Respiratory Medicine (2011) 105, 57–66

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Health-related quality of life in patients by COPD severity within primary care in Europe

P.W. Jones [a,*], G. Brusselle [b], R.W. Dal Negro [c], M. Ferrer [d], P. Kardos [e], M.L. Levy [f], T. Perez [g], J.J. Soler-Cataluña [h], T. van der Molen [i], L. Adamek [j], N. Banik [k]

[a] *Division of Clinical Science, St George's University of London, London, UK*
[b] *Respiratory Medicine, Ghent University Hospital, Belgium*
[c] *Lung Department, Orlandi General Hospital, Bussolengo, Italy*
[d] *Health Services Research Unit, IMIM – Hospital del Mar Research Institute, Barcelona, Spain*
[e] *Respiratory Medicine, Maingau Hospital, Frankfurt am Main, Germany*
[f] *Division of Community Health Sciences, University of Edinburgh, UK*
[g] *Pulmonology Department, Lille University Hospital, France*
[h] *Pneumology Unit, Requena General Hospital, Valencia, Spain*
[i] *University Medical Centre Groningen, The Netherlands*
[j] *Respiratory Centre of excellence, GlaxoSmithKline, Marly le Roi, France*
[k] *Biostatistics and Epidemiology, GlaxoSmithKline, Munich, Germany*

Received 28 April 2010; accepted 4 September 2010
Available online 6 October 2010

KEYWORDS
Chronic obstructive pulmonary disease;
Primary care;
Health-related quality of life;
SGRQ-C;
SF-12;
FACIT-Fatigue

Summary
Pan-European data on health-related quality of life (HRQL) in chronic obstructive pulmonary disease (COPD) are lacking.

This cross-sectional epidemiological study evaluated health status in 1817 COPD patients from an 'all-comers' primary care population in seven European countries (87% stable disease; 13% with current exacerbation) using: St George's Respiratory Questionnaire-COPD specific (SGRQ-C), the short form health survey (SF-12) and the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale.

Mean total score for SGRQ was 44.7 ± 19.4 showing marked impairment of HRQL. Scores differed little between countries (range 39.2–50.1). Impairment was associated with the severity of airway obstruction, but within each GOLD stage the variation (SD) was wide [Stage I: 38.5 ± 19.3 (n = 223); Stage II: 40.4 ± 18.1 (n = 868); Stage III: 50.2 ± 18.6 (n = 551); Stage IV: 58.6 ± 17.7 (n = 144)]. Patients suffering an exacerbation had a worse SGRQ score (54.9 ± 19.3) than those with stable disease (43.3 ± 19.0). The presence of ≥3 co-morbidities (CM) was also associated with a significantly worse score (49.9 ± 19.1) vs. 1–2 CM (42.1 ± 19.1)

* Corresponding author.
E-mail address: pjones@sghms.ac.uk (P.W. Jones).

0954-6111/$ - see front matter
doi:10.1016/j.rmed.2010.09.004

or no CM (42.3 ± 18.6). Findings with the SF-12 and FACIT-F results were consistent with those from the SGRQ-C.

This large observational primary care study shows that health status is significantly impaired in COPD patients of all severities, even in those with mild airway obstruction. Within each GOLD stage of severity there is considerable heterogeneity in HRQL impairment among patients.

(Study number: 111749).

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide resulting in a significant economic and social burden.[1] By 2020, COPD is estimated to become the fifth most common cause of morbidity and the third most common cause of death worldwide.[2] Spirometry remains the standard method for grading COPD severity in international treatment guidelines.[1,3,4] However, spirometry alone provides insufficient data on the effect of the disease on patients' lives.

Many studies have reported impaired health-related quality of life (HRQL) in patients with COPD[5–9] and a poor HRQL has been shown to be associated with high levels of dyspnoea,[6–8] physical impairment,[8] depression and anxiety,[5,8] a poor prognosis in terms of readmission to hospital[10] and death.[11] COPD exacerbations have also been associated with reduced health status, persisting after the exacerbations[12] as has an increased exacerbation frequency.[13] Some patients with severe airway obstruction may report few symptoms whilst others with mild obstruction report severe symptoms.[1] There is evidence of health status under-estimation by both patients and physicians.[1,14] When grading severity and the burden of the disease, it is now recognised that patient-reported outcomes provide important information that is complementary to lung function data.[15]

HRQL assessments may be performed using either generic or disease-specific questionnaires encompassing physical, psychological and social factors.[16] To our knowledge, the impact of COPD on both aspects of HRQL in a broadly sampled, multi-national population has not been previously studied. This cross-sectional, observational study was undertaken to provide data on the HRQL of a sample of COPD patients from primary care settings across seven European countries, using disease-specific and generic HRQL questionnaires.

Methods

Subjects

Eligible subjects were aged 40—80 years with an established COPD history (minimum six months from diagnosis) and a known post-bronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio of <70%. All subjects were either current or ex-smokers with a smoking history of at least 10 pack years. Exclusion criteria were asthma or any current respiratory disorder other than COPD, and serious, unstable cardiovascular disease. Recruitment took place between December 2008 and April 2009.

The study was approved by Institutional Review Boards or Ethics Committees according to local laws and regulations in the respective countries. Written informed consent was obtained from each subject.

Study design

The study was a cross-sectional, epidemiological, non-randomised survey, conducted in a primary care setting in Belgium, France, Germany, Italy, the Netherlands, Spain and the United Kingdom (UK). Primary care practitioners (PCPs) were identified using local GlaxoSmithKline contacts or by mass mailing to PCPs identified from publicly available sources. Patients with COPD, presenting at PCP practices for any reason and who fulfilled the entry criteria, were invited to participate. This paper presents the results for a sub-sample of patients who were, additionally, aged ≥30 years at diagnosis of COPD, had completed at least one HRQL questionnaire and fulfilled the Global Initiative for Chronic Obstructive Lung Disease criterion of FEV_1/FVC ratio <70%. In the UK, due to delays in gaining regulatory approval and therefore a shortened recruitment time, 39 patients (2.1% of the reported population) were recruited from a wider list of patients who had been independently pre-identified, in an anonymised manner, from PCP patient records. They were telephoned by their PCP to confirm eligibility and willingness to participate.

Demographic information, medical history, previous and current COPD medications were recorded. Severity by GOLD stage was calculated retrospectively from the lung function measurements documented. Information on blood gas values was not collected and thus patients are classified into GOLD stages III and IV without respect to this criterion. Physician-reported disease status (stable disease or presenting with an exacerbation), symptoms (cough, sputum, dyspnoea), and spirometry (post-bronchodilator FEV_1 and FVC and FEV_1/FVC) were also recorded. Spirometry had to be performed within six months before study entry or during the single study visit. The history of exacerbations in the previous 6 months was also recorded, using medical records and patient-recall as verification. An exacerbation was defined as a worsening of symptoms that required oral corticosteroids and/or antibiotics and/or hospitalizations. Based on the response of the patient, the investigator scored the patient's breathlessness using the Medical Research Council (MRC) Dyspnoea Scale.[17]

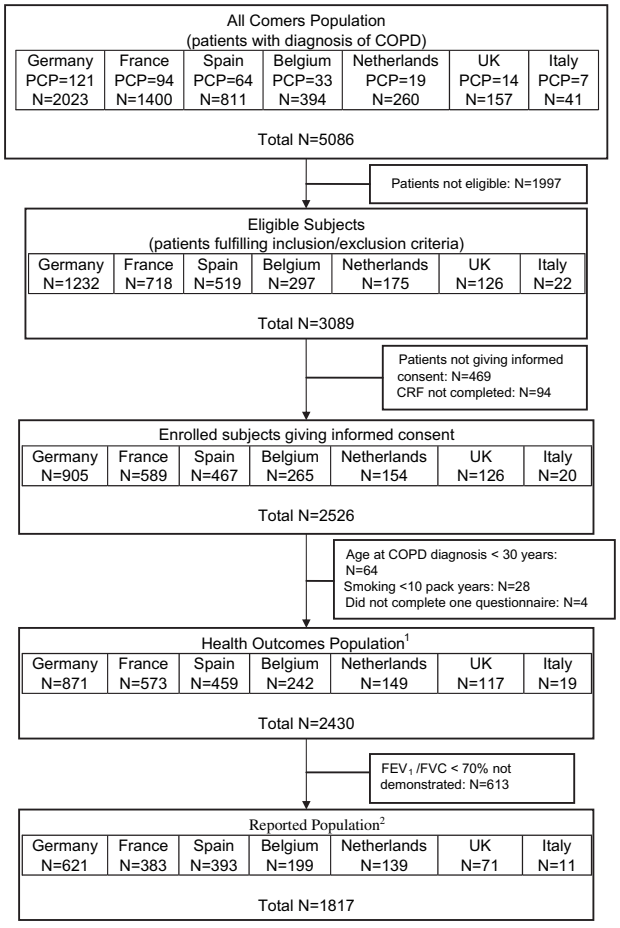

Figure 1 Patient flow through survey. PCP represents number of primary care physicians. [1]Health Outcomes Population consisted of patients with: (1) Age at diagnosis of COPD $\geq$30 (2) Number of pack years $>$10, and (3) At least one HRQL questionnaire completed. [2]Reported Population consisted of the Health Outcomes Population and demonstrating a FEV_1/FVC ratio $<$70%.

Questionnaires

Patients were asked to complete the following HRQL questionnaires at the single PCP visit, using validated translations. The questionnaires were completed after all other assessments had been conducted.

St George's respiratory questionnaire — COPD specific (SGRQ-C)

The SGRQ is a disease-specific HRQL questionnaire[18] and in this survey, the COPD specific version (SGRQ-C) was used.[19] It has a total and three component scores for: symptoms, activity and impacts; each score ranges from 0 (no impairment) to 100 (worst possible). SGRQ-C scores are transformed to be fully comparable with SGRQ scores, and are reported here as SGRQ scores exclusively.[19] A difference of four units in the SGRQ score is considered the minimum clinically important difference (MCID).[20] The SGRQ-C is designed to assess current health and does not specify a recall period.[20]

Short form health survey (SF-12)

Generic HRQL was assessed using the SF-12 (version 2).[21,22] This has two component summary scores (physical and mental or PCS-12 and MCS-12), ranging from 0 (worst) to 100 (best). Scores are normalised so that scores above or below 50 would be better or worse, respectively, than the general population. Excluding the first two general questions, the recall period for the SF-12 is seven days. The MCID is reported to be a change of 3 units for PCS and 3.5 units for MCS (Quality Metric Inc, private communication).

The functional assessment of chronic illness therapy (FACIT) fatigue scale

Fatigue was assessed using the generic, FACIT-Fatigue scale (FACIT-F) (version 4), designed to measure fatigue intensity and impact on daily life in a general population.[23] It assesses tiredness, weakness, and difficulty conducting usual activities due to fatigue. Recall period is one week and scores range from 0 to 52, corresponding to the most and least fatigue, respectively. A change of 3—4 units in the FACIT-F score has been deemed to be the MCID.[24]

Statistical analysis

The sample size was calculated to ensure a sufficient sample of patients in all participating countries and across all levels of COPD severity with the main intention of providing sufficient accuracy for the comparison of HRQL scores between stages of COPD severity. Using SGRQ data from other studies, the smallest acceptable subgroup sample size was estimated as 120 patients, pertaining to the subgroup with very severe COPD. According to the known distribution of disease severity grades this subgroup covers about 5% of all COPD patients. This resulted in a total estimated sample size of approximately 2300 subjects. Based on these sample sizes and a within-group standard deviation of 18 points of total SGRQ scores, the half-width of the 95% confidence interval for mean total SGRQ values were estimated to be less than 3.5 points thus allowing for reasonable and meaningful descriptive subgroup comparisons based on 95% confidence intervals of mean total SGRQ scores. Note, that the minimum important clinical difference (MCID) of total SGRQ scores is known to be 4 points.

Descriptive statistics, analysed using Statistical Analysis Systems version 9.1.3 software (SAS Inc, Cary, USA), were used to report demographic and baseline characteristics and distribution of HRQL questionnaire scores and subgroups split by country, sex, age, COPD status (stable disease vs. exacerbation), GOLD stage, number of co-morbidities and cardiovascular (CV) co-morbidities. Patients with CV co-morbidities were defined as those with at least one of: myocardial infarction, stroke, heart failure, treated hypertension, treated angina pectoris or treated arrhythmia.

Table 1 Demographic and clinical characteristics of COPD patients.

Characteristic	GOLD Staging[a]				Reported Population (N = 1817)
	I (N = 223)	II (N = 868)	III (N = 551)	IV (N = 144)	
Male sex, n (%)	144 (64.6)	610 (70.3)	413 (75.0)	122 (84.7)	1305 (71.8)
Age (years), mean (SD)	65.3 (9.7)	65.0 (9.8)	65.0 (9.5)	63.3 (9.5)	64.9 (9.6)
Reason for consultation[b], n (%):					
Scheduled appointment	102 (45.7)	500 (57.6)	319 (57.9)	78 (54.2)	1006 (55.4)
Prescription refill	77 (34.5)	228 (26.3)	113 (20.5)	30 (20.8)	451 (24.8)
Respiratory reasons	23 (10.3)	97 (11.2)	88 (16.0)	26 (18.1)	236 (13.0)
Non-respiratory reasons	41 (18.4)	139 (16.0)	60 (10.9)	16 (11.1)	262 (14.4)
Duration COPD (years), mean (SD)	8.4 (6.6)	8.8 (6.7)	10.4 (7.5)	10.3 (6.4)	9.4 (7.0)
Pack years, mean (SD)	36.9 (21.2)	39.2 (21.6)	42.4 (27.7)	43.8 (29.6)	40.4 (24.4)
Current smoker, n (%)	100 (44.8)	379 (43.7)	233 (42.3)	52 (36.1)	781 (43.0)
Number of co-morbididties,					
Mean (SD)	2.2 (1.7)	2.1 (1.7)	1.9 (1.5)	2.1 (1.6)	2.0 (1.6)
Number of cardiovascular co-morbidities, mean (SD)	0.8 (0.9)	0.9 (1.0)	1.0 (1.1)	0.9 (1.1)	0.9 (1.0)
Exacerbations on study day, n (%):					
Stable disease	204 (91.5)	777 (89.5)	461 (83.7)	110 (76.4)	1580 (87.0)
Exacerbation	19 (8.5)	91 (10.5)	90 (16.3)	34 (23.6)	237 (13.0)
Exacerbations in last 6 months, n (%), requiring:					
Antibiotics	117 (52.5)	458 (52.8)	318 (57.7)	93 (64.6)	1005 (55.3)
Oral corticosteroids	66 (29.6)	276 (31.8)	205 (37.2)	70 (48.6)	632 (34.8)
Hospitalisation	15 (6.7)	56 (6.5)	72 (13.1)	31 (21.5)	175 (9.6)
COPD symptoms on study day, n (%)					
Cough	165 (74.0)	656 (75.6)	440 (79.9)	125 (86.8)	1405 (77.3)
Sputum	141 (63.2)	556 (64.1)	415 (75.3)	106 (73.6)	1234 (67.9)
Dyspnoea	131 (58.7)	584 (67.3)	453 (82.2)	132 (91.7)	1321 (72.7)
Lung function, mean (SD):					
FEV_1 (L)	2.4 (0.5)	1.8 (0.4)	1.1 (0.3)	0.7 (0.2)	1.6 (0.6)
FEV_1% of predicted	92.2 (11.8)	63.3 (8.3)	40.6 (5.5)	24.1 (4.6)	56.7 (20.1)
MRC dyspnoea scale[c], n (%):					
1	65 (29.1)	207 (23.8)	55 (10.0)	15 (10.4)	344 (18.9)
2	88 (39.5)	392 (45.2)	180 (32.7)	23 (16.0)	694 (38.2)
3	42 (18.8)	181 (20.9)	166 (30.1)	29 (20.1)	427 (23.5)
4	25 (11.2)	70 (8.1)	125 (22.7)	43 (29.9)	271 (14.9)
5	3 (1.3)	17 (2.0)	24 (4.4)	34 (23.6)	79 (4.3)

MRC = Medical Research Council; FEV_1 = forced expiratory volume in 1 s. FVC = forced vital capacity.

[a] FEV_1 (% predicted) is missing for 31 patients due to missing information on height, therefore they are not classifiable into GOLD stages.

[b] Patients may have reported more than one reason.

[c] MRC scale: 1: 'only breathless with strenuous exercise'; 2: 'breathless when hurrying on level or up a slight hill'; 3: 'walk slower than people of same age on the level due to breathlessness or stop for breath when walking on level at own pace'; 4: 'stop for breath after walking 100 yards or a few minutes on the level'; 5: 'Too breathless to leave house or breathless when dressing'.

For testing the relationship between HRQL scores and GOLD stages, taking country into consideration, analysis of variance models were applied for all available HRQL scores with the factors GOLD stage, country and their interaction term. The test for statistical significance of the latter was used as a means of assessing the general association between GOLD stage and HRQL scores. As a global assessment, this test takes account of all patient characteristics simultaneously (including age, sex, duration of COPD and co-morbidities). If differences between countries in patients' characteristics have a relevant impact on the relationship between a HRQL score and GOLD stages, it would be shown as a significant interaction term in the respective model. All statistical tests were interpreted as descriptive ones and were performed at the nominal level of 0.05. Analysis of variance F-tests or two-sample *t*-tests for continuous data, or Fisher's exact tests for categorical data, were applied respectively.

Results

Study population

A total of 352 PCPs contributed patients to the survey and identified 5086 patients with COPD from their practices (Fig. 1). The Health Outcomes Population comprised 2430 patients of which 1817 fulfilled the GOLD criterion by demonstrating $FEV_1/FVC < 70\%$. Results for this population are reported here. FEV_1 as percent predicted was not available for 31 subjects due to missing information on patients' height.

Table 2 Health-related quality of life (HRQL) Scores by GOLD stage.

HRQL Questionnaire	Severity by GOLD Stage[a]				Reported Population (N = 1817)
	Stage I (N = 223)	Stage II (N = 868)	Stage III (N = 551)	Stage IV (N = 144)	
SGRQ[b]					
Total score:					
Mean (SD)	38.5 (19.3)	40.4 (18.1)	50.2 (18.6)	58.6 (17.7)	44.7 (19.4)
P25	22.3	26.5	37.3	45.7	29.6
Median	37.5	39.1	50.2	59.8	44.4
P75	52.1	53.1	63.9	73.2	58.9
Symptom score:					
Mean (SD)	56.2(24.0)	57.5 (21.6)	66.0 (20.4)	73.7 (16.8)	61.4 (21.9)
P25	37.4	42.9	53.1	61.1	45.9
Median	55.0	56.3	67.9	75.4	61.7
P75	75.4	73.9	83.0	88.1	78.7
Activity score:					
Mean (SD)	47.6 (21.8)	51.1 (20.8)	62.1 (20.6)	70.3 (18.8)	55.8 (21.9)
P25	32.9	33.3	50.8	58.6	39.7
Median	52.3	52.4	65.7	72.5	58.6
P75	59.6	65.8	79.6	86.8	72.5
Impacts score:					
Mean (SD)	27.8 (19.8)	28.7 (19.0)	38.0 (20.8)	46.6 (20.8)	33.0 (20.7)
P25	11.6	13.5	21.7	31.4	16.0
Median	23.9	24.7	37.1	46.2	30.2
P75	40.8	40.9	52.5	63.8	47.1
SF-12[c]					
PCS:					
Mean (SD)	39.8 (8.8)	39.3(8.7)	35.7 (8.7)	31.7 (8.6)	37.7 (9.1)
P25	33.3	32.7	29.5	25.9	30.8
Median	39.8	39.8	35.4	30.5	37.7
P75	46.5	45.6	42.0	37.4	44.5
MCS:					
Mean (SD)	47.4 (11.8)	47.9 (11.3)	47.0 (12.0)	43.7 (12.9)	47.2 (11.8)
P25	38.2	39.3	38.7	33.4	38.7
Median	48.0	48.7	47.8	42.3	48.0
P75	58.4	57.0	56.8	53.2	57.0
FACIT-F[d]					
Mean (SD)	36.4 (11.0)	36.3 (10.8)	32.5(12.1)	28.7 (12.1)	34.5 (11.6)
P25	29.5	29.0	23.0	20.0	26.0
Median	38.0	39.0	33.5	28.0	37.0
P75	46.0	45.0	43.0	37.0	44.0

P25 = 25th percentile; P75 = 75th percentile; SGRQ=St George's Respiratory Questionnaire; SF-12 = Short Form health survey; FACIT-F=Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale; PCS = Physical component score; MCS = Mental component score.

[a] FEV_1 (% predicted) is missing for 31 patients due to missing information on height, therefore they are not included in this table.

[b] Reported as SGRQ scores following transformation from SGRQ-C scores; SGRQ total score: a lower score represents a better QoL.

[c] SF-12 scores: a higher score represents a better QoL.

[d] FACIT-fatigue scores: higher score indicates less fatigue.

Patient characteristics

Demographic and clinical characteristics of study patients are presented by GOLD stage (Table 1). Approximately three quarters of patients were male. The mean age was 65 years and mean duration of COPD was 9 years. The mean FEV_1 was 1.6L (57% of predicted). Over 40% of all patients were current smokers with mean 40 smoking pack years. Over half of the patients in GOLD Stages II to IV had visited the PCP for a scheduled appointment on the study visit day. The proportion of patients attending for respiratory reasons was higher in those with more severe obstruction (10% of GOLD Stage I vs. 18% of GOLD Stage IV, most presenting with an exacerbation). A total of 13% of patients had an exacerbation at the study visit. In the previous six months, 10% of all patients had been hospitalised due to an exacerbation (Stage I: 6.7%, Stage II: 6.5%, Stage III: 13.1%, Stage IV: 21.5%) (Table 1). For exacerbations requiring antibiotics or oral corticosteroids there was no difference in numbers reported between GOLD Stages I and II. A high level of symptoms was reported even in patients in GOLD Stage I (cough 74.0%, sputum production 63.2% and dyspnoea

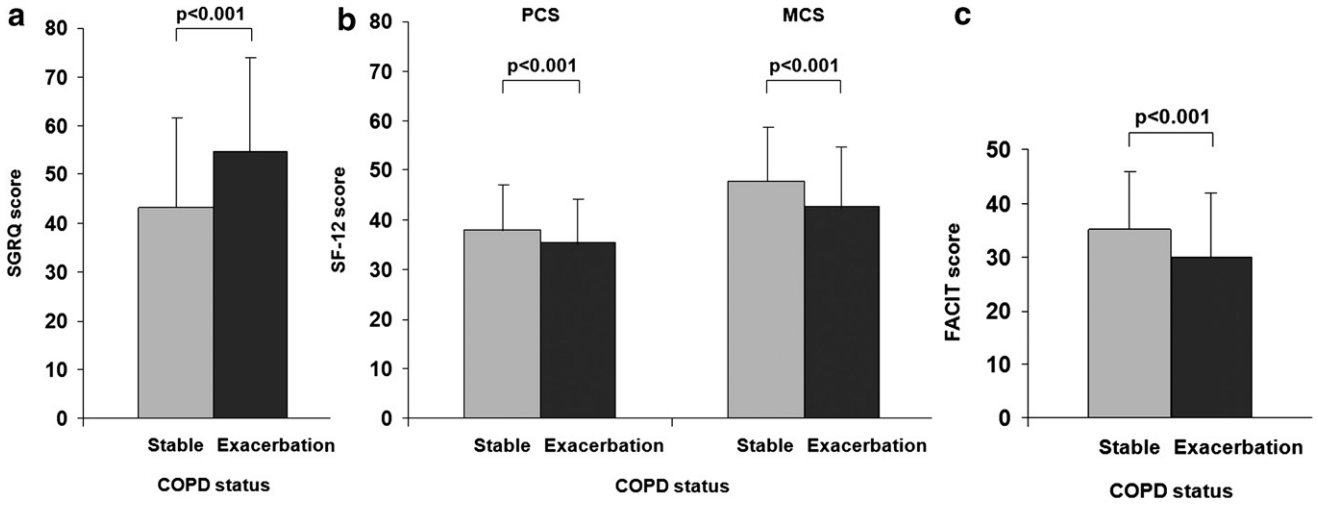

Figure 2 HRQL scores by COPD status on study day (mean + SD) (stable disease versus exacerbation) a) SGRQ total score by COPD status b) SF-12 component scores by COPD status c) FACIT-Fatigue score by COPD status.

58.7%), and increased symptoms were observed with more severe disease (Table 1).

Co-morbidities were frequent: hypertension 53%, hypercholesterolaemia 41%, osteoarthritis 26%, sleep disorder 25%, heartburn 21%, diabetes 19%, depression 17%, anxiety 15%. There was no difference in the mean number of co-morbidities reported by GOLD Stages (Table 1). In total, 89% of patients were receiving COPD treatment: inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) combination (55%), long-acting anticholinergics (41%), short-acting β_2-agonists (38%), short-acting anticholinergics (20%), LABA (17%) and ICS (12%). Smoking cessation treatment was being received by 4.4% of current smokers.

HRQL measures

All the HRQL questionnaires showed significant impairment across all levels of airway obstruction, even in patients with mild disease (Table 2). The differences between Stage I and II were less than the MCID with all questionnaires; by contrast differences between Stage II-III and Stage III-IV exceeded the MCIDs (with the single exception of SF-12 MCS). Within each severity group, there was considerable heterogeneity in impairment as evidenced by wide standard deviations.

Demographic factors had little effect on scores; although on the SF-12 MCS, males scored better than females: 48.4 (95% CI 47.7, 49.0) vs. 44.3 (95% CI 43.3, 45.4). Significant differences (smaller than the MCID) were noted for FACIT-F scores: males 35.0 (95% CI 34.4, 35.6) vs. females 33.1 (95% CI 32.0, 34.1), SF-12 PCS scores: younger ($\leq$65 years) 38.6 (95% CI 38.0, 39.2) vs. older 36.8 (95% CI 36.2, 37.4); SF-12 MCS younger: 46.0 (95% CI 45.2, 46.8) vs. older 48.4 (95% CI 47.7, 49.2).

Patients with stable disease showed statistically and clinically better HRQL scores and less fatigue than those suffering an exacerbation (Fig. 2). The presence of $\geq$3 reported co-morbidities (CM) was associated with worse HRQL compared with $<$3 co-morbidities (Fig. 3). Patients with cardiovascular co-morbidities (CV-CM) reported worse SGRQ scores (45.8 $\pm$ 19.5) than those without (43.2 $\pm$ 19.2), $p < 0.01$, but the difference was less than the MCID (Fig. 3). A similar picture was seen with the SF-12 PCS: no CV-CM 38.9 $\pm$ 9.2, presence of CV-CM 36.8 $\pm$ 8.8, $p < 0.001$.

HRQL by country

The average HRQL scores showed some inter-country variation. For example, the mean SGRQ score in The Netherlands differed by more than the MCID from the mean of all countries (Fig. 4a). Similarly there was also some variation in SF-12 and FACIT-F scores (Fig. 4b and c). MRC dyspnoea grades varied to a similar degree between countries for all grades.

These variations in HRQL scores appear to be due to differences in patient characteristics (i.e. age, sex, duration of disease, disease severity and co-morbidities) between the sub-samples per country, but not due to different relationships between HRQL scores and GOLD stages across countries. This was shown by the non-significant interaction terms in the linear models relating country and GOLD stage on HRQL scores. This was seen with all HRQL measures: total SGRQ, SF-12 MCS, SF-12 PCS, and FACIT.

Discussion

To our knowledge, this is the first large-scale study to use disease-specific and generic HRQL questionnaires to survey patients of all levels of COPD severity in primary care. HRQL was markedly impaired across all levels of severity of airway obstruction. A comparison of SGRQ scores from our study with those from the two population-based COPD studies, IBERPOC[25] and EPI-SCAN,[26] which included control subjects and patients classified as GOLD Stage '0', support our findings that patients with all severities had abnormal SGRQ scores, even those with mild disease. The most notable observations in our study are the marked impairments and small differences between patients in GOLD Stages I and II, whether assessed using generic or disease-specific HRQL questionnaires. The most likely explanation for our finding of poor health being associated with only mild-moderate obstructions is that patients with few symptoms are not detected and consequently not

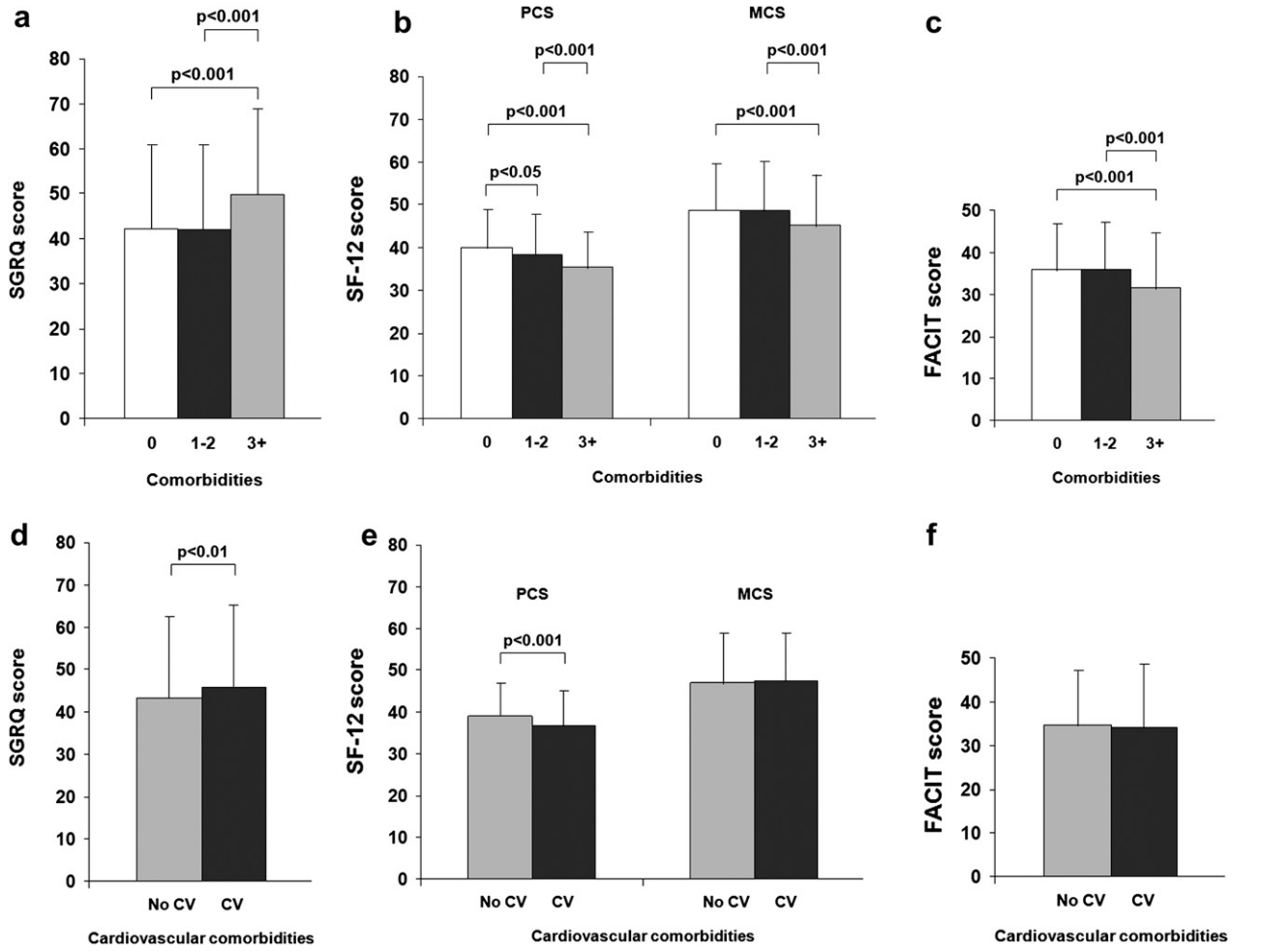

Figure 3 HRQL scores by number of co-morbidities and by cardiovascular co-morbidities
a) SGRQ total score by number of co-morbidities (mean + SD)
b) SF-12 component scores by number of co-morbidities (mean + SD)
c) FACIT-Fatigue score by number of co-morbidities (mean + SD)
d) SGRQ total score by cardiovascular co-morbidities (present[1] or absent) (mean + SD). CV = cardiovascular. ([1]defined as the patient having myocardial infarction, stroke or heart failure or patient being treated for hypertension, angina pectoris or arrhythmia)
e) SF-12 component scores by cardiovascular co-morbidities (present[1] or absent) (mean + SD). CV = cardiovascular; PCS = physical component score; MCS = mental component score. ([1]defined as the patient having myocardial infarction, stroke or heart failure or patient being treated for hypertension, angina pectoris or arrhythmia)
f) FACIT-Fatigue by cardiovascular co-morbidities (present[1] or absent) (mean + SD). ([1]defined as the patient having myocardial infarction, stroke or heart failure or patient being treated for hypertension, angina pectoris or arrhythmia)
No p-value shown indicates 'statistical non-significance'.

diagnosed. Our findings do not challenge the validity of GOLD staging when applied to all individuals with COPD in a population, whether diagnosed or not, but they do question the utility of GOLD staging alone (particularly I and II) for judging clinical severity in patients with diagnosed COPD, and suggest that burden of disease assessments provide additional complementary information.

Setting our findings into a broader context, the SGRQ scores from our population are comparable to baseline values from the UPLIFT study.[27] Our study did include data from a small number of patients who were experiencing an exacerbation whereas most other studies excluded recently exacerbated patients.[28,29] However, even patients with stable COPD and mild obstruction in our study reported SGRQ scores considerably higher than the upper limit of approximately 7 units expected in a healthy population.[25] SF-12 scores, particularly the physical component score, were lower (i.e. worse) than those obtained in a recent sample of 60—69 year olds from the general population in The Netherlands, in whom the mean MCS was 51.3 and mean PCS was 50.9.[30]

Our survey allowed us to compare SF-12 scores in COPD with scores in other chronic diseases. Xie et al. showed significant impairment in SF-12 scores in a US population of patients with coronary heart disease compared with a non-

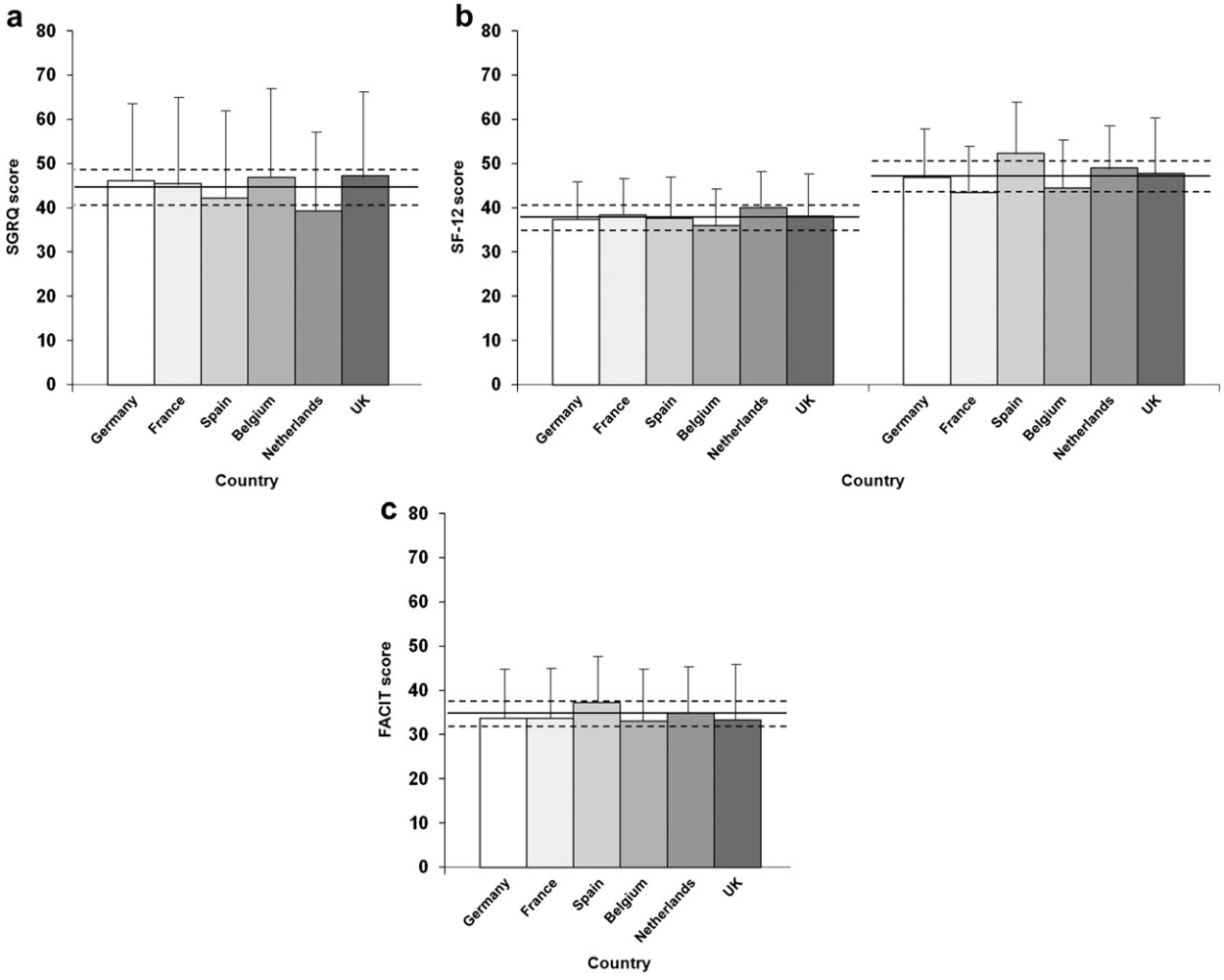

Figure 4 HRQL scores by country (Italy excluded due to small patient numbers)
a) SGRQ total score by country[1], b) SF-12 component scores by country[1], c) FACIT-Fatigue score by country[1] ([1]—represents mean score for all countries; - - - - - represents ± MCID).

coronary heart disease population. Scores for patients with coronary heart disease were comparable to our COPD population.[31] The SF-12 was derived from the SF-36 with which the scores are closely comparable.[22] In a study of patients with chronic conditions in six European countries, Japan and the USA, individuals reporting arthritis, congestive heart failure and chronic lung disease showed the highest impact on the SF-36, scoring around 47.5 for PCS, compared with 51.9 in respondents with no reported conditions. The score of 37.7 recorded for SF-12 PCS in our study indicates that primary care COPD patients suffer at least as much poor health as patients with other chronic conditions.[32]

Fatigue was prominent, even in GOLD Stage I patients. The data were consistent across countries. The FACIT-F scores were well below (i.e. worse than) the lower limit of 43 assessed in a US healthy population.[33] Data on COPD-related fatigue are scarce and to our knowledge, this is the largest set of data analysing FACIT scores in COPD, although a recent, smaller study also reported significantly greater fatigue in COPD patients during exacerbations.[34]

The symptom pattern differed with the degree of airway obstruction; cough was the prominent symptom in mild obstruction whereas dyspnoea was more frequently reported with severe and very severe obstruction. However, disability due to breathlessness was common even in patients with mild-moderate disease. The MRC dyspnoea scores showed that 70% of patients with mild disease and 74% of those with moderate obstruction experienced limitations in routine activities such as walking to the shops or keeping pace with their peers. The lack of complaint about cough in more severe disease may indicate that patients are overwhelmed by breathlessness rather than cough no longer being troublesome. The prominence of cough in mild disease could be an important indicator to PCPs to consider a diagnosis of COPD in patients presenting with persistent cough.

On all measures, there was an association between the presence of three or more reported co-morbidities and impaired HRQL. As might be expected, a step increase in co-morbidity count was associated with worsening of the generic SF-12 PCS score. By contrast, the SGRQ scores were almost identical in patients with under three co-morbidities, suggesting that the disease-specific SGRQ is not influenced by the presence of low levels of co-morbidity. There was a large step worsening in SGRQ in patients with $\geq$3 co-morbidities, which accords with the observation that more severe COPD is associated with a greater number of

co-morbidities.[35] In our own data, there was no relationship between mean number of co-morbidities and GOLD Stage.

The population recruited to this study was not a random sample of COPD patients within primary care; they were patients attending for a consultation. This may have biased the sample towards a more symptomatic group, explaining the high rate of reported exacerbations over the previous six months. New patients often consult because of a severe or persistent 'chest infection' (we noted over 50% of GOLD I and II patients required antibiotics for an exacerbation in the preceding six months). However, this is unlikely to have significantly influenced our study since the mean duration of COPD diagnosis was over 6 years, even in mild patients. Surprisingly, 7% of GOLD Stage I and II patients had been hospitalised for an exacerbation over the preceding 6 months. Scheduled appointment and prescription refill accounted for over three quarters of consultations suggesting that patients were being actively managed for chronic illness.

One of the criticisms of this study may be that the recruited patients were not fully representative of the whole COPD population. The method of patient recruitment meant that only patients with known diagnosed COPD were sampled. However, the sampling method did identify patients who reflect those seen in every-day practice in primary care across Europe, so the population is representative in that respect. It is believed that many patients with mild disease remain undiagnosed, so these patients would not have been included in this survey. Another limitation of the study is that countries were chosen on the basis of representing large COPD populations, so not all European countries are reflected in the dataset. Differences existed in the distribution of patient characteristics including COPD severity and consequently HRQL scores between countries in our sample. These are most likely caused by the different socio-demographic factors, differences between healthcare systems and therefore, the slightly different roles of PCPs in providing COPD care. In consequence, the mix of patients in terms of COPD severity, and some other characteristics, routinely showing up at their PCP, is likely to vary between countries. However, the relationship between HRQL impairment and GOLD Staging showed very similar patterns across countries, whether assessed in terms of MRC grade, or generic or disease-specific HRQL scores — suggesting that our findings may be applicable at the pooled (European) level, and generalised to other countries and healthcare systems.

In conclusion, this large observational European study confirms that health status is significantly impaired in COPD patients across all severities. We observed marked impairment in HRQL even in milder disease and there was little difference in the degree of impairment between GOLD Stage I and II patients. There was very wide variation in the patients' HRQL within each GOLD Stage. We conclude that a measurement of HRQL should be routinely included in the assessment and monitoring of COPD patients in primary care.

Conflict of interest statement

PWJ has received fees from pharmaceutical companies, including GSK, for speaking at meetings, participating in advisory board meetings and to support research. GB has received honoraria for lectures and has participated in advisory board meetings for various pharmaceutical companies including GSK. PK has received lecture fees, and participated in advisory boards and sponsored clinical trials for various pharmaceutical companies including GSK. MLL has served on advisory boards and received sponsorship, lecture fees and research funds from various pharmaceutical companies including GSK. JJSC has received lecture fees and research support from various pharmaceutical companies including GSK. LA and NB are employees of GSK.

Acknowledgements

Funding for this study was provided by GlaxoSmithKline (Study number: 111749). All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. The authors would like to thank all investigators who participated in this study and Tanja Hultsch from i3 Innovus who was the project leader for the operational conduct of the study. The authors would also like to acknowledge editorial support in the form of development of the manuscript first draft, editorial suggestions to draft versions of the paper, assembling tables and figures, collating author comments, copyediting, fact checking and referencing which was provided by Kate Hollingworth of LiveWire Communications. This support was funded by GlaxoSmithKline (GSK).

References

1. *The global initiative for chronic obstructive lung disease (GOLD) revised*, www.goldcopd.com; 2009.
2. Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990—2020: global burden of disease. *Lancet* 1997;**349**:1498—504.
3. Celli BR, MacNee W, Agusti A, Anzueto A, Berg B, Buist AS, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;**23**:932—46.
4. National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease: national clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004;**59**(Suppl. 1):1—232.
5. Cully JA, Graham DP, Stanley MA, Ferguson CJ, Sharafkhaneh A, Souchek J, et al. Quality of life in patients with chronic obstructive pulmonary disease and comorbid anxiety or depression. *Psychosomatics* 2006;**47**:312—9.
6. Garrido PC, Diez JM, Gutierrez JR, Centeno AM, Vázguez EG, Miguel G, et al. Negative impact of chronic obstructive pulmonary disease on the health-related quality of life of patients: results of the EPIDEPOC study. *Health Qual Life Outcomes* 2006;**4**:31—9.
7. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Oga T, Izumi T. A comparison of the level of dyspnoea vs. disease severity in indicating the health-related quality of life of patients with COPD. *Chest* 1999;**116**:1632—7.
8. Hu J, Meek P. Health-related quality of life in individuals with chronic obstructive pulmonary disease. *Heart Lung* 2005;**34**:415—22.
9. Spencer S, Calverley PM, Sherwood Burge P, Jones PW. Health status deterioration in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;**163**:122—8.

10. Osman IM, Godden DJ, Friend JA, Legge JS, Douglas JG. Quality of life and hospital re-admission in patients with chronic obstructive pulmonary disease. *Thorax* 1997;**52**:67—71.
11. Domingo-Salvany A, Lamarca R, Ferrer M, Garcia-Aymerich J, Alonso J, Félez M, et al. Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. *Am J Crit Care Med* 2002;**166**:680—5.
12. Donaldson GC, Wilkinson TMA, Hurst JR, Perera WR, Wedzicha JA. Exacerbations and time spent outdoors in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;**171**:446—52.
13. Seemungal TAR, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**157**:1418—22.
14. Rennard S, Decramer M, Calverly PMA, Pride NB, Soriano JB, Vermeire PA, et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of confronting COPD international survey. *Eur Respir J* 2002;**20**:799—805.
15. Cazzola M, MacNee W, Martinez FJ, Rabe KF, Franciosi LG, Barnes PJ, et al. On behalf of the American Thoracic Society/European Respiratory Society Task Force on outcomes of COPD. Outcomes of COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008;**31**:416—69.
16. Jones PW. Health status measurement in chronic obstructive pulmonary disease. *Thorax* 2001;**56**:880—7.
17. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;**54**:581—6.
18. Jones PW, Quirk FH, Baveystock CM. The St George's respiratory questionnaire. *Resp Med* 1991;**85**(Suppl. 2):25—31.
19. Meguro M, Barley EA, Spencer S, Jones PW. Development and validation of an Improved, COPD-Specific version of the St. George respiratory questionnaire. *Chest* 2007;**132**:456—63.
20. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J* 2002; **19**:398—404.
21. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;**34**:220—33.
22. Kontodimopoulos N, Pappa E, Niakas D, Tountas Y. Validity of SF-12 summary scores in a Greek general population. *Health Qual Life Outcome* 2007;**5**:55.
23. Webster K, Odom L, Peterman A, Lent L, Cella D. The Functional assessment of chronic illness Therapy (FACIT) measurement system: validation of version 4 of the core questionnaire. *Qual Life Res* 1999;**8**(7):604.
24. Yost KJ, Eton DT. Combining distribution- and anchor-based approaches to determine minimally important differences. The FACIT experience. *Eval Health Prof* 2005;**28**:172—91.
25. Ferrer M, Villasante C, Alonso J, Sobradillo V, Gabriel R, Villagut G, et al. Interpretation of quality of life scores from the St George's respiratory questionnaire. *Eur Respir J* 2002; **19**:405—13.
26. Miravitlles M, Soriano JB, Garcia-Rio F, Munoz L, Duran-Tauleria E, Sanchez G, Sobradillo V, Ancochea J. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. *Thorax* 2009;**64**:863—8.
27. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. for the UPLIFT study investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;**359**:1543—54.
28. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. for the TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;**356**:775—89.
29. Wedzicha JA, Calverley PMA, Seemungal TA, Hagan G, Ansari Z, Stockley RAfor the INSPIRE Investigators. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008;**177**:19—26.
30. Mols F, Pelle AJ, Kupper N. Normative data of the SF-12 health survey with validation using postmyocardial infarction patients in the Dutch population. *Qual Life Res* 2009;**18**: 403—14.
31. Xie J, Wu EQ, Zheng Z-J, Sullivan PW, Zhan L, Darwin R, et al. Patient-reported health status in coronary heart disease in the United States: age, sex, racial, and ethnic differences. *Circulation* 2008;**118**:491—7.
32. Alonso J, Ferrer M, Gandek B, Ware JE, Aaronson NK, Mosconi P. Health-related quality of life associated with chronic conditions in eight countries: results from the International Quality of Life Assessment (IQOLA) Project. *Qual Life Res* 2004;**13**:283—98.
33. Cella D, Lal J-S, Chang C-H, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer* 2002;**94**:528—38.
34. Baghai-Ravary R, Quint JK, Goldring JJP, Hurst JR, Donaldson GC, Wedzicha JA. Determinants and impact of fatigue in patients with chronic obstructive pulmonary disease. *Respir Med* 2009;**103**:216—23.
35. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008;**32**:962—9.