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Respiratory Medicine (in press)

ASTHMA CONTROL ASSESSED IN THE EGEA EPIDEMIOLOGICAL SURVEY AND HEALTH-RELATED QUALITY OF LIFE

Asthma control and health-related quality of life

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Key words: Asthma; Asthma control; Epidemiology; Health-related quality of life

SUMMARY

Background: The aims were to assess 1) the relationship of asthma control assessed by combining epidemiological survey questions and lung function to Health-Related Quality of Life (HRQL) and 2) whether individuals with controlled asthma reach similar generic HRQL levels as individuals without asthma.

Methods: The analysis included 584 individuals without asthma and 498 with asthma who participated in the follow-up of the Epidemiological study on Genetics and Environment of Asthma (EGEA). Asthma control was assessed from survey questions and lung function, closely adapted from the 2006-2009 Global Initiative for Asthma guidelines. The Asthma Quality of Life Questionnaire (AQLQ, scores range:1-7) and the generic SF-36 (scores range:0-100) were used.

Results: Adjusted mean total AQLQ score decreased by 0.5 points for each asthma control steps (6.4, 5.9 and 5.4 for controlled, partly-controlled and uncontrolled asthma respectively, $p<0.0001$). The differences in SF-36 scores between individuals with controlled asthma and those without asthma were minor and not significant for the PCS (-1, $p=0.09$), borderline significant for the MCS (-1.6, $p=0.05$) and small for the 8 domains (<5.1) although statistically significant for 4 domains.

Conclusion: These results support the discriminative properties of the proposed asthma control grading system and its use in epidemiology.

INTRODUCTION

Asthma control reflects the disease activity over a short period of time and incorporates exacerbations and current clinical control[1]. Asthma control is important in clinical practice to evaluate patients and their response to treatment (the Global Initiative for Asthma-GINA, the National Asthma Education and Prevention Program-NAEPP) as well as for public health and research. Studies on asthma control have mainly been conducted in clinical studies and few epidemiologic studies in large populations of asthmatics have addressed uncontrolled asthma assessed in a comprehensive manner by incorporating several dimensions of the disease [2, 3].

Poor asthma control is associated with generic and specific health-related quality of life (HRQL) indices [4-6]. Recent articles support the construct validity of the GINA asthma control classification by studying its relationship with specific control questionnaires in clinical populations [7, 8]. To our knowledge, no study has attempted to examine the HRQL impact of asthma control assessed in a comprehensive way following the GINA guidelines by combining subjective measures of asthma control through epidemiological survey questions (to assess daytime and nighttime symptoms level, rescue medication use and asthma exacerbation) and objective measures of asthma control (lung function). Asthma is associated with a decreased quality of life [9, 10], but it is unknown whether individuals with controlled asthma have a decreased HRQL compared to those without asthma. Such discriminative properties analysis, using a mixed traditional and clinical epidemiological approach, including healthy subjects and well characterized asthmatics, [11] would provide construct validity evidence of such a grading system of asthma control applicable in epidemiology [12].

In the frame of the Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy (EGEA), a French case-control and family study on asthma with detailed information for asthma control and quality of life for 1082 subjects, the specific hypotheses tested in this article are that 1) asthma control, assessed by combining data collected in that epidemiological survey closely adapted from the GINA guidelines, has an important impact on the quality of life among individuals with asthma; 2) the quality of life achieved in individuals with controlled asthma is similar to the quality of life of individuals without asthma.

METHODS

Population

EGEA is a cohort study (12 years follow-up) based on an initial group of patients with asthma recruited in chest clinics (probands, n=388) and their first-degree relatives (n=1244), and a group of population-based subjects (n=415). [13-15] Careful attention was given to address potential biases at inclusion and during examination. [15] The population of this cross sectional analysis included 1082 individuals (250 probands, 620 relatives of probands and 212 population-based subjects) who took part in EGEA2 (2003-2007), with data available for asthma, asthma control classification and HRQL (584 without asthma and 498 with current asthma) (Figure 1) [3]. Written consent was obtained from all participants at both surveys. Ethical approval to carry out the study was obtained for both surveys from the relevant committees (Cochin Port-Royal Hospital, Paris for EGEA1 and Necker-Enfants Malades Hospital, Paris for EGEA2).

Phenotypes

Current asthma was defined by a positive answer to one of the two standardized questions: “Have you ever had attacks of breathlessness at rest with wheezing?”, “Have you ever had asthma attacks?”, and at least to one question about asthma attack, respiratory symptoms (wheezing, nocturnal chest tightness, attack of shortness of breath following strenuous activity, at rest or at night) or treatment for asthma in the last 12 months [3]. Individuals without asthma were defined by negative answers to the first two questions and report of no treatment for asthma or respiratory problems in the past 12 months.

Asthma control was assessed by combining epidemiological data following as much as possible the 2006-2009 GINA (Global Initiative for Asthma) guidelines [16]. This classification has already been used in a previous publication assessing the determinants of asthma control [3]. Asthma was defined as 1) controlled if all the following features, assessed on average over the past 3 months except for FEV1, were present: trouble with breathing less than once a week, no asthma attacks, no nocturnal symptoms, short-acting ß2-agonists use twice or less per week in the last 3 months, no use of oral steroids in the last 12 months, FEV1 $\geq$ 80% of predicted value, 2) partly controlled if 1 or 2 of the above features were absent, 3) uncontrolled if $\geq$3 of these features were absent or if respiratory problems had caused hospital/emergency department admissions in the last 12 months, or if oral steroids had been used in the last 12 months or $\geq$12 asthma attacks in the past 3 months.

Quality of life questionnaires

Two standardized quality of life questionnaires were used:

1) The Asthma Quality of Life Questionnaire (AQLQ) [17] an asthma-specific instrument that consists of 32 questions, relating to the past 2 weeks and covering four domains: "symptoms", "activity limitation", "emotional function" and susceptibility to "environmental exposure". The minimal clinically important difference (MCID), which is the smallest difference that has been considered as clinically and socially relevant by the developers, is 0.5 [18]. As previously used in the literature [19], the HRQL score differences have been compared to the MCID when addressing the magnitude of the differences observed between groups, although the MCID was not initially developed to be used in this context.

2) The SF-36 (Medical Outcomes Survey 36 item Short Form health survey), a generic questionnaire composed of 36 items that covers eight health status domains: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health [20]. The computed scores for each domain and the two summary component scores (Physical Component Summary, PCS and Mental Component Summary, MCS) range from 0 to 100, with larger scores indicating better health status[21]. There are no recommended MCID for the summary scores, but MCIDs for the 8 domains have been described in an asthma population (between 10.0 and 16.7) [22].

Statistical analyses

Mixed models that take into account the dependence of the subjects within families were conducted with a robust estimate of the standard errors (SE) because of the non-normality of the HRQL scores. The assessment of comorbidity is important in HRQL research [23]. Since co-morbid conditions affect considerably less disease-specific than generic HRQL measures [24], the analysis using the SF-36 questionnaire were performed among individuals without co-morbidity (584 without asthma and 393 with asthma) whereas the analysis using the AQLQ were conducted on all individuals with asthma, with a further adjustment on co-morbidity (n=480). The analysis was further conducted separately in ICS users (ICS+) and non-ICS users (ICS-) over the past 12 months to account for disease severity [2]. All analyses were performed using the SAS 9.1 statistical software (SAS institute, Cary, NC).

RESULTS

Subject characteristics

The frequency of the allergy-related phenotypes (sensitization to aero-allergens, high level of total IgE and rhinitis) and bronchial hyperresponsiveness were much higher in individuals with asthma (n=498, mean age 39.4 years) than in individuals without asthma (n=584, mean age 43.8 years) (table 1). 93% of individuals with asthma, reported to have ever had doctor diagnosed asthma and half of them had used ICS in the past 12 months. In this population, 44.4%, 29.7% and 25.9% had controlled, partly-controlled and uncontrolled asthma.

Disease-specific and generic quality of life and asthma control

Uncontrolled asthma was associated with a significantly decreased total AQLQ score ($p<0.0001$) and partly-controlled asthma showed intermediate total AQLQ scores between controlled and uncontrolled asthma. A decrease by at least 0.5 point was observed for all domains and the total AQLQ score when comparing uncontrolled asthma to controlled asthma, but was only observed for the symptom score and the total AQLQ score when comparing partly-controlled asthma to controlled asthma (Table 2). The AQLQ scores were higher in ICS- compared to ICS+ (mean total AQLQ score were 6.4 and 5.7 respectively, $p<0.0001$), reflecting a milder disease among individuals not using ICS. Nevertheless, the multivariate analysis stratified on ICS use over the past 12 months showed that in both groups and for all domains, except for Activity Limitation in ICS-, uncontrolled asthma was related to significant decreased scores of at least 0.5 point compared to controlled asthma (table 2).

The physical and mental summary component scores and all SF-36 domains were significantly decreased in uncontrolled asthma compared to controlled asthma (Table 3). For three domains, Role Physical, General Health and Role Emotional, the score differences were stronger than the MCID thresholds defined for asthma (13.2, 12.6 and 16.7 respectively). Compared to controlled asthma, partly-controlled asthma was associated with a significantly lower PCS score, but no association was observed with the MCS score (table 3). Partly-controlled asthma showed similar SF-36 scores to controlled asthma for all domains, except for the General Health domain where a statistically significant difference was observed but the difference (6.4) was lower than the MCID previously proposed in asthma for this domain.

Generic quality of life (SF-36) in individuals with controlled asthma vs individuals without asthma

Mean SF-36 physical and mental summary scores were lower in the whole group of individuals with asthma as compared to individuals without asthma (adjusted means (SE) in individuals with asthma and individuals without asthma were for the PCS score 51.8 (0.45) *v*s 54.1 (0.31), p<0.0001 and for the MCS score 46.5 (0.65) vs 49.2 (0.56), p=0.0007).

Individuals with controlled asthma had similar PCS scores and lower MCS scores when compared to those without asthma (table 3). Similar results were observed even in subjects with controlled asthma who had used ICS in the past year (n=54) (adjusted mean (SE) PCS scores were 53.9 (0.8) and 54.3(0.4) and adjusted mean (SE) MCS score were 47.7 (1.4) and 49.2 (0.6) for controlled asthma and non asthma respectively). Regarding each SF-36 domain, individuals with controlled asthma showed statistically significantly lower scores for Physical Functioning, General Health, Social Functioning and Mental Health compared to individuals without asthma. However none of the observed differences reached 5 when the MCIDs defined in asthma for these domains are 10 or greater, indicating that although being statistically significant, the magnitudes of the differences were relatively small.

DISCUSSION

Uncontrolled asthma, assessed by combining epidemiological data on day and night symptoms, use of reliever therapy, lung function and exacerbation was significantly associated with a decreased HRQL, with differences compared to controlled asthmatics that exceeded the MCID. This study, by comparing HRQL between subjects with controlled asthma and healthy subjects, suggests that the health status impairment is minimal if asthma control is achieved.

The strength of the present analysis lies on the large and well characterized population of adults with asthma and without asthma recruited in the framework of the EGEA study. In the present analysis, a sensitive current asthma phenotype, supported by the high frequencies of the allergic phenotypes and of BHR among the individuals with asthma, and a specific definition of individuals without asthma were used. Another strength of the present analysis is the use of both a standardized generic questionnaire (SF-36) and an asthma specific questionnaire (AQLQ). Data available in the EGEA2 study made it possible to take into account a large number of confounders [3]. The comprehensive asthma control classification used allows accounting for multiple features of asthma control by combining both objective and subjective measures of asthma control. The inclusion of lung function in the asthma control assessment is supported by a previous factorial analysis showing that asthma health status is composed of distinct components, lung function being one of them [25], and by clustering analysis showing that an impaired lung function is observed for specific asthma phenotypes [26] . However, a limitation of this classification lies on the lack of data on activity limitation, one dimension of asthma control integrated in the GINA guidelines. Nevertheless, the lack of this dimension is expected to impair asthma control classification in only few subjects, as suggested by unpublished data in ECRHSII showing that among1032 patients with current asthma the activity limitation had an impact on the asthma control level in only 8.7% subjects. Compared to the time period used in some asthma control questionnaires or following the current clinical guidelines (one to four weeks), a longer time period was used in the EGEA study (3 months), which most likely results in decreasing the strength of the association with HRQL, as HRQL questionnaire relates to a much shorter time (2 weeks for the AQLQ and 4 weeks for the SF-36 questionnaire). However, there is no reason to expect a differential or systematic bias that would lead to underestimate or overestimate the association. The lack of asthma control in this population is due either to under-treatment (supported by the observation that 42% and 30% of the individuals with partly-controlled and uncontrolled asthma respectively did not use ICS in the past year) or to the lack of response to asthma treatment (supported by the observation that half of the subjects with uncontrolled asthma used high daily treatment level, GINA step 3 and 4, in the past 3 months) as previously reported[3].
Present findings show that uncontrolled asthma was significantly associated with decreased AQLQ scores, which confirm previous studies using standardized asthma control tools [4, 5]. Individuals with partly-controlled asthma had intermediate AQLQ scores between those with controlled and uncontrolled asthma. Our results, showing a greater impact of partly-controlled asthma on the symptoms domain compared to the emotional function and environmental exposure domains are in agreement with previous studies [19, 27]. The lack of difference between partly controlled asthma and controlled asthma using the SF-36 questionnaire, may be explained by a lower sensitivity of generic questionnaires to detect small differences in HRQL [28].

Clinical and epidemiological studies have shown a decreased HRQL in more severe asthma [29-31]. The similar pattern of association between asthma control and AQLQ score observed among subjects using ICS treatment and those not using ICS treatment suggests that the proposed asthma control classification is able to discriminate levels of HRQL in both individuals with mild and more severe asthma.

As expected and previously shown in other populations, individuals with asthma as a group had an impaired quality of life compared to individuals without asthma [9, 10]. Moreover, our results indicate that HRQL in individuals with controlled asthma is comparable to HRQL in individuals without asthma. The lack of

association between the SF-36 PCS score and controlled asthma is not due to a lack of statistical power as the power of 80% was reached for differences between control asthma and no asthma greater than 1.3; this represents a really reasonable difference compared with previous published articles in population-based study showing PCS decreased by 5 points with asthma [10]. The lack of difference between SF-36 component summary scores and controlled asthma was observed for the group of individuals with asthma who had used ICS in the past year and it may be an important message for encouraging the achievement of optimal control in populations. It is unlikely that potential misclassification could explain this result since asthma characterization was good. Although no major differences between individuals with asthma and those without asthma was observed on several personal and socio-economic characteristics (sex, smoking, educational level and BMI), selection bias may have occurred on other factors and a replication of our results in a larger population-based study is warranted.

Conclusion

The proposed approach to assess asthma control in epidemiology, using a comprehensive manner adapted from the GINA guidelines, is strongly associated with HRQL. Furthermore, although some of the SF-36 domain scores differences were statistically different between individuals with controlled asthma and those without asthma, the differences observed were of small magnitude, indicating that the health status impairment is minimal if asthma control is achieved. These results support the discriminative properties of such an asthma control grading system applicable in epidemiological studies. Its use in epidemiology could provide useful tools to identify risk factors for uncontrolled asthma and to compare the quality of asthma management between different populations.

Acknowledgments

We thank the EGEA cooperative group :
Coordination : F Kauffmann; F Demenais (genetics); I Pin (clinical aspects).
Respiratory epidemiology : Inserm U 700, Paris M Korobaeff (Egea1), F Neukirch (Egea1); Inserm U 707, Paris : I Annesi-Maesano ; Inserm CESP/U 1018, Villejuif : F Kauffmann, N Le Moual, R Nadif, MP Oryszczyn ; Inserm U 823, Grenoble : V Siroux
Genetics : Inserm U 393, Paris : J Feingold ; Inserm U 946, Paris : E Bouzigon , F Demenais, MH Dizier ; CNG, Evry : I Gut , M Lathrop.
Clinical centers : Grenoble : I Pin, C Pison; Lyon : D Ecochard (Egea1), F Gormand, Y Pacheco ; Marseille : D Charpin (Egea1), D Vervloet ; Montpellier : J Bousquet ; Paris Cochin : A Lockhart (Egea1), R Matran (now in Lille) ; Paris Necker : E Paty, P Scheinmann ; Paris-Trousseau : A Grimfeld, J Just.
Data and quality management : Inserm ex-U155 (Egea1) : J Hochez ; Inserm CESP/U 1018, Villejuif : N Le Moual, Inserm ex-U780 : C Ravault ; Inserm ex-U794 : N Chateigner ; Grenoble : J Ferran

The authors thank all those who participated to the setting of the study and on the various aspects of the examinations involved: interviewers, technicians for lung function testing and skin prick tests, blood sampling, IgE determinations, coders, those involved in quality control, data and sample management and all those who supervised the study in all centers. The authors are grateful to the three CIC-Inserm of Necker, Grenoble and Marseille who supported the study and in which subjects were examined. They are indebted to all the individuals who participated without whom that study would not have been possible.

Funding support : The EGEA study was supported in part by grants from Merck Sharp & Dohme (MSD); Hospital program of clinical research (PHRC)-Paris; National Research Agency - Health environment, health-work program; National Research Agency (ANR)- Biological collections for health program; French Agency of health safety, environment and work (AFSSET); the national scientific committee of the medico-technology support at home (AGIR à dom) and the Isere committee against respiratory diseases (COMARES).

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Figure 1: Flowchart of the EGEA population

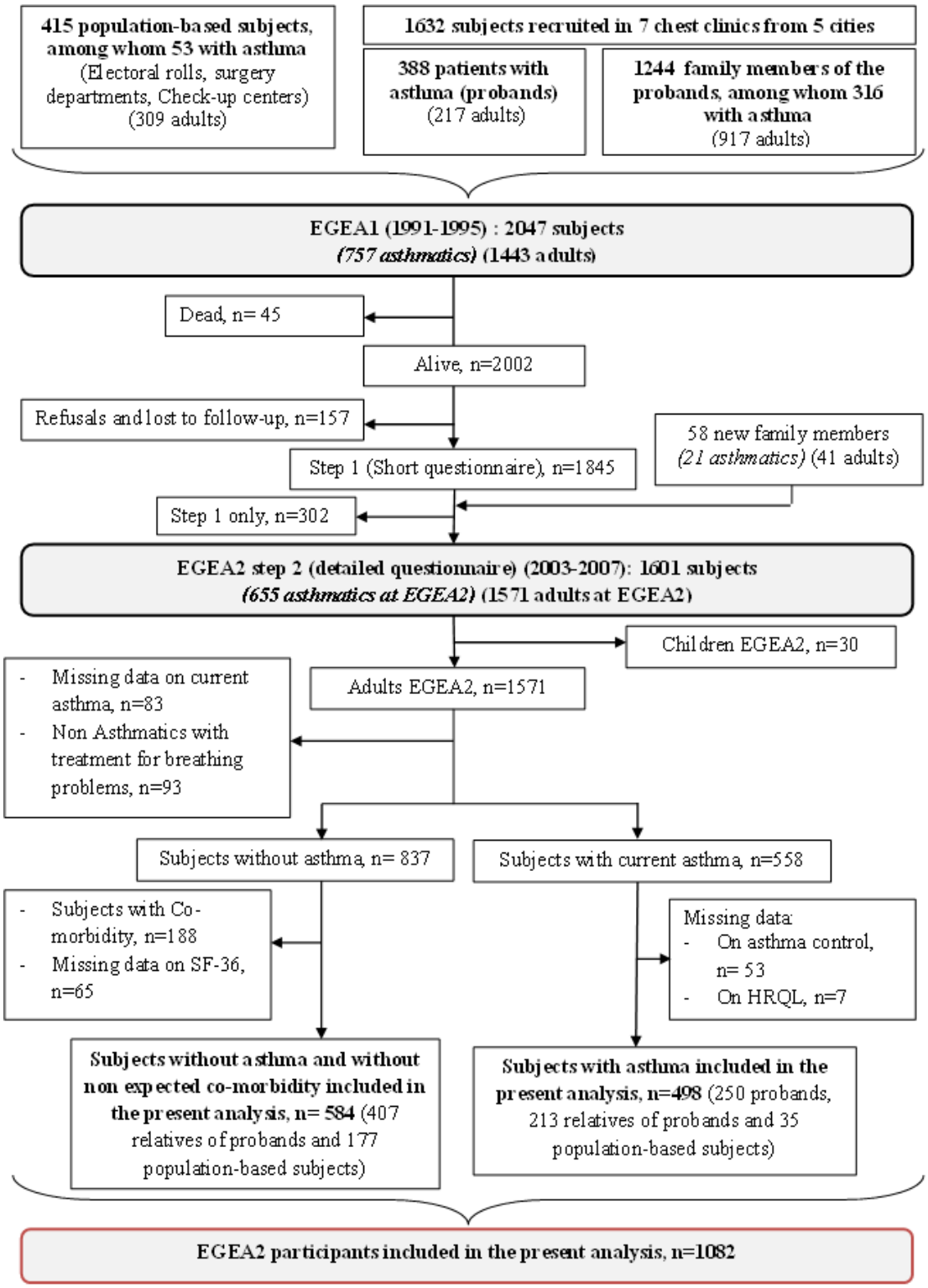

Table 1. Characteristics of the population

	Individuals without asthma and co-morbidity* n= 584	Individuals with asthma			
		All n= 498	**Controlled** n=221	**Partly controlled** n=148	**Uncontrolled** n=129
Age, m ± sd (n)	43.8 ± 15.6 (584)	39.4 ±16.4 (498) §	36.8±15.5 (221)	40.6±17.0 (148)	42.4±16.6 (129)
Sex, % males (n)	46.7 (273)	50.8 (253)	53.8 (119)	54.7 (81)	41.1 (53)
Educational level					
University, % (n)	51.1 (297)	49.3 (241)	49.3 (109)	53.1 (77)	44.7 (55)
Secondary, % (n)	25.5 (148)	29.0 (142)	31.2 (69)	24.1 (35)	30.9 (38)
Primary, % (n)	23.4 (136)	21.7 (106)	19.5 (43)	22.8 (33)	24.4 (30)
Current active/passive smoking					
Non/ex smokers and ETS†-, % (n)	39.0 (226)	34.2 (170)	33.0 (73)	33.8 (50)	36.7 (47)
Non/ex smokers and ETS†+, % (n)	39.4 (228)	40.2 (200)	38.5 (85)	45.3 (67)	37.5 (48)
Current smokers, % (n)	21.6 (125)	25.6 (127)	28.5 (63)	20.9 (31)	25.8 (33)
BMI ≥ 25 kg/m^2, % (n)	35.7 (199)	36.7 (178)	33.9 (75)	37.1 (53)	41.3 (50)
Co-morbidity*, % (n)	--	19.3 (96)	16.7 (37)	20.3 (30)	22.5 (29)
Sensitization, % (n)	40.1 (210)	81.1 (369) §	79.5 (167)	81.5 (110)	83.6 (92)
Active rhinitis, % (n)	18.9 (109)	60.8 (298) §	56.6 (124)	60.8 (87)	68.0 (87)
Total IgE ≥100 IU/ml, % (n)	29.2 (162)	61.5 (297) §	54.1 (118)	68.5 (98)	66.4 (81)
BHR, PD20≤4mg, % (n)	26.3 (103)	70.5 (198) §	66.7 (110)	74.6 (50)	77.5 (38)
Asthma					
Status in the study: Case, % (n)		50.2 (250)	37.2 (93)	30.8 (77)	32.0 (80)
Relatives or controls, % (n)		49.8 (248)	51.6 (128)	28.6 (71)	19.8 (49)
Asthma onset: ≤4 years, % (n)	--	31.1 (146)	31.5 (65)	30.3 (43)	31.4 (38)
]4-16] , % (n)	--	34.5 (162)	38.4 (79)	33.1 (47)	29.7 (36)
> 16, % (n)	--	34.3 (161)	30.1 (62)	36.6 (52)	38.8 (47)
ICS use in the past 12 months % (n)	--	49.4 (244)	31.0 (68)	58.2 (85)	70.5 (91)

* Non-expected co-morbidity was assessed by a positive answer to "Have you ever been treated or followed for rheumatism, Crohn disease, poly-arthritis, heart disease, diabetes, or other serious illnesses". For individuals who answered "other serious illnesses", the specific disease was reported and a medical doctor decided whether the condition(s) declared could be considered as a co-morbid condition in the context of this study of HRQL. † ETS : Environmental Tobacco Smoke. § $p<0.001$ for the difference between individuals without asthma those with asthma

Table 2. Disease-specific quality of life (AQLQ) according to asthma control

	Adjusted* mean (SE) AQLQ scores				
	Activity Limitation	Symptoms	Emotional Function	Environmental Exposure	**AQLQ total**
Among all individuals with asthma (n=429)					
Controlled asthma (ref.)	6.3 (0.06)	6.3 (0.07)	6.5 (0.08)	6.4 (0.09)	6.4 (0.06)
Partly-controlled asthma	6.0 (0.09) §	5.7 (0.10) §	6.1 (0.12) §	6.0 (0.11) §	5.9 (0.08) §
Uncontrolled asthma	5.7 (0.11) §	5.1 (0.12) §	5.7 (0.13) §	5.6 (0.12) §	5.4 (0.10) §
Among individuals with asthma who used ICS in the past 12 months (n=213)					
Controlled asthma (ref.)	6.3 (0.12)	6.1 (0.12)	6.4 (0.14)	6.2 (0.16)	6.2 (0.11)
Partly-controlled asthma	6.0 (0.12) †	5.7 (0.13) †	6.1 (0.15)	6.0 (0.14)	5.9 (0.11) †
Uncontrolled asthma	5.5 (0.14) §	4.9 (0.15) §	5.5 (0.16) §	5.5 (0.15) ‡	5.3 (0.13) §
Among individuals with asthma who did not used ICS in the past 12 months (n=212)					
Controlled asthma (ref.)	6.4 (0.08)	6.4 (0.08)	6.7 (0.08)	6.5 (0.12)	6.5 (0.07)
Partly-controlled asthma	6.3 (0.12)	5.8 (0.13) §	6.2 (0.15) §	6.1 (0.18) †	6.1 (0.11) §
Uncontrolled asthma	6.1 (0.13) †	5.7 (0.17) §	6.2 (0.17) ‡	5.8 (0.22) ‡	5.9 (0.13) §

* Models were adjusted by age, sex, educational level, smoking, BMI, sensitization, allergic rhinitis, IgE, co-morbidity and centre

† $p < 0.05$; ‡ $p < 0.01$; § $p < 0.001$ in comparison with the reference group (controlled asthma) and estimated with mixed model with a robust estimate of the standard errors

Table 3. Generic quality of life (SF36) according to asthma and asthma control

	Adjusted* mean (SE) SF-36 physical component scores					Adjusted* mean (SE) SF-36 mental component scores				
	Physical Functioning	Role Physical	Bodily Pain	General Health	**PCS**	Vitality	Social Functioning	Role Emotional	Mental Health	**MCS**
No asthma	93.1 (0.7)	91.3 (1.4)	78.3 (1.2)	75.3 (0.9)	54.1 (0.4)	60.3 (1.0)	84.8 (1.2)	84.5 (1.7)	68.9 (0.9)	49.0 (0.5)
Controlled asthma	89.4 (1.1)	88.3 (2.0)	78.9 (1.7)	70.2 (1.3)	53.1 (0.5)	58.0 (1.3)	79.7 (1.6)	80.5 (2.4)	65.5 (1.5)	47.4 (0.9)
Partly-controlled asthma	87.6 (1.3)	88.6 (2.5)	78.6 (2.3)	63.8 (1.9)	51.7 (0.7)	56.9 (1.6)	77.9 (2.0)	83.3 (3.1)	65.9 (1.6)	47.8 (0.9)
Uncontrolled asthma	82.8 (1.7)	75.1 (3.6)	70.6 (2.4)	57.6 (1.9)	49.2 (0.9)	51.7 (2.0)	68.8 (2.6)	63.8 (4.3)	60.2 (2.1)	43.1 (1.4)
Statistical test for the comparison of HRQL scores between controlled asthma and no asthma										
Controlled asthma vs. no asthma,										
Scores difference	-3.7	-3.0	0.6	-5.1	-1	-2.3	-5.1	-4.0	-3.4	-1.6
p value	0.002	0.19	0.79	0.0004	0.09	0.14	0.005	0.14	0.03	0.05
Statistical test for the comparison of HRQL scores between asthma control steps										
Partly-controlled vs. controlled asthma										
Scores difference	-1.8	0.3	-0.3	-6.4	-1.4	-1.1	-1.8	2.8	0.4	0.4
p value	0.25	0.90	0.91	0.002	0.05	0.55	0.42	0.43	0.82	0.74
Uncontrolled vs. partly-controlled asthma										
Scores difference	-4.8	-13.5	-8.0	-6.2	-2.5	-5.2	-9.1	-19.5	-5.7	-4.7
p value	0.02	0.001	0.01	0.02	0.02	0.03	0.004	0.0002	0.03	0.005
Uncontrolled vs. controlled asthma										
Scores difference	-6.6	-13.2	-8.3	-12.6	-3.9	-6.3	-10.9	-16.7	-5.3	-4.3
p value	0.0006	0.0006	0.004	<0.0001	<0.0001	0.008	0.0002	0.0006	0.03	0.008

* Models were adjusted by age, sex, educational level, smoking, BMI, sensitization, allergic rhinitis, IgE and centre
Adjusted means were estimated with mixed model with a robust estimate of the standard errors