

RESEARCH ARTICLE

Smoking and Subclinical ILD in RA versus the Multi-Ethnic Study of Atherosclerosis

Cheilonda Johnson¹, Jon T. Giles², Joan Bathon², David Lederer³, Eric A. Hoffman⁴, R. Graham Barr^{3,5,6}, Sonye K. Danoff^{1*}

1 Department of Medicine, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America, **2** Department of Medicine, Division of Rheumatology, Columbia University, College of Physicians & Surgeons, New York, New York, United States of America, **3** Department of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University, College of Physicians & Surgeons, New York, New York, United States of America, **4** Department of Radiology, University of Iowa Carver College of Medicine, Iowa City, Iowa, United States of America, **5** Department of Medicine, Division of General Medicine, Columbia University, College of Physicians & Surgeons, New York, New York, United States of America, **6** Department of Epidemiology, Columbia University, College of Physicians & Surgeons, New York, New York, United States of America

* sdanoff@jhmi.edu



OPEN ACCESS

Citation: Johnson C, Giles JT, Bathon J, Lederer D, Hoffman EA, Barr RG, et al. (2016) Smoking and Subclinical ILD in RA versus the Multi-Ethnic Study of Atherosclerosis. PLoS ONE 11(4): e0153024. doi:10.1371/journal.pone.0153024

Editor: Lynn M Schnapp, Medical University of South Carolina, UNITED STATES

Received: November 6, 2015

Accepted: March 21, 2016

Published: April 6, 2016

Copyright: © 2016 Johnson et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: The minimal anonymized dataset is attached as a Supporting Information file.

Funding: This research was funded by the Arthritis Foundation 6127, American College of Rheumatology Within Our Reach, and National Institutes of Health R01-H077162, RC1-100543, R01-093081, and R01-HL103676.

Competing Interests: The authors report the following competing interests; this does not alter the authors' adherence to PLOS ONE policies on sharing data and materials. Dr. Lederer reports grants from

Abstract

A population-based cohort showed an association between cigarette smoking and subclinical parenchymal lung disease defined as regions of increased computed tomography (CT) lung densitometry. This technique has not been applied to the rheumatoid arthritis (RA) population where associated ILD is highly prevalent. The association between cumulative cigarette smoking and volume of areas of high attenuation (HAA: >-600 and <-250 Hounsfield Units) on full inspiratory CT was compared in 172 RA participants and 3,969 controls in a general population sample. Multivariable regression models were used to adjust for demography, anthropometrics, percent emphysema, and CT parameters. The mean cumulative cigarette smoking exposure was 25 (IQR 10–42) and 15 (IQR 5–31) pack-years for the RA and non-RA cohorts, respectively. Mean HAA was 153(±57) cm³ and 129(±50) cm³ in the RA and non-RA cohorts, respectively. Each 10 cigarette pack-year increment was associated with a higher HAA by 0.03% (95% CI, 0.007–0.05%) in RA patients and by 0.008% (95% CI, 0.003–0.01%) in those without RA (interaction *p* = 0.001). Cigarette smoking was associated with higher lung attenuation; with a magnitude of association more pronounced in those with RA than in the general population. These data suggest that cigarette smoking may be a more potent ILD risk factor for RA patients than in the general population.

Introduction

Interstitial lung disease (ILD) is an important extrarticular manifestation of rheumatoid arthritis (RA) [1]. Since its first description over six decades ago, RA-associated ILD (RA-ILD) remains a significant source of morbidity and mortality [1–4]. This is due in part to poorly understood disease pathobiology and limited therapeutic options [1]. Identifying risk factors is

the NIH during the conduct of the study; personal fees from Intermune, Boehringer-Ingelheim, and Immuneworks, outside the submitted work. Dr. Hoffman reports grants from NIH, during the conduct of the study; other support from VIDA Diagnostics, outside the submitted work. Dr. Danoff reports grants from American College of Rheumatology Within Our Reach, grants from Arthritis Foundation, contract from National Institutes of Health, during the conduct of the study. All remaining authors declare that they have no competing interests.

the first step to understanding the mechanisms of this disease and eventually developing more efficacious treatment.

Smoking is a recognized risk factor for the development of RA, particularly among current and former heavy smokers [1, 5–8]. This has led many to hypothesize that smoking is a possible trigger of autoimmunity in RA [9]. Studies evaluating the role of smoking in the development of RA-ILD have shown conflicting results [1, 10, 11]. Some have shown a statistically significant increase in abnormalities on pulmonary function tests (PFT) and radiographic tests [12–14] in smokers with RA, while others have not [10]. While there is evidence that ILD may be statistically more prevalent in smokers with RA, there is no clear temporal or causal relationship between smoking and RA-ILD [15]. Nonetheless, many experts believe that smoking may act synergistically with other host and environmental factors to facilitate the development of ILD among those with RA [15–17]. For example, HLA-DRB1 shared epitope (SE) alleles, a significant genetic risk factor for the development of RA and RA-ILD, show strong gene-environment interactions with smoking [16, 18–20].

High resolution computed tomography (HRCT) is very sensitive at detecting lung abnormalities. In fact, many patients with RA exhibit HRCT evidence of ILD shortly after diagnosis before overt symptoms or PFT abnormalities develop [21, 22]. A large general population based study has shown that cumulative cigarette smoking is a risk factor for high attenuation lung lesions using CT densitometry that could represent preclinical interstitial lung disease [23]. This technique is highly reproducible and has been validated for quantifying the extent of lung parenchyma affected by lung injury, inflammation or fibrosis [23, 24]. Areas of high attenuation empirically correlate with parenchymal inflammation and fibrosis on imaging and restrictive physiology on PFTs [23, 24]. We sought to test the hypothesis that the association of smoking with early evidence of interstitial lung disease based on areas of high lung attenuation on CT would be greater in patients with RA compared with controls without RA.

Materials and Methods

Study Populations

Participants were enrolled in two separate but similar cohorts; RA patients in the Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis (ESCAPE RA) Study [25] and non-RA controls in the Multi-Ethnic Study of Atherosclerosis (MESA) [26]. Both prospectively investigated subclinical and progressive subclinical cardiovascular disease and have been previously described [25, 26]. MESA enrolled participants age 45–84 years old between July 2000 and December 2011. Participants were excluded if they had prevalent cardiovascular disease, weighed greater than 300 pounds, or underwent CT examination of the chest within one year of study enrollment. The ESCAPE RA study had the same inclusion/exclusion criteria as MESA, except subjects had to meet American College of Rheumatology RA criteria [27] for at least six months. ESCAPE RA enrolled participants from October 2004 to May 2006. All participants provided institutional review board (IRB) approved written informed consent. MESA was approved by the IRBs of all participating sites (Columbia University, Johns Hopkins University, Northwestern University, UCLA, University of Minnesota, and Wake Forest University) and the National Heart, Lung, and Blood Institute of the National Institutes of Health; the present study was approved by the Johns Hopkins University IRB (NA_32457).

CT Densitometry

Both groups underwent cardiac multi-detector row computed tomography (MDCT) scanning following the same protocol as part of the Baseline Visit [25, 26]. MESA cardiac MDCT scans

of 2.5 to 3.0 mm thickness capture approximately 70% of the lung from the carina to lung bases [28]. CT densitometry [29] is an automated method of CT interpretation where the Hounsfield units (HU) of each individual voxel are determined and summed yielding measures of low and high attenuation areas. Areas of high attenuation (HAA) were defined as voxels between -600 and -250 HU [23]; percent emphysema was defined as the percentage of lung voxels with attenuation less than -910 HU [28, 30]. Both measures are highly correlated with full-lung CT scans in MESA (Spearman correlation coefficient 0.87 for HAA) [23, 28].

Other Measures

Race/ethnicity were assessed by self-report. Anthropometrics and smoking history were assessed using standardized questionnaires for both groups [26]. Participants were considered ever smokers if they smoked at least 100 cigarettes in their lifetime and current smokers if they smoked in the last 30 days. ESCAPE RA participants had a baseline clinical evaluation including both RA specific and general health questionnaires and were assessed for the presence of the rheumatoid arthritis susceptibility alleles of *HLA-DRB1* (i.e. shared epitope) as previously described [25]. Additionally, ESCAPE RA participants underwent PFTs based on ATS guidelines [31, 32] at a Visit 2 (completed eighteen months after the Baseline Visit).

Analysis

The volume of high attenuation areas (HAA) was used in the regression models to allow for ease of comparison with published reports and reduce potential spurious correlations [23]. HAA had a natural log-normal distribution which was linear with all continuous variables. For the natural log HAA analysis, multivariable regression models were constructed with potential confounders included that were associated with HAA in univariate analyses at the $p < 0.20$ significance level, to allow for residual confounding. Akaike's information criterion is used to exclude non-contributory covariates in nested models. The natural log HAA (dependent variable) was regressed on cigarette pack-years (independent variable) after controlling for potential confounders. All calculations were performed using intercooled Stata 12 (StataCorp, College Station, TX). A two-tailed P value of less than 0.05 was used as the cutoff for statistical significance; estimates of uncertainty were presented as 95 percent confidence intervals (95% CI).

Results

CT densitometry data were available for 172 RA and 3,969 and non-RA control participants, respectively. Group participant characteristics are summarized in Table 1. The RA cohort was younger and comprised of primarily Caucasian women. The two groups were anthropometrically similar. Participants with RA were significantly more likely to have smoked and among former smokers, smoked more cigarettes on average. Participants from the RA cohort also had higher values of percent emphysema. Pulmonary characteristics of RA participants at Baseline and Visit 2 are summarized in Table 2. The mean RA duration was eight years. Thirty-eight percent were on prednisone therapy, 87% were on non-biologic DMARDs, and 46% were on biologic DMARDs at the start of the study (Table 2). Forty-one percent had respiratory symptoms with 8% showing a restrictive pattern on PFTs and 17% a diffusing capacity impairment (Table 2). The mean forced vital capacity percent predicted (FVC %) and carbon monoxide diffusing capacity percent predicted (DLCo %) was 101% (Table 2).

Areas of high attenuation were incrementally higher with higher cigarette smoking exposure in each group (Fig 1, S1 and S2 Figs). After adjusting for demography, anthropometrics, and total lung volume imaged, the volume of high attenuation areas (HAA) was 0.03% (95% CI,

Table 1. Participant Characteristics.

	MESA Controls (n = 3,969)	ESCAPE RA (n = 172)	P Value
Demographics			
Age, years	61 ± 10	60 ± 9	0.006
Men, %	49	41	0.04
Race/ethnicity			
White, %	35	88	<0.001
African American, %	26	7	
Asian, %	16	3	
Hispanic, %	23	2	
Anthropometrics			
Height, cm	166 ± 10	168 ± 10	0.18
Weight, kg	79 ± 17	80 ± 18	0.21
BMI, kg/m ²	28.1 ± 5.3	28.4 ± 5.3	0.56
BMI category, %			
<18.5	1	1	0.80
18.5–24.9	29	28	
25–29.9	39	37	
≥30	30	34	
Waist circumference, cm	98 ± 14	96 ± 16	0.14
Hip circumference, cm	105 ± 11	104 ± 14	0.14
Smoking			
Never smoker, %	52	38	<0.001
Former smoker, %	36	51	
Current smoker, %	12	11	
Cigarette pack-years (among ever smokers)	15 (5–31)	25 (10–42)	<0.001
Percent Emphysema, %*	20 ± 13	34 ± 14	<0.001
HAA, cm ³	129 ± 50	153 ± 57	<0.001

Data are mean ± SD, median (interquartile range), and percentage.

*Percent emphysema is the percentage of total voxels in the whole lung that fell below -910 Hounsfield units.

HAA: High attenuation areas are the volume of total voxels in the whole lung between -600 and -250 Hounsfield units.

doi:10.1371/journal.pone.0153024.t001

0.007–0.05%) higher for each 10 cigarette pack-year increase in smoking in the RA group compared with 0.008% (95% CI, 0.003–0.01%) in the non-RA group (interaction $p = 0.001$) (Table 3). After further adjustment for percent emphysema, this association was attenuated to 0.02% (95% CI, 0.001–0.04%) in the RA group and 0.005% (95% CI, 0.001–0.009%) in the non-RA group (interaction $p = 0.01$) (Table 4).

Patients from the RA cohort were stratified based on the presence or absence of HLA-DRB1 shared epitope (SE) alleles. After controlling for the same covariates as the unstratified model, areas of high attenuation were higher with greater cigarette smoking exposure in the SE positive group only (Table 5). HAA was 0.03% (95% CI, 0.006–0.06%) higher for each 10 cigarette pack-year increase in smoking in the SE positive RA group compared with 0.008% (95% CI, 0.003–0.01%) in the non-RA group (interaction $p = 0.002$).

Discussion

In this study we compared the association of cumulative cigarette smoking with areas of high lung attenuation on CT in a large number of individuals with RA (ESCAPE RA) and generally

Table 2. Baseline and Visit 2 RA Patient Characteristics.

Baseline Characteristics	N = 176
RA Disease Activity	
RA Duration, years	8 (4–17)
DAS28-CRP	3.7 (2.9–4.4)
CRP, mg/L	2.4 (1.1–7.7)
IL-6, pg/mL	3.7 (1.8–7.8)
Total SHS	8 (1–37)
RA Treatment	
Current prednisone, n (%)	67 (38)
Current non-biologic DMARDs, n (%)	150 (86)
Methotrexate, n (%)	114 (65)
Leflunomide, n (%)	19 (11)
Current biologic DMARDs, n (%)	81 (46)
TNF inhibitor, n (%)	78 (45)
Visit 2 Characteristics	
Pulmonary Function Tests	
Any abnormality, n (%)	38 (27)
Obstructive PFT pattern, n (%)	14 (10)
Restrictive PFT pattern, n (%)	12 (8)
Impaired Diffusion pattern, n (%)	24 (17)
Isolated impaired diffusion, n (%)	12 (9)
FVC (% predicted)	101 ± 19
DLCO (% predicted)	101 ± 59
Respiratory Symptoms	
Any respiratory symptoms, n (%)	69 (41)
Any cough, n (%)	37 (22)
Any breathlessness, n (%)	36 (21)

Data are mean ± SD, median (interquartile range) unless otherwise indicated.

RA = rheumatoid arthritis; DAS = disease activity score; CRP = C-reactive protein; IL = interleukin; SHS = Sharp-van-Heijde Score.

doi:10.1371/journal.pone.0153024.t002

healthy controls (MESA). We observed a higher proportion of high attenuation areas on cardiac CT with higher levels of cigarette smoke exposure. This association was significantly greater among patients with RA than in the general population. Our findings support the hypothesis that cigarette smoking acts synergistically with other host factors in RA patients to increase the risk of ILD.

Plausible biologic explanations for synergistic interactions with smoking include the antibody and genetic background of RA patients. Anticyclic citrullinated peptide antibodies (ACPA) are highly specific for RA and serum levels correlate with disease severity and response to therapy [33, 34]. Citrullination, a posttranslational protein modification, is present in the lung tissue of subjects with RA and certain citrullinated protein isoforms are highly specific for RA-ILD [33, 35, 36]. RA related lung abnormalities have been noted in patients with RA-specific autoantibodies in the serum and sputum prior to the onset of inflammatory arthritis [37, 38]. This has led to the hypothesis that the lung is the site of development or sequestering of RA autoantibodies [36, 37, 39]. Smoking enhances inflammatory cell recruitment, promoting pulmonary epithelial and endothelial injury [15, 40]. Through this process lung tissue citrullination is activated via altered expression of peptidylarginine deiminase (PAD) enzymes [1, 40,

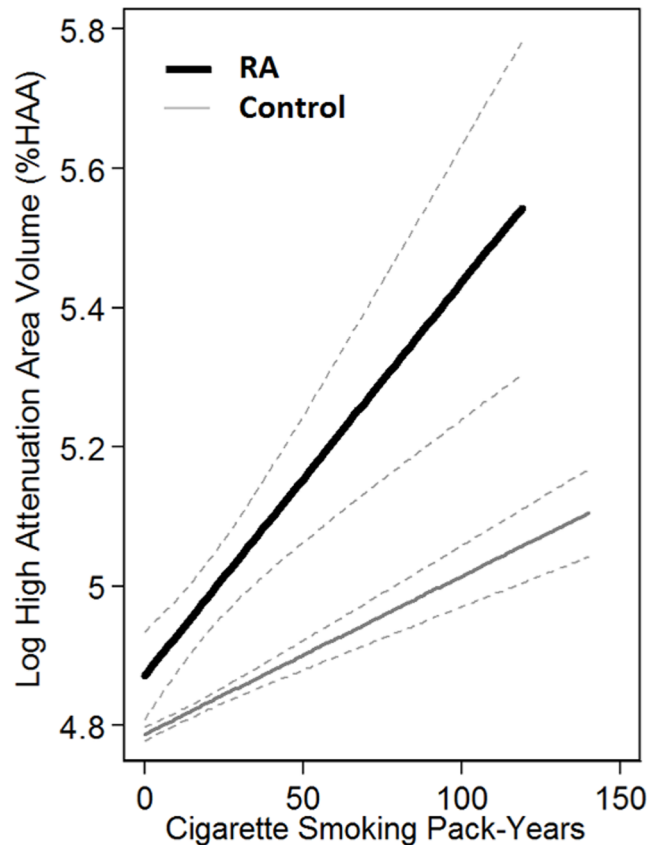


Fig 1. Association between Cigarette Pack-Years and Log High Attenuation Volume.

doi:10.1371/journal.pone.0153024.g001

[41]. The presence of smoking induced lung citrullination may lead to abnormal to lung injury repair increasing the risk of ILD in patients with RA [10].

Patients subtyped by ACPA positivity and negativity demonstrate distinct patterns of genetic variation and disease risk profiles by smoking status [16, 19]. For example, HLA-DRB1 shared epitope alleles show strong gene-environment interactions with smoking and are found exclusively in those with anticitrulline autoimmunity [16, 19]. Furthermore, smoking is a risk factor for RA in ACPA positive, but not ACPA negative RA patients [34]. We found that the

Table 3. CT Densitometry by Smoking History.

	Cigarette Pack-Years				Effect Estimate per 10 Pack-Yrs. (95% CI)	P Value
	0	1–10	11–20	>20		
ESCAPE RA						
No. of Subjects	67	23	17	58		
HAA Volume, cm ³	134 (±43)	148 (±44)	151 (±60)	176 (±68)	0.03% (0.007–0.05)	0.01
Controls						
No. of Subjects	2,119	601	344	742		
HAA Volume, cm ³	124 (±55)	128 (±20)	132 (±74)	139 (±61)	0.008% (0.003–0.01)	0.001

Primary Analysis. The full multivariate model includes age, sex, race/ethnicity, smoking status, height, body mass index, hip circumference, waist circumference, and total volume of imaged lung.

doi:10.1371/journal.pone.0153024.t003

Table 4. CT Densitometry by Smoking History, Controlled for Emphysema%.

	Cigarette Pack-Years				Effect Estimate per 10 Pack-Yrs. (95% CI)	P Value
	0	1–10	11–20	>20		
ESCAPE RA						
No. of Subjects	67	23	17	58		
HAA Volume, cm ³	134 (±43)	148 (±44)	151 (±60)	176 (±68)	0.02% (0.001–0.04)	0.04
Controls						
No. of Subjects	2,119	601	344	742		
HAA Volume, cm ³	124 (±55)	128 (±20)	132 (±74)	139 (±61)	0.005% (0.001–0.009)	0.009

Secondary Analysis. The full multivariate model includes age, sex, race/ethnicity, smoking status, height, body mass index, hip circumference, waist circumference, total volume of imaged lung, and emphysema %.

doi:10.1371/journal.pone.0153024.t004

association between higher cigarette smoke exposure and greater areas of high attenuation was restricted to the group of RA patients with any SE only. This suggests that smoking, in addition to potentially causing local injury and aberrant healing, interacts with individual genetic variation to cause systemic immune system dysregulation.

Our study has multiple strengths including large, well-characterized study populations and similar protocols for data collection and MDCT acquisition. Several limitations do warrant discussion. The study has the typical limitations of observational design and most importantly cannot determine causality. Although ILD typically predominates in the lung bases, important information including concomitant emphysema could be lost from the excluded lung apices, which may be particularly relevant here as the magnitude of the association for HAA was attenuated after controlling for percent emphysema. Given the significantly higher cumulative cigarette pack-years and percent emphysema in the RA group, the presence of this data could have further attenuated the differences between the two cohorts. As previously mentioned, however, cardiac CT scans are correlated with full-lung CT scans for both measures in MESA [23, 28]. Corresponding baseline visit PFTs were not available for the ESCAPE RA group to confirm a parallel association with spirometric restriction or reduced static lung volumes. The increased volume of high lung attenuation areas with greater cigarette smoking exposure captured in our study may represent areas of lung parenchyma inflammation and/or fibrosis that correspond with interstitial lung disease [23]. Areas of high attenuation noted on MDCT, however, could represent a range of pulmonary abnormalities including small airways inflammation and thickening and pulmonary edema [23, 37] that have noted to occur in increased frequency in smokers and patients with RA. The absolute change in the volume of areas of high attenuation with greater smoking was relatively small in both cohorts. The clinical significance of this degree of

Table 5. Shared Epitope Allele Stratified Model.

Group	N	Effect Estimate per 10 Pack-Years (95% CI)	P Value
ESCAPE RA:			
Any SE	119	0.03% (0.006–0.06)	0.02
No SE	46	0.009% (-0.06–0.08)	0.78
Controls	3927	0.008% (0.003–0.01)	<0.01

The full multivariate model includes age, sex, race/ethnicity, smoking status, height, body mass index, hip circumference, waist circumference, & total volume of imaged lung.

SE: HLA-DRB1 Shared Epitope Allele.

doi:10.1371/journal.pone.0153024.t005

change in patients without overt symptoms is unclear. Finally, the interaction between any SE and the association between cigarette smoking and HAA on CT is based on a small number of patients and warrants additional study in a larger RA cohort.

In conclusion, we found a stronger association between cigarette smoking and HAA on CT in those with RA compared with the general population. Areas of increased HAA on CT correlate with parenchymal inflammation and fibrosis and may represent subclinical ILD. Smoking is likely just one of many environmental exposures that act in combination with host (genetic) factors to initiate RA-ILD. Cigarette smoking, however, represents a major preventable risk factor for the development of RA-ILD and cessation efforts should be pursued aggressively.

Supporting Information

S1 Data. Anonymized Minimal Dataset.
(CSV)

S1 Fig. Scatterplot of the Association between Cigarette Pack-Years and Log High Attenuation Volume in MESA Participants.
(TIF)

S2 Fig. Scatterplot of the Association between Cigarette Pack-Years and Log High Attenuation Volume in ESCAPE RA Participants.
(TIF)

Acknowledgments

The MESA and MESA-Lung Studies were conducted and supported by the NHLBI in collaboration with the MESA and MESA-Lung Investigators. This manuscript has been reviewed by the MESA investigators for scientific content and consistency of data interpretation with previous MESA publications and significant comments have been incorporated prior to submission for publication. A full list of participating MESA investigators and institutions can be found at <http://www.mesa-nhlbi.org>. The authors thank the other investigators, staff, and participants of the MESA Study for their valuable contributions.

Author Contributions

Conceived and designed the experiments: CJ JTG. Analyzed the data: CJ JTG. Contributed reagents/materials/analysis tools: JB EAH RGB. Wrote the paper: CJ JTG JB DL EAH SKD. ESCAPE RA Principal Investigator: JB. MESA Lung Principal Investigator: RGB.

References

1. Cavagna L, Monti S, Grosso V, Boffini N, Scorletti E, Crepaldi G, et al. The Multifaceted Aspects of Interstitial Lung Disease in Rheumatoid Arthritis. *BioMed research international*. 2013; 2013:759760. Epub 2013/11/10. doi: [10.1155/2013/759760](https://doi.org/10.1155/2013/759760) PMID: [24205507](https://pubmed.ncbi.nlm.nih.gov/24205507/); PubMed Central PMCID: PMC3800606.
2. Ellman P, Ball RE. Rheumatoid disease with joint and pulmonary manifestations. *British medical journal*. 1948; 2(4583):816–20. Epub 1948/11/06. PMID: [18890308](https://pubmed.ncbi.nlm.nih.gov/18890308/); PubMed Central PMCID: PMC2091941.
3. Olson AL, Swigris JJ, Sprunger DB, Fischer A, Fernandez-Perez ER, Solomon J, et al. Rheumatoid arthritis-interstitial lung disease-associated mortality. *American journal of respiratory and critical care medicine*. 2011; 183(3):372–8. Epub 2010/09/21. doi: [10.1164/rccm.201004-0622OC](https://doi.org/10.1164/rccm.201004-0622OC) PMID: [20851924](https://pubmed.ncbi.nlm.nih.gov/20851924/).
4. Pappas DA, Giles JT, Connors G, Lechtzin N, Bathon JM, Danoff SK. Respiratory symptoms and disease characteristics as predictors of pulmonary function abnormalities in patients with rheumatoid

- arthritis: an observational cohort study. *Arthritis research & therapy*. 2010; 12(3):R104. Epub 2010/05/29. doi: [10.1186/ar3037](https://doi.org/10.1186/ar3037) PMID: [20507627](https://pubmed.ncbi.nlm.nih.gov/20507627/); PubMed Central PMCID: PMC2911894.
5. Hutchinson D, Shepstone L, Moots R, Lear JT, Lynch MP. Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. *Annals of the rheumatic diseases*. 2001; 60(3):223–7. Epub 2001/02/15. PMID: [11171682](https://pubmed.ncbi.nlm.nih.gov/11171682/); PubMed Central PMCID: PMC1753588.
 6. Mikuls TR, Sayles H, Yu F, Levan T, Gould KA, Thiele GM, et al. Associations of cigarette smoking with rheumatoid arthritis in African Americans. *Arthritis and rheumatism*. 2010; 62(12):3560–8. Epub 2010/08/20. doi: [10.1002/art.27716](https://doi.org/10.1002/art.27716) PMID: [20722010](https://pubmed.ncbi.nlm.nih.gov/20722010/); PubMed Central PMCID: PMC2995845.
 7. Yahya A, Bengtsson C, Lai TC, Larsson PT, Mustafa AN, Abdullah NA, et al. Smoking is associated with an increased risk of developing ACPA-positive but not ACPA-negative rheumatoid arthritis in Asian populations: evidence from the Malaysian MyEIRA case-control study. *Modern rheumatology / the Japan Rheumatism Association*. 2012; 22(4):524–31. Epub 2011/10/19. doi: [10.1007/s10165-011-0544-2](https://doi.org/10.1007/s10165-011-0544-2) PMID: [22006120](https://pubmed.ncbi.nlm.nih.gov/22006120/).
 8. Wolfe F. The effect of smoking on clinical, laboratory, and radiographic status in rheumatoid arthritis. *The Journal of rheumatology*. 2000; 27(3):630–7. Epub 2000/04/01. PMID: [10743800](https://pubmed.ncbi.nlm.nih.gov/10743800/).
 9. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis and rheumatism*. 2006; 54(1):38–46. Epub 2005/12/31. doi: [10.1002/art.21575](https://doi.org/10.1002/art.21575) PMID: [16385494](https://pubmed.ncbi.nlm.nih.gov/16385494/).
 10. Mori S, Koga Y, Sugimoto M. Different risk factors between interstitial lung disease and airway disease in rheumatoid arthritis. *Respiratory medicine*. 2012; 106(11):1591–9. Epub 2012/08/08. doi: [10.1016/j.rmed.2012.07.006](https://doi.org/10.1016/j.rmed.2012.07.006) PMID: [22867979](https://pubmed.ncbi.nlm.nih.gov/22867979/).
 11. Tsuchiya Y, Takayanagi N, Sugiura H, Miyahara Y, Tokunaga D, Kawabata Y, et al. Lung diseases directly associated with rheumatoid arthritis and their relationship to outcome. *The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology*. 2011; 37(6):1411–7. Epub 2010/10/05. doi: [10.1183/09031936.00019210](https://doi.org/10.1183/09031936.00019210) PMID: [20884744](https://pubmed.ncbi.nlm.nih.gov/20884744/).
 12. Saag KG, Kolluri S, Koehnke RK, Georgou TA, Rachow JW, Hunninghake GW, et al. Rheumatoid arthritis lung disease. Determinants of radiographic and physiologic abnormalities. *Arthritis and rheumatism*. 1996; 39(10):1711–9. Epub 1996/10/01. PMID: [8843862](https://pubmed.ncbi.nlm.nih.gov/8843862/).
 13. Luukkainen R, Saltyshev M, Pakkasela R, Nordqvist E, Huhtala H, Hakala M. Relationship of rheumatoid factor to lung diffusion capacity in smoking and non-smoking patients with rheumatoid arthritis. *Scandinavian journal of rheumatology*. 1995; 24(2):119–20. Epub 1995/01/01. PMID: [7747143](https://pubmed.ncbi.nlm.nih.gov/7747143/).
 14. Westedt ML, Hazes JM, Breedveld FC, Sterk PJ, Dijkman JH. Cigarette smoking and pulmonary diffusion defects in rheumatoid arthritis. *Rheumatology international*. 1998; 18(1):1–4. Epub 1998/07/22. PMID: [9672991](https://pubmed.ncbi.nlm.nih.gov/9672991/).
 15. Vassallo R, Ryu JH. Smoking-related interstitial lung diseases. *Clinics in chest medicine*. 2012; 33(1):165–78. Epub 2012/03/01. doi: [10.1016/j.ccm.2011.11.004](https://doi.org/10.1016/j.ccm.2011.11.004) PMID: [22365253](https://pubmed.ncbi.nlm.nih.gov/22365253/).
 16. Kallberg H, Padyukov L, Plenge RM, Ronnelid J, Gregersen PK, van der Helm-van Mil AH, et al. Gene-gene and gene-environment interactions involving HLA-DRB1, PTPN22, and smoking in two subsets of rheumatoid arthritis. *American journal of human genetics*. 2007; 80(5):867–75. Epub 2007/04/17. doi: [10.1086/516736](https://doi.org/10.1086/516736) PMID: [17436241](https://pubmed.ncbi.nlm.nih.gov/17436241/); PubMed Central PMCID: PMC1852748.
 17. Giles JT, Danoff SK, Sokolove J, Wagner CA, Winchester R, Pappas DA, et al. Association of fine specificity and repertoire expansion of anticitrullinated peptide antibodies with rheumatoid arthritis associated interstitial lung disease. *Annals of the rheumatic diseases*. 2013. Epub 2013/05/30. doi: [10.1136/annrheumdis-2012-203160](https://doi.org/10.1136/annrheumdis-2012-203160) PMID: [23716070](https://pubmed.ncbi.nlm.nih.gov/23716070/); PubMed Central PMCID: PMC3883892.
 18. Linn-Rasker SP, van der Helm-van Mil AH, van Gaalen FA, Kloppenburg M, de Vries RR, le Cessie S, et al. Smoking is a risk factor for anti-CCP antibodies only in rheumatoid arthritis patients who carry HLA-DRB1 shared epitope alleles. *Annals of the rheumatic diseases*. 2006; 65(3):366–71. Epub 2005/07/15. doi: [10.1136/ard.2005.041079](https://doi.org/10.1136/ard.2005.041079) PMID: [16014670](https://pubmed.ncbi.nlm.nih.gov/16014670/); PubMed Central PMCID: PMC1798061.
 19. Pedersen M, Jacobsen S, Garred P, Madsen HO, Klarlund M, Svejgaard A, et al. Strong combined gene-environment effects in anti-cyclic citrullinated peptide-positive rheumatoid arthritis: a nationwide case-control study in Denmark. *Arthritis and rheumatism*. 2007; 56(5):1446–53. Epub 2007/05/01. doi: [10.1002/art.22597](https://doi.org/10.1002/art.22597) PMID: [17469102](https://pubmed.ncbi.nlm.nih.gov/17469102/).
 20. Furukawa H, Oka S, Shimada K, Sugii S, Ohashi J, Matsui T, et al. Association of human leukocyte antigen with interstitial lung disease in rheumatoid arthritis: a protective role for shared epitope. *PloS one*. 2012; 7(5):e33133. doi: [10.1371/journal.pone.0033133](https://doi.org/10.1371/journal.pone.0033133) PMID: [22586441](https://pubmed.ncbi.nlm.nih.gov/22586441/); PubMed Central PMCID: PMC3346749.

21. Habib HM, Eisa AA, Arafat WR, Marie MA. Pulmonary involvement in early rheumatoid arthritis patients. *Clinical rheumatology*. 2011; 30(2):217–21. Epub 2010/05/27. doi: [10.1007/s10067-010-1492-5](https://doi.org/10.1007/s10067-010-1492-5) PMID: [20503061](https://pubmed.ncbi.nlm.nih.gov/20503061/).
22. Gochuico BR, Avila NA, Chow CK, Novero LJ, Wu HP, Ren P, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. *Archives of internal medicine*. 2008; 168(2):159–66. Epub 2008/01/30. doi: [10.1001/archinternmed.2007.59](https://doi.org/10.1001/archinternmed.2007.59) PMID: [18227362](https://pubmed.ncbi.nlm.nih.gov/18227362/).
23. Lederer DJ, Enright PL, Kawut SM, Hoffman EA, Hunninghake G, van Beek EJ, et al. Cigarette smoking is associated with subclinical parenchymal lung disease: the Multi-Ethnic Study of Atherosclerosis (MESA)-lung study. *American journal of respiratory and critical care medicine*. 2009; 180(5):407–14. Epub 2009/06/23. doi: [10.1164/rccm.200812-1966OC](https://doi.org/10.1164/rccm.200812-1966OC) PMID: [19542480](https://pubmed.ncbi.nlm.nih.gov/19542480/); PubMed Central PMCID: [PMC2742759](https://pubmed.ncbi.nlm.nih.gov/PMC2742759/).
24. Best AC, Lynch AM, Bozic CM, Miller D, Grunwald GK, Lynch DA. Quantitative CT indexes in idiopathic pulmonary fibrosis: relationship with physiologic impairment. *Radiology*. 2003; 228(2):407–14. Epub 2003/06/13. doi: [10.1148/radiol.2282020274](https://doi.org/10.1148/radiol.2282020274) PMID: [12802000](https://pubmed.ncbi.nlm.nih.gov/12802000/).
25. Giles JT, Szklo M, Post W, Petri M, Blumenthal RS, Lam G, et al. Coronary arterial calcification in rheumatoid arthritis: comparison with the Multi-Ethnic Study of Atherosclerosis. *Arthritis research & therapy*. 2009; 11(2):R36. Epub 2009/03/17. doi: [10.1186/ar2641](https://doi.org/10.1186/ar2641) PMID: [19284547](https://pubmed.ncbi.nlm.nih.gov/19284547/); PubMed Central PMCID: [PMC2688181](https://pubmed.ncbi.nlm.nih.gov/PMC2688181/).
26. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al. Multi-ethnic study of atherosclerosis: objectives and design. *American journal of epidemiology*. 2002; 156(9):871–81. Epub 2002/10/25. PMID: [12397006](https://pubmed.ncbi.nlm.nih.gov/12397006/).
27. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis and rheumatism*. 1988; 31(3):315–24. Epub 1988/03/01. PMID: [3358796](https://pubmed.ncbi.nlm.nih.gov/3358796/).
28. Hoffman EA, Jiang R, Baumhauer H, Brooks MA, Carr JJ, Detrano R, et al. Reproducibility and validity of lung density measures from cardiac CT Scans—The Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study. *Academic radiology*. 2009; 16(6):689–99. Epub 2009/05/12. doi: [10.1016/j.acra.2008.12.024](https://doi.org/10.1016/j.acra.2008.12.024) PMID: [19427979](https://pubmed.ncbi.nlm.nih.gov/19427979/); PubMed Central PMCID: [PMC2943871](https://pubmed.ncbi.nlm.nih.gov/PMC2943871/).
29. Hoffman EA, Ahmed FS, Baumhauer H, Budoff M, Carr JJ, Kronmal R, et al. Variation in the Percent of Emphysema-like Lung in a Healthy, Nonsmoking Multiethnic Sample. The MESA Lung Study. *Annals of the American Thoracic Society*. 2014; 11(6):898–907. doi: [10.1513/AnnalsATS.201310-364OC](https://doi.org/10.1513/AnnalsATS.201310-364OC) PMID: [24983825](https://pubmed.ncbi.nlm.nih.gov/24983825/).
30. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR Jr., et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. *Radiology*. 2005; 234(1):35–43. Epub 2004/12/25. doi: [10.1148/radiol.2341040439](https://doi.org/10.1148/radiol.2341040439) PMID: [15618373](https://pubmed.ncbi.nlm.nih.gov/15618373/).
31. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *American journal of respiratory and critical care medicine*. 2002; 165(2):277–304. Epub 2002/01/16. PMID: [11790668](https://pubmed.ncbi.nlm.nih.gov/11790668/).
32. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. *The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology*. 2005; 26(1):153–61. doi: [10.1183/09031936.05.00034505](https://doi.org/10.1183/09031936.05.00034505) PMID: [15994402](https://pubmed.ncbi.nlm.nih.gov/15994402/).
33. Bongartz T, Cantaert T, Atkins SR, Harle P, Myers JL, Turesson C, et al. Citrullination in extra-articular manifestations of rheumatoid arthritis. *Rheumatology (Oxford)*. 2007; 46(1):70–5. Epub 2006/06/20. doi: [10.1093/rheumatology/kei202](https://doi.org/10.1093/rheumatology/kei202) PMID: [16782731](https://pubmed.ncbi.nlm.nih.gov/16782731/).
34. Klareskog L, Malmstrom V, Lundberg K, Padyukov L, Alfredsson L. Smoking, citrullination and genetic variability in the immunopathogenesis of rheumatoid arthritis. *Seminars in immunology*. 2011; 23(2):92–8. Epub 2011/03/08. doi: [10.1016/j.smim.2011.01.014](https://doi.org/10.1016/j.smim.2011.01.014) PMID: [21376627](https://pubmed.ncbi.nlm.nih.gov/21376627/).
35. Harlow L, Rosas IO, Gochuico BR, Mikuls TR, Dellaripa PF, Oddis CV, et al. Identification of citrullinated hsp90 isoforms as novel autoantigens in rheumatoid arthritis-associated interstitial lung disease. *Arthritis and rheumatism*. 2013; 65(4):869–79. Epub 2013/02/13. doi: [10.1002/art.37881](https://doi.org/10.1002/art.37881) PMID: [23400887](https://pubmed.ncbi.nlm.nih.gov/23400887/).
36. Reynisdottir G, Olsen H, Joshua V, Engstrom M, Forsslund H, Karimi R, et al. Signs of immune activation and local inflammation are present in the bronchial tissue of patients with untreated early rheumatoid arthritis. *Annals of the rheumatic diseases*. 2015. doi: [10.1136/annrheumdis-2015-208216](https://doi.org/10.1136/annrheumdis-2015-208216) PMID: [26530319](https://pubmed.ncbi.nlm.nih.gov/26530319/).

37. Demoruelle MK, Weisman MH, Simonian PL, Lynch DA, Sachs PB, Pedraza IF, et al. Brief report: airways abnormalities and rheumatoid arthritis-related autoantibodies in subjects without arthritis: early injury or initiating site of autoimmunity? *Arthritis and rheumatism*. 2012; 64(6):1756–61. doi: [10.1002/art.34344](https://doi.org/10.1002/art.34344) PMID: [22183986](https://pubmed.ncbi.nlm.nih.gov/22183986/); PubMed Central PMCID: PMC3319006.
38. Willis VC, Demoruelle MK, Derber LA, Chartier-Logan CJ, Parish MC, Pedraza IF, et al. Sputum autoantibodies in patients with established rheumatoid arthritis and subjects at risk of future clinically apparent disease. *Arthritis and rheumatism*. 2013; 65(10):2545–54. doi: [10.1002/art.38066](https://doi.org/10.1002/art.38066) PMID: [23817979](https://pubmed.ncbi.nlm.nih.gov/23817979/); PubMed Central PMCID: PMC4066465.
39. Reynisdottir G, Karimi R, Joshua V, Olsen H, Hensvold AH, Harju A, et al. Structural changes and antibody enrichment in the lungs are early features of anti-citrullinated protein antibody-positive rheumatoid arthritis. *Arthritis Rheumatol*. 2014; 66(1):31–9. doi: [10.1002/art.38201](https://doi.org/10.1002/art.38201) PMID: [24449573](https://pubmed.ncbi.nlm.nih.gov/24449573/).
40. Thorley AJ, Tetley TD. Pulmonary epithelium, cigarette smoke, and chronic obstructive pulmonary disease. *International journal of chronic obstructive pulmonary disease*. 2007; 2(4):409–28. Epub 2008/02/14. PMID: [18268916](https://pubmed.ncbi.nlm.nih.gov/18268916/); PubMed Central PMCID: PMC2699967.
41. Baka Z, Buzas E, Nagy G. Rheumatoid arthritis and smoking: putting the pieces together. *Arthritis research & therapy*. 2009; 11(4):238. Epub 2009/08/15. doi: [10.1186/ar2751](https://doi.org/10.1186/ar2751) PMID: [19678909](https://pubmed.ncbi.nlm.nih.gov/19678909/); PubMed Central PMCID: PMC2745780.