Somatotypes trajectories during adulthood and its association with Chronic Obstructive Pulmonary Disease (COPD) phenotypes

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Abstract

Background Chronic obstructive pulmonary disease (COPD) comprises distinct phenotypes, all characterized by airflow limitation. Research Question We hypothesized that somatotype changes -as 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. An unbiased group-based trajectory modelling was used to determine somatotypes trajectories. We then compared the current COPD related clinical and phenotypic characteristics of subjects belonging to each trajectory.

Results At age 18, 88% of the participants described having a lean or medium somatotype (estimated BMI between 19-23 kg·m −2)while the other 12% a heavier somatotype (estimated BMI between 25-27 kg·m −2). 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 DLCO. A persistently lean trajectory was seen in 14% of the cohort. This group had lower FEV 1 , DLCO, more emphysema and worse BODE 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.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of illness and the third cause of death worldwide(1). COPD is recognized as a phenotypically heterogeneous clinical syndrome characterized 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 early stages of life as the result of the cumulative effect of different exposures and complex interactions between genetic, epigenetic, and age-related factors in susceptible individuals(2). 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 early age(3), however little is known as to why individuals develop distinct COPD phenotypes. The initial description of distinct COPD phenotypes dates back to the 1950's with the characterization of the predominantly emphysematous phenotype commonly called the "pink puffer" and a predominantly bronchitic phenotype called the "blue bloater" (4). More recently, studies using hypothesis-free cluster analysis resulted in the description of three to five discrete COPD phenotypes all with clear differences in response to therapy and prognosis(5–9). 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(10). More recently, the original “pink puffer” phenotype was refined and the term multi-organ loss of tissue phenotype (MOLT) was coined(11). These patients are characterized by having more emphysema, worse airflow obstruction, higher BODE score, are more prone to exacerbations, suffer a higher mortality and have 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(12). In support of this idea, investigators from two landmark epidemiologic cohorts (The Nurses’ Health Study and the Health Professionals Follow-up Study) demonstrated that adiposity changes throughout life course predict the subsequent risk for chronic diseases and mortality (13–15). They employed a Group-Based Multi-trajectory Modelling technique to participants’ recalled body builds at different age points to identify distinct subgroup of participants with similar trajectory of body shape from childhood to age 50.

We hypothesized 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 early age to manifest a different somatic response to the effects of cigarette smoke.

2. 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 approximately 12 to 24-month intervals. Subjects in COPDGene Boston cohort were included for this study at the follow-up visit, approximately 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 FEV_1 to forced vital capacity (FVC) of less than 0.7 measured 20 minutes after the administration of albuterol. Details of the inclusion and exclusion criteria for both cohorts have been described elsewhere(16,17). For the present analyses, participants were also asked to complete the validated Stunkard’s somatotype questionnaire(18) (Fig. 1) during their visit which occurred between October 2013 and June 2017. This study was conducted in accordance with the amended Declaration of Helsinki. The ethics committee at each of the participating centres approved the study (see “Declarations” section for details), and all patients provide written informed consent before enrolment.

Assessment Of Body Shape

The Stunkard’s Pictogram is a validated instrument of 9 line drawings of human figures reflecting the spectrum of body physiques or somatotypes (Fig. 1)(18). Participants were asked to select the

somatotype diagram that best depict their current body build and those at ages 18, 30, 40 and 50. 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(19). 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 more than 50 years ago. The utility of this instrument was also validated in large epidemiology studies to estimate adiposity trajectories across the life course(13–15,20,21).

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 $kg \cdot m^{-2}$), pulmonary function tests (FEV_1/FVC, FEV_1% predicted and DLCO % predicted) and six-minute walking distance test were performed according to international guidelines(22,23). The BMI, airflow obstruction, dyspnoea and exercise capacity (BODE) index was calculated as previously reported(17). 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(24,25). 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 more than 75% of emphysema in the lungs.

Statistical analysis

For categorical variables reported as proportions we used the chi-square test. For continuous variables reported as means (95% CI) we used the Student's t-test. To present a more meaningful interpretation of the Stunkard's Pictogram scale to BMI in $kg \cdot m^{-2}$, we fitted a linear regression model with current BMI as the outcome, somatotype at the time of study visit as predictor and gender as covariate and interaction term. We then used the regression coefficient and the reported somatotype at the time of visit to convert the 9-points scale and reported the strength of correlation between the Pictogram and BMI for each gender.

We used a group-based trajectory modelling approach to identify subjects that share similar somatotypes 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 5 trajectories for this analysis (see details in the supplemental material). After group trajectories were assigned, we then compared the phenotypic characteristics (gender, BMI, FEV1% predicted, FEV1/FVC, DLCO, BODE score, presence and extend of emphysema) and exposure to tobacco (age of smoking initiation, pack/years) between each of the 5 trajectory-based groups to determine if somatotype trajectories are associated with specific COPD phenotype. Differences in these phenotypic characteristics amongst the 5 trajectory-based groups were tested using ANOVA for continuous variables, a Chi-squared

test for categorical variables. Missing data was 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. For the Group-Based Trajectory Modelling analysis we used the Stata® (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) plug-in command "traj" available at https://www.andrew.cmu.edu/user/bjones/[27]. All other analyses were performed using SAS JMP Pro ® software, version 14.0 (SAS Institute).

3. Results

Descriptive

The combined cohorts included 356 COPD subjects with a mean age of 67 years (95% CI 66 -68), mean BMI of 27.2 $kg{\cdot}m^{-2}$ (95% CI 26.7-27.7) and 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 current somatotype score is:

a. BMI= 17.6 (95% CI 16.7 -18.5) + 1.9 (95% CI 1.8- 2.1) x somatotype score

This regression formula suggests that every increase in somatotype unit represents an increase of almost 2 $kg{\cdot}m^{-2}$ in BMI (Figure 2 and Figure E1 online supplemental material). The parameter estimates between males and females were similar.

Body shapes trajectories

As shown in Figure 3, we named each trajectory groups 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 is comprised of 14% (n=49) of the cohort, the second group with a "Lean-Increase" trajectory is comprised of 21% (n=74), the third group or "Medium-Increase" trajectory has 38% (n=138), the fourth group or "Medium-Parabolic" trajectory has 15% (n=54) subjects, and the final group with a "Heavy-Increase" trajectory has 41subjects or 12% of the cohort.

Table 1. Comparison of phenotypic features for each of the 5 trajectory-based groups.

Groups comparison was performed using ANOVA for continuous variables, a Chi-squared test for categorical variables. In Bold we highlighted those values that conferred a significant difference.

	Lean-Flat	Lean-Increase	Medium-Increase	Medium-Parabolic	Heavy-Increase	p-value
N	49 (14%)	74 (21%)	138 (38%)	54 (15%)	41 (12%)	
Age, yr	67 ± 9	69 ± 9	67 ± 9	67 ± 7	65 ± 10	0.3185
Males %	67%	70%	71%	51%	78%	0.0434
BMI ($kg \cdot m^{-2}$)	21.7 ± 4.0	27.2 ± 3.6	30.0 ± 4.1	23.3 ± 3.1	29.6 ± 4.9	< 0.0001
Current smokers (%)	42%	37%	32%	42%	42%	0.6399
Age of smoking initiation (years)*	17 ± 4	16 ± 3	17 ± 5	17 ± 4	17 ± 7	0.4198
Cumulative Smoking, pack-year ‡	67 ± 36	64 ± 28	56 ± 28	57± 33	62± 32	0.2418
FEV_1/FVC (%)	48 ± 13	52 ± 12	57 ± 11	53 ± 13	57 ± 11	< 0.0001
FEV_1 % predicted	60 ± 23	65 ± 19	71 ± 21	68 ± 24	68 ± 19	0.0142
DLCO % predicted§	48 ± 20	61 ± 21	68 ± 20	58 ± 19	67 ± 24	< 0.0001
% subject with emphysemaǁ	79%	52%	60%	63%	61%	0.1251
Emphysema severityǁ	1.5 ± 1.0	1.1 ± 1.1	0.7 ± 0.9	1.0 ± 1.0	0.9 ± 1.0	< 0.0001
BODE**	2.3 ± 1.6	1.4 ± 1.5	1.2 ± 1.6	1.5 ± 1.6	1.3 ± 1.9	0.0026

* data missing in 25 subjects with COPD.

‡ data missing in 75 subjects: 5 (10%) in Lean-flat group, 20 (27%) Lean-Increase, 24 (17%) in the Medium-Increase, 13 (24%) in the Medium-Parabolic, 11 (27%) in the Heavy-Increase group.

§ data missing in 71 subjects: 7 (17%) in Lean-flat group, 16 (22%) Lean-Increase, 30 (23%) in the Medium-Increase, 14 (26%) in the Medium-Parabolic, 4 (10%) in the Heavy-Increase group.

ǁ Data missing in 113 subjects: 21 (43%) in Lean-flat group, 25 (34%) Lean-Increase, 41 (30%) in the Medium-Increase, 13 (24%) in the Medium-Parabolic, 13 (32%) in the Heavy-Increase group.

** data missing in 11 subjects.

Results in the table reflect parameters estimates with imputed missing values.

From table 1, we can observe that subjects in all five groups have similar mean age, similar proportions of current smokers, they initiated smoking habit at a similar age and have the same cumulative smoking history. The majority have a tendency towards gaining and then sustaining, although at different rate and starting point, adiposity during adult life except for the “Lean-Flat” and Medium-Parabolic” groups. Phenotypically the 3 progressive adiposity groups share similar characteristics, namely less obstruction, higher BMI, DLCO 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 more obstructed, have a lower DLCO, lower BMI, worse BODE score and more severe emphysema, resembling the clinical features of the implosive or MOLT phenotype described by Celli et al(11). Next to the Lean-Flat group, is the Medium-Parabolic trajectory group, sharing some of the characteristics of the former including a lower BMI and second lowest DLCO. 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.

Table E2 in the online supplement material 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.

4. Discussion

Our study identified five distinct somatotypes 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 20–24 $kg{\cdot}m^{-2}$) 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 COPD(14,26). What is novel in this study is that patients with the MOLT phenotype seen at late adulthood, start from early age to follow a lean (lack of adiposity) trajectory throughout life. 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 DLCO, more severe emphysema and 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 DLCO (Fig. 3 and Table 1). Interestingly, this trajectory was also observed in the Nurses’ Health Study(14), 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 wasn't 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(28) 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(29,30) as well as in the general population(31). Third, the prevalence of certain comorbidities differs beyond chance between COPD patients with low and high BMI(32), and in addition the BMI is a salient feature between phenotypes in cluster analysis studies(5–8). However, this evidence cannot explain what separates COPD patients into different phenotypes. Based on our findings and suggestions from previous reviews(12,33,34) 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 the adipose tissue is not just an inert storage 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(12,35,36). It is also known that the fat mass and obesity–associated (FTO) genotype influences early adulthood and midlife weight(37–39) and in COPD is associated with low body mass and low lung function(40).

This study has several limitations. Our design referred as retrolective(41), where the outcomes variables to define the specific phenotypes where measured during the study visit and then the exposure (somatotypes at different age points) were 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 the 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(19). Further, seminal epidemiologic studies have demonstrated the validity of this simple instrument to draw somatotypes trajectories(13–15,39). 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 represents 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 smoking related COPD patients attending pulmonary clinics that reach their 60's and is possible that the proportion of individual belonging to each trajectory will vary over time as obesity became more prevalent over the last 30 years. Finally, we must be cautious to establish 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(42). 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 a strong evidence between the distinct trajectories and specific phenotypes. There is no doubt that the ideal methodology to address our hypothesis is to conduct a population-based study including subjects 18 years old (or younger) at risk to develop COPD with at least 40 years of follow

up. This is unlikely to be conducted. Unfortunately most COPD epidemiologic studies have a relative short observation period(43,44) and the cohorts used to establish lung function trajectories may not have detailed measurements over time to define the specific phenotypes(3).

5. Conclusions

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

Abbreviations

BMI
Body Mass Index
BODE index
Body mass index, Obstruction, Dyspnea, Exercise index
CI
Confidence Interval
COPD
Chronic Obstructive Pulmonary Disease.
DLCO
Diffusing Capacity for Carbon Monoxide
FEV1
Forced Expiratory Volume in the first second
FVC
Forced Vital Capacity
GOLD
Global Initiative for Chronic Obstructive Lung Disease
MOLT
Multi Organ Loss of Tissue

Declarations

Names and the approval numbers of the ethics committees from each of the participant sites.

- Boston, USA site: Partners Human Research Committee / N:2011P000857
- Pamplona, Spain site: Comité de Etica de la Investigación de la Universidad de Navarra/ N: 043-2010
- Tenerife, Spain site: Comité Etico de Investigación Clínica, Hospital Universitario NTRA. SRA. De Candelaria, Sant Cruz de Tenerife/ N:223/2004

- Gran Canaria, Spain site: Comité Etico de Investigación Clínica, Hospital de Gran Canaria/ N: 11/325
- Zaragoza, Spain site: Comité Etico de Investigación Clínica de Aragón/ N: 12/2010

Availability of data and materials:

The datasets generated and analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests:

1. Divo reports grants from NIH during the conduct of the study.
2. Silverman reports grants from NIH, during the conduct of the study; grants and other from GlaxoSmithKline, outside the submitted work.
3. Hersh reports grants from National Institutes of Health, during the conduct of the study; grants from Boehringer Ingelheim, grants from Novartis, personal fees from 23andMe, outside the submitted work.
4. Demeo reports grants from National Institutes of Health, during the conduct of the study.
5. Ross reports grants from NIH, during the conduct of the study.
6. No conflict exist for Dr. Marin Oto, Cabrera-Lopez, Casanova, de-Torres, Marin Trigo, Pinto-Plata, Ezponda, Polverino, Celli and Ms. Maguire.

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Author's contributions:

The listed authors attest that they made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) 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.

Doctors Edwin Silverman and Bartolome Celli contributed equally as senior authors.

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Figures

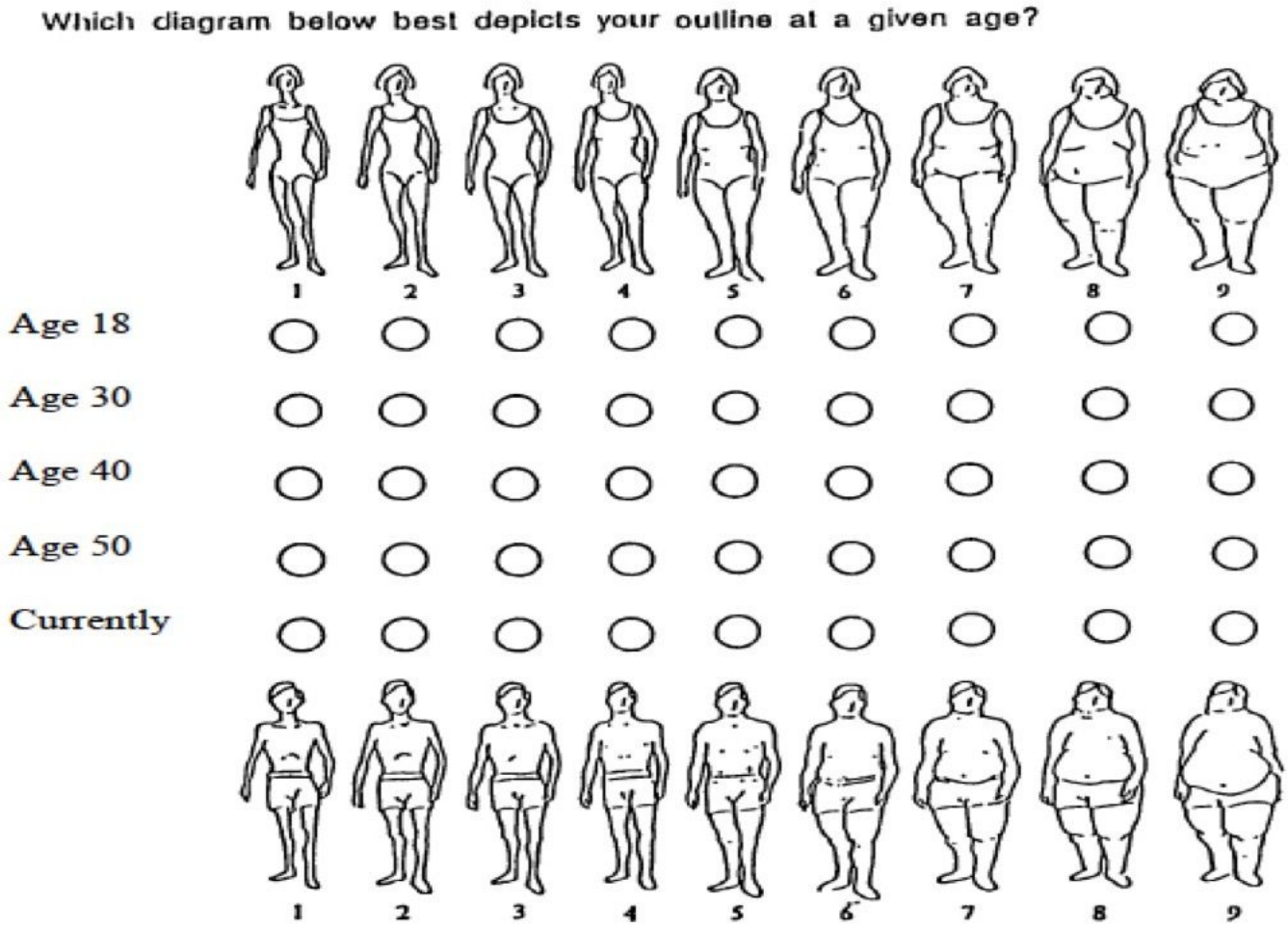
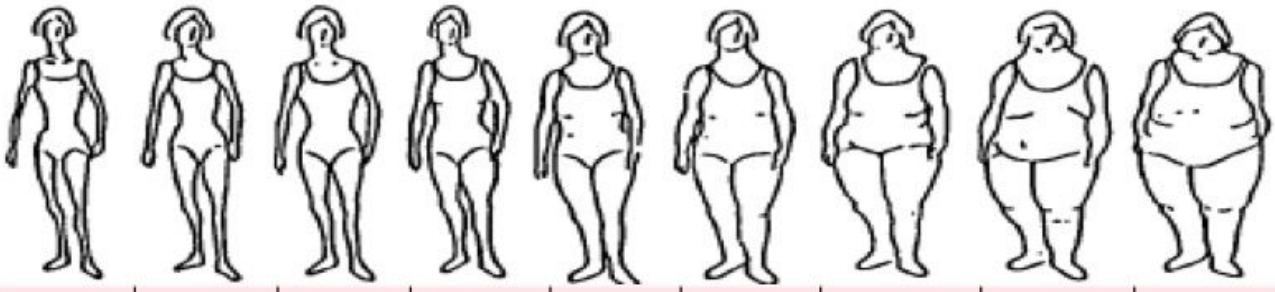
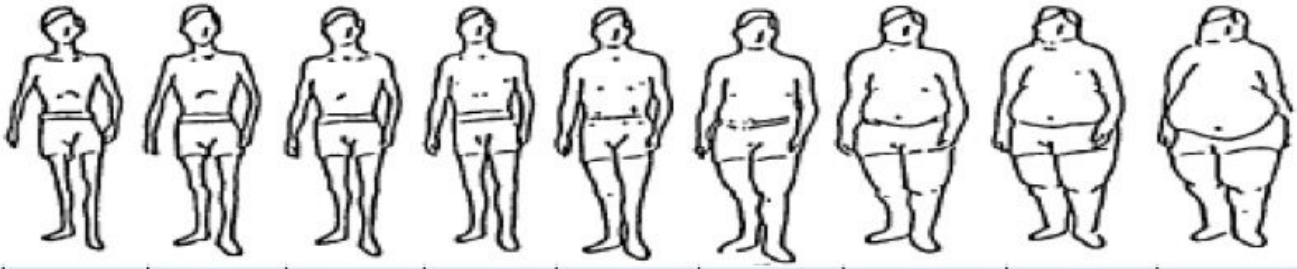


Figure 1

tunkard's Pictogram Footnote: Figure drawing used to assess body shape at ages 18, 30, 40, 50, and at study evaluation.



	1	2	3	4	5	6	7	8	9
BMI $kg \cdot m^{-2}$	19 (18-20)	21 (20-22)	23 (22-24)	25 (25-26)	27 (27-28)	29 (29-30)	31 (30-32)	34 (32-35)	36 (34-37)



	1	2	3	4	5	6	7	8	9
BMI $kg \cdot m^{-2}$	20 (19-21)	22 (21-22)	24 (23-24)	25 (25-26)	27 (27-28)	29 (29)	31 (30-31)	33 (32-33)	35 (34-35)

Figure 2

Predicted BMI for each of the somatotype's values. Footnote: We assigned a BMI value to each somatotype based on the regression formula obtained from participants current BMI and somatotype score. Values are expressed a mean and 95% confidence interval.

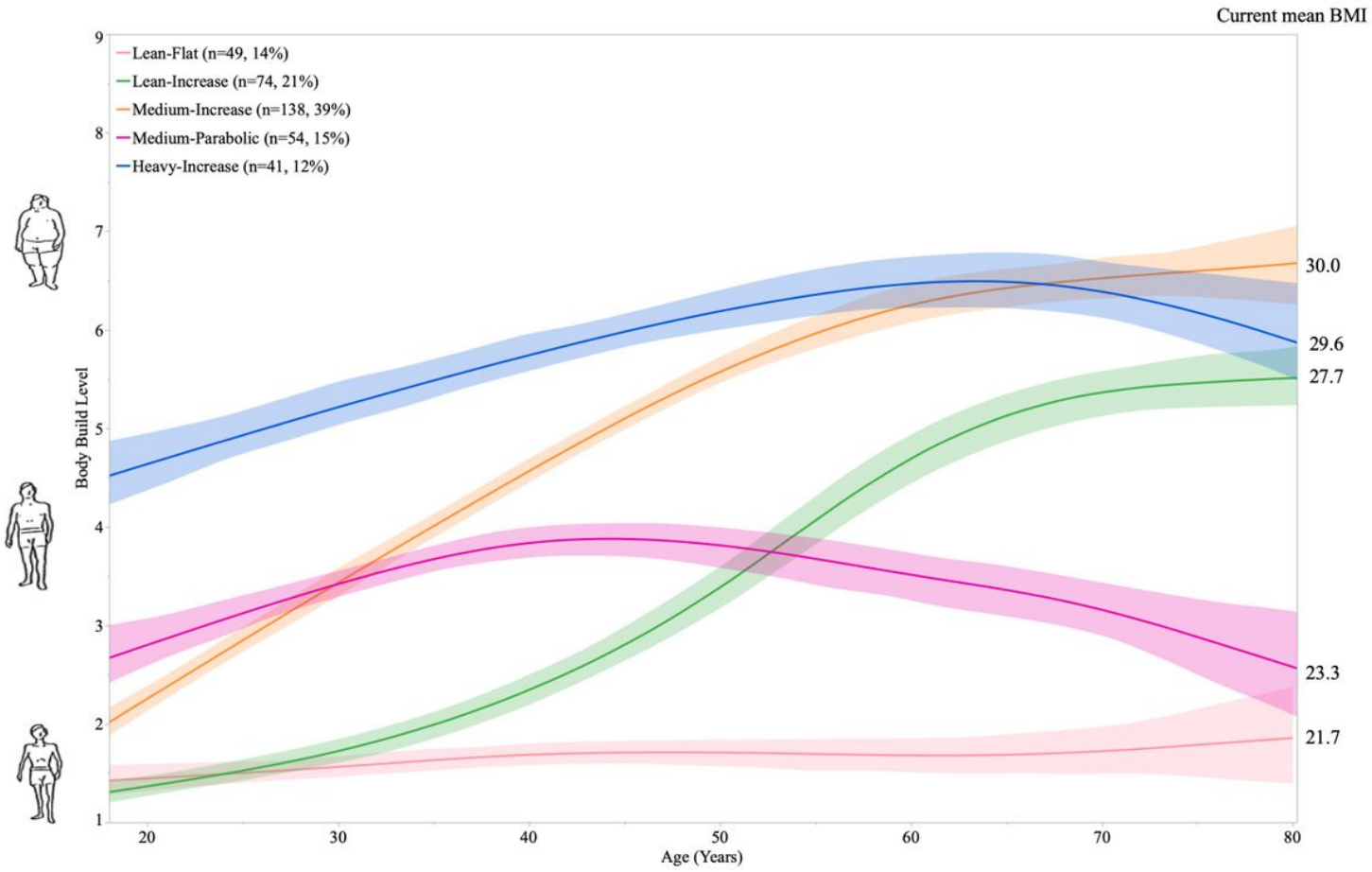


Figure 3

Somatotype trajectories throughout adult life. Footnote: Each line represents each trajectory estimates and the shaded bands the 95% confidence interval fit of the mean.

Supplementary Files

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- SupplementalMaterialReRe.docx