Association Between Interstitial Lung Abnormalities and All-Cause Mortality

39 AUTHORS, INCLUDING:

Thor Aspelund
Hjartavernd
389 PUBLICATIONS   13,066 CITATIONS

SEE PROFILE

Udo Hoffmann
Harvard University
517 PUBLICATIONS   16,506 CITATIONS

SEE PROFILE

Christopher J O'Donnell
National Institutes of Health
665 PUBLICATIONS   48,903 CITATIONS

SEE PROFILE

Lenore J Launer
National Institutes of Health
513 PUBLICATIONS   22,512 CITATIONS

SEE PROFILE

Association Between Interstitial Lung Abnormalities and All-Cause Mortality

Rachel K. Putman, MD; Hiroto Hatabu, MD, PhD; Tetsuro Araki, MD, PhD; Gunnar Gudmundsson, MD, PhD; Wei Gao, MS; Mizuki Nishino, MD; Yuka Okajima, MD; Josée Dupuis, PhD; Jeanne C. Latourelle, DSc; Michael H. Cho, MD, MPH; Souheil El-Chemaly, MD, MPH; Harvey O. Coxson, PhD; Bartolome R. Celli, MD; Isis E. Fernandez, MD; Oscar E. Zazueta, MD; James C. Ross, PhD; Rola Harmouche, PhD; Raúl San José Estépar, PhD; Alejandro A. Diaz, MD; Sigurdur Sigurdsson, BSc, MSc; Elías F. Gudmundsson, MSc; Gudny Eiríksdottír, MSc; Thor Aspelund, MSc, PhD; Matthew J. Budoff, MD; Gregory L. Kinney, PhD; John E. Hokanson, MPH, PhD; Michelle C. Williams, MD; John T. Murchison, MD; William MacNee, MD; Udo Hoffmann, MD, MPH; Christopher J. O'Donnell, MD, MPH; Lenore J. Launer, PhD; Tamara B. Harrris, MD, MS; Vilmundur Gudnason, MD, PhD; Edwin K. Silverman, MD, PhD; George T. O'Connor, MD; George R. Washko, MD; Ivan O. Rosas, MD; Gary M. Hunninghake, MD, MPH; for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) and COPDGene Investigators

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.

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

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.

Corresponding Author: Ivan O. Rosas, MD, Pulmonary and Critical Care Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (irosas@rics.bwh.harvard.edu).

nterstitial 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 participants[1-7] (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[6,9] 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 IPF[11] (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

Interstitial Lung Abnormalities and Mortality

Figure 1. Representative Examples of Definite Fibrosis from the FHS, AGES-Reykjavik, COPDGene, and ECLIPSE Studies
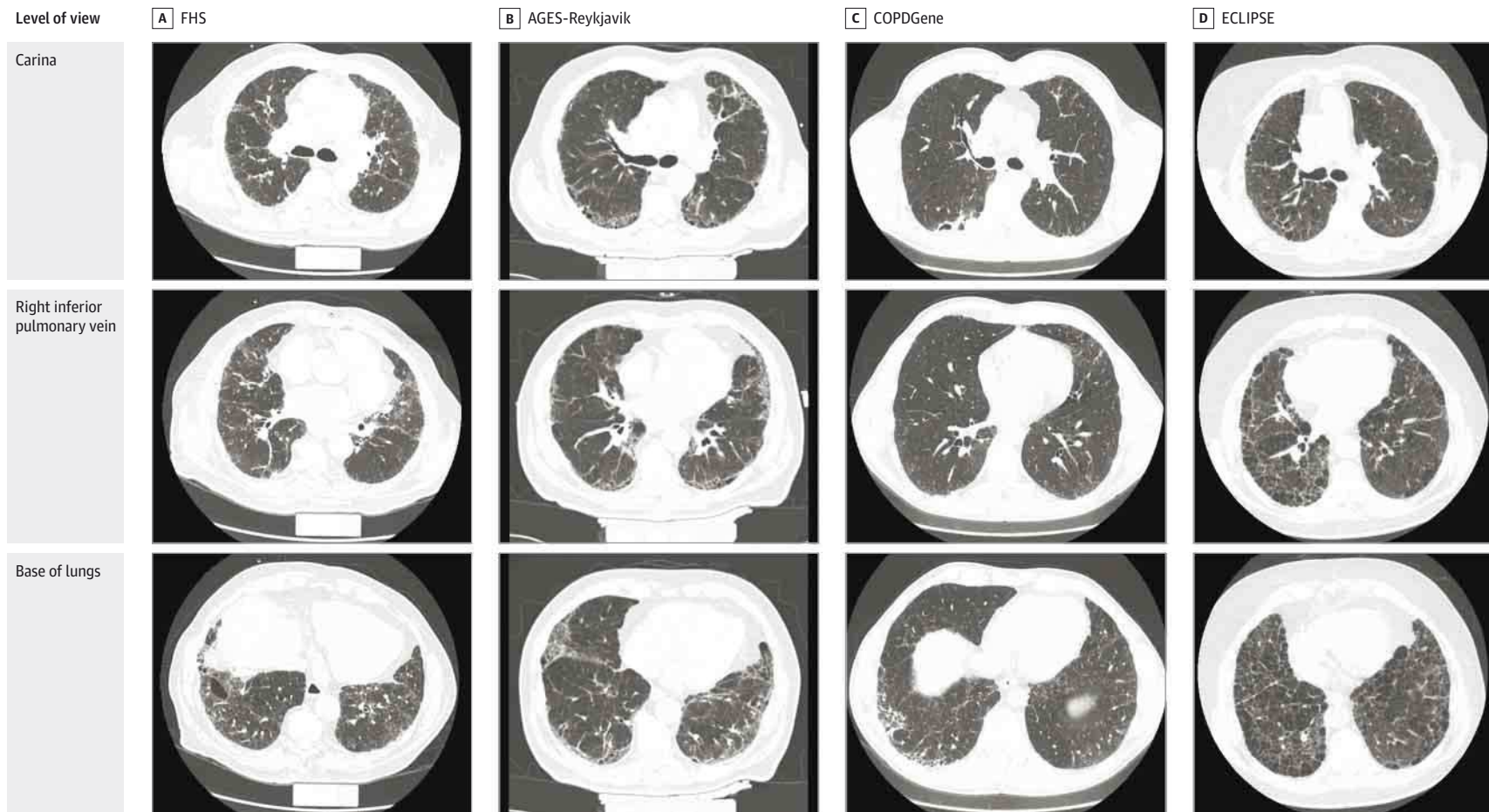
Chest computed tomographic (CT) axial images of 4 participants, one from each cohort, with interstitial lung abnormalities with definite fibrosis. Definite fibrosis is defined as pulmonary parenchymal architectural distortion diagnostic of fibrotic lung disease.[6] Panel A demonstrates subpleural reticular 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 FHS[6] and COPDGene cohorts[2] 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 (FEV_1) and FEV_1/forced vital capacity (FVC) ratio. In contrast, in the FHS, interstitial lung abnormalities were associated with a higher prevalence of COPD and a lower FEV_1/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

Interstitial Lung Abnormalities and Mortality

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; FEV$_1$, 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).

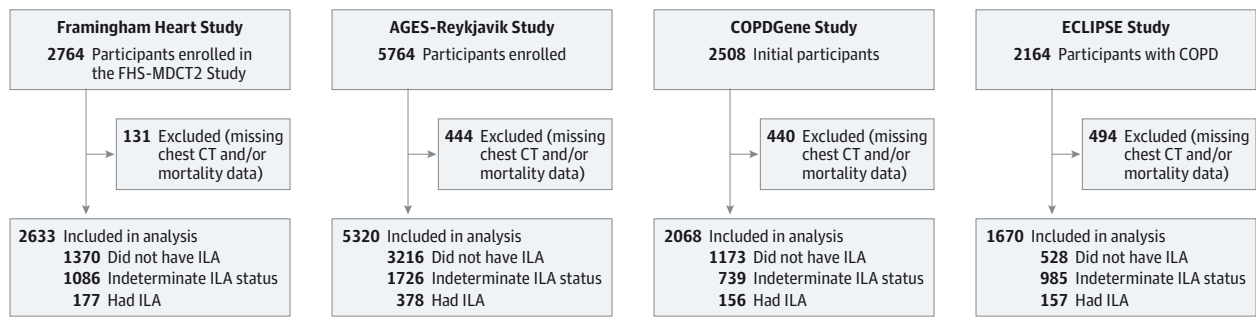[c] Missing current smoking status data for 3 (0.2%) participants in FHS.

[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 FEV$_1$ of less than 80% and FEV$_1$/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

Framingham Heart Study	**AGES-Reykjavik Study**	**COPDGene Study**	**ECLIPSE Study**
2764 Participants enrolled in the FHS-MDCT2 Study	5764 Participants enrolled	2508 Initial participants	2164 Participants with COPD
131 Excluded (missing chest CT and/or mortality data)	444 Excluded (missing chest CT and/or mortality data)	440 Excluded (missing chest CT and/or mortality data)	494 Excluded (missing chest CT and/or mortality data)
2633 Included in analysis 1370 Did not have ILA 1086 Indeterminate ILA status 177 Had ILA	5320 Included in analysis 3216 Did not have ILA 1726 Indeterminate ILA status 378 Had ILA	2068 Included in analysis 1173 Did not have ILA 739 Indeterminate ILA status 156 Had ILA	1670 Included in analysis 528 Did not have ILA 985 Indeterminate ILA status 157 Had ILA

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		AGES-Reykjavik		COPDGene		ECLIPSE	
	(N = 2633)		(N = 5320)		(N = 2068)		(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
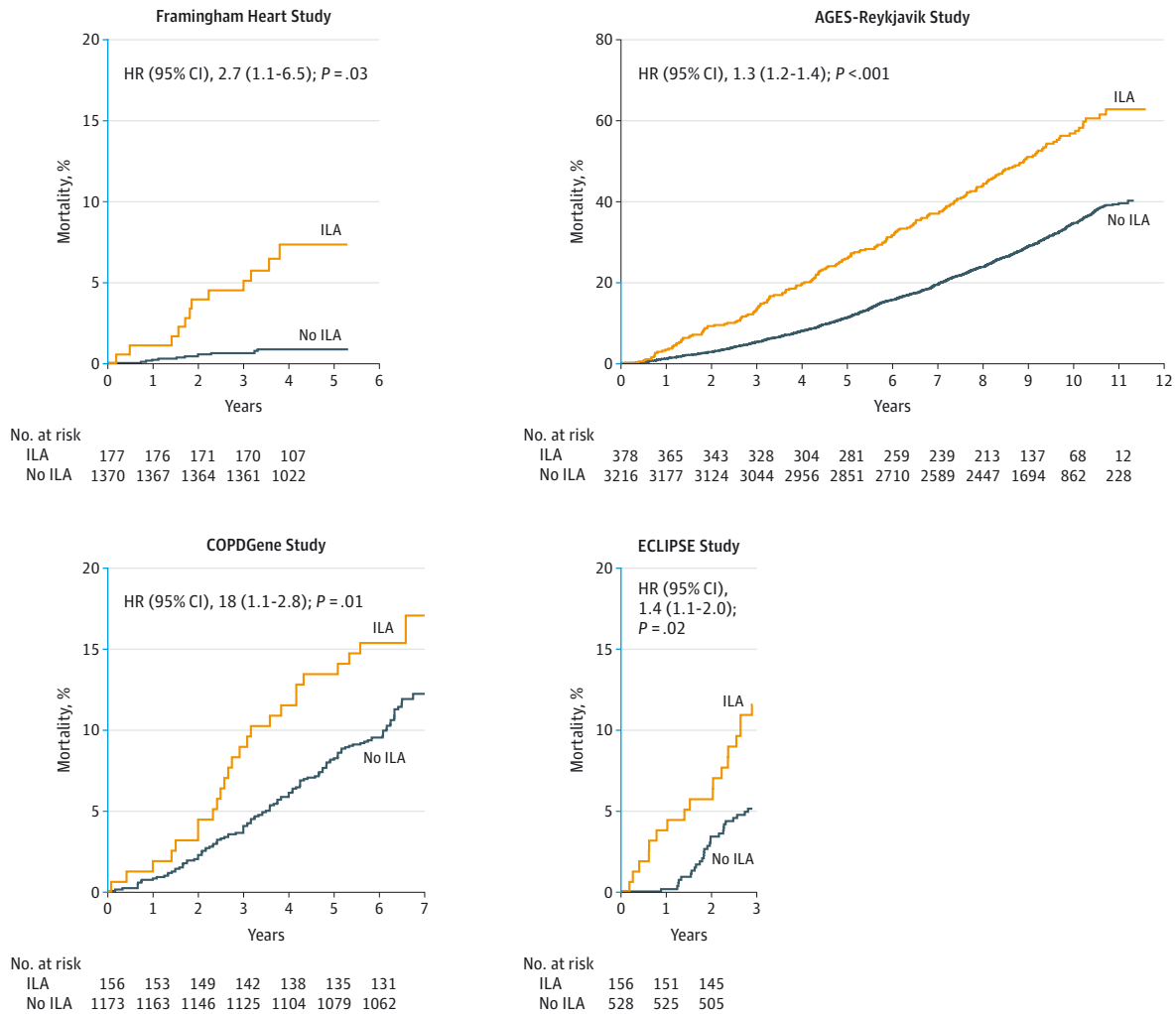
Blue segments of y-axes indicate mortality range from 0% to 20%. P values included in each panel are associated with hazard ratios (HRs [95% CIs]) from the adjusted Cox proportional hazards model including adjustments for age, sex, race, body mass index, pack-years of smoking, current or former smoking 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.

justments 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 FEV_1/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 lung[28] 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 samples [6]; 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.

REFERENCES

1. Lederer DJ, Enright PL, Kawut SM, et al. Cigarette smoking is associated with subclinical parenchymal lung disease: the Multi-Ethnic Study of Atherosclerosis (MESA)-lung study. *Am J Respir Crit Care Med*. 2009;180(5):407-414.

2. Washko GR, Hunninghake GM, Fernandez IE, et al; COPDGene Investigators. Lung volumes and emphysema in smokers with interstitial lung abnormalities. *N Engl J Med*. 2011;364(10):897-906.

3. Sverzellati N, Guerci L, Randi G, et al. Interstitial lung diseases in a lung cancer screening trial. *Eur Respir J*. 2011;38(2):392-400.

4. Jin GY, Lynch D, Chawla A, et al. Interstitial lung abnormalities in a CT lung cancer screening population: prevalence and progression rate. *Radiology*. 2013;268(2):563-571.

5. Tsushima K, Sone S, Yoshikawa S, Yokoyama T, Suzuki T, Kubo K. The radiological patterns of interstitial change at an early phase: over a 4-year follow-up. *Respir Med*. 2010;104(11):1712-1721.

6. Hunninghake GM, Hatabu H, Okajima Y, et al. MUC5B promoter polymorphism and interstitial lung abnormalities. *N Engl J Med*. 2013;368(23): 2192-2200.

7. Putman RK, Rosas IO, Hunninghake GM. Genetics and early detection in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2014;189(7):770-778.

8. Doyle TJ, Washko GR, Fernandez IE, et al; COPDGene Investigators. Interstitial lung abnormalities and reduced exercise capacity. *Am J Respir Crit Care Med*. 2012;185(7):756-762.

9. Kropski JA, Pritchett JM, Zoz DF, et al. Extensive phenotyping of individuals at risk for familial interstitial pneumonia reveals clues to the pathogenesis of interstitial lung disease. *Am J Respir Crit Care Med*. 2015;191(4):417-426.

10. Seibold MA, Wise AL, Speer MC, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. *N Engl J Med*. 2011;364(16): 1503-1512.

11. Raghu G, Collard HR, Egan JJ, et al; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183 (6):788-824.

12. American Thoracic Society; European Respiratory Society. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med*. 2002;165(2):277-304.

13. King TE Jr, Schwarz MI, Brown K, et al. Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality. *Am J Respir Crit Care Med*. 2001;164(6):1025-1032.

14. Raghu G, Chen SY, Yeh WS, et al. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11. *Lancet Respir Med*. 2014;2(7): 566-572.

15. Vancheri C, Failla M, Crimi N, Raghu G. Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology. *Eur Respir J*. 2010;35(3):496-504.

16. Hurst JR, Vestbo J, Anzueto A, et al; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363(12): 1128-1138.

17. Harris TB, Launer LJ, Eiriksdottir G, et al. Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. *Am J Epidemiol*. 2007;165(9):1076-1087.

18. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health Nations Health*. 1951;41(3):279-281.

19. Regan EA, Hokanson JE, Murphy JR, et al. Genetic epidemiology of COPD (COPDGene) study design. *COPD*. 2010;7(1):32-43.

20. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD. (Updated 2007). http://www.goldcopd.org. Accessed August 1, 2015.

21. Vestbo J, Anderson W, Coxson HO, et al; ECLIPSE investigators. Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE). *Eur Respir J*. 2008;31(4):869-873.

22. Washko GR, Lynch DA, Matsuoka S, et al. Identification of early interstitial lung disease in smokers from the COPDGene Study. *Acad Radiol*. 2010;17(1):48-53.

23. Ross JC, Estépar RS, Díaz A, et al. Lung extraction, lobe segmentation and hierarchical region assessment for quantitative analysis on high resolution computed tomography images. *Med Image Comput Comput Assist Interv*. 2009;12(pt 2): 690-698.

24. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;15(4):827-832.

25. Uh HW, Wijk HJ, Houwing-Duistermaat JJ. Testing for genetic association taking into account phenotypic information of relatives. *BMC Proc*. 2009;3(suppl 7):S123.

26. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(10): 1005-1012.

27. Panos RJ, Mortenson RL, Niccoli SA, King TE Jr. Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. *Am J Med*. 1990;88(4):396-404.

28. Copley SJ, Wells AU, Hawtin KE, et al. Lung morphology in the elderly: comparative CT study of subjects over 75 years old versus those under 55 years old. *Radiology*. 2009;251(2):566-573.

29. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2006;174(7):810-816.

30. Iwai K, Mori T, Yamada N, Yamaguchi M, Hosoda Y. Idiopathic pulmonary fibrosis: epidemiologic approaches to occupational exposure. *Am J Respir Crit Care Med*. 1994;150(3): 670-675.

31. Fernández Pérez ER, Daniels CE, Schroeder DR, et al. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study. *Chest*. 2010;137(1):129-137.

32. Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med*. 1994;150(4): 967-972.

33. King TE Jr, Bradford WZ, Castro-Bernardini S, et al; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2083-2092.

34. Richeldi L, du Bois RM, Raghu G, et al; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2071-2082.

Supplementary Online Content

Putman RK, Hatabu H, Araki T, et al. Association between interstitial lung abnormalities and all-cause mortality. *JAMA*. doi: 10.1001/jama.2016.0518

This supplementary material has been provided by the authors to give readers additional information about their work.

1   **Supplementary Online Content**

2

3   **Supplement to: Association Between Interstitial Lung Abnormalities and All-Cause Mortality**

4   Rachel K. Putman MD,[1]* Hiroto Hatabu MD PhD,[2,3]* Tetsuro Araki MD PhD,[2,3]* Gunnar Gudmundsson MD,[4]
5   Wei Gao MS,[5] Mizuki Nishino MD, [2,3] Yuka Okajima, MD,[2,6] Josée Dupuis PhD,[5, 7] Jeanne C. Latourelle, DSc,[8,9]
6   Michael H. Cho MD MPH,[1,10] Souheil El-Chemaly MD MPH[1], Harvey O. Coxson PhD,[11] Bartolome R. Celli MD,[1]
7   Isis E. Fernandez MD,[1,12] Oscar E. Zazueta MD,[1] James C. Ross PhD,[10,13] Rola Harmouche PhD,[1, 13] Raúl San José
8   Estépar, PhD.,[2,13] Alejandro A. Diaz, MD,[1] Sigurður Sigurdsson BSc MSc,[14] Elías F. Gudmundsson MSc,[14] Gudny
9   Eiríksdottír MSc,[14] Thor Aspelund MSc PhD,[14,15] Matthew J. Budoff MD,[16] Gregory L. Kinney PhD,[17] John E.
10   Hokanson MPH PhD,[17] Michelle C Williams MD,[18] John T. Murchison MD,[19] William MacNee MD,[20] Udo
11   Hoffmann MD MPH,[21] Christopher J. O'Donnell MD MPH,[7,22] Lenore J. Launer PhD,[23] Tamara B. Harrris MD
12   MS,[23] for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) and
13   COPDGene Investigators, Vilmundur Gudnason MD PhD,[14,15] Edwin K. Silverman MD PhD,[1,10] George T.
14   O'Connor MD,[7, 8] George R. Washko MD,[1,3] Ivan O. Rosas MD,[1] and Gary M. Hunninghake MD MPH[1,3]
15
16   [1]Pulmonary and Critical Care Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA;
17   [2]Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [3]Center for
18   Pulmonary Functional Imaging, Brigham and Women's Hospital, Harvard Medical School, Boston, MA;
19   [4]Department of Respiratory Medicine and Sleep, Landspital University Hospital, Reykjavik, Iceland. [5]Department of
20   Biostatistics, Boston University School of Public Health; [6]Department of Radiology, St. Luke's International
21   Hospital, Tokyo, Japan; [7]National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham MA;
22   [8]Pulmonary Center, Department of Medicine, Boston University, Boston, MA.; [9]Department of Neurology, Boston
23   University, Boston,[10]The Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard
24   Medical School, Boston, MA; [11]Department of Radiology, University of British Columbia, Vancouver, B.C.,
25   Canada; [12] Comprehensive Pneumology Center, Ludwig-Maximilians-University, University Hospital Grosshadern,
26   and Helmholtz Zentrum München; Member of the German Center for Lung Research, Munich, Germany; [13]Surgical
27   Planning Laboratory, Department of Radiology, Brigham and Women's Hospital, Boston MA; [14]Icelandic Heart
28   Association, Kopavogur, Iceland; [15]University of Iceland, Reykjavik, Iceland; [16]Department of Medicine, Los
29   Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, California; [17]Department of Epidemiology,
30   Colorado School of Public Health, University of Colorado Denver, Denver, Colorado; [18]Department University of
31   Edinburgh/British Heart Foundation Centre for Cardiovascular Science, Edinburgh, Scotland; [19]Royal Infirmary of
32   Edinburgh, University of Edinburgh, Edinburgh, Scotland; [20]Centre for Inflammation Research, University of
33   Edinburgh, Edinburgh, Scotland; [21]Cardiac MR PET CT Program, Department of Radiology, Massachusetts General
34   Hospital, Harvard Medical School, Boston, MA; [22]Cardiovascular Epidemiology and Human Genomics Branch,
35   NHLBI Division of Intramural Research, Bethesda, MD; [23]Intramural Research Program, National Institute of
36   Aging, NIH, Bethesda, MD
37
38   *These authors contributed equally to this manuscript
39

40

41

42

43

44

45

46 **Supplement Table of Contents**

63

64

65

66

67

68

69

70

71

72

73

74   **eMethods**

75   **Chest CT Data Acquisition**

76   In FHS, chest CT data sets were acquired during a single breath hold covering the entire lung. Slice thickness was

77   0.625 mm reconstructed in 1.5 mm intervals.

78

79   **CT Analysis**

80   The CT scans available from AGES-Reykjavik cohort included CTs of the thoracic aorta and cardiac CTs, the

81   images were evaluated jointly to determine ILA status. Chest CT scans were available for review from the

82   ECLIPSE cohort. Thoracic CT images were reviewed on AZE VirtualPlace Fujin Raijin workstations (AZE, Tokyo,

83   Japan) using axial images with a window level of -700 HU and a window width of 1500 HU. The chest CTs were

84   evaluated by three readers (one pulmonologist and two chest radiologists) using a sequential reading method as

85   previously described. All readers were blinded to participant specific information. The chest CT analysis was

86   divided into two stages. In the first stage the chest CTs were scored as follows: no evidence of ILA, indeterminate,

87   and ILA. The second reader would review all of the scans labeled as ILA, indeterminate, and 20% of the normal

88   scans. Finally, the third reader, provided majority opinion on those scans discordantly scored. Readers rotated

89   reading positions so that they read an approximately equivalent numbers of chest CTs as reader 1, reader 2, and

90   reader 3. ILA were defined as changes affecting >5% of any lung zone including, nondependent ground-glass or

91   reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, or traction

92   bronchiectasis[1-3]. Indeterminate scans were defined as focal or unilateral ground-glass attenuation, focal or

93   unilateral reticulation, and patchy ground-glass abnormality (5% of the lung).

94

95   In stage 2 of the visual chest CT analysis, ILA was further classified by defining a group of participants with ILA

96   limited to those evidence for architectural distortion defined as definite fibrosis[4]. All visual CT assessments and

97   subtyping were performed with a consensus of three readers who were blind to all participant information.

98

99   Coronary artery calcium (CAC) scores (defined as lesions with a density $\geq$ 130 Hounsfield units, with a minimum

100   area of $1.02mm^3$, and calculated by adding the individual lesion scores from the left main, left anterior descending,

101   circumflex and right coronary arteries) were calculated using the traditional Agatston scoring method[5].

3

102

Cohort Study Design

The Framingham Heart Study (FHS) began as a longitudinal epidemiologic study to determine the risk factors for

the development of cardiovascular disease, initially enrolling participants between the ages of 30 and 59. Over time

the study now includes the distinct cohorts and a range of phenotypic data; a subset of these two cohorts, the 2764

adult men and women who participated in the Multi-Detector Computed Tomography 2 (FHS-MDCT2) Study and

therefore had chest CTs available for review were included in this study.[6] The Age Gene/Environment

Susceptibility (AGES)-Reykjavik Study was designed with goal of better understanding the determinants of aging.

Participants included in the study were those who had participated in the Reykjavik Study, which originally

comprised a random sample of 30,795 men and women living in Rekjavik in 1967. From January 2002 through

February 2006, participants remaining from the initial Reykjavik Study were enrolled in the AGES-Reykjavik

Study.[7] Genetic Epidemiology of COPD or COPDGene is a multicenter observation study designed to identify

genetic factors associated with COPD. The study enrolled 10,300 non-Hispanic whites and African Americans ages

45-80, with a minimum of 10 pack-years of smoking history, with and without COPD across the GOLD stages.

Participants were excluded for a history of pulmonary disease except asthma, previous surgical excision of at least

one lung lobe (or lung volume reduction procedure), active cancer under treatment, suspected lung cancer (large or

highly suspicious lung mass), metal in the chest, recent exacerbation of COPD treated with antibiotics or steroids,

recent eye surgery, MI, other cardiac hospitalization, recent chest or abdominal surgery, inability to use albuterol,

multiple self-described racial categories, history of chest radiation therapy, and first or second degree relative

already enrolled in the study. Subjects with recent COPD exacerbations can be enrolled one month after their

exacerbation.[8] The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-Points (ECLIPSE)

study was a three year noninterventional study that planned to enroll 2,180 COPD subjects, GOLD stages II-IV,

ages 40-75 years and 500 smoking and non-smoking controls, that was designed to identify biomarkers and

mechanisms of COPD disease progression. Participants were excluded if they had known respiratory disorders

(other than COPD and severe α_1-antitrypsin deficiency), history of significant inflammatory disease other than

COPD, a COPD exacerbation within 4 weeks of enrolment, having undergone lung surgery, recent diagnosis of

cancer, having received a blood transfusion in the 4 weeks prior to study start, inability to walk, taking part in a

4

129   blinded drug study, therapy with oral corticosteroids at inclusion and participation in studies with radiation

130   exposure.[9]

131

Cause-of-Death Data Collection

133   Cause of death data from the AGES-Reykjavik cohort was available from a follow up period that ended on

134   December 31, 2009 (median follow up of 5.3 years, range of 1.4 months to 7.6 years). The causes of death were

135   determined from death certificates using the following ICD 9 and ICD 10 codes. Respiratory death ICD 9 codes

136   460-519, ICD 10 codes J00-J99. Cardiovascular death ICD 9 codes 390-459, ICD 10 codes I00-I99. Cancer death

137   ICD 9 codes 140-239, ICD 10 codes C00-D48; all other causes of death were included in the "other cause of death"

138   category. Pulmonary fibrosis deaths were deaths that corresponded to the following ICD 9 and ICDD 10 codes, ICD

139   9 515-519 and ICD 10 J67-J70, J80 and J84.

140

Statistical Models

142   In all multivariable Cox proportional hazards and logistic regression models, the following covariates were treated

143   as continuous variables; age, pack-years smoking, body mass index (BMI) and percentage of area under 950

144   Hounsfield units or the percentage of emphysematous lung. The following covariates were treated as categorical,

145   gender, race, current smoking status, GOLD stage of COPD, history of CAD, history of malignancy and coronary

146   calcium score. Coronary calcium scoring was done using the traditional Agatston scoring method. The coronary

147   calcium (CAC) scores were then divided into four categories: those with a CAC score of zero, scores between 1 and

148   99, scores between 100 and 399 and scores greater than 400; score of zero was used as the reference. Selection of

149   covariates for model building was based on clinical relevance and cohort characteristics, not an attempt to create the

150   most parsimonious models. In Cox models for each cohort, all variables were assessed, and none were noted to

151   violate the proportional hazards assumption. The proportional hazards assumption was tested using a multiplicative

152   interaction test of time by covariate; SAS was used for AGES-Reykjavik, COPDGene and ECLIPSE, R version

153   3.1.3 was used for the FHS. Kaplan-Meier plots were used to visually depict the mortality data (see **Figure 3** and

154   **eFigure 3**). Attributable fractions for mortality associated with the presence of ILA were calculated using the

155   formula HR-1/HR, where HR is hazard ratio; the hazard ratios from the baseline adjusted model were used.

156

5

157 **eResults**

158 **Chest CT Reading**

159 In the AGES-Reykjavik cohort, of the CT scans scored by at least two readers (2836), 1623 (57%) were concordant

160 reads. Of the 1213 discordant reads, 1155 (95%) involved one indeterminate read, while a discrepancy between

161 those with and without ILA was less common (58 [5%]). In the ECLIPSE cohort, of the CT scans scored by at least

162 two readers (1868), 1240 (66%) were concordant reads. Of the 628 discordant reads, 617 (98%) involved one

163 indeterminate read, while a discrepancy between those with and without ILA was rare (9 [1%]). These findings

164 are mostly consistent with levels of discordant reads we have noted in previous evaluations.

165

166 **ILA and Mortality**

167 The attributable fractions for mortality associated with ILA were calculated in each cohort, using the hazard ratios

168 that are adjusted for age, gender, race, body-mass-index, pack-years of smoking, current smoking status and GOLD

169 stage COPD where available. In the FHS the attributable fraction was 63%, 23% in AGES-Reykjavik, 44% in

170 COPDGene and 29% in ECLIPSE.

171

172 **ILA, Mortality and Definite Fibrosis**

173 Among participants with interstitial lung abnormalities, 25% (44 of 177) in the FHS, 37% (129 of 348) in the

174 AGES-Reykjavik, 21% (32 of 156) in COPDGene, and 18% (28 of 157) in ECLIPSE could be further classified as

175 having CT evidence of pulmonary fibrosis (Definite Fibrosis). The absolute mortality rates among those with

176 Definite Fibrosis were similar in the FHS ([6%], 3 deaths among 44) and COPDGene ([19%], 6 deaths among 32)

177 and increased in the AGES-Reykjavik ([71%], 91 deaths among 129) and ECLIPSE ([28%], 8 deaths among 28)

178 when compared to the mortality rates of interstitial lung abnormalities without definite fibrosis in each cohort. After

179 adjustment for covariates (age, sex, race, BMI, pack years and current smoking status) in AGES Reykjavik those

180 with definite fibrosis had an increase in the risk of death [HR=1.5, 95% Confidence Interval (CI) 1.2-2.0, P=0.003]

181 and in ECLIPSE after adjustment for the covariates above and GOLD stage COPD, participants with definite

182 fibrosis had an increased risk of death [HR=3.35, 95% CI 1.2-9.2, P=0.02]. While in COPDGene and the FHS,

183 there was not a significantly increased risk of death in participants with fibrotic ILA compared to those with ILA

184 without fibrosis; [HR=1.2, 95% CI 0.4-3.4, P=0.7] in COPDGene and [HR=0.9, 95% CI 0.3, 2.8, P=0.9] in FHS.

6

185

186   When subset to participants with interstitial lung abnormalities without definite fibrosis, after adjusting for age,

187   gender, race, body mass index, pack-years of smoking, current smoking status and GOLD stage (where available)

188   interstitial lung abnormalities were associated with an increased risk of death in all cohorts except ECLIPSE. In the

189   FHS (HR=2.8, 95% CI 1.1, 6.8, P=0.024), in AGES-Reykjavik (HR=1.2, 95% CI 1.05, 1.3, P=0.0026), in

190   COPDGene (HR=1.8, 95% CI 1.1, 2.9, P=0.003) and in ECLIPSE (HR=1.2, 95% CI 0.8, 1.8, P=0.3).

191

192   **ILA, Mortality and COPD**

193   To further evaluate confounding by measures of COPD severity, we used quartiles of BODE index instead of GOLD

194   stage of COPD in both COPDGene and ECLIPSE. The results were similar to those seen with adjustments for

195   GOLD stage. In COPDGene, HR=1.7, 95% CI 1.1-2.7, P=0.020; OR=1.7, 95% CI 1.01, 2.8, P=0.048. In

196   ECLIPSE, HR=1.4, 95% CI 1.03-1.9, P=0.03; OR=1.5, 95% CI 1.04-2.0, P=0.03.

197

198   **ILA Status and Cause-of-Death**

199   In the AGES-Reykjavik cohort we also evaluated the relationship between indeterminate ILA status and cause-of-

200   death. When compared to participants who were indeterminate for ILA, after adjustment for important covariates

201   (age, sex, BMI, pack years smoking and current smoking status) participants with ILA had an increase in the odds of

202   a respiratory death [OR=3.3, 95% CI 1.6-6.5, P<.001].

203

204

205

206

207

208

209

210

211

212

7

213

eTable 1. Baseline Characteristics of Participants From AGES-Reykjavik by ILA Status

	No ILA (3216, 61%)	Indeterminate (1726, 32%)	ILA (378, 7%)	P-Values			
	(0)	(1)	(2)	All	0vs1	0vs2	1vs2
Age – yrs, mean (SD)	76 (5)	77 (6)	78 (6)	<.001	<.001	<.001	0.19
Sex – no. female (%)	1910 (60)	962 (56)	172 (46)	<.001	0.01	<.001	<.001
Race – no. white (%)	N/A	N/A	N/A	--	--	--	--
Body Mass Index, mean (SD)	27 (4)	27 (4)	27 (5)	0.26	0.002	0.58	0.27
Pack Years Smoking, median, (IQR)[a]	0 (0, 16)	3 (0, 23)	11 (0, 29)	<.001	<.001	<.001	<.001
Current Smokers - no. (%)	374 (12)	205 (12)	307 (18)	0.006	0.82	<.001	.001
Mortality – no. (%)	1065 (33)	750 (43)	210 (56)	<.001	<.001	<.001	<.001

215   [a] IQR is interquartile range

216

217

218

219

220

221

222

223

224

225

226

227

228

229

230

8

231

232 **eTable 2.** Baseline Characteristics of Participants From ECLIPSE by ILA Status

233

	No ILA (528, 32%)	Indeterminate (985, 59%)	ILA (157, 9%)	P-Values			
	(0)	(1)	(2)	All	0 vs 1	0 vs 2	1 vs 2
Age – yrs, mean (SD)	62 (7)	64 (7)	64 (8)	<.001	<.001	<.001	0.7
Female Sex – no. (%)	182 (34)	357 (36)	41 (26)	0.30	0.50	0.05	0.02
Race – no. white (%)	515 (98)	958 (97)	154 (98)	0.91	0.87	1.0	0.79
Body Mass Index, mean (SD)	27 (6)	27 (6)	26 (5)	0.43	0.04	0.09	0.60
Pack Years Smoking, median, (IQR)[a]	45 (33, 62)	45 (33, 60)	43 (30, 60)	0.47	0.48	0.15	0.22
Current Smokers – no. (%)	202 (38)	315 (32)	72 (46)	<.001	0.02	0.10	<.001
FEV1 (% predicted), mean (SD)	44 (15)	43 (15)	47 (14)	0.001	0.09	0.020	<.001
FVC (% predicted), mean (SD)	79 (19)	79 (21)	80 (20)	0.70	0.73	0.78	0.80
FEV1/FVC (%),mean (SD)	45 (12)	43 (11)	48 (11)	<.001	0.05	0.006	<.001
GOLD Stage				<.001	0.02	0.01	<.001
Stage II – no. (%)	241 (46)	391 (40)	76 (48)				
Stage III – no. (%)	219 (41)	435 (44)	74 (47)				
Stage IV – no. (%)	68 (13)	159 (16)	7 (5)				
TLC (L)[b], mean (SD)	5.9 (1.5)	5.9 (1.5)	5.7 (1.4)	0.76	0.93	0.16	0.14
Fraction Volume -950 HU[c], mean (SD)	18.1 (11.5)	19.2 (12.7)	14.5 (10.8)	<.001	0.11	0.001	<.001
Mortality –no. (%)	27 (5)	120 (12)	18 (11)	<.001	<.001	0.009	0.90

234   [a] IQR is interquartile range
235   [b]Quantitative total lung capacity measurements were made using Airway Inspector (www.airwayinspector.org).
236   [c]Quantitative fraction volume below -950 Hounsfield unit measurements were made using Airway Inspector
237   (www.airwayinspector.org)
238

239

240

9

241

eTable 3. Association Between Interstitial Lung Abnormalities and Mortality, Including Additional Adjustments for Confounding[a]

	Framingham Heart Study		AGES-Reykjavik		COPDGene		ECLIPSE	
Median Follow Up Time – yrs, (IQR[b])	4.0 (3.3, 4.6)		8.9 (6.7, 9.9)		6.5 (6.2, 6.7)		2.9 (2.9, 2.9)	
	No ILA[c]	ILA	No ILA	ILA	No ILA	ILA	No ILA	ILA
Mortality – no. (%)	12 (1)	12 (7)	1065 (33)	210 (56)	133 (11)	25 (16)	27 (5)	18 (11)
Mortality Difference % (95% CI)[d]	6 (2, 10)		23 (18, 28)		5 (-1, 11)		6 (1, 11)	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Unadjusted Model	8.2 (3.6, 18.6)	<.001	1.6 (1.4, 1.8)	<.001	1.5 (0.9, 2.4)	0.09	1.6 (1.1, 2.1)	0.006
Adjusted Model[e]	2.8 (1.1, 7.3)	0.03	1.4 (1.2, 1.5)	<.001	1.8 (1.1, 3.1)	0.03	1.5 (1.1, 2.1)	0.02
Adjusted Model + Percentage Emphysema[f, g]	2.7 (1.0, 7.1)	0.04	--	--	1.9 (1.1, 3.2)	0.02	1.5 (1.04, 2.1)	0.03
Adjusted Model + Coronary Disease[h,g]	2.4 (0.9, 6.5)	0.09	1.3 (1.2, 1.5)	<.001	1.5 (0.9, 2.8)	0.15	1.6 (1.1, 2.5)	0.01
Adjusted Model + Cancer History[h,g]	2.8 (1.1, 7.0)	0.04	1.4 (1.2, 1.6)	<.001	1.8 (1.1, 3.1)	0.03	--	--

243 [a] All oddsratios are for the comparison between participants with and without interstitial lung abnormalities.
244 [b] IQR is interquartile range
245 [c] ILA is interstitial lung abnormalities
246 [d] 95% CI is 95% Confidence Interval

247 [e] Adjusted hazard ratios include adjustments for age, gender, race, body-mass index, pack-years of smoking, current or former smoking status, GOLD stage of COPD (where
248 available)
249
250 [f] Adjusted hazard ratios include adjustments for age, gender, race, body-mass index, pack-years of smoking, current or former smoking status, GOLD stage of COPD and amount of
251 emphysema (percentage below 950 Hounsfield units).
252 [g] Data for the variables used in addition to the adjusted model can be found in **eTable 4**
253 [h] Adjusted hazard ratios include adjustments for age, gender, race, body-mass index, pack-years of smoking, current or former smoking status, GOLD stage of COPD (except in the
254 AGES-Reykjavik where GOLD Stage was not available), history of coronary artery disease and coronary calcium score.
255 [i] Adjusted hazard ratios include adjustments for age, gender, race, body-mass index, pack-years of smoking, current or former smoking status, GOLD stage of COPD (except in the
256 AGES-Reykjavik where GOLD Stage was not available) and history of non-dermatologic malignancy in Framingham and AGES-Reykjavik, in COPDGene includes a history of lung,
257 breast, bladder, colon and prostate cancers.
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283

284 **eTable 4.** Baseline Characteristics by Interstitial Lung Abnormality Status for Additional Adjusted Covariates

Variable	Framingham Heart Study		AGES-Reykjavik		COPDGene		ECLIPSE	
	No ILA (1370) (52%)[a]	ILA (177) (7%)[a]	No ILA (3216) (60%)[a]	ILA (378) (7%)[a]	No ILA (1173) (57%)[a]	ILA (156) (8%)[a]	No ILA (528) (32%)[a]	ILA (157) (9%)[a]
Percentage of the lung less than -950 Hounsfield Units, median (IQR)[b]	30 (24, 33)	25 (18, 30)	--	--	4 (1, 13)	2 (1, 7)	16 (9, 25)	12 (6, 21)
History of Malignancy – no. yes (%)	102 (7)	33 (19)	990 (31)	135 (36)	41 (4)	10 (6)	--	--
History of Coronary Artery Disease – no. yes (%)	51 (4)	32 (18)	1089 (34)	187 (50)	66 (5)	14 (9)	73 (14)	24 (16)
Coronary Artery Calcium Scores – no. (%)*								
Score 0	768 (58)	33 (22)	423 (13)	25 (7)	682 (65)	71 (53)	99 (23)	22 (17)
Score 1-99	270 (20)	36 (24)	752 (23)	43 (12)	17 (1)	1 (1)	117 (27)	15 (12)
Score 100-399	173 (13)	34 (23)	763 (24)	84 (22)	209 (20)	33 (25)	93 (22)	41 (32)
Score > 400	113 (9)	48 (32)	1268 (40)	222 (59)	148 (14)	29 (22)	117 (27)	49 (29)

285   [a] Percentage of total population in each cohort

286   [b] IQR is interquartile range

287

288

289

290

291

292

293

294

295

296

297

eTable 5. Association Between Mortality and Indeterminate ILA Status[a]

	Framingham Heart Study		AGES-Reykjavik		COPDGene		ECLIPSE	
Median Follow Up Time – yrs, (IQR[b])	4.0 (3.3, 4.6)		8.9 (6.7, 9.9)		6.5 (6.2, 6.7)		2.9 (2.9, 2.9)	
Mortality – no. (%)	No ILA[c] 12 (1)	Indeterminate 24 (2)	No ILA 1065 (33)	Indeterminate 750 (43)	No ILA 133 (11)	Indeterminate 99 (13)	No ILA 27 (5)	Indeterminate 120 (12)
Mortality Difference % (95% CI)[d]	1 (0.4, 2)		10 (7, 13)		2 (-1, 5)		7 (4, 10)	
	Hazard or Odds Ratio (95% CI)	P-value	Hazard or Odds Ratio (95% CI)	P-value	Hazard or Odds Ratio (95% CI)	P-value	Hazard or Odds Ratio (95% CI)	P-value
Unadjusted Cox Proportional Hazards Model	2.5 (1.3, 4.9)	0.007	1.4 (1.3, 1.6)	<.001	1.2 (0.9, 1.5)	0.21	2.5 (1.6, 3.8)	<.001
Adjusted Cox Proportional Hazards Model[e]	1.4 (0.6, 2.9)	0.44	1.2 (1.1, 1.3)	<.001	1.2 (0.9, 1.5)	0.30	2.2 (1.4, 3.3)	<.001
Unadjusted Logistic Regression Model	2.6 (1.3, 5.1)	0.008	1.6 (1.4, 1.8)	<.001	1.2 (0.9, 1.6)	0.18	2.6 (1.7, 4.0)	<.001
Adjusted Logistic Regression Model[e]	1.4 (0.6, 3.1)	0.44	1.3 (1.1, 1.4)	<.001	1.2 (0.9, 1.6)	0.26	2.3 (1.5, 3.5)	<.001

[a]All hazard ratios are for the comparison between participants with and without interstitial lung abnormalities.
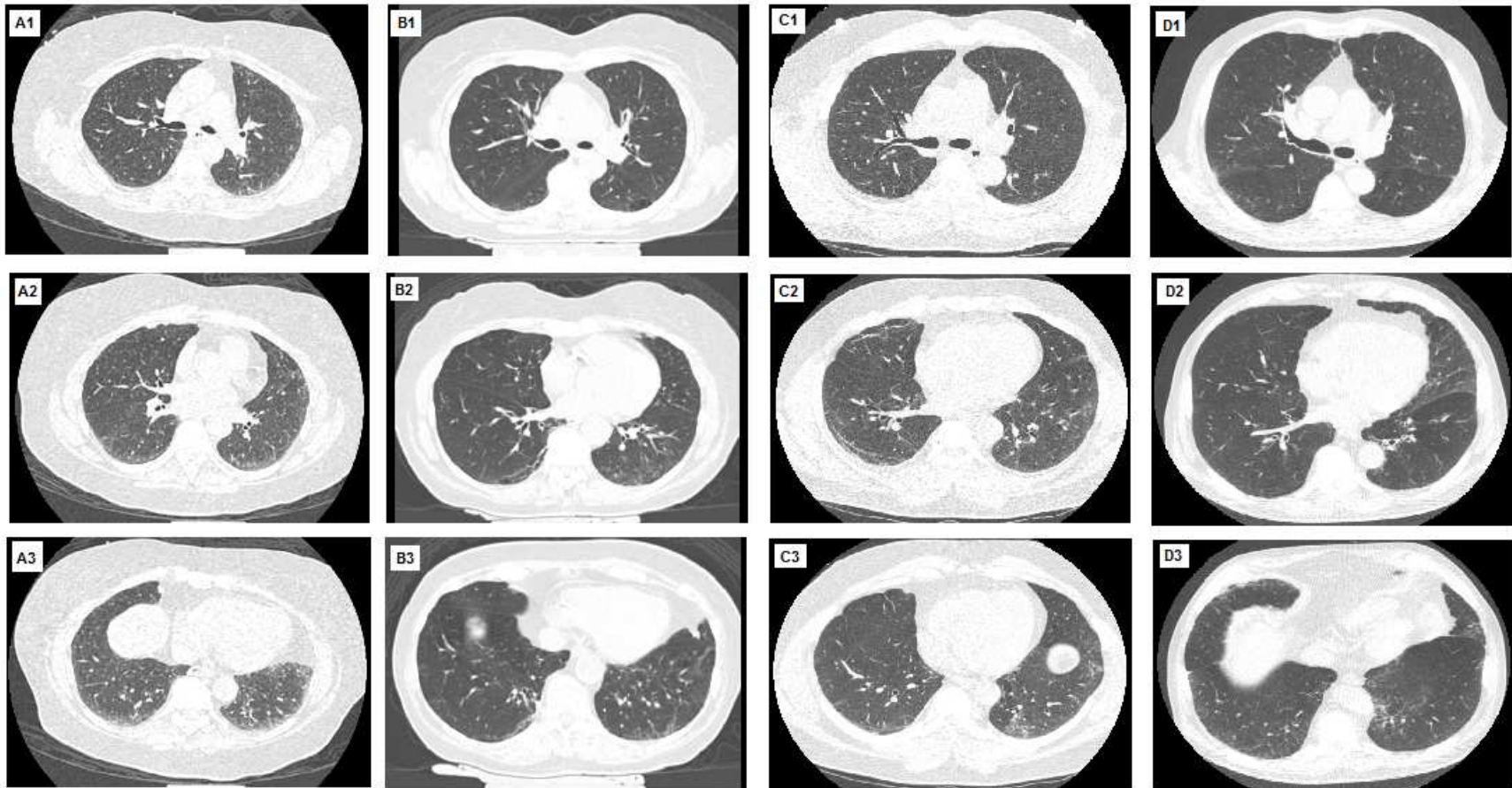[b] IQR is interquartile range
[c] ILA is interstitial lung abnormalities
[d] 95% CI is 95% Confidence Interval
[e] Adjusted hazard and odds ratios include adjustments for age, gender, race, body-mass index, pack-years of smoking, current or former smoking status, GOLD stage of COPD (where available)

13

eTable 6. Association Between Mortality and ILA Compared to Indeterminate ILA Status[a]

	Framingham Heart Study		AGES-Reykjavik		COPDGene		ECLIPSE	
Median Follow Up Time – yrs, (IQR[b])	4.0 (3.3, 4.6)		8.9 (6.7, 9.9)		6.5 (6.2, 6.7)		2.9 (2.9, 2.9)	
Mortality – no. (%)	Indeterminate 24 (2)	ILA[c] 12 (7)	Indeterminate 750 (43)	ILA 210 (56)	Indeterminate 99 (13)	ILA 25 (16)	Indeterminate 120 (12)	ILA 18 (11)
Mortality Difference % (95% CI)[d]	5 (1, 9)		13 (7, 19)		3 (-3, 9)		-1 (-6, 4)	
	Hazard or Odds Ratio (95% CI)	P-value	Hazard or Odds Ratio (95% CI)	P-value	Hazard or Odds Ratio (95% CI)	P-value	Hazard or Odds Ratio (95% CI)	P-value
Unadjusted Cox Proportional Hazards Model	3.1 (1.6, 5.9)	<.001	1.5 (1.3, 1.7)	<.001	1.2 (0.8, 1.9)	0.32	0.95 (0.6, 1.6)	0.8
Adjusted Cox Proportional Hazards Model[e]	1.6 (0.8, 3.4)	0.17	1.3 (1.1, 1.5)	0.002	1.6 (1.04, 2.6)	0.04	1.03 (0.6, 1.7)	0.9
Unadjusted Logistic Regression Model	3.2 (1.6, 6.5)	0.001	1.6 (1.3, 2.0)	<.001	1.2 (0.8, 2.0)	0.39	0.9 (0.6, 1.6)	0.8
Adjusted Logistic Regression Model[e]	1.8 (0.8, 3.9)	0.16	1.4 (1.1, 1.8)	0.006	1.7 (0.96, 2.8)	0.07	1.05 (0.6, 1.8)	0.87

308 [a] All hazard ratios are for the comparison between participants with and without interstitial lung abnormalities.
309 [b] IQR is interquartile range
310 [c] ILA is interstitial lung abnormalities
311 [d] 95% CI is 95% Confidence Interval
312 [e] Adjusted hazard and odds ratios include adjustments for age, gender, race, body-mass index, pack-years of smoking, current or former smoking status, GOLD stage of COPD (where
313 available)

314 **eFigure 1.** Chest Computed Tomographic Images of 4 Participants With Interstitial Lung Abnormalities Without Fibrosis
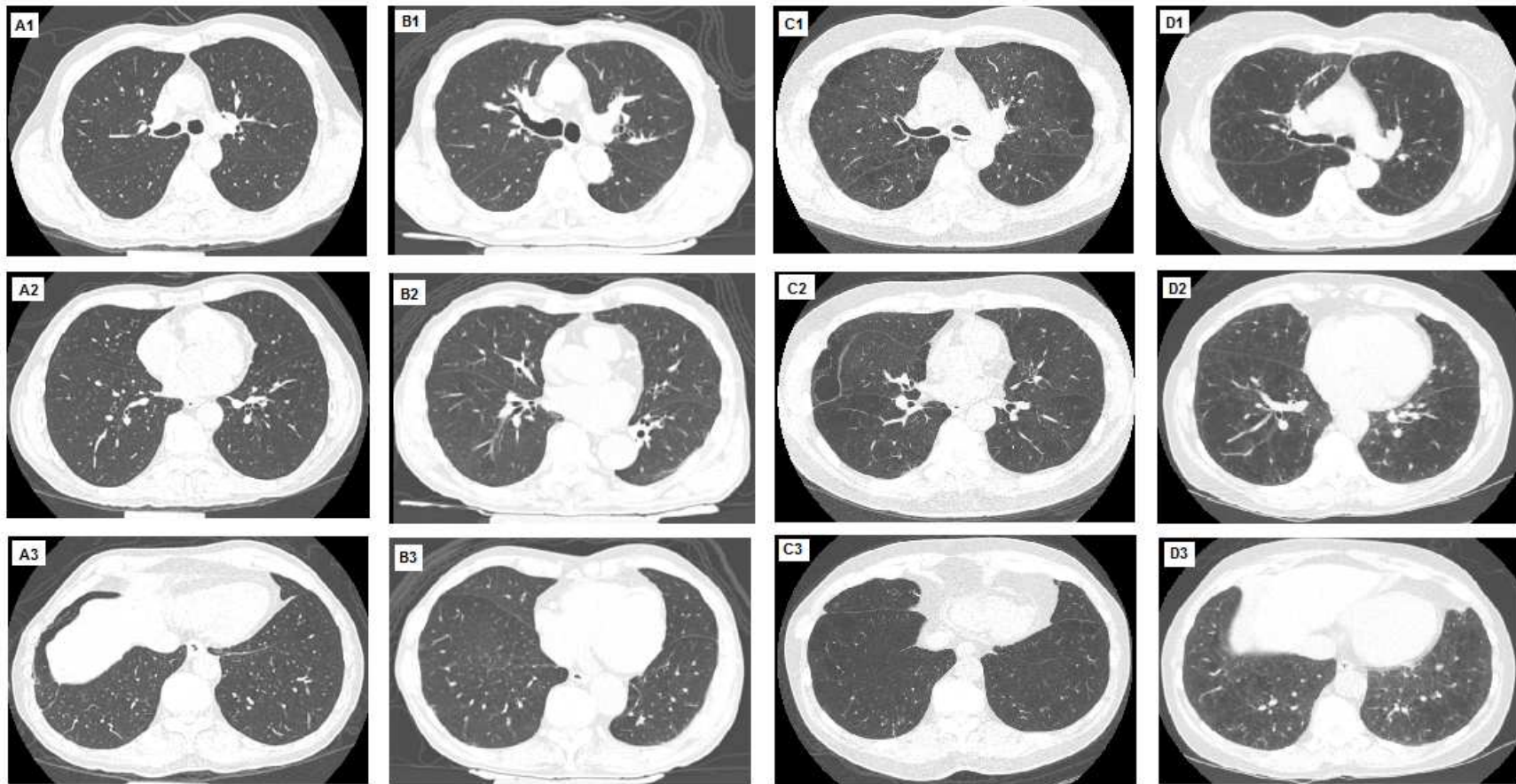

315

316 **eFigure 1:** Chest computed tomographic (CT) images of four participants with interstitial lung abnormalities without fibrosis. Each letter represents a different participant (A from FHS,

317 B from AGES Reykjavik, C from COPDGene, and D from ECLIPSE), in all panels images 1-3 are axial images, image 1 is at the level of the carina, image 2 is at the level of the right

318 inferior pulmonary vein and image 3 is at the base of the lungs. All panels demonstrate subpleural reticular markings; in addition in panels A2-A3, B2, C3, D1 and D3 also have

319 subpleural ground glass.

320

15

321

**eFigure 2.** Chest Computed Tomographic Images of 4 Participants With Indeterminate ILA Status

323

eFigure 2: Chest computed tomographic (CT) images of four participants with indeterminate ILA status. Each letter represents a different participant (A from FHS, B from AGES Reykjavik, C from COPDGene, and D from ECLIPSE), in all panels images 1-3 are axial images, image 1 is at the level of the carina, image 2 is at the level of the right inferior pulmonary vein and image 3 is at the base of the lungs. Each of the images has subpleural reticular changes that are either focal or account for less than 5% of a lung zone.

327

16

eFigure 3. Percent Mortality of Participants With Interstitial Lung Abnormalities (ILA), Indeterminate ILA Status, and Without ILA
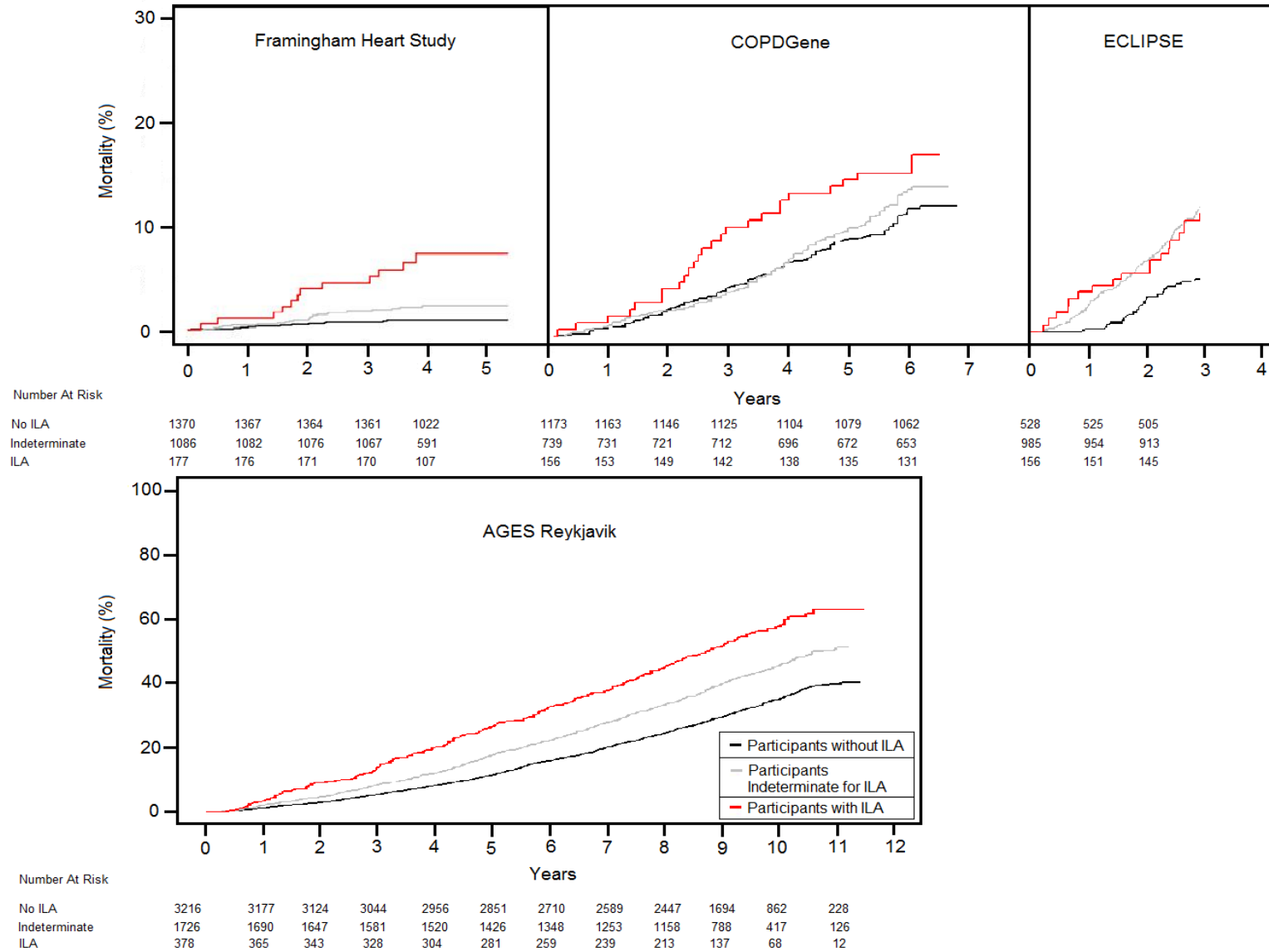
eFigure 3: Curves showing percent mortality comparing participants with interstitial lung abnormalities (ILA), indeterminate ILA status and those without ILA

eFigure 4. Mortality Rate by GOLD Stage and ILA Status in FHS, COPDGene and ECLIPSE
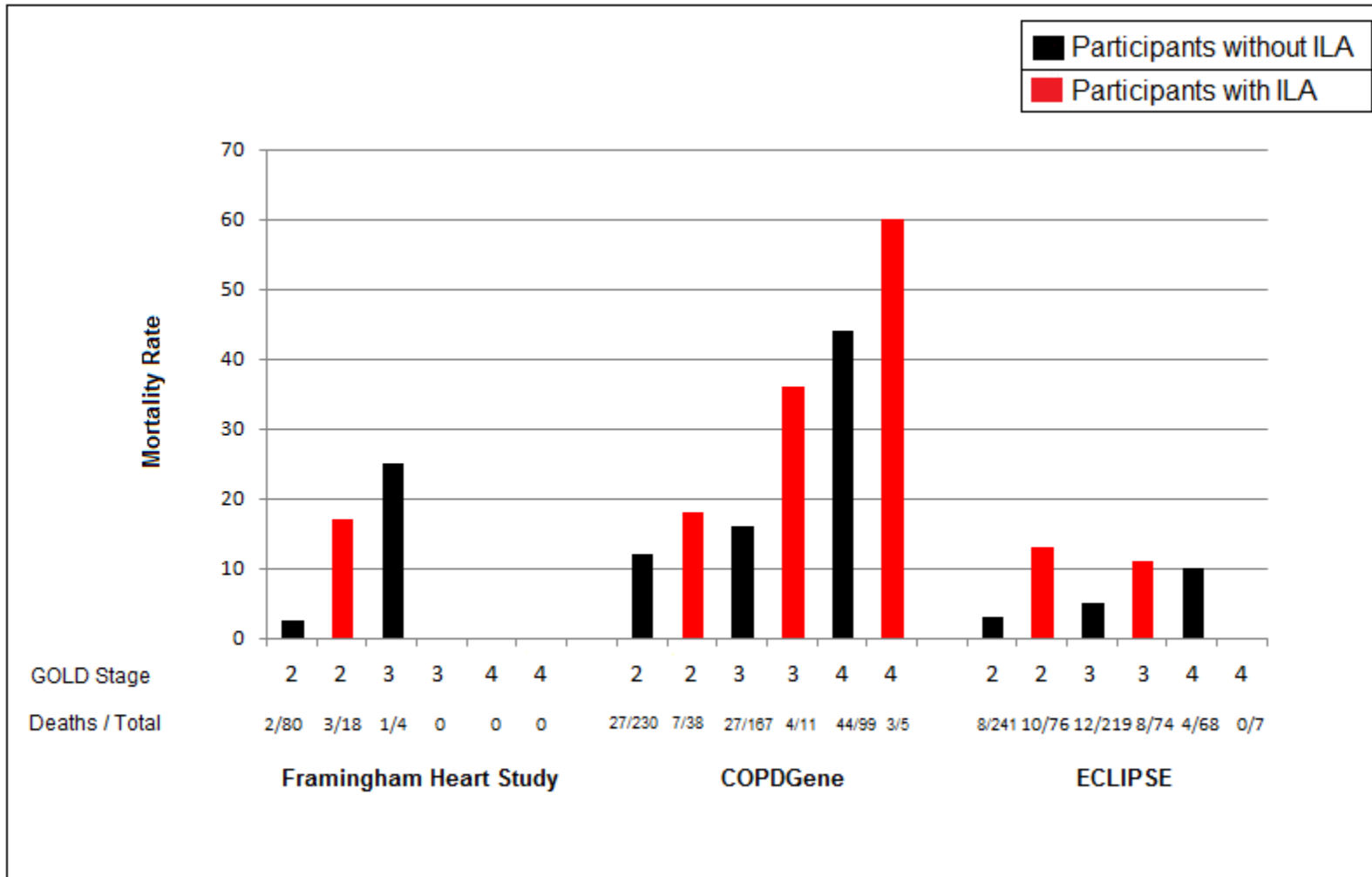
334 **eFigure 4:** Mortality rate by GOLD stage and ILA status in FHS, COPDGene and ECLIPSE.   Absolute mortality rate shown as a percentage is on the y-axis, GOLD stage and deaths

335 over the total are shown on the x-axis in each cohort.

References

1. Washko GR, Lynch DA, Matsuoka S, et al. Identification of early interstitial lung disease in smokers from the COPDGene Study. *Acad Radiol.* 2010;17(1):48-53.
2. Brantly M, Avila NA, Shotelersuk V, Lucero C, Huizing M, Gahl WA. Pulmonary function and high-resolution CT findings in patients with an inherited form of pulmonary fibrosis, Hermansky-Pudlak syndrome, due to mutations in HPS-1. *Chest.* 2000;117(1):129-136.
3. Gochuico BR, Avila NA, Chow CK, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. *Archives of internal medicine.* 2008;168(2):159-166.
4. Lee HY, Seo JB, Steele MP, et al. High-resolution CT scan findings in familial interstitial pneumonia do not conform to those of idiopathic interstitial pneumonia. *Chest.* 2012;142(6):1577-1583.
5. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *Journal of the American College of Cardiology.* 1990;15(4):827-832.
6. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. *American journal of public health and the nation's health.* 1951;41(3):279-281.
7. Harris TB, Launer LJ, Eiriksdottir G, et al. Age, Gene/Environment Susceptibility-Reykjavik Study: multidisciplinary applied phenomics. *American journal of epidemiology.* 2007;165(9):1076-1087.
8. Regan EA, Hokanson JE, Murphy JR, et al. Genetic epidemiology of COPD (COPDGene) study design. *Copd.* 2010;7(1):32-43.
9. Vestbo J, Anderson W, Coxson HO, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). *The European respiratory journal.* 2008;31(4):869-873.