






# Somatotypes trajectories during adulthood and their association with COPD phenotypes

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## ABSTRACT

**Rationale:** Chronic obstructive pulmonary disease (COPD) comprises distinct phenotypes, all characterised by airflow limitation.

**Objectives:** We hypothesised that somatotype changes – as a surrogate of adiposity – from early adulthood follow different trajectories to reach distinct phenotypes.

**Methods:** Using the validated Stunkard's Pictogram, 356 COPD patients chose the somatotype that best reflects their current body build and those at ages 18, 30, 40 and 50 years. An unbiased group-based trajectory modelling was used to determine somatotype trajectories. We then compared the current COPD-related clinical and phenotypic characteristics of subjects belonging to each trajectory.

**Measurements and main results:** At 18 years of age, 88% of the participants described having a lean or medium somatotype (estimated body mass index (BMI) between 19 and 23 kg·m<sup>-2</sup>) while the other 12% a heavier somatotype (estimated BMI between 25 and 27 kg·m<sup>-2</sup>). From age 18 onwards, five distinct trajectories were observed. Four of them demonstrating a continuous increase in adiposity throughout adulthood with the exception of one, where the initial increase was followed by loss of adiposity after age 40. Patients with this trajectory were primarily females with low BMI and  $D_{LCO}$  (diffusing capacity of the lung for carbon monoxide). A persistently lean trajectory was seen in 14% of the cohort. This group had significantly lower forced expiratory volume in 1 s (FEV<sub>1</sub>),  $D_{LCO}$ , more emphysema and a worse BODE (BMI, airflow obstruction, dyspnoea and exercise capacity) score thus resembling the multiple organ loss of tissue (MOLT) phenotype.

**Conclusions:** COPD patients have distinct somatotype trajectories throughout adulthood. Those with the MOLT phenotype maintain a lean trajectory throughout life. Smoking subjects with this lean phenotype in early adulthood deserve particular attention as they seem to develop more severe COPD.



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**In smoking-related COPD, somatotype trajectories are associated with the final COPD phenotype. Specifically, the “pink puffer” or multiorgan loss of tissue (MOLT) phenotype occurs where the patient remains lean.** <https://bit.ly/2YNhwfu>

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## Introduction

Chronic obstructive pulmonary disease (COPD) is recognised as a phenotypically heterogeneous clinical syndrome characterised by chronic respiratory symptoms, different degrees of structural pulmonary abnormalities, lung function impairment and extrapulmonary manifestations. COPD is usually diagnosed after the 5th decade of life, although its origin begins in the early stages of life as a result of the cumulative effect of different exposures and complex interactions between genetic, epigenetic and age-related factors in susceptible individuals [1]. This long latency period from the initial exposures to clinical diagnosis makes it difficult to study the natural history of COPD. In recent years we have learned that the development of airway obstruction can follow different trajectories starting at an early age [2]; however, little is known as to why individuals develop distinct COPD phenotypes.

The initial description of distinct COPD phenotypes dates back to the 1950s with the characterisation of the predominantly emphysematous phenotype commonly called the “pink puffer” and a predominantly bronchitic phenotype called the “blue bloater” [3]. More recently, studies using hypothesis-free cluster analysis resulted in the description of three to five discrete COPD phenotypes [4–8]. While the reproducibility of specific clusters among different COPD cohorts is modest, the classic “pink puffer” and “blue bloater” phenotypes tend to recur across multiple cohorts [9]. More recently, the original “pink puffer” phenotype was refined and the term multiorgan loss of tissue phenotype (MOLT) was coined [10]. These patients are characterised by having more emphysema, worse airflow obstruction and higher BODE (BMI, airflow obstruction, dyspnoea and exercise capacity) score, being more prone to exacerbations, suffering a higher mortality and having a lower body mass index (BMI).

Interestingly, in all of these studies one of the most salient clinical traits that differentiates between these phenotypes is the BMI, suggesting that adipose tissue may have a modulating effect in response to cigarette smoking [11]. In support of this idea, investigators from two landmark epidemiological cohorts (The Nurses’ Health Study and the Health Professionals Follow-up Study) demonstrated that adiposity changes throughout the life course predict the subsequent risk for chronic diseases and mortality [12–14]. They employed a Group-Based Multi-trajectory Modelling technique to participants’ recalled body builds at different age points to identify distinct subgroups of participants with a similar trajectory of body shape from childhood to age 50.

We hypothesised that changes in somatotypes – as a surrogate of the degree of adiposity – throughout adult life follow different trajectories to reach the subsequent COPD phenotype. More specifically, we sought to investigate if patients with the MOLT phenotype were signalled from an early age to manifest a different somatic response to the effects of cigarette smoke.

## Methods

### Study population

Participants were recruited from the BODE collaborative group (Tenerife, Gran Canarias, Pamplona and Zaragoza sites) and from the COPDGene study (Brigham and Women’s Hospital – Boston clinical site). In the BODE cohort, regular follow-up examination visits occur at ~12- to 24-month intervals. Subjects in COPDGene–Boston cohort were included for this study at the follow-up visit, ~5 years after the initial enrolment. In both cohorts, COPD was defined by a history of smoking of at least 10 pack-years and a ratio of forced expiratory volume in 1 s ( $FEV_1$ ) to forced vital capacity (FVC) of  $<0.7$  measured 20 min after the administration of albuterol. Details of the inclusion and exclusion criteria for both cohorts have been described elsewhere [15, 16]. For the present analyses, participants were also asked to complete the validated Stunkard’s somatotype questionnaire [17] (figure 1) during their visit that occurred between October 2013 and June 2017. The ethics committee at each of the participating centres approved the study, and all patients provided written informed consent before enrolment.

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Which diagram below best depicts your outline at a given age?

The figure displays two rows of nine line drawings each, representing a scale of body mass from 1 (slim) to 9 (obese). The top row shows female figures, and the bottom row shows male figures. Below each row is a grid of circles for selection. The rows are labeled: 'Age 18 years', 'Age 30 years', 'Age 40 years', 'Age 50 years', and 'Currently'. The columns are numbered 1 through 9.

	1	2	3	4	5	6	7	8	9
Age 18 years	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Age 30 years	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Age 40 years	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Age 50 years	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Currently	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**FIGURE 1** Stunkard's Pictogram. Figure drawings used to assess body shape at ages 18, 30, 40 and 50, and at study evaluation.

#### Assessment of body shape

The Stunkard's Pictogram is a validated instrument of nine line drawings of human figures reflecting the spectrum of body physiques or somatotypes (figure 1) [17]. Participants were asked to select the somatotype diagram that best depicted their current body build and those at ages 18, 30, 40 and 50 years. The validity of long-term recall of somatotypes and their correlation with related BMI was assessed among 181 participants aged 71–76 years in the Third Harvard Growth Study [18]. In this study they reported a correlation of 0.63 for men and 0.74 for women between the chosen figure and the subject's recall of height and weight >50 years ago. The utility of this instrument was also validated in large epidemiology studies to estimate adiposity trajectories across the life course [12–14, 19, 20].

#### Ascertainment of outcomes and other covariates

Demographics, smoking history (age of smoking initiation, number of cigarettes per day, date of smoking cessation), anthropometrics (assessed by the BMI in  $\text{kg}\cdot\text{m}^{-2}$ ), pulmonary function tests ( $\text{FEV}_1/\text{FVC}$ ,  $\text{FEV}_1$  % predicted and diffusing capacity of the lung for carbon monoxide ( $D_{\text{LCO}}$ ) % predicted) and 6-min walking distance tests were performed according to international guidelines [21, 22]. The BODE index was calculated as previously reported [16]. Emphysema was assessed by visual quantification of lung parenchyma from available chest computed tomography studies by two independent expert radiologists (GB and AE) using validated criteria [23, 24]. The extent of emphysema was graded from 0 to 4, with a grade of 0 indicating no emphysema, grade 1 indicating 1–25%, grade 2 indicating 25–50%, grade 3 indicating 50–75% and grade 4 indicating the presence in >75% of emphysema in the lungs.

#### Statistical analysis

For categorical variables reported as proportions we used the Chi-squared test. For continuous variables reported as means (95% CI) we used the t-test. To present a more meaningful interpretation of the Stunkard's Pictogram scale to BMI in  $\text{kg}\cdot\text{m}^{-2}$ , we fitted a linear regression model with current BMI as the outcome, somatotype at the time of study visit as predictor and sex as covariate and interaction term. We then used the regression coefficient and the reported somatotype at the time of visit to convert the nine-points scale and reported the strength of correlation between the pictogram and BMI for each sex.

We used a group-based trajectory modelling approach to identify subjects that share similar somatotype trajectories using subjects' chosen somatotype scores at the time of visit and those at ages 18, 30, 40 and

50. Thus, subjects are assigned to the trajectory group to which they have the highest probability of belonging. Based on the trajectory modelling analysis and clinical interpretability, we selected the model with five trajectories for this analysis (see details in the supplementary material). After group trajectories were assigned, we then compared the phenotypic characteristics (sex, BMI, FEV<sub>1</sub> % pred, FEV<sub>1</sub>/FVC, D<sub>LCO</sub>, BODE score, presence and extent of emphysema) and exposure to tobacco (age of smoking initiation, pack-years) between each of the five trajectory-based groups to determine if somatotype trajectories are associated with specific COPD phenotypes. Differences in these phenotypic characteristics amongst the five trajectory-based groups were tested using ANOVA for continuous variables and a Chi-squared test for categorical variables. Missing data were imputed using the low-rank matrix approximation provided as the Automated Data Imputation function in JMP.

We compared subjects' characteristics from the BODE and COPDGene cohorts to prevent selection bias and enhance internal validity. Statistical significance was considered at the level of p<0.05. For the group-based trajectory modelling analysis we used the Stata® (StataCorp. 2017, Stata Statistical Software: Release 15; StataCorp LLC, College Station, TX, USA) plug-in command "traj" available at [www.andrew.cmu.edu/user/bjones/](http://www.andrew.cmu.edu/user/bjones/) [25]. All other analyses were performed using SAS JMP Pro® software, version 14.0 (SAS Institute, Cary, NC, USA).

## Results

### Descriptive

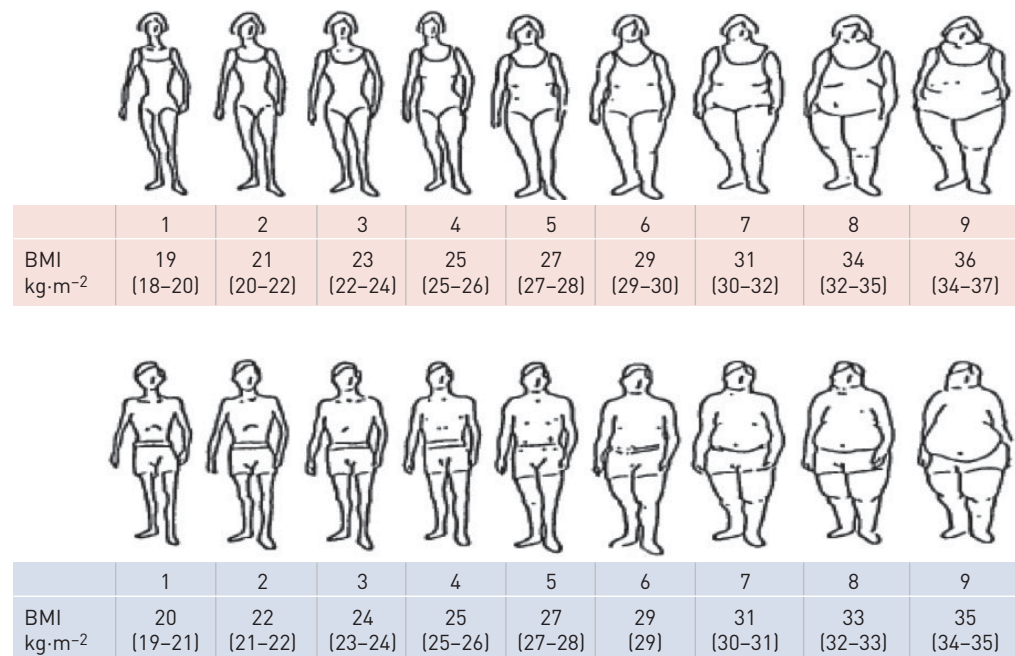
The combined cohorts included 356 subjects with COPD with a mean age of 67 years (95% CI 66–68) and mean BMI of 27.2 kg·m<sup>-2</sup> (95% CI 26.7–27.7); 68% were males. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric classification, 33% had mild, 45% had moderate and 22% had severe or very severe airflow limitation.

### Pictogram correlation

The Pearson correlation between the current body build and the BMI at time of visit was 0.77 (95% CI 0.73–0.81). The prediction equation for BMI obtained from fitting the current somatotype score is:

$$\text{BMI} = 17.6 \text{ (95\% CI 16.7–18.5)} + 1.9 \text{ (95\% CI 1.8–2.1)} \times \text{somatotype score}$$

This regression formula suggests that every increase in somatotype unit represents an increase of almost 2 kg·m<sup>-2</sup> in BMI (figure 2 and supplementary figure E1). There was no statistical difference in the parameter estimates between males and females.



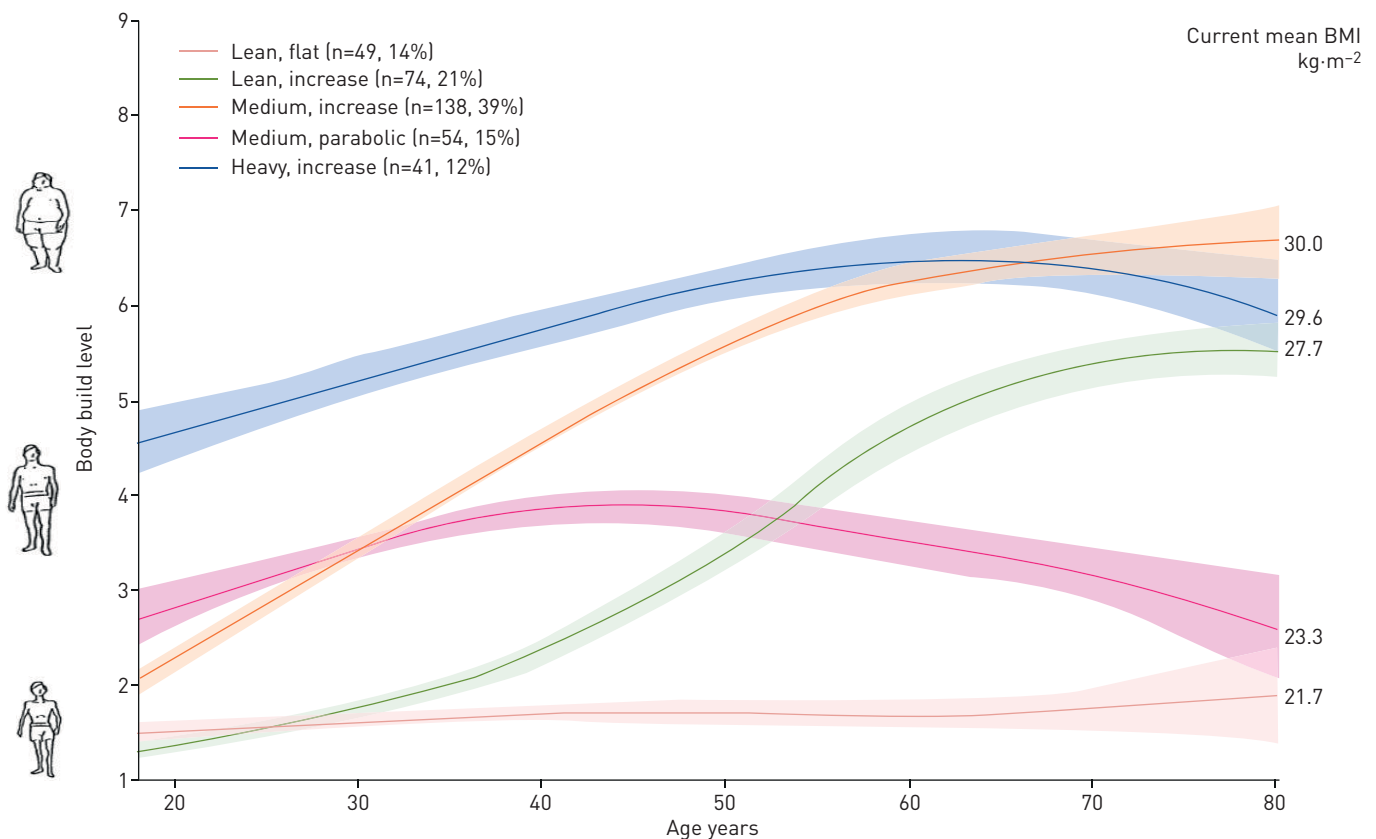
**FIGURE 2** Predicted BMI for each somatotype's values. We assigned a body mass index [BMI] value to each somatotype based on the regression formula obtained from participants' current BMI and somatotype score. Values are expressed as mean and 95% confidence interval.

### Body shapes trajectories

As shown in figure 3, we named each trajectory group using a descriptor based on their initial point at age 18 (intercept) and the directionality of the trajectory as Lean-Flat, Lean-Increase, Medium-Increase and Medium-Parabolic and Heavy-Increase. The first group with a “Lean-Flat” trajectory comprises 14% (n=49) of the cohort, the second group with a “Lean-Increase” trajectory comprises 21% (n=74), the third group or “Medium-Increase” trajectory has 38% (n=138) subjects, the fourth group or “Medium-Parabolic” trajectory has 15% (n=54) subjects and the final group with a “Heavy-Increase” trajectory has 41 subjects or 12% of the cohort.

From table 1, we can observe that subjects in all five groups have similar mean age and similar proportions of current smokers, they initiated their smoking habit at a similar age and have the same cumulative smoking history. The majority have a tendency towards gaining and then sustaining adiposity, although at a different rate and starting point, during adult life except for the “Lean-Flat” and Medium-Parabolic” groups. Phenotypically the three progressive adiposity groups share similar characteristics, namely less obstruction, higher BMI and  $D_{LCO}$  and lower BODE scores. In contrast, the Lean-Flat group is distinctively different in the trajectory and phenotypic characteristics compared to the other groups. They remain lean throughout adult life and are significantly more obstructed, have a lower  $D_{LCO}$ , lower BMI, worse BODE score and more severe emphysema, resembling the clinical features of the implosive or MOLT phenotype described by *CELLI et al.* [10]. Next to the Lean-Flat group is the Medium-Parabolic trajectory group, sharing some of the characteristics of the former including a significantly lower BMI and second lowest  $D_{LCO}$ . However, this group has a higher proportion of females (49%) and a particular trajectory demonstrating an initial increase in adiposity followed by loss after age 40.

Supplementary table E2 shows that the 301 patients from the BODE cohort and 55 from the COPDGene–Boston cohort were similar in their clinical characteristics except that subjects from the BODE cohort were slightly younger.



**FIGURE 3** Somatotype trajectories throughout adult life. Each line represents a trajectory estimate and the shaded bands the 95% confidence interval fit of the mean.



TABLE 1 Comparison of phenotypic features for each of the five trajectory-based groups

	Lean-Flat	Lean-Increase	Medium-Increase	Medium-Parabolic	Heavy-Increase	p-value
<b>Subjects</b>	49 (14%)	74 (21%)	138 (38%)	54 (15%)	41 (12%)	
<b>Age years</b>	67±9	69±9	67±9	67±7	<b>65±10</b>	NS
<b>Male %</b>	67%	70%	71%	<b>51%</b>	78%	0.0434
<b>BMI kg·m<sup>-2</sup></b>	<b>21.7±4.0</b>	27.2±3.6	30.0±4.1	<b>23.3±3.1</b>	29.6±4.9	<0.0001
<b>Current smokers %</b>	42%	37%	32%	42%	42%	NS
<b>Age of smoking initiation years<sup>#</sup></b>	17±4	16±3	17±5	17±4	17±7	NS
<b>Cumulative smoking pack-years<sup>¶</sup></b>	67±36	64±28	56±28	57±33	62±32	NS
<b>FEV<sub>1</sub>/FVC %</b>	<b>48±13</b>	52±12	57±11	53±13	57±11	<0.0001
<b>FEV<sub>1</sub> % pred</b>	<b>60±23</b>	65±19	71±21	68±24	<b>68±19</b>	0.0142
<b>D<sub>LCO</sub> % pred<sup>*</sup></b>	<b>48±20</b>	61±21	68±20	<b>58±19</b>	67±24	<0.0001
<b>Subjects with emphysema %<sup>§</sup></b>	79%	52%	60%	63%	61%	NS
<b>Emphysema severity<sup>§</sup></b>	<b>1.5±1.0</b>	1.1±1.1	0.7±0.9	1.0±1.0	0.9±1.0	<0.0001
<b>BODE<sup>f</sup></b>	<b>2.3±1.6</b>	1.4±1.5	1.2±1.6	1.5±1.6	1.3±1.9	0.0026

Data are presented as mean±SD, unless otherwise stated. Group comparison was performed using ANOVA for continuous variables, a Chi-squared test for categorical variables. Those values that conferred a significant difference are highlighted in bold. Results in the table reflect estimates of parameters with imputed missing values. BMI: body mass index; FEV<sub>1</sub>: forced expiratory volume in 1 s; FVC: forced vital capacity; % pred: % predicted; D<sub>LCO</sub>: diffusing capacity of the lung for carbon monoxide; BODE: BMI, airflow obstruction, dyspnoea and exercise capacity. <sup>#</sup>: Data missing in 25 subjects with chronic obstructive pulmonary disease (COPD); <sup>¶</sup>: data missing in 75 subjects: 5 (10%) in Lean-Flat, 20 (27%) in Lean-Increase, 24 (17%) in Medium-Increase, 13 (24%) in Medium-Parabolic, 11 (27%) in Heavy-Increase group; <sup>\*</sup>: data missing in 71 subjects: 7 (17%) in Lean-Flat group, 16 (22%) in Lean-Increase, 30 (23%) in Medium-Increase, 14 (26%) in Medium-Parabolic, 4 (10%) in Heavy-Increase group; <sup>§</sup>: data missing in 113 subjects: 21 (43%) in Lean-Flat, 25 (34%) in Lean-Increase, 41 (30%) in Medium-Increase, 13 (24%) in Medium-Parabolic, 13 (32%) in Heavy-Increase group; <sup>f</sup>: data missing in 11 subjects.

## Discussion

Our study identified five distinct somatotype trajectories throughout adulthood in subjects with smoking-related COPD. Importantly, those trajectories related to the final phenotypic expression of the disease.

In our cohort, 88% of participants started with a lean body shape (estimated BMI between 20 and 24 kg·m<sup>-2</sup>) at age 18. But after the 3rd and 4th decade of life, 59% reported a steady increase in somatotype, a trend that is not unique to patients with COPD [13, 26]. What is novel in this study is that patients with the MOLT phenotype in late adulthood were found to have followed a lean (lack of adiposity) trajectory throughout life, starting from an early age. The 14% of participants who demonstrated this trajectory have many of the features of the MOLT phenotype, namely a lower BMI, worse airway obstruction, lower D<sub>LCO</sub>, more severe emphysema and a worse BODE score than subjects in the other groups (table 1).

Another noteworthy finding is the parabolic trajectory observed in 15% of the cohort, where there is an initial adiposity gain that peaked at age 40, followed by progressive loss thereafter. This subgroup had the largest proportion of females (49%) and also manifest some of the features of the MOLT phenotype, in this case the second lowest BMI and D<sub>LCO</sub> (figure 3 and table 1). Interestingly, this trajectory was also observed in the Nurses' Health Study [13], with women showing a steeper decline in adiposity after age 40. The investigators in that study named the trajectory as 'Lean-Stable', but little attention or explanation was given to its meaning. We speculate that since it is observed primarily in women, it may relate to life events after age 40, such as the post-childbearing stage. It is unlikely to be related to cigarette smoking, as smoking was not more prevalent in the 11 000 participants with this trajectory.

The association between subjects' BMI and COPD has been extensively studied. First, in two longitudinal studies of asymptomatic young and middle-aged adults, a low BMI at baseline was associated with a higher risk for developing *airway obstruction* during the 10 [27] and 15 [25] years of follow-up. Second, there is strong evidence that a low BMI is associated with increased mortality risk from respiratory causes in COPD patients [28, 29] as well as in the general population [30]. Third, the prevalence of certain comorbidities differs significantly between COPD patients with low and high BMI [31], and in addition the BMI is a salient feature varying between phenotypes in cluster analysis studies [4–7]. However, this evidence cannot explain what separates COPD patients into different phenotypes. Based on our findings and suggestions from previous reviews [11, 32, 33] we can speculate that some of the differences in COPD phenotypes may relate to the accumulation (or lack thereof) of adipose tissue and its response to the repetitive and cumulative effect of cigarette smoking. It is well known that adipose tissue is not just an

inert store of energy, but rather another organ capable of modulating inflammation *via* signalling molecules (adipokines) and also a source of mesenchymal stem cells that can participate in tissue repair [11, 34, 35]. It is also known that the fat mass and obesity-associated (FTO) genotype influences early adulthood and midlife weight [36–38] and in COPD is associated with low body mass and low lung function [39].

This study has several limitations. Our design, referred to as *retropective* [40], where the outcome variables to define the specific phenotypes were measured during the study visit and the exposure (somatotypes at different age points) was collected by recall but treated as repeated measures over time, raises the possibility of recall and survivor bias. To reduce recall bias, we decided to use Stunkard's Pictogram. This instrument was validated by demonstrating a strong correlation of the long-term recall (up to 50 years) of subjects' somatotype with their historical BMI values [18]. Further, seminal epidemiological studies have demonstrated the validity of this simple instrument to draw somatotype trajectories [12–14, 38]. To enhance recall precision, we chose specific age points to draw the trajectories. We started at age 18, because it is the age when maximal height has already been reached and therefore changes in somatotype would likely represent changes in weight. After age 18, the scale defined each decade of life. It is also possible that we are showing the trajectories of COPD survivors, as our cohort has only 3% of subjects under the age of 50, and individuals with severe airway obstruction were likely underrepresented in this cohort. Thus, our findings reflect the trajectories for those patients with smoking-related COPD attending pulmonary clinics that have reached their 60s, and it is possible that the proportion of individuals belonging to each trajectory will vary over time as obesity becomes more prevalent over the last 30 years. Finally, we must be cautious about establishing causal inference between the type of trajectory and final phenotype. Nevertheless, we used the group-based trajectory modelling method, which is a hypothesis-free tool aimed to assign a membership to those participants with similar trajectories, without *a priori* inclusion of their clinical characteristics [41]. Once participants were assigned to a trajectory by the method, we compared their clinical characteristics. This sequence is particularly helpful to mitigate selection bias and provides strong evidence for the distinction between trajectories and specific phenotypes. There is no doubt that the ideal methodology to address our hypothesis is to conduct a population-based study that includes subjects 18 years old (or younger) at risk of developing COPD with at least 40 years of follow-up. This is unlikely to be conducted. Unfortunately, most COPD epidemiological studies have a relatively short observation period [42, 43], and there may not be detailed measurements over time to define the specific phenotypes in the cohorts used to establish lung function trajectories [2].

Our findings highlight the need to study the determinants for distinct COPD phenotypes and opens the possibility of establishing trajectories in the different dimensions that are known to exist in COPD. It confirms that we should look beyond the FEV<sub>1</sub> rate of decline to better understand the biology behind different phenotypes despite a single common exposure (tobacco smoking). Longitudinal follow-up studies should be carried out in cohorts established at an early age to determine anthropometric lung function beyond spirometry, imaging and biomarkers, aimed at deepening our understanding of the biology of the disease in its early stages. More specifically our findings suggest that adipose tissue is not just a fat deposit and may play a modulating role in the genesis of COPD.

In conclusion, our study provides evidence that individuals who develop COPD have distinct somatotype trajectories throughout adulthood leading to specific phenotypes. Subjects with the MOLT phenotype are programmed from an early age to maintain a lean trajectory through adult life. This particular subgroup of smokers deserves special attention as they are likely to become those patients with the most severe form of COPD.

**Author contributions:** The above listed authors attest that they made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be submitted for revision. All authors had full access to all the data in the study and accept responsibility for the submission of this work.

**Conflict of interest:** M.J. Divo has nothing to disclose. M. Marin Oto has nothing to disclose. C. Casanova Macario reports, in the last 3 years, to have received lectures and/or scientific advice from Laboratorios Bial, Boehringer Ingelheim, Gebropharma, GSK, Esteve, Menarini, Novartis and Rovi. C. Cabrera Lopez has nothing to disclose. J.P. de-Torres has nothing to disclose. J.M. Marin Trigo has nothing to disclose. C.P. Hersh reports grants from National Institutes of Health during the conduct of the study; and grants from Boehringer Ingelheim and Novartis, and personal fees from 23 and Me, outside the submitted work. A. Ezponda Casajús has nothing to disclose. C. Maguire has nothing to disclose. V.M. Pinto-Plata has nothing to disclose. F. Polverino has nothing to disclose. J.C. Ross reports grants from NIH during the conduct of the study. D. DeMeo has nothing to disclose. G. Bastarrica reports personal fees from General Electric, nonfinancial support from Siemens and grants from Guerbet, outside the submitted work. E.K. Silverman reports grants from NIH during the conduct of the study, and grants and travel support from GlaxoSmithKline outside the submitted work. B.R. Celli has nothing to disclose.

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