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Longitudinal follow-up of quadriceps strength and function in Chronic Obstructive Pulmonary Disease cohort after 3 years

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To the Editor:

Skeletal muscle weakness is a distinct extra-pulmonary manifestation of chronic obstructive pulmonary disease (COPD), associated with a poor prognosis (1) which may represent a novel therapeutic target (2). However, there exists sparse longitudinal data from prospective studies on skeletal muscle weakness and its relationship with disease progression in COPD. Previous studies have been cross-sectional in nature, and have failed to correlate data with baseline measures of exercise performance or systemic inflammation.

ERICA, (Evaluation of the Role of Inflammation in Chronic airways disease) is a multicentre prospective study in which quadriceps maximal voluntary contraction force (QMVC) was assessed in addition to other measures to provide a detailed evaluation of the extra-pulmonary manifestations of COPD.(4). Following ethical approval (NRES Harrow: **11/LO/1636**) at a single site, a subset of these patients underwent a more detailed evaluation with the aim of relating fibre type to phenotypic parameters (ClinicalTrials.gov number [NCT01471587](https://clinicaltrials.gov/ct2/show/study/NCT01471587)); the primary result has been presented elsewhere (5); here we present follow up data for the clinical parameters over a 3 year period.

Briefly 61 subjects were studied at baseline; key inclusion criteria were a clinical diagnosis of COPD confirmed by post-bronchodilator spirometry (FEV_1/FVC ratio <70% and FEV_1 <80% predicted) and >10 pack year smoking history. Patients with a history of exacerbation within 4 weeks of screening, other respiratory diagnoses or exercise-limiting musculoskeletal or neurological disease were excluded. After 3 years, participants were invited for follow up where baseline assessments were repeated. Key assessments included demographics,

anthropometrics, body composition as bioimpedance, post-bronchodilator spirometry and maximal sniff nasal inspiratory pressure (SNIP), physical activity (Sensewear Armband), short physical performance battery (SPPB), 6 minute walk test (6MWT), aortic pulse wave velocity (aPWV), quadriceps maximal voluntary contraction (QMVC), ultrasound determined rectus femoris muscle cross sectional area(RF_{CSA}), systemic inflammatory markers (fibrinogen, white cell count (WCC) and high sensitivity C-reactive protein (hsCRP) and health-related quality of life questionnaires. Mean change, between baseline and follow up, and rate of change per year were calculated and analysed using paired T-testing. Graphpad Prism version 5 was used for statistical analysis and significance was accepted as <0.05.

31 participants (61% male) returned for follow up; values are expressed as mean(SD) (Table 1). Reasons for not returning were; declined follow up for personal reasons (12, 20%), death, (10, 16%), inability to attend the study centre due to deterioration in COPD (6, 10%), lung transplant surgery (1, 1%) and being uncontactable (1, 1%). Non-returning participants were more nutritionally depleted judged by both BMI (p=0.002) and FFMI (p=0.03) and tended to poorer lung function at baseline judged my FEV_{1%} predicted (p=0.08)

At baseline the restudied subjects were aged 67 (8) years, with a 52 (40) pack year smoking history, FEV₁ 47.0 (20.2) % predicted, and Medical Research Council dyspnea (MRC) score 2.8 (1.3). 4 participants were current smokers at baseline; of these, 2 were still smoking at the time of follow up assessment.

Statistically significant decline was observed in both QMVC (-1.48 kg per year; 95% CI- 7.19 to -2.90, p =<0.0001), RF_{CSA} (-42.2 mm² per year; 95% CI-181 to -99.8, p =>0.0001) and fat

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3 free mass (FFM) (-0.58kg per year ; 95% CI -3.08 to -0.53, p=0.007) over three years without
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5 change in BMI. There was no relationship between QMVC change over time and gender
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7 (r=0.03, p=0.34) and a linear regression showed no correlation between co-morbidities
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9 (r=0.32, p=0.9) corticosteroid treatment (r=0.04, p=0.8), frequent exacerbations (r=0.045,
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11 p=0.9), or hospital admission (r=0.009, p=0.96) and QMVC decline. The magnitude of
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13 change is consistent with our earlier study (3) which found a reduction in quadriceps
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15 strength in COPD patients of 1.5kg over one year. The changes in FFM may be explained by
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17 skeletal muscle loss which is well documented in COPD and consistent with the observed
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19 decline in both QMVC and RF_{CSA} changes. Although there was no correlation between
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21 change in RF_{CSA} and QMVC there was a correlation between change in FFM and change in
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23 RF_{CSA} (r= 0.22p=0.007).
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32 As well as loss of skeletal muscle mass we also observed a significant decline in performance
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34 measures over 3 years. In particular the change in 6MWD showed a linear relationship with
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36 change in QMVC (r=0.52; p=0.003) but not with change in RF_{CSA} (r=0.27; p=0.19), with a
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38 similar order of magnitude to that previously reported in the ECLIPSE cohort, and which
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40 over three years exceeded the MCID (5). Similarly the SPPB significantly decreased from
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42 baseline to follow up; of the three individual components, the sit to stand test showed the
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44 greatest (and only statistically significant) contribution to this decline; this is consistent with
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46 the data of Bernabeu-Mora *et al* (6) which suggested that only the five-repetition sit to
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48 stand test sub component of the SPPB was a discriminative measure of self-reported
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50 mobility limitation. This is of importance as the European medical agency has recently
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52 indicated a favourable opinion for the SPPB as an endpoint in clinical trials for sarcopenia,
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54 yet little is known about how SPPB scores change over time in COPD. We acknowledge that
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a weakness of the current study is that we did not study healthy age matched controls. However available data suggest that progression in SPPB in our cohort (0.45 points/year) is faster than is reported in healthy seniors (0.1.-0.3 points/year) (7).

Our study failed to replicate the earlier finding of Bernabeu-Mora (6) and ourselves (8) of correlation between SPPB scores and quadriceps strength and we also observed no correlation between change in RF_{CSA} and individual components of SPPB. Several reasons could explain this including that our cohort was highly functioning at baseline (SPPB>10), giving a limited spread of SPPB values, as well as the small sample size. However we note that the annualised change observed in sit to stand test exceeded the time (1.7s) which we have previously established as the MCID for this test in COPD (9). Thus SPPB, or its sit to stand component, represents a relatively simple clinical outcome measure that can identify patients at risk of muscle weakness can be used as a tool in inpatient and outpatient environments without the need for specialist equipment or personnel, and which can detect change in a relatively small cohort.

In summary, our data, despite its small sample size and likely differential subject drop-outs, shows that a measurable decline in quadriceps strength and mass is observed over three years in patients with COPD, which in the case of QMVC correlates with clinically relevant changes in 6MWT and SPPB; consistent with this, change in SPPB was principally driven by the chair-stand element which we have previously shown to be related to quadriceps strength (10). Given the known predictive power of the SPPB for functional decline, hospitalisation and mortality (8), our data suggest that skeletal muscle dysfunction is an

appropriate target for intervention in COPD and that SPPB can be a useful endpoint in clinical trials assessing impact on skeletal muscle dysfunction.

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Figure 1: Pie chart showing the reasons for subjects declining follow up at 3 years.

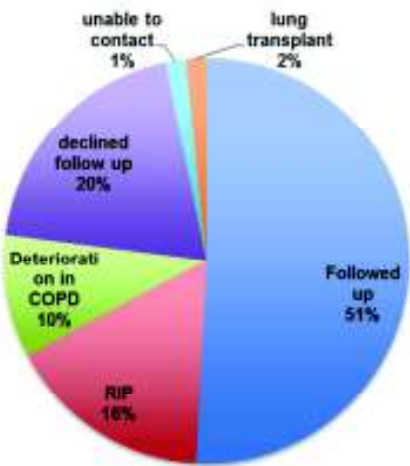


Table 1 Clinical characteristics at baseline and follow-up (n = 31)

	Baseline-not followed up (n=30)	Baseline-returning (n=31)	Follow up at 3 years (n=31)	Change: baseline to follow up	Change per year	95% confidence interval (based on change from Baseline to Follow up)	P value
Demographics							
Age (years)	65(9)	67(8)	70(8)				
Gender (%male)	77.3	61.3	61.3				
% current smokers	10.0	12.9	6.5				
Smoking history (pack years)	40(20)	52(40)	52(40)				
MRC dyspnoea score (of 5)	3 (1.4)	3(1.1)	3(1.3)	-0.16(1.24)	-0.05	-0.55 to 0.28	0.5
BMI (kg/m ²)	*22.6 (4.7)	26.7(5.1)	26.7(6.0)	-0.01(1.66)	0.00	-0.62 to 0.60	0.1
Respiratory Measurements							
FEV ₁ (%predicted)	38.3(17.5)	47.0(20.2)	42.8(21.5)	-5.56(15.0)	-1.62	-5.81 to -0.54	0.02
FEV ₁ /FVC ratio	0.34(0.14)	0.38(0.16)	0.40(0.16)	0.01(0.16)	0.00	-0.01 to 0.07	0.1
Exacerbations (per year)	2.1(2.4)	1.8(2.0)	2.1(2.2)	0.26(2.85)	0.07	-0.82 to 1.35	0.6
Muscle Indices							
6MWD(m)	408(116)	399(132)	325(172)	-71.7(162)	-16.8	-119 to -27.4	0.003
SPPB total score (of 12)	10(1.9)	11(1.4)	9(3.0)	-1.42(2.99)	-0.45	-2.70 to -0.40	0.01
Balance score (of 4)	4.0(0.4)	4.0(0.2)	3.7(1.0)	-0.39(1.21)	-0.1	-0.84 to 0.06	0.09
Gait speed score (of 4)	3.8(0.4)	3.8(0.5)	3.4(1.1)	-0.39(1.09)	-0.1	-0.79 to 0.01	0.06
4m gait speed time (s)	4.2(0.8)	4.2(0.9)	4.3(1.5)	-0.03(1.59)	-0.1	-0.64 to 0.45	0.7
Chair stand score (of 4)	*2.6(1.4)	3.1(1.0)	2.3(1.3)	-0.87(1.31)	-0.3	-1.35 to -0.39	0.0009

Chair stand time (s)	*16.1(13.3)	13.8(9.4)	19.3(14.7)	5.46(15.8)	1.6	0.47 to 13.1	0.05
FFM (kg)	*46.8(9.1)	52.1 (9.8)	50.3 (11.4)	-1.80(3.47)	-0.58	-3.08 to -0.53	<0.01
FFMI	14.3(3.4)42.3(5.6)	16.3(2.2)	16.3(3.2)	0.06(1.66)	0.02	-0.54 to 0.67	0.8
QMVC (kg)	28.8(9.5)	32.6(8.0)	27.2 (9.0)	-5.20(11.2)	-1.48	-7.19 to -2.90	<0.0001
QMVC (%predicted)	68.8(29.7)	72.7(16.7)	64.8 (18.8)	-7.39(12.9)	-2.20	-12.3 to -2.50	<0.01
RF(CSA)mm ²	516(184)	603(136)	449(126)	-154(245)	-42.2	-181 to -99.8	<0.0001
SNIP	56.0(19.2)	53.7(24.2)	60.6(19.2)	4.6(20.1)	1.94	-2.760 to 11.99	0.2
Cardiovascular Indices							
Systolic BP (mm Hg)	132(14.2)	140(16.3)	136(16.3)	-3.97(19.3)	-1.39	-11.1 to 3.12	0.7
APWV (m/s)	10.6(3.5)	10.7 (2.7)	10.3 (2.7)	-2.35(5.63)	-0.66	-1.44 to 0.96	0.7
Inflammatory Markers							
Fibrinogen (g/dL)	3.8(0.9)	3.4(0.7)	3.8(0.8)	0.35(0.51)	0.11	0.16 to 0.54	<0.001
WCC (x10 ⁹ /L)	7.2(1.7)	8.0(2.9)	7.9(2.3)	-0.10(2.62)	0.02	-10.5 to 4.66	0.4
hsCRP (mg/L)	9.8(16.3)	11.4(22.5)	8.1(19.6)	-13.1(22.1)	-4.02	-0.86 to 1.06	0.8

Table 1: baseline, follow up and change per year data.

Values expressed as mean (standard deviation) unless otherwise stated.

Abbreviations: **MRC:** medical research council; **BMI:** body mass index; **FEV₁:** forced expiratory volume in 1 second; **FVC:** forced vital capacity; **6MWD:** 6 Minute Walk Distance; **SPPB:** Short Physical Performance Battery; **FFM:** Fat Free Mass; **QMVC:** Quadriceps Maximal Voluntary Contraction; **RF (CSA):** Rectus Femoris (cross -sectional area); **SNIP:** maximal sniff nasal inspiratory pressure; **aPWV:** aortic pulse wave velocity; **APWV:** Aortic Pulse Wave Velocity; **WCC:** white cell count; **CRP:** C-reactive protein

*=baseline measure differed significantly between returning cohort and non-followed up cohort.

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