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Intercellular Adhesion Molecule 1 and Progression of Percent Emphysema: The MESA Lung Study

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Abstract

Endothelial intercellular adhesion molecule (ICAM) 1 binds neutrophils and facilitates their transmigration into the lung; E-selectin facilitates leukocyte rolling. As neutrophils contribute to tissue destruction in emphysema and chronic obstructive pulmonary disease, we hypothesized that

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CONTRIBUTIONS

CPA, SJB, EAH, RK, CB, JDK, DRJ, RPT and RGB contributed to study design. SJB, EAH, RK, CB, JDK, DRJ, RPT and RGB contributed to data acquisition. CPA, JES and RGB designed the longitudinal model and performed data analysis. CPA, JES, SJB, EAH, JHMA, ECO, KMD, CB, DRJ and RGB performed data interpretation. CPA drafted the manuscript, which was critically reviewed and revised by RGB and all coauthors. All coauthors gave final approval.

soluble ICAM-1 (sICAM-1) and E-selectin (sE-selectin) would be associated with longitudinal progression of emphysema and lung function decline.

The Multi-Ethnic Study of Atherosclerosis (MESA) enrolled participants 45-84 years old without clinical cardiovascular disease in 2000-02. The MESA Lung Study assessed percent emphysema (<-950 Hounsfield units) on cardiac (2000-07) and full-lung CT scans (2010-12), and spirometry was assessed twice over five years. sICAM-1 and sE-selectin were measured at baseline. Mixed-effect models adjusted for demographics, anthropometry, smoking, C-reactive protein, sphingomyelin and scanner factors.

Among 1,865 MESA Lung participants with measurement of sICAM-1 and percent emphysema the mean log-sICAM-1 was 5.5±0.3 ng/mL and percent emphysema increased 0.73 percentage points (95% CI: 0.34, 1.12; P<0.001) over ten years. A one SD increase in sICAM-1 was associated with an accelerated increase in percent emphysema of 0.23 percentage points over ten years (95% CI: 0.06, 0.39; P=0.007). No significant association was found for sE-selectin, or between any adhesion molecule and lung function.

Higher levels of sICAM-1 were independently associated with progression of percent emphysema in a general population sample.

Keywords

emphysema; CT imaging; endothelium; intercellular adhesion molecule-1

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined by spirometric airflow obstruction that does not fully reverse and is the 4th leading cause of death worldwide (1). Emphysema is defined pathologically as the permanent enlargement of airspaces and destruction of alveolar walls (2). Emphysema occurs in the majority of patients with COPD (3) and is not infrequent among smokers without COPD or older never-smokers (4). Emphysema assessed quantitatively on computed tomography (CT) has been associated with increased hospitalizations and mortality in those with and without COPD (5-7). However, the pathogenesis of COPD and emphysema remains incompletely understood and there are no medications targeting emphysema outside of alpha-1 antitrypsin deficiency.

Neutrophils, which are involved in the pathogenesis of emphysema and COPD, migrate into the lung via tight adhesion to intercellular adhesion molecule (ICAM) 1, an adhesion protein on endothelial cells (8, 9). E-selectin, an adhesion molecule expressed on activated endothelial cells, contributes to leukocyte rolling and thereby facilitates tight adhesion (8). ICAM-1 blocking antibodies reduce neutrophilic pulmonary inflammation by two-thirds in animals, suggesting that ICAM-1 may be critical in neutrophil access to the lung (10). Small studies have found altered ICAM-1 and E-selectin in COPD (11, 12), and cross-sectional studies have found inverse associations between soluble ICAM-1 (sICAM-1) and lung function (13, 14). However, no longitudinal study has assessed the relationship between ICAM-1 or E-selectin and the progression of emphysema or decline in lung function.

Since endothelial ICAM-1 correlates with plasma levels of sICAM-1 (15), we tested the *a priori* hypotheses (16) that sICAM-1 and soluble E-selectin (sE-selectin) are associated with longitudinal increases in the percentage of emphysema-like lung on CT and decline in lung function with the goal to understand subclinical disease progression. We tested this hypothesis in general population sample with mostly subclinical emphysema as it likely represents a biologically-relevant early stage in COPD pathogenesis, and may provide insight into strategies for disease prevention (17). In addition, subjects with clinical disease are more likely to have characteristics that may confound the relationship of interest (e.g., active infection, corticosteroid use). In order to test the specificity of the associations, we also examined soluble vascular cell adhesion molecule (sVCAM)-1, soluble L-selectin (sL-selectin), and soluble P-selectin (sP-selectin), adhesion molecules that increase with inflammation but are less relevant to neutrophil recruitment (8, 9).

METHODS

Multi-Ethnic Study of Atherosclerosis

The Multi-Ethnic Study of Atherosclerosis (MESA) recruited 6,814 participants ages 45 to 84 years and free of clinical cardiovascular disease in 2000-02 from six U.S. communities (18). Exclusion criteria were weight over 300 lbs, pregnancy, and impediments to long-term participation. The MESA Air Pollution Study recruited an additional 257 participants under the same criteria in 2004-07 (19).

The MESA Lung Study enrolled 3,965 MESA participants in 2004-06 who had flow-mediated dilation measured and consented to genetic analyses (20), all MESA Air participants at one site, and an additional 408 MESA participants in 2010-12. The current analysis includes participants in the MESA Lung Study with measurement of sICAM-1 and baseline percent emphysema.

The protocols of MESA and all studies described were approved by the institutional review boards of collaborating institutions and the National Heart, Lung, and Blood Institute. Written informed consent was obtained from all participants.

Measurement of Adhesion Molecules

Plasma sICAM-1 was measured at baseline among 2,621 MESA and the MESA Air participants using an ELISA assay (Parameter Human sICAM-1; R&D Systems, Minneapolis, MN). The coefficient of variation (CV) was 5.0%. Serum sE-selectin was measured at baseline for 998 MESA participants and the MESA Air participants (Parameter Human sE-selectin Immunoassay; R&D Systems; CV 5.7-8.8%).

Serum sVCAM-1 and sL-selectin were measured among 2,440 and plasma sP-selectin was measured among 2,572 participants an average of 1.7 years after baseline by ELISA (Parameter Human sVCAM-1, sL-selectin/CD62L, and sP-selectin Quantikine Immunoassays; R&D Systems). The laboratory CVs were 3.4-4.2%, 6.7-7.9%, and 6.7% respectively.

Genotyping

All consenting participants were genotyped with the ITMAT-Broad-CARe (IBC) microarray (Illumina, Inc; San Diego, CA) (21). The genotype of the ICAM-1 single-nucleotide polymorphism (SNP) rs5491 was obtained as it affects binding of sICAM-1 to the ELISA probe used (22). Genotypes for two advanced glycation endproduct-specific receptor (AGER) SNPs (rs2070600 and rs2071288) were also obtained as they have been associated with emphysema (23).

Measurement of Percent Emphysema

All participants underwent cardiac CT scans at baseline following a standardized protocol at full inspiration on electron-beam and multi-detector CT (MDCT) scanners at six centers (24). Participants were coached to total lung capacity and two scans were obtained; lung volume on replicate cardiac CTs were reproducible (r=0.95). The scan with the greatest lung volume was selected for analysis except where image quality differed. Follow-up cardiac CT scans used the same protocol; 45 off-protocol scans were excluded, as were 312 acquired on Aquilion scanners, which do not produce reliable lung density measures. Full-lung scans were performed on 3,204 MESA Lung participants at the ten-year follow-up exam at full inspiration on MDCT scanners following the SPIROMICS protocol (25).

Trained readers performed percent emphysema measurements at a reading center without knowledge of other participant information using modified Pulmonary Analysis Software Suite (PASS) software for cardiac scans and Apollo 1.2 (an updated version of PASS; VIDA Diagnostics, Coralville, IA) for full-lung scans. Percent emphysema was defined as the percentage of lung voxels below −950 Hounsfield units (HU), a threshold chosen based on pathologic comparisons (26), longitudinal study validity (27), and prognostic significance in this cohort (7). The −950 HU threshold on all scans was adjusted for attenuation of air outside the chest to account for scanner variation (28). As cardiac CTs image approximately 66% of lung volume (from the carina to lung bases), the upper-third of full-lung scans was excluded so as to compare the same lung region over time (28). Cardiac CT measures of percent emphysema have been previously validated against full-lung scans in this cohort (r=0.95 on MDCT scanners) (28). Examination of monthly averages of outside air from all scans demonstrated little scanner-drift over more than 11 years, with one exception (Supplement Figure 1). As an alternate measure of emphysema, lung density at the lower 15^{th} percentile was measured as the HU below which 15 percent of all lung voxels have a lower density value.

Spirometry

Spirometry was conducted between 2004-07 and repeated in 2010-12 in accordance with American Thoracic Society-European Respiratory Society guidelines. All participants attempted at least three acceptable maneuvers on the same dry-rolling seal spirometers (Occupational Marketing Inc., Houston, TX) following the MESA Lung protocol; all exams were reviewed by one investigator (29). Airflow obstruction was defined as FEV_1/FVC ratio less than 0.70 at the time of participants' first spirometry measurement.

Smoking and Other Covariates

Age, sex, race/ethnicity, educational attainment, smoking history, alcohol consumption, physical activity, second hand smoke exposure, and recent illness were self-reported. Smoking status was verified with urinary cotinine levels at baseline and ten-year follow-up (20). Height, weight, blood pressure, C-reactive protein, cholesterol, and fasting glucose were measured using standard techniques (30). Plasma sphingomyelin was measured with a validated four-step enzymatic assay (31). Medication-use was assessed by medication inventory (32). Hypertension and diabetes were defined by self-reported physician diagnoses, medication use, or abnormal blood pressure or glucose measurement. Estimates of residential exposure to ambient particulate matter <2.5μm ($PM_{2.5}$) used spatiotemporal models (19). High attenuation areas (HAAs) on CT were defined as lung regions between −600 and −250 HU, a measure of subclinical parenchymal lung disease (33).

Statistical Analysis

Participants were stratified by quintile of sICAM-1 for descriptive purposes. Mixed linear regression growth-curve models with random intercepts and slopes were used to assess the relationship of sICAM-1 and change in percent emphysema over time. sICAM-1 was log-transformed to improve normality. The initial model included CT scanner model, voxel size, and milliamperes (mAs); the subsequent model adjusted for age, sex, race/ethnicity, height, weight, and education; the final model included cigarettes per day, pack-years, C-reactive protein, and sphingomyelin. Scanner model, voxel size, mAs, height, weight, and cigarettes per day were time-variant. Effect measure modification was assessed for sex, smoking-status, race/ethnicity, age and presence of airflow obstruction. Secondary analyses were performed restricted to participants with AA genotype at rs5491, those with all adhesion molecules measured, scans acquired on Siemens, GE, or MDCT scanners, cardiac CT scans only, scanners with stable outside air attenuation and including scanners that were excluded for technical reasons. Secondary analyses were also performed adjusting for cardiovascular risk factors, relevant medications, alcohol-consumption, physical activity, second-hand smoke, $PM_{2.5}$ exposure, recent infection, percent HAA, total lung volume on CT and minor alleles at AGER SNPs. Analyses evaluating change in lung density at the lower 15^{th} percentile were also performed. Analyses for lung function and of other adhesion molecules used a similar statistical approach. Cross-sectional analyses used linear regression and were adjusted for baseline measures described above. Statistical significance was defined as two-tailed p-value <0.025, given the hypothesized two adhesion molecules. Analyses were performed using SAS 9.3 (SAS Institute; Cary, NC).

RESULTS

Study Participants

Of 4,473 participants, 1,865 had measures of sICAM-1 and percent emphysema and were included in the current analysis (Figure 1). The included participants did not differ from other MESA participants except they were younger and more likely to be female and white (Supplement Table 1). Eighty-one percent had a follow-up cardiac CT scan and 1,395 (75% of total; 77% of those still living) underwent a full-lung CT at the ten-year follow-up; 95% had at least one follow-up measure of emphysema.

Participants were 59±9 years old at baseline, 45% were male, and the race/ethnic distribution was: 47% white, 21% Hispanic, 18% African, and 14% Chinese-Americans. At baseline 15% were current-smokers, 39% former-smokers, and 46% never-smokers. The mean log-sICAM-1 was 5.5±0.3 ng/mL, median percent emphysema was 3.0% (IQR 1.2, 5.8), and mean FEV_1/FVC ratio was 0.75±0.08.

Compared to participants with the lowest sICAM-1 measurements, those in the highest quintile were more likely to be female, white or Hispanic, have lower educational attainment, higher BMI and currently smoke (Table 1). There were modest correlations between sICAM-1 and other adhesion molecules (Supplement Table 2).

sICAM-1, sE-selectin, and Longitudinal Change in Percent Emphysema

The 1,865 participants were scanned a median of three times over a median of 9.6 years (IQR 5.0, 10.0), resulting in 5,131 measures of percent emphysema. The mean increase in percent emphysema was 0.73 percentage points over ten years (95% CI: 0.34, 1.12; P<0.001).

sICAM-1 levels were significantly associated with longitudinal change in percent emphysema in minimally adjusted analyses (change in percent emphysema per SD log-sICAM-1 of 0.24 percentage points over 10 years, 95% CI: 0.08, 0.40; P=0.004). The fully adjusted model yielded very similar results (Table 2 and Figure 2).

Analyses restricted to 1,522 participants with AA genotype at SNP rs5491 yielded results of greater magnitude (0.37, 95% CI: 0.12, 0.62; P=0.003). There was no evidence for effect modification by sex, smoking status, race/ethnicity, age or presence of airflow obstruction (P-value for interaction 0.88, 0.56, 0.83, 0.65 and 0.88 respectively). The direction and magnitude of the association was similar when analyses were restricted to those with all adhesion molecules measured, scans acquired on Siemens, GE, MDCT scanners, cardiac CT scans or scanners with stable outside air attenuation and with inclusion of scans that were excluded for technical reasons. The results were similar after adjustment for cardiovascular risk factors, relevant medication use, alcohol consumption, physical activity, second hand smoke, $PM_{2.5}$ exposure, recent infection, percent HAA, total lung volume on CT or the minor alleles of AGER SNPs rs2070600 and rs2071288 (Figure 3). Analyses of the longitudinal change in lung density at the lower 15^{th} percentile showed an association of borderline statistical significance (change per SD log-sICAM-1 of −1.19 HU over 10 years, 95% CI: −2.39, 0.01; P=0.05) in minimally adjusted analyses; with further adjustment results were attenuated and not statistically significant.

Among 943 participants, sE-selectin was associated with longitudinal change in percent emphysema by a similar magnitude to sICAM-1 in minimally adjusted analyses; however, the relationship did not attain statistical significance and was further attenuated by multivariate adjustment (Table 2). There were no significant associations between sE-selectin and longitudinal change in lung density at the lower 15^{th} percentile.

In cross-sectional analyses, there was a significant negative association between sICAM-1 and percent emphysema (multivariate −0.24 percentage points per SD unit of log-sICAM-1,

95% CI: −0.43, −0.05, P=0.01). Cross-sectional associations were non-significant for sE-selectin (−0.15 percentage points per SD unit of log-sE-selectin, 95% CI: −0.41, 0.11, P=0.25). There was no evidence for effect modification of cross-sectional analyses by the presence of airflow obstruction (P-value for interaction 0.75 for sICAM-1, 0.49 for sE-selectin).

sICAM-1, sE-selectin and Longitudinal Change in Lung Function

Of participants with sICAM-1 measures, 1,629 had valid baseline spirometry and 1,149 completed repeat valid spirometry at a median of 4.7 years (71%; 73% of those living). The mean decline in FEV_1 was 23.1 mL/year (95% CI: −24.7, −21.4; P<0.001) and decline in FEV_1/FVC ratio was 0.22%/year (95% CI: −0.26, −0.19; P<0.001).

There was no evidence for an association between sICAM-1 or sE-selectin and decline in FEV_1 or FEV_1/FVC, although results for FEV_1/FVC were in the hypothesized direction for both adhesion molecules (Table 3).

Other Adhesion Molecules and Longitudinal Change in Percent Emphysema and Lung Function

Examination of sVCAM-1, sL-selectin, and sP-selectin revealed no evidence for an association with longitudinal change in percent emphysema or lung function (Table 4). Furthermore, 95% confidence intervals for all three of these adhesion molecules excluded an association of the magnitude observed for sICAM-1 and change in percent emphysema.

DISCUSSION

Higher levels of sICAM-1 were associated with accelerated progression of percent emphysema over ten years in this general population sample. The findings were consistent across multiple subgroups and robust to additional adjustment for a large number of possible confounders. Associations for sE-selectin were of similar magnitude in minimally adjusted analyses but did not attain statistical significance. In contrast, there was no evidence for association of other adhesion molecules with change in percent emphysema, or between any adhesion molecule and lung function. These findings suggest that ICAM-1, and associated neutrophil recruitment into the lung, may play a role in the progression of subclinical emphysema.

This is the first study of which we are aware to show an association between sICAM-1 levels and longitudinal progression of percent emphysema. These findings are consistent with small studies showing that circulating sICAM-1 is increased in patients with COPD (11, 12). The result for sE-selectin was of similar magnitude to sICAM-1 in minimally adjusted analyses, but was non-significant, in part due to the smaller sample size, and was further attenuated after full adjustment. Circulating sE-selectin has also been found to be increased in COPD in some (12), but not all prior studies (11).

ICAM-1 is critical to transendothelial migration of neutrophils into multiple organs including the lung (8, 9). ICAM-1 expression in the lung is upregulated in the setting of inflammation, and ICAM-1 blocking antibodies can significantly reduce neutrophilic

pulmonary inflammation in animal studies (10, 34). Furthermore, ICAM-1 and sE-selectin are upregulated in endothelial perturbation and dysfunction (35), which is directly linked to emphysema in mouse models (36) and has been observed in COPD (37, 38).

In contrast to results for sICAM-1 and sE-selectin, there was no evidence for association of other soluble adhesion molecules with progression of percent emphysema. VCAM-1 is important in transendothelial migration of basophils and eosinophils (9), leukocytes less relevant to the pathogenesis of emphysema. P-selectin and L-selectin are not affected by endothelial perturbation (8); in addition, selectins facilitate leukocyte rolling, which may be less relevant in the lung, given the small pulmonary capillaries and long neutrophil transit times (39). Alternative explanations for the specificity of the association of sICAM-1 appear less likely: all adhesion molecules were measured with similar precision; sVCAM-1, sL-selectin, and sP-selectin were measured one to two years after baseline, an interval that was short compared to follow-up; and sensitivity analyses limited to participants with measures of all adhesion molecules showed consistent results for sICAM-1.

The lack of an association of sICAM-1 with change in lung function may have several explanations. First, change in percent emphysema and a detectable decline in lung function may represent distinct processes. Findings from many recent biomarker and genetic studies support this contention (3, 40-43). Second, ICAM-1 expression on epithelial cells may have more relation to airflow obstruction and be less likely to be reflected in circulating sICAM-1 levels. Finally, the smaller sample size and shorter follow-up for lung function analyses raise the possibility of a false negative result; however, the confidence intervals suggest this was unlikely.

The major strengths of this study include repeated CT scans over ten years, large sample-size and the multi-ethnic, population-based sample. However, there are limitations that should be discussed. Adhesion molecules were measured in plasma or serum rather than membrane-bound on pulmonary endothelium. The latter was clearly infeasible in a study of this size and duration, and there is *in vivo* evidence that soluble adhesion molecules, including sICAM-1, relate to their endothelial expression (15). It is important to note that there are short term variations in plasma levels of sICAM-1 and sE-selectin in healthy individuals (variation coefficients of 7.9% and 11.3%, respectively) (44), although this would be expected to weaken the observed associations.

The magnitude of the association of sICAM-1 and progression of percent emphysema was modest; however, the progression for each SD of sICAM-1 represented nearly one-third of the average progression in this general population sample with mostly subclinical emphysema. In this cohort, percent emphysema has been associated with reduced LV filling, dyspnea and increased all-cause mortality (7, 45, 46). As such, the progression of subclinical emphysema likely represents an early stage in disease pathogenesis, and associated pathways may be relevant to disease prevention (17).

The cross-sectional association between percent emphysema and sICAM-1 was significant; however, in situations with divergent findings the longitudinal relationship is generally preferred (47).

Due to the long-term study, unequal loss to follow-up due may result in bias; however, a high proportion were rescanned at ten years. Confounding is also a concern, as it is in any observational study. The few studies on determinants of emphysema progression show that in addition to sex, BMI and active smoking, emphysema progression is associated with surfactant protein D (SPD), soluble receptor for advanced glycation endproducts (sRAGE) and sphingomyelin (3, 23, 48). Confounding by these factors is unlikely as adjustment for sphingomyelin and two AGER SNPs, which affect sRAGE levels, had little impact on the results and SPD is only weakly correlated with inflammatory markers, which relate to sICAM-1 levels (49). Conditions associated with sICAM-1 include cardiac risk factors, smoking, alcohol intake, rheumatoid arthritis, cancer and acute inflammatory conditions (50). However, MESA measured most of these factors precisely and additional adjustment had little effect on the results.

The sICAM-1 assay used does not reliably measure sICAM-1 in carriers of the T allele at rs5491 (22). This SNP is not uncommon among African-Americans and Hispanics. However, analyses restricted to AA genotype showed consistent results.

Percent emphysema was assessed on the lower 66% of the lungs and hence the lung apices were not included; however, percent emphysema measures from this region of the lung correlate well with those from full-lung scans in MESA (28). Due to the long follow-up time, there were inevitably changes in CT scanner models for each participant, as well as technological advances in image acquisition and processing that contribute to variation in quantitative emphysema measures. However, attenuation of air outside the body was remarkably stable over more than a decade and sensitivity analyses of scans acquired on similar scanners showed consistent results. True volume correction could not be performed as lung apices were not included, however lung volumes on repeat cardiac CT scans were highly reproducible. In addition, correction for lung volume may obscure relevant findings as CT lung volume may be a reflection of either improved inspiratory effort or disease-related hyperinflation. Analyses of the change in lung density at the lower 15^{th} percentile yielded results for sICAM-1 that were in the expected direction but not statistically significant. This lung density measure has been used and recommended for assessing longitudinal change in emphysema in diseased populations (3, 27, 51), but has not previously been studied in a population sample with largely subclinical emphysema.

In conclusion, sICAM-1 levels were associated with accelerated progression of percent emphysema on CT scan over ten years in this general population sample. These findings suggest that ICAM-1 may be important in the pathogenesis of emphysema, and further studies of this pathway in COPD and emphysema are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We measured plasma intercellular adhesion molecule (ICAM) 1 in a population sample
- We examined change in percent emphysema and lung function in mixed-effects models
- Percent emphysema was assessed on cardiac CT (2000-07) and full lung CT (2010-12)
- Higher soluble ICAM-1 was associated with faster progression of percent emphysema
- ICAM-1, involved in neutrophil migration in the lung may be important in emphysema

Figure 1.
Description of study sample

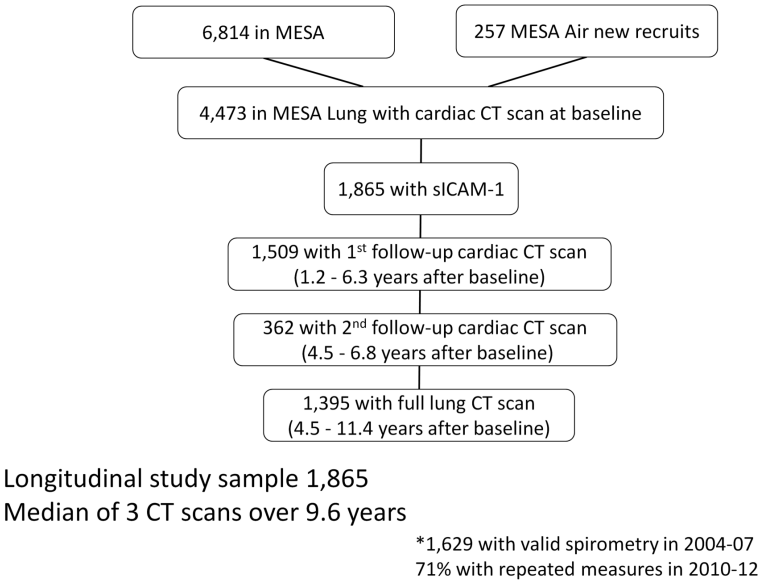

Figure 2.

Predicted change in percent emphysema over time by quintile of sICAM-1 among 1,865 participants followed for median of 9.6 years, results are shown for the fully adjusted model

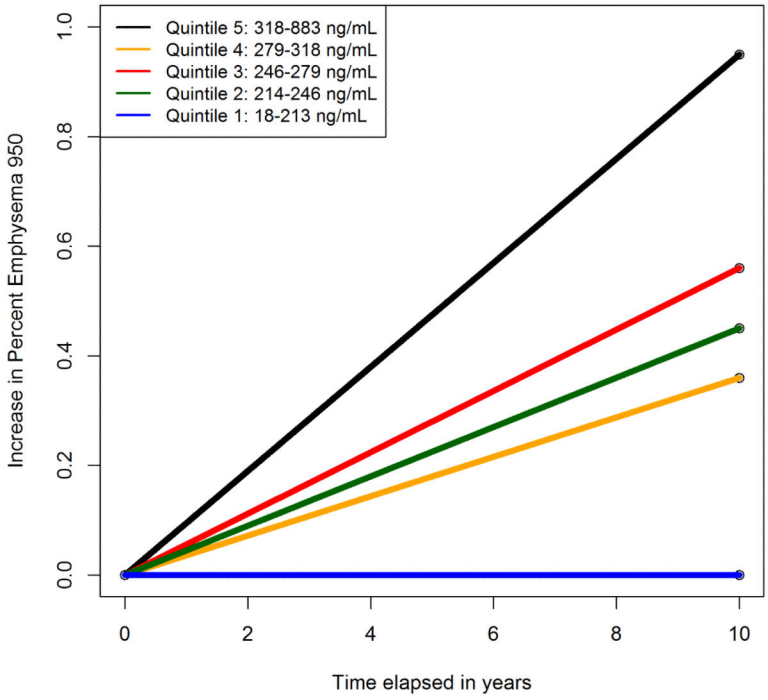

Figure 3.

Sensitivity analyses, showing the effect estimates of the change in percent emphysema over 10 years for 1 SD increase in log-sICAM-1

Table 1

Selected characteristics of study sample at baseline exam by quintile of sICAM-l

	Quintile of sICAM-1				
	Q1 (n=373)	**Q2 (n=373)**	**Q3 (n=373)**	**Q4 (n=373)**	**Q5 (n=373)**
sICAM-1 ng/mL (mean, SD)	170.3 ± 35.3	230.8 ± 9.3	262.6 ± 9.6	296.7 ± 11.5	383.7 ± 78.4
Age (mean ± SD)	58.1 ± 9.0	59.0 ± 9.6	59.1 ± 9.5	59.7 ± 9.6	59.6 ± 9.3
Percent male	46.6	49.9	44.8	40.8	41.8
Race (%)					
White, non-Hispanic	28.2	51.1	54.2	53.4	49.3
African-American	32.4	12.1	13.1	15.3	17.7
Hispanic/Latino	13.4	14.5	21.4	24.1	29.2
Chinese-American	26.0	22.3	11.3	7.2	3.8
Education (%)					
Incomplete High School	14.2	9.9	11.8	16.1	19.8
Completed High School	11.8	16.6	15.3	21.4	21.4
Some College	28.4	27.3	27.3	27.6	31.1
Completed College	23.1	20.4	17.4	14.2	15.0
Graduate Degree	22.3	25.5	27.9	20.7	12.7
Height (mean ± SD) cm	166.9 ± 9.5	168.2 ± 10.0	167.2 ± 9.9	165.8 ± 9.6	165.9 ± 9.9
Weight (mean ± SD) lbs	166.9 ± 39.5	166.8 ± 36.8	174.2 ± 38.1	177.9 ± 39.4	180.0 ± 38.2
BMI (mean ± SD) kg/m^2	27.0 ± 5.2	26.6 ± 4.5	28.2 ± 5.3	29.3 ± 5.9	29.7 ± 5.8
Smoking status (%)					
Never	51.5	53.4	48.8	43.4	32.4
Former	39.4	38.9	40.8	41.8	35.1
Current	9.1	7.8	10.5	14.7	32.4
Pack-years (mean ± SD)*	19.1 ± 20.8	23.9 ± 23.3	23.0 ± 22.9	23.4 ± 22.3	33.0 ± 32.7
Cigarettes/day (mean ± SD)†	11.4 ± 10.2	9.7 ± 7.5	8.4 ± 7.8	11.6 ± 10.6	16.4 ± 12.6
Recent cold or flu, % (No)	13.2 (49)	13.0 (48)	14.5 (54)	15.5 (58)	17.4 (64)
Oral steroid use, % (No)	0.54 (2)	0.54 (2)	1.9 (7)	0.27 (1)	1.1 (4)
C-reactive protein (mg/L)	3.0 ± 5.1	2.7 ± 6.0	3.0 ± 3.7	4.2 ± 5.7	5.6 ± 7.1
Sphingomyelin	43.9 ± 12.7	44.4 ± 13.2	44.9 ± 18.0	43.6 ± 12.3	44.9 ± 12.8
sE-selectin, ng/mL (mean, SD) n=928‡	40.8 ± 20.5	45.1 ± 17.0	49.7 ± 21.7	52.2 ± 21.3	66.3 ± 30.2
sVCAM1, ng/mL (mean, SD) n=1,054‡	633.1 ± 150	687.7 ± 193	728.8 ± 169	713.2 ± 194	765.5 ± 233
sL-selectin, ng/mL (mean, SD) n=1,054‡	894.5 ± 195	893.7 ± 186	915.1 ± 182	950.8 ± 201	946.2 ± 196
sP-selectin, ng/mL (mean, SD) n=1,100‡	25.9 ± 7.3	26.8 ± 9.1	28.4 ± 10.6	28.9 ± 10.3	31.6 ± 10.8

*for 904 ever-smokers reporting pack-years.

†for current smokers, n=278.

‡sample size includes those in the MESA Lung Study with both adhesion molecules measured.

Table 2

Predicted 10 year change in percent emphysema by quintile of sICAM-1 and sE-selectin

	Quintile of adhesion molecule					Change over 10 years per SD log-adhesion molecule (95% CI)*	P-value*
	1	2	3	4	5		
sICAM-1 (n=1,865)							
Model 1	Ref	0.29	0.36	0.25	0.96	0.24 (0.08, 0.40)	0.004
Model 2	Ref	0.45	0.54	0.37	1.07	0.27 (0.10, 0.43)	0.001
Model 3	Ref	0.45	0.57	0.38	1.02	0.23 (0.06, 0.39)	0.006
Model 4	Ref	0.45	0.56	0.36	0.95	0.23 (0.06, 0.39)	0.007
sE-selectin (n=943)							
Model 1	Ref	−0.14	−0.02	0.21	0.66	0.21 (−0.03, 0.45)	0.09
Model 2	Ref	−0.05	0.08	0.35	0.62	0.20 (−0.05, 0.45)	0.12
Model 3	Ref	−0.08	0.07	0.31	0.55	0.16 (−0.09, 0.40)	0.22
Model 4	Ref	−0.13	0.03	0.23	0.49	0.16 (−0.09, 0.41)	0.22

Model 1: adjusted for scanner model, voxel size and mAs

Model 2: additionally adjusted for age, sex, sex*time, race, race*time, height, weight and education

Model 3: additionally adjusted for cigarettes per day, pack-years and pack-years*time

Model 4: additionally adjusted for C-reactive protein and sphingomyelin

*Effect estimate and P-value derived from multivariate mixed model with log-adhesion molecule as a continuous variable

Table 3

Predicted change in FEV_1 and FEV_1/FVC per year for a 1 SD increase in log-adhesion molecule

	Change per year per SD log-adhesion molecule (95% CI)	P-value
sICAM-1		
FEV_1, mL (n=1,629)		
Model 1	−0.51 (−2.97, 1.95)	0.69
Model 2	−0.55 (−3.02, 1.93)	0.66
Model 3	−0.54 (−3.02, 1.93)	0.67
FEV_1/FVC, % (n=1,605)		
Model 1	−0.03 (−0.10, 0.03)	0.27
Model 2	−0.03 (−0.10, 0.02)	0.25
Model 3	−0.03 (−0.10, 0.02)	0.25
sE-selectin		
FEV_1, mL (n=899)		
Model 1	0.20 (−3.06, 3.45)	0.91
Model 2	0.10 (−3.17, 3.37)	0.95
Model 3	0.11 (−3.17, 3.38)	0.95
FEV_1/FVC, % (n=888)		
Model 1	−0.05 (−0.13, 0.03)	0.23
Model 2	−0.05 (−0.15, 0.03)	0.23
Model 3	−0.05 (−0.15, 0.03)	0.23

Model 1: adjusted for age, sex, race, educational attainment, height and weight (model for FEV_1 also adjusted for height^2)

Model 2: additionally adjusted for smoking status and pack-years for ever-smokers

Model 3: additionally adjusted for C-reactive protein

Table 4

Predicted change in percent emphysema, FEV_1 and FEV_1/FVC by levels of sVCAM-1, sL-selectin and sP-selectin

	Change per SD-log adhesion molecule (95% CI)	P-value
Percent emphysema, change per 10 years*†		
sVCAM-1 (n=1,932)	−0.024 (−0.18, 0.13)	0.77
sL-selectin (n=1,932)	0.001 (−0.16, 0.16)	0.99
sP-selectin (n=2,025)	−0.001 (−0.15, 0.14)	0.99
FEV_1 (mL), change per year*‡		
sVCAM-1 (n=1,771)	−0.33 (−2.80, 2.14)	0.79
sL-selectin (n=1,771)	−1.92 (−4.25, 0.41)	0.11
sP-selectin (n=1,858)	−0.52 (−2.78, 1.75)	0.66
FEV_1/FVC (%), change per year*		
sVCAM-1 (n=1,749)	0.02 (−0.04, 0.07)	0.56
sL-selectin (n=1,749)	0.01 (−0.04, 0.06)	0.76
sP-selectin (n=1,834)	−0.02 (−0.06, 0.03)	0.52

*The models shown are adjusted for age, sex, race, education, height, weight, cigarettes per day, pack-years and C-reactive protein

†The model for percent emphysema is also adjusted for scanner model, voxel size, mAs, sex*time, race*time, pack-years*time and sphingomyelin

‡The model for FEV_1 is also adjusted for height^2