higher or lower than estimated here, as patients experiencing alcohol-related symptoms are probably more likely to respond, but conversely certain subjects did not want to fill in the questionnaire because we asked for drinking habits, which is a sensitive issue. The questionnaire was not validated, and the extensiveness could result in bias due to 'responder fatigue'. Finally, alcohol abstainers were not questioned on characteristics of alcohol hyper-responsiveness. These patients were thus not included in the analysis of the hyper-responsive group, and consequently, we found a lower percentage of alcohol avoidance in this group as compared to the non-hyper-responsive group. Although the reason these patients abstained from alcohol was not asked in this questionnaire, many nasal polyp patients probably avoid alcoholic beverages after experiencing alcohol-induced symptom exacerbation.

In conclusion, we found that alcohol HR is significantly more prevalent in the case of chronic airway inflammation. Prevalence of these reactions increases with increasing disease severity and was highest in NERD, the severe end of the spectrum of chronic inflammatory nasal diseases. Furthermore, in CRSwNP, nasal alcohol HR is significantly more frequent in more severe and uncontrolled symptomatic subgroups. Local ECP levels are significantly higher in the alcohol HR CRSwNP population. To conclude, our results suggest that airway hyper-responsiveness to alcohol-containing liquids is related to the severity of airway inflammation.

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Conflict of interest

The authors declare no conflict of interest.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Comparison of patient characteristics in CRSwNP with and without nasal alcohol HR.

Figures S1. Shows the causal beverages for the induction of nasal alcohol HR in the different groups. In CRSwNP without asthma and in CRSsNP wines appear to be the most forceful triggers, whereas in all other groups all types of alcoholic beverages are most reported to cause nasal alcohol HR.

Figure S2. Demonstrates how often patients experience nasal alcohol HR after consumption of beverages.

Figure S3. Shows the latency between drinking and the occurrence of nasal symptoms in the different groups.

Figure S4. Demonstrates the duration of nasal symptoms in the different groups.

Figure S5. Shows the quantity of alcohol needed to elicit nasal alcohol HR.

Figure S6. Shows the severity of alcohol-elicited nasal symptoms.

Figure S7. Demonstrates that nasal alcohol HR was present before diagnosis or developed at the same time of diagnosis for the majority of CRSwNP or allergic rhinitis patients.

Table S1: comparison of patient characteristics in CRSwNP with and without nasal alcohol HR.

CRSwNP	Nasal alcohol HR	No alcohol HR	P-value
Number, n	129	231	NA
Gender, female/male (%/%)	38/62	28/72	0.045
Age, Median (IQR)	53 (44-62)	58 (50-66)	0.001
Smoker, n (%)	15 (11.6)	27 (11.7)	0.46
Allergy, n (%)	64 (49.6)	107 (46.5)	0.508
Asthma, n (%)	65 (50.4)	80 (34.6)	0.004
NSAID hypersensitivity, n (%)	26 (20.2)	23 (10.0)	0.010
Food allergy or hypersensitivity, n (%)	35 (27.1)	25 (10.9)	<0.0001
Nasal hyper-reactivity to chemical substances, n (%)	4 (3.2)	7 (3.1)	0.93
Previous FESS, n (%)	118 (91.4)	183 (79.1)	0.012
Recurrence, n (%)	68 (52.7)	87 (37.8)	0.008
Severity nasal symptom (VAS), Median (IQR)	4.5 (2.2-6)	2.0 (0.6-4.8)	<0.0001
Oral steroid treatment, n (%)	11 (8.7)	7 (3.1)	0.041
Oral Antibiotics, n (%)	17 (13.2)	9 (4.0)	0.002
Asthma treatment, n (%)	56 (42.5)	60 (26.9)	0.003

Table S1: shows the characteristics of CRSwNP patients and nasal alcohol HR. Patients with nasal alcohol HR are younger, predominantly female, and suffer more from recurrent disease, concomitant asthma, NSAID intolerance and food hypersensitivity or allergy. Prior surgery and treatment with oral steroids and oral antibiotics is more frequent in the nasal alcohol HR group and symptoms are more severe.

Figures S1 Summarize the characteristics of nasal alcohol HR, which was present in 35,8% of patients with CRSwNP. Among them, prevalence was highest in subjects with CRSwNP and asthma (40,9%) and in the subgroup with asthma and NSAID intolerance (57,1%). Nasal hyper-responsiveness to alcohol was also reported by 21,4% of CRSsNP subjects, 23,4% of AR patients and 3,1% of healthy controls. Data is thus shown for 129 CRSwNP patients (NERD n=20, CRSwNP with asthma n=45, CRSwNP patients without asthma n=64), 18 CRSsNP patients, 29 AR patients and 5 control subjects.

Figure S1

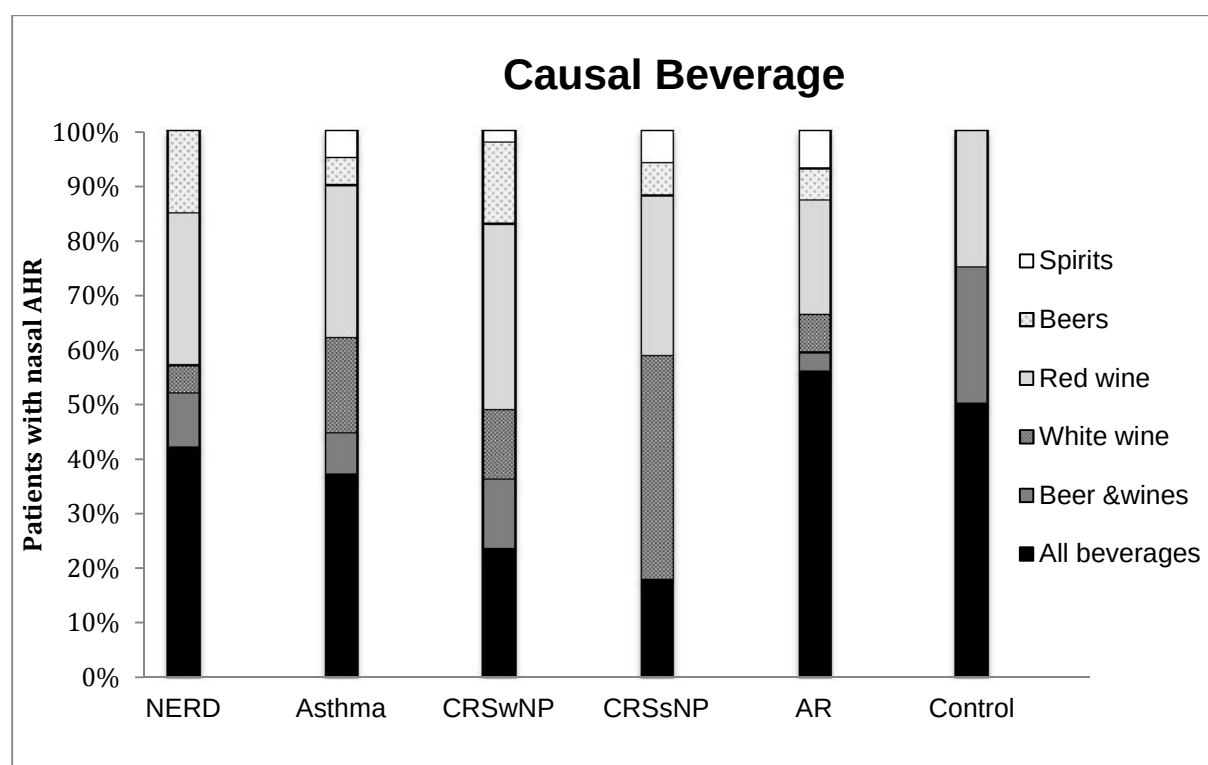


Figure S1 Shows the causal beverages for the induction of nasal alcohol HR in the different groups. In CRSwNP without asthma and in CRSsNP wines appear to be the most forceful triggers, whereas in all other groups all types of alcoholic beverages are most reported to cause nasal alcohol HR.

Figure S2

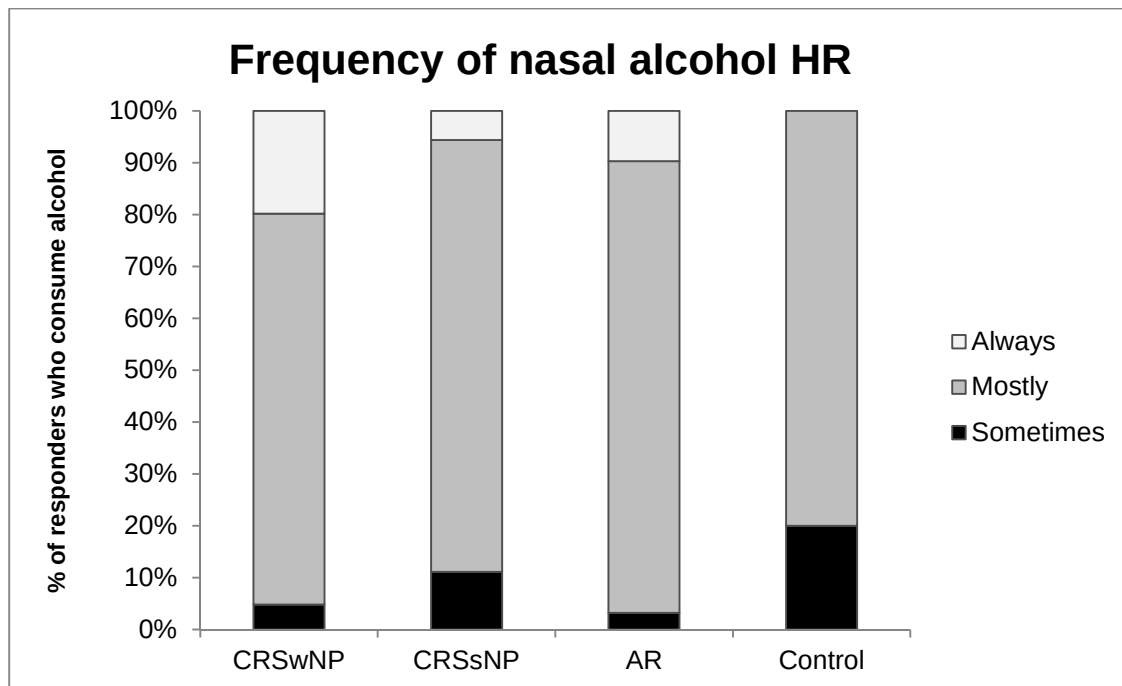


Figure S2 Demonstrates how often patients experience nasal alcohol HR after consumption of beverages. In patients with chronic nasal inflammation 5,6% - 19,8 % indicates nasal alcohol HR always occurs. None of the 6 healthy controls with nasal alcohol HR experiences symptoms each time alcohol is consumed. 'Mostly' is defined as in more than 50% of the times alcohol is consumed.

Figure S3

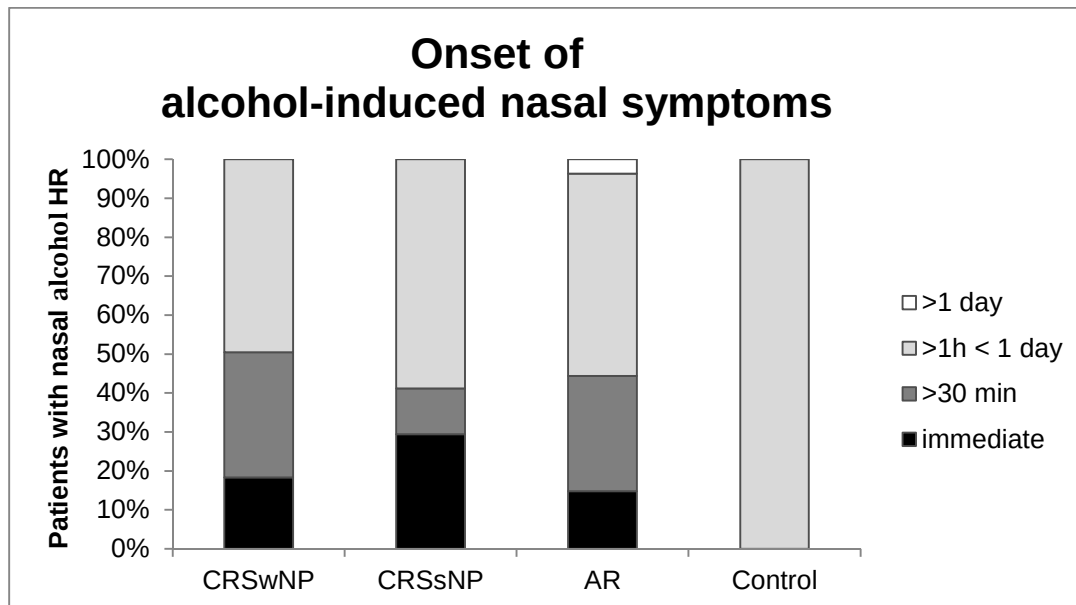


Figure S3 Shows the latency between drinking and the occurrence of nasal symptoms in the different groups. In approximately half of the patients diagnosed with a chronic inflammatory nasal disease, symptoms occur within an hour. In the other half symptoms develop within the day of alcohol consumption, except for 3,7 % of allergic rhinitis patients where it takes more than a day. In contrast, all 6 controls with nasal alcohol HR report it takes more than one hour but less than a day for symptoms to develop.

Figure S4

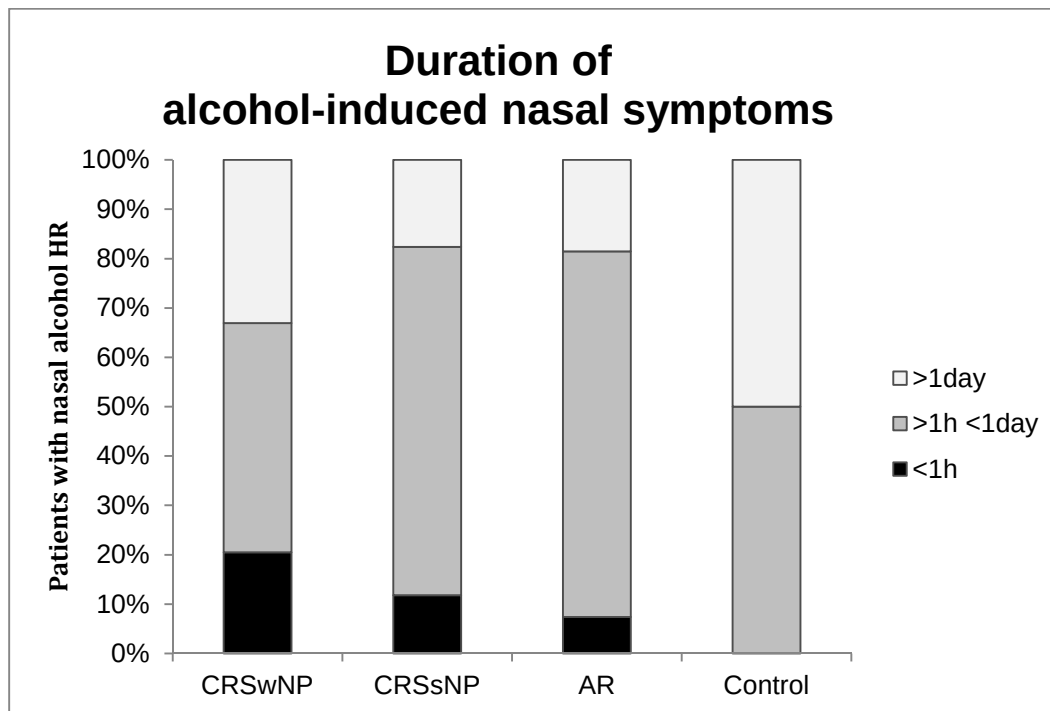


Figure S4 Demonstrates the duration of nasal symptoms in the different groups. The majority of patients with chronic inflammatory nasal disease report that symptoms resolve the same day as they develop. In contrast symptoms persist more than a day in 50% of controls with nasal alcohol HR.

Figure S5

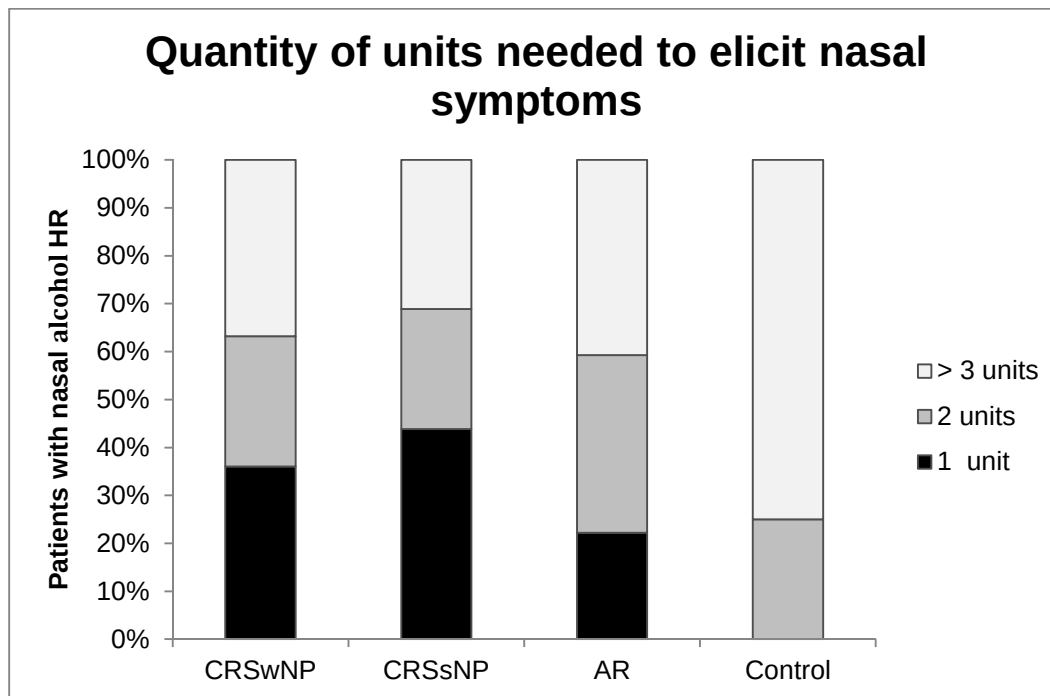


Figure S5 Shows the quantity of alcohol needed to elicit nasal alcohol HR. One unit is sufficient to develop nasal alcohol HR in about one-third of the chronic upper airway diseases. In control patients 1 unit is not sufficient to induce symptoms.

Figure S6

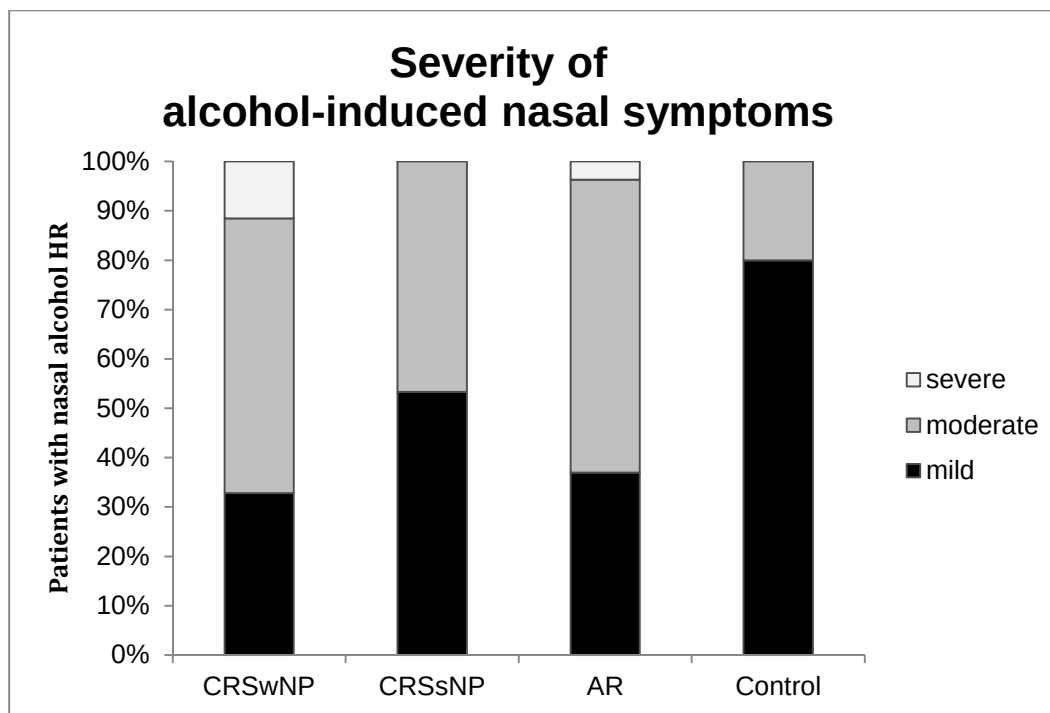


Figure S6 Shows the severity of alcohol-elicited nasal symptoms. Nasal alcohol HR symptoms are more severe in patients with chronic nasal inflammation as compared to healthy controls with nasal alcohol HR.

Figure S7

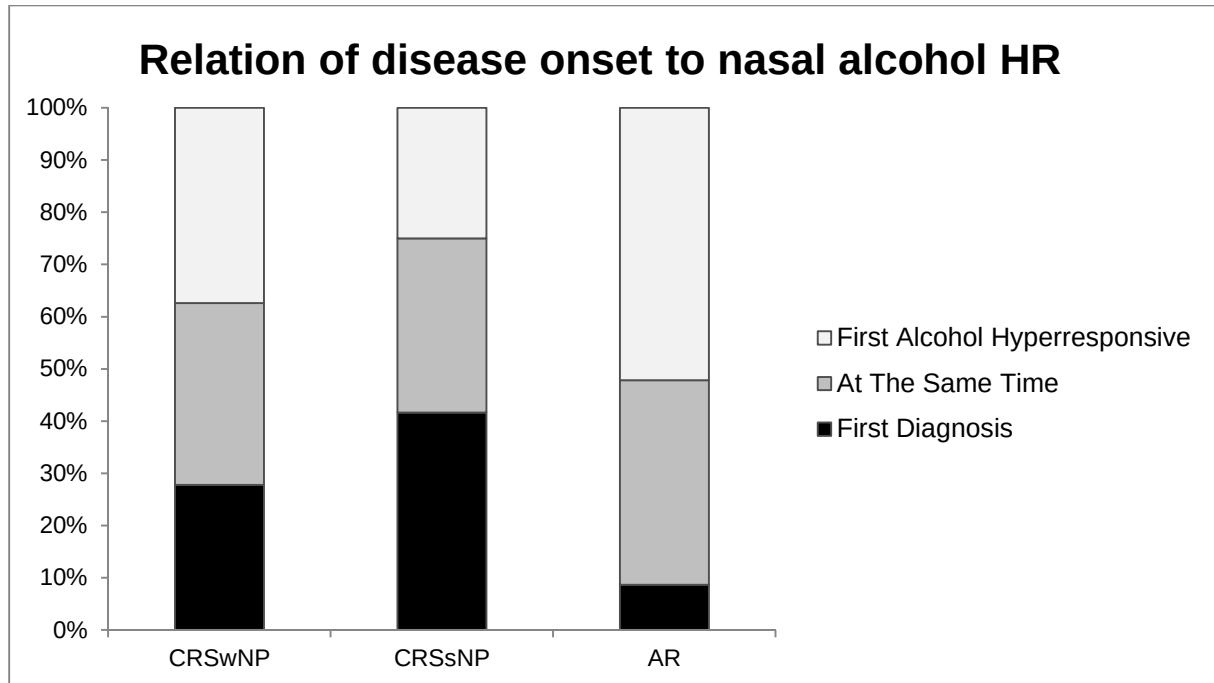


Figure S7 demonstrates that nasal alcohol HR was present before diagnosis or developed at the same time of diagnosis for the majority of CRSwNP or allergic rhinitis patients. In the case of CRSsNP, nasal alcohol HR developed after diagnosis