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Percent Emphysema and Daily Motor Activity Levels in the General Population

Multi-Ethnic Study of Atherosclerosis



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BACKGROUND: COPD is associated with reduced physical capacity. However, it is unclear whether pulmonary emphysema, which can occur without COPD, is associated with reduced physical activity in daily life, particularly among people without COPD and never smokers. We hypothesized that greater percentage of emphysema-like lung on CT scan is associated with reduced physical activity assessed by actigraphy and self-report.

METHODS: The Multi-Ethnic Study of Atherosclerosis (MESA) enrolled participants free of clinical cardiovascular disease from the general population. Percent emphysema was defined as percentage of voxels < -950 Hounsfield units on full-lung CT scans. Physical activity was measured by wrist actigraphy over 7 days and a questionnaire. Multivariable linear regression was used to adjust for age, sex, race/ethnicity, height, weight, education, smoking, pack-years, and lung function.

RESULTS: Among 1,435 participants with actigraphy and lung measures, 47% had never smoked, and 8% had COPD. Percent emphysema was associated with lower activity levels on actigraphy ($P = .001$), corresponding to 1.5 hour less per week of moderately paced walking for the average participant in quintile 2 vs 4 of percent emphysema. This association was significant among participants without COPD ($P = .004$) and among ever ($P = .01$) and never smokers ($P = .03$). It was also independent of coronary artery calcium and left ventricular ejection fraction. There was no evidence that percent emphysema was associated with self-reported activity levels.

CONCLUSIONS: Percent emphysema was associated with decreased physical activity in daily life objectively assessed by actigraphy in the general population, among participants without COPD, and nonsmokers. CHEST 2017; 151(5):1039-1050

KEY WORDS: actigraphy; computed tomography; emphysema; multicenter prospective cohort study; physical activity

ABBREVIATIONS: 6MWT = 6-minute walk test; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; MESA = Multi-Ethnic Study of Atherosclerosis; MET = metabolic equivalent of task

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COPD is the third leading cause of death in the United States.¹ COPD is defined by accelerated, age-related loss in lung function, resulting in airway obstruction that is not completely reversible.² Reduced functional status in COPD, characterized by reduced exercise tolerance, was described > 50 years ago by Filley et al³ and is well defined in more recent studies.⁴ Physical activity and exercise capacity are major predictors of mortality in COPD,^{5,6} but activity limitation in COPD is still poorly understood.^{7,8}

Emphysema is defined as nonreversible air space enlargement with parenchymal destruction resulting in loss of lung architecture.⁹ The percentage of emphysema-like lung (percent emphysema) on CT scan provides in vivo assessment of pulmonary emphysema.¹⁰ Quantitative CT-based measurements of emphysema have previously been correlated with morphometric measurements.¹¹ Parenchymal destruction in emphysema not just decreases the number of alveoli but is characterized by hyperinflation¹² in addition to destruction of the vasculature.^{9,13} These factors decrease maximal diffusion capacity and cardiac output,¹⁴ which lower peak O₂ absorption and therefore limit exercise tolerance and reduce physical activity.¹⁵ Physical activity is reduced in patients with COPD with hyperinflation,¹⁶ and is possibly mediated by factors such as dyspnea, increased respiratory muscle work, and lower cardiac output through reduced right ventricular preload and increased afterload.¹⁷ Increased percent emphysema occurs not infrequently in the general population, in the setting of which it is associated with decreased cardiac output,¹⁴ subclinical vascular changes,¹⁸ decreased exercise capacity on cardiopulmonary exercise testing¹⁹ and the 6-minute walk test (6MWT),⁴ and increased dyspnea.²⁰ However, exercise capacity

and physical activity in daily life are different constructs, and exercise capacity does not necessarily translate into physical activity in daily life.²¹ Emphysema occurs not infrequently in the absence of spirometrically defined COPD²² and is also associated with increased dyspnea on exertion and higher all-cause mortality.²³ Interestingly, the relationship of percent emphysema to dyspnea was not modified by current or former smoking,²⁰ which may suggest a mechanism independent of smoking and possibly be reflective of the generally modest relationships of smoking to percent emphysema²⁴ and some emphysema subtypes.²⁵

Although a classic clinical correlate of emphysema is reduced activity levels, at times in absence of complaints of dyspnea, little is known about the correlation between actual daily activity and the extent of emphysema, particularly in patients who do not have spirometrically defined COPD. Available studies and guidelines focus on COPD independent of emphysema.²⁶⁻²⁸ Studies that objectively quantified emphysema on CT scan used measures of exercise capacity, such as the 6MWT^{4,29,30} or cardiopulmonary exercise testing,^{20,31} which may not reflect general activity levels, did not adjust for lung function,³² focused on moderate to severe COPD,³³ or comprised small sample sizes.

We therefore hypothesized that percent emphysema on CT scan would be associated with reduced physical activity levels in daily life, including among participants without COPD and among nonsmokers, in a general population sample. We assessed activity levels by actigraphy, which has proven to be superior to self-report,³⁴ in addition to self-reported activity.

Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) recruited 6,814 whites, African Americans, Hispanics, and Asian Americans ages 45 to 84 years from six US communities in 2000 to 2002. The major exclusion criteria were clinical cardiovascular disease and weight > 136 kg.³⁵ There were 4,716 participants who attended the 10-year follow-up examination in 2010 through 2012, which included assessment of self-reported physical activity.

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The MESA Lung Study enrolled 3,965 MESA participants who were sampled randomly among those who underwent baseline measurements of endothelial function, consented to genetic analyses, and attended an examination during the MESA Lung Study recruitment period in 2004 and 2006. We excluded participants who had a restrictive pattern on spirometry (FVC < lower limit of normal [LLN], with a ratio of FEV₁ to FVC > 0.70).^{14,24} The MESA Lung participants plus a random selection of 851 of the 1,543 MESA participants that were not selected for MESA Lung, but attended examination 5 were invited to undergo full-lung CT scans in 2010 through 2012, resulting in 3,131 technically acceptable scans. Of this group, 2,808 had spirometry measures after we excluded participants who had a restrictive pattern on spirometry (FVC < LLN, with a ratio of FEV₁ to FVC > 0.70).¹⁴

The MESA Sleep Study enrolled 2,230 participants in 2010 through 2012. Of the sample with full-lung CT scans, 1,435 had valid

multiple day wrist actigraphy recording. Details of the recruitment of the present study sample are shown in [Figure 1](#).

All data assessed were obtained during 10-year follow-up (examination 5) of the MESA cohort. The median time between the CT scan examination and the beginning of the actigraphy assessment was 249 (interquartile range, 125–386) days.

Study procedures were approved by the institutional review boards of all participating institutions ([e-Appendix 1](#)) and by the National Heart, Lung, and Blood Institute. All participants provided informed consent.

Imaging

CT scans were acquired after coaching to full inspiration using 64-slice multidetector row CT scanners (Siemens Sensation 64 or General Electric V64). The CT scan acquisition followed the SPIROMICS/MESA-Lung full-inspiration protocol.³⁶

Trained technologists at a single center and blinded to patient information measured attenuation levels of the volumetric units (voxels) using APOLLO software (VIDA Diagnostics). Percent emphysema was defined as the percentage of lung voxels with an

attenuation level < −950 Hounsfield units, adjusted for attenuation of air outside the chest.³⁷ Emphysema on CT scan was defined as percent emphysema greater than the upper limit of normal, based on reference equations derived from healthy participants of this cohort. The reference values are a function of age, sex, race/ethnicity, height, current smoking, scanner manufacturer, and milliamperere seconds.³⁸

For secondary analyses, hyperinflation was assessed as percentage of the total pulmonary air volume on CT scan divided by predicted pulmonary air volume based on similarly derived CT scan reference equations.³⁸ Cardiac CT scans gated to the cardiac cycle were acquired in a subset at the same visit, and Agatston-adjusted coronary artery calcium score was measured.³⁹ Left ventricular ejection fraction (LVEF) was assessed by cardiac MRI in a subset at the same examination, as previously described.⁴⁰

Pulmonary Function Testing and COPD Case Status

Spirometry was assessed according to the American Thoracic Society/European Respiratory Society recommendations as previously described, and using predicted values and LLN based on the Hankinson reference equations. COPD was defined as a postbronchodilator FEV₁/FVC

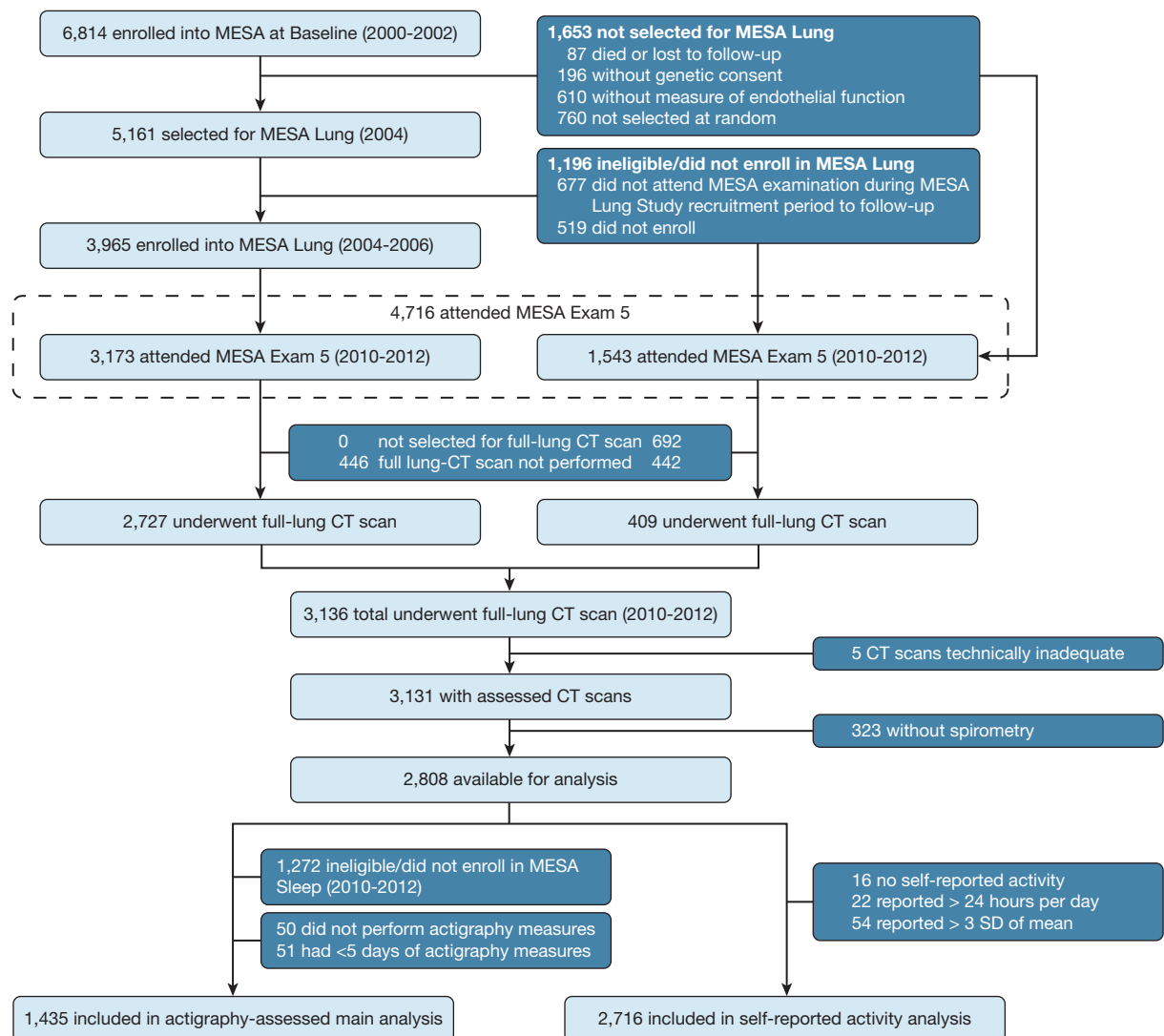


Figure 1 – Flow diagram of the study sample. MESA = Multi-Ethnic Study of Atherosclerosis.

ratio < 0.7, and airflow limitation was defined as prebronchodilator FEV₁/FVC ratio < 0.7 and secondary FEV₁/FVC ratio < LLN.²

Actigraphy

Participants were asked to wear a uniaxial actigraphy device (Actiwatch Spectrum; Philips Respironics) on the nondominant wrist for 7 consecutive days. Epoch length was set to 30 seconds, and activity count was then processed using the Actiware-Sleep version 5.59 analysis software (Mini Mitter Co., Inc.), a validated weighting algorithm,⁴¹ and scored at a central reading center. To assess motor activity in daily life, the mean daily activity count was assessed by analyzing the sum of the recorded accelerations per 24-hour period from 12 PM to 12 PM, which we then averaged over the measurement days (abbreviated as mean activity count). To account for possible increased need of sleep or rest and to avoid a bias toward underestimating inactivity or periods of low activity, these periods were included in the analysis.⁴² Time that the device was not worn, as indicated by the capacitive sensor, was excluded (time per day in percent: median, 0; interquartile range, 0-6.9). Based on current recommendations for healthy subjects and patients with COPD, a minimum of 4 weekdays and 1 weekend day were required for analysis,³³ resulting in the exclusion of 51 participants.

The uniaxial Actiwatch Spectrum has been shown to have a good correlation ($r = 0.68$, $P < .001$; regression equation: $y[\text{activity counts}] = 166.07 x[\text{kcal}] + 68,579$) to active energy expenditure as measured by the gold standard of doubly labeled water.⁴³

Results

The 1,435 participants with valid measures of percent emphysema and activity count on actigraphy had a mean age of 68 ± 9 years, 48% were male, and the median percent emphysema was 1.4% (interquartile range, 0.5%-2.9%). Of the participants, 47% were never smokers, and the prevalence of COPD was 8%. Participants wore their actigraphy device for an average of 7.1 ± 0.8 days, with an average of 180 (interquartile range, 138-229) accelerations per 24-hour period. This translates to an average active energy expenditure of 2,807 kJ (interquartile range, 1,735-4,045 kJ).

Table 1 summarizes the characteristics of the study sample, stratified by quintile of percent emphysema. Participants with greater percent emphysema were older, more likely to be men or white, and to have smoked cigarettes. Participants with greater percent emphysema also had lower BMI, were less likely to have diabetes, and more likely to have reduced LVEF and more coronary artery calcification.

Percent Emphysema and Mean Activity Count on Actigraphy

Greater percent emphysema was significantly associated with reduced activity levels assessed by actigraphy. This inverse association was significant in the unadjusted model ($P = .02$), minimally adjusted model ($P = .003$), and fully adjusted model (and

Self-Reported Physical Activity

The MESA Typical Week Physical Activity Survey was used as described previously, with moderate and vigorous physical activity levels as a summary measure (abbreviated as self-reported activity level).⁴⁴

Covariates

Anthropometry, height and weight, and other covariates were measured following the MESA protocol (<http://www.mesa-nhlbi.org>). Race/ethnicity was self-reported according to the 2000 US Census criteria.

Statistical Analysis

Multivariable linear regression was used to test the relationship and statistical significance between percent emphysema (independent variable) and physical activity (dependent variable) as continuous variables. Activity breakdowns by quintile of percent emphysema are shown for descriptive purposes. Percent emphysema was logarithmically transformed to account for the skewed data distribution. Additional analysis of untransformed percent emphysema using generalized additive models and linear regression with robust estimators is also provided. Covariates were chosen based on known associations with physical activity and with percent emphysema. SAS 9.3 (SAS Institute) was used for analyses.

For additional information on the methods, please refer to e-Appendix 1.

$P = .001$) (Table 2), with an effect estimate of percent emphysema in the full model of $-7,043$ activity counts. The difference between the mean absolute activity counts of quintiles 2 and 4 of percent emphysema (which avoids the impact of extreme values on either end of the range and happens to correspond roughly to 1 SD) (e-Appendix 2) in the fully adjusted model (Table 2) is approximately equivalent to a 237 kJ change in mean energy expenditure per day or 1,660 kJ per week.⁴³ This translates into 1.5 hours of moderately fast walking per week for an average weight participant (detailed calculations in e-Appendix 2, e-Table 1).⁴⁵

Additional adjustment for coronary artery calcium score and LVEF yielded highly consistent results that were also statistically significant (coefficient in thousands, -6 ; 95% CI, -11 to -1 ; $P = .03$). Consistent results were also obtained for the full model additionally adjusted for hyperinflation (coefficient in thousands, -7 ; 95% CI, -13 to -2 ; $P = 0.01$). Hyperinflation on CT scan was also associated with lower activity levels on actigraphy in unadjusted and fully adjusted models that did not include percent emphysema ($P = .049$ and $P = .035$, respectively). However, addition of percent emphysema rendered the association with hyperinflation null ($P = .90$), whereas the association of percent emphysema and actigraphy was largely unchanged.

TABLE 1] Characteristics of Study Participants Stratified by Quintiles of Percent Emphysema (N = 1,435)

Characteristic	Quintile of Percent Emphysema				
	1	2	3	4	5
No. of participants	287	287	287	287	287
Percent emphysema	0.3 (0.2-0.5)	0.7 (0.5-0.8)	1.4 (1.1-1.6)	2.5 (2.1-2.9)	5.5 (4.2-7.5)
Participants with percent emphysema > upper limit of normal, %	0	0	2	9	30
Age, y	66 ± 9	68 ± 9	69 ± 9	69 ± 9	70 ± 9
Male sex, %	23	34	46	60	76
Race or ethnic group, %					
Caucasian	23	28	35	37	52
African American	29	29	29	31	22
Hispanic	40	31	21	17	11
Chinese	8	12	15	15	15
Cigarette smoking, %					
Never smoker	54	52	49	43	37
Former smoker	33	37	43	49	54
Current smoker	13	11	8	8	9
Pack-years of smoking in never smokers	11 (2-32)	14 (2-30)	14 (2-31)	14 (3-29)	18 (5-35)
Height, cm	161 ± 9	164 ± 10	166 ± 10	168 ± 9	171 ± 9
Weight, kg	79 ± 16	79 ± 19	78 ± 18	80 ± 18	80 ± 17
BMI, kg/m ²	30.4 ± 5.6	29.5 ± 5.8	28.4 ± 5.3	28.2 ± 5.3	27.4 ± 5.0
Diabetes, %	24	19	18	14	12
COPD, ^a % (assessment available in n = 1,241)	2	4	6	9	23
Hypertension, %	57	61	58	60	51
Ejection fraction < 55%, % (assessment available in n = 1,074)	12	17	19	18	24
Coronary calcification (any), % (assessment available in n = 1,279)	57	64	69	68	71
Beta-blocker, %	20	17	16	16	14
FEV ₁ , % predicted	90 ± 18	95 ± 18	95 ± 18	99 ± 18	95 ± 22
FVC, % predicted	89 ± 16	94 ± 17	97 ± 16	100 ± 16	101 ± 18
FEV ₁ /FVC ratio	0.78 ± 0.07	0.77 ± 0.07	0.75 ± 0.08	0.74 ± 0.08	0.70 ± 0.10

Values are presented as median (interquartile range), mean ± SD, or as otherwise indicated. Race or ethnic group, smoking status, and pack-year history were self-reported.

^aDefined by postbronchodilator FEV₁/FVC ratio of < 0.7.

Male sex was also significantly associated with activity counts ($P = .03$) in the full model, whereas other covariates were not. Neither coronary artery calcium score nor LVEF were significantly associated with activity counts in the extended model.

The relationship of untransformed percent emphysema and mean activity count was approximately linear across the spectrum of percent emphysema (Fig 2), without evidence of a threshold (P value for nonlinearity = .32).

The findings were not driven by a small number of individuals with severe emphysema because exclusion of percent emphysema values above the 95th percentile showed similar results ($P = .002$). Further, the decrement in activity levels in the 121 participants with percent emphysema greater than the upper limit of normal was not statistically significant ($P = .50$).

Examination of untransformed percent emphysema with robust estimator led to similar results in the

TABLE 2] Mean Activity Counts by Quintile of Percent Emphysema and Mean Differences Per 1 Log-Unit Change in Percent Emphysema

Model	Mean Absolute Activity Counts in Thousands According to Quintile of Percent Emphysema					Mean Difference Actigraphy (95% CI) Per 1 Log-Unit Increase of Percent Emphysema	P Value
	1	2	3	4	5		
Quintile No.							
Measured mean activity count	192	177	178	175	174
Estimated active energy expenditure, ^a kJ/d	3,102	2,727	2,754	2,668	2,660
Estimated h/wk walking at 3.3 METS ^b	19.8	17.4	17.6	17.1	17.0
Minimally adjusted model ^c (n = 1,435)	193	187	183	180	175	-6 (-10 to -2)	.003
Estimated active energy expenditure, ^a kJ/d	3,135	2,984	2,883	2,807	2,681
Estimated h/wk walking at 3.3 METS ^b	20.0	19.0	18.4	17.9	17.1
Fully adjusted model ^d (n = 1,316)	196	189	184	180	174	-7 (-11 to -3)	.001
Estimated active energy expenditure, ^a kJ/d	3,218	3,043	2,916	2,806	2,650
Estimated h/wk walking at 3.3 METS ^b	20.5	19.4	18.6	17.9	17.0

Mean activity counts according to quintile of percent emphysema are adjusted as indicated by the model where applicable. CI = confidence interval.
^aEstimations of active energy expenditure (kJ/d) are based on the following formulas: $y[\text{activity counts}] = 166.07 x[\text{kcal}] + 68,579$, where 1 kcal = 4.184 kJ (ISO31-4 standard).⁴³

^bAssuming no other physical activity. Estimated active energy expenditure is calculated for the average participant with 79.4 kg, walking on level ground for 1 h with a 3 mi/h (= 4.8 km/h) pace (= 3.3 METs) = $79.4 \text{ kg} \times 3.3 \text{ MET} = 262 \text{ kcal/h} = 1,097.00 \text{ kJ/h}$.⁴⁵

^cMinimally adjusted multivariable linear regression model includes age, sex, race/ethnicity, education, and scanner manufacturer as covariates.

^dFully adjusted model also adds height, weight, BMI category, FEV₁, cotinine level, and pack-years (differentiating between current, former, and never smokers).

unadjusted and full model ($P = .09$ and $P = .04$, respectively) (e-Figure 1).

The association of percent emphysema on CT scan and mean activity count on actigraphy was consistent and statistically significant among ever smokers (coefficient in thousands, -7.5; 95% CI, -13.4 to -1.5; $P = .01$) and also among never smokers (coefficient in thousands, -6.7; 95% CI, -12.5 to -8.4; $P = .03$), without evidence for interaction by smoking status (interaction $P = .90$) (Fig 3).

There was a significant effect modification by age and site but not by sex, race/ethnicity, obesity, presence of cardiac risk factors, and resting oxygen saturation (Fig 4), with a stronger association among younger participants and consistent results at 4 of 6 sites. Findings were similar and statistically significant among participants without a history of myocardial infarction or heart failure (Fig 4).

The inverse association between percent emphysema and mean activity count persisted among participants

without COPD or without airflow limitation, regardless of its definition (Table 3). Effect estimates among these groups were highly similar to those in the full sample. Effect estimates restricted to participants with airflow limitation (prebronchodilator FEV₁/FVC ratio < 70%; n = 352) showed highly similar effect estimates in the unadjusted, minimally adjusted, and fully adjusted model (coefficient in thousands, -4; 95% CI, -11 to 2; coefficient in thousands, -4; 95% CI, -11 to 3; and coefficient in thousands, -5; 95% CI, -13 to 3, respectively), but failed to reach significance.

The variance in mean activity count explained by percent emphysema was modest at 0.8%; however, it accounted for 54% of the variance explained by the full model. The other significant predictor was male sex ($P = .03$).

Percent Emphysema and Self-Reported Activity Levels

e-Appendix 3, e-Table 2 summarize the characteristics of the 2,716 participants, with measures of percent

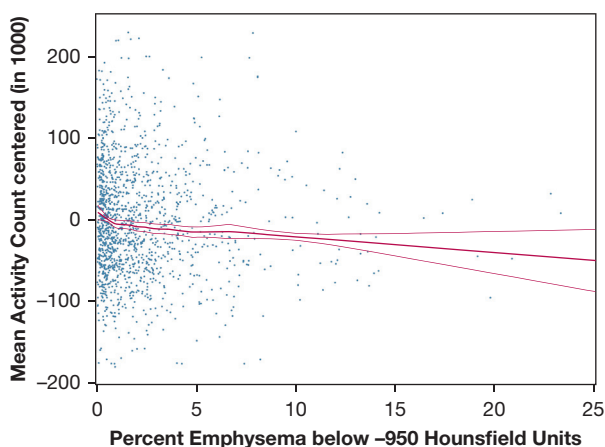


Figure 2 – Multivariate relationship between percent emphysema and mean activity count in a centered scatterplot and generalized additive model with local regression smoothing (LOESS) plot. Centered scatterplot and LOESS plot with 95% confidence interval and smoothing parameter of 0.6. Fully adjusted model includes age, sex, race/ethnicity, education, scanner manufacturer height, weight, BMI category, FEV₁, cotinine level, and pack-years (n = 1,316). The P value for the main association = .003. The deviation for nonlinearity was nonsignificant (P = .32). Excluding high percent emphysema values above the 95th percentile shows similar results (main association coefficient, -4.4; P = .002; nonlinearity P = .28; graph not shown). In a second generalized cross-validation model using the prediction of the sum of squares (df = 0.97), the P value for the main association was .001, and the deviation for nonlinearity stayed nonsignificant (P = .34; graph not shown).

emphysema and self-reported activity level stratified by quintile of percent emphysema.

Although there was an inverse association of percent emphysema with self-reported moderate and vigorous activity levels, results did not attain statistical significance (e-Appendix 3, e-Table 3). There was no association in the sample restricted to those with additionally available

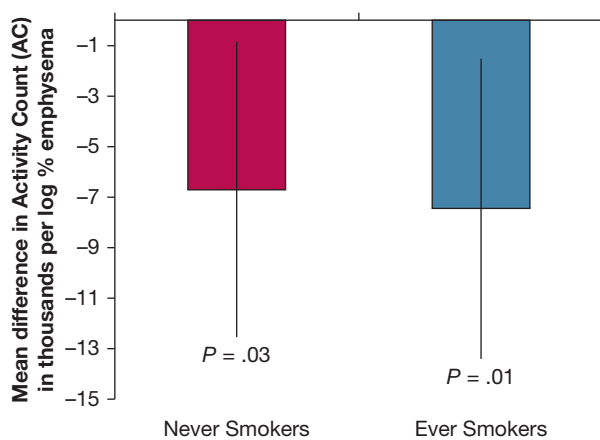


Figure 3 – Percent emphysema on CT scan and mean activity count by actigraphy stratified by smoking status. Activity counts in the thousands. Fully adjusted model includes age, sex, race/ethnicity, education, scanner manufacturer height, weight, BMI category, FEV₁, cotinine level, and pack-years. There was no significant interaction (P = .90). Never smokers: n = 671; ever smokers: n = 645.

actigraphy measures (e-Table 4). Stratified results demonstrated a generally inverse association (e-Fig 2).

Discussion

This study demonstrates that greater percent emphysema on CT scan was associated with reduced physical activity levels in daily life measured by actigraphy in a general population sample. The difference in physical activity between the average participant in quintile 2 vs 4 of percent emphysema was approximately equivalent to 1.5 hours of moderately fast walking per week. This relationship was independent of FEV₁, cardiac function, and hyperinflation; present among participants without COPD; and evident among never smokers.

This report, to our knowledge, presents the first large-scale assessment of objectively assessed percent emphysema and activity levels measured in real-world settings of a general population outside of the clinic. By assessing activity levels in the real-world setting, we extend findings from previous, much smaller (n ≤ 100) studies, which measured exercise capacity tests, such as the 6MWT⁴⁶ or incremental treadmill testing, instead of activity levels.^{19,31} Although the absolute change in activity associated with percent emphysema was modest, the aforementioned difference of 90 minutes of moderately fast walking per week was associated, in a different study, with 14% lower death rates over a follow-up of 8 years,⁴⁷ suggesting a difference of this magnitude might have an impact.

In contrast with previous studies, this study was sampled from the general population, without oversampling based on spirometrically defined COPD; had a large sample of participants without COPD; had more extensive control for potential confounders; and measured daily activity levels at home by actigraphy over 1 week.

Prior studies that oversampled patients with COPD among smokers demonstrated that percent emphysema was associated with lower 6MWT.^{4,33} Differences between the prior studies and ours include the case-control design of the prior studies, which required stratification of analyses into relatively small sample sizes; their over selection of more severe COPD, in which activity limitation is more likely to result from airflow obstruction than cardiac limitation; and the assessment of activity by 6MWT, which assesses provoked functional capacity at only one time point and which is known to be insensitive in mild disease.⁴⁶

In comparison, the current population-based study demonstrated a consistent inverse association between

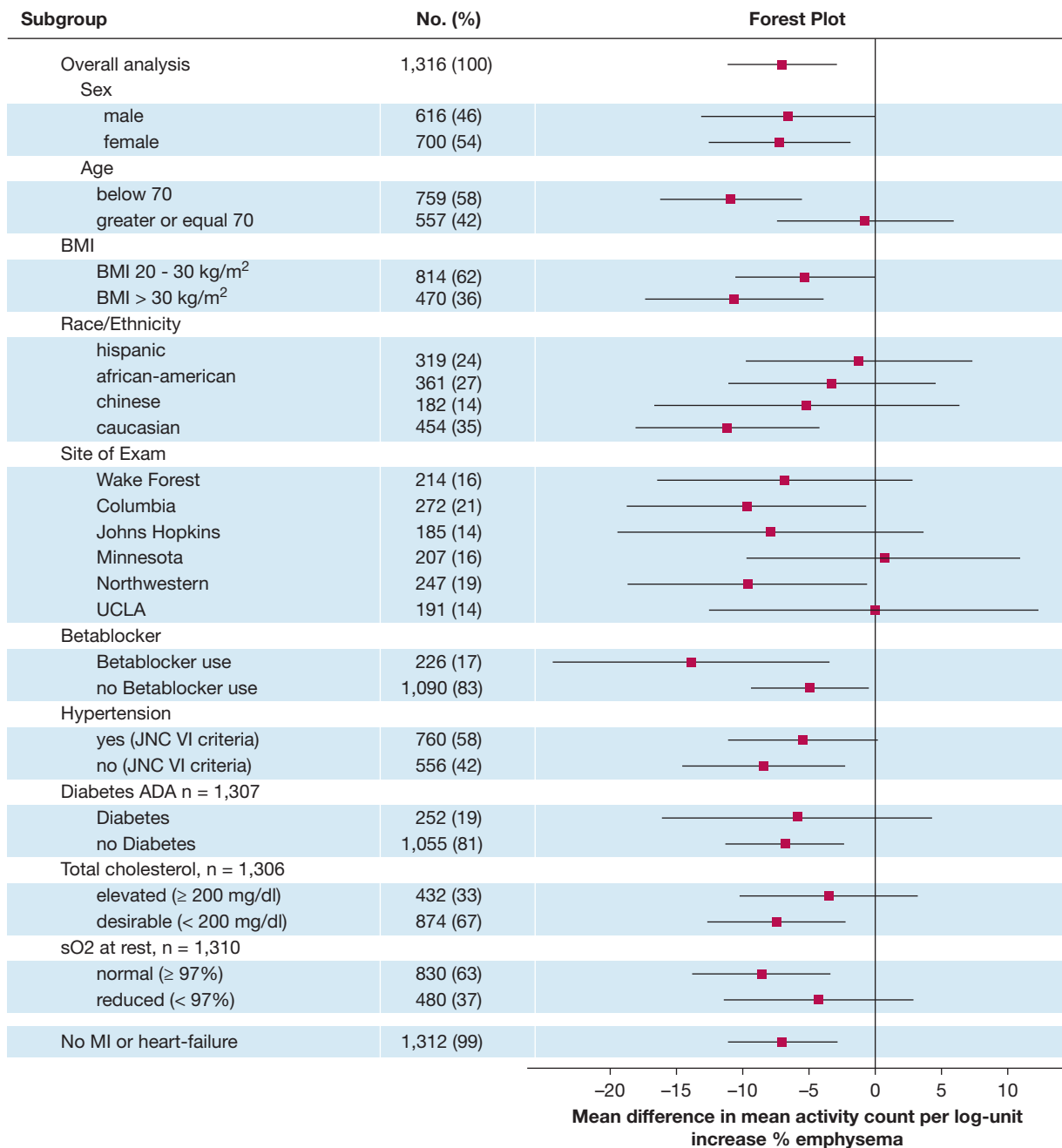


Figure 4 – Sensitivity analysis for association of percent emphysema on CT scan and mean activity count in actigraphy. Activity counts in the thousands (n = 1,316). Analysis for the fully adjusted model includes age, sex, race/ethnicity, education, scanner manufacturer, height, weight, BMI category, cotinine, pack-years, and FEV₁. No interactions besides age (P = .0413) and site (P < .0001) were significant (all other P values > .05). ADA = American Diabetes Association; JNC VI = Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; sO₂ = oxygen saturation; MI = myocardial infarction.

percent emphysema and week-long assessment of activity by means of actigraphy in unadjusted and extensively adjusted linear and nonlinear models, including among smokers and nonsmokers without COPD.

The mechanisms of reduced activity are not directly addressed in this report, and there are likely multiple factors at play. We hypothesize that emphysema is

characterized by destruction of the vasculature,^{9,13} decreasing maximal diffusion capacity and cardiac output,¹⁴ which lower peak O₂ absorption and therefore limit exercise tolerance and reduce physical activity in the general population.¹⁵ However, a systematic review of studies in patients with COPD implicated prior exacerbations, systemic inflammation, and hyperinflation with reduced physical activity (but not

TABLE 3] Association of Mean Activity Counts by Quintile of Percent Emphysema and Mean Differences Per 1 Log-Unit Change in Percent Emphysema Restricted to Participants Without COPD or Airflow Limitation

Model	Mean Absolute Activity Counts in Thousands According to Quintile of Percent Emphysema					Mean Difference Actigraphy (95% CI) Per 1 Log-Unit Increase of Percent Emphysema	P Value
	1	2	3	4	5		
Without COPD (n = 1,140)							
Minimally adjusted ^a	195	188	184	179	174	-7 (-12 to -2)	.003
Fully adjusted ^b	200	193	188	183	177	-7 (-12 to -2)	.004
Without airflow limitation (prebronchodilator FEV₁/FVC ratio ≥ 70%) (n = 1,083)							
Minimally adjusted ^a	194	188	184	180	175	-6 (-11 to -1)	.01
Fully adjusted ^b	198	192	188	183	178	-7 (-12 to -2)	.01
Without airflow limitation (prebronchodilator FEV₁/FVC ratio ≥ LLN) (n = 1,273)							
Minimally adjusted ^a	194	188	183	179	174	-7 (-11 to -2)	.003
Fully adjusted ^b	198	191	186	182	176	-7 (-12 to -3)	.002

LLN = lower limit of normal. See Table 2 legend for expansion of other abbreviations.

^aMinimally adjusted model includes age, sex, race/ethnicity, education, and scanner manufacturer as covariates.

^bFully adjusted model also adds height, weight, BMI category, FEV₁, cotinine level, and pack-years.

FEV₁, FVC, BMI, and comorbidities),⁷ all of which are also related to emphysema.⁴⁸⁻⁵⁰

Systemic inflammation has been shown to be associated with right ventricular impairment in MESA,⁵¹ and low to moderate percent emphysema has been shown to have a strong inverse association with function of the left and right ventricle,^{14,52} pulmonary blood flow,⁵³ and all-cause mortality in persons without airflow obstruction.²³

Therefore, systemic inflammation is a possible link between physical activity and emphysema.

Unfortunately, systemic inflammation markers were not available at the examination of the current analysis. Also, the number of exacerbations among the analyzed subjects was too small to find a correlation in our sample.

Hyperinflation assessed on CT scan, however, was inversely associated with activity. Although this measure has not yet been validated against total lung capacity on plethysmography and does not reflect gas trapping, we found that the association of percent emphysema with activity was independent of hyperinflation, rather than the other way around, suggesting a role of emphysema independent of hyperinflation.

Interestingly, a recent publication showed that fluticasone/vilanterol—a combination that has anti-inflammatory, bronchodilating, and vasodilatory properties—significantly improved cardiac function in patients with COPD with hyperinflation,¹³ suggesting that one or several mechanisms may be at work.

We found significant effect modification of the association of emphysema and activity counts by age and site. Aging generally lowers physical activity because of additional limiting factors besides those in the pulmonary system. However, the median age of the participants in our study is 67 years, and National Health and Nutrition Examination Survey data showed decreasing sex differences in total activity with ageing, with men and woman aged ≥ 60 years having similar activity counts on actigraphy.⁵⁴ Minor modification by site effect is not unusual and may be because of different socioeconomic composition of the participants, walkability of the areas of recruitment, and other factors. Stratification by resting O₂ saturation showed a more pronounced and significant result in participants with normal O₂ saturation. This might be explained with activity being associated more with percent emphysema than gas exchange in our population with a low to moderate degree of emphysema. In this manner, emphysema may contribute to cardiopulmonary failure,⁵⁵ likely producing a heart failure-like phenotype absent marked fluid overload, with reduced activity levels and increased dyspnea, even in the absence of airflow limitation.

The significant inverse association between percent emphysema and objectively assessed physical activity in daily life persisted among never smokers. This is particularly notable because this finding suggests that increasing percent emphysema may have a negative impact on physical activity in daily life independent of

an individual's direct exposure to cigarette smoke and related airway obstruction. Possible mechanisms for development of emphysema independent of direct proinflammatory stimuli of cigarette smoke on airways are thought to be mediated by inflammatory factors causing endothelial dysfunction, such as tumor necrosis factor- α , lipopolysaccharides, ionizing radiation, vascular endothelial growth factor receptor inhibition, or excess ceramides.⁵⁶ A hypothesized genetic cause of emphysema is the increase of α 1-antitrypsin degradation through α -mannosidase. Gene variants coding for α -mannosidase have been identified as a possible genetic cause of emphysema in Hispanics, African Americans, and Chinese, according to a genome-wide association study in MESA. In the same study, additional gene variants have been identified as a possible cause of emphysema in the general population.⁵⁷

In contrast, percent emphysema was not significantly associated with self-reported physical activity level. Self-reported activity questionnaires are the most widely used method to assess physical activity in epidemiologic research.⁴² However, in COPD, questionnaires have performed poorly in assessing physical activity.³⁴ This could be because of biased response in questionnaires, possibly with overreporting of self-reported activity level among those less active.⁵⁸ Also, low- or moderate-intensity activities for a longer duration may not be equivalent to strenuous activity for a shorter duration, despite equal resulting metabolic equivalent of task (MET) sums. Further inaccuracies include using MET hours through definition of association of MET to different tasks and ignoring both body weight and mechanical efficiency.⁴³ Furthermore, self-reported activity questionnaires typically perform worse in multiethnic samples such as the present.⁵⁹ Nonetheless, the overall observation is consistent with the clinically

perceived and classic phenotype of activity-limited patients with emphysema who deny symptoms.³

Our study has several limitations. First, actigraphy recording used a uniaxial and not a triaxial actigraphy, and there is no literature describing a minimally clinically important difference for actigraphy scores. However, our device has been shown to have a good correlation to the gold standard of the measurement of active energy expenditure, doubly labeled water.^{43,58} Second, CT scans were performed on different scanners across the study. Although the protocol was highly standardized with tight quality control and phantom data showing no substantial differences across the limited number of sites, there were differences in percent emphysema measurements by scanner manufacturer.³⁸ We addressed this problem by including scanner model as a covariate in our multivariable analyses. Nonetheless, scanner effects might account for the lack of association at two sites, as might chance. Third, the study was cross-sectional, and we infer that greater percent emphysema may contribute to less activity; however, we cannot rule out that the reverse may be true. Finally, residual confounding, particularly by socioeconomic status and smoking cannot be entirely excluded, as cannot unmeasured confounding. Nonetheless, precise measures were available on major confounders, including cardiovascular function.

In conclusion, greater percent emphysema on CT scan was associated with reduced physical activity levels in daily life assessed objectively, independent of lung function, among smokers and never smokers. Furthermore, greater percent emphysema on CT scan was also associated with reduced physical activity levels in daily life assessed objectively among participants without COPD on spirometry. Emphysema may contribute to reduced physical activity levels in daily life among patients with and without COPD.

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Additional information: The e-Appendices, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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