

Depressed Mood Modulates Impact of Chronic Rhinosinusitis Symptoms on Quality of Life



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What is already known about this topic? It is known that the burden of chronic rhinosinusitis (CRS) symptoms is negatively associated with general health-related quality of life (QOL). Patient factors and characteristics that can modulate this relationship remain unknown.

What does this article add to our knowledge? CRS symptom burden is negatively associated with general health-related QOL in patients with well-controlled symptoms. In patients with poorly controlled symptoms, only depressed mood—not overall CRS symptom burden—is negatively associated with general health-related QOL.

How does this study impact current management guidelines? Mood modulates the relationship between CRS symptom burden and general health-related QOL—in particular for patients with poorly controlled symptoms. This study therefore highlights the need for a holistic approach to management of CRS.

BACKGROUND: It is unknown how severity of depressed mood affects the well-recognized relationship between chronic rhinosinusitis (CRS) symptom burden and decreased general health-related quality of life (QOL).

OBJECTIVE: The objective of this study was to determine whether depressed mood would affect the relationship between CRS symptom burden and decreased general health-related QOL.

METHODS: For this cross-sectional study, 610 participants with CRS were prospectively recruited. CRS symptom burden was measured with the 22-item Sino-Nasal Outcome Test (SNOT-22). General health-related QOL was measured with the EuroQol 5-dimensional health utility value (EQ-5D HUV) and visual analog scale (EQ-5D VAS). Depressed mood was measured using the Patient Health Questionnaire-2 (PHQ-2). Participants were stratified as having well-controlled CRS

symptoms (SNOT-22 < 35) and poorly controlled CRS symptoms (SNOT-22 ≥ 35). Good general health-related QOL was determined as EQ-5D HUV ≥ 0.9 or EQ-5D VAS ≥ 80, in contrast to low general health-related QOL.

RESULTS: In participants with well-controlled CRS symptoms, both SNOT-22 and PHQ-2 were significantly and negatively associated with good general health-related QOL ($P < .020$ in all cases using multivariable regression). In participants with poorly controlled CRS symptoms, the PHQ-2 was significantly and negatively associated with good general health-related QOL using the EQ-5D HUV (adjusted odds ratio [OR] = 0.37, 95% confidence interval [CI]: 0.22-0.62, $P < .001$) or the EQ-5D VAS (adjusted OR = 0.74, 95% CI: 0.57-0.96, $P = .024$). In contrast, SNOT-22 was not associated with general health-related QOL in these patients.

CONCLUSIONS: Depressed mood modulates the association between CRS symptom burden and general health-related QOL. Our results suggest a threshold of CRS symptom burden or control, beyond which depressed mood—not CRS symptom burden—drives the association with general health-related QOL. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:2098-105)

Key words: Chronic rhinosinusitis; Depression; Depressed; Mood; Quality of life; EQ-5D

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication August 11, 2017; revised April 8, 2018; accepted for publication April 20, 2018.

Available online May 8, 2018.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2018.04.034>

Chronic rhinosinusitis (CRS) is an inflammatory disease of the sinonasal mucosa defined clinically based on subjective reporting of characteristic sinonasal symptomatology by patients in addition to objective evidence of sinonasal inflammation.^{1,2} CRS likely represents a common, clinical end point for a heterogeneous group of etiopathologies.³⁻⁸ Given the negative impact on physical and emotional aspects of daily functioning, CRS has

Abbreviations used

AUC- Area under the curve
CRS- Chronic rhinosinusitis
EQ-5D- 5-dimensional EuroQol questionnaire
HUV- Health utility value
OR- Odds ratio
PHQ-2- Patient Health Questionnaire-2
QOL- Quality of life
ROC- Receiver operating characteristic
SNOT-22- 22-item Sino-Nasal Outcome Test
VAS- Visual analog scale

been identified as one of the most taxing health conditions in the United States, responsible for billions of dollars in annual expenses, as well as a dramatic decrease in quality of life (QOL) for affected individuals.⁹

The chronic symptoms of CRS comprise the primary determinant of the decrease in QOL associated with CRS.¹⁰⁻¹³ These symptoms include not only sinonasal symptoms but also emotional symptoms, such as depressed mood.^{14,15} In the setting of infection, inflammation, or injury, it is common for patients to exhibit an organized suite of behavioral changes, called “sickness behavior,” which includes appetite disturbances, anhedonia, social withdrawal, and isolation.¹⁶ Sickness behavior is an evolutionarily conserved behavior and is beneficial in the acute setting as energy is conserved for the acute inflammatory response. However, in the setting of chronic inflammation, sickness behavior promotes the central nervous system to create and maintain a depressed mood.¹⁶ In this context, it is not surprising that nasal and extranasal symptoms of CRS have been shown to correlate with depressed mood in patients with CRS.^{17,18} The impact of depressed mood on CRS cannot be ignored, as it is associated with poorer outcomes in clinical management as well as increased direct and indirect costs related to CRS.^{15,19,20} In contrast, classic sinonasal symptoms seen in patients with CRS, such as nasal obstruction or drainage, are weakly associated with lost productivity and decreased general QOL.¹⁹ These findings suggest that depressed mood is an influential factor that can modulate patients’ perception of their disease.

Of all clinical manifestations of CRS, the chronic symptomatology associated with CRS is most commonly and strongly associated with decreased general health-related QOL.^{10,11,13} Given the fact that depressed mood plays a role in the perception of illness,²¹⁻²³ it is possible that depressed mood modulates the relationship between CRS symptom burden and the decrease in general health-related QOL seen in patients with CRS. The extent to which depressed mood may modulate this relationship has never been investigated. In this study, we explored the effect of depressed mood on the relationship between CRS symptom burden and general health-related QOL. We hypothesized that increasingly depressed mood would lead to a greater magnitude of association between increasing CRS symptom burden and decreasing general health-related QOL. In other words, we hypothesized that patients with more depressed mood would have lower general health-related QOL for a given level of CRS symptom burden.

METHODS

Study participants

This study was approved by the Massachusetts Eye and Ear Infirmary Human Studies Committee. Adult patients (aged 18 years or older) with CRS were recruited prospectively and provided informed consent for inclusion into this cross-sectional study. All participants met consensus guideline criteria for CRS established by the American Academy of Otolaryngology—Head and Neck Surgery.¹ Exclusion criteria included comorbid diagnoses of: (1) vasculitis, (2) cystic fibrosis, (3) sarcoidosis, and (4) immunodeficiency. Patients with active, acute CRS exacerbations were excluded so that all study participants’ symptom severities would be reflective of baseline CRS symptomatology. To remove the confounding effect of recent endoscopic sinus surgery, patients who had endoscopic sinus surgery within the last 6 months were also excluded.

Study design and data collection

This study was designed as a prospective cross-sectional study. All data were collected at enrollment. Demographic information including age, gender, and ethnic group was collected. Any patient who was an active smoker or reported a history of being a tobacco smoker in the past was considered to be a smoker for this study. At enrollment, participants were assessed by the evaluating physician for a history of asthma based on clinical history and prior diagnosis. A history of aeroallergen hypersensitivity was based on patient-reported formal (skin or serological) allergy testing. Participants were interviewed to determine whether they had a history of previous sinus surgery, a history of aspirin sensitivity (respiratory symptoms such as wheezing or shortness of breath after exposure to 1 or more nonsteroidal anti-inflammatory drugs) and whether they had comorbid diabetes, heart disease (coronary artery disease, myocardial infarction or heart failure), or history of stroke or cancer. Intranasal corticosteroid (spray or irrigation) use was also assessed. General health-related QOL was measured using the EuroQol 5-dimensional health utility value (EQ-5D HUV) derived from the validated EQ-5D questionnaire and the visual analog scale (EQ-5D VAS) given with the 5-level EQ-5D questionnaire.²⁴ Although the EQ-5D HUV assesses health status and ranges from 0 (lowest health state—death) to 1.0 (perfect health status), the EQ-5D VAS assesses patients’ self-reported 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.” All participants also completed the validated 22-item Sino-Nasal Outcome Test (SNOT-22) survey,²⁵ which provides a quantitative measure of CRS symptom burden. SNOT-22 nasal, otologic/facial pain, sleep, and emotional subdomain scores were also calculated.²⁶ The SNOT-22 nasal subdomain score was calculated by summing SNOT-22 items 1-6, 21, and 22. The SNOT-22 otologic/facial pain subdomain score was calculated by summing SNOT-22 items 7-10. The SNOT-22 sleep subdomain score was calculated by summing SNOT-22 items 11-18. The SNOT-22 emotional subdomain score was calculated by summing SNOT-22 items 19 and 20. The severity of each participant’s depressed mood was measured using the validated Patient Health Questionnaire-2 (PHQ-2) survey that queries the frequency over the prior 2 weeks of anhedonia and feeling down, depressed, or hopeless.²⁷ For each participant, the presence of nasal polyps was determined by nasal endoscopy.

TABLE I. Characteristics of study participants

	All study participants (N = 610)	Well-controlled CRS symptoms (N = 330)	Poorly controlled CRS symptoms (N = 280)	P value*
Demographics				
Age (y), mean (SD)	52.3 (15.9)	54.7 (15.8)	49.5 (15.5)	<.001
Gender (%)				
Male	48.7	53.0	43.6	.023
Female	51.3	47.0	56.4	
Ethnic group (%)				
White	60.8	61.8	59.6	.213
Black of African American	1.3	1.8	0.7	
Other	5.4	5.8	5.0	
Declined to respond	32.5	30.6	34.6	
Smoking (%)	27.9	26.7	29.3	.931
Comorbidities				
Aeroallergen hypersensitivity (%)	43.6	40.0	47.9	.059
Aspirin sensitivity (%)	5.4	5.2	5.7	.601
Asthma (%)	30.8	26.1	36.4	.009
Diabetes (%)	5.2	4.5	6.1	.467
Heart disease (%)	3.6	3.0	4.3	.514
Stroke (%)	1.3	1.2	1.4	1.00
Malignancy (%)	10.7	9.7	11.8	.431
CRS characteristics				
Nasal polyps (%)	45.1	47.9	41.8	.167
Previous sinus surgery (%)	37.0	34.5	40.0	.179
Intranasal corticosteroid use (%)	46.4	43.6	49.6	.143
SNOT-22 score, mean (SD)	35.8 (23.2)	18.2 (9.9)	56.6 (16.1)	<.001
EQ-5D HUV, mean (SD)	0.85 (0.15)	0.90 (0.10)	0.78 (0.16)	<.001
EQ-5D VAS, mean (SD)	71.7 (20.7)	79.7 (16.3)	62.3 (21.3)	<.001
PHQ-2, mean (SD)	0.8 (1.3)	0.4 (1.0)	1.3 (1.5)	<.001

CRS, Chronic rhinosinusitis; EQ-5D HUV, EuroQol 5-dimensional health utility value; EQ-5D VAS, EuroQol 5-dimensional visual analog scale; PHQ-2, Patient Health Questionnaire-2; SD, standard deviation; SNOT-22, 22-item Sino-Nasal Outcome Test.

*Comparison of participants with well-controlled CRS with those with poorly controlled CRS.

Statistical analysis

All analysis was performed using the statistical software package R (www.r-project.org).²⁸ Correlations were calculated using Spearman correlation. Participants were stratified based on previous work into 2 cohorts according to the SNOT-22 score (<35—“well-controlled CRS symptoms,” or ≥35—“poorly-controlled CRS symptoms”).²⁹ A total of 610 participants were recruited to have at least 280 participants in each cohort, which would provide 20 participants per variable for the multivariable regression models that were used to check for association between the EQ-5D and PHQ-2, while controlling for 13 other variables. This also provided at least 80% power to detect an association between the EQ-5D and PHQ-2 of small to medium effect size at a significance level of .05 using our multivariable model.

Participants were also stratified into 2 cohorts, having either good or low QOL, according to the EQ-5D HUV and EQ-5D VAS scores, using cutoff scores that were determined empirically based on the current data as described in the Results section. Associations between independent variables and having good versus low QOL were determined using logistic regression. A final multivariable model to examine the association between high versus low QOL (as a dependent variable) and the PHQ-2 score as our independent variable controlled for the SNOT-22 score, age, gender, history of aeroallergen hypersensitivity, history of smoking, previous sinus

surgery, nasal polyps, use of intranasal corticosteroids, and comorbid asthma, diabetes, heart disease, stroke, and malignancy. When needed, we generated receiver operating characteristic (ROC) curves with the pROC package.³⁰ The area under the ROC curve (AUC) was calculated with the trapezoid rule using the auc() function, and the 95% confidence interval of the AUC was calculated by performing 2000 bootstraps of the data with the ci() function. The *P* value for significance of the ROC curve was determined by the Wilcoxon rank-sum test.

RESULTS

Characteristics of study participants

We recruited a total of 610 participants, whose clinical and demographic characteristics are summarized in Table I. A total of 330 participants with well-controlled CRS symptoms and a total of 280 participants with poorly controlled CRS symptoms were recruited. In comparing these 2 cohorts, the participants with well-controlled CRS symptoms were found to be older ($P < .001$), consisted of a greater proportion of males ($P = .023$), and contained a lower proportion of asthmatics ($P = .009$) compared with the participants with poorly controlled CRS symptoms. The 2 cohorts were otherwise similar in their clinical and demographic characteristics.

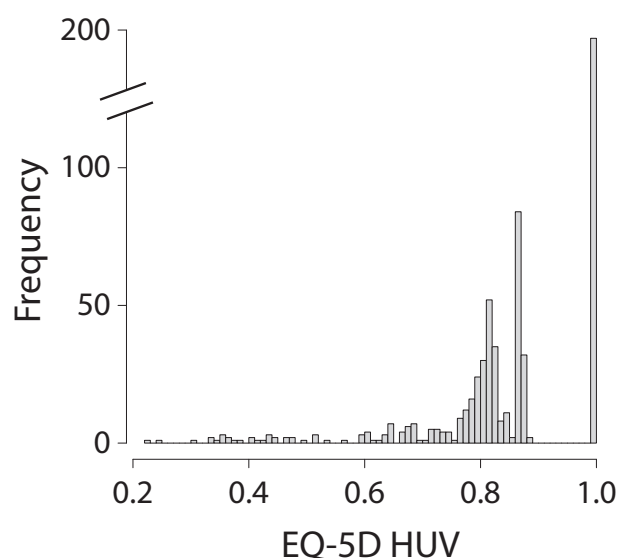


FIGURE 1. Histogram plot of EQ-5D HUV scores for study participants. *EQ-5D HUV*, EuroQol 5-dimensional health utility value.

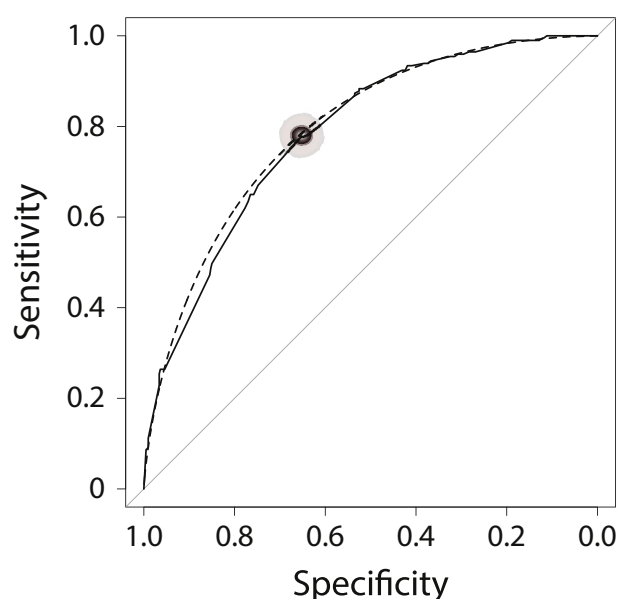


FIGURE 2. Receiver operating characteristic curve for the use of EQ-5D VAS to detect participants with EQ-5D HUV less than 0.9. The point reflecting an EQ-5D VAS cutoff of less than 80, which maximized the sum of sensitivity (77.7%) and specificity (65.4%), is shown. *EQ-5D HUV*, EuroQol 5-dimensional health utility value; *EQ-5D VAS*, EuroQol 5-dimensional visual analog scale.

Identifying a threshold for low general health-related QOL

To stratify patients in each cohort according to whether they had good or low general health-related QOL, we first examined a histogram plot of participants' EQ-5D HUV (Figure 1). This provided visualization of a clearly distinct population of

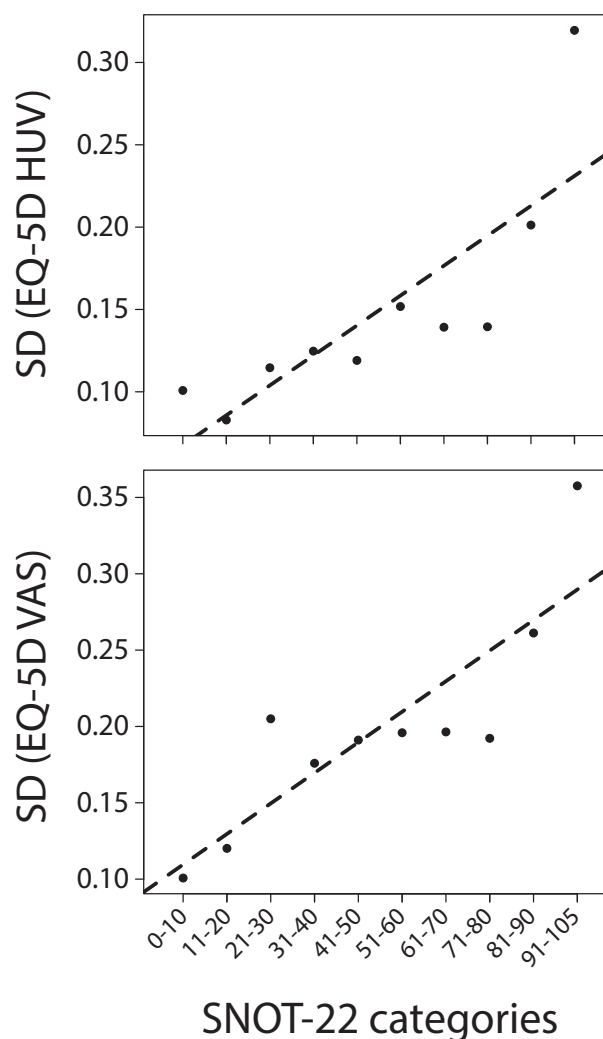


FIGURE 3. Scatter plot of the standard deviation of (top panel) EQ-5D HUV and (bottom panel) EQ-5D VAS versus SNOT-22 scores. *EQ-5D HUV*, EuroQol 5-dimensional health utility value; *EQ-5D VAS*, EuroQol 5-dimensional visual analog scale; *SD*, standard deviation; *SNOT-22*, 22-item Sino-Nasal Outcome Test.

participants who reported no problems in the 5 domains of the EQ-5D compared with all other participants. We therefore selected a threshold value of 0.9 for the EQ-5D HUV, below which participants were deemed to have low general health-related QOL, to formalize the natural separation of our study participants according to the EQ-5D HUV visualized in Figure 1. Our threshold is also consistent with prior studies showing that the mean value of the EQ-5D HUV in the general population is approximately 0.9.³¹ We next sought to extrapolate a threshold EQ-5D VAS value below which low general health-related QOL would be considered. The EQ-5D HUV was correlated with the EQ-5D VAS ($\rho = 0.59$, 95% confidence interval [CI]: 0.53-0.64). We next used an ROC analysis to find an EQ-5D VAS value that would most accurately identify participants with an EQ-5D HUV below 0.9. We found that an EQ-5D VAS score of less than 80 would best identify participants with an EQ-5D HUV below 0.9 (AUC = 0.78, 95% CI:

TABLE II. Associations between general health-related quality of life as a dependent variable and SNOT-22 and PHQ-2

	Well-controlled CRS							
	EQ-5D HUV				EQ-5D VAS			
	Univariate		Multivariable		Univariate		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
SNOT-22	0.93 (0.91-0.96)	<.001	0.93 (0.91-0.96)	<.001	0.93 (0.91-0.96)	<.001	0.94 (0.92-0.97)	<.001
PHQ-2	0.57 (0.42-0.78)	<.001	0.63 (0.45-0.86)	.005	0.75 (0.60-0.94)	.013	0.75 (0.58-0.97)	.028
	Poorly controlled CRS							
	EQ-5D HUV				EQ-5D VAS			
	Univariate		Multivariable		Univariate		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
SNOT-22	0.98 (0.96-1.00)	.065	1.00 (0.97-1.03)	.954	0.97 (0.95-0.99)	.003	0.98 (0.96-1.00)	.091
PHQ-2	0.36 (0.23-0.59)	<.001	0.37 (0.22-0.62)	<.001	0.66 (0.52-0.83)	<.001	0.74 (0.57-0.96)	.024

CI, Confidence interval; CRS, chronic rhinosinusitis; EQ-5D HUV, EuroQol 5-dimensional health utility value; EQ-5D VAS, EuroQol 5-dimensional visual analog scale; OR, odds ratio; PHQ-2, Patient Health Questionnaire-2; SNOT-22, 22-item Sino-Nasal Outcome Test.

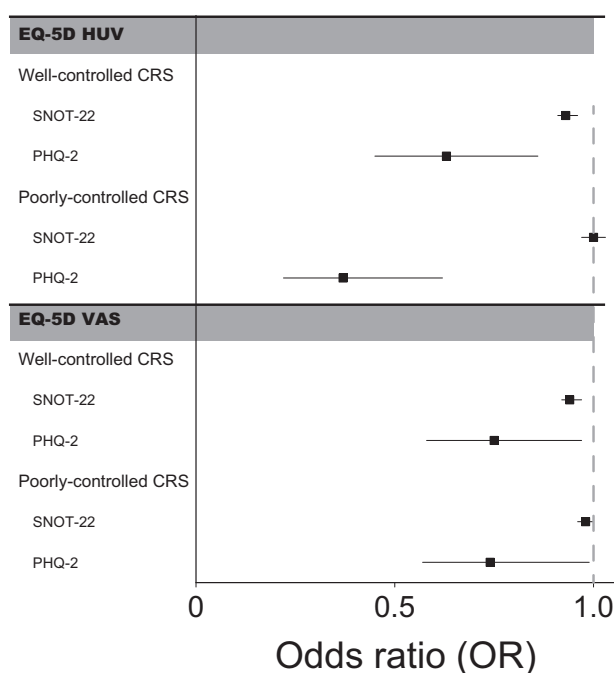


FIGURE 4. Forest plot reflecting the multivariable results in Table II, demonstrating the odds ratio (and associated 95% confidence intervals) for the association between general health-related quality of life—EQ-5D HUV (top) and EQ-5D VAS (bottom)—and SNOT-22 and PHQ-2. CRS, Chronic rhinosinusitis; EQ-5D HUV, EuroQol 5-dimensional health utility value; EQ-5D VAS, EuroQol 5-dimensional visual analog scale; PHQ-2, Patient Health Questionnaire-2; SNOT-22, 22-item Sino-Nasal Outcome Test.

0.75-0.82, $P < .001$), having a sensitivity of 77.7% and a specificity of 65.4% (Figure 2). We therefore considered an EQ-5D HUV < 0.9 or an EQ-5D VAS < 80 to indicate low general health-related QOL whereas EQ-5D scores equal to or greater than these thresholds were considered to reflect good general health-related QOL.

Association between depressed mood and general health-related QOL depends on the CRS symptom level

Previous work has demonstrated that the impact of subjective, patient-specific factors on general health-related QOL is most greatly felt at higher disease severities and that this is reflected in larger variability in general health-related QOL at higher disease severities.³² To examine whether this was the case, we examined the EQ-5D HUV and VAS scores for participants at 10-point levels of SNOT-22 score (eg, SNOT-22 score 0-10, 11-20, etc). We plotted the standard deviations of the EQ-5D HUV and VAS against the SNOT-22 score (Figure 3) and found statistically significant correlations ($\rho = 0.94$, 95% CI: 0.76-0.99 for the EQ-5D HUV; $\rho = 0.78$, 95% CI: 0.30-0.95 for the EQ-5D VAS), demonstrating that there is greater variability of general health-related QOL at higher CRS disease severities.

We next sought to determine whether depressed mood was one such subjective patient-specific factor that could influence the association between the SNOT-22 and EQ-5D. We first found that the SNOT-22 score significantly negatively correlated with the EQ-5D HUV ($\rho = -0.55$, 95% CI: -0.61 to -0.50) and EQ-5D VAS ($\rho = -0.52$, 95% CI: -0.58 to -0.46). We next stratified participants according to whether they had well-controlled (SNOT-22 score < 35) or poorly controlled (SNOT-22 ≥ 35) CRS symptoms with the goal of determining the impact of depressed mood on the relationship between CRS symptom burden and general health-related QOL in each cohort (Table II and Figure 4).

We first focused on the participants with well-controlled CRS symptoms (Table II, top). In this cohort, each single point increase in SNOT-22 was negatively associated with having good general health-related QOL based on an EQ-5D HUV cutoff of 0.9 (odds ratio [OR] = 0.93, 95% CI: 0.91-0.96, $P < .001$) or an EQ-5D VAS cutoff of 80 (OR = 0.93, 95% CI: 0.91-0.96, $P < .001$) on univariate analysis. All single point increases in SNOT-22 subdomain (nasal, otologic/facial pain, sleep, and emotional) scores were likewise negatively associated with having good general health-related QOL ($P < .05$), indicating that all types of CRS symptoms represented on the SNOT-22 are associated with decreased general health-related QOL. The

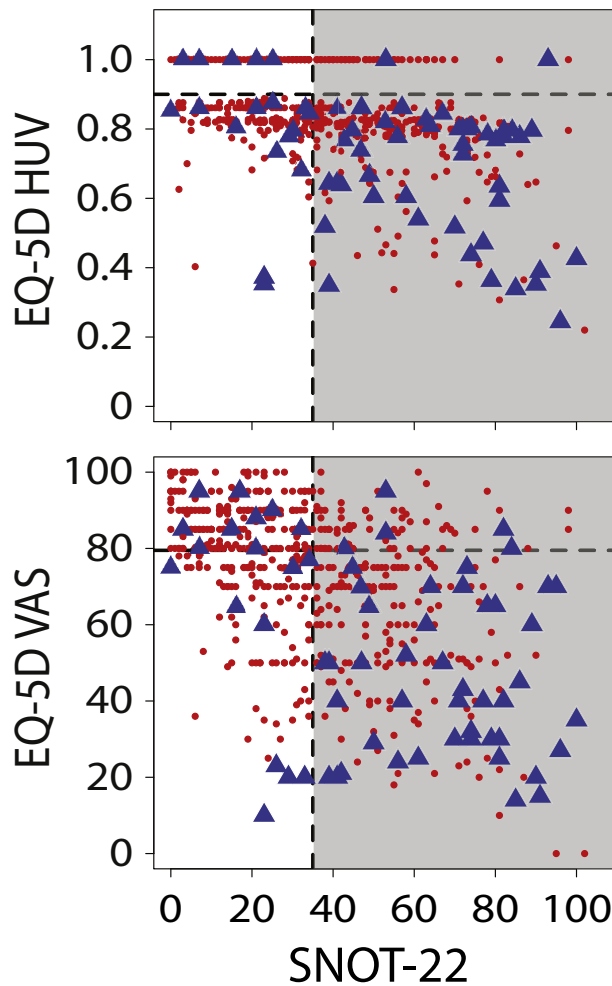


FIGURE 5. Scatter plot of (top panel) EQ-5D HUV and (bottom panel) EQ-5D VAS versus SNOT-22 score with data points color coded according to whether the participant's Patient Health Questionnaire-2 score was >2 (blue triangle), or ≤ 2 (red circle). Dashed lines indicate a SNOT-22 score of 35 (the threshold distinguishing poorly controlled from well-controlled chronic rhinosinusitis symptoms), an EQ-5D HUV score of 0.9 (the threshold distinguishing good from low general health-related QOL), and an EQ-5D VAS score of 80 (the threshold distinguishing good from low general health-related QOL). *EQ-5D HUV*, EuroQol 5-dimensional health utility value; *EQ-5D VAS*, EuroQol 5-dimensional visual analog scale; *QOL*, quality of life; *SNOT-22*, 22-item Sino-Nasal Outcome Test.

PHQ-2 score was also found to be negatively associated with the EQ-5D HUV (OR = 0.57, 95% CI: 0.42-0.78, $P < .001$) and EQ-5D VAS (OR = 0.75, 95% CI: 0.60-0.94, $P = .013$) on univariate analysis. In our multivariable regression models, we checked for the association between good general health-related QOL (based on EQ-5D HUV or VAS) as a dependent variable and the PHQ-2 score as an independent variable while controlling for SNOT-22 as well as age, gender, history of aeroallergen hypersensitivity, history of smoking, previous sinus surgery, nasal polyps, use of intranasal corticosteroids, and comorbid asthma, diabetes, heart disease, stroke, and

malignancy. We found that in the cohort with well-controlled CRS symptoms, the PHQ-2 remained significantly and negatively associated with having good general health-related QOL based on the EQ-5D HUV (adjusted OR = 0.63, 95% CI: 0.45-0.86, $P = .005$) or EQ-5D VAS (adjusted OR = 0.75, 95% CI: 0.58-0.97, $P = .028$). The SNOT-22 also remained significantly and negatively associated with having good general health-related QOL based on the EQ-5D HUV (adjusted OR = 0.93, 95% CI: 0.91-0.96, $P < .001$) or EQ-5D VAS (adjusted OR = 0.94, 95% CI: 0.92-0.97, $P < .001$).

We next focused on the participants with poorly controlled CRS symptoms (Table II, bottom). In this cohort, the SNOT-22 was much more weakly and negatively associated with having good general health-related QOL based on an EQ-5D HUV (OR = 0.98, 95% CI: 0.96-1.00, $P = .065$) or an EQ-5D VAS cutoff of 80 (OR = 0.97, 95% CI: 0.95-0.99, $P = .003$) on univariate analysis. The SNOT-22 sleep and emotional subdomain scores were most dominantly associated (negatively) with having good general health-related QOL ($P < .05$ for both EQ-5D HUV and VAS), whereas the SNOT-22 nasal subdomain score was not at all associated with good general health-related QOL ($P > .05$ for both EQ-5D HUV and VAS). The PHQ-2 score was also found to be negatively associated with the EQ-5D HUV (OR = 0.36, 95% CI: 0.23-0.59, $P < .001$) and EQ-5D VAS (OR = 0.66, 95% CI: 0.52-0.83, $P < .001$) on univariate analysis. Using our multivariable regression model we found that in the cohort with poorly controlled CRS symptoms, the PHQ-2 remained significantly and negatively associated with having good general health-related QOL based on the EQ-5D HUV (adjusted OR = 0.37, 95% CI: 0.22-0.62, $P < .001$) or EQ-5D VAS (adjusted OR = 0.74, 95% CI: 0.57-0.96, $P = .024$). However, the SNOT-22 was not significantly associated with having good general health-related QOL based on the EQ-5D HUV (adjusted OR = 1.00, 95% CI: 0.97-1.03, $P = .954$) or EQ-5D VAS (adjusted OR = 0.98, 95% CI: 0.96-1.00, $P = .091$). Because the SNOT-22 sleep or emotional subdomain scores were associated with decreased general health-related QOL on univariate regression as described above, we repeated our multivariable analysis by controlling for the SNOT-22 sleep and emotional subdomains instead of the overall SNOT-22 score. However, we still found no statistically significant association between these subdomains and general health-related QOL, whereas the PHQ-2 score remained significantly associated with decreased general health-related QOL.

Our results therefore show that the severity of acute depressed mood/anhedonia is the dominant symptom cluster that is associated with decreased general health-related QOL in patients with CRS with poorly controlled CRS symptomatology. In contrast, in patients with well-controlled CRS symptoms, all symptoms of CRS are associated with decreased general health-related QOL. These relationships are also illustrated in Figure 5.

DISCUSSION

CRS is associated with a significant general health-related QOL detriment that is comparable with the general health-related QOL detriment associated with other severe chronic conditions such as coronary artery disease and asthma.¹³ The chronic symptomatology associated with CRS is the clinical manifestation of the disease most commonly associated with

decreased general health-related QOL in affected patients.^{10,11,13} In fact, a very strong negative association between CRS symptom burden and general health-related QOL has been previously described.¹² However, research to identify patient characteristics that may impact the incremental general health-related QOL decrease associated with increasing CRS symptoms has not been undertaken. Prior work has demonstrated that patient mood may transform perception of illness and increase health care utilization for many diseases.^{21-23,33,34} In addition, the severity of depressed mood has been shown to be the principal determinant of missed work or school because of CRS; this is in contrast to sinonasal symptom burden, which was not associated with lost productivity because of CRS.¹⁹ In this study, we explored the effect of depressed mood on the relationship between CRS symptom burden and general health-related QOL. Specifically, we sought to determine whether the severity of depressed mood modulated the magnitude of association between increasing CRS symptom burden and decreased general health-related QOL. We found that the severity of depressed mood was a key factor in predicting decreased general health-related QOL and that the impact of depressed mood was largest in patients with severe, poorly controlled CRS symptoms. In fact, in patients with poorly controlled CRS symptoms, the burden of CRS symptoms was no longer associated with decreased general health-related QOL, whereas the severity of depressed mood was strongly associated with decreased general health-related QOL.

Measures of general health-related QOL, such as the EQ-5D, quantify patient health status in a standardized and generic (ie, not disease-specific) manner.^{35,36} When a measure of general health-related QOL is compared against a disease-specific measure of symptom burden, such as the SNOT-22, which quantifies CRS symptom burden, the confounding or modulating effect of subjective, patient-specific characteristics may become apparent.³² For example, previous work has shown that depressed mood may modulate the relationship between disease severity and general health-related QOL by influencing self-awareness, illness perception, pain, unpleasantness, vulnerability traits, and perceived need for health care utilization in a variety of chronic illnesses such as Parkinson's disease, chronic obstructive pulmonary disease, muscle disease, chronic lower back pain, and asthma.^{21-23,33,34} Previous studies of CRS have established strong associations between the severity of CRS symptoms and reduced general health-related QOL. However, no study has explored how exactly depressed mood may modulate the perceived burden of disease, as reflected by the association between symptom burden and general health-related QOL in patients with CRS.

In our study, we show that the severity of depressed mood influences the magnitude of association between CRS symptom burden and general health-related QOL. Specifically, patients with more depressed mood report larger incremental reductions in general health-related QOL for increasing CRS symptom burden, compared with mildly depressed or euthymic patients with CRS. In performing our study, we stratified patients according to whether their SNOT-22 score was below or above 35, which has previously been shown to be indicative of patients' perception of well- or poorly controlled CRS symptomatology, respectively.²⁹ Patient-reported CRS symptom control has previously been shown to be an important metric in the evaluation of patients with CRS.³⁷ In examining our study participants, those with poorly controlled CRS symptoms

exhibited a greater variability in general health-related QOL than those with well-controlled CRS symptoms. This suggested that the greatest impact for a hypothetical modulating factor in the relationship between CRS symptom burden and general health-related QOL would be expected to occur under conditions of greater CRS symptoms. In studying depressed mood in CRS, we found that for both cohorts of participants—those with well-controlled CRS symptoms and those with poorly controlled CRS symptoms—the severity of depressed mood was significantly associated with decreased general health-related QOL. However, we found the impact of depressed mood to be particularly important in patients with poorly controlled CRS. Although CRS symptom burden was also associated with decreased general health-related QOL in the participants with well-controlled CRS symptoms, this was not the case in participants with poorly controlled CRS symptoms. In the participants with poorly controlled CRS symptoms, increasing CRS symptom burden was no longer associated with decreased general health-related QOL, whereas increasing severity of depressed mood was very strongly associated with decreased general health-related QOL. This finding indicates that once patients are experiencing symptoms that exceed a certain threshold for symptom burden or poor control, additional increases in CRS symptom burden are less important in decreasing general health-related QOL, whereas, on the contrary, increasing depressed mood is very important in how patients report their general health-related QOL. It is important to note that calculation of the EQ-5D HUV incorporates patient-reported problems with anxiety and depression, whereas the EQ-5D VAS is independent of any explicit assessment of a patient's mood or anxiety level. The fact that we find the same dominant association between depressed mood and general health-related QOL regardless of whether we measure general health-related QOL with EQ-5D HUV or EQ-5D VAS shows that our results are not an artifact of the EQ-5D questionnaire.

Our findings are largely reflective of the segregation of patients with poorly controlled CRS symptoms into 2 populations. Despite having similarly high CRS symptom burden, one population reported remarkably high general health-related QOL, whereas the other population of patients reported substantially lower general health-related QOL. These populations were also distinguished by their respective severities of depressed mood, with significantly greater severity of depressed mood associated with the patients reporting low general health-related QOL. These findings may have potentially very important implications for CRS treatment. The goal of treatment for CRS is to improve the QOL of patients, and treatment is conventionally designed to reduce CRS symptomatology. However, our results suggest that modulation of mood may open new doors to improving general health-related QOL in patients whose symptoms are recalcitrant to conventional treatments such as intranasal corticosteroids. It is possible that comorbid mood disorders may be important to address as a component of a comprehensive management of patients with CRS, in particular those with poorly controlled symptomatology. Our results highlight the need for interventional studies to test and confirm these hypotheses.

Our results should be interpreted in the context of the limitations of our study. Our study identified a cross-sectional relationship between CRS symptom burden and general health-related QOL that was modulated by participants' severity of depressed mood. Nevertheless, the science behind patient

mood is complex, and we must therefore acknowledge that there may be additional variables that we have not accounted for that could be confounding our participants' depressed mood and illness perception. In addition, because our study is cross-sectional, it does not show how modulation of depressed mood would impact the relationship between CRS symptom burden and general health-related QOL, and so our results do not provide insight into the efficacy of improving mood on QOL in CRS. Nevertheless, we believe that the results shown here pave the way for future longitudinal studies to explore how addressing depressed mood may have a positive impact on CRS outcomes.

CONCLUSIONS

The burden of CRS symptoms is strongly associated with decreased general health-related QOL. This association, however, is modulated by the severity of depressed mood. For patients with a SNOT-22 score above 35—indicative of patient-perceived poor CRS symptom control—depressed mood is strongly associated with decreased general health-related QOL, whereas CRS symptom burden no longer has any association with general health-related QOL. The association of CRS symptom burden with decreased general health-related QOL is only up to a threshold of CRS symptom severity, beyond which the impact of symptoms on QOL is no longer driven by increasing sinonasal symptom burden but rather is driven by depressed mood instead. These results raise the possibility that modulation of depressed mood may impact the association of CRS symptom burden with general health-related QOL, but interventional studies are needed to test this hypothesis.

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