Computed tomography measure of lung injury and future interstitial features: the CARDIA Lung Study

Gabrielle Y. Liu [1], Laura A. Colangelo [2], Samuel Y. Ash [3,4], Raul San Jose Estepar [3,5], David R. Jacobs Jr [6], Bharat Thyagarajan [7], J. Michael Wells [8], Rachel K. Putman [5], Bina Choi [3,4], Christopher S. Stevenson [9], Mercedes Carnethon [2], George R. Washko [3,5] and Ravi Kalhan [1,2]

[1]Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. [2]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. [3]Applied Chest Imaging Laboratory, Brigham and Women's Hospital, Boston, MA, USA. [4]Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA, USA. [5]Department of Radiology, Brigham and Women's Hospital, Boston, MA, USA. [6]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, USA. [7]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA. [8]Division of Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL, USA. [9]Lung Cancer Initiative at Johnson & Johnson, London, UK.

Corresponding author: Gabrielle Y. Liu (gabrielle.liu@northwestern.edu)

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"CT lung injury" is an objective computed tomography feature that is associated with future interstitial features and restrictive spirometry https://bit.ly/3JliarO

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Abstract

Introduction Visually normal areas of the lung with high attenuation on computed tomography (CT) imaging, termed CT lung injury, may represent injured but not yet remodelled lung parenchyma. This prospective cohort study examined if CT lung injury is associated with future interstitial features on CT and restrictive spirometry abnormality among participants from the Coronary Artery Risk Development in Young Adults (CARDIA) study.

Methods CARDIA is a population-based cohort study. CT scans obtained at two time points were assessed objectively for amount of lung tissue characterised as CT lung injury and interstitial features. Restrictive spirometry was defined as having a forced vital capacity (FVC) <80% predicted with forced expiratory volume in 1 s/FVC ratio >70%.

Results Among 2213 participants, the median percentage of lung tissue characterised as CT lung injury at a mean age of 40 years was 3.4% (interquartile range 0.8–18.0%). After adjustment for covariates, a 10% higher amount of CT lung injury at mean age 40 years was associated with a 4.37% (95% CI 3.99–4.74%) higher amount of lung tissue characterised as interstitial features at mean age 50 years. Compared to those with the lowest quartile of CT lung injury at mean age 40 years, there were higher odds of incident restrictive spirometry at mean age 55 years in quartile 2 (OR 2.05, 95% CI 1.20–3.48), quartile 3 (OR 2.80, 95% CI 1.66–4.72) and quartile 4 (OR 3.77, 95% CI 2.24–6.33).

Conclusions CT lung injury is an early objective measure that indicates risk of future lung impairment.

Introduction

Investigations into the development of idiopathic interstitial lung disease (ILD) have been limited by incomplete understanding of the mechanisms and timing of transitions from ideal lung health to chronic idiopathic ILD [1]. Therefore, recent investigations have centred on identifying imaging markers of impaired respiratory health that may precede clinically overt ILD. Interstitial lung abnormalities (ILAs) are specific radiological patterns on visual assessment of computed tomography (CT) scans that may represent early ILD. ILAs are associated with accelerated decline in lung function and increased all-cause mortality [2–4].

Localised inflammation appears to be one of the earliest structural manifestations of lung injury and may begin decades prior to the development of pulmonary fibrosis [5–7]. Inflammatory markers, C-reactive

protein (CRP) and intercellular adhesion molecule (ICAM)-1, have been associated with future development of ILAs in population-based studies [8, 9]. Recent studies have also identified a novel tissue class on CT imaging that corresponds to visually normal-appearing areas of lung with high attenuation that we have termed "CT lung injury" [10]. It is hypothesised that this may represent injured but not yet remodelled lung tissue that precedes the development of ILAs. CT lung injury, even in those without ILA, has been associated in cross-section with increased CRP and ICAM-1, decreased lung function and 6-min walk distance, and increased future mortality [10].

Using longitudinal data from the CARDIA (Coronary Artery Risk Development in Young Adults) study [11], we examined whether CT lung injury in early middle age precedes the development of future interstitial changes and restrictive spirometry pattern. Additionally, we examined whether markers of systemic inflammation, CRP and ICAM-1, are associated with future CT lung injury.

Methods

Study design and participants

CARDIA is a prospective cohort study with Black and White participants aged 18–30 years who were recruited from 1985 to 1986 from four field centres (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA, USA). Recruitment achieved nearly equal numbers based on race, sex, education (more than high school, or high school or less), and age (18–24 or 25–30 years). Re-examination occurred after 2, 5, 7, 10, 15, 20, 25 and 30 years, with 71% of the surviving cohort returning for the year 30 examination. The detailed methods, instruments and quality control procedures for the CARDIA study have been previously described [11, 12]. The CARDIA study is reviewed annually by the internal review boards at each participating institution and participants sign a new informed consent form at every examination.

Study design

This is a prospective cohort study examining the association between CT lung injury at mean age 40 years (year 15 examination) and interstitial features at mean age 50 years (year 25 examination) and restrictive spirometry pattern at mean age 55 years (year 30 examination).

CT acquisition and analysis

CT scans of the chest were obtained at mean age 40 and 50 years. All CT scans were obtained at end-inspiration using a single breath hold. Details on CT acquisition at both time points are presented in the supplementary material. For this study, the primary predictor was the percentage of total lung tissue characterised as CT lung injury at mean age 40 years (year 15 examination). The primary outcome was the percentage of total lung tissue characterised as interstitial features at mean age 50 years (year 25 examination). The detailed methods used to objectively detect and quantify the volume of radiological feature subtypes have been previously described [10, 13–15]. In brief, the CT analysis tool was trained by two experts placing a total of 57 647 reference markers in CT scans from the CARDIA cohort on specific radiological features to create a library of training points. The radiological features included normal parenchyma, interstitial feature subtypes (reticular or ground glass) and emphysema (centrilobular or paraseptal). The tool then uses the properties of the local tissue and distance from the pleural surface to create a tissue classification vector for every portion of the lung. That vector is then evaluated using a k-nearest neighbours approach to determine its similarity to tissue classification vectors extracted from the library of training points previously placed. This process results in the classification of each area of the lung as being characterised as one of the following features: normal, CT lung injury, interstitial features or emphysema. To account for differences in CT acquisition protocol and technology between examinations at mean age 40 (year 15: 2000–2001) and 50 years (year 25: 2010–2011), this tool was trained separately for the mean age 40- and -50-year CT scans. The CT lung injury feature was defined as visually normal-appearing regions with high attenuation. High attenuation was defined as attenuation greater than the 95th percentile for visually normal parenchyma among training cases of never-smoking individuals with normal lung function.

Spirometry

Spirometry was measured at years 0, 2, 5, 10, 20 and 30, and followed standard procedures as recommended by the American Thoracic Society at all examinations [16–18]. Incident restrictive spirometry was defined as having a prebronchodilator forced vital capacity (FVC) <80% predicted at year 30 (mean age 55 years) with forced expiratory volume in 1 s (FEV_1)/FVC ratio ⩾0.7, but an FVC ⩾80% predicted at the time of their peak lung function [19, 20].

Inflammatory markers

CRP and ICAM-1 were selected as biomarkers of inflammation based on their availability and prior associations with ILA. CRP was measured at mean age 32, 40, 45 and 50 years (year 7, 15, 20 and 25

examinations). ICAM-1 was measured at mean age 32, 40 and 50 years. CRP and ICAM-1 measured at mean age 32 and 40 years were used for this study. CRP was measured using a BNII nephelometer (Dade Behring), with intra- and inter-assay coefficients of variation ranging from 2.3% to 4.4%, and 2.1% to 5.7%. ICAM-1 levels were measured using serum samples diluted 1:400 and an ELISA assay (R&D Systems). The limit of sensitivity of the ICAM-1 assay was 15 $pg \cdot mL^{-1}$ with a coefficient of variation of 9.4%.

Statistical analysis

Summary statistics including means and standard deviations were calculated as appropriate. Multivariable linear regression was used to assess the association between the percentage of lung characterised as CT lung injury at mean age 40 years and percentage of lung characterised as interstitial features at mean age 50 years. Multivariable logistic regression was used to determine the association between quartile of CT lung injury at mean age 40 years and odds of incident restrictive spirometry at mean age 55 years. Quartile of CT lung injury was used to account for the fact that CT lung injury was not normally distributed and there were several zero values. Secondary analyses included multivariable linear regression models to assess the associations between: CRP at mean age 40 years and percentage of lung characterised as CT lung injury at mean age 50 years; CRP at mean age 40 years and percentage of lung characterised as interstitial features at mean age 50 years; ICAM-1 at mean age 40 years and CT lung injury at mean age 50 years; and ICAM-1 at mean age 40 years and interstitial features at mean age 50 years. Multivariable logistic regression models were used to assess the association between CRP at mean age 40 years and odds of incident restrictive spirometry at mean age 55 years, and the association between ICAM-1 at mean age 40 years and odds of incident restrictive spirometry at mean age 55 years. There was no adjustment for multiple comparisons given that the secondary analyses were considered exploratory. CRP, ICAM-1 and the percentage of lung tissue characterised as CT lung injury, and interstitial features were log-transformed prior to being used in all regression models. Sensitivity analyses were also performed that examined the association between CT lung injury, CRP and ICAM-1 at mean age 40 years, and only reticular-type interstitial features at mean age 50 years. For these sensitivity analyses, ground-glass abnormalities were excluded from the outcome.

For CT lung injury and interstitial features values equal to zero, the datum was reset equal to half the minimum value of CT lung injury or interstitial features prior to log transformation. This resetting of the data points was performed for one CT lung injury datum point and 14 interstitial features data points. All models were adjusted for field centre, age, sex, self-reported race and years of education. Given that Black race and lower socioeconomic status have both been previously associated with elevated markers of systemic inflammation [21–23] and could therefore be potential confounders, we included self-reported race and years of education as covariates. Each model was also adjusted for: body mass index (BMI) at the year the predictor variable was measured; change in BMI from the year of predictor variable to the year of outcome measure; smoking status and cigarettes smoked per day at the year the predictor variable was measured; and smoking pack-years at the year the outcome was measured.

Results

Study participants

Of the 5115 initial participants, the analytic sample size for the association between CT lung injury at mean age 40 years and interstitial features at mean age 50 years was 2213, and was 1925 for its association with incident restrictive spirometry at mean age 55 years (figure S1). Missing covariates in each model account for the varying number of participants included in the different models. The median and interquartile range for amount of lung tissue characterised as CT lung injury at mean age 40 years was 3.4% (0.8–18.0%). The demographic characteristics of participants by quartile of CT lung injury at mean age 40 years are included in table 1. Compared to those in the lowest quartiles of CT lung injury, those in the highest quartiles were more likely to be female, self-identify as Black, have a high school education or less, and be a current smoker.

CT lung injury

Interstitial features

After adjustment for age, sex, race, field centre, BMI, smoking measures and years of education, a 10% higher percentage of lung tissue characterised as CT lung injury at mean age 40 years was associated with a 4.37% (95% CI 3.99–4.74%, $p<0.001$) higher percentage of lung tissue characterised as interstitial features at mean age 50 years. Figure 1 shows representative CT scan images from a participant with a high percentage of lung tissue characterised as CT lung injury at age 39 years who develops a high percentage of lung tissue characterised as interstitial features at age 49 years. The unadjusted association between CT lung injury and interstitial features is shown in figure 2.

TABLE 1 Characteristics of participants included in this analysis at mean age 40 years (year 15 examination) by quartile of computed tomography (CT) lung injury

	Quartile of CT lung injury[#]			
	Q1	Q2	Q3	Q4
Participants	553	554	552	554
CT lung injury, %, median (IQR)	0.4 (0.3)	1.6 (1.2)	7.7 (6.8)	36.2 (24.1)
Age, year	40.5±3.5	40.6±3.5	40.6±3.5	40.1±3.7
Female	46%	54%	57%	63%
Race				
Black	23%	41%	50%	58%
White	77%	59%	50%	42%
Education				
HS education or less	14%	19%	21%	26%
More than HS	86%	81%	79%	74%
Smoking status				
Never smoker	65%	63%	64%	55%
Former smoker	21%	21%	16%	16%
Current smoker	14%	16%	20%	30%
Cigarettes per day	1.4±4.4	2.3±6.7	2.4±6.0	4.1±8.3
Smoking pack-years	3.0±6.9	4.7±9.0	4.3±7.9	5.7±9.3
BMI, kg·m^{-2}	25.7±4.3	28.6±5.7	29.2±6.4	31.1±7.2
Peak FEV_1 % predicted	103±13	101±12	101±13	101±12
Peak FVC, % predicted	107±11	104±12	104±12	103±12

Data are presented as mean±SD unless otherwise stated. [#]: Quartile of percentage of lung characterised as CT lung injury, defined as visually normal-appearing regions with attenuation >95th percentile for normal lung tissue. IQR: interquartile range; HS: high school; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Incident restrictive spirometry

There were 3163 participants who had pulmonary function tests performed at mean age 55 years. Of these participants, 42 (1.3%) had an abnormal restrictive pattern of lung function (FVC <80% predicted with FEV_1/FVC >0.7) at the time of their peak lung function (when their FVC was highest). Of the 3121 participants without a restrictive pattern at their peak lung function, 396 (12.7%) developed an abnormal restrictive pattern of lung function by mean age 55 years. Analyses included 1925 participants who had complete data for spirometry and CT features at mean age 40 years.

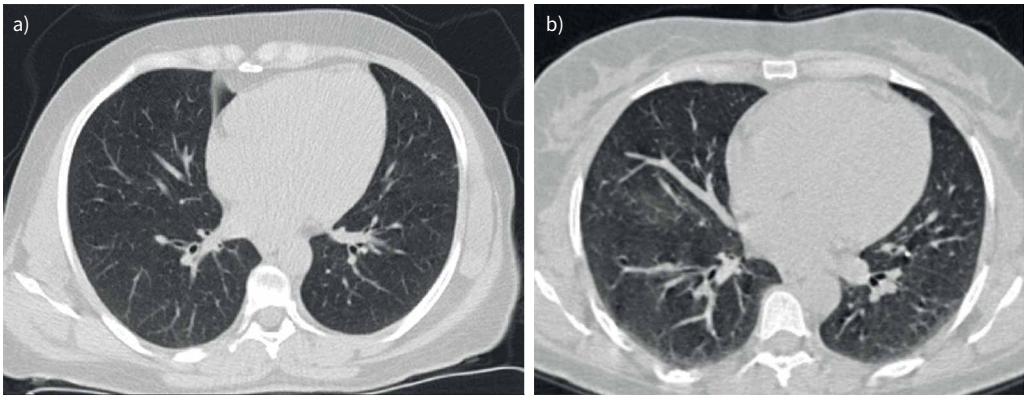

FIGURE 1 Representative computed tomography (CT) scan images from a participant with progression from high percentage of lung tissue characterised as CT lung injury to high percentage of lung tissue characterised as interstitial features. a) At age 39 years (year 15 examination), this participant had 33.9% of lung tissue characterised as CT lung injury (86th percentile for the cohort) and 1.1% of lung tissue characterised as interstitial features (76th percentile for the cohort). b) At age 49 years (year 25 examination), this participant had 55.9% of lung tissue characterised as CT lung injury (98th percentile for the cohort) and 26.6% of lung tissue characterised as interstitial features (99th percentile for the cohort).

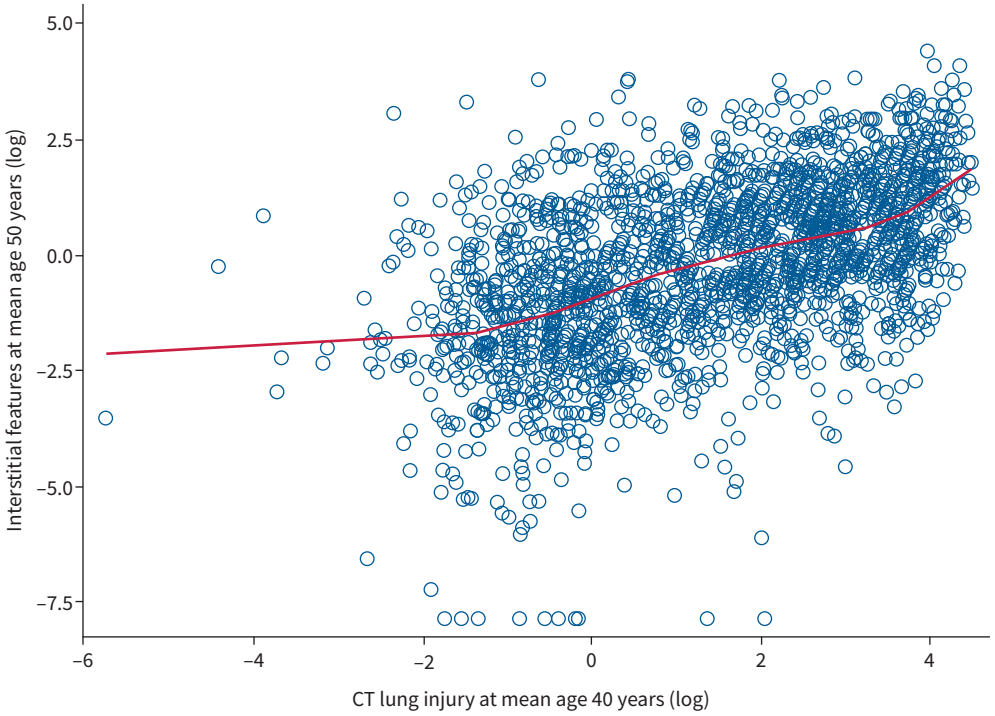

FIGURE 2 Scatterplot with locally weighted smoothing regression line depicting the association between the percent of lung tissue characterised as computed tomography (CT) lung injury at mean age 40 years and the percent of lung tissue characterised as interstitial features at mean age 50 years. Both variables were log-transformed due to non-normal distributions.

To examine the association between CT lung injury at mean age 40 years and incident restriction at mean age 55 years, we first divided the cohort by quartiles of percentage of lung characterised as CT lung injury. Quartile of CT lung injury was used due to the non-normal distribution of CT lung injury. We found that compared to those with the lowest quartile of CT lung injury, there were higher odds of incident restriction in quartile 2 (OR 2.05, 95% CI 1.20–3.48), quartile 3 (OR 2.80, 95% CI 1.66–4.72) and quartile 4 (OR 3.77, 95% CI 2.24–6.33) (table 2).

Inflammatory markers at mean age 40 years

CT features

To better understand the pathway from lung injury and inflammation to interstitial features, we performed exploratory secondary analyses examining the association between markers of systemic inflammation, CRP and ICAM-1, and future CT lung injury and interstitial features. At mean age 40 years, the mean±SD value of CRP was 3.12±4.99 $\mu g \cdot mL^{-1}$ and the value of ICAM-1 was 153.4±43.2 $ng \cdot L^{-1}$. After adjustment for

TABLE 2 Association between computed tomography (CT) lung injury at mean age 40 years (year 15 examination) and incident restrictive spirometry at mean age 55 years (year 30 examination) (N=1925)

	Quartile of CT lung injury[#] at mean age 40 years			
	Q1	Q2	Q3	Q4
Incident restriction[¶] OR (95% CI)	Ref (1.0)	2.05 (1.20–3.48)	2.80 (1.66–4.72)	3.77 (2.24–6.33)

Models adjusted for year 15 field centre, age, race, sex, years of education, smoking status, cigarettes smoked per day, body mass index (BMI), year 30–year 15 BMI change and year 30 smoking pack-years. [#]: quartile of percentage of lung characterised as CT lung injury, defined as visually normal-appearing regions with attenuation >95th percentile for normal lung tissue. [¶]: incident restriction was defined as having forced vital capacity (FVC) <80% predicted with forced expiratory volume in 1 s (FEV_1)/FVC ≥0.7 at mean age 55 years, but FVC ≥80% predicted with FEV_1/FVC ≥0.7 at peak lung function.

TABLE 3 Association between inflammatory markers at mean age 40 years (year 15 examination) and computed tomography (CT) features at mean age 50 years (year 25 examination)

	Quartile of inflammatory marker at mean age 40 years				Associated percent increase (95% CI) in lung characterised as each CT feature per 10% increase in inflammatory marker[#]
	Q1	Q2	Q3	Q4	
Quartile of CRP at mean age 40					
CRP, $\mu g \cdot mL^{-1}$	0.33±0.13	0.92±0.23	2.27±0.66	9.04±7.18	
CT lung injury[¶,+,§], %, median (IQR)	0.56 (0.10–2.90)	1.12 (0.17–6.52)	1.41 (0.24–7.84)	2.52 (0.44–15.76)	1.07 (0.34–1.80)
Interstitial features[¶,§,f]	0.44 (0.16–1.26)	0.72 (0.23–2.35)	0.92 (0.29–2.94)	1.28 (0.42–3.89)	0.87 (0.28–1.46)
Quartile of ICAM-1 at mean age 40					
ICAM-1, $ng \cdot L^{-1}$	111.6±10.7	135.7±5.6	157.5±7.3	208.5±46.1	
CT lung injury[¶,+,##], %	0.56 (0.09–3.30)	0.91 (0.16–5.03)	1.35 (0.21–8.48)	2.27 (0.37–14.03)	6.28 (2.34–10.4)
Interstitial features[¶,f,##], %	0.53 (0.16–1.61)	0.62 (0.22–2.28)	0.80 (0.26–2.73)	1.20 (0.35–3.85)	5.00 (1.85–8.24)

Data are presented as mean±SD or median (interquartile range). Models adjusted for year 0 field centre, age, race, sex, year 15 years of education, smoking status, cigarettes smoked per day, body mass index (BMI), year 25–year15 BMI change, and year 25 smoking pack-years. CRP: C-reactive protein; ICAM: intercellular adhesion molecule. [#]: based on multivariable linear regression, after log-transformation of inflammatory marker and log-transformation of CT feature; [¶]: unadjusted; [+]: defined as visually normal-appearing regions with attenuation >95th percentile for normal lung tissue; [§]: n=2570; [f]: defined as reticular or ground-glass abnormalities; [##]: n=2200.

covariates, higher levels of both CRP and ICAM-1 at mean age 40 years were associated with greater CT lung injury at mean age 50 years. For a 10% higher CRP, there was an associated 1.07% (95% CI 0.34–1.80%, p=0.004) higher percentage of lung characterised as CT lung injury (table 3). For a 10% higher ICAM-1, there was an associated 6.28% (95% CI 2.34–10.4%, p=0.002) higher percentage of lung characterised as CT lung injury.

We also examined the association between CRP and ICAM-1 at mean age 40 years and interstitial features at mean age 50 years. We found that for a 10% higher CRP, there was an associated 0.87% (95% CI 0.28–1.46%, p=0.004) higher percentage of lung characterised as interstitial features (table 2). For a 10% higher ICAM-1, there was an associated 5.00% (95% CI 1.85–8.24%, p=0.002) higher percentage of lung characterised as interstitial features. Distribution of CT lung features across quartiles of CRP and ICAM-1 at mean age 40 years are shown in figure 3 and table 3. Similar analyses were performed to examine the associations between CRP and ICAM-1 at an even earlier time point, mean age 32 years, and CT features at mean age 50 years. However, after adjustment for covariates, there were no statistically significant associations between CRP or ICAM-1 at mean age 32 years and CT lung injury or interstitial features at mean age 50 years (supplementary table 1).

Incident restrictive spirometry

We evaluated the relationship between systemic inflammation in early middle age and incident restriction 15 years later. CRP at mean age 40 years was associated with incident restriction at mean age 55 years (OR per standard deviation log-CRP 1.37, 95% CI 1.19–1.59) as was ICAM-1 (OR per standard deviation log-ICAM-1 1.23, 95% CI 1.07–1.42).

Sensitivity analyses

Given that reticular markings are an imaging pattern subtype of ILAs that are highly associated with increased risk of ILA progression and mortality [24], we performed sensitivity analyses to examine whether CT lung injury, CRP and ICAM-1 were associated specifically with reticular-type interstitial features. After adjustment for covariates, we found that there remained a significant association such that a 10% higher amount of lung tissue characterised as CT lung injury at mean age 40 years was associated with a 4.35% (95% CI 3.98–4.73%) higher amount of reticular-only interstitial features at mean age 50 years. Similarly, we found that a 10% higher CRP at mean age 40 years was associated with a 0.86% (95% CI 0.28–1.45%) higher amount of reticular-only interstitial features at mean age 50 years, and a 10% higher ICAM-1 was associated with a 4.93% (95% CI 1.79–8.16%) higher amount of reticular-only interstitial features.

Discussion

In this study, we demonstrated that CT lung injury, an imaging classifier suggestive of injured but not yet remodelled lung parenchyma in early middle age was associated with future interstitial features and

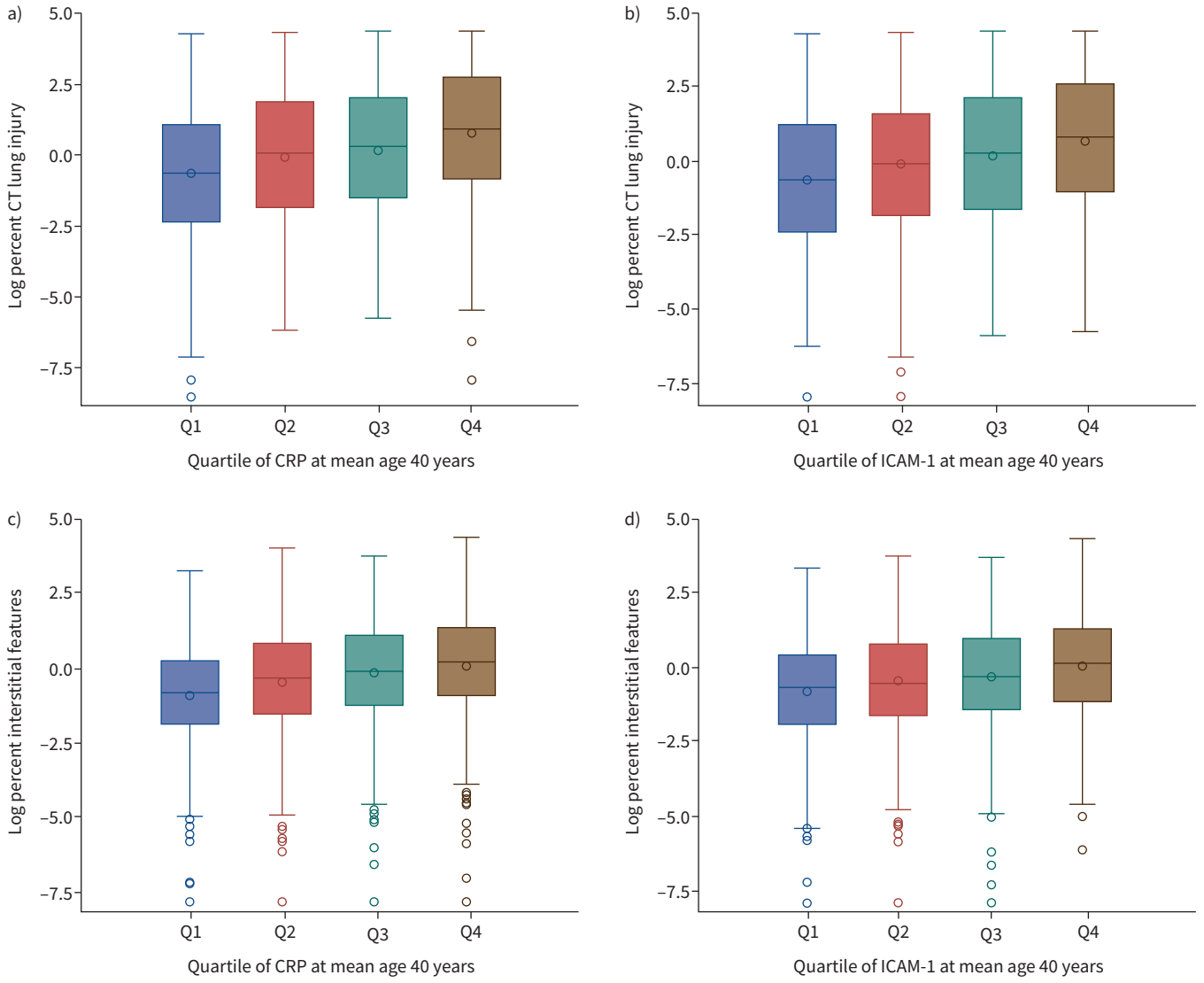

FIGURE 3 Differences in the log percentage of lung characterised as a, b) computed tomography (CT) lung injury and c, d) interstitial features at mean age 50 years by quartile of C-reactive protein (CRP) and intercellular adhesion molecule (ICAM)-1 at mean age 40 years. CT lung injury was defined as visually normal-appearing regions with attenuation >95th percentile for normal lung tissue. Interstitial features were defined as reticular or ground-glass abnormalities. The mean value of CRP from lowest to highest quartile was 0.33, 0.92, 2.27 and 9.04 $\mu g \cdot mL^{-1}$. The mean value of ICAM-1 from lowest to highest quartile was 112, 136, 158 and 209 $ng \cdot L^{-1}$.

restrictive spirometry. We also found that markers of systemic inflammation (CRP and ICAM-1) were positively associated with future CT lung injury, interstitial features on CT and restrictive spirometry; however, these secondary analyses were exploratory and not adjusted for multiple comparisons. These associations were independent of field centre, age, race, education, smoking status, cigarettes smoked per day, smoking pack-years and BMI at multiple time points. These findings suggest that identifying CT lung injury may be a way to detect some of the earliest changes which lead to interstitial features. Additionally, our study supports that elevations in markers of systemic inflammation may precede the development of lung injury and interstitial features by a decade.

The mechanisms involved in the pathogenesis of pulmonary fibrosis are complex and incompletely understood. One well-described pathway starts with repetitive microinjuries to the alveolar epithelium which lead to several maladaptive responses that promote the proliferation of myofibroblasts and excessive deposition of extracellular matrix proteins that lead to scar formation [25]. Inflammation and immune cells, particularly monocyte-derived macrophages, play an important role in promoting fibrogenesis [26, 27]. An

earlier cross-sectional study demonstrated that participants with more lung tissue characterised by CT lung injury had higher CRP and ICAM-1 levels, demonstrating its utility as a potential imaging biomarker for lung inflammation and injury [10]. CRP is a nonspecific acute phase reactant and is widely used as a clinical marker of inflammation [28]. ICAM-1 mediates trafficking of leukocytes into the alveolar space as part of the acute and chronic inflammatory response to lung injury [29, 30]. CRP and ICAM-1 have been associated with incident ILA in prior studies [8, 9]. Our research complements these studies by demonstrating similar findings in a younger cohort. This has important implications for the study of subclinical ILD in demonstrating that an inflammatory phenotype may precede the development of ILD by a decade and begin in early middle-age. The findings from our study also support that an inflammatory phenotype exists independent of smoking and obesity. Notably, a Mendelian randomisation study by Sunyer *et al.* found that specific polymorphisms in the CRP gene were associated with decreased CRP levels and higher FEV1 and FVC, suggesting heritability of lung function was at least partly controlled by the CRP gene [31].

We also found that higher levels of CT lung injury, CRP and ICAM-1 were all associated with increased odds of developing a restrictive pattern of abnormal lung function by age 55. At the time of this study, there has been conflicting data with regard to whether CRP is associated with lung function decline [32–36]. Given that ground-glass abnormalities are included in the definition of ILA put forth by the Fleischner Society [37], they were also included as part of the primary outcome of interstitial features in this study. However, in sensitivity analyses we also found that CT lung injury, CRP and ICAM-1 were also significantly associated with reticular-only interstitial features, when ground-glass abnormalities were excluded. This is notable given that the presence of reticular markings is associated with higher risk of ILA progression and increased mortality [24]. Our finding that CT lung injury is associated with both future interstitial features and incident restriction strengthen the argument that CT lung injury may be an important marker of vulnerable lung tissue which is injured but not yet fibrotic or remodelled. Areas for future research include examining whether interstitial features can be identified in the same locations where there were previously foci of CT lung injury.

Strengths of our study include that CARDIA is a large, multiracial cohort of healthy young adults who were followed for three decades. Additionally, repeated CT chest imaging, measures of inflammatory markers, and spirometry allow for the longitudinal assessment of the relationship between systemic inflammation and markers of subclinical ILD in an initially healthy population. We also have robust data on important covariates such as obesity and smoking, which allow for improved understanding of the relationship between systemic inflammation and future CT abnormalities.

There were limitations to our study. First, this study does not use specimens or biomarkers specific to lung inflammation, and therefore we are unable to definitively show that systemic inflammation leads to lung inflammation. Since CRP and ICAM-1 are non-specific markers of inflammation, we cannot rule out that elevations in these markers are associated with other disease states. Second, we do not have data on clinical diagnoses of ILD or clinical events such as ILD hospitalisations or death related to ILD, which limits our analyses to measures of subclinical ILD. Third, although we adjusted for BMI and smoking variables, there may be residual confounding due to more refined measures of obesity, such as visceral fat measures. Finally, because CARDIA is a longitudinal study that utilises evolving technology, there are differences in CT acquisition and quality from the examinations at mean age 40 years (conducted in the years 2000–2001) to mean age 50 years (conducted in 2010–2011), which may have affected the results of this study. However, because the CT analysis tool was trained separately for each examination year, it is unlikely that this would have led to an incorrect direction of association between higher amount of CT lung injury at mean age 40 years and higher amount of interstitial features at mean age 50 years. Additionally, we do not currently have data on visually defined ILAs in the CARDIA cohort; however, a prior study has shown that interstitial features characterised using the image processing tool from this study correlate with ILAs [14].

In conclusion, this study demonstrates the utility of CT lung injury as an objective and quantitative CT measure that can indicate risk of future ILD at the earliest stages, before significant remodelling has occurred. Additionally, this study reinforces that elevations in systemic inflammatory markers may precede the earliest imaging findings of parenchymal lung injury and damage. There remains a need for further research into how objective imaging processing tools can be used to further characterise phenotypes of impaired respiratory health and early disease.

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