Longitudinal change in ultrasound-derived rectus femoris cross-sectional area in COPD

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Ultrasound-derived rectus femoris cross-sectional area reduces over 12 months in people with COPD, but is not a useful surrogate measure for change in quadriceps strength, lower limb function or exercise capacity https://bit.ly/3TPmvsn

Cite this article as: Jenkins TO, Patel S, Edwards GD, *et al*. Longitudinal change in ultrasound-derived rectus femoris cross-sectional area in COPD. *ERJ Open Res* 2024; 10: 00123-2024 [DOI: 10.1183/23120541.00123-2024].

Received: 8 Feb 2024
Accepted: 27 March 2024

Abstract

Background Skeletal muscle dysfunction is common in COPD. Ultrasound-derived rectus femoris cross-sectional area (RFCSA) is a radiation free, non-invasive measure of muscle bulk that relates to quadriceps strength in people with COPD. However, there are limited longitudinal data for RFCSA, and it is not known whether longitudinal change in RFCSA reflects change in quadricep strength, exercise capacity, lower limb function or muscle mass. We aimed to quantify longitudinal change in ultrasound-derived RFCSA and assess its relationship with change in quadriceps maximal voluntary contraction (QMVC), incremental shuttle walk test (ISWT), five-repetition sit-to-stand (5STS) and fat-free mass (FFM) over 12 months in people with COPD.

Methods We measured ultrasound-derived RFCSA, QMVC, ISWT, 5STS and FFM (measured by bioelectric impedance analysis) at baseline and 12 months in 169 people with stable COPD. Change was correlated using Pearson's or Spearman's coefficients.

Results Baseline characteristics: mean±SD age 70.4±9.4 years; FEV_1 53.3±18.9% predicted. Over the course of 12 months mean RFCSA change was −33.7 mm^2 (99% CI −62.6– −4.9 mm^2; p=0.003) representing a mean±SD percentage change of −1.8±33.5%. There was a weak correlation between change in RFCSA and FFM (r=0.205, p=0.009), but not with change in QMVC, ISWT or 5STS.

Conclusion There is a statistically significant decrease in ultrasound-derived RFCSA over 12 months in people with stable COPD, but this decrease does not correlate with change in quadriceps strength, exercise capacity, FFM or lower limb function.

Introduction

Skeletal muscle dysfunction is common in COPD [1] and is associated with increased mortality and healthcare utilisation [2–4]. Skeletal muscle dysfunction is particularly prevalent in the lower limbs [5], and the quadriceps is one of the primary locomotor muscles. In COPD, quadriceps weakness is associated with reduced exercise tolerance [6], functional performance [7], quality of life [8] and physical activity [9], and can independently predict increased healthcare utilisation and mortality [2, 10].

Measurement of quadriceps muscle strength can be assessed by maximal voluntary contraction force, but this relies on maximum patient effort and motivation; 27% of patients perform quadriceps maximal voluntary contraction (QMVC) incorrectly in real-world practice [11]. Furthermore, measurement of QMVC force requires specialist, often cumbersome equipment such as a dedicated plinth or chair, which are not commonly available in most healthcare settings and difficult to use in clinical practice [12]. Although measurement of muscle strength is a core outcome for pulmonary rehabilitation, only 18.4% of services in the UK directly measure quadriceps strength [13].

Ultrasound imaging is a low-cost, non-invasive and non-ionising radiation method of measuring cross-sectional area of muscle and is becoming increasingly available in most clinical settings. Measurement of ultrasound-derived muscle cross-sectional area has been widely investigated in sarcopenia [14–16], intensive care [17, 18] and COPD [19]. Ultrasound-derived assessment of rectus femoris cross-sectional area (RFCSA) has been proposed as an attractive, effort-independent surrogate marker of quadriceps strength in COPD [20]. Previous studies have demonstrated that RFCSA correlates with QMVC and exercise capacity in patients with COPD [9, 21–26] and in critically ill patients [27] at a single time-point. To further validate ultrasound-derived RFCSA as a surrogate marker of quadriceps strength, longitudinal validity is important. However, there is a paucity of longitudinal data examining the natural course of RFCSA change in stable patients with COPD [22].

We conducted a longitudinal study to assess the relationship between ultrasound-derived RFCSA and quadriceps strength, exercise capacity, FFM and lower limb function over 12 months in patients with COPD. We hypothesised that longitudinal change in ultrasound-derived RFCSA would correlate with change in quadriceps strength over the same time period.

Materials and methods

Study participants

The current study was a planned secondary analysis of a prospective cohort study of people with chronic respiratory disease, approved by the London – Central Research Ethics Committee (13/LO/1161) and registered on ClinicalTrials.gov (NCT02261337). All participants provided informed written consent. The study was conducted according to the Declaration of Helsinki as most recently amended and Good Clinical Practice standards.

For this analysis, inclusion criteria were a physician diagnosis of stable COPD, based on the 2010 National Institute for Health and Clinical Excellence guidance on COPD [28], ability to provide written informed consent and agreement to attend two research visits 1 year apart. Exclusion criteria were significant comorbidities that would limit walking ability or measurement of QMVC (*e.g.* unstable ischaemic heart disease, neuromuscular disease, severe hip/lower limb joint pain or lower limb amputation), or the physician's expectation that that the participant would not be alive 1 year after recruitment (*e.g.* receiving specialist palliative care or presence of metastatic cancer).

Study procedures

Participants were assessed at baseline and 1 year later.

RFCSA was measured by B-mode ultrasonography using a Mindray DP-50 Ultrasound system (Mindray, Shenzhen, China). Imaging was conducted with the participant in a semirecumbent position with the leg rested in passive extension. Aquasonic ultrasonic transmission gel (Parker Laboratories, Fairfield, NJ, USA) was first applied to minimise soft tissue distortion. Ultrasound measurement was conducted on the dominant leg (same as the quadriceps strength measurements). The transducer was placed perpendicular to the long axis of the thigh on its anterior aspect, two-thirds of the distance from the anterior superior iliac spine to the superior patella border, similar to Seymour *et al*. [21]. Gentle contraction-relaxation techniques were employed to identify rectus femoris muscle borders. Scanning depth was adjusted to visualise the femur for orientation. A 5–10 MHz, 5.6 cm linear probe was used in the first instance for imaging; if the operator was unable to visualise the entire muscle due to increased size or excess adipose tissue, a 2–6 MHz curved abdominal probe was used. To ensure measurement reliability between baseline and 12 months, the same probe was used on both occasions. Distance from the anterior superior iliac spine and ultrasound probe used in the first visit was recorded for the repeat visit to maximise repeatability and reliability. Three images were taken, with removal and repositioning of the ultrasound probe between each. RFCSA was calculated using ImageJ (https://imagej.net) after the inner echogenic line of the rectus femoris was outlined by a movable cursor on a frozen image 3 times with measurements within 10% of each other. The average of these three separate RFCSA images was used for analysis.

Quadriceps strength was measured on the dominant leg using QMVC, as previously described [29]. Briefly, participants were seated in a chair with an inextensible strap placed around the ankle connected to a strain gauge, and performed six maximal isometric contractions maintained for 3 s with the knee joint at 90°, with the peak value recorded. If measured strength continued to increase, then additional measurements were performed until fatigue [29]. Data were recorded and analysed using LabChart 7 (ADInstruments, Oxford, UK). QMVC was adjusted for height and QMVC % predicted was calculated using the method described by Seymour *et al*. [21].

FFM, a surrogate marker of muscle mass, was determined using bioelectrical impedance analysis (Bodystat 1500; Bodystat, Douglas, Isle of Man). Participants were advised to do no strenuous exercise for 12 h prior to the test and avoid excessive alcohol consumption for 24 h before the test. Participants were advised to be "normally hydrated" and asked to empty their bladder before the test. When possible, tests were repeated at the same time of day at baseline and 12 months. A disease-specific regression equation was then used to calculate FFM [30]. FFM index (FFMI) was calculated by dividing FFM by height squared.

Lower limb functional capacity was measured using the five-repetition sit-to-stand (5STS) test as previously described [31], where a decreased time is associated with improved function, whilst exercise capacity was measured using the incremental shuttle walk test (ISWT) according to international technical standards [32]. Clinical information recorded at the 12-month follow-up included number of exacerbations in the last year, which was stratified into infrequent exacerbation history (0 or 1 exacerbations not leading to hospital admission) or frequent exacerbation history ($\geqslant$2 exacerbations or $\geqslant$1 exacerbations leading to hospital admission) [33].

Sample size

To demonstrate a weak correlation (r>0.3) between change in RFCSA and change in QMVC with 90% power at the 1% significance level required 158 participants. To account for 35% missing data or dropout, we aimed to include a minimum of 244 consecutive participants from the study cohort.

Statistical analysis

Data were tested for normality using Kolmogorov–Smirnov and Shapiro–Wilk tests. Baseline characteristics were reported using descriptive statistics and presented as mean with standard deviation. The relationship between RFCSA and outcome measures at baseline and 12 months was measured using Pearson's product-moment correlation (Spearman's rank correlation coefficient for non-parametric data). For this, a two-tailed level of p<0.01 was considered statistically significant to adjust for multiple correlation comparisons. A paired t-test was used to compare differences between paired outcome measures at baseline and 12 months. Univariate regression was used to assess the association between RFCSA change and plausible confounding variables based on previous evidence and expert opinion, including age, sex, body mass index (BMI), Medical Research Council (MRC) dyspnoea scale, smoker at baseline, ISWT at baseline, FFM, FFMI and exacerbation history or attending pulmonary rehabilitation during follow-up. A forced entry multivariate regression analysis used all the variables in the univariate analysis. Statistical analyses were performed using SPSS version 29.0.1.0 for Windows (IBM, Armonk, NY, USA).

Results

Recruitment

The flow of participants is presented in figure 1. 393 of the original cohort had an established diagnosis of COPD, with 240 attending both baseline and 1-year research assessments. Of these, 169 participants had both QMVC and RFCSA measured at both research visits.

Baseline

Baseline characteristics are presented in table 1. There were moderate strength correlations between RFCSA and measures of quadriceps strength and muscle mass (QMVC: r=0.508; FFM: r=0.523). However, the association between RFCSA and measures of walking exercise capacity and lower limb function were weaker (ISWT: r=0.329; 5STS: r= −0.261) (table 2).

Change in outcome measures over 12 months

Over the course of 12 months mean±SD RFCSA fell significantly from 521.3±197.5 to 487.6±174.3 mm^2 (mean change was −33.7 mm^2 (99% CI −62.6– −4.9 mm^2) (table 3). The changes in all outcomes over 12 months are shown in table 3, whilst figure 2 illustrates percentage change in RFCSA, QMVC, 5STS, ISWT and FFM over 12 months.

Change in RFCSA did not correlate with change in QMVC, 5STS or ISWT over 12 months. There was a weak correlation between change in RFCSA and change in FFM (r=0.205, p=0.009).

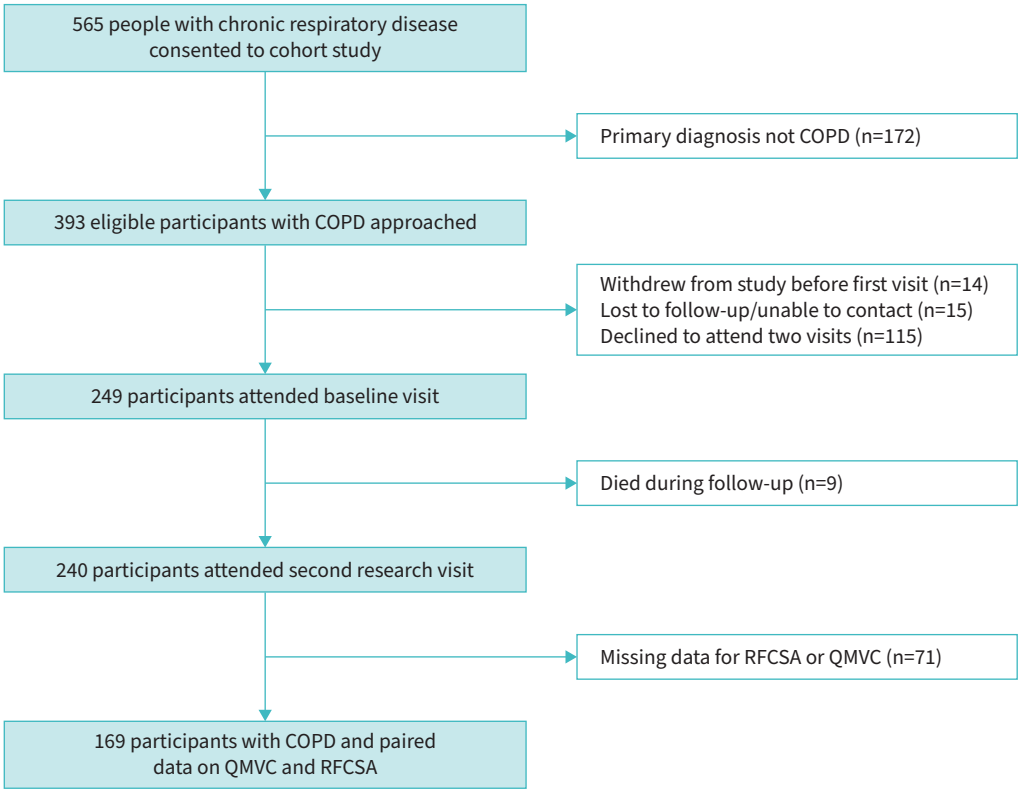

FIGURE 1 Flow of participants. RFCSA: rectus femoris cross-sectional area; QMVC: quadriceps maximal voluntary contraction.

Predictors of RFCSA change

Univariate and multivariate regression analyses found baseline age, sex, BMI, MRC dyspnoea scale, smoker, ISWT distance, FFM and FFMI did not predict change in RFCSA over 1 year, nor did exacerbation history or completion of pulmonary rehabilitation during follow-up (table 4).

TABLE 1 Baseline characteristics (n=169)

Male	90 (53.0)
Age (years)	70.4±9.4
BMI (kg·m^{-2})	27.9±6.0
FEV_1 (% pred)	53.3±18.9
FEV_1/FVC ratio	0.48±0.1
Current smoker	21 (12.4)
Smoking history (pack-years)	44.1±40.7
MRC dyspnoea score	3±1
RFCSA (mm^2)	521.3±197.5
QMVC (kg)	31.1±12.9
QMVC/height (kg·m^{-1})	18.6±7.3
QMVC (% pred)	75.2±25.6
ISWT (m)	330.2±177.6
5STS (s)	11.7±4.7
FFM (kg)	45.8±9.4
FFMI (kg·m^{-2})	16.7±2.4

Data are presented as n (%) or mean±SD. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; MRC: Medical Research Council; RFCSA: rectus femoris cross-sectional area; QMVC: quadriceps maximal voluntary contraction; ISWT: incremental shuttle walk test; 5STS: five-repetition sit-to-stand; FFM: fat-free mass; FFMI: fat-free mass index.

TABLE 2 Relationship (r-value[#]) between rectus femoris cross-sectional area and outcomes at baseline (n=169)

	r-value (99% CI)	p-value
QMVC (kg)	0.508 (0.328–0.652)	<0.001
QMVC/height (kg·m^{-1})	0.491 (0.308–0.639)	<0.001
QMVC (% pred)	0.300 (0.090–0.484)	<0.001
ISWT (m)	0.329 (0.133–0.500)	0.005
5STS (s)	−0.261 (−0.443– −0.058)	<0.001
FFM (kg)	0.523 (0.363–0.653)	<0.001
FFMI (kg·m^{-2})	0.441 (0.266–0.587)	<0.001

QMVC: quadriceps maximal voluntary contraction; ISWT: incremental shuttle walk test; 5STS: five-repetition sit-to-stand; FFM: fat-free mass; FFMI: fat-free mass index. [#]: Pearson's product-moment correlation (Spearman's rank correlation coefficient for non-parametric data).

Discussion

The main finding from this study is that ultrasound-derived RFCSA change does not reflect changes in quadriceps muscle strength, walking exercise capacity or lower limb functional performance over 12 months in individuals with COPD. This raises questions about the utility of RFCSA as a surrogate marker of quadriceps strength or lower limb performance in COPD.

Previous studies

Previous cross-sectional studies have shown that ultrasound-derived RFCSA correlates with QMVC in patients with COPD [9, 21, 22, 24], and this has led to proposals that ultrasound-derived RFCSA may be a useful surrogate measure of quadriceps strength. The technique has several advantages, including the non-invasive and painless nature, as well as not relying on patient motivation or effort. Therefore, it is particularly suitable in those unable to perform maximum volitional manoeuvres (*e.g.* in the intensive care setting) [18]. Demonstration of the longitudinal validity of RFCSA would provide further evidence to support a role as a surrogate measure of lower limb muscle strength or function. However, the only existing study exploring longitudinal validity in patients with COPD was conducted in a small cohort of patients; Buttery *et al.* [22] measured RFCSA over 3 years in 31 patients with COPD. RFCSA declined by a mean±SD of −154±245 mm^2 (95% CI −181– −99.8 mm^2) over 3 years, an annual rate of change similar to that observed in our study. The authors found no longitudinal correlation between RFCSA change and change in QMVC or exercise capacity measured by the 6-min walk test [22].

Other studies specifically measuring longitudinal change in RFCSA and QMVC in disease have investigated the relationship during a specific strengthening intervention or in critically ill patients, both over a short follow-up period. Menon *et al.* [23] measured RFCSA and QMVC before and after an 8-week resistance training programme in 45 patients with COPD and 19 healthy controls, and found no correlation between increase in RFCSA and increase in QMVC. In critically ill patients, Connolly *et al.* [18]

TABLE 3 Muscle, strength, exercise capacity and respiratory outcomes at baseline and 12-month follow-up

	Baseline	12 months	Absolute change	Percentage change	Absolute change 99% CI (p-value)
FEV_1 (% pred)	53.3±18.9	55.0±21.4	1.8±10.5	3.7±20.9	−0.53–4.04 (0.47)
RFCSA (mm^2)	521.3±197.5	487.6±174.3	−33.7±144.0	−1.8±33.5	−62.6– −4.9 (0.003)
QMVC (kg)	31.10±12.9	31.1±13.6	0.006±6.9	1.6±25.5	−1.6–1.6 (0.99)
QMVC/height (kg·m^{-1})	18.6±7.3	18.6±7.7	0.01±4.1	1.9±25.3	−0.93–0.95 (0.97)
QMVC (% pred)	62.3±22.2	62.2±23.3	−0.1±13.8	2.2±25.6	−4.2–4.1 (0.97)
ISWT (m)	330.2±177.6	299.8±168.4	−30.3±81.4	−8.1±34.5	−48.8– −10.7 (<0.001)
5STS time (s)	11.7±4.7	12.8±8.8	1.1±7.9	12.3±61.6	−0.55–2.8 (0.079)
FFM (kg)	45.6±9.4	46.0±9.6	0.45±2.8	1.1±6.1	−0.13–1.02 (0.066)
FFMI (kg·m^{-2})	16.6±2.4	16.8±2.4	0.15±1.0	1.1±6.1	−0.06–0.36 (0.97)

Data are presented as mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; RFCSA: rectus femoris cross-sectional area; QMVC: quadriceps maximal voluntary contraction; ISWT: incremental shuttle walk test; 5STS: five-repetition sit-to-stand; FFM: fat-free mass; FFMI: fat-free mass index.

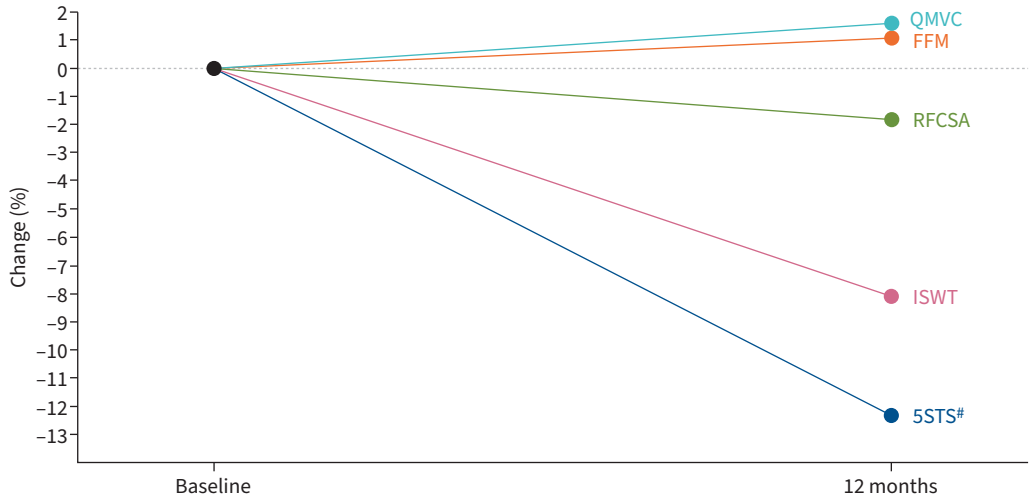

FIGURE 2 Mean percentage change in rectus femoris cross-sectional area (RFCSA), quadriceps maximal voluntary contraction (QMVC), fat-free mass (FFM), five-repetition sit-to-stand (5STS) time and incremental shuttle walk test (ISWT) time over 12 months. #: an increase in 5STS is associated with deterioration of lower limb function; the percentage change of 5STS has been inverted to demonstrate this negative change and its relationship to ISWT, RFCSA, FFM and QMVC.

demonstrated significant reductions in tibialis anterior cross-sectional area as measured by ultrasound but no changes in non-volitional strength when measured longitudinally over 7 days. Conversely, in health, data shows a weak correlation between increase in RFCSA and strength after a 24-week strengthening programme [34]. The weak correlation between RFCSA and FFM change in our data is similar to findings from Buttery *et al.* [22] who found a correlation coefficient of r=0.22. Longitudinal decline in FFM in patients with COPD is more pronounced in the lower limbs, which may explain these findings [35].

Significance of the findings

Despite previous cross-sectional studies showing moderate to strong correlations between RFCSA and QMVC, we have demonstrated in a prospective longitudinal study that change in RFCSA does not reflect change in QMVC, sit-to-stand performance or walking exercise capacity. There are several reasons that could explain the findings.

TABLE 4 Univariate and multivariate regression analyses to predict rectus femoris cross-sectional area change

	Univariate analysis		Multivariate analysis	
	Regression (β) coefficient (99% CI)	p-value	Regression (β) coefficient (99% CI)	p-value
Age (years)	−0.25 (−3.34–2.85)	0.836	−0.40 (−4.22–3.43)	0.787
Sex (male or female)	−36.88 (−94.4–20.67)	0.097	19.85 (−104.44–144.14)	0.677
BMI (kg·m^{-2})	−2.19 (−7.03–2.65)	0.24	2.43 (−7.39–12.26)	0.519
MRC dyspnoea score	6.43 (−20.5–33.3)	0.534	6.89 (−29.97–43.75)	0.055
Smoker at baseline	42.11 (−45.25–129.47)	0.211	62.79 (−34.85–160.43)	0.161
ISWT (m)	−0.075 (−0.24–0.095)	0.253	−0.13 (−0.37–0.12)	0.180
FFM (kg)	15.40 (−13.43–44.23)	0.166	−3.0 (−16.47–10.48)	0.562
FFMI (kg·m^{-2})	−9.49 (−34.46–15.49)	0.324	1.25 (−10.51–13.0)	0.087
Follow-up events				
Pulmonary rehabilitation course during follow-up	13.67 (−44.34–71.69)	0.540	21.45 (−50.12–93.01)	0.435
Exacerbation history during follow-up (GOLD ABCD tool)	−18.15 (−78.24–41.94)	0.432	−19.62 (−87.04–47.80)	0.448

BMI: body mass index; MRC: Medical Research Council; ISWT: incremental shuttle walk test; FFM: fat-free mass; FFMI: fat-free mass index; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

RFCSA reflects muscle size but not quality, and therefore a discordance between muscle size and function has been observed in previous studies [18, 22, 23]. RFCSA also reflects the size of the rectus femoris, which is only one of four muscles that constitute the quadriceps femoris, and therefore performance of QMVC and exercise performance. Also, inhomogeneous hypertrophy of quadriceps muscle compartments has been observed during intervention studies [36]. Whilst measurement of RFCSA using ultrasound correlates significantly with that measured by computed tomography (CT) in patients with COPD, the relationship between ultrasound-derived RFCSA and CT-derived total quadriceps cross-sectional area is much weaker [21]. Over time, other factors may have a heterogeneous impact on the lower limb variables, *e.g.* one would expect that deteriorating lung function may have a much greater impact on functional and exercise capacity levels than RFCSA.

Strengths and limitations

This is the largest study to prospectively examine the longitudinal change in RFCSA in people with COPD, with five-fold the number of participants in previous studies [22]. The study was designed to be adequately powered to detect even a weak correlation between RFCSA and quadriceps strength. Participants also had a detailed longitudinal evaluation of other relevant lower limb measures including quadriceps strength, lower limb function and exercise capacity. However, a weakness is that we did not use other imaging modalities such as CT, dual X-ray energy absorptiometry (DXA) or magnetic resonance imaging (MRI) due to ionising radiation or cost concerns. Despite this, ultrasound-derived RFCSA correlates well with CT-derived RFCSA in patients with COPD (intraclass coefficient r=0.88) [21] and in other disease [37]. In health, ultrasound-derived cross-sectional muscle area of the rectus femoris and the tibialis muscles highly correlates with that of MRI-derived cross-sectional area at a single time-point [38, 39]. Ultrasound-derived RFCSA has high levels of agreement against MRI-derived RFCSA in detecting cross-sectional area change after a 21-week strength training programme in healthy subjects [40]. DXA correlates well with ultrasound-derived RFCSA (r=0.68), but one major limitation of DXA is its lack of ability to assess specific muscles [23].

Future research using CT or MRI imaging to measure muscle mass could unequivocally confirm if there is a relationship between longitudinal change in muscle mass and measures of strength, lower limb function and exercise capacity in stable patients with COPD, but concerns regarding ionising radiation and cost could make studies of this nature unfeasible. Whilst echogenicity may have provided further information on muscle quality in this study [25, 41, 42], due to the variable reproducibility of echogenicity in the published literature [43, 44], we choose not to use this measure. Due to researcher availability over a longitudinal study, paired measurements at baseline and 12 months were conducted by the same researcher in 71% of participants, so some of the variance may be related to interrater variability. Although we did not measure RFCSA interrater agreement in our study, previous studies suggest interrater reliability of RFCSA is high [21, 23, 45, 46]; Seymour *et al.* [21] and Puthucheary *et al.* [45] found the mean±SD bias and 95% limits of agreement were 2±32 mm^2 and −61 to +65 mm^2 and 7±37 mm^2 and −66.1 to +80.5 mm^2, respectively, for interrater agreement of RFCSA measurement, Menon *et al.* [23] found inter-operator mean±SD differences in measured RFCSA of 8.73±25.39 and 5.90±15.01 mm^2 when comparing one primary operator to two others. To minimise inter-operator variability in our study, the same independent investigator performed all offline RFCSA calculations. Our cohort had largely stable disease and therefore the changes in RFCSA and other lower limb measures were relatively modest; our results cannot be extrapolated to other settings where more dramatic acute changes in RFCSA might be expected, *e.g.* in the acute hospitalisation setting [47] or in the intensive care setting [18]. We did not have an age-matched healthy control group so we cannot comment on the clinical significance of the observed RFCSA change over time and whether this is line with health ageing.

Conclusions

This study offers further insight into longitudinal change in RFCSA in stable COPD. Whilst RFCSA reduces significantly over 12 months, it does not correlate with change in quadriceps strength, exercise capacity nor lower limb function functional performance. Although ultrasound-derived assessment RFCSA may be an attractive, easy to access measure in both research and practice, our data suggest that RFCSA change is not a useful surrogate measure for longitudinal change in quadriceps strength, exercise capacity or lower limb function in stable COPD.

Provenance: Submitted article, peer reviewed.

Acknowledgements: The authors gratefully acknowledge the patients for agreeing to participate in the study.

This study is registered at ClinicalTrials.gov with identifier number NCT02261337.

Ethics statement: The current study was a planned secondary analysis of a prospective cohort study of people with chronic respiratory disease, approved by the London – Central Research Ethics Committee (13/LO/1161). All participants provided informed written consent.

Conflict of interest: T.O. Jenkins reports grants from the Royal Brompton and Harefield Hospital Charity, outside of the submitted work. T.O. Jenkins received funding from the National Institute for Health Research to undertake the submitted work. C.M. Nolan reports grants from the National Institute for Health and Care Research, Royal Brompton and Harefield Hospital Charities, and Brunel University London, outside of the submitted work. M. Maddocks reports grants from the National Institute for Health Research, the European Commission and UKRI Innovate UK, outside of the submitted work. M. Maddocks received funding from the National Institute for Health Research to undertake the submitted work. W.D-C. Man reports grants from the National Institute for Health Research, outside of the submitted work. W.D-C. Man received funding from the Medical Research Council to undertake the submitted work. W-D.C. Man is an Associate Editor of this journal. The remaining authors report no grants outside of the submitted work, or to undertake the submitted work.

Support statement: This cohort study was funded by a Medical Research Council (UK) New Investigator Research Grant (G1002113) awarded to W.D-C. Man. M. Maddocks is part funded by the National Institute for Health and Care Research (NIHR) Applied Research Collaboration South London. T.O. Jenkins is funded by a Health Education England and NIHR ICA Predoctoral Clinical and Practitioner Academic Fellowship. The views expressed in this publication are those of the author and not necessarily those of the CSC, NHS, NIHR or the Department of Health and Social Care.

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