

Impairment in quality of life is directly related to the level of allergen exposure and allergic airway inflammation

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Summary

Background Allergic disease has been shown to impair health-related quality of life (HRQL). The relationship between HRQL and either allergen exposure or allergic inflammation has not been previously assessed.

Objective To assess the relationship between HRQL and both grass pollen exposure and airway inflammation using the Paediatric Allergic Disease Quality of Life Questionnaire (PADQLQ). This is a novel questionnaire previously developed to assess the multi-system aspects of allergic disease.

Methods Eighty-four subjects, aged 6–17 years, with seasonal allergic rhinoconjunctivitis, asthma and/or cutaneous manifestations were assessed before and during the grass pollen season. They were assessed with the PADQLQ, a visual analogue scale (VAS) to assess quality of life, symptom diary and exhaled nitric oxide (FENO).

Results HRQL, as measured by the PADQLQ, significantly correlated with the average pollen count in the previous week (regression coefficient 0.038, 95% confidence interval (CI) 0.027–0.049, $P < 0.001$). The PADQLQ score was also found to be significantly associated with airway inflammation as measured by FENO (regression coefficient 0.410, 95% CI 0.175–0.646, $P = 0.001$). Additionally, PADQLQ showed a high degree of correlation with symptom scores and quality of life as measured by a VAS, good within-subject reliability and a small minimal important difference (0.20, 95% CI –0.09 to 0.49 on a seven-point scale).

Conclusion HRQL is related to both allergen load and allergic inflammation and the PADQLQ has excellent cross-sectional and longitudinal validity with respect to quality of life and symptoms.

Keywords asthma, children, eczema, multi-system allergic disease, quality of life, rhinoconjunctivitis, teenagers

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Introduction

It is increasingly accepted that health-related quality of life (HRQL) tools should be used as outcome measures in clinical trials as they are thought to represent more patient-orientated indicators rather than symptom scores or clinical measurement [1, 2]. Organ-specific quality of life questionnaires have been developed for diseases such as hayfever and asthma [3, 4]. Many allergic diseases have manifestations that include more than one system and these single-system questionnaires are unable to provide a valid global measure of HRQL for multi-system allergic disease. The Paediatric Allergic Disease Quality of Life Questionnaire (PADQLQ) [5] has been previously developed and validated, using well-established questionnaire development principles [6], to fill this gap. The PADQLQ aims to assess the HRQL of children or

teenagers with allergic disease affecting their eyes, ears, nose, lungs, skin, emotions and everyday activities. If the questionnaire were to fulfill this aim, it would be expected that the PADQLQ would reflect both allergen exposure and tissue inflammation as well as symptom severity. The relationship between HRQL, as measured by the questionnaires in current use, and either allergen exposure or airway inflammation has not been previously examined. In this study we aim to assess whether HRQL, as measured by the PADQLQ, is related to allergen exposure, airway inflammation and symptoms within a larger group of children and teenagers with seasonal grass pollen allergy. Additionally we aimed to provide more evidence of the validity of the PADQLQ within this larger group.

Methods

Study design

Subjects were assessed prior to the grass pollen season and at pre-planned weekly intervals during the pollen season in 2001.

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Subjects

Subjects, aged 7–16 years with seasonal allergic rhinoconjunctivitis, asthma and/or eczema, were recruited from the paediatric chest and allergy clinic at St Mary's Hospital. All subjects were required to have symptoms during the pollen season and a positive skin prick test to grass pollen (weal diameter >3 mm, six grass pollens, ALK-Abello, Horsholm, Denmark). The diagnosis of asthma was based on clinical history, examination and reversibility with inhaled bronchodilators [7]. A diagnosis of seasonal allergic rhinoconjunctivitis was made if there were typical symptoms during the pollen season [8]. Cutaneous symptoms were defined as the presence of urticaria, pruritis or eczema during the pollen season [9]. Outside the pollen season, they had minimal symptoms; in particular no subjects required inhaled corticosteroids over the winter period. They had no other illnesses that might affect their quality of life. Informed consent was obtained from all subjects and their parents and the study was approved by the local research ethics committee.

Outcome measures

Paediatric allergic disease quality of life questionnaire [5] The questionnaire has 26 questions, which naturally group into three domains: (i) practical problems (eight questions); (ii) symptoms (chest, three; nasal, four; ocular, two; cutaneous, two; and other symptoms, four); and (iii) emotional problems (three). Responses to each question were rated from not troubled (0) to extremely troubled (6). Subjects were asked to answer each question by thinking about the previous week. Parents were asked not to guide their child's answers. Individual items were equally weighted and results presented for each domain and the whole questionnaire. The PADQLQ was completed at the start of each assessment in clinic.

Visual analogue scales Subjects completed two visual analogue scales (VAS) to describe how troubled they were by their asthma or hayfever as previously described [5]. The VAS consisted of six faces ranging from very happy to very sad. The VAS was taken as a simple reference measurement of HRQL when evaluating the PADQLQ.

Symptom diary Subjects were asked to complete the symptom diary each evening during the week prior to an assessment, as previously described [5]. They were asked to rate the severity of ocular, nasal and chest symptoms on a fourpoint scale from no (0) to severe (3) symptoms. Parents were asked not to guide their child's answers.

Pollen count Daily atmospheric pollen counts for the North-West London area were measured during the pollen season with a Burkard 7-day volumetric spore trap (data supplied by the National Pollen Centre, University of Worcester, UK). The 2001 pollen season commenced at the start of May and extended until mid-August. The medium (inter-quartile range) pollen count during the season was 25 grains/m³ (10–80). Counts were at least moderately high (>50 grains/m³) through most of June and early July.

Measurement of exhaled nitric oxide levels FE_{NO} was measured in all subjects using the single expiratory breath method with a chemiluminescence analyser (Logan Research LR2500, Rochester, UK) according to the 1997 ERS guidelines [10]. The analyser is sensitive to nitric oxide concentrations of 0–5000 ppb and has a response time of <0.5 s. The analyser also measured carbon dioxide (resolution 0.1% CO₂ with <0.5 s response time) and exhalation pressure and flow in real time. A visual biofeedback arrangement was used to maintain a constant expiratory flow of 250 mL/min with subjects expiring against a low resistance. The FE_{NO} measurement was read from the plateau phase of the last part of exhalation when CO₂ concentration was 5–6%. Ambient NO levels were checked prior to measurement and exhaled NO values discarded if the ambient level was above 100 ppb, as previous work has shown that ambient NO up to these levels does not effect measured FE_{NO} using the single breath method [11]. The chemiluminescence analyser was calibrated daily with certified NO mixture (147 ppb, BOC Special Gases, Guildford, UK). FE_{NO} measurements were repeated until two consecutive results within 10% were obtained. This generally required two to four attempts. When asthmatic subjects have their FE_{NO} measured twice by different observers in our department, the inter-quartile range for the relative difference in the two measurements is –3.3% to 12.9%. The median FENO value for well, non-asthmatic, atopic children and teenagers in our department is 6.2 ppb (inter-quartile range 4.0–10.3).

Statistical methods

Relationship between Paediatric Allergic Disease Quality of Life Questionnaire and the pollen count or levels of exhaled nitric oxide The association between the PADQLQ score and both the average pollen count in the preceding days and the subject's exhaled nitric oxide level were determined using a time series regression approach [12]. This statistical model calculates the degree of association between PADQLQ score and the pollen count or exhaled nitric oxide level at the level of the subject. The model allows for multiple observations from individual subjects. Additionally we examined whether the PADQLQ was related to the cumulative pollen exposure over the preceding week. PADQLQ, FENO and the pollen count were transformed to normalize the data.

Relationship between Paediatric Allergic Disease Quality of Life Questionnaire and the visual analogue scales or symptom score The PADQLQ score was correlated with the VAS to establish its ability to distinguish between subjects with different degrees of impairment of HRQL. Given our previous experience [5], we expected to see a close relationship between these ($r > 0.6$). A comparison was also made between the PADQLQ and symptom scores; only a moderate degree of association was expected ($0.6 > r > 0.4$). The Bonferonni transformation was used to adjust for multiple comparisons.

Relationship between change in Paediatric Allergic Disease Quality of Life Questionnaire and the change in visual analogue scales The absolute change in VAS for all allergic

problems was classified into the following groups: 0 (no change), 1 (minimal appreciable difference), 2 and 3 or 4. The relationship between the change in PADQLQ and the change in VAS is assessed using ANOVA. The intra-class correlation coefficient for the repeated PADQLQ measurements where there was no change in the VAS is presented as a measure of repeatability. The change in PADQLQ was also correlated with the change in the average symptom scores. Again, the Bonferroni transformation is used to adjust for multiple comparisons. We expected that the change in the PADQLQ would be closely related to the change in the VAS ($r > 0.6$) and moderately associated with the change in symptoms ($r > 0.4$).

All statistical tests were undertaken using Stata 6.

Results

Subjects

Eighty-four children aged 6–17 years were enrolled into the study (Table 1). All had seasonal allergic rhinoconjunctivitis and most also suffered from seasonal allergic asthma. All were sensitized to grass pollen and a quarter were additionally sensitized to house dust mite. Subjects were assessed twice on average (range 1–4) during the grass pollen season. The medium (inter-quartile range) FE_{NO} measurement during the pollen season was 10.4 ppb (6.9–15.4). During the pollen season, 67 (79.8%), 43 (51.2%) and 27 (32.1%) subjects required therapy with long-acting oral antihistamines, intra-nasal corticosteroids and inhaled corticosteroids, respectively.

The Paediatric Allergic Disease Quality of Life Questionnaire score is related to the preceding average pollen count

The association between the PADQLQ score and both the average pollen count in the preceding days was determined using a time series regression approach to allow for multiple observations from individual subjects. As expected there was a strong relationship between the PADQLQ and the pollen count on the day of assessment with quality of life

deteriorating with increasing pollen exposure (regression coefficients 0.034, 95% CI 0.024–0.044, $P < 0.001$ with pollen count and PADQLQ both transformed by a square root to normalize the data). Similar levels of association were seen for the average pollen count in the previous week (regression coefficient 0.038, 95% CI 0.027–0.049, $P < 0.001$). Neither of these relationships were confounded by factors such as age, gender and a diagnosis of asthma. This means that a rise in the pollen count from 5 (low count day) to 100 grains/m³ (high count) is associated with a doubling of the PADQLQ score.

Subjects' Paediatric Allergic Disease Quality of Life Questionnaire score is related to their exhaled nitric oxide level

Using a time series regression analysis, a significant relationship was found between each subject's PADQLQ and their FE_{NO} (regression coefficient 0.410, 95% CI 0.175–0.646, $P = 0.001$, $n = 213$ with FE_{NO} logarithmically transformed and PADQLQ square rooted to normalize each). This relationship was not affected by factors such as age, gender or a diagnosis of asthma. Again as expected, quality of life deteriorated with increasing airway inflammation as measured by FE_{NO} . A rise in FE_{NO} from 6 to 20 ppb was associated with a doubling of the PADQLQ score.

Paediatric Allergic Disease Quality of Life Questionnaire score is related to both the visual analogue scales and symptom scores

The PADQLQ and each of its domains showed an excellent degree of association (ANOVA $P < 0.001$) with the VAS for both rhinoconjunctivitis and asthma-related problems (Table 2). Additionally, the data presented in Table 2 demonstrate that the PADQLQ and each of its domains show excellent correlation with ocular, nasal and chest symptoms. As might be expected, the correlation was generally less for the activities and emotions domains. Similar results for both

Table 1. Subject characteristics

Number	84 (100%)
Mean age in years (range)	11.5 (6–17.5)
Female	28 (33.3%)
Ethnicity	59 (70.2%)
White	
Black	9 (10.7%)
Indian subcontinent	7 (8.3%)
Other	9 (10.7%)
Seasonal allergic asthma	71 (84.5%)
Seasonal allergic rhinoconjunctivitis	84 (100%)
Eczema	38 (45.2%)
Food allergy	19 (22.6%)
Therapy with inhaled corticosteroids	33 (39.3%)
Therapy with long-acting oral antihistamines	41 (48.8%)
Therapy with long-acting topical nasal corticosteroid	20 (23.8%)

Clinical characteristics and therapy refer to preceding pollen season. Data presented as mean (range) or number (%) of subjects.

Table 2. Association between PADQLQ and symptoms

	PADQLQ score			
	All domains	Activities	Symptoms	Emotions
Eye/nose symptoms*	0.661 (< 0.001)	0.389 (< 0.001)	0.688 (< 0.001)	0.425 (0.001)
Chest symptoms*	0.630 (< 0.001)	0.489 (< 0.001)	0.618 (< 0.001)	0.348 (0.029)
All symptoms*	0.723 (< 0.001)	0.738 (< 0.001)	0.738 (< 0.001)	0.506 (0.001)
Rhinoconjunctivitis VAS†	34.1 (< 0.001)	13.0 (< 0.001)	32.5 (< 0.001)	6.7 (< 0.001)
Asthma VAS†	15.2 (< 0.001)	9.1 (< 0.001)	14.4 (< 0.001)	4.9 (0.01)

P-values modified using Bonferroni's transformation to allow for multiple comparisons.

*Results presented as Pearson's correlation coefficient (*P*-value) for symptoms or

†ANOVA *F*-score (*P*-value) for VAS.

VAS, visual analogue scale; PADQLQ, Paediatric Allergic Disease Quality of Life Questionnaire.

Table 3. Change in PADQLQ vs. change in symptom and VAS scores

Change in	PADQLQ			
	All domains	Practical	Symptoms	Emotions
Eyes and nose symptoms*	0.426 (0.036)	0.440 (0.025)	0.406 (0.056)	0.468 (0.012)
Chest symptoms*	0.559 (0.001)	0.502 (0.004)	0.509 (0.004)	0.264 (0.802)
All symptoms*	0.542 (0.001)	0.526 (0.002)	0.507 (0.04)	0.445 (0.022)
Rhinoconjunctivitis VAS†	3.6 (0.012)	3.0 (0.048)	3.7 (0.009)	5.2 (<0.001)
Asthma VAS†	7.0 (<0.001)	6.2 (<0.001)	5.3 (0.001)	4.5 (0.005)

P-values modified using Bonferroni's transformation to allow for multiple comparisons.

*Results presented as Pearson's correlation coefficients (*P*-value) for symptoms or

†ANOVA *F*-score (*P*-value) for VAS.

VAS, visual analogue scale; PADQLQ, Paediatric Allergic Disease Quality of Life Questionnaire.

symptoms and the VAS (data not shown) were seen when children (≤ 12 years) and teenagers were analysed separately. These data together suggest that the PADQLQ has good cross-sectional validity.

The responsiveness to change of the PADQLQ was assessed by comparing the change in the PADQLQ score between two successive visits with the change in VAS and symptom scores. As expected, a significant relationship was found for the change in hayfever, asthma and total symptom scores (Table 3). There was also a significant relationship between the change in PADQLQ and the change in VAS scores for both hayfever and asthma (Table 3). Similar relationships were found for almost all the PADQLQ domains (Table 3).

To determine the reliability of the PADQLQ, we calculated the change in PADQLQ for subjects with no change in their average of their average hayfever and asthma VAS. The change in PADQLQ was found to be -0.14 (95% CI -0.37 to 0.08 , $n = 24$). The intra-class correlation coefficient for these repeated measurements, when quality of life was stable, was 0.95 . For the practical problems, symptoms and emotions domains it was 0.94 , 0.96 and 0.86 , respectively. To determine the sensitivity of the PADQLQ, change in PADQLQ associated with a change of 1 in the average of their hayfever and asthma VAS (minimal important difference (MID)) was calculated. The MID was 0.20 (95% CI -0.09 to 0.49 , $n = 39$).

Discussion

The PADQLQ is a novel multi-system HRQL questionnaire (PADQLQ) designed to assess how multi-system allergic diseases impinge on the lives of children and teenagers. For the first time we have shown that an allergy HRQL questionnaire correlates with the burden of allergen exposure and airway inflammation as measured by exhaled nitric oxide. This would be expected for a questionnaire designed to assess HRQL in allergic disease although, to

our knowledge, such a relationship has not been demonstrated for other HRQL questionnaires. Unsurprisingly, HRQL correlates with pollen exposure on the day of assessment or the average exposure in the previous week in keeping with the fact that allergen inflammatory changes result from chronic allergen exposure [13]. Additionally, given that exhaled nitric oxide is a measure of allergic inflammation associated with of the late rather than the early phase [14], it is not surprising to find a relationship between FE_{NO} and PADQLQ. The correlation coefficients for the relationship between PADQLQ and both grass pollen and exhaled NO levels are not large, but this would be expected as a multitude of environmental, biological and psychological factors influence how individual subjects react to disease. These may have been larger if we had recruited a homogeneous population who all suffered from asthma and excluded subjects exposed to other allergens such as household pets.

In this paper we have presented further validation data for the PADQLQ from a larger paediatric population. In this large group of children and teenagers with seasonal allergic asthma, rhinoconjunctivitis and/or eczema, the PADQLQ effectively discriminated between subjects with different degrees of impairment as measured by a VAS or a total symptom score (Table 3). The close relationship with allergen exposure, inflammation and symptoms provides good evidence for the cross-sectional validity of this questionnaire. Data are also presented that demonstrate that the PADQLQ correlates with changes in both the VAS and the total symptom score (Tables 3). Additionally, the PADQLQ shows good repeatability (intra-class correlation coefficient 0.95) in subjects with no change in their perceived HRQL as measured by VAS. The minimally important difference for the PADQLQ is small (0.20 , 95% CI -0.09 to 0.49) and similar to those seen for other HRQLQ [4, 15]. The relationship between the change in PADQLQ and the change in both VAS and symptoms, as well as the good repeatability and small MID provide further evidence for the longitudinal validity of the PADQLQ.

Given the close relationship with allergen exposure, inflammation and symptoms, the multi-system PADQLQ should be a valuable instrument for delineating the effects of systemic allergic diseases on children and teenagers in cross-sectional studies. With its good reliability and small MID, the questionnaire is also a potentially useful outcome measure for interventional studies in children with systemic allergic disease. A sample size analysis (Table 4) demonstrates that a relatively modest-sized study is powered to detect a 1–2 MID difference between two groups. The PADQLQ could be used instead of a battery of organ-specific tools to assess children and teenagers with multi-system allergic disease. This novel HRQL questionnaire, which reflects airway inflammation, could be used to assess the effect of new systemic immunomodulatory and anti-inflammatory therapies, for example anti-IgE, leukotriene receptor antagonists, antihistamines and immunotherapy.

This study has a number of limitations. Firstly, airway inflammation was only measured non-invasively by measuring levels of exhaled nitric oxide. This technique has now been well validated as a marker of airway inflammation in childhood [16–19], and we have data from this group of

Table 4. Sample sizes for clinical trial

Difference between the two groups	Number required in each group			
	$\alpha = 0.05$ (one-sided test)		$\alpha = 0.05$ (two-sided test)	
	$\beta = 0.1$	$\beta = 0.2$	$\beta = 0.1$	$\beta = 0.2$
MID	155	112	190	142
1.5 MID	68	49	83	62
2 MID	39	28	48	36

Assuming: MID = 0.33; pooled SD = 0.99; average season score = 1.31; parallel group study design; level of statistical significance = α and power = β . MID is assumed to be 0.33 as this larger value was the MID from the first validation study [5].

MID, minimal important difference.

children and teenagers demonstrating that there is a close and significant relationship between FE_{NO} and sputum eosinophilia (data not shown). A flow rate of 250 mL/s was used to sample exhaled nitric oxide as suggested by the only guidelines available when the study was commenced [10]. This is higher than the current recommendations [19]. It is unlikely that the use of a lower flow rate would have substantially altered the pattern of the results and it may have actually increased the sensitivity of exhaled NO in measuring differences in airway inflammation [20]. Secondly, pollen counts were only measured at one site in North West London although the residences of the subjects were spread across this area. While the trends of exposure for all subjects will be similar within this small geographical area, these values may not accurately reflect personal pollen exposure. In spite of this, we were still able to demonstrate relationships between the PADQLQ and both FE_{NO} and pollen exposure indicating that, within a longitudinal model, these relationships are very robust. Thirdly, the subjects did not additionally complete the rhinoconjunctivitis or asthma HRQLQ as in our previous study [5]; we therefore cannot comment on whether these might correlate better with airway inflammation than the PADQLQ. Lastly, the questionnaire was validated only in a group of children and teenagers with seasonal allergic asthma and rhinoconjunctivitis. As with any new questionnaire, it is important that it is tested in as many populations as possible. In particular it would be useful to assess the validity of the PADQLQ in children with perennial problems. Children and teenagers with perennial allergic symptoms were included in the development stage [5]. As their other scores were similar to the subjects with seasonal allergy, it might be expected that the PADQLQ would also provide reliable and valid results in this group. However, this requires further validation.

We have demonstrated that the HRQL as assessed by the PADQLQ is related to allergen load, airway inflammation and allergic symptoms. This single questionnaire can be used instead of a battery of organ-specific tools in children with systemic allergic disease. The PADQLQ has good cross-sectional and longitudinal validity and reliability enabling it to discriminate between subjects and detect changes in HRQL. The PADQLQ is therefore a potentially useful outcome measure for assessing the effectiveness of systemic immunomodulatory and anti-inflammatory therapies. This

approach is likely to prove to be more sensitive than ones that utilize organ-based HRQL questionnaires.

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