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The relevance of patient-reported outcomes in a grass pollen immunotherapy trial in children and adolescents with rhinoconjunctivitis

Esther Röder^{1,2}, Marjolein Y. Berger^{2,3}, Wim C. J. Hop⁴, Hans de Groot⁵ & Roy Gerth van Wijk¹

¹Department of Allergology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands; ²Department of General Practice, Erasmus MC-University Medical Center, Rotterdam, The Netherlands; ³Department of General Practice, University Medical Center Groningen, Groningen, The Netherlands; ⁴Department of Biostatistics, Erasmus MC-University Medical Center, Rotterdam, The Netherlands; ⁵Department of Pediatric Allergology, Reinier de Graaf Groep, Delft, The Netherlands

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Keywords

allergic rhinitis; child; adolescent; grass pollen; patient-reported outcome; quality of life; diary card.

Correspondence

Roy Gerth van Wijk, Erasmus MC, Department of Allergology (GK 324), PO Box 2040, 3000 CA Rotterdam, The Netherlands.
Tel.: +31 10 70 33981
Fax: +31 10 70 34202
E-mail: r.gerthvanwijk@erasmusmc.nl

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Abstract

Background: Patient-reported outcomes (PROs) are the only instruments available to assess the efficacy of an intervention in patients with allergic rhinoconjunctivitis. As allergic rhinoconjunctivitis is a systemic disease, it is now recommended to use not only PROs focusing at classical symptoms, but also health-related quality of life (HRQL) instruments in immunotherapy trials.

Methods: A previously published immunotherapy trial in children and adolescents (6–18 yr) with hay fever provided us with data to assess the relevance of two of these additional outcome measures, the disease-specific rhinoconjunctivitis quality of life questionnaire (RQLQ) and the generic COOP/WONCA-charts (CWC). A PRO was considered relevant if it was responsive to pollen exposure and at least had a moderate correlation with the classical symptoms of allergic rhinoconjunctivitis. Furthermore, we evaluated a post-season PRO, that is, a global assessment of symptoms (GAS). This assessment is used in clinical trials as a tool for selecting participants with sufficient symptoms and in daily practice to evaluate the patient's complaints during the preceding season. We assessed the correlation of this retrospective score with the actual symptoms during the previous pollen season.

Results: Data from 36 children and 63 adolescents were analysed. On the basis of the total scores of the paediatric and adolescent version of the RQLQ, both questionnaires were considered relevant as they were responsive to exposure and showed a moderate to strong correlation with the rhinoconjunctivitis symptoms. However, in both children and adolescents, 40% of the RQLQ items were not relevant according to our definition. The CWC as a whole and the separate charts appear less relevant because of the weak correlations with the daily symptom score from the diary. The correlation between our post-season GAS and the in season daily symptom score was weak.

Conclusion: The paediatric and adolescent RQLQ are relevant, but could be shortened as they contain a substantial number of irrelevant items. The CWC are not relevant in the monitoring of children and adolescents with allergic rhinoconjunctivitis caused by grass pollen. The retrospective GAS does not sufficiently reflect the actual symptoms during the preceding season.

Abbreviations

Δ, changes of scores between high and low pollen period; AdolRQLQ, adolescent rhinoconjunctivitis quality of life questionnaire; CWC, COOP/WONCA-charts; DC, diary card; GA²LEN, global allergy and asthma european network; GAS, global assessment of symptoms; HRQL, Health-related quality of life; MID, minimal important difference; PRO, patient-reported outcome; PRQLQ, paediatric rhinoconjunctivitis quality of life questionnaire; RCT, randomized controlled trial; RQLQ, rhinoconjunctivitis quality of life questionnaire; WAO, World Allergy Organization.

Allergy is a systemic disease. Patients with allergic rhinoconjunctivitis do not only suffer from nose and eye symptoms, but also suffer from general complaints such as fatigue, sleeping problems and difficulty concentrating (1). As a result, allergic rhinoconjunctivitis interferes with many aspects of daily life (2). Focusing on symptoms alone might therefore not fully reflect the impact of this allergic disease. To estimate the burden of a disease as perceived by the patient, health-related quality of life (HRQL) can be assessed. Nowadays, the demonstration of the effects on quality of life in immunotherapy trials is recommended by the World Allergy Organization (WAO) and the Global Allergy and Asthma European Network (GA²LEN) (3, 4). So far, quality of life outcome measures were included in only a few immunotherapy trials with inhalant allergens in children (5–7). Although well accepted, it is not known how relevant the inclusion of these HRQL instruments is. A previously published immunotherapy trial in children and adolescents (6–18 yr) with hay fever provided us with data to investigate the relevance of a disease-specific and a general HRQL measure. For the assessment of the disease-specific quality of life, the most widely used and validated paediatric and adolescent version of the rhinoconjunctivitis quality of life questionnaire (RQLQ) was used (8, 9). Several generic quality of life questionnaires for children have been developed. However, most lists are long (up to 153 items), the applicability in different cultures is often unknown and none of the lists are widely used (10). We explored the use of the COOP/WONCA-charts (CWC) (11–13) in our population, in spite of the fact that this instrument has been validated for adults only and not for children or adolescents. The CWC measure the functional health status and have three major advantages. First, it is a short questionnaire consisting of six questions. Secondly, the answers are illustrated with a simple drawing, which might facilitate the use in our age group. Thirdly, the CWC appear to have low susceptibility to cultural differences (13).

In addition to these two in season patient-reported outcomes (PROs), we also asked the participants to complete a global assessment of symptoms after the grass pollen season to evaluate their complaints in the preceding months. This assessment is often used as a tool for selecting participants with sufficient symptoms in clinical trials. In daily clinical practice, physicians often rely on such retrospective statements from their patients to evaluate symptoms and treatment effects during the previous season.

In this study, we first aimed to assess the relevance of the HRQL PROs by studying the influence of pollen exposure and the relationship with the classical features of allergic rhinoconjunctivitis. A PRO was considered relevant if it was responsive to pollen exposure and at least had a moderate correlation with the daily symptom score. Secondly, we were also interested in the most important impairments as perceived by the participants in a low and a high pollen period as well as possible differences between periods. Finally, we investigated how well the retrospective global assessment of symptoms represented the actual complaints during the season. We considered the retrospective score to be an adequate

reflection of these complaints if the correlation with the daily symptom score was strong.

Methods

Participants

A detailed description of the randomized double-blind placebo-controlled trial has been reported elsewhere (5). A total of 204 children and adolescents aged 6–18 yr (mean age [SD] 12.9 [2.8] yr; 114 boys and 90 girls) with hay fever were enrolled from general family practices in the Netherlands. All participants had IgE antibodies to grass pollen ≥ 0.7 kU/l (Phadia) and a history of rhinoconjunctivitis. The latter was assessed by a retrospective symptom score: participants scored five symptoms (sneezing, itching nose, watery running nose, nasal blockage and itching eyes) during the previous grass pollen season (May–August) on a 0–3 scale (0 = none, 1 = mild, 2 = moderate and 3 = severe; maximum total score = 15). Participants with a score ≥ 5 were included.

Participants with daily pulmonary inhaled glucocorticoids during ≥ 3 months in the preceding year, or immunotherapy in the preceding 3 yr were excluded. Other exclusion criteria were sensitization (specific IgE ≥ 0.7 kU/l; Phadia) to pets present in the family home, nasal abnormalities requiring surgery and general contra-indications for immunotherapy (14). The participants were allowed to be sensitized to birch pollen and house dust mite. In the Netherlands, the birch pollen season precedes the grass pollen season, whereas the peak of the house dust mite season follows the grass pollen season.

Participants were included in two consecutive years. Both cohorts entered the trial and started treatment after the grass pollen season, in September–October and participated for 2 yr. Data from the overlapping year (i.e. the second pollen season of the first cohort and the first pollen season of the second cohort) were selected for the present analysis. Most importantly, data from both treatment groups were pooled, as there were no differences between treatment groups in the primary and secondary outcome measures of the trial, including symptom score and disease-specific quality of life (5).

Exposure

Daily pollen counts were obtained from the pollen monitoring station in Leiden (Burkard pollen trap, Leiden University Medical Centre, the Netherlands). These counts represent the pollen exposure in the region where the participants were recruited and evaluated. In the Netherlands, the grass pollen season starts in May, with low pollen counts, and the highest pollen counts are recorded in June.

Patient-reported outcomes

In general, the PROs were interview-administered in children and self-administered in adolescents. A parent or research assistant was allowed to assist, provided that they would not influence the response of the participant. The study design is presented in Fig. 1.

Rhinoconjunctivitis-specific quality of life questionnaire (RQLQ)

The disease-specific quality of life was assessed using the validated paediatric (6–11 yr; PRQLQ) (8) and adolescent (12–17 yr; AdolRQLQ) (9) rhinoconjunctivitis quality of life questionnaire. The PRQLQ consists of 23 items in five domains: 'nose symptoms', 'eye symptoms', 'practical problems', 'activities' and 'other symptoms'. The AdolRQLQ consist of 25 items in six domains: 'nose symptoms', 'eye symptoms', 'practical problems', 'activities', 'emotional symptoms' and 'non-hay fever symptoms'. For the domain 'activities', the adolescents identified three activities from a predefined list that were performed on a regular basis and that were impaired by their nose/eye symptoms. These activities were identified at the first visit and remained specific for that participant throughout the trial.

The participants were asked to recall their experiences during the previous 7 days. Each item is scored on a 7-point ordinal scale ranging from 0 ('no impairment') to 6 ('maximum impairment'). The RQLQs were completed during two house visits: one in a period with low exposure (May) and the other in a period with high pollen counts (June). Only complete questionnaires were analysed. The mean overall score and the mean score for each domain separately in the low and high pollen period were calculated (range 0–6).

COOP/WONCA-charts (CWC)

The CWC measure six core aspects of functional status: 'physical fitness', 'feelings', 'daily activities', 'social activities', 'change in health' and 'overall health'. Each domain is rated on a 5-point ordinal scale ranging from one ('no limitation at all') to five ('severely limited'); for the domain 'change in health' score one indicates 'much better' and score five 'much worse'. The recall period is 14 days (13). The questionnaire was completed during the same visits as the RQLQ and only complete questionnaires were analysed. The mean overall score and the mean score for each domain separately in the low and high pollen period were calculated (range 1–5).

Diary card (DC)

Participants scored five symptoms – sneezing, itching nose, watery running nose, nasal blockage and itching eyes – on a 0–3 scale (0 = none, 1 = mild, 2 = moderate and 3 = severe) on diary cards during the period May–August

31. For the comparison with the RQLQ, the 7 days in the diary card that corresponded with the recall period of the RQLQ were analysed, provided that on at least 4 days all five symptoms were recorded. For the comparison with the CWC, the 14 days in the diary card that corresponded with the recall period of the CWC were analysed, provided that on at least 8 days all five symptoms were recorded. The mean total symptom score (range 0–15), the mean total nose symptom score (range 0–12) and the mean total eye symptom score (range 0–3) during the low and high pollen period were calculated. Also, the mean total symptom score for the whole season (May–August) was calculated (range 0–15). For the latter analysis, only pollen relevant days were analysed (i.e. days with a pollen count that exceeded the median pollen count of that season), provided that on at least 50% of the days all five symptoms were recorded.

Global assessment of symptoms

After the grass pollen season, the participants evaluated their complaints during the previous season (i.e. May–August in the second year of the first cohort and the first year of the second cohort) by scoring five symptoms – sneezing, itching nose, watery running nose, nasal blockage and itching eyes on a 0–3 scale (0 = none, 1 = mild, 2 = moderate and 3 = severe). The mean total score was calculated (range 0–15).

Statistical analysis

Only participants with an analysable RQLQ, CWC and DC, in both the RQLQ-week and CWC-weeks, were analysed. Children (6–11 yr) and adolescents (12–17 yr) were analysed separately, because the PRQLQ and AdolRQLQ contain different items and therefore cannot be combined.

Comparison of the scores between the low and high pollen period was performed using the paired Wilcoxon test. The limit of significance in these comparisons was considered $p = 0.05$ (two-sided).

The minimal important difference (MID) for the RQLQ is 0.5 (15). Changes larger than 1.0 and 1.5 are considered moderate and large differences, respectively (15). The MID for the CWC is unknown.

The correlation between the different PROs was analysed using Spearman's correlation. In view of the multitude of

Figure 1 Study design. CWC, COOP/WONCA-charts; DC, Diary Card; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; GAS, Global assessment of symptoms.

correlations analysed, we set the level of significance at $p = 0.01$ (two-sided) in these analyses. A correlation coefficient (r) ≥ 0.7 is generally considered to represent a strong correlation, a coefficient between 0.5 and 0.7 a moderate correlation, between 0.3 and 0.5 a weak correlation and below 0.3 as little if any correlation (16).

To identify the most important impairments as perceived by the patients in both periods, the items and domains of the HRQL questionnaires were ranked according to severity (i.e. from highest to lowest mean score).

Determination of relevance

The overall RQLQ and CWC were considered relevant if the following conditions were met:

1. The total score was responsive to exposure: the score in the high pollen period was higher compared with the score in the low pollen period and this difference was statistically significant and, in case, a minimal important difference (MID) is known, also clinically relevant.
2. The total score correlated with the rhinoconjunctivitis symptoms: the score in the high pollen period had at least a statistically significant moderate correlation with the DC total score in the same period and the change in the HRQL total score had at least a statistically significant moderate correlation with the change in DC total score (changes in outcomes are represented by the symbol ' Δ ' in text and tables).

The same conditions were used for the determination of the relevance of the separate RQLQ and CWC-domains. Only condition 1 was considered for the RQLQ items.

The retrospective GAS was considered a relevant representative of the actual complaints during the season if the correlation with the mean total symptom score of the DC for the whole season was at least strong.

Results

At the beginning of the grass pollen season, 55 children and 116 adolescents were participating in the study. Owing to drop-out and incomplete diary cards and/or questionnaires, 18 children and 53 adolescents could not reliably be evaluated and were excluded from the analyses. The data from one child were not analysed because both house visits took place in a high pollen period. In total, 36 children (mean age [SD] 9.4 [1.3] yr; 25 boys/11 girls) and 63 adolescents (mean age [SD] 14.0 [1.7] yr; 33 boys/30 girls) were analysed. In both age groups, there were no significant differences with respect to age, gender and the retrospective symptom score at the start of the trial between participants who were included in the analyses compared with those who were excluded.

Relevance of the RQLQ and CWC

For all children and adolescents, the mean grass pollen count in the evaluated RQLQ-week and CWC-weeks was higher in the high pollen period. The total scores of all PROs (RQLQ, CWC and related DCs) were significantly higher in the high pollen period in both age groups (Table 1 and E1).

The change in total scores (Δ) of the PRQLQ and Adol-RQLQ reached the MID-limit. The total scores of the RQLQs in the high pollen period showed a strong correlation with the DC total scores and the changes in scores of both RQLQs showed a moderate correlation with the changes in DC total scores (Table 2, column 'DC total'). Consequently, the overall PRQLQ and AdolRQLQ are considered relevant.

The PRQLQ domain 'other symptoms' and the Adol-RQLQ domains 'non-hay fever symptoms' and 'emotional symptoms' did not reach the MID threshold, nor did they fulfil our criteria for the correlations. Therefore, those domains are not considered relevant. We found strong associations ($r \geq 0.70$) between the DC and the RQLQ domains covering nasal or eye symptoms. If RQLQ total scores are calculated without the nose and eye symptom domains, the changes in both adjusted total scores were significant ($p \leq 0.01$). The change in the adjusted total score of the PRQLQ was 0.7 and the difference in the adjusted Adol-RQLQ total score just failed to reach the MID-limit. The correlations with the DC total scores were also lower, but still significant (Children: low pollen $r = 0.44$ /high pollen $r = 0.65/\Delta r = 0.60$. Adolescents: low pollen $r = 0.67$ /high pollen $r = 0.68/\Delta r = 0.57$. All p -values ≤ 0.01).

As stated before, the CWC total scores were responsive to exposure. This was also the case for the domain 'overall health' in both age groups and the domain 'change in health' in children and 'daily activities' in adolescents (Table E1). Analysis of the relationship between the CWC and DC yielded mainly weak correlations ($r < 0.50$; Table E2, column 'DC total'). Therefore, the overall CWC and its separate domains cannot be considered relevant in both age groups, although in children the CWC total score and the domain 'overall health' just failed to meet the conditions concerning the correlation with symptoms.

We also investigated the correlation between the separate DC domains 'nose symptoms' and 'eye symptom' and the total and domain scores of both HRQLs (Table 2 and E2, column 'DC-nose' and 'DC-eye'). The results of these analyses correspond with the results of the correlations between the DC total score and the HRQLs.

All RQLQ items had a higher mean score in the high pollen period, except the item 'headache' in the adolescent group. Changes in 4 of 23 PRQLQ items and 10 of 25 Adol-RQLQ items were below the MID-limit of 0.5. In children, 7 items of various domains fulfilled the criterion of a moderate change, whereas in adolescents only the item 'red eyes' reached this limit. The change in PRQLQ item 'take medications' was the only large difference. For an item to be considered relevant, the change in scores had to reach the MID-limit and be statistically significant. In children, 13 of the 23 items met these criteria, and in adolescents 15 of 25.

Most important impairments

In both age groups and both pollen periods the RQLQ domain 'nose symptoms' had the highest score followed by the practical problems domain in children and the activity domain in adolescents (Table 1).

Table 1 Paediatric and adolescent rhinoconjunctivitis quality of life questionnaire: Relevance and most important impairments

	Low pollen		High pollen		Δ		
(A) 6–11 yr							
Pollen	Median (range) 3.0 (2.4 to 24.7)		Median (range) 93.7 (57.0 to 239.3)				
DC	Mean (range)		Mean (range)		Mean (range)	p value	
Total	2.5 (0 to 9.6)		4.3 (0 to 10.6)		1.8 (–6.0 to 10.4)	#	
RQLQ	Mean (range)	Rank	Mean (range)	Rank	Mean (range)	p value	
Total	1.1 (0.3 to 2.8)		1.8 (0.1 to 5.4)		0.8 (–0.9 to 4.6)	#	R
Domain							
Nose symptoms	1.9 (0.5 to 4.0)	1	2.8 (0.3 to 6.0)	1	0.9 (–1.8 to 4.3)	#	R
Practical problems	1.2 (0 to 3.8)	2	2.0 (0 to 5.8)	2	0.8 (–1.4 to 5.2)	#	R
Other symptoms	0.9 (0 to 2.2)	3	1.3 (0 to 4.0)	5	0.4 (–0.8 to 3.0)	#	–
Eye symptoms	0.8 (0 to 3.3)	4	1.9 (0 to 5.5)	3	1.0 (–1.3 to 5.0)	#	R
Activities	0.6 (0 to 3.3)	5	1.4 (0 to 6.0)	4	0.8 (–1.8 to 6.0)	#	R
Item†							
Sneezing* (N)	2.7 (0 to 5)	1	3.3 (1 to 6)	2	0.6 (–4 to 4)	ns	–
Rub nose/eyes (PR)	2.4 (0 to 6)	2	3.4 (0 to 6)	1	1.1 (–4 to 6)	\$	R
Thirst (O)	2.4 (0 to 6)	3	3.0 (0 to 6)	3	0.7 (–3 to 5)	ns	–
Itchy eyes* (E)	2.0 (0 to 6)	4	2.9 (0 to 6)	4	0.9 (–5 to 4)	#	R
Itchy nose* (N)	1.8 (0 to 5)	5	2.6 (0 to 6)	6	0.8 (–2 to 4)	\$	R
Blow nose (PR)	1.8 (0 to 6)	6	2.5 (0 to 6)	8	0.7 (–5 to 5)	ns	–
Stuffy/blocked nose* (N)	1.7 (0 to 5)	7	2.9 (0 to 6)	5	1.2 (–2 to 5)	#	R
Playing outdoors (A)	1.3 (0 to 6)	8	2.5 (0 to 6)	7	1.2 (–2 to 6)	#	R
Runny nose* (N)	1.2 (0 to 6)	9	2.4 (0 to 6)	9	1.2 (–3 to 5)	#	R
Take medications (PR)	0.9 (0 to 5)	10	2.4 (0 to 6)	10	1.5 (–3 to 6)	#	R
Headache (O)	0.9 (0 to 5)	11	1.0 (0 to 4)	17	0.1 (–2 to 4)	ns	–
Carry kleenex (PR)	0.8 (0 to 6)	12	1.5 (0 to 6)	12	0.8 (–3 to 6)	\$	R
Scratchy/itchy throat (O)	0.7 (0 to 6)	13	1.3 (0 to 6)	15	0.6 (–3 to 6)	ns	–
Watery eyes (E)	0.6 (0 to 5)	14	1.8 (0 to 6)	11	1.3 (–1 to 5)	#	R
Sore eyes (E)	0.5 (0 to 3)	15	1.2 (0 to 6)	16	0.7 (–2 to 6)	\$	R
Hard to get to sleep (A)	0.5 (0 to 2)	16	1.3 (0 to 6)	14	0.8 (–2 to 6)	#	R
Tired (O)	0.4 (0 to 2)	17	0.9 (0 to 5)	18	0.5 (–2 to 4)	\$	R
Do not feel well all over (O)	0.4 (0 to 2)	18	0.7 (0 to 6)	22	0.3 (–1 to 6)	ns	–
Hard to pay attention (A)	0.4 (0 to 2)	19	0.9 (0 to 6)	19	0.5 (–2 to 6)	ns	–
Irritable (O)	0.3 (0 to 3)	20	0.8 (0 to 5)	21	0.4 (–1 to 4)	\$	–
Wake up during night (A)	0.3 (0 to 3)	21	0.9 (0 to 6)	20	0.5 (–2 to 6)	ns	–
Swollen/puffy eyes (E)	0.3 (0 to 2)	22	1.5 (0 to 5)	13	1.2 (–1 to 5)	#	R
Feel embarrassed (PR)	0.1 (0 to 2)	23	0.3 (0 to 5)	23	0.1 (–1 to 5)	ns	–

N = 36; Low pollen, May; High pollen, June; Δ , Difference: High pollen minus Low pollen.

DC, Diary Card (scale 0–15). RQLQ, Paediatric rhinoconjunctivitis quality of life questionnaire (scale 0–6, a higher score indicates a lower quality of life).

*Symptoms also recorded in the diary card.

†Corresponding domains: A = Activities; E = Eye symptoms; N = Nose symptoms; O = Other symptoms; PR = Practical problems.

#p ≤ 0.01; \$p ≤ 0.05.

R, relevant; for the total and domain scores, the results from the correlation analyses (see Table 2) were also incorporated.

Looking at the RQLQ items, there were no major differences between the low and high pollen period. The PRQLQ and AdolRQLQ items with the highest mean scores were the five nose and eye symptoms that were also recorded in the DC, practical problems (like ‘rub eyes/nose’ and ‘blow nose’) and activities. Notable is the high score for ‘thirst’ in children, rank three in both periods.

In both age groups and in both pollen periods, the CWC-domains ‘change in health’ and ‘overall health’ are the items with the highest mean scores (Table E1).

Relevance of the GAS

The mean GAS in children and adolescents was 6.5 (range 1–12) and 6.8 (range 0–13), respectively. The mean DC total

Table 1 (Continued)

	Low pollen		High pollen		Δ		
(B) 12–17 yr							
Pollen	Median (range) 3.0 (2.4 to 24.7)		Median (range) 87.0 (46.3 to 239.3)				
DC	Mean (range)		Mean (range)		Mean (range)	p value	
Total	3.2 (0 to 10.0)		4.7 (0 to 12.0)		1.5 (–3.6 to 7.9)	#	
RQLQ	Mean (range)	Rank	Mean (range)	Rank	Mean (range)	p value	R
Total	1.3 (0 to 4.7)		1.8 (0 to 4.5)		0.5 (–1.5 to 3.2)	#	R
Domain							
Nose symptoms	2.2 (0 to 6.0)	1	2.8 (0 to 6.0)	1	0.7 (–2.5 to 4.8)	#	R
Activities	1.9 (0 to 5.0)	2	2.4 (0 to 6.0)	2	0.5 (–2.0 to 4.7)	#	R
Eye symptoms	1.4 (0 to 5.5)	3	2.3 (0 to 6.0)	3	0.9 (–2.8 to 5.8)	#	R
Practical problems	1.3 (0 to 5.4)	4	2.0 (0 to 5.4)	4	0.7 (–2.0 to 3.6)	#	R
Non-hay fever symptoms	0.8 (0 to 5.0)	5	1.1 (0 to 5.0)	5	0.3 (–3.0 to 2.4)	#	–
Emotional symptoms	0.4 (0 to 3.5)	6	0.6 (0 to 4.3)	6	0.2 (–1.3 to 3.0)	\$	–
Item†							
Rub nose/eyes (PR)	2.7 (0 to 6)	1	3.4 (0 to 6)	1	0.7 (–3 to 5)	#	R
Sneezing* (N)	2.5 (0 to 6)	2	3.1 (0 to 6)	2	0.5 (–2 to 4)	#	R
Itchy eyes* (E)	2.2 (0 to 6)	3	3.0 (0 to 6)	3	0.8 (–4 to 6)	#	R
Stuffy/blocked nose* (N)	2.1 (0 to 6)	4	2.9 (0 to 6)	4	0.8 (–3 to 6)	\$	R
Itchy nose* (N)	2.1 (0 to 6)	5	2.8 (0 to 6)	5	0.7 (–3 to 6)	#	R
Activity 2 (A)	2.0 (0 to 6)	6	2.5 (0 to 6)	8	0.5 (–3 to 6)	ns	–
Runny nose* (N)	1.9 (0 to 6)	7	2.5 (0 to 6)	6	0.6 (–5 to 6)	\$	R
Activity 1 (A)	1.9 (0 to 6)	8	2.3 (0 to 6)	12	0.4 (–3 to 5)	\$	–
Activity 3 (A)	1.7 (0 to 6)	9	2.3 (0 to 6)	11	0.6 (–3 to 6)	#	R
Blow nose (PR)	1.7 (0 to 6)	10	2.5 (0 to 6)	7	0.8 (–4 to 5)	#	R
Watery eyes (E)	1.6 (0 to 6)	11	2.4 (0 to 6)	9	0.8 (–4 to 6)	#	R
Carry kleenex (PR)	1.4 (0 to 6)	12	2.1 (0 to 6)	13	0.7 (–4 to 6)	#	R
Tired/worn out (NH)	1.2 (0 to 6)	13	1.3 (0 to 5)	17	0.1 (–4 to 4)	ns	–
Red eyes (E)	1.2 (0 to 5)	14	2.4 (0 to 6)	10	1.2 (–5 to 6)	#	R
Thirst (NH)	1.1 (0 to 6)	15	1.6 (0 to 6)	14	0.5 (–2 to 3)	#	R
Headache (NH)	0.8 (0 to 5)	16	0.8 (0 to 5)	22	–0.1 (–3 to 3)	ns	–
Irritable (F)	0.7 (0 to 5)	17	1.0 (0 to 6)	18	0.3 (–4 to 5)	ns	–
Swollen eyes (E)	0.7 (0 to 5)	18	1.4 (0 to 6)	15	0.8 (–5 to 6)	#	R
Lack of good night’s sleep (PR)	0.5 (0 to 6)	19	1.4 (0 to 6)	16	0.9 (–4 to 5)	#	R
Generally do not feel well (NH)	0.5 (0 to 5)	20	0.9 (0 to 5)	20	0.4 (–3 to 5)	\$	–
(school) work‡ (PR)	0.5 (0 to 6)	21	0.8 (0 to 5)	21	0.3 (–6 to 5)	\$	–
Can not concentrate (NH)	0.4 (0 to 6)	22	1.0 (0 to 5)	19	0.5 (–6 to 4)	#	R
Frustrated (F)	0.4 (0 to 5)	23	0.4 (0 to 5)	24	0.0 (–3 to 2)	ns	–
Restless (F)	0.3 (0 to 2)	24	0.7 (0 to 5)	23	0.4 (–2 to 5)	\$	–
Upset/embarrassed§ (F)	0.2 (0 to 2)	25	0.3 (0 to 6)	25	0.1 (–2 to 6)	ns	–

N = 63; Low pollen, May; High pollen, June; Δ , Difference: High pollen minus Low pollen.

DC, Diary card (scale 0–15); RQLQ, Adolescent rhinoconjunctivitis quality of life questionnaire (scale 0–6, a higher score indicates a lower quality of life).

*Symptoms also recorded in the diary card.

†corresponding domains: A = Activities; E = Eye symptoms; F = Emotional symptoms; N = Nose symptoms; NH = Non-hay fever symptoms; PR = Practical problems.

‡Complete description: unable to do (school) work as well as usual.

§Complete description: upset/embarrassed by other's response to your hay fever symptoms.

#p ≤ 0.01; p ≤ 0.05.

R, relevant; for the total and domain scores the results from the correlation analyses (see Table 2) were also incorporated.

symptom score in children and adolescents was 3.7 (range 0.6–8.2) and 3.8 (range 0.3–9.8), respectively. The correlation between the GAS and the DC total symptom score of the

whole season was 0.42 both in children and adolescents. The correlation between the GAS and other in season PRO total scores was lower, except for the RQLQ total score in the low

and high pollen period in adolescents ($r = 0.49$ and $r = 0.53$, respectively; Table 3).

Discussion

Patient-reported outcomes, which are subjective measures, are the only outcomes available to evaluate the effects of medication or other interventions in patients with allergic rhinoconjunctivitis. The acknowledgement that allergic rhinoconjunctivitis can significantly influence the patient's quality of life because of its impact on daily activities,

school and work performance (1) led to the development of disease-specific questionnaires. Rhinoconjunctivitis quality of life questionnaires (RQLQs) designed for adults (17), adolescents (9) and children (8) are now available. The items of the RQLQs reflect the most important impairments as reported by patients in each specific age group. Nowadays, assessment of disease-specific quality of life is an essential part of randomized controlled trials (RCTs) in allergic rhinoconjunctivitis. On the other hand, generic quality of life instruments are not commonly used in these RCTs. Generic HRQL measures are less sensitive

Table 2 Correlation between diary card and paediatric and adolescent rhinoconjunctivitis quality of life questionnaire

				DC Total	DC Nose	DC Eye
RQLQ	6–11 yr	Total	Low pollen	0.64	0.62	–
			High pollen	0.74	0.72	0.67
			Δ	0.64	0.60	0.52
		Nose	Low pollen	0.64	0.67	–
			High pollen	0.74	0.75	0.57
			Δ	0.68	0.67	0.43
		Eye	Low pollen	0.51	–	0.75
			High pollen	0.64	0.57	0.74
			Δ	0.60	0.49	0.68
		Activities	Low pollen	–	–	–
			High pollen	0.58	0.58	0.50
			Δ	0.61	0.59	0.50
		Practical	Low pollen	–	–	–
			High pollen	0.67	0.65	0.62
			Δ	0.67	0.60	0.56
		Other	Low pollen	–	–	–
			High pollen	0.52	0.51	0.49
			Δ	–	–	–
	12–17 yr	Total	Low pollen	0.77	0.75	0.51
			High pollen	0.77	0.74	0.71
			Δ	0.68	0.68	0.54
		Nose	Low pollen	0.80	0.82	0.40
			High pollen	0.78	0.77	0.61
			Δ	0.67	0.71	0.44
		Eye	Low pollen	0.63	0.52	0.76
			High pollen	0.70	0.64	0.79
			Δ	0.69	0.62	0.70
		Activities	Low pollen	0.61	0.59	0.45
			High pollen	0.56	0.52	0.56
			Δ	0.55	0.52	0.53
		Practical	Low pollen	0.68	0.69	0.34
			High pollen	0.69	0.68	0.55
			Δ	0.55	0.59	0.33
		Emotional	Low pollen	0.40	0.40	–
			High pollen	0.49	0.48	0.37
			Δ	–	–	–
		Non-hay fever	Low pollen	0.41	0.39	–
			High pollen	0.61	0.58	0.58
			Δ	0.35	0.40	–

6–11 yr $n = 36$; 12–17 yr $n = 63$. In the rows labelled 'low pollen' and 'high pollen' the correlations are shown for the scores in May and June, respectively. In the rows labelled 'Δ', the correlations are shown for the changes (high pollen minus low pollen) of both scores.

Spearman's correlation; only significant correlations ($p \leq 0.01$) are shown.

DC, Diary card; RQLQ, Rhinoconjunctivitis quality of life questionnaire.

Table 3 Correlation between the global assessment of symptoms, diary card, rhinoconjunctivitis quality of life questionnaire and COOP/WONCA-charts

				GAS
6–11 yr	DC	Whole season		0.42
		Low pollen	RQLQ-week	–
			CWC-weeks	–
		high pollen	RQLQ-week	–
	RQLQ	low pollen		–
		high pollen		–
	CWC	low pollen		–
		high pollen		–
12–17 yr	DC	whole season		0.42
		low pollen	RQLQ-week	0.36
			CWC-weeks	0.37
		high pollen	RQLQ-week	0.41
	RQLQ	low pollen		0.49
		high pollen		0.53
	CWC	low pollen		–
		high pollen		0.36

6–11 yr n = 36; 12–17 yr n = 61. In the rows labelled 'whole season', 'low pollen' and 'high pollen', the correlations are shown for the total scores in May–August, May and June, respectively. Spearman's correlation; only significant correlations ($p \leq 0.01$) are shown. DC, Diary card; CWC, COOP/WONCA-charts; GAS, global assessment of symptoms; RQLQ, rhinoconjunctivitis quality of life questionnaire.

to capture small but important changes that may occur in the course of a disease, for instance before and after treatment. On the other hand, they can be used to compare the impairments caused by different diseases and some generic HRQL measures are used in cost-effectiveness analyses. In contrast to the disease-specific RQLQ, no widely accepted generic list is available for children. We wished to explore the properties of the CWC being a simple and short instrument. The CWC were developed as a screening instrument in general practice. If the responses indicate a decrease in health status, a longer and more sophisticated instrument can be used to get more precise information (11–13). As the CWC are validated for adults only, we did not incorporate the CWC in our analysis of the efficacy of sublingual immunotherapy in children and adolescents. However, the immunotherapy trial provided us with the opportunity to test the responsiveness to pollen exposure and to correlate the outcome of the CWC with rhinoconjunctivitis symptoms. In case of responsiveness and moderate correlation, a formal validation would be the next step.

In this study, we looked at the relevance of the RQLQ and CWC in an immunotherapy trial in young patients with hay fever. First, we evaluated the outcome measures in terms of responsiveness to pollen exposure. In our opinion, symptoms or problems not responding to increased pollen exposure are irrelevant in the context of well-established pollen allergy. All PROs appeared to be responsive to higher pollen

exposure. The clinical significance of the observed changes of the CWC cannot be estimated as information about the MID of this instrument is not available. The RQLQs showed heterogeneity in responsiveness. Although changes in total scores and most domains reached the limit of 0.5, one-sixth of differences in the PRQLQ items and almost one-third of the changes in AdolRQLQ items remained under the level of clinical significance.

Secondly, we expected a relationship with the classical symptoms of rhinoconjunctivitis as recorded with diary cards. It does not make sense to assess symptoms or problems that are apparently not related to the features of nasal disease. The PRQLQ and the AdolRQLQ both performed better than the CWC, with respect to the total scores as well as to the separate domains. The CWC showed predominantly weak correlations or no significant correlations with daily symptoms at all. The analysis of the different domains of both RQLQs however revealed again domains that did not fulfil the correlation criteria.

In a clinical trial, participants should not be burdened with questions that address the same aspects of a disease. In our study, we found strong correlations between the nasal and eye domains of the DC and the RQLQ. This is not unexpected, as answers to questions about severity, frequency and impact of symptoms – although differently phrased – will be inter-related, in particular if they are put to patients in the same time frame. When the nose and eye domains were removed from the RQLQs, the PRQLQ was still responsive to exposure, but the AdolRQLQ just failed to reach the MID-limit. As anticipated, the correlations with the DC were somewhat lower, but still highly significant. It would be interesting to investigate whether an adjusted version of the RQLQ without nose and eye symptoms might be a relevant addition to the DC in clinical trials. Another option to minimize overlap is replacing the diary card with the RQLQ and using the RQLQ as a primary outcome. In a GA²LEN paper on the conduct of immunotherapy trials, it was stated that HRQL measures may soon become primary outcomes (18). In contrast, the WAO stated on the same issue that this is not possible, partly because there is no accepted way of correcting the use of rescue medication (3). However, this is also true for the classical symptom scores as still no widely used standardized method of combining symptom severity and medication use is available. Recently, three interesting articles were published addressing these issues. Häfner et al. as well as Grouin et al. (19, 20) validated a new combined symptom-medication score. Franzke et al. (21) on the other hand, focussed on the patient's needs and benefits and developed a new instrument for the assessment of patient-defined benefit that can be used for the evaluation of allergic rhinitis treatments. Besides addressing the same issues in different questionnaires, asking questions that are not relevant should be avoided. In both age groups, 40% of the RQLQ items were not relevant. Removing these items from the questionnaires results in shorter lists with mere relevant questions, which will enhance compliance. For adults such a shortened version of the RQLQ, the mini-RQLQ, is already available (22). Furthermore, both PRQLQ and Adol-

RQLQ are developed by and validated in patients with pollen-induced allergic rhinitis. It has been suggested that the lists might be missing some important items for patients with persistent rhinitis caused by exposure to indoor allergens, such as snoring and mouth breathing (23). Therefore, it would be interesting to assess the relevance of the complete and/or shortened questionnaires in for instance house dust mite allergic patients.

Clinically relevant differences in symptom or HRQL scores can only be detected if patients with sufficient symptoms are included in a study. To select such patients a baseline period (i.e. observation during the season before randomization) could be used. In grass pollen immunotherapy trials, a baseline season is not mandatory, because of the variability in exposure between seasons (23). In some trials, participants are selected only on the basis of having experienced rhinoconjunctivitis symptoms during the previous year(s) (24, 25). Others also assess the severity of symptoms by using a retrospective assessment of symptoms during the previous season to select patients with sufficient symptoms (26). In our study, the GAS overrated the severity of the actual symptoms during the season and the correlation between the GAS and the DC was statistically significant, but not strong. This result resembles the outcome of a study performed in adults where the retrospective assessment also overrated the severity of and only had a fair to moderate agreement with the in season assessment (27). The phrasing of the GAS is not the same in all trials. For instance, Wahn et al. (26) asked the patients to assess the worst symptoms during the season and not evaluate the symptoms during the whole of the season. Further research is needed to determine whether rephrasing the questions might improve the correlation of this retrospective assessment with the in season symptom scores. Our findings on the GAS have implications going beyond RCTs. Physicians often see patients after the season and rely on the severity of symptoms and the effect of treatment as perceived retrospectively by patients. Our results point at the imprecision of such statements.

Another result that can be helpful for physicians when treating children and adolescents with hay fever is the analysis of the separate items of the RQLQs, as this analysis may give valuable information on the problems these patients experience. In general, children and adolescents are bothered by the same issues. In daily practice, evaluation of symptoms, practical problems (like rubbing nose/eyes) and impairment in activities will give a good impression of the impact of the disease. It appears that children also perceive thirst as an important issue, a complaint that is not spontaneously brought to the physician's attention. In children, special

attention should also be paid to medication use. When pollen exposure rises, taking their medication becomes much more bothersome to children, which might lead to non-compliance and consequently more symptoms. As the pollen season progresses, both adolescents and children experience a substantial impact from eye symptoms. Emotional problems, such as embarrassment and frustration, are considered least important in both age groups.

This study has a few limitations. First, the study is mainly exploratory and derived from a dataset from a RCT. However, as the instruments are designed to be used in clinical trials, this study population is appropriately composed to evaluate the properties of the instruments. Secondly, the numbers of participants are small, however they appeared to be sufficient for the analyses we made. Larger study groups and an extension to adults may however strengthen our findings. Thirdly, the relevance of the HRQL questionnaires was based on assumptions about the meaning of the correlations. Such assumptions are helpful in deciding what is important, but they have to be used with caution.

In conclusion, we demonstrated that the paediatric and adolescent RQLQ are relevant as they both are responsive to exposure and correlate well with rhinoconjunctivitis symptoms in pollen seasons. However, both RQLQs contain a substantial number of irrelevant items and therefore both questionnaires could be shortened. Furthermore, our data showed that the CWC are not relevant in the monitoring of children and adolescents with allergic rhinoconjunctivitis. In this study, the retrospective GAS was not a relevant representative of the actual symptoms during the previous season. Because the GAS is used as an evaluation tool in research as well as in daily practice, further research is needed to determine whether for instance rephrasing the questions, for example, focusing on days with severe symptoms, might improve this retrospective assessment.

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References

1. Bousquet J, Van Cauwenberge P, Khaltaev N; ARIA Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; **108**: s147.
2. Baiardini I, Braido F, Brandi S, Canonica GW. Allergic diseases and their impact on quality of life. *Ann Allergy Asthma Immunol* 2006; **97**: 419–28.
3. Canonica GW, Baena-Cagnani CE, Bousquet J, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy

- Organization (WAO) taskforce. *Allergy* 2007; **62**: 317–24.
4. Baiardini I, Bousquet PJ, Brzoza Z, et al. Recommendations for assessing patient-reported outcomes and health-related quality of life in clinical trials on allergy: a GA²LEN taskforce position paper. *Allergy* 2010; **65**: 290–5.
 5. Röder E, Berger MY, Hop WCJ, Bernsen RMD, de Groot H, Gerth van Wijk R. Sublingual immunotherapy with grass pollen is not effective in symptomatic youngsters in primary care. *J Allergy Clin Immunol* 2007; **119**: 892–8.
 6. Kuna P, Kaczmarek J, Kupezyk M. Efficacy and safety of immunotherapy for allergies to *Alternaria alternata* in children. *J Allergy Clin Immunol* 2011; **127**: 502–8.
 7. Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. *J Allergy Clin Immunol* 2011; **127**: 64–71.
 8. Juniper EF, Howland WC, Roberts NB, Thompson AK, King DR. Measuring quality of life in children with rhinoconjunctivitis. *J Allergy Clin Immunol* 1998; **101**: 163–70.
 9. Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. *J Allergy Clin Immunol* 1994; **93**: 413–23.
 10. Eiser C, Morse R. A review of measures of quality of life for children with chronic illness. *Arch Dis Child* 2001; **84**: 205–11.
 11. Nelson EC, Wasson J, Kirk J, et al. Assessment of function in routine medical practice: description of the COOP Chart method and preliminary findings. *J Chron Dis* 1987; **40** (Suppl. 1): s55–63.
 12. Scholten JHG, Van Weel C. Functional Status Assessment in Family Practice: The Dartmouth COOP Functional Health Assessment Charts/WONCA. Lelystad: Meditekst, 1992.
 13. Van Weel C, König-Zahn C, Touw-Otten FWMM, et al. Measuring Functional Health with the COOP/WONCA Charts – a Manual. Groningen: Northern Centre for Health Care Research, 1995.
 14. Bousquet J, Lockey RF, Malling H-J. WHO position paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Allergy* 1998; **53** (Suppl. 44): 1–42.
 15. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. *J Clin Epidemiol* 1994; **47**: 81–7.
 16. Hinkle DE, Wiersma W, Jurs SG. Applied Statistics for the Behavioral Sciences, 4th edn. Boston: Houghton Mifflin Company, 1998.
 17. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991; **21**: 77–83.
 18. Bousquet PJ, Brozek J, Bachert C, et al. The CONSORT statement checklist in allergen-specific immunotherapy: a GA²LEN paper. *Allergy* 2009; **64**: 1737–45.
 19. Häfner D, Reich K, Matricardi PM, Meyer H, Kettner J, Narkus A. Prospective validation of 'Allergy-Control-SCORETM': a novel symptom-medication score for clinical trials. *Allergy* 2011; **66**: 629–36.
 20. Grouin J-M, Vicout E, Jean-Alphonse S, et al. The average Adjusted Symptom Score, a new primary efficacy end-point for specific allergen immunotherapy trials. *Clin Exp Allergy* 2011; **41**: 1282–8.
 21. Franzke N, Schäfer I, Jost K, et al. A new instrument for the assessment of patient-defined benefit in the treatment of allergic rhinitis. *Allergy* 2011; **66**: 665–70.
 22. Juniper EF, Thomson AK, Ferrie PJ, Roberts JN. Development and validation of the Mini Rhinoconjunctivitis Quality of Life Questionnaire. *Clin Exp Allergy* 2000; **30**: 132–40.
 23. Bousquet J, Schünemann HJ, Bousquet PJ, et al. How to design and evaluate randomized controlled trials in immunotherapy for allergic rhinitis: an ARIA-GA²LEN statement. *Allergy* 2011; **66**: 765–74.
 24. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; **118**: 434–40.
 25. Bufe A, Eberle P, Franke-Beckmann E, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009; **123**: 167–73.
 26. Wahn U, Tabar A, Kuna P, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009; **123**: 160–6.
 27. Bodtger U, Poulsen LK, Malling HJ. Retrospective assessment of seasonal allergic symptoms: over-rating but useful. *Clin Exp Allergy* 2003; **33**: 496–500.

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Table E1 COOP/WONCA-charts: Relevance and most important impairments.

Table E2 Correlation between diary card and COOP/WONCA-charts.

Table E1 COOP/WONCA-charts: Relevance and most important impairments

	Low pollen		High pollen		Δ		
(A) 6–11 yr							
Pollen	Median (range) 2.6 (1.9 to 16.6)		Median (range) 102.6 (61.1 to 175.4)				
DC	Mean (range)		Mean (range)		Mean (range)	p value	
Total	2.4 (0 to 8.5)		4.5 (0.1 to 12.5)		2.1 (–3.2 to 12.3)	#	
CWC	Mean (range)	Rank	Mean (range)	Rank	Mean (range)	p value	R
Total	1.6 (1.0 to 2.7)		1.8 (1.2 to 4.2)		0.2 (–0.8 to 2.3)	\$	–
Domain							
Change in health	2.3 (1 to 4)	1	2.8 (1 to 5)	1	0.6 (–1 to 4)	#	–
Overall health	1.8 (1 to 3)	2	2.3 (1 to 5)	2	0.5 (–2 to 4)	\$	–
Feelings	1.6 (1 to 5)	3	1.6 (1 to 5)	3	0.0 (–3 to 4)	ns	–
Physical fitness	1.5 (1 to 3)	4	1.5 (1 to 4)	4	0.0 (–1 to 1)	ns	–
Daily activities	1.3 (1 to 3)	5	1.4 (1 to 4)	5	0.2 (–2 to 3)	ns	–
Social activities	1.2 (1 to 4)	6	1.1 (1 to 3)	6	–0.1 (–2 to 1)	ns	–
(B) 12–17 yr							
Pollen	Median (range) 2.6 (1.9 to 16.6)		Median (range) 99.7 (51.6 to 79.6)				
DC	Mean (range) 3.2 (0 to 8.4)		Mean (range) 4.8 (0 to 10.3)		Mean (range) 1.6 (–2.4 to 7.0)	p value #	
CWC	Mean (range)	Rank	Mean (range)	Rank	Mean (range)	p value	R
Total	1.8 (1.0 to 3.7)		1.9 (1.2 to 3.5)		0.2 (–1.2 to 1.8)	\$	–
Domain							
Change in health	2.7 (1 to 4)	1	2.8 (1 to 5)	1	0.1 (–3 to 3)	ns	–
Overall health	2.3 (1 to 5)	2	2.6 (1 to 5)	2	0.3 (–2 to 3)	\$	–
Feelings	1.8 (1 to 5)	3	1.7 (1 to 4)	4	–0.1 (–3 to 2)	ns	–
Daily activities	1.5 (1 to 4)	4	1.9 (1 to 4)	3	0.4 (–2 to 3)	#	–
Physical fitness	1.4 (1 to 3)	5	1.5 (1 to 3)	5	0.1 (–1 to 2)	ns	–
Social activities	1.1 (1 to 4)	6	1.2 (1 to 4)	6	0.1 (–2 to 3)	ns	–

6–11 yr n = 36; 12–17 yr n = 63.

Low pollen, May; High pollen, June; Δ , Difference: High pollen minus Low pollen.

CWC, COOP/WONCA-charts (scale 1–5, a higher score indicates a lower quality of life); DC, Diary card (scale 0–15).

#p ≤ 0.01; \$p ≤ 0.05.

R, relevant; for the total and domain scores the results from the correlation analyses (see Table E2) were also incorporated.

Table E2 Correlation between diary card and COOP/WONCA-charts

			DC Total	DC Nose	DC Eye
CWC	6–11 yr	Total	Low pollen	–	–
			High pollen	0.47	0.47
			Δ	0.5	0.54
		Physical fitness	Low pollen	–	–
			High pollen	–	0.48
			Δ	0.56	0.54
		Feelings	Low pollen	–	–
			High pollen	–	–
			Δ	–	–
		Daily activities	Low pollen	–	–
			High pollen	–	–
			Δ	–	–
		Social activities	Low pollen	–0.43	–0.45
			High pollen	–	–
			Δ	–	–
	12–17 yr	Total	Low pollen	–	–
			High pollen	0.35	0.35
			Δ	0.38	0.4
		Physical fitness	Low pollen	–	–
			High pollen	–	–
			Δ	–	–
		Feelings	Low pollen	–	–
			High pollen	0.31	0.29
			Δ	–	0.32
		Daily activities	Low pollen	–	–
			High pollen	0.38	0.39
			Δ	0.35	0.33
		Social activities	Low pollen	–	–
			High pollen	0.35	0.34
			Δ	–	–
		Change in health	Low pollen	–	–
			High pollen	–	–
			Δ	–	–
		Overall health	Low pollen	0.39	0.39
			High pollen	–	–
			Δ	0.47	0.48

6–11 yr n = 36; 12–17 yr n = 63. In the rows labelled 'low pollen' and 'high pollen', the correlations are shown for the scores in May and June, respectively. In the rows labelled ' Δ ', the correlations are shown for the changes (high pollen minus low pollen) of both scores. Spearman's correlation; only significant correlations ($p \leq 0.01$) are shown.

DC, Diary card; CWC, COOP/WONCA-charts.