The effects of priming on rhinologic patient reported outcome measures: a randomized controlled trial*

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Abstract

Background: Patient-reported outcome measures (PROMs) are questio-nnaires designed to assess a patient's perception of their medical condition. The 22-item Sino-Nasal Outcomes Test (SNOT-22), the Rhinosinusitis Disability Index (RSDI) and the mini-Rhino-conjunctivitis Quality of Life Questionnaire (MiniRQLQ) are validated PROMs commonly used to assess rhinologic conditions. The objective of this study is to determine if responses on these PROMs may be influenced by priming respondents with positive or negative health-related questionnaires.

Methods: Nine hundred patients were prospectively randomized to one of nine groups. Groups A, D and G were positively primed prior to completing the SNOT-22, the RSDI and MiniRQLQ, respectively. Groups B, E, and H were negatively primed. Groups C, F, and I served as control groups, completing the PROMs without priming. Priming was performed by administering a survey designed to make patients think about their health-related quality of life in a positive or negative way.

Results: Patients who were primed negatively had statistically significantly worse scores on the SNOT-22, RSDI and MiniRQLQ when compared to patients who were primed positively. When compared to the control group, patients who were primed negatively had statistically worse scores on the SNOT-22 and RSDI. There was no significant difference in scores between the positive priming and the control groups for any PROM.

Conclusions: Priming subjects regarding their health-related quality of life impacts their responses on rhinologic PROMs. Further study is required to understand the clinical and research implications of this novel finding and to clarify the optimal manner for administering and interpreting PROMs.

Key words: patient-reported outcome measure, PROM, SNOT-22, RSDI, MiniRQLQ, priming

Introduction

Patient reported outcome measures (PROMs) are clinical assessment tools completed by a patient without input from a health care professional [(1)]. These standardized questionnaires are essential tools for understanding and delivering patient-centered care, as they provide unique information from a patient's perspective to capture domains of conditions or illnesses that may not be measured by traditional objective outcome measures [(2)]. Numerous PROMS have been developed and validated across disciplines and specialties [(3-6)]. Their use as endpoints in clinical trials has dramatically increased over last two decades [(7)].

Chronic rhinosinusitis (CRS) significantly impacts quality of life (QOL); therefore, the subjective patient experience as measured through PROMs is essential to both the clinician and the researcher. The Sino-Nasal Outcome Test (SNOT) is a PROM designed to capture the impacts of CRS on QOL [(6)]. The 22-item Sino-Nasal Outcome Test (SNOT-22) spans five domains including rhinologic symptoms, extra-nasal rhinologic symptoms, ear and facial symptoms, psychological dysfunction, and sleep dysfunction [(8-

[9]. The SNOT-22 has become one of the most widely used PROMs for CRS, along with the Rhinosinusitis Disability Index (RSDI) [8-10]. The RSDI is a 30-item PROM designed to measure the impact of CRS on the emotional, functional, and physical state [10]. Meanwhile, the mini-Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) is a 14-item PROM for patients with rhinoconjunctivitis, encompassing five domains: activity limitations, practical problems, nose symptoms, eye symptoms, and other symptoms [11]. The MiniRQLQ has demonstrated strong evidence of construct validity and high intra-class correlation coefficients [11].

Although these instruments have rigorous data supporting their validity and reliability, responses to PROMs could be influenced by a number of patient-level factors which have not been well explored or described [12,13]. Numerous factors including interactions with health-care providers and clinical settings,may impact responses to PROMs, and therefore understanding such factors is crucial [14]. Priming is a psychological phenomenon whereby exposure to one stimulus influences responses to another stimulus because specific associations are activated prior to performing a task without conscious intention [15]. Countless patient-specific or environment-specific factors may be priming patients without the knowledge of the healthcare providers administering the PROMs. The impact of priming on PROMs in otolaryngology or in rhinology specifically has not been previously reported.

The objective of this randomized controlled prospective study is to determine whether responses to PROMs may be influenced by external factors. Since priming may occur in the clinical setting and can be reproduced in an experimental setting, this study explores the impact of priming on three commonly used rhinologic PROMs: the SNOT-22, the RSDI, and the MiniRQLQ [15,16].

We hypothesize that priming individuals with a health-related questionnaire using either positive or negative health-related associations prior to completion of the PROMs will significantly impact their responses. Developing and validating PROMs requires a rigorous understanding of responses in both healthy and diseased populations. Indeed, the development and validation of the SNOT-22, RSDI, and MiniRQLQ is based on data derived by the administration of these instruments to broad populations, including those with and without rhinologic disease. Due to the paucity of data on the subject, we first test our hypothesis in a broad population without regard to suspected or confirmed rhinologic disease. This study thus serves as a foundation for subsequent research exploring the impact of priming and other factors on responses to PROMs in subjects with specific rhinologic disease states.

Materials and methods

Trial design

A web-based randomized clinical trial (RCT) with two behavioral intervention groups and one control group was designed for each PROM. Participants were distributed in a 1:1:1 allocation among the three groups for each PROM. Approval was obtained by the Institutional Review Board (AAAT8186) of the Columbia University Irving Medical Center. No important changes to the trial methodology were made after trial commencement. This RCT was registered on clinicaltrials.gov as NCT05229016.

Participants and recruitment

Using the online recruitment platform Prolific (www.prolific.co), 900 voluntary adults were recruited from over 50,000 eligible participants between November 2021 and February 2022. Prolific is a validated platform for administering survey and psychometric response forms [17]. Individuals interested in taking part in research studies voluntarily join the Prolific platform, and are notified by email when they are eligible for a study. This matching process is based on the verified demographic information volunteered by the Prolific users, and the inclusion criteria entered by the researchers. Eligible participants were thus notified and encouraged to participate to the study during the recruitment period. The first 900 participants who consented to participate to the study were recruited. For this study, participants were compensated $10.50 USD prorated per hour for participating. Inclusion criteria included: adults 18 years of age and older, citizenship in the United States, fluency in English, and ability to provide informed consent. Participants were excluded if they did not meet all inclusion criteria. Participants were not screened for rhinologic disorders or other co-morbidities prior to enrollment.

Blinding

Prospective participants were informed that they were being recruited to complete a series of surveys related to activity, health, medical history, and demographic information, in order to help researchers determine which surveys work best for collecting such information. Participants were also informed that all responses would be de-identified. They were not informed of the objective of the study. Participants were also not informed that they were randomized into groups or that priming was being performed.

Interventions

After informed consent was obtained, participants were randomized to one of nine groups. Participants in Groups A, B and C completed the SNOT-22. Participants in Groups D, E and F completed the RSDI. Participants in Groups G, H, and I completed the MiniRQLQ. Prior to completing the PROM, participants in Groups A, D and G were primed positively by responding to a positive health-related questionnaire. Participants in Groups B, E and H

- In which season do you feel the healthiest? _____
- Which type of outdoor activity do you prefer the most? _____
- Have you ever experienced an environment (in the mountains, at the beach, etc.) where the air feels cleaner or purer to you?
  ○ A little bit ○ Yes, definitely
- What is your favorite sport? _____
- If you take a deep breath and exhale slowly, do you ever feel your shoulders relax?
  ○ A little bit ○ Yes, definitely
- Have you ever laughed so hard that you had to catch your breath?
  ○ A little bit ○ Yes, definitely
- Have you ever experienced an environment (in the mountains, at the beach, etc.) where it really felt good to take a deep breath?
  ○ A little bit ○ Yes, definitely
- Do you think more clearly when you feel happy?
  ○ A little bit ○ Yes, definitely
- Do you feel happier on days where you wake up feeling energized?
  ○ A little bit ○ Yes, definitely
- Have you ever experienced an environment (in the mountains, at the beach, etc.) where you felt physically happier?
  ○ A little bit ○ Yes, definitely
- Do you have more energy on days where you eat healthy foods?
  ○ A little bit ○ Yes, definitely
- Have you ever felt that a day full of sunshine makes you feel healthier and stronger?
  ○ A little bit ○ Yes, definitely
- Do you feel more relaxed and calmer on days where you woke up feeling energized?
  ○ A little bit ○ Yes, definitely
- Have you ever experienced an environment (in the mountains, at the beach, etc.) where you felt your body relax?
  ○ A little bit ○ Yes, definitely
- Do you think more clearly when you feel relaxed?
  ○ A little bit ○ Yes, definitely
- What are you looking forward to in the future? _____
- In which month can you breathe the most comfortably? _____
- Does taking a deep breath ever make you feel better?
  ○ A little bit ○ Yes, definitely
- Are there people in your life who make you feel better or calmer?
  ○ A little bit ○ Yes, definitely
- Do you ever feel calmer when you know that you are going to be well rested for tomorrow's responsibilities?
  ○ A little bit ○ Yes, definitely
- Do warm sunny days make you feel more relaxed?
  ○ A little bit ○ Yes, definitely
- When you feel good, is it easier to concentrate on work?
  ○ A little bit ○ Yes, definitely
- When you feel good physically, do you feel that your mood is positively impacted?
  ○ A little bit ○ Yes, definitely

Please list 3 things about your health for which you feel grateful
1.
2.
3.

Please list 3 activities or experiences that make you feel healthy and strong
1.
2.
3.

Figure 1. Positive health-related survey.

- How frequently do you feel tension in your neck, shoulders or head?
  ○ Once in a while ○ Frequencly
- Are there foods that reliably give you an upset stomach?
  ○ A few ○ Yes, many
- How often do you feel tired or fatigued in a typical week?
  ○ Some of the time ○ Most of the time
- Do you have memories of being very sick or feeling nauseous when you were younger?
  ○ A few ○ Yes, many
- Do you worry about your health for the future?
  ○ A little bit ○ Yes, definitely
- Do you get very thick mucus when you are sick?
  ○ A few ○ Yes, many
- What potential health condition concerns you most about the future? _____
- Are you concerned that you will have to rely on people to take care of you in the future, or when you become elderly or sick?
  ○ A little bit ○ Yes, definitely
- Does it sometimes feel harder to take a deep breath if you are in a stuffy room?
  ○ A little bit ○ Yes, definitely
- In which month do you feel the most nasal congestion? _____
- In which season do you get sick the most? _____
- Does unhealthy or greasy food ever make you feel nauseous or queasy?
  ○ A little bit ○ Yes, definitely
- When you feel nauseous or queasy, is it harder to feel happy?
  ○ A little bit ○ Yes, definitely
- When you feel nauseous or queasy, is it harder to concentrate?
  ○ A little bit ○ Yes, definitely
- Does very thick mucus ever make you feel nauseous?
  ○ A little bit ○ Yes, definitely
- Are there people in your life who make you feel sad or stressed?
  ○ A few ○ Yes, many
- Do you ever feel anxiety when you know that you are going to be tired for tomorrow's responsibilities?
  ○ A little bit ○ Yes, definitely
- Do cold dreary days make you feel sad?
  ○ A little bit ○ Yes, definitely
- When you feel sick, is it harder to concentrate on work?
  ○ A little bit ○ Yes, definitely
- When you feel sick, do you feel sad?
  ○ A little bit ○ Yes, definitely
- Have you ever worried that a chronic health condition could lead to loneliness?
  ○ A little bit ○ Yes, definitely
- Have you ever experienced "brain fog" or just felt "out of it" even if you did not have a fever?
  ○ A little bit ○ Yes, definitely
- Do you feel stressed or depressed about not being healthy enough?
  ○ A little bit ○ Yes, definitely
- Do you worry that certain habits could lead to become overweight or obese?
  ○ A little bit ○ Yes, definitely
- Have you ever experienced an environment (in the city, near a factory, etc.) where the air feels heavier or more polluted to you?
  ○ A little bit ○ Yes, definitely
- Have you ever experienced tinnitus or ringing in your ears due to stress, fatigue or exposure to loud noise?
  ○ A little bit ○ Yes, definitely
- Have you ever felt embarrassed because you were sick or due to a medical condition?
  ○ A little bit ○ Yes, definitely

Figure 2. Negative health-related survey.

were primed negatively by responding to a negative health-related questionnaire prior to completing the PROM. Participants in Groups C, F and I served as control groups and were not primed prior to completing the PROM.

The two priming surveys were developed based on previous evidence that asking people to reflect on positive or negative experiences and exposing them to specific words or images may unconsciously influence them [18-20]. These priming surveys are shown in Figures 1 and 2. After completion of PROMs, all participants then rated their mood on a 10cm visual analog scale (VAS), and finally submitted basic demographic and health-related information.

Outcomes

The primary outcomes of interest were the mean total score on the SNOT-22 for Groups A, B and C, the mean total score on the RSDI for Groups D, E and F, and the mean total score on the MiniRQLQ for Groups G, H and I.

The SNOT-22 asks participants to rate 22 symptoms on a severity scale of 1 to 5, with 1 representing "no problem" and 5 "problem as bad as it can be". The RSDI asks participants to rate 30 items on a severity scale of 0 to 4, with 0 representing the least severe response and 4 the most. There are 11 items for the physical domain, 9 for the functional, and 10 for the emotional. RSDI scores range between 0 and 120 points. The MiniRQLQ is a 14-item questionnaire with a 0 to 6 response scale for each item. There are 3 items for the activities domain, 2 for practical problems, 3 for nose symptoms, 3 for eye symptoms, and 3 for other symptoms. MiniRQLQ scores thus range between 0 and 84 points. Scores for each of these PROMs are calculated by adding the individual scores for each item, with higher scores representing worse disease severity.

The secondary outcomes for this study were the mean scores for each domain of the SNOT-22 for Groups A, B and C, the mean scores for each domain of the RSDI for Groups D, E and F, and the mean scores for each domain of the MiniRQLQ for Groups G, H and I. Scores from each domain are calculated by summing the scores from all items of the domain [10, 11, 21]. Finally, the mean mood score on the mood VAS for each group was determined.

Sample size

The sample size was calculated based on the primary outcome. With an alpha error of 0.05, a power of 0.90, and a medium effect size of 0.5, a sample size of 86 was estimated for each group. In order to account for potential refusal to consent, and survey incompletion, 100 participants were recruited per group.

Randomization

Randomization was performed independently through the online survey platform Qualtrics (www.qualtrics.com) which generated a random allocation sequence, and implemented it by assigning participants to one of the nine groups. No restriction such as block randomization were used. Using a third party allowed to conceal the allocation sequence and protect the randomization.

Statistical analysis

Demographic data were reported as means for continuous variables and frequencies for categorical variables. In order to assess if the groups were balanced, continuous demographic data were compared using one-way ANOVA, and categorical variables were tested with Chi squared test. For the primary and secondary outcomes, one-way ANOVA were calculated to determine if mean scores differed statistically between the three groups for each PROM. Pair-wise comparison was performed by calculating 95% confidence intervals (CIs). Statistical significance was achieved if $p<0.05$. All statistical analyses were performed with SPSS (IBM Corp. Released 2020. Version 27.0. Armonk, NY, USA).

Results

Participants

Nine hundred participants were recruited from November 2021 to February 2022.

For the SNOT-22, one patient declined to participate prior to the start of the survey, while 299 provided informed consent and underwent randomization. Three participants in Group A and two in Group B failed to complete the surveys. Thus, a total of 294 (98%) participants completed the SNOT-22. Groups A, B, and C were balanced for all demographic and health-related variables (Table 1A).

For the RSDI, 3 participants (3%) in Group D and two (2%) in Group F did not complete the questionnaires. Groups D, E, and F were balanced for all demographic and health-related variables (Table 1B).

For the MiniRQLQ, 2 participants (2%) in Group G and 2 in Group I (2%) did not complete the study. Demographic and health-related variables were also balanced between all three groups, except for history of lung disease; fewer respondents in the control Group F had a positive history of lung disease (Table 1C).

Primary and secondary outcomes

For the primary outcome, the mean total SNOT-22 score with 95%CI for the positively primed Group A was 34.3 (95%CI [30.6-30.8]), for the negatively primed Group B was 45.1 (95%CI [41.8-48.4]), and for the control Group C was 36.8 (95%CI [33.1-40.5]). One-way ANOVA revealed a statistically significant difference among the three groups ($p<0.001$ ($df=2$, $F=9.8$)). Pair-wise comparison with 95% CIs demonstrated that Group B after negative priming had statistically significantly worse scores when compared to Group A after positive priming and control Group C, by a margin of 8.3. There was no difference between the positive intervention Group A and the control Group C. For the secondary outcomes, one-way ANOVA revealed a statistically significant difference among the three groups for the mean score of each SNOT-22 domain. Pair-wise comparison with 95%CI demonstrated that the negative intervention Group B had statistically significant worse scores in all domains of the SNOT-22 when compared to the positive intervention Group A. When comparing the negative intervention Group B to the control Group C, there was a statistically significant difference for 2 out of the 5 domains: rhinologic symptoms and extra-nasal rhinologic symptoms. When comparing the positive intervention Group A to the control Group C, there were no statistically significant differences for any domain. For scores on the mood VAS, one-way ANOVA did not reveal any statistically significant difference among the three groups. For each group, the mean total score for the SNOT-22 and the mean score for each domain are presented in Table 2 (Supplemental Figure 1). The mean score for the mood VAS is also presented in Table 2.

For the RSDI, the mean total score for the positively primed Group D was 19.2 (95%CI[15.2-23.2]), for the negatively primed Group E 33.4 (95%CI[28.9-37.9]), and for the control Group F 17.2 (95%CI[13.4-21.0]). One-way ANOVA revealed a statistically significant difference between the three means ($p<0.001$ ($df=2$, $F=18.3$)). Pair-wise comparison using the 95%CIs demonstrated that the mean total score for negatively primed Group E was worse than the score for positively primed Group D and for control Group F. There was no difference between the positively primed Group D and the control Group F. These statistical findings were also true for the mean score of all three domains of the RSDI. The mean mood VAS score for participants in Group D was 68.2 (95%CI[64.7-71.8]), in Group E 60.9 (95%CI[57.2-64.7]), and in Group F 64.2 (95%CI[60.2-68.2]). One-way ANOVA revealed a statistically significant difference between the three groups ($p<0.026$ ($df=2$, $F=3.7$)). The difference was observed between Group D and Group E. Mean RSDI total scores, domain scores, and corresponding mood VAS scores can be found in Table 3 (Supplemental Figure 2).

For the MiniRQLQ, the mean total score for the positively primed Group G was 17.3 (95%CI[14.4-20.1]), for the negatively primed Group H 24.8 (95%CI[21.0-28.5]), and for the control Group I 18.6 (95%CI[15.6-21.5]). One-way ANOVA revealed a statistically significant difference between the three means ($p=0.002$ ($df=2$, $F=6.2$)). Using the 95% CIs for pair-wise comparison, the

Table 1A. Patients' characteristics for the SNOT-22.

VARIABLE	GROUP A Positive (n=96)	GROUP B Negative (n=98)	GROUP C Control (n=100)	P VALUE
AGE, MEAN (SD), YEARS	33.3 (12.6)	34.6 (13.9)	33.0 (12.1)	0.663
GENDER, N (%)				0.770
Male	46 (47.9)	47 (48.0)	51 (51.0)	
Female	49 (51.0)	48 (49.0)	46 (46.0)	
Non-binary	1 (1.0)	3 (3.1)	3 (3.0)	
ETHNICITY, N (%)				0.754
Non-Hispanic white	73 (76.0)	74 (75.5)	71 (71.0)	
Hispanic or Latino	8 (8.3)	10 (10.2)	10 (10.0)	
Black or African American	4 (4.2)	6 (6.1)	12 (12.0)	
Asian or Asian American	8 (8.3)	6 (6.1)	6 (6.0)	
Other	3 (3.1)	2 (2.0)	1 (1.0)	
INCOME, N (%)				0.202
0-24,999	18 (18.8)	24 (24.5)	16 (16.0)	
25,000-49,999	29 (30.2)	23 (23.5)	24 (24.0)	
50,000-74,999	18 (18.8)	12 (12.2)	24 (24.0)	
75,000-99,999	13 (13.5)	23 (23.5)	12 (12.0)	
100,000 +	18 (18.8)	16 (16.3)	24 (24.0)	
ALLERGIES, N (%)				0.875
Yes	33 (34.4)	33 (33.7)	33 (33.0)	
RECURRENT SINUSITIS, N (%)				0.901
Yes	5 (5.2)	4 (4.1)	4 (4.0)	
CHRONIC SINUSITIS, N (%)				0.356
Yes	2 (2.1)	5 (5.1)	2 (2.0)	
DEVIATED SEPTUM, N (%)				0.628
Yes	3 (3.1)	5 (5.1)	6 (6.0)	
NASAL POLYPS, N (%)				0.142
Yes	0 (0.0)	0 (0.0)	2 (2.0)	
ENT SURGERY, N (%)				0.417
Yes	17 (17.7)	17 (17.3)	24 (24.0)	
SINUS SURGERY, N (%)				0.248
Yes	2 (2.1)	0 (0.0	3 (3.0)	
SEPTOPLASTY, N (%)				0.882
Yes	2 (2.1)	2 (2.0)	3 (3.0)	
CHRONIC PAIN, N (%)				0.264
Yes	17 (17.7)	26 (26.5)	19 (19.0)	
PSYCHIATRIC HISTORY, N (%)				0.692
Yes	48 (50.0)	45 (45.9)	44 (44.0)	
SMOKING, N (%)				0.717
Never a smoker	73 (76.0)	67 (68.4)	76 (76.0)	
Current smoker	10 (10.4)	12 (12.2)	10 (10.0)	
Former smoker	13 (13.5)	19 (19.4)	14 (14.0)	
MEDICATIONS, N (%)				0.554
0	48 (50.0)	54 (55.1)	55 (55.0)	
1-3	33 (34.4)	30 (30.6)	38 (38.0)	
4 +	15 (15.6)	14 (14.3)	7 (7.0)	
CARDIAC HISTORY, N (%)				0.125
Yes	17 (17.7)	29 (29.6)	16 (16.0)	
PULMONARY HISTORY, N (%)				0.587
Yes	24 (25.0)	20 (20.4)	22 (22.0)	
DIABETES HISTORY, N (%)				0.585
Yes	9 (9.4)	6 (6.1)	6 (6.0)	
STROKE HISTORY, N (%)				0.758
Yes	2 (2.1)	1 (1.0)	1 (1.0)	

Table 1B. Patients' characteristics for the Rhinosinusitis Disability Index.

VARIABLE	GROUP D Positive (n=97)	GROUP E Negative (n=100)	GROUP F Control (n=98)	P VALUE
AGE, MEAN (SD), YEARS	34.2 (13.9)	36.4 (15.0)	34.0 (14.8)	0.429
GENDER, N (%)				0.667
Male	51 (52.6)	52 (52.0)	45 (45.9)	
Female	43 (44.3)	47 (47.0)	50 (51.0)	
Non-binary	3 (3.1)	1 (1.0)	3 (3.1)	
ETHNICITY, N (%)				0.830
Non-Hispanic white	67 (69.1)	72 (72.0)	72 (73.5)	
Hispanic or Latino	11 (11.3)	8 (8.0)	8 (8.2)	
Black or African American	6 (6.2)	8 (8.0)	9 (9.2)	
Asian or Asian American	10 (10.3)	10 (10.0)	6 (6.1)	
Other	3 (3.1)	2 (2.0)	3 (3.1)	
INCOME, N (%)				0.925
0-24,999	12 (12.4)	21 (21.0)	16 (16.3)	
25,000-49,999	28 (28.9)	26 (26.0)	30 (30.1)	
50,000-74,999	21 (21.6)	18 (18.0)	17 (17.3)	
75,000-99,999	13 (13.4)	11 (11.0)	12 (12.2)	
100,000 +	23 (23.7)	24 (24.0)	23 (23.5)	
ALLERGIES, N (%)				0.763
Yes	35 (36.1)	41 (41.0)	39 (39.8)	
RECURRENT SINUSITIS, N (%)				0.800
Yes	6 (6.2)	6 (6.0)	8 (8.2)	
CHRONIC SINUSITIS, N (%)				0.416
Yes	8 (8.2)	4 (4.0)	5 (5.1)	
DEVIATED SEPTUM, N (%)				0.768
Yes	4 (4.1)	6 (6.0)	4 (4.1)	
NASAL POLYPS, N (%)				0.611
Yes	0 (0.0)	1 (1.0)	1 (1.0)	
ENT SURGERY, N (%)				0.737
Yes	20 (20.1)	18 (18.0)	22 (22.4)	
SINUS SURGERY, N (%)				0.604
Yes	1 (1.0)	2 (2.0)	3 (3.1)	
SEPTOPLASTY, N (%)				0.357
Yes	2 (2.1)	1 (1.0)	0 (0.0)	
CHRONIC PAIN, N (%)				0.561
Yes	19 (19.6)	26 (26.0)	23 (23.5)	
PSYCHIATRIC HISTORY, N (%)				0.083
Yes	38 (39.2)	48 (48.0)	54 (55.1)	
SMOKING, N (%)				0.358
Never a smoker	74 (76.3)	73 (73.0)	65 (66.3)	
Current smoker	5 (5.2)	9 (9.0)	13 (13.3)	
Former smoker	18 (18.6)	18 (18.0)	20 (20.4)	
MEDICATIONS, N (%)				0.126
0	47 (48.5)	53 (53.0)	40 (40.8)	
1-3	39 (40.2)	43 (43.0)	43 (43.9)	
4 +	11 (11.3)	4 (4.0)	15 (15.3)	
CARDIAC HISTORY, N (%)				0.052
Yes	17 (17.5)	21 (21.0)	31 (31.6)	
PULMONARY HISTORY, N (%)				0.674
Yes	16 (16.5)	16 (16.0)	20 (20.4)	
DIABETES HISTORY, N (%)				0.237
Yes	7 (7.2)	4 (4.0)	10 (10.2)	
STROKE HISTORY, N (%)				0.773
Yes	1 (1.0)	1 (1.0)	2 (2.0)	

Table 1C. Patients' characteristics for the mini-Rhinoconjunctivitis Quality of Life.

VAR--IABLE	GROUP G Positive (n=98)	GROUP H Negative (n=100)	GROUP I Control (n=98)	P VALUE
AGE, MEAN (SD), YEARS	31.8 (11.6)	36.1 (14.1)	34.7 (12.2)	0.053
GENDER, N (%)				0.625
Male	52 (53.1)	50 (50.0)	46 (46.9)	
Female	42 (42.9)	47 (47.0)	51 (52.0)	
Non-binary	4 (4.1)	3 (3.0)	1 (1.0)	
ETHNICITY, N (%)				0.774
Non-Hispanic white	69 (70.4)	69 (69.0)	64 (65.3)	
Hispanic or Latino	9 (9.2)	7 (7.0)	11 (11.2)	
Black or African American	6 (6.1)	11 (11.0)	8 (8.2)	
Asian or Asian American	8 (8.2)	10 (10.0)	11 (11.2)	
Other	6 (6.1)	3 (3.0)	4 (4.1)	
INCOME, N (%)				0.211
0-24,999	26 (26.5)	20 (20.0)	17 (17.3)	
25,000-49,999	27 (27.6)	21 (21.0)	27 (27.6)	
50,000-74,999	17 (17.3)	27 (27.0)	21 (21.4)	
75,000-99,999	15 (15.3)	7 (7.0)	13 (13.3)	
100,000 +	13 (13.3)	25 (25.0)	20 (20.4)	
ALLERGIES, N (%)				0.859
Yes	40 (40.8)	39 (39.0)	42 (42.9)	
RECURRENT SINUSITIS, N (%)				0.999
Yes	4 (4.1)	4 (4.0)	4 (4.1)	
CHRONIC SINUSITIS, N (%)				0.105
Yes	7 (7.1)	5 (5.0)	1 (1.0)	
DEVIATED SEPTUM, N (%)				0.608
Yes	5 (5.1)	6 (6.0)	3 (3.1)	
NASAL POLYPS, N (%)				0.374
Yes	0 (0.0)	1 (1.0)	0 (0.0)	
ENT SURGERY, N (%)				0.175
Yes	11 (11.2)	21 (21.0)	17 (17.3)	
SINUS SURGERY, N (%)				0.770
Yes	2 (2.0)	1 (1.0)	1 (1.0)	
SEPTOPLASTY, N (%)				0.885
Yes	3 (3.1)	3 (3.0)	2 (2.0)	
CHRONIC PAIN, N (%)				0.073
Yes	22 (22.4)	31 (31.0)	17 (17.3)	
PSYCHIATRIC HISTORY, N (%)				0.232
Yes	50 (51.0)	39 (39.0)	43 (43.9)	
SMOKING, N (%)				0.197
Never a smoker	76 (77.6)	73 (73.0)	64 (65.3)	
Current smoker	5 (5.1)	8 (8.0)	14 (14.3)	
Former smoker	17 (17.3)	19 (19.0)	20 (20.4)	
MEDICATIONS, N (%)				0.636
0	52 (53.1)	48 (48.0)	60 (61.2)	
1-3	37 (37.8)	39 (39.0)	31 (31.6)	
4 +	9 (9.2)	13 (13.0)	7 (7.1)	
CARDIAC HISTORY, N (%)				0.801
Yes	17 (17.3)	21 (21.0)	16 (16.3)	
PULMONARY HISTORY, N (%)				**0.019**
Yes	20 (20.4)	27 (27.0)	11 (11.2)	
DIABETES HISTORY, N (%)				0.310
Yes	4 (4.1)	9 (9.0)	5 (5.1)	
STROKE HISTORY, N (%)				0.374
Yes	2 (2.0)	5 (5.0)	2 (2.0)	

Table 2. Primary and Secondary Outcomes for the SNOT-22.

OUTCOME Mean [95% confidence interval]	GROUP A Positive (n=96)	GROUP B Negative (n=98)	GROUP C Control (n=100)	P VALUE (df, F)
Total SNOT-22 Score	34.3 [30.6-38.0]	45.1 [41.8-48.4]	36.8 [33.1-40.5]	<0.001 (2, 9.8)
Rhinologic Symptom Domain Score	8.2 [7.2-9.2]	10.9 [9.8-11.9]	8.2 [7.2-9.1]	<0.001 (2, 9.9)
Extra-Nasal Rhinologic Symptom Domain Score	3.7 [3.2-4.3]	5.7 [5.1-6.2]	4.1 [3.6-4.7]	<0.001 (2, 13.8)
Ear and Facial Symptom Domain Score	6.1 [5.0-7.2]	8.2 [7.3-9.1]	6.9 [5.8-8.0]	0.017 (2, 4.1)
Psychological Dysfunction Domain Score	14.8 [13.2-16.5]	18.9 [17.5-20.4]	16.1 [14.4-17.7]	0.001 (2, 6.9)
Sleep Dysfunction Domain Score	8.2 [7.2-9.2]	10.5 [9.5-11.5]	9.1 [8.0-10.1]	0.006 (2, 5.1)
Mood Visual Analogue Scale Score	62.1 [58.1-66.1]	63.5 [60.0-67.2]	63.8 [60.0-67.6]	0.817 (2, 0.2)

Table 3. Primary and Secondary Outcomes for the RSDI.

OUTCOME Mean [95% confidence interval]	GROUP D Positive (n=97)	GROUP E Negative (n=100)	GROUP F Control (n=98)	P VALUE (df, F)
Total RSDI Score	19.2 [15.2-23.2]	33.4 [28.9-37.9]	17.2 [13.4-21.0]	<0.001 (2, 18.3)
Physical Domain Score	7.9 [6.4-9.4]	13.3 [11.7-14.8]	7.6 [5.9-9.2]	<0.001 (2, 16.2)
Functional Domain Score	6.0 [4.6-7.4]	10.1 [8.5-11.7]]	5.2 [4.0-6.5]	<0.001 (2, 13.1)
Emotional Domain Score	5.2 [3.9-6.6]	10.1 [8.3-11.8]	4.5 [3.2-5.7]	<0.001 (2, 17.1)
Mood Visual Analogue Scale Score	68.2 [64.7-71.8]	60.9 [57.2-64.7]	64.2 [60.2-68.2]	0.026 (2, 3.7)

Table 4. Primary and Secondary Outcomes for the MiniRQLQ.

OUTCOME Mean [95% confidence interval]	GROUP G Positive (n=98)	GROUP H Negative (n=100)	GROUP I Control (n=98)	P VALUE (df, F)
Total MiniRQLQ Score	17.3 [14.4-20.1]	24.8 [21.0-28.5]	18.6 [15.6-21.5]	0.002 (2, 6.2)
Activities Domain Score	3.1 [2.5-3.7]	4.6 [3.9-5.4]	3.5 [2.9-4.2]	0.008 (2, 4.9)
Practical problems Domain Score	2.4 [1.9-2.9]	3.8 [3.1-4.5]	3.2 [2.6-3.8]	0.004 (2, 5.6)
Nose symptoms Domain Score	3.4 [2.7-4.2]	5.3 [4.3-6.2]	4.2 [3.4-5.0]	0.009 (2, 4.8)
Eye symptoms Domain Score	2.9 [2.2-3.6]	4.5 [3.6-5.5]	3.1 [2.3-3.9]	0.009 (2, 4.8)
Other symptoms Domain Score	5.4 [4.5-6.3]	6.5 [5.6-7.5]	4.6 [3.8-5.4]	0.007 (2, 5.0)
Mood Visual Analogue Scale Score	62.2 [58.3-66.2]	64.8 [61.3-68.3]	62.1 [58.1-66.1]	0.533 (2, 0.6)

mean total score for participants who were primed negatively in Group H was worse than the score for those primed positively in Group G. There were, however, no differences between the control group I, and the positively primed Group G and the

negatively primed Group H. These statistical findings were also observed for all domains of the MiniRQLQ, except for "Other Symptoms". The mean mood score on the VAS for participants in Group G was 62.2 (95%CI[58.3-66.2]), in Group H 64.8 (95%CI[61.3-68.3]), and in Group I 62.1 (95%CI[58.1-66.1]). One-way ANOVA did not reveal any difference between the three groups (p=0.533 (df=2, F=0.6)). Mean MiniRQLQ total scores, domain scores, and corresponding mood VAS scores can be found in Table 4 (Supplemental Figure 3).

Harm

No adverse effects from the interventions were reported by participants.

Discussion

PROMs measure the personal and subjective experience of health conditions, which may fluctuate and be influenced by numerous patient-specific, disease-specific, and environment-specific circumstances [13]. This RCT aims to determine if responses to the most commonly used rhinology PROMs can be influencing by priming. Participants in the intervention groups were thus primed prior to completing the SNOT-22, RSDI and MiniRQLQ with surveys that exposed them to positive or negative health-related questions.

For the SNOT-22 and the RSDI, negatively primed respondents had significantly worse scores than those primed positively and those in the control group. This difference was true not only for the total PROM scores, but also for almost all domains of each PROM. For the MiniRQLQ, although statistical significance was almost reached when comparing scores from the negatively primed to the control group, a statistically significant difference was only detected when comparing the negatively primed to the positively primed group. This difference was significant for each of the five domain scores within the MiniRQLQ. Furthermore, for the RSDI, negatively priming participants affected scores not only in a statistically significant way, but also in a clinically significant way. The MCID is the minimum change in outcome score signifying a clinical difference. For the SNOT-22, negatively primed respondents scored on average 8.3 points worse than the control group, with an MCID of 8.9 for surgically managed patients, and 12.0 for medically managed pateints [21-23]. For the RSDI, the average difference between the negatively primed group and the control group was 16.2, with a MCID of 10.35 [24]. To our knowledge, there is no validated MCID for the MiniRQLQ. Conversely, there was no statistically significant difference between positively primed patients and control groups. This finding could be explained by the fact that the study was performed in a general population rather than exclusively patients with rhinologic disorders, where baseline scores tend to be lower and difficult to improve [6, 25]. However, given that PROMs scores in all control groups were higher than expected for the general population, positive priming could simply not have an impact on PROMs.

Our findings appear to be supported by a recent study demonstrating that depression and anxiety may confound and affect scoring on the SNOT-22, as the sleep and psychological dysfunction domains correlated with other PROMs for depression and general anxiety disorder [26]. Moreover, patient-level factors may affect physical domains, such as rhinologic, extra-nasal rhinologic, and ear and facial symptoms. Although priming is a well-known concept in the field of social psychology, its impact on PROMs is poorly understood [15]. Our study suggests that priming does not appear to affect VAS mood scores significantly. Although positively primed participants in the RSDI group had statistically the best mood and negatively primed participants had the worst mood, this pattern was not observed for the SNOT-22 or the MiniRQLQ groups. This finding suggests that participants' responses to rhinologic PROMs may be influenced regardless of general mood VAS scores.

Although participants in this study were intentionally primed, such phenomena occur all around us in daily life, and may occur unintentionally in clinical practice. For instance, positive priming could occur if a PROM is administered after a pleasant encounter with an upbeat provider who discusses which aspects of the patient's health are feeling good. Conversely, negative priming could occur if a PROM is completed after unpleasant events such as long wait time, or a conversation about which aspects of the patient's health are symptomatic and troublesome. External sources, such as social media or news reports, could also impact patients' state of mind. These effects may be minimal in large RCTs if the randomization distributes both known and unknown variables equally across participants. However, without a clear understanding of what these effects are or the degree of their influence, it is impossible to measure them or assure their equal distribution among clinical trial cohorts. In smaller studies or clinical series, the context in which PROMs are administered may be playing an outsize role. Understanding the factors that influence, distort, or otherwise impact the administration or interpretation of clinical assessment tools is thus absolutely essential.

As PROMs are considered validated and reliable instruments, it may be surprising that a simple and seemingly unrelated survey could prime subjects to impact their responses to a rhinologic disease-specific PROM to such a significant degree. We interpret this very significant finding to suggest that PROMs are clinical assessment tools like any other, and as such, they require certain parameters for their accurate administration. Blood pressure, for example, is generally measured in the upper extremity with the patient seated at rest, serum cortisol levels are measured in the morning, and lipid panels are performed fasting. We hypothesize that PROMs may similarly require a standardized clinical context for consistent, reliable, and resilient results to withstand external influences and factors such as priming.

One strength of this study is that respondents were randomized, reducing the risk of known and unknown confounders; all measured demographic, socioeconomic, and health-related data, except for one variable for the MiniRQLQ, were balanced among the nine groups, suggesting proper randomization. Furthermore, participants were blinded to the hypothesis and methodology, which also minimized risks of bias. The results from this study should however be interpreted considering its limitations. First, respondents were sampled from the general population, and only a minority had a history of sinusitis or deviated nasal septum. The effects of priming could potentially differ if the study were performed in a population of patients with CRS. As previously mentioned, the basis of any PROM development and validation requires its study in a normal population. Therefore, this study was first performed in the general population irrespective of suspected or confirmed rhinologic disease to provide baseline data on the impact of patient-level factors on rhinologic PROMs. Further studies will be required to determine if the same effects are observed in rhinologic specific populations. Although recruitment for these subsequent studies would be more labour-intensive, data from this preliminary study could facilitate study design, especially for sample size considerations. Furthermore, although participants were recruited from the general US population, the demographic data from our sample differed from the US census [27]. Notably, the participants' younger age and the under-representation of African Americans were demographic features inconsistent with the US population; the importance of concordance between study populations and treatment populations in rhinology clinical trials has been described by our group previously [27-29]. In fact, notable demographic characteristics in our study population that may limit the generalizability of the study include the young age of participants, and the high prevalence of mental illness and chronic pain. Although it is uncertain why these characteristics were observed in our population, it is possible that individuals who volunteer to participate to research projects online tend to be younger, as younger individuals tend to be more facile with technology. The ease with which anonymity may be preserved online could also lead participants to be more honest about their mental and physical health. Alternatively, participants interested in participating in clinical studies could have more comorbidities than the general population. Moreover, the mean SNOT-22 score of 36.8 for the control group was higher than previously described scores for the general population [30]. This could potentially be explained by the high prevalence of psychiatric history, leading to higher scores in the sleep and psychological dysfunction domains of the PROM [25]. Lastly, given that the study was performed through an online platform, it was not possible to monitor the quality of the participants' responses until the final analysis. In the end, only 15 participants out of 900 did not complete the questionnaire, which is an event that could also occur in the clinical setting, and no obviously aberrant responses required exclusion from analysis.

Conclusion

Although the SNOT-22, the RSDI and the MiniRQLQ are validated PROMs that are commonly used for rhinologic conditions, the optimal setting and conditions in which these questionnaires should be administered are still unclear. This study suggests that healthy volunteers who are negatively primed prior to completing fundamental rhinologic PROMs have worst scores on the questionnaires. Further studies are required to better characterize these effects in disease-specific populations and in settings more closely reflecting the standard clinical or research environment.

Trial registration

This clinical trial was registered on clinicaltrials.gov under the ID NCT05229016.

Authorship contribution

Study design: NY, AW, ZMS, JBO, DA; Data collection: NY, AW, DA; Data analysis: NY, DA; Data interpretation: NY, AW, ZMS, JBO, DA; Manuscript: NY, AW, ZMS, JBO, DA

Conflict of interest

None

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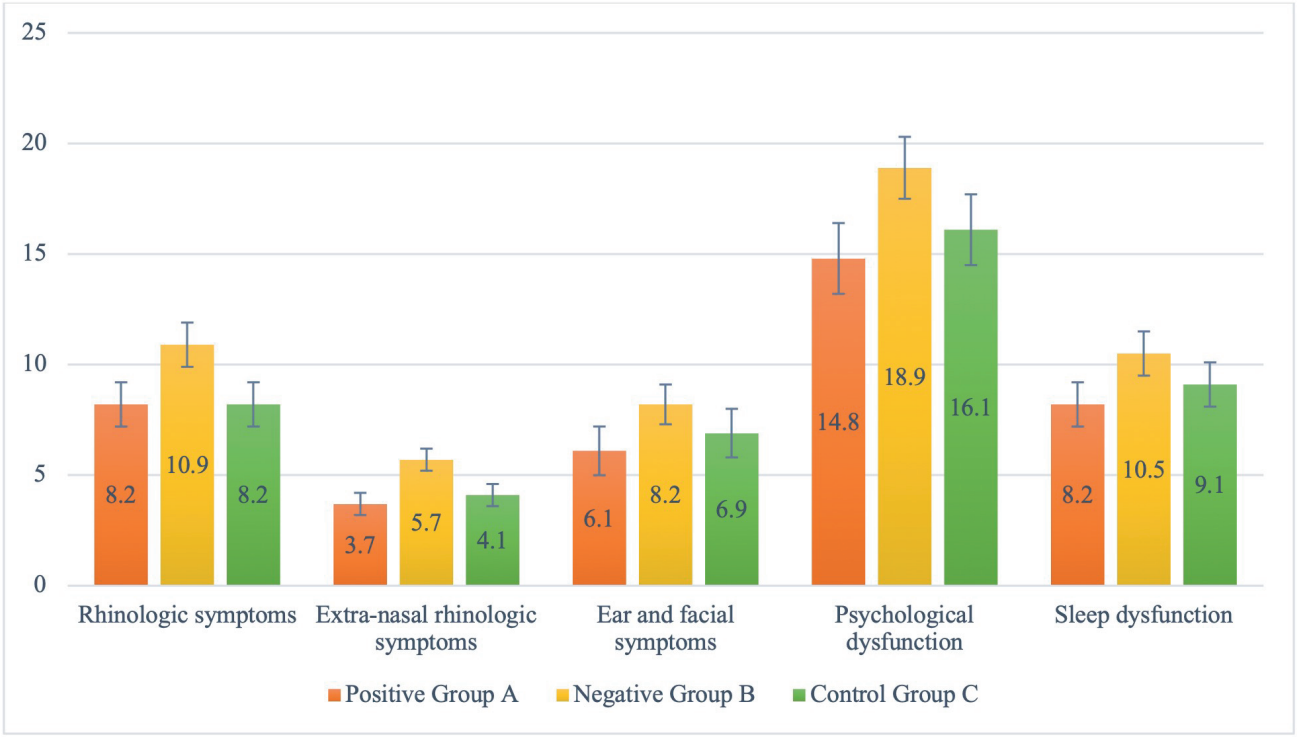
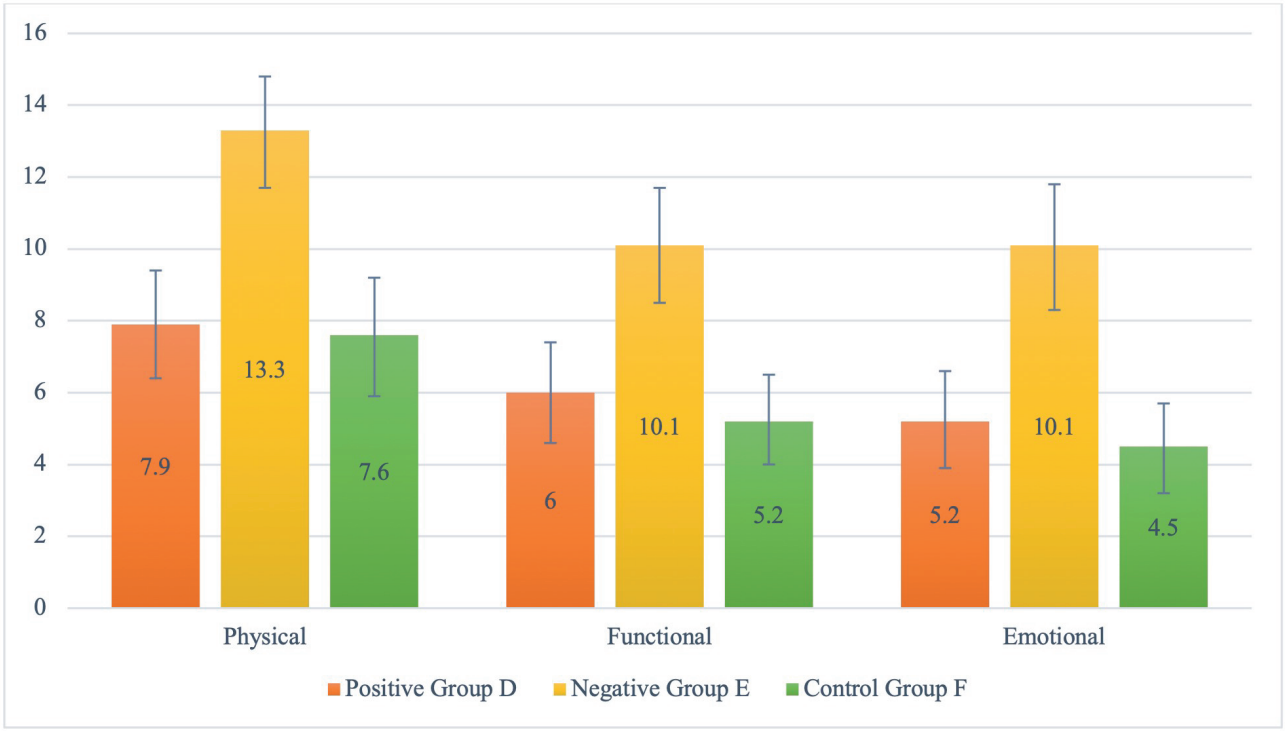
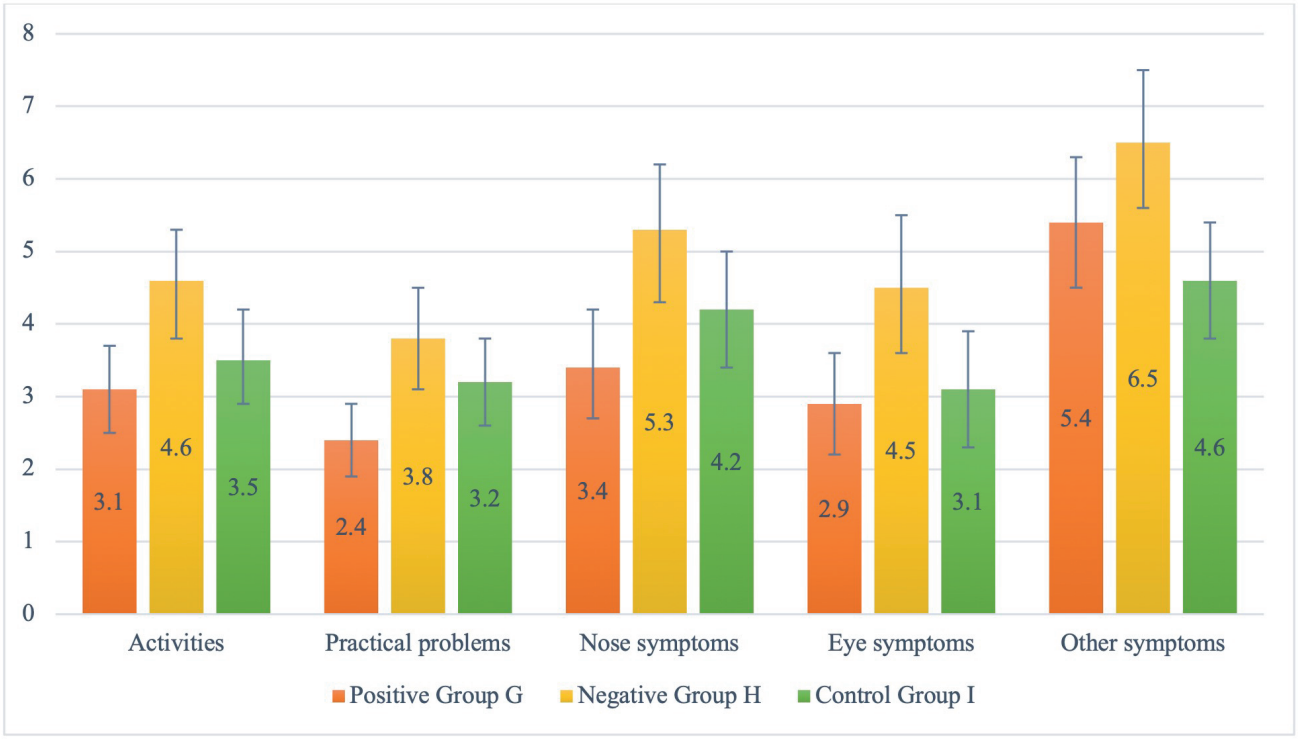
SUPPLEMENTARY MATERIAL



Supplemental Figure 1. SNOT-22 Domain Scores (Mean with 95% Confidence Interval).



Supplemental Figure 2. RSDI Domain Scores (Mean with 95% Confidence Interval).



Supplemental Figure 3. MiniRQLQ Domain Scores (Mean with 95% Confidence Interval).