Can health status questionnaires be used as a measure of physical activity in COPD patients?

To the Editor:

Acting to address the amount of physical activity of patients with chronic obstructive pulmonary disease (COPD) is recommended as part of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations [1]. A level lower than approximately 5000 steps for day (sedentary lifestyle index) is associated with significantly increased health risks [2, 3]. Actively screening to identify patients below this threshold could be an important step towards targeting interventions to increase physical activity. Potential screening tools include activity monitors (objective assessment) or self-reported questionnaires (subjective assessment) to measure the amount of physical activity [4]. The latter method, which is feasible in clinical practice, may not result in an accurate representation in an individual patient, as questionnaire responses tend to misclassify physical activity [5]. Although more accurate and widely used in research, activity monitoring is not yet commonly included in patients' routine assessment. Several health status questionnaires in routine clinical use contain a domain or dimension related to physical activity [6]. In the analytical framework of Leidy [7], functional performance has been defined as the physical, psychological, social, occupational and spiritual activities that people actually do in the normal course of their lives to meet basic needs, fulfil usual roles, and maintain their health and wellbeing. A review by Kocks *et al.* [8] proposed that these questionnaires could be used in the measurement of functional performance (defined as "what a patient is actually doing") and that this would be a more practical alternative to physical activity monitoring. Whether this approach is sufficiently valid as a representation of physical activity levels in clinical practice remains to be established.

The aims of the present analyses were 1) to describe the relationship between objectively measured physical activity and responses to health status questionnaires, and 2) to assess the utility of these questionnaires to screen for severe physical inactivity (SPI) in this population.

Data from 235 COPD patients (diagnosis confirmed by post-bronchodilator spirometry) recruited from five centres across Europe (Leuven, Belgium; Athens, Greece; Groningen, The Netherlands; and London and Edinburgh, UK), as part of the PROactive project (www.proactivecopd.com), were included in this analysis. Patients were current or ex-smokers (⩾10 pack-years) without comorbidities significantly interfering with their ability to exercise and without respiratory conditions other than COPD. Further study details are available in the article reporting the primary analyses of the present study [9]. Physical activity was measured for 14 days during waking hours using the Dynaport Movemonitor (McRoberts, The Hague, the Netherlands), which has been validated in this population [10, 11]. Patients with a minimum of four valid days, defined as days with ⩾8 h of wearing time, were included in this analysis [12]. SPI was defined as a step count <5000 per day [2]. At the end of this measurement period, several questionnaires were administered including: the Chronic Respiratory Disease Questionnaire Self-Administered Standardised Format (CRDQ-SAS), COPD Assessment Test (CAT), Clinical COPD Questionnaire (CCQ) and modified Medical Research Council dyspnoea questionnaire (mMRC). Relations between physical activity (number of daily steps) and different health status questionnaires were investigated using Spearman correlations. The ability of questionnaires to predict SPI was analysed using logistic regression analysis with SPI as the outcome and different questionnaires as explanatory variables, each included in a separate analysis. Area under the curve (AUC) was retrieved if the regression analysis was significant. AUC values are a measure of accuracy and are considered excellent (⩾0.90), good (0.80–0.89), fair (0.70–0.79) or poor (<0.70). Receiver operating characteristic (ROC) curves were drawn for the different questionnaires, including total scores and the subdomain with the best discriminative property. A cut-off was suggested for each of the questionnaires (using the total score or subdomain, giving the highest AUC), giving an equal weight to sensitivity and specificity. Likelihood ratios were calculated as the ratio between sensitivity and 1−specificity. Likelihood ratios >10 are considered to provide strong evidence for diagnostic purposes [13].

Nine patients did not have a valid physical activity measurement and were excluded from the analysis, and one patient did not complete the questionnaires, resulting in 225 patients (67% male, mean±SD age 67±8 years, forced expiratory volume in 1 s 56±20% pred, 6-min walk distance 426±129 m (68±19% pred) with a median (interquartile range) step count of 4287 (2971–6331) steps per day representing all GOLD stages (I/II/III/IV: 12%/47%/32%/9%, respectively) included in the present analyses. 60% of patients were defined as severely inactive. The health status questionnaires (and their subdomains) $CCQ_{symptoms}$,

CRDQ-SAS$_{mental}$ and CRDQ-SAS$_{mastery}$ were poorly correlated (absolute r<0.3), CAT, CCQ$_{total}$, CCQ$_{mental}$, CCQ$_{functional\ state}$, CRDQ-SAS$_{total}$, CRDQ-SAS$_{dyspnoea}$ and CRDQ-SAS$_{fatigue}$ were weakly related (absolute r=0.3–<0.5), and the mMRC score was moderately related (r=−0.52) to steps (p<0.01 for all). All scores, except for the CRDQ-SAS$_{mental}$ score, were significant predictors of SPI (p⩽0.01 for all). Only mMRC and CCQ$_{functional\ state}$ scores showed a fair discriminative property (AUC 0.719 and 0.724, respectively). Other questionnaires resulted in a poor discrimination (AUC<0.7). ROC curves were plotted for the different questionnaires including the total score and the best discriminative subdomain (figure 1). To predict SPI, a mMRC score ⩾2 resulted in a positive predictive value (PPV) of 79%, accuracy of 67% and positive likelihood ratio (LR^+) of 2.27. A CAT score ⩾13 resulted in a PPV of 73%, accuracy of 64% and LR^+ of 1.78. A CCQ$_{functional\ state}$ score ⩾1.5 resulted in a PPV of 76%, accuracy of 67% and LR^+ of 2.06. A CRDQ-SAS$_{dyspnoea}$ score ⩽5.3 results in PPV of 76%, accuracy of 68% and LR^+ of 2.10.

The present data show that responses to health status questionnaires are only loosely related to the amount of physical activity, and their use cannot therefore be recommended as a standalone screening tool for SPI because of low sensitivity and specificity. Two explanations can be proposed for the very low to moderate associations observed between these questionnaires, which mainly capture symptoms and physical activity. First, none of these questionnaires use physical activity as a main concept and, thus, they are not designed to give a reliable assessment of the physical activity level [6]. The questionnaires mainly reflect symptoms that are indirectly associated with physical activity. Second, it is plausible that there is interplay between the volume (amount×intensity) of physical activity and the symptom experience. Patients may decrease their level of physical activity to avoid symptoms. This leads to the hypothesis that symptoms can depend on the physical activity level and, therefore, fail to give a reliable estimate of the actual underlying physical activity level. Indeed, patients' perception of physical activity includes not only the amount of physical activity but also symptoms experienced during and adaptations related to physical activity [9, 14].

A good screening tool for inactive patients would be able to identify truly inactive patients (sensitivity) without including too many active patients (specificity). DEPEW *et al.* [15] concluded that the mMRC is the best predictor of SPI, compared to two physical activity questionnaires, self-efficacy and the ADO (age, dyspnoea and airflow obstruction) index. Those authors proposed a mMRC score of 3 as a triage for SPI (defined as physical activity level <1.4, *i.e.* the ratio of active to total energy expenditure) [15]. Above this

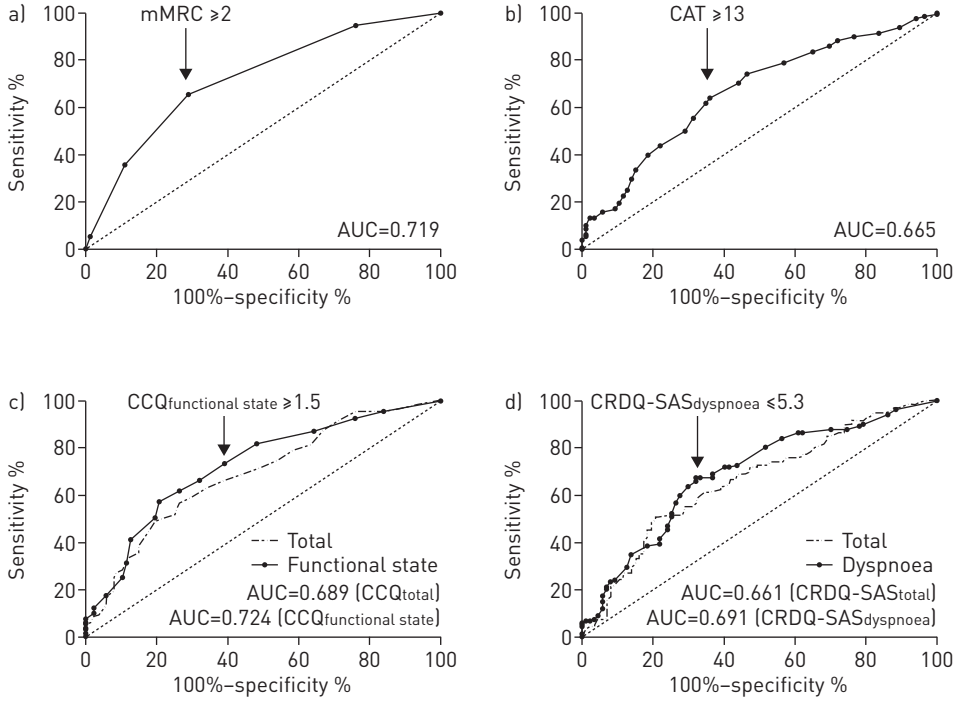

FIGURE 1 Receiver operating characteristic analyses of: a) the modified Medical Research council dyspnoea questionnaire (mMRC), with a range of 0–4; b) COPD Assessment Test (CAT), with a range of 0–40; c) total score and functional state domain score of the Clinical COPD Questionnaire (CCQ), with a range of 0–6 for both; and d) total score and dyspnoea domain score of the Chronic Respiratory Disease Questionnaire Self-Administered Standardised format (CRDQ-SAS), with a range of 1–7 for both. mMRC ⩾2 resulted in a sensitivity of 65% and specificity of 71%; CAT ⩾13 resulted in 64% sensitivity and 64% specificity; CCQ$_{functional\ state}$ ⩾1.5 in 66% sensitivity and 68% specificity; and CRDQ-SAS$_{dyspnoea}$ ⩽5.3 in 67% sensitivity and 68% specificity.

cut-off, 84% of patients identified as severely inactive were indeed inactive (PPV 84%). However, it resulted in a sensitivity of 36%, meaning that only a minority of inactive patients were identified by this screening tool. Based on the ROC analysis, for mMRC, we chose a cut-off of 2 points, which also resulted in a majority of patients above this threshold to be inactive (PPV 79%) with a sensitivity of 65%. These results suggest that this cut-off could be used in clinical practice as a first screening tool to identify severely inactive patients. However, a significant proportion of patients with an mMRC of 0 or 1 are inactive (negative predictive value (NPV) 56%). Therefore, physical activity should still be measured to identify inactive patients with a mMRC <2. A comparable conclusion can be drawn based on the CCQ$_{\text{functional state}}$ domain, using a cut off ⩾1.5 (PPV 76%, NPV 57%). In the review by KOCKS *et al.* [8], the questionnaires were judged mainly based on their use in a primary care setting (*e.g.* practical use and responsiveness). These authors also concluded the mMRC and CCQ$_{\text{functional state}}$ to be the most suited questionnaires to measure functional performance [8]. The present study shows that this conclusion only holds true in terms of PPV, whereas NPV is poor.

The use of simple clinical tests, such as the 6-min walk test, were also shown to fail to predict SPI [16]. Taking all this into account, we can conclude that neither health status questionnaires nor simple clinical tests can replace objective measurement of physical activity in COPD patients. The mMRC dyspnoea and CCQ$_{\text{functional state}}$ score could be recommended as easy first screening tests to identify severely inactive patients but will misclassify patients as "not severely inactive" below the proposed thresholds. Therefore, objective physical activity measurement should be recommended in the clinical routine assessment of COPD patients.

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Health status questionnaires provide only limited insight into the physical activity of patients with COPD http://ow.ly/X7oUb

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Urokinase plasminogen activator receptor polymorphisms and airway remodelling in asthma

To the Editor:

In the past decade, several asthma genes have been identified [1]; however, the key challenge is to determine how these genetic changes contribute to the underlying lung biology. We identified the urokinase plasminogen activator receptor (*PLAUR*) as an asthma susceptibility gene by positional cloning [2]. We showed that the same single nucleotide polymorphisms (SNPs) were associated with soluble PLAUR levels in blood, airway hyperresponsiveness (AHR) and accelerated lung function decline in asthma; a clinical feature linked to airway wall remodelling [2]. Therefore, we hypothesised that PLAUR may contribute to structural changes in asthma *via* increased levels of the membrane bound or soluble receptor. We subsequently showed that PLAUR levels were elevated in the airway epithelium of asthma patients and that PLAUR has a role in epithelial repair responses [3]. The aim of the current study was to 1) test for association between *PLAUR* SNPs and markers of airway remodelling using bronchial biopsies from asthma patients; and 2) test for association between SNPs and staining for PLAUR in airway tissue.

This study utilised bronchial biopsy samples from 137 asthma patients. These subjects were previously recruited in the northern Netherlands and re-examined during 2002–2006 [4]. Lung function testing and AMP provocation tests were performed and subjects were considered to have AHR when an AMP concentration of <320 mg·mL^{-1} caused a 20% fall in forced expiratory volume in 1 s (FEV_1). DNA samples were available in all 137 subjects. Bronchoscopy, collection and processing of the bronchial biopsies were performed as previously described, including quantification of remodelling markers [4]. Quantification was performed on the largest of three biopsy sections taken. Clinical characteristics of the asthma patients investigated and details on genotyping and immunohistochemistry are available on request. The study was approved by the University Medical Center Groningen ethics committee and participants signed informed consent forms.

Bronchial biopsies were characterised for: 1) basement membrane thickness (μm); 2) sub-epithelial vasculature (number of $CD31^+$ vessels per 0.1mm^2 of submucosa); 3) percentage intact epithelium; 4) basal