

Longitudinal changes in total and regional body composition in patients with chronic obstructive pulmonary disease

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Abstract

Background and objective: Low fat-free mass (FFM) is common in patients with chronic obstructive pulmonary disease (COPD) and contributes to morbidity and mortality. Few studies have evaluated longitudinal changes in body composition in patients with COPD compared with non-COPD controls. This study aimed to compare longitudinal changes in total and regional body composition between patients with COPD and non-COPD controls and investigate predictors of changes in body composition in COPD.

Methods: Patients with COPD and non-COPD controls participating in the Individualized COPD Evaluation in relation to Ageing (ICE-Age) study, a single-centre, longitudinal, observational study, were included. Subjects were assessed at baseline and after 2 years of follow-up. Among other procedures, body composition was measured by dual-energy X-ray absorptiometry scan. The number of exacerbations/hospitalizations 1 year before inclusion and during follow-up were assessed in patients with COPD.

Results: A total of 405 subjects were included (205 COPD, 87 smoking and 113 non-smoking controls). Patients with COPD and smoking controls presented a significant decline in total FFM (mean [95% CI]: -1173 [$-1527/-820$] g and -486 [$-816/-156$] g, respectively) while body composition remained stable in non-smoking controls. In patients with COPD, the decline in FFM was more pronounced in legs (-174 [$-361/14$] g) and trunk (-675 [$-944/406$] g) rather than in arms (54 [$-19/126$] g). The predictors of changes in total and regional FFM in patients with COPD were gender, number of previous hospitalizations, baseline values of FFM and BMI.

Conclusion: Patients with COPD present a significant decline in FFM after 2 years of follow-up, this decline is more pronounced in their legs and trunk.

KEYWORDS

body composition, chronic obstructive pulmonary disease, longitudinal change, low fat-free mass, physical activity, pulmonary rehabilitation

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease known to be a leading cause of morbidity and mortality worldwide and inducing a substantial economic and social burden.¹ Patients with COPD present chronic airflow obstruction and respiratory symptoms; however, there is a substantial variation in risk of exacerbations, exercise

capacity, level of physical activity and other characteristics among patients.¹ Thus, COPD is considered a complex and heterogeneous disease and studies have identified different patients' clusters based on a comprehensive assessment of lung function,² response to pulmonary rehabilitation,³ comorbidities,^{4,5} physical activity⁶ and body composition.^{7,8}

Body composition abnormalities have been extensively investigated in patients with COPD.⁹ Studies have found a

higher prevalence of body composition abnormalities in this population compared with non-COPD control groups, affecting surrogate markers of muscle mass and fat mass (FM).^{7,10} There is evidence showing a 'cachectic' comorbidity cluster that is specifically related to COPD and represents a disease-specific phenotype.^{5,11} In addition, a population-based cohort study found that the presence of sarcopenia appears to be independent of chronic diseases apart from COPD.¹² Indeed, changes in body composition are expected with normal ageing and are gender dependent.¹³ However, patients with COPD present an accelerated ageing process,¹⁴ raising the hypothesis that the changes in body composition may also be different in COPD compared with non-COPD controls.

Only few studies investigated longitudinal changes in body composition in patients with COPD.^{10,15–17} In these studies, the time of follow-up ranged from 1 to 7 years and body composition variables were measures of total body or legs, whereas no specific variables for trunk and arms were available. The studies that included a control group found small changes in body composition in patients with COPD which were comparable with the changes of smoking and non-smoking controls.^{10,15,16} In the case of regional assessment of body composition (with stratification in trunk and limbs), only a few cross-sectional studies are available.^{18–20} The findings from these studies suggest that limbs are more affected in patients with COPD, whereas changes in trunk body composition are more present in patients with worse disease severity and/or presenting emphysema.^{18–20} To our knowledge, no previous study has investigated longitudinal changes in regional body composition in patients with COPD compared with non-COPD controls, neither identified a subgroup of patients with a different body composition trajectory.

Therefore, this study aimed: (1) to compare longitudinal changes in total and regional body composition between patients with COPD, smoking and non-smoking controls; (2) to investigate baseline predictors of longitudinal changes in body composition in patients with COPD; and (3) to investigate the associations of longitudinal changes of body composition with longitudinal changes of symptoms, lung function, health-related quality of life (HRQL) and occurrence of exacerbations/hospitalizations in patients with COPD after 2 years of follow-up.

METHODS

Study design and subjects

The Individualized COPD Evaluation in relation to Ageing (ICE-Age) study, was a single-centre, prospective, observational study performed in Ciro (Horn, The Netherlands) with 2 years of follow-up. Detailed information regarding inclusion and exclusion criteria as well as the enrolment process were previously described.¹⁴ Patients with COPD were recruited on referral to pulmonary rehabilitation at

SUMMARY AT A GLANCE

Patients with chronic obstructive pulmonary disease (COPD) present a significant decline in total, leg and trunk low fat-free mass (FFM), while arms FFM remains stable after 2 years of follow-up. We identified a subgroup of patients with preserved FFM at baseline and history of previous hospitalizations that present greater decline in total and leg FFM compared to other patients with COPD.

CIRO during a clinically stable phase (absence of respiratory tract infection or exacerbation of the disease for <4 weeks before study entry). Smoking and non-smoking controls were recruited from the same region (south of the Netherlands) from December 2010 to August 2016.

Assessments

Anthropometric and demographic data were collected. Body weight and height were assessed and used to calculate BMI (weight divided by height squared [kg/m^2]). Subjects were classified into BMI categories according to the World Health Organization (WHO) criteria: underweight ($<18.5 \text{ kg}/\text{m}^2$), normal weight ($18.5\text{--}24.9 \text{ kg}/\text{m}^2$), overweight ($25\text{--}29.9 \text{ kg}/\text{m}^2$) or obese ($\geq 30 \text{ kg}/\text{m}^2$).²¹ In patients with COPD, the number of exacerbations and hospitalizations due to COPD in the previous year and use of long-term oxygen therapy were recorded. An exacerbation was defined as an acute need to use a course of oral glucocorticosteroids or antibiotics and/or hospitalization due to acute respiratory worsening.

Body composition was assessed by dual-energy X-ray absorptiometry (DEXA) scan (Lunar Prodigy system; GE Healthcare, Madison, WI, USA). Total and regional body composition, including lean, fat and bone mass, was analysed. Fat-free mass (FFM) was calculated as the sum of lean mass plus bone mineral content and described as total FFM, legs FFM, trunk FFM and arms FFM. FM was calculated as the difference between weight and total FFM. Bone mineral density was measured in the lumbar spine and proximal femur (hips) and the respective *T*-scores were calculated. FFM index (FFMI) and FM index (FMI) were calculated by dividing total FFM and FM by height², respectively. Patients were classified into low FFMI and high FMI according to the 10th and 90th percentiles of age-gender-BMI-specific cut-offs,²² respectively.

Post-bronchodilator lung function tests were performed to assess forced expiratory volume in the first second (FEV₁), forced vital capacity (FVC) and its ratio (FEV₁/FVC), using a standardized spirometer method (Masterlab[®], Jaeger, Germany), following the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.²³ Residual volume

TABLE 1 Baseline characteristics of the sample

| Variables | COPD (N = 205) | Smoking controls (N = 87) | Non-smoking controls (N = 113) |
|------------------------------------|---------------------|----------------------------------|-----------------------------------|
| Male, n (%) | 119 (58) | 51 (59) | 39 (34) ^{ab} |
| Age (years) | 62 (57–67) | 61 (59–65) | 60 (55–64) ^a |
| BMI (kg/m ²) | 27.0 (22.9–30.4) | 27.2 (25.4–29.1) | 25.8 (24.0–28.4) |
| Underweight, n (%) | 10 (5) | 0 (0) | 0 (0) |
| Normal weight, n (%) | 63 (31) | 18 (21) | 42 (37) ^b |
| Overweight, n (%) | 72 (35) | 56 (64) ^a | 52 (46) ^b |
| Obese, n (%) | 60 (29) | 13 (15) ^a | 19 (17) ^a |
| Body composition | | | |
| FFMI (kg/m ²) | 17.4 (15.6–19.4) | 18.9 (16.4–20.2) ^a | 17.2 (15.6–19.4) ^b |
| Low FFMI, n (%) | 82 (40) | 19 (22) ^a | 23 (20) ^a |
| FMI (kg/m ²) | 9.2 (6.3–11.4) | 8.5 (6.8–10.6) | 8.7 (7.0–10.7) |
| High FMI, n (%) | 72 (35) | 20 (23) | 24 (21) ^a |
| Arms FFM (kg) | 4.67 (3.67–5.86) | 5.84 (4.05–6.70) ^a | 4.33 (3.66–6.38) ^b |
| Legs FFM (kg) | 13.99 (11.24–17.15) | 16.49 (12.27–18.70) ^a | 13.07 (11.78–17.16) ^b |
| Trunk FFM (kg) | 23.59 (19.30–28.86) | 24.80 (19.84–27.56) | 20.78 (18.70–25.35) ^{ab} |
| BMD L2–L4 (g/cm ²) | 1.10 (0.95–1.23) | 1.19 (1.05–1.36) | 1.22 (1.08–1.34) ^a |
| BMD hip (g/cm ²) | 0.84 (0.76–0.92) | 0.91 (0.83–1.06) | 0.94 (0.87–1.03) ^a |
| Lumbar spine T-score | −1.1 (−1.8 to 0.2) | −0.2 (−1.3 to 1.1) ^a | 0.1 (−1.1 to 1.1) ^a |
| Hip T-score | −1.5 (−2.1 to −0.9) | −1.0 (−1.6 to 0.1) ^a | −0.6 (−1.3 to 0.2) ^a |
| Osteopenia, n (%) | 109 (53) | 40 (46) | 37 (33) ^a |
| Osteoporosis, n (%) | 41 (20) | 6 (7) | 6 (5) ^a |
| Smoking status | | | |
| Ex-smoker, n (%) | 174 (85) | 65 (75) | 50 (44) ^a |
| Habitual smoker, n (%) | 28 (14) | 22 (25) ^a | 4 (3) ^{ab} |
| Non-smoker, n (%) | 3 (1) | 0 (0) | 59 (52) ^a |
| Pack-years | 43 (31–59) | 21 (14–31) ^a | 0 (0–4) ^{ab} |
| Lung function | | | |
| FEV ₁ (% predicted) | 50 (36–62) | 116 (107–125) ^a | 120 (109–130) ^a |
| FVC (% predicted) | 98 (82–111) | 122 (110–132) ^a | 124 (114–135) ^a |
| FEV ₁ /FVC | 40 (32–49) | 77 (75–83) ^a | 79 (76–83) ^a |
| ITGV (% predicted) | 144 ± 33 | 98 ± 17 ^a | 101 ± 19 ^a |
| RV (% predicted) | 152 (130–184) | 95 (84–104) ^a | 95 (83–106) ^a |
| TL _{CO} (% predicted) | 52 (43–66) | 91 (81–101) ^a | 92 (85–104) ^a |
| LTOT use, n (%) | 32 (16) | 0 (0) ^a | 0 (0) ^a |
| Self-reported comorbidities | | | |
| Hypertension, n (%) | 46 (22) | 23 (26) | 19 (17) |
| Peripheral vascular disease, n (%) | 40 (19) | 1 (1) ^a | 2 (2) ^a |
| Joint disease, n (%) | 27 (13) | 17 (19) | 20 (18) |
| Diabetes mellitus, n (%) | 19 (9) | 4 (5) | 2 (2) ^a |
| Gastrointestinal disease, n (%) | 20 (10) | 3 (3) | 6 (5) |
| Psychological disorder, n (%) | 17 (8) | 2 (2) | 4 (3) |
| Hypercholesterolaemia, n (%) | 15 (7) | 8 (9) | 5 (4) |
| Cardiac disease, n (%) | 40 (19) | 6 (7) ^a | 4 (3) ^a |
| Sleep apnoea, n (%) | 13 (6) | 3 (3) | 1 (1) |
| Other, n (%) | 34 (17) | 16 (18) | 17 (15) |

Abbreviations: BMD, bone mineral density; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in the first second; FFM, fat-free mass; FFMI, FFM index; FMI, fat mass index; FVC, forced vital capacity; ITGV, intra-thoracic gas volume; LTOT, long-term oxygen therapy; RV, residual volume; TL_{CO}, transfer factor for carbon monoxide.

^ap < 0.05 compared with COPD.

^bp < 0.05 compared with smoking control.

(RV) and intra-thoracic gas volume (ITGV) were determined by body plethysmography (Masterlab) following the quality control guidelines.²⁴ Transfer factor for carbon monoxide (TL_{CO}) was assessed by using single-breath method (Masterlab).²⁵ All parameters were expressed as percentage of reference values.^{26–28} The number of pack-years smoked and smoking status (habitual smokers, ex-smokers [≥10 pack-years] and non-smokers [<10 pack-years]) were recorded.

In patients with COPD, the Medical Research Council (MRC) scale²⁹ and the COPD-specific version of St George Respiratory Questionnaire (SGRQ)³⁰ were applied to assess the level of functional limitation due to breathlessness in activities of daily living and disease-related quality of life, respectively. All the previously described assessments were performed at baseline and repeated after 2 years of follow-up. In the time between, the occurrence of exacerbations during follow-up was recorded by telephone contact every 3 months.

Statistical analysis

Normality in data distribution was evaluated using the Shapiro–Wilk test. Quantitative variables were described as mean \pm SD or median (interquartile range 25%–75%) as appropriate. Categorical variables were described as absolute and relative frequency. The longitudinal change in variables were calculated by subtracting the data at Year 2 from baseline data. For the comparisons of the baseline characteristics between patients with COPD, smoking and non-smoking controls, the one-way analysis of variance (ANOVA) or Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables were performed as appropriate. The paired *t*-test or Wilcoxon signed-rank test was used to compare differences between paired observations (baseline vs. 2 years of follow-up) within each group. To evaluate the predictive value of the different baseline factors to explain the variance in the change of total and regional body composition of patients with COPD, a stepwise multiple regression analysis was performed. Since baseline values of FFMI and number of hospitalizations 1 year before baseline were found to be associated with changes in total and regional body composition (see Results), further analyses to examine whether patients with COPD classified as normal (or low) FFMI and with (or without) at least one hospitalization in the previous year present different body composition trajectories were performed using the two-way ANOVA test. All the tests with comparisons between more than two groups were followed by Bonferroni post hoc test for pairwise comparisons.

Correlations between changes in total and regional body composition with changes in lung function and HRQL in patients with COPD were assessed by Pearson's *r* or Spearman's *r* as appropriate. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS v 25 for Windows; SPSS Inc., Chicago, IL, USA). Figures were

created using GraphPad Prism 9.0 (GraphPad Software Inc., USA). Significance level was set at $p < 0.05$.

RESULTS

A total of 205 patients with COPD and 200 subjects without COPD (87 smoking controls and 113 non-smoking controls) were included for these analyses. The baseline characteristics of the sample are presented in Table 1. The group of non-smoking controls was younger, presented a higher proportion of female subjects and, as expected, reduced smoking history compared with patients with COPD. Per definition, patients with COPD presented impaired lung function compared with smoking and non-smoking controls. Baseline BMI was comparable between groups. Frequency of peripheral vascular disease, cardiovascular disease and osteoporosis was significantly increased in COPD compared with smoking and non-smoking controls. In general, patients with COPD were classified as overweight, heavy smokers, with moderate to severe airflow obstruction, moderately impaired diffusion capacity and increased static lung volumes. A total of 82 (40%) patients with COPD were classified as low FFMI, whereas 72 (35%) were classified as high FMI. In addition, patients with COPD presented moderate to severe functional limitation due to breathlessness in activities of daily living and reduced quality of life (Table 2).

After 2 years of follow-up, 10 patients with COPD, one non-smoking control and three smoking controls did not return for outcome assessments at the second visit but were followed up by a phone call. Eleven patients with COPD declined to participate or were not available to perform outcome assessments at the second visit. Ten patients with

TABLE 2 Level of functional limitation due to breathlessness in activities of daily living, disease-related quality of life, number of exacerbations and hospitalizations in patients with COPD

| Variables | COPD |
|---|------------------|
| Questionnaires | |
| MRC | 3 (2–4) |
| SGRQ symptoms | 59.6 (42.7–72.1) |
| SGRQ impact | 41.3(28.2–54.3) |
| SGRQ activity | 56.4(42.0–67.0) |
| SGRQ total | 56.4(42.0–67.0) |
| Number of exacerbations in the previous year | |
| 0, <i>n</i> (%) | 44 (23) |
| 1, <i>n</i> (%) | 57 (29) |
| 2 or more, <i>n</i> (%) | 93 (48) |
| Number of hospitalizations in the previous year | |
| 0, <i>n</i> (%) | 140 (69) |
| 1, <i>n</i> (%) | 60 (30) |
| 2 or more, <i>n</i> (%) | 3 (1) |

Abbreviations: COPD, chronic obstructive pulmonary disease; MRC, Medical Research Council; SGRQ, St George Respiratory Questionnaire.

COPD and one non-smoking control died during the study. The remaining 174 (85%) patients with COPD, 84 (96%) smoking controls and 111 (98%) non-smoking controls repeated the measurements. As presented in Figure 1, weight remained stable in all groups; however, patients with COPD and smoking controls presented a significant decline in FFM and increase in FM, while non-smoking controls presented no

significant differences in body composition. Regarding regional body composition, patients with COPD presented a significant decline in legs and trunk FFM. The decline in FFM in smoking controls is mostly explained by a decline in trunk FFM, as an increase in legs and arms FFM was observed. Non-smoking controls presented a significant increase in legs FFM, but no differences in trunk and arms FFM.

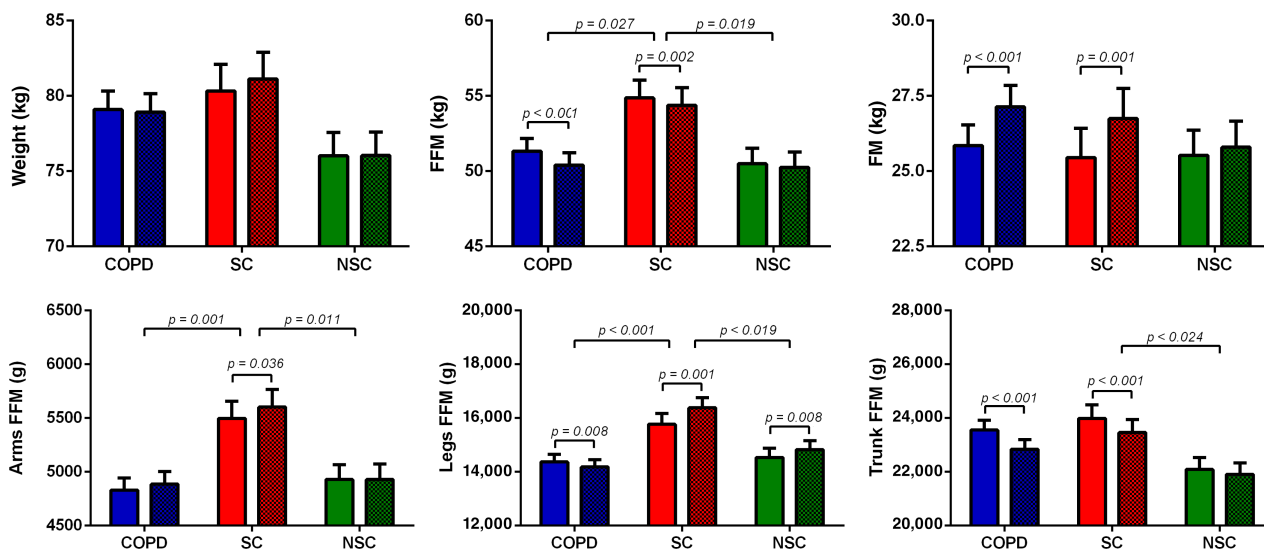


FIGURE 1 Comparison of changes in total and regional body composition among patients with chronic obstructive pulmonary disease, smoking and non-smoking controls after 2 years of follow-up. Figure displays the mean and SE. Clean bars: baseline. Hatched bars: 2 years of follow-up. NSC, non-smoking controls; SC, smoking controls

TABLE 3 Multiple stepwise regression to identify independent contributors to the variance in the change of total and regional body composition in patients with COPD after 2 years of follow-up

| Model | Correlates | Beta | 95% CI (lower/upper) | p-Value |
|--|------------------------------------|-------|----------------------|---------|
| Δ FFMI (kg/m ²) Adjusted R ² = 0.20 p-Value < 0.001 | Constant | 2.01 | 0.79/3.24 | <0.01 |
| | Baseline FFMI (kg/m ²) | -0.28 | -0.40/-0.16 | <0.001 |
| | BMI (kg/m ²) | 0.09 | 0.04/0.14 | <0.001 |
| | Gender (male) | 0.59 | 0.14/1.04 | 0.01 |
| | Previous hospitalization (n) | -0.30 | -0.56/-0.04 | 0.02 |
| Δ Legs FFM (g) Adjusted R ² = 0.16 p-Value < 0.001 | Constant | -860 | -1952/231 | 0.12 |
| | Baseline leg FFM (g) | -0.13 | -0.20/-0.07 | <0.001 |
| | BMI (kg/m ²) | 96 | 49/142 | <0.001 |
| Δ Trunk FFM (g) Adjusted R ² = 0.16 p-Value < 0.001 | Constant | 3818 | 1967/5668 | <0.001 |
| | Baseline trunk FFM (g) | -0.22 | -0.31/-0.12 | <0.001 |
| | Gender (male) | 1145 | 259/2032 | 0.04 |
| | Previous hospitalization (n) | -142 | -280/-4 | 0.04 |
| Δ Arms FFM (g) Adjusted R ² = 0.15 p-Value < 0.001 | Constant | -109 | -570/353 | 0.64 |
| | BMI (kg/m ²) | 33 | 15/51 | <0.001 |
| | Baseline arm FFM (g) | -0.2 | -0.3/-0.1 | <0.001 |
| | Gender (male) | 443 | 176/710 | 0.001 |

Note: Excluded variables: age, pack-years, lung function in percent of predicted (forced expiratory volume in the first second, forced vital capacity, intra-thoracic gas volume, residual volume and transfer factor for carbon monoxide), number of previous exacerbations, number of exacerbations during the follow-up and number of hospitalizations during the follow-up.

Abbreviations: COPD, chronic obstructive pulmonary disease; FFM, fat-free mass; FFMI, FFM index.

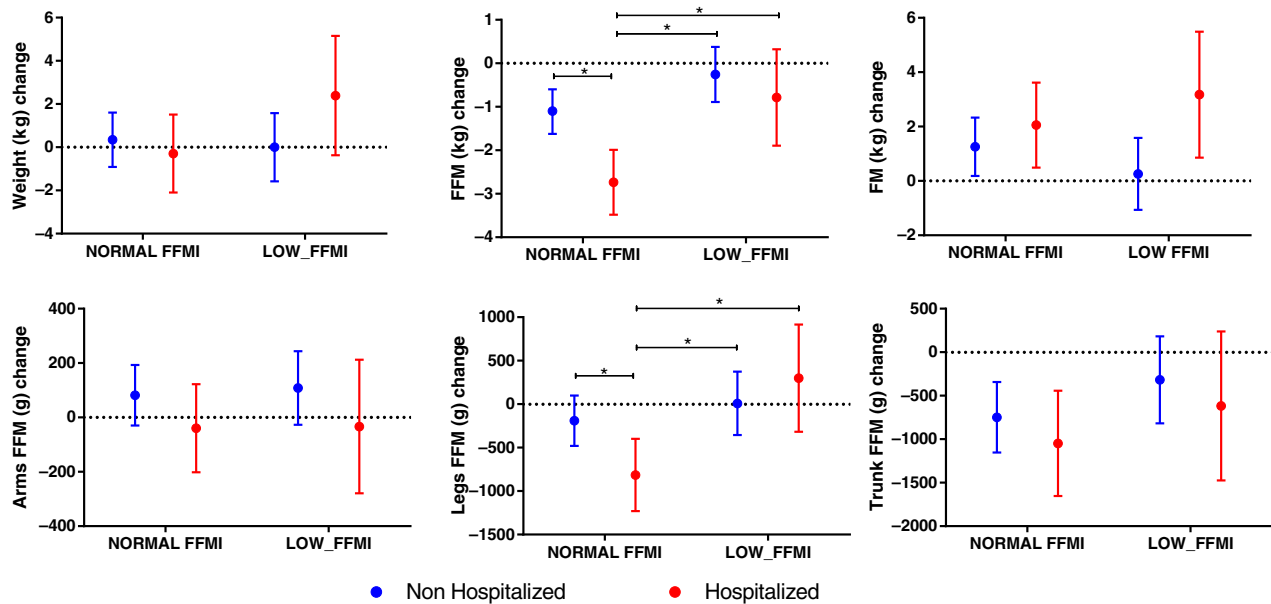


FIGURE 2 Comparison of changes, after 2 years of follow-up, in total and regional body composition among patients with chronic obstructive pulmonary disease stratified according to baseline fat-free mass index (FFMI) (normal/low) and occurrence of previous hospitalization (hospitalized/non-hospitalized). Mean (95% CI) values are reported. Normal FFMI and non-hospitalized ($n = 69$); Normal FFMI and hospitalized ($n = 33$); low FFMI and non-hospitalized ($n = 45$); low FFMI and hospitalized ($n = 15$); $p < 0.05$

TABLE 4 Correlations between changes in total and regional body composition with changes in lung function, symptoms of dyspnoea and health-related quality of life in patients with COPD

| | Change in weight | Change in FFM | Change in FM | Change in legs FFM | Change in trunk FFM | Change in arms FFM |
|--|-----------------------------|-----------------------------|----------------------------|---------------------------|-----------------------------|-----------------------------|
| Change in FEV ₁ % predicted | $r = -0.03$ $p = 0.70$ | $r = -0.01$ $p = 0.88$ | $r = -0.02$ $p = 0.69$ | $r = -0.02$ $p = 0.80$ | $r = -0.17^*$ $p = 0.04$ | $r = 0.09$ $p = 0.25$ |
| Change in FVC % predicted | $r = -0.13$ $p = 0.09$ | $r = -0.05$ $p = 0.54$ | $r = -0.10$ $p = 0.19$ | $r = 0.01$ $p = 0.92$ | $r = -0.13$ $p = 0.10$ | $r = 0.05$ $p = 0.50$ |
| Change in ITGV % predicted | $r = -0.18^*$ $p = 0.02$ | $r = -0.14$ $p = 0.09$ | $r = -0.14$ $p = 0.85$ | $r = -0.07$ $p = 0.40$ | $r = 0.05$ $p = 0.58$ | $r = -0.20^*$ $p = 0.01$ |
| Change in RV % predicted | $r = 0.01$ $p = 0.89$ | $r = -0.06$ $p = 0.50$ | $r = 0.04$ $p = 0.59$ | $r = -0.10$ $p = 0.23$ | $r = 0.18^*$ $p = 0.03$ | $r = -0.16^*$ $p = 0.04$ |
| Change in TL _{CO} % predicted | $r = 0.07$ $p = 0.42$ | $r = 0.14$ $p = 0.09$ | $r = 0.03$ $p = 0.69$ | $r = 0.09$ $p = 0.25$ | $r = 0.05$ $p = 0.56$ | $r = 0.21^*$ $p = 0.01$ |
| Change in MRC | $r = 0.23^*$ $p = 0.04$ | $r = -0.14$ $p = 0.22$ | $r = 0.29^*$ $p = 0.01$ | $r = 0.05$ $p = 0.64$ | $r = -0.18$ $p = 0.13$ | $r = 0.02$ $p = 0.87$ |
| Change in SGRQ symptoms | $r = 0.02$ $p = 0.82$ | $r = -0.22^*$ $p = 0.03$ | $r = 0.14$ $p = 0.16$ | $r = -0.08$ $p = 0.42$ | $r = -0.14$ $p = 0.18$ | $r = 0.00$ $p = 0.93$ |
| Change in SGRQ impact | $r = 0.09$ $p = 0.38$ | $r = 0.00$ $p = 0.98$ | $r = 0.09$ $p = 0.36$ | $r = -0.04$ $p = 0.65$ | $r = -0.00$ $p = 0.98$ | $r = 0.08$ $p = 0.41$ |
| Change in SGRQ activity | $r = 0.16$ $p = 0.11$ | $r = -0.05$ $p = 0.65$ | $r = 0.20$ $p = 0.04$ | $r = -0.02$ $p = 0.84$ | $r = -0.11$ $p = 0.26$ | $r = -0.10$ $p = 0.30$ |
| Change in SGRQ total | $r = 0.13$ $p = 0.18$ | $r = -0.06$ $p = 0.56$ | $r = 0.17$ $p = 0.08$ | $r = -0.08$ $p = 0.41$ | $r = -0.08$ $p = 0.41$ | $r = -0.04$ $p = 0.70$ |

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in the first second; FFM, fat-free mass; FM, fat mass; FVC, forced vital capacity; ITGV, intra-thoracic gas volume; MRC, Medical Research Council; RV, residual volume; SGRQ, St George Respiratory Questionnaire; TL_{CO}, transfer factor for carbon monoxide. $*p < 0.05$.

Table 3 shows the results of the stepwise multiple regression performed to identify the baseline predictors of longitudinal changes in total and regional body composition in patients with COPD. Baseline values of total and regional FFM were significant predictors of their own change. In addition, the number of hospitalizations 1 year before baseline was associated with greater decline in FFMI and arms FFM. In contrast, higher baseline values of BMI were associated with lower decline in FFMI, legs and arms FFM. Male gender showed a protective effect for the decline in FFMI, trunk and arms FFM. There were no associations between longitudinal changes in body composition with smoking status, lung function and number of exacerbations/hospitalizations during follow-up. Patients classified as normal FFMI and presenting hospitalizations 1 year before baseline presented a greater decline in total and leg FFM compared with patients with normal FFMI, but no hospitalizations and patients with low FFMI (Figure 2).

Table 4 presents the single correlations between changes in total and regional body composition with changes in lung function and HRQL in patients with COPD. The change in body weight was negatively associated with the change in ITGV ($r = -0.18$) and positively associated with the change in MRC ($r = 0.23$). The change in total FFM was negatively associated with change in SGRQ symptoms score ($r = -0.22$). The changes in FM were positively associated with change in MRC ($r = 0.29$) and SGRQ activity score ($r = 0.20$). Finally, change in trunk FFM was negatively associated with change in FEV₁ ($r = -0.17$) and positively associated with changes in RV ($r = 0.18$), whereas arms FFM was negatively associated with changes in ITGV ($r = -0.20$) and RV ($r = -0.16$) and positively associated with changes in TL_{CO} ($r = 0.21$). No additional associations were found between other variables of body composition and lung function or HRQL.

DISCUSSION

This was the first study to compare longitudinal changes in total and regional body composition between patients with COPD, smoking and non-smoking controls, during 2 years of follow-up. The study shows that patients with COPD present a significant decline in total, leg and trunk FFM compared with smoking and/or non-smoking controls, while no changes were observed in arms FFM. In addition, preserved total and regional FFM at baseline and a history of previous hospitalizations were associated with longitudinal changes in FFM in patients with COPD, and these characteristics could discriminate a subgroup of patients presenting greater decline in total and legs FFM. Lastly, changes in lung function, symptoms of dyspnoea and HRQL were weakly associated with changes in body composition in patients with COPD.

Previous studies found no difference in longitudinal changes of body composition between patients with COPD and non-COPD controls.^{10,16} In contrast, the present study found a significant decline of FFM in patients with COPD

after 2 years of follow-up, whereas no changes in FFM were observed in non-smoking controls. We hypothesize that the difference between these findings is caused by differences in the population included (e.g., older subjects with obstructive lung disease [OLD])¹⁶ and methods of assessment of body composition (bio-electrical impedance analysis vs. DEXA scan).¹⁰ The strengths of the present study are the inclusion of a relatively large sample of patients with COPD and smoking and non-smoking controls as well as a comprehensive assessment of body composition by DEXA scan, including total and regional variables.

The study from van den Borst et al.¹⁶ aimed to investigate whether OLD and smoking accelerate ageing-related decline in lean mass. Subjects were followed up for a period of 7 years. While at baseline large differences were observed in body composition between OLD and smoking controls compared with non-smoking controls, the longitudinal changes in body composition were similar between the groups. However, this study included subjects with OLD with ages from 70 to 79 years. Therefore, the results may not be generalizable to younger subjects and middle-aged patients with clinical diagnosis of COPD.

Another study by Rutten et al.¹⁰ evaluated changes in body composition over 3 years in a cohort of patients with COPD in comparison with smoking and non-smoking controls. This study showed that the changes in body composition in patients with COPD were comparable with the change in smoking and non-smoking controls after 3 years and were independent of the initial body weight. In this previous study, the changes in FFMI and FMI of patients with COPD were less pronounced ($-0.1 [-0.6/0.5]$, $-0.1 [-1.1/0.8]$, respectively) than the changes of the present study ($-0.4 [-0.9/0.1]$, $0.3 [-0.5/1.5]$, respectively). Later, Rutten et al.¹⁵ showed that the proportion of patients with continuous FFM decline was small, but higher in patients with COPD compared with non-COPD controls. The authors suggested that there may be a subgroup of patients with disease-specific muscle wasting defined by continuous FFM decline, which might be partly explained by higher number of exacerbations.¹⁵

The present study found that, despite presenting a significant decline in legs FFM, patients with COPD present no changes in arms FFM after 2 years of follow-up. A possible explanation is that most of self-care activities and activities of daily living are done with the arms, whereas legs dysfunction is closely related to higher intensity physical activity (legs are directly involved in locomotion and exercise capacity), which is usually reduced in this population.³¹ Previous studies have found that patients with COPD present relatively preserved characteristics in arms compared with legs regarding muscle strength and endurance,³²⁻³⁴ mechanical efficiency,³⁵ oxidative capacity³⁶ and duration of daily arm activities, despite lower intensity and at cost of higher effort of trapezius compared with healthy control subjects.³² In addition, previous findings support that patients with severe disease exhibit disproportional leg muscle wasting compared with patients with mild COPD.¹⁸ In relation to the changes in trunk body composition, previous findings suggest that the

reduction in trunk FFM is present specifically in patients with worse disease severity and/or presenting emphysema.^{19,20} In the present study, we did not find any lung function factor independently associated with the change in trunk FFM.

This is not the first study to find association between higher baseline values of FFM and higher decline in FFM over time. Hopkinson et al.¹⁷ found that baseline values of FFM were retained in a stepwise regression analyses as a predictor of the change in FFM after 1 year of follow-up. Our results suggest an interaction effect in which the impact of hospitalizations is higher for patients with preserved FFMI, since patients presenting these features were identified as a subgroup with greater decline in total and legs FFM after 2 years of follow-up (Figure 2). Notably, during hospitalization, patients with COPD present very low level of baseline physical activity.^{33,34} A similar effect has been reported for the impact of exacerbations on longitudinal changes of FEV₁, which is higher for patients with COPD with mild disease.³⁷ Our hypothesis is the existence of a floor effect, in which patients with lower FFM values may have experienced a significant decline in FFM before the inclusion in the study and are less susceptible to the negative effects of hospitalizations.

Changes in body composition were weakly associated with changes in lung function, symptoms of dyspnoea and HRQL in patients with COPD ($r < 0.3$, for all) (Table 4). Our models could explain only 15%–20% of the variance in changes in body composition (Table 3) suggesting that these changes are affected by a great number of different factors, beyond the factors covered by this study (e.g., nutrition, physical activity, use of drugs and systemic inflammation). The knowledge of COPD as a complex, multidimensional and heterogeneous disease, in which patients may present comparable degrees of airflow obstruction, but considerable differences in their MRC and SGRQ scores³⁸ or body composition,^{8,39} may be extended for a longitudinal perspective. Thus, patients may also present different patterns of longitudinal changes in the aforementioned outcomes which are mildly associated.

Some limitations of the present study include: (1) most of the patients with COPD were recruited in a tertiary care pulmonary rehabilitation and results should not be generalized for other stages of the disease or patient profiles; (2) the lack of additional variables that could also be related with longitudinal changes in body composition, such as physical activity and dietary habits; (3) this study could not assess the impact of longitudinal changes in body composition to other outcomes (e.g., mortality, exercise capacity and muscle strength); and (4) patients with COPD underwent an 8-week pulmonary rehabilitation programme, but the effect of this short-term intervention on body composition was not assessed in this study. Based on a previous study from our centre, no substantial changes were anticipated.⁴⁰ Future studies should be conducted in order to investigate longitudinal changes in body composition in a broader sample of patients with COPD in comparison with non-COPD controls, during a longer period

of time, to confirm the present findings and to provide information regarding the prognostic value of changes in total and regional body composition. Furthermore, studies investigating strategies to slow down (or prevent) the decline in regional FFM in patients with COPD and its benefits are an interesting topic.

In conclusion, patients with COPD and smoking controls present a significant decline in FFM after 2 years of follow-up, and this decline is more pronounced in their legs and trunk. Patients with COPD with higher baseline FFMI and occurrence of recent hospitalizations were identified as a subgroup presenting greater decline in total and legs FFM. Longitudinal changes in body composition are weakly associated with longitudinal changes in lung function, symptoms of dyspnoea and HRQL.

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AUTHOR CONTRIBUTIONS

Felipe Machado: Conceptualization; data curation; formal analysis; methodology; visualization; writing-original draft; writing-review & editing. **Martijn Spruit:** Conceptualization; methodology; supervision; visualization; writing-review & editing. **Miranda Coenjaerds:** Conceptualization; methodology; visualization; writing-original draft; writing-review & editing. **Fabio Pitta:** Conceptualization; methodology; visualization; writing-review & editing. **Niki Reynaert:** Conceptualization; methodology; visualization; writing-original draft; writing-review & editing. **Frits Franssen:** Conceptualization; methodology; project administration; supervision; visualization; writing-review & editing.

CONFLICT OF INTEREST

Martijn A. Spruit reports grants from Netherlands Lung Foundation and Stichting Astma Bestrijding, and grants and personal fees from AstraZeneca and Boehringer Ingelheim, all outside the submitted work. Frits M. E. Franssen reports grants and personal fees from AstraZeneca and Novartis, and personal fees from Boehringer Ingelheim, Chiesi, GlaxoSmithKline and TEVA, outside the submitted work. The other authors declare that they have no conflicts of interest that could have influenced the present study.


HUMAN ETHICS APPROVAL DECLARATION

The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines and has been approved by the local ethics review board of the Maastricht University Medical Centre (Maastricht, The Netherlands; MEC 10-3-033). All subjects provided written informed consent prior to study participation. In addition, the study analyses were approved by the board of directors of CIRO (Horn, The Netherlands).


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