Occupational Exposures and Subclinical Interstitial Lung Disease:

The MESA (Multi-Ethnic Study of Atherosclerosis) Air–Lung Study

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Abstract

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RATIONALE: The impact of a broad range of occupational exposures on subclinical interstitial lung disease (ILD) has not been studied.

OBJECTIVES: To determine whether occupational exposures to vapors, gas, dust, and fumes (VGDF) are associated with high-attenuation areas (HAAs) and interstitial lung abnormalities 4 (ILAs), which are quantitative and qualitative computed tomography (CT)–based measurements of subclinical ILD, respectively.

METHODS: We performed analyses of participants enrolled in MESA (Multi-Ethnic Study of Atherosclerosis), a population-based cohort aged 45–84 years at recruitment. HAA was measured at baseline and on serial cardiac CT scans in 5,702 participants. ILA was ascertained in a subset of 2,312 participants who underwent full-lung CT scanning at 10-year follow-up. Occupational exposures were assessed by self-reported VGDF exposure and by job-exposure matrix (JEM). Linear mixed models and logistic regression were used to determine whether occupational exposures were associated with log-transformed HAA and ILA. Models were adjusted for age, sex, race/ethnicity, education, employment status, tobacco use, and scanner technology.

RESULTS: Each JEM score increment in VGDF exposure was associated with 2.64% greater HAA (95% confidence interval [CI], 1.23–4.19%). Self-reported vapors/gas exposure was associated with an increased odds of ILA among those currently employed (1.76-fold; 95% CI, 1.09–2.84) and those less than 65 years old (1.97-fold; 95% CI, 1.16–3.35). There was no consistent evidence that occupational exposures were associated with progression of HAA over the follow-up period.

CONCLUSIONS: JEM-assigned and self-reported exposures to VGDF were associated with measurements of subclinical ILD in community-dwelling adults.

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INTRODUCTION

The interstitial lung diseases (ILDs) encompass a diverse group of chronic lung diseases, characterized by recurrent alveolar injury, parenchymal inflammation and extracellular fibrosis. Despite a low incidence rate, the ILDs are associated with significant morbidity and mortality, and remain the primary indication for lung transplantation in the United States [1]. As symptoms typically present late in the disease course, the inciting cause of injury is often unclear and difficult to distinguish from other chronic and mixed exposures.

Although the underlying etiology of the ILDs is largely unknown, occupational exposures are important risk factors, and specific disease subtypes are characteristically associated with certain exposures. For example, specific fibrogenic particulates, such as asbestos, silica or coal dust are prerequisites for the development of the pneumoconioses [2]. Inhalational exposures to a range of environmental and occupational organic antigens precipitate the immunologic reaction that characterizes hypersensitivity pneumonitis. There is also evidence suggesting that occupational exposures may contribute to the pathobiology of idiopathic forms of disease [3]. Individuals with occupational dust exposure, particularly wood and metal, have an increased risk of idiopathic pulmonary fibrosis [4-6].

Identification of subclinical radiographic forms of ILD provides a unique opportunity to study potential antecedent causes of disease in an asymptomatic population. Interstitial lung abnormalities (ILA), a qualitative assessment of early interstitial changes in nondependent portions of the lung, and high attenuation areas (HAA), a quantitative CT attenuation-based phenotype, are two validated measurements of subclinical ILD [7-9]. Even in the absence of clinical ILD, populations with subclinical interstitial lung disease have more respiratory symptoms, physiologic decrements and higher mortality [8, 10, 11].

The association between a broad range of self-reported and independently- assigned occupational exposures and subclinical ILD has not been previously investigated in a population-based study. We hypothesized that exposure to vapors, gas, dust and fumes (VGDF) would be associated with qualitative and quantitative measurements of subclinical ILD in community-dwelling adults.

Some of these results have been previously reported in the form of an abstract [12].

METHODS

Study design and participant selection

The Multi-Ethnic Atherosclerosis Study (MESA) is a prospective cohort study funded by the National Heart Lung and Blood Institute to investigate subclinical cardiovascular disease. MESA and ancillary studies, MESA Lung and MESA Air, are described in depth elsewhere and served as the sampling frame for this study [8, 13-15]. Informed consent was obtained for all participants and the study was approved by the Institutional Review Board at collaborating centers.

Briefly, MESA enrolled participants that were free of known cardiovascular disease from six centers around the United States: Baltimore, MD; Chicago, IL; Los Angeles County, CA; New York City, NY; St Paul, MN; and Winston Salem, NC. 6,814 participants, with ages between 45-84, were recruited between 2000-2002 and underwent questionnaires regarding demographics, family history, medical history, lifestyle habits and psychosocial factors. At enrollment and during the four subsequent exams, participants had noninvasive assessment of cardiovascular status including cardiac CT scans. By design, all returning participants had a repeat cardiac CT scan at either exam 2 (2955 participants) or 3 (2805 participants), 30% of the cohort (1405 participants) had a third cardiac CT scan at exam 4. 3,200 participants underwent cardiac CT scan again at exam 5 during years 2010 -12, nearly all of whom also had a full CT scan at this time.

The sampling scheme of participants included in our qualitative and quantitative assessments of subclinical ILD are described in detail in the results.

Interstitial Lung Abnormalities

Full lung MESA CT scans were acquired at suspended full inspiration using the MESA Lung/ SPIROMICS protocol, as previously described [8, 16]. One of five board-certified radiologists reviewed the full lung CT scans for ILA, which was defined as the presence of ground- glass, reticular abnormality, diffuse centrilobular nodularity, honeycombing, traction bronchiectasis, non-emphysematous cysts or architectural distortion in at least 5% of nondependent portions of the lung (inter-reader kappa 0.4706 (0.1368-0.8044)) [17].

High Attenuation Areas

HAA was measured on non-contrast cardiac CT scans performed at the MESA baseline visit and selected follow up exams using standardized protocols [18]. These cardiac CT scans image approximately 65 -70% of the total lung volume, capture most of the lower lobes and exclude much of the lung apexes. Quantitative image attenuation was measured by trained readers using a modified version of the Pulmonary Analysis Software developed by Dr. Eric Hoffman at the University of Iowa. HAA was defined as the percent of the imaged lung volume having attenuation values between -600 and -250 Hounsfield Units (HU) [8, 9]. This range of CT lung attenuation includes ground-glass and reticular abnormalities, and excludes denser areas that characterize atelectasis, medium and large blood vessels and pulmonary nodules. Percent emphysema was defined as the percentage of voxels below -950 HU.

Exposure Assessment

Occupational exposures were assessed using 2 methods: 1) by self-reported exposure to VGDF and 2) by a job-exposure matrix (JEM) previously created by the National Institute for Occupational Safety and Health (NIOSH) [19]. Self-reported exposures were obtained during MESA Exam 4 and included presence/ absence, duration and severity of exposure to VGDF. Participants were asked separately about exposure to dusts, fumes and vapors/ gas (combined into one category). Demographic questionnaires at each exam ascertained current occupation if participants were employed or the occupation where last employed if the participants were retired (see supplementary appendix). These reported occupations were coded using Bureau of Census 2002 occupational codes by trained staff from NIOSH. One industrial hygienist assigned an initial score based on the four-digit US Census Occupation code, representing the likelihood and severity of exposure (low, intermediate or high) to vapors/ gas, fumes, dust, subcategories of dust (inorganic versus organic) and combined VGDF exposure. The other 2 hygienists reviewed the preliminary scoring and reached a final consensus score.

Statistical Analysis

All statistical tests were performed in SAS version 9.3 (SAS institute, Cary, NC) using a two-tailed p-value with α of 0.05 to define statistical significance.

Occupational risk factors were defined according to self-reported exposures and the exposures established using the NIOSH JEM. Occupational exposure variables that were individually evaluated in models included self-reported exposures to vapors/ gas, dust or fumes (VGDF); any VGDF exposure (none versus any); severity of VGDF exposure (none, mild, moderate or severe); years of exposure to VGDF; and JEM- assigned VGDF exposure scores (low, intermediate or high). In the main analyses, exposures with more than one category were treated as ordinal variables and duration of exposure to VGDF was treated as a continuous variable. As the difference in severity between categories of exposures may not be linear, these exposure variables were treated as dummy variables in sensitivity analyses.

Multivariable logistic regression was used to examine associations between occupational exposures and the odds of ILA on full lung CT scan at exam 5. Models were adjusted for age, gender, ethnicity, tobacco use (current smoking status and pack years) and site. We assessed for effect modification through models stratified on age, gender, ethnicity, employment status and smoking status. Where stratified models showed differential effects, we tested for statistical significance with nested models including an interaction term between the exposure and potential effect modifier.

A linear mixed model was used to analyze the cross sectional association between occupational exposures and HAA at baseline examination and the relationship between occupational exposures and the rate of progression of HAA. HAA was log transformed in the model, and back transformed to obtain an estimate of percent change. Repeat measurements were modeled as a function of study time, and time varying exposures modeled as an interaction with time to examine the associations with the linear rate of change of HAA over time. Participant-specific random intercepts and slopes were included. Models were adjusted for potential confounders selected *a priori*: age, gender, educational attainment, employment status, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate, total volume of imaged lung, percent emphysema on CT scan, scanner type and study site. Potential effect modification was examined with stratification based on smoking status, gender, ethnicity, age and employment status.

RESULTS

Subject Characteristics

A total of 6,813 MESA participants underwent a cardiac CT scan that was assessed for HAA at baseline, and 5,965 participants had at least one follow up cardiac CT scan. The average number of cardiac CT scans per participant was 2.4, with mean follow up time of 5.9 years (range 0.9 to 11.4 years). After excluding participants missing adjustment covariates or occupational exposures, 5702 participants were included in the longitudinal assessment of progression of HAA (see Figure 1 below).

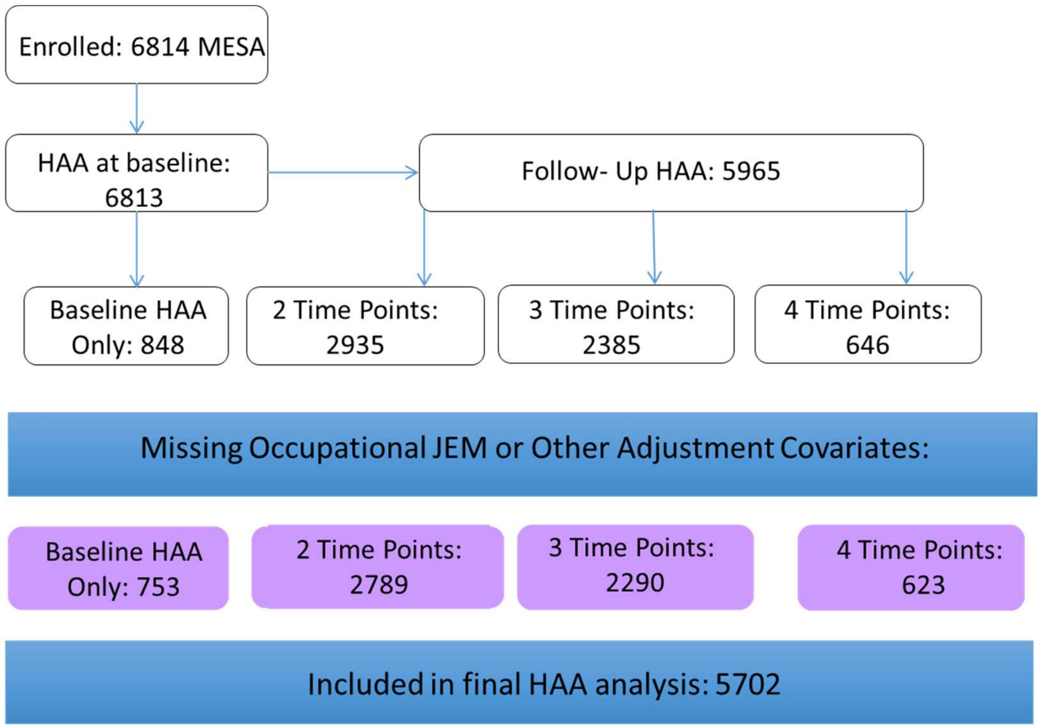


Figure 1: Number of participants included in the analysis of HAA prevalence and progression. The number in the shaded box (last row) represents the number of measurements included in the analysis of JEM –estimated occupational exposures. JEM - job exposure matrix, HAA- high attentuation area

A total of 3,137 MESA participants, including some of the participants recruited under MESA Air, had a full lung CT scan that was assessed by a radiologist, 128 were not read for ILA, and 34 had unreadable scans. As previously done, we further excluded 491 full lung CT scans that were read as "indeterminate" for ILA [17]. Additional participants that were missing occupational exposures or other covariates were excluded from final ILA analyses (see Figure 2), leaving 2,312 participants for analysis.

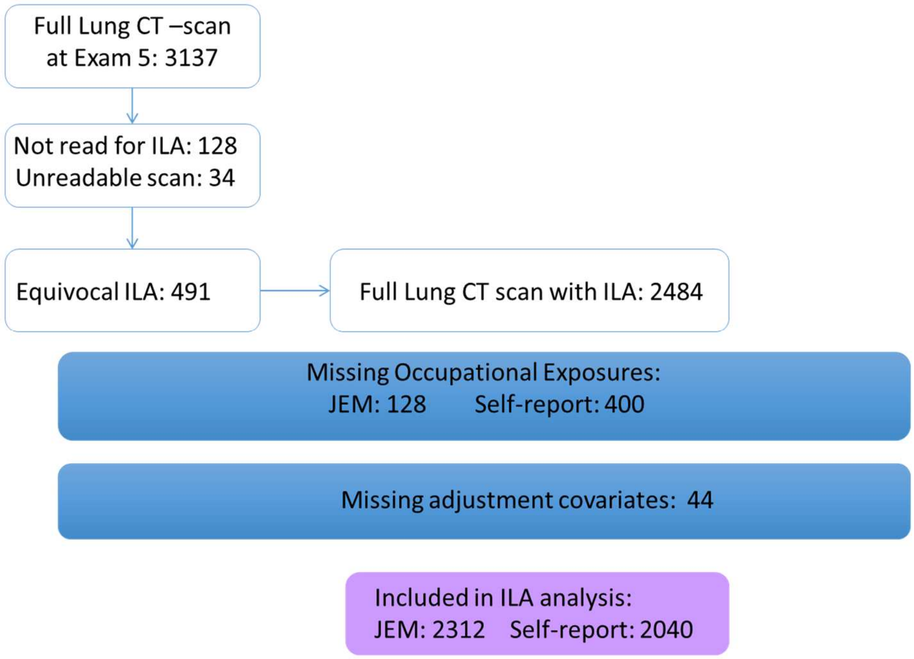


Figure 2: Number of participants included in the analyses of ILA prevalence. The number in the purple shaded box (last row) represents the number of measurements included in the analysis of occupational exposures. ILA- interstitial lung abnormalities

Baseline characteristics were similar in the analytic groups used for ILA and HAA analyses (Table 1). A total of 2,528 (44.3%) of the participants included in the HAA analysis had never smoked, whereas 1,287 (55.7%) of the participants in the ILA analysis had never smoked. The mean age of the MESA cohort at baseline was 62 years (SD 10) and 3214 (47%) were male. Racial/ ethnic differences were based on study design: 2621 (39%) participants were white, 1893 (28%) were African American, 1496 (22%) were Hispanic and 803 (12%) were Asian (Chinese).

TABLE 1: Baseline Characteristics at Participant Recruitment

	HAA measured at Exam 1	Cohort included in HAA Model	Cohort included in ILA Model+
Participants (number)	6813	5702	2312
Age (years)	62.2 (10.2)	61.7 (10.1)	59.5 (9.3)
Male	3214 (47.2)	2813 (49.3)	1108 (47.9)
Race			
White	2621 (38.5)	2304 (40.4)	934 (40.4)
African-American	1893 (27.8)	1566 (27.5)	617 (26.7)
Hispanic	1496 (22)	1198 (21.0)	461 (19.9)
Asian (Chinese)	803 (11.8)	634 (11.1)	300 (13.06)
BMI, kg/m^2	28.3 (5.5)	28.3 (5.4)	28.3 (5.3)
Height, cm	166.4 (10)	166.8 (10.0)	167.0 (10)
Weight, lbs	173.4 (38.2)	174.3 (37.9)	174.4 (37.6)
Smoking status			
Never smokers	3085 (45)	2528 (44.3)	1287 (55.7)
Former smokers	2761 (41)	2370 (41.5)	776 (33.6)
Current smokers	967 (14)	804 (14.1)	249 (10.8)
Cigarette pack- years*	13 (2.0-31.5)	13.5 (2.2-31)	13.5 (4.0 -30.0)
Socioeconomic status			
Education			
≤ High school	2460 (36.2)	1878 (32.9)	675 (29.2)
Some college	1937 (28.5)	1669 (29.3)	675 (29.2)
≥ College	2393 (35.2)	2155 (37.8)	962 (41.6)
Income++			
< 25,000	2059 (31.5)	1560 (28.3)	536 (23.8)
25,000- 74,999	3003 (45.9)	2606 (47.3)	1118 (49.7)
≥ 75,000	1478 (22.6)	1348 (24.4)	596 (26.5)
Percent emphysema	4.2 (4.5)	4.3 (4.5)	4.0 (4.0)
Study Site			
Winston Salem, NC	1077 (15.8)	937 (16.4)	439 (19.0)
New York, NY	1102 (16.2)	963 (16.9)	408 (17.7)
Baltimore, MD	1086 (15.9)	872 (15.3)	305 (13.2)
St. Paul, MN	1066 (15.7)	921 (16.2)	330 (14.3)
Chicago, IL	1164 (17.1)	1010 (17.7)	467 (20.2)
Los Angeles, CA	1318 (19.4)	999 (17.5)	363 (15.7)

Data presented as mean ± SD, n (%) unless otherwise stated. All parameters collected at MESA baseline visit in years 2000-2002, unless otherwise stated. ILA = interstitial lung abnormalities; HAA = high attenuation areas; BMI = Body Mass Index

*median (interquartile range) among ever smokers

+ includes demographics from 53 MESA Air new recruits at time of recruitment, with exception of age, which is backdated to year 2000

++missing data on 188 participants in HAA cohort, 62 in ILA cohort

Occupational Exposures

Occupational exposures are presented in Table 2. In the entire MESA cohort, 1454 (37%) of participants reported exposure to dust, 735 (18.8%) reported exposure to vapors or gases and 929 (23.7%) reported exposures to fumes. According to the JEM, 16.4% of participants had intermediate exposures and 7.5% of participants had high exposures to VGDF; which was similar to self-reported severity of exposures. At the start of the study, 3220 (48.1%) of participants were employed and 2543 (38%) were retired. Of the participants studied at Exam 5, 2059 (44%) were still employed and 1968 (42.3%) had retired (data not shown). There was a low Spearman correlation (0.20, $p< 0.001$) between self-reported severity of exposures and exposures assigned per JEM (see Table 3).

TABLE 2: Occupational Characteristics of Participants at Recruitment

	HAA measured at Exam 1	Cohort included in HAA Model	Cohort included in ILA Model
Participants (number)	6813	5702	2312
Employment status[1]			
Homemaker	774 (11.6)	391 (6.9)	151 (6.5)
Employed	3220 (48.1)	2973 (52.1)	1385 (59.9)
Unemployed	154 (2.3)	127 (2.2)	45 (1.9)
Retired	2543 (38.0)	2211 (38.8)	731 (31.6)
Job Exposure Matrix assigned exposures			
VGDF score			
Low	4913 (76.2)	4389 (77.0)	1816 (78.6)
Intermediate	1055 (16.4)	901 (15.8)	341 (14.8)
High	481 (7.5)	412 (7.2)	155 (6.7)
Gas/ Vapor[2]	1180 (18.3)	1008 (17.7)	379 (16.4)
Dust[2]	910 (14.1)	782 (13.7)	281 (12.2)
Inorganic	397 (6.2)	350 (6.1)	125 (5.4)
Organic	468 (7.3)	393 (6.9)	146 (6.3)
Fumes[2]	306 (3.7)	262 (4.6)	98 (4.2)
Self-reported exposures[3]			
Dust	1454 (37.0)	1398 (38.1)	776 (38.9)
Gas/ Vapor	735 (18.8)	709 (19.4)	418 (21.1)
Fumes	929 (23.7)	895 (24.4)	502 (25.2)
Any VGDF exposure[4]	1713 (43.5)	1651 (44.9)	923 (46.3)
Severity[5]			
None	2212 (56.4)	2017 (55)	1070 (53.7)
Mild	977 (24.9)	946 (25.8)	537 (27.0)
Moderate	537 (13.7)	514 (14)	286 (14.4)
Severe	196 (5.0)	188 (5.1)	99 (5.0)
# of VGDF agents[6]			
0	2212 (56.7)	2017 (55.4)	1070 (54.0)
1	798 (20.5)	772 (21.2)	429 (21.7)
2	386 (9.9)	370 (10.2)	197 (10.0)
3	503 (12.9)	484 (13.3)	284 (14.3)
Years exposure to VGDF	18.2 (12.7)	18 (12.8)	17.6 (12.5)

Occupational characteristics obtained from questionnaires administered during exam 4
[1] Employment status at recruitment
[2] exposure score dichotomized into "low" versus "intermediate/ high"
[3] self- reported exposures missing dust in 2029, vapors/ gas in 2047, fumes in 2037 in HAA cohort; dust in 317, vapors/ gas in 327 and fumes in 323 in ILA cohort
[4] self-reported exposure to any VGDF agent missing in 2024 in HAA cohort, 332 in ILA cohort
[5] self- reported severity missing in 2037 in HAA cohort, 320 in ILA cohort
[6] total number of VGDF- constituent agents, calculated from self-reported exposure

Table 3: Correlation between Self-Reported and JEM-assigned Exposures				
	Self- reported			
	Any VGDF	Gas/ Vapor	Dust	Fumes
JEM- assigned				
Any VGDF	0.20			
Gas/ Vapor		0.18		
Dust			0.13	
Fumes				0.11

Association with High Attenuation Areas

At recruitment, MESA participants had a mean HAA of 5.1% (3.1% SD) with a range of 1.4% to 46.6%. HAA decreased slightly (0.35% per year [95% CI 0.21% to 0.48%]) over follow-up.

In our mixed model that adjusted for potential confounders (Table 4, Figure 3), occupational exposures were significantly associated with higher measurements of HAA in the entire cohort. With increasing exposure to VGDF as assigned by the JEM, HAA increased by 2.39% (95%CI 1.23% to 3.57%, p-value <0.001; Figure 3) per exposure category (low to intermediate to high). Sex may be an effect modifier (p-value for interaction with gender < 0.001): in females, HAA increased by 3.93% (95%CI 1.94% to 5.96%, p-value <0.001) per exposure category, compared to males, where HAA increased 1.05% (95%CI -0.30% to 2.42%, p-value 0.13) per exposure category. Sensitivity analyses treating JEM exposures as dummy variables had similar results: in general, associations were strongest in the higher compared to lower exposure categories (see Appendix).

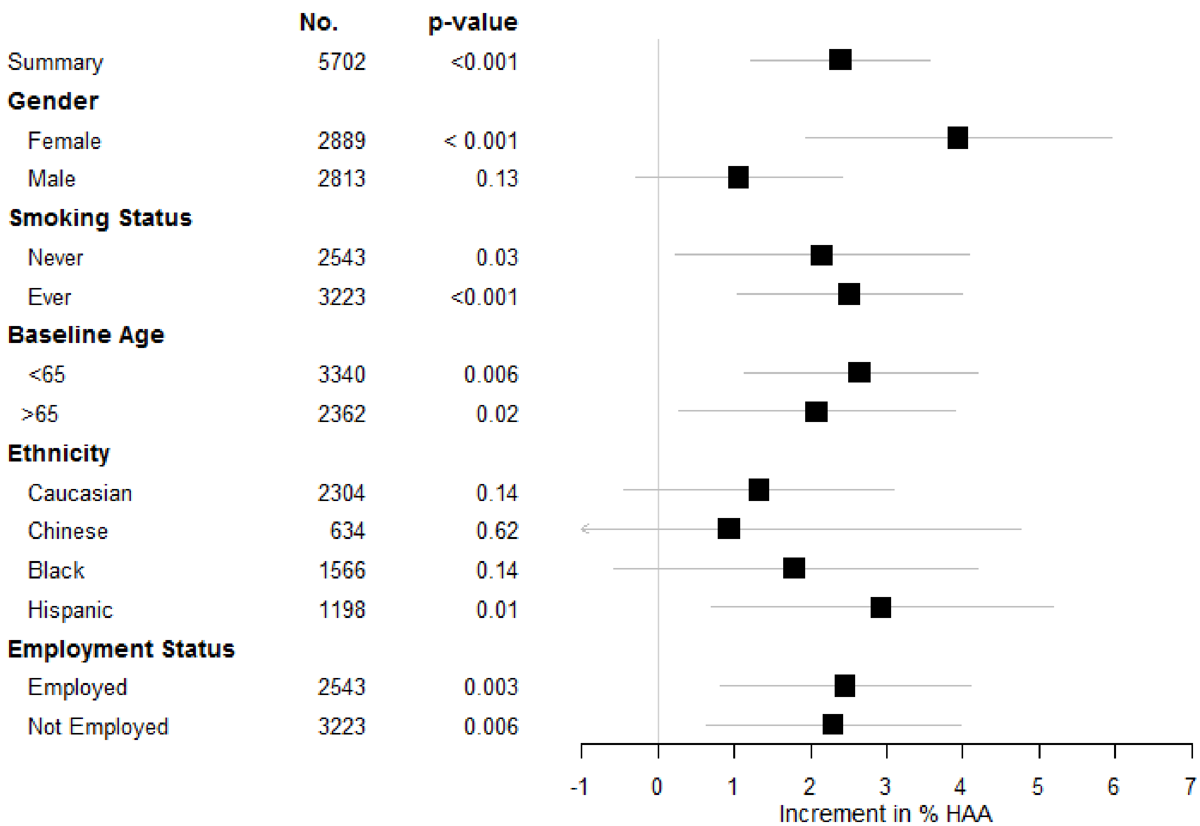
TABLE 4: Association between JEM- assigned and Self-reported Exposure to VGDF and High Attenuation Areas

	Overall Difference in % HAA (95% CI)	**Females** Difference in % HAA (95% CI)	**Males** Difference in % HAA (95% CI)	**Gender** P-interaction	**Currently Employed** Difference in % HAA (95% CI)	**Not Employed** Difference in % HAA (95% CI)	**Employment** P-interaction
JEM-assigned Exposure							
VGDF	**2.39 (1.23 to 3.57)**	**3.93 (1.94 to 5.96)**	1.05 (-0.30 to 2.42)	< 0.001	**2.45 (0.82 to 4.10)**	**2.29 (0.64 to 3.97)**	0.77
Gas/ Vapor	**1.82 (0.57 to 3.09)**	**4.80 (2.41 to 7.25)**	0.54 (-0.84 to 1.94)	< 0.001	**1.70 (0 to 3.46)**	**1.76 (0 to 3.58)**	0.99
Combined Dust	1.36 (-0.07 to 2.82)	**4.09 (1.11 to 7.15)**	-0.02 (-1.54 to 1.53)	0.002	-0.63 (-2.61 to 1.40)	**3.04 (1.00 to 5.12)**	0.02
Inorganic Dust	**2.29 (0.25 to 4.37)**	**10.1 (2.85 to 17.9)**	1.16 (-0.81 to 3.17)	0.03	-1.21 (-4.07 to 1.73)	**4.88 (2.00 to 7.83)**	0.05
Organic Dust	1.82 (-0.28 to 3.96)	**3.78 (0.19 to 7.50)**	0.25 (-0.54 to 2.72)	0.009	0.34 (-2.73 to 3.50)	2.81 (-0.07, to 5.76)	0.29
Fumes	0.14 (-1.91 to 2.23)	-0.76 (-5.13 to 3.85)	0.17 (-1.98 to 2.37)	0.45	0.48 (-2.62 to 3.68)	-0.09 (-2.84 to 2.73)	0.52
Self- Reported Exposure							
Gas/ Vapor	0.33 (-1.63 to 2.32)	-2.36 (-3.23 to 2.93)	-0.24 (-2.41 to 1.98)	0.55	1.05 (-1.36 to 3.52)	-0.21 (-3.32 to 3.01)	0.78
Dust	0.28 (-1.34 to 1.93)	0.81 (-1.57 to 3.25)	-0.33 (-2.35 to 1.75)	0.87	-0.25 (-2.27 to 1.81)	0.69 (-1.84 to 3.30)	0.63
Fumes	0.07 (-1.14 to 2.57)	0.57 (-2.33 to 3.56)	0.05 (-2.10 to 2.24)	0.43	0.80 (-1.49 to 3.15)	0.58 (-2.29 to 3.54)	0.99
Any VDGF exposure	-0.14 (-1.72 to 1.46)	-0.33 (-2.33 to 1.71)	-0.33 (-2.33 to 1.71)	0.89	-0.69 (-2.67 to 1.34)	0.13 (-2.30 to 2.61)	0.70
Severity	-0.19 (-1.05 to 0.69)	-0.44 (-1.71 to 0.85)	-0.13 (-1.22 to 0.98)	0.42	-0.67 (-1.80 to 0.48)	0.14 (-1.16 to 1.46)	0.53
Per 10 years exposure	-0.06 (-0.98 to 0.87)	-1.40 (-2.88 to 0.10)	0.64 (-0.46 to 1.76)	0.42	-0.15 (-1.39 to 0.28)	-0.02 (-1.37 to 1.35)	0.88

Adjusted for age, race, smoking status (pack years, current smoking), gender, employment status, educational attainment, percent emphysema, BMI, height, scanner, type, total voxels, site

Shown is the cross- sectional association of JEM-assigned and self- reported VGDF exposures and percent change in high attenuation areas (HAA), from linear mixed models adjusted for age, gender, race/ ethnicity, educational attainment, employment status, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate, total volume of lung imaged, percent emphysema on CT scan, CT scanner type and study site

FIGURE 3: Forest plots of multivariable-adjusted associations between JEM-assigned exposures and HAA, stratified on selected clinical and demographic variables. Boxes represent point estimates, whiskers are 95% confidence intervals. P values for stratified analyses are shown. P-values for interactions are < 0.001, 0.96, 0.88, 0.87, 0.77 for gender, smoking status, baseline age, ethnicity and employment status respectively.



When JEM-assigned exposures were separated into constituent agents, associations with HAA were strongest with dust and gas exposure (Table 4). HAA increased by 2.29% (95%CI 0.25% to 4.37%, p-value < 0.001) per exposure category (low to intermediate to high) of inorganic dust and by 1.82% (95%CI -0.28% to 3.96%, p-value 0.09) per exposure category of organic dust.

Overall, there was no consistent association between self-reported exposures and HAA or with occupational exposures and progression of HAA over time. In ethnicity-stratified models, self-reported VGDF exposure was associated with an increased rate of progression of HAA in Caucasians (p-value for interaction with race 0.16, Table 4).

TABLE 5: Association between JEM-assigned and Self- Reported VGDF Exposures and Progression of High Attenuation Areas

	Overall Annual % Change in HAA (95% CI)	Caucasians Annual % Change in HAA (95% CI)	Race p- interaction
JEM exposure			
VGDF	0 (-0.20 to 0.19)	0.13 (-0.16 to 0.4)	0.35
Gas/ Vapor	0.03 (-0.19 to 0.24)	0.07 (-0.24 to 0.38)	0.97
Combined Dust	0.15 (-0.09 to 0.39)	0.12 (-0.20 to 0.44)	0.51
Inorganic Dust	0.15 (-0.19 to 0.49)	0.32 (-0.11 to 0.76)	0.56
Organic Dust	-0.19 (-0.78 to 0.40)	-0.09 (-0.61 to 0.43)	0.56
Fumes	0.21 (-0.15 to 0.57)	0.18 (-0.30 to 0.67)	0.66
Self-reported Exposure			
Gas/ Vapor	0.37 (-0.34 to 1.09)	**0.58 (0.16 to 1.01)**	0.66
Dust	0.04 (-0.23 to 0.31)	**0.42 (0.07 to 0.78)**	0.12
Fumes	0.19 (-0.12 to 0.50)	**0.61 (0.21 to 1.01)**	0.13
Any VDGF exposure	0.05 (-0.10 to 0.19)	**0.53 (0.19 to 0.88)**	0.16
Severity	0.08 (-0.17 to 0.35)	**0.31 (0.12 to 0.51)**	0.11
Per 10 years exposure	0.01 (-0.15 to 0.16)	0 (0 to 0.3)	0.17

Adjusted for age, race, smoking status (pack years, current smoking), gender, employment status, educational attainment, percent emphysema, BMI, height, scanner, type, total voxels, site

Shown is the linear longitudinal association of JEM-assigned and self- reported VGDF exposures with percent change in high attenuation areas (HAA), from linear mixed models adjusted for age, gender, race/ ethnicity, educational attainment, employment status, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate, total volume of lung imaged, percent emphysema on CT scan, CT scanner type and study site

Association with Interstitial Lung Abnormalities

A total of 310 (9.9%) of the 3137 participants who underwent full lung CT scan had ILA: 289 (9.2%) had scans read as suspicious for ILD and 21 (0.67%) had scans that met standard criteria for usual interstitial pneumonia (UIP) pattern with bilateral fibrosis associated with honeycombing and traction bronchiectasis in a subpleural distribution.

In our multivariable- adjusted analyses, overall estimates did not show a significant association between occupational exposures and odds of ILA at Exam 5 (Table 6). However, there was an increasing trend in the odds of ILA with exposures to VGDF, both per self-report and per JEM.

Among those currently employed, there was a 1.39-fold increase in odds of ILA (95%CI 0.94 to 2.08) for each increase in exposure category. In the *a priori* specified sub-group analyses, self-reported exposure to vapor or gas was associated with a 1.76-fold increase in odds of ILA (95% CI 1.09 to 2.84, p-value 0.02; p-value for interaction with age = 0.7) in participants who were less than 65 years and a 1.97-fold increase in odds of ILA (95%CI 1.16 to 3.35, p-value 0.01; p-value for interaction with employment status = 0.22) in participants who were employed during exam 5.

TABLE 6: Association between JEM-assigned and Self-Reported VGDF Occupational Exposures and Interstitial Lung Abnormalities

	Overall	**Baseline Age < 65**	**Baseline Age ≥ 65**	**Currently Employed***	**Not Employed***
	OR (95% CI)	OR (95%CI)	OR (95%CI)	OR (95% CI)	OR (95%CI)
JEM- assigned Exposure					
VGDF	1.04 (0.83 to 1.30)	1.22 (0.85 to 1.73)	0.95 (0.71 to 1.29)	1.39 (0.94 to 2.08)	0.95 (0.72 to 1.25)
Combined Dust	1.10 (0.82 to 1.46)	1.22 (0.75 to 2.00)	1.08 (0.75 to 1.56)	1.57 (0.93 to 2.64)	0.98 (0.68 to 1.40)
Inorganic Dust	1.21 (0.82 to 1.81)	0.45 (0.12 to 1.75)	1.52 (0.96 to 2.39)	0.48 (0.12 to 1.86)	1.47 (0.95 to 2.29)
Organic Dust	0.92 (0.59 to 1.42)	1.76 (0.84 to 3.69)	0.91 (0.42 to 1.96)	**2.33 (1.13 to 4.80)**	0.60 (0.33 to 1.12)
Self-reported Exposure					
Gas/ Vapor	1.30 (0.93 to 1.83)	**1.76 (1.09 to 2.84)**	1.02 (0.61 to 1.68)	**1.97 (1.16 to 3.35)**	0.99 (0.63 to 1.57)
Dust	0.94 (0.69 to 1.28)	0.96 (0.62 to 1.48)	0.93 (0.60 to 1.42)	1.14 (0.69 to 1.87)	0.85 (0.56 to 1.26)
Fumes	1.13 (0.81 to 1.58)	1.39 (0.86 to 2.25)	0.87 (0.53 to 1.41)	1.57 (0.90 to 2.72)	0.97 (0.63 to 1.49)
Any VGDF agents**	0.93 (0.70 to 1.25)	0.90 (0.58 to 1.38)	0.96 (0.63 to 1.42)	1.17 (0.72 to 1.92)	0.83 (0.57 to 1.20)
Severity	1.00 (0.86 to 1.17)	1.07 (0.84 to 1.35)	0.95 (0.77 to 1.19)	1.12 (0.86 to 1.48)	0.95 (0.76 to 1.16)
Per 10 years exposure	0.92 (0.78 to 1.09)	1.17 (0.91 to 1.51)	**0.97 (0.95 to 1.00)**	1.08 (0.81 to 1.44)	0.98 (0.96 to 1.01)

Adjusted for age, race, smoking status (pack years, current smoking), gender, site
*employment status at exam 5
**self-reported exposure to vapors/ gas, dust or fumes

Shown is the cross sectional association of JEM-assigned and self-reported exposures to VGDF with the odds of interstitial lung abnormalities (ILA), from stratified multivariable logistic regression models adjusted for age, gender, ethnicity, tobacco use (current smoking status and pack years) and study site

DISCUSSION

We found that occupational exposures to vapors/ gas, dusts and fumes were associated with quantitative and, among those currently employed, qualitative subclinical ILD phenotypes. Exposure based on JEM-score was associated with increased HAA and demonstrated evidence of a dose response relationship, with higher estimated exposure levels associated with increased HAA. There was a trend towards increased ILA with occupational exposures, which was strongest in the sub-group of younger participants and those who were currently employed.

This is the first study to show that a broad range of occupational exposures, categorized as VGDF, is linked to markers of lung inflammation and fibrosis. With the exception of specific exposures that are known causes of ILD, such as welding fumes or tobacco smoke; vapors, fumes and gases have been traditionally classified as risk factors for obstructive lung disease [20]. However, it is common for similar environmental triggers to produce different pathologic responses in the genetically susceptible host.

While the biologic pathways leading to pulmonary fibrosis are still poorly understood, current evidence suggests that ILD arises from recurrent epithelial injury and dysregulated repair. Animal models of pneumoconiosis have led to important insights into lung injury and disease mechanisms; demonstrating how inhaled particles are up-taken by alveolar epithelial cells, sequestered in the lung and cause parenchymal injury. When animals are exposed to aerosolized silica, the particles are transported into the interstitium and enter the lymphatics, where they induce oxidative stress and initiate an inflammatory cascade characterized by T-cell and macrophage activation [21]. Similarly, rats that are exposed to high doses of intra-tracheal instilled welding fumes show nodular aggregates containing particulate matter in the alveolar and alveolar ductal regions [22]. These models provide evidence that a variety of environmental insults produce the same pathologic response that can lead to fibrinogenesis.

The advantage of using a broad exposure metric, such as VGDF, is the ability to capture multiple, mixed exposures that may act synergistically to cause disease over time. When JEM-assigned exposures were separated into constituent agents, the associations with HAA were most robust with dust exposure, and in particular, inorganic dust exposure. This observation is consistent with the known pathogenicity of fibrogenic dusts, such as asbestos, silica and coal dust. Interestingly, associations with self-reported exposures were strongest with vapors/ gas and fume exposure. The ability to draw conclusions about the relative pathogenicity of these different agents is limited by small sample size and different exposure assessment techniques.

One of the more interesting aspects of our study was the suggestion of a temporal relationship between VGDF exposure and subclinical ILD. Subclinical ILD is often presumed to be a progressive process, and a recent study found that 20-46% of individuals with ILA showed worsening imaging abnormalities over time [10]. In our study, however, we only saw a significant association between some self-reported exposures and progression of HAA in Caucasians. This association was not seen with JEM-assigned exposures, in other stratified analyses or in the overall cohort.

A potential explanation for the lack of a consistent temporal progression that we observed may be attributed to the demographics of the population studied, with a relatively advanced age (mean 62 years at recruitment) and, subsequently a higher rate of retirement (38% at recruitment) than the general population. Consequently, we presume that the heaviest burden of occupational exposure in the MESA cohort took place before study recruitment. This would suggest that damage to the lungs from VGDF is more likely to occur early in the exposure, rather than after a prolonged latency period. Without ongoing inhalational exposures to incite inflammation and alveolar injury, some phenotypes of subclinical ILD may stabilize or partially resolve.

This hypothesis is supported by the observation that the odds of ILA were greatest in the subgroup of younger participants and those who were actively employed. Both of these groups were more likely to have current inhalational exposures. Although we did not find statistical evidence of effect modification by age or employment status, our ability to detect a difference was limited by sample size.

In contrast, we found the opposite relationship in some of the JEM-assigned exposures where associations were stronger in females, older participants and those who were not actively employed. This may reflect the heterogeneity of the underlying disease process and susceptible population: subclinical ILD may represent early changes in a diverse group of chronic lung diseases, from autoimmune diseases to pneumoconioses. Fibrogenic dust inhalation, which is captured by JEM-assigned inorganic dust exposure, typically leads to slowly progressive disease that manifests after a prolonged latency period. In this exposure category, we would expect associations to be stronger in those with remote exposures. In addition, there are significant temporal trends in exposure levels as stricter worker regulations have led to dramatic reductions in dust exposure over the past several decades. While provocative, it is difficult to draw definitive conclusion due to the inherent limitations of observation studies and the specific limitations to our study.

Exposure assessment in occupational epidemiology research is an important source of error, with concerns for both over- and under- reporting biasing estimates [23]. To mitigate this limitation, we used two separate methods of VGDF assessment: self-reported exposure and JEM-assigned exposure. JEM-assigned exposure was assessed at baseline for each participant, based on the participant's current or most recent occupation. Change of employment status was also recorded at each subsequent exam and adjusted for in the analyses. This method of exposure assessment did not capture remote exposures from prior jobs, or the longest held position.

The self-reported VGDF questionnaire was administered during MESA exam 4: a median of 4.7 years (range 3.5- 6.8 years) after exam 1 during which the baseline HAA was assessed. The questionnaire (relevant questions replicated in the online supplement) assessed for VGDF exposure at any time during the employment history, not just the most current occupation. Despite the lag time between baseline HAA assessment and the self-exposure questionnaire, we do not feel that this is likely to be a major source of exposure misclassification. This assumption is based on 1) the advanced age of the MESA cohort with a high proportion of retired participants at the study start 2) the prolonged exposures reported on the VGDF questionnaire (median duration 16 years).

Self-reported exposures may be subject to recall bias with significant inter- and intra- respondent inconsistency and inaccuracy. The occupational questionnaires used in this study tried to capture a more comprehensive exposure history by asking separately about kinds of exposures, severity, and duration. Nonetheless, participants may have been unaware of certain exposures or unable to distinguish between technical classes of exposures (for example, the difference between vapors/ gas versus fumes). Additionally, where participants perceived a work-related health outcome, they may have systemically over-report exposures.

While JEM exposure was assigned by independent experts, there was also a risk of substantial misclassification. There is considerable heterogeneity in exposures within the same job title: not all road workers are substantially exposed to dust while some office employees may have vapors/

gas exposures [24]. These sources of misclassification in JEM-assigned exposures would be expected to bias towards the null and attenuate the estimates that we observed.

Both methods of exposure assessment in our study were associated with different sources of exposure misclassification, yet each captured different aspects of VGDF exposure. By using both methods, we hoped to achieve a more comprehensive assessment of the participant's exposure history. While there was low correlation between exposure levels calculated by self-report versus JEM-assignment, a similar discordance has been previously reported in many other studies and is representative of the difficulty in assigning occupational exposures in epidemiologic studies [25, 26].

In this study, exposure levels predicted by the JEM were more consistently associated with phenotypes of subclinical ILD than self-reported exposures on questionnaires. This pattern is in contrast to epidemiologic studies that have compared the risk of asthma and COPD with multiple approaches to the assessment of occupational exposures. These usually find more significant associations with self-reported exposures rather than JEM- assigned exposures [19, 23, 24, 27]. Once again, this could be attributed to limited power in our study, especially since a smaller number of participants answered the self-reported exposure questionnaires in comparison to the number of participants assigned an exposure through the JEM.

In addition to potential errors from exposure misclassification, our study had some additional limitations. It is possible that the cohort that completed the entire study, from recruitment to MESA exam 5, had less comorbidities than participants who were censored due to death or loss to follow up. It is somewhat reassuring that the baseline characteristics of the participants who had a full lung CT at exam 5 were similar to the overall cohort, however, there may be some unmeasured effects due to survivorship bias in our estimates. Another limitation of this study was the use of cardiac, rather than full lung, CT scans to measure HAA. While this method could potentially miss some areas of affected lung, we previously showed that HAA on cardiac CT scan strongly agrees with HAA on full lung CT scan [9].

CONCLUSIONS

Despite these limitations, this observational study has several novel findings. We observed significant associations with two different approaches to exposure assessment and two separate subclinical ILD phenotypes. There was evidence of a dose-response relationship and a possible temporal association between exposures and the outcome. In combination with a plausible biologic mechanism, these findings suggest a relationship between occupational exposures and subclinical ILD. More studies are needed to determine the significance of this association, distinguish the importance between different exposures classes, and follow disease progression in those with occupational exposures over time.

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APPENDIX

Pertinent Occupational Questionnaire:

The occupational exposure was determined by the following questions, reproduced below from the "MESA-Lung field Center Manual of Operations and Procedures" Version 1.9 April 8, 2008. A trained interviewer administered the questionnaire to participants. The interviewers were instructed to read each question exactly as written and to record responses verbatim. If participants asked for clarification of the terms used in the questions, the interviewer provided separate definitions from the "note" section of the manual.

Q.13. Have you ever been exposed at work to:
(This is "ever" exposure, and it does not have to be daily exposure).
Vapors or gas Answer "yes" or "no" or "don't know".
Note: vapors are really synonymous with gas, that is the form into which liquids are naturally converted by the action of a sufficient degree of heat.
Dust Answer "yes" or "no" or "don't know".
Note: dust is fine particulate matter which is light enough to be to be easily raised and carried up into the air.
Fumes Answer "yes" or "no" or "don't know".
Note: fumes are volatile matter produced by and usually accompanying combustion (where there's smoke, there's fumes -- although the converse is not completely true).
If yes to any of the above, answer the following:
For how many years were you exposed at work to vapors, gas, dust or fumes?
Provide the number of years. ___ years
How long ago was your last exposure?
Select "current" or provide the number in months OR in years.
____ current OR ___ months OR ____years
Was the exposure "mild" or moderate" or severe'? ___ mild ___ moderate ___severe
Select one. Note that the exposure is in order of increasing level.

The occupation was determined by the following four open-ended questions from the survey:
Q.9 For whom do/did you work? (name of company, business, organization or other employer) If you are are not working now, please respond regarding your main occupation before you stopped working.
Q.10 What type of business or industry is/was this? (e.g., hospital, newspaper publishing, mail order house, auto repair shop, bank, etc.)
Q.11 What kind of work do/did you do or what was your job title? (e.g. registered nurse, personnel manager, auto mechanic, accountant, grinder operator, etc.)
Q.12 What are/were your most important activities or duties? (e.g. patient care, directing hiring policies, repairing automobiles, reviewing financial records, operating grinding mill, etc.)

The JEM used in this study was developed by the National Institute for Occupational Safety and Health (NIOSH). It was constructed using general principles from UCSF COPD Job Exposure Matrix (10/14/2008, modified 1/06/09) [1], expert knowledge, and information from the Encyclopedia of Occupational Safety and Health, 4th ed [2]. For each Bureau of Census 2002 occupational code, a score was assigned that represented the likelihood and severity of exposure (low, intermediate or high) to vapors/ gas, dust, fumes, subcategories of dust (inorganic versus organic) and combined VGDF exposure. A representative example of exposure assignment using the JEM is shown below.

TABLE A1: Representative Census Code and JEM-Score Assignment

Census	Category Title	JEM Score				
		VGDF	Gas/ Vapor	Inorganic Dust	Organic Dust	Fumes
2400	Archivist Curators Museum technician	2	2	1	2	1
2830	Editors	1	1	1	1	1
4250	Grounds Maintenance Workers	3	3	1	3	1
6520	Sheet Metal Worker	3	2	2	1	3

Shown is a representative table of Bureau of Census 2002 occupational codes and JEM – assignments. For exposure scores, 1 represents low exposure, 2 represents intermediate exposure and 3 represents high exposure. JEM- job exposure matrix, VGDF – vapors/ gas, dust, fume.

This section contains fully stratified models from the main analysis that may be of interest. Table A2 presents stratified analyses from multivariable logistic regression of the association between occupational exposures and ILA. Table A3 and A4 present stratified analyses from the linear mixed model of the association between occupational exposures and HAA.

TABLE A2: Association between Occupational Exposures to VGDF and Interstitial Lung Abnormalities

	Overall		**Caucasians**		**Asians**		**Black**		**Hispanics**	
	OR (95% CI)	p	OR (95%CI)	p	OR (95%CI)	P	OR (95%CI)	p	OR (95% CI)	
JEM exposure										
VGDF	1.04 (0.83, 1.30)	0.74	1.24 (0.84 to 1.84)	0.28	0.62 (0.2 to 1.30)	0.21	0.64 (0.36 to 1.17)	0.15	1.43 (0.97 to 2.10)	0.07
Gas/ Vapor	0.99 (0.77 to 1.29)	0.96	1.08 (0.68 to 1.72)	0.74	0.43 (0.15 to 1.21)	0.11	0.70 (0.38 to 1.30)	0.26	1.61 (1.03 to 2.49)	0.03
Combined Dust	1.10 (0.82 to 1.46)	0.53	1.25 (0.77 to 2.04)	0.36	0.70 (0.28 to 1.76	0.45	0.85 (0.41 to 1.75	0.65	1.47 (0.87 to 2.47)	0.15
Inorganic Dust	1.21 (0.82 to 1.81)	0.33	0.46 (-2.31 to 3.32)	0.75	11.8 (4.45 to 19.6)	0.001	3.28 (-1.00 to 7.74)	0.13	1.50 (0.78 to 2.90)	0.22
Organic Dust	0.92 (0.59 to 1.42)	0.69	0.04 (-3.24 to 3.43)	0.98	4.26 (-1.91 to 10.8)	0.18	-0.15 (-0.04 to 3.40)	0.94	1.37 (0.64 to 2.95)	0.42
Fumes	0.95 (0.60 to 1.50)	0.82	1.54 (0.77 to 3.09)	0.22	0.99 (0.14 to 7.02)	1.00	0.47 (0.15 to 1.49)	0.20	1.19 (0.47 to 2.98)	0.71
Self-reported Exposure										
Gas/ Vapor	1.30 (0.93 to 1.83)	0.13	1.51 (0.87 to 2.64)	0.14	1.29 (0.43 to 3.89)	0.66	1.08 (0.54 to 2.18)	0.83	1.05 (0.52 to 2.11)	0.90
Dust	0.94 (0.69 to 1.28)	0.70	0.97 (0.60 to 1.57)	0.90	0.51 (0.11 to 2.34)	0.39	1.23 (0.69 to 2.23)	0.48	0.66 (0.35 to 1.25)	0.20
Fumes	1.13 (0.81 to 1.58)	0.49	1.50 (0.89 to 2.51)	0.12	0.68 (0.07 to 6.24)	0.74	1.14 (0.61 to 2.13)	0.69	0.60 (0.29 to 1.26)	0.18
Any VGDF exposure	0.93 (0.70 to 1.25)	0.64	0.93 (0.59 to 1.48)	0.77	1.03 (0.41 to 2.63)	0.95	1.50 (0.82 to 2.75)	0.19	**0.44 (0.23 to 0.84)**	**0.01**
Severity	1.00 (0.86, 1.17)	0.98	1.09 (0.84 to 1.42)	0.50	1.02 (0.57 to 1.81)	0.96	1.23 (0.91 to 1.66)	0.18	**0.63 (0.44, 0.90)**	**0.01**
Per 10 years exposure	0.99 (0.98, 1.01)	0.34	0.99 (0.97 1.02)	0.67	N/A		0.98 (0.95 to 1.01)	0.16	1.02 (0.98 to 1.06)	0.34

Adjusted for age, race, smoking status (pack years, current smoking), gender, site

TABLE A2: Association between Occupational Exposures to VGDF and Interstitial Lung Abnormalities

	Baseline Age < 65		**Age ≥ 65**		**Not currently employed***		**Currently Employed***	
	OR (95%CI)	p	OR (95%CI)	P	OR (95%CI)	p	OR (95% CI)	p
JEM exposure								
VGDF	1.22 (0.85 to 1.73)	0.27	0.95 (0.71 to 1.29)	0.21	0.95 (0.72 to 1.25)	0.71	1.39 (0.94 to 2.08)	0.10
Gas/ Vapor	1.10 (0.74 to 1.66)	0.63	0.88 (0.62 to 1.23)	0.45	0.91 (0.65 to 1.26)	0.56	1.23 (0.80 to 1.89)	0.35
Combined Dust	1.22 (0.75 to 2.00)	0.43	1.08 (0.75 to 1.56)	0.69	0.98 (0.68 to 1.40)	0.91	1.57 (0.93 to 2.64)	0.09
Inorganic Dust	0.45 (0.12 to 1.75)	0.25	1.52 (0.96 to 2.39)	0.07	1.47 (0.95 to 2.29)	0.08	0.48 (0.12 to 1.86)	0.29
Organic Dust	1.76 (0.84 to 3.69)	0.14	0.91 (0.42 to 1.96)	0.81	0.60 (0.33 to 1.12)	0.11	2.33 (1.13 to 4.80)	0.02
Fumes	0.91 (0.39 to 2.12)	0.82	0.95 (0.54 to 1.67)	0.86	0.92 (0.54 to 1.55)	0.75	1.13 (0.41 to 3.07)	0.82
Self-reported Exposure								
Gas/ Vapor	**1.76 (1.09 to 2.84)**	**0.02**	1.02 (0.61 to 1.68)	0.95	0.99 (0.63 to 1.57)	0.98	**1.97 (1.16 to 3.35)**	**0.01**
Dust	0.96 (0.62 to 1.48)	0.84	0.93 (0.60 to 1.42)	0.73	0.85 (0.56 to 1.26)	0.42	1.14 (0.69 to 1.87)	0.61
Fumes	1.39 (0.86 to 2.25)	0.17	0.87 (0.53 to 1.41)	0.56	0.97 (0.63 to 1.49)	0.88	1.57 (0.90 to 2.72)	0.11
Any VGDF agents	0.90 (0.58 to 1.38)	0.62	0.96 (0.63 to 1.42)	0.79	0.83 (0.57 to 1.20)	0.32	1.17 (0.72 to 1.92)	0.52
Severity	1.07 (0.84 to 1.35)	0.59	0.95 (0.77 to 1.19)	0.67	0.95 (0.76 to 1.16)	0.60	1.12 (0.86 to 1.48)	0.40
Per 10 years exposure	1.02 (0.99 to 1.04)	0.22	**0.97 (0.95 to 1.00)**	**0.03**	0.98 (0.96 to 1.01)	0.16	1.01 (0.98 to 1.04)	0.59

Adjusted for age, race, smoking status (pack years, current smoking), gender, site
*employment status at exam 5

TABLE A2: Association between Occupational Exposures to VGDF and Interstitial Lung Abnormalities

	Females		Males		Never Smokers		Ever smokers	
	OR (95%CI)	p	OR (95%CI)	P	OR (95%CI)	p	OR (95% CI)	p
JEM exposure								
VGDF	0.82 (0.56 to 1.19)	0.30	1.20 (0.90 to 1.61)	0.22	0.87 (0.62 to 1.23)	0.44	1.22 (0.91 to 1.65)	0.18
Gas/ Vapor	0.72 (0.44 to 1.20)	0.21	1.15 (0.84 to 1.56)	0.39	0.92 (0.62 to 1.36)	0.67	1.11 (0.79 to 1.56)	0.52
Combined Dust	0.78 (0.44 to 1.41)	0.41	1.23 (0.87 to 1.74)	0.25	0.94 (0.60 to 1.48)	0.80	1.22 (0.82 to 1.81)	0.32
Inorganic Dust	0.82 (0.20 to 3.41)	0.79	1.19 (0.78 to 1.83)	0.42	1.08 (0.58 to 2.04)	0.80	1.25 (0.75 to 2.09)	0.39
Organic Dust	0.83 (0.41 to 1.69)	0.61	0.98 (0.55 to 1.73)	0.93	0.66 (0.32 to 1.37)	0.27	1.18 (0.67 to 2.08)	0.56
Fumes	0.30 (0.205 to 1.77)	0.18	1.12 (0.68 to 1.85)	0.66	1.09 (0.56 to 2.13)	0.79	0.81 (0.43 to 1.51);	0.51
Self-reported Exposure								
Gas/ Vapor	1.27 (0.76 to 2.14)	0.36	1.27 (0.80 to 2.03)	0.30	1.46 (0.89 to 2.38)	0.13	1.08 (0.68 to 1.72)	0.75
Dust	0.75 (0.48 to 1.16)	0.20	1.19 (0.76 to 1.87)	0.45	0.92 (0.59 to 1.42)	0.70	0.91 (0.59 to 1.38)	0.64
Fumes	0.95 (0.57 to 1.58)	0.83	1.24 (0.78 to 1.97)	0.36	1.18 (0.70 to 1.97)	0.53	1.01 (0.65 to 1.58)	0.95
Any VGDF agents	0.68 (0.45 to 1.02)	0.07	1.30 (0.83 to 2.04)	0.26	0.92 (0.61 to 1.38)	0.68	0.89 (0.59 to 1.35)	0.60
Severity	0.86 (0.69, 1.09)	0.21	1.13 (0.90, 1.42)	0.30	0.93 (0.73, 1.18)	0.55	1.03 (0.83, 1.28)	0.76
Per 10 years exposure	0.98 (0.95 to 1.01)	0.26	0.99 (0.97, 1.01)	0.48	0.98 (0.96 to 1.01)	0.25	1.00 (0.98 to 1.03)	0.67

Adjusted for age, race, smoking status (pack years, current smoking), gender, site

Table A2: Estimates of Occupational Exposures to VGDF and Risk of Interstitial Lung Abnormalities. Cross sectional association of JEM-assigned and self-reported exposures to VGDF with the odds of interstitial lung abnormalities (ILA), from stratified multivariable logistic regression models adjusted for age, gender, ethnicity, tobacco use (current smoking status and pack years) and site.

TABLE A3: Association between Occupational Exposures to VGDF and High Attenuation Areas

	Overall		Females		Males		Never smoker		Ever Smoker	
	Difference in % HAA (95% CI)	p	Difference in % HAA (95% CI)	p	Difference in % HAA (95% CI)	P	Difference in % HAA (95% CI)	p	Difference in % HAA (95% CI)	p
JEM exposure										
VGDF	**2.39 (1.23 to 3.57)**	**< 0.001**	**3.93 (1.94 to 5.96)**	**< 0.001**	1.05 (-0.30 to 2.42)	0.13	**2.14 (0.23 to 4.09)**	**0.03**	**2.50 (1.04 to 3.98)**	**<0.001**
Gas/ Vapor	**1.82 (0.57 to 3.09)**	**0.004**	**4.80 (2.41 to 7.25)**	**< 0.001**	0.54 (-0.84 to 1.94)	0.44	**2.10 (0.02 to 4.22)**	**0.05**	**1.67 (0.10 to 3.26)**	**0.04**
Combined Dust	1.36 (-0.07 to 2.82)	0.06	**4.09 (1.11 to 7.15)**	**0.007**	-0.02 (-1.54 to 1.53)	0.98	**2.44 (0.01 to 4.92)**	**0.05**	0.93 (-0.84 to 2.72)	0.31
Inorganic Dust	**2.29 (0.25 to 4.37)**	**0.03**	**10.1 (2.85 to 17.9)**	**0.006**	1.16 (-0.81 to 3.17)	0.24	**6.18 (2.19 to 10.3)**	**0.002**	1.18 (-1.16 to 3.58)	0.32
Organic Dust	1.82 (-0.28 to 3.96)	0.09	**3.78 (0.19 to 7.50)**	**0.04**	0.25 (-0.54 to 2.72)	0.84	2.13 (-1.22 to 5.59)	0.21	1.47 (-1.22 to 4.23)	0.29
Fumes	0.14 (-1.91 to 2.23)	0.90	-0.76 (-5.13 to 3.85)	0.75	0.17 (-1.98 to 2.37)	0.87	0.18 (-3.55 to 1.20)	0.93	-0.11 (-0.40 to 2.37)	0.93
Self-reported Exposure										
Gas/ Vapor	0.33 (-1.63 to 2.32)	0.75	-2.36 (-3.23 to 2.93)	0.78	-0.24 (-2.41 to 1.98)	0.82	1.07 (-2.16 to 4.39)	0.52	-0.32 (-2.68 to 2.09)	0.79
Dust	0.28 (-1.34 to 1.93)	0.74	0.81 (-1.57 to 3.25)	0.51	-0.33 (-2.35 to 1.75)	0.76	-0.13 (-2.65 to 2.45)	0.92	0.72 (-1.34 to 2.82)	0.49
Fumes	0.07 (-1.14 to 2.57)	0.46	0.57 (-2.33 to 3.56)	0.70	0.05 (-2.10 to 2.24)	0.97	1.08 (-1.95 to 4.22)	0.49	0.44 (-1.78 to 2.71)	0.70
Any VGDF	-0.14 (-1.72 to 1.46)	0.86	-0.33 (-2.33 to 1.71)	0.75	-0.33 (-2.33 to 1.71)	0.75	-0.55 (-2.95 to 1.91)	0.66	0.53 (-1.51 to 2.61)	0.61
Severity	-0.19 (-1.05 to 0.69)	0.68	-0.44 (-1.71 to 0.85)	0.50	-0.13 (-1.22 to 0.98)	0.82	-0.32 (-1.70 to 1.07)	0.65	0.06 (-1.02 to 1.15)	0.91
Per 10 years exposure	-0.06 (-0.98 to 0.87)	0.90	-1.40 (-2.88 to 0.10)	0.07	0.64 (-0.46 to 1.76)	0.37	-0.81 (-2.33 to 0.73)	0.30	0.21 (-0.93 to 0.29)	0.72

Adjusted for age, race, smoking status (pack years, current smoking), gender, employment status, educational attainment, percent emphysema, BMI, height, scanner, type, total voxels, site
p-values interactions for JEM VGDF: **gender 0.0004** smoking 0.96 employment status 0.77 age 0.88 race 0.87
JEM combined dusts**: gender 0.002** smoking 0.48 **employment status 0.02** age 0.08 race 0.69
JEM organic dusts: **gender 0.009** smoking 0.59 employment status 0.29 age 0.30 race 0.28
JEM mineral dusts**: gender 0.03** smoking 0.65 **employment status 0.05** age 0.09 race 0.69
JEM gas**: gender 0.0002** smoking 0.75 employment status 0.99 age 0.29 race 0.39
JEM fumes: gender 0.45 smoking 0.77 employment status 0.52 age 0.65 race 0.95
self-reported fumes: gender 0.43 smoking 0.54 employment status 0.99 age 0.87 race 0.90
self-reported dust: gender 0.87 smoking 0.37 employment status 0.63 age 0.10 race 0.13
self-reported gas: gender 0.55 smoking 0.70 employment status 0.78 age 0.69 race 0.71
self-reported any: gender 0.89 job 0.70
self-reported severity: employment status 0.53 gender 0.42 race 0.21
self-reported 10 yr: race 0.08 employment status 0.88 gender 0.42

TABLE A3: Association between Occupational Exposures to VGDF and High Attenuation Areas

	Age < 65		Age ≥ 65		Caucasian		Asian		Black	
	Difference in % HAA (95% CI)	p	Difference in % HAA (95% CI)	p	Difference in % HAA (95% CI)	P	Difference in % HAA (95% CI)	p	Difference in % HAA (95% CI)	
JEM exposure										
VGDF	**2.64 (0.12 to 4.19)**	**0.006**	**2.08 (0.28 to 3.91)**	**0.02**	1.32 (-0.44 to 3.10)	0.14	0.93 (-2.74 to 4.76)	0.62	1.78 (-0.59 to 4.20)	0.14
Gas/ Vapor	1.14 (-0.47 to 2.77)	0.17	**2.61 (0.63 to 4.63)**	**0.01**	1.86 (-0.06 to 3.81)	0.06	0.06 (-4.00 to 4.29)	0.98	1.27 (-1.15 to 3.75)	0.31
Combined Dust	-0.06 (-1.91 to 1.83)	0.95	**2.88 (0.64 to 5.16)**	**0.01**	-0.54 (-2.57 to 1.53)	0.61	3.02 (-1.59 to 7.84)	0.20	0.79 (-2.04 to 3.70)	0.17
Inorganic Dust	-0.10 (-2.73 to 2.61)	0.94	**4.90 (1.71 to 8.18)**	**0.002**	0.24 (-2.52, to 3.08)	0.87	**9.50 (1.47 to 18.2)**	**0.02**	2.00 (-2.25 to 6.44)	0.36
Organic Dust	0.43 (-2.48 to 3.44)	0.77	2.78 (-0.24 to 5.89)	0.07	-0.04 (-3.35, 3.39)	0.73	1.16 (-4.79 to 7.48)	0.71	-0.65(-4.61 to 3.47)	0.75
Fumes	0.23 (-2.53 to 3.07)	0.87	-0.20 (-3.26 to 2.95)	0.90	-1.48 (-4.32 to 1.46)	0.32	-0.34 (-9.62, 11.4)	0.95	0.82 (-2.71, 4.50)	0.66
Self-reported Exposure										
Gas/ Vapor	1.29 (-1.03 to 3.66)	0.28	-0.83 (-4.36 to 2.82)	0.65	-1.48 (-4.05 to 1.15)	0.27	-1.49 (-7.64 to 5.08)	0.65	1.72 (-1.94 to 5.53)	0.86
Dust	-0.04 (-1.99 to 1.95)	0.97	1.69 (-1.18 to 4.64)	0.25	-1.33 (-3.46 to 0.84)	0.23	3.24 (-2.10 to 8.87)	0.24	1.29 (-1.73 to 4.40)	0.40
Fumes	1.54 (-0.64 to 3.78)	0.17	-0.58 (-3.76 to 2.70)	0.73	-0.67 (-3.08 to 1.80)	0.59	0.81 (-6.88 to 9.13)	0.84	0.57 (-2.66 to 3.91)	0.73
Any VDGF	0.01 (-1.91 to 1.98)	0.99	0.24 (-2.46 to 3.02)	0.86	-1.54 (-3.62 to 0.58)	0.15	1.69 (-2.82 to 6.41)	0.47	0.89 (-2.12 to 4.00)	0.57
Severity	0.41 (-0.66 to 1.48)	0.46	-0.63 (-2.10 to 0.86)	0.40	-0.99 (-2.18 to 0.22)	0.11	1.17 (-1.50 to 3.92)	0.39	1.06 (-0.64 to 2.78)	0.22
Per 10 years exposure	-0.61 (-1.77 to 0.56)	0.30	0.79 (-0.74 to 2.34)	0.31	0.10 (-1.04 to 1.24)	0.87	0.95 (-2.53 to 4.55)	0.59	0.71 (-1.07 to 2.52)	0.43

Adjusted for age, race, smoking status (pack years, current smoking), gender, employment status, educational attainment, percent emphysema, BMI, height, scanner, type, total voxels, site

TABLE A3: Association between Occupational Exposures to VGDF and High Attenuation Areas

	Hispanic		Employed		Not currently employed	
	Difference in % HAA (95% CI)	P	Difference in % HAA (95% CI)	p	Difference in HAA (95% CI)	p
JEM exposure						
VGDF	**2.92 (0.71 to 5.18)**	**0.01**	**2.45 (0.82 to 4.10)**	**0.003**	**2.29 (0.64 to 3.97)**	**0.006**
Gas/ Vapor	**2.42 (0 to 4.92)**	**0.05**	**1.70 (0 to 3.46)**	**0.05**	**1.76 (0 to 3.58)**	**0.05**
Combined Dust	**3.01 (0.09 to 6.02)**	**0.04**	-0.63 (-2.61 to 1.40)	0.54	**3.04 (1.00 to 5.12)**	**0.003**
Inorganic Dust	**4.45 (0.44 to 8.62)**	**0.03**	-1.21 (-4.07 to 1.73)	0.42	**4.88 (2.00 to 7.83)**	**< 0.001**
Organic Dust	3.25 (-0.84 to 7.50)	0.12	0.34 (-2.73 to 3.50)	0.83	2.81 (-0.07, to 5.76)	0.06
Fumes	1.71 (-2.61 to 6.23)	0.44	0.48 (-2.62 to 3.68)	0.76	-0.09 (-2.84 to 2.73)	0.95
Self-reported Exposure						
Gas/ Vapor	1.98 (-2.47 to 6.63)	0.39	1.05 (-1.36 to 3.52)	0.40	-0.21 (-3.32 to 3.01)	0.90
Dust	1.12 (-2.56 to 4.93)	0.56	-0.25 (-2.27 to 1.81)	0.81	0.69 (-1.84 to 3.30)	0.59
Fumes	2.20 (-1.94 to 6.53)	0.30	0.80 (-1.49 to 3.15)	0.50	0.58 (-2.29 to 3.54)	0.70
Any VGDF exposure	0.66 (-2.98 to 4.44)	0.72	-0.69 (-2.67 to 1.34)	0.57	0.13 (-2.30 to 2.61)	0.92
Severity	-0.37 (-2.19 to 0.29)	0.69	-0.67 (-1.80 to 0.48)	0.25	0.14 (-1.16 to 1.46)	0.83
Per 10 yr exposure	-1.29 (-3.37 to 0.84)	0.23	-0.15 (-1.39 to 0.28)	0.82	-0.02 (-1.37 to 1.35)	0.81

Adjusted for age, race, smoking status (pack years, current smoking), gender, employment status, educational attainment, percent emphysema, BMI, height, scanner, type, total voxels, site

TABLE A3: Estimates of self-reported and JEM- assigned occupational exposures to VGDF and HAA. Cross- sectional association of self- reported VGDF exposures and percent change in high attenuation areas (HAA), from linear mixed models adjusted for age, gender, race/ ethnicity, educational attainment, employment status, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate, total volume of lung imaged, percent emphysema on CT scan, CT scanner type and study site. Interaction for gender: 0.007

TABLE A4: Association between Occupational Exposures to VGDF and Progression of High Attenuation Areas

	Age < 65		**Age ≥ 65**		**Caucasian**		**Asian**		**Black**	
	Annual % Change in HAA (95% CI)	P	Annual % Change in HAA (95% CI)	p	Annual % Change in HAA (95% CI)	P	Annual % Change in HAA (95% CI)	p	Annual % Change in HAA (95% CI)	p
JEM exposure										
VGDF	-0.15 (-0.32 to 0.14)	0.45	0.15 (-0.20 to 0.49)	0.41	0.13 (-0.16 to 0.4)	0.38	0.17 (-0.33 to 0.67)	0.50	0.30 (-0.20 to 0.79)	0.24
Gas/ Vapor	0.02 (-0.23 to 0.27)	0.88	0.08 (-0.30 to 0.48)	0.14	0.07 (-0.24 to 0.38)	0.67	-0.03 (-0.57 to 0.51)	0.92	0.07 (-0.44 to 0.59)	0.78
Combined Dust	0.03 (-0.25 to 0.32)	0.81	0.43 (0 to 0.87)	0.05	0.12 (-0.20 to 0.44)	0.46	-0.06 (-0.66 to 0.55)	0.85	0.44 (-0.19 to 1.08)	0.17
Inorganic Dust	0.14 (-0.27 to 0.55)	0.51	0.27 (-0.32 to 0.87)	0.37	0.32 (-0.11 to 0.76)	0.14	-0.22 (-1.24 to 0.81)	0.67	0.63 (-0.38 to 1.64)	0.22
Organic Dust	-0.23 (-0.67 to 0.22)	0.32	0.04 (-0.56 to 0.65)	0.89	-0.09 (-0.61 to 0.43)	0.73	-0.23 (-1.10 to 0.64)	0.60	0.32 (-0.56 to 1.20)	0.48
Fumes	0.08 (-0.36 to 0.52)	0.72	0.43 (-0.19 to 1.06)	0.17	0.18 (-0.30 to 0.67)	0.46	0.50 (-0.90 to 1.92)	0.48	0.55 (-0.16 to 1.28)	0.13
Self-reported Exposure										
Gas/ Vapor	0.23 (-0.13 to 0.59)	0.21	**0.67 (0.01 to 1.35)**	**0.05**	**0.61 (0.12 to 1.01)**	**0.004**	0.08 (-0.08 to 0.98)	0.86	0.06 (-0.62 to 0.75)	0.86
Dust	0 (-0.31 to 0.31)	0.97	0.07 (-0.47 to 0.61)	0.80	**0.46 (0.12 to 0.84)**	**0.009**	-0.34 (-1.12 to 0.44)	0.39	-0.13 (-0.68 to 0.42)	0.64
Fumes	0.14 (-0.21 to 0.49)	0.43	0.14 (-0.50 to 0.77)	0.67	**0.66 (0.26 to 1.05)**	**0.001**	0.34 (-0.89 to 1.58)	0.59	-0.21 (-0.81 to 0.41)	0.51
Any VGDF agents	-0.02 (-0.33 to 0.28)	0.88	0.21 (-0.26 to 0.07)	0.35	**0.57 (0.22 to 0.89)**	**0.001**	-0.19 (-0.84 to 0.47)	0.57	-0.21 (-0.75 to 0.34)	0.45
Severity	-0.05 (-0.22 to 0.12)	0.59	0.18 (-0.10 to 0.46)	0.20	**0.32 (0.13 to 0.52)**	**0.001**	-0.13 (-0.52 to 0.27)	0.53	-0.13 (-0.43 to 0.18)	0.42
Years exposure	0.10 (-0.10 to 0.29)	0.33	-0.12 (-0.40 to 0.15)	0.37	0.09 (-0.09 to 0.26)	0.34	-0.44 (-0.99 to 0.12)	0.12	-0.07 (-0.35 to 0.21)	0.64

Adjusted for age, race, smoking status (pack years, current smoking), gender, employment status, educational attainment, percent emphysema, BMI, height, scanner, type, total voxels, site

p-value for interactions JEM VGDF: gender 0.02 smoking 0.82 age 0.60 employment status 0.05 (?) race 0.35
JEM combined dusts: gender 0.02 smoking 0.29 age 0.54 employment status 0.43 race 0.51
JEM organic dusts: gender 0.63 smoking 0.51 age 0.73 employment status 0.94 race 0.56
JEM mineral dusts: gender 0.07 smoking 0.41 age 0.91 employment status 0.003 race 0.56
JEM gas: gender 0.007 smoking 0.72 age 0.92 employment status 0.25 race 0.97
JEM fumes: gender 0.80 smoking 0.89 age 0.67 employment status 0.38 race 0.42
self-reported fumes: gender 0.29 smoking 0.68 employment status 0.96 age 0.98 race 0.13
self-reported dust: gender 0.78 smoking 0.87 employment status 0.13 age 0.88 race 0.12
self- reported gas: gender 0.95 smoking 0.84 employment status 0.44 age 0.42 race 0.66
self-reported any: race 0.16 gender 0.33 employment status 0.16
self-reported severity: employment status 0.35 gender 0.08 race 0.11
self-reported ten year: race 0.17 employment status 0.82 gender 0.80

TABLE A4: Association between Occupational Exposures to VGDF and Progression of High Attenuation Areas

	Overall		Females		Males		Never Smoker		Ever Smoker	
	Annual % Change in HAA (95% CI)	p	Annual % Change in HAA (95% CI)	p	Annual % Change in HAA (95% CI)	P	Annual % Change in HAA (95% CI)	p	Annual % Change in HAA (95% CI)	p
JEM exposure										
VGDF	0 (-0.20 to 0.19)	0.95	-0.28 (-0.60 to 0.04)	0.08	0.19 (-0.04 to 0.43)	0.10	0.09 (-0.20 to 0.37)	0.54	-0.08 (-0.34 to 0.17)	0
Gas/ Vapor	0.03 (-0.19 to 0.24)	0.81	**-0.41 (-0.80 to -0.03)**	**0.03**	0.23 (-0.01 to 0.47)	0.06	0.10 (-0.21 to 0.41)	0.54	-0.02 (-0.30 to 0.26)	0.90
Combined Dust	0.15 (-0.09 to 0.39)	0.23	-0.23 (-0.71 to 0.25)	0.35	**0.34 (0.08 to 0.60)**	**0.01**	-0.05 (-0.41 to 0.32)	0.79	0.26 (-0.06 to 0.57)	0.11
Inorganic Dust	0.15 (-0.19 to 0.49)	0.40	-0.91 (-2.06 to 0.25)	0.12	0.3 (-0.02 to 0.64)	0.07	-0.09 (-0.65 to 0.47)	0.75	0.27 (-0.14 to 0.69)	0.20
Organic Dust	-0.19 (-0.78 to 0.40)	0.52	-0.11 (-0.54 to 0.32)	0.61	-0.20 (-0.72 to 0.32)	0.45	-0.12 (-0.60 to 0.35)	0.61	-0.23 (-0.67 to 0.22)	0.32
Fumes	0.21 (-0.15 to 0.57)	0.25	0.19 (-0.56 to 0.94)	0.62	0.19 (-0.19 to 0.58)	0.32	**0.59 (0 to 1.20)**	**0.05**	0.04 (-0.40 to 0.48)	0.87
Self-reported Exposure										
Gas/ Vapor	0.37 (-0.34 to 1.09)	0.31	0.36 (-0.18 to 0.91)	0.19	0.37 (-0.01 to 0.75)	0.06	0.46 (-0.03 to 0.95)	0.07	0.40 (- 0.02 to 0.82)	0.06
Dust	0.04 (-0.23 to 0.31)	0.78	-0.07 (-0.47 to 0.34)	0.75	0.11 (-0.24 to 0.47)	0.54	0.05 (-0.35 to 0.45)	0.82	0.05 (-0.31 to 0.41)	0.80
Fumes	0.19 (-0.12 to 0.50)	0.24	-0.08 (-0.57 to 0.41)	0.74	**0.39 (0.01 to 0.77)**	**0.04**	0.31 (-0.16 to 0.79)	0.20	0.10 (-0.29 to 0.50)	0.61
Severity	0.05 (-0.10 to 0.19)	0.54	-0.07 (-0.29 to 0.14)	0.49	**0.20 (0.01 to 0.39)**	**0.04**	0.06 (-0.16 to 0.28)	0.59	0.04 (-0.15 to 0.23)	0.69
Any VDGF exposure	0.08 (-0.17 to 0.35)	0.54	-0.09 (-0.47 to 0.30)	0.65	0.18 (-0.01 to 0.62)	0.13	0.14 (-0.23 to 0.52)	0.46	0.01 (-0.34 to 0.37)	0.94
Years exposure	0.01 (-0.15 to 0.16)	0.94	0.10 (-0.13 to 0.34)	0.40	-0.09 (-0.46 to 0.11)	0.37	-0.81 (-0.33 to 0.19)	0.59	0.09 (-0.10 to 0.29)	0.35

Adjusted for age, race, smoking status (pack years, current smoking), gender, employment status, educational attainment, percent emphysema, BMI, height, scanner, type, total voxels, site

TABLE A4: Association between Occupational Exposures to VGDF and Progression of High Attenuation Areas

	Hispanic		**Employed**		**Not Employed**	
	Annual % Change in HAA (95% CI)	P	Annual % Change in HAA (95% CI)	p	Annual % Change in HAA (95% CI)	P
JEM exposure						
VGDF	-0.11 (-0.46 to 2.42)	0.53	-0.13 (-0.39 to 0.13)	0.34	0.04 (-0.25 to 0.32)	0.81
Gas/ Vapor	0.06 (-0.34 to 0.46)	0.77	0.01 (-0.28 to 0.29)	0.96	0.01 (-0.30 to 0.33)	0.93
Combined Dust	0.10 (-0.38 to 0.58)	0.69	0.09 (-0.25 to 0.43)	0.61	0.13 (-0.22 to 0.48)	0.48
Inorganic Dust	-0.31 (-0.95 to 0.33)	0.34	0.21 (-0.28 to 0.69)	0.40	0.05 (-0.44 to 0.55)	0.84
Organic Dust	-0.18 (-0.84 to 0.53)	0.62	-0.18 (-0.71 to 0.35)	0.51	-0.17 (-0.68 to 0.34)	0.51
Fumes	-0.25 (-0.97 to 0.48)	0.50	-0.16 (-0.68 to 0.36)	0.54	0.36 (-0.15 to 0.88)	0.17
Self-reported Exposure						
Gas/ Vapor	0.37 (-0.34 to 1.09)	0.31	0.12 (-0.29 to 0.53)	0.56	**0.62 (0.09 to 1.15)**	**0.02**
Dust	-0.09 (-0.69 to 0.51)	0.77	-0.07 (-0.41 to 0.27)	0.67	0.15 (-0.28 to 0.59)	0.48
Fumes	0.05 (-0.61 to 0.71)	0.89	0 (-0.40 to 0.41)	0.99	0.20 (-2.29 to 0.74)	0.33
Any VGDF agent	0 (-0.60 to 0.60)	0.99	-0.14 (-0.49 to 0.20)	0.41	0.27 (-0.15 to 0.67)	0.20
Severity	0 (-0.31 to 0.29)	0.96	-0.02 (-0.20 to 0.17)	0.87	0.27 (-0.10 to 0.34)	0.30
Per 10 year exposure	-0.06 (-0.45 to 0.33)	0.77	0.06 (-0.16 to 0.28)	0.61	-0.03 (-0.26 to 0.21)	0.81

Adjusted for age, race, smoking status (pack years, current smoking), gender, employment status, educational attainment, percent emphysema, BMI, height, scanner, type, total voxels, site

TABLE A4: Estimates of occupational exposures to VGDF and progression of HAA. Linear longitudinal association of JEM-assigned and self-reported VGDF exposures with percent change in high attenuation areas (HAA), from linear mixed models adjusted for age, gender, race/ ethnicity, educational attainment, employment status, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate, total volume of lung imaged, percent emphysema on CT scan, CT scanner type and study site

TABLE A5: Association between VGDF Occupational Exposures and Interstitial Lung Abnormalities

	JEM- assigned VGDF OR (95% CI) compared to low		Severity OR (95% CI) compared to none		
	Medium	High	Mild	Moderate	Severe
Overall	0.98 (0.70 to 2.36)	1.17 (0.72 to 1.91)	0.93 (0.67 to 1.32)	0.73 (0.46 to 1.15)	1.45 (0.83 to 2.52)
Gender					
Female	0.74 (0.39 to 1.39)	0.75 (0.32 to 1.73)	0.66 (0.40 to 1.09)	0.59 (0.31 to 1.14)	1.04 (0.46 to 2.34)
Male	1.17 (0.70 to 1.95)	1.55 (0.83 to 1.9)	1.37 (0.83 to 2.28)	0.89 (0.45 to 1.76)	1.95 (0.88 to 4.32)
Smoking Status					
Never	0.82 (0.47 to 1.42)	0.82 (0.47 to 1.42)	0.99 (0.61 to 1.60)	0.82 (0.42 to 1.58)	0.83 (0.31 to 2.23)
Ever	1.17 (0.70 to 1.95)	1.17 (0.70 to 1.95)	0.85 (0.53 to 1.39)	0.62 (0.33 to 1.17)	1.85 (0.92 to 3.71)
Baseline Age					
< 65 years	0.99 (0.54 to 1.83)	1.72 (0.81 to 3.66)	0.80 (0.48 to 1.33)	0.75 (0.39 to 1.45)	2.08 (0.96 to 4.50)
≥ 65 years	0.94 (0.56 to 1.59)	0.92 (0.48 to 1.76	1.05 (0.66 to 1.70)	0.71 (0.36 to 1.38)	1.05 (0.47 to 2.34)
Ethnicity					
Caucasian	1.50 (0.74 to 3.07)	1.36 (0.55 to 3.35)	0.75 (0.42 to 1.32)	1.05 (0.51 to 2.16)	1.89 (0.74 to 4.78)
Asian	0.37 (0.12 to 1.17)	0.77 (0.15 to 3.87)	1.10 (0.37 to 3.22)	0.67 (0.08 to 5.62)	1.44 (0.13 to 15.6)
Black	0.65 (0.27 to 1.55)	0.41 (0.09 to 1.87)	1.53 (0.78 to 3.01)	1.00 (0.40 to 2.48)	2.60 (0.84 to 7.17)
Hispanic	1.52 (0.74 to 3.12)	2.01 (0.91 to 4.46)	0.61 (0.29 to 1.29)	0.25 (0.09 to 0.68)	0.47 (0.14 to 1.59)
Employment status					
Employed	1.08 (0.55 to 2.14)	2.37 (1.01 to 5.57)	1.17 (0.67 to 2.04)	0.89 (0.40 to 1.95)	2.12 (0.80 to 5.61)
Not employed	0.93 (0.57 to 1.52)	0.91 (0.49 to 1.68)	0.8 (0.54 to 1.31)	0.66 (0.37 to 1.18)	1.21 (0.61 to 2.41)

Adjusted for age, race, smoking status (pack years, current smoking), gender, site
*employment status at exam 5

Shown is the Cross sectional association of JEM-assigned and self-reported severity to VGDF with the odds of interstitial lung abnormalities (ILA), from stratified multivariable logistic regression models adjusted for age, gender, ethnicity, tobacco use (current smoking status and pack years) and site.

This section contains results from analyses encoding occupational exposures as dummy variables. This does not make the assumption that the distance between different categories of exposures are equidistant. The lowest exposure category is encoded as the reference value

TABLE A6: Association between Job Exposure Matrix estimation of VGDF and High Attenuation Areas

	JEM Difference in % HAA (95% CI) compared to Low		Severity Difference in % HAA (95% CI) compared to None		
	Medium	High	Mild	Moderate	Severe
Overall	4.15 (2.25 to 6.07)	3.49 (0.90 to 6.15)	-0.01 (-1.86 to 1.87)	0.15 (-2.13 to 2.47)	-1.41 (-4.80 to 2.10)
Gender					
Female	5.78 (2.53 to 9.12)	6.35 (1.73 to 11.2)	0.39 (-2.34 to 3.20)	0.02 (-3.30 to 3.46)	-3.26 (-8.25 to 2.01)
Male	2.32 (0.14 to 4.54)	1.24 (-1.62 to 4.24)	-0.40 (-2.69 to 1.95)	-0.40 (-3.24 to 2.52)	-0.83 (-4.25 to 4.27)
Smoking Status					
Never	5.75 (2.70 to 8.89)	1.09 (-3.15 to 5.51)	-0.63 (-3.45 to 2.28)	0.02 (-3.60 to 3.78)	-1.89 (-7.55 to 4.13)
Ever	2.92 (0.51 to 5.38)	4.77 (1.54 to 8.11)	0.82 (-1.59 to 3.22)	0.39 (-2.44 to 3.29)	-0.36 (-4.43 to 3.88)
Baseline Age					
< 65 years	4.65 (2.19 to 7.16)	3.68 (0.25 to 7.22)	-0.60 (-2.79 to 1.64)	0.44 (-2.26 to 3.21)	2.28 (-2.03 to 6.78)
≥ 65 years	3.05 (0.10 to 6.08)	3.52 (-0.43 to 7.62)	1.60 (-1.68 to 4.88)	0.67 (-3.38 to 4.88)	-5.52 (-10.8 to 0.21)
Ethnicity					
Caucasian	1.25 (-1.73 to 4.34)	2.69 (-1.26 to 6.80)	-1.65 (-4.02 to 0.77)	0.52 (-2.74 to 3.88)	-5.82 (-10.3 to -1.12)
Asian	4.71 (-0.31 to 9.99)	-4.96 (-13.7 to 4.72)	1.37 (-4.24 to 7.31)	0.94 (-6.34 to 8.79)	6.17 (-6.83 to 21.0)
Black	2.05 (-1.58 to 5.82)	3.32 (-2.09 to 9.02)	-0.12 (-3.50 to 3.39)	2.26 (-2.03 to 6.73)	3.50 (-3.36 to 10.8)
Hispanic	4.77 (0.94 to 8.74)	5.13 (0.47 to 10.0)	3.02 (-1.55 to 7.80)	-1.42 (-6.04 to 3.42)	-0.48 (-7.16 to 6.67)
Employment Status					
Employed	2.77 (0.21 to 5.38)	4.69 (0.93 to 8.59)	-0.08 (-2.37 to 2.25)	-1.67 (-4.50 to 1.26)	-1.77 (-6.37 to 3.04)
Not employed	4.77 (2.03 to 7.59)	2.99 (-0.58 to 6.70)	-0.39 (-3.29 to 2.60)	1.73 (-1.81 to 5.41)	-1.19 (-6.06 to 3.93)

Adjusted for age, race, smoking status (pack years, current smoking), gender, employment status, educational attainment, percent emphysema, BMI, height, scanner, type, total voxels, site

Shown is the cross- sectional association of self- reported VGDF exposures and percent change in high attenuation areas (HAA), from linear mixed models adjusted for age, gender, race/ ethnicity, educational attainment, employment status, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate, total volume of lung imaged, percent emphysema on CT scan, CT scanner type and study site. Severity is encoded as a dummy variable with none as the reference range.

TABLE A7: Association between Occupational Exposures and Progression of High Attenuation Areas

	JEM Annual % Change in HAA (95% CI) compared to Low		Severity Annual % Change in HAA (95% CI) compared to None		
	Medium	High	Mild	Moderate	Severe
Overall	-0.06 (-0.27 to 0.25)	0.04 (-0.39 to 0.46)	0.09 (-0.22 to 0.40)	-0.03 (-0.41 to 0.35)	0.30 (-0.29 to 0.90)
Gender					
Female	-0.32 (-0.83 to 0.20)	-0.53 (-1.27 to 0.21)	0.06 (-0.41 to 0.53)	-0.44 (-1.00 to 0.12)	0.16 (-0.72 to 1.05)
Male	0.19 (-0.19 to 0.58)	0.39 (-0.11 to 0.89)	0.08 (-0.32 to 0.43)	0.53 (0.03 to 1.03)	0.46 (-0.32 to 1.25)
Smoking Status					
Never	-0.23 (-0.68 to 0.22)	0.47 (-0.18 to 1.12)	0.25 (-0.20 to 0.70)	-0.18 (-0.74 to 0.38)	0.60 (-0.37 to 1.57)
Ever	0.01 (-0.42 to 0.43)	-0.22 (-0.77 to 0.33)	-0.08 (-0.49 to 0.34)	0.08 (-0.42 to 0.58)	0.15 (-0.59 to 0.89)
Baseline Age					
< 65 years	-0.14 (-0.51 to 0.22)	-0.13 (-0.64 to 0.39)	0.07 (-0.28 to 0.42)	-0.20 (-0.64 to 0.23)	0 (-0.70 to 0.70)
≥ 65 years	0.13 (-0.46 to 0.72)	0.31 (-0.43 to 1.06)	0.05 (-0.56 to 1.72)	0.34 (-0.41 to 1.09)	0.61 (-0.49 to 1.72)
Ethnicity					
Caucasian	0.24 (-0.27 to 0.75)	0.18 (-0.45 to 0.81)	0.51 (0.12 to 0.90)	0.44 (-0.08 to 0.97)	1.12 (0.34 to 1.92)
Asian	-0.17 (-0.86 to 0.54)	0.88 (-0.45 to 2.23)	-0.18 (-0.99 to 0.65)	-0.07 (-1.13 to 1.00)	-0.69 (-2.68 to 1.33)
Black	0.14 (-0.61 to 0.90)	0.76 (-0.40 to 1.93)	-0.23 (-0.86 to 0.41)	-0.25 (-1.01 to 0.52)	-0.32 (-1.61 to 0.99)
Hispanic	-0.18 (-0.64 to 0.61)	-0.26 (-0.99 to 0.46)	0.01 (-0.71 to 0.74)	-0.07 (-0.85 to 0.71)	0.05 (-1.09 to 1.21)
Employment Status					
Employed	0.04 (-0.38 to 0.45)	-0.41 (-1.01 to 0.19)	-0.13 (-0.52 to 0.26)	-0.12 (-0.60 to 0.36)	0.22 (-0.60 to 1.04)
Not employed	-0.18 (-0.66 to 0.31)	0.20 (-0.42 to 0.83)	0.29 (-0.21 to 0.79)	0.07 (-0.52 to 0.68)	0.48 (-0.39 to 1.36)

Adjusted for age, race, smoking status (pack years, current smoking), gender, employment status, educational attainment, percent emphysema, BMI, height, scanner, type, total voxels, site

Shown is the linear longitudinal association of JEM-assigned and self- reported VGDF exposures with percent change in high attenuation areas (HAA), from linear mixed models adjusted for age, gender, race/ ethnicity, educational attainment, employment status, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate, total volume of lung imaged, percent emphysema on CT scan, CT scanner type and study site