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Incidence of interstitial lung abnormalities: the MESA Lung Study

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Abstract

Background—The incidence of newly developed interstitial lung abnormalities (ILA) and fibrotic ILA has not been previously reported.

Methods—Trained thoracic radiologists evaluated 13 944 cardiac computed tomography scans for the presence of ILA in 6197 Multi-Ethnic Study of Atherosclerosis longitudinal cohort study participants >45 years of age from 2000 to 2012. Five percent of the scans were re-read by the same or a different observer in a blinded fashion. After exclusion of participants with ILA at baseline, incidence rates and incidence rate ratios for ILA and fibrotic ILA were calculated.

Results—The intra-reader agreement of ILA was 92.0% (Gwet's AC1 0.912, interclass correlation coefficient (ICC) 0.982) and the inter-reader agreement of ILA was 83.5% (Gwet's AC1 0.814, ICC 0.969). Incidence of ILA and fibrotic ILA was estimated to be 13.1 and 3.5 cases per 1000 person-years, respectively. In multivariable analyses, age (hazard ratio (HR) 1.06 (95% CI 1.05–1.08); p<0.001 and HR 1.08 (95% CI 1.06–1.11); p<0.001), high attenuation area at baseline (HR 1.05 (95% CI 1.03–1.07); p<0.001 and HR 1.06 (95% CI 1.02–1.10); p=0.002) and the *MUC5B* promoter single nucleotide polymorphism (HR 1.73 (95% CI 1.17–2.56); p=0.01 and HR 4.96 (95% CI 2.68–9.15); p<0.001) were associated with incident ILA and fibrotic ILA, respectively. Ever-smoking (HR 2.31 (95% CI 1.34–3.96); p=0.002) and an idiopathic pulmonary fibrosis polygenic risk score (HR 2.09 (95% CI 1.61–2.71); p<0.001) were associated only with incident fibrotic ILA.

Conclusions—Incident ILA and fibrotic ILA were estimated by review of cardiac imaging studies. These findings may lead to wider application of a screening tool for atherosclerosis to identify pre-clinical lung disease.

Shareable abstract (@ERSpublications)

Incidence rates of ILA and fibrotic ILA were calculated from single-reader evaluations of cardiac CT scans, with good inter-reader correlation. ILA incidence was found to be associated with age, baseline lung attenuation and polygenic risk scores. https://bit.ly/3ZUAM9v

Introduction

Interstitial lung abnormalities (ILA), defined as incidental radiological findings on computed tomography (CT) scans of the chest, are common and have been increasingly recognised as an early form of pulmonary fibrosis given their common risk factors [1]. Large population-

based cohorts and lung cancer screening cohorts estimate that the prevalence of ILA ranges from 3% to 10% in middle- to older-aged adults [2–5]. Advanced age, smoking and biomarkers of alveolar ageing have been associated with higher odds of prevalent ILA and idiopathic pulmonary fibrosis (IPF), suggesting shared underlying pathophysiology [2, 6, 7]. Additionally, a common variant in the promoter of the *MUC5B* gene (rs35705950) has been found to be associated with prevalent ILA and IPF [8, 9], indicating shared genetic risk.

A multidisciplinary position paper by the Fleischer Society recommends the reporting of ILA as they are associated with adverse clinical outcomes in numerous populations, including progression, mortality and cancer-associated treatment toxicities [1]. If ILA reporting was incorporated into clinical practice, then these reads would be made by a single radiologist instead of by consensus across multiple observers, a practice widely adopted in the research setting [5, 10, 11]. However, the concordance of single-radiologist ILA has never been systematically studied.

The prevalence of ILA is several hundred-fold higher than the prevalence of IPF, which is a rare disease [12–15]. Given the differences in prevalence, it is possible that the majority of ILA either regress or never progress to symptomatic pulmonary fibrosis. Longitudinal studies have identified patterns of ILA that have a greater proclivity for progression and, thus, may be more specific indicators of early IPF [16]. ILA with features of fibrosis or with a basal-peripheral predominance has been proposed to fit within an algorithm for the management of ILA and surveillance for transformation to interstitial lung diseases (ILD) [17]. However, no formal analysis of incident ILA or fibrotic ILA has been previously calculated or investigated. Studying newly detected ILA or fibrotic ILA, as opposed to prevalent abnormalities, may lead to a better understanding of causation.

The goal of this study was to estimate the incidence of ILA and fibrotic ILA in a multi-ethnic population through evaluation of cardiac CT scans. Secondary aims were to assess the reproducibility of single-observer ILA and to define risk factors of incident ILA and incident fibrotic ILA.

Methods

More detailed methodology is available in the supplementary material.

Study participants

The Multi-Ethnic Study of Atherosclerosis (MESA) is a National Heart, Lung, and Blood Institute-sponsored prospective cohort study that originally enrolled 6814 adults between the ages of 45 and 84 years from six US communities. At enrolment and during the subsequent four exams (2000–2012), participants had non-contrast cardiac CT scans. Smoking status, as previously defined, was assessed at each exam visit [2].

Cardiac CT analysis of ILA

Training of thoracic radiologists for scoring ILA is described in the supplementary material. Lung windows of cardiac CT scans were assessed for the presence or absence of ILA as

previously described [1]. The superior portions of the lungs above the aortic arch were not assessed, but most of the lower lobes were included in the cardiac imaging. ILA was defined as the presence of non-dependent ground-glass abnormalities, reticulations, non-emphysematous cysts, traction bronchiectasis or honeycombing in ⩾5% of any lung zone [1]. Scans with ILA patterns found to involve <5% of a lung zone were considered indeterminate. Fibrotic ILA was defined as the subset of ILA that displayed honeycombing, traction bronchiectasis or architectural distortion and findings were categorised as unilateral or bilateral. CT-derived high attenuation area (HAA: percent lung voxels > −600 and < −250 HU) was obtained using an automated approach as was previously described and correlated with ILD [18].

Common variant genotypes

MUC5B (rs35705950) was obtained from whole-genome sequencing as part of the TOPMed program (https://topmed.nhlbi.nih.gov). Polygenic risk scores are described in the supplementary material.

Statistical analysis

Approximately 5% of the scans were randomly assigned to the same or different radiologist to determine intra- and inter-reader variability, respectively. Agreement was based on radiologists' grouping of scans into one of three categories: ILA, indeterminate ILA and no ILA. We used Gwet's first-order agreement coefficient (AC1) [19] to calculate chance-corrected agreement, as it is more reliable than Cohen's κ in the absence of an even balance across categories [20]. The interclass correlation coefficient (ICC) [21] was calculated from a logistic regression that models the feature with random effects for participant and radiologist.

For the incidence analyses, indeterminate scans were grouped with normal scans. Participants with ILA or fibrotic ILA present at Exam 1 were excluded from their respective incidence analyses and all subsequent CT scans were evaluated for the presence of new ILA or fibrotic ILA. Incidence rates of ILA were calculated as the ratio of the number of new cases to the number of at-risk person-years (per 1000). We calculated stratified analyses to identify risk factors for ILA development. Unadjusted incidence rates ratios and confidence intervals were obtained using Poisson regression. Kaplan–Meier curves were created to illustrate the proportion of individuals who developed ILA.

Hazard ratios were estimated using Cox proportional hazard models adjusting for the covariables of age, race/ethnicity, sex, smoking status (defined as ever versus never), body mass index (BMI), percent HAA, *MUC5B* (rs35705950) single nucleotide polymorphism (SNP) and polygenic risk score. In the models in which HAA was included, we adjusted for CT scanner parameters, percent total lung imaged and percent emphysema. When performing Cox regression models using genetic data, we included the first four principal components as covariates for multivariable adjustment of ancestry.

Results

A total of 14 022 cardiac CT scans from Exam 1 through Exam 5 of the MESA study were analysed for the presence of ILA. 78 scans with insufficient images were excluded, leaving 13 944 CT scans for review (table 1).

A total of 6197 individuals had baseline cardiac CT scans (figure 1 and supplementary table S1). Of these, 53% were female, with a mean±SD age of 62.0±10.2 years. 39% were non-Hispanic White, 28% were Black, 21% were Hispanic and 12% were Asian. 50% were ever-smokers with a median 15 pack-year smoking history.

Five percent of the scans were analysed in a blinded fashion to evaluate the intra- and inter-reader reliability in identifying ILA. The intra-reader agreement of ILA was 92.0% (Gwet's AC1 0.912, ICC 0.982) and the inter-reader agreement of ILA was 83.5% (Gwet's AC1 0.814, ICC 0.969) (supplementary tables S2–S4). Advanced participant age was associated with increased intra- and inter-reader ILA disagreement (supplementary table S5).

Prevalent and incident interstitial lung abnormalities

The proportion of participants with prevalent ILA ranged from 4.3% to 7.3% (table 1 and supplementary figure S1). Representative examples of ILA are included in figure 2. Prevalent ILA on cardiac CT scan at Exam 1 was associated with older age, race/ethnicity and higher BMI (supplementary table S1). After excluding participants with ILA at Exam 1 and those without a CT assessment after Exam 1 (n=714), 5195 participants had at least one follow-up cardiac CT scan assessed for incident ILA. Of those included in the incident ILA analysis, 48% were female, with a mean±SD age of 61.4±10.0 years. 41% were White, 27% were Black and 21% were Hispanic. Half had a history of smoking. Each participant had an average of 2.3 cardiac CT scans over the course of the study period with a mean (range) follow-up time of 3.9 (1.2–11.2) years. The participants were followed for a total of 19 748 person-years. A total of 259 new cases of ILA were found after Exam 1, corresponding to an ILA incidence of 13.1 per 1000 person-years (table 1). In a sensitivity analysis in which indeterminate ILA scans were removed from the analysis, the rate was 12.7 per 1000 person-years (supplementary table S6). Ground-glass opacities and reticulations were the most common ILA pattern seen in incident ILA cases (supplementary table S7).

Incident ILA increased with age, from 7.8 per 1000 person-years for those aged 45–54 years to 31.7 per 1000 person-years for those aged 75–84 years (table 2 and figure 3). The crude incidence rate ratio for individuals aged 75–84 years was 4.05 (95% CI 2.75–5.97) compared with the youngest group.

After adjusting for confounders, every 1-year increase in age was associated with 6% higher risk of ILA over the follow-up period (HR 1.06 (95% CI 1.05–1.08); $p<0.001$) (table 3). Every 1% increase in HAA was associated with a 5% increased risk in ILA (HR 1.05 (95% CI 1.03–1.07); $p<0.001$). Race/ethnicity, sex, smoking and BMI were not independently associated with incident ILA.

Prevalent and incident fibrotic interstitial lung abnormalities

Prevalent fibrotic ILA ranged from 1.1% to 2.8% across exams (table 1 and supplementary figure S2). Prevalent fibrotic ILA on cardiac CT scan at Exam 1 was associated with older age and ever-smoking (supplementary table S8). We repeated the incident analysis, this time only taking fibrotic ILA patterns into consideration. After excluding the 76 participants with fibrotic ILA on Exam 1, 5373 participants had at least one follow-up cardiac CT scan assessed for incident fibrotic ILA. There were 71 incident fibrotic ILA cases over 20 525 person-years, correlating to an incidence of 3.5 per 1000 person-years. Traction bronchiectasis was the most common pattern (supplementary table S9).

Age and baseline HAA were again associated with the development of incident fibrotic ILA. Incident fibrotic ILA increased with older age, from 0.9 per 1000 person-years for those aged 45–54 years to 6.0 per 1000 person-years for those aged 75–84 years of age (table 2). The crude incidence rate ratio for individuals aged 75–84 years was 6.52 (95% CI 2.31–20.93) compared with the (reference) youngest group. The incidence rate of fibrotic ILA for ever-smokers was 4.5 per 1000 person-years compared with 2.3 per 1000 person-years in never-smokers, corresponding to an incidence rate ratio of 1.94 (95% CI 1.16–3.34). The incidence of fibrotic ILA was similar in males and females, and there was no difference among different race/ethnicity or BMI categories.

In an adjusted model that included smoking and HAA, every 1-year increase in age was associated with an 8% higher risk for incident fibrotic ILA (HR 1.08 (95% CI 1.06–1.11); p<0.001) (table 3). Ever-smokers had 2.31 times higher risk of developing fibrotic ILA patterns compared with never-smokers (HR 2.31 (95% CI 1.34–3.96); p=0.002). Every 1% increase in HAA was associated with 6% higher risk of incident fibrotic ILA (HR 1.06 (95% CI 1.02–1.10); p=0.002). Race/ethnicity, sex and BMI were not independently associated with incident fibrotic ILA.

Genomic factors

The incidence rate ratio for fibrotic ILA was associated with the *MUC5B* promoter variant (rs35705950) (table 2 and figure 3). In a multivariable model adjusting for age, sex, race/ethnicity and smoking, the *MUC5B* SNP was associated with incident ILA and with fibrotic ILA (OR 1.73 (95% CI 1.17–2.56); p=0.01 and OR 4.96 (95% CI 2.68–9.15); p=0.001, respectively) (table 3). We examined the associations between polygenic risk scores calculated for SNPs associated with ILA [8] and IPF [9] (table 4). The ILA polygenic risk score was dependent on the *MUC5B* promoter SNP for both incident ILA and incident fibrotic ILA. The IPF polygenic risk score was associated only with incident fibrotic ILA. Every 1-point increase in the IPF polygenic risk score was associated with 2.09 times higher risk (HR 2.09 (95% CI 1.61–2.71); p<0.001) for fibrotic ILA and the association remained significant even after the removal of the *MUC5B* SNP. There was no association between the telomere length polygenic risk score [22] and either incident ILA or incident fibrotic ILA.

Discussion

To the best of our knowledge, this is the first study to calculate the incidence of ILA and fibrotic ILA in a multi-ethnic population. We report an overall ILA incidence of 13.1 cases per 1000 person-years in a large population-based cohort of adults >45 years of age. Similarly, we report the incidence of fibrotic ILA, as defined as the subset of incident ILA cases with honeycombing, traction bronchiectasis, architectural distortion or bilateral fibrosis, at 3.5 cases per 1000 person-years in this cohort. Our estimations of ILA incidence are similar to those of COPD (2.3–8.9 per 1000 person-years) [23–25], indicating a significant burden in the general population. Nearly all prior ILA studies have been cross-sectional in design and have studied its prevalence. Although a few studies have evaluated a change in the presence of ILA over time [16, 26], the overall incidence of new cases in prior studies seems to be broadly concordant with these results, although not formally calculated.

This study differs from other ILA studies in that 5% of all scans were analysed in a blinded fashion by highly experienced thoracic radiologists to evaluate their intra- and inter-reader reliability in identifying ILA. While there was 92% and 83.5% agreement of ILA in intra- and inter-reader analyses, respectively, these values are inflated by the large numbers of CT scans for which the readers agreed had no evidence of ILA. It is worth noting that among the scans that were read as positive for ILA by a radiologist, 58% (11 out of 19) were re-read as being positive for ILA by the same radiologist and 46% (11 out of 24) were re-read as being positive for ILA by a different chest radiologist. So, while the ICC values for intra- and inter-reader reliability for ILA were high (0.982 and 0.969, respectively), Gwet's AC1 values were lower (0.912 and 0.814, respectively) but still within the range considered indicative of good agreement. We find that both increased age and higher baseline HAA are associated with a higher odds of reader disagreement, and postulate that this finding is likely confounded by the relationship between these variables and ILA. Whereas many ILA studies rely on consensus between two or more radiologists [4, 16, 26], our findings provide a single-reader estimate of ILA. This study highlights the difficulty of thoracic radiologists, even after completing training and testing modules, to agree upon this subtle imaging phenotype. In the future, other quantitative pattern analyses and machine learning techniques may bypass this limitation [27, 28].

We find that both incident ILA and incident fibrotic ILA are robustly associated with age, similar to nearly all other studies of prevalent ILA [1]. Similarly, we find a strong association between the *MUC5B* promoter SNP (rs35705950) and incident ILA as well as incident fibrotic ILA. This SNP accounts for the largest proportion of genetic risk of IPF of all common genetic loci [29], as further evidenced by the considerable lessening of the polygenic risk scores association without it. Interestingly, we also find that the IPF polygenic risk score is associated only with incident fibrotic ILA, with or without inclusion of the *MUC5B* SNP. These findings underscore a key difference between incident ILA and incident fibrotic ILA, and reinforce the similarity of genetic underpinnings between fibrotic ILA and IPF [8, 9, 30, 31]. Although a telomere length polygenic risk score has been causally linked to IPF [32], the lack of an association between the telomere polygenic risk score and incident ILA may indicate that different genomic risk factors confer risk for progression of ILA to IPF. Additional studies will be needed to further probe the

contributions of individual and composite SNPs with regard to ILA subtypes and risk of progression.

In contrast to other studies that have linked exposure to tobacco smoke prevalent ILA [33], we find that smoking is a not a risk factor for incident ILA but is specifically associated with incident fibrotic ILA. We also report the novel finding that HAA measurement at Exam 1 is associated with both incident ILA and incident fibrotic ILA. HAA represents an objective and quantitative measure of radiological abnormality that has been independently associated with reduced lung function, biomarkers of lung injury and inflammation, and ILD-related mortality/hospitalisation [2, 18]. Choi *et al.* [34] found that MESA participants with greater HAA at Exam 1 had a greater likelihood of having prevalent ILA on full lung CT scans by Exam 5. This study suggests that HAA may represent one of the earliest CT manifestations and may predict the later onset of incident ILA or fibrotic ILA.

There are a number of limitations of this study. We assessed ILA on cardiac CT scans, which only include 60–70% of the lung zones and often exclude the upper lung zones above the heart. The ILA prevalence on Exam 5 cardiac CT scans was 7.3% compared with 10.5% on full lung CT scans [18]. The exclusion of the upper lung zones may explain this variance. Cardiac CT scans parameters, including size thickness and kernel reconstruction, are also different than those used in high-resolution CT scans. The use of cardiac CT scans may also explain the relatively low number of indeterminate scans compared with a prevalence of up to 44% reported in studies using full lung CT scans [5, 18, 26, 35]. Differences in scan protocols across different MESA sites, followed during various MESA exam periods, or set by participant weight, may have contributed to differences in the incidence of fibrotic ILA, as fine reticulations and traction bronchiectasis may have been obscured by lower resolution imaging. Incidence data of ILA and fibrotic ILA were determined for a cohort with no known baseline cardiovascular disease, and so may not be fully representative of the older adult population. This study differs from others by the variable amount of time between qualified scans for participants. Only a portion of the cohort was captured at each time-point for subsequent exams by design, so it is difficult to ascertain differential loss to follow-up. Because of the low number of incident cases, there was limited power to assess other risk factors and outcomes, such as progression. In addition, the polygenic risk scores were based upon known SNPs and did not include other SNPs that did not rise to a similar level of statistical significance.

In conclusion, the single-observer assessment of ILA and fibrotic ILA from longitudinal imaging studies has allowed calculations of incident ILA and fibrotic ILA to be 13.1 and 3.5 cases per 1000 person-years, respectively, in a multi-ethnic population >45 years of age. These rates are ~100-fold greater than the incidence of IPF, which ranges between 5.8 and 17.4 per 100 000 person-years in the USA [12, 15]. This study highlights the utility of cardiac CT scans to detect incipient pulmonary fibrosis and the significant burden of abnormal scans in the general population. Even as these scans are typically ordered to assess cardiovascular risk, findings from the evaluation of the extra-cardiac portions may detect early stages of lung disease. Additional follow-up of this cohort and others may lead to a better understanding of the clinical variables, biomarkers and timespan that predicts progression of ILA to pulmonary fibrosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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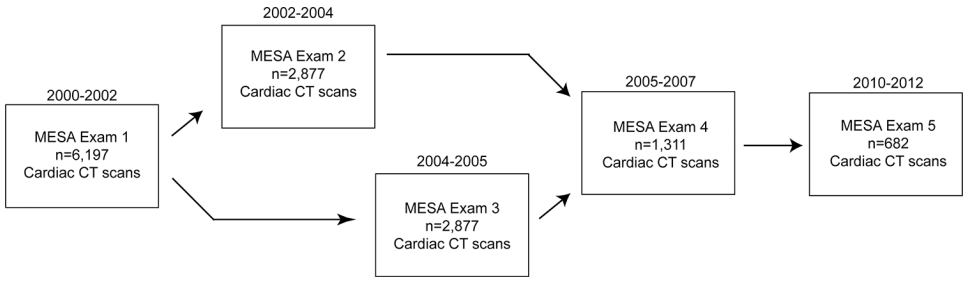

FIGURE 1.

Study timeline with longitudinal cardiac scan imaging of Multi-Ethnic Study of Atherosclerosis (MESA) participants. At enrolment and during the subsequent four exams (2000–2012), participants had non-invasive assessment of cardiovascular status, including cardiac computed tomography (CT) scans. The number of cardiac CT scans included in this study's incidence analysis are shown for each of the five different exam periods. By design, after Exam 1, all returning participants had a repeat cardiac CT scan at either Exam 2 (2955 participants) or at Exam 3 (2805 participants). Approximately 30% (1405 participants) had a cardiac CT scan at Exam 4. Only a subset of the Exam 5 cardiac CTs were analysed in this study.

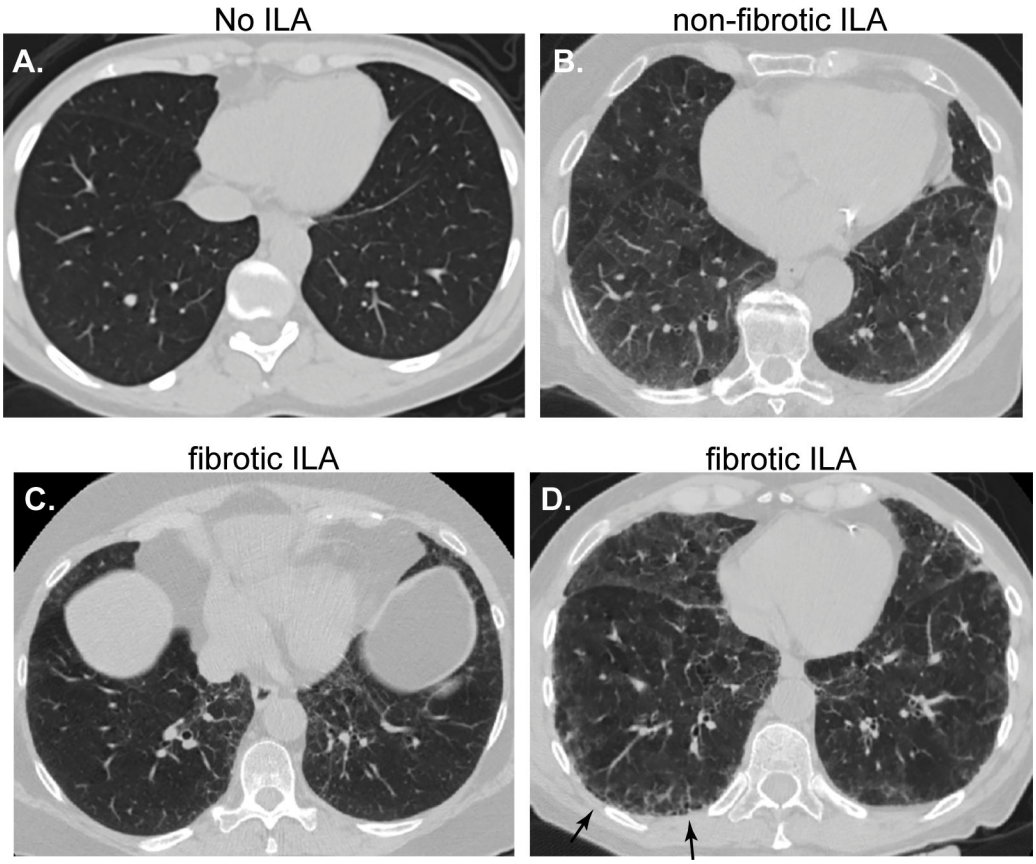

FIGURE 2.

Representative cardiac computed tomography scan imaging of Multi-Ethnic Study of Atherosclerosis participants. Example scans with a) no interstitial lung abnormalities (ILA), b) non-fibrotic ILA characterised by increased ground-glass opacities, and fibrotic ILA with c) bilateral peripheral reticulations and traction bronchiolectasis, and d) extensive bilateral peripheral reticulation, ground-glass opacities and honeycombing (arrows).

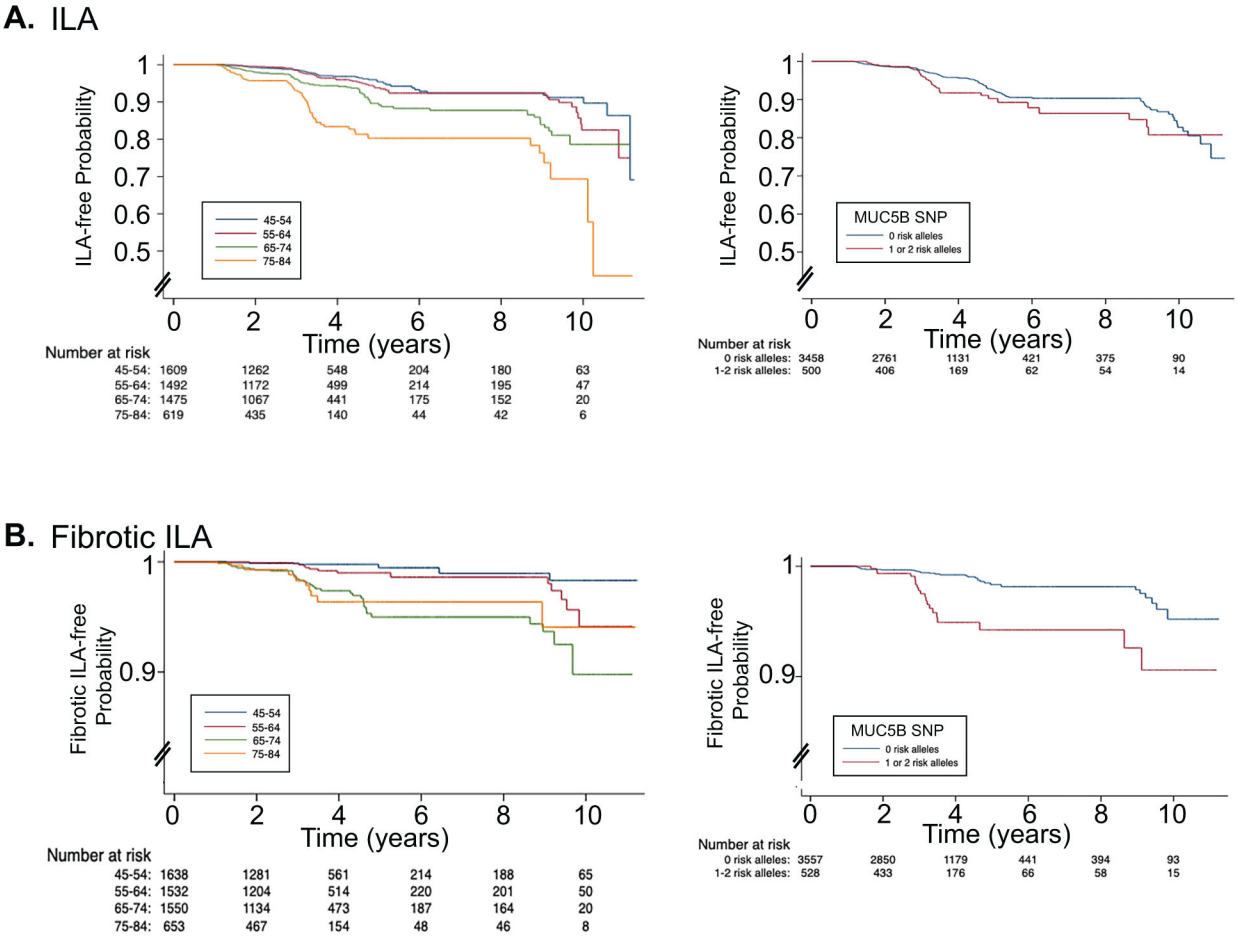

FIGURE 3.

Kaplan–Meier curves of time to a, b) interstitial lung abnormalities (ILA) and c, d) fibrotic ILA for a, c) age and b, d) *MUC5B* minor allele. a, c) Proportion of participants who are ILA- or fibrotic ILA-free are shown for subjects of increasing decades of age: 45–54, 55–64, 65–74 and 75–84 years. b, d) Proportion of participants who are ILA- or fibrotic ILA-free of those without the *MUC5B* minor allele and those with at least one minor risk allele.

TABLE 1

Prevalent interstitial lung abnormalities (ILA), incident ILA, prevalent fibrotic ILA and incident fibrotic ILA by Multi-Ethnic Study of Atherosclerosis (MESA) exam

	MESA Exam 1	MESA Exam 2	MESA Exam 3	MESA Exam 4	MESA Exam 5	Total
Years	2000–2002	2002–2004	2004–2005	2005–2007	2010–2012	
Prevalent ILA						
Follow-up time, years (mean±SD)		1.7±0.3	3.2±0.3	4.9±0.5	9.6±0.6	
Reads, n	6197	2877	2877	1311	682	13 944
ILA present, n	288	123	155	79	50	
Prevalence, %	4.7	4.3	5.4	6.0	7.3	
Incident ILA						
Reads, n		2506	2516	1116	569	
Incident ILA, n		78	103	47	31	259
At risk[#], n		5195	3716	1544	569	19 748 person-years at risk
Incidence, %		3.1	4.1	4.1	5.3	13.1 per 1000 person-years
Prevalent fibrotic ILA						
Reads, n	6197	2877	2877	1311	682	13 944
Fibrotic ILA present, n	76	33	45	21	19	
Prevalence, %	1.2	1.1	1.6	1.6	2.8	
Incident fibrotic ILA						
Reads, n		2583	2612	1165	599	
Incident ILA, n		18	31	11	11	71
At risk[#], n		5373	3863	1614	599	20 525 person-years at risk
Incidence, %		0.7	1.2	0.9	1.8	3.5 per 1000 person-years

[#]: number of participants at risk for developing ILA prior to the indicated MESA exam period. Participants who developed ILA and those who did not have a subsequent valid cardiac CT scan for analysis (censored) were removed from the at-risk group for the subsequent exam.

TABLE 2

12-year incidence of interstitial lung abnormalities (ILA) and fibrotic ILA in the Multi-Ethnic Study of Atherosclerosis cohort followed from 2000 to 2012

	Incident ILA					Incident fibrotic ILA				
	Participants, n (%)	**Person-years**	**Cases (n)**	**IR (per 1000 person-years)**	**Crude IRR (95 CI)**	**Participants, n (%)**	**Person-years**	**Cases (n)**	**IR (per 1000 person-years)**	**Crude IRR (95% CI)**
Age, years										
47–54	1609 (31)	6371	50	7.8	1	1638 (30)	6509	6	0.9	1
55–64	1492 (29)	5980	58	10	1.23 (0.83–1.84)	1532 (29)	6152	14	2.3	2.47 (0.89–7.83)
65–74	1475 (28)	5380	87	16.2	**2.06 (1.44–2.98)**	1550 (29)	5702	38	6.7	**7.23 (3.03–20.92)**
75–84	619 (12)	2015	64	31.7	**4.05 (2.75–5.97)**	653 (12)	2161	13	6.0	**6.52 (2.31–20.93)**
Sex										
Female	2718 (52)	10 293	137	13.3	1	2821 (52)	10 731	38	3.5	1
Male	2477 (48)	9455	122	12.9	0.97 (0.75–1.25)	2552 (48)	9794	33	3.4	0.95 (0.58–1.56)
Race/ethnicity										
White	2127 (41)	8360	99	11.8	1	2180 (40)	8599	29	3.4	1
Asian	613 (12)	2083	30	14.4	1.22 (0.78–1.85)	631 (12)	2165	6	2.8	0.82 (0.28–2.01)
Black	1394 (27)	5191	68	13.1	1.11 (0.80–1.52)	1450 (27)	5419	21	3.9	1.15 (0.62–2.09)
Hispanic	1061 (20)	4113	62	15.1	1.27 (0.91–1.77)	1112 (21)	4342	15	3.5	1.02 (0.51–1.97)
Smoking status [#]										
Never-smoker	2600 (50)	9456	116	12.3	1	2692 (50)	9865	23	2.3	1
Ever-smoker	2580 (505)	10 238	143	14.0	1.14 (0.88–1.47)	2666 (50)	10 607	48	4.5	**1.94 (1.16–3.34)**
BMI, kg·m^{-2}										
Normal (18.5–24.9)	1493 (29)	5428	57	10.5	1	1525 (28)	5552	18	3.2	1
Underweight (<18.5)	41 (1)	177	2	11.3	1.07 (0.13–4.05)	41 (1)	177	1	5.6	1.73 (0.04–11.01)

	Incident ILA					Incident fibrotic ILA				
	Participants, n (%)	**Person-years**	**Cases (n)**	**IR (per 1000 person-years)**	**Crude IRR (95 CI)**	**Participants, n (%)**	**Person-years**	**Cases (n)**	**IR (per 1000 person-years)**	**Crude IRR (95% CI)**
Overweight (25–29.9)	2022 (39)	7826	118	15.1	1.43 (1.04–2.00)	2097 (39)	8177	32	3.9	1.22 (0.65–2.28)
Obese (>29.9)	1639 (31)	6315	82	13.0	1.23 (0.87–1.77)	1710 (32)	6618	20	3.0	0.93 (0.47–1.87)
***MUC5B* risk alleles** ¶										
0	3458 (87)	13 445	162	12.0	1	3557 (87)	13 903	36	2.5	1
1 or 2	500 (13)	1974	35	17.7	1.47 (0.99–2.13)	528 (13)	2092	20	9.6	**3.80 (2.08–6.76)**
Overall cohort	5195	19 748	259	13.1		5373	20 525	71	3.5	

IR: incidence rate; IRR: incidence rate ratio; BMI: body mass index.

#: missing smoking status for 15 participants;

¶: genetic information missing for 1227 participants in the incident ILA analysis and 1288 participants in the incident fibrotic ILA analysis. Bold indicates statistical significance (p<0.05).

TABLE 3

Predictors of incident interstitial lung abnormalities (ILA) and incident fibrotic ILA

	Incident ILA		Incident fibrotic ILA	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Model 1				
Age	1.06 (1.05–1.07)	**<0.001**	1.09 (1.06–1.11)	**<0.001**
Race/ethnicity				
(White)	1		1	
Asian	1.34 (0.89–2.04)	0.16	1.03 (0.42–2.52)	0.95
Black	1.22 (0.89–1.04)	0.22	1.26 (0.72–2.22)	0.42
Hispanic	1.35 (0.98–1.86)	0.06	1.10 (0.59–2.06)	0.76
Male sex	0.93 (0.72–1.19)	0.56	0.83 (0.55–1.36)	0.49
Ever-smoking[#]	1.19 (0.93–1.54)	0.17	2.07 (1.24–3.48)	**0.01**
Model 2				
Age	1.06 (1.05–1.08)	**<0.001**	1.08 (1.06–1.11)	**<0.001**
Race/ethnicity				
(White)	1		1	
Asian	1.16 (0.72–1.88)	0.54	1.35 (0.50–3.64)	0.55
Black	1.12 (0.81–1.56)	0.50	1.44 (0.79–2.65)	0.24
Hispanic	1.19 (0.84–1.68)	0.32	1.24 (0.63–2.47)	0.53
Male sex	1.11 (0.82–1.50)	0.51	0.67 (0.38–1.19)	0.17
Ever-smoking	1.26 (0.97–1.63)	0.08	2.31 (1.34–3.96)	**0.002**
BMI, $kg \cdot m^{-2}$	1.01 (0.98–1.03)	0.72	0.99 (0.94–1.04)	0.75
HAA, % baseline[¶]	1.05 (1.03–1.07)	**<0.001**	1.06 (1.02–1.10)	**0.002**
Model 3 [+]				
Age	1.06 (1.04–1.08)	**<0.001**	1.09 (1.06–1.12)	**<0.001**
Male sex	1.07 (0.80–1.44)	0.66	0.93 (0.53–1.64)	0.79
Ever-smoking	1.31 (0.97–1.77)	0.08	3.20 (1.65–6.22)	**0.001**
MUC5B risk allele[§]	1.73 (1.17–2.56)	**0.01**	4.96 (2.68–9.15)	**<0.001**

HR: hazard ratio; BMI: body mass index; HAA: high attenuation area.

[#]: missing smoking status for 15 participants;

[¶]: HAA model also adjusted for computed tomography scanner, total volume of imaged lung and percent emphysema;

[+]: Model 3 adjusted for the first four principal components of genomic ancestry as described in the Methods *(MUC5B* genotype data missing for 1227 participants in the incident ILA analysis and 1288 participants in the incident fibrotic ILA analysis, thus in Model 3 n=3950 and n=4077 for incident ILA and incident fibrotic ILA, respectively);

[§]: risk allele of rs35705950 GG *versus* GT or TT. Bold indicates statistical significance (p<0.05).

TABLE 4

Association between polygenic risk score (PRS) with incident interstitial lung abnormalities (ILA) and incident fibrotic ILA

Model[#]	Incident ILA		Incident fibrotic ILA	
	HR (95% CI)	p-value	HR (95% CI)	p-value
+ILA PRS [¶]	1.89 (1.26–2.83)	**0.002**	3.26 (1.62–6.40)	**0.001**
+ILA PRS without *MUC5B* SNP	1.72 (0.93–3.18)	0.08	0.48 (0.13–1.73)	0.26
+IPF PRS [+]	1.17 (0.99–1.39)	0.07	2.09 (1.61–2.71)	**<0.001**
+IPF PRS without *MUC5B* SNP	1.01 (0.81–1.28)	0.90	1.63 (1.07–2.48)	**0.02**
+Telomere length PRS [§]	0.58 (0.20–1.65)	0.31	0.51 (0.08–3.65)	0.51

HR: hazard ratio; SNP: single nucleotide polymorphism.

[#]: the multivariable model was adjusted for age, sex, the first four principal components of genomic ancestry (as described in the Methods), smoking and one of the listed PRSs;

[¶]: the following loci were included in the calculation of the ILA PRS with an associated β (in parentheses): rs73199442 (0.519), rs6886640 (0.247) and rs35705950 (0.678);

[+]: the following loci were included in the calculation of the IPF PRS with an associated β (in parentheses): rs78238620 (0.457), rs12699415 (0.247), rs28513081 (−0.198), rs537322302 (2.067), rs41308092 (0.751), rs12696304 (0.270), rs2013701 (−0.248), rs7725218 (−0.329), rs2076295 (0.378), rs2897075 (0.262), rs35705950 (1.577), rs9577395 (−0.261), rs59424629 (−0.261), rs62023891 (0.239) and rs12610495 (0.270);

[§]: the following loci were included in the calculation of the telomere length PRS with an associated β (in parentheses): rs3219104 (0.042), rs10936600 (−0.086), rs4691895 (−0.058), rs7705526 (0.082), rs2853677 (−0.064), rs59294613 (−0.041), rs9419958 (−0.064), rs228595 (−0.029), rs2302588 (0.048), rs7194734 (−0.037), rs8105767 (0.039), rs75691080 (−0.067), rs34978822 (−0.140), rs73624724 (0.051), rs55749605 (−0.037), rs13137667 (0.077), rs34991172 (−0.061), rs2736176 (0.035), rs3785074 (0.035) and rs62053580 (−0.039). Bold indicates statistical significance ($p<0.05$).