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

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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 comorbidities (CM) was also associated with a significantly worse score (49.9 ± 19.1) vs. 1–2 CM (42.1 ± 19.1).
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.\(^1\) 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.\(^1\)\(^,\)\(^6\)\(^,\)\(^14\) 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 <0.70. 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 <0.70. 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.\(^17\)
Health-related QoL in COPD patients in primary care, Europe

In this survey, the COPD specific version (SGRQ-C) was used. The SGRQ is a disease-specific HRQL questionnaire and in other assessments had been conducted. The functional assessment of chronic illness therapy (FACIT) fatigue scale 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. 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 -4 units in the FACIT-F score has been deemed to be the MCID.

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 5 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.
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 FEV₁/FVC < 70%. Results for this population are reported here. FEV₁ as percent predicted was not available for 31 subjects due to missing information on patients’ height.
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 FEV1 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

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

<table>
<thead>
<tr>
<th>HRQL Questionnaire</th>
<th>Severity by GOLD Stagea</th>
<th>Reported Population (N = 1817)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage I (N = 223)</td>
<td>Stage II (N = 868)</td>
</tr>
<tr>
<td>SGRQb</td>
<td>Total score:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>38.5 (19.3)</td>
</tr>
<tr>
<td></td>
<td>P25</td>
<td>22.3</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>37.5</td>
</tr>
<tr>
<td></td>
<td>P75</td>
<td>52.1</td>
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<tr>
<td>Symptom score:</td>
<td>Mean (SD)</td>
<td>56.2 (24.0)</td>
</tr>
<tr>
<td></td>
<td>P25</td>
<td>37.4</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>55.0</td>
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<tr>
<td></td>
<td>P75</td>
<td>75.4</td>
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<tr>
<td>Activity score:</td>
<td>Mean (SD)</td>
<td>47.6 (21.8)</td>
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<tr>
<td></td>
<td>P25</td>
<td>32.9</td>
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<tr>
<td></td>
<td>Median</td>
<td>52.3</td>
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<tr>
<td></td>
<td>P75</td>
<td>59.6</td>
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<tr>
<td>Impacts score:</td>
<td>Mean (SD)</td>
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<td></td>
<td>P25</td>
<td>11.6</td>
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<tr>
<td></td>
<td>Median</td>
<td>23.9</td>
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<tr>
<td></td>
<td>P75</td>
<td>40.8</td>
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<tr>
<td>SF-12c</td>
<td>PCS:</td>
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</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>39.8 (8.8)</td>
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<tr>
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<td>Median</td>
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<td></td>
<td>MCS:</td>
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<td></td>
<td>Mean (SD)</td>
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<td></td>
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<td></td>
<td>P75</td>
<td>58.4</td>
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<tr>
<td></td>
<td>FACIT-Fd</td>
<td></td>
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<tr>
<td></td>
<td>Mean (SD)</td>
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<tr>
<td></td>
<td>P25</td>
<td>29.5</td>
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<tr>
<td></td>
<td>Median</td>
<td>38.0</td>
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<tr>
<td></td>
<td>P75</td>
<td>46.0</td>
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</tbody>
</table>

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 FEV1 (% 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.
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 β₂-agonist (ICS/LABA) combination (55%), long-acting anticholinergics (41%), short-acting β₂-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 (<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 ≥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 ± 19.5) than those without (43.2 ± 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 ± 9.2, presence of CV-CM 36.8 ± 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, IBERPOC25 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
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-
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

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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).
co-morbidities. 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.

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