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ORIGINAL ARTICLE

Treatment history and association between allergic rhinitis symptoms and quality of life

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Abstract

Background Recalcitrance of allergic rhinitis (AR) to medical management may be reflective of patient-specific impact of AR symptoms.

Aims To understand the relationship between AR symptoms and general health-related quality of life (QOL) or AR control, based on treatment status.

Methods Cross-sectional cohort study of 130 adult participants—65 using no allergy medications and 65 consistently using intranasal corticosteroid sprays (ICS) in the last 3 months—presenting with persistent AR. General health-related QOL was measured using the EuroQol 5-dimensional visual analog scale (EQ-5D VAS). Severity and control of AR symptoms were measured using the 22-item Sinonasal Outcome Test (SNOT-22) and the Rhinitis Control Assessment Test (RCAT), respectively. We compared associations between AR symptoms and general health-related QOL and AR control in patients presenting with persistent AR with and without ICS use.

Results Severity of AR symptoms was similar between cohorts. In participants using no allergy medications, extranasal AR symptom severities were most dominantly associated with decreased EQ-5D VAS and RCAT score. In participants using ICS, only nasal symptom severities were associated with decreased EQ-5D VAS and RCAT scores. Consistently, only in participants on ICS was a deviated septum associated with decreased EQ-5D VAS ($\beta = -12.1$, 95% CI −21.1 to −3.1, $p = 0.011$) and poorly controlled AR (OR = 4.27, 96% CI 1.27 to 14.33; $p = 0.019$).

Conclusions In persistent AR despite consistent ICS use, nasal symptoms may be the dominant drivers of AR-associated decreased general health-related QOL in contrast to persistent AR on no medication, when extranasal symptoms of AR are most significant. Longitudinal study is needed to investigate whether these results are predictive of responsiveness to ICS.

Keywords Allergic rhinitis · Extranasal symptoms · General health-related quality of life · Intranasal corticosteroid spray · Nasal symptoms

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Introduction

Allergic rhinitis (AR) is an inflammatory condition of the nasal cavity with symptoms such as sneezing, nasal obstruction, pruritus, and rhinorrhea, which can have a profound impact on the daily life of patients [1]. Its symptoms further affect psychosocial functions, life at home, and productivity at work or in school [2–5]. The prevalence of AR is reportedly as high as 40% [1, 6, 7], which makes this a disease with a significant quality of life (QOL) detriment and economic burden on society as a whole.

The first-line therapy for AR includes either antihistamines or intranasal corticosteroid sprays (ICS). However, ICS are generally considered the most effective form of monotherapy [8] and are often the medical treatment of choice used prior to

determining whether endonasal surgical interventions for nasal obstruction would be warranted [9]. In the treatment of AR, ICS have been shown to block multiple inflammatory pathways and to ameliorate both nasal and extranasal symptoms [10]. Yet, despite treatment with an ICS, some patients still experience persistently severe AR symptoms or poor control of their AR and it is still unclear why this may be the case. Although allergen exposure and host-specific pathophysiology (e.g., intensity of the allergic response) very likely play a role in the efficacy of ICS, it is unknown whether the patient-specific impact or perception of AR symptomatology may have some role in the ICS treatment response.

There is a potential to gain some insight into this possibility by studying patients who present for clinical care due to complaints about their persistent AR. It has previously been shown that in the general population of patients with persistent AR, extranasal symptoms of AR (such as sleep or ear/facial discomfort symptoms) may have the greatest impact on general health-related QOL [11]. In this study, we hypothesized that the possible role of patients' perceptions of their persistent AR symptomatology in determining treatment response would be reflected in the differential association of AR symptom severities and general health-related QOL-based AR treatment status. Specifically, we determined the association between AR symptoms with the level of AR control as well as general health-related QOL, comparing patients presenting with persistent AR who had been using no allergy medication to AR patients who had been using an ICS. We believe that our results will be clinically informative by providing insight into the symptoms that have the greatest impact on patients with persistent AR, depending treatment history with an ICS.

Materials and methods

Study participants

This study was approved by the Massachusetts Eye and Ear Infirmary Human Studies Committee. We prospectively recruited adult patients aged 18 years or older with persistent AR based on formal skin or serological allergy testing [12] and a history consistent with the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [1]. All study participants were recruited at the time of initial presentation to our clinics for management of AR and provided informed consent for inclusion in this study. Exclusion criteria included comorbid diagnoses of chronic rhinosinusitis, vasculitis, cystic fibrosis, sarcoidosis, or immunodeficiency.

Study design and data collection

This is a cross-sectional cohort study. A total of 130 study participants were prospectively recruited. Specifically, we recruited 65 participants with persistent AR who presented to our clinic and reported using an ICS consistently, at least 6 days per week, and under the recommendation of their primary care physicians for the preceding 3 months. We also recruited 65 participants with persistent AR who presented to our clinic and had not used any allergy medication—including ICS, antihistamines, leukotriene receptor antagonists, or mast cell stabilizers—in the preceding 3 months. All data were collected at the time of enrollment. Age, gender, race, and smoking history of all participants were recorded. Any participant who was a current or former tobacco smoker was considered a smoker for this study. At enrollment, participants were assessed by the evaluating physician for a history of asthma based on clinical evaluation and clinical history/prior diagnosis. As clinical assessment by an otolaryngologist of a clinically significant deviated septum has been shown to be highly accurate [9], all participants were evaluated using anterior rhinoscopy and nasal endoscopy for nasal septal deviation by an experienced otolaryngologist while blinded to the participants' responses on validated surveys quantifying AR control, AR symptom severity, and general health-related QOL. All participants completed the Rhinitis Control Assessment Test (RCAT), which assesses the control of rhinitis and its associated symptomatology [13]. All participants completed the 22-item Sinonasal Outcome Test (SNOT-22) questionnaire [14]. The SNOT-22 assesses 22 symptoms, which are related to either nasal symptoms, sleep quality, ear/facial discomfort symptoms, or emotional symptoms, on an integer scale of 0—"no problem," 1—"very mild problem," 2—"mild to slight problem," 3—"moderate problem," 4—"severe problem," or 5—"problem as bad as it can be." General health-related QOL was measured by the validated EuroQol 5-dimensional visual analog scale (EQ-5D VAS) given with the 5-level EQ-5D questionnaire [15]. EQ-5D VAS measures the current state of health—with 0 as the minimum, representing the "worst health you can imagine" and 100 as the maximum, representing the "best health you can imagine."

Statistical analysis

All analysis was performed with the statistical software package R [16]. A total of 65 participants were recruited in each cohort in order to be able to detect an association of medium effect size (Cohen's $f^2 = 0.15$) between the severity of an individual symptom reflected by the SNOT-22 (as the independent variable) and EQ-5D VAS as our primary outcome variable with a power of 0.9 and at a significance level of 0.05. Associations were sought using linear regression for EQ-5D VAS as the dependent variable and logistic regression for poor AR control as the secondary dependent variable.

Results

Characteristics of study participants

A total of 130 participants with persistent AR, with 65 participants reporting the use of an ICS for at least 6 days per week over the preceding 3 months and 65 participants reportedly taking no allergy medication (including an ICS or antihistamine), were recruited. The demographic and clinical characteristics of these study participants are characterized in Table 1. Of all participants, 68.5% had poorly controlled AR (RCAT < 22)—76.9% of the participants using an ICS and 60.0% of the participants using no allergy medication had poorly controlled AR. Although the difference in the distribution of participants in each cohort having poorly controlled AR did not reach statistical significance ($p = 0.060$), the cohort using no allergy medication did have a significantly higher mean RCAT score ($p = 0.028$). There was otherwise no statistically significant difference between those two cohorts with respect to the SNOT-22 or EQ-5D VAS scores ($p > 0.05$). Additionally, when we compared the severity of scores of the individual SNOT-22 items between the two cohorts, we found almost completely identical symptom severities (Fig. 1) with no statistically significant differences in the scores of any of the individual SNOT-22 items ($p > 0.05$).

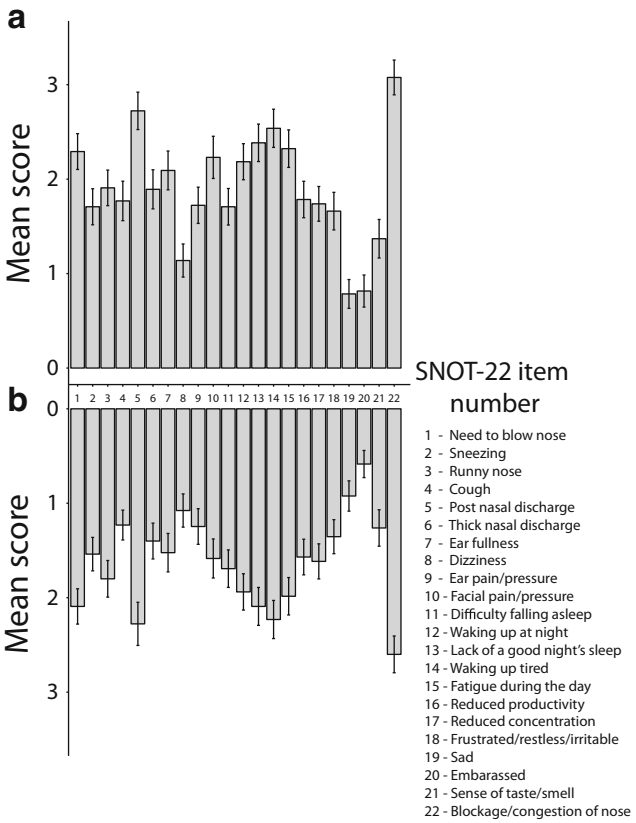

Fig. 1 Bar graph for the mean score of each SNOT-22 item for **a** participants using an intranasal corticosteroid spray (N=65) and **b** participants not using any allergy medication. Error bars reflect standard error. The symptom assessed for each of the SNOT-22 items is listed to the right of the figure

Association between AR symptoms and AR control

We first sought to determine the association between sinonasal symptoms and AR control in the two cohorts (Table 2). When we checked for an association between the severity of sinonasal symptoms and poor AR control, we found only the severity of nasal symptoms, such as nasal obstruction and sneezing, to be associated with poor AR control in the cohort using an ICS. In contrast, we found not only the severity of nasal symptoms of AR but also extranasal symptoms related to sleep quality, ear/facial discomfort, and depressed mood to be associated with poor AR control in the cohort using no allergy medication. These

Table 1 Characteristics of study participants

	All study participants ($N = 130$)	Using an ICS ($N = 65$)	No allergy medication ($N = 65$)
Clinical and demographic characteristics			
Age, mean in years (SD)	43.8 (16.9)	46.4 (17.4)	41.2 (16.0)
Gender			
Male (%)	33.1	26.2	40.0
Female (%)	66.9	73.8	60.0
Smoking history (%)	21.5	21.5	21.5
Asthma (%)	18.5	21.5	15.4
Allergic rhinitis characteristics			
Using an antihistamine (%)	30.0	60.0	0.0
RCAT score, mean (SD)	19.3 (4.4)	18.4 (4.5)	20.1 (4.1)
SNOT-22 score, mean (SD)	38.7 (21.4)	41.8 (20.8)	35.6 (21.7)
EQ-5D VAS, mean (SD)	70.1 (18.9)	71.1 (18.3)	69.2 (19.5)

SD standard deviation

Table 2 Association of individual SNOT-22 items with poorly controlled AR

SNOT-22 item	ICS		No allergy medication	
	OR	*p* value	OR	*p* value
1—Need to blow nose	2.31	0.001	1.97	0.001
2—Sneezing	4.85	0.001	2.97	< 0.001
3—Runny nose	1.99	0.008	1.74	0.006
4—Cough	1.57	0.035	1.49	0.078
5—Post nasal discharge	1.36	0.107	1.77	0.001
6—Thick nasal discharge	1.44	0.073	1.85	0.007
7—Ear fullness	1.33	0.139	1.39	0.056
8—Dizziness	1.16	0.520	1.27	0.215
9—Ear pain/pressure	1.03	0.871	1.62	0.022
10—Facial pain/pressure	1.27	0.169	1.36	0.067
11—Difficulty falling asleep	1.35	0.155	1.85	0.003
12—Waking up at night	1.35	0.141	2.40	< 0.001
13—Lack of a good night's sleep	1.22	0.288	1.86	0.002
14—Waking up tired	1.37	0.106	2.02	0.001
15—Fatigue during the day	1.38	0.109	1.84	0.002
16—Reduced productivity	1.43	0.103	2.08	0.001
17—Reduced concentration	1.51	0.077	1.95	0.003
18—Frustrated/restless/irritable	1.42	0.108	1.95	0.005
19—Sad	1.42	0.263	1.77	0.026
20—Embarrassed	1.50	0.199	2.85	0.034
21—Sense of taste/smell	1.57	0.072	1.05	0.768
22—Blockage/congestion of nose	2.24	0.001	2.07	< 0.001

OR odds ratio

divergent associations between the burden of AR symptoms and poor AR control were confirmed after controlling for age, gender, smoking history, comorbid asthma, and antihistamine use (Supplemental Table S1 and Fig. 2). We additionally sought to confirm the role of nasal symptomatology in AR control between these two cohorts by examining whether the presence of a deviated nasal septum—which would result in nasal obstruction—was associated with AR control. We found that having a clinically significant septal deviation was associated with poor AR control (odds ratio [OR] = 4.27, 95% CI 1.27–14.33, $p = 0.019$) in participants who were using an ICS but not in participants who had used no allergy medication in the past 3 months (OR = 0.64, 95% CI 0.22–1.82, $p = 0.403$).

Association between AR symptoms and general health-related QOL

In order to understand why participants using an ICS associated the burden of AR symptoms with the level of AR control differently compared to participants not using any allergy medication, we sought associations between the symptoms reflected by the SNOT-22 and general health-related QOL, as reflected by the EQ-5D VAS for each cohort. In investigating these associations, we sought to determine whether symptoms of AR differentially impacted patients using an ICS in comparison to patients using no allergy medications. As expected from the findings described above, we found that the severity of nasal symptoms was associated with the greatest decrease in EQ-5D VAS in the ICS cohort while the severity of extranasal symptoms (most dominantly symptoms related to poor sleep quality) was associated with the greatest decreases in EQ-5D VAS in participants using no allergy medication (Table 3). For the latter participants, the severity of nasal symptoms had essentially no impact on the EQ-5D VAS score. These associations were confirmed after controlling for age, gender, smoking history, comorbid asthma, and antihistamine use (Supplemental Table S2 and Fig. 3). We likewise used the presence of nasal septal deviation as a possible clinical correlate for nasal symptomatology (i.e., nasal obstruction) and found that while nasal septal deviation was associated with decreased EQ-5D VAS (linear regression coefficient [β] = − 12.1, 95% CI − 21.1 to − 3.1, $p = 0.011$) for the participants using an ICS, this was not the case for the participants using no allergy medications (β = − 5.4, 95% CI − 15.3 to 4.4, $p = 0.281$).

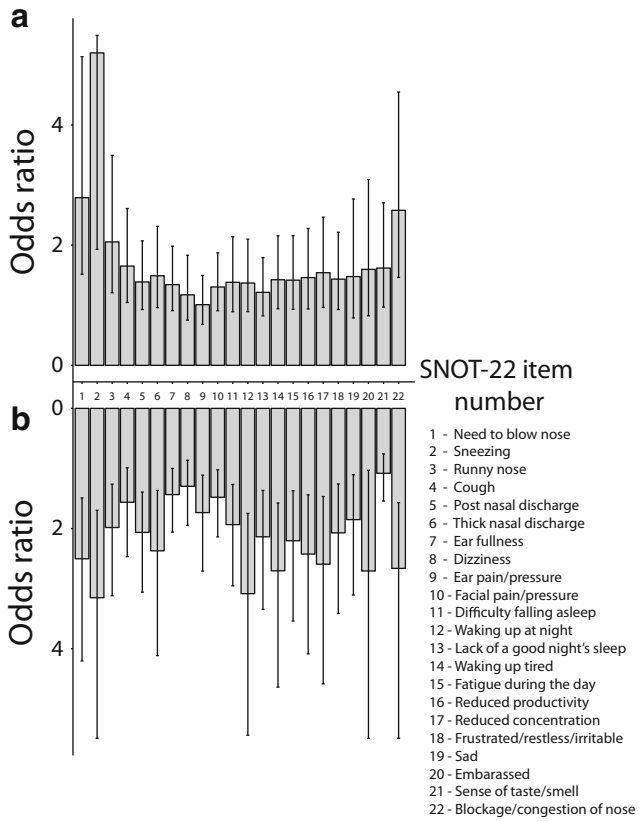

Fig. 2 Bar graph for showing the multivariable odds ratio (controlling for age, gender, smoking history, comorbid asthma, and antihistamine use) for the association between having poorly controlled AR (RCAT < 22) and each SNOT-22 item for **a** participants using an intranasal corticosteroid spray ($N = 65$) and **b** participants not using any allergy medication. Error bars reflect the 95% CIs. The symptom assessed for each of the SNOT-22 items is listed to the right of the figure

Discussion

The classic symptoms of AR are of nasal origin and the clinical diagnosis of AR is made based on the presence of nasal symptomatology (in addition to positive skin or serological testing). However, AR also affects individuals through extranasal symptoms such as ear/facial discomfort or sleep-related symptoms that may have a profound impact on the QOL of patients [11]. Because the goal of AR treatment is to improve symptomatology in order to improve QOL, the AR symptoms associated with the greatest decrease in QOL should ideally be the focus of evaluation and response to treatment. The patient population with persistent AR symptoms is not entirely homogeneous as it consists of both patients who are not using allergy medication as well as patients who are failing allergy medication. It is possible that the impact of AR symptoms on these patients' QOL may be different as well. In this study, we compared the association between AR symptoms and general health-related QOL (and AR control) in a cohort of patients who presented with persistent AR and no use of allergy medication in the last 3 months with the same associations in a cohort of patients who presented with persistent AR symptoms despite using at least an ICS on a consistent basis over the same amount of time. We found that both nasal and extranasal symptoms of AR were significantly associated with decreased general health-related QOL. However, in patients presenting with persistent AR symptoms despite using an ICS (reflective of patients failing appropriate first-line medication), the association between nasal symptoms and decreased general health-related QOL or AR control was most dominant while in patients using no allergy medication, the extranasal symptoms of AR were most greatly associated with decreased general health-related QOL and poor AR control.

Previous studies have demonstrated that uncontrolled AR and its symptoms including both nasal and extranasal symptoms can lead to impairments at work and in daily life [17]. Consequently, the impact of AR on patients' lives leads to a significant general health-related QOL detriment [18]. The different symptoms of AR include extranasal symptoms, such as sleep-related symptoms largely reflecting poor sleep quality, as well as ear/facial discomfort, such as ear pressure or facial pressure, and emotional symptoms, such as depressed mood [17, 19–21]. Most well-known are the classic nasal symptoms of AR, including sneezing, rhinorrhea, nasal obstruction, and pruritus [1]. Previous study of the different symptoms of AR has shown that among all of the different symptoms of AR, extranasal symptoms may be most dominantly associated with a decreased general health-related QOL, compared to nasal symptoms, in the general population of patients with persistent AR [11].

In this study, we questioned whether real-time AR treatment status may bias—and therefore inform the clinical care of—the disease perception (how the disease impacts QOL) of patients presenting with persistent AR symptoms. In persistent AR patients who were not using any allergy medication, extranasal symptoms of AR related to poor sleep quality, ear/facial discomfort, and depressed mood had the greatest association with decreased general health-related QOL and poor AR control. By contrast, we found that participants in our cohort using an ICS were impacted very differently by their persistent AR symptoms. In participants using an ICS, the severity of nasal symptoms—including nasal obstruction, rhinorrhea, and sneezing—was most associated with having poorly controlled AR and with decreased general health-related QOL. These two cohorts of patients with persistent AR—those on an ICS and those using no allergy medication—had similar severities of nasal and extranasal symptoms so it was surprising to find that these two cohorts could be so differently impacted by nasal and extranasal symptoms of AR.

Based on our results, we can consider several possibilities and make some hypotheses to motivate future study. Our results suggest the possibility that AR treatment status may bias the AR disease perception of patients who present with complaints of persistent AR. However, why might that be the case? Previous work has demonstrated that ICS are the most effective topical medication for improving the severity of nasal symptoms (such as obstruction) of AR [8, 22, 23]. Our results suggest the

Table 3 Association of individual SNOT-22 items with EQ-5D VAS

	ICS		No allergy medication	
SNOT-22 item	β^a	p value	β^a	p value
1—Need to blow nose	− 5.71	< 0.001	− 1.80	0.270
2—Sneezing	− 4.65	0.001	− 1.76	0.307
3—Runny nose	− 3.78	0.012	− 1.29	0.412
4—Cough	− 3.29	0.015	− 4.82	0.011
5—Post nasal discharge	− 3.84	0.007	− 3.91	0.003
6—Thick nasal discharge	− 3.53	0.010	− 0.84	0.604
7—Ear fullness	− 2.13	0.125	− 3.22	0.029
8—Dizziness	− 2.32	0.155	− 4.64	0.006
9—Ear pain/pressure	− 3.96	0.009	− 2.55	0.112
10—Facial pain/pressure	− 2.06	0.113	− 2.87	0.049
11—Difficulty falling asleep	− 2.92	0.047	− 4.87	0.001
12—Waking up at night	− 1.43	0.344	− 4.10	0.008
13—Lack of a good night's sleep	− 2.22	0.124	− 4.96	0.001
14—Waking up tired	− 3.62	0.009	− 6.04	< 0.001
15—Fatigue during the day	− 3.91	0.005	− 6.99	< 0.001
16—Reduced productivity	− 2.78	0.060	− 7.20	< 0.001
17—Reduced concentration	− 2.92	0.058	− 5.74	< 0.001
18—Frustrated/restless/irritable	− 3.84	0.007	− 4.48	0.007
19—Sad	− 4.40	0.017	− 6.20	0.001
20—Embarrassed	− 2.51	0.135	− 6.60	0.001
21—Sense of taste/smell	− 1.86	0.186	− 1.52	0.336
22—Blockage/congestion of nose	− 5.25	< 0.001	1.63	0.297

[a] Linear regression coefficient

possibility of an important link between the QOL impact of nasal symptoms and failure of ICS for controlling persistent AR. Participants in both of our cohorts experienced similar severities of AR symptomatology; the primary difference between these two cohorts was the association of specific AR symptoms with general health-related QOL and patient-reported AR control. Based on our results, it could be possible that ICS may be less effective in AR patients whose nasal symptoms have the greatest impact on their QOL or that, while ICS are generally effective at blunting the QOL impact of AR symptoms, ICS may be ineffective at eliminating the impact of nasal symptoms that may be related to fixed, anatomic problems. Both of these possibilities may likely contribute to our findings and both findings are also supported by our analysis showing that the physical exam finding of significant nasal septal deviation was strongly associated with decreased general health-related QOL in our cohort using an ICS but not for the cohort taking no allergy medication. These possible explanations certainly need further study in order to be confirmed but we nevertheless believe that our results will be clinically informative for the care of patients with AR for several reasons. First, this study suggests for the first time that the patient-specific impact of AR symptom severities on QOL may modulate patient perception of AR control as well as response to ICS (or perhaps other treatments as well). In assessing AR patients, it is therefore beneficial to evaluate the impact of AR symptoms on patients (e.g., on their QOL) rather than focusing just simply on the overall severity of symptoms. Second, our findings demonstrate that the most significant symptoms of AR may vary between different cohorts of AR patients and we show that although extranasal symptoms of AR are most associated with QOL detriment and poor AR control in untreated patients, nasal symptoms of AR should potentially be more focused upon in the evaluation of AR patients who are failing treatment with an ICS.

Our results should be interpreted within the context of the limitations of our studies. The primary limitation of this study is its cross-sectional design. The definitive means to prove our results would be through a longitudinal study of AR patients' symptomatology before and after treatment with an ICS to compare the symptomatology patterns of those who did and did not respond to ICS. Our results here certainly do not replace such a longitudinal study but they certainly provide some novel insights that importantly serve as justification and motivation for future longitudinal study. Because ICS are generally quite effective, such a longitudinal study would require large numbers of AR patients in order to recruit a reasonable number of patients who continue to have persistent symptoms despite taking an ICS. Before undertaking such a study, it is necessary to

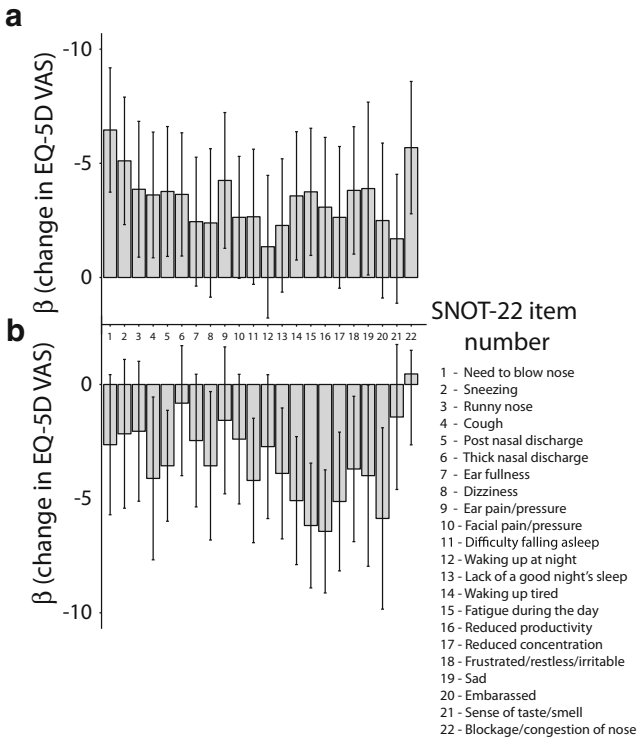

Fig. 3 Bar graph showing the linear regression coefficient (β) for the association between EQ-5D VAS and each SNOT-22 item for **a** participants using an intranasal corticosteroid spray ($N = 65$) and **b** participants not using any allergy medication. Error bars reflect the 95% CIs. The symptom assessed for each of the SNOT-22 items is listed to the right of the figure

establish the likelihood of whether a relationship exists between patient-specific impact of AR symptoms on QOL and treatment response, which we have now done using our simple cross-sectional design. Additionally to be considered as a limitation, although we do not know if the patients in the no medication cohort have never used any allergy medications, we do know that they had not used any allergy medications in the preceding 3 months, which we believe is enough time for the patients' persistent AR symptomatology and quality of life to be reflective of the untreated state. We believe that the novel insights provided by our study should serve as the basis for future longitudinal studies as well as inform the design of clinical trials. In particular, we believe that our results represent an important contribution as they highlight the need to investigate whether patients' perceptions of their AR, for example as reflected by patient-specific associations between individual AR symptoms and general health-related QOL, may be predictive of future AR treatment response.

Conclusion

In patients presenting for complaints of persistent AR symptoms despite consistent utilization of an ICS, nasal symptoms are associated with the greatest QOL impact. In contrast, for persistent AR patients presenting in the setting of no AR medication usage, the extranasal symptoms of AR are associated with the greatest QOL impact. Evaluation of patients presenting with persistent AR should take into account the patients' AR treatment status. Further study is needed to determine if the patient-specific impact of AR symptoms on QOL may be used to inform the focus of the clinical assessment and subsequent treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This study was approved by the Massachusetts Eye and Ear Infirmary Human Studies Committee.

Informed consent Informed consent was obtained from each participant.

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