Airway to Lung Volume Ratio on CT is Associated with Pulmonary Function Transition from Obstructive to Restrictive Pattern in Obesity

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Abstract

Background: Obesity is associated with excessive airway collapse and reduced lung volume; it is unknown whether it affects airway-lung interactions. We sought to compare the airway tree to lung volume ratio, assessed by CT, in obese individuals with and without ventilation disorders.

Methods: Participants underwent inspiratory chest CT and pulmonary function. The percentage ratio of the whole airway tree to lung volume, automatically segmented via deep learning, was defined as CT airway volume percent (AWV%). Total airway count (TAC), airway wall area percent (WA%), and other CT indexes were also measured.

Results: We evaluated 88 participants including adolescents(age: 14-18, n= 12) and adults (age: 19-25, n= 17; age: 26-35, n= 39; age> 35, n= 20). Obese adolescents had higher forced vital capacity (FVC) (P = 0.001) and lower AWV% (P = 0.008) than obese adults (age >35). Among obese adults, participants with restrictive disorders had larger AWV% (P < 0.001) and those with obstructive disorders showed smaller AWV% (P < 0.001) compared to participants with normal ventilation. AWV% was positively correlated with age and forced expiratory volume in 1 second (FEV1)/FVC and adversely related to FVC ($P < 0.05$ for all), and in multivariate models, AWV% independently predicted FEV1/FVC (R^2 = 0.49, P < 0.001) and FVC (R^2 = 0.60, P < 0.001).

Conclusion: Transitions in lung function patterns between obese adolescents and adults are associated with airway to lung ratios. The obesity-induced disproportion between the airway tree and lung volume may adversely affect and complicate lung ventilation.

Introduction

Obesity is a global epidemic that has nearly tripled since the 1970s [1]. Obesity increases the risk of several respiratory symptoms and diseases, such as asthma and chronic obstructive pulmonary disease (COPD), and exerts detrimental effects on lung function [2].

Obesity can directly alter the respiratory system's mechanical properties through fat deposits in the mediastinum, chest wall, and abdominal and thoracic cavities[2, 3]. These alterations can reduce lung volume [4], increase the risk of airway collapse and closure[5], and decrease total respiratory system compliance [6], which may eventually contribute to pulmonary defects in obese individuals[3]. Moreover, the effects of obesity on pulmonary function change from an obstructive pattern[7, 8] in adolescence to a restrictive pattern in adulthood [9-11].

Previous CT/MRI studies showed that obesity adversely affects both the airway tree and lung volume [4, 12]. However, their data did not elucidate the effects of obesity on the interaction between airway and lung sizes, which is essential for maintaining lung mechanics and pulmonary function [13].

Recently, a few works have shown that a new CT marker, airway volume percent (AWV%), defined as a percentage ratio of the airway tree to lung volume, is related to pulmonary function and lung disease severity[14, 15]. Therefore, we hypothesized that changes in airway tree to lung volume ratio are also associated with transitions in lung function in obesity. The purpose of this study was to measure and compare the CT airway to lung volume ratio between obese adolescents and adults with and without pulmonary ventilation disorders and evaluate its relationships with lung function.

Methods

Study design

This cross-sectional study compared obese adolescents with normal pulmonary function, obese adults with normal pulmonary function, and obese adults with ventilation disorders.

Human subjects

We enrolled obese participants(BMI >30 kg/m^2) 14 to 57 years of age with the following exclusion: (1) history of thoracic surgery and lung disease, (2) current or former smokers, (3) history of thoracic congenital skeletal abnormality, (4) occupational history that may lead to impairment of lung function. The study was approved by the institutional review board of the First Affiliated Hospital of Jinan University and informed written consent was obtained from all participants.

CT Image Acquisition

Unenhanced chest computed tomography (CT) was acquired using a 320-row CT scanner (Toshiba Aquilion ONE, Japan) from the apex to the lung base in the supine position during a brief breath-hold after inspiration. All participants received respiratory training prior to the CT examination to ensure successful breathing maneuvers during image acquisition. CT parameters for image acquisition were as follows:140 peak kVp, variable mAs, 0.5-second gantry rotation, the pitch of 1.0 or 1.25mm slice thickness, contiguous slices. Reconstruction was performed with a high spatial frequency algorithm (FC56).

CT Image Analysis

Airway Segmentation via Deep Learning

Based on the work of Minghui Zhang et al.[16] , we first preprocess the CT scans and train an encoder-decoder network (), cooperating with the distance-related loss function to segment the airway tree structure, aiming to preserve the completeness of the airway tree as much as possible. Specifically, during the preprocessing, we set the window level at -300 HU with a width of 900 HU and rescale voxel values into [0, 255]. Besides, we cropped the lung field to remove unrelated background regions. The encoder extracts the semantic feature of the input image, and the symmetrical decoder receives the output of the encoder and the skip connection to predict the category of each voxel (i.e., airway or background).

Secondly, we conducted a manual edition by two experienced radiologists based on the previous automatic airway segmentation step. The overall framework can be seen in Fig 1.

Fig 2 shows the segmentation results by different methods. a) represents the automatic segmentation results by the software embedded in our hospital (VIMS, Vitrea® 2), b) shows the automatic segmentation results by deep learning methods, c) shows the result of the edition based on b)). The blue dotted boxes highlight the significant differences among these three methods. We can observe that deep learning-based methods segment more accurately than the software. Furthermore, with manual refinement by experienced radiologists, we can correct some small breakage regions and obtain satisfactory airway segmentation results.

Airway Volume (AV)

The airway volume (AV) can be counted as below:

$$\mathrm{AV} = \sum_i x_i,$$

where x_i denotes each voxel belongs to the airway.

Airway volume percent (AWV%)

The airway volume percent measures the percentage of airways occupying the lung volume. The formulation can be written as below:

$$\mathrm{AWV\%} = 100 * \frac{\sum_i x_i}{\sum_i y_i}$$

where x_i denotes each voxel belongs to the airway and the y_i denotes each voxel belongs to the lung.

Total airway count (TAC)

The total airway count (TAC) denotes the number of branches by the segmented airway tree.

Airway fractal dimension（AFD）

The fractal complexity of the segmented airway luminal tree was measured by the Minkowski-Bougliand box-counting dimension [17]. Precisely, the AFD can be calculated by the following formula:

$$dim_{box}(Airway) := \lim_{\varepsilon \to 0} \frac{logN(\varepsilon)}{log(1/\varepsilon)},$$

where N stands for the number of sticks, ε stands for the scaling factor, and dim_{box} (Airway)stands for the fractal dimension.

Wall area percent (WA%)

Using 3D SLICER (http://www.slicer.org/), the wall area percent (WA%: (wall area/total bronchial area)×100) and the square root of wall area with an internal perimeter of 10mm (Pi10) were obtained as previously described[18, 19]. The mean WA% was calculated as the average of six segmental bronchi in each subject.

Pulmonary Function Tests

Pulmonary function tests (PFT) were performed on computerized spirometers (Masterscreen, Jaeger, Hochberg, Germany) according to the ATS/ERS recommendations[20, 21]. Each spirometer was calibrated daily, and a minimum of three satisfactory slow and forced vital capacity manoeuvers were required of each subject. All the data of PFT enrolled in this study were measured without using bronchodilators. The Basic information concerning age (years), height (cm), weight (kg), body mass index (BMI; kg/m^2) were collected before PFT. Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and their ratios (FEV1/FVC), expiratory reserve volume (ERV), and vital capacity (VC) were acquired. A restrictive ventilation disorder was defined as FEV1/FVC >0.70 and FVC <80% predicted[20]. FEV1/FVC <92% of predicted value was identified as an obstructive ventilation disorder, recommended by the guidelines for PFTs published by the Chinese Thoracic Society[22].

Statistical Analysis

The SPSS 26.0 software (IBM Corporation, Chicago, IL, USA) and GraphPad Prism 8.40 (GraphPad Software Inc., San Diego, CA) were utilized to perform statistical tests and plot charts. Data were tested for normality using the Shapiro-Wilk test and non-parametric test if not normally distributed. One-way analysis of variance (ANOVA) or Kruskal-Wallis test was used to compare differences in demographics, pulmonary function tests, and CT measurements for age groups and pulmonary ventilation groups. Spearman (r_s) correlation analysis was used to estimate associations between variables.

Multivariable models were generated using the enter approach to determine variables with significant associations with FEV1, FEV1/FVC, FVC. All variables were log-transformed. A P value < 0.05 was considered a statistically significant difference.

Results

Demographics and lung function

We evaluated 88 obese participants(mean age, 30 years ± 9 [standard deviation]); 50 females) with a clinical diagnosis of obesity as shown in Table 1, which summarizes the demographic data, PFT results, and CT measurements for the entire study cohort grouped into four age range groups.

Association between Pulmonary Function, AWV%, and Age in Obesity

As expected, The FVC decreased with the age of the groups (104.25 [interquartile range {IQR}: 98.33-110.40] vs 93.15 [IQR 89.22-99.87] vs 96.90 [IQR 89.15-99.85] vs 90.62 [IQR 76.05-96.33], respectively, P =0.001). However, AWV% and TAC tended to increase with age and were significantly higher in group 4 (age > 35) compared to group 1(14≤ age ≤18) (1.15 [IQR 0.76-1.19] vs 0.79 [IQR 0.70-0.86], 134.00 [IQR 120.25-161.25] vs. 89.50 [IQR 72.50-107.50], respectively, $P < 0.01$) (Fig 3). There were no differences in WA%, Pi10 ,and AFD between the groups.

Relationships between AWV% and Ventilation Disorders in Obesity

As shown in Table S1, 27 of the 76 obese adults had pulmonary ventilation disorders, where 17 were restrictive disorders and the remaining 10 with obstructive disorders. There were differences in AWV% between the groups. Compared to the normal ventilation group (0.89 [IQR 0.82-1.00]), AWV% was higher in group A (1.20 [IQR 1.15-1.32, $P < 0.001$) and lower in group B (0.65 [IQR 0.60-0.68], $P < 0.001$) (Fig 3).

Table 1: Demographic data and CT measurements by age groups in obesity

Parameter	Group 1	Group 2	Group 3	Group 4	*P*
Number (female)	12 (6)	17 (9)	39 (24)	20 (11)	
Age (years)	16 (14-17)	22 (21-24)	31 (29-34)	41 (38-44)	
BMI (kg/m^2)	42.8 (34.7-44.58)	43.10 (35.75-45.45)	40.50 (33.30-49.30)	35.20 (32.85-42.50)	0.60
Pulmonary Function					
ERV (L)	1.43 (1.27-1.56)	1.54 (1.41-1.67)	1.29 (1.23-1.50) ‡	1.28 (1.10-1.44) ‡	0.002
VC (L)	4.01 (3.66-4.56)	4.20 (3.57-4.62)	3.65 (3.35-4.11)	3.47 (2.71-3.89) ‡	0.005
FEV1%$_{pred}$ #	96.71 ± 12.22	93.62 ± 12.97	93.68 ± 15.26	90.63 ± 21.22	0.78
FEV1/FVC%$_{pred}$	101.45 (98.91-103.50)	102.30 (96.10-106.55)	102.30 (99.40-104.30)	101.80(96.37-105.14)	0.89
FVC%$_{pred}$	104.25 (98.33-110.40)	93.15 (89.22-99.87) *	96.90 (89.15-99.85) *	90.62 (76.05-96.33) *	0.001
IMAGING					
WA%	0.70(0.63-0.76)	0.69(0.64-0.74)	0.68(0.60-0.72)	0.65(0.57-0.75)	0.22
Pi10(mm) #	4.31 ± 0.62	4.26 ± 0.53	3.94 ± 0.93	3.89 ± 0.74	0.26
AWV%	0.79 (0.70-0.86)	0.80 (0.70-0.98)	0.91 (0.84-1.1)	1.15 (0.76-1.19) *	0.008
TAC (n)	89.50 (72.50-107.50)	108.00(86.50-123.50)	115.00 (89.00-153.00)	134.00(120.25-161.25)*	0.003
AFD #	1.84 ± 0.01	1.83 ± 0.02	1.83 ± 0.02	1.83 ± 0.02	0.84

Unless otherwise specified, data are medians, with interquartile ranges in parentheses. Group 1, 14≤ age ≤18, (*n* =12); Group 2,18< age ≤ 25, (*n* =17); Group 3, 25< age ≤ 35, (*n* =39); Group 4, 35 < age ≤ 57, (*n* =20). BMI=body mass index; ERV= expiratory reserve volume; VC= vital capacity; FEV1= forced expiratory volume in one second; FVC= forced vital capacity; %$_{pred}$=percent predicted; WA%=wall area percent; Pi10= the square root of the airway wall area for a theoretical airway with 10mm internal perimeter; AWV%= airway volume percent; AFD= airway fractal dimension; TAC= total airway count. Significance of difference (P < 0.05): * Significantly different from Group 1; ‡ Significantly different from Group 2. # Data are means ± standard deviations.

Associations between AWV% and Lung Function

In Fig 4, AWV% was moderately related to age (r_s = 0.31, P = 0.004), FEV1/FVC (r_s = 0.63, P < 0.001) and FVC (r_s = -0.70, P < 0.001). FEV1 was significantly, albeit weakly to moderately, related to AWV% (r_s = -0.23, P= 0.03) and TAC (r_s=0.43, P < 0.001) (Fig 4). In addition, TAC was negatively related to BMI (r_s = -0.29, P = 0.006); WA% (r_s = 0.58, P < 0.001) and Pi10 (r_s = 0.51, P < 0.001) were positively correlated with BMI. Moreover, TAC was negatively related to WA% (r_s = -0.32, P= 0.003).

Multivariable models to determine the relative influence of CT measurements on FEV1, FEV1/FVC, and FVC, adjusted for age, sex, and BMI, are shown in Table 2. Among all CT measurements investigated, the standardized beta coefficients (β) indicated that AWV% (β = -0.61, P < 0.001) had the greatest relative influence on FVC, followed by TAC (β = 0.23, P = 0.009). For FEV1/FVC, AWV% (β = 0.77, P < 0.001) was the only imaging predictor. For FEV1, significant association was shown for TAC (β = 0.62, P < 0.001).

Table 2 Multivariable models

	Unstandardized		standardized		
Parameter	B	Standard Error	β	Variance Inflation Factor	P value
MODEL 1: FEV1%$_{pred}$ (R^2= 0.32, P < 0.001)					
AWV%	-11.93	7.12	-0.17	1.21	0.10
TAC	31.68	5.82	0.62	1.50	<0.001
AFD	-32.97	160.77	-0.02	1.10	0.84
WA%	17.28	20.91	0.20	6.84	0.41
Pi10	-10.51	17.78	-0.14	6.75	0.56
MODEL 2: FEV1/FVC%$_{pred}$ (R^2= 0.49, P < 0.001)					
AWV%	18.39	2.12	0.77	1.21	<0.001
TAC	-0.04	1.73	-0.002	1.51	0.98
AFD	8.52	47.84	0.02	1.10	0.86
WA%	2.10	6.22	0.07	6.84	0.74
Pi10	1.07	5.29	0.04	6.75	0.84
MODEL 3: FVC%$_{pred}$ (R^2= 0.60, P < 0.001)					
AWV%	-38.36	4.96	-0.61	1.21	<0.001
TAC	10.89	4.05	0.23	1.51	0.009
AFD	56.91	111.90	0.038	1.10	0.61
WA%	20.44	14.55	0.26	6.84	0.16
Pi10	-19.90	12.38	-0.30	6.75	0.11

All variables were log-transformed. Models adjusted for age, sex, BMI. B = regression coefficient; β = standardized regression coefficient; AWV%= airway volume percent; TAC = total airway count; AFD = airway fractal dimension; WA%= wall area percent; Pi10= the square root of the airway wall area for a theoretical airway with 10mm internal perimeter; FEV1= forced expiratory volume in one second; FVC = forced vital capacity; %$_{pred}$ = percent predicted.

Discussion

Several pulmonary function studies have shown that obesity is associated with increased airway closure and reduced lung volume [3, 5, 23], adversely affecting lung function. Physiological studies have highlighted the importance of the relationship between airway and lung volume in structure-function terms [24], and recent works have shown that a new CT marker, airway volume percent (AWV%), is related to lung function and lung disease severity[13, 25]. Based on these findings, we wondered whether obesity affects the interaction between airway and lung volume and the potential relationship of CT AWV% with pulmonary function. We evaluated 88 obese participants with obesity and made the following important and novel findings: *(a)* increasing age was associated with lower FVC and greater AWV%, *(b)* among obese adults, participants with restrictive disorders had larger AWV% and those with obstructive disorders showed smaller AWV% compared to participants with normal lung ventilation, *(c)* AWV% correlated with age, FVC, and FEV1/FVC, and in multivariate models, *(d)* AWV% independently predicted FEV1/FVC and FVC.

Due to the fine-grained pulmonary airway structure, manual annotation is time-consuming, error-prone, and highly relies on the expertise of clinicians. Deep learning methods, especially fully convolutional networks(FCNs) [26], achieved state-of-the-art performance in the segmentation task of volumetric medical data to relieve the burden of manual delineation. In the experiments of automatic airway segmentation based on deep learning methods, we have set the random seed to 777 for reproducible research, and the automatic segmentation results have shown no significant difference compared with the refinement results by experienced radiologists. Hence, the proposed automatic segmentation algorithm is reliable and can relieve the burden of clinicians.

Recent works have demonstrated that the effects of obesity on pulmonary function change from the obstructive pattern in childhood and adolescence[9, 23] to the restrictive pattern in adulthood[27, 28]. The effects of obesity reach the maximum obstructive pattern at ages 16 to 20, diminish at about 30, and then shift to the restrictive pattern after age 35 [29]. We observed a similar age-related lung function transition in the present study: FVC decreased with age. Meanwhile, AWV% and TAC showed an increasing tendency with age, and the most remarkable differences were seen between the adolescent group and the adults' group aged >35 years. Thus, in our study, a relatively smaller AWV% in obese adolescents may represent a disproportionate growth between lung parenchyma (faster) and airway count and caliber (slower) [8, 9, 30-32], which leads to a more rapidly increasing FVC value compared with the FEV1 value. On the other hand, obese adults exhibited restricted lung volume and thoracic cage growth and reduced lung compliance[7, 33, 34], which eventually affects the airway to lung volume ratio, resulting in increased AWV% and decreased FVC. Therefore, AWV% is a characteristic CT marker reflecting lung structure-function in obese people across a range of ages.

In addition, we found that the disproportionate AWV% was associated with ventilation disorders in obese adults. Although obese adults are more inclined to develop restrictive ventilatory disorders due to their characteristic restrictive lung function pattern, we found that obese adults can also develop obstructive ventilatory disorders in the present study. Compared to the group of normal ventilation, the restrictive disorders group had higher AWV% and the obstructive disorder group had lower AWV%. These results suggest that the overall effect of obesity on pulmonary function is multifactorial and complex, and the greater changes in the airway to lung volume ratio adversely affect ventilation in obesity.

AWV% was moderately related to FEV1/FVC, FVC, and age. Moreover, FVC was inversely and positively correlated with age and AWV%, respectively, which may help explain the transition of pulmonary function patterns between obese adolescents and adults. In multivariate models, AWV% was independently predicated FEV1/FVC and FVC. Thus, AWV% provided unique information related to pulmonary ventilation in obesity, independent of airway and lung morphology. Furthermore, our study also indicated that TAC had influences on FEV1, which is consistent with previous reports[35, 36] and indicated that TAC is an accurate indicator of airflow limitation.

Some limitations do need to be acknowledged. It is important to note that CT lung volume acquisition differences may affect the airway to lung volume ratio; therefore, we performed standardized breathing training for each participant to ensure that the CT acquisition was close to TLC. However, we acknowledge the lack of repeatable and longitudinal follow-up CT imaging at present. Future work will be required to estimate the reproducibility of AWV% in participants with obesity and the potential changes in AWV% over time. The study is based on a convenience sample dominated by obese adults with normal pulmonary function; thus, we are underpowered to individually estimate obese adolescents and obese individuals with abnormal pulmonary ventilation. A population-based sample will provide a broader range of ages and participants with abnormal lung function, which will allow the detection of differences between all ages and subgroups of pulmonary ventilation disorders.

Conclusion

In summary, Ours is the first study to examine the effects of obesity on the interaction between airway tree and lung volume. We found that the ratio of airway tree to lung volume was associated with the pattern of lung function between obese adolescents and adults. Our results also indicate that obesity is associated with the disproportion between the airway tree and lung volume, which may adversely affect and complicate lung ventilation.

Abbreviations

BMI: Body mass index; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; VC: Vital capacity; ERV: Expiratory reserve volume; IQR: Interquartile range; AWV%: Airway volume percent; AV: Airway volume; LV: Lung volume; TAC: Total airway count; AFD: Airway fractal dimension; WA%: Wall area percent; Pi10: The square root of the airway wall area for a theoretical airway with 10mm internal perimeter

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XY and MHZ analyzed and interpreted the CT data, and wrote the manuscript. XY, MHZ, YZF, YD and YHH contributed to the conception and interpretation of the data. XRC and YG contributed to the interpretation of CT data and the editing of the manuscript. All authors read and approved the final manuscript.

Authors' information

Not applicable

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki.This study was approved by the ethics committee of the First Affiliated Hospital of Jinan University, Guangzhou, China. All parents, guardians or next of kin provided written informed consent for the minors to participate in this study. All adult participants provided written informed consent to participate in this study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no conflicts of interest.

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Figures

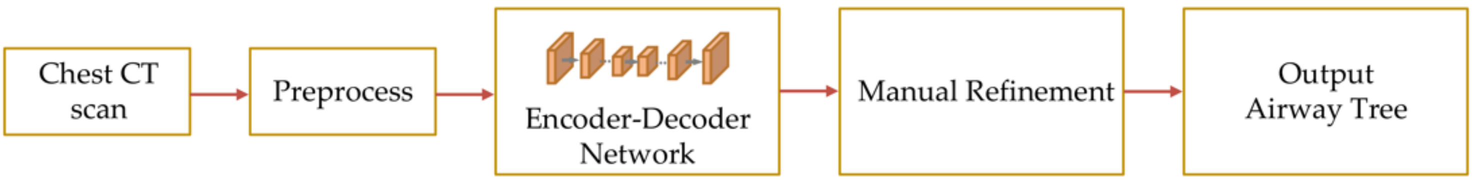

Figure 1

The overall framework of airway segmentation and refinement.

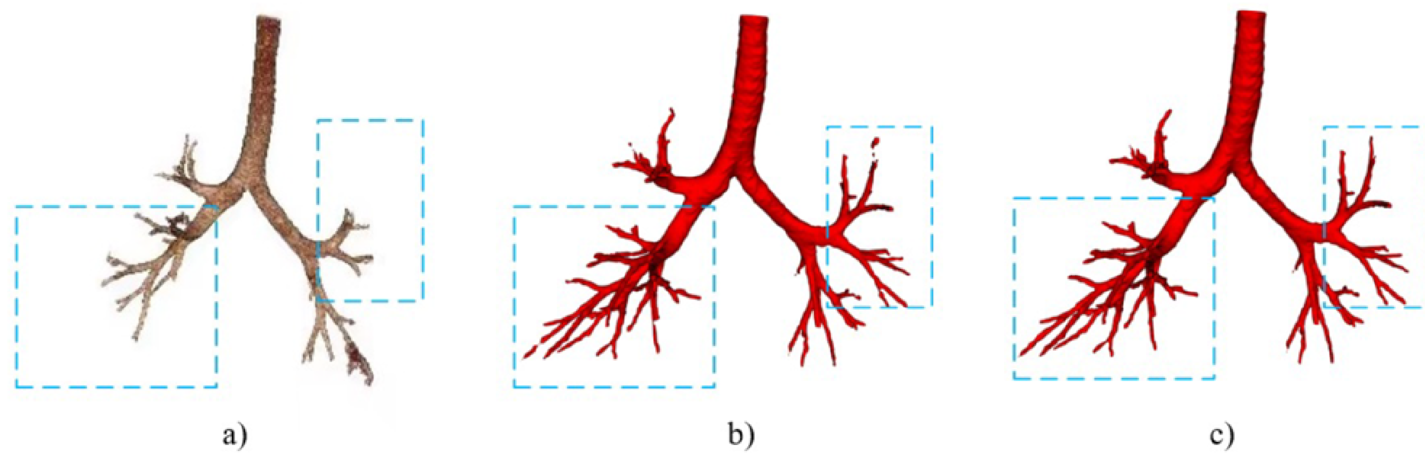

Figure 2

The visualization of airway segmentation results by different methods. **a**) shows the segmentation result by hospital tool. **b**) shows the automatic segmentation result through deep learning methods, and **c**) shows the manual refinement results based on **b**).

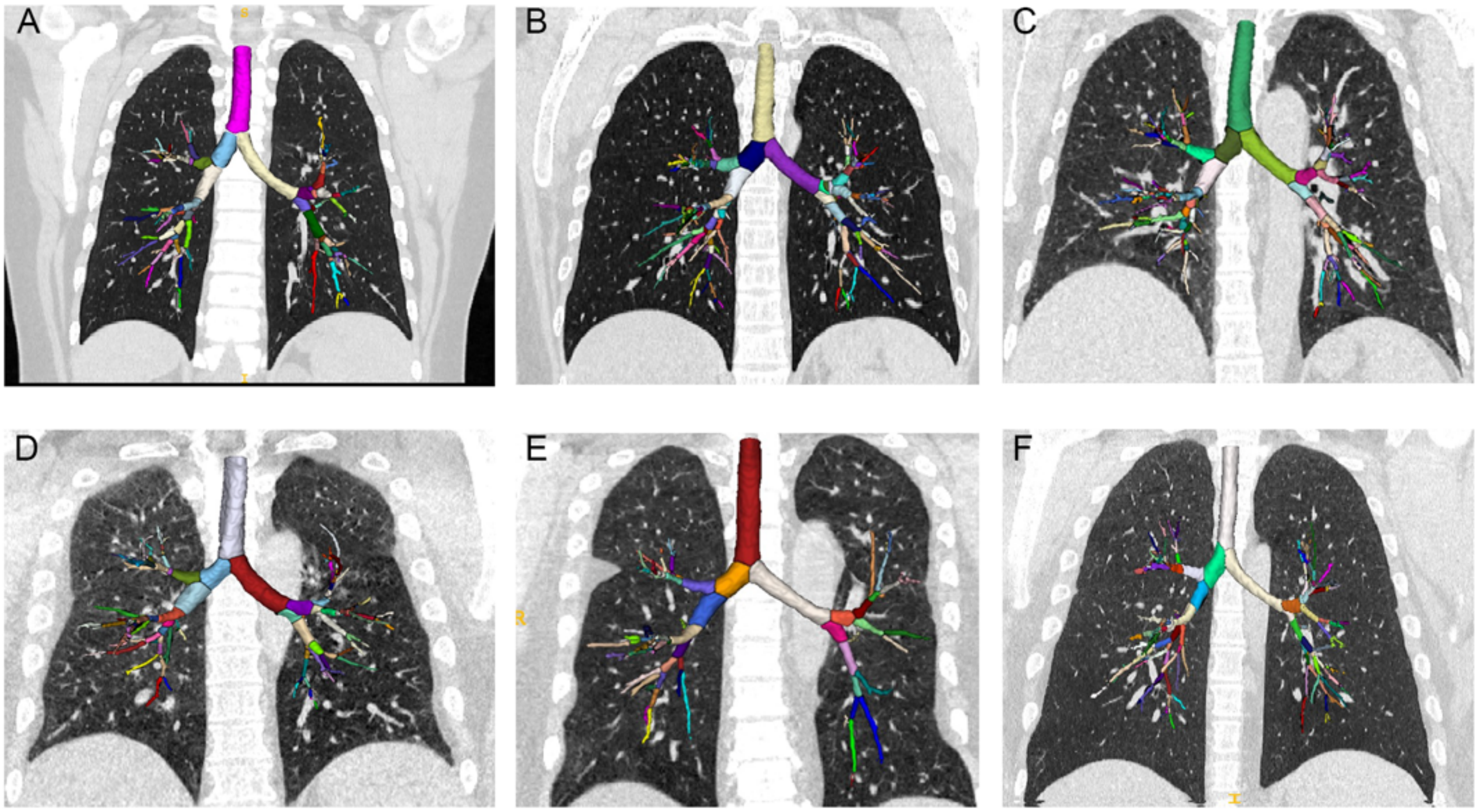

Figure 3

Representative coronal CT images with segmented central airway trees, and corresponding airway to lung ratio, body mass index (BMI), forced vital capacity (FVC), and forced expired volume in the first second to FVC(FEV1/FVC) ratio from 6 obesity cases. **A-C** shows that the airway to lung volume ratio changes from adolescence to adulthood with normal lung ventilation. **D-F** displays the airway to lung volume ratio in obese adults with or without ventilation disorders. **A** (a 14-year-old boy with AWV% = 0.73, BMI= 38.6 kg/m^2, FVC%$_{pred}$ =102.4, and FEV1/FVC%$_{pred}$=101.3). **B** (a 29-year-old woman with AWV% = 0.98, BMI=36.0 kg/m^2, FVC% $_{pred}$ = 99.85, and FEV1/FVC% $_{pred}$ = 102.40). **C** (a 49-year-old woman with AWV%=1.03, BMI=39.1 kg/m^2, FVC%$_{pred}$= 93.0, and FEV1/FVC% $_{pred}$ =108.80). **D** (a 39-year-old man with normal ventilation: AWV%= 0.93, BMI= 55.80 kg/m^2, FVC%$_{pred}$ = 96.6, and FEV1/FVC%$_{pred}$ =102.90). **E** (a 34-year-old man with restrictive disorders: AWV%=1.22, BMI=55.60 kg/m^2, FVC%$_{pred}$ = 68.80, and FEV1/FVC%$_{pred}$ =103.20). **F** (a 30-year-old man with obstructive disorders: AWV% = 0.60, BMI= 51.70 kg/m^2, FVC%$_{pred}$ =111.70, and FEV1/FVC%$_{pred}$ = 89.50).

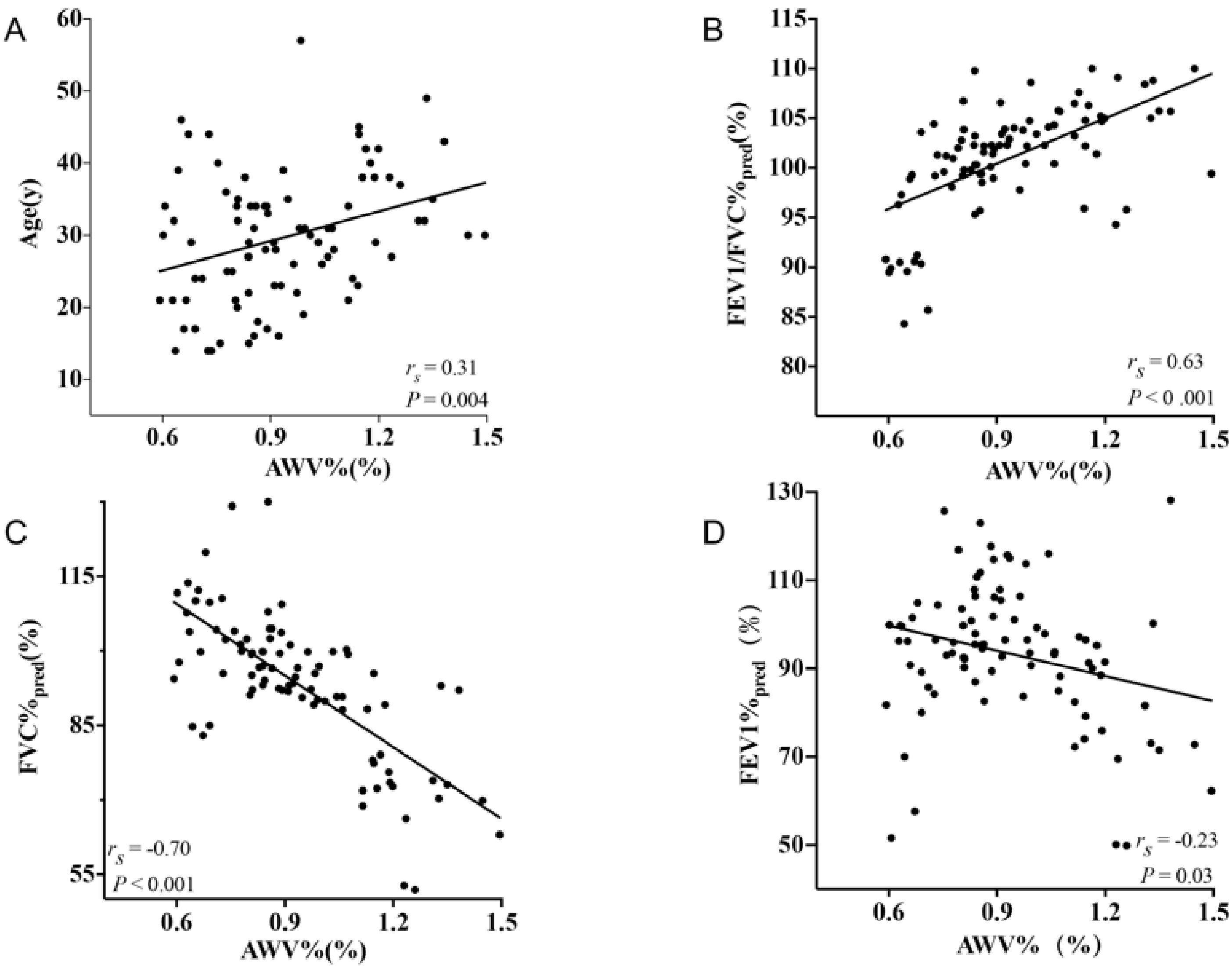

Figure 4

Associations of the airway to lung volume ratio (AWV%) with age, FEV1, FEV1/FVC, and FVC. FEV1= forced expiratory volume in one second; FVC= forced vital capacity. $\%_{pred}$=percent predicted. r_s value indicates the Spearman correlation coefficient.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TableS1.docx