Supplementary Appendix

High Attenuation Areas on Chest CT in Community-Dwelling Adults: The MESA Study

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Participants and Study Design

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multi-center, prospective cohort study sponsored by the National Heart Lung and Blood Institute (NHLBI) to investigate the progression of subclinical cardiovascular disease. Participant selection criteria have previously been described [1]. Briefly, the study enrolled 6,814 adults age 45 and 84 years free of clinical cardiovascular disease from six communities in the United States between 2000 and 2002. Exclusion criteria included weight greater than 136 kg, limited life expectancy, any impediment to long-term participation, and chest CT imaging in the preceding 12 months. Notably, there were no selection criteria based on lung disease, respiratory symptoms, or smoking history.

MESA participants were followed longitudinally and attended serial follow-up visits, with the most recent visit completed between 2010 and 2012 (Figure S1). All participants completed a detailed questionnaire on demographics, family history, medical history, medication use, lifestyle habits and psychosocial factor during the MESA baseline visit between years 2000 and 2002, as previously described [1]. Height, weight, and waist circumference were measured using standard techniques [1]. Smoking history and number of pack-years were self-reported, with never-smoking defined as fewer than 100 cigarettes smoked in a lifetime and current smoking defined as cigarette use within the past 30 days. A subset of participants had urine cotinine measured and participants with levels greater than 100 ng/mL were reclassified as current smokers. Blood was drawn for biomarker measurements and participants completed cardiac CT scans at the MESA baseline visit.

In the current study, we included participants from the MESA study (n=6,814, Figure S2A) as well as three substudies: biomarkers (Figure S2B), lung function & ILA measurement (Figure S2C) and exercise testing (Figure S2D).

We sampled 908 MESA participants for measurement of MMP-7 and SP-A (Figure S2B). We performed a case-cohort study [2]. In this substudy, for sampling purposes, cases were defined as an HAA greater than 9% of imaged lung at baseline. A randomly selected subcohort of 600 MESA participants served as the comparator group, consistent with the case-cohort study design [2]. 33 participants sampled for the subcohort met case definition, leaving 567 as the comparator group in our analyses. MMP-7 and SP-A were chosen based on prior studies showing associations of these biomarkers with lung injury and extracellular matrix remodeling in ILD [3, 4]. We additionally examined the associations between HAA and two biomarkers of inflammation (IL-6 and CRP) [5] that had already been measured in nearly all participants in the MESA parent cohort.

In 2004-2006, 3,965 participants were randomly sampled from the MESA parent study to undergo spirometry and complete additional questionnaires (Figure S2C) [6]. 3,834 of these participants had complete spirometry data and were included in our analyses. The median time between baseline HAA measurement and completion of spirometry was 4.6 years (range 2.1 to 6.0 years). 2,727 of these participants also completed full lung CT scans at the MESA exam 5 follow-up visit (in years 2010-2012; Figure S1). There were an additional 410 participants newly sampled from the original MESA cohort in 2010 that also underwent full lung CT scans. 2,907 of these 3137 participants had scans with valid baseline measurement of HAA and a valid

assessment of interstitial lung abnormalities (ILA) and were included in our analyses. The median time between baseline HAA measurement and subsequent ILA measurement was 9.5 years (range 8.0 to 11.4 years).

The exercise substudy enrolled 89 MESA participants from the Columbia University MESA Field Center in 2010-2012 for 6-minute walk testing (6-MWT) and cardiopulmonary exercise testing (CPET) (Figure S2D). Exclusion criteria included airflow obstruction by spirometry, body mass index (BMI) >35, clinical diagnosis of asthma, chronic obstructive pulmonary disease (COPD), or another condition that limits the respiratory system mechanics, perceived inability to exercise, recent acute coronary syndrome, known angina, and known left ventricular systolic dysfunction. Participants with clinical ILD were excluded. The recruited participants were predominantly African-American or Hispanic, reflecting the demographics of MESA participants at Columbia University. The study enrolled 30 cases, which we defined as participants with HAA above the 90^{th} percentile (7.5% of total imaged lung) on MESA cardiac CT scans completed at the MESA baseline visit (between 2000 and 2002). 59 controls with HAA below the 90^{th} percentile were frequency matched on age, gender, race/ethnicity, BMI and smoking status. The median time between HAA measurement and completion of the walk test and CPET was 10.8 years (range 9.6 to 12.1).

We also measured HAA in 48 adults with clinically diagnosed ILD, 75% of whom had IPF diagnosed by ATS criteria. These patients were seen at one of 3 centers (Columbia, Penn, or Duke) and were enrolled in the NHLBI-funded Lung Transplant Body Composition (LTBC) study.

MESA, LTBC and all ancillary studies were approved by Institutional Review Boards at all collaborating centers and all participants provided informed consent.

High Attenuation Areas on CT Scan

Baseline cardiac CT scans were performed during the years 2000-2002 on multi-detector CT scanners (three sites) or electron beam tomography scanners (three sites) using a standardized protocol, as previously described [7, 8]. Each participant underwent two sequential scans on separate breath-holds in succession at full inspiration, with transverse fields of view capturing the whole lung field from the carina to the lung bases. The scan with higher air volume was used for analyses, except in cases of discordant scan quality control score, in which case the higher quality scan was used. A prior validation study using MESA full lung scans showed that these cardiac CT scans image approximately 65% of total lung volume, excluding most of the upper lobes but capturing most of the lower lobes [9]. High attenuation areas (HAA) were defined as the volume of imaged lungs having CT attenuation values between -600 and -250 Hounsfield Units (HU). This range of attenuation values includes ground-glass and reticular changes but excludes more dense areas such as parenchymal consolidation, blood vessels, and solid nodules. HAA of at least 10% of imaged lung volume is moderately specific for subclinical ILD (~70%), has good positive and negative predictive value (96% and 67% respectively compared to interpretation by blinded pulmonologist as the "gold standard"), and is independently associated with cumulative cigarette smoke exposure, as we have previously described [10]. Percent emphysema was defined as the percentage of the voxels in the lung below -950 HU, as previously described [9, 11]. Quantitative image attenuation was measured using a modified

version of the Pulmonary Analysis Software Suite at a single reading center by trained readers from the University of Iowa Imaging Lab.

Biomarker Measurements

C-reactive protein (CRP) and interleukin-6 (IL-6) levels were measured at the MESA Core Laboratory at University of Vermont in serum collected from all MESA participants at the MESA baseline visit. Valid CRP results were available for 6,761 MESA participants and valid IL-6 results were available for 6,621 MESA participants. CRP was measured using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, IL). This instrument utilizes a particle enhanced immunonepholometric assay to determine CRP. Polystyrene particles are coated with monoclonal antibodies to CRP that agglutinate in the presence of antigen (CRP) to cause an increase in the intensity of scattered light. The increase in scattered light is proportional to the amount of CRP in the sample. The assay range is 0.175 – 1100 mg/L. Expected values for CRP in normal, healthy individuals are ≤ 3 mg/L. The mean CRP concentration in our sample was 3.78 mg/L. Intra-assay CVs range from 2.3 to 4.4% and inter-assay CVs range from 2.1 to 5.7%.

IL-6 was measured using ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN). The lower detection limit is <0.0.094 pg/mL with a detection range of 0.156-10.0 pg/mL. A monoclonal anti-IL6 antibody is coated on the plastic support and a polyclonal anti-IL6 antibody is used as the sandwich antibody. The amount of IL-6 bound is determined by a color reaction. The expected normal range per the manufacturer is 0.24 to 12.5

pg/mL. The mean concentration in our sample was 1.56 mg/L. The laboratory CV for this assay is 6.3%.

MMP-7 and SP-A were measured in banked baseline serum samples from MESA participants at the MESA Core Laboratory at the University of Vermont's Laboratory for Clinical Biochemistry Research. Samples were stored at -70ºC. MMP-7 was measured using a quantitative sandwich ELISA assay from R&D systems. The lower detection limit for this assay is 0.094 ng/mL and the detection range is 0.2-10 ng/mL. The expected normal range per manufacturer is 1.07-4.40 ng/mL. The mean concentration in our sample was 4.33 ng/mL (4.09 in subcohort only). The laboratory inter-assay CVs range from 2.9 to 6.9%.

SP-A was measured using a quantitative sandwich ELISA from Biovendor. The lower detection limit for this assay is 0.16 ng/mL and the upper limit of detection is 500 ng/mL. The expected normal range per manufacturer is 13-65 ng/mL. The mean concentration in our sample was 76.25 ng/mL (79.87 in subcohort only). The laboratory inter-assay CVs range from 10.9 to 14.2%.

Spirometry and Exercise Testing

Spirometry was conducted in years 2004 to 2006 according to the American Thoracic Society (ATS)/European Respiratory Society guidelines [12], using equipment and protocol that have previously been described [13]. Six-minute walk test was conducted in 2010-2012 in accordance with ATS guidelines [14]. Oxygen saturation, distance walked, and Borg dyspnea and fatigue scores were measured at the end of the walk. CPET was performed on a Vmax Encore 29 Metabolic Exercise System, Viasprint 150P (Viasys Respiratory Care, Yorba Linda, CA) with an

electrically braked cycle ergometer. Continuous 12-lead telemetry was monitored via CardioSoft electrocardiogram software (GE/CardioSoft, Houston, TX). After 5 min of rest and 3 minutes of unloaded pedaling, an individualized ramping protocol was determined based on the participant's maximum voluntary ventilation (MVV). Individuals who achieved ≤ 40 L/min MVV performed a 5-watt per minute ramping protocol, and those attaining > 40 L/min MVV performed a 10-watt ramping protocol. CPET variables were collected breath-by-breath and included the rate of carbon dioxide output ($\dot{V}CO_2$ in $mL.min^{-1}.kg^{-1}$), workload (peak watts), oxygen uptake ($\dot{V}O_2$ in $mL.min^{-1}.kg^{-1}$), minute ventilation ($\dot{V}E$ in liters per min), partial pressure of end-tidal CO_2 ($PetCO_2$ in millimeters of mercury), heart rate (HR) in beats per minute (bpm), and volume of O_2 uptake per heartbeat (O_2 pulse) in milliliters per beat.

Interstitial Lung Abnormalities

Full lung CT scans were acquired at MESA exam 5 (years 2010 to 2012) without intravenous contrast at suspended full inspiration on 64-slice scanners (GE and Siemens) using the MESA-Lung/SPIROMICS protocol [15]. Images were reconstructed using 0.625 mm slice thickness. In order to standardize measurement of ILA, five expert thoracic radiologists (J.H.M.A, J.N., P.H.N., S.K.S., J.R.W.) first reviewed the Fleischner Society's definitions of 6 key findings (ground-glass opacity, reticular pattern, nonemphysematous cysts, honeycombing, traction bronchiectasis and centrilobular nodules) [16] and then reviewed 4 publications describing ILA [17-20]. Scans were read as "suspicious" for ILD if they had 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 [17-19]. Scans were read as "definite ILD" if they had bilateral fibrosis in multiple lobes

associated with honeycombing and traction bronchiectasis in a subpleural distribution. Scans that had either “suspicious” or “definite” ILD were then defined as having ILA. Scans with a solitary focus of ground-glass attenuation, reticulation or multifocal ground-glass abnormality in less than 5% of the lung were read as “equivocal” for ILA and were excluded from further analysis, as previously described [18, 19]. During the training period, each radiologist independently reviewed 20 randomly selected MESA exam 5 full lung CT scans and scored the presence or absence of each ILA finding [17] using a pre-formatted case-report form. All 20 scans were then reviewed as a group by teleconference. Each of the 3,010 exam 5 full lung CT scans was then assigned to 1 of the 5 radiologists for formal ILA reading. All formal readings used an electronic case-report form developed by the MESA Coordinating Center at the University of Washington.

Cardiac MRI

Cardiac magnetic resonance imaging (MRI) was performed at the MESA baseline visit in 5,098 participants, of whom 5,004 had interpretable images of the left ventricle (LV). The MRI protocol has been described previously [21]. Images were acquired using 1.5-T magnets, using a four-element, phased-array surface coil placed anteriorly and posteriorly, with ECG gating. Imaging was consisted of fast gradient echo cine images with temporal resolution of 50 msec or less. Data were analyzed using MASS software, version 4.2 (Medis) at a single reading center [8]. LV end-diastolic volume was calculated as the summation of areas on each separate slice multiplied by the sum of slice thickness and image gap. LV mass was determined by the sum of the myocardial areas times slice thickness plus image gap in the end-diastolic phase, multiplied by the specific gravity of the myocardium [21]. LV ejection fraction was calculated as the stroke volume divided by the end-diastolic volume [8].

Longitudinal Follow-up

MESA participants were followed prospectively and vital status was determined by contacting each MESA participant or family member by interviewers every 9 to 12 months. This was supplemented through review of the National Death Index (NDI) to ensure complete follow-up of mortality through the most recent NDI update (March 13, 2015). Five participants were excluded from follow-up by the MESA parent study because of discovery of pre-baseline cardiovascular events, and no mortality data is available for these participants.

Analysis Approach

We present a number of analyses to establish the validity of HAA as a measure of subclinical ILD. We treated HAA as a continuous independent variable and expressed it as the log base 2-transformed percentage of imaged lung volume with an attenuated value between -600 and -250 HU.

For most analyses, we used generalized linear models to adjust for age, gender, race, educational attainment, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate (GFR), study site, mA dose, total volume of imaged lung and percent emphysema. Since FVC and imaged lung volume were highly collinear (Pearson correlation coefficient of 0.69), we excluded imaged lung volume from analyses examining the association between HAA and FVC. We used logistic regression to estimate adjusted odds ratios for ILA for each quartile of HAA and per doubling of HAA. We present age- and gender-adjusted least-square mean values of exercise measurements for HAA cases and controls from the MESA exercise study.

For MMP-7 and SP-A models, we performed sensitivity analyses using inverse probability weighting to account for sampling of cases and the subcohort.

We examined associations between HAA and survival time using Cox proportional hazards models and additive Cox models, as previously described [22]. Survival time was calculated as the age at death or last follow-up or the most recent NDI update, whichever occurred later. Analyses were left-truncated at age of study entry. Primary analyses were adjusted for the same covariates as the generalized linear models above. Secondary analyses were adjusted for additional risk factors and potential confounders: alcohol use, exercise, coronary artery calcium, diabetes medication use, insulin use, fasting glucose level, hypertension, antihypertensive medication use, systolic and diastolic blood pressures, cholesterol medication use, total and high-density lipoprotein cholesterol levels, c-reactive protein level, d-dimer level and history of cancer.

All biomarkers as well as HAA were log base 2-transformed in all analyses. We used multiple imputation (proc mi and proc mianalyze in SAS version 9.3) to account for missing covariate values, which were infrequent (<1%). We used generalized additive models to examine non-linear associations and visually inspect the form of the adjusted relationships between variables. We examined models stratified by smoking status, age, gender, race and BMI. Log-likelihood tests were used to test for interactions between HAA and potential effect modifiers. Additional sensitivity analyses included models adjusted for LV ejection fraction, LV end-diastolic volume and LV end-diastolic mass in the subset of participants who had valid cardiac MRI

measurements. All statistical tests were performed in SAS version 9.3 (SAS Institute) and R version 3.2.0 (R Foundation for Statistical Computing).

Additional Stratified Analyses

Additional analyses included models stratified by age, gender, race and BMI (Table S10). For FVC, there was evidence of effect modification by gender (p for interaction <0.001), with stronger association between HAA and FVC among males (adjusted estimate -146 mL, 95% CI -216 to -77) than among females (adjusted estimate -54 mL, 95% CI -92 to -16). The association between HAA and FVC was also modified by race (p for interaction 0.01), with the strongest association among African-Americans (adjusted estimate -216 mL, 95% CI -294 to -137) and the weakest association among Hispanics (adjusted estimate 9 mL, 95% CI -53 to 71).

The association between MMP7 and HAA was modified by gender (p for interaction 0.03) and race (p for interaction <0.001). Males had a stronger association than females (adjusted estimate 13.67%, 95% CI 5.05 to 23.01 for males; adjust estimate 3.29%, 95% CI -3.28 to 10.31 for females). In models stratified by race, the strongest association between MMP7 and HAA was found among African-Americans (adjusted estimate 11.46%, 95% CI 1.52 to 22.39).

We did not find any evidence of effect modification by gender, age, race or BMI on the association between HAA and ILA (Table S10).

Additional Sensitivity Analyses

We examined models adjusted for measurements of LV systolic and diastolic dysfunction (LV ejection fraction, LV end-diastolic mass and LV end-diastolic volume) in a subset of MESA participants who underwent cardiac MRI at the baseline visit (Table S11). We found slight attenuation of the effect estimates for FVC, IL-6, ILA and HR for death. However, the association between HAA and these outcomes remained significant. The adjusted effect estimate for MMP-7 decreased from 6.26 to 2.51% (95% CI -3.07 to 8.41) and was no longer significant (p=0.39). However, LV function parameters were not available for 286 of the 908 participants who completed MMP-7 measurements. In a model limited to only the participants who had complete LV function parameters, but unadjusted for these parameters, the effect estimate for MMP-7 was 3.69% (95% CI -1.98 to 9.69; p=0.21), suggesting minimal confounding by LV measures.

We examined models after exclusion of participants with HAA above the 90^{th} percentile (>7.5%; Table S12). In the fully adjusted model, the association between HAA and FVC increased from -82 to -261 mL (95% CI -328 to -194; p<0.001). The association between HAA and MMP-7 (among subcohort participants only) increased from 6.26 to 22.66% (95% CI 7.18 to 40.38, p=0.003). The association between HAA and IL-6 increased from 8.78 to 20.56% (95% CI 13.13 to 28.49; p<0.001). The OR for the association between HAA and ILA increased from 1.95 to 3.00 (95% CI 1.63 to 5.51; p<0.001). In the model fully adjusted for a number of cardiovascular disease risk factors and cancer, the HR for the association between HAA and mortality increased from 1.55 to 1.94 (95% CI 1.52 to 2.49; p<0.001).

Table S1. Computed tomography protocols for baseline cardiac scans in MESA (adapted from ref [9]).

Scanner	Scan Mode	mA/mAs*	kV	Rotation Time (s)	Slice Thickness (mm)	Slice Spacing (mm)	Field of View (cm) †	Kernel
GE Light Speed QXi	Axial	200 mA	120	0.800	2.5	2.5	35	Standard
GE Light Speed Plus	Axial	320 mA	120	0.500	2.5	2.5	35	Standard
Siemens Volume Zoom	Axial	139 mA/ 50 mAs	120	0.361	2.5	2.5	35	Standard
Imatron C-150	Axial	630 mA	120	0.100	2.5	2.5	35	Sharp

∗ For the multidetector computed tomographic (MDCT) systems the mA was increased by 25% in individuals who weighed 100 kg (220 lbs) or greater to maintain a similar level of image noise.
† Ref [23]

Table S2: Baseline characteristics of 6,813 MESA participants stratified by quartiles of HAA.

	HAA			
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
HAA %, range	2.0 to 3.5%	3.5 to 4.2%	4.2 to 5.4%	5.4 to 75.2%
Participants, n	1703	1703	1704	1703
Age, years	62±10	62±10	62±10	63±10
Male	952 (56)	839 (49)	750 (44)	672 (39)
Race/ethnicity				
White	942 (55)	666 (39)	586 (34)	428 (25)
African-American	385 (23)	481 (28)	524 (31)	502 (29)
Hispanic	238 (14)	349 (21)	394 (23)	514 (30)
Chinese	138 (8)	207 (12)	200 (12)	259 (15)
BMI, kg/m^2	27±5	28±5	29±6	30±6
Height, cm	169±10	167±10	166±10	164±10
Weight, lbs	166±35	172±38	178±39	177±40
Waist circumference, cm	94±13	97±14	100±14	101±15
Hip circumference, cm	103±10	105±11	107±12	108±12
Smoking				
Never-smokers	707 (42)	744 (43)	786 (46)	848 (50)
Former smokers	785 (46)	724 (43)	645 (38)	607 (36)
Current smokers	211 (12)	235 (14)	273 (16)	248 (15)
Cigarette pack-years*	13 (3-32)	15 (4-34)	16 (4-34)	14 (3-31)
Spirometry†				
FVC, L	3.63±0.94	3.26±0.90	3.04±0.89	2.85±0.92
FVC, % predicted	101.50±15.64	96.16±15.42	93.06±15.59	91.38±17.01
FEV1, L	2.61±0.74	2.43±0.71	2.30±0.70	2.20±0.72
FEV1, % predicted	97.52±18.79	94.08±17.66	92.42±17.68	92.34±18.28
FEV1/FVC ratio	0.72±0.09	0.75±0.09	0.75±0.08	0.77±0.07
Computed tomography				
Total imaged lung volume, mL	3312 (2857-3861)	2866 (2449-3362)	2569 (2201-3006)	2045 (1711-2466)
Emphysema, %	6.7 (3.8-10.1)	3.6 (2.1-6.0)	2.3 (1.3-4.0)	0.9 (0.4-1.9)
Respiratory diseases				
Self-reported asthma, %	9.4	10.3	10.5	9.0
Self-reported pulmonary fibrosis, %†	0.1	0.2	0.1	0.1
Self-reported emphysema, %	2.4	1.9	0.9	0.9

Data presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. All parameters collected at MESA baseline visit in years 2000-2002, unless otherwise stated. HAA = high attenuation areas; BMI: body mass index

* Among ever-smokers

† Completed at MESA exam 3-4 (years 2004-2006) in 3,834 MESA participants

Table S3. Baseline characteristics of MESA participants in parent cohort and participants sampled for selected ancillary studies.

	MESA Parent*	MESA lung substudy		Exercise subgroup‡		Biomarker subgroup§	
		Spirometry subgroup	ILA subgroup	Controls	Cases	Subcohort	Cases
N	6813	3834	2430	59	30	600	341
Age, years	62±10	61±10	60±9	60±8	58±9	63±10	65±10
Male	3213 (47)	1895 (49)	1144 (47)	24 (41)	12 (40)	285 (48)	128 (38)
Race/ethnicity							
White	2622 (38)	1351 (35)	953 (39)	1 (2)	1 (3)	220 (37)	54 (16)
African-American	1892 (28)	986 (26)	636 (26)	19 (32)	4 (13)	187 (31)	79 (23)
Hispanic	1495 (22)	872 (23)	503 (21)	39 (66)	25 (84)	125 (21)	131 (38)
Chinese	804 (12)	625 (16)	338 (14)	0 (0)	0 (0)	68 (11)	77 (23)
BMI, kg/m^2	28±5	28±5	28±5	28±3	28±3	28±6	29±5
Height, cm	166±10	167±10	167±10	166±7	162±8	166±10	162±10
Weight, lb	173±38	172±38	174±37	167±20	162±20	174±40	170±38
Hip circumference, cm	106±11	105±11	106±11	104±6	105±6	106±12	106±11
Waist circumference, cm	98±14	97±14	97±14	95±9	96±9	98±14	101±13
Smoking							
Never-smokers	3085 (45)	1786 (47)	1211 (50)	44 (74)	19 (63)	274 (45)	199 (58)
Former smokers	2761 (41)	1505 (39)	905 (37)	11 (19)	8 (27)	268 (45)	112 (33)
Current smokers	967 (14)	543 (14)	314 (13)	4 (7)	3 (10)	58 (10)	30 (9)
Cigarette pack-years†	14.5 (3-33)	14.9 (3-33)	12.8 (3-30)	8.8 (2-23)	4.7 (1-23)	12.6 (2-30)	12.6 (2-30)
Total volume imaged lung, cm^3	2691 (2208-3253)	2692 (2219-3244)	2687 (2226-3255)	2461 (2207-3026)	1685 (1461-1923)	2682 (2212-3266)	1607 (1345-1962)
Emphysema, %	2.9 (1.2-5.7)	3.0 (1.3-5.8)	2.7 (1.2-5.5)	3.1 (1.8-6.6)	0.2 (0.1-0.4)	2.9 (1.2-5.7)	0.4 (0.2-0.8)
HAA, %	4.2 (3.5-5.4)	4.3 (3.6-5.4)	4.2 (3.6-5.3)	4.2 (3.8-4.7)	12.0 (9.3-18.7)	4.3 (3.6-5.3)	11.9 (10.2-15.1)

Data presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. All parameters collected at MESA baseline visit in years 2000-2002. BMI = body mass index; ILA = interstitial lung abnormalities; HAA = high attenuation areas

* Excludes 1 participant without baseline HAA measurement.

† Among ever-smokers.

‡ Cases were defined by HAA greater than the 90^{th} percentile (7.5% of total imaged lung). Controls were defined as HAA values less than the 90^{th} percentile.

§ Cases were defined by HAA greater than 9% of total imaged lung. Subcohort was randomly selected from MESA parent. 33 participants in the subcohort also met case definition.

Table S4. Cross-sectional associations between HAA and serum biomarkers of lung injury, extracellular matrix remodeling and inflammation at the MESA baseline exam stratified by smoking status and using inverse probability weighting to account for case/subcohort sampling.*

	Overall		Ever-smokers		Never-smokers		P for interaction
	Percent change in biomarker†	P value	Percent change in biomarker†	P value	Percent change in biomarker†	P value	
MMP-7, ng/mL	7.20 (0.62 to 14.22)	0.03	17.71 (7.09 to 29.38)	<0.001	1.64 (-6.97 to 11.03)	0.72	0.01
SP-A, ng/mL	2.32 (-10.30 to 16.70)	0.73	3.80 (-13.62 to 24.73)	0.69	5.15 (-13.20 to 27.37)	0.61	0.67

HAA = high attenuation areas; MMP-7 = matrix metalloproteinase-7; SP-A = surfactant protein-A

* 908 MESA participants include 341 cases defined as having HAA>9% and a randomly selected subcohort of 600 MESA participants; 33 participants in the subcohort also met case definition.

† Adjusted for age, gender, race, educational attainment, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate (GFR), study site, percent emphysema, mA dose and total volume of imaged lung (adjustment for smoking status and pack-years not included is smoking-stratified models). All covariates measured at baseline examination in 2000 to 2002. Percent change is reported per 2-fold increase in HAA.

Table S5. Associations between HAA and FVC among 3,834 MESA participants stratified by smoking status.

	HAA						
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**P for trend**	**Overall (95% CI)§**	**P value**
FVC, all MESA lung function participants*							
Unadjusted, mL	Ref	-370.39	-581.36	-765.57	<0.001	-466.93 (-519.78 to -414.09)	<0.001
Unadjusted, % predicted	Ref	-5.27	-8.28	-9.90	<0.001	-5.50 (-6.42 to -4.57)	<0.001
Adjusted, mL†	Ref	-137.67	-197.02	-212.56	<0.001	-81.54 (-118.73 to -44.35)	<0.001
Adjusted, % predicted†	Ref	-3.58	-5.63	-6.56	<0.001	-2.78 (-3.90 to -1.66)	<0.001
FVC, ever-smokers‡							
Unadjusted, mL	Ref	-332.92	-585.69	-708.05	<0.001	-464.42 (-543.73 to -385.10)	<0.001
Unadjusted, % predicted	Ref	-5.20	-8.51	-10.85	<0.001	-6.80 (-8.21 to -5.38)	<0.001
Adjusted, mL†	Ref	-169.75	-251.54	-303.61	<0.001	-156.50 (-216.49 to -96.52)	<0.001
Adjusted, % predicted†	Ref	-4.09	-6.94	-8.77	<0.001	-4.84 (-6.55 to -3.13)	<0.001
FVC, never-smokers‡							
Unadjusted, mL	Ref	-408.11	-561.00	-782.75	<0.001	-433.68 (-502.45 to -364.91)	<0.001
Unadjusted, % predicted	Ref	-5.39	-8.10	-9.19	<0.001	-4.64 (-5.83 to -3.44)	<0.001
Adjusted, mL†	Ref	-94.95	-135.71	-104.50	0.33	-14.64 (-60.24 to 30.97)	0.53
Adjusted, % predicted†	Ref	-3.11	-4.47	-4.23	0.06	-0.96 (-2.44 to 0.52)	0.20

HAA = high attenuation areas; FVC = forced vital capacity

* Excludes MESA lung function participants without valid spirometry measurements (n=131).

† Adjusted for age, gender, race, educational attainment, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate (GFR), study site, percent emphysema and mA dose (adjustment for smoking and cigarette pack-years not included in stratified models). Models for percent predicted FVC exclude adjustment for age, gender and height. All covariates measured at baseline examination in 2000 to 2002.

‡ P values for the interaction between HAA as a continuous variable and smoking status as a binary variable are 0.002 for FVC and 0.03 for ppFVC.

§ Overall effect estimate is reported as the change in FVC and percent predicted FVC per 2-fold increase in HAA.

Table S6. Associations between HAA, FEV1 and FEV1/FVC ratio among 3,834 MESA participants stratified by smoking status.

	Change per 2-fold increase in HAA	P value
FEV1, all MESA lung function participants*		
Unadjusted, mL	-241.43 (-282.75 to -200.12)	<0.001
Unadjusted, % predicted	-1.56 (-2.60 to -0.51)	0.003
Adjusted, mL†	-62.42 (-94.11 to -30.73)	<0.001
Adjusted, % predicted†	-2.14 (-3.39 to -0.88)	<0.001
FEV1, ever-smokers‡		
Unadjusted, mL	-199.08 (-262.32 to -135.85)	<0.001
Unadjusted, % predicted	-1.53 (-3.16 to -0.10)	0.07
Adjusted, mL†	-105.38 (-158.96 to -51.79)	<0.001
Adjusted, % predicted†	-3.57 (-5.57 to -1.57)	<0.001
FEV1, never-smokers‡		
Unadjusted, mL	-262.88 (-316.46 to -209.31)	<0.001
Unadjusted, % predicted	-2.21 (-3.50 to -0.93)	<0.001
Adjusted, mL†	-12.38 (-49.92 to 25.17)	0.52
Adjusted, % predicted†	-0.57 (-2.19 to 1.06)	0.50
FEV1/FVC ratio, all MESA lung function participants		
Unadjusted, %	3.47 (2.99 to 3.95)	<0.001
Adjusted, %†	0.29 (-0.25 to 0.83)	0.30
FEV1/FVC, ever-smokers§		
Unadjusted, %	4.41 (3.64 to 5.18)	<0.001
Adjusted, %†	0.51 (-0.40 to 1.41)	0.27
FEV1/FVC, never-smokers§		
Unadjusted, %	2.29 (1.73 to 2.84)	<0.001
Adjusted, %†	0.34 (-0.33 to 1.02)	0.32

HAA = high attenuation areas; FEV1 = forced expired volume in 1 second; FVC = forced vital capacity

* Excludes MESA lung function participants without valid spirometry measurements (n=131).

† Adjusted for age, gender, race, educational attainment, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate (GFR), study site, percent emphysema and mA dose. Models for percent predicted FEV1 exclude adjustment for age, gender and height. Models stratified by smoking status exclude adjustment for smoking status and cigarette pack-years. All covariates measured at baseline examination in 2000 to 2002.

‡ P for interaction between HAA as a continuous variable and smoking status as a binary variable (never/ever smoker) for FEV1 is 0.49, for ppFEV1 is 0.84.

§ P for interaction between HAA as a continuous variable and smoking status as a binary variable (never/ever smoker) for FEV1/FVC ratio is 0.02.

Table S7. Associations between baseline HAA and exercise capacity in 30 cases with elevated HAA and 59 controls without elevated HAA.*

	Controls HAA<7.5%	Cases HAA>7.5%	LS Mean Controls (SE)†	LS Mean Cases (SE)†	P value‡
6-minute walk test					
Walk distance, m	485	453	491 (11.58)	451 (16.21)	0.045
O_2 saturation at end of study	95.6	94.3	95.6 (1.03)	94.2 (1.44)	0.43
Borg dyspnea score	0.66	0.72	0.67 (0.14)	0.72 (0.19)	0.84
CPET					
$\dot{V}O_2$ peak, L/min	1.45	1.32	1.47 (0.04)	1.28 (0.06)	0.01
$\dot{V}O_2$ peak, ml/kg/min	19.35	17.96	19.56 (0.53)	17.55 (0.74)	0.03
$\dot{V}O_2$ at AT, L/min§	1.13	1.03	1.15 (0.04)	1.00 (0.05)	0.02
$\dot{V}O_2$ predicted %	82.24	73.47	82.78 (2.19)	72.40 (3.07)	0.01
Peak Watts	86.71	78.73	88.12 (2.86)	75.96 (4.02)	0.02
$\dot{V}O_2$/Watts, %	1.76	1.78	1.76 (0.06)	1.80 (0.09)	0.71
Peak HR, beats/min	131.54	130.23	132.46 (2.09)	128.42 (2.93)	0.27
O_2 pulse, ml/beat (peak)	11.05	10.19	11.12 (0.34)	10.04 (0.48)	0.07
Breathing reserve ($\dot{V}E$/MVV)	60.27	54.21	60.72 (2.02)	53.34 (2.84)	0.04
$\dot{V}E$/ $\dot{V}CO_2$ at AT§	30.86	31.82	30.73 (0.60)	32.09 (0.87)	0.20
$\dot{V}E$/ $\dot{V}CO_2$ peak	31.51	31.83	31.44 (0.50)	31.96 (0.71)	0.56
$PetCO_2$ peak, mm Hg	36.53	36.84	36.52 (0.53)	36.87 (0.75)	0.71

HAA = high attenuation areas; LS = least squares; CPET = cardiopulmonary exercise test; $\dot{V}O_2$ = oxygen uptake; AT = anaerobic threshold; $\dot{V}E$ = minute ventilation; MVV = maximum voluntary ventilation; $\dot{V}CO_2$ = carbon dioxide output; $PetCO_2$ = end-tidal partial pressure of carbon dioxide

* Cases were defined by HAA greater than the 90th percentile (7.5% of total imaged lung). Controls were defined as HAA values less than the 90th percentile.

† LS mean is adjusted for age and gender.

‡ P value is for adjusted analyses.

§ Excludes 3 participants who did not reach AT.

Table S8. Types of abnormalities seen on scans of participants with ILA.

Type of abnormality	N*
Nondependent ground-glass	166
Nondependent reticular changes	196
Diffuse centrilobular nodularity with ground-glass abnormality	24
Honeycombing	27
Traction bronchiectasis	64
Non-emphysematous cysts	11
Architectural distortion	15
Bilateral fibrosis in multiple lobes associated with honeycombing and traction bronchiectasis in a subpleural distribution	21

*ILA was defined as the presence of one or more these abnormalities.

Table S9. Associations between baseline HAA and ILA at 9.5 years of follow-up in 2,907 MESA participants.

	HAA				P for trend	Overall	P value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4			
Number of participants	726	727	727	727		2907	
Number with ILA	61	72	72	101		306	
ILA prevalence, %	8.4	9.9	9.9	13.9	<0.001	10.5	
OR (95% CI)						**OR (95% CI) per doubling of HAA**	
Unadjusted	Ref	1.20 (0.84 to 1.71)	1.20 (0.84 to 1.71)	1.76 (1.26 to 2.46)	<0.001	1.43 (1.18 to 1.73)	<0.001
Adjusted†	Ref	1.50 (0.99 to 2.26)	1.76 (1.11 to 2.80)	3.02 (1.77 to 5.14)	<0.001	1.91 (1.42 to 2.56)	<0.001
Adjusted, stratified by smoking status‡							
Ever-smokers	Ref	1.38 (0.80 to 2.36)	1.72 (0.95 to 3.12)	2.68 (1.34 to 5.35)	0.004	2.31 (1.56 to 3.43)	<0.001
Never-smokers	Ref	2.19 (1.12 to 4.29)	2.31 (1.06 to 5.00)	4.97 (2.05 to 12.05)	<0.001	1.60 (1.01 to 2.53)	0.04

HAA = high attenuation areas; ILA = interstitial lung abnormalities; OR = odds ratio; CI = confidence interval

† Adjusted for age, gender, race/ethnicity, educational attainment, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate (GFR), study site, mA dose, total volume of imaged lung and percent emphysema. Adjustment for smoking status and pack-years was excluded from smoking-stratified models. All covariates measured at baseline examination in 2000 to 2002.

‡ P for interaction 0.26.

Table S10. Associations between HAA, FVC, MMP7 and ILA stratified by age, gender, race and BMI.

	Estimate*	95% CI	P value	P for interaction
FVC†				
Gender				<0.001
Male	-146.12	-215.71 to -76.54	<0.001	
Female	-54.19	-92.32 to -16.06	0.005	
Age				0.09
<55	-1.55	-72.28 to 59.19	0.97	
55-64	-144.38	-214.66 to -74.09	<0.001	
65-74	-73.21	-138.89 to -7.54	0.03	
>=75	-149.11	-248.33 to -49.88	0.003	
Race				0.01
White	-93.86	-173.16 to -14.56	0.02	
Chinese	-87.54	-165.78 to -9.31	0.03	
African-American	-215.91	-294.34 to -137.48	<0.001	
Hispanic	9.19	-53.01 to 71.39	0.77	
BMI				0.96
<25	-97.21	-169.43 to -24.99	0.008	
25-30	-57.77	-117.29 to 1.75	0.06	
>30	-103.00	-166.07 to -39.93	0.001	
MMP-7‡				
Gender				0.03
Male	13.67	5.05 to 23.01	0.001	
Female	3.29	-3.28 to 10.31	0.33	
Age				0.17
<55	12.07	2.79 to 22.18	0.01	
55-64	17.89	7.34 to 29.47	<0.001	
65-74	0.01	-9.26 to 10.23	1.0	
>=75	-4.03	-12.96 to 5.82	0.41	
Race				<0.001
White	8.45	-0.44 to 18.14	0.06	
Chinese	-4.76	-16.49 to 8.63	0.47	
African-American	11.46	1.52 to 22.39	0.02	
Hispanic	10.59	0.32 to 21.90	0.04	
BMI				0.07
<25	-0.37	-8.28 to 8.22	0.93	
25-30	14.04	6.01 to 22.67	<0.001	
>30	3.77	-5.60 to 14.08	0.44	
ILA§				
Gender				0.07
Male	3.04	1.78 to 5.20	<0.001	
Female	1.59	1.04 to 2.42	0.03	
Age				0.08
<55	1.87	0.84 to 4.17	0.13	
55-64	2.79	1.59 to 4.87	<0.001	
65-74	1.62	0.95 to 2.73	0.07	
>=75	1.28	0.52 to 3.17	0.59	
Race				0.19
White	1.32	0.73 to 2.38	0.36	
Chinese	2.03	0.82 to 5.00	0.12	
African-American	2.29	1.26 to 4.18	0.007	
Hispanic	2.36	1.23 to 4.52	0.01	
BMI				0.57
<25	1.52	0.82 to 2.80	0.18	

25-30	2.10	1.32 to 3.34	0.002
>30	1.85	1.02 to 3.35	0.04

HAA = high attenuation areas; FVC = forced vital capacity; MMP-7 = matrix metalloproteinase-7; ILA = interstitial lung abnormalities; BMI = body mass index

* Adjusted for age, gender, race, educational attainment, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate (GFR), study site, percent emphysema, mA dose and total volume of imaged lung. All covariates measured at baseline examination in 2000 to 2002.

† Estimate is equal to change in FVC per 2-fold increase in HAA.

‡ Estimate is equal to percent change in MMP-7 per 2-fold increase in HAA.

§ Estimate is equal to OR of ILA per 2-fold increase in HAA.

Table S11. Association between HAA, FVC, MMP-7, IL-6, ILA and mortality adjusted for measurements of left ventricular systolic and diastolic dysfunction on MRI.

	n	Estimate per doubling of HAA*	95% CI	P value
FVC				
Change in mL	2944	-53.94	-95.91 to -11.97	0.01
MMP-7				
% change	622	2.51	-3.07 to 8.41	0.39
% change†	622	3.69	-1.98 to 9.69	0.21
IL-6				
% change	4879	8.67	3.87 to 13.69	<0.001
ILA				
OR	1943	1.51	1.18 to 1.93	0.001
Mortality				
HR, model 1	4999	1.37	1.15 to 1.62	<0.001
HR, model 2‡	4999	1.37	1.16 to 1.63	<0.001

HAA = high attenuation areas; FVC = forced vital capacity; MMP-7 = matrix metalloproteinase-7; IL-6 = interleukin-6; ILA = interstitial lung abnormalities; OR = odds ratio; HR = hazard ratio

* Adjusted for age, gender, race, educational attainment, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate (GFR), study site, percent emphysema, mA dose, total volume of imaged lung, left ventricular (LV) ejection fraction, LV end-diastolic mass and LV end-diastolic volume. All covariates measured at baseline examination in 2000 to 2002.

† Model is not adjusted for left ventricular (LV) ejection fraction, LV end-diastolic mass or LV end-diastolic volume, but limited to only the subset of participants who had these complete cardiac MRI parameters.

‡ Additionally adjusted for alcohol use, exercise, coronary artery calcium, diabetes medication use, insulin use, fasting glucose level, hypertension, antihypertensive medication use, systolic and diastolic blood pressures, cholesterol medication use, total and high-density lipoprotein cholesterol levels, c-reactive protein level, d-dimer level and history of cancer.

Table S12. Association between HAA, FVC, MMP-7, IL-6, ILA and mortality after exclusion of participants above the 90th percentile of HAA.

	n	Estimate per doubling of HAA*	95% CI	P value
FVC				
Change in mL	3450	-261	-328 to -194	<0.001
MMP-7†				
% change	540	22.66	7.18 to 40.38	0.003
IL-6				
% change	5958	20.56	13.13 to 28.49	<0.001
ILA				
OR	2187	3.00	1.63 to 5.51	<0.001
Mortality				
HR, model 1	6127	2.01	1.57 to 2.56	<0.001
HR, model 2‡	6127	1.94	1.52 to 2.49	<0.001

HAA = high attenuation areas; FVC = forced vital capacity; MMP-7 = matrix metalloproteinase-7; IL-6 = interleukin-6; ILA = interstitial lung abnormalities; OR = odds ratio; HR = hazard ratio

* Adjusted for age, gender, race, educational attainment, height, BMI, waist circumference, smoking status, cigarette pack-years, glomerular filtration rate (GFR), study site, percent emphysema, mA dose and total volume of imaged lung. All covariates measured at baseline examination in 2000 to 2002.

† Analysis performed only in subcohort.

‡Additionally adjusted for alcohol use, exercise, coronary artery calcium, diabetes medication use, insulin use, fasting glucose level, hypertension, antihypertensive medication use, systolic and diastolic blood pressures, cholesterol medication use, total and high-density lipoprotein cholesterol levels, c-reactive protein level, d-dimer level and history of cancer.

Figure S1. Longitudinal follow-up in MESA and substudies, schedule of study visits, measurements. Green = MESA parent cohort; purple = MESA lung function and imaging substudy; pink = MESA exercise subgroup.

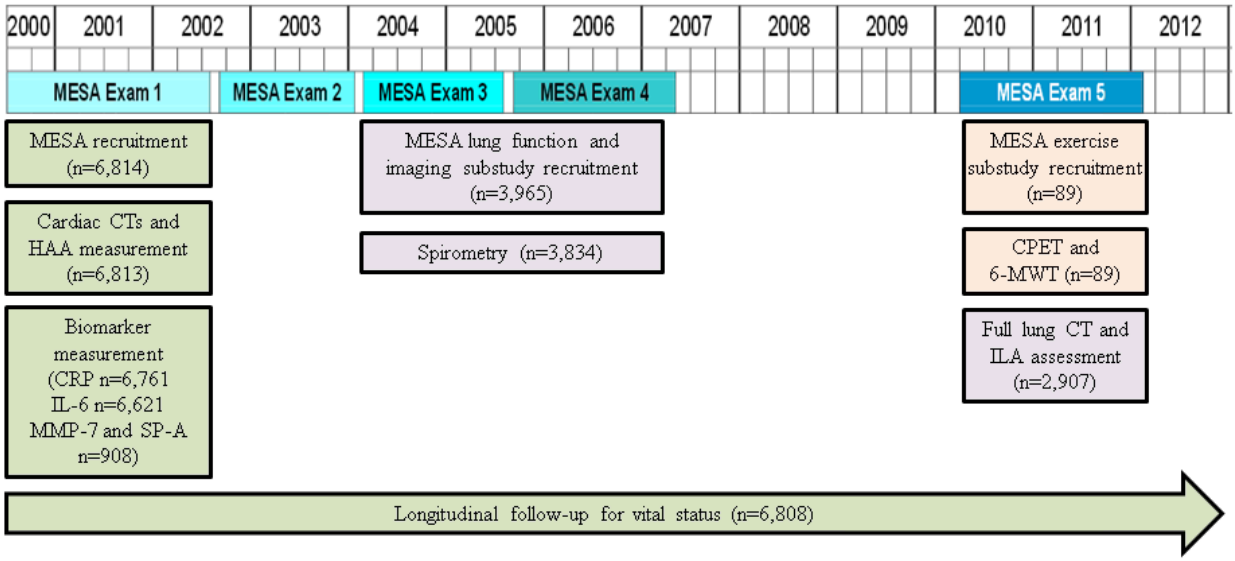
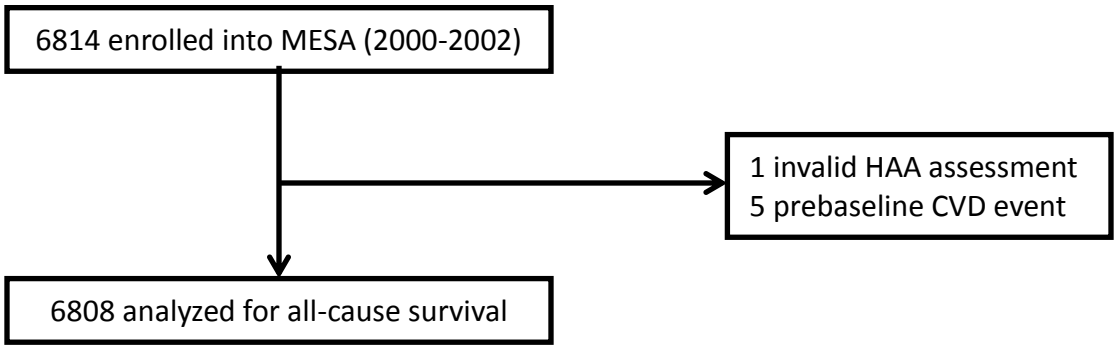
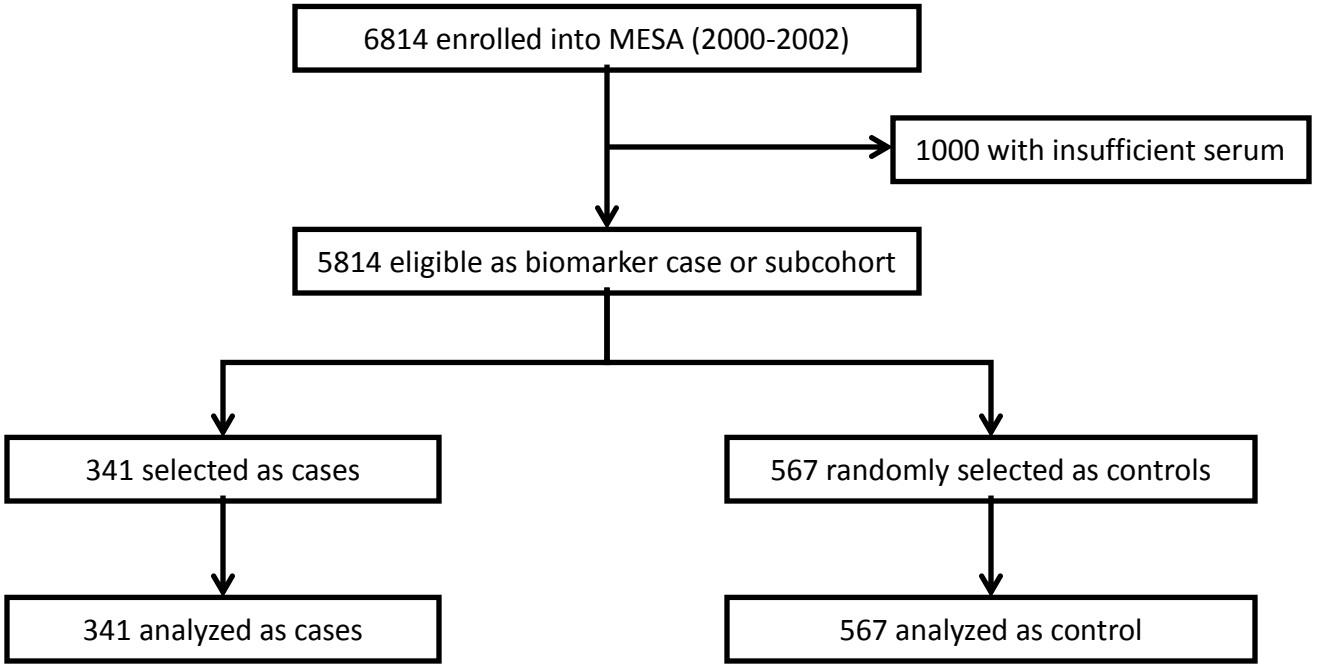


Figure S2. Flow charts of study populations for (A) MESA parent cohort, (B) biomarker substudy, (C) lung function & ILA substudy, and (D) exercise substudy.

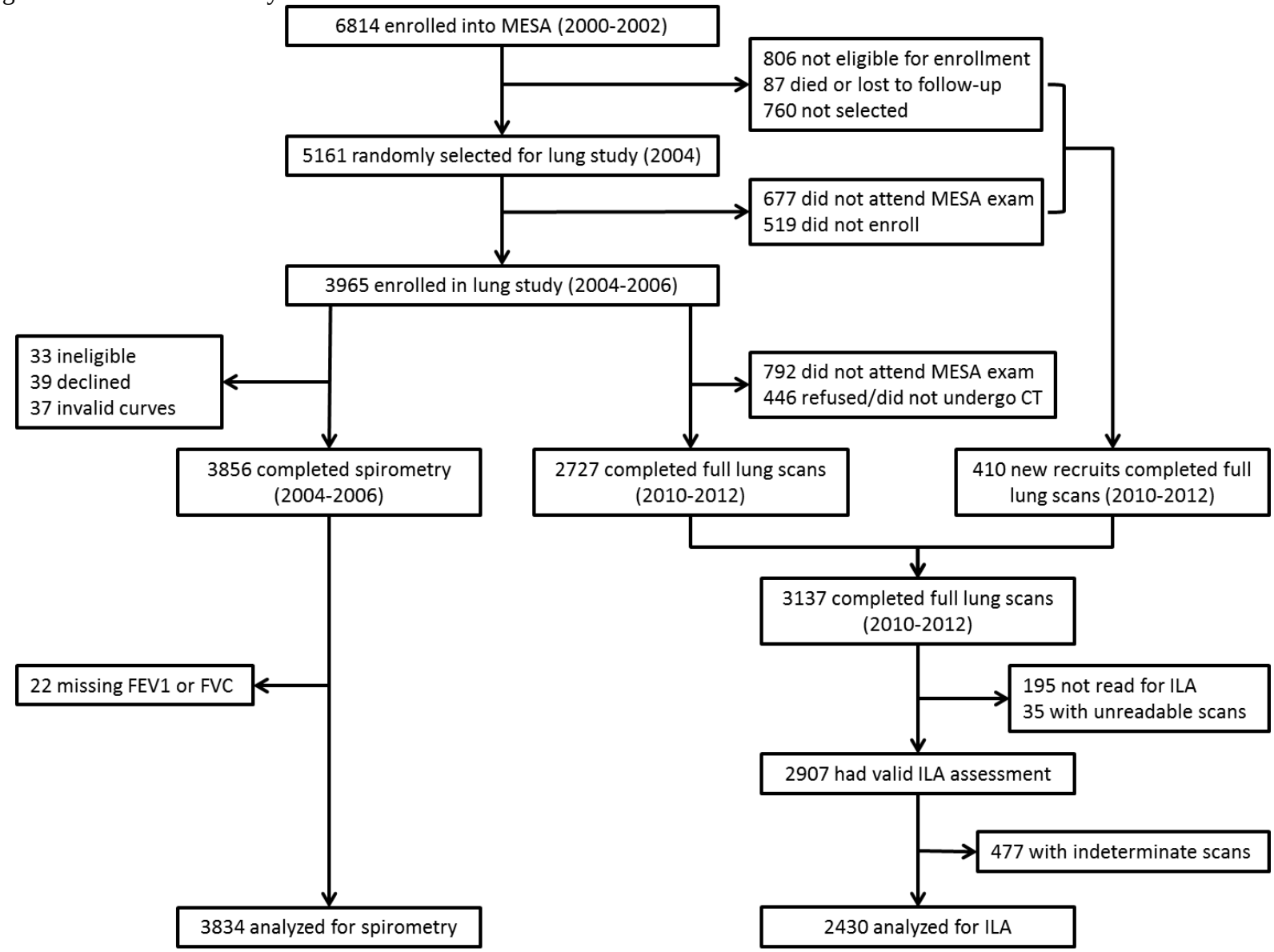
(A) MESA parent cohort



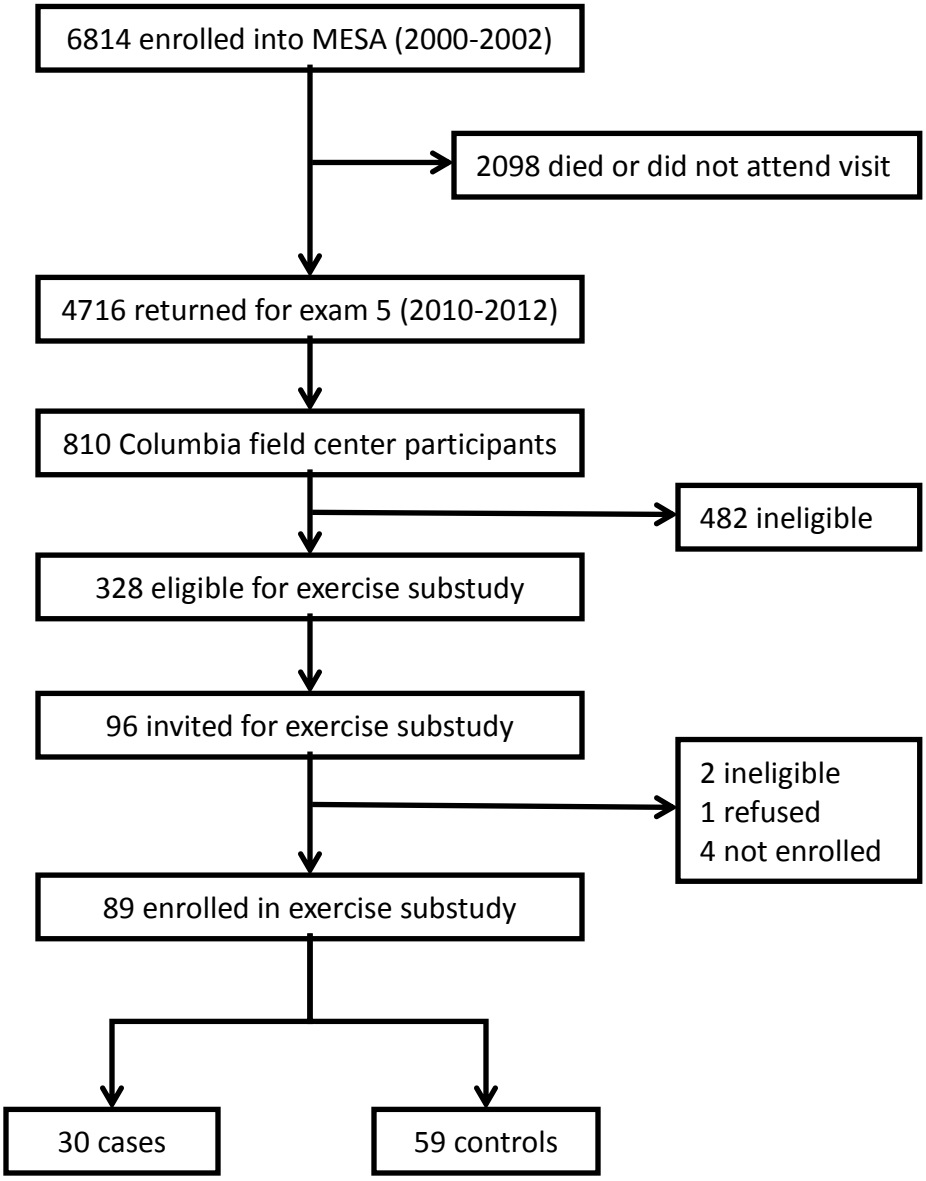
(B) Biomarker substudy



(C) Lung function & ILA substudy



(D) Exercise substudy



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