Global airways – a novel Standard Tests for Asthma, allergic Rhinitis, and chronic Rhinosinusitis (STARR-15)*

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Abstract

Background: Global airway disease, with symptoms from both upper and lower airways, is a challenging problem for clinicians. Our goal is to design one single standard test for the awareness of global airway diseases to be used in clinical setting.

Material and Methods: During 2019, rhinologists and pulmonologists generated a pool of items based on literature, patient-reported outcome measures and clinical experience. The items were administered to 206 patients with known asthma, CRS, allergic rhinitis, or a combination thereof. The patients also completed the Asthma Control Questionnaire (ACQ-5) and the Sino-Nasal Outcome Test (SNOT-22). Using a mix of clinical knowledge and data-driven methods a global airways questionnaire was developed,

Results: Mean ACQ score was highest in patients with all three, whereas the highest SNOT-22 score was observed in patients with CRS and asthma. After the development process, analysis of responses from 206 patients to 44 items on a new global airway's questionnaire led to identification of 15 items that form the STARR-15 questionnaire with three underlying domains (an allergic rhinitis sub-factor, a CRS sub-factor and an asthma sub-factor).

Conclusion: STARR-15 represents the first global airways questionnaire, to be used when examining patients with upper and lower airways symptoms. Future analyses are warranted to evaluate the clinical and psychometric properties of STARR-15.

Key words: allergic rhinitis, asthma, chronic rhinosinusitis, global airways, PROM's, questionnaire

Introduction

Patient-reported outcome measures (PROMs) are questionnaires measuring patients' views of their own health status [1, 2]. PROMs are self-completed questionnaires, in which patients are asked about their own perspectives of their feelings, symptoms, and anxiety before and after treatment [3, 4].

The asthma control questionnaire (ACQ) is the most widely used PROM [5], especially in severe asthma, all countries including data in International Severe asthma registry (ISAR) and the Nordic severe asthma registry are recommended to use ACQ [6, 7]; it includes a subdivision in scales, with a weighted value indicating the level of control independent of severity of asthma, where the original ACQ-7 has been reduced to the ACQ-5 [8]. ACQ is the only questionnaire fulfilling all essential characteristics, including validity, responsiveness, stability, internal consistency, and interpretability. ACQ does not have diagnostic potential, the recall period is seven days, and the level of asthma control is measured by a score of ACQ when used in patients with diagnosed asthma [9].

When examining patients with upper airway symptoms (e.g., nasal stenosis, nasal discharge, loss of smell and facial pain), various questionnaires are available, including the most often used Sino-Nasal Outcome Test (SNOT-22). SNOT-22 is a disease-specific PROM used in chronic rhinosinusitis (CRS) and is considered the most suitable tool for assessing the level of severity in patients diagnosed with CRS with or without nasal polyps (CRSwNP and CRSsNP) [10, 11], but is however not restricted to nasal symptoms only.

Disease of upper and lower airways is often present in the same patients, so a considerable overlap between the two diseases as well as inflammation exists and in such a degree that it is named, global airways disease [12]. The reason is that both diseases and especially the moderate to severe level of disease often are driven by type 2 inflammation [13, 14]. Several different PROMs are routinely used in clinical settings within both pulmonology and rhinology, but no combined questionnaire exists covering the global airway diseases. No sinonasal symptoms are included in any of the asthma questionnaires used, whereas the SNOT-22 includes various symptoms, also some asthma-like symptoms. Patients with upper and lower airway disease happen to be examined and treated by either rhinologists or pulmonologists, and identifying co-morbidities are often lacking in both clinical settings [15]. As diseases simultaneously occur in global airways, patients should be evaluated at both upper and lower airways, as better disease control are gained, when both upper and lower airways are treated.

The objective of this study was to take the first steps towards developing one single standardised questionnaire (Standard Test for Asthma, allergic Rhinitis, and chronic Rhinosinusitis, entitled STARR-15)) comprising of symptoms of both upper and lower airways in patients with known disease with the goal of providing increased awareness of the global airway disease. In this study, we describe the development process using a sample of 206 patients.

Methods

The development of a global airway's questionnaire was conducted in several phases. First, identification of potential items was performed and put together to form a first version of the questionnaire (item identification phase and pilot phase), then a sample of patients completed the questionnaire (data collection phase), and their responses were analyzed to form a reduced form of the questionnaire (item reduction phase). This reduced questionnaire underwent further statistical analyses. All phases are described in detail below. In all phases, we used a mix of data-driven approaches and our clinical experience to guide the analyses. The project was approved by the Capital Region in Denmark with project no VD-2018-383, the Local ethical commitee no FSP 21064988, and informed consent was obtained from all patients.

Item identification and pilot phase

Item identification was performed by the authors through brainstorms and face-to-face meetings. Items from existing measures such as the ACQ and the SNOT-22 were reviewed and considered for inclusion. This process generated a pool of 55 candidate items. A Likert scale with six response options was selected ("no problem", "very mild problem", "mild or slight problem", "moderate problem", "severe problem", "problem as bad as it can be").

This first version of the questionnaire underwent pilot testing in eleven patients with asthma, CRS, allergic rhinitis, or a combination of the diseases. The patients were interviewed by one of the authors immediately after completing the questionnaire to explore the items' comprehensiveness, relevance, and clarity.

Data collection

Patients above the age of 18 years, who could read and write Danish, were followed in a specialist clinic, and had prior to the inclusion been diagnosed with asthma, CRS, or allergic rhinitis (or with a combination of these diseases) were included. All patients were diagnosed by a specialist trained in global airways diseases. The patients were managed in the clinic and was diagnosed at the time of referral; CRS was diagnosed according to the EPOS2020 guidelines, thus all patients diagnosed with CRS had a sinus CT scan a nasal endoscopy and symptoms registered; allergic rhinitis was based on symptoms and a skin prick test; asthma was diagnosed based on symptoms and a mannitol provocation or response to beta2-agonist. All with asthma had lung function performed and skin prick test measured at the time of referral.

Patients were recruited from respiratory and ear-nose-throat (ENT) outpatient clinics, at five different sites in the Copenhagen County of Denmark. All patients completed the new questionnaire as well as the ACQ-5 and SNOT-22 questionnaires.

Item reduction phase

A reduction in the number of items was performed in several steps, using a mix of data-driven approaches but also using our clinical experience. First, we applied two a priori defined exclusion criteria: 1) any item with less than 20% of subjects indicating a symptom to be "a moderate problem", "a severe problem", or "problem as bad as it can be" to avoid floor and ceiling effects [16]; or 2) one of any two items whose Pearson's correlation coefficient was 0.70 or higher to avoid including items with the same meaning.

Statistical analyses

To assess the questionnaire's ability to discriminate between patients suffering from asthma, CRS, allergic rhinitis or a combination thereof, we compared item means between the disease groups and evaluated associations by a Kruskal-Wallis test.

Using PROC IRT in SAS, we fitted unconstrained graded response models (GRM) treating item responses as ordinal variables. Eigen values were used to assess dimensionality and latent trait parameter estimates and item characteristic curves were obtained. We estimated factor scores using maximum a posteriori estimation and used the criterion that items were assigned to the factor on which the item had a higher factor load. Factor scores were compared using F-statistics among the patients with different underlying diseases to evaluate their ability to dif-

Tabel 1. Characteristics of the study population according to disease group.

		Physician reported diagnoses Five groups*					Physician reported diagnoses Three groups**			
	Total	CRS only	Asthma only	CRS and asthma	Asthma and AR	Asthma, CRS, AR	p	CRS only (± AR)	Asthma only (± AR)	Asthma and CRS (±AR)	p
Number of respondents	206	54 (28%)	39 (20%)	29 (15%)	54 (28%)	18 (9%)		61 (30%)	93 (46%)	47 (23%)	
Male	107 (52%)	39 (72%)	9 (23%)	14 (48%)	30 (56%)	9 (50%)	0.004	42 (69%)	39 (42%)	23 (49%)	0.004
Age (years)	47 (17)	47 (19)	46 (17)	51 (16)	44 (14)	60 (12)	0.004	46 (19)	45 (15)	54 (15)	0.003
BMI (kg/m^2)	26 (5)	26 (6)	25 (3)	25 (4)	26 (5)	28 (6)	0.42	26 (6)	26 (5)	26 (5)	0.90
ACQ-5 score	1.15 (1.21)	0.21 (0.74)	1.34 (1.03)	1.72 (1.27)	1.54 (1.14)	1.84 (1.24)	<0.001	0.19 (0.69)	1.45 (1.10)	1.77 (1.25)	<0.001
SNOT-22 score	52 (19)	59 (16)	42 (15)	62 (22)	44 (17)	58 (14)	<0.001	59 (16)	43 (16)	51 (19)	<0.001

Values are n (%) or mean (sd), AR: allergic rhinitis, *12 patients with AR only not included, **5 patients with AR only and AR and CRS not included.

ferentiate between patients. Internal consistency was evaluated using Cronbach's α. To test the discriminant validity, we also analyzed the association between the factor scores and ACQ-5 and SNOT-22 scores using simple linear regression evaluated by the R2 and Root Mean Square Errors (RMSE). During the analysis, patients with allergic rhinitis only, were excluded as this disease could not be grouped during the process of 5 disease categories (n=12) and 3 disease categories (n=5). We used SAS Enterprise Guide 7.1 to analyze our data, and all reported p-values were two-sided with an α of 0.05.

Results

First, the modifications to the list of items resulting from the pilot phase are presented, followed by a presentation of the results obtained from the data collection and item reduction phases.

Pilot testing

After the pilot testing in 11 patients, modifications were made to the list of the original 55 items. First, an additional response category was added to some items ("not relevant"), and two items were combined ("facial pain" and "facial pressure" to form one item). Some items were deleted ("middle ear problems", "deafness", "decreased sense of taste", "use of nasal rinse with saline", "avoid social contact", "frequent infections", "frustration", "restlessness", "irritation", "administration of Xylometazoline drops") due to the more general character of these questions. After the pilot phase, the questionnaire consisted of 44 items that formed the questionnaire that was completed in the full patient sample.

Data collection

At total of 207 patients were included during 2019–2020. Out of these, 206 returned their response. Patient demographics and clinical variables are shown in Table 1 and Supplementary Table 1. Dividing the total population into five categories, led to 54 (28%) patients having a CRS diagnosis only, 39 (20%) an asthma diagnosis only, 29 (15%) a combination of CRS and asthma, 54 (28%) asthma with allergic rhinitis, and 18 (9%) patients having all three conditions (Table 1). Mean ACQ-5 score was highest in patients with all three conditions [1.84 (SD=1.24)], whereas the highest SNOT-22 score was observed in patients with CRS and asthma [62 (SD=22)] (Table 1).

Item reduction phase

The patients' responses to the 44 included items are presented in Table 2. Based on these responses in the 206 patients, we observed that items 3, 4, 5, 6, 7, 8, 9, 10, 20, 21, 24, 25, 26, 42, 43 met exclusion criterion 1 (floor and ceiling effects), and items 13 and 14, items 14 and 17, items 16 and 17, items 18 and 19, items 23 and 27, items 24 and 28, item 38 and 39, items 42 and 43, and items 31, 33, 34, 35, 36, 38 met exclusion criterion 2 (correlated items) (data not shown).

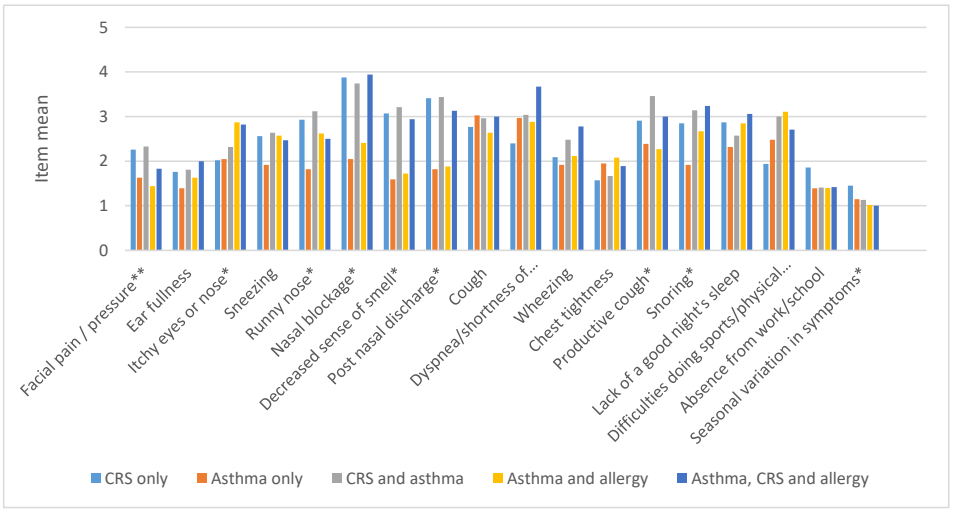
Despite some items fulfilling the exclusion criteria, our clinical knowledge overruled some findings based on significant clinical importance of the items. The authors decided to keep items 25 and 26 ("wheezing" and "chest tightness") despite the fact that fewer than 20% indicated these symptoms to be moderate, severe, or as bad as can be. Further, it was decided not to consider items 1 ("headache",) 29 ("common cold"), and 38 ("tiredness") since they were deemed too unspecific, and items 18 ("dry mucous membranes") and 19 ("morning dryness in the throat") since they were not considered as relevant for the diseases compared to some of the other items. Two sets of items (items 6 and 21 "itchy eyes" and "itchy nose", respectively and items 23 and 27 "shortness of breath" and "shortness of breath/difficult to breath", respectively) were combined to form one item each

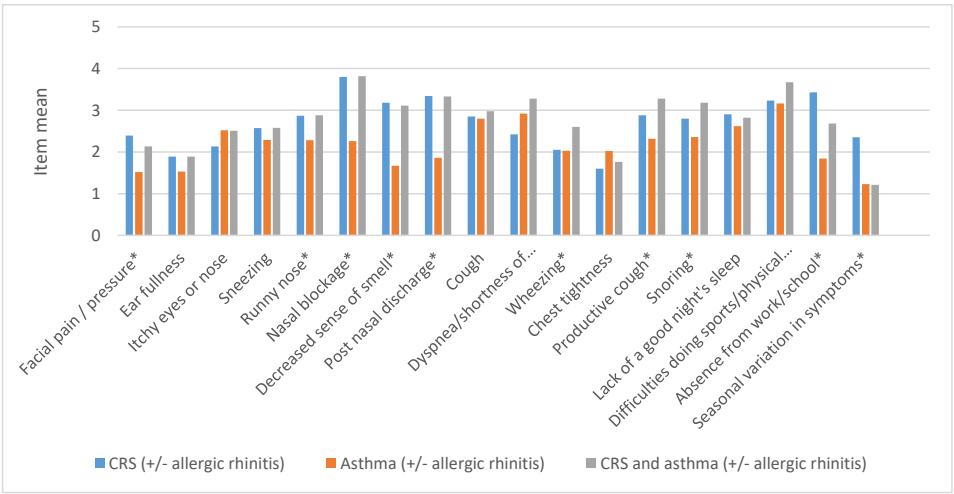
Table 2. Item response frequencies on the full questionnaire. Items marked in blue were retained on the reduced questionnaire, including18 items.

Item content			Response value						
Item full Q	Item reduced Q	During the past 12 weeks, how often have you been bothered by the following symptoms:	No problem	A very mild problem	Mild or slight problem	A moderate problem	A severe problem	Problem as bad as can be	Not relevant
1		Headache	36%	21%	14%	23%	5%	2%	
2	**1**	**Facial pain / pressure#**	**63%**	**11%**	**6%**	**13%**	**6%**	**1%**	
3		Ear pain#	74%	12%	7%	4%	4%	0%	
4	**2**	**Ear fullness pressure#**	**63%**	**16%**	**11%**	**5%**	**2%**	**1%**	
5		Dizziness#	57%	20%	11%	8%	3%	0%	
6	**3**	**Itchy eyes***	**40%**	**28%**	**16%**	**13%**	**3%**	**0%**	
7		Red eyes	64%	19%	9%	7%	2%	0%	
8		Itchy skin	55%	18%	15%	8%	2%	1%	
9		Itchy ears	67%	13%	12%	8%	2%	0%	
10		Ichty palate	70%	16%	8%	4%	1%	1%	
11		Need to blow nose#	17%	23%	21%	18%	16%	5%	
12	**4**	**Sneezing#**	**28%**	**30%**	**17%**	**19%**	**4%**	**1%**	
13	**5**	**Runny nose#**	**33%**	**21%**	**16%**	**17%**	**11%**	**3%**	
14	**6**	**Nasal blockage#**	**28%**	**17%**	**11%**	**18%**	**17%**	**10%**	
15	**7**	**Decreased sense of smell#**	**51%**	**11%**	**7%**	**13%**	**9%**	**8%**	
16	**8**	**Post nasal discharge#**	**35%**	**20%**	**14%**	**13%**	**12%**	**6%**	
17		Thick nasal discharge#	44%	16%	15%	10%	11%	5%	
18		Dry mucous membranes	45%	20%	15%	13%	6%	2%	
19		Morning dryness in the throat	43%	15%	11%	17%	11%	4%	
20		Nose bleeding	75%	13%	5%	4%	2%	0%	
21	**3**	**Itchy nose***	**54%**	**23%**	**12%**	**8%**	**2%**	**1%**	
22	**9**	**Cough#**	**24%**	**24%**	**18%**	**14%**	**14%**	**5%**	
23	**10**	**Shortness of breathe****	**35%**	**20%**	**18%**	**12%**	**11%**	**4%**	
24		Phlegm or expectoration	52%	15%	12%	9%	9%	1%	
25	**11**	**Wheezing*****	**44%**	**24%**	**13%**	**11%**	**7%**	**1%**	
26	**12**	**Chest tightness *****	**62%**	**14%**	**11%**	**8%**	**4%**	**1%**	
27	**10**	**Shortness of breath / difficulties breathing ****	**35%**	**20%**	**18%**	**16%**	**8%**	**4%**	
28	**13**	**Productive cough**	**30%**	**22%**	**14%**	**17%**	**12%**	**3%**	
29		Common cold	34%	18%	21%	14%	9%	2%	
30	**14**	**Snoring**	**37%**	**17%**	**15%**	**13%**	**13%**	**6%**	
31		Difficulty falling asleep#	43%	21%	14%	11%	5%	4%	
32		Symptoms at night	48%	16%	12%	10%	8%	4%	
33		Wake up at night#	33%	24%	14%	13%	13%	5%	
34	**15**	**Lack of a good night's sleep#**	**31%**	**22%**	**13%**	**17%**	**11%**	**5%**	
35		Shortened sleep	36%	20%	13%	18%	7%	5%	
36		Wake up tired#	22%	24%	17%	20%	9%	7%	
37		Tendency to fall asleep during the day	46%	17%	17%	11%	6%	3%	
38		Tiredness	21%	24%	19%	18%	12%	5%	
39		Reduced concentration#	43%	24%	15%	11%	5%	2%	
40	**16**	**Difficulties doing sports / training / physical activity**	**28%**	**18%**	**14%**	**13%**	**7%**	**4%**	**15%**

Item full Q	Item reduced Q	Item content: During the past 12 weeks, how often have you been bothered by the following symptoms:	Response value: No problem	A very mild problem	Mild or slight problem	A moderate problem	A severe problem	Problem as bad as can be	Not relevant
41		Limitations in your domestic daily activities (including vacuum, cleaning, mowing the lawn)	47%	20%	11%	10%	7%	3%	2%
42		Difficulties doing work work / school	46%	21%	10%	6%	3%	2%	13%
43	**17**	**Absence from work or school**	**59%**	**11%**	**6%**	**4%**	**3%**	**1%**	**17%**
			Yes	No	Not relevant				
44	**18**	**Seasonal variation in symptoms**	**69%**	**9%**	**22%**				

Items marked in bold were kept for analysis. *Items were combined to form one item. **Items were combined to form one item.***Items were kept in the questionnaire despite fewer than <20% of patients indicating the symptom to be moderate, severe, or the worst possible symptom, #Indicates items on SNOT-22.





*Denotes statistical significance by a Kruskal-Wallis test

Figure 1. Item means on the reduced questionnaire according to disease group. Figure 1A include all 5 groups, and 1B three groups, with same questionnaire response.

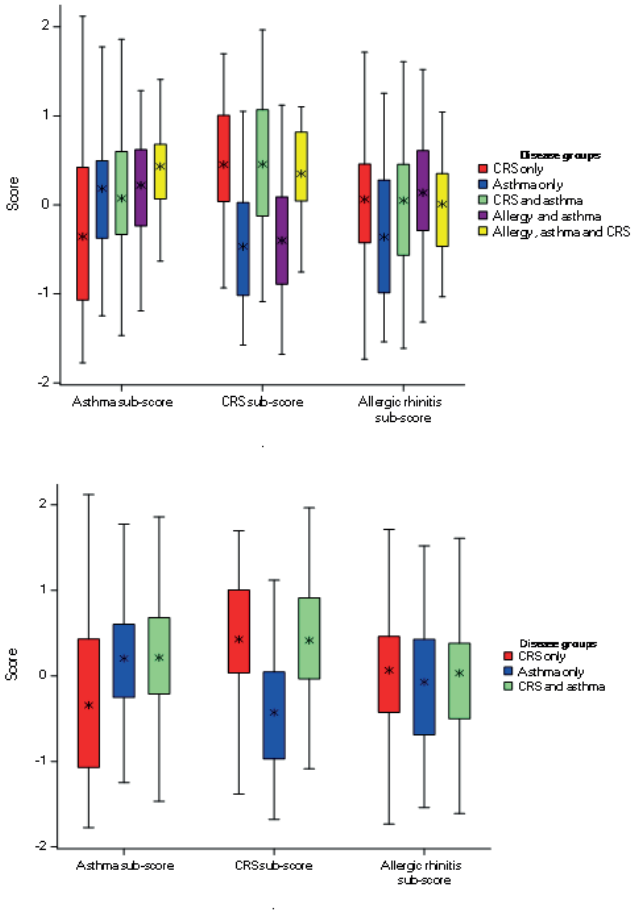


Figure 2. Factor scores from the IRT model against disease groups. Figure A include all five groups, whereas figure B include the 3 merged groups.

based on considerations that they covered the same underlying construction. The highest endorsed response value on the two items was chosen as response value on the combination item. For any two items that showed pearson's correlations > 0.70, the authors went through the pairwise items and discussed which should be kept for analysis based on clinical importance. which resulted in retaining items 13 ("runny nose"), 14 ("nasal blockage"), 16 ("postnasal discharge"). For Items 31, 33, 34, 35, 36, and 38 that were all correlations > 0.70, the authors decided to retain item 34 ("lack of a good night's sleep").

The above-mentioned modifications led to a modified version of the questionnaire with 18 items that underwent further statistical analyses and marked in blue in Table 2.

Statistical testing of the final questionnaire

The reduced questionnaire including 18 items was first analyzed with respect to item means. In Figure 1, item means are illustrated according to underlying disease (A with all five and B with three groups). Means of items 2, 4, 9, 11, 12, 15, and 17 were not significantly different among the disease groups in five categories, whereas means of items 1, 3, 5, 6, 7, 8, 10, 13, 14, 16, and 18 were significantly different. The patients' responses to ACQ-5 and SNOT-22 are seen in Supplementary Figure 1.

Item response theory analyses

We fitted a model using the 18 items with responses on the 6-point Likert scale. The item characteristics curves indicated a large overlap in the probability of endorsing response categories "very small problem", "a small problem", "moderate problem" and "severe problem" across the latent trait suggesting limited discriminative ability about the latent trait of these response categories (data not shown). We therefore fitted a model where we combined the six response categories to form a 3-point Likert scale with the options "no problem", "a small problem" (this was a combination of the previous categories "a very small problem", "a small problem", and "a moderate problem") and "a large problem" (this was a combination of the previous categories "a severe problem" and "problem as bad as it can be"). Based on the eigen values, this model appeared to have 3 underlying factors. Three separate factors were therefore calculated with factor loads seen in Supplementary Table 2A. One factor comprised of four items (items 1, 2, 15, 17) that could not be categorized into a clinically meaningful dimension. We therefore decided to test a new model without these items; however, based on clinical importance, item 1 ("facial pain") was retained leading to a model with 15 items (Supplementary Table 2B). The eigen values and scree plot suggested three underlying dimensions explaining 58% of the variance (Supplementary Figure 2). Factor loads are seen in Supplementary Table 2B and item characteristics curves in Supplementary Figure 3.

Factor 1 was labelled "Asthma factor", Factor 2 "CRS factor", and Factor 3 "Allergic rhinitis factor". Cronbach's alpha was 0.73, 0.76, and 0.63 for the three factors, respectively, suggesting acceptable internal consistency for the "Asthma factor" and "CRS factor". The ability of the three factors to differentiate between patients with CRS only, asthma only, CRS and asthma, asthma and allergy, and a combination of all three diseases is seen in Figure 2, where 2A represent all 5 groups, and 2B the 3 merged disease groups (numbers in Supplementary Table 3). CRS only patients scored lower on the asthma factor compared to the other disease groups, whereas patients with CRS either alone or in combination with asthma and/or allergic rhinitis scored higher on the CRS factor. The asthma patients scored low on the CRS factors, although a substantial overlap exists (Figure 2 A and B). There was little difference among patients on the allergic rhinitis factor. The associations between the asthma factor scores and the ACQ-5 as well as the CRS factor and SNOT-22 scores are seen in Figure 3 (A: the 5 groups and B: 3 groups). The asthma factor score explained (R2-value) 0.35-0.58 of the variances in ACQ-5 for patients with asthma alone or in combination with CRS and/or allergic rhinitis. However, the association was weaker as illustrated by a smaller R2 (0.12) and larger residual variance (RMSE=0.90) for patients with CRS only. When comparing the

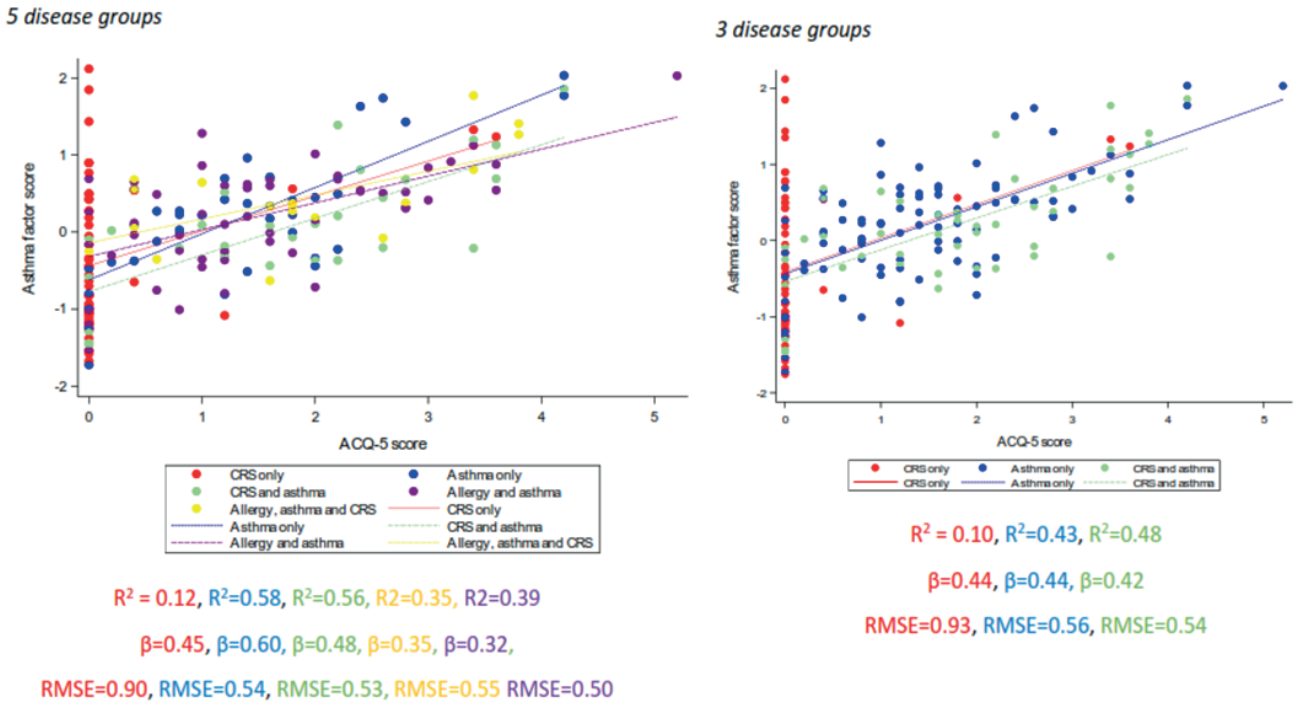


Figure 3. The asthma factor from the IRT model against ACQ-5 score. Figure 3A include the 5 disease groups, and 3B the merged 3 disease groups.

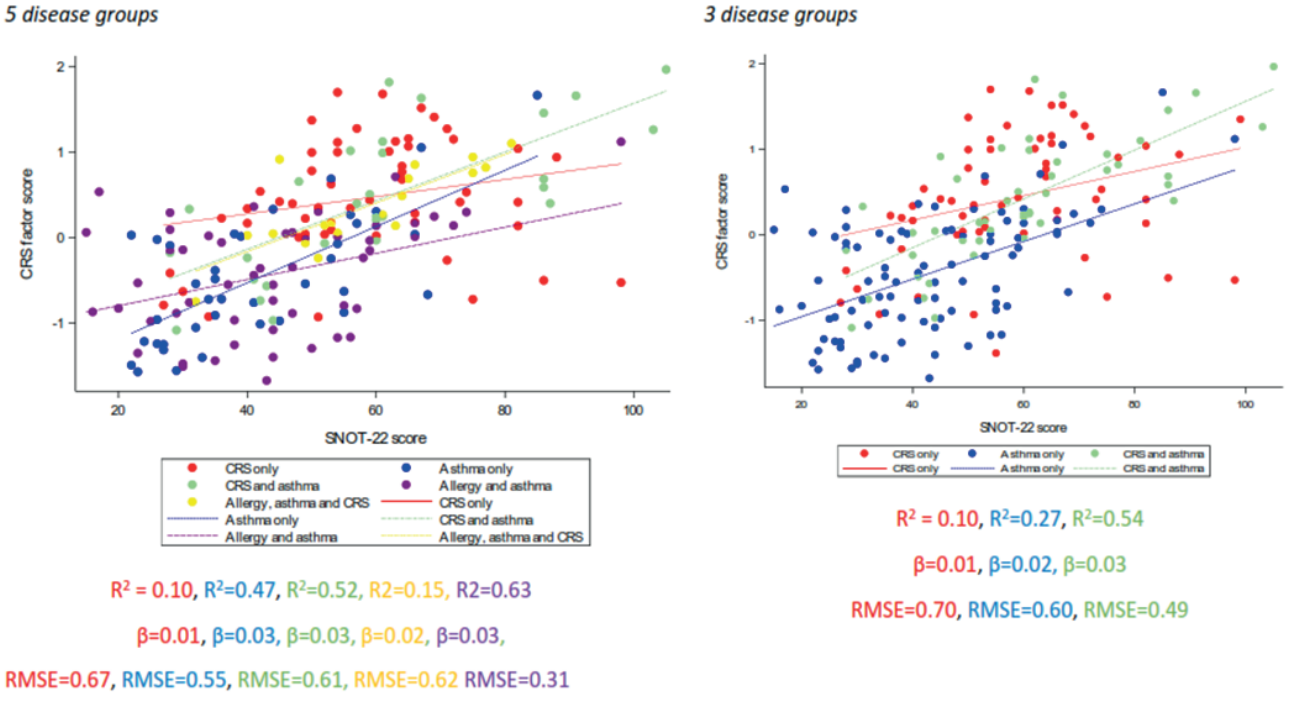


Figure 4. CRS sub-factor from the IRT model against SNOT-22. Figure A include all 5 disease groups, and Figure B the 3 groups of merged disease.

CRS factor to SNOT-22 there was a larger variation in the association depending on the disease group. Weakest association was observed for CRS only patients (R2 = 0.10) (Figure 4). The final STARR-15 questionnaire resulting from the above analyses and to be validated further using another patient sample is shown in Supplementary Table 2B and in Table 3.

Table 3. The STARR-15 questionnaire.

Item	During the past 12 weeks, how have you been bothered by the following symptoms:	No problem	A moderate problem	A severe problem
1	Itchy eyes or nose			
2	Sneezing			
3	Runny nose			
4	Seasonal variation in symptoms			
5	Facial pain			
6	Nasal blockage			
7	Decreased sense of smell			
8	Postnasal discharge			
9	Snoring			
10	Productive cough			
11	Cough			
12	Dyspnea/shortness of breath/difficulties breathing			
13	Wheezing			
14	Chest tightness			
15	Difficulties doing sports			

Discussion

In this survey, we examined a bucket of upper and lower respiratory questions and complains, in a relevant group of patients diagnosed in secondary care prior to inclusion, and we succeeded in the development of global airways standard test with 15 items. The 15 items were selected resulting from analyses using a data-driven approach and by applying our knowledge from more than 20 years in the clinic. Interestingly these 15 included symptoms are in alliance with symptoms suggested by GINA [17], EPOS2020 [18] and ARIA [19]. All patients were suffering from either allergic rhinitis, CRS and/or asthma and were diagnosed in rhinology or pulmonology setting, with interest in global airways. We found a large overlap in the responses to this questionnaire among patients with the three diseases, which supports the concept of global airway disease possibly with similar inflammatory mechanisms; however, this complicates the diagnostic potential of a global airway questionnaire. On the other hand, this STARR-15 tool provides the clinician with a reasonable indication of upper and lower airway symptoms. In case of one or more positive responses occurs, patients should thus be examined systematically to identify global airway disease [20].
The median ACQ-5 score was over 1.5 and the median SNOT22 score was above 60 point, and the majority of the patients had CRSwNP (>90%) indicating somewhat uncontrolled diseases with current respiratory symptoms during both 1 and 2 weeks. Furthermore, more than half of the asthma patients suffered from upper airway diseases as well, and likewise more than half of the patients with CRS, suffered from lower airway disease. Therefore, it is important, to develop an easy-to-use tool, which can enlighten the clinician of double disease. The ACQ questionnaire is widely used in asthma and allergy clinics as the most valid and robust tool [5], furthermore ACQ was used in the present study, as ACQ correlated with level of GINA in real life setting [21] and are used in severe asthma clinic, although it might be troublesome in an ENT clinic or in a general clinic where the patients do not have any knowledge of asthma, as they have respiratory symptoms only, but no diagnose of asthma. Moreover, the SNOT-22 score is not specific enough and consequently, an asthma patient can obtain a higher SNOT-22 score without having CRS. In a former study of CRS performed in specialist ENT clinic out-side hospital, we found 40% had asthma, of whom 50% did not know about having asthma on top of CRS [15], similarly in patients referred for nasal surgery in hospital setting [22]. The ENT surgeon was not aware of current double disease, which support the need for focus on global airways. We developed a 15-item questionnaire, STARR-15, that is thought to be used in clinic setting to screen for possible co-morbidity. Traditionally pulmonologist use to be more aware of allergic rhinitis symptoms [23] and need of treatment of airway allergies, whereas the knowledge of CRS are limited. It is evident that the upper and lower airways influence on another and both should be optimally treated, this awareness of triple disease is also important in general praxis, where the majority of patients are taken care of. Of the 15-item questionnaire, three items pointed in the direction of variable upper airway disease, related to histamine induced symptoms, five turned out to point in the direction of chronic upper respiratory disease, and lastly six pointed in the direction of lower airway disease. Interestingly,

cough was included both as productive cough as part of the claims among the patients suffering of CRS and cough as part of asthma. This is also knowledge supported by the clinical and scientific experience [24, 25], where the productive cough might be due post-nasal drip, where the dry cough might be signs of hyperresponsiveness. Some questions, which were less associated with the new STARR-15 questionnaire developed through analysis of 49 items were the questions concerning sleep, nighttime awakenings, and daytime sleepiness. Questions concerning sleep are of importance, as nighttime awakenings in asthma are related with substantial uncontrolled disease. Sleep could have been importance in evaluation of severity of both asthma and CRS, but the current questionnaire did not support the possibility of grading the severity of the global airway's diseases. Likewise, another question, which was erased during analysis was "exercise" or "physical activity". However, all three patient categories complain of exercise limitation to some degree by responding on the question "difficulties doing sport" which was included in the STARR-15, on behalf of the asthma group. Physical limitations is in alliance with the symptoms suggested in both GINA guidelines [17] and EPOS2020 [18]. Lastly, "facial pain" was also eliminated from the questionnaire, during the analysis. However, facial pain is a diagnostic criterion in the EPOS2020 evaluation of patients with CRS [18, 20]. We therefore included this question, independent of the deletion through the analyses. When testing patients, it seems to be possible to screen for upper and lower airway disease by the STARR-15 questionnaire, it was however, not possible in the current set-up to diagnose the two or three diseases, as the diagnosis was already known. Furthermore, although the primary aim was to include a severity score in the current global airway questionnaire, the STARR-15 test was not able to examine the degree of disease severity.
The strengths of the current questionnaire are that it is a symptom-based test, asking for respiratory complains, without naming allergy, CRS or asthma. The questionnaire is manageable without an excess of questions and calculations. No arithmetic's are needed. This makes our questionnaire more usable in several settings, that being upper or lower respiratory specialist clinics, as well as in general practice. The focus is building up awareness of co-morbidity in the global airways. We were inspired by the paper "Developing a valid patient-reported outcome measure" by Rothrock et al. [26] and their suggestion for how to develop a PROM. Our starting point was that there's a need for a new PROM, and for the present study, we have completed the phases of item generation, item improvement, consolidate revisions, initial testing and analysis and finalization stages of the PROM development. We still need to complete the phases of clinical validation studies and the resulting ongoing instrument improvement.

A limitation of our study is the selection of patients, who were already followed and diagnosed by clinicians in either an ENT with endoscopy setting or pulmonary with asthma provocation and allergy testing setting. Referral were different in time, and therefore, the absolute values measured at referral were not included in the present study. This will most likely have resulted in patients being more aware of symptoms related to their underlying disease in either upper or lower airways which will in turn have affected their responses. The selection of patients without a focus on allergic rhinitis only (five/five patients with AR only were included) may also explain the low discriminative ability of the allergic rhinitis sub-factor in our IRT analyses. Furthermore, only three items were included in the allergic rhinitis sub-factor, which may also have hampered the internal consistency that was lower than for the other two sub-factors. In a subsequent/future validation study, the questionnaire should be evaluated in a group of patients newly referred to the GP or specialist setting, and they should be undiagnosed, prior to filling out the questionnaire. It will also be important to include a group of patients with a broader distribution of severity of disease for all three disease groups (allergic rhinitis, CRS, asthma) ranging from no disease (healthy controls) to severe disease, although the patients included had uncontrolled disease (ACQ 1.5 an SNOT22 60).
Another limitation of our first attempt to develop a global airways questionnaire was the selection of too many response categories to each item. Furthermore, although 200 patients participated in the survey, it might have been too few for the item response theory analyses. We used several questions concerning seasonal variation suggested from the ARIA guidelines [27], but in this kind of survey, it might have been better to ask for seasonal variation as such or no variation, as we found no differences between all the different questions of variation.
Several key validity indicators, such as reliability and responsiveness, were not considered in the present study. The focus of the present study was to take the first steps in designing a PROM that can set the focus of both upper and lower disease. It is therefore important to continue developing this disease management tool, to ensure one tool to cover all demands, and a future validation study is therefore warranted. This will be performed using another patient sample, and with a focus on recruiting patients with different levels of severity of disease in order to extend our understanding of how well the questionnaire performs. New analyses of the psychometric properties of the sub-factors and the items will also be necessary to conduct to evaluate the performance of the scale.

Conclusion

Our new PROMs questionnaire STARR-15, is designed to be used in rhinology, pulmonology and allergology as well as GP settings, when examining patients with Type 2 inflammation associated respiratory complains as the STARR-15 can facilitate

the awareness of the diseases being in both upper and lower airways. In parallel with the introduction of biologics for Type 2 global airways inflammation the STARR-15 may have an important role representing a PROM embracing the global airways.

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Authorship contribution

VB, KA, CvB, SH have developed the project, VB and KA have examined all patients. SH and JP have perfromed statistical analysis. VB, KA, CvB, SH and JP have written and reviewed the manuscript.

Conflict of interest

No conflict of interest.

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