# Supplementary Material

## Participants

The Healthy adult control (HC) group and the COPD-PC were participants in the Physical Activity and Respiratory Health (PhARaoH) Study in which healthy adults were recruited through community advertisement and patients with COPD through primary care clinics located in Leicestershire, UK[1]. The following inclusion criteria for the HC group were used for analysis; $FEV_1$> 80% predicted, $FEV_1$/FVC ratio >0.7, mMRC <2, age ≤40. Patients were included if they had a physician diagnosis of COPD that was confirmed by spirometric testing at baseline using established guidelines[2].

The COPD-CC was recruited from a Leicestershire based hospital complex COPD service designed for patients with advanced COPD. Referrals were from General Practitioners and other respiratory specialists as previously described[3]. The two studies from which participants for this study are drawn had relevant ethical approval (13-EM-0389, 13/EM/0287).

## Measurements

In all three groups height was measured using a stadiometer to the nearest 0.01 metre (m) and weight using digital weighing scales to the nearest kilogram (kg). Body Mass Index (BMI($kg/m^2$)) was then derived from these measures (weight(kg)/height($m)^2$). In the HC group and the COPD-PC body composition was measured using Bio-electrical impedance analysis (BIA) (Tanita MC780MA). Body composition was measured by Dual energy x-ray absorptiometry (DEXA) (LUNAR DEXA scanner) in the COPD-CC. Fat-free mass (FFM) was then calculated using the established method of the sum of lean mass and bone mineral content[4]. All participants underwent spirometry and measurements are expressed as a percentage of reference values[5].

**QMVC measurement**

The methodology for QMVC measurement was consistent across the cohorts[6]. Measurements were performed with participants seated, knees bent at a 90° angle, with the torso secured with adjustable belts. The dynamometer was attached to the lower leg just above the level of the malleoli ensuring a straight vector. Participants were encouraged to push out the lower leg and exert maximal effort for six seconds. The best reading from the dominant leg following at least 3 attempts was recorded (in kg).

**Statistical Analysis**

The prediction equations were derived within the HC group using multiple linear regression with bootstrapping of 1000 samples. Forced entry method was used for the model without fat-free mass (FFM-). Age, gender, weight and height were entered initially as they are theoretically implicated and previous relationships have been found[7, 8]. A hierarchical approach was then used for the second model (FFM+) with fat-free mass entered first followed by age and gender and then weight and height. This order was chosen to prioritise the inclusion of fat-free mass. Only variables that reached significance ($p \leq 0.05$) were retained in the models. Weight and height were removed from the second model due to collinearity and non-significance. The distribution of residual values was assessed for normality and models checked for absence of multicollinearity and heteroscedasticity. There was one extreme outlier (>3 standard deviations above mean QMVC) which skewed the distribution of the residuals so was removed from further analyses. The linearity of relationships was also assessed and established. Only complete cases were entered in the analyses.

The prediction equations were used to classify weakness in each of the cohorts using a threshold of the lower limit of normal (LLN) corresponding to the threshold above which 95% of the healthy cohort lie. This equates to a standardised residual below -1.645 using the

prediction equations and the standard error of the estimate (SEE) for the healthy cohort. The standardised residual for an individual was calculated as:

**(Measured QMVC-Predicted QMVC)/standard error of the estimate (SEE)***

*SEE from HC

Participants with QMVC values below this would therefore be classified as having quadriceps weakness.

A sub-analysis was performed to calculate the percent predictions and the number classified as weak for each model in those within the COPD-CC without a low fat-free mass index ($FFM/height^2$)[10]. The results of this are shown in Table S2.

Differences in baseline characteristics between the HC and COPD cohorts, and between the standardised residuals of the models within the cohorts, were analysed using independent t-tests, or Mann-Whitney U tests if parametric assumptions were not met. All analyses were performed using SPSS (version 22). The TRIPOD checklist for developing prediction models was used to check the methodology and reporting[9].

**Table S1: Baseline characteristics of the Healthy Control, Primary Care COPD and Complex Care COPD cohorts**

| | HC | Primary Care COPD | Complex Care COPD |
|---|---|---|---|
| n | 175 | 112 | 189 |
| Age (yrs) | 54 (14) | 68 (9)* | 66 (12)† |
| BMI(kg/m$^2$) | 25.8 (6.3) | 27.4 (6.4) | 24.7 (9.5)† |
| FFM (kg) | 47.7 (14.9) | 58.1 (17.6)* | 45.4 (14.6)† |
| QMVC (kg) | 32.0 (18) | 33.0 (16.8) | 17.1 (8.4)† |
| FEV1 (%predicted) | 102.0 (20) | 66.1 (24.8)* | 29.0 (16)† |
| Gender | M=55(31.4%) | M=74(66.1%)* | M=108(57.1%)† |

Displayed as median and Interquartile Range (IQR) unless stated.
Abbreviations: n: number of subjects, HC: Healthy Control, IQR: interquartile range, BMI: body mass index, FFM: fat-free mass, QMVC: quadriceps maximal voluntary contraction, $FEV_1$: forced expiratory volume in 1 second, M: male. *Statistical difference between Healthy Control Group and Primary Care COPD group ($P<0.05$) †Statistical difference between Healthy Control Group and Complex Care COPD group ($P<0.05$).

**Table S2: QMVC values expressed as percent predicted values and number classed as weak using the FFM- and FFM+ models in COPD-CC without low Fat-free Mass Index**

| | |
|---|---|
| n | 56 |
| FFM- Model %pred QMVC: | 60.4 (16.8) |
| Number classed as weak (%): | 22 (35.5%) |
| FFM+ Model %pred QMVC: | 66.7 (18.5) |
| Number classed as weak (%): | 19 (30.6%) |

Mean values and SD of measured Quadriceps Maximal Voluntary Contraction (QMVC) presented as a percentage of the values predicted (%pred) and the number classed as weak using the FFM- and FFM+ models.
Abbreviations: FFM+: Fat-free mass model, FFM- model without fat-free mass, SD: standard deviation, n: number in COPD-CC without low fat-free mass index.

References


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