Original research

Respiratory exacerbations are associated with muscle loss in current and former smokers

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ABSTRACT

Objectives Muscle wasting is a recognised extra-pulmonary complication in chronic obstructive pulmonary disease and has been associated with increased risk of death. Acute respiratory exacerbations are associated with reduction of muscle function, but there is a paucity of data on their long-term effect. This study explores the relationship between acute respiratory exacerbations and long-term muscle loss using serial measurements of CT derived pectoralis muscle area (PMA).

Design and setting Participants were included from two prospective, longitudinal, observational, multicentre cohorts of ever-smokers with at least 10 pack-year history.

Participants The primary analysis included 1332 (of 2501) participants from Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) and 4384 (of 10 198) participants from Genetic Epidemiology of COPD (COPDGene) who had complete data from their baseline and follow-up visits.

Interventions PMA was measured on chest CT scans at two timepoints. Self-reported exacerbation data were collected from participants in both studies through the use of periodic longitudinal surveys.

Main outcome measures Age-related and excess muscle loss over time.

Results Age, sex, race and body mass index were associated with baseline PMA. Participants experienced age-related decline at the upper end of reported normal ranges. In ECLIPSE, the exacerbation rate over time was associated with an excess muscle area loss of 1.3% (95% CI 0.6 to 1.9, p<0.001) over 3 years and in COPDGene with an excess muscle area loss of 2.1% (95% CI 1.2 to 2.8, p<0.001) over 5 years. Excess muscle area decline was absent in 273 individuals who participated in pulmonary rehabilitation.

Conclusions Exacerbations are associated with accelerated skeletal muscle loss. Each annual exacerbation was associated with the equivalent of 6 months of age-expected decline in muscle mass. Ameliorating exacerbation-associated muscle loss represents an important therapeutic target.

Key messages

What is the key question?

► Are respiratory exacerbations associated with chronic muscle loss in ever-smokers?

What is the bottom line?

► Each annual exacerbation is associated with excess muscle loss equivalent to 6 months of age-related decline.

Why read on?

► Muscle wasting is noted across the spectrum of obstructive lung disease severity and is associated with increased risk of death; finding and addressing potential drivers represents an important therapeutic avenue.

INTRODUCTION

Sarcopenia is defined as an age-related loss of skeletal muscle mass and function and is closely linked to frailty.[1] Over age 40, healthy adults lose muscle mass at a rate of 0.64%–0.7% per year for women and 0.8%–0.98% per year for men.[2 3] Chronic disease can accelerate sarcopenia through inflammation, metabolic derangement, hospitalisation and activity reduction.[4 5]

There is an extensive body of literature demonstrating increased rates of sarcopenia in persons with COPD, but muscle wasting is not universal.[5–8] van den Borst and colleagues found lower baseline fat free mass, but no difference in the rate of decline in fat free mass over 8 years of follow-up when comparing smokers with obstructive lung disease to smokers without obstruction.[9] In the acute setting, respiratory events are associated with reductions in muscle function.[10 11] Hopkinson and colleagues demonstrated subacute persistence of muscle volume loss at 1 year in those with two or more exacerbations in that period.[12] These data suggest that respiratory events may contribute to chronic muscle wasting in smokers, but there is a paucity of longitudinal data to examine the durability of these effects.

Several methods for quantitatively measuring muscle mass have been endorsed in international guidelines including dual-energy X-ray absorptiometry, bioelectrical impedance analysis (BIA) and CT.[1] Pectoralis muscle area (PMA), unlike lumbar, psoas

or thigh muscle area, can be derived from routine chest CT. In patients with COPD, PMA correlates well with the whole-body fat free mass index derived from BIA and is more closely associated with mortality than body mass index (BMI).[13–17]

Using baseline and 3-year or 5-year follow-up data from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) and Genetic Epidemiology of COPD (COPDGene) studies, we sought to identify the relationship between respiratory exacerbation rate over time and long-term muscle loss. We hypothesised that higher rates of respiratory exacerbation would be associated with an accelerated loss of skeletal muscle beyond what would be expected with age in ever smokers with and without COPD.

METHODS

Study population

The study populations used in our analysis were derived from two previously described multicentre, longitudinal, observational, cohort studies. The ECLIPSE (NCT00292552, SCO104960) study enrolled 2164 COPD patients and 337 controls, aged 45–75, with a smoking history of at least 10 pack years.[18] Participants were enrolled from 26 centres across 12 countries and followed for a total of 3 years with assessments completed at baseline, 12 months and 36 months. For our primary analysis, we included those subjects who had complete data for both their baseline and 36-month visits.

The COPDGene study (NCT00608764) is ongoing and has enrolled 10 198 non-Hispanic White or African American ever smokers with and without COPD, aged 45–80, with a history of at least 10 pack years of smoking.[19] Enrolment occurred at 21 centres in the USA with assessments every 5 years; the 10-year follow-up visit is ongoing. Our primary analysis used data from those participants with complete data for their baseline and year 5 visits.

Assessments

Both studies collected self-reported acute respiratory event data at each visit and between visits. Study visits were delayed if a patient was currently having an event. COPDGene participants were contacted every 6 months by telephone or web systems and ECLIPSE participants were contacted monthly by telephone.[18 20] In both studies, an acute respiratory event (hereafter referred to as an exacerbation) was considered to be an increase in respiratory symptoms requiring antibiotics or systemic steroids; a severe event was one that required emergency department evaluation or hospitalisation.[18 19] For each participant, the number of reported events was divided by the observed follow-up time to generate an annualised exacerbation rate.

Spirometry was obtained at baseline and each follow-up visit in both studies, before and after the administration of an inhaled short-acting beta agonist. Expiratory airflow obstruction was defined spirometrically by the presence of a post-bronchodilator FEV_1/FVC ratio of less than 0.7. Additional categorisation of disease severity was performed based on decrements in the FEV_1. COPD was defined as those with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2 or higher disease (ie, FEV_1 per cent predicted <0.8).[21] Ever smokers without obstruction and those with an FEV_1/FVC ratio less than 0.7, but an FEV_1 >80% of predicted (GOLD 1), were categorised as 'at risk'.

Six-minute walk testing was completed according to international guidelines at study visits for all participants in COPDGene and in participants diagnosed with COPD in ECLIPSE.[22] The minimum clinically important change in distance on serial testing was taken as 30 m.[23]

Participants in both studies underwent CT scanning of the chest at full inflation at each in-person visit.[18 19] Quantitative assessments of the PMA were obtained as described previously from a single axial slice of the CT scan above the aortic arch.[24 25] Each resulting segmentation was reviewed for quality control and segmentation failures (eg, malposition of the arm, distortion from an implanted device) were visually identified and excluded. The calculated PMA reported for each scan was expressed in cm^2 and represented the aggregate cross-sectional area of the right and left pectoralis major and minor muscles.

Statistical analyses

Models were checked for normality of residuals, homoscedasticity and multicollinearity. When the 154 observations with residuals more than 2.5 SD away from the residuals mean were excluded, the effect estimates and CIs did not change. Variance inflation factors were between 1 and 2 for all covariates. Histogram and quantile-quantile plots revealed the distribution of the PMA values to be non-normal. Linear mixed effects models were used to fit the log-transform of PMA longitudinally. Primary predictors of interest in these models included phase of study (baseline or follow-up), annual exacerbation rate, and their interaction. The PMA loss associated with the interaction term is described as 'excess loss'. Additional time-invariant covariates were race, sex and smoking history on enrolment (measured in pack years); time dependent covariates included age, BMI, chronic oral steroid use and current smoking status. Covariates were selected a priori as potential confounders of the relationship between exacerbations and PMA or their role as independent predictors of the outcome of interest. Repeated measures were accounted for by including random intercepts for subjects, which induced a compound symmetric covariance structure on the repeated measures. The Satterthwaite method for df was used to obtain p values for fixed effects.[26] CIs were generated by the Wald method. Annual severe exacerbation rate and its effect on PMA was similarly and separately modelled. GOLD stage and participation in intercurrent pulmonary rehabilitation (PR) were explored as model covariates in separate, exploratory models.

Study participants were then divided into quintiles of per cent PMA decline, with quintile 0 representing those whom gained PMA and quintile 5 representing the largest decline over the study interval. The Kruskal-Wallis test was used to assess for differences in distribution of 6 min walk distance and BMI across quintiles. The Fisher exact test was used to assess for differences in the per cent of participants with a minimum clinically important gain or loss in 6 min walk distance across quintiles.

To account for bias due to missing data, we repeated the analysis in both cohorts including participants with complete data for only one of the time points, which we term the expanded cohort. For more details, see online supplemental file 1. All analyses were performed using R V.3.5.1, with longitudinal models using the lme4 and lmerTest packages.

RESULTS

For the primary analysis, 1332 participants from ECLIPSE and 4384 participants from COPDGene had complete data for the baseline and follow-up visits (figure 1A,B, respectively). Baseline clinical characteristics of the cohorts are shown in table 1. The ECLIPSE cohort was 63.6% men, 97.7% non-Hispanic White, had a mean PMA of 36.6 cm^2 (±10.9), and 0.5% of the participants reported using chronic oral steroids. The COPDGene

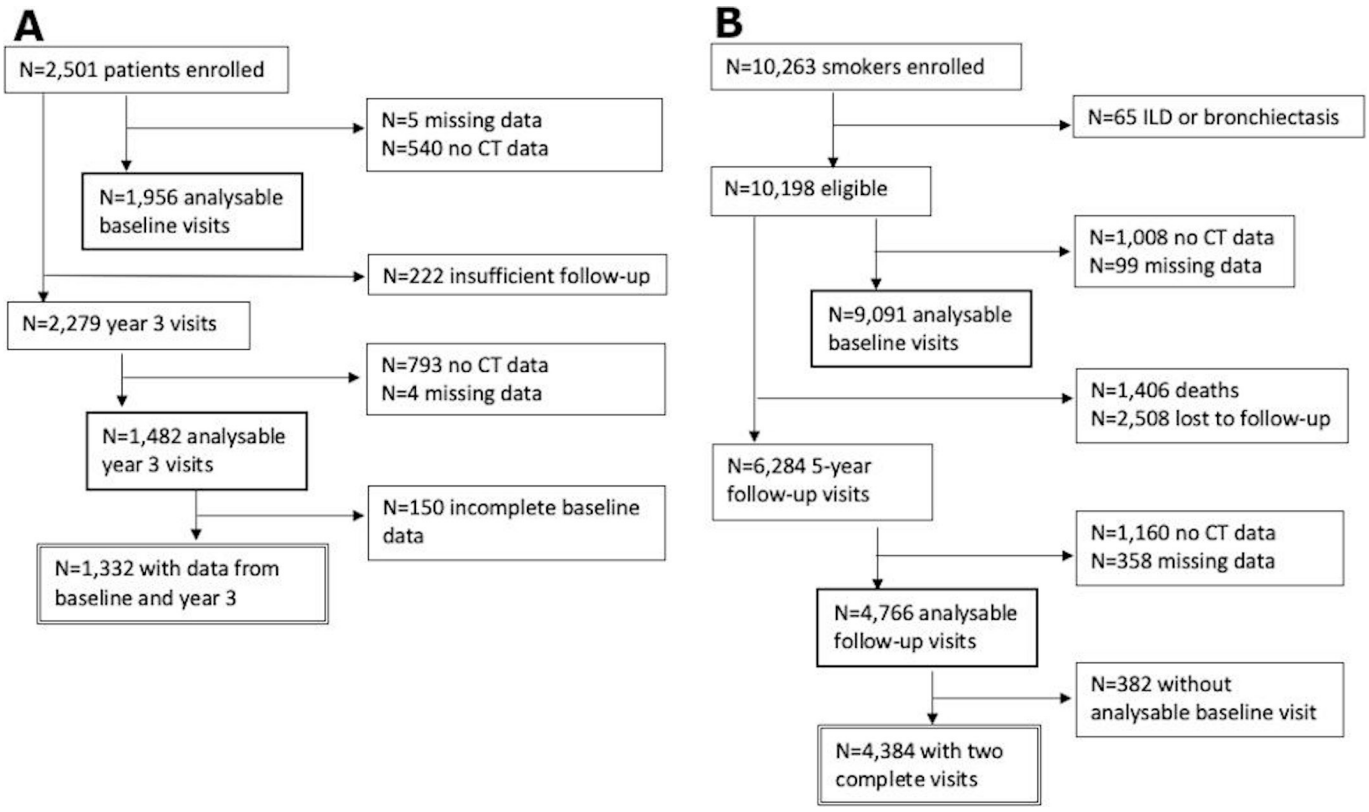

Figure 1 Consort diagram. (A) Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints cohort; (B) Genetic Epidemiology of COPD cohort. ILD, interstitial lung disease.

cohort was 50.5% men, 70.6% non-Hispanic White, had a mean PMA of 41.3 cm^2 (±15.3), and 1.5% of the participants reported using chronic oral steroids.

Exacerbations were common in both cohorts prior to enrolment as well as during the intercurrent follow-up interval (table 1). In the 12 months preceding study entry, 45.9% of participants in ECLIPSE and 20.5% of participants in COPDGene reported at least one exacerbation, with 15.3% and 4.6% reporting at least one severe exacerbation, respectively. During the follow-up interval, 59% of ECLIPSE participants and 39.9% of COPDGene participants reported at least one exacerbation, with 21.0% and 17.4% reporting at least one severe exacerbation, respectively.

In the mixed models for both cohorts, age($p<0.001$), sex ($p<0.001$), BMI ($p<0.001$) and race (ECLIPSE $p=0.004$, COPDGene $p<0.001$) were significant correlates of PMA. Men and women experienced age-related decline at the upper end of reported normal ranges. Women lost 0.8% (95% CI 0.6 to 1.0, $p<0.001$) and 0.8% (95% CI 0.7 to 0.9, $p<0.001$) of their PMA annually in ECLIPSE and COPDGene, respectively while men lost 1.0% (95% CI 0.8 to 1.2, $p<0.001$) and 1.0% (95% CI 0.9 to 1.1, $p<0.001$) of their PMA annually in the ECLIPSE and COPDGene cohorts, respectively.

The exacerbation rate by time interaction was associated with a statistically significant excess PMA loss. In ECLIPSE, an annual exacerbation rate of one per year was associated with an excess loss of 1.3% (95% CI 0.6 to 1.9, $p<0.001$) over 3 years. The severe exacerbation rate by time interaction was associated with an excess PMA loss of 2.6% (95% CI 1.2 to 4.0, $p<0.001$) over that same time period. In COPDGene, an exacerbation rate of one per year was associated with an excess loss of 2.1% (95% CI 1.2 to 2.8, $p<0.001$) over 5 years. An equivalent severe exacerbation rate was associated with an excess PMA loss of 2.9% (95% CI 1.1 to 4.8, $p=0.002$) over that same time period (figure 2).

The exacerbation rate by time interaction in women was associated with an excess PMA loss of 1.1% (95% CI 0.1 to 2.2, $p=0.043$) in ECLIPSE and 1.8% (95% CI 0.8 to 2.9, $p=0.001$) in COPDGene, compared with 1.4% (95% CI 0.6 to 2.2, $p<0.001$) in ECLIPSE and 2.6% (95% CI 1.4 to 4.0, $p<0.001$) in COPDGene for men (figure 2).

In both the at-risk and COPD groups, the exacerbation by time interaction was associated with excess loss of PMA (figure 2). In participants with COPD, an annual exacerbation rate of one per year was associated with a 0.7% (95% CI 0 to 1.4, $p=0.050$) excess loss of PMA in ECLIPSE and 1.5% (95% CI 0.3 to 2.6, $p=0.017$) in COPDGene. In participants at-risk, an effect estimate could not be calculated for those in ECLIPSE due to their low rates of exacerbation (online supplemental table 2), but for those in COPDGene, an annual exacerbation rate of one per year was associated with a 1.9% (95% CI 0.7 to 3.1, $p=0.002$) excess loss of PMA.

When included as a fixed effect in the model, GOLD stage was negatively associated with PMA ($p=0.062$ for GOLD 1 in COPDGene and $p<0.001$ for each GOLD 2–4 stage in both studies). When included as a fixed effect, intercurrent PR was also a significant predictor of PMA ($p=0.001$) in the COPDGene cohort. In the group whom attended PR (n=273), there was no significant excess decline in PMA (−0.2%, 95% CI −2.2 to 2.5, $p=0.882$) attributable to the exacerbation by time interaction despite a mean annual exacerbation rate of 1.0.

Participants whose PMA decreased over time had a corresponding decrease in BMI ($p<0.001$ for both cohorts, table 2). Greater decreases in PMA were not associated with changes in

Table 1 Clinical characteristics of the cohorts

	ECLIPSE	COPDGene
Baseline characteristics		
Sample size	1332	4384
Age, years (mean, SD)	61.8 (7.9)	59.8 (8.6)
Male (n, %)	847 (63.6)	2214 (50.5)
Caucasian (n, %)	1302 (97.7)	3093 (70.6)
Current smoker (n, %)	512 (38.4)	2122 (48.4)
Pack years on study entry (mean, SD)	45.8 (27.5)	42.8 (23.8)
BMI (mean, SD)	26.5 (5.1)	29.1 (5.9)
Chronic oral steroid use (n, %)	7 (0.5)	64 (1.5)
Pectoral muscle area, cm^2 (mean, SD)	36.6 (10.9)	41.3 (15.3)
6-minute walk distance, m (mean, SD)	386.4 (118.3)	434.7 (113.1)
Baseline exacerbation history		
An event in past year (%)	45.9	20.5
Mean rate, per year	0.93	0.33
A severe event in past year (%)	15.3	4.6
Mean severe rate, per year	0.25	0.06
Intercurrent exacerbation history		
An event during follow-up (%)	59.0	39.9
≥1 event per year (%)	41.7	11.7
Mean rate, per year	0.94	0.33
A severe event during follow-up (%)	21.0	17.4
≥1 severe event per year (%)	7.7	2.4
Mean severe rate, per year	0.19	0.09

Baseline exacerbation history represents participants' self-reported 12-month exacerbation frequency at study enrolment. Intercurrent exacerbations are those that occurred during the study and were assessed using periodic surveys during the study follow-up period. These data are available by Global Initiative for Chronic Obstructive Lung Disease stage in online supplemental tables E1 and E2.
BMI, body mass index; COPDGene, Genetic Epidemiology of COPD; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints.

6 min walk distance as measured by median per cent change (p=0.379 in ECLIPSE, p=0.363 in COPDGene), per cent gaining 30 m or more metres (p=0.965 in ECLIPSE, p=0.738 in COPDGene) or per cent losing 30 m or more metres (p=0.332 in ECLIPSE, p=0.520 in COPDGene, table 3).

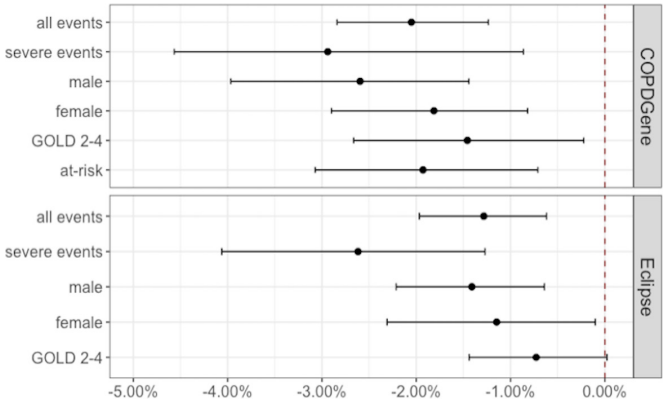

Figure 2 Estimated excess per cent loss of pectoral muscle area per annual exacerbation. The 1332 participants from ECLIPSE were followed for 3 years and the 4384 participants in COPDGene were followed for 5 years. The dot represents the effect estimate for excess per cent muscle loss and the whiskers correspond to the 95% CI. COPDGene, Genetic Epidemiology of COPD; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 2 Percent change in pectoral muscle area and BMI by quintile of PMA loss

	ECLIPSE			COPDGene		
Quintile of PMA decline	n	Median % change PMA	Median % change BMI	n	Median % change PMA	Median % change BMI
0	503	8.2	0.8	1516	9.4	1.8
1	166	−2.1	−0.3	574	−2.5	0.1
2	166	−6.3	−1.3	574	−7.6	0.1
3	166	−9.7	−2.5	573	−12.5	−1.4
4	166	−14.7	−2.2	574	−18.6	−1.2
5	165	−22.4	−2.6	573	−27.9	−3.9

The 0th quintile represents those subjects who had an increase in their PMA during the study.
BMI, body mass index; COPDGene, Genetic Epidemiology of COPD; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; PMA, pectoral muscle area.

DISCUSSION

The results of this longitudinal study in two observational cohorts demonstrate that acute respiratory exacerbations are associated with accelerated loss of skeletal muscle cross-sectional area over 3-year and 5-year periods of observation. The association was present in both men and women, as well as both those diagnosed with COPD, and current and former smokers at risk for COPD. In annualised terms, our data suggest that for each exacerbation, a person loses the equivalent of 6 months of age-related pectoral muscle area. That is, a person who has one exacerbation per year would be expected to lose 1.5 times their age-expected muscle area and a person who has two exacerbations per year would lose two times their age expected muscle area in that year.

Our findings extend and reinforce the conclusions of Hopkinson and colleagues who found that persons with two or more exacerbations in 1 year of follow-up had a larger decrease in fat free mass.[12] Two or more exacerbations in 12 months allows little recovery time, making their described change in body composition potentially attributable to the acute effect of those exacerbations. By observing participants for multiple years, our study demonstrates a persistent decrement despite periods of intercurrent stability and provides a potential explanation as to why people with COPD may have accelerated muscle loss.

Similar to van den Borst and colleagues, we found that persons with COPD had lower baseline muscle mass than those without obstruction. However, van den Borst found no difference in the body composition trajectories over 8 years comparing participants with COPD to smoking controls.[9] Their study did not report data on exacerbations and had only 260 obstructive lung disease participants, of whom one third were GOLD stage 1. It is possible that their cohort had a low exacerbation frequency, which limited their power to detect differences attributable to exacerbations. Taken in concert, our two studies suggest that exacerbations are a potential mechanism for accelerated decline in muscle mass and that absence of exacerbations could result in a body composition trajectory similar to that of non-obstructed individuals.

Exercise programmes, such as PR, are the most widely available, recommended intervention in persons with skeletal muscle dysfunction.[1 27 28] Exercise programmes improve skeletal muscle function and increase muscle mass in the short-term.[8 29–31] For the small number of people in this study whom underwent intercurrent PR, there was no association between exacerbations over time and PMA. This raises the possibility that PR attenuates the effect of exacerbations on the skeletal musculature; however, replication in a larger cohort is necessary to confirm this hypothesis. PR immediately following exacerbations may be of

Table 3 Changes in 6 min walk testing by quintile of PMA loss

	ECLIPSE*				COPDGene†			
Quintile of PMA decline	n	Median % change 6MW distance	% with ≥30 m gain	% with ≥30 m loss	n	Median % change 6MW distance	% with ≥30 m gain	% with ≥30 m loss
0	357	−3.1	25.5	42.3	1482	−8.2	22.3	53.8
1	113	−2.8	26.5	39.8	560	−9.2	20.2	54.1
2	121	−2.2	24.0	37.2	561	−5.8	22.3	49.5
3	136	−3.4	23.5	39.0	559	−7.3	23.1	53.1
4	121	−3.6	26.4	38.0	556	−8.1	24.1	54.1
5	131	−5.9	22.1	49.6	560	−9.4	22.7	54.5

The 0th quintile represents those subjects who had an increase in their PMA during the study.
*N=353 subjects from ECLIPSE did not have 6 min walk data available.
†N=106 subjects from COPDGene did not have 6 min walk data available.
COPDGene, Genetic Epidemiology of COPD; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; 6MW, 6 min walk; PMA, pectoral muscle area.

particular benefit; multiple studies have demonstrated improvement in 1-year mortality when PR was initiated within 90 days of hospital discharge.[32 33] Unfortunately, long-term mortality has not shown a similar improvement, which may be related to the inconsistency with which PR results in sustained increases in physical activity.[29 32 34]

Surprisingly, those individuals with the greatest percentage of PMA loss did not have reduced performance on 6 min walk testing compared with those with little or no PMA loss (table 3). This may reflect the fact that the 6 min walk is a submaximal test and is more akin to a test of functional performance rather than a test of endurance exercise capacity or force generation. Muscle weakness does manifest predominantly in the lower limbs; however, a disconnect between skeletal muscle mass and quadriceps weakness has also been previously described.[5 8 35] This underscores the point that low muscle mass does not necessarily equate to muscle weakness and that a test of functional performance is not necessarily a strong correlate of muscle mass. Similarly, following BMI clinically would underestimate the impact on muscle mass, as we found the change in skeletal muscle area to be 10-fold the change in BMI (table 2). Identifying and potentially intervening in those patients with muscle mass loss, regardless of BMI or physical performance, is important, however, as muscle wasting is demonstrated to carry a poor prognosis.[13 36–38] Indeed, weight loss, even in the absence of low BMI, is associated with increased mortality in COPD, likely because it often represents loss of muscle, rather than fat, mass.[39]

Strengths of our study include the replicability in two large, multicentre cohorts, our longitudinal model design, and our examination of both muscle mass and function. The smaller effect estimates reported for the ECLIPSE cohort are likely a reflection of the shorter duration of follow-up: 3 years in ECLIPSE compared with 5 years in COPDGene, given the annualised effects were consistent between cohorts. While loss to follow-up presents a concern for bias in our results, our expanded analysis using partial data and application of inverse probability weighting methods suggest that missing data did not alter estimates notably (see online supplemental file 1).

Other limitations to our investigation include lack of data on physical activity, having only two time points, and lack of causal inference. Due to the long time intervals used, we could not observe acute muscle decrement associated with exacerbations and the potential mechanism of incomplete recovery remains a hypothesis. The low exacerbation rate in the at-risk subjects in the ECLIPSE cohort prevented us from replicating the effect noted in the at-risk subjects in the COPDGene cohort. Nonetheless, fat free mass index has been previously associated with higher risk of exacerbations in ECLIPSE, corroborating our findings.[40] The true effect on those at-risk or with mild disease is of interest not only for the possibility of early intervention, but because lung function decline was most prominent in GOLD stage 1 participants in a recent longitudinal analysis of the COPDGene cohort.[41] Further, all of the exacerbation data was self-reported, which introduces recollection bias, especially in the baseline data in which subjects were asked to recall the prior 12 months. Subjects in COPDGene were contacted every 6 months, compared with monthly in ECLIPSE, which may have resulted in relative under-reporting of exacerbations in the COPDGene cohort.

In summary, we used clinical and radiological data from two cohorts of patients at risk for, or diagnosed with, COPD to demonstrate an association between exacerbation rate over time and an accelerated loss of skeletal muscle. Neither BMI nor 6 min walk performance reflected the degree of skeletal muscle loss. CT phenotyping could prove to be a useful methodology for assessing body composition as many patients already undergo imaging scans for lung cancer screening or clinical concerns. Further work is needed to determine whether PR attenuates muscle loss and whether intervention to preserve muscle mass can alter prognosis.

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REFERENCES

1 Dent E, Morley JE, Cruz-Jentoft AJ, *et al*. International clinical practice guidelines for sarcopenia (ICFSR): screening, diagnosis and management. *J Nutr Health Aging* 2018;22:1148–61.
2 Wilkinson DJ, Piasecki M, Atherton PJ. The age-related loss of skeletal muscle mass and function: measurement and physiology of muscle fibre atrophy and muscle fibre loss in humans. *Ageing Res Rev* 2018;47:123–32.
3 Mitchell WK, Williams J, Atherton P, *et al*. Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. *Front Physiol* 2012;3:260.
4 Marzetti E, Calvani R, Tosato M, *et al*. Sarcopenia: an overview. *Aging Clin Exp Res* 2017;29:11–17.
5 Jaitovich A, Barreiro E. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. what we know and can do for our patients. *Am J Respir Crit Care Med* 2018;198:175–86.
6 Benz E, Trajanoska K, Lahousse L, *et al*. Sarcopenia in COPD: a systematic review and meta-analysis. *Eur Respir Rev* 2019;28. doi:10.1183/16000617.0049-2019. [Epub ahead of print: 31 Dec 2019].
7 Maddocks M, Kon SSC, Canavan JL, *et al*. Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study. *Thorax* 2016;71:988–95.
8 Jones SE, Maddocks M, Kon SSC, *et al*. Sarcopenia in COPD: prevalence, clinical correlates and response to pulmonary rehabilitation. *Thorax* 2015;70:213–8.
9 van den Borst B, Koster A, Yu B, *et al*. Is age-related decline in lean mass and physical function accelerated by obstructive lung disease or smoking? *Thorax* 2011;66:961–9.
10 Spruit MA, Gosselink R, Troosters T, *et al*. Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax* 2003;58:752–6.
11 Pitta F, Troosters T, Probst VS, *et al*. Physical activity and hospitalization for exacerbation of COPD. *Chest* 2006;129:536–44.
12 Hopkinson NS, Tennant RC, Dayer MJ, *et al*. A prospective study of decline in fat free mass and skeletal muscle strength in chronic obstructive pulmonary disease. *Respir Res* 2007;8:25.
13 McDonald M-LN, Diaz AA, Rutten E, *et al*. Chest computed tomography-derived low fat-free mass index and mortality in COPD. *Eur Respir J* 2017;50. doi:10.1183/13993003.01134-2017. [Epub ahead of print: 14 Dec 2017].
14 Marquis K, Debigaré R, Lacasse Y, *et al*. Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;166:809–13.
15 Vestbo J, Prescott E, Almdal T, *et al*. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City heart study. *Am J Respir Crit Care Med* 2006;173:79–83.
16 Tanimura K, Sato S, Fuseya Y, *et al*. Quantitative assessment of erector spinae muscles in patients with chronic obstructive pulmonary disease. novel chest computed Tomography-derived index for prognosis. *Ann Am Thorac Soc* 2016;13:334–41.
17 McDonald M-LN, Diaz AA, Ross JC, *et al*. Quantitative computed tomography measures of pectoralis muscle area and disease severity in chronic obstructive pulmonary disease. A cross-sectional study. *Ann Am Thorac Soc* 2014;11:326–34.
18 Vestbo J, Anderson W, Coxson HO, *et al*. Evaluation of COPD longitudinally to identify predictive surrogate end-points (eclipse). *Eur Respir J* 2008;31:869–73.
19 Regan EA, Hokanson JE, Murphy JR, *et al*. Genetic epidemiology of COPD (COPDGene) study design. *COPD* 2010;7:32–43.
20 Stewart JI, Moyle S, Criner GJ, *et al*. Automated telecommunication to obtain longitudinal follow-up in a multicenter cross-sectional COPD study. *COPD* 2012;9:466–72.
21 Rabe KF, Hurd S, Anzueto A, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: gold executive summary. *Am J Respir Crit Care Med* 2007;176:532–55.
22 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. Ats statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–7.
23 Celli B, Tetzlaff K, Criner G, *et al*. The 6-Minute-Walk distance test as a chronic obstructive pulmonary disease stratification tool. insights from the COPD biomarker qualification Consortium. *Am J Respir Crit Care Med* 2016;194:1483–93.
24 Moreta-Martinez RO, Onieva J, Pascau J. Pectoralis muscle and subcutaneous adipose tissue segmentation on CT images based on convolutional networks. *Int J Comput Assist Radiol Surg* 2017;12:31–3.
25 Cano-Espinosa C, Gonzalez G, Washko GR, *et al*. Biomarker localization from deep learning regression networks. *IEEE Trans Med Imaging* 2020;39:2121–32.
26 Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest package: tests in linear mixed effects models. *J Stat Softw* 2017;82:26.
27 Maltais F, Decramer M, Casaburi R, *et al*. An official American thoracic Society/European respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2014;189:e15–62.
28 Spruit MA, Singh SJ, Garvey C, *et al*. An official American thoracic Society/European respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;188:e13–64.
29 Spruit MA, Pitta F, McAuley E, *et al*. Pulmonary rehabilitation and physical activity in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015;192:924–33.
30 Yoshimura Y, Wakabayashi H, Yamada M, *et al*. Interventions for treating sarcopenia: a systematic review and meta-analysis of randomized controlled studies. *J Am Med Dir Assoc* 2017;18:553.e1–553.e16.
31 De Brandt J, Spruit MA, Hansen D, *et al*. Changes in lower limb muscle function and muscle mass following exercise-based interventions in patients with chronic obstructive pulmonary disease: a review of the English-language literature. *Chron Respir Dis* 2018;15:182–219.
32 Ryrsø CK, Godtfredsen NS, Kofod LM, *et al*. Lower mortality after early supervised pulmonary rehabilitation following COPD-exacerbations: a systematic review and meta-analysis. *BMC Pulm Med* 2018;18:154.
33 Lindenauer PK, Stefan MS, Pekow PS, *et al*. Association between initiation of pulmonary rehabilitation after hospitalization for COPD and 1-year survival among Medicare beneficiaries. *JAMA* 2020;323:1813–23.
34 Puhan MA, Gimeno-Santos E, Cates CJ, *et al*. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2016;12:CD005305.
35 Gosselink R, Troosters T, Decramer M. Distribution of muscle weakness in patients with stable chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2000;20:353–60.
36 Diaz AA, Martinez CH, Harmouche R, *et al*. Pectoralis muscle area and mortality in smokers without airflow obstruction. *Respir Res* 2018;19:62.
37 Celis-Morales CA, Welsh P, Lyall DM, *et al*. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. *BMJ* 2018;361:k1651.
38 Massierer D, Alsowayan W, Lima VP, *et al*. Prognostic value of simple measures of physical function and muscle strength in COPD: a systematic review. *Respir Med* 2020;161:105856.
39 McDonald M-LN, Wouters EFM, Rutten E, *et al*. It's more than low BMI: prevalence of cachexia and associated mortality in COPD. *Respir Res* 2019;20:100.
40 Rutten EPA, Spruit MA, McDonald M-LN, *et al*. Continuous fat-free mass decline in COPD: fact or fiction? *Eur Respir J* 2015;46:1496–8.
41 Dransfield MT, Kunisaki KM, Strand MJ, *et al*. Acute exacerbations and lung function loss in smokers with and without chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017;195:324–30.

Online Data Supplement

Title: Respiratory exacerbations are associated with muscle loss in current and former smokers

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Table E1. Expanded baseline demographics by presence or absence of COPD.

	ECLIPSE		COPDGene	
	At-risk	GOLD stage II-IV	At-risk	GOLD stage II-IV
Sample size	226	1106	2,976	1,387
Age, years	55.0 (8.7)	63.2 (6.9)	58.4 (8.5)	62.9 (8.1)
Male	126 (55.8)	721 (65.2)	1,444 (48.5)	759 (54.7)
Caucasian	220 (97.3)	1082 (97.8)	2,006 (67.4)	1,082 (78.0)
Current smoker	134 (59.3)	378 (34.2)	1535 (51.6)	569 (41.0)
Pack years at study entry	32.4 (24.4)	48.6 (27.3)	39.0 (21.6)	51.0 (26.0)
BMI	26.7 (4.3)	26.5 (5.3)	28.3 (5.9)	28.6 (5.8)
Chronic oral steroid use	0.0 (0.0)	0.0 (0.0)	22 (0.7)	42 (3.0)
Pectoral muscle area, cm^2	42.61 (13.25)	34.96 (9.85)	42.60 (16.01)	38.43 (13.18)
6-minute walk distance, m	--	386.4 (118.3)	455.0 (108.3)	391.3 (110.9)

Table E2. Expanded summary of exacerbation data, by Gold stage.

	ECLIPSE[a]				**COPDGene[b]**			
Sample size	At-risk	GOLD 2	GOLD 3	GOLD 4	At-risk	GOLD 2	GOLD 3	GOLD 4
Baseline exacerbation history	226	516	460	130	2976	866	421	100
% with an event in past year	5.8	44.8	59.8	71.5	13.1	30.5	43.7	57.0
Mean rate, per year	0.09	0.92	1.19	1.52	0.20	0.50	0.74	1.09
% with a severe event in past year	0.0	12.8	20.4	33.8	2.4	6.0	13.1	21.0
Mean severe rate, per year	0.0	0.25	0.31	0.50	0.03	0.08	0.17	0.27
Intercurrent exacerbation history								
% with an event during follow-up	0.0	62.4	77.2	83.8	29.6	53.1	75.3	81.0
% ≥ 1 event per year	0.0	39.9	56.5	69.2	7.0	16.4	28.7	37.0
Mean rate, per year	0.00	0.85	1.28	1.79	0.21	0.45	0.78	0.94
% with a severe event during follow-up	0.0	15.1	31.3	46.9	11.0	24.8	40.1	45.0
% ≥1 severe event per year	0.0	3.7	11.5	23.8	1.6	2.9	5.7	10.0
Mean severe rate, per year	0.00	0.11	0.28	0.53	.06	0.12	0.23	0.27

[a] N=2 subjects in ECLIPSE did not have GOLD stage data.

[b] N=21 subjects in COPDGene did not have GOLD stage data.

Analysis with an expanded cohort

As with any longitudinal study, loss to follow-up may introduce bias into the effect estimates. Fully addressing missing data is challenging with only two time-points, as no information can be inferred on progression for those with only one visit. Our primary analysis using only patients who completed two visits implicitly assumes subjects lost to follow-up are missing completely at random (MCAR), which implies that none of the observed (or unobserved) variables impacted their continued participation. In contrast, an analysis using partial data assumes only missing at random (MAR), which allows their loss to follow-up to be related to the observed data (but not the missing data). If the analysis correctly adjusts for the conditional variable(s), unbiased estimates are possible.

For the expanded analysis, 3,562 visits (2,224 unique patients) from ECLIPSE and 13,857 visits (9,473 unique patients) from COPDGene had complete data available. Baseline clinical characteristics of the cohorts are shown in Table E3. As would be expected, there were more baseline visits with complete data than follow-up visits in both studies.

Effect estimates for the excess loss of PMA per annual exacerbation were lower in the expanded cohort than in the primary analysis, however all of them remained statistically significant (Figure E1). While these results are re-assuring, they do not eliminate the potential for bias if the missingness is not random. For example, patients who died or who became too sick to attend their study visits would potentially introduce survivor bias. If these patients had frequent exacerbations but preserved muscle mass or few exacerbations with accelerated muscle loss, their exclusion would make the association demonstrated in this study appear stronger than it is.

We also repeated the analysis using inverse probability weighting (IPW), which is different method to assess the impact of missingness. Specifically, the probability of missingness was modeled as a function of key predictors, leading to the construction of weights that were then used in the pectoral muscle area (PMA) model to essentially give dropouts higher weighting, with the aim to reduce bias in estimates caused by missing data. Logistic regression was used to model data presence (1=yes, 0=no) as a function of phase (baseline or follow-up), exacerbation rate, age, BMI, race, smoking status, and 2-way interactions between phase and the other variables. From this model fit, the probability of data presence was determined for each subject and phase, and weights were then calculated as the inverse of these probabilities. In the model fit for PMA, the weights were applied to records, resulting in an up-weighting of records when the probability of missingness was greater and a down-weighting of records association with lower probability of missingness. In order to have the weights have the desired impact, correlation was not modeled and empirical standard errors were used (Fitzmaurice et al, Applied Longitudinal Analysis 2nd edition, 2011).

As might be expected, small compositional cohort differences in the missing subjects increased the impact of those variables in the IPW model. For example, there are more current smokers in the excluded cohort and the effect of smoking went from a 1% effect on pectoral muscle area under the complete case analysis to a 10% effect in the IPW analysis. The estimated coefficients describing the association with exacerbations; however, were not changed greatly relative to the estimates presented in the primary analysis. Specifically, for the primary analysis, the estimated excess PMA loss for subjects experiencing one exacerbation per year remained 2.1% after applying the IPW methods.

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Table E3. Characteristics of the expanded analysis cohort.

	ECLIPSE		COPDGene	
	Expanded cohort	Excluded from primary analysis	Expanded cohort	Excluded from primary analysis
Total visits	3,562	898	13,857	5,089
Baseline	2,067	735	9,091	4,707
Follow-up	1,495	163	4,766	382
Deaths prior to follow-up	172	172	1,198	1,198
Age, years	63.1 (8.1)	62.6 (8.5)	61.5 (9.3)	59.7 (9.4)
Male	1,368 (61.5)[a]	524 (58.4)	5,108 (53.9)[a]	2894 (56.9)
Caucasian	2,168 (97.5)[a]	872 (97.1)	6,318 (66.7)[a]	3,225 (63.4)
Current smoker	1,339 (37.6)	315 (35.2)	6,676 (48.2)	2832 (55.6)
Pack years on study entry	43.9 (28.3)[a]	40.8 (29.4)	44.13 (24.7)[a]	45.3 (25.4)
BMI	26.5 (5.4)	26.8 (6.0)	28.9 (6.2)	28.6 (6.4)
Chronic oral steroid use	69 (1.9)	16 (1.8)	310 (2.2)	172 (3.4)
Pectoral muscle area, cm^2	35.7 (11.2)	36.0 (11.8)	41.0 (15.7)	42.6 (16.8)
6-minute walk distance[b], m	370.1 (126.2)	334.3 (120.4)	406.5 (125.0)	391.9 (125.9)
BODE score[c]	3.2 (2.1)	3.7 (2.2)	1.8 (2.2)	2.2 (2.5)
Pulmonary rehabilitation	--	--	370 (3.9)[d]	97 (7.8)

[a] these time-independent covariates are expressed as a function of unique patients. The time-varying covariates use the total number of visits as the denominator.

[b] 6MW data available for n=2,732 visits in ECLIPSE and n= 13,667 visits in COPDGene.

[c] BODE data available for n=2,654 visits in ECLIPSE and n=13,458 visits in COPDGene

[d] No pulmonary rehabilitation data is available for ECLIPSE subjects.

Figure E1. **Comparison of effect estimates for the primary and expanded cohorts**.
The dot represents the effect estimate for excess percent muscle loss and the whiskers correspond to the 95% confidence interval. The primary cohort is comprised of the 1,332 participants from ECLIPSE and the 4,384 participants in COPDGene who had complete data for the baseline and 3- or 5-year follow-up visit, respectively. The expanded cohort includes an additional 898 visits from ECLIPSE and 5,089 visits from COPDGene representing participants who had complete data at only one of the two time-points.

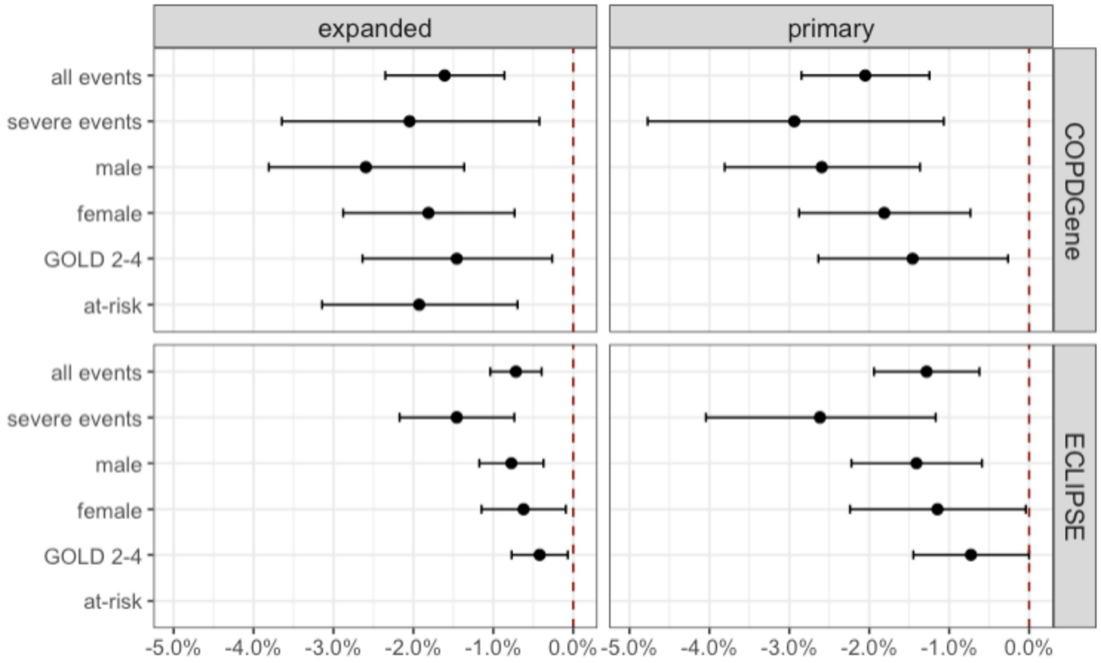

Table E4: Ethics Review Boards: ECLIPSE

Inv/Site No.	Institution & Address	IEC/IRB Committee
027904/023622	Asthma Centre Ivan Vazov Street Nr 31 PO Box 1018 Pleven, 5800 Bulgaria	Ethics Committee for Multicentre Trials 8, Damyan Gruev str., Sofia 1303 Bulgaria
076209/023623	Military Medical Academy Georgi Sofiiski 3 str Sofia 1606 Bulgaria	Ethics Committee for Multicentre Trials 8, Damyan Gruev str., Sofia 1303 Bulgaria
006269/023794	Montreal Chest Institute 3650 St-Urbain, Room K307 Montreal, QC H2X 2P4 Canada	McGill University Health Center Research Ethics Board 3650 St Urbain Montreal, QC H2X 2P4
006610/023668	The Lung Center 2775 Laurel St., 7th Floor Vancouver, BC V5Z 1M9 Canada	The University of British Columbia Office of Research Services Clinical Research Ethics Board Room210, 828 West 10th Ave Vancouver, BC V5Z 1L8 Canada
004970/023483	Queen Elizabeth II Health Sciences Centre Halifax Infirmary 1796 Summer St., Room 5452 Halifax, NS B3H 3A7 Canada	Capital Health Research Ethics Board Centre for Clinical Research Building 118-5790 University Avenue Halifax, NS B3H 1V7 Canada
029347/023796	McMaster University, Health Sciences Center 1200 Main St. West, Room 3U25 Hamilton, ON L8N 3Z5 Canada	Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board 293 Wellington St N, Suite 102 Hamilton, Ontario L8L 8E7 Canada
035031/023795	Pacific Lung Health Center 1081 Burrard Street 8B Providence Wing Vancouver, BC V6Z 1Y6 Canada	Office of Research Services (ORS) Providence Health Care Research Institute Room 1125, 11th Floor 1190 Hornby Street c/o 1081 Burrard Street Vancouver, BC V6Z 1Y6
006193/023547	Hopital Laval, Recherche Clinic Centre de Pneumologie 2725 Chemin Sainte Foy Pavillion U, Locale U 1751 Sainte Foy, QC G1V 4G5 Canada	Comité d'éthique de la recherche Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ) 2725, chemin Ste-Foy Quebec, Qc Canada G1V 4G5
004395/02409 4	Kingston General Hospital Richardson House 102 Stuart Street Kingtson, ON K7L 2V6 Canada	Queens University Office of Research Services Fleming Hall, Jemmett Wing, Room 301 Queens University Kingston, ON, Canada
000309/024204	SPLiN s.r.o. Oddeleni TRN Cimicka 37/446 Praha 8 18200 Czech Republic	Multicentric Ethics Committee Fakultni nemocnice v Motole V Uvalu 84 Prague 5 ZIP: 150 06 Czech Republic
000683/023960	H:S Hvidovre Hospital Hjerte-Lungemedicinsk afdeling Kettegaard Alle 30 Opgang 1 Hvidovre 2650 Denmark	Den videnskabsetiske komité for region hovedstaden Regionsgaarden Kongensvænge 2 3400 Hillerød
001687/024403	Astmacentrum Hornerheide Hornerheide 1 Horn 6085 NM Netherlands	METC Zuidwest-Holland M.H.H.A. Kirkels-Breukers P.O Box 5011 2600 GA Delft The Netherlands

082272/023579	Haukeland Universitets sykehus Chest department Jonas Liesvei 65 Bergen N 5021 Norway	Regional Ethic Committee West Haukeland University Hospital, N-5021 Bergen, Norway
014566/024144	P3 Research Bown Hospital Churchill Drive Crofton Downs Wellington 6035 New Zealand	c/- Ministry of Health 1-3 The Terrace Level 1 Wellington 6011
136098/024146	KOPA Golnik Golnik 36 4204 Golnik Slovenia	The National Medical Ethics Committee of the Republic of Slovenia University Institute of Clinical Neurophysiology, Medical Center Ljubljana, Zaloška c. 7, SI-1525 Ljubljana
108244/026658	Hospital Son Dureta C/ Andrea Doria 55 Palma de Mallorca 07014 Spain	Comité ètic d´investigació clínica Illes Balears Conselleria de Salut i Consum Direcció General d'Avaluació i Acreditació Comitè Ètic d'Investigació Clínica de les Illes Balears (CEIC-IB) Camí de Jesús, 38 A 07011 Palma - Illes Balears
000473/023973	Aintree University Hospitals NHS Foundation Trust Respiratory Research Department Longmoor Lane, Ward 14a Liverpool L9 7AL United Kingdom	Oxfordshire REC C 2nd Floor, Astral House Chaucer Business Park Granville Way Bicester OX26 4JT
082424/023706	Cambridge Institute for Medical Research Department of Medicine Hills Road, Wellcome Trust / MRC Building Cambridge CB2 2XY United Kingdom	Oxfordshire REC C 2nd Floor, Astral House Chaucer Business Park Granville Way Bicester OX26 4JT
029855/023707	New Royal Infirmary of Edinburgh Little France Crescent, Old Dalkeith Road 51 Little France Crescent Edinburgh Midlothian EH16 4SA United Kingdom	Oxfordshire REC C 2nd Floor, Astral House Chaucer Business Park Granville Way Bicester OX26 4JT
023731/023974	Wythenshawe Hospital Medicine Evaluation Unit Southmoor Road The Langley Building, North West Lung Research Centre Manchester M23 9LT United Kingdom	Oxfordshire REC C 2nd Floor, Astral House Chaucer Business Park Granville Way Bicester OX26 4JT
029742/024037	The Royal Free Hospital Academic Unit of Respiratory Medicine Pond Street London NW3 2QG United Kingdom	Oxfordshire REC C 2nd Floor, Astral House Chaucer Business Park Granville Way Bicester OX26 4JT
001069/024393	Institute of Phthisiatry and Pulmonology Department of Pulmonology 10, Amosova Str Kiev 03680 Ukraine	
001047/024392	Institute of Phthisiatry and Pulmonology Department of Pulmonology 10, Amosova Str Kiev 03680 Ukraine	
001071/024362	Institute of Phthisiatry and Pulmonology Department of Pulmonology 10, Amosova Str Kiev 03680 Ukraine	
001063/024364	Donetsk State Medical University Department of Therapy 16 Illicha prospect Donetsk 83003 Ukraine	

044783/023140	University of Texas Health Science Center Pulmonary Diseases 7400 Merton Minter Blvd., (111E) San Antonio, TX 78229 United States	University of Texas Health Science Center 7703 Floyd Curl Drive, Mail Code 7830 San Antonio, TX 78229-3900
077534/023146	Rhode Island Hospital Division of Pulmonary, Sleep & Critical Care Medicine 593 Eddy Street, APC 7th Floor Providence, RI 02903 United States	Lifespan Office of Research Administration 167 Point Street Providence, RI 02903
013075/023147	Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center Rehab Clinical Trials Center 1124 W. Carson St., Bldg. J4 Torrance, CA 90502 United States	John F. Wolf, MD Human Subjects Committee Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center 1124 West Carson Street Torrance, CA 90502
008578/023354.	St. Elizabeth's Medical Center Pulmonary STN-3 736 Cambridge Street Boston, MA 02135 Unites States	Research/Human Subjects Committee Caritas St. Elizabeth's Medical Center Cambridge St., HOQ3 Boston, MA 02135
021992/023148	Pulmonary Associates of Richmond, Inc. 1000 Boulders Parkway, Suite 201 Richmond, VA 23225 United States	Goodwyn Institution Review Board 9380 Main Street Cincinnati, OH 45242
010875/023149	Pulmonary Associates, PA 1112 East McDowell Road Phoenix, AZ 85006 United States	Goodwyn Institution Review Board 9380 Main Street Cincinnati, OH 45242
011553/023150	Advances in Medicine 42362 Bob Hope Drive Rancho Mirage, CA 92270 Unites States	Western International Review Board 3535 Seventh Ave SW Olympia, WA 98508
010094/023355	Baylor Clinic-Baylor College of Medicine 6620 Main Street Suite 11B, 16 Houston, TX 77030 United States	Baylor College of Medicine IRB Clinical Research Studies One Baylor Plaza, Mail stop 600D Houston, TX 77030
015497/023356	Dartmouth-Hitchcock Medical Center Pulmonary & Critical Care Center One Medical Center Drive Lebanon, NH 03756 Unites States	Dartmouth-Hitchcock Medical Center Committee for the Protection of Human Subjects 11 Rope Ferry Road #6210 Hanover, NH 03755
008005/023357	National Jewish Medical & Research Center Weinberg Clinical Research Unit 1400 Jackson Street Denver, CO 80206 United States	National Jewish Medical & Research Center IRB 1400 Jackson Street Denver, CO 80206
009021/023358	University of Nebraska Medical Center Pulmonary Clinical Studies Unit 982465 Nebraska Medical Center DRC II1022 Omaha, NE 68198 United States	University of Nebraska Medical Center IRB Academic & Research Services Bldg. 3000 987830 Nebraska Medical Center Omaha, NE 68198
083482/023571	Yale University School of Medicine Internal Medicine/Pulmonary 1 Gilbert Street, TAC S 441 New Haven, CT 06520 United States	Yale University School of Medicine Human Investigation Committee 47 College Street, Suite 204 New Haven, CT 06520
015449/023359	Mayo Clinic Pulmonary Clinical Research Center Lanmark 2-46 14 - 2nd Street SW Rochester, MN 55905 United States	Mayo Foundation IRB 201 Building, Room 4-60 200 First Street SW Rochester, MN 55905
080801/023389	Creighton University Medical Center Pulmonary & Critical Care Division 601 N. 30th Street, Suite 3820 Omaha, NE 68131 United States	Creighton University Medical Center IRB 2500 California Plaza Omaha, NE 68178

010532/023489	University of Pittsburgh Medical Center Emphysema Research Center 3471 5th Ave., Suite 1211 Pittsburgh, PA 15213 United States	University of Pittsburgh IRB 3500 Fifth Ave, Ground Level Pittsburgh, PA 15213

021093/023390	Houston VA Medical Center 2002 Holcombe Blvd. Pulmonary 111-1, Room 3C-220 Houston, TX 77030 United States	Baylor College of Medicine IRB Clinical Research Studies One Baylor Plaza, Mail stop 600D Houston, TX 77030
008864/023392	Midwest Chest Consultants, PC 330 First Capital Drive, Suite 470 St. Charles, MO 63301 United States	Goodwyn Institution Review Board 9380 Main Street Cincinnati, OH 45242
077533/023391	Harvard University-Brigham & Women's Hospital Channing Laboratory 181 Longwood Ave. Boston, MA 02115 United States	Brigham & Women's Hospital IRB Partners Human Research Office 116 Huntington Ave, Suite 1002 Boston, MA 02116
016586/023393	University of Miami School of Medicine 1600 NW 10th Ave, #7064-A (R-47) Miami, FL 33136	Western International Review Board 3535 Seventh Ave SW Olympia, WA 98508
057745/023394	Johns Hopkins Asthma & Allergy Center 5501 Hopkins Bayview Circle, Room 3B-58 Baltimore, MD 21224 United States	John Hopkins School of Medicine Office of Human Subject Research 1620 McElderry St., Reed Hall Suite B 130 Baltimore, MD 21205
012252/023395	St. Francis Hospital & Medical Center Pulmonary Medicine 114 Woodland Street Hartford, CT 06105 United States	St. Francis Hospital & Medical Center IRB Department of Research 114 Woodland St. Hartford, CT 06105

Table E5: Ethics Review Boards: COPDGene

Clinical Center	Institution Title	Protocol Number
National Jewish Health	National Jewish IRB	HS-1883a
Brigham and Women's Hospital	Partners Human Research Committee	2007-P-000554/2; BWH
Baylor College of Medicine	Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals	H-22209
Michael E. DeBakey VAMC	Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals	H-22202
Columbia University Medical Center	Columbia University Medical Center IRB	IRB-AAAC9324
Duke University Medical Center	The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB)	Pro00004464
Johns Hopkins University	Johns Hopkins Medicine Institutional Review Boards (JHM IRB)	NA_00011524
Los Angeles Biomedical Research Institute	The John F. Wolf, MD Human Subjects Committee of Harbor-UCLA Medical Center	12756-01
Morehouse School of Medicine	Morehouse School of Medicine Institutional Review Board	07-1029
Temple University	Temple University Office for Human Subjects Protections Institutional Review Board	11369
University of Alabama at Birmingham	The University of Alabama at Birmingham Institutional Review Board for Human Use	FO70712014
University of California, San Diego	University of California, San Diego Human Research Protections Program	070876
University of Iowa	The University of Iowa Human Subjects Office	200710717
Ann Arbor VA	VA Ann Arbor Healthcare System IRB	PCC 2008-110732
University of Minnesota	University of Minnesota Research Subjects' Protection Programs (RSPP)	0801M24949
University of Pittsburgh	University of Pittsburgh Institutional Review Board	PRO07120059
University of Texas Health Sciences Center at San Antonio	UT Health Science Center San Antonio Institutional Review Board	HSC20070644H
Health Partners Research Foundation	Health Partners Research Foundation Institutional Review Board	07-127
University of Michigan	Medical School Institutional Review Board (IRBMED)	HUM00014973
Minneapolis VA Medical Center	Minneapolis VAMC IRB	4128-A
Fallon Clinic	Institutional Review Board/Research Review Committee Saint Vincent Hospital – Fallon Clinic – Fallon Community Health Plan	1143