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Comparison of outcome measures in allergic rhinitis in children, adolescents and adults

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Running title

AR in children, adolescents and adults

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Abstract page

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Comparison of outcome measures in allergic rhinitis in children, adolescents and adults

Abstract

Background: Grass-pollen-induced allergic rhinoconjunctivitis (AR) is very common worldwide. However, its symptoms may vary with the patient's age. The present study compared symptom profiles and quality of life (QoL) in children, adolescents and adults with grass-pollen-induced AR.

Methods: This was a four-week, multicentre, observational study of children (aged 6–11), adolescents (12–17) and adults (18–65) consulting specialist physicians in France. The management of AR was at the physicians' discretion. Participants regularly rated their symptoms (the Rhinoconjunctivitis Total Symptom Score (RTSS) and a visual analogue scale (VAS)), and QoL (the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)).

Results: 806 patients (253 children, 250 adolescents and 303 adults, of whom 83.5% suffered from moderate-to-severe, persistent AR) provided data for at least the first two weeks of the study. Ocular pruritus (the most bothersome symptom in children (35%), adolescents (22%) and adults (16%)) was associated with poor QoL in all groups, whereas nasal obstruction and pruritus were associated with poor QoL in adolescents and children. Over 4 weeks, the weekly mean RTSS and VAS scores fell by around half. This change was associated with an improvement in the RQLQ scores. In all age groups, the VAS score was well correlated with the weekly mean RTSS score (Pearson's r : 0.79–0.88) and moderately correlated with the weekly mean RQLQ score (Pearson's r : 0.64–0.80).

Conclusions: In moderate-to-severe grass-pollen-induced AR, symptom perception differs in children vs. older patients. However, the assessments of treatment outcomes (using the RTSS, VAS and RQLQ) were similar in all age groups.

Keywords

Allergic rhinoconjunctivitis; grass pollen; nasal congestion; ocular pruritus; patient profile; quality of life; rhinorrhoea, visual analogue scale.

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Introduction

Allergic rhinoconjunctivitis (AR) is one of the most common chronic disease worldwide (1,2). In Europe, it has been estimated that approximately 25% of the general adult population suffers from respiratory allergies, and that around 40% of these cases are caused by pollens in general and grass pollens in particular (2). AR has a marked impact on quality of life (QoL), and impairs activities of daily living (ADL) and work/school performance in adults and children (3-8).

Symptoms and evaluations of the severity of AR may differ in children, adolescents and adults. In clinical trials, AR severity is commonly evaluated through patient-reported assessments of the intensity of six common individual symptoms (sneezing, rhinorrhoea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes) on a scale of 0 to 3. Individual symptom scores are summed for the

Rhinoconjunctivitis Total Symptom Score (RTSS) (9-11). However, little information of this type is available in school-age children. It is important to determine whether tools for the measurements of AR severity and other outcomes have similar characteristics in different age groups.

The primary objective of the present observational study was to establish the minimally important difference in the RTSS in patients with grass-pollen-induced AR during the grass pollen period; the corresponding results were published recently (12). Here, we describe the study's secondary endpoints (symptom profiles, VAS and QoL), with a focus on three age groups (i.e. children, adolescents and adults).

Methods

Study design

EQUINOXE 2 was an observational, prospective study of patients consulting 298 specialists (allergists, paediatricians, chest or ear, nose & throat specialists) from across France for grass-pollen-induced allergic AR during the grass pollen period (12).

Study participants

Briefly, patients between 6 and 65 years were included if they (i) had documented grass-pollen-induced AR, (ii) were consulting an allergy specialist for the management of their AR symptoms, and (iii) had an RTSS ≥ 6 on the day of inclusion and on each of the two preceding days (12). The main exclusion criteria were persistent or intermittent asthma that increased in severity during the grass pollen season, and any diagnosed disease (including atopic dermatitis, eczema, food allergy) or any concomitant condition that may interfere with the evaluation of allergic rhino-conjunctivitis' related symptoms, quality of life, fatigue, and daily activities (3,13). Recruitment of the participants was stratified so that similar numbers of adults (aged 18-65), adolescents (12-17) and children (6-11) were included.

Assessments

Physicians completed a questionnaire on the day of consultation to gather data on sociodemographic variables, rhinitis symptoms, any concomitant diseases, and the treatment(s) prescribed. Each physician was free to decide how to manage AR in his/her patients.

At inclusion and for the four weeks thereafter, each patient (with the help of a parent, if required – mainly for the younger children) rated (i) the RTSS on a daily basis ranging from 0 to 18, (ii) the overall intensity of the allergy symptoms (on a 100 mm visual analogue scale (VAS) ranging from 0 – “no symptoms” – to 100 mm – “very severe symptoms”) on a daily basis and (iii) age- and disease-specific QoL (according to the Rhinoconjunctivitis Quality of Life Questionnaire, RQLQ) (14) on a weekly basis. In the VAS for children, the qualifiers “no symptoms” and “very severe symptoms” were replaced by appropriate emoticons. The RQLQ includes questions on activities of daily living, practical problems, general well-being, nose symptoms, eye symptoms (for all age groups), emotional state (for adults and adolescents only) and sleep (for adults only). Each area is rated on a 7-point scale from 0 (“not at all bothersome”) to 6 (“extremely bothersome”) for adults and adolescents, and from 1 (“extremely bothersome”) to 7 (“not at all bothersome”) for children (i.e. a reversed scale for the latter group). The observation period was limited to four weeks to maintain compliance to questionnaire return and reduce drop outs.

Ethics

The study was approved by an independent ethics committee (*Comité de Protection des Personnes Ile-de-France VIII*; reference: SC110319). In line with the French legislation on clinical research (and as approved by the IEC), only verbal informed consent (rather than written consent) was required for this observational, non-interventional study. A brief note from the physician (stating that consent had been requested and verbally granted at the time of the consultation) was included in the patient's medical records.

Statistical analysis

The statistical analyses were performed with SAS software (version 9.2, SAS Institute Inc., Cary NC, USA). Correlations between datasets were measured using Pearson's correlation coefficient. Fisher's exact test, the odds ratio (OR) and the latter's 95% confidence interval (CI) were calculated using GraphPad Prism[®] software (version 5.01, San Diego, CA, USA).

RESULTS

Study population

A total of 1353 patients were screened for eligibility (Fig. E1, online repository). Valid data for analysis were obtained from 806 patients (303 adults (37.6%), 250 adolescents (31.0%) and 253 children (31.4%)), all of whom had filled out the daily questionnaires on symptoms and QoL for at least the first two weeks of the study (Tables E1-E3, Fig. E1, online repository). Overall, 619 patients (75.7%) were found to be sensitized to at least one allergen in addition to grass pollen. The proportion of patients monosensitized to grass pollen did not vary significantly with age (Table E1, online repository). There were no significant differences between the age groups in terms of exposure to tobacco smoke or to pets. Most patients had already been treated for AR before inclusion in the study (Table E1); the most frequently used symptomatic treatments prior to the study consultation were oral antihistamines (76.9%), nasal corticosteroids (29.9%), cromone eye drops (20.4%) and topical antihistamines (9.9%) (12). 401 participants (49.8%) had been or were being treated with allergen immunotherapy.

Symptom profiles on inclusion

Data on the persistence and severity of AR (according to the Allergic Rhinitis and its Impact on Asthma (ARIA) classification (3)) were available for 796 patients (Table E2); 83.5% suffered from persistent moderate-to-severe AR, and only 9% had mild AR.

The three age groups had similar values for the RTSS, VAS and RQLQ scores (Tables E2 & E3) at inclusion. The AR symptoms variously reported to be the single most bothersome symptom in adults, adolescents and children are described in Fig. 1. Ocular pruritus was reported to be the single most bothersome symptom more frequently by children than by adolescents ($p=0.001$) and adults ($p=0.001$). In contrast, sneezing and rhinorrhoea were less frequently reported by children than by adolescents and adults (sneezing: $p<0.05$ vs. both adolescents and adults; rhinorrhoea: $p=0.066$ vs. adolescents and $p<0.001$ vs. adults). Lastly, nasal pruritus was less frequently reported by children and adolescents than by adults ($p<0.05$). There were no differences between the age groups in terms of the frequency with which nasal congestion and watery eyes were reported to be the single most bothersome symptom.

Quality of life on inclusion

The mean RQLQ scores on inclusion showed that AR was associated with a moderate impact on the patients' QoL in the three age groups (Table E3). To facilitate comparison, the three sets of RQLQ data in Table E3 are expressed on the same scale (i.e. from 0 (no impairment) to 6 (maximal impairment), meaning that the paediatric RQLQ score was inversed). The scores in the "nasal symptoms" and "eye symptoms" RQLQ domains were similar in the three age groups, except that the score in the "eye symptoms" domain was significantly higher in children than in adults ($p<0.05$).

We next calculated an OR [95%CI] to characterize the relationship between moderate-to-severe scores for individual symptoms on one hand and poor QoL (defined as an RQLQ score ≥ 4) on the other (Table 1). Ocular symptoms were associated with poor QoL in all three age groups, whereas nasal obstruction and nasal pruritus were associated with poor QoL in children and adolescents but not in adults. Rhinorrhoea and sneezing were not associated with poor QoL in any of the three groups.

Changes in symptoms and QoL during the study

All patient-reported outcomes were measured over a 4-week period, and the changes over this time for children ($n=209$), adolescents ($n=207$) and adults ($n=255$) are shown in Fig. 2. The weekly mean RTSS scores fell to a similar extent in all three age groups (by 52.5% in children, 49.7% in

adolescents and 47.3% in adults). The same was found for the VAS score, with a reduction of 50.0% in children, 47.3% in adolescents and 49.1% in adults. In all age groups, the RTSS score and the VAS score were correlated (Table 2).

The reduction in symptom intensity was associated with a relative mean improvement in RQLQ levels by 27.6% (+1.18 points), 43.1% (-1.09 points) and 43.7% (-1.19 points) in children, adolescents and adults, respectively; these values correspond mostly to large changes (13) (Fig. 2). Weekly changes in RQLQ were correlated with changes in VAS and RTSS scores (Table 2). The correlation coefficients (Pearson's r) for the changes in weekly mean VAS and RQLQ scores were similar in the three age groups but were somewhat lower than the correlation coefficients for the VAS and RTSS scores (Table 2).

Furthermore, the score for the most bothersome symptom was also correlated with the VAS and RQLQ scores throughout the four weeks (with Pearson's r ranging from 0.64 to 0.83 for the VAS score and from 0.54 to 0.73 for the RQLQ score) and with the RTSS (range: 0.74 to 0.84). There were no significant differences between the age groups in this respect.

Discussion

In the present study carried out in children, adolescents and adults, we found that (i) ocular symptoms have a strong impact (particularly in children), (ii) a VAS can be used to assess AR severity and was highly responsive to change in all three age groups, and (iii), most importantly, all the treatment outcomes had similar values across the three age groups.

Study strengths and limitations

This is the first study to have compared outcomes in three age groups (children, adolescents and adults) in a “real-life” setting. Importantly, children assessed the symptoms and other outcomes themselves. This is noteworthy, since patient-reported outcomes are not often available for children. Thus, the similar evaluations of all outcomes in the three age groups indicate that the instruments used with adults can also be used with children suffering from grass pollen seasonal allergic rhinitis. The

study's "real-life" design was not optimal for assessing absolute treatment efficacy. However, the study was appropriate for comparing efficacy measurements in three age groups.

Discussion of the results

Our findings in adults and (to a lesser extent) in adolescents (i.e. that ocular symptoms are the most bothersome) are consistent with most studies of AR (15-21). However, some studies have suggested that nasal congestion is the most bothersome symptom (22-24). In the present study, ocular pruritus was more likely to be reported as the most bothersome symptom in adolescents than in adults, and was even the most frequent bothersome symptom in children. In all three age groups, watery eyes were much less likely to be reported as the most bothersome symptom. Moreover, we found that ocular symptoms were associated with poor QoL in the three age groups. Rhinorrhoea and sneezing were not associated with poor QoL in any of the three groups, as also recently reported in adults (15).

The results of the present study confirm the particular impact of ocular symptoms on the symptom profile and QoL in adults suffering from grass pollen AR and extend this finding to adolescents and children. Indeed, our results emphasize ocular symptoms as a major unmet need in grass pollen-induced AR (whatever the age of the patients, and notably in children) and suggest that particular attention should be paid to ocular symptoms in the management of this allergic condition.

In agreement with our present results, several surveys of the paediatric population have found that ocular symptoms are also bothersome (24) - particularly in children sensitized to grass pollen (19).

Our study results also provided insights into the value of VASs, as previously explored in the literature. In a large, cross-sectional study of adults in primary care, a nasal symptom VAS was shown to be appropriate for evaluating the severity of AR (25). In the latter study, there was a moderate but highly significant correlation (0.46) between the VAS and RQLQ scores. In a pragmatic, randomized cluster trial in adults with grass pollen AR, a VAS for overall symptom severity was highly responsive to change during a two-week treatment period; there were moderate-to-high correlations between the change in the VAS on one hand and the change in the RQLQ (0.54) or the nasal symptom score on the other (0.66) (26). In patients with moderate-to-severe, persistent AR, a correlation (0.62) was also found between a summary score of two VASs (evaluating nasal and ocular symptoms,

respectively) and the RQLQ score (27). Recently, in an observational prospective study of adults in primary care, a VAS evaluating the overall discomfort caused by AR was found to be appropriate for the highly sensitive detection of changes in symptoms and QoL (28). The correlations between changes over two weeks in the VAS on one hand and the RQLQ and RTSS scores on the other were large and highly significant (0.77 and 0.80, respectively). In the present study, we confirmed the correlation between a VAS score for AR symptom-related discomfort and the RTSS and RQLQ scores in adults suffering from grass pollen AR and also extended this finding to adolescents and children. Lastly, the VAS score was also correlated with the score for the most bothersome symptom. Hence, the VAS appears to be a simple tool with much the same properties in adults, adolescents and children. Our results support the ongoing implementation of the VAS-based “MASK aerobiology” smartphone application (promoted by the Integrated Care Pathways for Airway Diseases initiative) for adolescents and (with the help of a parent) children over the age of 6 (29). In the present study the VAS, RQLQ and RTSS were rated by the children. In a recent study in children with moderate/severe seasonal AR, the efficacy of the combination of azelastine hydrochloride and fluticasone propionate was found for the RQLQ but not for nasal and ocular symptom scores. However, when children rated their own symptoms instead of their caregivers by proxy, the efficacy of the combination became also apparent highlighting that caregivers are less able than children to accurately assess response and the need for simple and easy efficacy assessment tool in paediatric study. Our data are therefore in line with this study.

Generalizability

The present study was a “real-life” assessment of patients treated by specialist physicians in France. The three age groups had similar values for the RTSS, VAS and RQLQ, which were also similar to those previously observed in populations of adults (25,26). Hence the present results can probably be generalized to clinical practice (30). The study was performed in France, and so the findings may differ in other countries. However, VAS data from adults are similar in European countries and Japan.

In conclusion, our study of 806 adults, adolescents and children with grass-pollen-induced AR showed that the most bothersome self-reported symptom was rhinorrhoea in adults and adolescents and ocular pruritus in children. Particular attention should be paid to ocular symptoms in the management of this allergic condition. We confirmed the correlation between a VAS score for AR symptom-related discomfort and the RTSS and RQLQ scores in adults suffering from grass pollen AR but also extended this finding to adolescents and children – confirming the value of the VAS as an easy-to-use tool for investigating the impact of AR on a patient's life.

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Authors' contributions

PhD conceived the study, participated in its design and coordination, helped to draft the manuscript and participated in data collection and statistical analysis. PJB, SGD, HS and PaD interpreted data and helped to revise the manuscript for critical content. JB interpreted data and helped to draft the manuscript. OdB participated in the study's design and coordination. All authors read and approved the final manuscript.

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Figure 1. Distribution of the self-reported, single most bothersome symptom, by age group at inclusion (n=802; missing data=4)

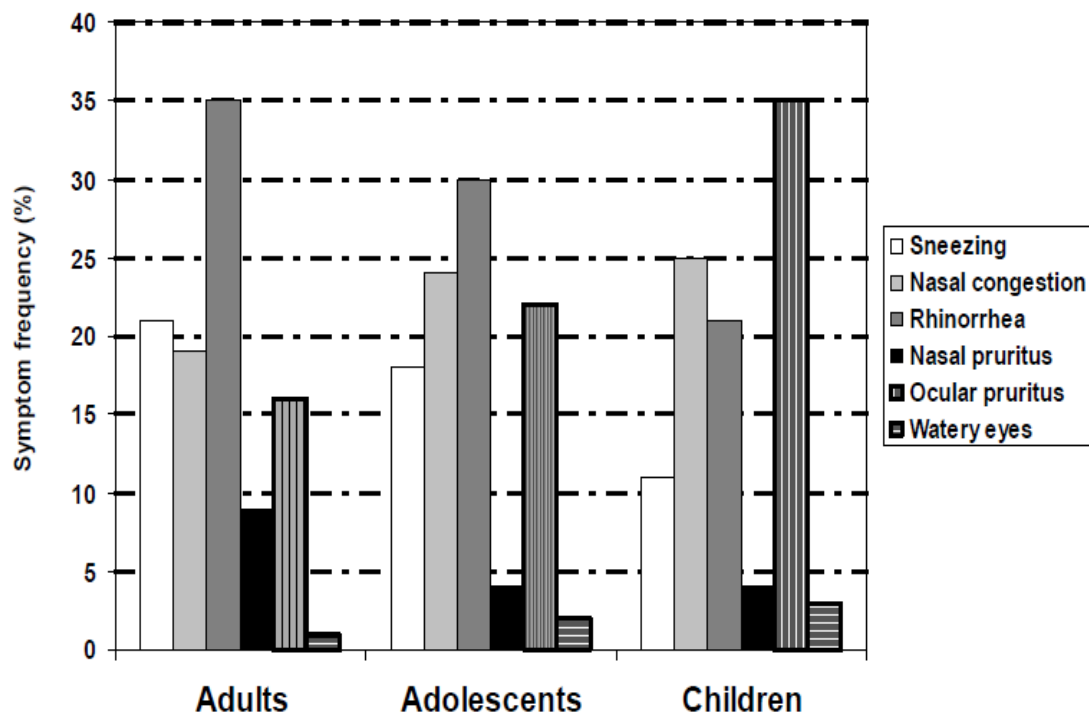
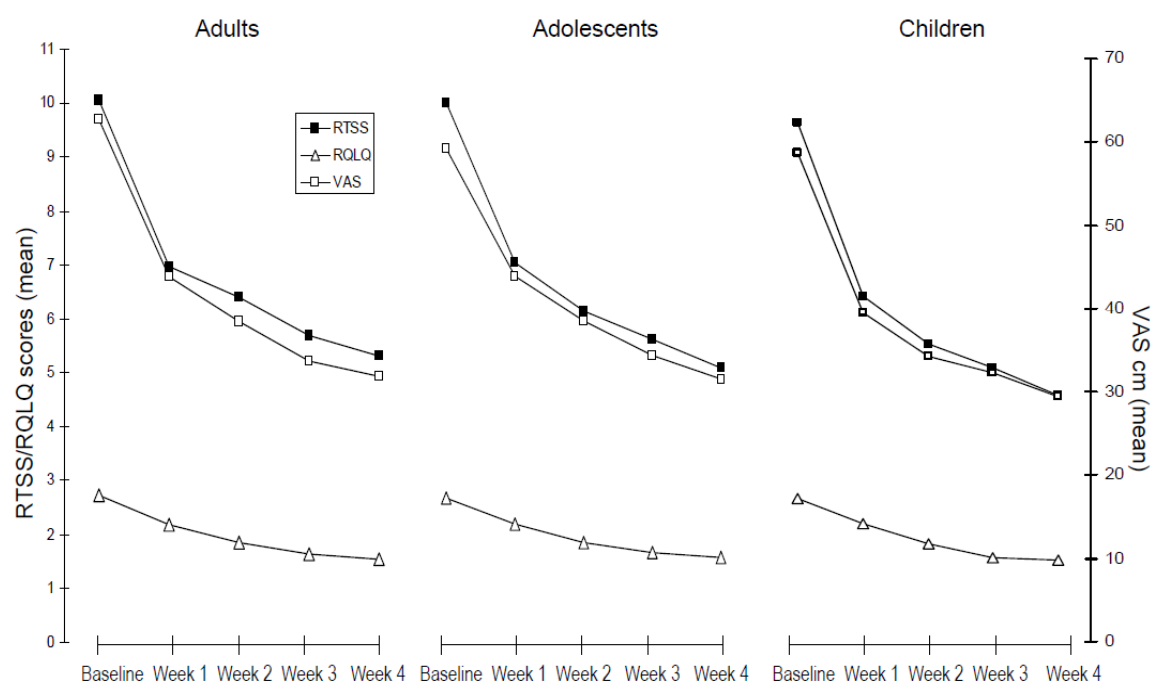


Figure 2. Change in symptom scores and quality of life over the 4-week study period in the three age groups.



Tables

Table 1. Impact of symptoms on the RQLQ score. Poor quality of life was defined as a RQLQ ≥ 4 and the presence of moderate-to-severe symptoms as a mean individual symptom score (ranging from 0 to 3) ≥ 2 over three days (the day of the inclusion visit and the two previous days). The OR [95%CI] (generated using the Miettinen method) was calculated with regard to the absence of symptoms or the presence of mild symptoms only (mean score < 2).

Symptom	Adults (n = 303)	Adolescents (n = 250)	Children (n = 253)
Sneezing	1.57 (0.71–3.46) <i>n.s.</i>	1.29 (0.48–3.43) <i>n.s.</i>	1.50 (0.63–17.59) <i>n.s.</i>
Rhinorrhoea	1.24 (0.57–2.68) <i>n.s.</i>	1.97 (0.65–5.99) <i>n.s.</i>	1.33 (0.59–2.98) <i>p</i> < 0.01
Nasal pruritus	1.22 (0.59–2.52) <i>n.s.</i>	3.78 (1.42–10.09) <i>p</i> < 0.01	2.82 (1.22–6.50) <i>p</i> < 0.02
Nasal obstruction	1.84 (0.87–3.89) <i>n.s.</i>	3.30 (1.13–9.60) <i>p</i> < 0.05	1.71 (0.71–4.15) <i>n.s.</i>
Ocular pruritus	3.10 (1.48–6.51) <i>p</i> < 0.01	5.67 (1.83–17.59) <i>p</i> < 0.01	2.32 (1.00–5.38) <i>p</i> < 0.05
Ocular watering	4.48 (2.25–8.93) <i>p</i> < 0.001	3.07 (1.25–7.52) <i>p</i> < 0.02	2.54 (1.16–5.58) <i>p</i> < 0.05

Table 2: The correlations (Pearson's coefficient) between VAS, RQLQ and RTSS scores and between changes in these scores.

		VAS						Changes in VAS		
		W1	W2	W3	W4			W1/2	W2/3	W3/4
RQLQ	Children	0.64	0.74	0.71	0.75	Changes in RQLQ	Children	0.51	0.58	0.50
	Adolescents	0.69	0.73	0.74	0.78		Adolescents	0.56	0.51	0.60
	Adults	0.60	0.74	0.76	0.80		Adults	0.61	0.69	0.63
RTSS	Children	0.80	0.81	0.80	0.81	Changes in RTSS	Children	0.77	0.81	0.73
	Adolescents	0.85	0.86	0.86	0.88		Adolescents	0.80	0.80	0.84
	Adults	0.79	0.83	0.83	0.83		Adults	0.82	0.85	0.80

W = week

Table E1. Characteristics of the study population, by age group.

	Adults n=303	Adolescents n=250	Children n=253
Demographics			
Males	99 (33.7%)	144 (57.6%)	157 (62.1%)
Females	204 (67.3%)	106 (42.4%)	96 (37.9%)
Age (years)	34.3 ± 11.4	14.8 ± 1.7	9.3 ± 1.6
BMI	24 ± 4.3	20 ± 3.1	17 ± 2.5
Risk factors			
Exposure to smoking	74 (24.4%)	48 (19.2%)	47 (18.6%)
Active smokers	42 (13.9%)	7 (2.8%)	1 (0.4%)
Exposure to pets	120 (39.6%)	129 (51.6%)	115 (45.6%)
Duration of AR, and sensitization status			
Duration of AR* (years)	12.5 ± 9.1	5.7 ± 3.1	3.4 ± 1.7
Monosensitization to grass pollen	73 (24.1%)	52 (20.8%)	61 (24.1%)
Symptomatic medication use prior to study inclusion (% of patients)			
Oral antihistamines	237 (78.2%)	186 (74.4%)	189 (74.7%)
Nasal corticoids	95 (31.4%)	76 (30.4%)	65 (25.7%)
Cromone eye drops	7 (2.3%)	52 (20.8%)	63 (24.9%)
Nasal antihistamines	28 (9.2%)	28 (11.2%)	24 (9.5%)
Leukotriene receptor antagonist (montelukast)	10 (3.3%)	19 (7.6%)	18 (7.1%)
Vasoconstrictors	9 (3.0%)	2 (0.8%)	0

AR: allergic rhinoconjunctivitis; BMI: body mass index. Data are expressed as the number (percentage) or the mean ± SD.

Table E2. Classification of the patients according to the ARIA classification and symptom severity (n=796, MD=10).

	Adults (n=301, MD=2)	Adolescents (n=245, MD=5)	Children (n=250, MD=3)	Total
Classification of AR (n=796, MD=10)				
Intermittent mild	4 (1.3%)	12 (4.9%)	8 (3.2%)	24 (3.0%)
Intermittent moderate-to-severe	17 (5.6%)	20 (8.2%)	22 (8.8%)	59 (7.4%)
Persistent mild	13 (4.3%)	18 (7.3%)	17 (6.8%)	48 (6.0%)
Persistent moderate-to-severe	267 (88.7%)	195 (79.6%)	203 (81.2%)	665 (83.5%)
Severity of AR at inclusion (n=796, MD=10)				
RTSS (mean $\pm$ SD)	10.1 $\pm$ 2.9	9.8 $\pm$ 2.8	9.8 $\pm$ 2.6	
VAS (mm)	61.7 $\pm$ 20.3	56.8 $\pm$ 21	58.7 $\pm$ 23.6	

MD: missing data; AR: allergic rhinoconjunctivitis; RTSS: Rhinoconjunctivitis Total Symptom Score; SD: standard deviation; VAS: visual analogue scale.

13 **Table E3.** RQLQ score at inclusion in the three age groups.

RQLQ	Adults <i>(n = 303)</i>	Adolescents <i>(n = 250)</i>	Children <i>(n = 253)</i>
Global score	2.72 ± 1.09	2.53 ± 1.03	2.66 ± 1.02
Nasal symptoms	3.35 ± 1.30	3.50 ± 1.34	3.33 ± 1.21
Eye symptoms	2.26 ± 1.50	2.46 ± 1.65	2.72 ± 1.73 ^{\$}
Non-hay fever symptoms	1.94 ± 1.35	1.70 ± 1.26	1.90 ± 1.27
Activities	3.20 ± 1.30	3.03 ± 1.58	2.49 ± 1.27
Practical problems	4.03 ± 1.35	2.88 ± 1.27	3.15 ± 1.19
Emotions	2.11 ± 1.53	1.76 ± 1.31	<i>nd</i>
Sleep	1.98 ± 1.67	1.93 ± 1.79*	<i>nd</i>

14

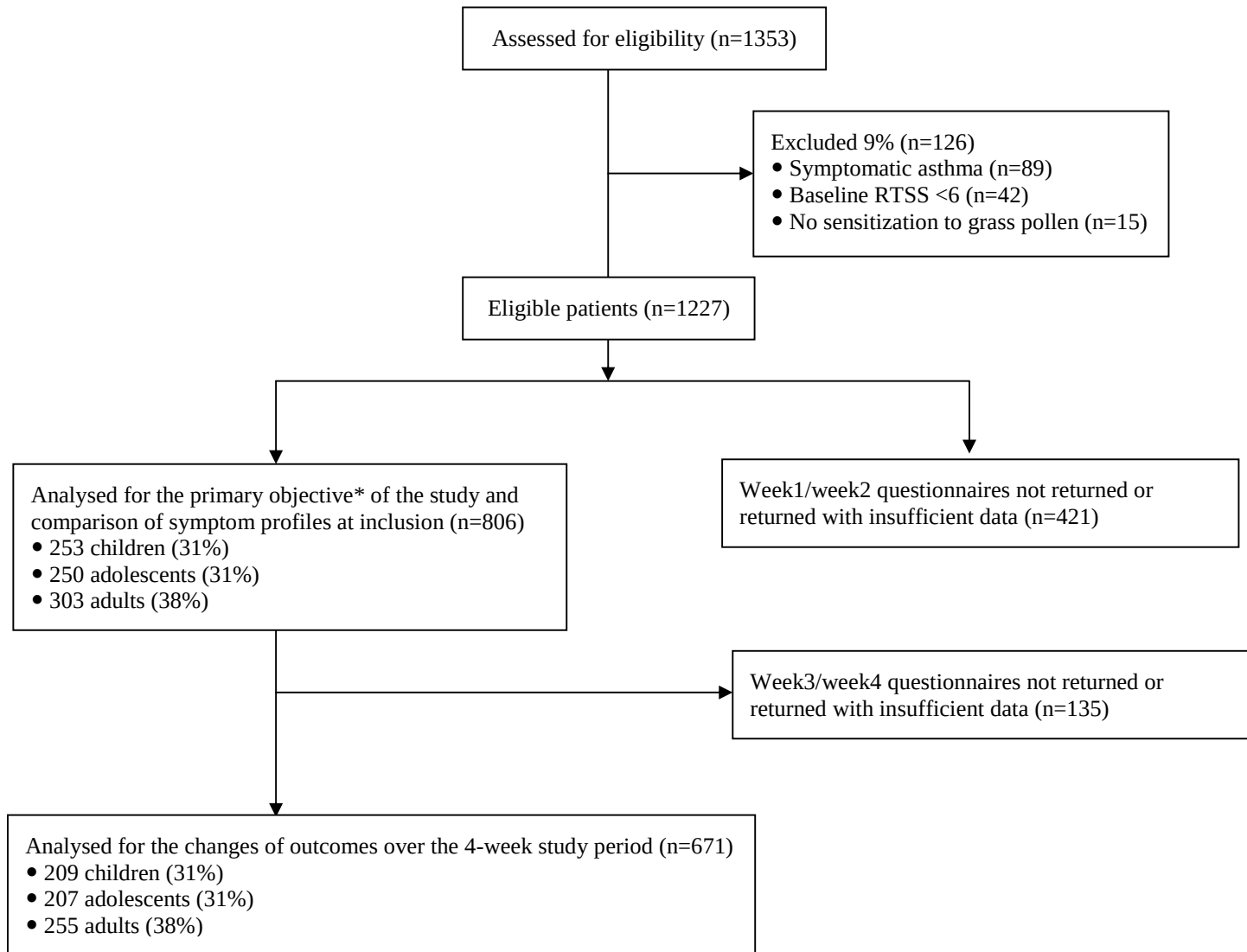
15 Results are expressed as the mean ± SD. * This score corresponds to a single item in the “practical
16 problem” section (“lack of a good night’s sleep”) in the RQLQ for adolescents. \$ p<0.05 vs. adults.

17 *nd*: not determined because these items do not feature in the paediatric RQLQ.

18

19 **Figure E1. Patient disposition**

20



* NB: this was the full analysis set for determination of the study's primary objective (the minimally important difference; see reference 12).