ABSTRACT

Background: Pulmonary Rehabilitation (PR) is an important treatment for patients with chronic obstructive pulmonary disease (COPD) but it is not established whether any baseline parameter can predict response or compliance.

Aim: To identify whether baseline measures can predict who will complete the programme and who will achieve a clinically significant benefit from a Minimum Clinical Important Difference (MCID) in terms of exercise capacity and health-related quality of life (HRQoL).

Methods: Data were collected prospectively from patients with COPD at their baseline assessment for an outpatient PR programme in one of eight centres across London. 'Completion' was defined as attending at least 75% of the designated PR visits and return for the follow-up evaluation. The MCID for outcome measures was based on published data.

Results: 787 outpatients with COPD (68.1±10.5 years old; 49.6% males) were included. Patients who completed PR (n=449, 57.1%) were significantly older with less severe airflow obstruction, lower anxiety and depression scores, less dyspnoea and better HRQoL. Only baseline CAT score (OR=0.925; 95% CI 0.879 to 0.974; p=0.003) was retained in multivariate analysis. Patients with the lowest baseline walking distance were most likely to achieve the MCID for exercise capacity. No baseline variable could independently predict achievement of an MCID in HRQoL.

Conclusions: Patients with better HRQoL are more likely to complete PR while worse baseline exercise performance makes the achievement of a positive MCID in exercise capacity more likely. However, no baseline parameter could predict who would benefit the most in terms of HRQoL.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disorder characterised by high morbidity and mortality. Pulmonary rehabilitation (PR) is a multidimensional, non-pharmacological intervention that has been established as the standard of care for the management of this condition. PR programmes (which include supervised exercise training) have been shown in clinical trials to improve exercise capacity, reduce dyspnoea, anxiety and depression while improving quality of life among patients with COPD, and these findings are supported by data from clinical practice.

Drop-out rates for those who attend a PR programme are high, with up to 50–75% of the initial COPD population referred for PR declining to take part or failing to complete the programme. Although PR has a compelling evidence base, some patients with COPD do not achieve a clinically significant improvement. Maximising the efficiency of services is important as limited health resources allocated to PR programmes mean that not every patient with COPD who might benefit has access to them. It is important therefore to be able to identify patients with COPD who may need additional support to complete a PR programme and also to identify those who may need additional input to achieve a useful improvement.

Demographic factors, physiological measurements and health-related quality of life (HRQoL) questionnaires have been used to investigate outcomes of interest in PR, such as programme completion or impact on exercise

KEY MESSAGES

- In a real-life clinical setting of PR those COPD patients most likely to benefit from PR appeared the least likely to complete it.
- Improvement in different aspects following PR was generally measure-specific so no single baseline factor could predict a minimum clinical important improvement in exercise capacity as well as health status.
capacity. To date, the optimum strategy for baseline assessment in PR has not been defined so published studies and clinical programmes use a range of measures. We conducted a multicentre study aiming to identify whether there is an optimal tool or universal measure that could independently predict: (1) the completion of the PR programme and (2) achievement of the accepted minimum clinically important difference (MCID) in terms of exercise capacity and quality of life.

**MATERIAL-METHODS**

**Population**

We analysed data collected routinely from 787 patients with COPD who attended at least the initial assessment visit of an outpatient PR programme in one of eight centres across London between March 2012 and March 2013. Diagnosis of COPD was based on postbronchodilator forced expiratory volume in 1 s to forced vital capacity ratio \( (FEV_1/FVC) \) being <0.7. Patients were included in the study when baseline anthropometric characteristics, \( FEV_1 \) and \( FEV_1/FVC \) ratio had been recorded, along with at least one outcome measure (exercise capacity, dyspnoea score, or a HRQL questionnaire). Patients with a clinical diagnosis of asthma or heart failure (New York Heart Association (NYHA) III-IV) were excluded. The collation of data from the different programmes was approved by the Riverside Research Ethics Committee.

All programmes followed British Thoracic Society (BTS) guidelines regarding a combination of aerobic and strength training. The programme included a mixture of two supervised sessions and one or more unsupervised home exercise sessions each week over 8–12 weeks. Exercise prescription was based on the outcome of initial exercise assessment and was increased through the programme as tolerated. Programmes were multidisciplinary with an educational component covering issues including exercise (which was recommended during the programme and was to continue after its completion), medication use, diet and coping strategies, according to BTS recommendations.

All patients underwent an initial evaluation before the beginning of the programme and a second evaluation immediately after PR completion. Patients with COPD who completed at least 75% of the designated PR programme and returned for the follow-up evaluation were characterised as completers. Demographic characteristics and pulmonary function testing variables were recorded only once (before PR), while dyspnoea score, exercise capacity measurements, anxiety and depression scale scores and HRQL variables were recorded for COPD completers prerehabilitation and postrehabilitation.

**Measurements**

Pulmonary function testing was completed according to established guidelines. \( FEV_1/FVC \) was recorded and normal predicted values were calculated based on the European Community for Steel and Coal reference equations. Exercise capacity was evaluated using either the incremental shuttle walk test (ISWT) or the 6 min walk test (6MWWT). Both exercise tests were conducted according to the published literature. Dyspnoea was assessed in a 5-point instrument during rest, using the Medical Research Council (MRC) dyspnoea scale.

The Hospital Anxiety and Depression (HAD) Scale was utilised to assess the level of anxiety and depression. The HAD is a 14-item questionnaire consisting of two seven-item subscales: one for assessing anxiety (HAD-A) and one for assessing depression (HAD-D). Subscales are rated between 0 and 21 and the higher the scores, the higher the level of anxiety and depression, correspondingly. Scores of 0–7 in either HAD-A or HAD-D subscale are considered normal, 8–10 borderline and ≥11 clinical caseness.

Quality of life was evaluated using the COPD assessment test (CAT) or the Chronic Respiratory Disease Questionnaire (CRDQ). The CAT consists of eight items which are rated using a Likert-type scale of 0–5, with higher scores representing worse quality of life. The CRDQ consists of four domains: dyspnoea (five items) \( (CRDQ-D) \), fatigue (four items) \( (CRDQ-F) \), emotional function (seven items) \( (CRDQ-E) \) and mastery (four items) \( (CRDQ-M) \); each domain is rated using a modified 7-point Likert scale and higher scores represent better quality of life. Subscores were obtained for each domain and a total score for the whole CRDQ by adding the four subscores, as previously described.

**Minimum clinical important difference**

MCID was used to characterise which patients benefited from PR. This allowed comparison between programmes using different outcome measures. The MCID for each variable tested was defined according to the published literature. An increase of more than 30 m and an increase of more than 47.5 m was defined as the MCID for the 6MWWT and ISWT, correspondingly. The MCID for MRC was defined as a decrease of ≥1 in the dyspnoea score, while for HAD-A and HAD-D questionnaires it was defined as an increase of ≥1.5. An increase of >0.5 was used as the MCID for each of the CRDQ domains (dyspnoea, fatigue, emotional function and mastery). For the CAT a reduction of >2 points was defined as MCID.

**Statistical analysis**

Statistical analysis was performed using the Predictive Analytics Software (PASW, SPSS Inc) V.18. Data are presented as mean±1 SD or as % percentages. Comparisons before and after PR were conducted using paired-sample t test. Independent samples t test and \( \chi^2 \) test were utilised, as appropriate, for comparisons between completer and non-completer groups and between those who established an MCID or not for all the outcomes of interest. All parameters that were univariately associated with either completion or MCID in each outcome were...
entered in a multivariate regression analysis model, to allow independent predictors of PR completion and PR effectiveness to be identified. OR with corresponding 95% CIs are reported for each independent predictor. A level of p<0.05 was considered significant.

RESULTS
The study population consisted of 787 outpatients with COPD (68±10.5 years old; 49.6% males). Most patients (42%) presented with Global Initiative for Obstructive Lung Disease (GOLD) stage II (FEV1%predicted: 89.9±9.3%); 6.8% presented with GOLD stage I (FEV1%predicted: 62.4±8.7%), 32.4% with GOLD stage III (FEV1%predicted: 39.7±5.6%) and 18.8% with GOLD stage IV (FEV1%predicted: 23.4±4.2%). In 30 patients (3.8%) COPD was accompanied with bronchiectasis, while one patient had α 1 antitrypsin deficiency.

Prior to entering PR, all 787 patients had completed the MRC dyspnoea score and the CAT questionnaire. Data on baseline exercise capacity were available for 664 patients (ISWT for N=406 and 6MWT for N=258). Baseline anxiety and depression score was available for 640 patients, while 340 patients completed a second HRQL questionnaire. The baseline differences in demographic and clinical characteristics of the patient with COPD subgroup that completed the extra-HRQL questionnaire, which was CRDQ. No baseline differences in demographic and clinical characteristics were noted in the patient with COPD subgroup that completed the extra-HRQL questionnaire. The baseline demographic and clinical characteristics of the patient population are presented in table 1.

Overall, 57.1% of patients (n=449) completed the PR programme; reasons for not completing PR were not systematically recorded. Patients who completed the PR were older, had less severe disease (indicated by FEV1% predicted), less anxiety and depression, (indicated by the HAD-A and HAD-D questionnaires), less dyspnoea prior to referral (indicated by the MRC score), and better quality of life identified by lower scores in CAT, and higher scores in CRDQ-E, CRDQ-M, CRDQ-F and Total CRDQ (table 2). Baseline variables (FEV1/FVC ratio, body mass index (BMI), CRDQ-D and exercise capacity prior to referral) did not differ between the groups.

Assessment at the end of the programme indicated that PR had been beneficial for participants as a group (table 3), with significant improvements in exercise capacity, in terms of either 6MWT (p<0.001) or ISWT (p<0.001) distance. Anxiety and depression scores fell (both p<0.001) post PR. Quality of life also improved with significant fall in CAT score (p<0.001) while CRDQ (Total CRDQ, CRDQ-D, CRDQ-E, CRDQ-M and CRDQ-F) increased (p<0.027; p<0.001; p<0.001 and p<0.001, correspondingly). MRC dyspnoea score was also significantly less (p<0.001).

Predictors of completion
All parameters univariately associated with PR completion were entered in a stepwise multivariate logistic regression analysis model. In order to avoid
multicollinearity issues, only the total score of CRDQ entered the analysis, since its individual domains were very highly correlated to the total score (Pearson r=0.85). Variables entered were: age, FEV1 %predicted, baseline CRDQ total, CAT, HAD-A, HAD-D and MRC scores. The only independent predictor of PR completion was baseline CAT score (OR=0.925; 95% CI 0.879 to 0.974; p=0.003); the higher the baseline CAT score, the lower the probability of completing the PR programme.

Predictors of achieving the MCID in exercise capacity
Among COPD completers, 68.3% (45.1% male; 67.7±9.7 years old; 54±4±20.3 FEV1 %predicted) improved exercise capacity by greater than the published MCID after PR (group A), compared to patients who did not establish this improvement (group B). Group A had worse exercise capacity prior to PR, according to either 6MWT (236.1±92.4 m vs 284±80.9 m, p=0.014) or ISWT (254.5±137.7 m vs 315.5±174.8 m, p=0.022) and this was the only predictor of exercise MCID. Age, sex, lung function, BMI, baseline CRDQ, SGRQ, CAT and MRC dyspnoea score were not discriminatory in terms of exercise capacity.

Predictors of MCID in HRQoL
PR had a significant impact on CAT, CRDQ, HAD-A and HAD-D scores. Since there is a variety of different HRQoL questionnaires in use in clinical practice, MCID predictors of HRQoL were investigated individually.

CAT
53.2% of completers achieved the MCID for the CAT score. These patients were younger (66.7±9.7 vs 71.5±9.9, p<0.001) and had lower CAT scores, that is, better health status at baseline (22.5±7.5 vs 16.7±7.2, p<0.001).

Both these variables remained strong independent predictors of MCID in HRQoL after entering a stepwise multivariate regression analysis model (OR for age=0.960; 95% CI 0.938 to 0.983 and OR for CAT pre-PR=1.101; 95% CI 1.068 to 1.135).

CRDQ
Predictors of MCID were identified for each of the four domains individually. 56.2% of completers achieved the MCID in CRDQ-D domain. These patients had a higher FEV1/FVC ratio (51.1±12.9 vs 41.3±12, p=0.026), a worse CRDQ-D baseline score (2.6±0.9 vs 3.5±1.6, p<0.001) and were predominately female (67% vs 45.9%, p=0.003). However, none of these variables remained an independent predictor in the multivariate analysis; nor did age, BMI, FEV1 %predicted, exercise capacity and MRC score differ between the groups.

For CRDQ-E domain, MCID was achieved in 42.8% of completers. These patients had higher baseline MRC score (3.4±0.7 vs 2.9±0.8, p<0.001) and lower baseline CRDQ-E score (3.7±1.2 vs 4.8±1.4, p<0.001). When entered in a stepwise regression analysis model, baseline MRC (OR=1.682, 95% CI 1.076 to 2.631; p=0.023) as well as baseline CRDQ-E (OR=0.610, 95% CI 0.476 to 0.783; p<0.001) could predict MCID in CRDQ-E.

MCID for CRDQ-F domain was achieved in 58.6% of patients with COPD who completed the PR programme. These were younger (66±10.4 vs 70±10.8 years old, p=0.003), had a higher MRC dyspnoea score (3.5±0.8 vs 2.9±0.8) and a lower baseline CRDQ-F score (3±1.1 vs 4.3±1.4, p<0.001) compared to the rest. In the multivariate analysis, only age (OR=0.967; 95% CI 0.937 to 0.998, p=0.039) and baseline CRDQ-F (OR=0.457; 95% CI 0.347 to 0.603, p<0.001) remained independent predictors of achieving the CRDQ-F MCID.

Finally, 37.6% of completers achieved the MCID in the CRDQ-M domain. These patients had higher MRC dyspnoea score (3±0.7 vs 3±0.8, p=0.002) compared to the rest of the completers. No other demographic or clinical characteristic was found to be different between these two groups.

Predictors of MCID in HAD scores
Among COPD completers, 31.7% achieved an improvement above MCID in HAD-A. They had higher baseline MRC dyspnoea score (3.5±0.9 vs 3.1±0.9, p=0.004) and greater baseline anxiety (9.5±4.4 vs 5.8±4.1, p<0.001). Age, sex, BMI, severity of obstruction and exercise capacity were not associated with HAD-A improvement. In the stepwise multivariate regression analysis, only baseline HAD-A (OR=1.221; 95% CI 1.151 to 1.294, p<0.001) could independently predict the presence of MCID in HAD-A. Alternatively, HAD-A score was analysed based on symptom severity subscale. Prior to PR, 51.6% of patients were considered normal, 20.9% were considered borderline and the remaining 27.5% were potential clinical cases. After PR completion, 64.5% of patients were normal, 20.8% were borderline and only 14.7% were normal, 20.9% were considered borderline and the remaining 27.5% were potential clinical cases.

Table 3
Table 3 Comparisons between pre and post pulmonary rehabilitation among completers

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pre PR</th>
<th>Post PR</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISWT (m)</td>
<td>264.9±148</td>
<td>350.1±158.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>246.8±99</td>
<td>316±94.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAT</td>
<td>20.7±8</td>
<td>17.8±7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CDRQ_Total</td>
<td>15.2±4.4</td>
<td>15.8±4.7</td>
<td>0.027</td>
</tr>
<tr>
<td>CDRQ_D</td>
<td>2.9±1.3</td>
<td>3.6±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CDRQ_E</td>
<td>4.3±1.4</td>
<td>4.8±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CDRQ_F</td>
<td>3.8±2.1</td>
<td>4.1±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CDRQ_M</td>
<td>4.6±1.7</td>
<td>3.2±2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAD-A</td>
<td>7.1±4.6</td>
<td>6.3±4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAD-D</td>
<td>6.4±4</td>
<td>5.3±3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRC</td>
<td>3.2±0.9</td>
<td>2.6±0.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Italics indicate significant p values (<0.05).

6MWT, 6 min walking test; CRDQ, Chronic Respiratory Disease Questionnaire; CRDQ_D, CRDQ Dyspnoea domain; CRDQ_E, CRDQ Emotional function domain; CRDQ_F, CRDQ Fatigue domain; CRDQ_M, CRDQ Mastery domain; HAD, Hospital Anxiety (A) and Depression (D) Scale; ISWT, Incremental Shuttle Walking Test; MRC, Medical Research Council Dyspnoea Scale; PR, Pulmonary rehabilitation.
were potential cases, and this difference was significant (p<0.001).

Improvement above HAD-D MCID threshold was noted in 37.2% of completers. Similar to the HAD-A results, patients were more breathless, according to MRC dyspnoea score (3.3±0.8 vs 3±0.9, p<0.001) and had worse baseline depression (8.3±3.7 vs 5.1±3.6, p<0.001), compared to the rest of completers. Age, sex, BMI, FEV1/predicted, FEV1/FVC ratio and exercise capacity prior to PR were similar between the two groups. Baseline HAD-D score was the only multivariate predictor of HAD-D MCID (OR=1.265; 95% CI 1.179 to 1.358, p<0.001). An analysis based on HAD-D symptom severity subscale was also conducted. Prior to PR 61.1% of patients were normal, 21.3% were borderline and the remaining 17.6% were potential cases. The corresponding percentages after PR completion were 74.5%, 16.9% and 8.6% and the differences were statistically significant (p<0.001).

**DISCUSSION**

This is a multicentre study in a large population of patients with COPD attending baseline assessment for PR, which aimed to identify whether baseline factors could predict completion of the programme and which patients would achieve the MCID for exercise and HRQoL in a clinical context. Participants who completed PR had less severe disease with HRQoL the only independent predictor, but it was those with the most severe disease who derived the greatest benefit. Improvement in different aspects following PR was generally measure-specific so no single baseline factor could predict improvement in exercise capacity as well as health status.

**PR completion**

The study identifies a paradox: those most likely to benefit from PR appear least likely to complete it. Approximately 57% of patients with COPD completed the programme consistent with previous UK data. Others have reported much higher rates of PR completion ranging from more than 80% to approximately 70%. Clinical practice differs from the controlled environment of clinical trials where patients have made a commitment to participation by signing a consent form, have fewer comorbidities and are usually under closer follow-up. Moreover, the definition of PR completion varies; in the current study completers attended at least 75% of sessions and returned for a follow-up visit, while other authors have used much lower thresholds to define PR completion, so results are not easily comparable.

The specific reasons for not completing PR were not systematically collected and, thus, could not be further analysed in the current study. Keating et al reported that being unwell, having major difficulties travelling to the PR centre, inconvenient running hours of the programme, family issues, work responsibilities, lack of social support and lack of perceived benefit were the most common reasons of dropping out from a PR programme in a small group of 18 patients with COPD. Identifying the barriers of PR attendance and completion in real-life PR settings is an area of further research, as resolving them could give the essential input for patients to complete the PR programme.

CAT score was the only independent predictor of PR completion, with completers having lower baseline CAT scores, indicating a better health status. The COPD assessment tool is a recently introduced questionnaire that responds to PR in COPD as well as non-COPD populations and takes less time to complete than other HRQoL questionnaires. The present data add to evidence of its utility as an assessment measure in PR. To the authors’ knowledge, this is the first time that CAT has been identified as an independent predictor of PR completion and this result needs to be further confirmed in large, prospective studies in the future.

Interestingly, HAD scores were not independent predictors of PR completion. In a cohort of 51 patients, Garrod et al have previously shown that depressed patients were in a significantly higher risk of drop-out compared to non-depressed patients. However, that study utilised the Brief Assessment Schedule Depression Cards and not the HAD-D score, in order to assess depression. In another cohort of 111 COPD outpatients enrolled in a community based programme, better mood independently predicted PR completion among female participants. In this study depression was assessed utilising another tool, the Epidemiologic Studies Depression Scale (CED-D). Several reliable, adult, self-report measures of depression, such as the PHQ-9, the Beck Depression Inventory (BDI), the Geriatric Depression Scale (GDS) and the CED-D, have been developed and used in research and in clinical practice, making the decision for the optimal measure to screen depression among patients with COPD rather difficult. Given the fact that the presence of depression is associated with poor adherence to treatment in COPD as well as in other chronic conditions, more studies are needed in order to identify the best tool when it comes to evaluating the impact of depression on PR completion.

**PR outcome measures**

There is a huge body of evidence demonstrating PR programmes that include supervised exercise training improve functional status, reduce symptom severity and improve HRQoL among patients with COPD and, as expected, these effects were seen in the present study. Since the programmes studied used a variety of tools for evaluation (all employed the CAT score and the vast majority of them the HADS) we used achievement of the accepted MCID as an outcome measure to allow exercise and HRQoL effects to be combined. A previous evaluation of PR programmes suggested that although the response to rehabilitation was good on average, some patients achieved little or no benefit. A further
study indicated that almost 30% of patients who entered a PR programme did not respond in terms of exercise capacity or health status, even though the mean impact of PR was beneficial.42

No single parameter was found to predict achievement of MCID for exercise and HRQoL. Poor exercise capacity prior to PR was the only independent predictor of clinically significant improvement in exercise capacity following completion of the programme. Some previous studies have failed to establish a significant association between baseline physical condition, lung function parameters and exercise MCID,2,35 43 which may have been due to insufficient sample size. Troosters et al16 reported that patients with reduced exercise capacity and reduced respiratory and peripheral muscle strength were more likely to improve after attendance at PR.

For the various HRQoL measures the achievement of the MCID was best predicted by a worse baseline value (CAT score, CRDQ-D, E, F). A higher MRC dyspnoea score at baseline also predicted improvement in CRDQ emotional function and fatigue domains and was the only predictor of improvement in CRDQ-M. In a previous study, Selzler et al2 failed to identify any predictor of improvement in HRQoL; however, this study utilised the SF-36 and the SGRQ. In another study, Garrod et al35 identified a higher baseline 6MWT as the only predictor of improvement in HRQoL, assessed by the use of SGRQ. No baseline physiological measurement has yet been shown to predict significant improvements in HRQoL.16 43

The greatest improvements in anxiety and depression were in those with the highest scores at baseline, which is understandable, as PR would not be expected to relieve a condition that was not present. PR is partly effective as a behavioural therapy, with graded exposure to dyspnoea and learning coping strategies similar to the sort of approaches applied in cognitive behavioural therapy.

METHODOLOGICAL ISSUES

The use of different outcome measures across the participating study sites is a limitation of the current study; however, it reflects the variability of baseline clinical assessment in real life PR settings. Moreover, PR outcomes were evaluated based on the MCID, an approach which minimises the variability of measures applied. A strength of the study is that it reflects clinical practice with a less selected population than is generally recruited to clinical trials and thus has greater relevance. Data were entered prospectively onto a clinical database and then anonymised by local staff before being collated centrally, meaning that source verification was not possible. It is unlikely that this would have introduced any systematic bias. The clinical data available were limited being based on those collected routinely as part of the various PR programmes, so other factors such as motivation, sociodemographic status and reasons for drop-out could not be considered. Moreover, some missing data on baseline evaluation of exercise capacity and/or HRQoL reduce somewhat the study sample size; however, this is a random phenomenon, unlikely to have produced any systematic bias.

CONCLUSION

The present study suggests that those with the worst health status may need additional support to continue to attend and complete PR programmes with possible strategies including support for transport and lay-support. Non-completion is an event rather than a permanent state and health practitioners should review reasons for non-completion with patients, reinforce the benefits, and encourage further participation as appropriate.

Contributors AKB and RJT contributed substantially in study design, data collection, analysis and interpretation and manuscript drafting. VML, LH, JN, HJ, EJC, CF, CL and RG contributed substantially in data collection and interpretation and critically corrected the manuscript draft. MIP and NSH contributed substantially in study conception and design, in data interpretation and critically corrected the manuscript draft. All authors approved the final version of the manuscript to be published.

Competing interests None.

Ethics approval Riverside Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES