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Title

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Permalink

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Journal

JAMA, 315(7)

ISSN

0098-7484

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Publication Date

2016-02-01

DOI

10.1001/jama.2016.0518

Peer reviewed

Original Investigation

Association Between Interstitial Lung Abnormalities and All-Cause Mortality

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IMPORTANCE Interstitial lung abnormalities have been associated with lower 6-minute walk distance, diffusion capacity for carbon monoxide, and total lung capacity. However, to our knowledge, an association with mortality has not been previously investigated.

OBJECTIVE To investigate whether interstitial lung abnormalities are associated with increased mortality.

DESIGN, SETTING, AND POPULATION Prospective cohort studies of 2633 participants from the FHS (Framingham Heart Study; computed tomographic [CT] scans obtained September 2008-March 2011), 5320 from the AGES-Reykjavik Study (Age Gene/Environment Susceptibility; recruited January 2002-February 2006), 2068 from the COPDGene Study (Chronic Obstructive Pulmonary Disease; recruited November 2007-April 2010), and 1670 from ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; between December 2005-December 2006).

EXPOSURES Interstitial lung abnormality status as determined by chest CT evaluation.

MAIN OUTCOMES AND MEASURES All-cause mortality over an approximate 3- to 9-year median follow-up time. Cause-of-death information was also examined in the AGES-Reykjavik cohort.

RESULTS Interstitial lung abnormalities were present in 177 (7%) of the 2633 participants from FHS, 378 (7%) of 5320 from AGES-Reykjavik, 156 (8%) of 2068 from COPDGene, and in 157 (9%) of 1670 from ECLIPSE. Over median follow-up times of approximately 3 to 9 years, there were more deaths (and a greater absolute rate of mortality) among participants with interstitial lung abnormalities when compared with those who did not have interstitial lung abnormalities in the following cohorts: 7% vs 1% in FHS (6% difference [95% CI, 2% to 10%]), 56% vs 33% in AGES-Reykjavik (23% difference [95% CI, 18% to 28%]), and 11% vs 5% in ECLIPSE (6% difference [95% CI, 1% to 11%]). After adjustment for covariates, interstitial lung abnormalities were associated with a higher risk of death in the FHS (hazard ratio [HR], 2.7 [95% CI, 1.1 to 6.5]; $P = .03$), AGES-Reykjavik (HR, 1.3 [95% CI, 1.2 to 1.4]; $P < .001$), COPDGene (HR, 1.8 [95% CI, 1.1 to 2.8]; $P = .01$), and ECLIPSE (HR, 1.4 [95% CI, 1.1 to 2.0]; $P = .02$) cohorts. In the AGES-Reykjavik cohort, the higher rate of mortality could be explained by a higher rate of death due to respiratory disease, specifically pulmonary fibrosis.

CONCLUSIONS AND RELEVANCE In 4 separate research cohorts, interstitial lung abnormalities were associated with a greater risk of all-cause mortality. The clinical implications of this association require further investigation.

JAMA. 2016;315(7):672-681. doi:10.1001/jama.2016.0518

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Group Information: A list of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators was published in the *N Engl J Med*. 2010;363(12):1128-1138 and of the COPDGene Investigators, *JAMA Intern Med*. 2015;175(9):1539-1549.

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Interstitial lung abnormalities are defined as specific patterns of increased lung density noted on chest computed tomography (CT) scans identified in participants with no prior history of interstitial lung disease. In studies of adults, interstitial lung abnormalities are present in approximately 2% to 10% of research participants¹⁻⁷ (and 7% of a general population sample)⁶ and are associated with reductions in lung capacity,^{1,2,6} exercise capacity,⁸ gas exchange,^{5,6} and genetic abnormalities^{5,9} common to patients with familial interstitial pneumonia and idiopathic pulmonary fibrosis (IPF).¹⁰ These data suggest that interstitial lung abnormalities may, in some cases, represent an early and/or mild form of pulmonary fibrosis.

While radiologic abnormalities, worsening pulmonary function, and decreased exercise tolerance are important diagnostic features of IPF¹¹ (the most common and severe form of pulmonary fibrosis),¹² IPF is also associated with a high mortality rate.^{13,14} Although the survival rate of people with IPF appears to have increased slightly in recent years,¹⁴ median survival time after diagnosis is 3 to 5 years,^{13,14} which is worse than that of most malignancies.¹⁵ Given the other correlations between IPF and interstitial lung abnormalities, we hypothesized that the presence of interstitial lung abnormalities would be associated with an increased rate of mortality.

Methods

Study Design and Mortality Ascertainment

Protocols for participant enrollment and phenotyping in the FHS (Framingham Heart Study), the AGES-Reykjavik Study (Age Gene/Environment Susceptibility), the COPDGene Study (Genetic Epidemiology of COPD), and the ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) have been described previously.^{2,6,16,17} In all cohorts, race was self-reported based on fixed categories. Analyses were adjusted for race, given the known influence of race on mortality in other pulmonary diseases. In all cohorts, mortality refers to all-cause mortality unless otherwise indicated. Written informed consent was obtained from all participants. The institutional review boards of the Brigham and Women's Hospital and individual participating centers approved this study.

The FHS is a longitudinal study originally designed to identify risk factors for cardiovascular disease in the general population.¹⁸ The AGES-Reykjavik study is a longitudinal birth cohort from the Reykjavik Study (established in 1967) that now includes men and women born in Reykjavik, Iceland, between 1907 and 1935 who are monitored by the Icelandic Heart Association. The COPDGene study is a multicenter longitudinal study designed to identify the epidemiologic and genetic risk factors for chronic obstructive pulmonary disease (COPD). Participants with known active lung diseases other than asthma, emphysema, or COPD were excluded.¹⁹ For this analysis, COPDGene refers to the first 2508 participants.² ECLIPSE is a multicenter and multinational 3-year observational study of 2164 COPD patients (GOLD [Global Initiative for Chronic Obstructive Lung Disease]

stages 2-4)²⁰ and 582 controls aged 40 to 75 years.²¹ Participants with known respiratory disorders other than COPD were excluded.²¹ For these analyses, only the 2164 COPD participants from ECLIPSE were included because longitudinal mortality data from control participants was not collected (see eMethods in the Supplement for further details on cohort study design).

Chest CT Analysis

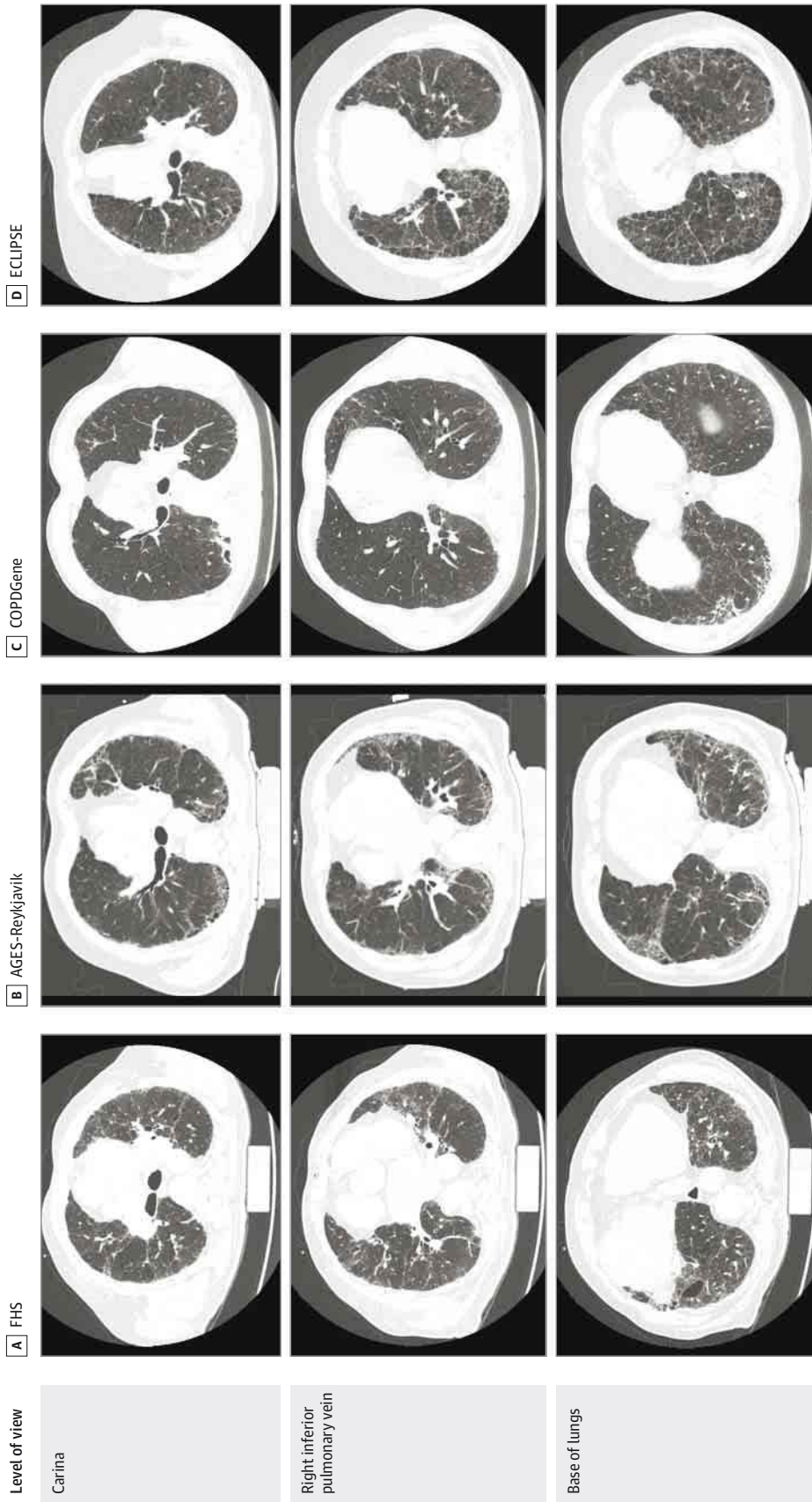
The methods for chest CT characterization for interstitial lung abnormalities in the FHS and COPDGene cohorts^{2,6} were used to characterize interstitial lung abnormalities in AGES-Reykjavik and ECLIPSE (eMethods in the Supplement). In all cohorts, the chest CT scans were evaluated by as many as 3 readers (2 chest radiologists and 1 pulmonologist) using a sequential reading method.²² Interstitial lung abnormalities were defined as nondependent changes affecting more than 5% of any lung zone, including reticular or ground-glass abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, or traction bronchiectasis (eFigure 1 in the Supplement). Chest CT images with focal or unilateral ground-glass attenuation, focal or unilateral reticulation, or patchy ground-glass abnormalities (<5% of any lung zone) were considered indeterminate (eFigure 2 in the Supplement). To explore the association between undiagnosed pulmonary fibrosis and mortality, an additional subset of interstitial lung abnormalities with pulmonary parenchymal architectural distortion diagnostic of fibrotic lung disease (definite fibrosis; Figure 1) was created.⁶ Quantitative total lung volume and emphysema (percentage < -950 Hounsfield units [HU]), where reported, were measured with Airway Inspector.²³ Coronary artery calcium scores were calculated using the traditional Agatston scoring method.²⁴

Statistical Analyses

In all cohorts except the FHS, association analyses between pairs of variables were conducted using Fisher exact tests for categorical variables and 2-tailed *t* tests for continuous variables. In the FHS, all analyses accounted for familial relationships using generalized estimating equations.²⁵ To evaluate the association between interstitial lung abnormalities and mortality, logistic regression was used to analyze rates of absolute mortality and Cox proportional hazards models were used to analyze time to mortality, with robust standard errors to account for familial correlation in FHS. In Cox models, all variables were assessed and none violated the proportional hazards assumption. Multivariable models included adjustments for age, race, sex, body mass index, pack-years of smoking, smoking status (current vs former), and GOLD stage (if available).

Additional covariates were measures of coronary artery disease (CAD [self-report of CAD or adjudicated in the FHS and also of coronary artery calcium scores]) and history of self-reported nondermatologic malignancy. In the COPD cohorts, additional analyses were implemented using the BODE index (body mass index, air flow obstruction, dyspnea, and exercise)²⁶ as an alternative measure of COPD severity. All *P* values were 2-sided and a level of .05 was considered

Figure 1. Representative Examples of Definite Fibrosis from the FHS, AGES-Reykjavik, COPDGene, and ECLIPSE Studies



Chest computed tomographic (CT) axial images of 4 participants, one from each cohort, with interstitial lung abnormalities with definite fibrosis. Definite fibrosis is defined as pulmonary parenchymal architectural distortion diagnostic of fibrotic lung disease.⁶ Panel A demonstrates subpleural reticular markings, ground glass abnormalities, and traction bronchiectasis in all images. Panel B shows more advanced fibrosis with subpleural reticular markings, traction bronchiectasis, and honeycombing. Panel C shows upper lobe-predominant emphysema with fibrosis; evidence of subpleural reticular changes and traction bronchiectasis are most prominent in the top and bottom images. The white spot in the center of the left lung field is the dome of the left diaphragm. Panel D demonstrates severe emphysema combined with fibrosis; subpleural reticular markings and traction bronchiectasis are seen in all 3 images.

statistically significant. SAS version 9.4 (SAS Institute Inc) was used for analyses in the AGES-Reykjavik, COPDGene, and ECLIPSE cohorts and R version 3.1.3 was used for analyses in the FHS.

Results

Of the 2764 participants in the FHS (Framingham Heart Study Multidetector Computed Tomography 2 study between September 2008 and March 2011), 2633 (95%) participants had chest CT and mortality reports as of December 2013 (median follow-up time, 4.0 years) and were included. In AGES-Reykjavik (of the 5764 participants recruited between January 2002 and February 2006), 5320 (92%) had chest CT and mortality data as of December 2013 (median follow-up time, 8.9 years) and were included. Additionally, cause-of-death data obtained from death certificates (*International Classification of Diseases, Ninth Revision [ICD-9]* and *ICD-10* codes; see eMethods in the Supplement) were collected in December 2009 (median follow-up time, 5.3 years). In COPDGene (of the first 2508 participants recruited between November 2007 and April 2010), 2068 (82%) had chest CT and mortality information as of October 2015 (median follow-up time, 6.5 years) and were included. In ECLIPSE (of the 2164 participants recruited between December 2005 and December 2006), 1670 (77%) had chest CT and mortality information (median follow-up time, 2.9 years) and were included.

Interstitial Lung Abnormality Prevalence

The prevalence of participants with interstitial lung abnormalities, without interstitial lung abnormalities, and with indeterminate interstitial lung abnormality status in the FHS⁶ and COPDGene cohorts² have been previously reported and similar percentages were noted in these subsets (in the FHS, interstitial lung abnormalities were present in 177 [7%], were not present in 1370 [52%], and were indeterminate in 1086 [41%]; in COPDGene, interstitial lung abnormalities were present in 156 [8%], were not present in 1173 [57%], and were indeterminate in 739 [36%]; Table 1; Figure 2). In the AGES-Reykjavik cohort, interstitial lung abnormalities were present in 378 (7%), were not present in 3216 (61%), and were indeterminate in 1726 (32%) (Table 1; Figure 2). In ECLIPSE, interstitial lung abnormalities were present in 157 (9%), were not present in 528 (32%), and were indeterminate in 985 (59%) (Table 1; Figure 2). Additional results about reading methodology are included in eResults (in the Supplement).

Baseline Characteristics and Interstitial Lung Abnormalities

The baseline characteristics of the participants from all 4 cohorts, stratified by the presence or absence of interstitial lung abnormalities, are presented in Table 1. Baseline characteristics of AGES-Reykjavik and ECLIPSE participants, including those who were indeterminate for interstitial lung abnormalities, are included in eTable 1 and eTable 2 (in the Supplement). Across all cohorts, interstitial lung abnormalities were associated with older age when compared with the absence of interstitial lung abnormalities. As noted in the COPDGene

study,² among participants in ECLIPSE,²³ interstitial lung abnormalities (when compared with absence of interstitial lung abnormalities) were associated with less-severe airway obstruction, as demonstrated by a higher forced expiratory volume in the first second (FEV₁) and FEV₁/forced vital capacity (FVC) ratio. In contrast, in the FHS, interstitial lung abnormalities were associated with a higher prevalence of COPD and a lower FEV₁/FVC ratio.

Mortality and Interstitial Lung Abnormalities

For all cohorts except the COPDGene Study, the absolute mortality rates were significantly higher among participants with interstitial lung abnormalities when compared with those who did not have interstitial lung abnormalities (Table 2). In the FHS, 7% (12 deaths) of participants with interstitial lung abnormalities died over 4 years compared with 1% (12 deaths) of those who did not have interstitial abnormalities; in the AGES-Reykjavik study, 56% (210 deaths) of participants with interstitial lung abnormalities vs 33% (1065 deaths) of participants without interstitial lung abnormalities died over 8.9 years. Among smokers with and without COPD from COPDGene, 16% (25 deaths) of participants with interstitial lung abnormalities died vs 11% (133 deaths) of participants without interstitial lung abnormalities over 6.5 years. Among smokers with COPD from ECLIPSE, 11% (18 deaths) of participants with interstitial lung abnormalities died over 2.9 years vs 5% (27 deaths) of participants without interstitial lung abnormalities. These findings resulted in a 6% difference (95% CI, 2%-10%) in the FHS, a 23% difference (95% CI, 18%-28%) in AGES-Reykjavik, a 5% difference (95% CI, -1% to 11%) in COPDGene, and a 6% difference (95% CI, 1% to 11%) in ECLIPSE in the absolute mortality rates associated with interstitial lung abnormalities. The mortality rates among participants with indeterminate status were 2% (24 deaths) in FHS, 43% (750 deaths) in AGES-Reykjavik, 13% (99 deaths) in COPDGene and 12% (120 deaths) in ECLIPSE (eTable 5 in the Supplement).

When compared with participants who did not have interstitial lung abnormalities in multivariable Cox proportional hazards models adjusted for age, sex, race, body mass index, pack-years of smoking, current smoking status, and GOLD stage (where available), interstitial lung abnormalities were associated with a higher risk of death in the FHS (hazard ratio [HR], 2.7 [95% CI, 1.1-6.5]; $P = .03$), AGES-Reykjavik (HR, 1.3 [95% CI, 1.2-1.4]; $P < .001$), COPDGene (HR, 1.8 [95% CI, 1.1-2.8]; $P = .01$), and ECLIPSE (HR, 1.4 [95% CI, 1.1-2.0]; $P = .02$) (Figure 3). Similar results were seen, with higher odds of death, when using multivariable logistic regression (eTable 3 in the Supplement). For further analyses regarding definite fibrosis and participants who were indeterminate for interstitial lung abnormalities see eTable 5, eTable 6, and eFigure 3 in the Supplement.

Mortality, Interstitial Lung Abnormalities, and Never Smokers

To determine if unmeasured differences in smoking behavior among smokers could explain the associations between interstitial lung abnormalities and mortality, associations between interstitial lung abnormalities and mortality in never

Table 1. Baseline Characteristics of Participants From Framingham Heart, AGES-Reykjavik, COPDGene, and ECLIPSE Studies Stratified by Interstitial Lung Abnormality Status

Variable	FHS ^{a,b} (N = 2633)			AGES-Reykjavik ^b (N = 5320)			COPDGene ^{a,b} (N = 2068)			ECLIPSE (N = 1670)		
	No ILA 1370 ^c	ILA 177 ^c	P Value	No ILA 3216 ^c	ILA 378 ^c	P Value	No ILA 1173 ^c	ILA 156 ^c	P Value	No ILA 528 ^c	ILA 157 ^c	P Value
Age, mean (SD), y	56 (11)	70 (12)	<.001	76 (5)	78 (6)	<.001	60 (9)	64 (9)	<.001	62 (7)	64 (8)	<.001
Women, No. (%)	675 (49)	89 (50)	.81	1910 (59)	172 (45)	<.001	564 (48)	80 (51)	.50	182 (34)	41 (26)	.05
White race, No. (%)	1370 (100)	177 (100)	NA	3216 (100)	378 (100)	NA	929 (79)	112 (72)	.04	515 (98)	154 (98)	1.0
Body mass index, mean (SD)	29 (6)	28 (5)	.38	27 (4)	27 (5)	.58	28 (6)	30 (7)	.008	27 (6)	26 (5)	.09
Smoking pack-years, median (IQR)	11 (4-23)	19 (9-33)	<.001	0 (0-16)	11 (0-29)	<.001	40 (30-54)	44 (30-64)	.06	45 (33-62)	43 (30-60)	.15
Current smokers, No. (%) ^c	73 (5)	17 (10)	.04	374 (12)	69 (18)	<.001	505 (43)	71 (46)	.61	202 (38)	72 (46)	.10
FEV ₁ % predicted, mean (SD)	98 (15)	98 (17)	.49				75 (28)	78 (22)	.10	44 (15)	47 (14)	.02
FVC % predicted, mean (SD)	101 (13)	101 (15)	.99				87 (19)	88 (17)	.49	79 (19)	80 (20)	.78
FEV ₁ /FVC ratio, mean (SD)	75 (7)	73 (7)	<.001				64 (18)	67 (14)	.03	45 (12)	48 (11)	.006
COPD, No. (%) ^d	84 (6)	19 (12)	.01				561 (41)	63 (33)	.02	528 (100)	157 (100)	NA
GOLD stage, No. (%) ^e			0.04						<.001			.01
Unclassified ^f	55 (4)	6 (4)					87 (7)	17 (11)				
Stage 0	983 (76)	105 (66)					508 (43)	63 (41)				
Stage 1	175 (14)	29 (18)					82 (7)	21 (14)				
Stage 2	80 (6)	18 (11)					230 (20)	38 (25)		241 (46)	76 (48)	
Stage 3	4 (0.3)	1 (1)					167 (14)	11 (7)		219 (41)	74 (47)	
Stage 4							99 (8)	5 (3)		68 (13)	7 (5)	
TLC, L, mean (SD) ^g	5.2 (1.2)	4.5 (1.3)	<.001	NA	NA		5.8 (1.4)	5.2 (1.4)	<.001	5.9 (1.5)	5.7 (1.4)	.16

Abbreviations: AGES, Age Gene/Environment Susceptibility; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; FEV₁, forced expiratory volume in the first second; FHS, Framingham Heart Study; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ILA, interstitial lung abnormality; IQR, interquartile range; NA, not available; TLC, total lung capacity.

^a Baseline characteristics from the FHS and COPDGene are similar to what has been previously published and are now limited to participants with chest CT and mortality data.^{2,6}

^b Missing spirometry data for 91 (6%) participants in FHS, 1 (0.05%) participant in COPDGene, and for approximately 80% of participants in AGES-Reykjavik (categorical data not shown).

^c Missing current smoking status data for 3 (0.2%) participants in FHS.

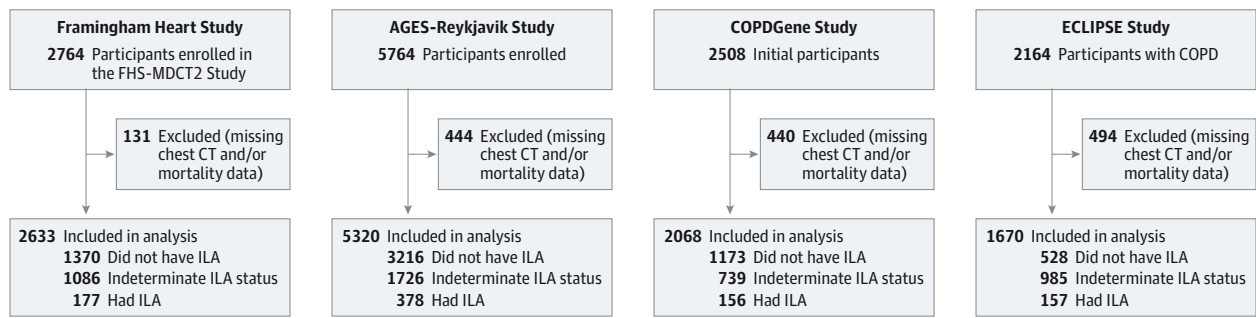
^d COPD category includes participants with GOLD stage 2 or greater.

^e Missing GOLD stage data for 1 (0.05%) participant in COPDGene.

^f GOLD unclassified category indicates FEV₁ of less than 80% and FEV₁/FVC ratio of 0.70 or greater.

^g TLC measurements were NA for AGES-Reykjavik (categorical data not shown) and missing TLC data for 93 (6%) participants in FHS and for 1 (0.05%) participant in COPDGene. Quantitative CT measurements for TLC were made using Airway Inspector.

Figure 2. Participant Flow for the FHS, AGES-Reykjavik, COPDGene, and ECLIPSE Studies



AGES indicates the Age Gene/Environment Susceptibility; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; FHS-MDCT2, Framingham Heart Study Multidetector Computed Tomography 2; ICD, International Classification of Diseases; ILA, interstitial lung abnormalities.

Table 2. Association Between Interstitial Lung Abnormalities and Mortality

	FHS (N = 2633)		AGES-Reykjavik (N = 5320)		COPDGene (N = 2068)		ECLIPSE (N = 1670)	
Median follow-up time, (IQR), y	4.0 (3.3 to 4.6)		8.9 (6.7 to 9.9)		6.5 (6.2 to 6.7)		2.9 (2.9 to 2.9)	
Mortality, No. (%)								
No ILA	12 (1)		1065 (33)		133 (11)		27 (5)	
ILA	12 (7)		210 (56)		25 (16)		18 (11)	
Mortality difference % (95% CI)	6 (2 to 10)		23 (18 to 28)		5 (-1 to 11)		6 (1 to 11)	
Models	HR (95% CI) ^a	P Value	HR (95% CI) ^a	P Value	HR (95% CI) ^a	P Value	HR (95% CI) ^a	P Value
Unadjusted model	7.7 (3.7-16.1)	<.001	1.4 (1.3-1.6)	<.001	1.5 (0.98-2.3)	.08	1.5 (1.1-2.1)	.005
Adjusted model ^b	2.7 (1.1-6.5)	.03	1.3 (1.2-1.4)	<.001	1.8 (1.1-2.8)	.01	1.4 (1.1-2.0)	.02
Plus % emphysema ^{c,d}	2.6 (1.03-6.7)	.04			1.9 (1.2-3.0)	.007	1.4 (1.03-2.0)	.03
Plus coronary disease ^{d,e}	2.2 (0.9-5.9)	.10	1.2 (1.1-1.3)	<.001	1.5 (0.9-2.0)	.12	1.7 (1.1-2.4)	.008
Plus cancer history ^{d,e}	2.6 (1.1-6.2)	.03	1.25 (1.2-1.3)	<.001	1.8 (1.1-2.8)	.008		

Abbreviations AGES, Age Gene/Environment Susceptibility; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; FHS, Framingham Heart Study; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; ILA, interstitial lung abnormality; IQR, interquartile range.

^a All HRs are for the comparison between participants with and without interstitial lung abnormalities.

^b Adjusted HRs include adjustments for age, sex, race, BMI (calculated as weight in kilograms divided by height in meters squared), pack-years of smoking, current or former smoking status, and GOLD stage of COPD (where available).

^c Adjusted HRs include adjustments for age, sex, race, BMI, pack-years of smoking, current or former smoking status, GOLD stage of COPD, and amount of emphysema (% < -950 Hounsfield units [HU]).

^d See eTable 4 (Supplement) for variables used in addition to the baseline adjusted model.

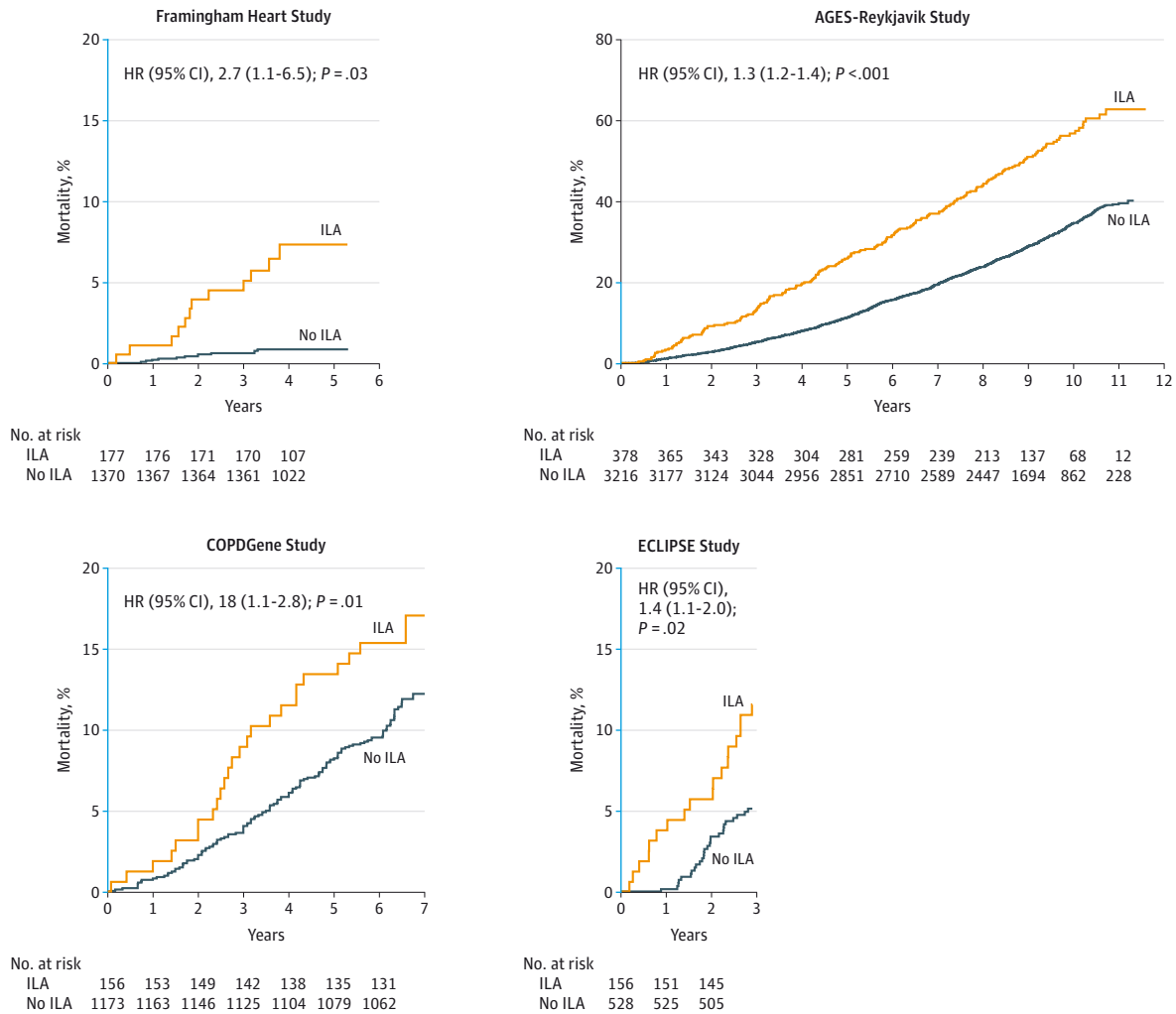
^e Adjusted HRs include adjustments for age, sex, race, BMI, pack-years of smoking, current or former smoking status, GOLD stage of COPD (except in the AGES-Reykjavik where GOLD stage was not available), history of coronary artery disease, and coronary calcium score.

smokers from both the FHS and AGES-Reykjavik cohorts were analyzed. In the FHS, 6% of never smokers with interstitial lung abnormalities died compared with 0.3% of never smokers who did not have interstitial abnormalities, a difference of 5.7% (95% CI, 1%-12%) and an HR of 19.9 (95% CI, 5.1-78.1; $P < .001$). In AGES-Reykjavik, 52% of never smokers with interstitial lung abnormalities died compared with 31% of those who did not have interstitial lung abnormalities, a difference of 21%, (95% CI, 11%-31%) and an HR of 1.3 (95% CI, 1.1-1.4; $P = .002$).

Mortality, Interstitial Lung Abnormalities, COPD, CAD, and Cancer

To determine if the presence of other chronic diseases could explain the associations between interstitial lung abnormalities and mortality, analyses were performed in each cohort, additionally adjusting for the percentage of emphysematous lung, measures of CAD or reports of malignancy (where available). The association between interstitial lung abnormalities and mortality remained statistically significant after additional ad-

Figure 3. Mortality Rates by ILA Status for the Framingham Heart Study, AGES-Reykjavik, COPDGene, and ECLIPSE Studies



Blue segments of y-axes indicate mortality range from 0% to 20%. P values included in each panel are associated with hazard ratios (HRs [95% CIs]) from the adjusted Cox proportional hazards model including adjustments for age, sex, race, body mass index, pack-years of smoking, current or former smoking status, and GOLD stage of COPD (except in AGES-Reykjavik where GOLD stage

was not available). AGES indicates the Age Gene/Environment Susceptibility; COPD, chronic obstructive pulmonary disease; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ILA, interstitial lung abnormalities.

adjustments for disease-specific measures (Table 2), except in the FHS and COPDGene, in which additional adjustment for adjudicated or self-report of CAD and coronary artery calcium scores resulted in no association (Table 2). Similar associations between interstitial lung abnormalities and mortality were seen in COPDGene and ECLIPSE studies when adjusting for BODE index (eResults in the Supplement). Additionally, the absolute mortality rates of each GOLD stage were consistently greater among participants with interstitial lung abnormalities compared with those who did not have interstitial lung abnormalities (eFigure 4 in the Supplement).

Mortality, Interstitial Lung Abnormalities, and Cause of Death

To determine the causes of death among participants with interstitial lung abnormalities, data from the AGES-Reykjavik

cohort were assessed (where causes-of-death were available) from death certificates on an interim follow-up date (December 31, 2009, median follow-up time, 5.4 years). Participants with interstitial lung abnormalities in the AGES-Reykjavik cohort were more likely to die of a respiratory cause (13%) compared with those who did not have interstitial lung abnormalities (4%) or those with indeterminate status (6%; see Table 3). After adjusting for covariates (age, sex, race, BMI, pack-years of smoking, current smoking status), participants with interstitial lung abnormalities had a higher odds ratio (OR) of death from a respiratory cause (OR, 2.4 [95% CI, 1.7-3.4]; $P < .001$) compared with those who did not have interstitial lung abnormalities. Results were similar when comparing participants with interstitial lung abnormalities with those who were indeterminate for interstitial lung abnormalities (eResults in the Supplement). After adjusting

Table 3. Mortality, Interstitial Lung Abnormalities, and Cause of Death for the AGES-Reykjavik Study

	No. (%) ^a			
	ILA	Indeterminate	No ILA	Overall
No. of participants	378	1726	3216	5320
Deaths				
Total	115 (100)	382 (100)	468 (100)	965
Cardiovascular ^b	48 (42)	161 (42)	204 (44)	413
Cancer ^c	29 (25)	111 (29)	151 (32)	291
Respiratory ^d	15 (13)	22 (6)	20 (4)	57
Pulmonary fibrosis	7	1	0	8
Other	8	21	20	49
Other ^e	23 (20)	88 (23)	93 (20)	204

Abbreviations: AGES, Age Gene/Environment Susceptibility; *ICD*, *International Classification of Diseases*; ILA, interstitial lung abnormality.

^a Percentages were all rounded to the nearest whole number. Some of the percentages may sum to greater than 100%.

^b Cardiovascular deaths included the following: *ICD-9* codes 390-459 and *ICD-10* codes I00-I99.

^c Cancer deaths included the following: *ICD-9* codes 140-239 and *ICD-10* codes C00-D48.

^d Respiratory deaths included the following: *ICD-9* codes 460-519 and *ICD-10* codes J00-J99.

^e All causes of death not contained in these *ICD-9* and *ICD-10* codes were included in the category of *other*.

for covariates, there was no association between interstitial lung disease status and death due to cardiovascular disease, cancer, or other causes. Among participants who died of a respiratory cause, interstitial lung abnormalities were associated with an increased rate of death from pulmonary fibrosis ([47%], 7 of the 15 respiratory deaths among those with interstitial lung abnormalities were from pulmonary fibrosis; Table 3). Of the 8 deaths due to pulmonary fibrosis, 5 participants had evidence of definite fibrosis on chest CT, 2 had interstitial lung abnormalities without definite fibrosis, and 1 participant was indeterminate for interstitial lung abnormality status. Only 1 of these participants had previously diagnosed pulmonary fibrosis at the time of the CT scan.

Discussion

In this study, interstitial lung abnormalities, a set of imaging abnormalities noted among approximately 7% of adult participants,⁶ were associated with a higher rate of all-cause mortality. The associations between interstitial lung abnormalities and mortality were not attenuated after adjustment for smoking, cancer, COPD, or CAD. Among an older population from Iceland, the higher rate of mortality in those with interstitial lung abnormalities was associated with a higher rate of death from respiratory failure and pulmonary fibrosis. These findings, in conjunction with those previously published,^{2,6,8} demonstrate that despite often being undiagnosed and asymptomatic,^{2,6} interstitial lung abnormalities may be associated with lower survival rates among older persons.

This study builds on prior studies,⁷ demonstrating that interstitial lung abnormalities were associated with older age, smoking, and a restrictive lung deficit. The findings in ECLIPSE are similar to those previously reported in COPDGene,² which demonstrated that among smokers with COPD, interstitial lung abnormalities were identified among those with more preserved FEV₁/FVC ratios. Although COPD was associated with interstitial lung abnormalities in

the FHS, this association may be related to older age and history of smoking, which are common in both COPD and interstitial lung abnormalities.

It is important to consider the higher mortality rates associated with interstitial lung abnormalities in context. The mortality rates associated with interstitial lung abnormalities are lower than the well-documented mortality rates associated with clinically identified IPF.^{13,14} In addition, although data from the AGES-Reykjavik cohort demonstrated that interstitial lung abnormalities were associated with death caused by respiratory failure and pulmonary fibrosis, respiratory failure death is more common in patients with IPF.^{11,27}

The absolute mortality rates differed between the cohorts. This was due, in part, to differences in recruitment criteria and follow-up time. Compared with the FHS (which included a general population sample of adults), the higher absolute mortality rates in COPDGene and ECLIPSE are likely explained by a longer follow-up time (COPDGene) and the inclusion of greater numbers of COPD patients (COPDGene and ECLIPSE). Although the FHS and AGES-Reykjavik participants were recruited from community-dwelling men and women, the higher mortality rates in the AGES-Reykjavik cohort are likely explained by the older age and longer follow-up times of the average participants in this cohort.

This study has some limitations. First, participants with interstitial lung abnormalities were older than those without interstitial lung abnormalities.⁷ Therefore, residual confounding is possible even after adjustment. Second, further study is needed to determine the prognostic significance of interstitial lung abnormalities in younger age groups. Third, further studies are needed to identify imaging findings on CT scan that may simply reflect a normal variant of the aging lung²⁸ rather than an early stage of progressive interstitial lung disease. Fourth, interstitial lung abnormalities were associated with a higher risk of death among never smokers from 2 cohorts; however, the large hazard of mortality associated with interstitial lung abnormalities in the FHS among never smokers was driven by a small number of deaths. Fifth,

although an association between interstitial lung abnormalities and increased risk of respiratory death was identified in the AGES-Reykjavik study, data regarding the cause of death were not available from other cohorts. Sixth, despite the correlations presented between research participants with interstitial lung abnormalities and patients with IPF (as well as other forms of interstitial lung disease), this study cannot explain the large discrepancy between the prevalence of interstitial lung abnormalities (7% in general population samples⁶; Table 1) and the reported prevalence of IPF (\approx 0.002%-0.04% of the general population)²⁹⁻³¹ and interstitial lung disease. Of note, the prevalence of definite fibrosis in each cohort (\approx 1.6%-2.4%) is similar to the prevalence of IPF noted in an autopsy study of 510 cases from New Mexico (1.8%) even though IPF was suspected as a cause of death in less than one-tenth of these cases.³² Seventh, unmeasured confounders could explain these findings. Eighth, there are differences in the estimates of the association of interstitial

lung abnormalities on mortality in unadjusted and adjusted models in the FHS. Ninth, although data on interobserver variability in interstitial lung abnormality scoring are presented, data on intraobserver variability in interstitial lung abnormality scoring were not recorded.

Follow-up studies should determine the risk factors for and the events that lead to death among persons with interstitial lung abnormalities. Given the ability to treat more advanced stages of pulmonary fibrosis,^{33,34} future clinical trials attempting to reduce the overall mortality associated with pulmonary fibrosis should consider including early stages of the disease.

Conclusions

In 4 separate research cohorts, interstitial lung abnormalities were associated with a greater risk of all-cause mortality. The clinical implications of this association require further investigation.

ARTICLE INFORMATION

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Author Contributions: Dr Hunninghake had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Putman, Hatabu, and Araki contributed equally to this article.

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Statistical analysis: Putman, Gao, Dupuis, Latourelle, Zazueta, Ross, Aspelund, Kinney, Rosas, Hunninghake.

Obtained funding: Gudmundsson, Eiríksdóttir,

Hoffmann, Harris, Gudnason, Silverman, O'Connor, Washko, Rosas, Hunninghake.

Administrative, technical, or material support:

Hatabu, Gudmundsson, Okajima, Coxson, Fernandez, Ross, Estépar, Sigurdsson, Gudmundsson, Eiríksdóttir, Aspelund, Hokanson, Harris, Silverman, Washko, Hunninghake.

Study supervision: Hatabu, Gudmundsson, Dupuis,

Budoff, Silverman, O'Connor, Rosas, Hunninghake.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Budoff reports receipt of grant support from General Electric. Dr Celli reports receipt of a research grant support from AstraZeneca and serving on advisory boards for GlaxoSmithKline, Boehringer-Ingelheim, AstraZeneca, Almirall, and Takeda. Dr Coxson reports receipt of grant support from GlaxoSmithKline and serving on the advisory boards of GlaxoSmithKline and Samsung. Dr Diaz reports having served as a speaker for Novartis. Dr Hatabu reports receipt of research grant support from Canon USA Inc and Toshiba Medical Inc. Dr Hunninghake reports having consulted for Medna LLC and the George Lehman Group and serving on the board of advisors for Patients Like Me and Genentech. Dr Nishino reports receipt of grant support from Canon Inc and serving as a consultant for Bristol-Myers Squibb. In the past 3 years, Dr Silverman reports receipt of honoraria and consulting fees from Merck, grant support and consulting fees from GlaxoSmithKline, and honoraria from Novartis. Dr Washko reports having consulted for Merck and GlaxoSmithKline.

Funding Support: Dr Putman is supported by a National Institutes of Health (NIH) grant (T32 HL007633). Dr Gudmundsson is supported by a project grant from the Icelandic Research Fund (141513-051) and from the Landspítali Scientific Fund (A-2015-030). Dr Nishino is supported by a National Cancer Institute grant (1K23CA157631). Dr Cho is supported by 2 NIH grants (K08 HL097029 and R01 HL13264). Dr El-Chemaly is supported by an NIH grant (R21 HL119902). Dr San Jose Estépar is supported by 3 NIH grants (K25 HL104085, R01 HL116931, and R01 HL116473). Dr Diaz is supported by an NIH grant (K01 HL118714). This work was partially supported by the National Heart,

Lung, and Blood Institute's Framingham Heart Study contract (N01-HC-25195). COPDGene is supported by 2 NIH grants (R01 HL089897 and R01 HL089856). The ECLIPSE study was sponsored by GlaxoSmithKline (NCT00292552; GSK code SCO104960). The AGES (Age, Gene/Environment Susceptibility)-Reykjavik study was supported by a National Institute on Aging (NIA) grant (27120120022C), 2 NIH contracts (N01-AG-1-2100 and HHSN27120120022C), the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). Dr Gudnason is supported by an NIA grant (27120120022C) and an Icelandic Research Fund project grant (141513-051). Dr Silverman is supported by 3 NIH grants (R01 HL089856, P01 HL105339, and P01 HL114501). Dr Washko is supported by 3 NIH grants (R01 HL107246, R01 HL116473, and R01 HL122464). Dr Rosas is supported by an NIH grant (P01 HL114501). Dr Hunninghake and this study are supported by 2 NIH grants (P01 HL114501 and R01 HL11024) and a project grant from the Icelandic Research Fund (141513-051).

Role of the Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: Dr O'Connor, JAMA Associate Editor, was not involved in the editorial review of or decision to publish this article.

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