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Longitudinal HRQoL shows divergent trends and identifies constant decliners in asthma and COPD

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Summary
Background/aim: Monitoring of lung function alone does not adequately identify the high-risk patients among elderly asthma and COPD cohorts. The additional value of Health-Related Quality of Life (HRQoL) development in the detection of patients with a disabling disease in clinical practice is unclear. The aim of this study was to statistically examine the individual development of HRQoL measured using respiratory-specific AQ20 and generic 15D questionnaires.
Materials and methods: The HRQoL of COPD ($N = 739$) and asthma ($N = 1329$) patients was evaluated at 0, 1, 2, and 4 years after recruitment. To determine a five-year HRQoL change for each patient we used mixed-effects modelling for linear trend.
Results: In COPD, the majority (60–80%) of the individuals showed declining trend, whereas in asthma, the majority (46–71%) showed no attenuation in HRQoL. The proportion of constant decliners was estimated higher with the 15D both in asthma (6.3%) and COPD (6.3%) than with AQ20 (3.5 and 4.5%, respectively). The first measurement of HRQoL was found to predict future development of HRQoL. In asthma, obesity-related diseases such as hypertension, diabetes and gastro-esophageal reflux disease best explained the decline, whereas in COPD, age and the level of bronchial obstruction were the main determinants.
Conclusion: Based on the five-year follow-up, the HRQoL trends significantly diverging from each other could be identified both among the asthma and COPD patients. Compared to

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cross-sectional HRQoL, the HRQoL trend over a clinically relevant period of time allows us to ignore, to a great extent, the random error of self-assessed HRQoL and thus, it may offer a more accurate measure to describe the disease process.

Introduction

Several cross-sectional studies comparing the clinical findings and Health-Related Quality of Life (HRQoL) in asthma and chronic obstructive pulmonary disease (COPD) have lately been published [1—5]. In COPD, HRQoL has been shown to correlate with lung function, exercise capacity, exacerbations, dyspnoea and comorbidities, but all the correlations found are rather weak when linked to clinical manifestations [6]. In asthma, severity of the disease, comorbidities such as chronic rhinosinusitis and allergic rhinitis have been found to be associated with impaired HRQoL [7,8]. Different clinical determinants might be identified with different types of instruments e.g. due to better sensitivity of disease-specific instruments.

HRQoL instruments have proven valuable in clinical interventions and as the primary or secondary endpoint in efficacy studies [9—13]. In clinical practice when chronic diseases are managed, the value of HRQoL remains however, unclear. Potentially HRQoL can provide important information on patients' perception of disease burden. Both asthma and COPD are complex diseases. We have used to consider COPD as a progressive disease leading to disabilities through severe dyspnoea and disease exacerbations, while in asthma the lung functions are stored and long-term prognosis is generally good. In the elderly patient populations the features of asthma and COPD are often overlapping [14]. Monitoring of lung functions alone does not necessarily dissect these patients having either progressive or non-progressive disease [15,16]. As the treatments in obstructive lung diseases have evolved rapidly, there is a need for better diagnostics. The assessment of longitudinal HRQoL together with other clinical measures might improve the identification of the high-risk patients.

Several HRQoL questionnaires have been evaluated and compared in chronic obstructive airway diseases, both generic and airway-specific [17—32]. None of them has shown to be superior to others [33]. The questionnaires are usually designed to assess the patients' present HRQoL, which is a highly subjective measure and by definition leads to some degree of random error in the analysis and thus demands caution when interpreting of the results. However, if several repeated measurements are available over a clinically relevant period of time and the within-patient variation is acceptable in relation to the number of cross-sectional measurements, the error could be greatly ignored. Consistency of multiple consecutive measurements and thus the potential predictive value of the first measurement are poorly understood at the moment.

The aim of this study was to examine the individual development of HRQoL among elderly asthma and COPD patients. Patients' clinical status was assessed at baseline and HRQoL followed by prospective measurements at cross-sectional time points 0, 1, 2, and 4 years. Our main objective was to study whether it was possible to identify patients with constantly poor development of HRQoL. We also studied the predictive value of a first HRQoL measurement and finally determined the risk factors for poor development of HRQoL.

Materials and methods

Subjects

The patients with asthma, smoking-related COPD or chronic bronchitis were recruited from Turku and Helsinki University Hospitals in Finland. We invited all adult patients with ICD10 J44 and J45 codes who had visited the hospitals in the years 1995—2006 [34,35]. A total of 2068 patients (27% of all invited) contacted the research staff by phone and visited the research clinic. The comprehensive retrospective medical records covered at least 5 years prior to the enrolment. Based on clinical and diagnostic data, the main component of their obstructive disease was defined as smoking-related COPD or chronic bronchitis in 739 and as asthma in 1329 patients (**Finn**ish **C**hronic **A**irway **D**isease (FinnCAD) cohort) [35].

Clinical characteristics

From the medical records, we identified the results of the latest flow-volume spirometry including bronchodilatation test, weight, and height and smoking status of the patient. The reference value for FEV_1 (forced expiratory volume in 1 s) was used [36]. All the given diagnoses stated in the medical records were carefully evaluated, especially time of the onset and certainty of the diagnosis. Common co-existing diseases were classified at the time of recruiting based on a diagnosis often made by a specialist of the field. Deaths were tracked from the population registry.

The Ethics Committee of the Hospital District of Helsinki and Uusimaa has approved the study.

HRQoL

Patients' HRQoL was assessed at 0, 1, 2 and, 4 years using both the generic 15D and Airway-specific Questionnaire 20 (AQ20) [25,37]. The AQ20 questionnaire is a modification of the St. George's Respiratory Questionnaire (SGRQ) consisting of 20 'yes'/'no'/'does not concern me' questions. The AQ20 has discriminative properties and responsiveness comparable to more complex questionnaires such as the SGRQ and CRQ [26]. The summary score is obtained by summing up the 'yes' —answers. The summary score is

given between 0 and 20, 0 being perfect respiratory health and 20 indicating multiple symptoms of airway-specific health.

The 15D questionnaire consists of 15 dimensions (mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity) of health status, each having 5 levels on an ordinal scale. The scaled score is given on a 0—1 scale, where 0 = being dead, 1 = full HRQoL. The 15D questionnaire has been shown to be reliable, valid and sensitive for many different chronic diseases [27,37,38] including asthma and COPD and comparable to EQ-5D, SF-6D, and HUI3 [20,23,27,37,39]. A change of $\geq$0.03 in the 15D score is considered to be the Minimum Clinically Important Difference (MCID) in the sense that people can on average feel the difference [40].

The change in the total scores for each participant over time is expressed as HRQoL trends separately for both instruments. The trend was computed only for those who had $\geq$3 measurements within the five-year follow-up period. Due to the scoring systems the trends show in opposite directions.

Analysis

In order to incorporate the variation between patients' self-reported measurements of HRQoL, we used a mixed-effects model. The development of HRQoL in the five-year period for each patient was modelled as linear in time since the entry into the study.

Intraclass correlations were used to determine the amount of resemblance between sequential measurements for each patient. Zero correlation indicates that the past measurement of a particular patient yields no information about the future scores and one indicates that the measurements of a patient are perfectly correlated.

To identify the uncertainty related to individual trends we used a Markov Chain Monte Carlo (MCMC)-sampler. The algorithm was used to produce 10,000 possible trends of development for each patient (the posterior distribution of trends) based on the actual data. When more than 8500 out of 10,000 samples were negative, a patient was considered to be a constant decliner (85% probability level). Highest Posterior Density intervals were determined to describe the variation of development at population level parameters.

The value of the baseline HRQoL score in predicting future development of patients HRQoL was evaluated using Receiver Operating Characteristic (ROC). The constantly declining development was explained with the baseline HRQoL measurement in a binary logistic regression model, in which the entire study population of each cohort was included. Area Under Curve (AUC) was then derived to describe the diagnostic value of a first measurement of HRQoL.

To further analyse the risk factors of poor development of HRQoL, we performed Bayesian Models Averaging (BMA). Scaled posterior effect probability varies from 0 to 100, indicating the relevance of a variable in describing the poor development of QoL. In contrast to *p*-value, low values of effect probabilities are also informative suggesting no association between endpoint and a variable. We only show the risk factors with a posterior effect probability of >20%, using each instrument in both asthma and COPD. Factors with posterior effect probabilities lower than 20% were considered not to be associated with poor development of HRQoL [41].

All analysis was done using R Statistical Software version 2.15.

Results

Patient populations

The HRQoL of COPD (N = 739) and asthma (N = 1329) patients was evaluated by a generic (15D) and airway-specific (AQ20) HRQoL instrument at cross-sectional time points 0, 1, 2, and 4 years. The patients were clinically profiled at baseline based on retrospective clinical data. All participants having $\geq$3 measurements of HRQoL and relevant clinical data available were included in the analysis (Table 1). Compared to the COPD patients, the asthma patients were younger (mean 58 vs. 68 years, $p < 0.001$), showed female majority (mean 74 vs. 33%, $p < 0.001$), and had suffered the disease longer (mean 14 vs. 8 years, $p < 0.001$). COPD patients had more pack years (mean 42 vs. 7 years, $p < 0.001$), poorer lung functions (mean FEV_1 59 vs. 89% of expected, $p < 0.001$), and more frequently co-existing chronic diseases such as cardiovascular disease (28 vs. 7%, $p < 0.001$), diabetes (16 vs. 6%, $p < 0.001$), and alcohol abuse (15 vs. 3%, $p < 0.001$) than the asthma patients. At any given time point, the mean HRQoL level was constantly lower in the COPD cohort compared to that of the asthma cohort by both instruments (Table 1).

Five-year-trends in COPD showed significantly poorer development than those in asthma

The variation of HRQoL measurements within a patient was evaluated using the intraclass correlations for both patient groups and for both instruments. The correlations were acceptable and equal for each subgroup: for asthma in AQ20 0.80 and in 15D 0.82; and for COPD 0.81 and 0.81, respectively.

In COPD, the majority (60.1—80.1%) of the individuals showed declining HRQoL. The overall mean decline in the 15D score was −0.005/year (95% CI −0.007 to −0.002), and in the AQ20 score 0.092/year (95% CI −0.02 to 0.19) (Fig. 1). In asthma, the majority (45.9—70.5% % of the patients) of the trends suggested no decline. For the 15D the overall mean change in the score was −0.002/year (95% CI −0.003 to 10^{-5}) and in AQ20 the mean trend was slightly improving −0.10/year (95% CI −0.17 to −0.05).

The proportion of patients with declining trends was higher both in asthma (539/54.1%) and COPD (443/80.1%) when 15D was used. With AQ20 the proportion of decliners was 308/29.5% in asthma and 357/60.1% in COPD, respectively.

Table 1 Clinical characteristic of the asthma and COPD patients studied with two separate HRQoL instruments.

	Asthma		COPD	
	15D (N = 996) N (%)	AQ 20 (N = 1045) N (%)	15D (N = 548) N (%)	AQ 20 (N = 594) N (%)
Age, yrs[a]	58.3, (57.5, 59.1)	59.9, (35.6, 84.2)	68.1, (55.0, 81.1)	68.3, (55.1, 81.5)
Male[b]	256, (25.7)	265, (25.3)	347, (62.7)	371, (62.5)
FEV_1% predicted[a]	88.9, (87.8, 89.9)	88.6, (87.5, 89.6)	58.6, (56.9, 60.2)	58.6, (57.0, 60.1)
Pack years[a]	7.2, (6.5, 8.0)	7.3, (6.5, 8.0)	42.0, (41.2, 42.8)	42.4, (41.0, 44.0)
Body mass index[a]	27.3, (27.0, 27.6)	27.4, (27.1, 27.8)	26.8, (26.4, 27.3)	27.0, (26.5, 27.4)
Coronary disease[b]	52, (5.2)	51, (4.8)	111, (20.3)	119, (20.0)
Cerebrovascular disease[b]	22, (2.2)	23, (2.2)	40, (7.3)	42, (7.1)
Peripheral arterial occlusive disease[b]	NA	NA	32, (5.8)	37, (6.2)
Hypertension[b]	313, (31.4)	338, (32.3)	227, (41.4)	249, (41.9)
Alcohol abuse[b]	32, (3.2)	34, (3.3)	81, (14.8)	89, (15.0)
Hypothyreosis[b]	79, (7.9)	103, (10.3)	42, (7.7)	45, (7.6)
Cancer[b]	83, (8.3)	98, (9.8)	49, (8.9)	51, (8.6)
Gastro-esophageal reflux[b]	257, (25.8)	274, (27.5)	139, (25.4)	148, (25.0)
Arrhythmia[b]	114, (11.4)	124, (11.9)	99, (18.1)	116, (19.5)
Chronic sinusitis[b]	168, (16.9)	177, (17.8)	NA	NA
Diabetes[b]	50, (5.2)	62, (5.9)	87, (15.9)	93, (15.7)
Psychiatric conditions[b]				
Yes, mild depression/	45, (4.5)	49, (4.7)	15, (2.7)	17, (2.9)
anxiety meds needed occasionally	65, (6.5)	70, (6.7)	34, (6.2)	36, (6.1)
Yes, moderate, meds needed regularly	145, (14.6)	155, (14.8)	87, (15.9)	90, (15.2)
Yes, psychotic conditions, meds and/or hospital admissions needed regularly	38, (3.8)	45, (4.3)	40, (7.3)	39, (6.6)
Duration of disease, years[a]	14.4, (13.7, 15.2)	14.6, (13.8, 15.3)	8.2, (7.8, 8.5)	8.3, (7.9, 8.6)
Mean HRQoL score at:				
Baseline[a]	0.865, (0.859, 0.871)	7.20, (6.91, 7.48)	0.799, (0.793, 0.811)	8.05, (7.66, 8.45)
1 Follow-up[a]	0.868, (0.861, 0.874)	6.84, (6.54, 7.13)	0.792, (0.785, 0.804)	8.15, (7.74, 8.57)
2 Follow-up[a]	0.864, (0.858, 0.871)	6.70, (6.41, 6.98)	0.788, (0.782, 0.801)	8.20, (7.79, 8.62)
4 Follow-up[a]	0.862, (0.855, 0.870)	6.67, (6.36, 6.97)	0.783, (0.773, 0.794)	8.13, (7.68, 8.58)

NA = not available.
[a] Mean (95% CI).
[b] Number (%).

Identification of the patients with constantly declining HRQoL

The accuracy of identifying patients with constantly declining trends was dependent on the within-patient variation between the sequential HRQoL measurements and the number of measurements available for each patient. Markov Chain Monte Carlo sampling showed that only a fraction of decliners presented in Fig. 1 showed constantly poor development of HRQoL. The majority of the constant decliners were identified based on four measurements (95-71%). The proportion of constant decliners was higher for 15D both in asthma (6.3%) and COPD (6.3%) than with AQ20 (3.5 and 4.5%, respectively) (Fig. 2). The vast majority of the patients were thus considered non-decliners (the patients who showed either non-significant decline or improving trends).

To evaluate the clinical significance of the difference in trajectories found between the constant decliners and rest of the patients, we used the MCID value determined for 15D. Among constant decliners, MCID occurred in 2.2 years (95% CI 1.9—2.5 years) in asthma, whereas among the non-decliners, it took 75 years (42.9—300 years, $p < 0.0001$). In COPD the difference was not that extreme, but still clinically meaningful and significant 1.7 (1.5—2.0 years) vs. 6.8 years (6.1—7.7 years, $p = 0.0007$). The decline rates for AQ20 were significantly accelerated in constant decliners both in asthma ($p < 0.0001$) and in COPD ($p < 0.0001$).

A large majority of constant decliners were identified based on four measurements of HRQoL (15D Asthma 83%, COPD 77% and AQ20 Asthma 95%, COPD 96%).

Baseline HRQoL score had predictive value

Since the poor individual baseline HRQoL showed correlation with the declining individual HRQoL trend (Fig. 2), we studied the value of the baseline HRQoL score in predicting the future change of HRQoL using the area under ROC curve (AUC) statistic. We estimated the proportion of patients who would be correctly classified as constant decliners based on the baseline HRQoL measurement only (Fig. 3), when the entire study population of each cohort was included in the analysis. Models showed good accuracy: AUC in asthma was 0.84 when 15D and 0.80 when AQ20 was used. In COPD, the AUCs were 0.83 and 0.78,

respectively. The optimal cut-off point for detecting the constant decliners in asthma were 0.84 (Odds Ratio for constant decline = 5.6, 95% CI 3.31—9.59) for 15D and >9.5 (OR = 3.7, 95% CI 1.5—9.2) for AQ20. For COPD the cut-off points were <0.77 (OR = 11.7, 95% CI 4.8—28.6) and >9.5 (OR = 4.8, 95% CI 1.2—20.1), respectively.

Distinct profiles of risk factors accelerate the poor development of HRQoL in asthma and COPD.

All clinical variables (Table 1) characterizing the patient at baseline were included in the BMA analysis. The risk factors accelerating the poor development exceeding statistical significance for each subgroup and instrument are shown in Table 2. The risk factors of poor development were mostly parallel regardless of the instrument (15D or AQ20), but the profile was remarkably different in asthma and COPD. In asthma, obesity-related diseases such as hypertension, diabetes, and GERD were the most important risk factors of poor development of HRQoL. In COPD, age and the level of bronchial obstruction were the main determinants. The effect of the most severe psychiatric conditions was seen in both asthma and COPD.

Discussion

The present longitudinal study among elderly COPD and asthma patients combined both prospective and retrospective study elements. HRQoL was followed in a prospective manner while the patients' clinical profile was based on retrospective medical records at baseline. The results showed that both the airway-specific AQ20 and generic 15D show trends in HRQoL, and identified constant decliners both among COPD and elderly asthma patients over a period of 5 years.

As expected, the mean development of HRQoL was significantly weaker in COPD than in asthma, and this difference was found both by the generic and the respiratory-specific instrument. In COPD, the declining trend was observed in 60—80% of the patients, while in asthma, HRQoL was sustained or even improved, and the declining trend was observed only in 30—54% of the patients. At the posterior probability level of >85%, 6.3% of the patients in both disease groups were identified as constant decliners by the generic HRQoL instrument, and 3.5—4.5% using the airway-specific instrument. In the identification of the

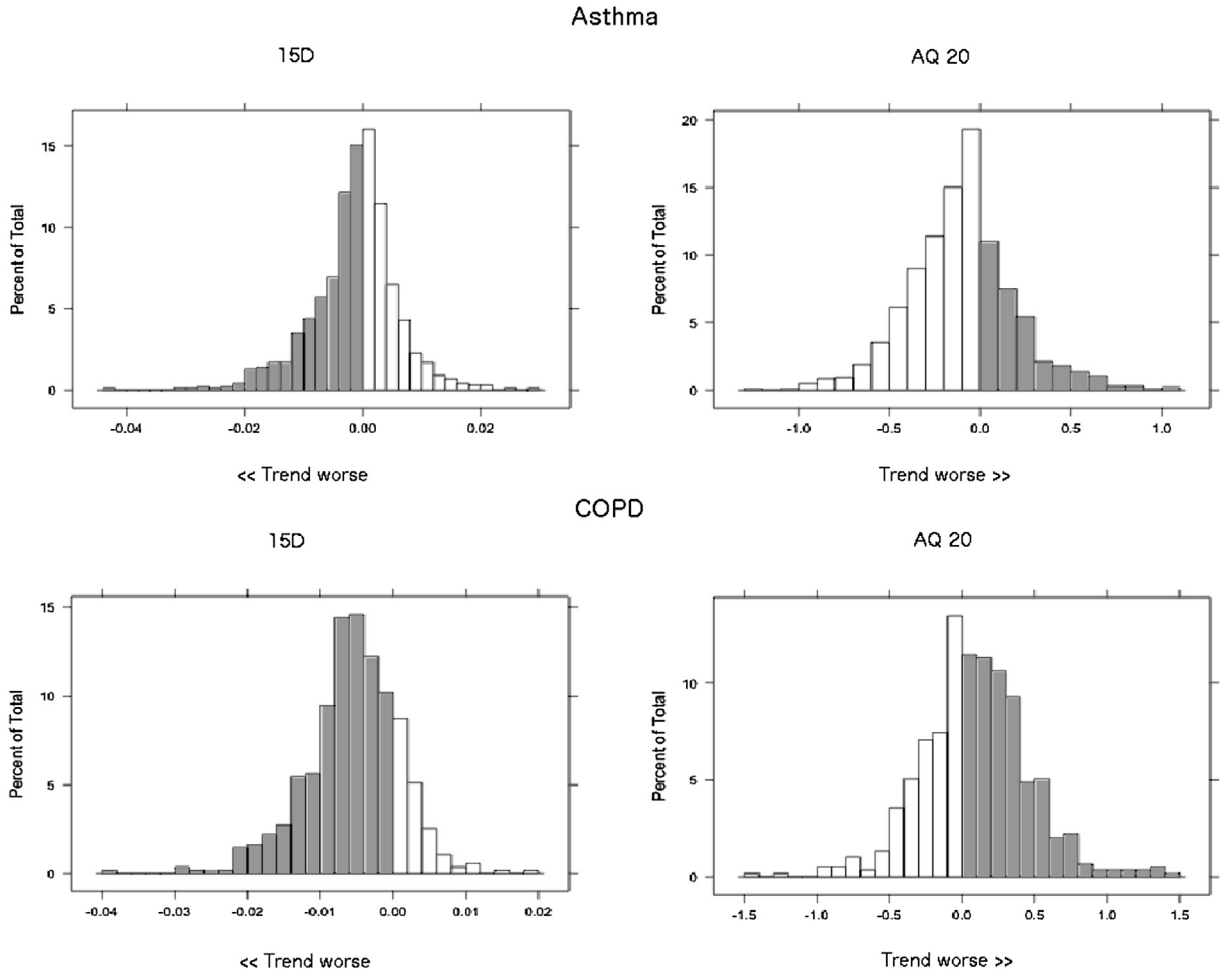

Figure 1 Posterior distribution of regression coefficients (=HRQoL trends) for the 15D and AQ20 trends among the asthma and COPD patients. For both questionnaires, 0 trend means no change based on the 5 year follow-up, the declining trends are shown in grey and improving trends in white, note the opposite scales.

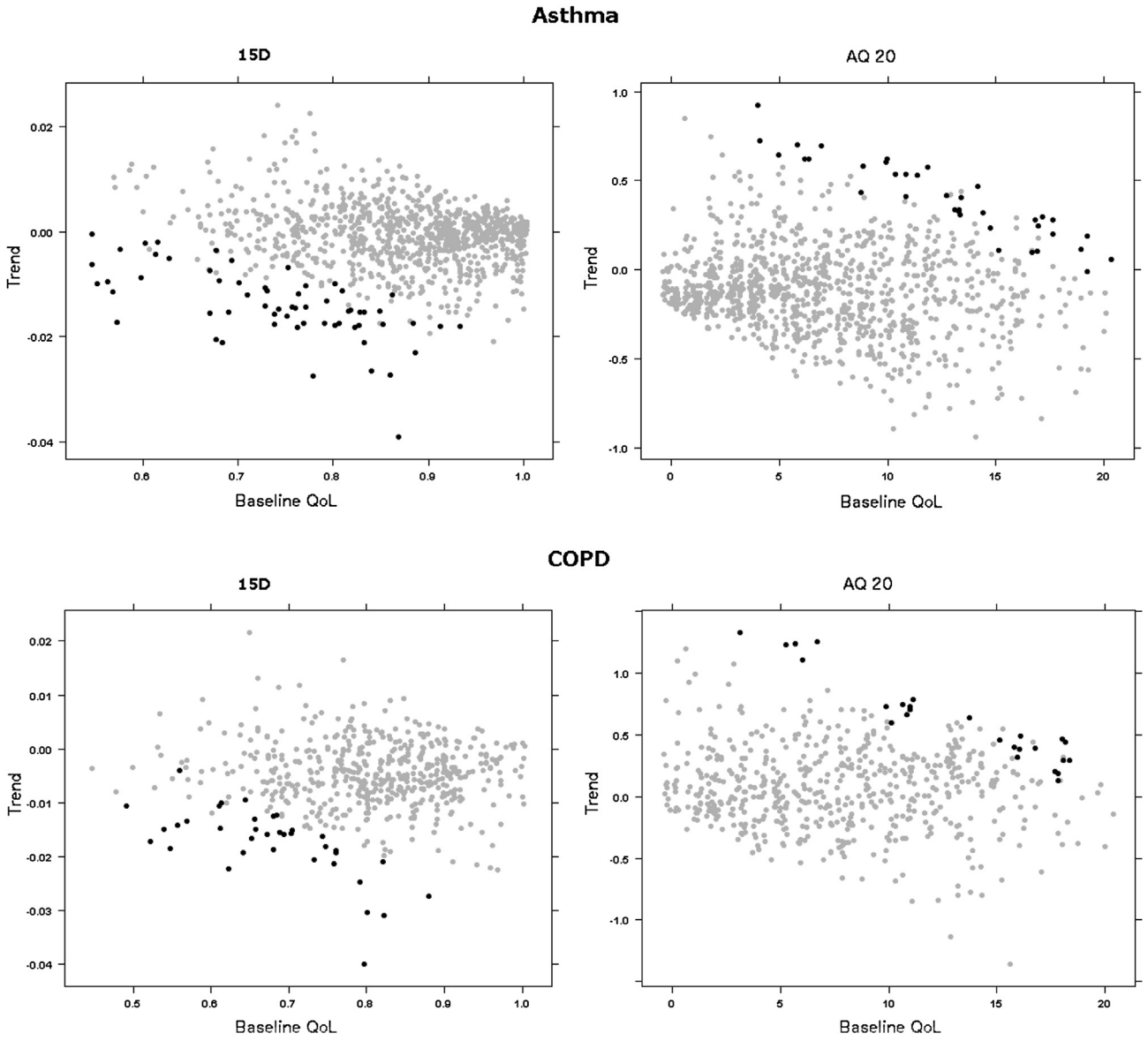

Figure 2 15D and AQ20 trends in relation to the baseline HRQoL level among the asthma and COPD patients, note the opposite scales. Black dots represent the individuals who were defined as patients with constantly declining trends.

constant decliners, among both asthma and COPD patients, the baseline HRQoL score was shown to have a strong predictive value. In asthma, obesity-related diseases such as hypertension, diabetes, and GERD explained the poor development, while in COPD, the level of bronchial obstruction was the main determinant.

Traditionally, in the study of HRQoL, the mean score of a study population is computed at one cross-sectional point of time, or the mean scores before and after an intervention are compared. These approaches ignore an essential proportion of uncertainty, since the differences in each patient's individual development are discarded. In the present study design, multiple consecutive measurements of HRQoL allowed us to evaluate individual development over time and to further analyse the clinical variables explaining the differences between the patients. Considering the nature of asthma and COPD, a five-year follow-up time is long enough to bring out significant variation between patients. In this study, we concentrated especially on the patients who showed declining trend and assessed them individually in contrast to methods traditionally used in clinical studies.

The limitations of the study were related to the retrospective study design and the number of HRQoL measurements performed per patient. Some clinical variables such as 6 Minute Walk Test and certain lung function measurements determining the nature of the disease were not available for majority of the patients and thus, those were excluded from the study. Individual differences in medication were not incorporated into the mixed-effects model either, which might have some effects on outcomes. In Finland asthma and COPD are treated according to national guidelines that follow the international recommendations [42,43]. In asthma, inhaled corticosteroids form a strong basis for the treatment, while in COPD, the medication is still mostly directed to symptom relief.

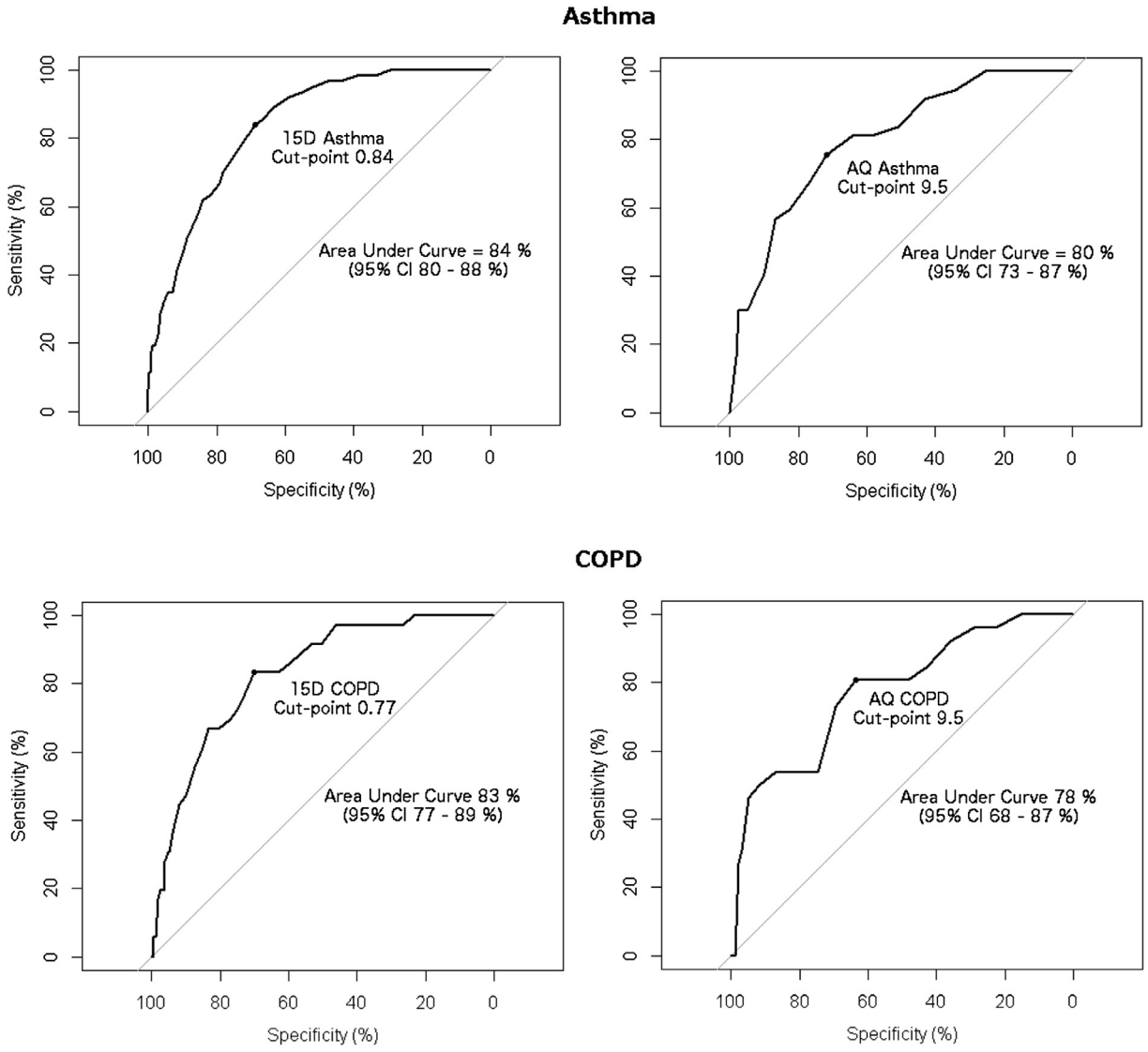

Figure 3 ROC curves and AUC statistics of the baseline HRQoL measurements in prediction of the constant decliners within the next five years.

The identification of the constant decliners is dependent on the number of patients studied in each sub-cohort, the number of the HRQoL measurements available for each particular patient, and the within-patient variation between the measurements. Statistical power of the analysis improved clearly when the number of measurements increased from three to four: for 15D 77—83% of the constant decliners were found among patients with four measurements. For AQ20 the corresponding proportions were even higher, 95%—96%. Thus the probability to identify constant decliners would improve substantially with one more measurement for each patient. The results are also dependent on the probability level at which the results are examined. The higher probability level, the more stringent threshold for the dissection of each patient into a risk or a non-risk patient (in this case a constant decliner or non-decliner). In this study, we used the probability level of 85%, which represented a rather conservative threshold, and thus the number of reported decliners is also rather cautious. Due to the progressive nature of COPD, one would have expected to find more constant decliners in COPD than in asthma. The difference between the disease groups was most likely equalized due to discontinuation of the study in the COPD group due to deaths ($N = 60$) and very severe disease ($N = 26$) before the 3-4 cross-sectional HRQoL measurements were gathered.

To demonstrate the difference among the constant decliners compared to that in the rest of the patients, we used MCID available for 15D. A change in HRQoL equal to the MCID accumulated among constant decliners in approximately two years in both COPD and in asthma. Among COPD non-decliners it took 7 years, and in asthma 75 years.

When the value of a first HRQoL measurement in predicting whether the patient will be a constant decliner during the next five years was estimated, the test showed robustness in both disease groups (AUC for 15D 0.78—0.84) as future decliners were successfully identified. The patient's baseline HRQoL level and HRQoL trend for the next

Table 2 Clinical risk factors that accelerated the individual decline of HRQoL determined among the asthma and COPD patients by two separate HRQoL instruments.

Clinical variable	Constant decliners in asthma				Constant decliners in COPD			
	15D ($N = 63$)		AQ20 ($N = 37$)		15D ($N = 35$)		AQ20 ($N = 26$)	
	Posterior effect probability[a]	Effect	Posterior effect probability	Effect	Posterior effect probability	Effect	Posterior effect probability	Effect
Age (+1 year)					64.9	−0.0004		
BMI (+1 unit)	100.0	−0.0008						
Hypertension	77.0	−0.0055	22.9	0.050				
Diabetes			60.6	0.115				
Gastro oesophageal reflux disease	51.4	−0.0038						
Severe psychiatric conditions			22.5	0.105	31.2	−0.0042		
FEV_1 % of predicted								
40–64	24.1	−0.0022						
<40	31.5	−0.0070			73.9	−0.007	65.5	0.365

[a] Posterior effect probabilities (PEP) and posterior means of the effects (5-year effect) for risk factors with PEP exceeding 20%.

five years were significantly correlated in constant decliners. Baseline 15D < 0.8 and AQ20 score >9.5 predicted both in asthma and COPD constantly declining trend during the forthcoming 5 years.

Several earlier reports have shown that cross-sectional HRQoL is only weakly or not at all correlated with FEV_1 among COPD patients [18,21,26]. These results are in line with the results found in the present cohort. FEV_1 affected HRQoL only in the late stages of the disease (Kilpeläinen et al. unpublished data). Therefore, it was to some extent surprising that FEV_1, in addition to age, was the strongest risk factor for the HRQoL trend in COPD.

The method presented here is to our knowledge a novel approach in HRQoL analyses and so far rarely used in clinical medicine in general. The results suggest that the HRQoL trend over time may serve as a more robust outcome than the HRQoL level at a certain cross-sectional time point. In addition the method allows labelling a patient as a high or low risk patient at certain probability level. This quality may become beneficial when more personalised health care is developed. In asthma, obesity-related comorbidities were the most important risk factors of the poor development of HRQoL. The comparison between generic and airway-specific instruments suggested that more decliners could be found using a generic instrument, most likely due to its ability to detect changes also in co-existing diseases.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.rmed.2013.12.001.

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