Title
Variation in the Percent of Emphysema-like Lung in a Healthy, Nonsmoking Multiethnic Sample. The MESA Lung Study

Journal
Annals of the American Thoracic Society, 11(6)

ISSN
2329-6933

Authors
Hoffman, Eric A
Ahmed, Firas S
Baumhauer, Heather
et al.

Publication Date
2014-07-01

DOI
10.1513/annalsats.201310-364oc

Peer reviewed

ORIGINAL RESEARCH

Variation in the Percent of Emphysema-like Lung in a Healthy, Nonsmoking Multiethnic Sample

The MESA Lung Study

Eric A. Hoffman[1,2,3], Firas S. Ahmed[4,5], Heather Baumhauer[1], Mathew Budoff[7], J. Jeffrey Carr[8], Richard Kronmal[9], S. Reddy[1], and R. Graham Barr[4,6]

[1]Department of Radiology, [2]Department of Medicine, Carver College of Medicine, and [3]Department of Biomedical Engineering, College of Engineering, University of Iowa, Iowa City, Iowa; [4]Department of Medicine, [5]Department of Radiology and [6]Department of Epidemiology, Columbia University Medical Center, New York, New York; [7]Department of Medicine, Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, Los Angeles, California; [8]Department of Radiology, Vanderbilt University Medical Center, Nashville, Tennessee; and [9]Department of Biostatistics, University of Washington, Seattle, Washington

Abstract

Rationale: Computed tomography (CT)-based lung density is used to quantitate the percentage of emphysema-like lung (hereafter referred to as percent emphysema), but information on its distribution among healthy nonsmokers is limited.

Objectives: We evaluated percent emphysema and total lung volume on CT scans of healthy never-smokers in a multiethnic, population-based study.

Methods: The Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study investigators acquired full-lung CT scans of 3,137 participants (ages 54–93 yr) between 2010–12. The CT scans were taken at full inspiration following the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) protocol. "Healthy never-smokers" were defined as participants without a history of tobacco smoking or respiratory symptoms and disease. "Percent emphysema" was defined as the percentage of lung voxels below −950 Hounsfield units. "Total lung volume" was defined by the volume of lung voxels.

Measurements and Main Results: Among 854 healthy never-smokers, the median percent emphysema visualized on full-lung scans was 1.1% (interquartile range, 0.5–2.5%). The percent emphysema values were 1.2 percentage points higher among men compared with women and 0.7, 1.2, and 1.2 percentage points lower among African Americans, Hispanics, and Asians compared with whites, respectively ($P < 0.001$). Percent emphysema was positively related to age and height and inversely related to body mass index. The findings were similar for total lung volume on CT scans and for percent emphysema defined at −910 Hounsfield units and measured on cardiac scans. Reference equations to account for these differences are presented for never, former and current smokers.

Conclusions: Similar to lung function, percent emphysema varies substantially by demographic factors and body size among healthy never-smokers. The presented reference equations will assist in defining abnormal values for percent emphysema and total lung volume on CT scans, although validation is pending.

Keywords: emphysema; lung volumes; quantitative computed tomography; reference equations

(Received in original form October 18, 2013; accepted in final form May 14, 2014)

Supported by the National Heart, Lung and Blood Institute, National Institutes of Health (R01 HL077612, R01 HL093081, N01 HC95159-HC95169, BRP HL064368, and HL112986).

Author Contributions: drafting the manuscript: E.A.H., R.G.B.; collecting the data: E.A.H., H.B., M.B., J.J.C., R.K., S.R., R.G.B.; obtaining funding: E.A.H., R.G.B., R.K.; statistical analysis: F.S.A.; oversight of statistical analysis: R.G.B., R.K.; final review: all authors.

Correspondence and requests for reprints should be addressed to R. Graham Barr, M.D., Dr.P.H., Columbia University Medical Center, 630 West 168th Street, PH 9 East, Room 105, New York, NY 10032. E-mail: rgb9@columbia.edu

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Ann Am Thorac Soc Vol 11, No 6, pp 898–907, Jul 2014

DOI: 10.1513/AnnalsATS.201310-364OC
Internet address: www.atsjournals.org

Computed tomography (CT) of the lung has long been used to provide an index of regional lung density (1–3), which, when acquired at full inspiration, yields measures of the presence and distribution of emphysema-like lung (4–7). The percentage of emphysema-like lung (also called "percent low attenuation area" and hereafter referred to as "percent emphysema") correlates with the presence and extent of emphysema on autopsy (3, 8, 9) and is associated with a poor prognosis in chronic obstructive pulmonary disease (COPD) (10–14), among smokers (15), and in the general population (16) independent of lung function.

Percent emphysema, in addition to lung volumes and airway measures (17–19), is being obtained on scans from tens of thousands of participants in research studies. In some of these studies, the researchers have inferred differences in disease susceptibility by sex and race/ethnicity using percent emphysema (20–23). To interpret variation in disease, however, it is helpful to understand the variation of percent emphysema in the nonsmoking, normal population (24).

In a normal population including never-smokers, differences in percent emphysema may occur because of altered stretch or compression of the lung related to gravity, height of the lung and support of the heart (1, 25), variation in residual peripheral airway structures (a voxel inside an airway will be emphysema-like), and scatter effects (26), which differ by scanner manufacturer, or may represent the presence of subclinical emphysema due to secondhand smoke exposure during childhood and other environmental exposures, as well as genetic factors (27–32). Indeed, researchers in small studies have suggested that percent emphysema varies among healthy never-smokers by demographic factors (33–36); however, these studies were limited by modest sample sizes, restricted racial and ethnic distributions, and lack of population-based sampling. Investigators in a larger study recently reported that lobar lung volumes on CT scans vary by sex, height, and race (37); however, that study included mostly older smokers, who are unlikely to have structurally normal lungs, and the researchers did not address percent emphysema or total lung volumes.

In the present article, we describe normal variation in percent emphysema in a large sample of nonsmokers recruited from the general population and provide normal reference equations for the four major racial and ethnic groups in the United States using a highly standardized lung CT protocol used in several other large research studies. For completeness, we provide in the online supplement similar equations for percent emphysema acquired on cardiac scans, which were previously presented in abstract form (38).

Methods

Multiethnic Study of Atherosclerosis

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study initially designed to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease (39). The MESA investigators recruited 6,814 men and women ages 45–84 years old from six U.S. communities from 2000–02: Forsyth County, NC; northern Manhattan and Bronx, NY; Baltimore City and Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles, CA. Exclusion criteria included clinical cardiovascular disease, weight >300 lbs., pregnancy, or impediment to long-term participation. The protocols of MESA and all studies described herein were approved by the institutional review boards of all collaborating institutions and the National Heart, Lung, and Blood Institute (NHLBI).

The MESA Lung Study researchers enrolled 3,965 MESA participants of the 4,484 selected who were sampled randomly from among those who consented to genetic analyses, underwent baseline measures of endothelial function, and attended an examination during the MESA Lung recruitment period from 2004–06. Asians, who were predominantly of Chinese background, were oversampled to improve the precision of estimates for that group.

We selected the following sample to undergo full-lung CT scans between 2010–12: (*1*) all MESA participants who were enrolled into the MESA Lung Study from 2004–06, (*2*) all MESA participants who were selected for participation but were not enrolled into the MESA Lung Study from 2004–06, and (*3*) a random sample of MESA participants selected for magnetic resonance imaging. Of these participants, 3,137 underwent full-lung CT scans between 2010–12 (Figure 1).

Healthy Never-Smoker Sample

The selection of healthy never-smoker MESA Lung participants followed the strategy for the derivation of spirometry reference equations recommended for use in the United States (40) and previously validated in this cohort (41). Participants with a history of tobacco smoking, respiratory symptoms or diagnoses, and poor CT scan acquisition were excluded (Figure 1). Participants with a recent respiratory infection or body mass index (BMI) >40 kg/m^2 were also excluded to avoid, respectively, potential infiltrates or the effects of severe obesity on inspiration level and beam attenuation.

Healthy Active Smoker Sample

Because active smoking affects CT lung density measurements (42), we also defined a healthy active smoker sample to estimate reference equations for percent emphysema for current smokers. This sample met the same exclusion criteria as the healthy never-smoker sample, except that it was limited to participants who reported active smoking.

Imaging

The full-lung scans were acquired at six centers in 2010–12 using four models of 64-slice multidetector row CT (MDCT) scanners from two manufacturers (four Siemens SOMATOM Sensation and one Siemens SOMATOM Definition [Siemens Medical Solutions, Erlangen, Germany], two GE LightSpeed and one GE Discovery [GE Healthcare, Waukesha, WI]) following the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS)/MESA Lung CT protocol (0.984 pitch, 0.5 seconds, 120 kVp) (43, 44). Scans were acquired at suspended full inspiration following coaching to inspire to total lung capacity. The milliampere level was based on BMI: 145 mA for <20 kg/m^2, 180 mA for 20–30 kg/m^2, and 270 mA for >30 kg/m^2. Images were reconstructed at 0.625 mm. Scanner calibration was confirmed throughout the study with monthly lung phantom measures. All participants also underwent cardiac CT scans between 2000 and 2002. The cardiac scan acquisition and reading protocol are described in the online supplement.

Percent Emphysema and Total Lung Volume

Image attenuation was assessed on full-lung scans using APOLLO Version 1.2 software (VIDA Diagnostics, Coralville IA) at a single reading center by trained readers without knowledge of other participant information. All voxels in the lung were identified, and lung volume was calculated. “Percent emphysema” is defined as the percentage of total voxels within the lung field that fell below −950 Hounsfield units (HUs) based upon pathological comparisons (3), and also the percentage below −910 HU, as the

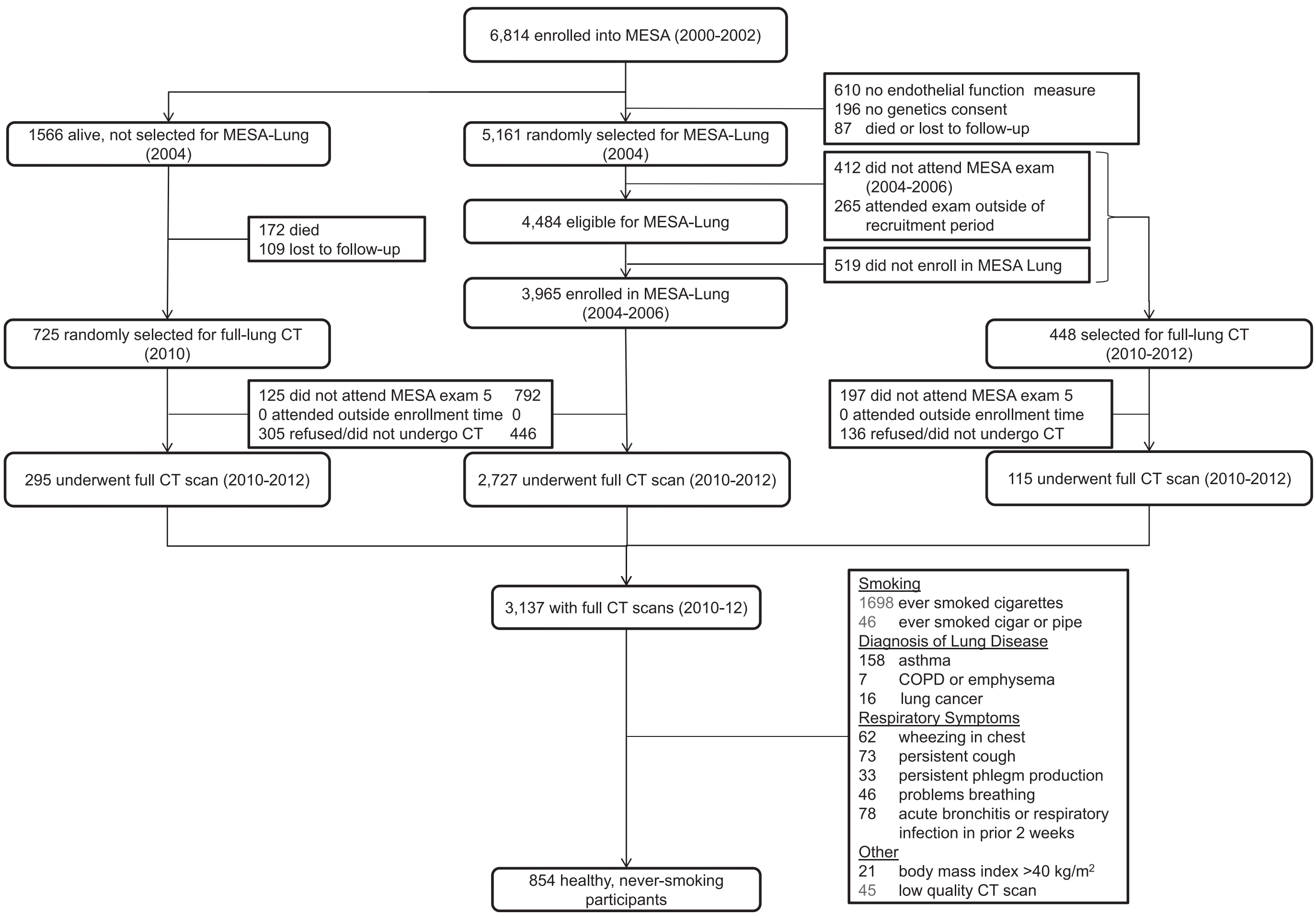

Figure 1. Flow diagram of Multi-Ethnic Study of Atherosclerosis (MESA) participants who underwent full-lung computed tomography (CT) scanning between 2010–12. COPD = chronic obstructive pulmonary disease.

latter has also been validated compared with pathology (2) and is often used in cohorts of less severe disease. These thresholds were not corrected for tracheal or outside air attenuation for the main analyses. The apical and basal regions were defined as the apical and basal one-thirds of the lung and the apical/basal ratio in percent emphysema was calculated. In addition, lobes were segmented, and the ratio of upper/lower lobe percent emphysema was calculated.

Total lung volume visualized on full-lung scans was defined as the number of voxels within the lung mask times the voxel volume, as determined by the slice spacing and the reconstructed field of view. Air and tissue volume were determined by the mean lung HU and the reconstructed HU values of pure air and blood (1). Knowing the value of air and blood, and assuming the HU scale is linear between air and water, coupled with the assumption that lung voxels represent only air or tissue (blood), allows attribution of a percent air and tissue value to the lung based upon the mean lung HU. Multiplying percent air or percent tissue by the total lung provides a total air or tissue volume.

Lung Function

Spirometry was conducted from 2010–12 in accordance with the American Thoracic Society/European Respiratory Society guidelines (45) on a dry-rolling-sealed spirometer (Occupational Marketing, Inc., Houston, TX). One investigator reviewed all spirometry examinations and graded each test for quality (41).

Covariates

Race/ethnicity was defined by self-report during the baseline MESA examination according to 2000 U.S. census criteria as race (white, African-American, Asian) and ethnicity (Hispanic or non-Hispanic) (39). Any smoking history was defined by self-report as a lifetime history of >100 cigarettes, >20 cigars, or >20 pipefuls of tobacco. Respiratory diagnoses and symptoms were assessed with standard questionnaire items (46). Height, weight, and waist and hip circumferences were measured using standometers, calibrated scales, and metal tapes, respectively.

Statistical Analysis

Measures of percent emphysema and lung volumes were stratified by categorical variables of interest and are expressed as medians or means, as appropriate. The distribution of the CT measures was examined using the PROC TRANSREG statement, and appropriate transformations were made to yield approximate normal distributions. The λ value of log-transformed percent emphysema at −950 Hounsfield units was 0.030, suggesting that a log transformation was appropriate for this outcome. The relationships between the CT-based measures and the demographic, anthropomorphic, and scanner variables were examined in linear regression models. Variables that were significantly related to CT-based measures at $P < 0.05$ were considered for inclusion, although consideration was also made for consistency across models and variables previously related to pulmonary function (40).

Reference equations were estimated in the healthy never-smoker sample using linear regression for transformed percent emphysema measures. Analyses were repeated in the combined sample of healthy never-smoker and healthy current smoker samples. Interactions by age, sex, race and ethnicity, milliamperes, manufacturer, and smoking status were tested, and none were found. Quadratic and other nonlinear terms were also tested and did not improve the model fit. The intercept for the upper limit of normal was calculated as the intercept of the predicted equation plus 1.645 multiplied by the standard error of the estimate of the prediction equation. Analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC).

Results

The 3,137 participants who underwent full-lung CT scans were similar to the 1,580 participants who completed the MESA examination between 2010 and 2012 but did not have full-lung CT scans, except for being slightly younger and comprising a lower proportion of women and whites and a higher proportion of Asian Americans, the latter by design (*see* Table 1 in the online supplement).

Of the 3,137 participants who underwent full-lung CT scanning, 854 had never smoked, reported no respiratory diagnoses or symptoms, had a BMI below 40 kg/m^2 and had adequate-quality scans (Figure 1). The characteristics of these participants are shown in Table 1. They had a mean age of 69 ± 9 years, and 62% were female. Most were between 54 and 89 years of age (*see* Supplement 2 online for distribution by decade of age). The racial and ethnic distribution was 32% white, 23% African American, 20% Hispanic, and 25% Asian American. Lung function was normal, as expected. The median percent emphysema was 1.1% at a −950 HU threshold and 16% at a −910 HU threshold. The mean total lung volume was 4,412 ml.

The characteristics of the 99 healthy current smokers are shown in online supplement Table 3. Compared with healthy nonsmokers, these participants were younger and more likely to be male, African American, and of lower socioeconomic status and also had lower lung function and greater percent emphysema.

Percent Emphysema and Total Lung Volume in Healthy Never-Smoker Participants

Percent emphysema increased with age and was substantially greater among men than among women, although there was considerable overlap between individuals (Figure 2A). Percent emphysema increased with height and was greater among whites than among other racial and ethnic groups,

Table 1. Characteristics of healthy, never-smoker participants in the MESA Lung Study who underwent full-lung CT scans between 2010 and 2012

Characteristics	Healthy, Never-Smoker Sample (*n = 854*)
Age, mean ± SD, yr	69 ± 9
Male sex, %	38
Race, %	
White	32
Asian	25
African-American	23
Hispanic	20
Height, mean ± SD, cm	163 ± 9
Weight, mean ± SD, lbs.	159 ± 34
Body mass index, mean ± SD, kg/m^2	27 ± 4
Waist circumference, cm	94 ± 13
Hip circumference, cm	102 ± 10
Waist/hip ratio, mean ± SD	0.93 ± 0.09
Educational attainment, %	
Less than high school	14
High school graduate	18
Some college	25
College graduate	20
Less than bachelor's degree	22
Scanner, %	
Siemens SOMATOM Sensation 64	60
Siemens SOMATOM Definition 64	7
GE LightSpeed VCT 64	20
GE Discovery 64	14
Lung function	
Percent predicted FVC, mean ± SD*	99 ± 17
Percent predicted FEV_1, mean ± SD*	99 ± 18
FEV_1/FVC ratio, mean ± SD*	76 ± 8
Emphysema measurements	
Percent emphysema$_{-950}$ median (IQR)	1.1 (0.49–2.49)
Percent emphysema$_{-910}$ median (IQR)	15.8 (7.5–26.9)
Apical/basal ratio of percent emphysema$_{-950}$ median (IQR)	0.90 (0.54–1.42)
Ratio of upper/lower lobe percent emphysema$_{-950}$ median (IQR)	1.31 (0.94–1.93)
Volumes	
Total lung volume, mean ± SD, ml	4,526 ± 1,216
Total air volume, mean ± SD, ml	3,797 ± 1,109
Total tissue volume, mean ± SD, ml	730 ± 143

Definition of abbreviations: FVC = forced expiratory capacity; FEV_1 = forced expiratory volume in 1 second; IQR = interquartile range; Percent emphysema$_{-950}$ = percentage of emphysema-like lung at −950 Hounsfield units; MESA = Multi-Ethnic Study of Atherosclerosis.
*n = 766.

Table 2. Multivariate mean differences in percent emphysema and total lung volume among healthy, never-smoker participants in the MESA lung study

Sample Demographics (*N* = *854*)	Total Percent Emphysema$_{-950}$ (%)	Apical/Basal Ratio of Emphysema$_{-950}$	Ratio of Upper/Lower Lobe Emphysema$_{-950}$	Total Lung Volume (*ml*)
Age, per 10 yr	0.2*	−0.1*	−0.1*	−54
Male sex	1.3*	0.2	0.3*	577*
Race and Ethnicity				
White	Reference	Reference	Reference	Reference
Asian	−1.1*	0.1	−0.2	−681*
African-American	−0.7*	0.1	−0.3	−783*
Hispanic	−0.9*	−0.1	−0.1	−406*
Height per 10 cm	0.21	−0.3*	−0.2*	654*
BMI, kg/m^2				
<20	0.3	−0.2	0.2	234
20–30	Reference	Reference	Reference	Reference
>30	−0.6*	−0.2	−0.5*	−235*
GE scanner (vs. Siemens)	−1.3*	−0.2	−0.4*	−10

Definition of abbreviations: BMI = body mass index; Percent emphysema$_{-950}$ = percentage of emphysema-like lung at −950 Hounsfield units; MESA = Multi-Ethnic Study of Atherosclerosis.
Multivariate models included the variables are in addition to educational attainment. The values shown are the back-transformed (i.e., unlogged) multivariate mean differences per unit of the independent variable (i.e., 10 yr for age).
*$P < 0.05$.

again with great overlap (Figure 2B). In addition, percent emphysema varied by weight, educational attainment, and scanner manufacturer (all $P < 0.05$).

Table 2 shows the multivariate relationships of percent emphysema to these factors. Percent emphysema varied substantially by age, sex, race and ethnicity, height, and BMI. Despite efforts to standardize the protocol across scanner manufacturers and phantom data confirming calibration, participants scanned on GE scanners had a lower average percent emphysema than those scanned on Siemens scanners. In contrast, the apical/basal ratio in percent emphysema varied significantly by age and height only, whereas the upper/lower lobe ratio in percent emphysema varied by age, sex, height, BMI, and scanner manufacturer.

Total lung volume also varied by age, sex, race and ethnicity, height, and BMI, but was unaffected by scanner manufacturer.

Most measures of percent emphysema and total lung volume were associated with lung function, even in this healthy never-smoker sample (Table 3).

Reference Equations for Percent Emphysema and Total Lung Volume on CT Scans

Given the large and significant differences by demographic and body size variables, we derived reference equations for percent emphysema that included terms for age, sex, race and ethnicity, height, BMI category as defined in the protocol, and manufacturer (Table 4). Reference equations for apical-basal emphysema included terms for age, height, and BMI and those for total lung volume on CT scans included all terms except scanner manufacturer. Equations for percent emphysema were stratified by current smoking status due to the large artifactual effect of current smoking on percent emphysema. The variables included in the equations accounted for approximately one-third of the variation in percent emphysema and almost two-thirds of the variation in total lung volume in these normal individuals.

The reference equations provide one intercept for the calculation of predicted values and a different intercept for the

Table 3. Multivariate mean differences in lung function per standard deviation unit of percent emphysema and lung volume on CT among healthy never-smoker participants in the MESA lung study

Statistics	Total Emphysema (SD)	Apical/Basal Ratio of Emphysema (SD)	Upper/Lower Ratio of Emphysema (SD)	Total Lung Volume (*ml*) (SD)
Sample size n = 767	Mean Difference	Mean Difference	Mean Difference	Mean Difference
FVC, ml	126 (<0.001)	8 (0.69)	62 (<0.001)	463 (<0.001)
FEV_1, ml	37 (0.025)	2 (0.87)	35 (0.017)	292 (<0.001)
FEV_1/FVC ratio, %	−1.55 (<0.001)	0.34 (0.29)	−0.47 (0.094)	−2.43 (<0.001)

Definition of abbreviations: BMI = body mass index; CT = computed tomography; FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second.
Models are adjusted for age, sex, race and ethnicity, height, BMI <20, BMI >30, educational attainment, and scanner type. *P*-values are given in parentheses.

Table 4. Reference equations for predicted and limits of normal values for percent emphysema and total lung volume on CT scans derived from the MESA lung study for former, never-, and current smokers

Statistics	Intercept (Predicted)	Intercept (Upper Limit of Normal)	Intercept (Lower Limit of Normal)	Covariates	R^2
Percent Emphysema$_{-950}$ for former smokers and never-smokers					
% Emphysema	0.140	0.534	—	Age$^{0.336}$·Height$^{2.160}$·Sex$^{0.996}$·AA$^{-0.451}$·Hispanic$^{-1.022}$·Chinese$^{-0.838}$·Manufacturer$^{-1.017}$·Low BMI$^{0.579}$·High BMI$^{-0.647}$	0.32
Apical/basal ratio	31.218	119.104	—	Age$^{-0.662}$·Height$^{-1.640}$	0.02
Percent emphysema$_{-950\ HU}$ for current smokers					
% Emphysema	0.081	0.322	—	Age$^{0.453}$·Height$^{2.345}$·Sex$^{0.977}$·AA$^{-0.444}$·Hispanic$^{-1.022}$·Chinese$^{-0.902}$·Manufacturer$^{-1.087}$·Low BMI$^{0.741}$·High BMI$^{-0.663}$·Cigarettes/day$^{-0.102}$	0.34
Apical/basal ratio	15.705	61.252	—	Age$^{-0.510}$·Height$^{-1.554}$·Cigarettes/day$^{-0.051}$	0.02
Lung volumes: all for all persons					
Total lung volume	2,805	—	2,105	Age$^{-0.145}$·Height$^{2.285}$·Sex$^{0.180}$·AA$^{-0.241}$·Hispanic$^{-0.157}$·Chinese$^{-0.233}$·Low BMI$^{0.069}$·High BMI$^{-0.086}$	0.59
Total air volume	2,535	—	1,814	Age$^{-0.170}$·Height$^{2.368}$·Sex$^{0.194}$·AA$^{-0.263}$·Hispanic$^{-0.195}$·Chinese$^{-0.253}$·Low BMI$^{0.090}$·High BMI$^{-0.122}$	0.54

Definition of abbreviations: BMI = body mass index; CT = computed tomography; AA = African-American; low BMI = body mass index <20 kg/m^2; high BMI = body mass index >30 kg/m^2; Percent emphysema$_{-950}$ = Percentage of emphysema-like lung at −950 Hounsfield units; MESA = Multi-Ethnic Study of Atherosclerosis.

Note. Separate equations are necessary for percent emphysema among former smokers and never-smokers compared to current smokers because of effects of current smoking on percent emphysema (see HEALTHY ACTIVE SMOKER SAMPLE for details). The first set of equations should be used for former smokers and never-smokers, and the second set should be used for current smokers. The equations for lung volumes apply to never, former, and current smokers. For all equations, multiply the relevant intercept by the values of the covariates to the given powers to obtain the relevant values (e.g., to obtain the upper limit of normal for percent emphysema$_{-950\ HU}$ among former smokers, multiply 0.543 by the covariates to the given powers, making sure to specify the covariates as follows. Age was measured in years, and height was measured in meters. Categorical variables were coded as sex (1 = female; 2 = male); AA, Hispanic, Chinese, low BMI, and high BMI (1 = no; 2 = yes); and manufacturer (1 = Siemens; 2 = GE).

calculation of the limits of normal. Use of the predicted values to remove residual variation by scanner manufacturer and BMI makes clear the need for reference equations to account for sex, height, race and ethnicity, and, to a lesser extent, age (Figure 3).

Reference equations are also provided for percent emphysema on full-lung scans corrected for the attenuation of outside air and defined at a −910-HU threshold, as well as for lung density measurements, including percent high attenuation areas, on cardiac scans (see Tables 4–6 in the online supplement). The equations for cardiac scans included the same variables as those derived for full-lung CT scans and explained a similar proportion of the variance in percent emphysema.

Discussion

The results of the present study demonstrate significant variation in percent emphysema and total lung volume visualized on CT scans by demographic factors, body size, and scanner manufacturer among healthy never-smokers in a unique, multiethnic, population-based sample. We provide reference equations to account for this normal variation and to more accurately define abnormal values of percent emphysema and total lung volume visualized on CT scans of current, former, and never smokers. Validation of these equations in an external cohort is pending.

Although researchers in several small studies have described CT characteristics in a normal nonsmoking population (33–36), this study is the first, to the best of our knowledge, with a cohort of normal nonsmokers that is large enough to define normal variation in percent emphysema in the general population. In a relatively large number of disease-based, multicenter studies, researchers have or are using CT to define lung structure, including the National Emphysema Treatment Trial, SPIROMICS, COPDGene, and Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints studies in COPD, the Severe Asthma Research Project (SARP) in asthma, and the Lung Tissue Research Consortium in interstitial lung disease. Several papers on these studies have suggested differing susceptibilities to pathologic processes based upon sex, race, and demographic characteristics (20–22). On the basis of the data we present herein, we think that some of their conclusions may have been influenced by normal variation, as the differences observed for percent emphysema based upon sex, race and ethnicity, and body size among healthy never-smokers were consistent with or more extreme than those previously observed in patients with COPD (20–22).

It is of interest that the only factors in those studies that influenced differences between apical basal aspects were age and height. Because an important determination of emphysema phenotypes (α_1- versus

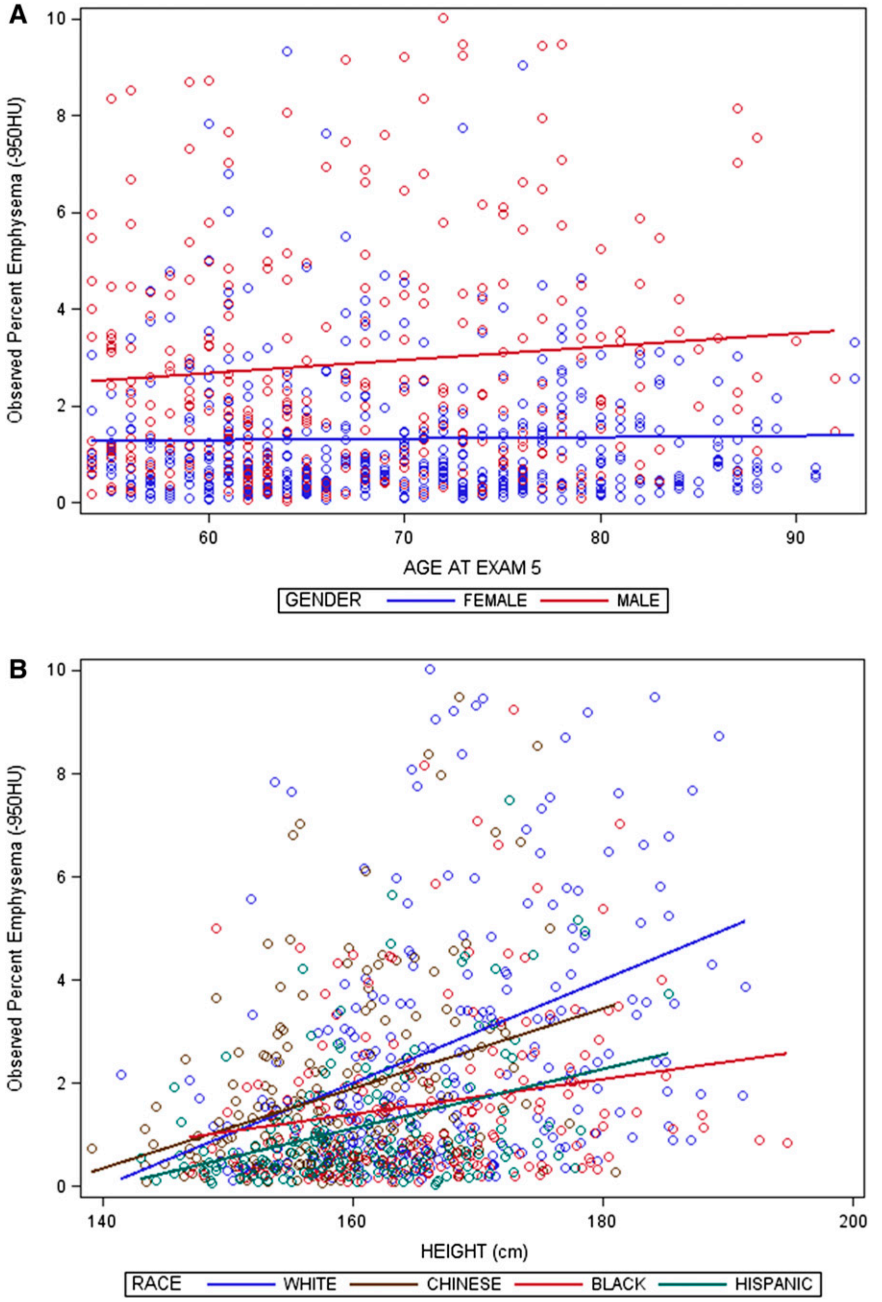

Figure 2. Observed values of percent emphysema among healthy never-smoker adults by sex, and age (*A*) and by race, ethnicity, and height (*B*). *Note*: Lines in the figure are regression lines. HU = Hounsfield units.

smoking-associated), as well as trigger points for lung volume (surgical or endobronchial), has been the apical and basal differences in emphysema-like lung, the homogeneity of this measure across the normal population in all but measures of age and height demonstrates the robust nature of the apical and basal phenotype (47–49). Interestingly, the more refined measure of upper/lower lobe ratio in percent emphysema varied with all factors except for race and ethnicity.

The current findings for lung structure, perhaps not surprisingly, are similar to those for spirometric measures. For example, mean normal values of the forced vital capacity (FVC) have long been recognized to decline with age and to be greater among men compared with women, among whites compared with nonwhites, and among taller compared with shorter individuals (40), as we observed for total lung volumes on CT scans.

Similar differences in percent emphysema among healthy never-smokers may reflect differences in airway size between men and women and between large compared with small individuals that persist out to the lung periphery and that contribute to "parenchymal density" in the lung periphery. CT measurements also varied by obesity, likely due to greater compression of the lung at suspended full inspiration in the supine position in obese compared with lean individuals, and, in the case of percent emphysema, beam attenuation by adipose tissue, in addition to protocol differences. Age, obesity, and other factors related to ability to attain total lung capacity (50) may also have affected our measurements. Unlike spirometric measurements, percent emphysema is known to be affected acutely by cigarette smoking (42). We did not examine this relationship directly in this study, but we present separate equations for percent emphysema for use with current smokers.

The variance explained by the current reference equations for lung volumes on CT scans was comparable to that for reference equations for volumes measured on spirometry in the Third National Health and Nutrition Examination Survey (40). Similarly, the variance explained by the reference equations for percent emphysema was similar to that for the ratio of forced expiratory volume in 1 second (FEV_1) to FVC, the lower limit of normal of which is used to define airflow limitation (45). The variance explained by reference equations for the apical/basal ratio in percent emphysema was lower.

A major strength of the current study is that the acquisition protocol and the software used for the full-lung analyses are identical to those used in other major NHLBI-supported studies, including SPIROMICS and SARP; hence, the reference equations developed in our study are likely directly applicable to those studies and other research studies using the same CT scan data acquisition protocol. The reference equations for percent emphysema on cardiac scans presented in the online

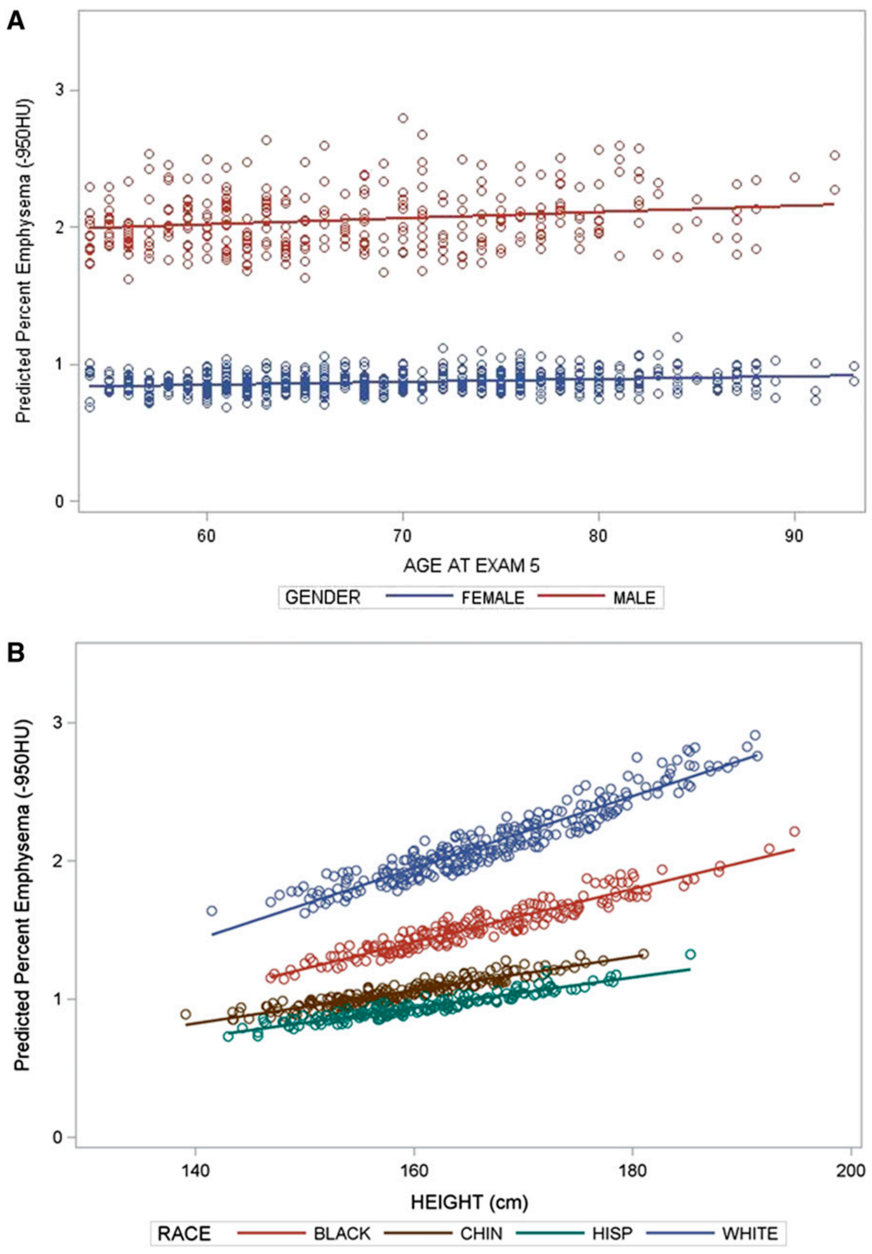

Figure 3. Predicted normal values of percent emphysema among healthy never-smoker adults by sex and age (*A*) and by race, ethnicity, and height (*B*). *Note*: Lines in the figure are regression lines. HU = Hounsfield units.

supplement are likely to be applicable in studies using cardiac CT protocols based upon the MESA protocol, including the Framingham Heart Study, the Coronary Artery Risk Development in Young Adults Study, and the Reykjavik Study. As manufacturers, and presumably protocols, did not affect total lung volume, the reference equations for lung volumes visualized on CT scans apply broadly, potentially including well-performed clinical scans.

As reconstructed CT scan-visualized densities are influenced by scanner manufacturer and model, slice thickness, reconstruction kernel, and more (51–54), the equations for percent emphysema may or may not be applicable directly to studies in which other techniques are used; however, the current equations provide a benchmark against which other studies can test their results. The differences by manufacturer and model reinforce the need for scanner manufacturers to standardize measurements for lung imaging.

No other similarly large cohort of nonsmokers is available for validation of the full-lung equations, although the authors of a recent publication on lobar volumes visualized on CT scans of smokers found somewhat similar differences by sex, height, and African-American race/ethnicity, but not age and body mass index (other racial and ethnic groups were not included) (37).

Similarly to findings for spirometry (55), we found no evidence that the relationship of age and height to percent emphysema varied by race or ethnicity. This observation implies that separate reference equations for quantitative CT-based lung measurements for separate racial and ethnic groups are unnecessary, although terms for race and ethnicity in the equations are still needed.

The limitations of the present study include its modest sample size after stratification by race, ethnicity, and sex and the lack of an independent validation set. Nonetheless, the sample sizes for most race-, ethnicity-, and sex-specific cells were comparable to those for spirometry reference equations (40), and the sample size of the present study was considerably larger than those of prior studies on reference equations for lung volumes on phlethysmography (56, 57). We did not validate the reference equations in an independent cohort, owing to the absence of an appropriate cohort with full-lung scans; however, we anticipate future validation in the control group in SPIROMICS.

In conclusion, herein we present a large population-based assessment of percent emphysema and total lung volume measured on CT scans among healthy never-smokers. We demonstrate that there are significant differences based upon sex, age, race, ethnicity, body habitus, and scanner manufacturer with regard to percent emphysema, and we provide reference equations to account for these differences. The reference equations were not validated in an independent cohort, owing to the current lack of a large cohort of healthy never-smokers with CT scans.

It is possible that changes in scanning protocols and scanners might alter the coefficients in the equations for percent emphysema; however, the relative differences between the subsets of the population identified in our study should remain unchanged. Scanner factors did not affect equations for total lung volume. Thus, the equations represent the present state-of-the-art definition of abnormal values for percent emphysema in research settings and, for total lung volume on CT, in clinical research and settings. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Megha Parikh, Tess Pottinger, and Joe Schwartz for assistance with statistical analyses, David Lederer for high attenuation area analyses, and the participants of the MESA and MESA Lung studies for their valuable contributions. A full list of participating MESA investigators and institutions can be found at www.mesa-nhlbi.org

References

1 Hoffman EA. Effect of body orientation on regional lung expansion: a computed tomographic approach. *J Appl Physiol (1985)* 1985;59: 468–480.
2 Coxson HO, Mayo JR, Behzad H, Moore BJ, Verburgt LM, Staples CA, Paré PD, Hogg JC. Measurement of lung expansion with computed tomography and comparison with quantitative histology. *J Appl Physiol (1985)* 1995;79:1525–1530.
3 Gevenois PA, de Maertelaer V, De Vuyst P, Zanen J, Yernault JC. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1995;152: 653–657.
4 Coxson HO. Quantitative chest tomography in COPD research: chairman's summary. *Proc Am Thorac Soc* 2008;5:874–877.
5 Hoffman EA, Simon BA, McLennan G. A structural and functional assessment of the lung via multidetector-row computed tomography: phenotyping chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2006;3:519–532.
6 Washko GR, Criner GJ, Mohsenifar Z, Sciurba FC, Sharafkhaneh A, Make BJ, Hoffman EA, Reilly JJ. Computed tomographic-based quantification of emphysema and correlation to pulmonary function and mechanics. *COPD* 2008;5:177–186.
7 Stolk J, Ng WH, Bakker ME, Reiber JH, Rabe KF, Putter H, Stoel BC. Correlation between annual change in health status and computer tomography derived lung density in subjects with α_1-antitrypsin deficiency. *Thorax* 2003;58:1027–1030.
8 Müller NL, Staples CA, Miller RR, Abboud RT. "Density mask": an objective method to quantitate emphysema using computed tomography. *Chest* 1988;94:782–787.
9 Madani A, De Maertelaer V, Zanen J, Gevenois PA. Pulmonary emphysema: radiation dose and section thickness at multidetector CT quantification—comparison with macroscopic and microscopic morphometry. *Radiology* 2007;243:250–257.
10 Haruna A, Muro S, Nakano Y, Ohara T, Hoshino Y, Ogawa E, Hirai T, Niimi A, Nishimura K, Chin K, *et al*. CT scan findings of emphysema predict mortality in COPD. *Chest* 2010;138:635–640.
11 Sverzellati N, Cademartiri F, Bravi F, Martini C, Gira FA, Maffei E, Marchianò A, La Vecchia C, De Filippo M, Kuhnigk JM, *et al*. Relationship and prognostic value of modified coronary artery calcium score, FEV_1, and emphysema in lung cancer screening population: the MILD trial. *Radiology* 2012;262:460–467.
12 Johannessen A, Skorge TD, Bottai M, Grydeland TB, Nilsen RM, Coxson H, Dirksen A, Omenaas E, Gulsvik A, Bakke P. Mortality by level of emphysema and airway wall thickness. *Am J Respir Crit Care Med* 2013;187:602–608.
13 Mohamed Hoesein FAA, de Hoop B, Zanen P, Gietema H, Kruitwagen CLJJ, van Ginneken B, Isgum I, Mol C, van Klaveren RJ, Dijkstra AE, *et al*. CT-quantified emphysema in male heavy smokers: association with lung function decline. *Thorax* 2011;66:782–787.
14 Mohamed Hoesein FAA, van Rikxoort E, van Ginneken B, de Jong PA, Prokop M, Lammers J-WJ, Zanen P. Computed tomography-quantified emphysema distribution is associated with lung function decline. *Eur Respir J* 2012;40:844–850.
15 McAllister D, Ahmed FS, Austin JHM, Henschke C, Keller BM, Lemeshow A, Reeves AP, Mesia-Vela S, Pearson GD, Shiau MC, *et al*. Emphysema predicts hospitalisation and incident airflow obstruction among older smokers: a prospective cohort study. *PLoS ONE* 2014;9:e93221.
16 Tan WC, Bourbeau J, Hernandez P, Chapman KR, Cowie R, FitzGerald JM, Marciniuk DD, Maltais F, Buist AS, O'Donnell DE, *et al*.; CanCOLD Collaborative Research Group. Exacerbation-like respiratory symptoms in individuals without chronic obstructive pulmonary disease: results from a population-based study. *Thorax* (In press)
17 Nakano Y, Müller NL, King GG, Niimi A, Kalloger SE, Mishima M, Paré PD. Quantitative assessment of airway remodeling using high-resolution CT. Chest 2002;122(6 Suppl):271S–275S.
18 Martinez CH, Chen YH, Westgate PM, Liu LX, Murray S, Curtis JL, Make BJ, Kazerooni EA, Lynch DA, Marchetti N, *et al*.; COPDGene Investigators. Relationship between quantitative CT metrics and health status and BODE in chronic obstructive pulmonary disease. *Thorax* 2012;67:399–406.
19 Han MK, Kazerooni EA, Lynch DA, Liu LX, Murray S, Curtis JL, Criner GJ, Kim V, Bowler RP, Hanania NA, *et al*.; COPDGene Investigators. Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes. *Radiology* 2011;261:274–282.
20 Kim WJ, Silverman EK, Hoffman E, Criner GJ, Mosenifar Z, Sciurba FC, Make BJ, Carey V, Estépar RS, Diaz A, *et al*.; NETT Research Group. CT metrics of airway disease and emphysema in severe COPD. *Chest* 2009;136:396–404.
21 Dransfield MT, Washko GR, Foreman MG, Estepar RS, Reilly J, Bailey WC. Gender differences in the severity of CT emphysema in COPD. *Chest* 2007;132:464–470.
22 Camp PG, Coxson HO, Levy RD, Pillai SG, Anderson W, Vestbo J, Kennedy SM, Silverman EK, Lomas DA, Paré PD. Sex differences in emphysema and airway disease in smokers. *Chest* 2009;136: 1480–1488.
23 Grydeland TB, Dirksen A, Coxson HO, Pillai SG, Sharma S, Eide GE, Gulsvik A, Bakke PS. Quantitative computed tomography: emphysema and airway wall thickness by sex, age and smoking. *Eur Respir J* 2009;34:858–865.
24 Smith BM, Barr RG. Establishing normal reference values in quantitative computed tomography of emphysema. *J Thorac Imaging* 2013;28:280–283.
25 Hoffman EA, Ritman EL. Heart-lung interaction: effect on regional lung air content and total heart volume. *Ann Biomed Eng* 1987;15: 241–257.
26 Mobberley SD, Fuld MK, Sieren JP, Primak AN, Hoffman EA. Scatter correction associated with dedicated dual-source CT hardware improves accuracy of lung air measures. *Acad Radiol* 2013;20: 1334–1343.
27 Lovasi GS, Diez Roux AV, Hoffman EA, Kawut SM, Jacobs DR Jr, Barr RG. Association of environmental tobacco smoke exposure in childhood with early emphysema in adulthood among nonsmokers: the MESA Lung study. *Am J Epidemiol* 2010;171:54–62.
28 Peisl A, Doney B, Hoffman EA, Graziani M, Kullman G, Kaufman JD, Burchfiel C, Donohue KM, Hinckley Stukoysky K, Fujishiro K, *et al*. Occupational risk factors for percent emphysema on computed tomography in the Multi-Ethnic Study of Atherosclerosis [abstract]. *Am J Respir Crit Care Med* 2014;189:A5099.
29 Madrigano J, Adar SD, Schwartz J, Hoffman EA, Enright P, Austin J, Szpiro A, Hinckley Stukoysky K, Kinney P, Vedal S, *et al*. Ambient fine particulate matter (PM2.5) exposure and longitudinal change in percent emphysema on computed tomography (CT): the Multi-Ethnic Study of Atherosclerosis (MESA) lung and air pollution studies [abstract]. *Am J Respir Crit Care Med* 2014;189:A2438.

30 Yamashiro T, Matsuoka S, Estépar RSJ, Diaz A, Newell JD, Sandhaus RA, Mergo PJ, Brantly ML, Murayama S, Reilly JJ, *et al*. Quantitative airway assessment on computed tomography in patients with α_1-antitrypsin deficiency. *COPD* 2009;6:468–477.
31 Wielpütz MO, Weinheimer O, Eichinger M, Wiebel M, Biederer J, Kauczor H-U, Heußel CP, Mall MA, Puderbach M. Pulmonary emphysema in cystic fibrosis detected by densitometry on chest multidetector computed tomography. *PLoS ONE* 2013;8:e73142.
32 Manichaikul A, Hoffman EA, Smolonska J, Gao W, Cho MH, Baumhauer H, Budoff M, Austin JH, Washko GR, Carr JJ, *et al*. Genome-wide study of percent emphysema on computed tomography in the general population: the Multi-Ethnic Study of Atherosclerosis Lung/SNP Health Association Resource Study. *Am J Respir Crit Care Med* 2014;189:408–418.
33 Mets OM, van Hulst RA, Jacobs C, van Ginneken B, de Jong PA. Normal range of emphysema and air trapping on CT in young men. *AJR Am J Roentgenol* 2012;199:336–340.
34 Irion KL, Marchiori E, Hochhegger B, da Silva Porto N, da Silva Moreira J, Anselmi CE, Holemans JA, Irion PO. CT quantification of emphysema in young subjects with no recognizable chest disease. *AJR Am J Roentgenol* 2009;192:W90-W96.
35 Zach JA, Newell JD Jr, Schroeder J, Murphy JR, Curran-Everett D, Hoffman EA, Westgate PM, Han MK, Silverman EK, Crapo JD, *et al*.; COPDGene Investigators. Quantitative computed tomography of the lungs and airways in healthy nonsmoking adults. *Invest Radiol* 2012; 47:596–602.
36 Gevenois PA, Scillia P, de Maertelaer V, Michils A, De Vuyst P, Yernault JC. The effects of age, sex, lung size, and hyperinflation on CT lung densitometry. *AJR Am J Roentgenol* 1996;167:1169–1173.
37 Come CE, Diaz AA, Curran-Everett D, Muralidhar N, Hersh CP, Zach JA, Schroeder J, Lynch DA, Celli B, Washko GR; COPDGene Investigators. Characterizing functional lung heterogeneity in COPD using reference equations for CT scan-measured lobar volumes. *Chest* 2013;143:1607–1617.
38 Hoffman EA, Jiang R, Baumhauer H, Brooks MA, Carr JJ, Detrano R, Reinhardt J, Rodriguez J, Stukovsky K, Wong ND, *et al*. CT lung density measures in a healthy multiethnic population: the MESA Lung Study. Presented at the American Thoracic Society Annual Meeting, 2007, San Francisco, CA, Abstract.
39 Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, *et al*. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol* 2002;156: 871–881.
40 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–187.
41 Hankinson JL, Kawut SM, Shahar E, Smith LJ, Stukovsky KH, Barr RG. Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults: the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study. *Chest* 2010;137:138–145.
42 Ashraf H, Lo P, Shaker SB, de Bruijne M, Dirksen A, Tønnesen P, Dahlbäck M, Pedersen JH. Short-term effect of changes in smoking behaviour on emphysema quantification by CT. *Thorax* 2011;66: 55–60.
43 Sieren JP, Hoffman EA, Baumhauer H, Barr RG, Goldin JG, Rennard S. CT imaging protocol standardization for use in a multicenter study: SPIROMICS (abstract LL-CHE4631). Radiological Society of North America, December 1, 2011, Chicago, IL.
44 Couper D, Lavange LM, Han M, Barr RG, Bleecker E, Hoffman EA, Kanner R, Kleerup E, Martinez FJ, Woodruff PG, *et al*.; SPIROMICS Research Group: Design of the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS). *Thorax* 2014;69: 491–494.
45 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, *et al*.; ATS/ ERS Task Force. Standardisation of spirometry. *Eur Respir J* 2005; 26:319–338.
46 Ferris BG. Epidemiology Standardization Project (American Thoracic Society). *Am Rev Respir Dis* 1978;118:1–120.
47 Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, Weinmann G, Wood DE; National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059–2073.
48 Shah PL, Herth FJ. Current status of bronchoscopic lung volume reduction with endobronchial valves. *Thorax* 2014;69:280–286.
49 Parr DG, Stoel BC, Stolk J, Stockley RA. Pattern of emphysema distribution in α_1-antitrypsin deficiency influences lung function impairment. *Am J Respir Crit Care Med* 2004;170:1172–1178.
50 Lovasi GS, Diez Roux AV, Hoffman EA, Smith LJ, Jiang R, Carr JJ, Barr RG. Socioeconomic status is positively associated with percent emphysema on CT scan: the MESA Lung Study. *Acad Radiol* 2011; 18:199–204.
51 Sieren JP, Newell JD, Judy PF, Lynch DA, Chan KS, Guo J, Hoffman EA. Reference standard and statistical model for intersite and temporal comparisons of CT attenuation in a multicenter quantitative lung study. *Med Phys* 2012;39:5757–5767.
52 Stoel BC, Bakker ME, Stolk J, Dirksen A, Stockley RA, Piitulainen E, Russi EW, Reiber JH. Comparison of the sensitivities of 5 different computed tomography scanners for the assessment of the progression of pulmonary emphysema: a phantom study. *Invest Radiol* 2004;39:1–7.
53 Boedeker KL, McNitt-Gray MF, Rogers SR, Truong DA, Brown MS, Gjertson DW, Goldin JG. Emphysema: effect of reconstruction algorithm on CT imaging measures. *Radiology* 2004;232:295–301.
54 Hochhegger B, Irion KL, Marchiori E. Thresholds to lung density measures. *Acad Radiol* 2010;17:339–401.
55 Kiefer EM, Hankinson JL, Barr RG. Similar relation of age and height to lung function among Whites, African Americans, and Hispanics. *Am J Epidemiol* 2011;173:376–387.
56 Garcia-Rio F, Dorgham A, Pino JM, Villasante C, Garcia-Quero C, Alvarez-Sala R. Lung volume reference values for women and men 65 to 85 years of age. *Am J Respir Crit Care Med* 2009;180: 1083–1091.
57 Crapo RO, Morris AH, Clayton PD, Nixon CR. Lung volumes in healthy nonsmoking adults. *Bull Eur Physiopathol Respir* 1982;18:419–425.