

Original article

Quality-of-life and asthma-severity in general population asthmatics: results of the ECRHS II study

Background: Health-related quality-of-life (HRQL) has been poorly studied in large samples of asthmatics from the general population. HRQL and its relationship to asthma-severity were assessed among 900 asthmatics enrolled in the European Community Respiratory Health Survey.

Methods: Among asthmatics, 864 completed the short form-36 (SF-36) questionnaire and 477 also completed the Asthma Quality-of-life Questionnaire (AQLQ). A 4-class asthma-severity scale, combining clinical items, forced expiratory volume in 1 s and the level of treatment and the different asthma-severity components (each of the clinical items and hospitalization) were studied in relation to HRQL.

Results: Mean SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores (45.5 and 48.8 respectively) were lower than expected in a general population. The mean total AQLQ score was 5.8. The AQLQ score and to a lesser extent the PCS score were significantly related to the 4-class asthma-severity scale, although the risk of having a lower HRQL score did not vary proportionally across the levels of severity. Asthma-severity had no impact on the MCS score. Asthma attack frequency and hospitalization were associated with both total AQLQ and PCS scores, whereas nocturnal symptoms and lung function were more strongly related to the AQLQ and PCS score respectively.

Conclusion: In population-based asthmatics, the specific AQLQ questionnaire, and also to a lesser extent the generic SF-36 questionnaire, were sensitive to asthma-severity. Frequencies of asthma attacks, of nocturnal symptoms and hospitalization for asthma have independent impact on HRQL.

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Many studies conducted both in clinical and population-based samples show that the quality-of-life is impaired in asthmatic patients (1–3). One of the major goals in the management of asthma is to improve the health-related quality-of-life (HRQL) of patients. Standardized questionnaires, either generic applied over all diseases or specific for asthma, have been developed in tandem with clinical criteria to measure the impact of the disease on daily life in clinical trials (4, 5). Results from Juniper et al. (6) indicated that HRQL measures add complementary

information to conventionally-used clinical outcomes. There are few data on HRQL in asthmatics selected from community-based samples and determinants of HRQL remain poorly addressed. Although the quality-of-life decreased with the degree of asthma-severity (7, 8), HRQL is not simply a further index of severity, as the degree to which disease is perceived to affect daily life may vary between patients with the same asthma-severity.

The assessment of asthma-severity is not straightforward and has evolved over the years. In 2006 the Global

Initiative for Asthma (GINA) classification, initially developed in clinical practice for the management of individual asthmatic patients, shifted from asthma-severity to asthma-control, where treatment is no longer part of the classification (9). However, taking the medication into account may provide useful additional information in population-based studies including both treated and untreated asthmatics (10). In parallel, items combined in these classifications, such as asthma attack frequency and lung function, are not always interrelated (11, 12) and may have different impact on the self-perception of the patient. In clinical trials, Moy et al. (8) found that the intensity of asthma symptoms significantly predicted HRQL in asthmatics whereas lung function was not an independent determinant of HRQL. Poor asthma-control and frequent exacerbations have also been shown to be related to a decreased HRQL (13, 14). It is still unknown whether these observations in specific clinical populations remain in population-based asthmatics. The European Community Respiratory Health Survey II (ECRHS II) study collected data in a European general population sample including around 1500 asthmatics. The aim of this analysis is to (i) describe HRQL assessed both by an asthma-specific questionnaire (AQLQ) and a generic questionnaire [short form-36 (SF-36)] in asthmatics from a large general population and (ii) assess the relations between HRQL and an asthma-severity classification and its different components.

Methods

Population

The ECRHS is an international study of asthma (15). From a short questionnaire sent to a random sample of young adults aged between 20 and 44 years in 48 centres, a random sample of the responders enriched with a symptomatic sample was examined in ECRHS I ($n = 18\,668$). About 10 years later, 10933 individuals in 29 centres from the initial cohort were re-examined (ECRHS II) (16). Previous analysis showed no major participation bias in the follow-up of the cohort, except that the nonparticipants were slightly older and more often smokers at ECRHS I compared to the participants (17).

Among the subjects participating in ECRHS II, 1528 individuals were considered as current asthmatics using the following criteria: report of diagnosis of asthma confirmed by a doctor and at least one respiratory symptom (wheeze; nocturnal chest tightness; attack of breathlessness after activity, at rest or at night) or asthma attack or use of inhaled/oral medicines because of breathing problem in the last 12 months. Because ventilatory data from Melbourne were not comparable with other centres, asthmatic subjects from Melbourne were initially excluded from the analysis ($n = 171$). Among the remaining 1357 asthmatics, 457 individuals were excluded because of missing data for either asthma-severity or for both HRQL questionnaires (225 with missing asthma-severity only, 79 with missing HRQL data only and 153 missing for both criteria). Finally, the analysis was conducted on 900 asthmatics among which 864 and 477 have filled in the SF-36 and the AQLQ questionnaires respectively.

Health-related quality-of-life

The generic SF-36 questionnaire (version 1.3) was part of the ECRHS II core protocol and was administered to all subjects, whereas the asthma-specific questionnaire was part of an optional protocol, and was administered to asthmatic subjects in centres that chose to take part. The SF-36 questionnaire is a standardized and widely used tool (18). This questionnaire is composed of 36 items, which are combined to measure four physical and four psychological scales. We used the three-step scoring system to calculate the values for the concepts from the items of the questionnaire as described in the SF-36 manual and interpretation guide and as previously used in a study of the HRQL in allergic rhinitis in ECRHS (2, 19). The Physical (PCS) and Mental (MCS) Component Summary measures were then computed as recommended by the developers (20). By construction, PCS and MCS score means expected in a general population are 50. Asthmatics from 17 centres completed an asthma-specific HRQL questionnaire: the Asthma Quality-of-life Questionnaire (AQLQ) (21). The AQLQ is composed of 32 questions which cover four domains: activity limitation, symptoms, environmental stimuli and emotional function. Subjects recall their experiences during the previous 2 weeks and score a number of asthma-related problems on a 7-point likert scale from 1 (maximum impairment) to 7 (no impairment) either in term of frequency, duration or amount. We used an overall summary index, which is the mean of the responses to the 32 items (total AQLQ score). The AQLQ was found to be valid, reproducible and responsive to change over time (21) and these properties have been conserved in translated versions (22). A change in score of 0.5 points has been determined to be the minimal clinically important difference (23). The PCS, MCS and total AQLQ scores are lower when HRQL is decreased. Among the 423 subjects who did not complete the AQLQ, 227 (53.7%) were examined in one of the centres that did not include the AQLQ in their protocol.

Asthma-severity

Based on both clinical features and the level of daily treatment, the subjects were classified according to a 4-step asthma-severity scale (intermittent, mild, moderate and severe persistent asthma) following the 2005 revised GINA guidelines (9). This 4-step asthma-severity scale has already been used to assess prognostic factors of asthma-severity in ECRHS (24).

In order to cover several components of asthma-severity and burden, different items were assessed: (i) the frequency of asthma attacks in the last 3 months (0; 1–2; > 2); (ii) the frequency of being woken up because of asthma attacks or attacks of shortness of breath in the last 3 months (0; < 1/week; ≥ 1/week); (iii) forced expiratory volume in 1 s ($FEV_{1\%}$) predicted (≥ 80%; < 80%) and (iv) emergency room visits or night spent in the hospital because of breathing problems in the past 12 months (yes; no).

Statistical analysis

None of the HRQL scores was normally distributed in this population. Mean HRQL scores were presented for comparison to other populations, but median and nonparametric tests (Kruskal–Wallis and Wilcoxon tests) were used. The analyses were further conducted considering each HRQL score as a binary variable defined with the first quartile for threshold, to contrast one-fourth of the subjects with the worst HRQL scores to others.

Confounding factors considered in the analysis were age, gender, body mass index (BMI), current active and passive smoking

(3-classes variable: nonsmokers and not exposed to passive smoking; nonsmokers but currently exposed to passive smoking; current smokers), occupational status (5-classes variable : manager/professionals; technicians; other non manual; manual; unclassified/unknown), allergic rhinitis (binary variable assessed using the answer to the following question: 'do you have any nasal allergies, including hay fever?') co-morbidity (3-classes variable assessed using the answer to the following question: 'do you have any long-term limiting illness?': no limiting illness, limiting illness, missing) and the level of daily treatment.

We performed generalized estimated equation models allowing to take into account the dependence of the observations within the same sample and country (Proc GENMOD in the SAS statistical software).

Results

There was no difference in the socio-demographic characteristics between asthmatic subjects included in the analysis ($n = 900$) and asthmatic subjects enrolled in ECRHSII but not included because of missing data ($n = 457$) (Table 1). Regarding asthma-severity, although asthmatics included in the analyses had higher FEV₁ and less nocturnal symptoms than asthmatics not included, there was no difference for the 4-class asthma-severity scale (Table 1). The HRQL scores did not differ between subjects included to those excluded (Table 1). There was no difference for socio-demographic factors, SF-36 scores and any of the asthma-severity items studied between subjects who filled in the AQLQ questionnaire ($n = 477$) and those who did not ($n = 423$), but using the 4-class asthma-severity scale, results showed that asthmatics with AQLQ tended to have more severe asthma than the asthmatics without AQLQ (frequencies of subjects in the intermittent, mild, moderate and severe persistent asthma were 51.4, 9.2, 20.1, 19.3 and 57.0, 12.0, 14.2, 16.8 in asthmatics with and without AQLQ respectively, $P = 0.04$).

Descriptive characteristics

The mean age of participants in the analysis was 42.4 years and 41.7% were males (Table 1). The mean asthma duration was 22.7 years (range: 0.2–54.4). Mean total AQLQ, PCS and MCS scores were 5.8, 45.5 and 48.6 respectively (Table 2). The total AQLQ score and the PCS score significantly decreased with age, female sex, lower occupational status and co-morbidities (Table 2). The PCS score also significantly decreased with increasing BMI. The MCS score was significantly associated with gender (decreased in women) and with asthma duration (increased with longer asthma duration).

Relation between the HRQL scores and asthma-severity

Univariate analysis showed that the total AQLQ score and the SF-36 PCS score were significantly decreased in

Table 1. Comparison between asthmatics included in the analysis to asthmatics not included because of missing data on asthma-severity or HRQL data

	Asthmatics included in the analysis	Asthmatics not included	<i>P</i> -value
<i>n</i>	900	457	
Age (year), mean $\pm$ SD	42.4 $\pm$ 7.3	42.5 $\pm$ 7.3	0.77
Gender, % men	41.7	41.4	0.91
Active/passive smoking: never, %	55.6	53.8	0.81
Passive smoking only, %	18.5	19.4	
Active smoking, <i>n</i> %	25.9	26.8	
Occupational status: manager/ professionals, %	29.7	28.5	0.95
Technicians, %	19.1	19.0	
Other nonmanual, %	29.8	29.8	
Manual, %	21.4	22.7	
BMI: <25, (<i>n</i> = 418)	47.1	46.8	0.46
25–30, (<i>n</i> = 319)	35.9	33.1	
>30, (<i>n</i> = 151)	17.0	20.2	
Asthma duration (year), mean $\pm$ SD	22.7 $\pm$ 12.5	22.1 $\pm$ 12.7	0.74
Rhinitis, %	65.9	66.1	0.93
Co-morbidity, <i>n</i>	648	190	
Yes, %	28.9	31.0	0.56
Level of asthma treatment, past 12 months, <i>n</i>	900	276	
Level 1, %	76.1	82.6	0.09
Level 2, %	4.9	5.1	
Level 3, %	13.1	8.3	
Level 4, %	5.9	4.0	
<i>Asthma-severity</i>			
4-class asthma-severity scale, <i>n</i>	900	79	
Intermittent, %	54.0	54.4	0.87
Mild persistent, %	10.6	11.4	
Moderate persistent, %	17.3	13.9	
Severe persistent, %	18.1	20.2	
Asthma attacks frequency, past 3 months, <i>n</i>	881	444	
None, %	69.8	71.2	0.87
1 or 2, %	17.9	16.9	
>2, %	12.3	11.9	
Nocturnal symptoms frequency, past 3 months, <i>n</i>	896	437	
None, %	69.7	64.8	0.06
≥ 1 /month and <1/week, %	20.8	21.7	
≥ 1 /week, %	9.5	13.5	
FEV ₁ , <i>n</i>	900	237	
FEV ₁ $\leq$ 80% predicted, %	13.9	24.1	0.0001
Emergency visits/ hospitalization, past 12 months, %	6.6	5.6	0.47
<i>Quality-of-life scores</i>			
AQLQ, <i>n</i>	477	83	
Mean	5.8	5.7	
Median (Q1–Q3)	6.1 (5.2–6.7)	6.1 (5.3–6.7)	0.68
PCS, <i>n</i>	864	222	
Mean	45.5	44.1	
Median (Q1–Q3)	48.9 (40.7–53.7)	48.4 (38.2–54.3)	0.54
MCS, <i>n</i>	864	222	
Mean	48.6	47.5	
Median (Q1–Q3)	51.6 (42.2–57.4)	51.9 (40.3–57.0)	0.47

HRQL, health-related quality-of-life; BMI, body mass index; FEV₁, forced expiratory volume in 1 s; AQLQ, Asthma Quality-of-life Questionnaire; PCS, physical component summary; MCS, mental component summary.

Table 2. Factors related to HRQL

	AQLQ			SF-36 PCS			SF-36 MCS		
	Mean	Median (Q1–Q3)	P-value	Mean	Median (Q1–Q3)	P-value	Mean	Median (Q1–Q3)	P-value
Total	5.8	6.1 (5.2–6.7)		45.5	48.9 (40.7–53.7)		48.6	51.6 (42.2–57.4)	
Age: <35 years, (<i>n</i> = 183)	6.1	6.2 (5.5–6.7)	0.005	48.5	50.9 (44.6–54.4)	<0.0001	48.0	51.6 (40.4–57.3)	0.11
35–45, (<i>n</i> = 348)	5.9	6.2 (5.3–6.8)		46.4	49.7 (41.5–54.0)		47.9	51.3 (41.4–56.4)	
≥45, (<i>n</i> = 369)	5.7	6.0 (4.8–6.6)		43.3	46.7 (36.0–53.1)		49.5	52.5 (43.4–57.8)	
Gender: men, (<i>n</i> = 375)	6.0	6.3 (5.6–6.8)	0.0004	47.3	50.2 (43.5–54.2)	0.001	50.2	52.1 (46.1–57.7)	0.005
Women, (<i>n</i> = 525)	5.7	6.0 (5.0–6.6)		44.2	48.1 (37.6–53.3)		47.4	51.3 (38.4–57.0)	
BMI: <25, (<i>n</i> = 418)	5.9	6.2 (5.3–6.8)	0.13	47.5	50.9 (43.1–54.9)	<0.0001	48.0	51.4 (42.1–56.7)	0.26
25–30, (<i>n</i> = 319)	5.8	6.0 (5.1–6.6)		45.2	48.6 (39.7–53.1)		49.1	51.6 (42.6–57.8)	
>30, (<i>n</i> = 151)	5.8	6.2 (5.1–6.7)		41.2	44.4 (34.0–50.7)		49.2	52.6 (42.5–57.8)	
Active/passive smoking:									
Never, (<i>n</i> = 493)	5.9	6.2 (5.2–6.7)	0.93	46.2	49.5 (41.7–54.2)	0.11	49.2	52.1 (43.2–57.6)	0.09
Passive smoking only, (<i>n</i> = 164)	5.8	6.2 (4.9–6.7)		44.8	48.3 (38.5–54.4)		47.7	51.1 (40.7–57.5)	
Active smoking, (<i>n</i> = 229)	5.9	6.1 (5.4–6.7)		44.7	48.6 (39.6–52.9)		47.6	50.6 (41.3–56.7)	
Occupational status:									
Manager/professional, (<i>n</i> = 246)	6.2	6.5 (5.8–6.8)	<0.0001	47.8	51.1 (43.2–54.9)	<0.0001	49.2	52.0 (45.3–57.3)	0.15
Technicians, (<i>n</i> = 158)	6.0	6.2 (5.5–6.8)		47.2	51.2 (41.8–54.7)		50.0	52.1 (45.5–57.7)	
Other nonmanual, (<i>n</i> = 247)	5.7	5.8 (4.9–6.6)		44.5	48.2 (40.1–53.2)		47.5	51.4 (39.5–56.7)	
Manual, (<i>n</i> = 177)	5.6	5.9 (4.8–6.5)		44.1	47.7 (38.1–51.8)		49.3	51.7 (42.1–57.9)	
Unclassified/unknown, (<i>n</i> = 72)	5.3	5.7 (3.7–6.4)		40.8	46.7 (33.2–50.1)		45.3	49.0 (36.8–56.9)	
Rhinitis: no, (<i>n</i> = 306)	5.8	6.1 (5.1–6.7)	0.96	45.8	49.0 (41.2–53.2)	0.95	47.4	51.3 (38.8–57.0)	0.06
Yes, (<i>n</i> = 592)	5.9	6.1 (5.2–6.7)		45.4	48.8 (40.1–53.8)		49.2	51.9 (43.2–57.7)	
Co-morbidity: no, (<i>n</i> = 461)	6.0	6.4 (5.6–6.8)	0.0008	48.8	51.3 (45.0–54.7)	<0.0001	47.9	51.4 (41.9–56.6)	0.75
Yes, (<i>n</i> = 187)	5.6	6.0 (4.9–6.6)		39.7	43.8 (28.4–51.2)		47.9	51.5 (39.7–57.6)	
Asthma duration (years): <10, (<i>n</i> = 152)	5.7	5.9 (5.1–6.7)	0.41	45.2	48.3 (38.8–52.8)	0.20	47.6	50.3 (40.6–56.8)	0.01
10–20, (<i>n</i> = 247)	5.8	6.1 (5.1–6.7)		46.1	49.4 (41.6–54.7)		46.8	50.9 (38.0–56.8)	
20–30, (<i>n</i> = 206)	6.0	6.2 (5.4–6.7)		46.4	50.0 (42.0–54.0)		49.7	51.8 (43.4–57.3)	
≥30, (<i>n</i> = 272)	5.9	6.1 (5.3–6.7)		44.6	48.2 (39.7–53.6)		50.2	53.1 (46.6–57.9)	

HRQL, health-related quality-of-life; BMI, body mass index; AQLQ, Asthma Quality-of-life Questionnaire; PCS, physical component summary; MCS, mental component summary. P-values assessed from nonparametric tests.

more severe asthma (Tables 3 and 4). However, the associations did not show a clear trend, as moderate persistent asthma had a higher median than mild persistent asthma. Adjustment for confounders did not change the results: for both the total AQLQ score (Table 3) and the PCS score (Table 4), the risk of being in the first quartile was significantly higher for mild, moderate and severe persistent asthmatics compared to intermittent asthmatics. The association was similarly observed in men and women (*P*-values for the interaction term in the multivariate analysis were 0.41 and 0.67 for the AQLQ score and the PCS score respectively). The MCS score was not related to the 4-class asthma-severity scale (*P* = 0.10) (Table 4).

To assess the respective impact of each asthma-severity aspect on quality-of-life, each clinical item was studied in relation to the HRQL scores. Whatever the asthma-severity item studied, an increased asthma-severity was significantly related to a reduced total AQLQ and PCS scores (Tables 3 and 4). For the AQLQ score, a clear trend was observed with the frequencies of asthma attacks and of nocturnal symptoms. In the multivariate model including all asthma-severity components and confounding factors, the diurnal and nocturnal symptom frequency remained highly related to the total AQLQ

score (*P* < 0.0001). Hospitalization also remained significantly related to the total AQLQ score but to a lesser extent (*P* = 0.02) (Table 3). With regard to the SF-36 scores, in the multivariate model all asthma-severity items remained significantly related to a lower PCS score and none to the MCS score (Table 4).

Discussion

In a large sample of asthmatics from the general European population, we confirmed the previous reports from clinical populations, showing that asthma-severity is a significant predictor of the AQLQ score and of the physical component of the SF-36 generic tool, but not of the SF-36 mental component. The impact of the different asthma-severity components on HRQL varies according to both the severity items and the HRQL questionnaire considered. Asthma attack frequency and hospitalization for asthma were associated with measures from both quality-of-life instruments. Nocturnal symptoms altered HRQL measured by AQLQ whereas lung function had an independent impact only on the PCS score.

The analysis has been conducted in a large sample of asthmatics recruited in the general population from

Table 3. Relation between the total AQLQ score and asthma-severity

	Univariate analyses, <i>n</i> = 477		Multivariate analyses, <i>n</i> = 457, OR (95% CI)
	Median (IQ range)	<Q1, %†	
<i>Model 1‡:</i>			
4-class asthma-severity scale			
Intermittent	6.5 (1.0)	13.5	1.0
Mild persistent	5.6 (1.4)	36.4	3.1 (1.6–6.1)
Moderate persistent	6.0 (1.6)	29.2	2.4 (1.4–4.2)
Severe persistent	5.4 (1.7)	44.6	4.3 (2.3–7.8)
<i>P</i> -value*	<0.0001	<0.0001	<0.0001
<i>Model 2‡:</i>			
Asthma attacks frequency, past 3 months			
None	6.4 (1.1)	15.8	1.0
1 or 2	5.7 (1.3)	31.1	1.7 (0.9–3.0)
>2	5.0 (1.8)	55.6	4.6 (2.4–8.6)
<i>P</i> -value*	<0.0001	<0.0001	<0.0001
Nocturnal symptoms frequency, past 3 months			
None	6.4 (1.1)	14.6	1.0
≥1/month and <1/week	5.5 (1.4)	38.5	2.3 (1.2–4.3)
≥1/week	4.8 (1.6)	66.7	6.1 (2.5–14.7)
<i>P</i> -value*	<0.0001	<0.0001	0.0002
FEV ₁ % predicted			
>80%	6.2 (1.4)	23.5	1.0
≤ 80% pred	5.9 (1.6)	31.9	1.7 (0.8–3.7)
<i>P</i> -value	0.02	0.10	0.17
≥1 emergency visits or hospitalization, past year			
No	6.2 (1.4)	22.9	1.0
Yes	5.4 (2.0)	44.7	2.1 (1.1–3.9)
<i>P</i> -value*	0.0006	0.0008	0.02

AQLQ, Asthma Quality-of-life Questionnaire; FEV₁, forced expiratory volume in 1 s.
 **P*-value taking into account the correlation between observations from the same sample and country (GEE model), except for the median comparison (*P*-value assessed from the nonparametric test).

†Per cent of subjects with a quality-of-life score lower than the first quartile observed in the whole population (5.2).

‡Model 1 multivariate analysis: GEE models using the total AQLQ score (binary variable using the first quartile for threshold) as dependant variable and the 4-class asthma-severity scale and confounders (gender, age, occupational status, tobacco smoking, co-morbidity, rhinitis and BMI) as independent variables.

Model 2 multivariate analysis: GEE models using the total AQLQ score (binary variable using the first quartile for threshold) as dependant variable and the asthma-severity items and confounders (gender, age, occupational status, tobacco smoking, co-morbidity, rhinitis, BMI and level of treatment) as independent variables.

several European countries with a detailed questionnaire allowing good characterization of the asthma phenotypes. Major confounders were taken into account in the analyses. Although one-third of the asthmatics from ECRHSII could not be included in this analysis because of missing data, the sub-sample of asthmatics participating in this analysis were similar in many ways excepting that they had a better lung function than those not included. It indicates that results observed are probably not driven by any major selection bias. The main reason for noncompletion of the AQLQ was that 12 out of the 29 centres did not take part in that part of the study.

However, the population with AQLQ data had similar SF36 scores, asthma-severity and socio-demographic characteristics than asthmatics who did not complete the AQLQ. Despite these similarities between participants and nonparticipants, there is a probability that people who are more sensitive to disease and its symptoms are more willing to answer to the AQLQ questionnaire than others, regardless of asthma-severity. This aspect could not be assessed in our population but if it happens it would not have any impact in the relation between asthma-severity and the total AQLQ score.

The physical and mental health scores of the quality-of-life were lower than the score of 50 achieved in the random sample of ECRHS participants, although overall scores and disease-specific scores were higher than that which was reported from clinical studies (5, 8, 25). Results observed in our data support previous findings indicating a reduced HRQL in women and in older subjects among the asthmatics (3, 26). Nevertheless our results suggest that asthma-severity has a similar impact on HRQL in both genders. Our results also confirm the impact of the socioeconomic status in HRQL in asthmatics, assessed both using the AQLQ and SF-36 PCS scores (25). As previously found, we observed that co-morbidity in asthmatics has a major impact on HRQL (27). Asthmatics with higher BMI had lower SF-36 PCS score, in contrast to the previous finding where BMI was not related to the AQLQ score in our data (28). An association between smoking and HRQL has been previously shown in asthmatics (29), but smoking was not a major predictor of HRQL in our population.

The HRQL assessed using the total AQLQ score was significantly decreased with increasing asthma-severity defined using the 4-class asthma-severity scale. Interestingly, compared to intermittent asthma, the differences between the medians observed in mild, moderate and severe persistent asthma were ≥0.5 point, the clinically meaningful difference defined by the authors of the AQLQ (23). This is in line with the results from previous clinical studies (8). As opposed to the report of Fonseca et al. (7) in their clinical population, we did not observe a dose-response relationship between the HRQL scores and the asthma-severity grades, which indicates that patients with the intermediate form of asthma-severity did not perceive a different HRQL.

Although the magnitude of the relation between quality-of-life and asthma-severity was stronger for the total AQLQ score than for the PCS, the physical component and not the mental component of the generic questionnaire was able to detect the differences in asthma-severity in this population-based study. There are conflicting results regarding the role of asthma-severity on SF-36 scores (3, 30, 31). But these reports are difficult to compare as the principal aim, the population studied, the asthma-severity assessment and the statistical tools differ widely.

We acknowledge that it remains particularly difficult to measure asthma-severity in a population-based study.

Table 4. Relation between the PCS and the MCS scores and asthma-severity

	PCS			MCS		
	Univariate analyses, <i>n</i> = 864			Univariate analyses, <i>n</i> = 864		
	Median (IQ range)	<Q1, %†	Multivariate analyses, <i>n</i> = 837, OR (95% CI)	Median (IQ range)	<Q1, %‡	Multivariate analyses, <i>n</i> = 837, OR (95% CI)
<i>Model 1‡:</i>						
4-class asthma-severity scale						
Intermittent	50.8 (11.1)	19.6	1.0	51.5 (17.9)	23.8	1.0
Mild persistent	48.4 (14.8)	27.8	1.5 [0.8–2.9]	51.3 (17.1)	31.1	1.6 (1.0–2.3)
Moderate persistent	48.2 (14.9)	29.3	1.4 [1.0–2.0]	53.3 (13.9)	22.7	1.0 (0.7–1.7)
Severe persistent	44.4 (17.0)	35.7	1.8 [1.3–2.4]	51.3 (17.5)	27.3	1.3 (0.7–2.4)
<i>P</i> value*	<0.0001	<0.0001	0.0015	0.97	0.02	0.10
<i>Model 2‡:</i>						
Asthma attacks frequency, past 3 month						
None	49.9 (11.6)	21.2	1.0	52.2 (14.8)	23.5	1.0
1 or 2	46.6 (15.9)	32.0	1.5 [0.9–2.4]	51.3 (12.0)	23.5	1.0 (0.7–1.4)
>2	46.5 (20.0)	32.7	1.7 [1.3–2.4]	48.9 (17.4)	32.7	1.9 (1.0–3.4)
<i>P</i> value*	0.002	<0.0001	0.001	0.06	0.06	0.12
Nocturnal symptoms frequency, past 3 month						
None	50.5 (11.4)	20.5	1.0	52.0 (14.5)	23.6	1.0
≥1/month and <1/week	46.8 (17.4)	32.0	1.5 [1.1–2.2]	50.8 (15.0)	25.8	1.1 (0.7–1.6)
≥1/week	42.8 (19.1)	43.4	1.6 [0.8–3.1]	50.3 (21.1)	32.9	1.0 (0.5–1.7)
<i>P</i> value*	<0.0001	0.0004	0.05	0.22	0.32	0.88
FEV ₁ % predicted:						
> 80%	49.4 (12.6)	23.5	1.0	51.5 (15.4)	25.2	1.0
≤ 80% pred	45.4 (16.5)	34.5	1.7 [1.0–2.9]	53.6 (15.1)	23.5	1.1 (0.6–1.8)
<i>P</i> value*	0.0002	0.003	0.05	0.17	0.71	0.82
≥1 emergency visits or hospitalization, past year						
No	49.2 (12.5)	23.5	1.0	51.8 (14.8)	24.1	1.0
Yes	41.2 (22.7)	49.1	2.3 [1.4–3.7]	48.7 (17.5)	35.8	1.7 (0.9–3.1)
<i>P</i> value*	0.0001	<0.0001	0.001	0.09	0.03	0.12

FEV₁, forced expiratory volume in 1 s; PCS, physical component summary; MCS, mental component summary.

* *P*-value taking into account the correlation between observations from the same sample and country (GEE model), except for the median comparison (*P*-value assessed from the nonparametric test).

† Per cent of subjects with a quality-of-life score lower than the first quartile observed in the whole population (5.2).

‡ Model 1 multivariate analyses: GEE models using the PCS or MCS score (binary variable using the first quartile for threshold) as dependant variable and the 4-class asthma-severity scale and confounders (gender, age, occupational status, tobacco smoking, co-morbidity, rhinitis and BMI) as independent variables.

Model 2 multivariate analyses: GEE models using the PCS or MCS score (binary variable using the first quartile for threshold) as dependant variable and the several asthma-severity items and confounders (gender, age, occupational status, tobacco smoking, co-morbidity, rhinitis, BMI and level of treatment) as independent variables.

Here, we chose to combine clinical items and the level of treatment, following the 2005 GINA guidelines and results from Liard et al. (9, 10). We are aware that the last GINA recommendations (2006) have evolved and shifted from severity to control (9). However, if this approach is adapted to clinical practice for the management of individual asthmatic patients, it seems that taking medication into account may provide both useful and additional information in population-based studies (10).

There is more and more evidence supporting that asthma and asthma-severity are heterogeneous (32, 33). The respective role of the different asthma-severity components (frequency of symptoms, level of ventilatory function and healthcare utilization) on HRQL remains poorly addressed. Our results are in accordance with previous analyses showing that the frequency of asthma attacks is the major predictor of HRQL (8, 30, 34). More convincingly, a clear dose-response relationship with

both the AQLQ and the PCS scores was found in our study. Interestingly, in addition to the frequency of asthma attacks, the frequency of nocturnal asthma symptoms was found to be an independent determinant of the total AQLQ score, suggesting that the control of both diurnal and nocturnal symptoms is an important target for therapeutic intervention. As opposed to the AQLQ, the SF-36 is not specific for asthma and contains no questions on nocturnal symptoms. It may explain why the frequency of nocturnal symptoms was not found to be a predictor of the PCS score.

In our study low FEV₁ was significantly related to the PCS independent of the other severity criteria. However, in 50 moderate/severe asthmatics with FEV₁ < 80% predicted, Apter et al. (25) did not find any correlation between FEV₁ and PCS or MCS; the lack of relation may result from the limited sample size or perhaps because, below a certain degree of airflow limitation, the subjects

do not perceive further effects. The lack of association between the FEV₁ and the total AQLQ in our study is consistent with the previous findings (8, 25). Altogether, these findings add evidence that distinct dimensions may be identified within asthma-severity and support the recommendation that HRQL should be measured in addition to clinical parameters using both generic and specific questionnaires.

Independent of the other predictors, emergency visit or hospitalization for asthma in the past year was similarly associated with the SF-36 PCS score and the total AQLQ score with OR between 2.5 and 3.0 for being in the lowest quartile score. Despite the low occurrence of hospitalization in our population, it seems to have a major independent impact on HRQL.

In conclusion, this study conducted in asthmatics from the general population confirmed that increased asthma-severity is associated with impaired quality-of-life, but the risk of worse quality-of-life does not follow a linear trend across the levels of severity. Asthmatic patients are obviously bothered by the frequency of asthma attacks, but the frequency of nocturnal symptoms and emergency visits for asthma have additional independent impact on their HRQL. These are all important objectives to target in the management of the disease.

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References

1. Ford ES, Mannino DM, Redd SC, Moriarty DG, Mokdad AH. Determinants of quality of life among people with asthma: findings from the Behavioral Risk Factor Surveillance System. *J Asthma* 2004;**41**:327–336.
2. 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.
3. Bousquet J, Knani J, Dhivert H, Richard A, Chicoye A, Ware JE Jr et al. Quality of life in asthma. I. Internal consistency and validity of the SF-36 questionnaire. *Am J Respir Crit Care Med* 1994;**149**:371–375.
4. Mahajan P, Okamoto LJ, Schaberg A, Kellerman D, Schoenwetter WF. Impact of fluticasone propionate powder on health-related quality of life in patients with moderate asthma. *J Asthma* 1997;**34**:227–234.
5. Juniper EF, Svensson K, O'Byrne PM, Barnes PJ, Bauer CA, Lofdahl CG et al. Asthma quality of life during 1 year of treatment with budesonide with or without formoterol. *Eur Respir J* 1999;**14**:1038–1043.
6. Juniper EF, Johnston PR, Borkhoff CM, Guyatt GH, Boulet LP, Haukioja A. Quality of life in asthma clinical trials: comparison of salmeterol and salbutamol. *Am J Respir Crit Care Med* 1995;**151**:66–70.
7. Fonseca JA, Delgado L, Costa-Pereira A, Tavares C, Moreira A, Morete A et al. Evaluation of the asthma life quality test for the screening and severity assessment of asthma. *Allergy* 2004;**59**:1198–1204.
8. Moy ML, Israel E, Weiss ST, Juniper EF, Dube L, Drazen JM. Clinical predictors of health-related quality of life depend on asthma severity. *Am J Respir Crit Care Med* 2001;**163**:924–929.
9. Global Initiative for Asthma. Global strategy for asthma management and prevention. Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health, 1995 NIH publication no. 95-3659. Available at: <http://www.ginasthma.org>.
10. Liard R, Leynaert B, Zureik M, Beguin FX, Neukirch F. Using Global Initiative for Asthma guidelines to assess asthma severity in populations. *Eur Respir J* 2000;**16**:615–620.
11. Teeter JG, Bleecker ER. Relationship between airway obstruction and respiratory symptoms in adult asthmatics. *Chest* 1998;**113**:272–277.
12. Bailey WC, Higgins DM, Richards BM, Richards JM Jr. Asthma severity: a factor analytic investigation. *Am J Med* 1992;**93**:263–269.
13. Vollmer WM, Markson LE, O'Connor E, Sanocki LL, Fitterman L, Berger M et al. Association of asthma control with health care utilization and quality of life. *Am J Respir Crit Care Med* 1999;**160**:1647–1652.
14. Chen H, Gould MK, Blanc PD, Miller DP, Kamath TV, Lee JH et al. Asthma control, severity, and quality of life: quantifying the effect of uncontrolled disease. *J Allergy Clin Immunol* 2007;**120**:396–402.
15. The European Community Respiratory Health Survey II Steering Committee. The European Community Respiratory Health Survey II. *Eur Respir J* 2002;**20**:1071–1079.
16. Chinn S, Jarvis D, Burney P, Luczynska C, Ackermann-Liebrich U, Anto JM et al. Increase in diagnosed asthma but not in symptoms in the European Community Respiratory Health Survey. *Thorax* 2004;**59**:646–651.
17. Cazzoletti L, Marcon A, Janson C, Corsico A, Jarvis D, Pin I et al. Asthma control in Europe: a real-world evaluation based on an international population-based study. *J Allergy Clin Immunol* 2007;**120**:1360–1367.
18. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36) I. Conceptual framework and item selection. *Med Care* 1992;**30**:473–483.
19. Ware JE Jr, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey: Manual and Interpretation Guide. Boston, MA: The Health Institute, New England Medical Center, 1993.
20. Ware JE Jr, Kosinski M, Keller SD. SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston, MA: Health Assessment Lab, New England Medical Center, 1994.
21. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. *Am Rev Respir Dis* 1993;**147**:832–838.
22. Sanjuas C, Alonso J, Ferrer M, Curull V, Broquetas JM, Anto JM. Adaptation of the Asthma Quality of Life Questionnaire to a second language preserves its critical properties: the Spanish version. *J Clin Epidemiol* 2001;**54**:182–189.

23. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol* 1994;**47**:81–87.
24. de Marco R, Marcon A, Jarvis D, Accordini S, Almar E, Bugiani M et al. Prognostic factors of asthma severity: a 9-year international prospective cohort study. *J Allergy Clin Immunol* 2006;**117**:1249–1256.
25. Apter AJ, Reisine ST, Affleck G, Barrows E, ZuWallack RL. The influence of demographic and socioeconomic factors on health-related quality of life in asthma. *J Allergy Clin Immunol* 1999;**103**:72–78.
26. Wijnhoven HA, Kriegsman DM, Snoek FJ, Hesselink AE, de HM. Gender differences in health-related quality of life among asthma patients. *J Asthma* 2003;**40**:189–199.
27. Wijnhoven HA, Kriegsman DM, Hesselink AE, de HM, Schellevis FG. The influence of co-morbidity on health-related quality of life in asthma and COPD patients. *Respir Med* 2003;**97**:468–475.
28. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med* 2006;**100**:648–657.
29. Sippel JM, Pedula KL, Vollmer WM, Buist AS, Osborne ML. Associations of smoking with hospital-based care and quality of life in patients with obstructive airway disease. *Chest* 1999;**115**:691–696.
30. Schatz M, Mosen D, Apter AJ, Zeiger RS, Vollmer WM, Stibolt TB et al. Relationships among quality of life, severity, and control measures in asthma: an evaluation using factor analysis. *J Allergy Clin Immunol* 2005;**115**:1049–1055.
31. Ekici A, Ekici M, Kara T, Keles H, Kocyigit P. Negative mood and quality of life in patients with asthma. *Qual Life Res* 2006;**15**:49–56.
32. Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet* 2006;**368**:804–813.
33. Bel EH. Severe asthma. *Breathe* 2006;**3**:128–139.
34. Osman LM, Calder C, Robertson R, Friend JA, Legge JS, Douglas JG. Symptoms, quality of life, and health service contact among young adults with mild asthma. *Am J Respir Crit Care Med* 2000;**161**:498–503.