The relationship of fat and muscle measurements with emphysema and bronchial wall thickening in smokers

Stijn A.O. Bunk[1], Jetty Ipema[1], Grigory Sidorenkov[2], Edwin Bennink[1], Rozemarijn Vliegenthart[3], Pim A. de Jong[1], Esther Pompe[1], Jean-Paul Charbonnier[4], Bart H.D. Luijk[5], Joachim Aerts[6], Harry J.M. Groen[7] and Firdaus A.A. Mohamed Hoesein[1]

[1]Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands. [2]University of Groningen, University Medical Center Groningen, Department of Epidemiology, Groningen, The Netherlands. [3]University of Groningen, University Medical Center Groningen, Center for Medical Imaging-North East Netherlands, Groningen, The Netherlands. [4]Thirona, Nijmegen, The Netherlands. [5]Department of Pulmonology, University Medical Center Utrecht, Utrecht, The Netherlands. [6]Department of Respiratory Medicine, ErasmusMC, Rotterdam, The Netherlands. [7]Department of Pulmonary Diseases, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

Corresponding author: Stijn A.O. Bunk (S.A.O.Bunk-2@umcutrecht.nl)

Shareable abstract (@ERSpublications)
In a group of long-time smokers, CT-derived fat and muscle measurements related to mild emphysema and bronchial wall thickening. This finding could help inform early detection of fat and muscle loss during routine screening. https://bit.ly/3S8jns9

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Abstract

Introduction Differences in body composition in patients with COPD may have important prognostic value and may provide opportunities for patient-specific management. We investigated the relation of thoracic fat and muscle with computed tomography (CT)-measured emphysema and bronchial wall thickening.

Methods Low-dose baseline chest CT scans from 1031 male lung cancer screening participants from one site were quantified for emphysema, bronchial wall thickening, subcutaneous fat, visceral fat and skeletal muscle. Body composition measurements were performed by segmenting the first slice above the aortic arch using Hounsfield unit thresholds with region growing and manual corrections. COPD presence and severity were evaluated with pre-bronchodilator spirometry testing.

Results Participants had a median age of 61.5 years (58.6–65.6, 25th–75th percentile) and median number of 38.0 pack-years (28.0–49.5); 549 (53.2%) were current smokers. Overall, 396 (38.4%) had COPD (256 Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1, 140 GOLD 2–3). Participants with COPD had less subcutaneous fat, visceral fat and skeletal muscle ($p<0.001$ for all). With increasing GOLD stages, subcutaneous ($p=0.005$) and visceral fat values ($p=0.004$) were higher, and skeletal muscle was lower ($p=0.004$). With increasing severity of CT-derived emphysema, subcutaneous fat, visceral fat and skeletal muscle values were lower ($p<0.001$ for all). With increasing CT-derived bronchial wall thickness, subcutaneous and visceral fat values were higher ($p<0.001$ for both), without difference in skeletal muscle. All statistical relationships remained when adjusted for age, pack-years and smoking status.

Conclusion COPD presence and emphysema severity are associated with smaller amounts of thoracic fat and muscle, whereas bronchial wall thickening is associated with fat accumulation.

Introduction

Among smokers, COPD is the second leading cause of death and in some countries, it is even the primary cause of smoking-related deaths [1]. For COPD patients the number of pack-years smoked contributes to disease severity [2]. The airflow limitation in COPD can be caused by airway disease and/or emphysema. In the end-stages of the disease a typical bronchitis patient, also called “blue bloater”, classically presents as obese, whereas a typical emphysema patient, also called “pink puffer”, is cachectic [3, 4]. Previous studies including early-stage disease information did not perform an in-depth analysis of the statistical relationship between early-stage disease and body composition [5].

Multiple studies have shown a negative association between anthropometric fat measurements and pulmonary function [6, 7], but other studies showed a higher body mass index (BMI) in persons with bronchial wall thickening compared to persons with emphysema [8]. Another study showed that the fat mass index was positively associated with bronchial wall thickness [9]. The ratio of fat types may be important too, as visceral fat is known to be more metabolically active than subcutaneous fat [10]. Mediastinal fat has been shown to be associated with decreased incremental shuttle walk distance and increased interleukin-6 levels, and subcutaneous fat with reduced emphysema progression [11]. In addition to fat, lower intercostal muscle mass was shown to be associated with a higher risk for repeated hospital admissions due to COPD exacerbations [12] and a higher Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage [13]. Previous research also showed that persons with lower pectoral muscle mass tended to have more severe airflow obstruction at expiration, a lower quality of life and a reduced exercise capacity [14]. Studies also showed that the fat-free mass index is negatively associated with emphysema [9, 15].

Computed tomography (CT) is a widely used and effective method for not only visualising early signs of COPD, but also quantifying fat and muscle quantity. CT is an easy and accurate method to investigate fat and muscle in larger cohort studies [16–18] when paired with automated analysis of body composition [19, 20]. The aim of our study was to investigate fat and muscle quantity in the chest in relation to subtypes of COPD, namely emphysema and bronchial wall thickening, in cases at an early disease stage.

Materials and methods

Study population

The Dutch and Belgium Lung Cancer Screening Trial (NELSON) is a randomised controlled population-based trial. Participants were current or former smokers with a smoking history of >15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years. Inclusion and exclusion criteria have previously been described [21–23]. The screening group underwent low-dose inspiratory chest CT scanning. For the current study, a subsample of participants who underwent pulmonary function testing at the University Medical Center Utrecht was used, as previously described [24]. The Medical Ethics Committee approved the ancillary study protocol, and written informed consent for side studies was obtained from all participants included in the present study. This study was conducted as part of the NELSON-POP project, which is an extension of NELSON [25].

Pulmonary function testing

Pre-bronchodilator pulmonary function tests were performed according to the European Respiratory Society/American Thoracic Society guidelines [26]. Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were recorded [24]. FEV_1 was expressed as per cent predicted, calculated by FEV_1 of the patient divided by the mean FEV_1 in the population. COPD was defined as a FEV_1/FVC ratio <70%. GOLD stage was defined as: 1) mild, when FEV_1 was equal to or higher than 80% predicted; 2) moderate, when FEV_1 was between 50 and 80% predicted; and 3) severe, when FEV_1 was <50% predicted [27]. Given the limited number of participants staged as GOLD 3, they were grouped with GOLD 2 in the analysis.

Image acquisition

The scanning protocol has been previously described [24, 28]. Emphysema and airway measurements were performed on 1-mm axial slices at 0.7-mm increments. Pixel spacing ranged from 0.5 mm to 1.0 mm, with a mean±SD of 0.7±0.06 mm. Fat and muscle measurements were performed on post-processed slices with a thickness of 3.1 mm at 1.4-mm increments. These slices were created by averaging the 1-mm slices with a window of four slices and a step size of two slices. This post-processing step was performed to reduce image noise.

Emphysema and airway measurements

CT emphysema was defined as the Hounsfield unit (HU) value at the 15th percentile (Perc15) of the attenuation–distribution curve of all pulmonary voxels. The procedure for calculating Perc15 has been previously described [24, 29]. Bronchial wall thickness was defined as the square root of wall area at a theoretical internal lumen perimeter of 10 mm (Pi10). The procedure for calculating Pi10 has been previously described [29, 30]. All quantifications were performed with CIRRUS Lung 12.03 (Cirrus, Diagnostic Image Analysis Group, Radboud University Medical Center, Nijmegen, the Netherlands; Fraunhofer MEVIS, Bremen, Germany) [31].

Fat and muscle measurements

Fat and muscle measurements were performed using in-house developed manual segmentation software, with the observers adhering to a structured procedure. To start, the observer, a medical student, selected the correct axial slice. This was the first CT slice above the aortic arch. On the CT slice, areas containing

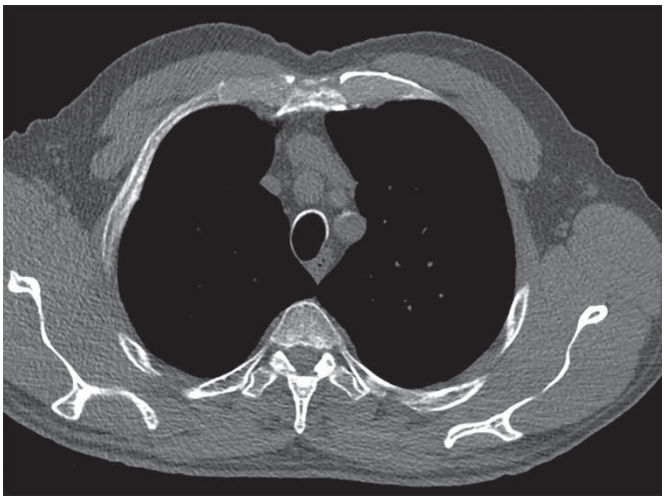

FIGURE 1 A computed tomography slice at the level just above the aortic arch.

visceral fat, subcutaneous fat and skeletal muscle were visually identified. Fat in the mediastinum was segmented as visceral fat. Skeletal muscle was segmented into four groups as determined visually by the observer: dorsal, shoulder, intercostal and pectoral muscle. These four groups were aggregated into an overall measurement of skeletal muscle. Manually initiated 2D region growing, based on a tissue's HU range, was used to label the tissue types. For visceral fat this was −150 to −50 HU, for subcutaneous fat −190 to −30 HU and for muscles −29 to 150 HU [32]. Inaccuracies were manually corrected. In figure 1 an example of an unsegmented slice is shown. In figure 2 multiple segmented slices are shown. To assess interobserver variability, two medical students, blinded for each other's results, performed fat and muscle measurements on the same 200 scans.

Statistical analysis

SPSS (version 26 for Windows) was used for data analysis. The intraclass correlation coefficient was used to test interobserver variability between the two observers. A coefficient above 0.7 was considered good and above 0.8 excellent [33]. Normality of data distribution was determined by visual analysis of Q-Q plots and histograms. Pi10 was divided into quartiles, from lowest bronchial wall disease (quartile 1) to highest bronchial wall disease (quartile 4). Perc15 was also divided into quartiles, from lowest amount of emphysema (quartile 1) to highest amount of emphysema (quartile 4). Differences in fat and muscle areas between the group with and without COPD, GOLD stages, Perc15 quartiles and Pi10 quartiles were

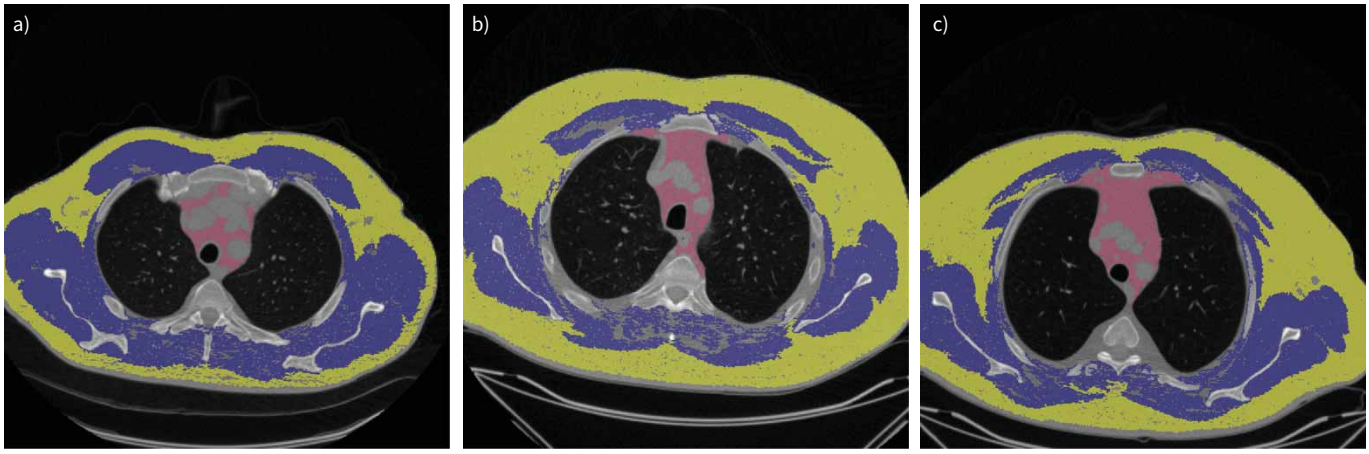

FIGURE 2 Population overview showing large variation in tissue distribution. Yellow: subcutaneous fat; pink: visceral fat; blue: skeletal muscle. a) Large amount of muscle. b) Large amount of subcutaneous fat. c) Large amount of visceral fat.

analysed using the independent t-test (ANOVA). A p-value of 0.05 or lower was considered significant. *Post hoc* Tukey was used to determine the significantly different groups.

To understand the possible effect of confounders on the association of emphysema and bronchial wall thickness with the measures of thoracic fat and muscle, general linear models (GLM) were specified adjusting for age, pack-years and smoking status. Separate GLMs were created for the Perc15 and Pi10 quartiles. Separate GLMs were used because Perc15 and Pi10 are correlated, and thus should not be part of the same model. Subcutaneous fat, visceral fat and skeletal muscle area were chosen to be the dependent variables. Data are presented as mean±SD and median (interquartile range (IQR)) depending on the distribution unless stated otherwise.

Results

Study population

The study population comprised 1031 male participants who underwent pre-bronchodilator spirometry in addition to the lung cancer screening CT scan. The participants had a median (IQR) age of 61.5 (58.6–65.6) years and median pack-years of 38.0 (28.0–49.5). 549 (53.2%) participants were current smokers. Based on spirometry, COPD was diagnosed in 396 participants (38.4%), including 256 staged GOLD 1, 117 GOLD 2 and 23 GOLD 3. Detailed characteristics for the No COPD and COPD groups are shown in table 1. The COPD group was significantly older, had more pack-years and comprised relatively more current smokers. Age, number of pack-years and smoking status did not differ between the groups based on GOLD stage (supplementary table E1). Bronchial wall thickness data were only available for 1012 participants. BMI data were only available for 849 participants and were not analysed, but are reported. Intraclass correlation coefficients between observers were excellent for subcutaneous fat area (0.988), visceral fat area (0.937) and skeletal muscle area (0.957). The fat and muscle measurements stratified by the Perc15 quartiles, Pi10 quartiles and COPD stage are shown visually in figure 3. Distribution histograms of fat and muscle measurements, Perc15 and Pi10 can be seen in supplementary figures E1 to E9, showing they are all normally distributed.

COPD and body composition differences

The outcomes of the fat and muscle measurements stratified by the presence of COPD are reported in table 1. Individuals with COPD had less subcutaneous fat (no COPD: 150.5 cm^2, COPD: 126.4 cm^2, 16% less)

TABLE 1 Characteristics of the 1031 included male participants subdivided by COPD status

	Total group	No COPD	COPD	p-value (between no COPD and COPD)
Participants n	1031	635	396	
Age years, median (IQR)	61.5 (7.1)	61.2 (6.9)	62.3 (7)	**0.013**
Pack-years smoked, median (IQR)	38 (21.5)	34.2 (18.3)	38.7 (19.8)	**0.002**
Current smoker, n (%)	549 (53.20)	316 (49.80)	233 (58.80)	**0.004**
FEV_1 % predicted, mean±SD	96.8±17.3	103.5±13.7	86±17.2	**<0.001**
FEV_1/FVC %, mean±SD	71.7±9	76.7±4.9	63.6±8.1	**<0.001**
Subcutaneous fat cm^2, mean±SD	141.2±53.3	150.5±51.8	126.4±52.4	**<0.001**
Visceral fat cm^2, mean±SD	12.6±5.2	13.3±5.3	11.6±4.8	**<0.001**
Skeletal muscle cm^2, mean±SD	227.2±30.2	231.5±30.3	220.4±28.7	**<0.001**
Dorsal muscle cm^2, mean±SD	42.5±6.3	42.8±6.1	42.0±6.5	0.074
Shoulder muscle cm^2, mean±SD	123.5±19.6	125.7±19.9	119.9±18.4	**<0.001**
Intercostal muscle cm^2, mean±SD	14.4±3.6	14.6±3.5	13.9±3.8	**0.002**
Pectoral muscle cm^2, mean±SD	46.9±9.6	48.5±9.6	44.5±9.0	**<0.001**
Perc15 HU, mean±SD	−907.9±19	−902.5±17.8	−916.7±17.5	**<0.001**
Pi10 mm, mean±SD	2.4±0.5	2.3±0.4	2.6±0.5	**<0.001**
BMI $kg \cdot m^{-2}$, mean±SD	26.3±3.4	26.9±3.3	25.3±3.4	**<0.001**
Missing, n	182	107	75	

p-values for age and pack-years smoked calculated using Kruskal–Wallis, all others calculated using ANOVA. Significant data ($p<0.05$) are highlighted in bold. IQR: interquartile range; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; HU: Hounsfield unit; Perc15: computed tomography emphysema HU value at percentile 15; Pi10: bronchial wall thickness at lumen perimeter 10 mm; BMI: body mass index.

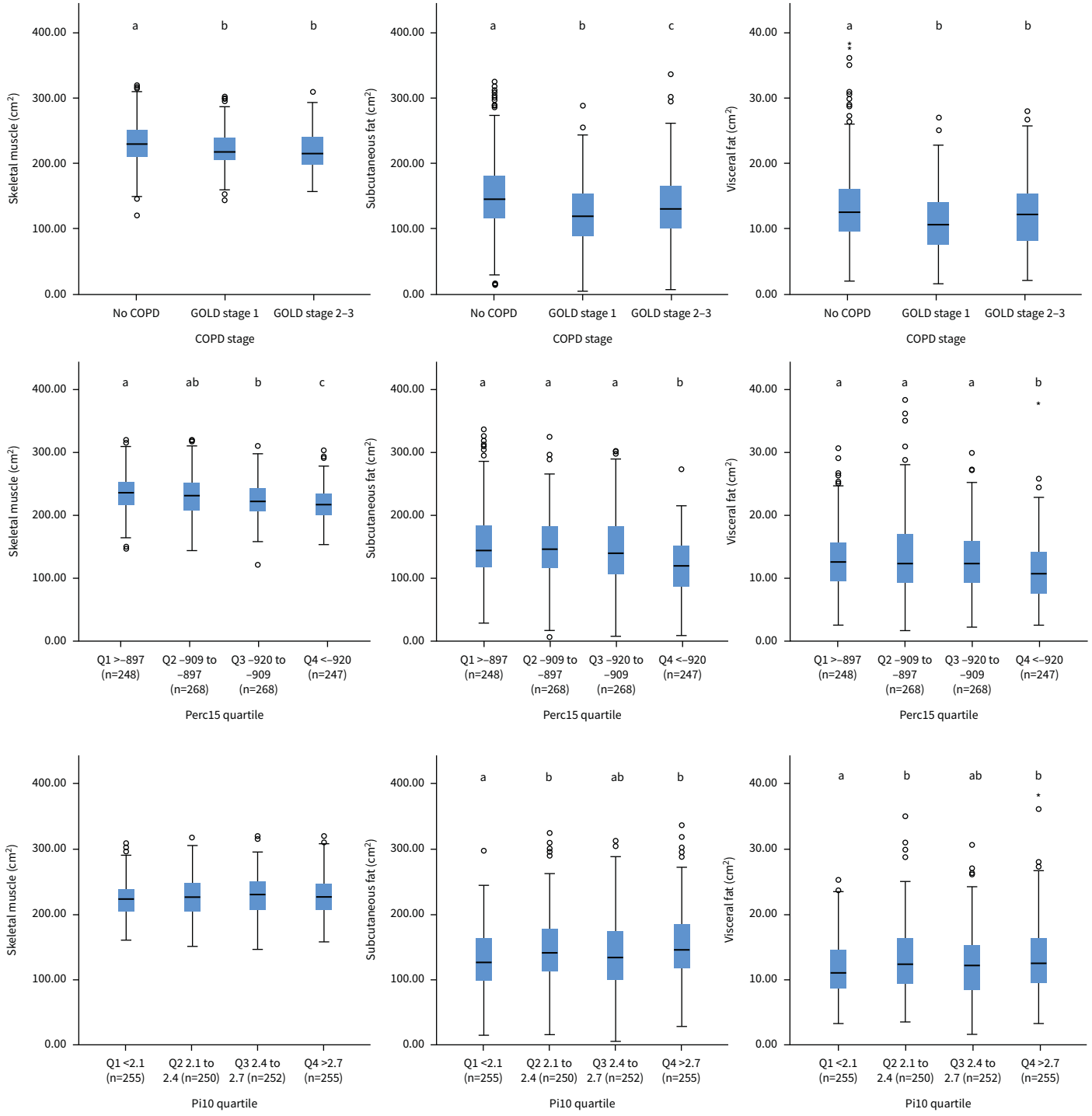

FIGURE 3 Boxplots showing group quartile differences for COPD stages in the first row, Perc15 quartiles in the second row and Pi10 quartiles in the third row. The letters above the columns indicate *post hoc* Tukey group. Perc15: computed tomography emphysema Hounsfield unit value at percentile 15; Pi10: bronchial wall thickness at lumen perimeter 10 mm; GOLD: Global Initiative for Chronic Obstructive Lung Disease. Values more than 1.5 times IQR below Q1 or above Q3 are indicated by circles, and values more than 3.0 times IQR below Q1 or above Q3 are indicated by asterisks.

and visceral fat (no COPD: 13.3 cm^2, COPD: 11.6 cm^2, 12.9% less), as well as less skeletal muscle (no COPD: 231.5 cm^2, COPD: 220.4 cm^2, 4.7% less) ($p<0.001$ for all). With increasing GOLD stages (GOLD 1 to GOLD 2–3) the subcutaneous fat amount (121.7 *versus* 135.0 cm^2, $p=0.017$) was higher (figure 3, supplementary table E1).

Emphysema and body composition differences

More severe emphysema was correlated with reductions in fat and muscle (figure 3). With increasing severity of CT-derived emphysema (Q1 Perc15 *versus* Q4 Perc15), subcutaneous fat decreased on average by 22.3%, from 153.3 to 119.1 cm^2. Visceral fat decreased on average by 13.8%, from 13.0 to 11.2 cm^2, while skeletal muscle decreased on average by 7.6%, from 235.0 to 217.2 cm^2 ($p<0.001$ for all). The *post hoc* Tukey test result shows that the amount of skeletal muscle was already significantly different in Q2 *versus* Q1 (supplementary table E2).

Bronchial wall thickening and body composition differences

In contrast to emphysema, a higher value of Pi10, indicating thicker bronchial walls, showed significant association with higher amounts of subcutaneous and visceral fat (figure 3). From Q1 Pi10 to Q4 Pi10, subcutaneous fat increased on average by 14.7% from 130.7 cm^2 to 149.9 cm^2 ($p<0.001$). Visceral fat increased by 13.6% from 11.7 cm^2 to 13.2 cm^2 ($p<0.001$). No significant difference was found for muscle area ($p=0.065$). The *post hoc* Tukey test result shows that the amount of fat was already significantly different in Q2 *versus* Q1 (supplementary table E3).

Separate analysis of former and current smokers

For Perc15 and Pi10, when splitting the dataset by former and current smokers, no differences in the presence of statistical relationships were observed. Both groups (former *versus* current smoker) showed significant differences between Perc15 quartiles for subcutaneous ($p<0.001$ for both) and visceral ($p<0.001$ and $p=0.001$) fat, and for skeletal muscle ($p<0.001$ and $p=0.004$). For Pi10 quartiles there were significant differences for subcutaneous ($p=0.032$ and $p=0.001$) and visceral ($p=0.019$ and $p=0.012$) fat but not for skeletal muscle ($p=0.090$ and $p=0.664$).

Significance of separate muscle groups

The separate dorsal, shoulder, intercostal and pectoral muscle areas had different statistical relationships from each other with COPD, Perc15 and Pi10. Boxplots of these muscle group areas are shown in supplementary figure E10. Individuals with COPD had less shoulder ($p<0.001$), intercostal ($p=0.002$) and pectoral ($p<0.001$) muscle (table 1). No muscle groups were significantly different between GOLD 1 and GOLD 2–3 (supplementary table E1).

More severe emphysema was correlated with less shoulder and pectoral muscle ($p<0.001$ for both). The *post hoc* Tukey test result shows the amount of muscle was already significantly different in Q2 *versus* Q1 (supplementary table E2).

Higher values of Pi10 were correlated with less shoulder muscle ($p=0.012$). The *post hoc* Tukey test result shows the amount of muscle was already significantly different in Q2 *versus* Q1 (supplementary table E3).

Relation of confounders and outcomes

In GLM analysis of the influence of confounders on the association of emphysema and bronchial wall thickness with the thoracic fat and muscle measurements, some significant relationships between the thoracic fat and muscle measurements and age, pack-years, or smoking status were observed (tables 2 and 3). For Perc15, age had a significant effect on skeletal muscle ($p<0.001$), smoking status had a significant effect on subcutaneous and visceral fat and skeletal muscle ($p<0.0001$ for all), and pack-years had a significant effect on subcutaneous fat ($p=0.008$). For Pi10, age had a significant effect on skeletal muscle ($p<0.001$), smoking status had a significant effect on subcutaneous and visceral fat ($p<0.001$) and skeletal muscle ($p=0.011$), and pack-years had a significant effect on subcutaneous fat ($p=0.003$). However, based on these analyses, when corrected for confounders, no significant relationships of interest changed (supplementary table E1 to E3).

Discussion

In a cohort of male current and former smokers with and without COPD who participated in lung cancer screening, we investigated the relation of early CT signs of emphysema and bronchial wall thickening with CT-derived measures of thoracic fat and muscle. We observed significant differences in amounts of fat and muscle by GOLD stage, emphysema severity and bronchial wall thickness. The group with COPD had smaller areas of fat and muscle. Increasing emphysema severity was associated with smaller areas of fat and muscle, whereas increasing bronchial wall thickening was associated with more subcutaneous and visceral fat but not muscle. Interestingly, a smaller muscle area was already seen in participants in the 2nd quartile of Perc15, and larger areas of fat were already seen in the 2nd quartile of Pi10. The findings remained similar in GLM that adjusted for confounders. This suggests that the classic end-stage COPD phenotypes characterised by either cachexia and emphysema (pink puffers) or fat accumulation and

TABLE 2 Parameter estimates for the general linear models with only quartiles of Perc15 as fixed independent variable

Dependent variable	Parameter estimate	Standard error	p-value
Subcutaneous fat cm^2			
Intercept	129.268	20.261	**<0.001**
Age	−0.131	0.314	0.677
Current smoker	−21.51	3.339	**<0.001**
Pack-years	0.244	0.091	**0.008**
GOLD stage	−3.494	2.228	0.117
Perc15 Q1	37.697	5.058	**<0.001**
Perc15 Q2	31.409	4.778	**<0.001**
Perc15 Q3	24.077	4.638	**<0.001**
Perc15 Q4	reference[#]		
Visceral fat cm^2			
Intercept	11.47	2.034	**<0.001**
Age	0.004	0.032	0.904
Current smoker	−1.649	0.335	**<0.001**
Pack-years	0.011	0.009	0.222
GOLD stage	−0.287	0.224	0.199
Perc15 Q1	2.052	0.508	**<0.001**
Perc15 Q2	2.316	0.48	**<0.001**
Perc15 Q3	1.484	0.466	**0.001**
Perc15 Q4	reference[#]		
Skeletal muscle cm^2			
Intercept	302.521	11.450	**<0.001**
Age	−1.218	0.178	**<0.001**
Current smoker	−6.692	1.887	**<0.001**
Pack-years	−0.037	0.052	0.475
GOLD stage	−3.580	1.259	**0.005**
Perc15 Q1	14.126	2.859	**<0.001**
Perc15 Q2	11.402	2.700	**<0.001**
Perc15 Q3	5.907	2.621	**0.024**
Perc15 Q4	reference[#]		
Dorsal muscle cm^2			
Intercept	60.243	2.457	**<0.001**
Age	−0.273	0.038	**<0.001**
Current smoker	−0.754	0.405	0.063
Pack-years	−0.008	0.011	0.449
GOLD stage	−0.352	0.270	0.193
Perc15 Q1	−0.058	0.613	0.924
Perc15 Q2	0.564	0.579	0.330
Perc15 Q3	0.347	0.562	0.537
Perc15 Q4	reference[#]		
Shoulder muscle cm^2			
Intercept	162.419	7.553	**<0.001**
Age	−0.651	0.117	**<0.001**
Current smoker	−3.343	1.245	**0.007**
Pack-years	−0.023	0.034	0.492
GOLD stage	−1.228	0.831	0.140
Perc15 Q1	9.312	1.886	**<0.001**
Perc15 Q2	7.428	1.781	**<0.001**
Perc15 Q3	3.735	1.729	**0.031**
Perc15 Q4	reference[#]		
Intercostal muscle cm^2			
Intercept	21.360	1.432	**<0.001**
Age	−0.101	0.022	**<0.001**
Current smoker	−0.457	0.236	0.053
Pack-years	−0.005	0.006	0.395
GOLD stage	−0.482	0.157	**0.002**
Perc15 Q1	0.063	0.357	0.860
Perc15 Q2	−0.033	0.338	0.922

Continued

TABLE 2 Continued

Dependent variable	Parameter estimate	Standard error	p-value
Perc15 Q3	0.008	0.328	0.980
Perc15 Q4	reference[#]		
Pectoral muscle cm^2			
Intercept	58.499	3.683	**<0.001**
Age	−0.194	0.057	**0.001**
Current smoker	−2.139	0.607	**<0.001**
Pack-years	0.000	0.017	0.980
GOLD stage	−1.519	0.405	**<0.001**
Perc15 Q1	4.809	0.920	**<0.001**
Perc15 Q2	3.443	0.869	**<0.001**
Perc15 Q3	1.817	0.843	**0.031**
Perc15 Q4	reference[#]		

Significant data (p<0.05) are highlighted in bold. The parameter estimate indicates how much of the difference in measured tissue area is caused relative to the reference by every year of age, being a current smoker, every pack-year, GOLD stage group and specific quartile of Perc15. Perc15: computed tomography emphysema HU value at percentile 15; GOLD: Global Initiative for Chronic Obstructive Lung Disease. [#]: this parameter is set to zero because it is redundant.

TABLE 3 Parameter estimates for the general linear models with only quartiles of Pi10 as fixed independent variable

Dependent variable	Parameter estimate	Standard error	p-value
Subcutaneous fat cm^2			
Intercept	178.392	20.336	**<0.001**
Age	−0.264	0.32	0.408
Current smoker	−16.162	3.3	**<0.001**
Pack-years	0.28	0.094	**0.003**
GOLD stage	−14.915	2.248	**<0.001**
Pi10 Q1	−31.292	4.835	**<0.001**
Pi10 Q2	−13.843	4.797	**0.004**
Pi10 Q3	−14.98	4.636	**0.001**
Pi10 Q4	reference[#]		
Visceral fat cm^2			
Intercept	14.698	1.991	**<0.001**
Age	−0.004	0.031	0.9
Current smoker	−1.298	0.323	**<0.001**
Pack-years	0.014	0.009	0.142
GOLD stage	−1.061	0.22	**<0.001**
Pi10 Q1	−2.49	0.473	**<0.001**
Pi10 Q2	−0.759	0.47	0.106
Pi10 Q3	−1.349	0.454	**0.003**
Pi10 Q4	reference[#]		
Skeletal muscle cm^2			
Intercept	313.889	11.130	**<0.001**
Age	−1.277	0.175	**<0.001**
Current smoker	−4.168	1.806	**0.011**
Pack-years	−0.043	0.051	0.524
GOLD stage	−7.282	1.230	**<0.001**
Pi10 Q1	−8.733	2.646	**<0.001**
Pi10 Q2	−5.687	2.625	**0.013**
Pi10 Q3	−1.030	2.537	0.631
Pi10 Q4	reference[#]		
Dorsal muscle cm^2			
Intercept	60.455	2.443	**<0.001**
Age	−0.273	0.038	**<0.001**
Current smoker	−0.763	0.396	0.054

Continued

TABLE 3 Continued

Dependent variable	Parameter estimate	Standard error	p-value
Pack-years	−0.009	0.011	0.404
GOLD stage	−0.408	0.270	0.131
Pi10 Q1	0.014	0.581	0.981
Pi10 Q2	0.023	0.576	0.968
Pi10 Q3	0.331	0.557	0.553
Pi10 Q4	reference[#]		
Shoulder muscle cm^2			
Intercept	173.407	7.540	**<0.001**
Age	−0.687	0.118	**<0.001**
Current smoker	−2.069	1.223	0.091
Pack-years	−0.016	0.035	0.642
GOLD stage	−4.043	0.833	**<0.001**
Pi10 Q1	−7.346	1.793	**<0.001**
Pi10 Q2	−3.933	1.778	**0.027**
Pi10 Q3	−0.792	1.719	0.645
Pi10 Q4	reference[#]		
Intercostal muscle cm^2			
Intercept	21.929	1.420	**<0.001**
Age	−0.105	0.022	**<0.001**
Current smoker	−0.475	0.230	**0.040**
Pack-years	−0.008	0.007	0.210
GOLD stage	−0.550	0.157	**<0.001**
Pi10 Q1	−0.118	0.338	0.727
Pi10 Q2	−0.237	0.335	0.479
Pi10 Q3	−0.188	0.324	0.561
Pi10 Q4	reference[#]		
Pectoral muscle cm^2			
Intercept	64.554	3.693	**<0.001**
Age	−0.218	0.058	**<0.001**
Current smoker	−1.458	0.599	**0.015**
Pack-years	8.246E-05	0.017	0.996
GOLD stage	−2.969	0.408	**<0.001**
Pi10 Q1	−3.161	0.878	**<0.001**
Pi10 Q2	−2.577	0.871	**0.003**
Pi10 Q3	−0.609	0.842	0.470
Pi10 Q4	reference[#]		

Significant data (p<0.05) are highlighted in bold. The parameter estimate indicates how much of the difference in measured tissue area is caused relative to the reference by every year of age, if the patient is a smoker, every pack-year, GOLD stage group and specific quartile of Pi10. Pi10: bronchial wall thickness at lumen perimeter 10 mm; GOLD: Global Initiative for Chronic Obstructive Lung Disease. [#]: this parameter is set to zero because it is redundant.

bronchial wall thickening (blue bloaters) may already exist at a mild stage of disease in smokers fit enough for potential lung surgery.

Visceral fat is known to produce hormones and cytokines that may induce inflammation [10], as seen in bronchitis and emphysema. Patients with thicker bronchial walls did have more visceral fat. It could represent a vicious circle of inflammatory bronchitis that is enhanced by inflammation from the metabolically active visceral fat compartment, similar to some other chronic inflammatory diseases such as atherosclerosis [34]. The decrease observed for visceral and subcutaneous fat with increasing emphysema severity was significant, with a larger reduction of subcutaneous fat than visceral fat. This suggests that in the early stage of emphysema fat loss occurs in both compartments, but more rapidly in the subcutaneous fat compartment. It also suggests that emphysema has a different underlying disease process compared to bronchitis, which is mainly caused by chronic inflammation. We speculate that the physical exertion of breathing in patients with emphysema could play a role in cachexia, but other mechanistic processes could also lead to wasting in emphysema.

Owing to clear inclusion and exclusion criteria, our cohort consisted of heavy (former) male smokers who were relatively healthy. Most patients in the COPD group were classified as GOLD 1, despite smoking on

average 38 pack-years. We observed significantly less fat and muscle in the COPD group compared to the group without COPD. This shows that even in patients with mild COPD, fat and muscle areas are affected. A significantly higher age in the COPD group compared to the group without COPD might, to some extent, also contribute to the differences in the amount of fat and muscle, as increasing age is related to lower subcutaneous fat and muscle amounts [35, 36]. However, age did not differ significantly between GOLD stages. The GLM analysis showed that age, when stratified by COPD presence or GOLD stage, had a small but significant effect on amount of skeletal muscle but not on the amount of fat. The relationship between age and skeletal muscle did not affect the observed statistical relationship between COPD and skeletal muscle.

Clinical importance

Using CT scans to quantify thoracic fat and muscle may help in diagnosing cachexia or sarcopenia and accumulation of visceral fat in an early stage of smoking-related disease, even when using low-dose scans. Early diagnosis might be helpful for effective management and prognosis, and prevention of muscle loss or fat accumulation by rehabilitation and lifestyle modification may be effective [37]. COPD and emphysema patients with loss of muscle or muscle weakness may benefit from muscle strengthening, as this may reduce exacerbations [12, 38, 39]. Furthermore, there may be a role for diet optimisation or supplementation to improve body composition and reduce cachexia. On the contrary, weight loss without reduction of skeletal muscle mass may be important for bronchitis-dominant patients as this is associated with improved clinical status [40].

Strengths and limitations

Strengths of our study are that we included a large cohort with low-dose CT scans and mostly participants without or with mild COPD, based on lung function criteria. Even stronger associations may be present in COPD patients with poorer disease condition and health status.

Our study has several limitations. First, our study group comprises only men. Fat distribution differs between men and women [41, 42]. This may have an impact when investigating a whole population, especially since susceptibility to COPD development in women seems to be greater than in men [43]. Second, in some cases the field of view of the CT scan did not cover the entire chest. This results in a bias towards underestimation of the amount of subcutaneous fat and muscle (figure 2), which could potentially result in bias towards zero effect. Nevertheless, significant differences were still found in subcutaneous fat between patients with emphysema and bronchial wall thickening. Methods are being developed to correct for an insufficient field of view [44]. Third, each type of fat and muscle was measured as an area on a single 3.1-mm CT slice. Therefore, the position of the patient and the slice selection may have influenced the results to some extent, as we did not employ full volumetric measurements. The associations we found might differ slightly in strength when looking at volume instead of area. Fourth, the quantitative methods for scoring emphysema are influenced by the low-dose scanning protocol, as this protocol decreases the signal to noise ratio, reducing measurement accuracy. Fifth, we also wished to analyse if specific muscle groups had individual significant differences based on disease severity, but only a composite measurement of all muscle groups added together showed significant relationships with disease severity. This is likely due to insignificant individual differences adding up to a larger, statistically significant difference. Sixth, a lower visceral fat measurement in Pi10 Q3 compared to Q2 and Q4 was observed. This can likely be attributed to measurement noise, as the overall correlation between Pi10 and visceral fat remains. Seventh, only pre-bronchodilator spirometry was performed, due to the limited time available in the lung cancer screening setting, while COPD is defined as post-bronchodilator FEV_1/FVC <70%. Eighth, in 2.2% of patients (23) in our dataset lung cancer was detected during one of the screening rounds. This is unlikely to affect our overall conclusion.

Conclusion

In patients with smoking-related pulmonary disease, mild COPD and mild emphysema are already associated with lower amounts of fat and muscle, and mild bronchial wall thickening is associated with fat accumulation. This may provide important information for prognosis and for personalised management of changes in body composition caused by early or mild smoking-related lung disease.

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