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Acute Exacerbations Are Associated with Progression of Emphysema

To the Editor:

Emphysema is associated with substantial respiratory morbidity and mortality. Although commonly regarded as a progressive disease, the rate of progression of emphysema is not uniform, and the factors affecting its progression are poorly understood. Although disease progression can be attenuated by smoking cessation, lung function decline remains higher in those who quit smoking compared with healthy individuals. Several studies suggest that the presence of emphysema itself is a risk factor for progression and that emphysema begets more emphysema (1, 2). The pathologic underpinning of this association likely lies in mechanotransduction; regions of emphysema impact surrounding normal lung regions by mechanical stretch resulting in further destruction of alveolar septae (1, 2). Given that this stretch is likely to be greater with coughing, such as during exacerbations, we hypothesized that acute exacerbations would be associated with a faster progression of emphysema.

Methods

We analyzed data from the COPD (Genetic Epidemiology of chronic obstructive pulmonary disease) Gene study (3). At enrollment (Visit 1) and approximately 5 years later (Visit 2), spirometry and computed tomography (CT) were acquired. LungQ, v1.0.0 (Thirona), was used to quantify emphysema on inspiratory scans using adjusted lung density (ALD), calculated as the 15th percentile of the attenuation histogram + 1,000 HU, adjusted for total lung volume on CT using Multi-Ethnic Study of Atherosclerosis normative equations (predicted lung volume using baseline age but time-varying height and body mass index [BMI]) (4). Image noise, which can affect lung density measurement, was estimated in each CT scan using an implementation of a method proposed for the quality assessment of clinical CT scans (5). Between the two visits, participants were prospectively contacted every 3 to 6 months to ascertain interval exacerbations (6). Exacerbations were defined as worsening of respiratory symptoms beyond the baseline, requiring the use of either systemic steroids or antibiotics. We categorized exacerbation frequency over 5 years into three categories:

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Table 1. Adjusted associations of exacerbation categories with lung density change

Exacerbation Category*	Sample Size	Change in Adjusted Lung Density (g/L)	
		Multivariable Model: Mean (95% CI)	*P* Value
Overall cohort			
Former smokers			0.0005†
0	1501	−3.27 (−3.81 to −2.74)	<0.0001
1–4	567	−4.16 (−4.91 to −3.41)	<0.0001
⩾5	284	−5.22 (−6.23 to −4.21)	<0.0001
Active smokers			0.494†
0	1089	−4.89 (−5.63 to −4.16)	<0.0001
1–4	297	−5.58 (−6.84 to −4.32)	<0.0001
⩾5	136	−5.61 (−7.39 to −3.83)	<0.0001
Emphysema <5%			
Former smokers			0.058†
0	1013	−2.88 (−3.55 to −2.21)	<0.0001
1–4	287	−3.68 (−4.76 to −2.60)	<0.0001
⩾5	111	−4.74 (−6.39 to −3.09)	<0.0001
Active smokers			0.545†
0	942	−4.40 (−5.18 to −3.62)	<0.0001
1–4	246	−4.84 (−6.22 to −3.47)	<0.0001
⩾5	106	−5.46 (−7.47 to −3.46)	0.0001
Emphysema ⩾5%			
Former smokers			0.005†
0	488	−3.73 (−4.60 to −2.87)	<0.0001
1–4	280	−4.68 (−5.67 to −3.69)	<0.0001
⩾5	173	−5.92 (−7.13 to −4.71)	<0.0001
Active smokers			0.492†
0	147	−8.66 (−10.55 to −6.77)	<0.0001
1–4	51	−8.98 (−11.77 to −6.19)	<0.0001
⩾5	30	−6.62 (−10.12 to −3.12)	0.0002

Definition of abbreviation: CI = confidence interval.
All models adjusted for age, sex, race, height, body mass index, body mass index-squared, computed tomography noise, computed tomography noise-squared, study center, and computed tomography scanner type (random terms used for the last two).
*Exacerbation categories on the basis of the total number over 5 years.
†*P* value for interaction between exacerbation category and time (compares rates of change over time between exacerbation groups).

0, 1–4 (less than one exacerbation per year), and ⩾5 (at least one exacerbation per year). The institutional review boards of all 21 centers approved the COPDGene study, and all participants provided written informed consent.

Statistical Analyses. Linear mixed models were used to fit ALD longitudinally. The primary predictors were exacerbation frequency category, Visit 1 or 2, and the interaction between these terms. Fixed-effect terms were also included for baseline age, sex, race/ethnicity, height, BMI, BMI-squared, CT noise, CT noise-squared, and random terms were included for the CT scanner model and study center. Some subjects used different scanners at Visits 1 and 2; consequently, the scanner model was allowed to be time-varying. The primary estimates of interest derived from this model were changes in average ALD between visits by exacerbation category, derived from the visit and visit*exacerbation terms. Because baseline age was included as a predictor (rather than actual age at visit), these estimates include progression because of illness as well as changes because of aging. An unstructured error covariance structure was included to model repeated measures on subjects. Because active smoking significantly increases lung density, likely in a nonlinear fashion, we stratified participants by smoking status into persistently former and persistently active smokers at both visits and excluded those with a change in smoking status between visits. In additional analyses, we evaluated whether the relationship between exacerbations and emphysema progression was modified by the presence of baseline emphysema. For these analyses, we stratified subjects by the percentage of emphysema on the basis of lung volume occupied by low attenuation areas <−950 HU, using a 5% cut point, in addition to stratifying on the basis of smoking groups (i.e., groups were active smoker with low emphysema, active smoker with high emphysema, former smoker with low emphysema, and former smoker with high emphysema). Reported *P* values are on the basis of two-sided tests. Analyses were performed using SAS 9.4.

Results

Among 4,668 subjects with available data for the first two visits, including baseline emphysema measures, 794 changed smoking status; the remaining 3,874 subjects (either persistently current or persistently former smokers) were included in the analyses. The mean age at enrollment was 63.4 (standard deviation, 9.2) years. A total of 1,944 (50.2%) were females, and 969 (25%) were African American. A total of 1,829, 357, 756, 365, and 87 had GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages 0 through 4, respectively, 463 had preserved ratio impaired spirometry, and 17 did not have baseline spirometry data to be evaluated. A total of 2,590 (67%) had no exacerbations, and 1,284 (33%) suffered at least one exacerbation over 5 years; 864 (22%) had one to four exacerbations, and 420 (11%) had at least five exacerbations over 5 years.

In persistently former smokers, the relationship between exacerbation frequency and change in lung density was significant, such that a greater number of exacerbations was associated with a greater decrease in lung density after adjusting for age, sex, race, height, BMI, and CT noise (Table 1). In contrast, this effect modification was not observed in persistently active smokers, although mean ALD declines were greater in this group. On analyses stratified by the presence of emphysema at baseline, a higher number of exacerbations were associated with a greater reduction in ALD in only those persistently former smokers with at least 5% emphysema at baseline (Table 1). In contrast, in those with less than 5% emphysema at baseline, exacerbations were not significantly associated with a change in lung density, regardless of smoking status. Estimates of change in ALD reported in Table 1 include aging effects as well as disease progression effects. The decline in ALD because of aging (separate from disease progression) was estimated to be 0.36 g/L/year in our data, consistent with reports by Shaker and colleagues (0.33 g/L/yr in the reference group) (7). Thus, we would expect a change in mean ALD of between −1.5 and −2 g/L over a 5-year period because of aging in a healthy population. Disease progression estimates could then be obtained by subtracting these amounts from the estimates shown in Table 1.

Discussion

We found that exacerbations were associated with progression of emphysema in persistently former but not active smokers and that this association was especially pronounced in those with more than a minimal amount of preexisting emphysema.

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are associated with lung function decline (8), but the structural basis for this decline has not been previously adequately explored. In a small study of 60 individuals, Tanabe and colleagues found that the rate of progression of emphysema was greater in those who had at least one exacerbation over a period of 2 years compared with those without exacerbations (9). These associations were, however, not adjusted for other factors known to affect emphysema progression, such as age and cigarette smoking. Coxson and colleagues found no relationship between exacerbation and emphysema progression over 3 years, but exacerbations were ascertained over the year before enrollment and not prospectively between the scans (10).

Given the relatively small annual change in lung density and the low frequency of exacerbations overall, we categorized exacerbation frequency into clinically meaningful bins of none, less than one, and at least one exacerbation a year. We found a stepwise greater loss of lung density with increasing exacerbation frequency, predominantly in former smokers who already had some preexisting emphysema. We have previously shown that areas of emphysema subtend a mechanical influence over the penumbra of a normal lung (2). This mechanical influence is likely exaggerated during periods of coughing, as is observed during exacerbations. Our finding that exacerbations impact emphysema progression mainly in those with some amount of preexisting emphysema is consistent with the concept of mechanotransduction. Other pathophysiologic mechanisms pertinent to alveolar destruction are also likely activated during an exacerbation, including parenchymal inflammation and oxidative stress (11, 12). Our findings raise the possibility that disease progression in COPD is likely stepwise when impacted by exacerbations and not necessarily linear. It is unclear why the same impact of exacerbations was not noted in active smokers. There are likely several reasons. One, emphysema progression was the highest in active smokers in whom baseline emphysema was present, and this may have masked smaller changes associated with exacerbations. Two, there was also a higher drop-out rate among active smokers compared with former smokers. Active smokers with worse symptoms are also more likely to have quit smoking between visits, and fewer current smokers had available data to estimate progression. Three, the increased lung density associated with cigarette smoking may have masked emphysema progression. It should be noted that the number of cigarettes smoked has a variable effect on lung density and that this relationship is likely not linear.

Limitations

Some limitations should be noted. Emphysema was quantified at only two time points. Approximately one-third of participants in the original cohort were lost to follow-up; however, in a prior study of the change of forced expiratory volume in 1 second, it was determined that those lost to follow-up were similar to those who followed up at 5 years (8).

Conclusions

Exacerbations are related to emphysema progression in a dose-dependent manner. Even low exacerbation frequency is associated with a high risk of emphysema progression, especially once emphysema has already set in. As emphysema is irreversible, these results underscore the importance of preventing exacerbations. ■

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Chronic Obstructive Pulmonary Disease in the LGBTQI+ Population

To the Editor:

We read with great interest the article by Krishnan and colleagues (1), "Race and Sex Differences in Mortality in Individuals with Chronic Obstructive Pulmonary Disease," recently published in *AnnalsATS*.

The authors examined, by race and sex and underlying mechanisms, mortality differences in chronic obstructive pulmonary disease (COPD). They used Medicare claims among REGARDS (Reasons for Geographic and Racial Differences in Stroke) cohort participants to identify COPD and found no race and sex differences in all-cause mortality. For all race and sex groups with COPD, the most common cause of death was cardiovascular disease (CVD).

Krishnan and colleagues concluded that CVD comorbidity management, especially among Black individuals, may improve mortality outcomes, as Black women with COPD more frequently die of CVD (1). We sadly note that the authors do not mention sexual and gender minorities (SGMs). Unfortunately, the study seems to confirm the invisibility of the LGBTQI+ (agender, asexual, bisexual, gay, gender diverse, genderqueer, genderfluid, intersex, lesbian, nonbinary, pansexual, queer, and transgender people) population in the analyzed data. In this regard, we would like to remind readers that SGMs represent approximately 10% or more of the U.S. population. Yet the LGBTQI+ population, which should not be considered as a whole but divided into its various specific components, is a population at greater risk for both COPD and CVD (2, 3). Data and results from studies not including LGBTQI+ people perpetuate disparities for SGM populations (4). There is the urgency to also consider the LGBTQI+ population in studies together with the need to increase and improve the delivery of health care for SGMs. Protocols and guidelines for caring for LGBTQI+ patients are poorly defined. Furthermore, data on targeted screening, as well as validated reference data for laboratory and imaging/diagnostic testing or information on the efficacy of drugs and their adverse effects, are lacking among SGMs. To identify and characterize the population of interest is the first and most critical step to better understand and eliminate health disparities and deliver culturally competent care. To promote equality of care and provide patient-centered care, it is essential to collect and document patients' sexual orientations and gender identity information in healthcare settings, but to date, most healthcare organizations have yet to implement this aspect. To better understand the unique needs of the LGBTQI+ population, more research is needed, and the availability of data is critical. To enhance data availability for analysis of the LGBTQI+ population, it is necessary to improve data collection and analysis methods incorporating claims and other sources, such as surveys and electronic health record data among others (5).

Unfortunately, at the moment, the collection and availability of data relating to sex and gender identity are still a critical point. The LGBTQI+ community has historically experienced bias, discrimination, and perceived inadequate or inappropriate care (6). Reduction of this barrier can begin involving the whole scientific community, which must include LGBTQI+ populations in studies, trials, protocols, and guidelines. ■

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