Published in final edited form as:

Eur Respir J. 2016 January ; 47(1): 104–112. doi:10.1183/13993003.00996-2015.

Sex-specific features of emphysema among current and former smokers with COPD

Megan Hardin, MD, MPH[1,2], **Marilyn Foreman, MD, MPH**[3], **Mark T. Dransfield, MD**[4], **Nadia Hansel, MD**[5], **MeiLan K Han, MD**[6], **Michael H Cho, MD, MPH**[1,2], **Surya P Bhatt, MD**[7], **Joe Ramsdell, MD**[8], **David Lynch, MB**[9], **Jeffrey L. Curtis, MD**[6,10], **Edwin K. Silverman, MD, PHD**[1,2], **George Washko, MD, MS**[2], **Dawn DeMeo, MD, MPH**[1,2], and **For the COPDGene Investigators**

[1]Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[2]Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[3]Morehouse School of Medicine, Department of Internal Medicine, Atlanta, GA

[4]Division of Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL

[5]Johns Hopkins School of Medicine, Baltimore, MD

[6]University of Michigan Health System, Ann Arbor, MI

[7]University of Alabama, Birmingham, AL

[8]Division of Internal Medicine, University of California, San Diego, San Diego, CA

[9]Department of Radiology, National Jewish Health, Denver, CO

[10]VA Ann Arbor Healthcare System, Ann Arbor, MI

Abstract

Rationale—Recent studies suggest that men with COPD have more emphysema than women. It is not known if these differences persist across degrees of COPD severity.

Objectives—Our aim was to identify sex-specific differences in quantitative emphysema within COPD subgroups based on COPD severity.

Methods—We included non-Hispanic white and African American subjects from the COPDGene study with at least ten pack-years of smoking and COPD GOLD spirometry grade II or greater. We examined sex-specific differences in log-transformed emphysema (%LAA) by GOLD spirometry grade, among subjects with early-onset COPD (<55 years old) and advanced emphysema (>25 % emphysema).

Corresponding Author: Megan Hardin, MD, MPH, Channing Division of Network Medicine, 181 Longwood Ave, Boston, MA 02116, remeh@channing.harvard.edu.

Measurements and Main Results—Compared to women, men had higher log %LAA: overall (1.97 ± 1.4 v 1.69±1.6, ß=0.32(0.04), $P=1.34\times10^{-14}$), among non-Hispanic whites ($P=8.37\times10^{-14}$), and African American subjects (P=0.002). Women with early-onset COPD, severe emphysema, and GOLD grade IV COPD had similar emphysema as men but markedly fewer pack-years smoking (early-onset P=0.01, severe emphysema and GOLD grade IV P<0.001).

Conclusions—This study identifies subsets of female smokers with COPD who are particularly susceptible to parenchymal destruction.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death in the US, with over 15 million Americans affected(1). COPD prevalence and mortality among women have risen rapidly in the last several decades and are now equal to COPD prevalence and mortality among men(2, 3). Multiple studies suggest that women experience greater lung function decline than men for the same amount of cigarette exposure(4-7). Although the prevalence of COPD among African Americans (AA) is less than among non-Hispanic whites (NHW) (2), AA demonstrate greater lung function decline in response to cigarette smoke, with some studies suggesting that AA women are particularly susceptible to tobacco smoke(4). Despite the growing recognition that COPD is not just a men's disease, research into sex-specific features of COPD has been limited and is needed(8).

Radiographic emphysema is a clinically relevant COPD phenotype that correlates with loss of lung function(9, 10), expiratory airflow limitation(11), decreased diffusing capacity(12), decreased exercise capacity(13, 14), increased respiratory exacerbations(15), and respiratory mortality(16-18). Identifying sex differences in emphysema may lead to insights into sex-specific differences in COPD susceptibility, severity, co-morbidities and treatments.

Several prior studies have compared cross-sectional radiographic emphysema between men and women. These studies have suggested that, as a group, men with COPD have more overall emphysema than women for the same degree of airflow obstruction (19-22). Based on these studies, it would appear that women are less sensitive to parenchymal damage from cigarette smoke than men. This would run counter to evidence suggesting that women have greater lung function decline in response to smoking(5). However, COPD is a complex disease with multiple subphenotypes. These studies were underpowered to identify whether the trend for greater emphysema among male COPD subjects persists among severe COPD subtypes including severe emphysema, advanced, or early-onset COPD. In addition, these trends have not been fully explored among African American populations. One study among a subset of subjects from COPDGene demonstrated that AA had less overall emphysema than NHW (23). A further analysis of emphysema differences within these subgroups and across different races is an essential step towards understanding how COPD can develop and progress by sex, insights which may inform sex-specific clinical care of patients.

This study responds to a call from the National Institutes of Health for more investigation in to the sex-based differences in disease(24), and specifically the need for increased investigation into the sex-specific features of COPD. The goals of this study were to investigate sex-specific differences in emphysema across a large population of COPD

subjects with a comprehensive range of lung function and to investigate sex-specific associations between cigarette smoke dosage and emphysema. We hypothesized that male predominance of emphysema would not persist among severe COPD subgroups.

Materials and Methods

Subjects

All subjects signed informed consent and IRB approval was obtained at Brigham and Women's Hospital [2007P000554; Partners Human Research Committee] and all study sites (Supplementary Table 11). All subjects were NHW or AA current or former smoking participants in the COPDGene study(25). All subjects completed a modified ATS respiratory questionnaire and standardized pulmonary function testing. Our main analysis was among subjects with COPD by ATS/ERS criteria (post-bronchodilator $FEV_1/FVC < 70\%$, $FEV_1 <$ 80% predicted), GOLD spirometry grade II-IV, based on the GOLD 2006 classifications scheme. We examined %LAA differences among all subjects and stratified by race, GOLD spirometry grade, among those subjects with early-onset COPD, and severe emphysema. Early-onset COPD subjects were < 55 years old with $FEV_1 < 50$ percent predicted(26). Severe emphysema was defined as > 25% LAA on CT(27). We additionally investigated smoking controls from COPDGene (current or former smokers with greater than 10 pack-years smoking history and normal spirometry).

Radiographic measurements

Quantitative emphysema, percent low attenuation area (%LAA), was measured using inspiratory CT scans performed at each clinical center and analyzed with Slicer software(25) (15). The total emphysema (%LAA) was defined as the percentage of lung with low attenuation areas less than -950 Hounsfield units (HU)(28). We additionally examined %LAA at -910 HU.

Statistical Analysis

All analyses were performed using R (v2.15.1). We compared means of continuous variables using Student's t-tests and binary variables using Pearson chi-squared analysis. We used Pearson correlations to measure the correlation between pack-years of smoking and emphysema by sex. We transformed %LAA to the natural log scale(29), and performed univariate comparisons of log %LAA using student's T test. We performed logistic regression for log %LAA, adjusting for age, pack-years smoking, current smoking status, and body-mass index. Analyses including both NHW and AA subjects were additionally adjusted for race. We adjusted for CT scanner model using indicator variables for each CT scanner model included in COPDGene(30). Logistic regression for mean %LAA are additionally presented in the online material. We performed a sensitivity analysis among subjects scanned with a single scanner (Siemens© Definition), comparing log %LAA between men and women by sex and race (online material). We performed an additional analysis to examine sex differences in additional exposures and their impact on emphysema, including: age at starting smoking, adult second-hand smoke exposure, and occupational smoke, dust and fumes exposure. We performed backwards selection to identify variables

associated with log %LAA and performed multivariate linear regression for the outcome log % LAA additionally adjusting for these covariates.

Results

Subject demographics

A total of 3690 subjects with GOLD spirometry grade II-IV COPD were included in the analyses (Table 1). Of these subjects, 836 were AA. Both NHW and AA female subjects had fewer pack-years of smoking than males (NHW: 50.3±23.7 vs. 60.7±30.2 pack-years, P<0.001; AA: 38.7±21.3 vs. 45.6±24.0 pack-years, P<0.001).

Quantitative emphysema

In multivariate analyses comparing log %LAA between males and females with COPD, stratified by race, and adjusted for age, BMI, pack-years, current smoking status, and CT scanner type (Figure 1 and Table 2), males had greater emphysema than females, both among NHW (2.06±1.3 vs. 1.79±1.5, β=0.34±0.05, $P=8.37\times10^{-14}$) and AA (1.63±1.5 vs. 1.31±1.7, β=0.31±0.10, P=0.002). This trend persisted with the mean %LAA outcome (Supplementary Table 1), and among subjects scanned with a single CT scanner type (Supplementary Table 2). A similar trend was observed when comparing the outcome %LAA-910 (Supplementary Table 3). The sex-specific difference in log %LAA was also observed among 4,388 current or former smokers with normal lung function (Supplementary Tables 4-5).

Pack-years of smoking and emphysema

Overall, men had greater pack-years of smoking than women (Table 1). Pack-years of smoking was significantly but weakly correlated with log %LAA in males and females (males: R=0.12, P<0.001; females: R=0.08, P=0.002). Among all COPD subjects, there was not a significant interaction between sex and pack-years for the outcome log %LAA (P=0.69 for NHW, P=0.97 for AA, and P=0.78 for all subjects). However, the interaction between sex and current smoking status was significant for this outcome among all subjects (P=0.004) and NHW (P=0.01), but only a trend among African Americans (P=0.06). Among the smoking controls, males demonstrated more emphysema per pack-year smoked than females (P<0.001), but there was no difference in the amount of emphysema per pack year smoked among all of the COPD subjects (P=0.74) (Supplementary Table 6).

Quantitative CT traits and the sex-specific relationship with lung function

To evaluate whether the relationship between amount of emphysema and lung function differed by sex, we examined sex-specific differences in log %LAA by GOLD spirometry grade (Table 3 and Figure 2). Log %LAA increased with each GOLD spirometry grade in men and women. The disparity between the sexes in log %LAA was seen most strongly among the GOLD II subjects (males: 1.39±1.3% vs. females: 1.09±1.5%, β=0.36±0.05, P<0.001) and decreased to non-significant among subjects with GOLD grade III and IV COPD. Similarly, for grade IV COPD, there was no difference in log %LAA between males and females among all subjects combined, (3.05±0.85 vs. 3.03±0.91, β=0.12±0.06, P=0.07) or among AA subjects. Among NHW subjects, males with GOLD grade IV COPD

demonstrated statistically significant but clinically minimal difference in log %LAA (males: 3.08±0.8vs. females: 3.02±1.0, β=0.17±0.07, P=0.02). Males had significantly more pack-years smoking than females overall (Table 1), and at all GOLD stages, including GOLD IV (Males: 61.8±31.4 vs. females: 49.2±24.3, β=11.1±2.3, P<0.001). These same trends persisted when comparing mean %LAA by sex among each GOLD group (Supplementary Table 7). When baseline FEV_1 was included in the model examining the relationship between log %LAA and sex, males continued to have significantly more emphysema than women (β=0.7±0.04, P<0.001).

Sex-specific emphysema patterns among early-onset COPD subjects

There were 260 subjects with early-onset COPD (Table 4). Females with early-onset COPD had statistically similar log %LAA as males (Females: 1.78±1.6 vs. Males: 2.06±1.4, β=0.13±0.18, P=0.47). As seen previously(26), the females demonstrated similar lung function as measured by FEV_1 percent predicted (Females: 35.52±10.6% vs. Males: 35.52±9.8%, P=0.99), but fewer pack-years of smoking (Females: 41.0±20.0 vs. Males: 48.2±25.4 pack-years, P=0.01). There was no interaction between sex and pack years smoking (P=0.42). These same trends persisted when comparing mean %LAA (Supplementary Table 8).

Sex-specific emphysema patterns among emphysema-predominant subjects

There were 627 subjects with greater than 25% LAA on chest CT scans (Table 4). There were more men than women in this group. Males and females with emphysema predominance were similar in age and lung function (Table 4). However, the females in this group had significantly fewer pack-years than males (Females: 49.1±22.1 vs. Males: 56.3±25.8 pack-years, P<0.001), despite similar log %LAA (Females: 3.54±0.2 vs. Males: 3.54±0.2, P=0.19). This same trend was seen when comparing mean %LAA (Supplementary Table 8).

Environmental exposures

We examined the relationship between environmental exposures and log %LAA. Overall, males had greater second-hand smoke exposure, including smoke exposure at work, were more likely to have worked in a job with dust or fumes, and were more likely to be currently working in a job with dust or fumes (Supplementary Table 9). In a multivariate analysis, passive smoke (β=0.003±0.001, P=0.02) and fumes exposure at work (β=0.20±0.05, P<0.001) were significantly associated with log %LAA, and years of second hand smoke exposure at work approached significance (β=0.003±0.001, P<0.07). The addition of these covariates to the multivariate regression examining log %LAA did not change the general trends noted in our main analysis. (Supplementary Table 10). We additionally included maternal smoking and maternal history of COPD in our model examining the relationship between sex and %LAA among all subjects and early-onset subjects; the inclusion of these variables did not impact the overall trends of our results.

Discussion

In this analysis of COPDGene subjects, we demonstrate that although men displayed greater radiographic emphysema extent than women overall, women in three phenotypic subgroups (early-onset COPD, subjects with severe emphysema, and GOLD grade IV COPD) had comparable radiographic emphysema, despite fewer pack-years of smoking. These findings suggest a subset of female smokers who are particularly susceptible to parenchymal lung destruction. Our results significantly extend previous studies showing that among COPD subjects in aggregate, men tend to have an emphysema-predominant phenotype, and women have airway involvement(19, 21, 22, 31). Those prior studies were limited by sample size or subject ascertainment, and therefore had limited generalizability to specific subsets of COPD subjects. Given the increasing recognition that radiographic emphysema is a clinically meaningful COPD phenotype, even in the absence of airflow obstruction, our findings fill an important knowledge gap on sex-based differences in lung disease.

Early-onset COPD is an extreme COPD subgroup, and may prove especially useful for investigating the role of sex-specific genetic factors in COPD development and progression. Prior studies have suggested a distinct pathogenesis for early-onset COPD encompassing sex-specific immune responses, genetic or epigenetic effects(26). Subjects with early-onset COPD have been shown to be predominantly female(32), a finding replicated in an analysis of the first 2500 subjects from COPDGene(26). Linkage and familial aggregation studies have identified potential genetic risk factors for early-onset COPD(33-35); the finding of markedly reduced lung function in female first-degree relatives of probands with early-onset COPD(36) suggests that women may be particularly susceptible to this COPD subtype. Our finding that women with early-onset COPD have equivalent emphysema with fewer pack-years of smoking is consistent with these suggestions. In contrast to our findings, however, Camp and colleagues examined probands and their siblings with COPD from the ICGN study(19). In that population, they found that more men had an emphysema pattern and women an airway predominant pattern. Although probands in that study were selected for COPD occurring before age 65, the subjects overall were different than those included here, including fewer subjects with severe COPD.

Our findings among the emphysema-predominant subgroup differ from the observations among subjects with severe emphysema being considered for lung volume reduction surgery from the National Emphysema Treatment Trial (NETT). Martinez and colleagues demonstrated that among these subjects, males had more emphysema than females, as measured by whole lung percent emphysema on CT scan(21). However, their study contrasts with COPDGene in several ways. NETT study subjects were defined by the presence of severe COPD ($FEV_1pp < 45\%$), and subjects considered high-risk for lung-volume reduction surgery were excluded, including those with very severe COPD ($FEV_1pp < 20\%$). NETT subjects had significant pack-years smoking history with a mean of 71 pack-years in males and 55 in females. Among COPDGene subjects we observed that the sex-specific differences in emphysema were less distinct among the heaviest smokers, as well as those with the most severe reductions in lung function.

Our finding that the sex-based differences were most striking at early grades of the disease (GOLD II), but equivalent by later-grade disease is important because it may suggest that sex-based emphysema patterns begin early in the disease process but later progress differently in men and women depending on additional susceptibility factors. This result contrasts with a prior study of 396 subjects with COPD GOLD II-IV from the National Lung Screening Trial (31). In that study, men overall had greater emphysema than women. However, the differences in percent emphysema were not significantly different between men and women with GOLD II COPD, but were for GOLD III/IV males and females. COPDGene includes more subjects with severe COPD, and is better powered to examine differences in emphysema among this subset of subjects. In addition, this current study accounts for pack-years and smoking status when comparing emphysema between the sexes.

Our study also demonstrated similar, but less marked, sex-based differences in COPD among the AA subjects, relative to NHW sex-based differences. In a previous analysis among the first 2500 subjects from the COPDGene study, Hansel and colleagues observed that AA subjects had less overall emphysema, as well as less lower lobe emphysema than NHW (23). We demonstrate that the sex-based differences in emphysema are less marked in AA subjects but the trend is still present. It is of note that in our study, AA females had higher BMI than AA males, while the converse was seen in NHW. This trend mirrors that seen among US adults as a whole(37). Theoretically, increased BMI could lead to decreased effective radiation dose and artifactually increase %LAA measurement(30, 38), however, we have adjusted for BMI in our model.

We chose to use log %LAA as our measure of emphysema. This endpoint is determined by calculating the percentage of voxels on the chest CT that are below a certain Hounsfield unit, in this case, less than 950. The SLICER method is a computer algorithm and therefore not subject to inter-observer variability. However, while it provides a quantitative assessment of overall emphysema, it does not yet parse subtypes such as panlobular, paraseptal, and centrilobular emphysema. Several other methods for calculating emphysema have been developed(39, 40), and this is an area of active research. While analyzing sex-based differences in all of these outcomes is of interest, and is an area for future work, for this current analysis we chose an established and validated method.

Our study has several limitations. First, because %LAA is a highly skewed variable, we log-transformed this outcome as has been done previously(29), however, we recognize that log-transformed values are less straightforward. We have included the analysis of untransformed mean emphysema for our main analyses (Supplementary Material). Second, we attempted to identify sex-specific differences in emphysema related to smoking history. Our findings were mixed, which might reflect either that quantitative emphysema is poorly correlated with pack-years of smoking history or that pack-years is not the best metric to characterize cigarette smoke exposure. The pack-years variable is a best estimation of prior cigarette smoke exposure; however this variable is limited in the ability to assess the impact of smoke exposure as it assumes a continuous exposure and linear dosage relationship. Additionally, one pack of cigarettes could represent a different dose for men and women as women have smaller lung size. Differences in emphysema between men and women may be related to sex-specific differences in the response to cigarette smoke: %LAA is correlated with

decreased lung function(9), and women with COPD demonstrated greater lung function decline per cigarette smoked than men(4, 5). Although cigarette smoke is clearly the most important factor in COPD development in industrialized nations, other exposures may impact the progression of emphysema. We attempted to examine the role of such additional exposures including second-hand smoke, and occupational dust and fumes. Although women exposed to biomass fuels have demonstrated distinct emphysema patterns from women with lung function decline from smoking(41), our cohort was ascertained with an emphasis on current and former smokers. These results may be less generalizable to areas where biomass fuel exposure is more prevalent. While males in our study had greater exposures to second-hand smoke, and occupational dust and fumes, the general trends from our main analysis remained significant after adjusting for additional exposures. Third, we cannot exclude the possibility of selection bias, i.e, that women with lung disease and fewer pack-years of smoking history may have been more willing to enroll in the COPDGene study. Finally, body composition can impact radiographic assessment of emphysema, and sex-based differences in subcutaneous tissue could impact our findings; to overcome this, as has been done in prior studies, we adjusted for body mass index as a covariate in our regression models. The potential for differential attenuation by breast tissue remains. Current CT scan techniques do not account for breast tissue attenuation, and this is an area for methods development.

The apparent sexual dimorphism in radiographic emphysema may relate to sex-specific differences in the biologic impact of cigarette smoke dosage. The finding that women demonstrate equivalent emphysema despite fewer pack-years of smoking in the early-onset and emphysema-predominant subsets suggests an increased susceptibility among women in these groups to parenchymal injury associated with smoking. COPD is a complex disorder impacted by heterogeneous susceptibility factors. Identifying susceptibility factors within distinct phenotypic subgroups is an important advance to understanding the variable susceptibility of COPD in general, and sex-specific features specifically. Longitudinal studies following changes in emphysema will be necessary to clarify sex-specific effects of cigarette smoke on emphysema development and progression and potentially to identify additional sex-specific factors contributing to irreversible parenchymal lung destruction.

Conclusions

Among subgroups of non-Hispanic white and African American smokers, including advanced COPD, early-onset COPD, and severe emphysema, men and women demonstrate equivalent emphysema despite significantly fewer pack-years of cigarette smoking among women. COPD is a heterogeneous disease, and identifying phenotypically distinct subsets remains an important step in our understanding of the sexually dimorphic features of disease pathogenesis. Continued research on sex-differences in COPD is mandatory, with a hope to proceed toward sex-specific primary prevention, diagnostics and therapeutics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank participants and field investigators in COPDGene for their willingness to contribute to medical research.

Grant support: R01 HL089438, K12 HL120004, R01 HL089856, R01 HL089897, P01HL105339, 2013 Sheila J. Goodnight, MD, FCCP Clinical Research Grant in Women's Lung Health

NIH Grant Support and Disclaimer: The COPDGene project described was supported by Award Number R01HL089897 and Award Number R01HL089856 from the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, And Blood Institute or the National Institutes of Health.

COPD Foundation Funding: The COPDGene project is also supported by the COPD Foundation through contributions made to an Industry Advisory Board comprised of AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Siemens, Sunovion, and GlaxoSmithKline.

References

1. Diaz-Guzman E, Mannino DM. Epidemiology and prevalence of chronic obstructive pulmonary disease. Clinics in chest medicine. 2014; 35(1):7–16. [PubMed: 24507833]
2. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance--United States, 1971-2000. MMWR Surveill Summ. 2002; 51(6):1–16.
3. Thun MJ, Carter BD, Feskanich D, Freedman ND, Prentice R, Lopez AD, et al. 50-year trends in smoking-related mortality in the United States. N Engl J Med. 2013; 368(4):351–64. [PubMed: 23343064]
4. Dransfield MT, Davis JJ, Gerald LB, Bailey WC. Racial and gender differences in susceptibility to tobacco smoke among patients with chronic obstructive pulmonary disease. Respiratory medicine. 2006; 100(6):1110–6. [PubMed: 16236491]
5. Sorheim IC, Johannessen A, Gulsvik A, Bakke PS, Silverman EK, DeMeo DL. Gender differences in COPD: are women more susceptible to smoking effects than men? Thorax. 2010; 65(6):480–5. [PubMed: 20522842]
6. Gan WQ, Man SF, Postma DS, Camp P, Sin DD. Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respiratory research. 2006; 7:52. [PubMed: 16571126]
7. Prescott E, Bjerg AM, Andersen PK, Lange P, Vestbo J. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. The European respiratory journal. 1997; 10(4):822–7. [PubMed: 9150319]
8. Han MK, Postma D, Mannino DM, Giardino ND, Buist S, Curtis JL, et al. Gender and chronic obstructive pulmonary disease: why it matters. Am J Respir Crit Care Med. 2007; 176(12):1179–84. [PubMed: 17673696]
9. Nakano Y, Muro S, Sakai H, Hirai T, Chin K, Tsukino M, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. Am J Respir Crit Care Med. 2000; 162(3 Pt 1):1102–8. [PubMed: 10988137]
10. Timmins SC, Diba C, Farrow CE, Schoeffel RE, Berend N, Salome CM, et al. The relationship between airflow obstruction, emphysema extent, and small airways function in COPD. Chest. 2012; 142(2):312–9. [PubMed: 22345381]
11. Diaz AA, Morales A, Diaz JC, Ramos C, Klaassen J, Saldias F, et al. CT and physiologic determinants of dyspnea and exercise capacity during the six-minute walk test in mild COPD. Respir Med. 2013; 107(4):570–9. [PubMed: 23313036]
12. Baldi S, Miniati M, Bellina CR, Battolla L, Catapano G, Begliomini E, et al. Relationship between extent of pulmonary emphysema by high-resolution computed tomography and lung elastic recoil in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001; 164(4): 585–9. [PubMed: 11520720]

13. Diaz AA, Bartholmai B, San Jose Estepar R, Ross J, Matsuoka S, Yamashiro T, et al. Relationship of emphysema and airway disease assessed by CT to exercise capacity in COPD. Respir Med. 2010; 104(8):1145–51. [PubMed: 20385477]
14. Spruit MA, Watkins ML, Edwards LD, Vestbo J, Calverley PM, Pinto-Plata V, et al. Determinants of poor 6-min walking distance in patients with COPD: the ECLIPSE cohort. Respir Med. 2010; 104(6):849–57. [PubMed: 20471236]
15. Han MK, Kazerooni EA, Lynch DA, Liu LX, Murray S, Curtis JL, et al. Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes. Radiology. 2011; 261(1):274–82. [PubMed: 21788524]
16. Johannessen A, Skorge TD, Bottai M, Grydeland TB, Nilsen RM, Coxson H, et al. Mortality by level of emphysema and airway wall thickness. Am J Respir Crit Care Med. 2013; 187(6):602–8. [PubMed: 23328525]
17. Haruna A, Muro S, Nakano Y, Ohara T, Hoshino Y, Ogawa E, et al. CT scan findings of emphysema predict mortality in COPD. Chest. 2010; 138(3):635–40. [PubMed: 20382712]
18. Dawkins PA, Dowson LJ, Guest PJ, Stockley RA. Predictors of mortality in alpha1-antitrypsin deficiency. Thorax. 2003; 58(12):1020–6. [PubMed: 14645964]
19. Camp PG, Coxson HO, Levy RD, Pillai SG, Anderson W, Vestbo J, et al. Sex differences in emphysema and airway disease in smokers. Chest. 2009; 136(6):1480–8. [PubMed: 19617404]
20. Dransfield MT, Bailey WC. COPD: racial disparities in susceptibility, treatment, and outcomes. Clinics in chest medicine. 2006; 27(3):463–71. vii. [PubMed: 16880056]
21. Martinez FJ, Curtis JL, Sciurba F, Mumford J, Giardino ND, Weinmann G, et al. Sex differences in severe pulmonary emphysema. Am J Respir Crit Care Med. 2007; 176(3):243–52. [PubMed: 17431226]
22. Tatsumi K, Kasahara Y, Kurosu K, Tanabe N, Takiguchi Y, Kuriyama T, et al. Clinical phenotypes of COPD: results of a Japanese epidemiological survey. Respirology. 2004; 9(3):331–6. [PubMed: 15363004]
23. Hansel NN, Washko GR, Foreman MG, Han MK, Hoffman EA, DeMeo DL, et al. Racial differences in CT phenotypes in COPD. COPD. 2013; 10(1):20–7. [PubMed: 23413893]
24. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. Nature. 2014; 509(7500):282–3. [PubMed: 24834516]
25. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, et al. Genetic epidemiology of COPD (COPDGene) study design. COPD. 2010; 7(1):32–43. [PubMed: 20214461]
26. Foreman MG, Zhang L, Murphy J, Hansel NN, Make B, Hokanson JE, et al. Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPDGene Study. Am J Respir Crit Care Med. 2011; 184(4):414–20. [PubMed: 21562134]
27. Diaz AA, Come CE, Ross JC, San Jose Estepar R, Han MK, Loring SH, et al. Association between airway caliber changes with lung inflation and emphysema assessed by volumetric CT scan in subjects with COPD. Chest. 2012; 141(3):736–44. [PubMed: 21940776]
28. 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(2):653–7. [PubMed: 7633722]
29. Cho MH, Castaldi PJ, Hersh CP, Hobbs BD, Barr RG, Tal-Singer R, et al. A Genome-wide Association Study of Emphysema and Airway Quantitative Imaging Phenotypes. Am J Respir Crit Care Med. 2015
30. Yuan R, Mayo JR, Hogg JC, Pare PD, McWilliams AM, Lam S, et al. The effects of radiation dose and CT manufacturer on measurements of lung densitometry. Chest. 2007; 132(2):617–23. [PubMed: 17573501]
31. 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(2):464–70. [PubMed: 17573503]
32. Silverman EK, Speizer FE, Weiss ST, Chapman HA Jr, Schuette A, Campbell EJ, et al. Familial aggregation of severe, early-onset COPD: candidate gene approaches. Chest. 2000; 117(5 Suppl 1):273S–4S. [PubMed: 10843948]

33. Silverman EK, Mosley JD, Palmer LJ, Barth M, Senter JM, Brown A, et al. Genome-wide linkage analysis of severe, early-onset chronic obstructive pulmonary disease: airflow obstruction and chronic bronchitis phenotypes. Human molecular genetics. 2002; 11(6):623–32. [PubMed: 11912177]

34. Silverman EK, Palmer LJ, Mosley JD, Barth M, Senter JM, Brown A, et al. Genomewide linkage analysis of quantitative spirometric phenotypes in severe early-onset chronic obstructive pulmonary disease. American journal of human genetics. 2002; 70(5):1229–39. [PubMed: 11914989]

35. DeMeo DL, Carey VJ, Chapman HA, Reilly JJ, Ginns LC, Speizer FE, et al. Familial aggregation of FEF(25-75) and FEF(25-75)/FVC in families with severe, early onset COPD. Thorax. 2004; 59(5):396–400. [PubMed: 15115866]

36. Silverman EK, Weiss ST, Drazen JM, Chapman HA, Carey V, Campbell EJ, et al. Gender-related differences in severe, early-onset chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000; 162(6):2152–8. [PubMed: 11112130]

37. Wang Y, Beydoun MA. The obesity epidemic in the United States--gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. Epidemiologic reviews. 2007; 29:6–28. [PubMed: 17510091]

38. Ogawa E, Nakano Y, Ohara T, Muro S, Hirai T, Sato S, et al. Body mass index in male patients with COPD: correlation with low attenuation areas on CT. Thorax. 2009; 64(1):20–5. [PubMed: 18852156]

39. Castaldi PJ, San Jose Estepar R, Mendoza CS, Hersh CP, Laird N, Crapo JD, et al. Distinct quantitative computed tomography emphysema patterns are associated with physiology and function in smokers. Am J Respir Crit Care Med. 2013; 188(9):1083–90. [PubMed: 23980521]

40. Galban CJ, Han MK, Boes JL, Chughtai KA, Meyer CR, Johnson TD, et al. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. Nature medicine. 2012; 18(11):1711–5.

41. Camp PG, Ramirez-Venegas A, Sansores RH, Alva LF, McDougall JE, Sin DD, et al. COPD phenotypes in biomass smoke- versus tobacco smoke-exposed Mexican women. The European respiratory journal. 2014; 43(3):725–34. [PubMed: 24114962]

Appendix

Contributions

Conception and design: MH, DD, MF, NH, MC, GW, EKS

Acquisition of data: GW, DL, EKS, DD, MF

Interpretation of data: MH, DD, MF, NH, MC, EKS, GW

Drafting of manuscript: MH, DD, EKS

Revision of Manuscript: MH, MF, MD, NH, MKH, SPB, JR, DL, EKS, GW, DD, JLC

MH had full access to all of the data in this study and takes responsibility for the integrity of data and accuracy of data analysis.

COPDGene® Investigators – Core Units

Administrative Core: James Crapo, MD (PI), Edwin Silverman, MD, PhD (PI), Barry Make, MD, Elizabeth Regan, MD, PhD

Genetic Analysis Core: Terri Beaty, PhD, Nan Laird, PhD, Christoph Lange, PhD, Michael Cho, MD, Stephanie Santorico, PhD, John Hokanson, MPH, PhD, Dawn DeMeo, MD, MPH, Nadia Hansel, MD, MPH, Craig Hersh, MD, MPH, Peter Castaldi, MD, MSc, Merry-Lynn McDonald, PhD, Emily Wan, MD, Megan Hardin, MD, Jacqueline Hetmanski, MS, Margaret Parker, MS, Marilyn Foreman, MD, Brian Hobbs, MD, Robert Busch, MD, Adel El-Bouiez, MD, Peter Castaldi, MD, Megan Hardin, MD, Dandi Qiao, PhD, Elizabeth Regan, MD, Eitan Halper-Stromberg, Ferdouse Begum, Sungho Won, Brittney Fredericksen, Sharon Lutz, PhD

Imaging Core: David A Lynch, MB, Harvey O Coxson, PhD, MeiLan K Han, MD, MS, MD, Eric A Hoffman, PhD, Stephen Humphries MS, Francine L Jacobson, MD, Philip F Judy, PhD, Ella A Kazerooni, MD, John D Newell, Jr., MD, Elizabeth Regan, MD, James C Ross, PhD, Raul San Jose Estepar, PhD, Berend C Stoel, PhD, Juerg Tschirren, PhD, Eva van Rikxoort, PhD, Bram van Ginneken, PhD, George Washko, MD, Carla G Wilson, MS, Mustafa Al Qaisi, MD, Teresa Gray, Alex Kluiber, Tanya Mann, Jered Sieren, Douglas Stinson, Joyce Schroeder, MD, Edwin Van Beek, MD, PhD

PFT QA Core, Salt Lake City, UT: Robert Jensen, PhD

Data Coordinating Center and Biostatistics, National Jewish Health, Denver, CO: Douglas Everett, PhD, Anna Faino, MS, Matt Strand, PhD, Carla Wilson, MS

Epidemiology Core, *University of Colorado Anschutz Medical Campus, Aurora, CO*: John E. Hokanson, MPH, PhD, Jennifer Black-Shinn, MPH, PhD, Gregory Kinney, MPH, PhD, Sharon Lutz, PhD, Katherine Pratte, MSPH

COPDGene® Investigators – Clinical Centers

Ann Arbor VA: Jeffrey Curtis, MD, Carlos Martinez, MD, MPH, Perry G. Pernicano, MD

Baylor College of Medicine, Houston, TX: Nicola Hanania, MD, MS, Philip Alapat, MD, Venkata Bandi, MD, Mustafa Atik, MD, Aladin Boriek, PhD, Kalpatha Guntupalli, MD, Elizabeth Guy, MD, Amit Parulekar, MD, Arun Nachiappan, MD

Brigham and Women's Hospital, Boston, MA: Dawn DeMeo, MD, MPH, Craig Hersh, MD, MPH, George Washko, MD, Francine Jacobson, MD, MPH

Columbia University, New York, NY: R. Graham Barr, MD, DrPH, Byron Thomashow, MD, John Austin, MD, Belinda D'Souza, MD, Gregory D.N. Pearson, MD, Anna Rozenshtein, MD, MPH, FACR

Duke University Medical Center, Durham, NC: Neil MacIntyre, Jr., MD, Lacey Washington, MD, H. Page McAdams, MD

Health Partners Research Foundation, Minneapolis, MN: Charlene McEvoy, MD, MPH, Joseph Tashjian, MD

Johns Hopkins University, Baltimore, MD: Robert Wise, MD, Nadia Hansel, MD, MPH, Robert Brown, MD, Karen Horton, MD, Nirupama Putcha, MD, MHS,

Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, Los Angeles, CA: Richard Casaburi, MD, Alessandra Adami, PhD, Janos Porszasz, MD, PhD, Hans Fischer, MD, PhD, Matthew Budoff, MD, Dan Cannon, PhD, Harry Rossiter, PhD

Michael E. DeBakey VAMC, Houston, TX: Amir Sharafkhaneh, MD, PhD, Charlie Lan, DO

Minneapolis VA: Christine Wendt, MD, Brian Bell, MD

Morehouse School of Medicine, Atlanta, GA: Marilyn Foreman, MD, MS, Gloria Westney, MD, MS, Eugene Berkowitz, MD, PhD

National Jewish Health, Denver, CO: Russell Bowler, MD, PhD, David Lynch, MD

Reliant Medical Group, Worcester, MA: Richard Rosiello, MD, David Pace, MD

Temple University, Philadelphia, PA: Gerard Criner, MD, David Ciccolella, MD, Francis Cordova, MD, Chandra Dass, MD, Robert D'Alonzo, DO, Parag Desai, MD, Michael Jacobs, PharmD, Steven Kelsen, MD, PhD, Victor Kim, MD, A. James Mamary, MD, Nathaniel Marchetti, DO, Aditti Satti, MD, Kartik Shenoy, MD, Robert M. Steiner, MD, Alex Swift, MD, Irene Swift, MD, Gloria Vega-Sanchez, MD

University of Alabama, Birmingham, AL: Mark Dransfield, MD, William Bailey, MD, J. Michael Wells, MD, Surya Bhatt, MD, Hrudaya Nath, MD

University of California, San Diego, CA: Joe Ramsdell, MD, Paul Friedman, MD, Xavier Soler, MD, PhD, Andrew Yen, MD

University of Iowa, Iowa City, IA: Alejandro Cornellas, MD, John Newell, Jr., MD, Brad Thompson, MD

University of Michigan, Ann Arbor, MI: MeiLan Han, MD, Ella Kazerooni, MD, Fernando Martinez, MD,

University of Minnesota, Minneapolis, MN: Joanne Billings, MD, Tadashi Allen, MD

University of Pittsburgh, Pittsburgh, PA: Frank Sciurba, MD, Divay Chandra, MD, MSc, Joel Weissfeld, MD, MPH, Carl Fuhrman, MD, Jessica Bon, MD

University of Texas Health Science Center at San Antonio, San Antonio, TX: Antonio Anzueto, MD, Sandra Adams, MD, Diego Maselli-Caceres, MD, Mario E. Ruiz, MD

summary

Among severe COPD subgroups, women demonstrate greater susceptibility to smoking-related parenchymal lung damage/emphysema.

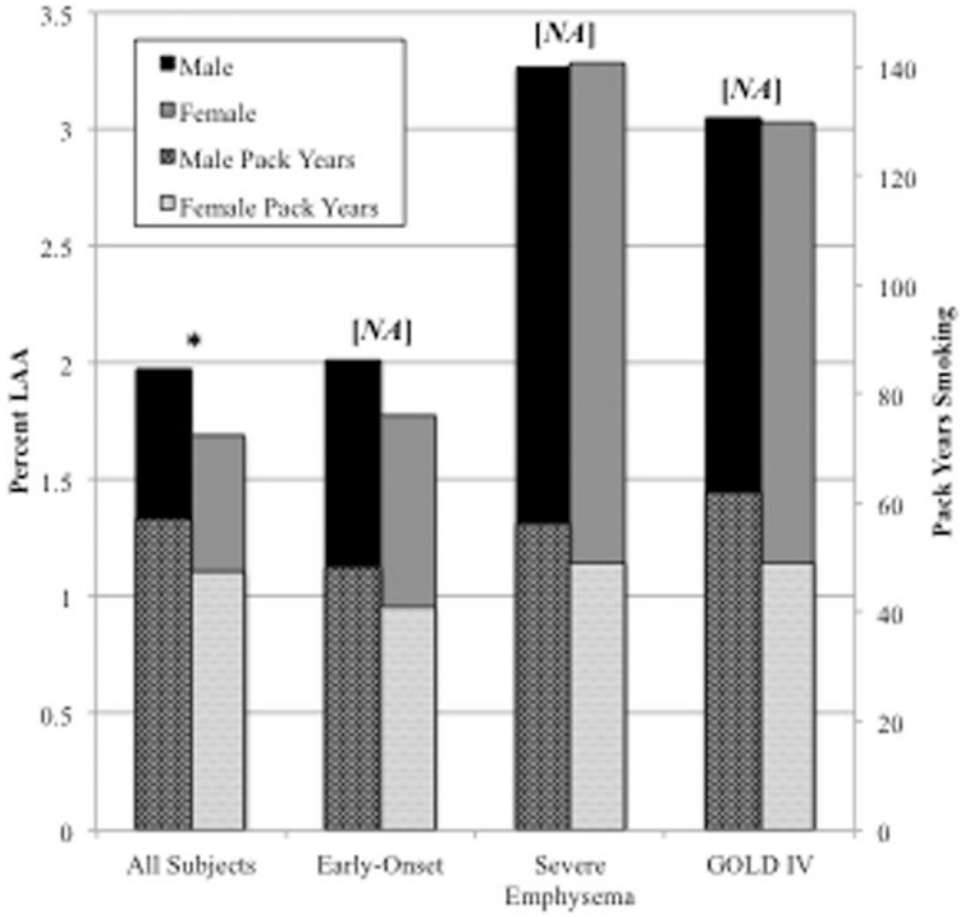

Figure 1.

Log percent LAA and pack-years across severe COPD phenotypes.

All subjects: NHW and AA subjects with COPD; Early-onset: early onset COPD subjects; Severe emphysema: COPD subjects with > 25% LAA; GOLD IV: All NHW and AA subjects with GOLD grade IV. P values from the generalized linear model adjusted for age, race, BMI, pack-years smoking, current smoking status, and CT scanner type. *P<0.001; NA: P>0.05. P<0.01 for the difference in pack-years by sex for each COPD subtype.

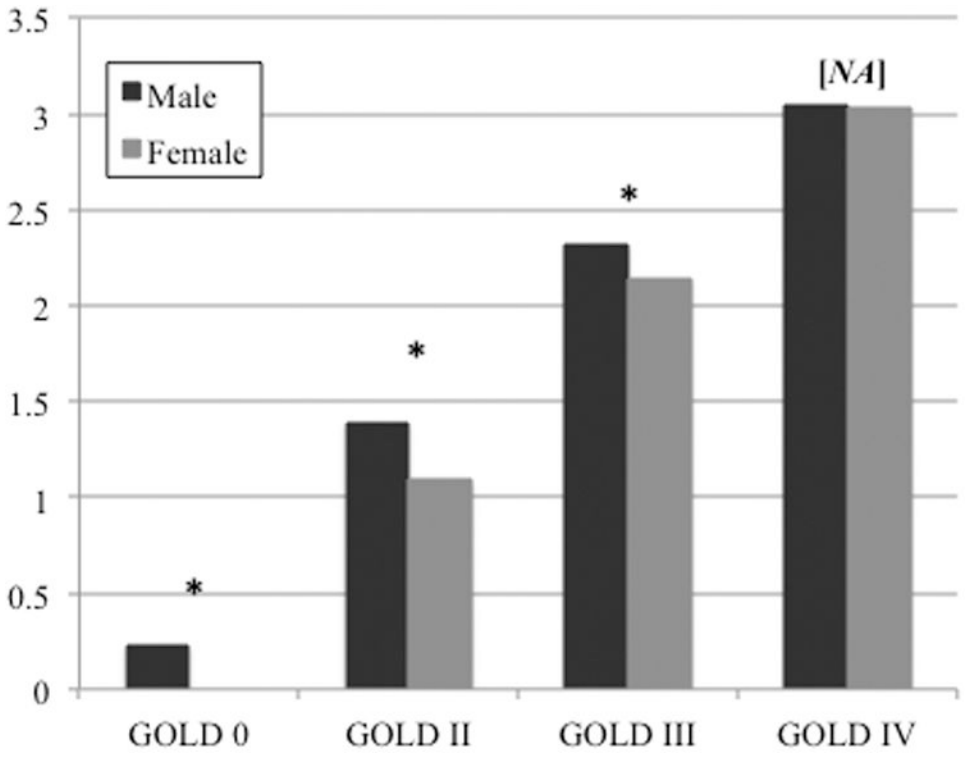

Figure 2.

Log percent LAA by spirometric GOLD grade.

P values are obtained from generalized linear models adjusted for age, race, BMI, pack-years smoking, current smoking status, and CT scanner type.

Table 1

Demographic data

	Non-Hispanic White			African American		
	Male	**Female**	**P value**	**Male**	**Female**	**P value**
COPD subjects	1593	1261	NA	459	377	NA
Age	65.1 (8.2)	64.1 (8.3)	0.002	58.8 (8.0)	59.2 (8.3)	0.46
Pack-years	60.7 (30.2)	50.3 (23.7)	<0.001	45.6 (24.0)	38.7 (21.3)	<0.001
Current Smoker (%)	556 (34.9)	436 (34.6)	0.89	301 (65.6)	208 (55.2)	0.003
BMI (kg/m2)	28.4 (5.6)	27.7 (6.7)	0.008	26.7 (6.0)	29.5 (7.3)	<0.001
FEV_1pp	49.12 (18.1)	50.28 (17.8)	0.09	51.79 (18.2)	52.81 (17.2)	0.41
FEV_1/FVC	0.48 (0.1)	0.50 (0.1)	<0.001	0.52 (0.1)	0.53 (0.1)	0.13
GOLD 2 (%)	776 (48.7)	668 (53.0)	NA	252 (54.9)	226 (60.0)	NA
GOLD 3	531 (33.3)	388 (30.8)	NA	136 (29.6)	107 (28.4)	NA
GOLD 4	286 (18.0)	205 (16.3)	NA	71 (15.5)	44 (11.7)	NA
%LAA	14.2 (12.9)	12.9 (12.8)	0.008	11.4 (12.5)	9.7 (11.7)	0.06
Log %LAA	2.06 (1.3)	1.79 (1.5)	<0.001	1.63 (1.5)	1.31 (1.7)	0.006
Early-onset COPD (%)	78 (4.9)	81 (6.4)	0.09	52 (11.3)	49 (13.0)	0.53
Emphysema predominant (%)	304 (19.1)	216 (17.1)	0.20	68 (14.8)	39 (10.3)	0.07

Data are presented as mean (sd) or N (%). BMI: body-mass index; FEV_1pp: FEV_1 percent predicted; GOLD II-IV: Spirometric GOLD grade; Early-onset COPD: < 55 yo, GOLD grade III or IV; Emphysema predominant: subjects with ≥ 25% emphysema on CT. P value: univariate comparison of NHW and AA males vs. females, respectively.

Table 2

Log %LAA by sex and race

	Male	Female	Beta (se)	P value
All subjects	1.97 (1.4)	1.69 (1.6)	0.32 (0.04)	<0.001[a]
NHW	2.06 (1.3)	1.79 (1.5)	0.34 (0.05)	<0.001[b]
AA	1.63 (1.5)	1.31 (1.7)	0.31 (0.1)	0.002[c]

Including all subjects with GOLD grade 2-4 COPD. Data are presented as mean (sd). Adjusted for age, pack-years, current smoking status, BMI, CT scanner. Percent emphysema log transformed for normality. Beta represents the difference for males compared to female subjects. Interaction between current smoking and sex on log emphysema:

[a] All subjects: P=0.004;

[b] NHW subjects: P=0.01;

[c] AA subjects: P=0.06

Table 3

Log %LAA by GOLD grade

GOLD Grade	Male	Female	Beta (se)	P value
All subjects				
2	1.39 (1.28)	1.09 (1.47)	0.36 (0.05)	<0.001
3	2.32 (1.25)	2.14 (1.39)	0.25 (0.07)	0.001
4	3.05 (0.85)	3.03 (0.91)	0.12 (0.06)	0.07
Non-Hispanic whites				
2	1.49 (1.24)	1.20 (1.43)	0.37 (0.06)	<0.001
3	2.37 (1.21)	2.22 (1.37)	0.30 (0.07)	<0.001
4	3.08 (0.82)	3.02 (0.95)	0.17 (0.07)	0.02
African Americans				
2	2.34 (1.07)	2.1 (1.27)	0.35 (0.10)	<0.001
3	2.13 (1.4)	1.87 (1.43)	0.24 (0.17)	0.14
4	2.39 (1.13)	2.1 (1.28)	0.27 (0.19)	0.14

Presenting mean (sd). Adjusted for age, gender, pack-years, BMI, current smoking status, CT scanner. “All subjects” additionally adjusted for race. Beta refers to male subjects compared to female subjects.

Table 4

Log %LAA among severe COPD subtypes

	Early-onset COPD				Severe Emphysema			
	Males	**Females**	**Beta (se)**	**P value**	**Males**	**Females**	**Beta (se)**	**P value**
N	130	130			372	255		
Age	51.31 (2.6)	50.96 (2.6)		0.27	65.64 (7.8)	64.71 (7.8)		0.14
Pack-years	48.2 (25.4)	41.0 (20.0)		0.01	56.31 (25.8)	49.11 (22.1)		<0.001
FEV_1pp	35.52 (9.8)	35.52 (10.6)		0.99	33.5 (14.1)	32.93 (13.5)		0.61
Log %LAA	2.06 (1.4)	1.78 (1.6)	0.13 (0.18)	0.47	3.54 (0.2)	3.54 (0.2)	0.022 (0.02)	0.19

Early-onset COPD defined as COPD GOLD grade III and IV and age< 55. Severe emphysema defined as %LAA greater than 25%. FEV_1pp: FEV_1 percent predicted. %LAA: percent lung attenuation area less than -950Hu. Univariate comparisons performed for age, pack-years and FEV1pp. %LAA adjusted for age, race, pack-years, smoking status, BMI, and CT scanner.