

Original article

Does asthma control correlate with quality of life related to upper and lower airways? A real life study

Background: The goal of asthma therapy is to achieve an optimal level of disease control, but the relationship between asthma control, impact of comorbid rhinitis and health related quality of life (HRQoL) in real life remains unexplored.

Objective: The aims of this real life study were to evaluate asthma control, the impact of asthma (with and without rhinitis) on HRQoL, the relationship between asthma control and HRQoL, and the role of rhinitis on asthma control and HRQoL.

Methods: 122 asthma patients completed the Asthma Control Test, Rhinitis Symptoms score (T5SS) and RHINASTHMA.

Results: Asthma control was unsatisfactory (44.27% of uncontrolled patients), as well as HRQoL. Controlled patients showed significantly lower scores in all the RHINASTHMA domains compared to uncontrolled. Irrespective of their level of control, patients with rhinitis symptoms showed worse HRQoL in Upper Airways (UA) ($P < 0.0001$), Lower Airways (LA) ($P < 0.001$), and Global Summary (GS) ($P < 0.0001$). In patients with symptomatic rhinitis, RHINASTHMA were lower in controlled asthma patients (UA $P = 0.002$; LA $P < 0.0001$; RAI $P < 0.01$; GS $P < 0.0001$). Asthma control was associated with lower T5SS score ($P = 0.034$).

Conclusion: Asthma control in real life is unsatisfactory. Rhinitis and asthma influence each other in terms of control and HRQoL. The control of rhinitis in asthma patients can lead to an optimization of HRQoL related to the upper airways, while this phenomenon is not so evident in asthma. These results suggest to strengthen the ARIA recommendation that asthma patients must be evaluated for rhinitis and vice versa.

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As suggested by the international guidelines, the goals of asthma therapy should be to achieve and maintain an optimal level of disease control to minimize daytime and night-time symptoms, activity limitation, airway narrowing, the need for reliever medications and thus to reduce the risk of life-threatening exacerbations and long-term morbidity (1). It is reasonable to assume that better asthma control is associated with less of an impact on health related quality of life (HRQoL), but few studies have specifically addressed this association utilizing validated instruments. In a retrospective analysis by Bateman et al. (2) of three randomized, double-blind, controlled studies, the effect of salmeterol/fluticasone propionate combination therapy on HRQoL, utilizing the Asthma Quality of Life Questionnaire (AQLQ), in patients with different levels of asthma severity was evaluated. The results from this study showed that the patients who achieved disease control according to GINA guidelines reported better AQLQ scores than patients who did not achieve control. The QoL of controlled

asthma patients was very similar to healthy control subjects. In particular, the correlation between asthma control and HRQoL was analysed in 1994 in a cohort of 3416 patients involved in the GOAL (3) study. The AQLQ questionnaire was administered. Combination therapy treatment was shown to improve HRQoL. The average AQLQ score at end-point was significantly higher in patients achieving total control compared with those achieving good control ($P < 0.001$), and in patients achieving good control compared to patients not well controlled ($P < 0.001$). Previous studies have assessed HRQoL by using instruments to specifically address either asthma or rhinitis in populations with different levels of disease control. As 60–80% of asthma patients also have rhinitis symptoms (4–6), their upper airway symptoms could be impacting their HRQoL. Although commonly considered a trivial disease by nonsufferers, this condition frequently results in a significant impairment of patient performance and wellbeing, in addition to their more typical nasal and ocular symptoms. Numerous

clinical studies have highlighted how rhinitis may negatively affect health status (7), sleep (8), concentration (9), performance at work (10), learning and school activities (11), social life (7), sexuality (12) and sports (13).

The relative burden of allergic rhinitis and asthma on HRQoL was addressed by Leynaert in a large population study (14). The presence of respiratory allergy was associated with impairment of social and mental health in patients with both asthma and rhinitis, as well as in patients with rhinitis alone. In addition, patients with both rhinitis and asthma, reported significant impairment in items related to physical health, suggesting from the patient's perspective, comorbid asthma and rhinitis resulting in an additional QoL burden.

The relationship between asthma control, co-morbid rhinitis and patient's HRQoL, especially in a real life context still needs to be clarified to identify the relevance of each on influencing patient's wellbeing.

Objective

The aims of this study were to explore asthma control in real life, to assess the impact of respiratory diseases (asthma with and without rhinitis symptoms) on patients' HRQoL, to investigate the relationship between the level of asthma control and HRQoL domains and to evaluate the role of rhinitis symptoms on asthma control and HRQoL.

Material and methods

In this study, we assessed outpatients affected by bronchial asthma, referred to the pneumological division for a follow-up visit from April to June 2007. Patients prior to being seen were asked to fill out the Asthma Control Test (ACT), Rhinitis Symptoms score (T5SS) and RHINASTHMA questionnaire.

The ACT is an effective questionnaire to determine the level of asthma control (15, 16). The ACT was developed by Nathan et al. through a stepwise regression analysis on data from a 22-item survey, administered to 471 asthma patients in a respiratory specialist office. The final five items selected assessed limitations at work, school and home because of asthma, the amount of dyspnoea, the presence of nocturnal symptoms and the use of rescue medications; as well as the patient's subjective perception of their level of asthma control over the previous 4 weeks. Patients assigned a score from 1 to 5 from poorest control to total control. By adding the five item scores, three levels of control are identified: scores from 5 to 19 indicate uncontrolled asthma; scores from 20 to 24 indicate well-controlled asthma and a score of 25 indicates the total control. Nathan et al. found that ACT correlate with forced expiratory volume in 1 s (FEV₁), (although ACT was a better predictor of uncontrolled asthma), and the specialist recommendations on needing a change in asthma therapy. Therefore, ACT proved to be a simple and rapidly self-administered instrument for assessing the level of asthma control, which takes into consideration not only asthma symptoms, but also its impact on daily life and the subjects' perception of their disease control.

Nasal and ocular symptoms were assessed using the T5SS which measures five symptoms: rhinorrhoea, nasal itching, sneezing, nasal

congestion and ocular itching. Symptoms were rated using the following scale: 0, no signs/symptoms; 1, mild (easily tolerated); 2, moderate (bothersome but tolerable); 3, severe (hard to tolerate, interferes with activity or sleep). The T5SS is derived from the sum of the five individual symptoms scores (range 0–15).

The RHINASTHMA questionnaire evaluates the impact of rhinitis and asthma on patient HRQoL (17). The questionnaire is made up of 30 items, whose analysis provides scores relating to the Upper Airways (UA), Lower Airways (LA) and Respiratory Allergy Impact (RAI). Moreover, RHINASTHMA also provides a composite score, the Global Summary (GS), which computes the aggregate score to indicate the overall impact of the disease. This instrument utilizes a five-point Likert scale (not at all, a little, fairly, much, very much) to measure the extent to which patients are bothered by every item during the previous 2 weeks. Answers to the RHINASTHMA items are then converted into a score from 0 to 100. Questions and scores are formulated so that the higher score corresponds to worse HRQoL.

After completing the questionnaires, patients gave them to the nursing staff and underwent an evaluation which included an accurate anamnesis (previous rhinitis symptoms, results of allergy testing, and ongoing therapies for asthma and rhinitis were recorded) and clinical examination. Afterwards, spirometry was performed according to ATS recommendations to detect the presence of airway obstruction.

Statistical analysis

Exploratory data analysis of demographic (gender and age) and clinical data was performed using univariate and bivariate statistical procedures. Pairwise association between categorical variables were assessed through chi-squared test for heterogeneity. Nonparametric statistics (median test) was applied to test differences in RHINASTHMA domains (continuous variables) by asthma-control and rhinitis symptom groups. Discriminant power of T5SS score on anamnestic ascertainment of rhinitis and on gravity of ongoing symptoms was assessed through the receiver operating characteristic (ROC) analysis (18). The main result of this statistical methodology is given by the area under the ROC curve (AUC), which can be interpreted as a measure of classification accuracy: the larger the AUC, the greater is the overall ability of the statistical model to discriminate between the two considered groups. A ROC analysis was also applied to each HRQoL domain and GS between asthma-controlled and -uncontrolled subjects. Finally, to estimate the joint effect of asthma control and rhinitis symptoms on RHINASTHMA domains, a logistic regression model was applied, including gender, age and smoking habit as confounding factors (19). All the study domains were dichotomized by using a score value of 20 as cut-off. This value represents the threshold under which patients are considered as having a good HRQoL level (corresponding to 80% of best possible QoL). An ROC analysis was applied within this context too. Specifically, the relative role played by asthma-control and rhinitis symptoms was further investigated by comparing the AUC based on the full logistic model with the AUCs computed from the logistic models including only the covariate asthma-control or rhinitis.

Results

Data from 122 asthma patients were collected from April to June. Patients' age ranged from 15 to 75, the average age being 44.16 (SD 14.882). Forty-seven were males

Table 1. Demographic and clinical characteristics

Frequencies		Frequency	Percentage
Gender	Males	47	38.52
	Females	75	61.48
Smoke	Smoker	24	19.67
	Ex smoker	26	21.31
	Never smoked	72	59.02
Allergy	Not allergic	29	23.77
	Allergic	91	74.59
	Missing	2	1.64
Kind of allergy	Perennial	74	81.32
	Seasonal	17	18.68
FEV ₁	≤ 60	6	4.92
	60–80	32	26.23
	>80	83	68.03
	Missing	1	0.82
Rhinitis	Absent	32	26.33
	Present	90	73.77
Rhinitis presence	Absent (T5SS < 3.5)	43	35.25
	Present (T5SS ≥ 3.5)	79	64.75
Rhinitis therapy	No	44	55.70
	Yes	35	44.30

(38.52%), 75 were females (61.48%). FEV₁ values ranged from 36% to 117%. By means of the ROC analysis, 3.5 was identified as the T5SS score that best discriminated between anamnestic datum of rhinitis presence and gravity of ongoing symptoms (sensitivity – specificity) in the examined population. Demographic and clinical parameters of the patients are summarized in Table 1. One hundred and nineteen patients were on inhaled steroids for their asthma, of which 59 were on the combination of an inhaled steroid and LABA and 42 patients were also on an antileukotriene; three patients were only on salbutamol as needed. Among the patients on rhinitis therapy, nine were taking antihistamines, antileukotrienes and nasal steroids; 31 patients were taking antihistamines and antileukotrienes; two patients were taking antihistamines only. Of the patients with T5SS ≤ 3.5, 34 were not taking medication for rhinitis while nine were; of the patients with a T5SS > 3.5, 44 were not on medication for rhinitis while 35 were.

Asthma control

The results obtained from ACT showed that 10 patients (8.19% of the total sample) reported optimal control, an ACT score of 25; an additional 58 patients (47.54%) were controlled with an ACT score between 20 and 24, with the mean score 22.23; 54 patients (44.27%) were not controlled, with an ACT score between 5 and 19, mean score 14.27 (Fig. 1). Due to the small percentage of patients who achieved total control, further analyses were performed by considering two populations; controlled (ACT score ≥ 20; *n* = 68) and not controlled (ACT < 20; *n* = 54). Females appeared to be less controlled than males (*P* = 0.001). A significant Spearman correlation

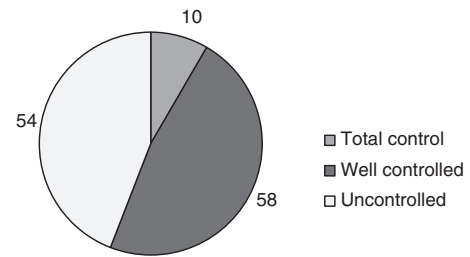


Figure 1. Level of asthma control according to Asthma Control Test.

(*P* = 0.01) was observed between ACT score and FEV₁, but no significant association was found when airway obstruction was stratified into three groups (FEV₁ ≥ 80; FEV₁ > 60 < 80; FEV₁ ≤ 60) (*P* = 0.219).

No significant differences were found between controlled and not controlled patients when allowing for smoking habits, allergic sensitization, kind of aeroallergen sensitization and treatment for rhinitis. The presence of rhinitis symptoms is not associated with the level of asthma control assessed by means of ACT if we analyse the overall population (*P* = 0.247). In the overall population sample, the patients with controlled asthma show lower T5SS score than uncontrolled (*P* = 0.034). By analysing only patients with rhinitic symptoms (T5SS > 3.5), asthma control is associated with a lower T5SS score (*P* = 0.005).

Quality of life

The RHINASTHMA questionnaire revealed a mean score of 25.18 (SD 21.22) for the UA, 29.29 (SD 21.44) for the LA, 24.93 (SD 17.82) for the RAI, and 26.89 (SD 17.08) for the GS.

There was a significant difference between males and females for the LA domain (*P* = 0.009) and the GS (*P* < 0.001) with females reporting worse HRQoL. Patients with controlled asthma (ACT ≥ 20), showed significantly lower scores for all RHINASTHMA domains, indicating better quality of life compared with uncontrolled patients (Fig. 2). Irrespective of their level of asthma control, patients showed significantly lower scores in UA (*P* < 0.0001), LA (*P* = 0.001) and GS (*P* < 0.0001) if their T5SS was ≤ 3.5, (Fig. 3). When considering patients with T5SS ≤ 3.5 only, a significant difference was found between controlled and uncontrolled patients for the LA (13.11 ± 9.13 vs 38.46 ± 24.89, *P* = 0.024), RAI (15.63 ± 12.59 vs 26.76 ± 18.64, *P* = 0.044), GS (11.70 ± 7.04 vs 26.09 ± 14.47, *P* = 0.008), but not for the UA (*P* = 0.495). In patients with T5SS > 3.5, all RHINASTHMA scores were significantly lower in controlled patients than in uncontrolled patients (UA: 29.20 ± 16.26 vs 41.74 ± 21.15, *P* = 0.002; LA: 20.45 ± 15.20 vs 46.46 ± 18.09, *P* < 0.001; RAI: 21.95 ± 16.54 vs 33.97 ± 18.21, *P* = 0.01; GS: 23.48 ± 11.87 vs 41.71 ± 16.57, *P* < 0.001). Further-

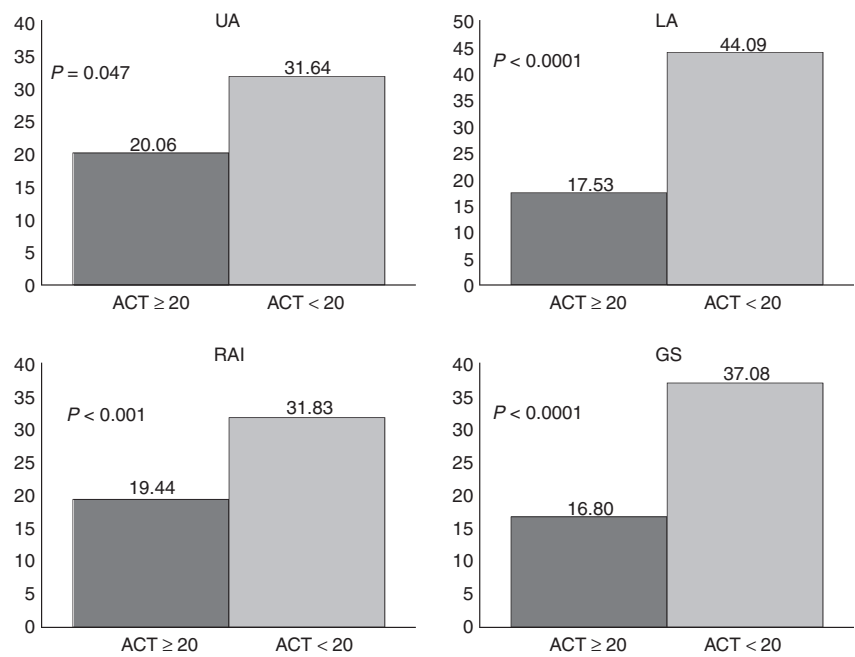


Figure 2. Differences in quality of life domains between controlled and uncontrolled patients.

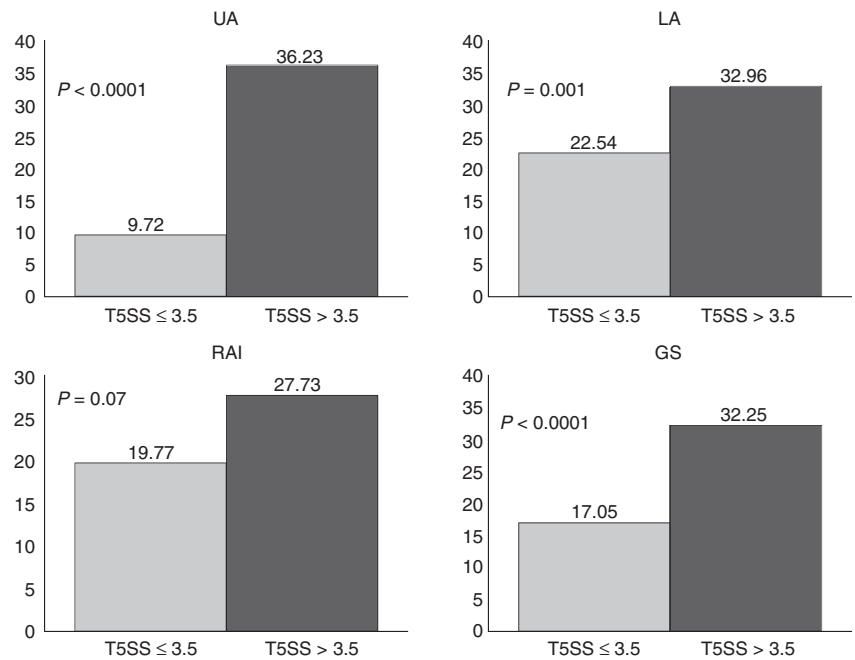


Figure 3. Differences in RHINASTHMA domains on the basis of the level of rhinitis symptoms measured by means of T5SS.

more, in patients with controlled asthma, the presence of rhinitis symptoms was associated with poorer quality of life as assessed by RHINASTHMA. Patients with rhinitis symptoms had significantly higher scores for UA (29.20 ± 16.26 vs 6.17 ± 5.63 , $P < 0.001$), RAI (21.95 ± 16.54 vs 15.63 ± 12.59 , $P = 0.026$) and GS (23.48 ± 11.37 vs 11.70 ± 7.04 , $P = 0.001$). On the contrary, in patients with uncontrolled asthma, there was a statistically significant difference between patients with

rhinitis symptoms and patients without rhinitis symptoms only in the UA domain (41.74 ± 21.15 vs 7.64 ± 7.28 , $P < 0.001$).

Relationship between asthma control and quality of life

With the aim of identifying the link between ACT score and HRQoL, we performed an ROC analysis (see Table 2) to establish the probability that a controlled or

Table 2. ROC analysis

	ACT			
	Cut-off	Accuracy (AUC)	Sensitivity	Specificity
UA	23.6	0.65	0.65	0.57
LA	31.73	0.87	0.90	0.74
RAI	23.44	0.71	0.68	0.63
GS	27.09	0.82	0.81	0.72

Table 3. Logistic regression

Logistic regression	Accuracy (AUC)	Without ACT			Without rhinitis symptoms		
		Delta AUC	Test χ^2	P	Delta AUC	Test χ^2	P
UA	0.913	0.008	1.20	0.274	0.181	18.78	<0.0001
LA	0.913	0.1	9.70	0.0018	0.048	5.43	0.0198
RAI	0.774	0.047	2.32	0.128	0.023	2.02	0.1553
GS	0.929	0.046	4.83	0.028	0.08	8.07	0.0045

uncontrolled patient has or does not have good HRQoL, after having fixed the cut-off that better discriminated between the two groups (controlled and uncontrolled).

For this analysis, the probability for controlled subjects to have good HRQoL, is 90% in the LA domain with a cut-off = 31.73, 81% in GS with a cut-off = 27.08, 65% in UA with a cut-off = 23.5, and 68% in RAI with a cut-off = 23.44.

The logistic regression analysis underscores that UA and GS are influenced by rhinitis symptoms while LA is influenced more by ACT score. The more influencing element in UA and GS is the rhinitis symptoms; in LA, the ACT score (see Table 3).

Discussion

The GOAL study showed that total control of asthma is an achievable target. Therefore, it appears reasonable to assess if this outcome is being reached in a real life setting. Bateman et al. not only showed that well controlled patients have better HRQoL compared with uncontrolled asthma patients, but they can also achieve an almost normal level of quality of life (2, 3). Recent real life observational studies (AIRE, INSPIRE, GAPP) (20–22) have shown that many asthma patients still have symptoms despite medication and moreover, that some factors (i.e. adherence, co-morbidities, inadequate treatment) influence their ability to achieve control. The availability of a composite multidimensional test, like ACT, appears to be a useful tool for both patients and physicians in monitoring and improving asthma control.

In light of the above, we evaluated the level of asthma control and its impact on quality of life in asthma patients, many with concomitant rhinitis in a real life

setting. The incidence of rhinitis in this study of 122 asthma patients was very high, in accordance with what is reported in the literature. The use of RHINASTHMA, a specific tool for measuring HRQoL in patients suffering from respiratory allergy, made it possible to determine the impact of rhinitis and asthma on impairing patients' daily life.

Our results confirmed that women with asthma are less controlled than men, in line with previous findings that female patients have more severe asthma and greater bronchial hyper-responsiveness than male patients (23, 24). As others previously reported, a weak correlation existed between pulmonary function and the level of asthma control (16, 25). As seen in the GOAL study (3) and in the ACT validation study (15), our results confirm that asthma severity, as defined by a reduction in FEV₁, does not always correlate with asthma control. Furthermore, rhinitis symptoms may influence pulmonary function (FEV₁) and also the ability to achieve asthma control.

If patients have suboptimal asthma control, their quality of life is usually far from ideal. As in other studies, women tend to report HRQoL scores that are inferior to those of men (26).

Assuming that patients with a T5SS score ≤ 3.5 have rhinitis of little impact on concomitant asthma, a majority of our patients (64.75%) were symptomatic: some because of not having treatment and others because their treatment was insufficient to control their disease.

Although ACT is a useful instrument for providing information on asthma control, if used alone, it is not sufficient to capture all aspects of patients' respiratory diseases.

The RHINASTHMA composite score (GS), representing the overall impact on HRQoL, showed that only 74% achievable wellbeing is reached. The UA score, reflecting the pathological impact of the UA on HRQoL, is nearly optimal (6) in patients without symptoms, whereas in treated/not treated symptomatic patients, it is around 35, indicating a considerable reduction in their wellbeing. The limited number of patients treated for rhinitis and their different treatments did not allow us to analyse the real effect of drugs on these parameters. The LA domain score, which reflects the pathological impact of the LA on HRQoL, was reduced considerably in controlled asthma patients compared to uncontrolled patients, but remained far from the achievable best value. It can be deduced that controlling rhinitis symptoms may optimize HRQoL related to the UA, but this does not occur in asthma. In fact, even though HRQoL in asthma improves when patients are controlled, optimal values are not always achieved: achieving asthma control does not necessarily mean to reach the best possible HRQoL. The presence of the disease, the necessity to be cured and to manage it along the time represent a cost in terms of HRQoL. Therefore, it is important to bear in mind that measuring asthma

control and measuring HRQoL should be performed in parallel and that achieving one does not guarantee achieving the other. The phenotype of an asthma patient is relevant in defining outcomes and the treatment plan to accomplish these outcomes. Although rhinitis symptoms do not influence asthma control as measured by ACT, controlling rhinitis symptoms in asthma patients can lead to better HRQoL. We can hypothesize that the wellbeing acquired with better control leads the patient to feel globally better; another hypothesis is that patients that achieve the control are those who, due to their personal characteristic, can better perform a global therapeutic strategy.

Since the evaluation of a patients' HRQoL is not always feasible in daily practice, it would be interesting to be able to predict the level of HRQoL on the basis of achieved level of asthma control, knowing different components of HRQoL influence disease control differently.

The logistic regression analysis confirmed that both the level of asthma control and the presence of rhinitis

symptoms influence HRQoL, but each one impacts different aspects of HRQoL.

The assessment of HRQoL utilizing the patient's viewpoint is increasingly being recommended by the regulatory authorities for the evaluation of new pharmaceutical products (27, 28), which supports the GRADE approach (29) and assessing the global effect of a treatment on patients with respiratory allergy (30, 31).

Our real life data strengthen the ARIA guidelines recommendation that asthma patients must be evaluated for rhinitis and rhinitis patients must be evaluated for asthma (32).

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References

- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Revised 2006. Available at: <http://ginasthma.com>. Accessed 10 December 2007.
- Bateman DE, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control Study. *Am J Respir Crit Care Med* 2004;**170**:836–844.
- Bateman ED, Bousquet J, Keech ML, Busse WW, Clark TJ, Pedersen SE. The correlation between asthma control and health status: the GOAL study. *Eur Respir J* 2007;**29**:56–62.
- Spector SL. Overview of comorbid associations of allergic rhinitis. *J Allergy Clin Immunol* 1997;**99**:773–780.
- Passalacqua G, Ciprandi G, Canonica GW. United airways disease: therapeutic aspects. *Thorax* 2000;**55**:26–27.
- Passalacqua G, Ciprandi G, Canonica GW. The nose-lung interaction in allergic rhinitis and asthma: the United Airways Disease. *Curr Opin* 2001;**1**:7–13.
- Bousquet J, Bullinger M, Fayol C, Marquis P, Valentin B, Burtin B. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. *J Allergy Clin Immunol* 1994;**94**:182–188.
- Stuck BA, Czajkowski J, Hagner AE, Klimek L, Verste T, Hörmann K et al. 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**:663–668.
- Juniper EF, Stahl E, Doty RL et al. Clinical outcomes and adverse effect monitoring in allergic rhinitis. *J Allergy Clin Immunol* 2005;**115**:S390–S413.
- Shedden A. Impact of nasal congestion on quality of life and work productivity in allergic rhinitis. *Treat Respir Med* 2005;**4**:438–445.
- Bender BG, Fisher TL. Differential impacts of allergic rhinitis and allergy medication on childhood learning. *Pediatr Asthma Allergy Immunol* 1998;**12**:1–11.
- Kirmaz C, Aydemir O, Bayrak P et al. Sexual dysfunction in patients with allergic rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 2005;**95**:525–529.
- Bonini S, Bonini M, Bousquet J et al. Rhinitis and asthma in athletes: an ARIA document in collaboration with GALEN. *Allergy* 2006;**61**:681–692.
- 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.
- Nathan RA, Sorkness CA, Kosinski M et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;**113**:59–65.
- Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006;**117**:549–556.
- Baiardini I, Pasquali M, Giardini A, Specchia C, Passalacqua G, Venturi S et al. Rhinasthma: a new specific QoL questionnaire for patients with rhinitis and asthma. *Allergy* 2003;**58**:289–294.
- Sullivan Pepe M. The statistical evaluation of medical tests for classification and prediction. Oxford, UK: Oxford University Press, 2003.
- Hosmer DW Jr, Lemeshow S. Applied logistic regression, 2nd ed. New York, NY: Wiley, 2000.
- Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;**16**:802–807.
- Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. *BMC Pulm Med* 2006;**6**:13.

22. Canonica GW, Baena-Cagnani CE, Blaiss MS, Dahl R, Kaliner MA, Valovirta EJ et al. Unmet needs in asthma: Global Asthma Physician and Patient (GAPP) Survey: global adult findings. *Allergy* 2007;**62**:668–674.
23. Leynaert B, Bousquet J, Henry C, Liard R, Neukirch F. Is bronchial hyperresponsiveness more frequent in women than in men? A population-based study. *Am J Respir Crit Care Med* 1997;**156**:1413–1420.
24. Bottema RW, Reijmerink NE, Koppelman GH, Kerkhof M, Postma DS. Phenotype definition, age, and gender in the genetics of asthma and atopy. *Immunol Allergy Clin North Am* 2005;**25**:621–639.
25. Rodrigo GJ, Arcos JP, Nannini LJ, Neffen H, Broin MG, Contrera M et al. Reliability and factor analysis of the Spanish version of the asthma control test. *Ann Allergy Asthma Immunol* 2008;**100**:17–22.
26. Sullivan M, Karlsson J. The Swedish SF-36 health survey III. Evaluation of criterion-based validity: results from normative population. *J Clin Epidemiol* 1998;**51**:1105–1113.
27. FDA. Draft guidance for industry on patient-reported outcome measures: use in medicinal product development to support labeling claims. *Fed Regist* 2006;**71**:5862–5863.
28. Committee for Medicinal Products for Human Use. Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. Available at: <http://www.emea.europa.eu/pdfs/human/ewp/1393104en.pdf> (25 July 2005) (accessed 7 December 2006).
29. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924–926.
30. Baiardini I, Braido F, Tarantini F, Porcu A, Bonini S, Bousquet PJ et al. ARIA-suggested drugs for allergic rhinitis: what impact on quality of life? A GA2LEN review. *Allergy* 2008;**63**:660–669.
31. Baiardini I, Braido F, Brandi S, Tarantini F, Bonini S, Bousquet J et al. The impact of GINA suggested drugs for the treatment of asthma on health-related quality of life: a GA²LEN review. *Allergy* 2008;**63**:1015–1030.
32. Bousquet J, van Cauwenberge PB, Khaltayev N, ARIA Workshop Group, WHO. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**:S1–S334.