

Received Date : 28-Apr-2016

Revised Date : 18-Jul-2016

Accepted Date : 09-Aug-2016

Article type : Original Article-Epidemiology of Allergic Disease

In allergic rhinitis, work, classroom and activity impairments are weakly related to other outcome measures.

Philippe Devillier^{1,2}, Jean Bousquet³, Hélène Salvator^{1,2}, Emmanuel Naline^{1,2}, Stanislas Grassin-Delye², and Olivier de Beaumont⁴

¹ UPRES EA 220, Université de Versailles Saint-Quentin, Suresnes, France

² Clinical Pharmacology Unit, Department of Airway Diseases, Foch Hospital, Suresnes, France

³ INSERM, VIMA: Ageing and chronic diseases. Epidemiological and Public Health Approaches, U1168, Paris, and Université de Versailles Saint-Quentin, UMR-S 1168, Versailles, France.

⁴ Stallergenes SA, Antony, France

Running title

Impact of allergic rhinitis

Correspondence

Professor Philippe Devillier

UPRES EA 220, Foch Hospital, 11 rue Guillaume Lenoir, F-92150 Suresnes, France

p.devillier@hopital-foch.org

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cea.12801

This article is protected by copyright. All rights reserved.

Abstract

Background: The impact of grass-pollen-induced allergic rhinoconjunctivitis (AR) on classroom/work productivity and activities can be assessed with a specific instrument: the Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI-AS). The present study evaluated the relationships between the WPAI-AS and other outcome measures in AR.

Methods: Adolescents (aged 12–17) and adults (aged 18–65) consulting specialists for AR were enrolled in a four-week, multicentre, observational study. The management of AR was left to the physicians' discretion. Participants regularly rated the WPAI-AS, their symptoms (using the Rhinoconjunctivitis Total Symptom Score (RTSS) and a 0-to-100 mm visual analogue scale (VAS)), and quality of life (according to the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)).

Results: 247 adolescents and 292 adults showed similar baseline impairments in classroom/work productivity and activities other than work. In both age groups, the WPAI-AS scores were moderately correlated with the RQLQ score and, to a lesser extent, with the VAS score and the RTSS. A multiple regression analysis indicated that the RQLQ score was a weak but statistically significant predictor of both impaired work/classroom productivity and daily activities. A 50 mm VAS cut-off categorized patients in whom AR had the greatest impact on productivity.

Conclusions: Grass-pollen-induced AR impairs work/classroom and daily activity to a similar extent in adults and adolescents. The weak-to-moderate correlations with AR symptom scores and quality of life scores suggest that a specific tool (such as the WPAI-AS) should be used to assess AR's impact on word/classroom productivity and daily activities.

Abstract: 250 words

Keywords

Allergic rhinoconjunctivitis; grass pollen, productivity, activities, outcomes.

Introduction

As a very common disease, allergic rhinitis (AR) is often trivialized, and its detrimental effects are often underestimated by both sufferers and physicians (1-3). Allergic rhinitis can significantly disrupt quality of life (QoL) and impair work productivity or classroom performance and other daily activities in sufferers (4-10). The symptoms of AR can also disturb sleep, which further degrades QoL, activities of daily living and performance at work or in the classroom (11-13). AR can occur throughout life, and so the disease's socioprofessional impact may differ when comparing adolescents and adults.

In clinical studies, the severity of AR is commonly evaluated through patient-reported assessments of the intensity of the main individual symptoms (sneezing, rhinorrhoea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes). The individual symptom scores are then summed to yield the Rhinoconjunctivitis Total Symptom Score (RTSS) (14-15). The overall intensity of the symptoms can also be easily assessed by scoring a visual analogue scale (VAS) (16-17). The impact on QoL can be measured by administering a disease-specific questionnaire, such as the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (18,19). Although AR's impact on productivity can be evaluated with various instruments, the psychometric properties of the Work Productivity and Activity Impairment Questionnaire have been assessed most extensively (20). Furthermore, an allergy-specific version has been developed (the Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI+CIQ:AS, further abbreviated hereafter to WPAI-AS)) and used to measure the productivity changes associated with AR (21).

The EQUINOXE 2 study was an observational, prospective, multicentre study of adults, adolescents and children consulting specialist physicians (including allergists, paediatricians, chest physicians and ear, nose & throat specialists) across France for grass-pollen-induced allergic AR during the grass pollen period (15). EQUINOXE 2's primary objective was to establish the minimally important difference in the RTSS in this population (15). The study's secondary objectives were to (i) compare symptom profiles and impacts in the three age groups (22) and (ii) assess AR's impact on work/classroom and daily activities (according to the WPAI-AS) and sleepiness (according to the Epworth Sleepiness Scale (ESS)).

There is a paucity of data on the relationships between the RTSS, VAS and RQLQ on one hand and the impact of AR on the productivity and daily activities (as assessed with the WPAI-AS) on the other. The aim of the present study was to investigate the relationship between the WPAI-AS and various measures of AR severity (the VAS and RQLQ scores, and the RTSS). If this relationship is weak, one can consider that (i) AR symptom scores and quality of life scores should not be used as proxy measures of impaired work/classroom productivity, and (ii) a specific instrument (such as the WPAI-AS) should always be applied. Lastly, since the symptom profiles for adolescents and adults differ (22), these putative relationships were studied in the two age groups separately.

Methods

Study design and participants

The EQUINOXE 2 study was an observational, prospective, multicentre study conducted during the 2011 grass pollen season (between April 11th and June 30th). Briefly, patients between 12 and 65 years were included if they (i) had physician-documented grass pollen-induced AR, (ii) were consulting an specialist physician with expertise in allergy 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 (12,15). Sensitization to grass pollen and other allergens had to be documented by skin prick tests and/or specific IgE assays at or prior to the inclusion visit. 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, and food allergy) or concomitant condition that might interfere with the evaluation of the symptoms of allergic rhinoconjunctivitis, QoL, fatigue, and daily activities (15). The evaluation of persistent or intermittent asthma (the main confounding factor) was based on the physician's assessment, the patient's medical history and the use of reliever and/or controller asthma medications. Recruitment was stratified so that similar numbers of adults and adolescents were included. Each physician was free to decide how to manage AR in his/her patients.

Assessments

On the day of consultation, the physicians completed a questionnaire in order to record the patient's sociodemographic variables, AR symptoms, concomitant diseases (if any) and the treatment(s) prescribed. At inclusion and for the four weeks following inclusion in the study, each patient was asked to complete several questionnaires.

The patients completed the French version of the WPAI-AS on a weekly basis (21). The WPAI-AS scale measures the impact of allergies on work/classroom productivity and on activities other than work. It is scored from 0 ("allergies had no effect on my work/classwork/daily activities") to 10 ("allergies completely prevented me from working/doing my class work/doing my daily activities"). The WPAI-AS calculates the overall work or classroom impairment due to allergies as a percentage by adding the percentage of hours missed to the percentage of impairment while working or in the classroom during the hours worked. The WPAI-AS also calculates the percentage activity impairment due to allergies. WPAI-AS scores range from 0 to 100%, with higher scores reflecting greater impairment and thus lower productivity.

Furthermore, the patients provided data on (i) the RTSS on a daily basis, using the four-point scale (0 = absence of symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms) to score four individual nasal symptoms (sneezing, rhinorrhoea, congestion and itching) and two ocular symptoms (tearing and itching), (ii) the overall intensity of the allergy symptoms (on a 100 mm VAS ranging from 0 – "no symptoms" – to 100 mm – "very severe symptoms") on a daily basis and (iii) QoL (using an adult- or adolescent-specific version of the RQLQ) on a weekly basis. Each of the items in the RQLQs for adults and adolescents is rated on a 7-point scale from 0 ("not at all bothersome") to 6 ("extremely bothersome") (18,19).

Lastly, the adults (but not the adolescents) completed the ESS questionnaire on a weekly basis [20]. The ESS is rated from 0 ("would never doze") to 3 ("a high chance of dozing") for eight everyday situations, giving an overall score that ranges from 0 to 24 (23).

The study's observation period was limited to four weeks, in order to boost the questionnaire return rate and reduce the drop-out rate.

Ethics

The study was approved by an independent ethics committee (IEC: *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

All statistics were performed with SAS (version 9.2) or Statview (version 5) software (both from SAS Institute Inc., Cary, NC, USA). In each of the two age groups, the strength of the association between the WPAI-AS score and the other outcome measures was examined using Pearson's correlation coefficient (denoted as r) and a backward stepwise multiple regression analysis. r was calculated for (i) the correlation between the WPAI-AS scores and the average RTSS, RQLQ score and VAS score at the inclusion visit and then every week over the four weeks of follow-up, and (ii) the correlation between the weekly changes in WPAI-AS scores and the weekly changes in the RTSS, RQLQ score and VAS score over the four weeks. The p value for r was calculated using Fisher's r to z test. A score of over 60 mm on a 0-to-100 mm VAS has been validated for categorizing patients with moderate/severe rhinitis (16). Three groups were considered: patients with a VAS score below 50 mm (categorized as having mild rhinitis), those with a score of 60 mm or more (categorized as having severe rhinitis), and those with a score of 50 mm or more. These subgroups were compared using a Mann-Whitney test, to determine whether these VAS score thresholds distinguish between subgroups of patients with different WPAI-AS scores.

RESULTS

The study population

Valid data for analysis were obtained from 247 adolescents and 292 adults, all of whom had filled out the WPAI-AS (at least for the daily activity impairment) and the symptom scores at the inclusion visit and for at least the first two weeks of the study (Table 1, Figure 1). The great majority of patients were suffering from moderate-to-severe AR, according to the ARIA classification (Table 1).

Thirty-six percent of the adolescents were attending junior high ("*college*") and 62% were attending high school ("*lycée*"). Sixteen percent of the adults were attending high school or were in higher education, 67% were salaried employees or self-employed, and 17% were unemployed or retired.

Adults were more likely than adolescents to be active smokers (56.7% vs. 14.6%, respectively). Symptomatic treatments for AR were prescribed to the same extent in adolescents and adults. The proportion of patients taking leukotriene receptor antagonists was higher for adolescents than for adults (7.7% vs. 3.4%, respectively). Vasoconstrictors were rarely prescribed (Table 1). Overall, half of the participants (52%, for both adults and adolescents) had been treated or were being treated with allergen immunotherapy. The proportion of polysensitized patients did not differ significantly according to the age group (75.7% in adults and 78.8% in adolescents), and the sensitisation profiles were similar (Table 1). There were no significant differences between the age groups in terms of exposure to pets and or the prevalence of concomitant co-morbidities (Table 1).

WPAI-AS scores on inclusion

The baseline (inclusion) WPAI-AS scores ranged from 27.3% to 39.8%, and were similar in adults and adolescents (Table 1). The WPAI-AS scores were significantly ($p<0.0001$) and positively correlated with the other outcome measures (Table 2).

The weakest correlations ($r=0.26$ to 0.35) were observed for the WPAI-AS scores and the RTSS calculated over three days (i.e. scored on the day of the inclusion visit and recalled for each of the previous two days). The strongest correlations were observed for the RQLQ score and (to a lesser extent) the VAS score (Table 2). In both adolescents and adults, a multiple regression analysis indicated that both the RQLQ and VAS scores were significant predictors of activity impairment but that only the RQLQ score was predictive of work/classroom impairment.

The correlations between the WPAI-AS scores and the RQLQ's "no hay fever" domain (including items on fatigue, productivity and concentration) and "activities limitation" domain ranged from $r=0.51$ to 0.66 , and thus were similar to those calculated for the overall RQLQ score. The strongest correlation ($r=0.71$) was found for work/classroom impairment and the adolescence-specific RQLQ's "unable to do your work (school work) as well as usual" item.

In adults, the correlations between the WPAI-AS scores and the ESS score were weak ($r=0.34$ for work/classroom impairment and $r=0.28$ for activity impairment). The correlations between either the overall RQLQ score or the RQLQ's sleep domain score and the ESS score were also weak ($r=0.43$ and 0.31 , respectively). The strongest correlation ($r=0.45$) was found for the ESS score and the "tiredness" item in the RQLQ, while the weakest correlations were found for the VAS and the RTSS ($r=0.18$ and 0.16 , respectively; $p<0.05$).

The use of VAS cut-off levels to categorize adults and adolescents with mild or moderate/severe AR to grass pollen was associated with clear, highly significant differences in the WPAI-AS scores (Table 3). Furthermore, the ESS score also differed when comparing patients with mild vs. moderate/severe AR. Lastly, the use of a cut-off level of 50 mm (rather than 60 mm) to categorize patients with severe AR did not change the results in this respect (Table 3).

Changes in WPAI-AS scores and other outcome measures during the study

The WPAI-AS scores and the other patient-reported outcome measures were measured weekly over a 4-week period, and the changes over this period for adolescents and adults are shown in Figure 2. The reductions (relative to baseline) in either the classroom/work or activity impairment were similar in adolescents (33% and 45%, respectively) and adults (30% and 43%, respectively) and were associated with reductions (relative to baseline) in RTSS, VAS, and RQLQ levels.

In both adolescents and adults, the strongest correlations were seen for the WPAI-AS scores and the weekly RQLQ (range: $r=0.55-0.82$) and for the changes in these two scores (range: $r=0.44-0.68$) from one week to the next (Table 4). The correlations between the WPAI-AS scores and the weekly average VAS and those between the changes in these two scores from one week to the next were in the same range as the correlations between the WPAI-AS and the RTSS scores in both adolescents and adults (Table 4).

Lastly, the AR's impact on sleepiness in the adult group (which was modest at inclusion) barely changed over the 4-week assessment period, with a 14.5% fall in the ESS score and non-significant or very weak correlations with the VAS or RQLQ scores (data not shown).

Discussion

In the present prospective, observational study of equivalent numbers of adolescents and adults suffering from AR (15), our main findings were that (i) the impact of AR on WPAI-AS scores is similar in adolescents vs. adults, (ii) impairments in work/classroom productivity and daily activities are weakly to moderately correlated with the RQLQ score, the VAS score and the RTSS, (iii) patients with troublesome symptoms (VAS score ≥ 50) have higher WPAI-AS scores and greater ESS scores than those with milder disease (VAS score < 50), and (iv) changes in WPAI-AS scores are also weakly to moderately correlated with the changes in the RQLQ score, the VAS score and the RTSS.

Study strengths and limitations

This is the first study to have (i) compared AR-associated impairments in adolescents and adults, and (ii) studied the relationship between the WPAI-AS and three conventional AR outcome measures (and particularly the VAS) in a “real-life” setting (given the observational nature of the study, the representative sample of the population of patients consulting allergists and other specialist physicians, and the fact that each physician was free to decide how to manage AR in his/her patients). Although the study's design was not optimal for assessing absolute treatment efficacy, it was appropriate for comparing outcome measures. Furthermore, we cannot rule out the possibility that the characteristics of patients who completed the questionnaires differ from those of patients who chose not to complete them. However, we did not observe any differences in characteristics on inclusion when comparing patients screened for eligibility with evaluable patients having returned the

questionnaires with appropriate data. Furthermore, the risk of heterogeneity in the way the questionnaires were administered by the investigating physicians and/or interpreted by the patients was reduced by the standardization of data collection (i.e. the provision of comprehensive written instructions on filling out the questionnaires).

Discussion of the results

The two age groups had similar values for the RTSS, VAS and RQLQ, which in turn were similar to those reported previously for populations with moderate-to-severe AR consulting in primary care (16,17,24). The impairment of work/classroom productivity and the restriction of daily activities in patients suffering from AR has been assessed in various types of study over the last ten years. In two French studies (a cross-sectional study of a large population of patients with moderate-to-severe AR consulting in primary care, and a pragmatic, randomized study in grass pollen-induced AR), the WPAI-AS scores for work/classroom productivity and daily activities were somewhat higher than in the present study (6,26), as were the scores in three US clinical trials measuring the efficacy of antihistamines in seasonal AR (27-29). In contrast, the WPAI-AS scores at inclusion for daily activities and classroom impairment in a Japanese clinical trial evaluating the effect of an antihistamine on productivity during the peak cedar pollinosis season were similar to the values noted in the present study (although the work impairment score was somewhat higher) (30). Overall, the WPAI-AS scores in the present study are of the same order of magnitude as those reported in the literature on patients with AR.

Few studies have studied the putative correlation between the WPAI-AS and other outcome measures. In earlier work, the WPAI-AS score has been weakly to moderately correlated with the AR total symptom score (21) or the ARIA severity score (6). Changes in the WPAI-AS score were correlated with changes in the total nasal symptom score recorded in three clinical trials of antihistamines, and the strength of the correlation was similar to that observed in the present study (21,28). However, the present study extended these findings by documenting the relationship between the WPAI-AS and other outcome measures in AR (the RQLQ, a VAS and the RTSS). The strongest (but moderate) correlations were found for the RQLQ. This result might be because the domains explored by the RQLQ cannot be assessed with the RTSS or a VAS. We conclude that neither the RQLQ, a VAS nor the RTSS can reliably replace specific tools (such as the WPAI-AS) for evaluating AR's impact on productivity. However, the VAS is a simple tool with similar characteristics in adults and adolescents for assessing AR-symptom-related discomfort (22). Patients with a score ≥ 50 on a 0-to-100 VAS can be ascribed to a "troublesome symptoms" group and had a significantly greater WPAI-AS score than those with a VAS score < 50 . Furthermore, the VAS-based "MASK aerobiology" smartphone application (promoted by the Integrated Care Pathways for Airway Diseases initiative) is freely available in 15 European countries (31,32). In this context, the cut-off level of 50 (on a 0-to-100

VAS) may be particularly useful for identifying and monitoring adults and adolescents with a high risk of impairment at work, in the classroom and in other daily activities.

Lastly, we found that grass-pollen AR had a relatively weak impact on daytime sleepiness (as previously reported in seasonal AR)(33). The ESS score was weakly correlated with the VAS score. However, sleep impairment can be observed in patients with severe AR (11,29), as found in the present study for patients with a VAS score ≥ 50 mm. There was also a weak correlation between the ESS score and all the other outcome measures.

Generalizability

The present study was a “real-life” assessment of patients treated by specialist physicians. Hence, the present results can probably be generalized to clinical practice, for the following reasons.

In the present study, the two age groups (adolescents and adults) had similar values for the RTSS, VAS and RQLQ, which in turn were similar to those reported previously for populations consulting in primary care for AR (16,17,24). For example, the values of the RTSS, RQLQ and VAS quoted in a study of 990 unselected adults consulting for AR were respectively 9.7 ± 3.8 , 2.7 ± 1.1 , and 60.9 ± 19.8 (17). These values are similar to the values in the present study, in both adults and adolescents, respectively: RTSS (10.1 ± 2.9 and 9.8 ± 2.8), RQLQ (2.7 ± 1.1 and 2.5 ± 1.0), VAS (61.7 ± 20.3 and 56.8 ± 21.0).

Lastly, the present study was performed in France, and so the findings may differ in other countries.

Conclusion

In addition to conventional outcome measures in AR (such as the RTSS, the RQLQ and easy-to-use tools like the VAS), a specific instrument (such as the WPAI-AS) should be used when assessing AR-associated impairments in work/classroom productivity and in daily activities. However, a score of 50 mm and more on a 0-to-100 mm VAS (corresponding to patients with mainly moderate to severe AR) could also be very useful for identifying patients at risk of productivity impairments (particularly through the use of the MASK smartphone application).

List of abbreviations

Abbreviation	Meaning
AR	allergic rhinoconjunctivitis
ARIA	Allergic Rhinitis and its Impact on Asthma
ESS	Epworth Sleepiness Scale
QoL	quality of life
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RTSS	Rhinoconjunctivitis Total Symptom Score
SD	standard deviation
VAS	visual analogue scale
WPAI+CIQ:AS and WPAI	Work Productivity and Activity Impairment Questionnaire + Classroom Impairment Questions: Allergy Specific

Competing interests

Philippe Devillier has received consulting fees, honoraria for lectures and/or research funding from Schering-Plough-MSD, Sanofi-Aventis, GlaxoSmithKline, Chiesi, AstraZeneca, ALK and Stallergenes. Jean Bousquet has received honoraria for participation in scientific advisory boards (from Almirall, Meda, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva and Uriach) and seminars at scientific meetings (from Almirall, AstraZeneca, Chiesi, GSK, Meda, Menarini, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva and Uriach) and is a board member at Stallergenes. Stanislas Grassin-Delyle, Hélène Salvator and Emmanuel Naline have no competing interests. Olivier de Beaumont is an employee of Stallergenes.

Authors' contributions

Philippe Devillier conceived the study, participated in its design and coordination, participated in data collection, performed the statistical analysis, participated in data interpretation and drafted the manuscript. Jean Bousquet interpreted data and helped to draft the manuscript. Stanislas Grassin-Delyle, Hélène Salvator, and Emmanuel Naline helped to manage data and draft the manuscript. Olivier de Beaumont participated in the study's design and coordination. All authors read and approved the final manuscript. This study was funded by Stallergenes and the study sponsor was Foch Hospital. A contract research organization (Universal Medica, Saint-Cloud, France) was in charge of the logistic aspects of data collection.

Acknowledgements

We thank David Fraser D.Phil. (Biotech Communication SARL, Damery, France) for medical writing support (funded by Stallergenes).

References

1. Asher MI, Montefort S, Björkstén B, Lai CKW, Strachan DP, Weiland SK, Williams H: Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**:733-743.
2. D'Amato G, Cecchi L, Bonini S, Nunes C, Annesi-Maesano I, Behrendt H, Liccardi G, Popov T, van Cauwenberge P: Allergenic pollen and pollen allergy in Europe. *Allergy* 2007;**62**:976-990.
3. Bousquet J, Khaltayev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, Zuberbier T, Baena-Cagnani CE, Canonica GW, van Weel C, et al: Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;**63** Suppl 86:8-160.
4. Leynaert B, Neukirch C, Liard R, Bousquet J, Neukirch F. Quality of life in allergic rhinitis and asthma. A population-based study of young adults. *Am J Respir Crit Care Med*. 2000;**162**:1391–1396.
5. 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**:413–423.
6. Bousquet J, Neukirch F, Bousquet PJ, Gehano P, Klossek JM, Le Gal M, et al. Severity and impairment of allergic rhinitis in patients consulting in primary care. *J Allergy Clin Immunol* 2006;**117**:158–162.
7. Szeinbach SL, Seoane-Vazquez EC, Beyer A, Williams PB. The impact of allergic rhinitis on work productivity. *Prim Care Respir J* 2007;**16**:98–105.

- Accepted Article
8. Walker S, Khan-Wasti S, Fletcher M, Cullinan P, Harris J, Sheikh A. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study. *J Allergy Clin Immunol* 2007;**120**: 381–387.
 9. Meltzer EO: Quality of life in adults and children with allergic rhinitis. *J Allergy Clin Immunol* 2001;**108**:S45-53.
 10. Simons FE. Learning impairment and allergic rhinitis. *Allergy Asthma Proc* 1996 ;**17**:185-9.
 11. Leger D, Annesi-Maesano I, Carat F, Rugina M, Chanal I, Pribil C, et al. Allergic rhinitis and its consequences on quality of sleep: an unexplored area. *Arch Intern Med* 2006;**16**:1744–1748.
 12. Santos CB, Pratt EL, Hanks C, McCann J, Craig TJ: Allergic rhinitis and its effect on sleep, fatigue, and daytime somnolence. *Ann Allergy Asthma Immunol* 2006;**97**:579-586.
 13. Stull DE, Schaefer M, Crespi S, Sandor DW: Relative strength of relationships of nasal congestion and ocular symptoms with sleep, mood and productivity. *Curr Med Res Opin* 2009;**25**:1785-1792.
 14. European Medicines Agency. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases CHMP/EWP/18504/2006.
 15. Devillier P., Chassany O, Vicaut E, Beaumont OD, Robin B, Dreyfus J, Bousquet P.J. The Minimally Important Difference in the Rhinoconjunctivitis Total Symptom Score in Grass-Pollen-Induced Allergic Rhinoconjunctivitis. *Allergy* 2014;**69**:1689-1695.
 16. Bousquet PJ, Combescure C, Neukirch F, Klossek JM, Mechin H, Daures JP, et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. *Allergy* 2007;**62**:367-372.
 17. Demoly P, Bousquet PJ, Mesbah K, Bousquet J, Devillier P. Visual analogue scale in patients treated for allergic rhinitis: an observational prospective study in primary care: asthma and rhinitis. *Clin Exp Allergy* 2013;**43**:881-888.
 18. Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol* 1996;**98**:843-845.
 19. 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**:413-423.

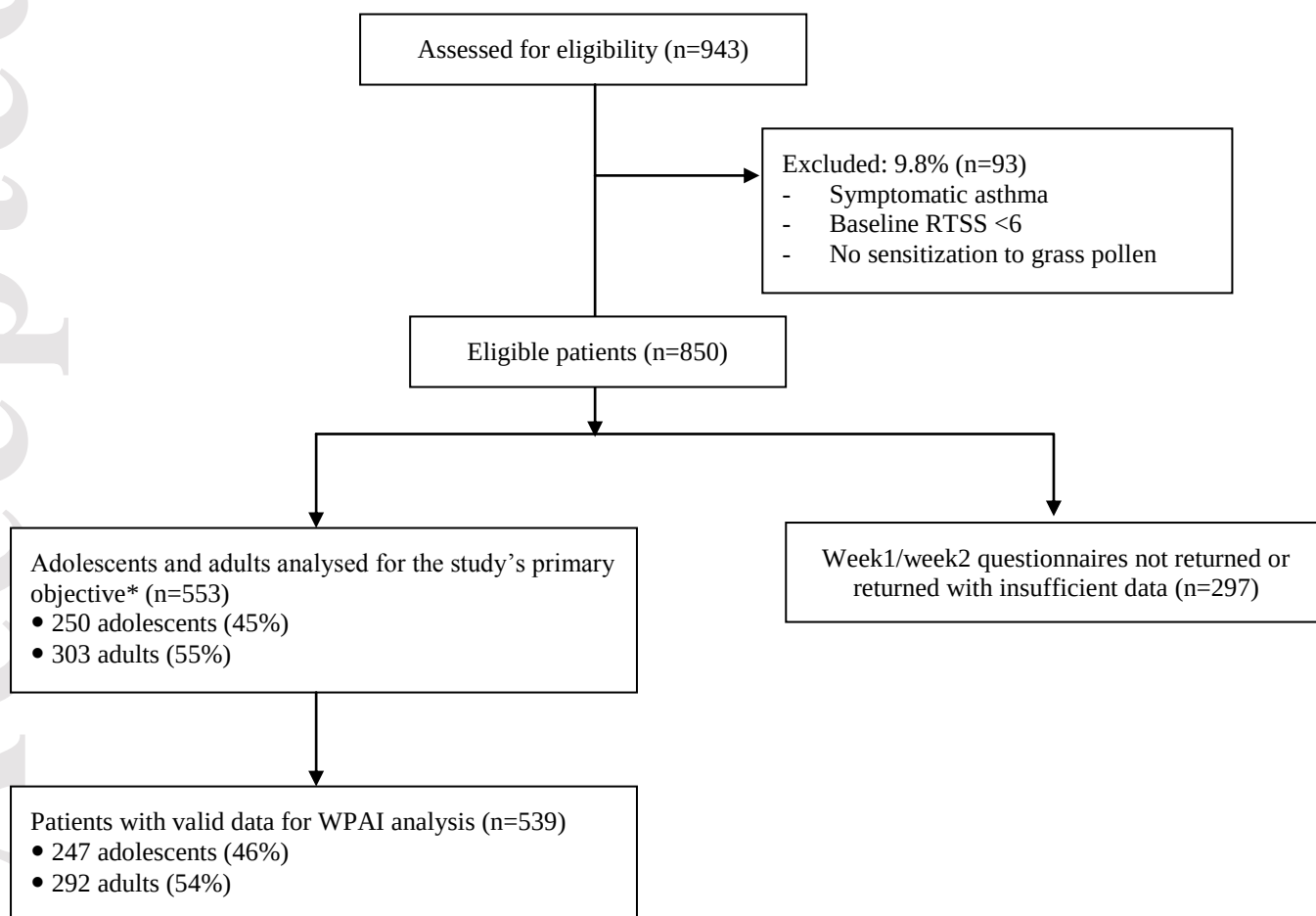
20. Prasad M, Wahlqvist P, Shikhar R, Shih YC. A review of self-report instruments measuring health-related work productivity: a patient-reported outcomes perspective. *Pharmacoeconomics* 2004;**22**:225-44.
21. Reilly MC, Tanner A, Meltzer EO: Work, classroom, and activity impairment instruments. Validation studies in allergic rhinitis. *Clinical Drug Investigations* 1996;**11**:278-288.
22. Devillier P, Bousquet PJ, Grassin-Delye S, Salvator H, Demoly P, Bousquet J, de Beaumont O. Comparison of outcome measures in allergic rhinitis in children, adolescents and adults. *Pediatr Allergy Immunol.* 2016 ;27 :375-81.
23. Johns MW: A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;**14**:540-545.
24. Bousquet PJ, Demoly P, Devillier P, Mesbah K, Bousquet J. Impact of allergic rhinitis symptoms on quality of life in primary care. *Int Arch Allergy Immunol* 2013;**160**:393-400.
25. de la Hoz Caballer B, Rodríguez M, Fraj J, Cerecedo I, Antolín-Amérigo D, Colás C. Allergic rhinitis and its impact on work productivity in primary care practice and a comparison with other common diseases: the Cross-sectional study to evaluate work Productivity in allergic Rhinitis compared with other common diseases (CAPRI) study. *Am J Rhinol Allergy* 2012;**26**:390-4.
26. Bousquet J, Bodez T, Gehano P, Klossek JM, Liard F, Neukirch F, Le Gal M, Janin N, Allaf B. Implementation of guidelines for allergic rhinitis in specialist practices. A randomized pragmatic controlled trial. *Int Arch Allergy Immunol* 2009;**150**:75-82.
27. Mansfield LE, Hampel F, Haeusler JM, Georges G. Study of levocetirizine in seasonal allergic rhinitis. *Curr Med Res Opin* 2010;**26**:1269-75.
28. Fairchild CJ, Meltzer EO, Roland PS, Wells D, Drake M, Wall GM. Comprehensive report of the efficacy, safety, quality of life, and work impact of Olopatadine 0.6% and Olopatadine 0.4% treatment in patients with seasonal allergic rhinitis. *Allergy Asthma Proc* 2007;**28**:716-23.
29. Segall N, Gawchik S, Georges G, Haeusler JM. Efficacy and safety of levocetirizine in improving symptoms and health-related quality of life in US adults with seasonal allergic rhinitis: a randomized, placebo-controlled study. *Ann Allergy Asthma Immunol* 2010;**104**:259-67.
30. Okubo K, Gotoh M, Shimada K, Ritsu M, Okuda M, Crawford B. Fexofenadine improves the

quality of life and work productivity in Japanese patients with seasonal allergic rhinitis during the peak cedar pollinosis season. *Int Arch Allergy Immunol* 2005;**136**:148-54.

31. Bousquet J, Schunemann HJ, Fonseca J, Samolinski B, Bachert C, Canonica GW, MACVIA-ARIA Sentinel Network for allergic rhinitis (MASK-rhinitis): the new generation guideline implementation. *Allergy* 2015;**70**:1372-92.
32. Bourret R, Bousquet J, Mercier J, Camuzat T, Bedbrook A, Demoly P, et al. MASK rhinitis, a single tool for integrated care pathways in allergic rhinitis. *World Hosp Health Serv* 2015;**51**:36-9.
33. Stuck BA, Czajkowski J, Hagner AE, Klimek L, Verse T, Hörmann K, Maurer JT. Changes in daytime sleepiness, quality of life, and objective sleep patterns in seasonal allergic rhinitis: a controlled clinical trial. *J Allergy Clin Immunol* 2004;**113**:663-8.

Illustrations and figures

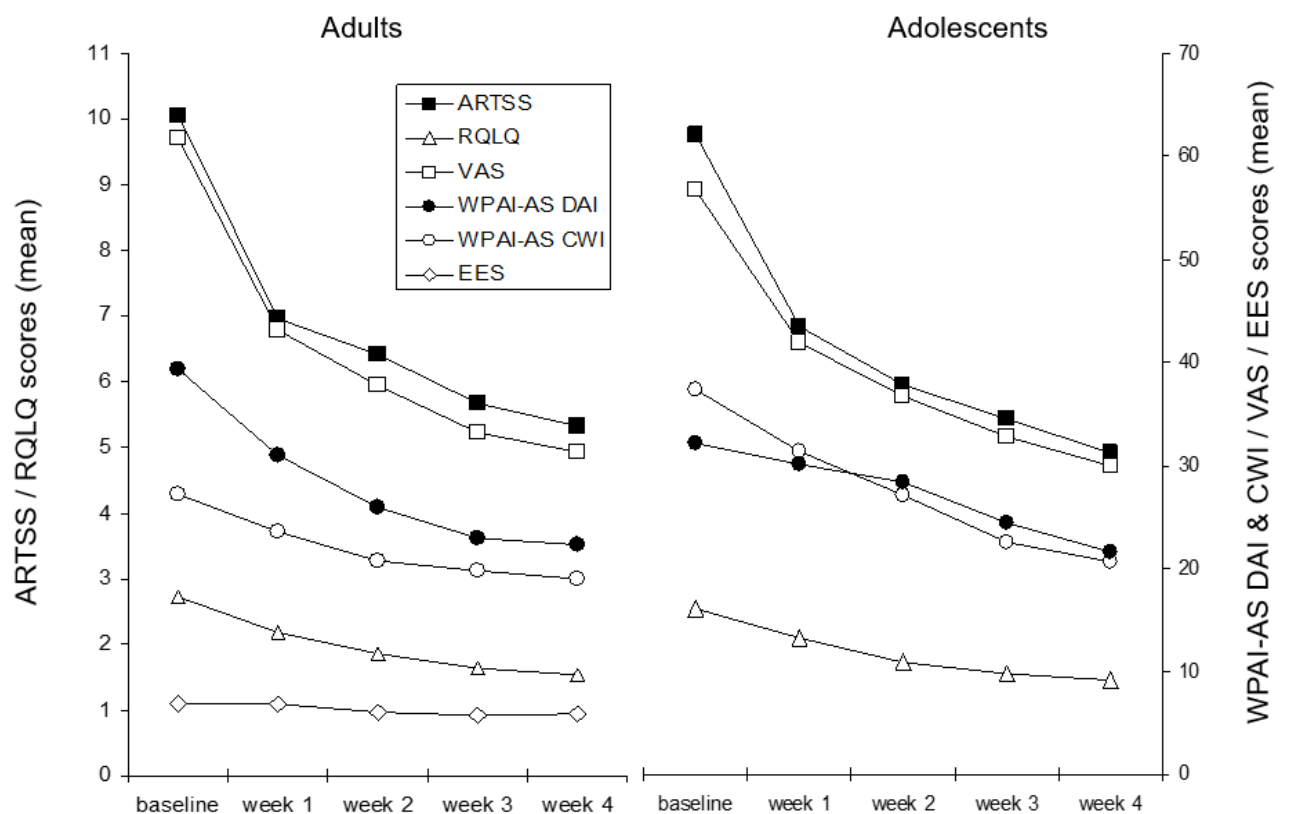
Figure 1 Patient disposition



* NB: this was the full analysis set for determination of the study's primary objective (the minimally important difference; see reference 15).

Accepted Article

Figure 2. Change in classroom/work impairment (CWI according to the WPAI-AS), daily activity impairment (DAI, according to the WPAI-AS), visual analogue scale (VAS) score and (for adults only) the Epworth Sleepiness Scale score (ESS) (right axis), symptom scores (average RTSS, ARTSS) and quality of life score (RQLQ) (left axis), over the 4-week study period in adults and adolescents.



Tables

Table 1. Demographic and clinical characteristics of the study population at the inclusion visit (by age group).

	<i>Adolescents aged 12-17 (n=247)</i>	<i>Adults aged ≥18 (n=292)</i>
Male (n, %)	142 (57.5%)	94 (33.5%)
Age (years), mean ± SD	14.8 ± 1.7	34.2 ± 11.3
ARIA classification (n, %):		
mild intermittent/persistent	28 (11.3)	17 (5.8)
moderate-to-severe intermittent	19 (7.7)	14 (4.8)
moderate-to-severe persistent	199 (80.5)	261 (89.4)
Time since diagnosis (years)	5.8 ± 3.1	12.4 ± 9.1
AR assessments at baseline		
WPAI-AS work/classroom impairment (%)	32.2 ± 25.0	27.3 ± 24.2
WPAI-AS daily activity impairment (%)	37.3 ± 25.5	39.8 ± 26.5
RTSS	9.8 ± 2.8	10.1 ± 2.9
RQLQ	2.7 ± 1.0	2.5 ± 1.0
VAS	56.8 ± 21.0	61.7 ± 20.3
EES	-	6.9 ± 4.9
Sensitisations other than to grass pollen (n, %):		
tree pollen	105 (42.5)	118 (40.2)
mites	114 (46.1)	107 (36.5)
pets	60 (24.3)	70 (24.0)
Treatments for AR on the day of the consultation (n, %):		
oral antihistamines	186 (76.1)	231 (79.1)
nasal corticosteroids	76 (31.6)	95 (32.5)
nasal antihistamines	28 (11.3)	27 (9.2)
leukotriene receptor antagonist	19 (7.7)	10 (3.4)
decongestants	2 (0.8)	9 (3.0)
ocular cromone	52 (21.5)	47 (16.1)
Concomitant co-morbidities (n, %):		
intermittent asthma	21 (8.5)	14 (4.8)

sinusitis	14 (5.7)	36 (12.3)
atopic dermatitis	37 (15.0)	26 (8.9)
food allergy	23 (9.3)	22 (7.5)

AR: allergic rhinoconjunctivitis; WPAI-AS: Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific; RTSS: average Rhinoconjunctivitis Total Symptom Score; VAS: visual analogue scale; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; ESS: Epworth Sleepiness Scale

Results are expressed as the mean $\pm$ SD

Table 2: Correlation (*r*) between WPAI-AS scores and the average RTSS (ARTSS), the RQLQ score and the VAS score in adults and in adolescents at inclusion.

		WPAI-AS work/classroom impairment	WPAI-AS daily activity impairment
RQLQ	Adolescents	0.66	0.65
	Adults	0.52	0.62
VAS	Adolescents	0.48	0.50
	Adults	0.41	0.51
ARTSS	Adolescents	0.29	0.34
	Adults	0.25	0.36

Table 3: WPAI-AS scores in patients with mild AR (VAS score <50 mm) and in patients with moderate/severe AR (VAS score $\geq$ 50 or 60 mm) at inclusion.

		WPAI-AS work/classroom impairment	WPAI-AS daily activity impairment	Epworth Sleep Scale score
Adolescents	VAS<50	10.00 [0.00 – 30.00] (n=70)	20.00 [10.00-40.00] (n=79)	NA
	VAS $\geq$ 50	40.00** [20.00 – 70.00] (n=149)	40.00** [22.50 – 70.00] (n=160)	NA
	VAS $\geq$ 60	50.00** [23.75 - 70.00] (n=122)	50.00** [30.00 – 70.00] (n=129)	NA
Adults	VAS<50	10.00 [0.00 – 20.00] (n=62)	20.00 [10.00 – 40.00] (n=71)	5.00 [2.00 – 8.00] (n=75)
	VAS $\geq$ 50	30.00** [10.00 – 50.00] (n=178)	40.00** [20.00 – 70.00] (n=210)	7.00* [3.00 – 10.00] (n=214)
	VAS $\geq$ 60	30.00** [10.00 – 50.00] (n=144)	50.00** [30.00-70.00] (n=168)	7.00* [3.00 – 10.50] (n=169)

Results are expressed as the median [25th-75th percentiles]; * p<0.025, ** p<0.0001 (Mann-Whitney test vs. data for a VAS score <50 mm). NA: not assessed.

Table 4: Correlations (r) between WPAI-AS scores and the RQLQ score, the RTSS and the VAS score over the 4-week study period in adults and in adolescents.

		WPAI-AS work/classroom impairment						Changes in WPAI-AS work/classroom impairment		
		W1	W2	W3	W4			W1/2	W2/3	W3/4
RQLQ	Adolescents	0.65	0.75	0.74	0.76	Changes in RQLQ	Adolescents	0.65	0.68	0.54
	Adults	0.60	0.55	0.76	0.78		Adults	0.44	0.61	0.51
VAS	Adolescents	0.58	0.65	0.69	0.71	Changes in VAS	Adolescents	0.42	0.44	0.35
	Adults	0.38	0.43	0.63	0.68		Adults	0.26	0.48	0.36
ARTSS	Adolescents	0.47	0.59	0.63	0.64	Changes in ARTSS	Adolescents	0.39	0.48	0.42
	Adults	0.38	0.40	0.64	0.66		Adults	0.27	0.41	0.44

		WPAI-AS daily activity impairment						Changes in WPAI-AS daily activity impairment		
		W1	W2	W3	W4			W1/2	W2/3	W3/4
RQLQ	Adolescents	0.73	0.74	0.68	0.76	Changes in RQLQ	Adolescents	0.65	0.55	0.65
	Adults	0.68	0.76	0.79	0.82		Adults	0.60	0.62	0.53
VAS	Adolescents	0.59	0.68	0.63	0.74	Changes in VAS	Adolescents	0.48	0.41	0.45
	Adults	0.50	0.57	0.67	0.75		Adults	0.48	0.53	0.49
ARTSS	Adolescents	0.56	0.62	0.55	0.72	Changes in ARTSS	Adolescents	0.45	0.37	0.50
	Adults	0.50	0.57	0.65	0.68		Adults	0.48	0.44	0.47