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Rheumatoid Arthritis and Lung Disease

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Updates in Rheumatology
University of Nebraska Medical Center

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HARVARD MEDICAL SCHOOL

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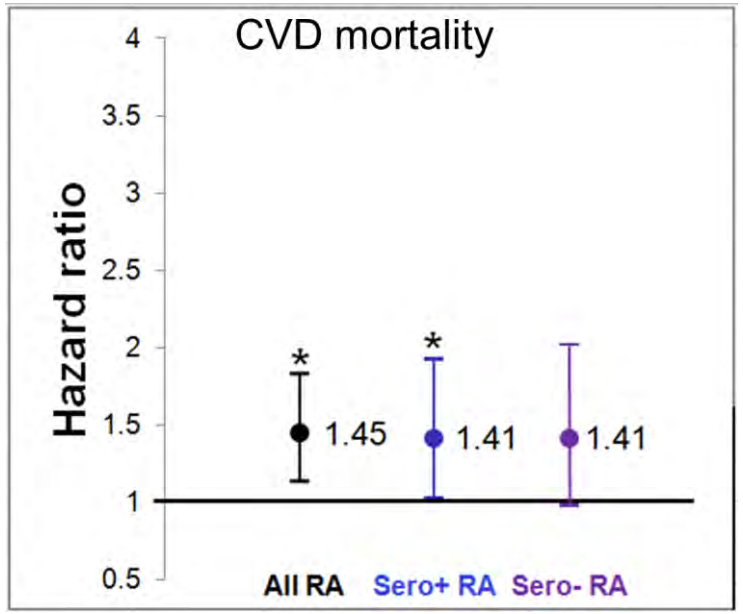
National Institutes of Health

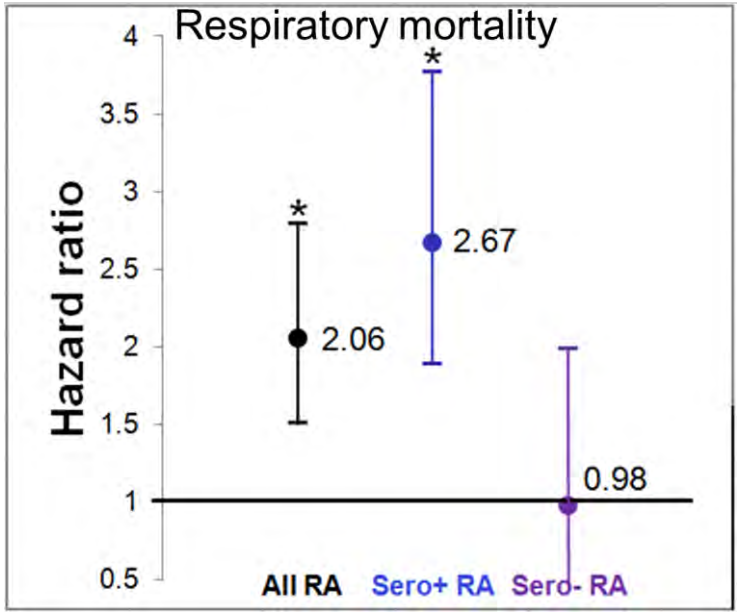
NIAMS
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Rheumatology Research Foundation

Respiratory burden of RA

- RA is associated with <u>excess total, cardiovascular, and respiratory mortality</u>
  - Nurses' Health Study: 121,700 women followed since 1976
  - All RA: **HR 1.40 (95%CI 1.25-1.57)** for total mortality
  - Seropositive RA: **HR 1.51 (95%CI 1.31-1.74)** for total mortality
  - Seronegative RA: HR 1.15 (95%CI 0.95-1.39) for total mortality

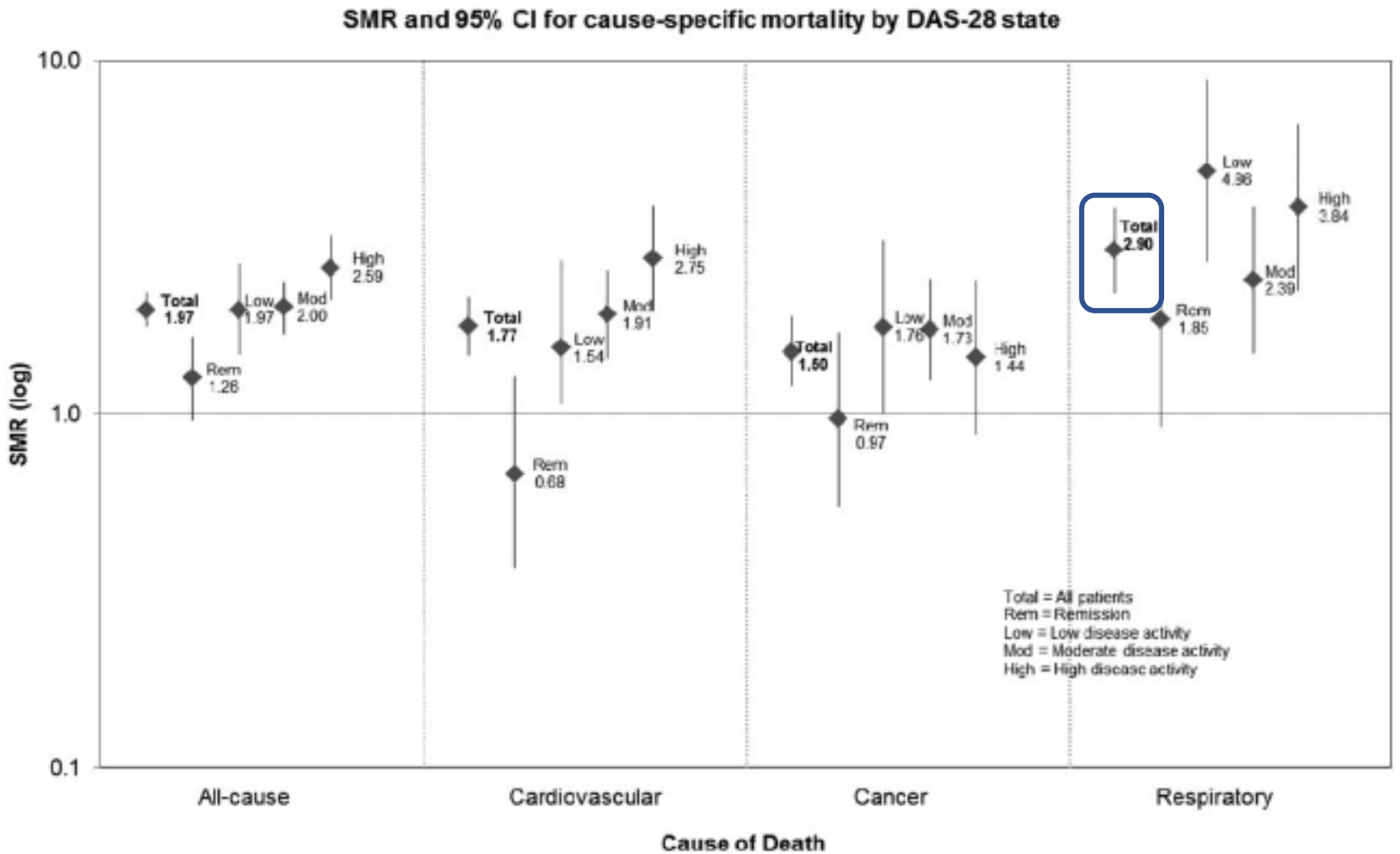




Sparks JA, *et al, Arthritis Care Res*, 2016

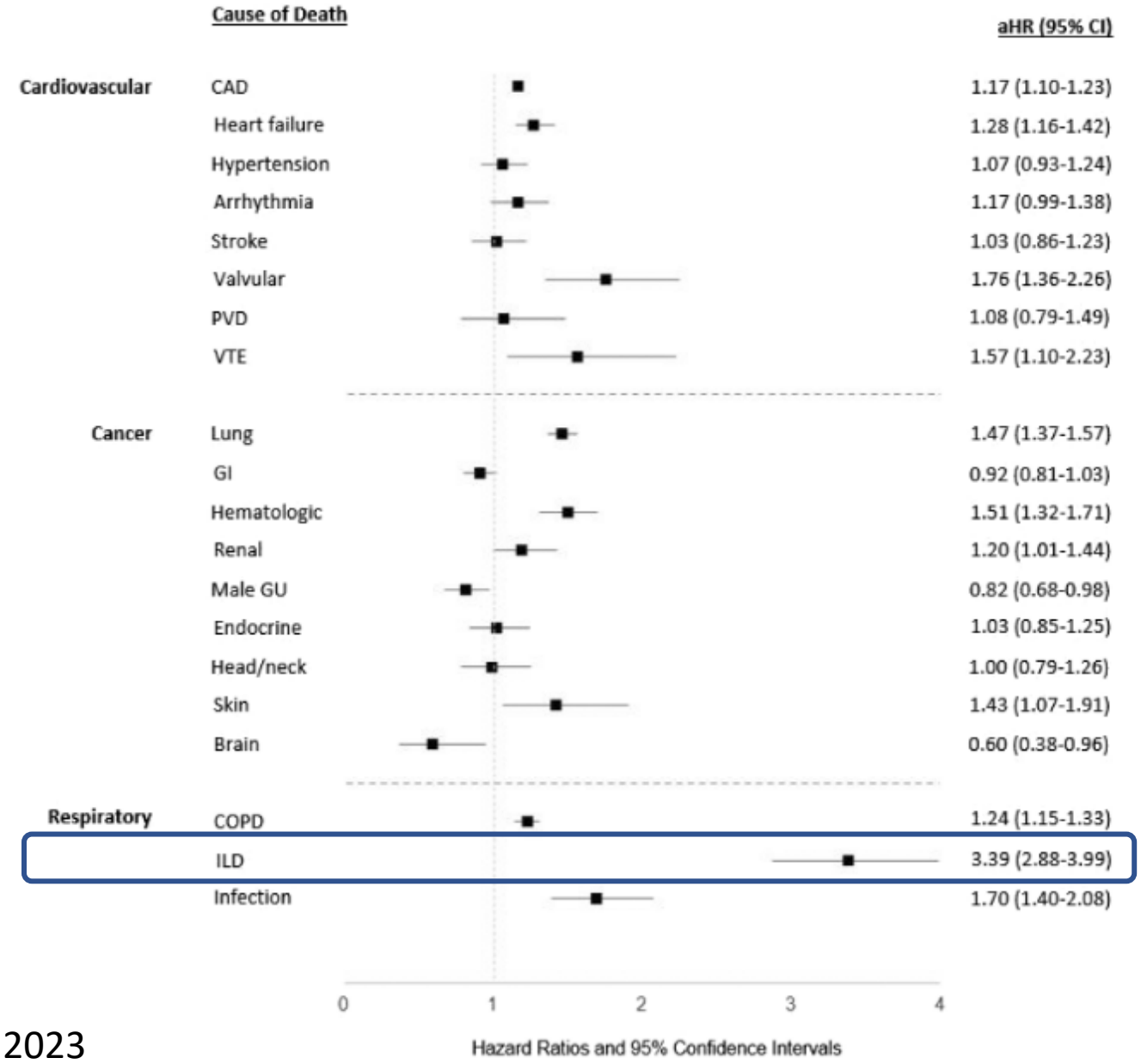
Respiratory burden of RA

- Total and cause-specific mortality among male US veterans



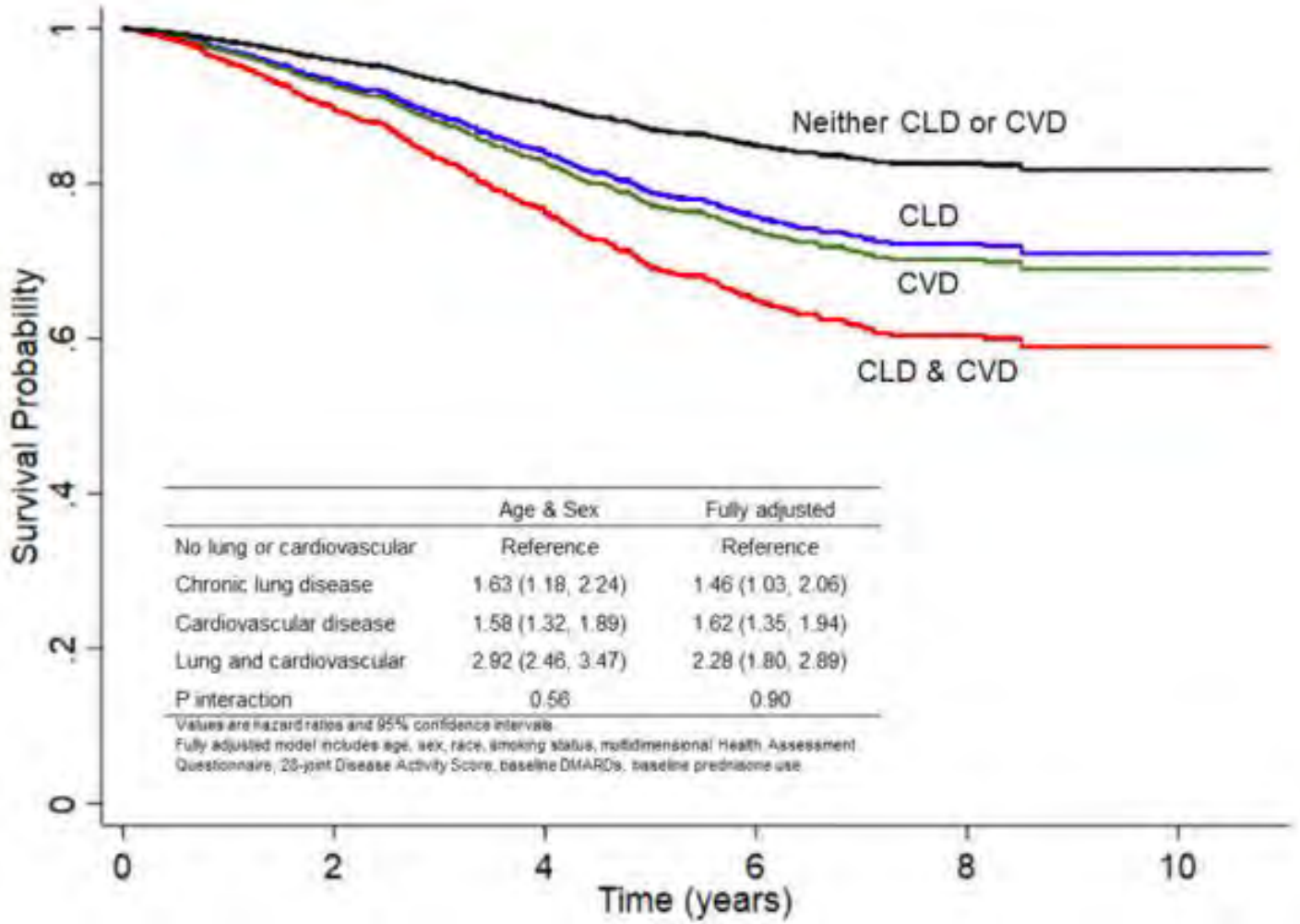
England BR, *et al, Arthritis Care Res*, 2016

RA and cause-specific mortality



Johnson T, *et al, Arthritis Care Res*, 2023

Chronic lung disease and CVD and mortality



	Age & Sex	Fully adjusted
No lung or cardiovascular	Reference	Reference
Chronic lung disease	1.63 (1.18, 2.24)	1.46 (1.03, 2.06)
Cardiovascular disease	1.58 (1.32, 1.89)	1.62 (1.35, 1.94)
Lung and cardiovascular	2.92 (2.46, 3.47)	2.28 (1.80, 2.89)
P interaction	0.56	0.90

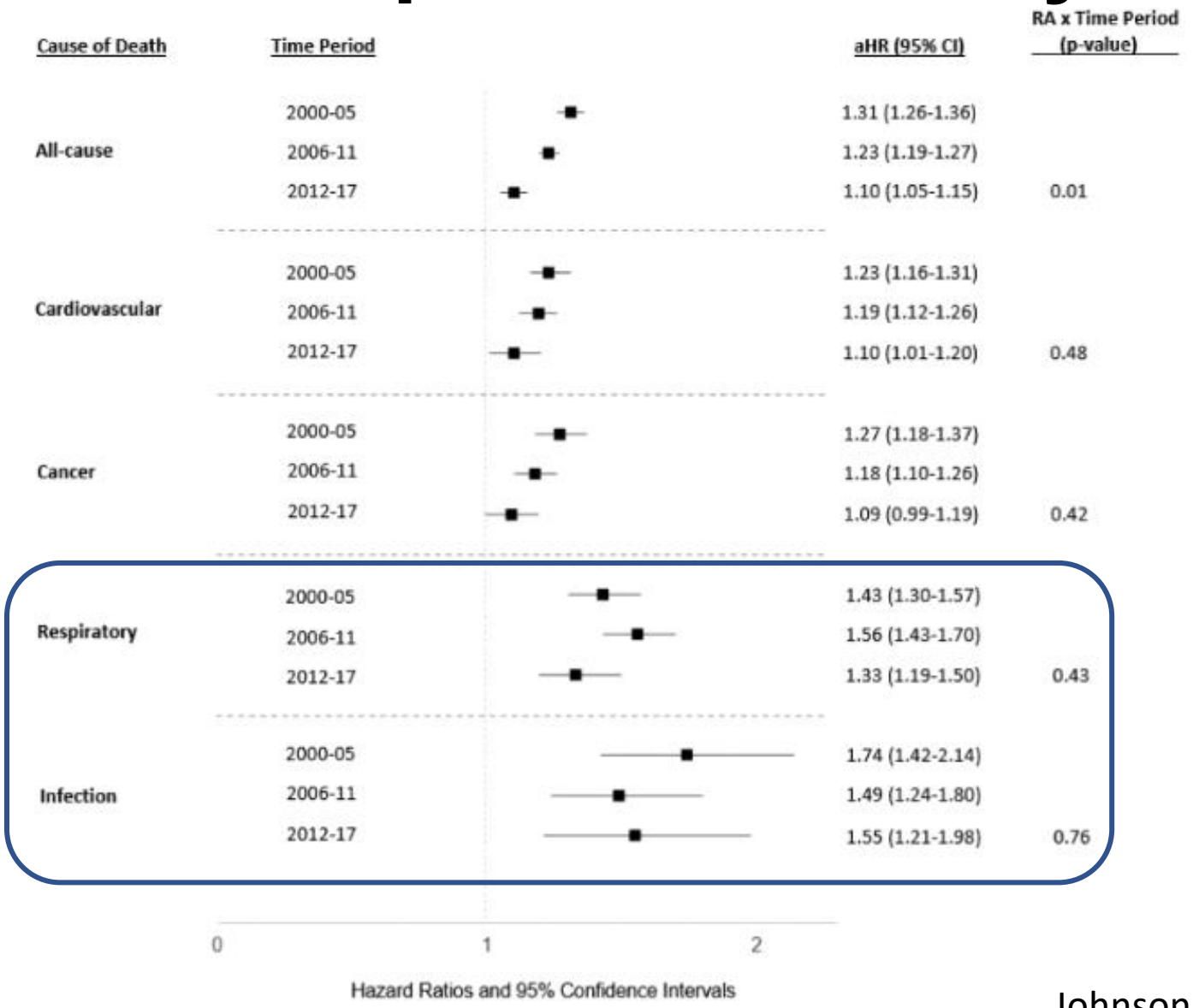
Values are hazard ratios and 95% confidence intervals
Fully adjusted model includes age, sex, race, smoking status, multidimensional Health Assessment Questionnaire, 28-joint Disease Activity Score, baseline DMARDs, baseline prednisone use

Frequency of specific chronic lung disease comorbidities (N = 2,053).

Lung disease	N	% of Patients
Any HCUP-CCS chronic lung disease	554	27.0
HCUP-CCS, COPD and bronchiectasis	301	14.7
HCUP-CCS, asthma	62	3.0
HCUP-CCS, lung disease due to external agents	2	0.1
HCUP-CCS, other lower respiratory disease†	330	16.1
Physician entered, ILD‡	106	5.2
Physician entered, COPD	371	18.1

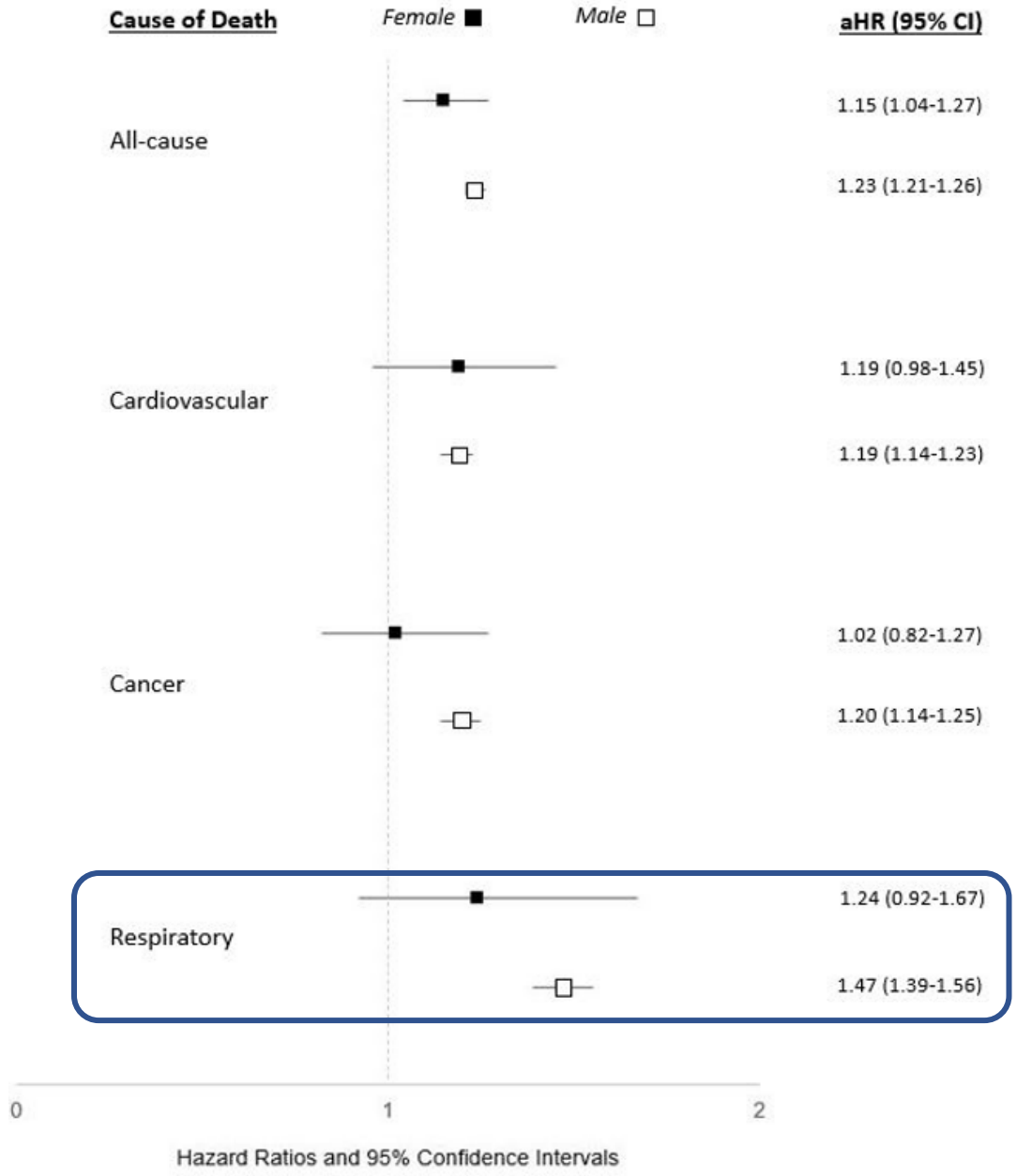
England BR, *et al, Clin Rheumatol,* 2018

RA and cause-specific mortality over time



Johnson T, *et al, Arthritis Care Res*, 2023

RA and cause-specific mortality by sex



Johnson T, *et al, Arthritis Care Res*, 2023

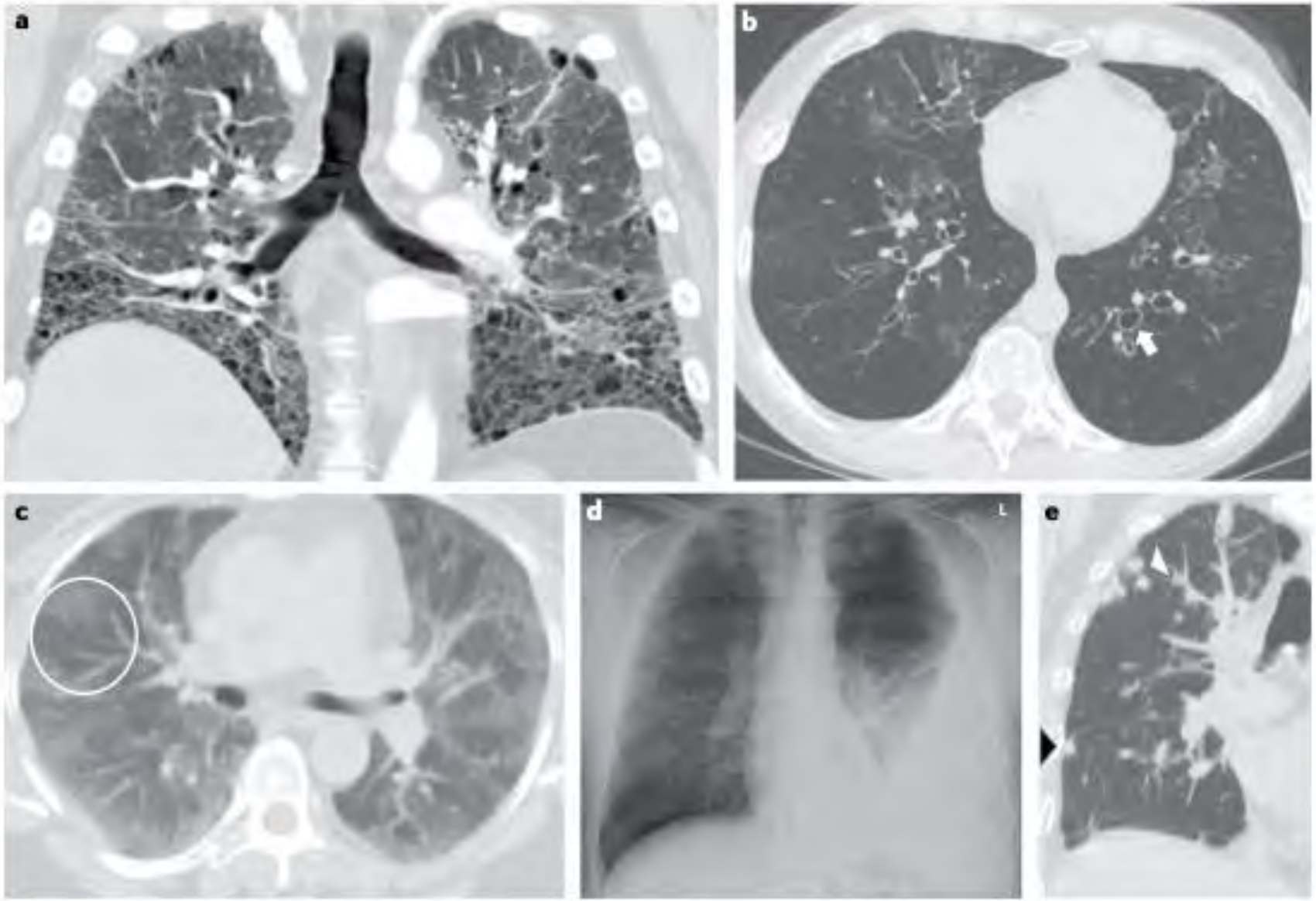
Differential diagnosis of dyspnea

- RA-related
  - ILD
  - Bronchiectasis/airways
  - Pleuritis
  - Vasculitis
  - Nodules
- Deconditioning
- Obesity
- GERD/aspiration
- Infection
- Smoking/inhalant-related
- Silicosis/berylliosis
- Reactive airways disease
- COPD
- Asthma
- Cancer
- Drug-induced pneumonitis
- Hypersensitivity pneumonitis
- Pulmonary hypertension
- Clinically insignificant radiologic abnormality
- Venous thromboembolism
- Respiratory muscle weakness
- Heart failure/CAD
- Many others

GERD = Gastroesophageal reflux disease; COPD = chronic obstructive pulmonary disease; CAD = Coronary Artery Disease

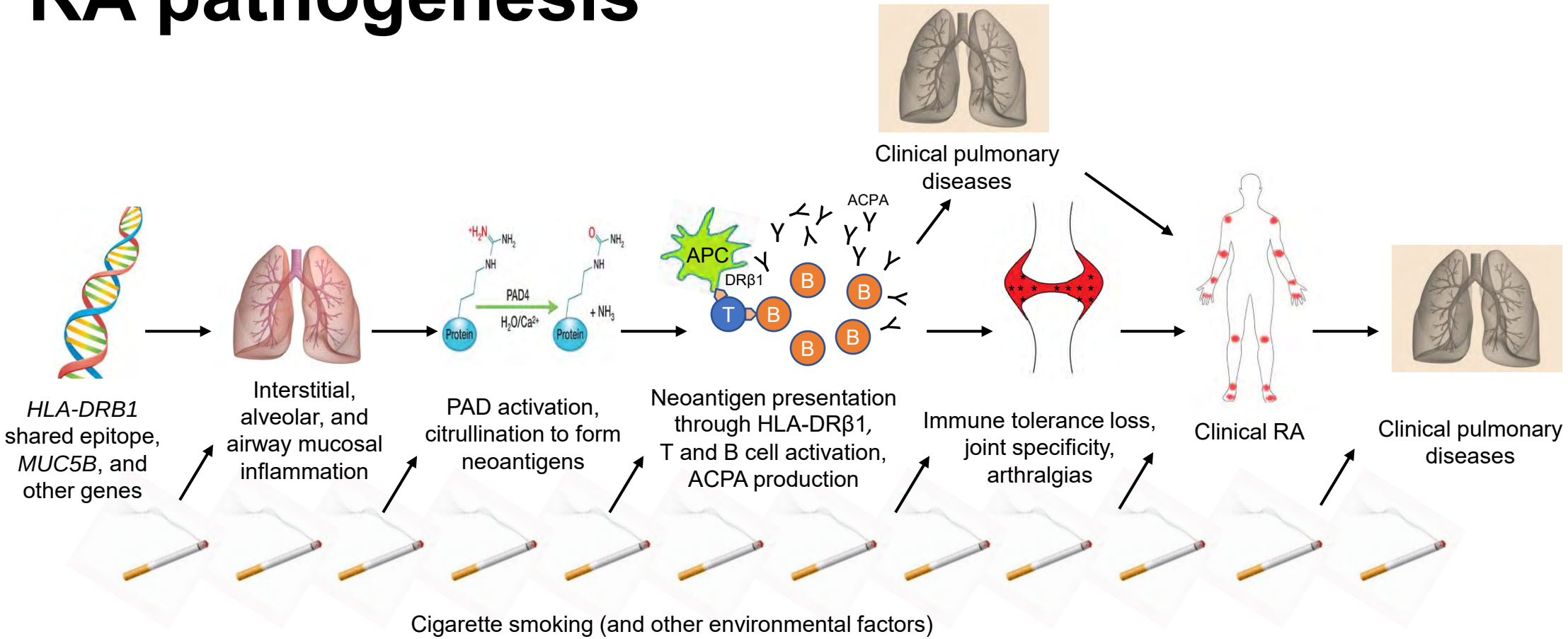
Parshall MB, et al. *Am J Respir Crit Care Med.* 201

a. Advanced RA-ILD
b. Bronchiectasis
c. Obliterative bronchiolitis
d. Pleural effusion
e. Rheumatoid pulmonary nodules



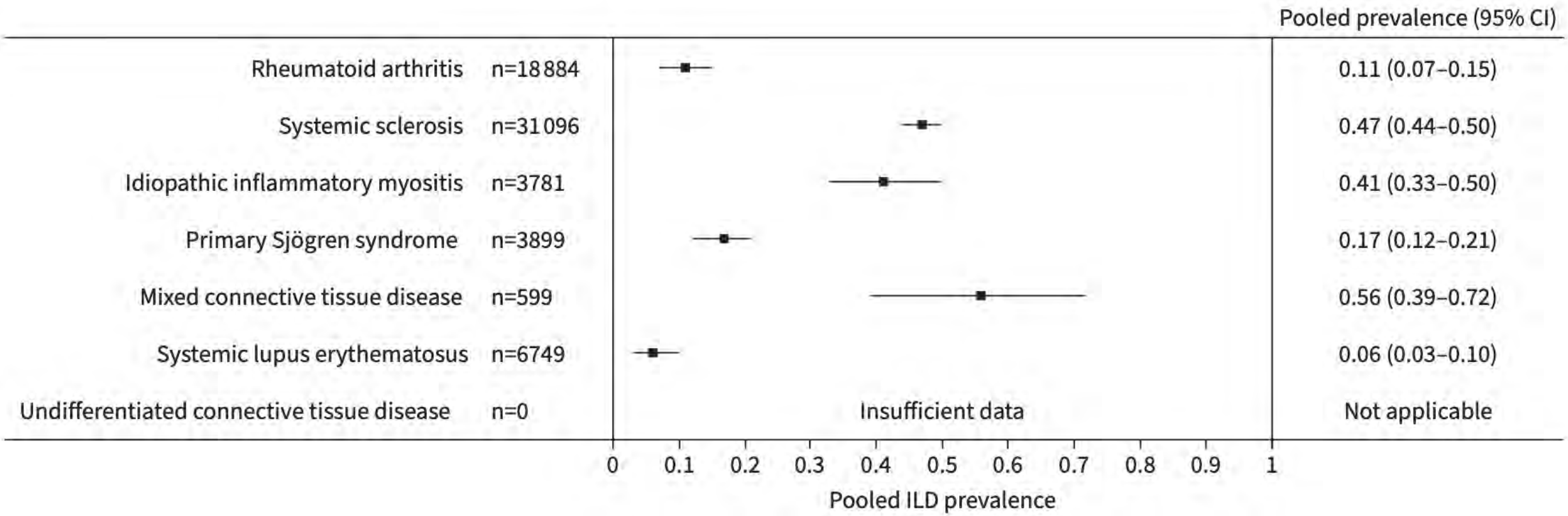
Wang D, et al. *Nat Rev Rheumatol.* 2019

ACPA elevation, lung inflammation, and RA pathogenesis



Sparks JA, et al. *Curr Rheumatol Rep.* 2016

ILD prevalence in rheumatic diseases



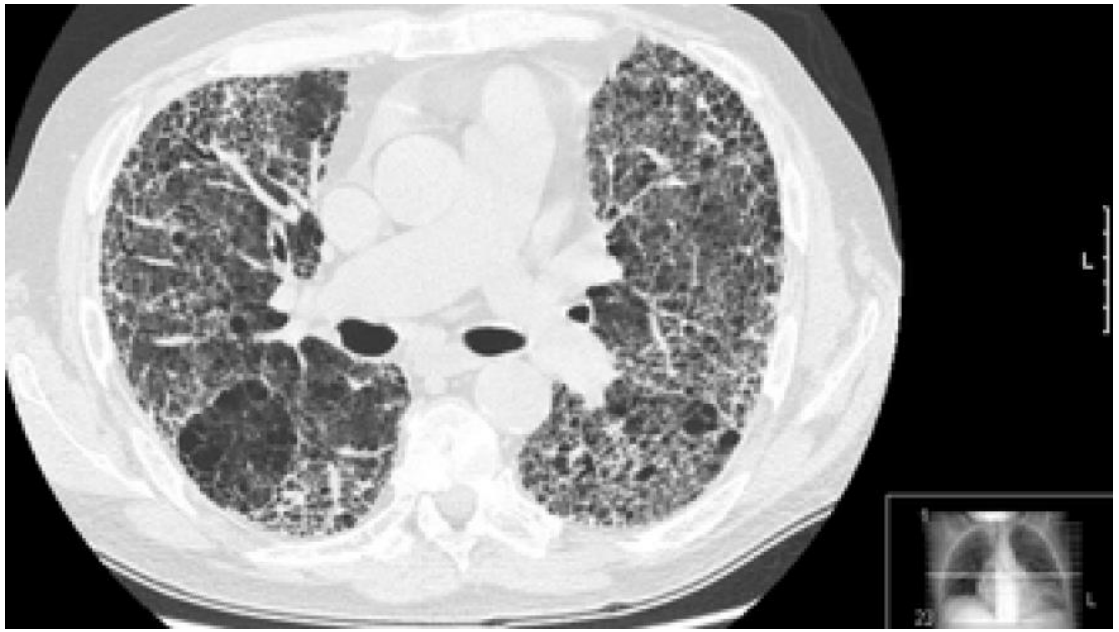
Joy GM, et al. *Eur Respir Rev,* 2023

RA-ILD subtypes

RA-ILD subtypes	Proportion of RA-ILD	
Usual Interstitial PNA (**UIP**)	50-60%	***Fibrotic***
Nonspecific Interstitial PNA (**NSIP**) -Cellular NSIP -Fibrotic NSIP	30-40%	***Inflammatory***
Desquamative Interstitial PNA (**DIP**) -Smoking-related	2-5%	
Respiratory Bronchiolitis (**RB**)	2-5%	
Diffuse Alveolar Damage (**DAD**)	2-5%	
Organizing PNA (**OP**)	2-5%	
Lymphoid Interstitial PNA (**LIP**)	2-5%	

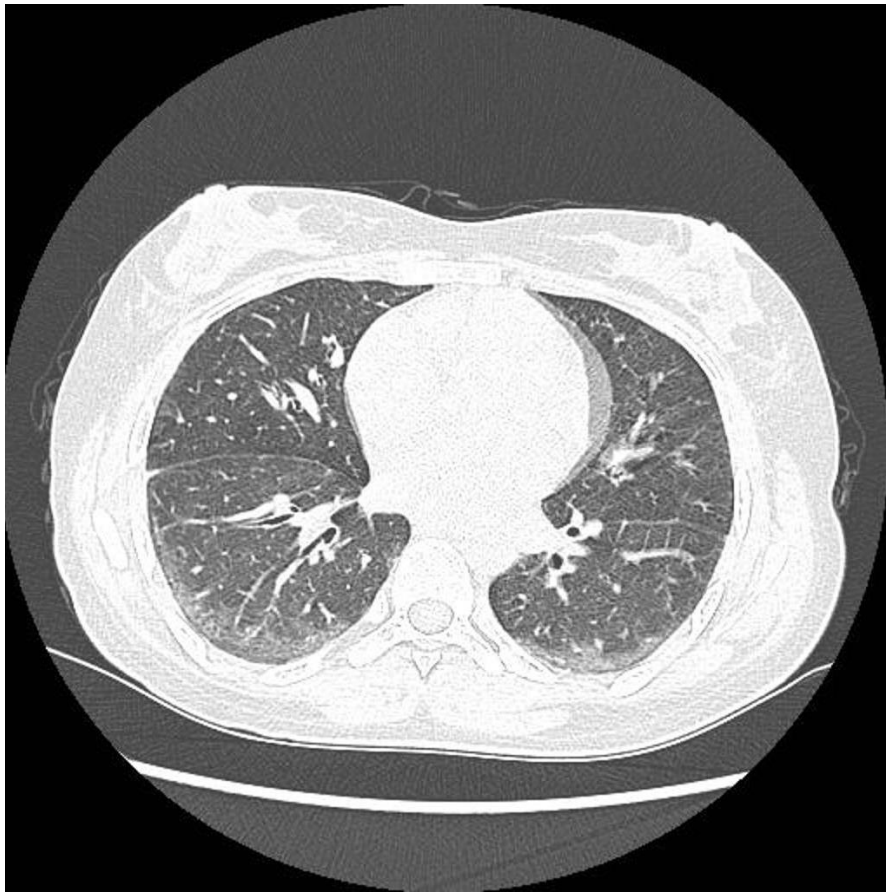
Consider smoking, inhalants, GERD, infection, malignancy, overlap syndromes
Lung biopsy sometimes needed for ambiguous CT chest imaging

UIP



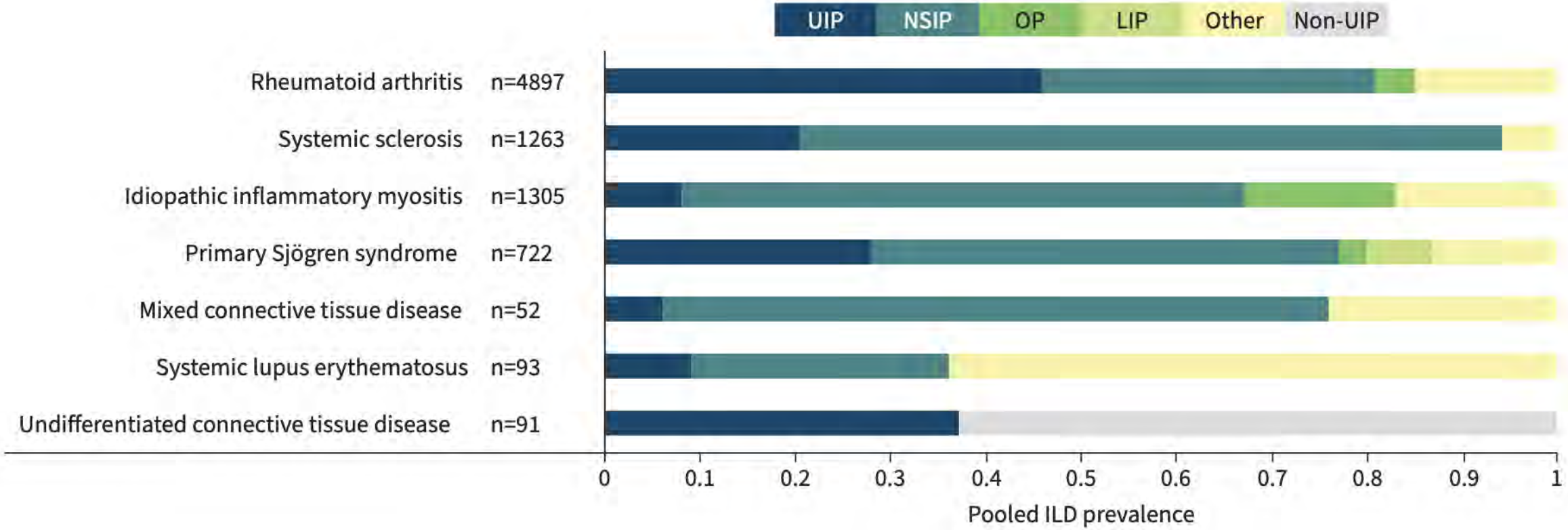
- Scarring
- Reticulation
- Mosaicism
- Traction bronchiectasis
- Honeycombing

NSIP



- Ground-glass opacities
- Lower lobe volume loss
- Reticulonodular opacities

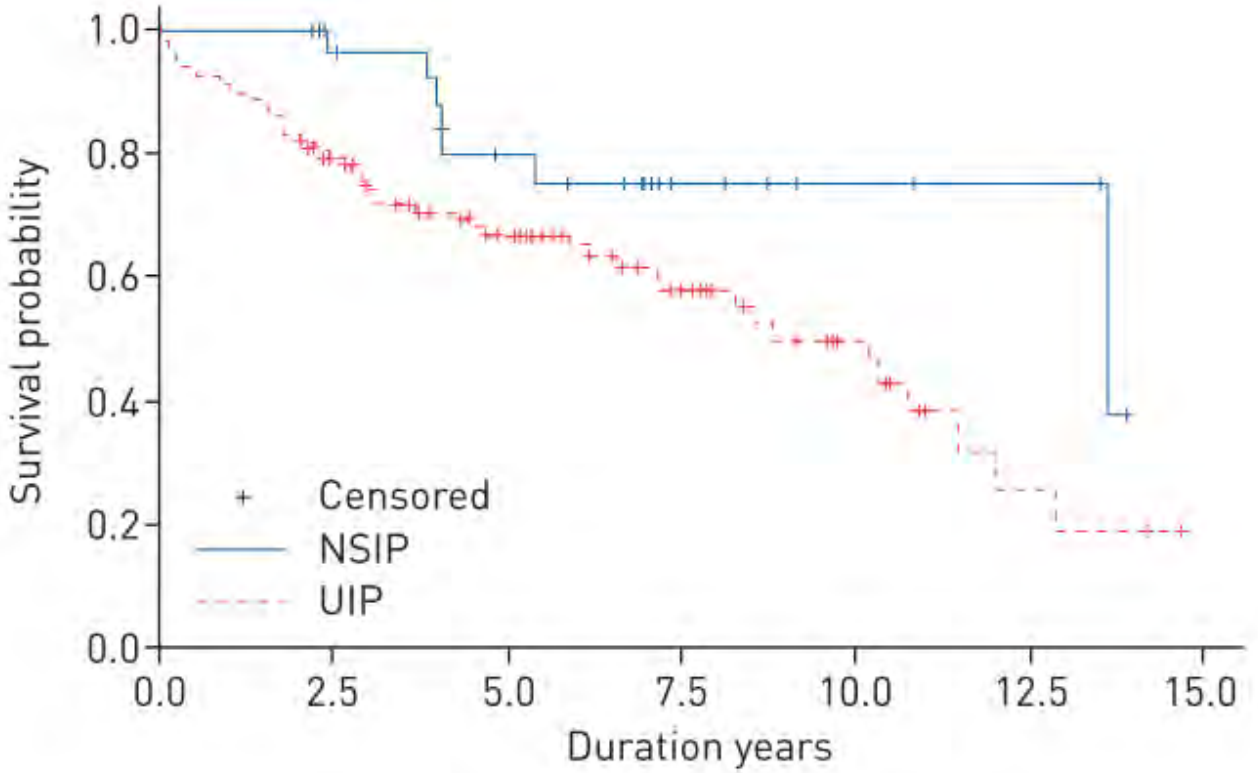
UIP is more common in RA than other SARDs



Joy GM, et al. *Eur Respir Rev,* 2023

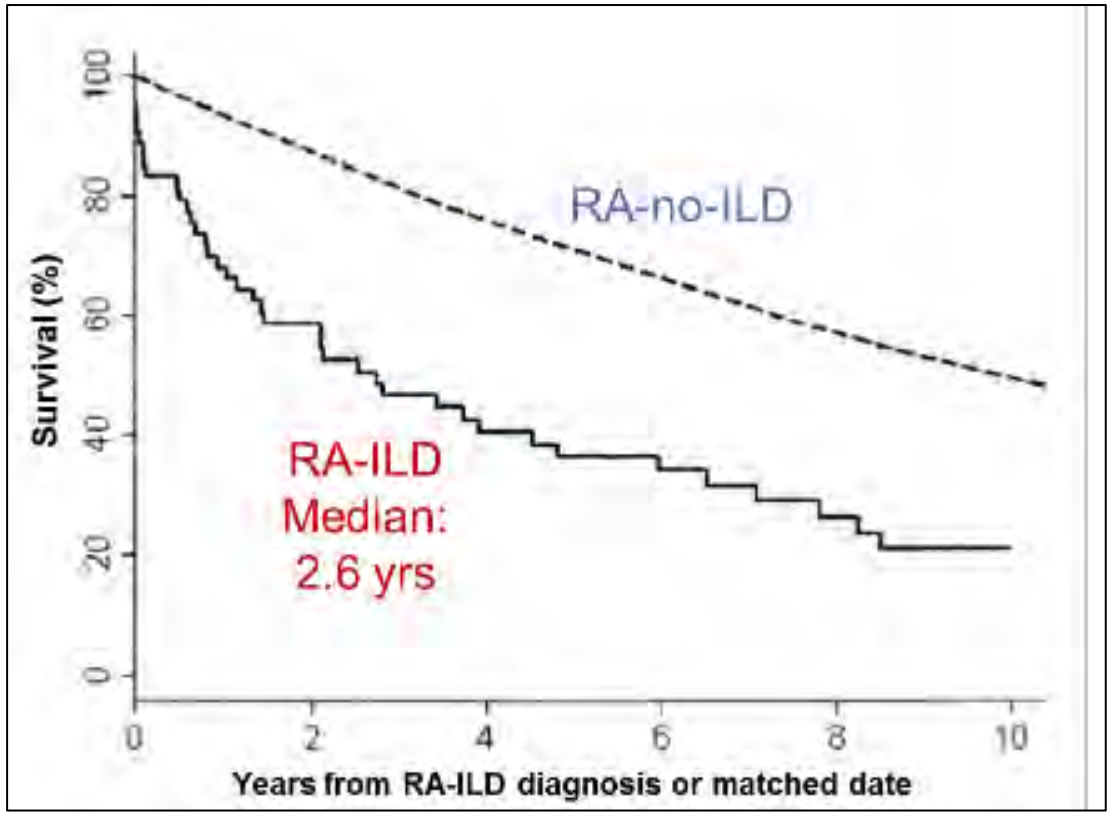
UIP prognosis

- UIP: 3-fold higher risk for progression by DLCO (<40% predicted) than NSIP
- UIP: 66% increased risk for mortality compared to other subtypes
    - Note: DAD is uncommon, but highly lethal

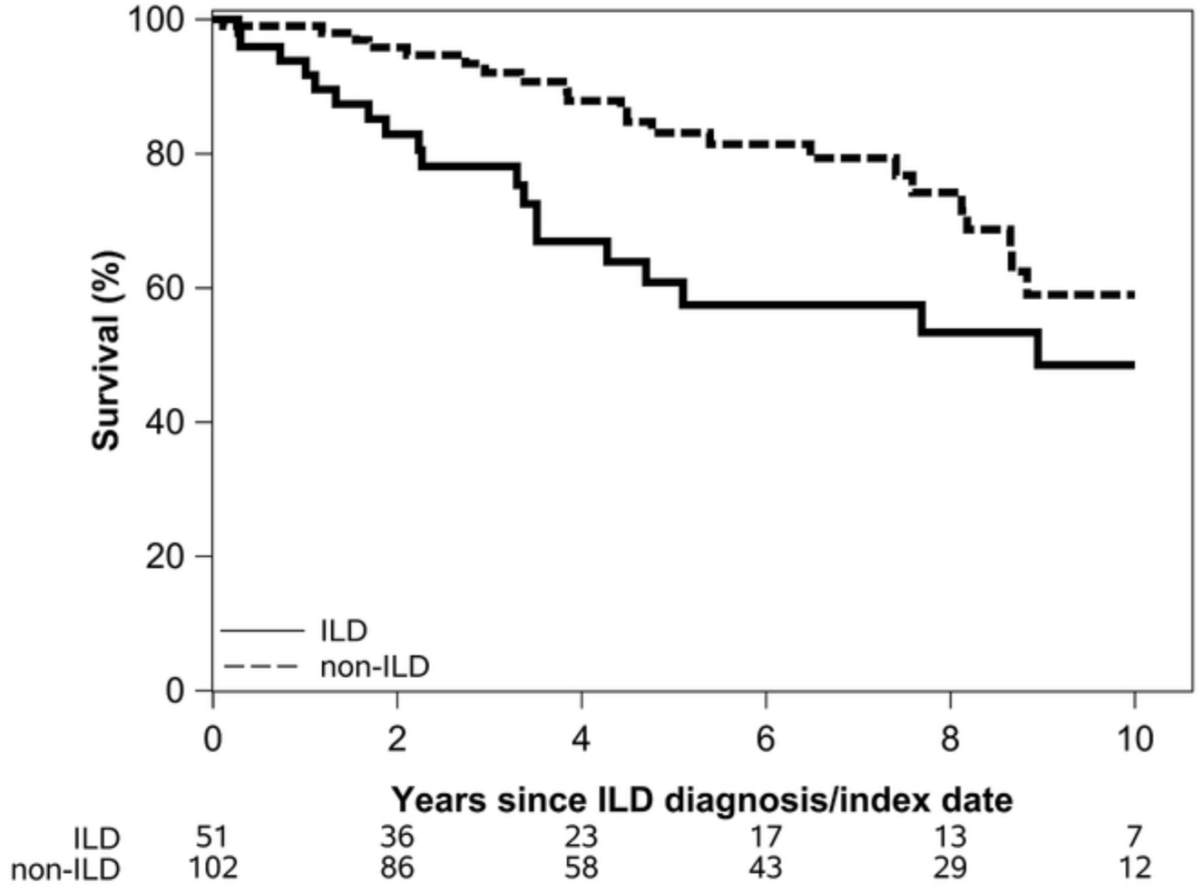


Zamora-Legoff JA, *et al, Arthritis Rheumatol*, 2017
Singh N, *et al, Semin Arthritis Rheum*, 2019

RA-ILD survival in Olmsted County, MN



Incidence 1955-1995; followed to 2006



Incidence 1999-2014; followed to 2019

Bongartz T, *et al, Arthritis Rheum*, 2010
Samhouri BF, *et al, Arthritis Care Res*, 2022

RA-ILD in Medicare

- Retrospective cohort study (2008-2017)
- Claims definitions of RA and RA-ILD (both validated)

- Among 509,787 RA patients, 10,306 (2.0%) had prevalent RA-ILD
- 13,372 (2.6%) developed incident RA-ILD during 1,873,127 person-years of follow-up (median 3.0 years/person; IR 7.14 per 1000 person-years)
  - Nearly 5% had or developed RA-ILD

- 38.7% of RA-ILD died compared to 20.7% of RA without ILD (HR 1.66)
- RA-ILD had excess respiratory (HR 4.39) and cancer (HR 1.56) mortality

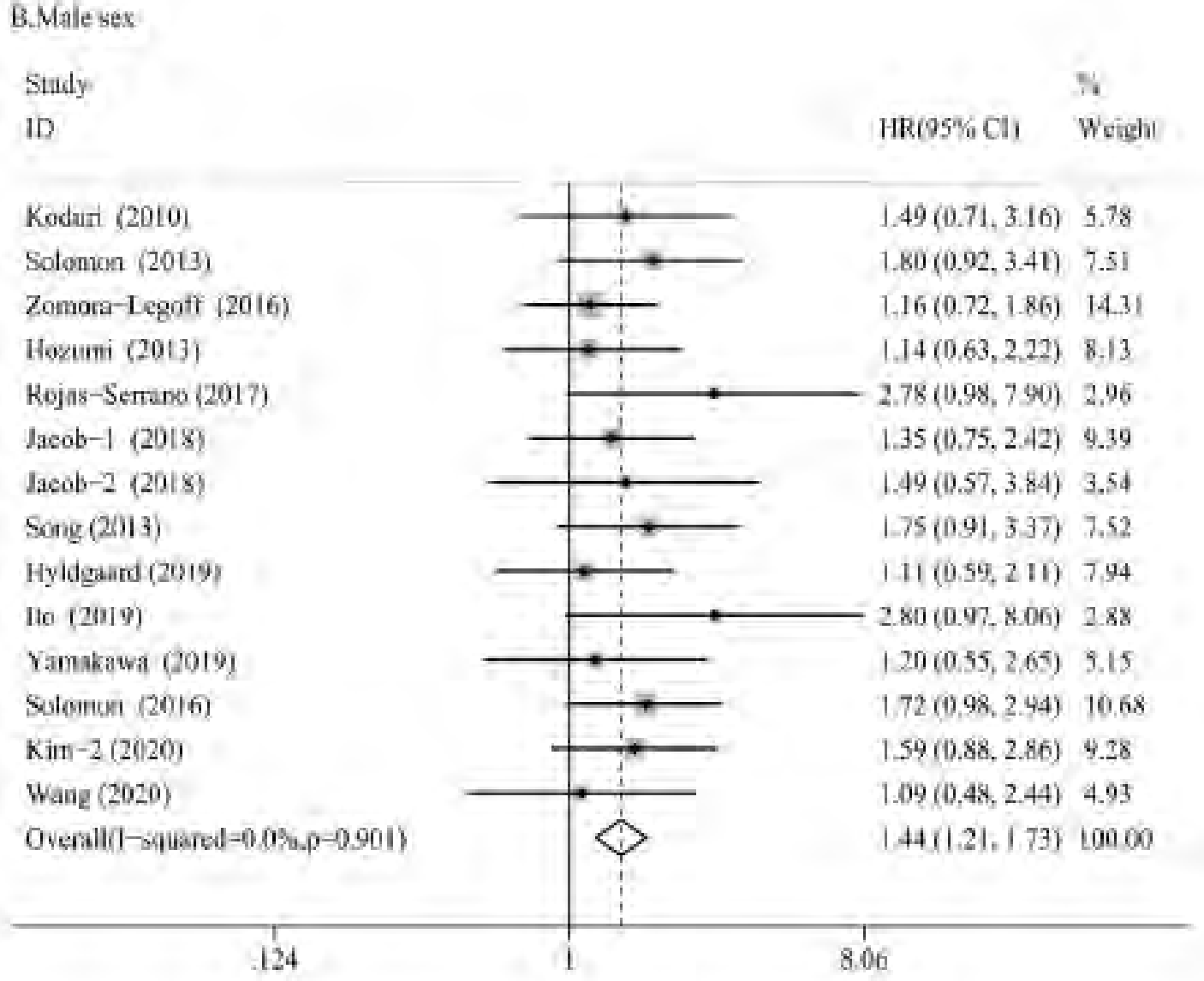
Sparks JA, *et al, Rheumatology*, 2021

RA-ILD risk factors

- Demographics
  - Male sex
- Genetics: *MUC5B* promoter variant
- Lifestyle
  - Smoking
  - Obesity
- Comorbidities
  - Asthma
  - COPD
- RA characteristics
  - Older age at RA diagnosis
  - Longer RA duration
  - Articular disease activity
  - Higher CRP
  - Worse MHAQ scores
  - High RF and ACPA titers

Esposito AJ, *et al, Clin Chest Med,* 2019
Sparks JA, *et al, Arthritis Rheumatol*, 2019
Huang S, *et al, Curr Treat Opt Rheumatol*, 2020
Kronzer V, *et al, J Rheumatol*, 2020
Sparks JA, *et al, Rheumatology*, 2020

Sex and RA-ILD mortality

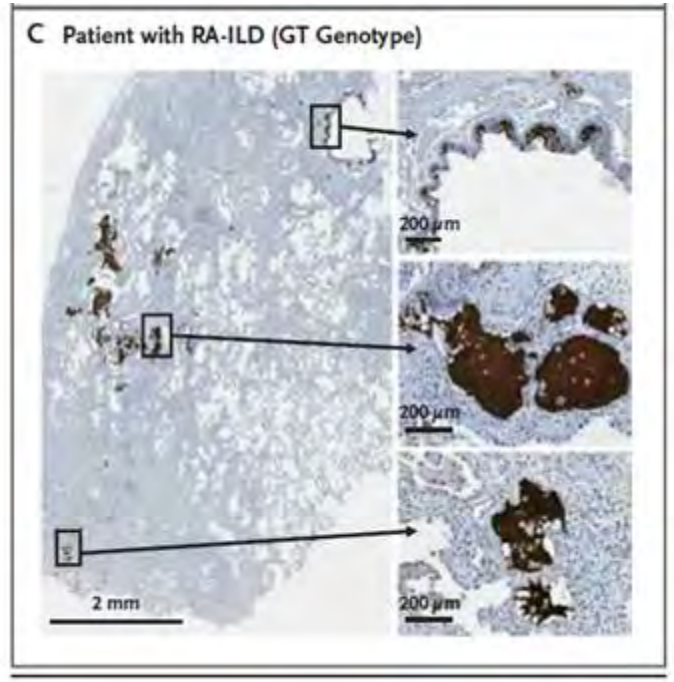


Qiu M, *et al, Respir Res*, 2021

MUC5B: RA-ILD genetic risk factor

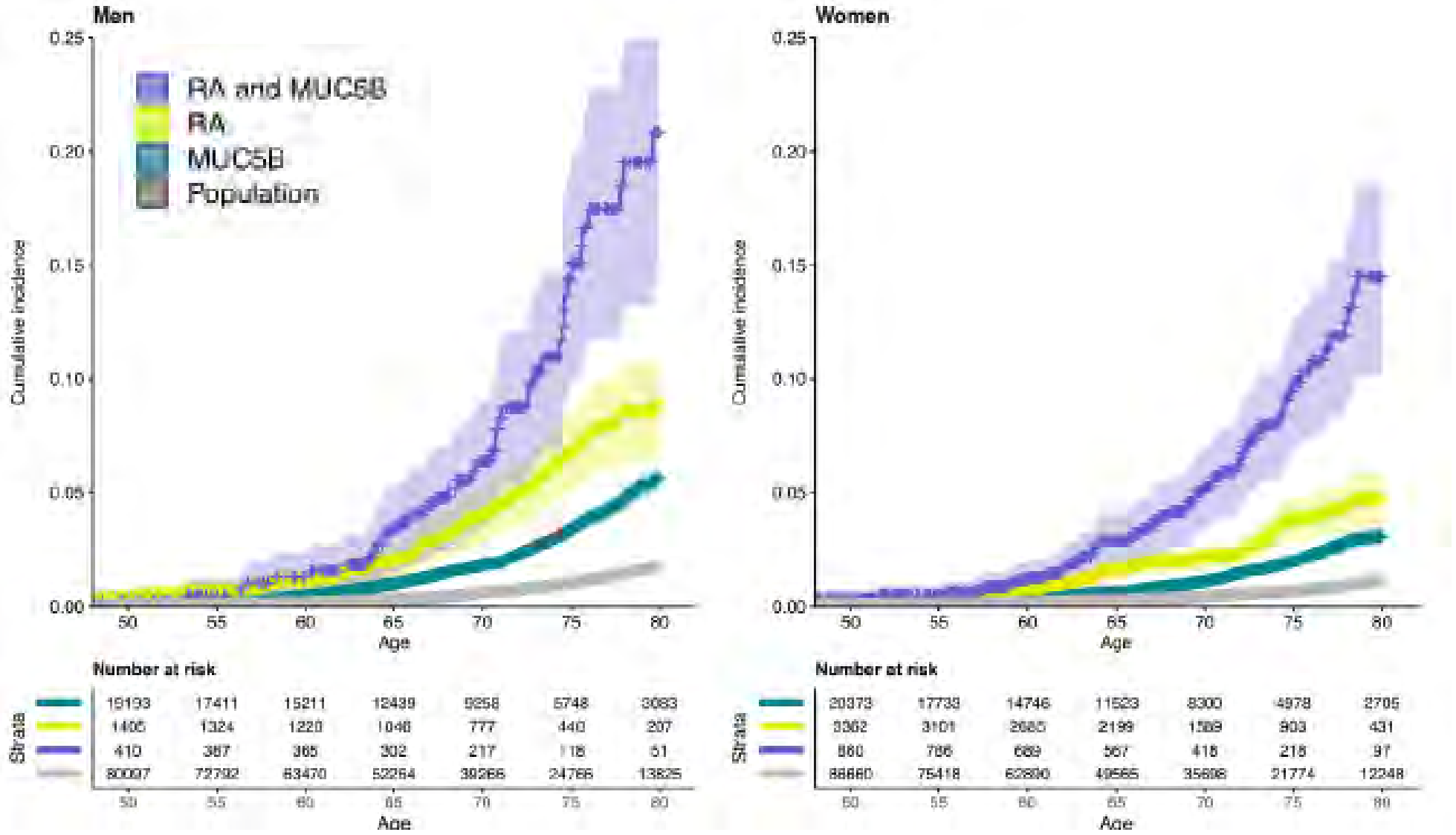
- Promoter variant: strongest genetic risk factor for IPF
  - T risk allele associated with higher expression of mucin 5B
- Presence of promoter variant and ORs for RA-ILD
    - 4.7 compared to general population
    - 3.1 compared to RA-no-ILD

- Specifically associated with <u>UIP subtype of RA-ILD</u>
- Honeycombed lung tissue with RA-ILD overexpressed MUC5B
- Also associated with:
  - ILD earlier in RA course
  - Older-onset RA



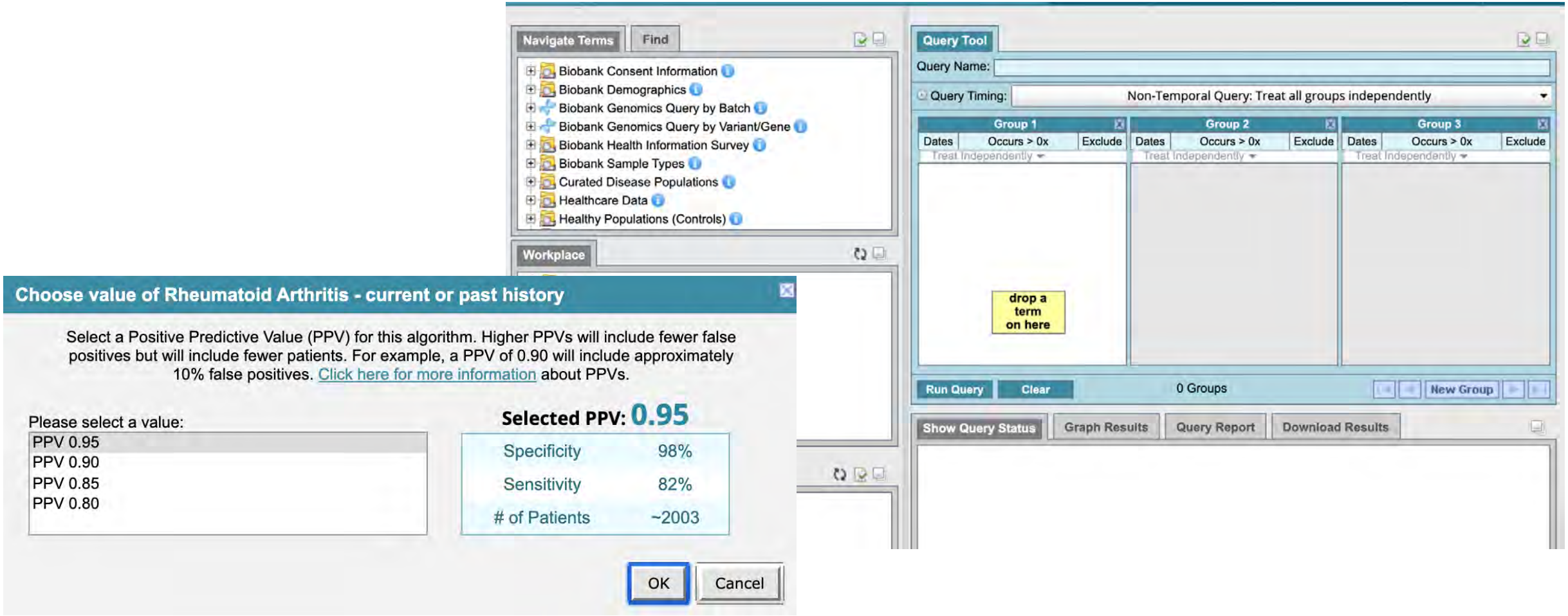
Juge PA, *et al, N Engl J Med*, 2018
McDermott G, *et al, Rheumatology*, 2022

Lifetime risk of ILD by RA/sex/*MUC5B*



Palomaki A, *et al, Ann Rheum Dis*, 2021

IDENTIFICATION OF RA IN MGB BIOBANK



Welcome to the Biobank Portal | Overview

Close

Announcement

Introducing Quantitative Imaging Data

The Biobank Portal now offers Quantitative Image Data for querying. These are metrics derived from medical images using automated and/or semi-automated machine learning (ML) algorithms. The new folder can be found in the *Navigate Terms* section on the left. Read More...

Quick Start: Perform advanced search queries! Click an example below to load it.

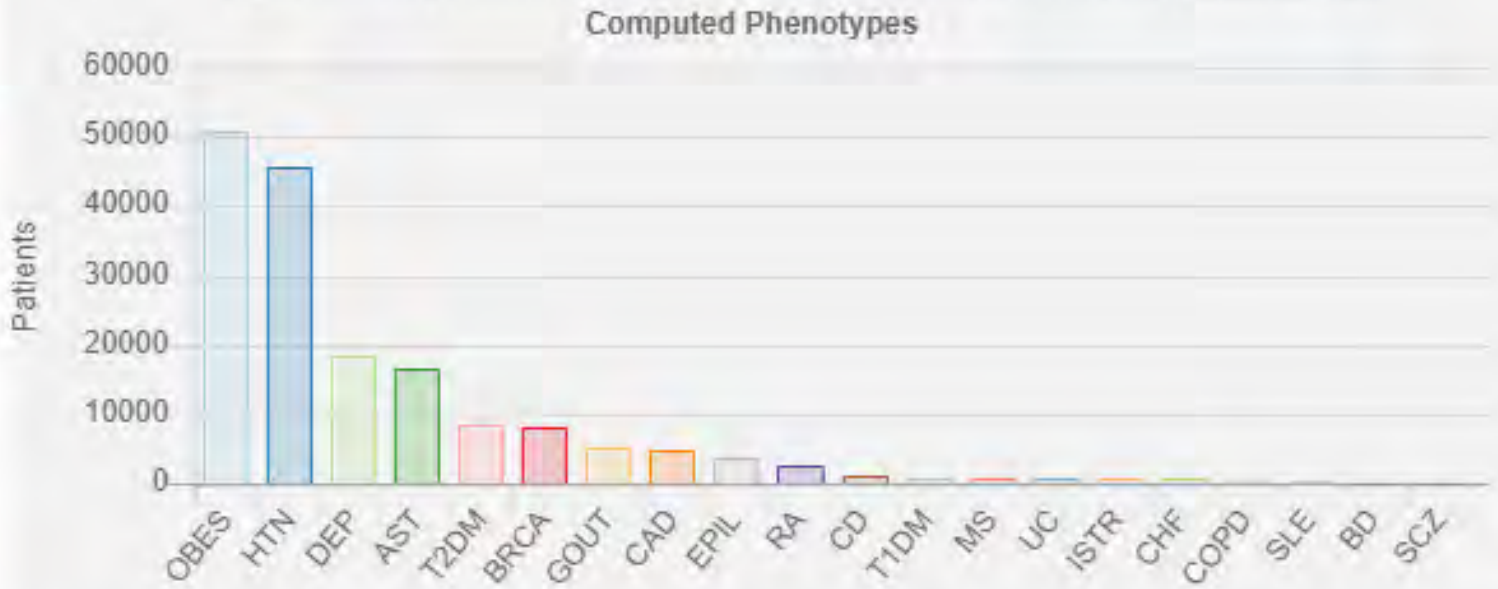
- Healthy males between 20 and 49 years old
- Genotyped patients with HBA1C > 6.5% in 2015
- Hispanics with plasma or serum samples and hypertension (PPV 0.90)

Additional Resources:

- Step-by-Step Tutorial
- Biobank Portal Wiki Site
- Contact Us

Data last updated on 04/16/2024

Current Data: Computed Phenotypes | Computed Phenotypes with Genotype Data
Age | Gender | Ethnicity | Race | Vital Status | BMI | Consent site | Consent year

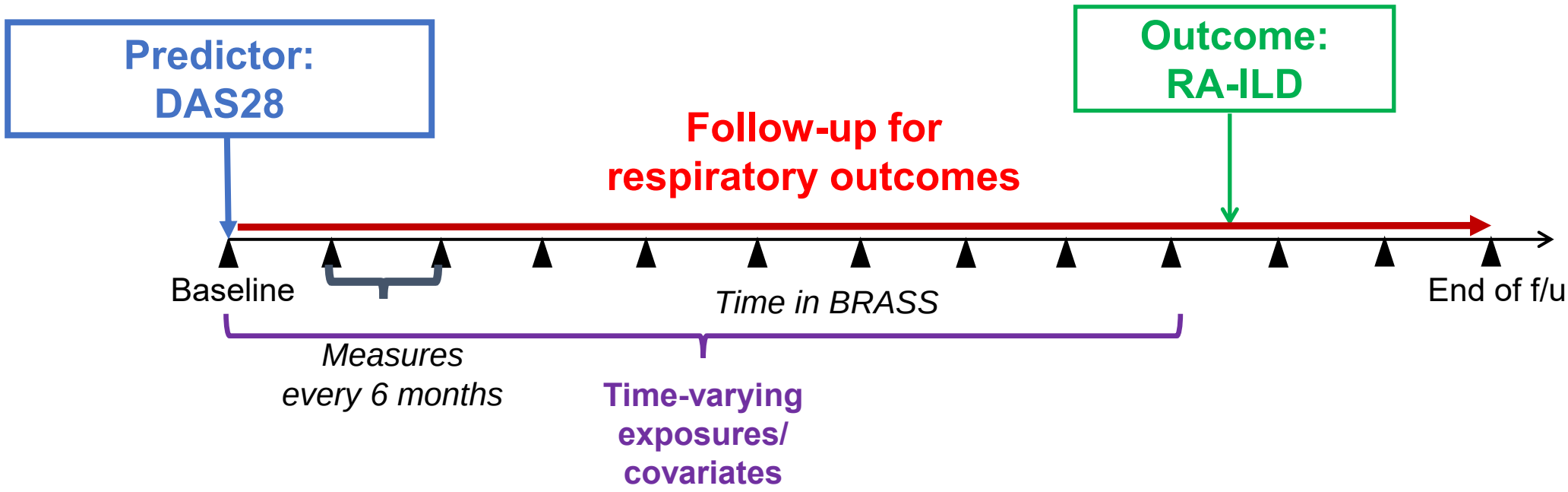


CONSENTED SUBJECTS	BIOBANK SAMPLES	GENOMIC DATA	COMPUTED PHENOTYPES	HEALTH SURVEYS
148,786	100,289	65,568	20	70,505
▲156 since last week				

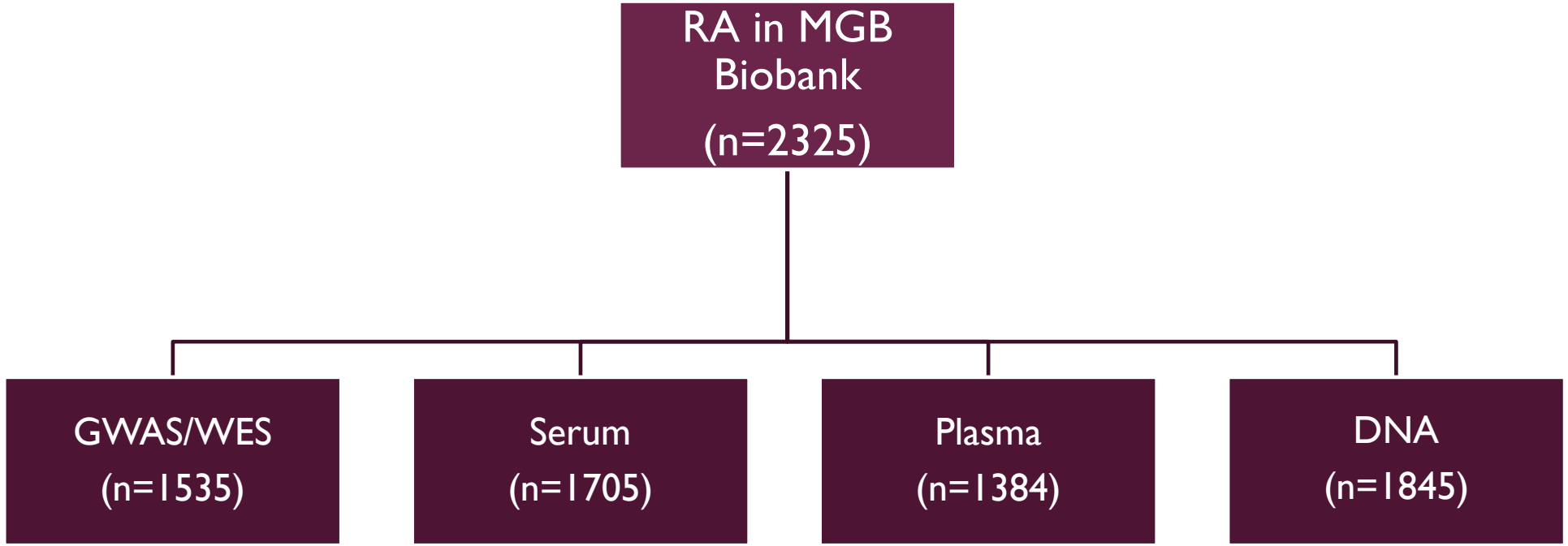
BRASS
Brigham and Women's Hospital
Rheumatoid Arthritis Sequential Study.

Prospective RA recruitment: BRASS (n = 1,600)

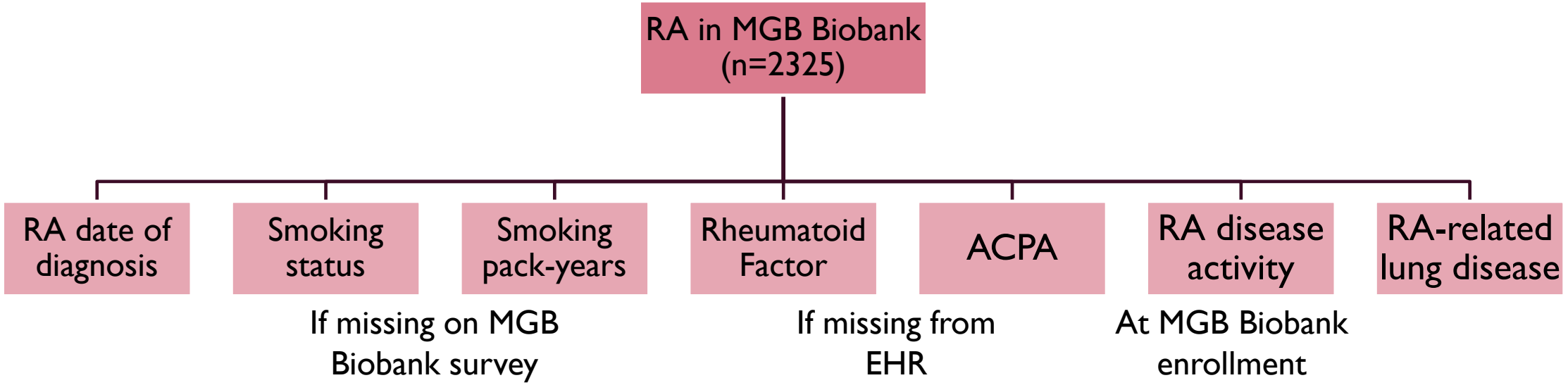
Up to 15 years of follow-up / recruitment ongoing



RA IN THE MGB BIOBANK



DATA COLLECTION BY MEDICAL RECORD REVIEW



RA patients with available CT chest imaging or pathology

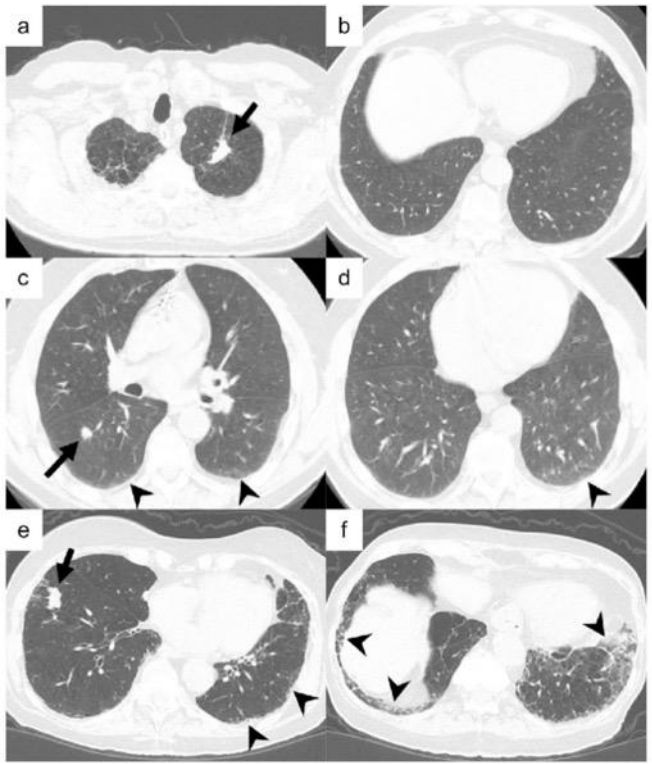
Radiology Reviews

Medical Record Reviews

Well-Phenotyped RA Patient Population

(+/- RA-related lung diseases)

Hida, 2021



Bongartz, 2010

Table 1. Classification criteria for ILD in RA*

Probable ILD	Chest radiography/CT report containing terms such as "pulmonary fibrosis," "fibrotic changes," "fibrosis," "RA-lung," "fibrosing alveolitis," and presence of nonspecific abnormalities that can be observed in ILD *and* Treating physician's diagnosis of "pulmonary fibrosis," "RA-lung," "fibrosing alveolitis," or other terms in the medical record consistent with ILD
Definite ILD	Diagnosis of ILD by a pulmonologist *and* Two of the following 3 criteria: ILD observed on CT or chest radiograph Restrictive pattern observed on PFT (TLC ≤80% predicted) Bronchoscopic or surgical lung biopsy results consistent with ILD

* ILD = interstitial lung disease; RA = rheumatoid arthritis; CT = computed tomography; PFT = pulmonary function testing; TLC = total lung capacity.

Phenotyping RA-ILD + subtypes in MGB Cohorts

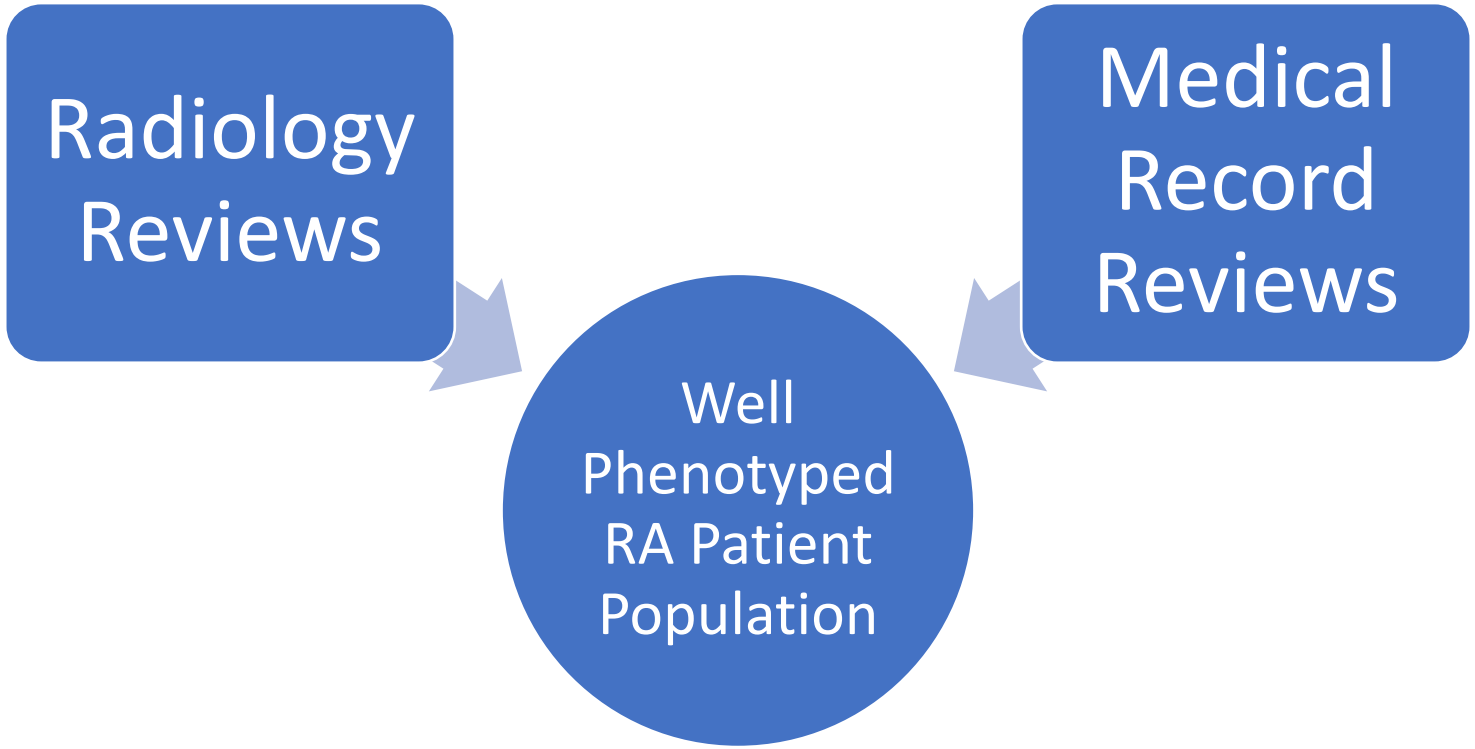
MGB Biobank

n=2325 RA patients

Biobank RA algorithm
ICD codes
Overlapping with other cohorts (BRASS, Prod4)

n=866 with CT chest imaging
n=197 with surgical lung pathology

Confirmed by clinical chart review



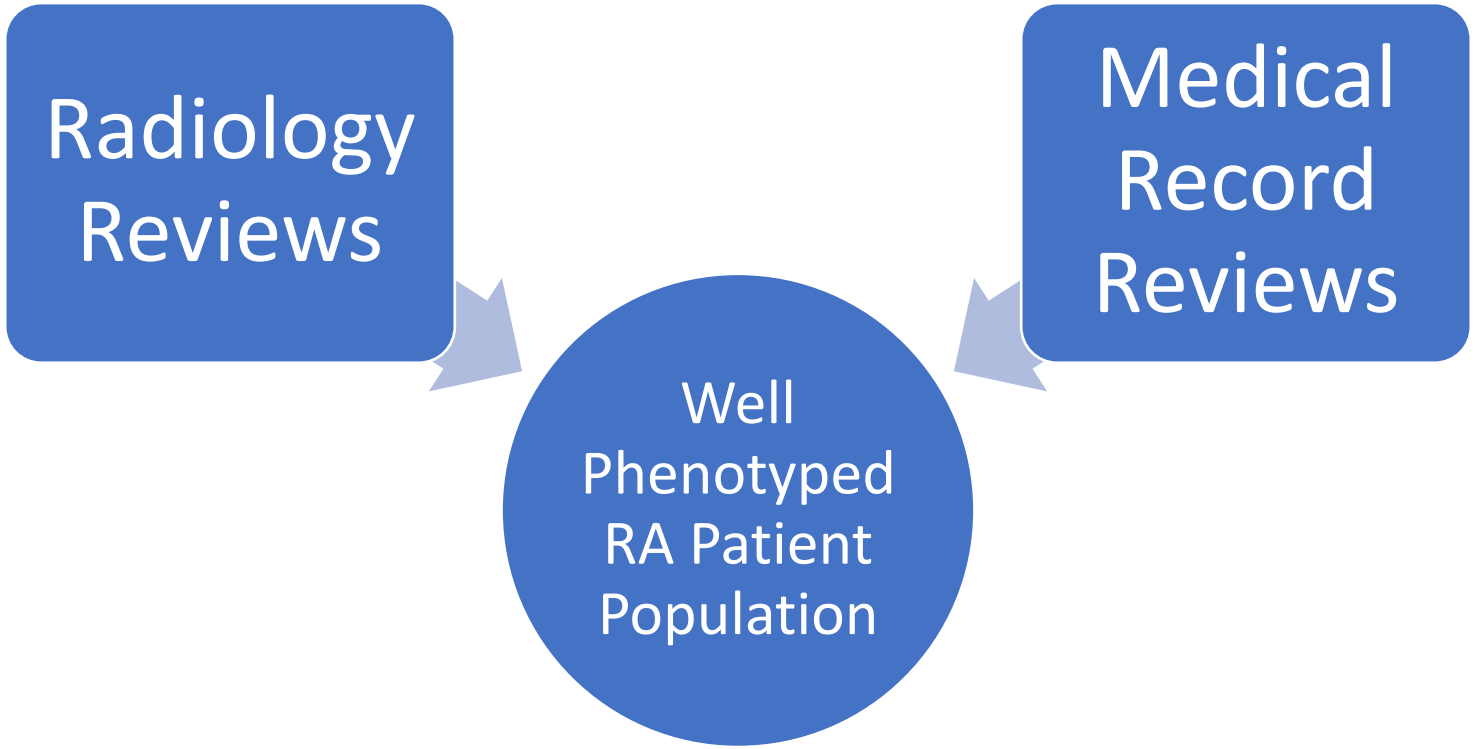
(with and without RA-related lung diseases)
(genotyping and/or WES)

Phenotyping RA-ILD + subtypes in MGB Cohorts

BRASS

n=1598 RA patients

n=410 with CT chest imaging
n=43 with surgical lung pathology



(with and without RA-related lung diseases)

BRASS
Brigham and Women's Hospital
Rheumatoid Arthritis Sequential Study.

DAS28 and RA-ILD risk

	Remission/Low HR (95%CI)	Moderate/High HR (95%CI)
Cases/person-years	26/5,459	35/2,509
Multivariable*	1.00 (Ref)	**2.22 (1.28,3.82)**

*Adjusted for age, sex, smoking, RA duration, serostatus

Sparks JA, *et al, Arthritis Rheumatol*, 2019

BRASS
Brigham and Women's Hospital
Rheumatoid Arthritis Sequential Study.

4-level ordinal DAS28 and RA-ILD risk

	Remission HR (95%CI)	Low HR (95%CI)	Moderate HR (95%CI)	High HR (95%CI)	*p* for trend
Cases/person-years	18/4,232	8/1,227	20/1,828	15/681	
Multivariable*	1.00 (Ref)	1.41 (0.61,3.28)	**2.08 (1.06,4.05)**	**3.48 (1.64,7.38)**	**0.001**

	HR (95%CI) per unit increase in DAS28
Cases/person-years	61/7,968
Multivariable*	**1.35 (1.14,1.60)**

*Adjusted for age, sex, smoking, RA duration, serostatus

Sparks JA, *et al, Arthritis Rheumatol*, 2019

Lifestyle and clinical factors for RA-ILD risk

- 84 RA-ILD cases; 233 RA-noILD controls

- Sociodemographic
  - Age
  - Sex
  - Education
- Lifestyle
  - Smoking status
  - Pack-years
  - Obesity
- RA factors
  - RF status
  - CCP status
  - DAS28-CRP
  - DMARDs
  - Glucocorticoids
  - MD-HAQ
  - Erosions
  - Nodules

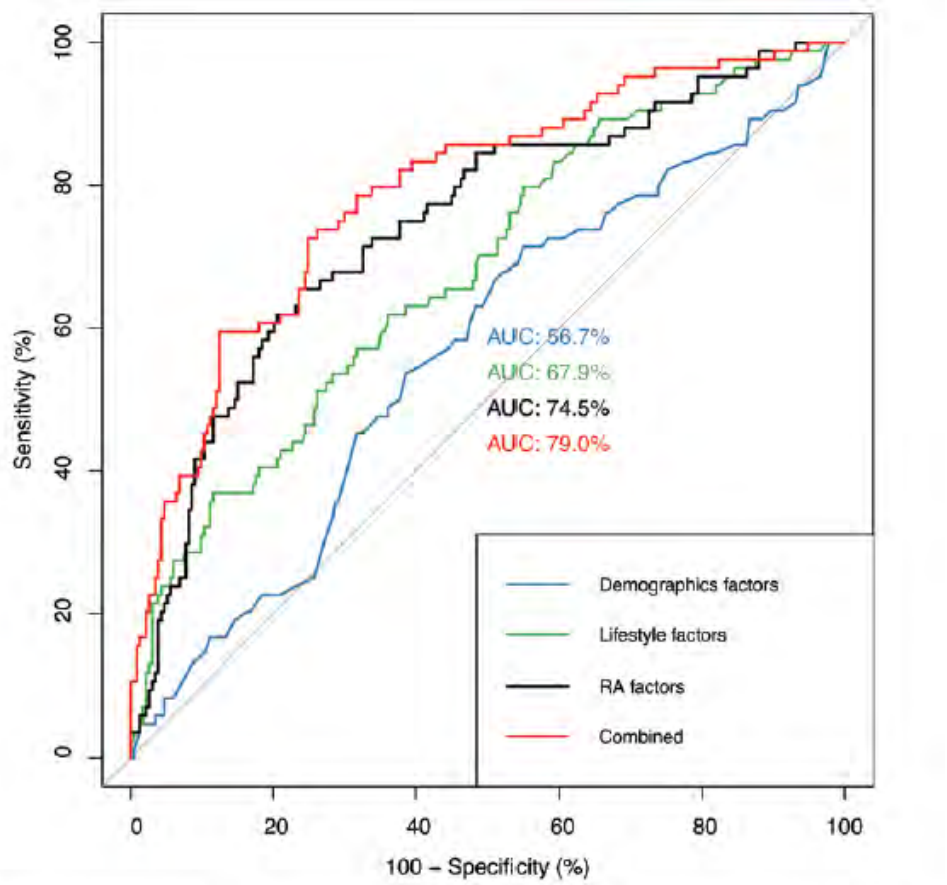


Figure 1. Receiver-operating characteristic curve for incident RA-ILD risk. These curves were fit using the 84 RA-ILD cases and 233 RA non-ILD controls in BRASS using known demographic, lifestyle, and RA clinical risk factors. AUC: area under the curve; BRASS: Brigham Rheumatoid Arthritis Sequential Study; ILD: interstitial lung disease; RA: rheumatoid arthritis.

Kronzer VL, *et al, J Rheumatol*, 2021

BRASS
Brigham and Women's Hospital
Rheumatoid Arthritis Sequential Study.

Novel autoantibodies and RA-ILD risk

	Adjusted* odds ratio (95% CI)	FDR pvalue
Citrullinated antigens		
H4 33–48 citrullinated 39 (IgA2)	0·08 (0·03–0·22)	<0·0001
H2A/a-2 1–20 citrullinated (IgA2)	4·03 (2·03–8·00)	0·0027
Filaggrin 48–65 cit2 cyclic (IgG)	3·47 (1·71–7·01)	0·014
FibrinogenB 36–52 citrullinated (IgA2)	0·37 (0·16–0·86)	0·397
Clusterin 231–250 citrullinated cyclic (IgG)	1·27 (1·03–1·56)	0·397
H4 33–48 citrullinated 39–40 (IgG)	1·25 (1·02–1·53)	0·397
Filaggrin 48–65 cit2 cyclic (IgA2)	5·04 (1·10–23·1)	0·419
H2A/a 1–20 citrullinated cyclic (IgA2)	1·60 (1·00–2·57)	0·455
Fibronectin citrullinated 1035–36 (IgG)	1·22 (0·99–1·50)	0·455
Filaggrin 48–65 cit2 cyclic (IgA1)	1·87 (0·98–3·59)	0·455
Non-citrullinated (native) antigens		
H2A/a 1–20 cyclic (IgA2)	5·52 (2·38–12·78)	0·0013
H2A/a-2 1–20 (IgA2)	4·60 (2·18–9·74)	0·0013
Filaggrin 48–65 cyclic (IgG)	2·53 (1·47–4·34)	0·010
H2A/a 1–20 cyclic (IgG)	1·91 (1·18–3·10)	0·088
H2A/a-2 1–20 (IgG)	1·86 (1·14–3·05)	0·105
Tenascin C 1 (IgG)	0·69 (0·50–0·95)	0·148
Tenascin C 1 (IgA1)	0·73 (0·54–0·98)	0·195
Vimentin 58–77 cyclic (IgG)	1·51 (1·02–2·24)	0·195
Tenascin C 1 (IgA2)	0·50 (0·22–1·15)	0·455
Vimentin 58–77 cyclic (IgA2)	1·75 (0·84–3·63)	0·530

6 novel autoantibodies associated with incident RA-ILD

Cit-histone-4
Cit-histone-2A
Cit-filaggrin
Histone-2A cyclic
Histone-2A
Filaggrin

All models were conditioned on matching factors (age, sex, RA duration, RF status, and time from blood draw to index date) and adjusted for smoking pack-years and BMI

Kronzer VL, *et al, Lancet Rheumatol*, 2023

BRASS
Brigham and Women's Hospital
Rheumatoid Arthritis Sequential Study.

Models for RA-ILD prediction

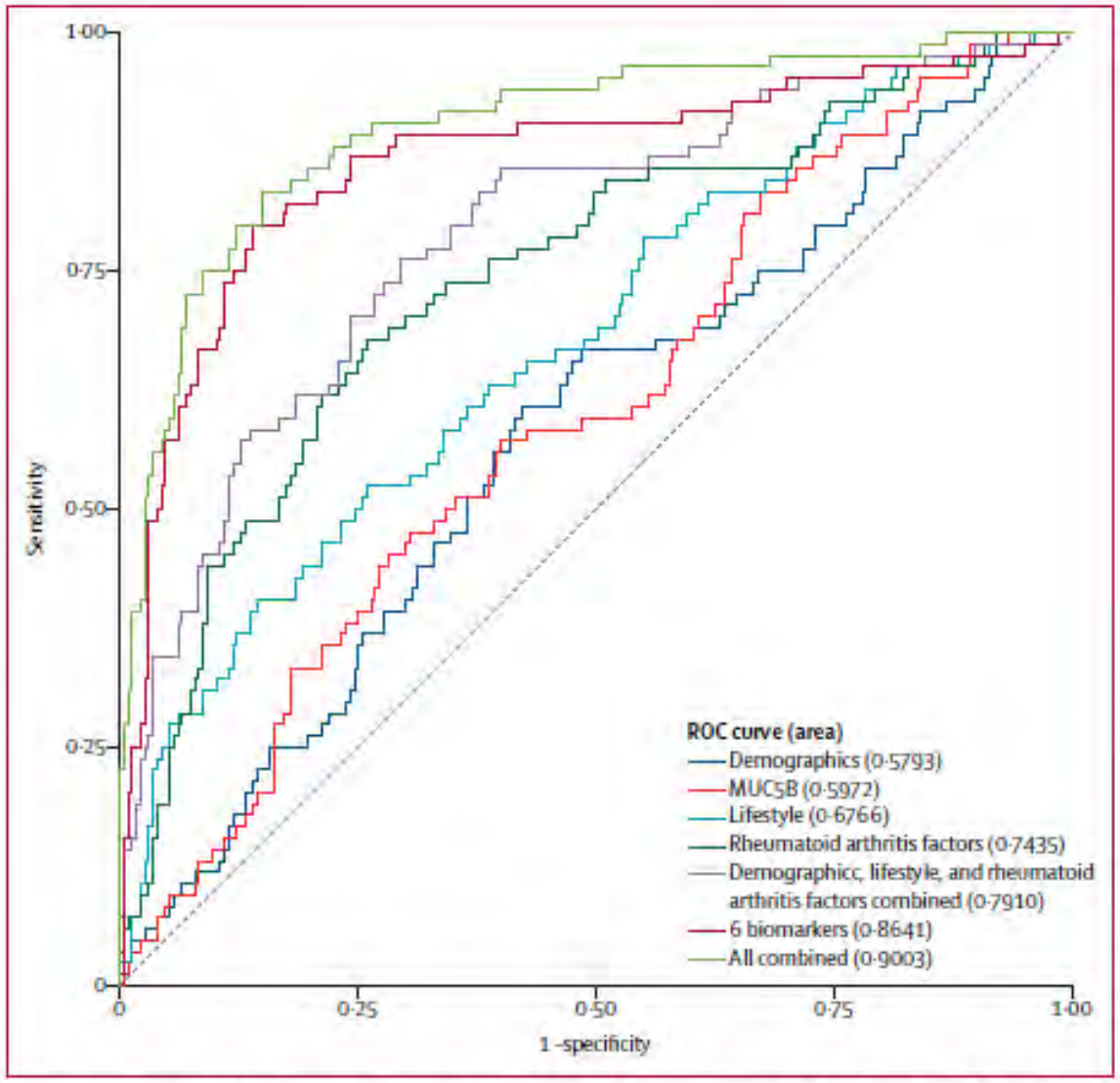


Figure: Comparison of ROC curves for incident rheumatoid arthritis-associated ILD risk among 84 cases and 233 rheumatoid arthritis controls without ILD, adding novel biomarkers and *MUC5B* to clinical factors

Optimism corrected AUC=0.84

	Score points without biomarkers	Score points with biomarkers
Smoking pack-years ≥30	1·9	2·3
DAS28-CRP ≥3·2	1·2	1·2
Current glucocorticoid use	1·0	1·2
BMI ≥30 kg/m²	0·4	0·8
Filaggrin 48–65 citrullinated 2 cyclic (IgG), highest tertile	..	2·0
H4 33–48 citrullinated 39 (IgA2), lowest tertile	..	1·9
H2A/a-2 1–20 (IgA2), highest tertile	..	1·8
MUC5B promoter variant present	..	0·1

Score of 5.0 had 83% sensitivity and 87% specificity for RA-ILD

Kronzer VL, *et al, Lancet Rheumatol*, 2023

Combined MGB Biobank/BRASS

- n=208 clinically-apparent RA-ILD cases
  - Subtype based on radiology review of HRCT (or path when available)
- n=547 RA no-ILD controls with HRCT
- Total unique patients: n=3339

RA-ILD subtypes (n=208 total)	
UIP	99 (47.6%)
NSIP	38 (18.3%)
Organizing Pneumonia	17 (8.2%)
RB-ILD	6 (2.9%)
Other/Indeterminate	48 (23.1%)

VARA: RA-related autoantibodies and RA-ILD

- Retrospective cohort of 2,328 RA patients in VARA cohort
- Median age 64 years, 89.3% male
- 100 prevalent RA-ILD at baseline, 83 incident RA-ILD during follow-up

- RF+/ACPA+ RA: OR 2.90 (1.24-6.78) for **prevalent RA-ILD** at baseline compared to seronegative RA
  - Low titer RF+: OR 2.69
  - High titer RF+: OR 3.40
  - High titer ACPA+: OR 1.91

- Few associations of RF/ACPA with **incident RA-ILD**
  - Very high titer RF+: HR 1.68

Natalini JG, *et al, Ann Am Thorac Soc*, 2021

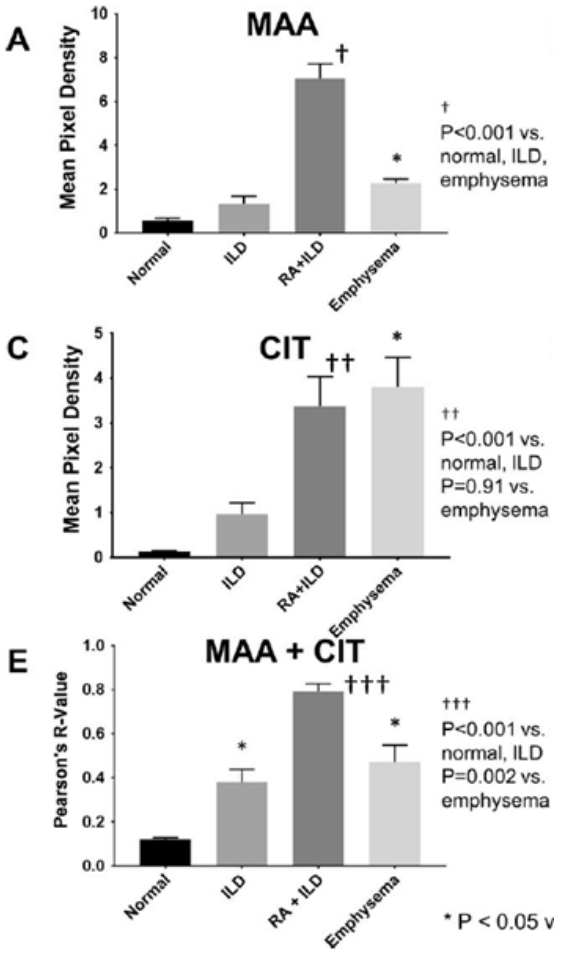
Anti-MAA and RA-ILD risk

- VARA registry (n=1,885 with anti-MAA measured)
  - n=90 prevalent RA-ILD cases
  - n=294 prevalent RA with COPD

- MAA: Malondialdehyde–acetaldehyde
  - Immunogenic products of oxidative stress
  - Smoking and heavy alcohol intake increase MAA

- **High IgA and IgM anti-MAA** associated with about **2-fold increased odds for RA-ILD**

- Lung tissue with RA-ILD has co-localized MAA and citrulline



England BR, *et al, Arthritis Rheumatol*, 2019

Anti-CarP antibodies and RA-ILD risk

- Spanish RA cohort
- Enrolled n=37 with ILD and n=142 without ILD

- Measured antibodies to anti-carbamylated antibodies (anti-CarP)

- Carbamylation: non-enzymatic conversion of lysine residues (homocitrulline)

- All Anti-CarP associated with RA-ILD
- No association of RF and ACPA with RA-ILD

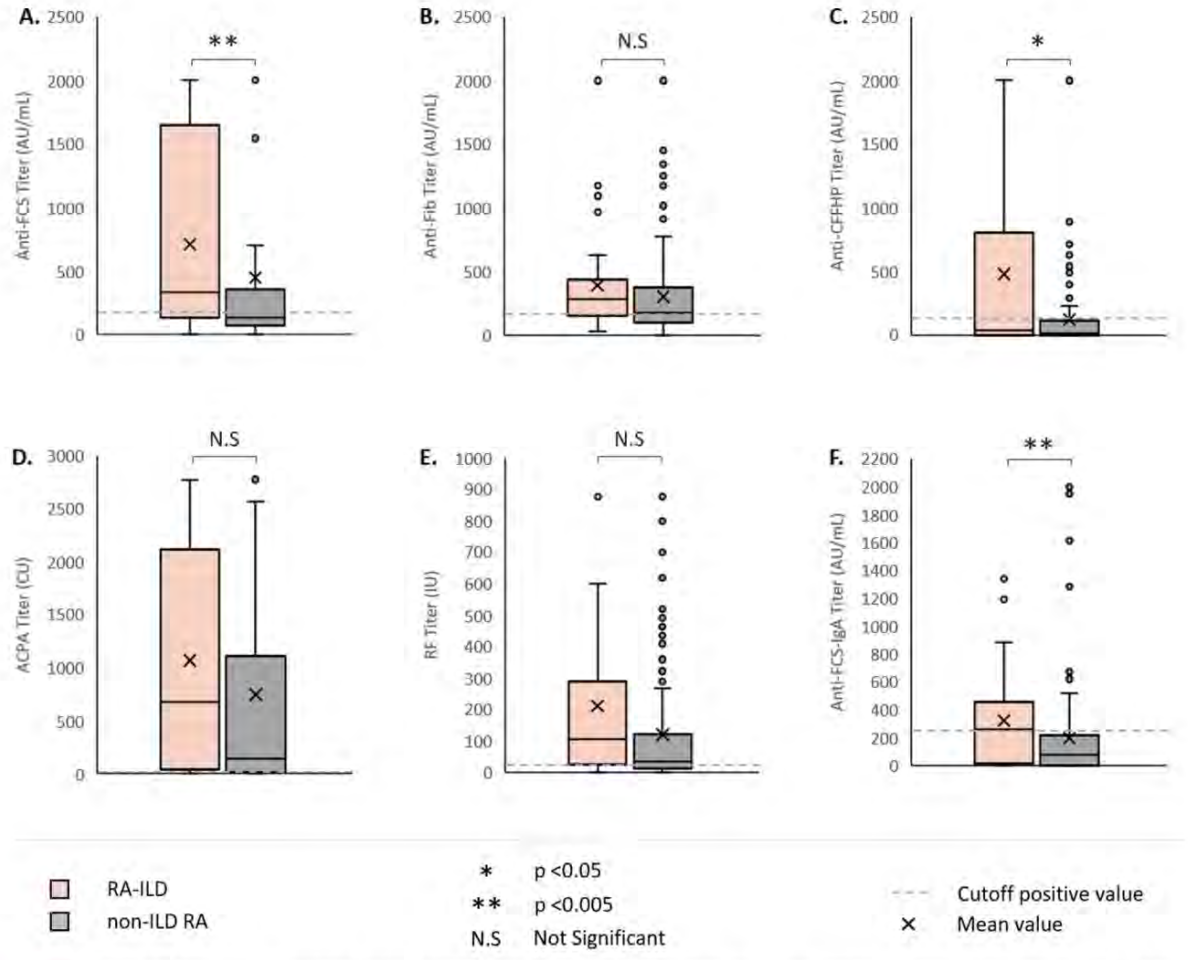


Figure 2 Boxplots of autoantibody titers in patients with and without ILD. ACPA, anticitrullinated protein antibody; Anti-CFFHP, IgG antibodies against chimeric fibrine/filagrine homocitrullinated peptide; Anti-FCS, IgG antibodies against carbamylated fetal calf serum; Anti-Fib, IgG antibodies against carbamylated fibrinogen; Anti-FCS-IgA, IgA antibodies against carbamylated fetal calf serum immunoglobulin A; AU, arbitrary units; CU, chemiluminescence units; ILD, interstitial lung disease; IU, international units; RA, rheumatoid arthritis; RF, rheumatoid factor.

Castellanos-Moreira, *et al, Ann Rheum Dis*, 2020

Methotrexate and incident RA-ILD risk

- Methotrexate-induced pneumonitis: rare, but occurs
  - CIRT: 7 cases on MTX (0.3%) vs. 1 case on placebo (<0.1%)

- Methotrexate and incident RA-ILD
  - **No increased risk**
  - ERAS/ERAN: OR 0.48 (0.30-0.79)
  - International case-control study: OR 0.46 (0.24-0.90)
  - BRASS: OR 0.36 (0.17-0.77)

- Case reports for and against most other DMARDs
  - Trials needed

Sparks JA, *et al, Arthritis Rheumatol,* 2020
Kiely P, *et al, BMJ Open*, 2019
Juge P, *et al, Eur Respir J*, 2021
Kronzer V, *et al, J Rheumtol*, 2021

b/ts DMARD and incident RA-ILD risk

Table 2. Incidence and Adjusted HRs of ILD in Patients With Rheumatoid Arthritis by Treatment

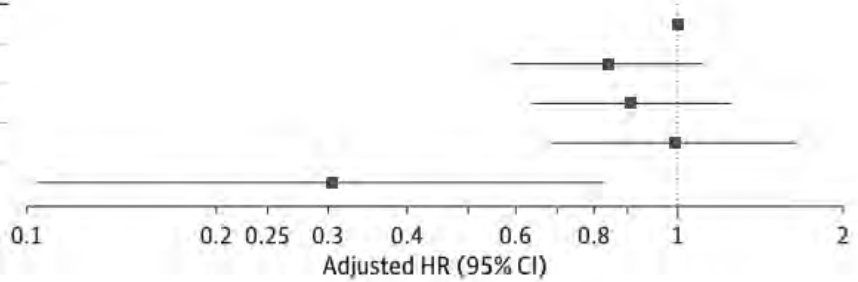
Characteristic	Total cohort (N = 28 559)	Adalimumab (n = 13 326)	Abatacept (n = 5676)	Rituximab (n = 5444)	Tocilizumab (n = 2548)	Tofacitinib (n = 1565)
Incident ILD, No. (%)	276 (0.97)	119 (0.89)	60 (1.06)	62 (1.14)	30 (1.18)	5 (0.32)
Person-years, No.	67 087	34 682	13 447	10 074	5492	3392
IR (95% CI)	4.11 (3.65-4.62)	3.43 (2.85-4.09)	4.46 (3.44-5.70)	6.15 (4.76-7.84)	5.05 (3.47-7.12)	1.47 (0.54-3.27)
IRR (95% CI)	NA	1 [Reference]	1.30 (0.95-1.77)	1.79 (1.32-2.44)	1.47 (0.99-2.20)	0.43 (0.18-1.05)
HR (95% CI)						
Crude	NA	1 [Reference]	1.28 (0.94-1.74)	1.71 (1.26-2.33)	1.53 (1.03-2.29)	0.41 (0.17-1.01)
Adjusted[a]	NA	1 [Reference]	0.79 (0.57-1.09)	0.85 (0.61-1.20)	0.99 (0.65-1.50)	0.31 (0.12-0.78)

Abbreviations: HR, hazard ratio; ILD, interstitial lung disease; IR, incidence rate per 1000 person-years; IRR, incidence rate ratio with adalimumab as the reference group; NA, not applicable.

[a] Adjusted for age, sex, race, education, geographical region, Charlson comorbidity score, outpatient visit frequency, and concomitant immunosuppressive medication use.

Figure. Adjusted Hazard Ratios (HRs) of Interstitial Lung Disease in Patients With Rheumatoid Arthritis by Treatment

Treatment cohort	Adjusted HR (95% CI)
Adalimumab	1 [Reference]
Abatacept	0.79 (0.57-1.09)
Rituximab	0.85 (0.61-1.20)
Tocilizumab	0.99 (0.65-1.50)
Tofacitinib	0.31 (0.12-0.78)



Baker MC, *et al, JAMA Netw Open,* 2023

No association of JAKi vs. TNFi for incident RA-ILD risk in Oral Surveillance RCT

Table S10. Summary of Additional AEs of Special Interest (Safety Analysis Set, 28-Day On-Treatment Time)

	Tofacitinib 5 mg BID (N=1455)	Tofacitinib 10 mg BID* (N=1456)	TNFi (N=1451)
Adjudicated interstitial lung disease			
n (%)	15 (1.0)	17 (1.2)	17 (1.2)
Total patient-years of exposure	5155.72	4849.88	5025.54
IR (95% CI)	0.29 (0.16 to 0.48)	0.35 (0.20 to 0.56)	0.34 (0.20 to 0.54)
HR (95% CI) (versus TNFi)	0.86 (0.43 to 1.73)	1.04 (0.53 to 2.03)	Referent
HR (95% CI) (versus tofacitinib 5 mg BID)	Referent	1.20 (0.60 to 2.40)	—

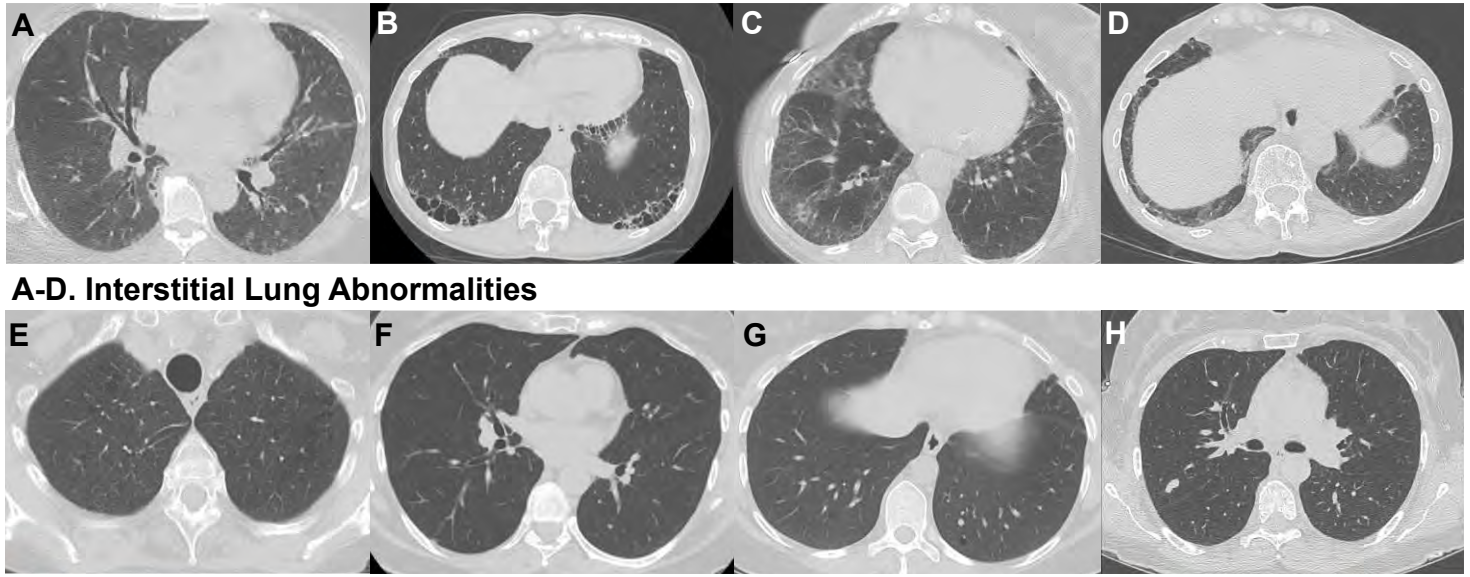
Ytterberg SR, *et al, N Engl J Med,* 2022

Preclinical parenchymal lung abnormalities

- BRASS-ILD study without known lung diseases (n=106)
  - Research protocol to obtain HRCT and other lung measures

- **Any "preclinical" parenchymal lung disease: 44%**
  - Associations: older age, lower DLCO/diffusion defect

- **Emphysema: 36%**
  - Ever smokers (42%)
  - Never smokers (31%)
- **Bronchiectasis: 22%**
- **RA-ILD: 15%**



Esposito A*, Sparks JA*, *et al, Rheumatology*, 2021

Risk score for subclinical RA-ILD

- French RA cohorts
  - ESPOIR (n=163) and TRANSLATE2 (n=89)

- RA patients without pulmonary symptoms underwent research HRCT
  - Median RA duration 14 years
- Subclinical RA-ILD identified in 19% and 17%, respectively

- Identified independent risk factors for subclinical RA-ILD
  - ***MUC5B* promoter variant** (OR 3.74)
  - **Male sex** (OR 3.93)
  - **Older age at RA onset** (OR 1.10 per year)
  - **Higher mean DAS28 over follow-up** (OR 2.03 per unit)

- **AUC 0.82 and 0.78**, respectively

Juge PA, *et al, Arthritis Rheumatol*, 2022

Risk score for subclinical RA-ILD

		DAS28-ESR ≤ 2.9		DAS28-ESR]2.9 – 4.3]		DAS28-ESR > 4.3	
Age at RA onset (years)	*MUC5B* rs35705950 genotypes	Female	Male	Female	Male	Female	Male
Risk matrix							
≤ 49	GG	2.0 [0.3–5.7]	7.1 [1.0–18.6]	6.7 [1.2–16.5]	21.3 [3.2–50.3]	12.5 [2.0–29.7]	34.9 [5.9–71.4]
	GT/TT	6.7 [1.4–17.6]	21.3 [5.4–48.0]	20.3 [5.2–38.2]	48.9 [16.0–80.1]	33.5 [6.3–59.4]	65.4 [16.3–90.8]
]49 – 58]	GG	6.2 [1.5–15.6]	19.9 [4.5–41.6]	18.9 [5.9–30.6]	46.8 [15.0–71.7]	31.6 [8.3–57.1]	63.4 [18.1–87.5]
	GT/TT	18.9 [3.8–50.1]	46.8 [13.0–80.8]	45.2 [15.6–71.7]	75.6 [39–94.6]	62 [17.9–87.4]	86.0 [40.7–97.7]
> 58	GG	16.7 [5.0–39.1]	42.9 [20.6–72.0]	41.4 [15.0–69.5]	72.7 [35.6–92.3]	58.3 [25.1–84.8]	84.0 [48.3–97.2]
	GT/TT	41.4 [17.4–76.6]	72.7 [46.9–92.7]	71.4 [40.8–91.7]	90.4 [66.9–98.3]	83.1 [47.3–96.8]	94.9 [72.1–99.3]

Probabilities to have subclinical RA-ILD with their respective 95% confidence intervals are shown.

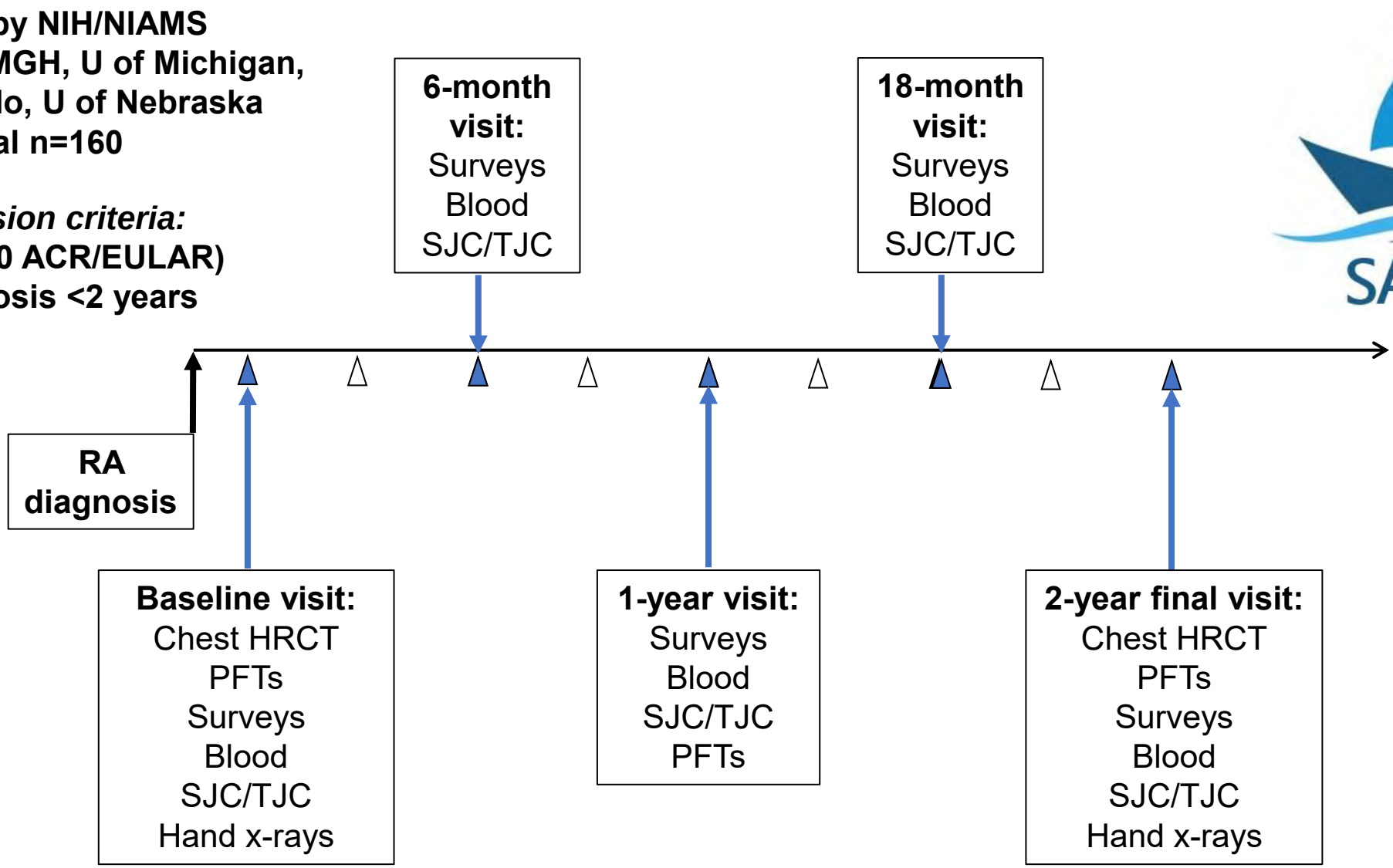
RA: rheumatoid arthritis; ILD: interstitial lung disease; DAS28-ESR: Disease Activity Score in 28 joints-erythrocyte sedimentation rate

Juge PA, *et al, Arthritis Rheumatol*, 2022

SAIL-RA: Study of Inflammatory Arthritis and ILD in EarLy RA

Funded by NIH/NIAMS
5 sites: BWH, MGH, U of Michigan, U of Colorado, U of Nebraska
Goal n=160

Inclusion criteria:
RA (2010 ACR/EULAR)
Diagnosis <2 years



ANCHOR-RA

- Sponsored by Boehringer Ingelheim
- Enrolling n=1200 RA patients for screening study (6 countries, 30 sites)
  - HRCT
  - PFTs
  - Lung U/S (subset)
- All have at least 2 ILD risk factors
  - Autoantibodies (ACPA/RF >3x ULN)
  - Non-articular RA manifestations
  - Cigarette smoking (ever)
  - He/him (male sex)
  - Older age (60+ years)
  - RA high disease activity

COPDGene: Prospective smoker cohort (n=10,371)

Prevalence and mortality associations of interstitial lung abnormalities in rheumatoid arthritis within a multicentre prospective cohort of smokers

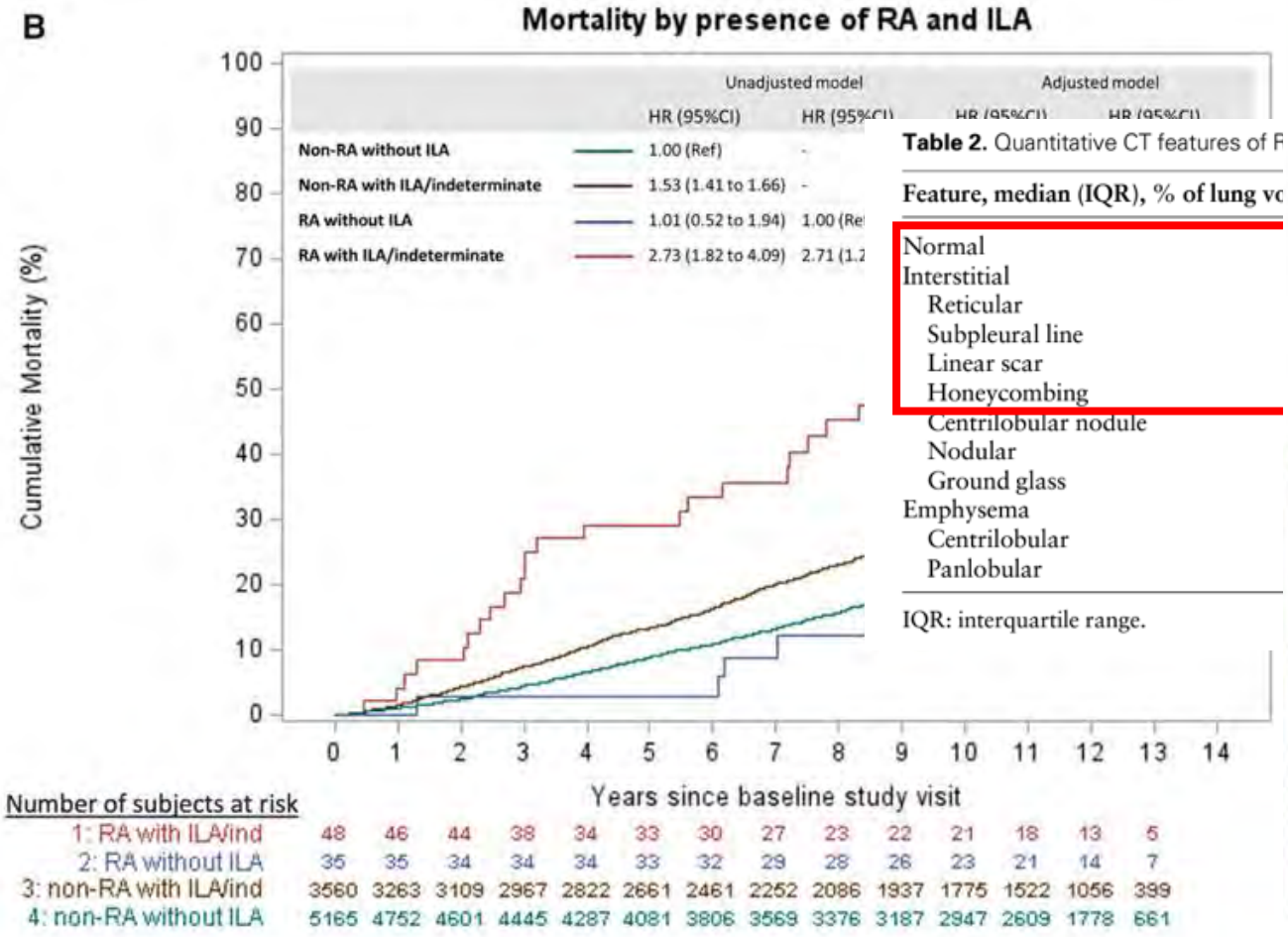
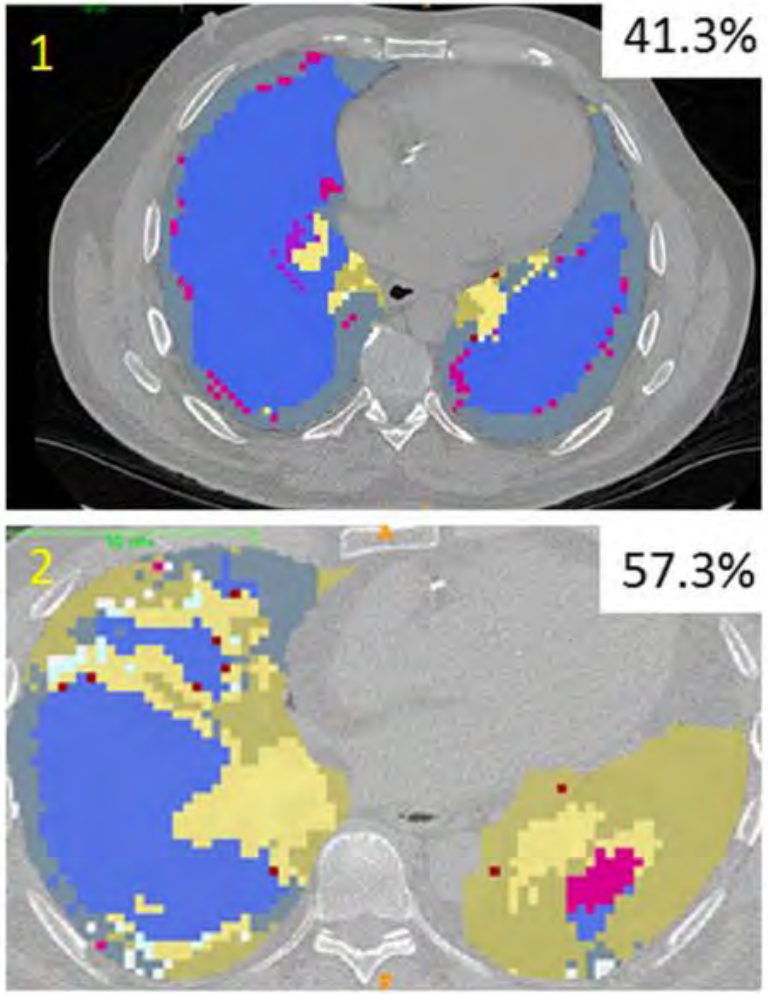


Table 2. Quantitative CT features of R

Feature, median (IQR), % of lung vo
Normal
Interstitial
Reticular
Subpleural line
Linear scar
Honeycombing
Centrilobular nodule
Nodular
Ground glass
Emphysema
Centrilobular
Panlobular

IQR: interquartile range.

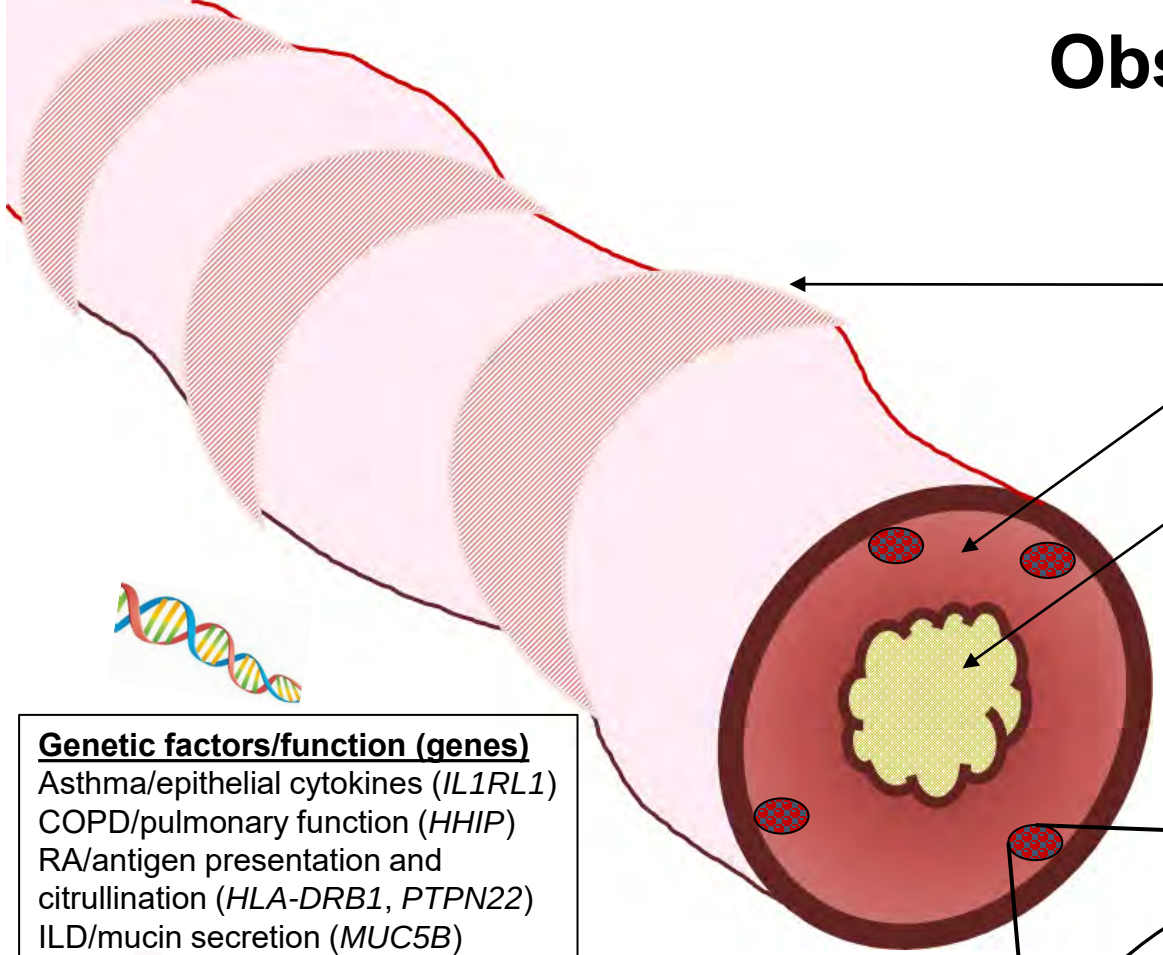
Rheumatoid arthritis, quantitative parenchymal lung features and mortality among smokers



McDermott GC, *et al*, *Rheumatology*, 2023

Ash, Respiratory Research, 2017

Obstructive lung disease in RA



Mechanisms of airway obstruction

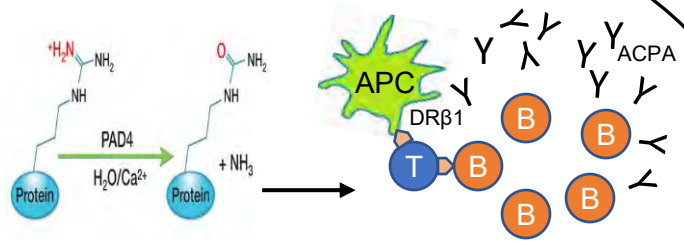
- Tightened smooth muscle and bronchoconstriction
- Inflamed, thickened, airways with mucus and secretions
- Distal air trapping and emphysema

Genetic factors/function (genes)
Asthma/epithelial cytokines (*IL1RL1*)
COPD/pulmonary function (*HHIP*)
RA/antigen presentation and citrullination (*HLA-DRB1*, *PTPN22*)
ILD/mucin secretion (*MUC5B*)

Environmental factors
Smoking
Pollution
Infections
Other inhalants/allergens
Dietary intake
Physical activity

Biologic processes
Cytokine production
Neutrophil extracellular traps
ROS and hypoxia
Microbial peptides
PAD activation
Citrullination and other PTM
Neoantigen production
Immune tolerance loss
Autoantibody production
Lymphoid aggregates

Formation of lymphoid aggregates

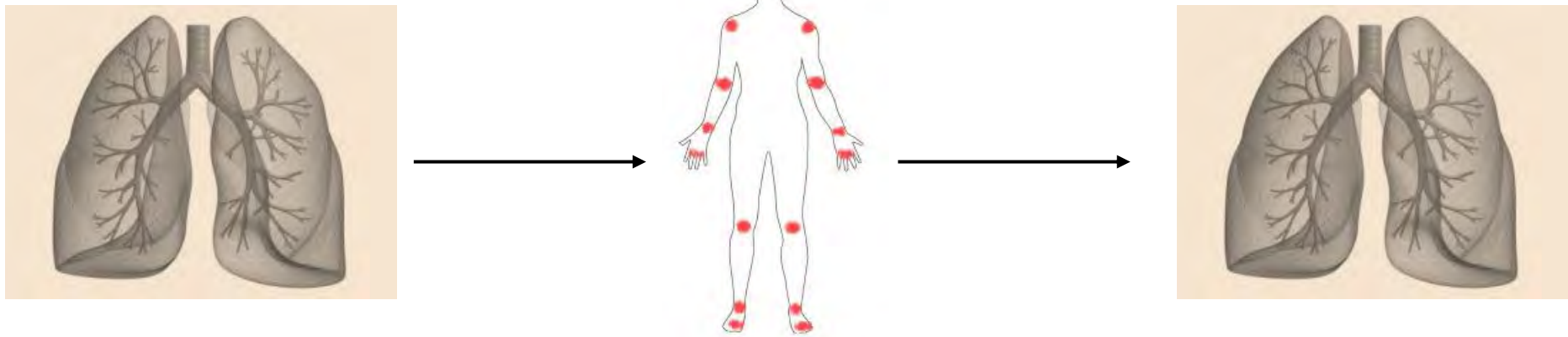


PAD activation, citrullination to form neoantigens

Neoantigen presentation through HLA-DRβ1, T and B cell activation, ACPA production

Friedlander M, *et al*, *Expert Rev Clin Immunol*. 2019

RA and COPD risk



COPD *before* RA

Ford JA, *et al, Arthritis Rheumatol*, 2020
COPD: ↑ incident seropositive RA risk, adjusted for smoking pack-years

- Strongest association for older smokers

Clinical RA

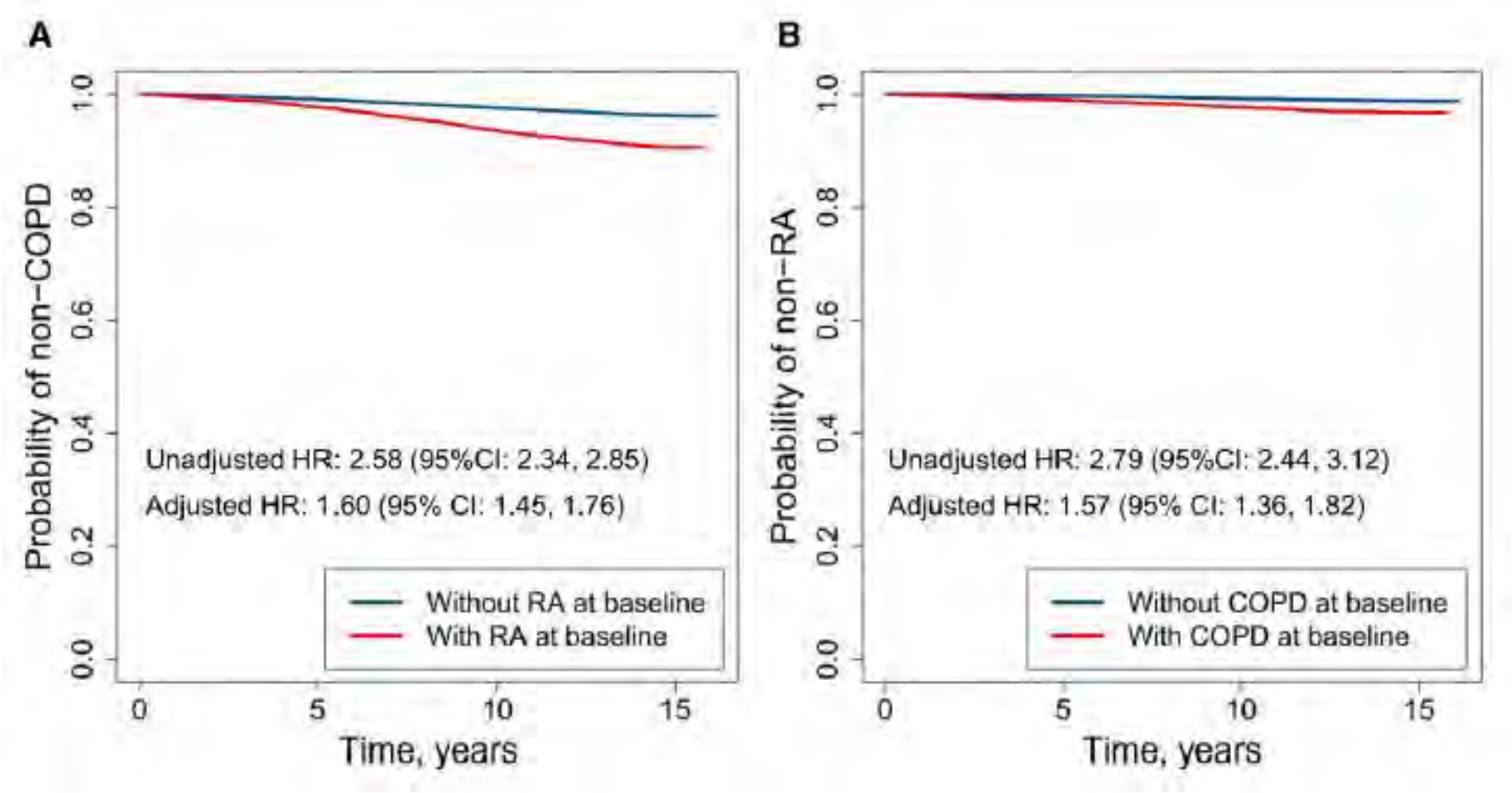
COPD *after* RA

Sparks JA, *et al, Semin Arthritis Rheum*, 2018
Meta-analysis of 6 studies:
RA: ↑ incident COPD risk

Ma Y, *et al, Respir Res,* 2019
Sparks JA, *et al, Semin Arthritis Rheum,* 2018

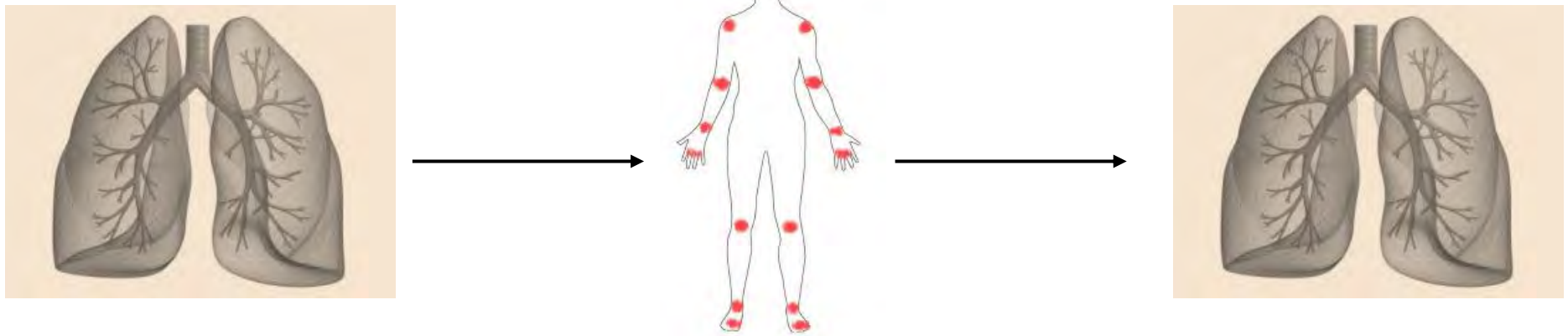
Bi-directional association of RA and COPD

- UK Biobank (n=403,045)



Yang K, *et al, Rheumatology,* 2023

RA and asthma risk



Asthma *before* RA

10 previous studies:
Asthma: ↑ incident RA risk
- 4-fold ↑ odds of pre-RA ACPA+
- Most were case-control studies

Clinical RA

Asthma *after* RA

2 retrospective cohorts:
RA: ↑ incident asthma risk
- No smoking or RA serostatus data

Hemminki K, *et al, Eur Respir J,* 2011
Hou YC, *et al, Allergy Asthma Proc,* 2017
Shen TC, *et al, QJM,* 2014
Zaccardelli A, *et al*, *Arthritis Res Ther*, 2019

RA and incident obstructive lung disease

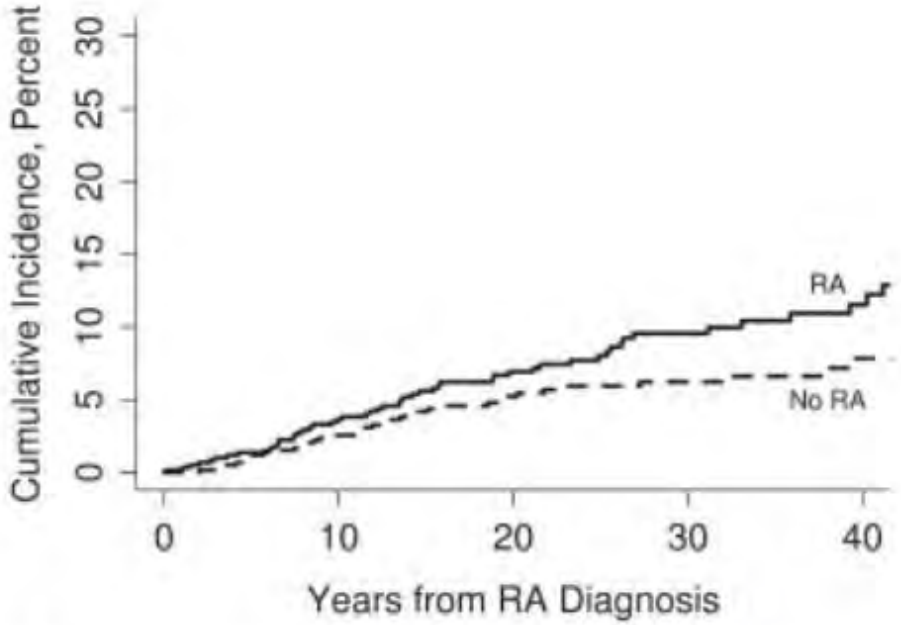


Figure 1. Incidence of obstructive lung disease in patients with rheumatoid arthritis (RA; solid line) and subjects without RA (broken line).

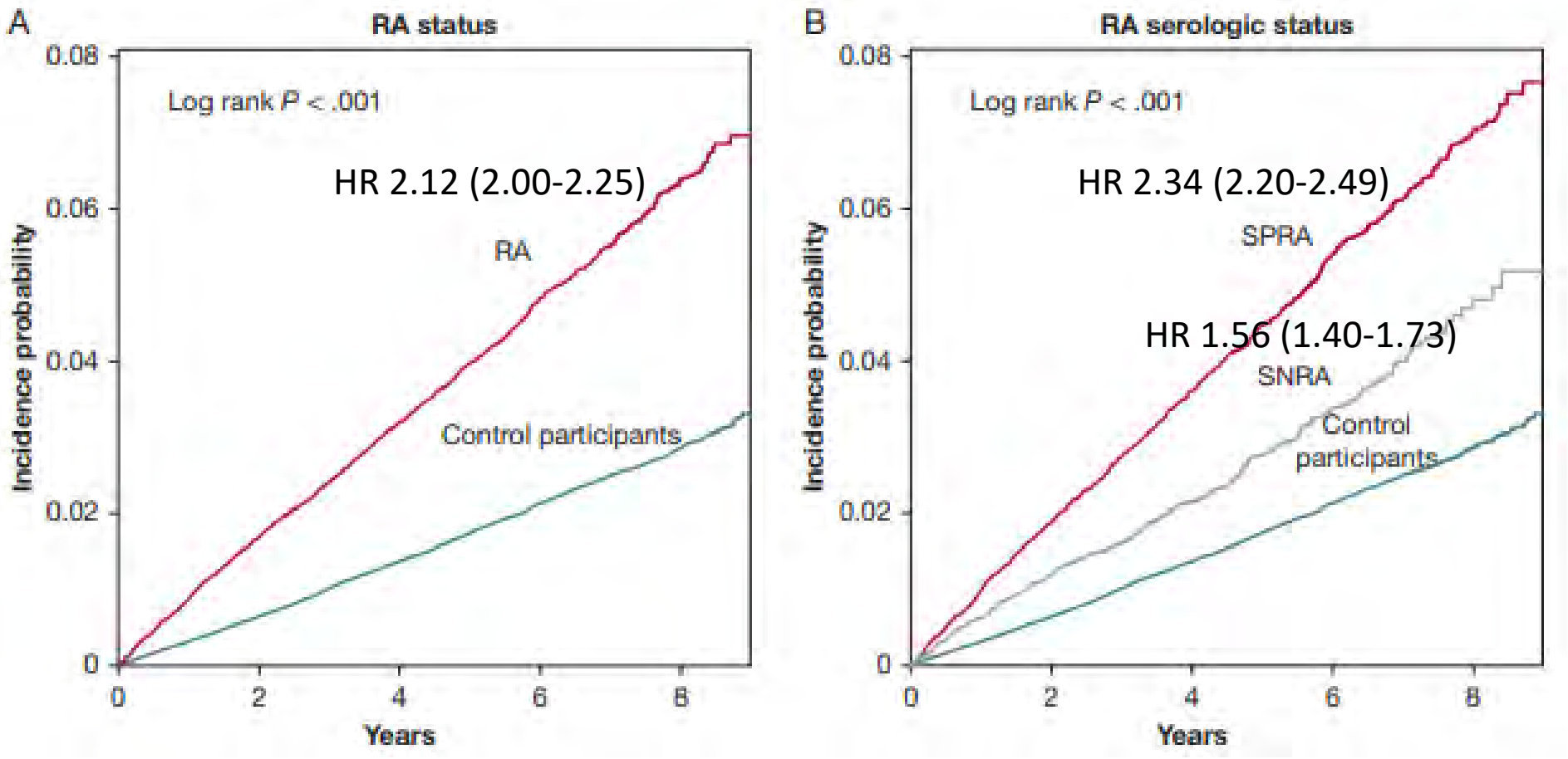
Table 3. Types of lung disease (including overlap of 2 different pathologies) underlying airway obstruction in RA and non-RA patients*

Type of lung disease	RA cohort	Non-RA cohort
COPD	38	23
ILD	1	0
Asthma	1	11
Bronchiectasis	3	0
COPD + ILD	6	1
COPD + asthma	1	4
COPD + bronchiectasis	1	1
ILD + bronchiectasis	1 (traction bronchiectasis)	0

Nannini C, *et al, Arthritis Care Res,* 2013

Incidence of bronchiectasis in RA

- Korean insurance database: 50,651 RA cases and 253,255 comparators



Choi H, *et al, Chest,* 2024

Risk factors for bronchiectasis in RA

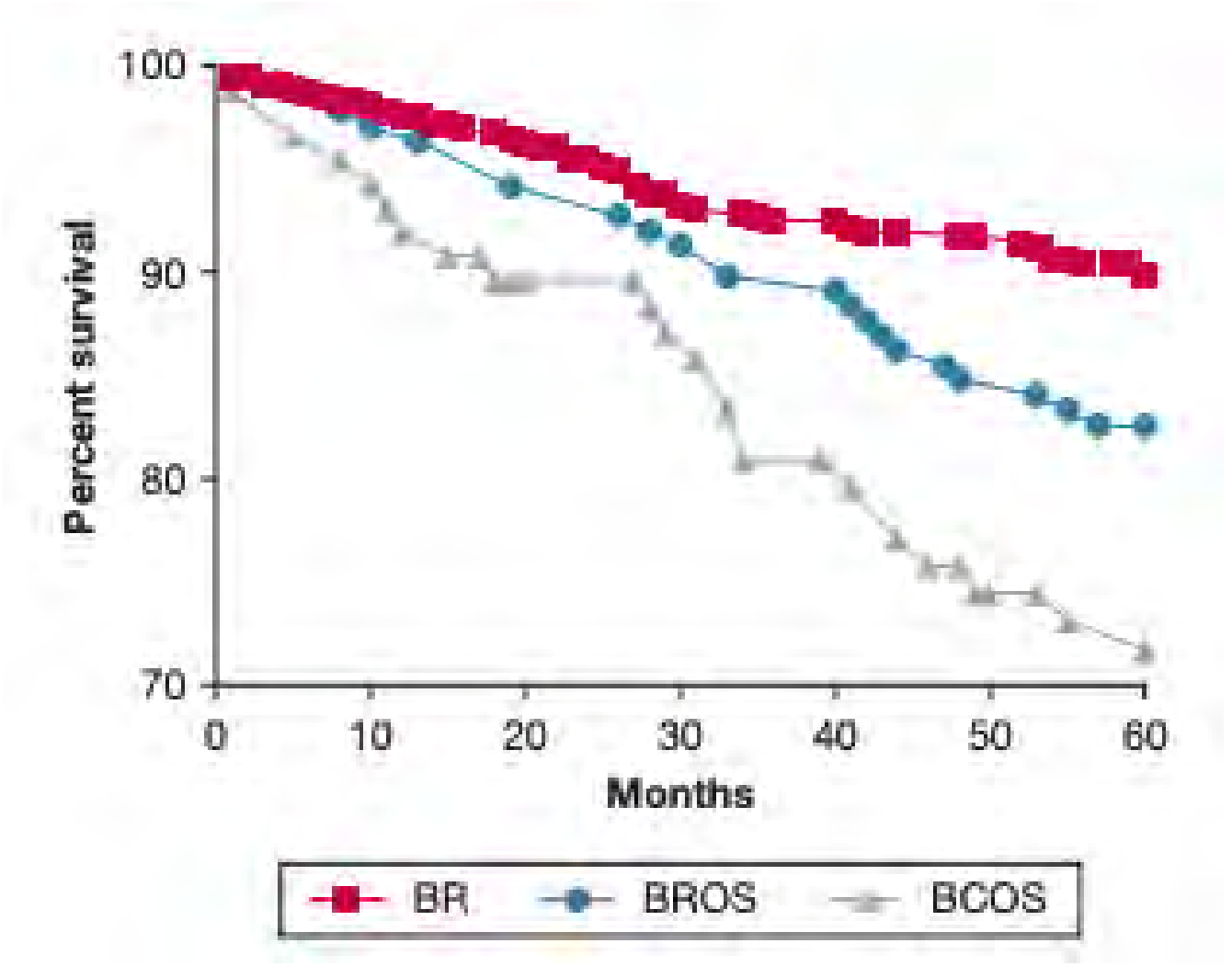
- Case-control study in MGB Biobank
  - Cases: Bronchiectasis on CT scan, no ILD
  - Controls: normal chest CT scan
- Associations
  - Seropositivity
  - Lower BMI
- No associations
  - Age at RA diagnosis
  - RA duration
  - Sex
  - Smoking

Table 3. Associations of RA-related autoantibodies with isolated RA-BR.

RA-related Autoantibody Status[a]	Multivariable[b] OR for Isolated RA-BR (95% CI)	*P*
RF negative	1.00 (Ref)	
RF positive (> 1× ULN)	**4.40 (2.14–9.07)**	**< 0.0001**
RF negative	1.00 (Ref)	
RF low positive (> 1–3× ULN)	1.95 (0.67–5.66)	0.22
RF high positive (> 3× ULN)	**5.44 (2.57–11.54)**	**< 0.0001**
Anti-CCP negative	1.00 (Ref)	
Anti-CCP positive (> 1× ULN)	**3.47 (1.65–7.31)**	**0.001**
Anti-CCP negative	1.00 (Ref)	
Anti-CCP low positive (> 1–3× ULN)	1.45 (0.29–7.32)	0.65
Anti-CCP high positive (> 3× ULN)	**3.73 (1.76–7.90)**	**0.0006**

McDermott GC, *et al, J Rheumatol,* 2022

Bronchiectasis in RA and survival



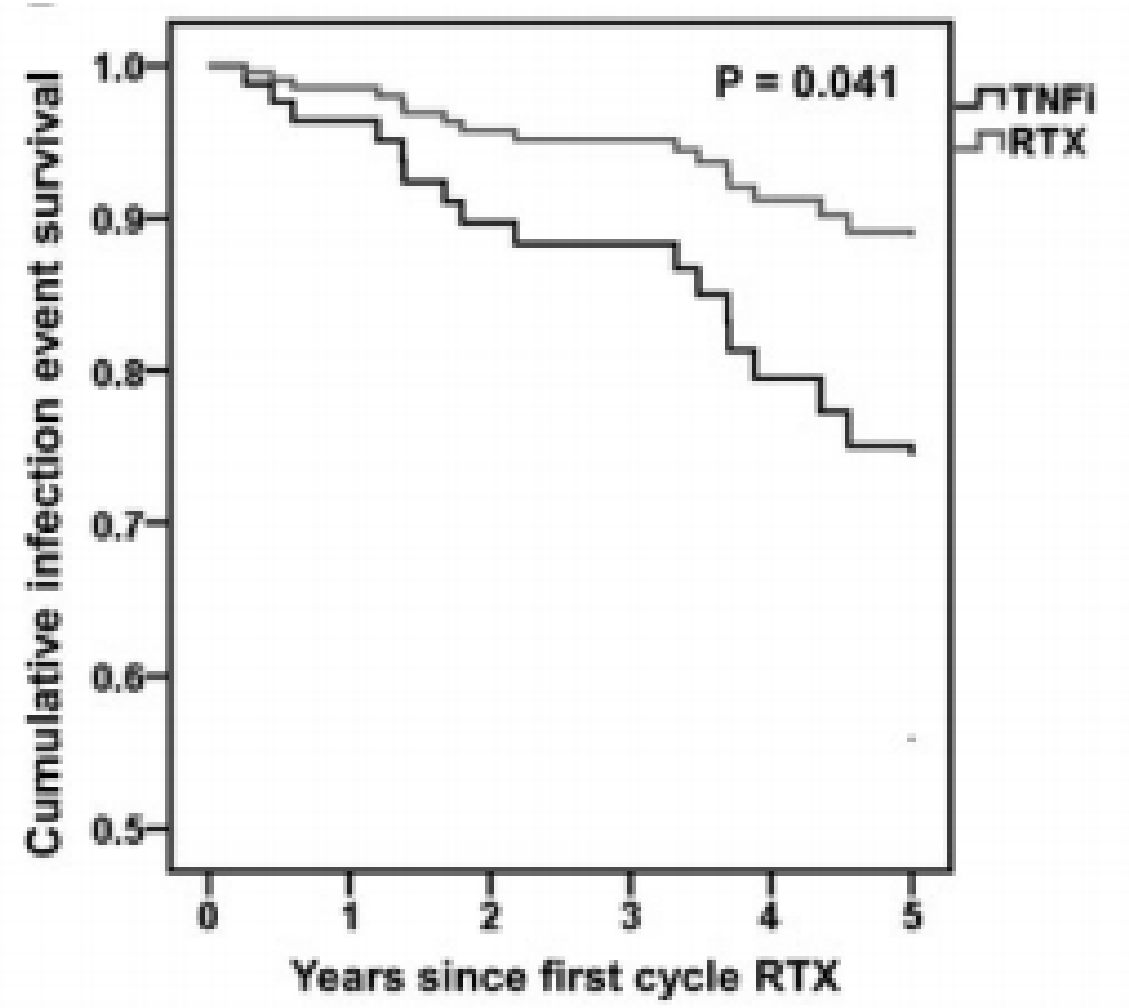
BR=bronchiectasis alone

BROS=bronchiectasis RA overlap syndrome

BCOS=bronchiectasis COPD overlap syndrome

De Soyza, *et al, Chest,* 2017

Rituximab and infection-free survival in RA-BR



Yusof M, *et al, Rheumatology,* 2019

Pleural disease

- Often subclinical
- Moderate effusions: avoid methotrexate due to third spacing
- Typically exudative effusion
  - Pleural to serum glucose ratio <0.5
- May also have pericardial effusions
- Chronic effusions can cause chyliform/pseudochylous effusions
  - Nonexpandable lung due to entrapment

- Thoracentesis sometimes needed
- Consider drug-induced lupus from TNF inhibitors

Pulmonary nodules

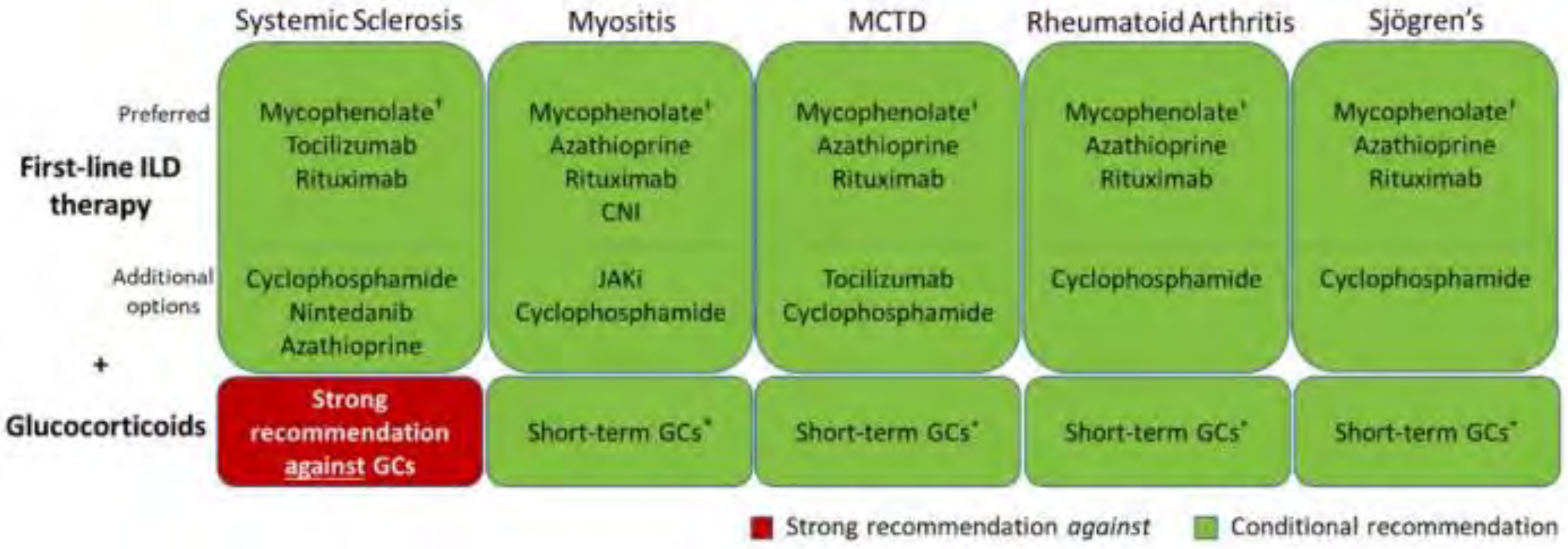
- Very common
- Monitor for malignancy similar to general population

- Caplan syndrome: RA and pneumoconiosis related to occupational dust (coal, asbestos, silica) exposure
  - Pulmonary nodules (peripheral, basilar)
  - Airway obstruction
  - Progressive fibrosis

RA-ILD treatment considerations

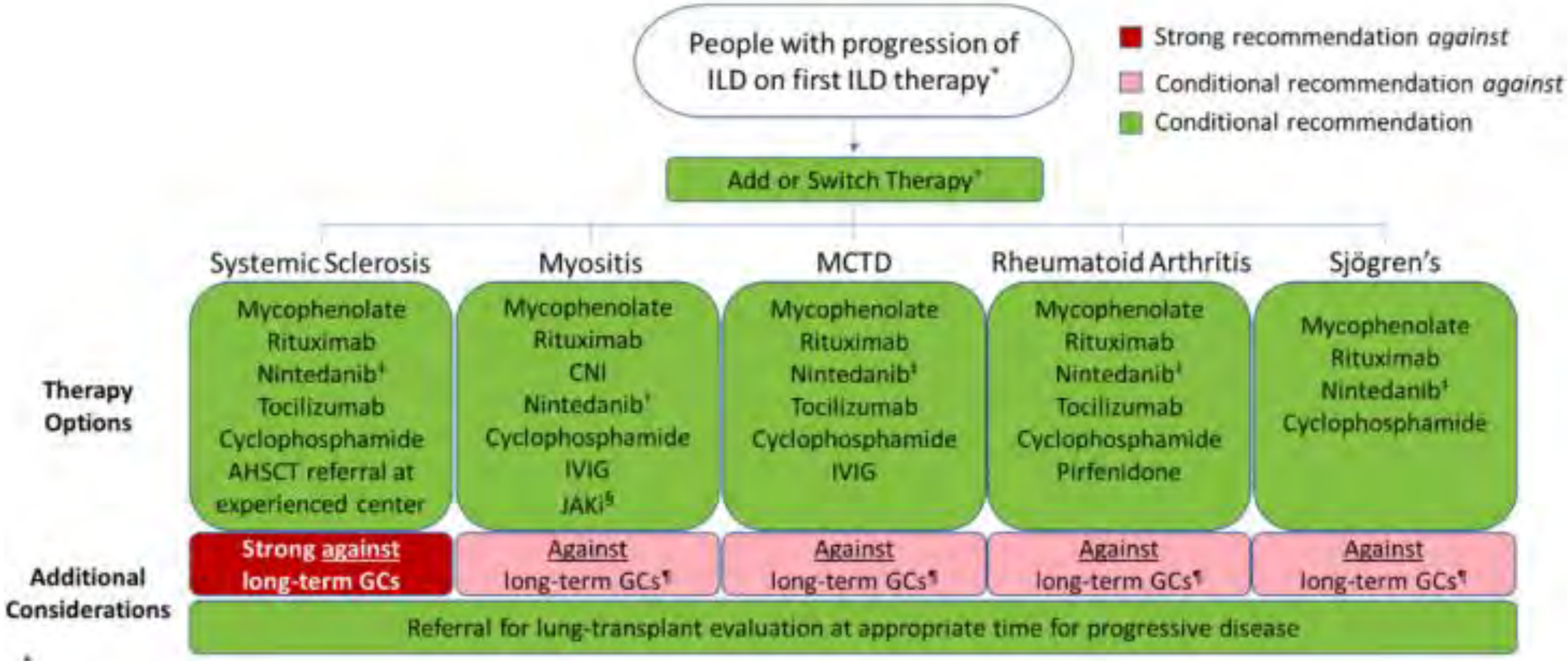
- Arthritis activity/damage
- Pulmonary activity/damage
  - Inflammatory
  - Fibrotic
  - Mixed
  - Masquerading/concomitant conditions (smoking, infection, COPD, asthma, aspiration)
- Potential for infection/pneumonitis with immunosuppressants
- Organ systems may not be active in parallel
- Multidisciplinary approach

ACR/Chest SARD-ILD treatment guideline: <u>First line</u>



Johnson S, *et al, Arthritis Rheumatol*, 2024

ACR/Chest SARD-ILD treatment guideline: Progression after first line



Johnson S, *et al, Arthritis Rheumatol*, 2024

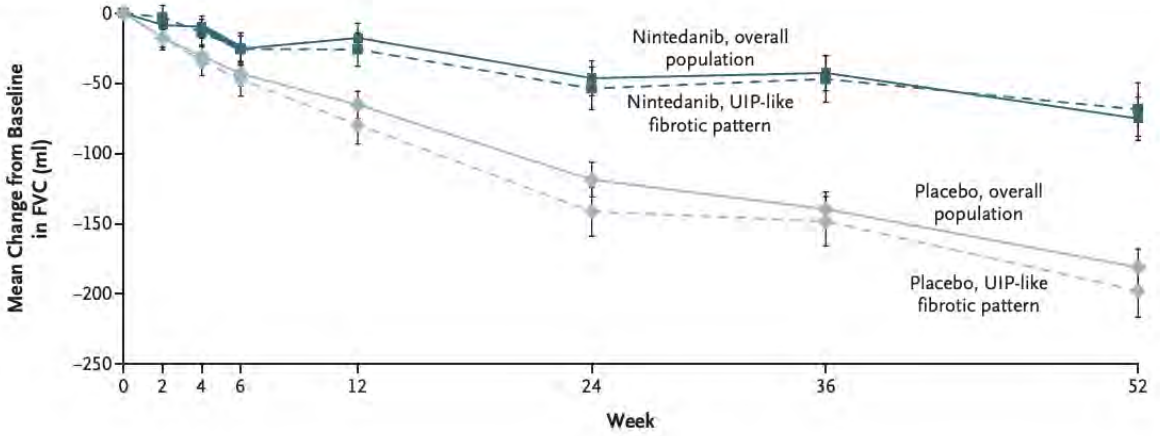
“Fibrotic” RA-ILD

- UIP, fibrotic NSIP, cystic LIP

- Controlled trial data
  - Nintedanib
  - Pirfenidone

Nintedanib

- INBUILD trial (n=663): randomized placebo-controlled trial of patients with progressive fibrosing ILDs
  - 13% had RA-ILD
  - 67% of nintedanib group had diarrhea



No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

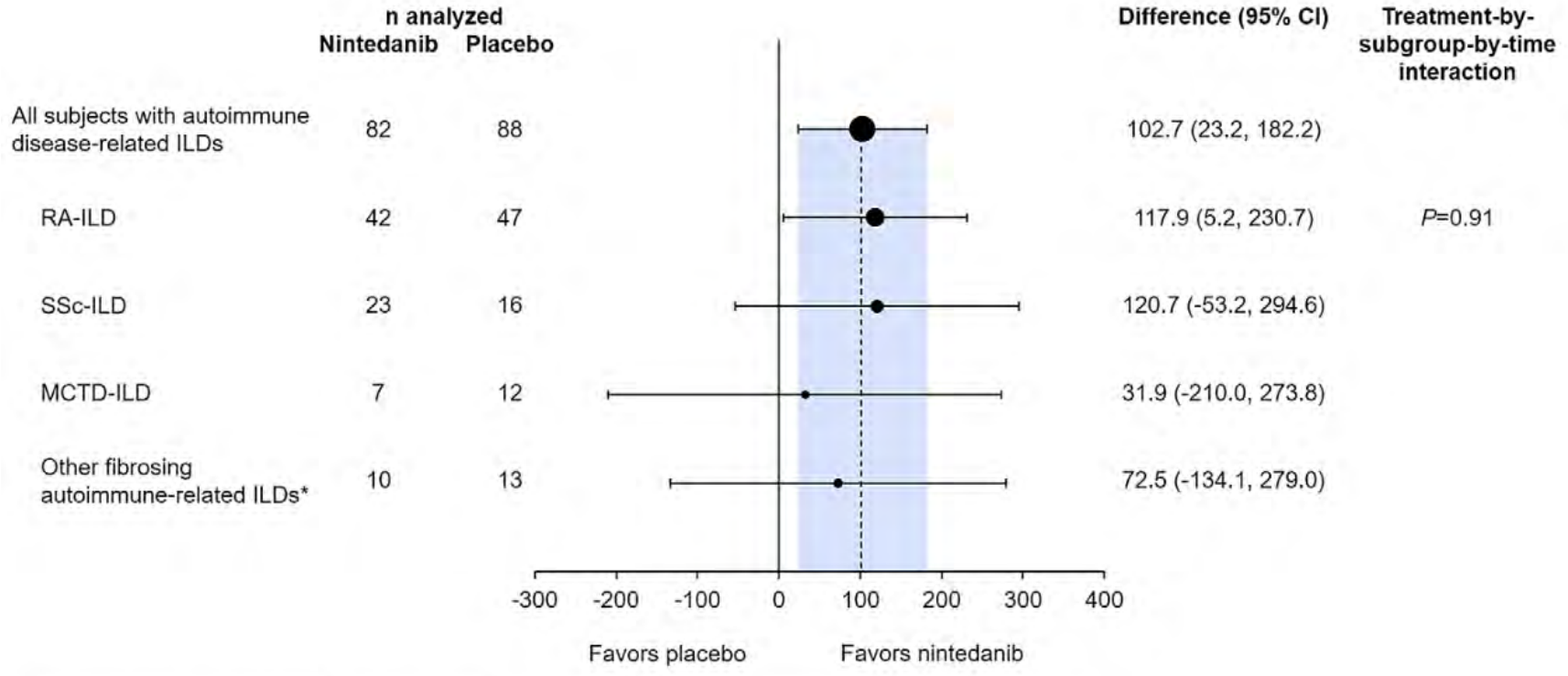
Figure 2. Decline from Baseline in Forced Vital Capacity (FVC).

Shown is the observed mean change from baseline in FVC over the 52-week trial period in the overall population and in patients with an imaging pattern of usual interstitial pneumonia (UIP) on high-resolution computed tomography in the nintedanib group and the placebo group. The I bars indicate the standard error.

Flaherty KR, *et al, N Engl J Med*, 2019

INBUILD subgroup analysis

- Subgroup analysis of n=170 with fibrosing autoimmune disease ILD



*Subjects with an autoimmune disease noted in the "Other fibrosing ILDs" category of the case report form.

Matteson EL, *et al, Arthritis Rheumatol*, 2022

Pirfenidone

- TRAIL1 trial (n=123): randomized placebo-controlled trial of patients with RA-ILD
  - Goal enrollment n=270
- Primary outcome: decline in %FVC by 10% or more or death
  - 11% vs. 15% (p=0.48)
- Pirfenidone group had slower decline in FVC
- Nausea in 53% of pirfenidone group

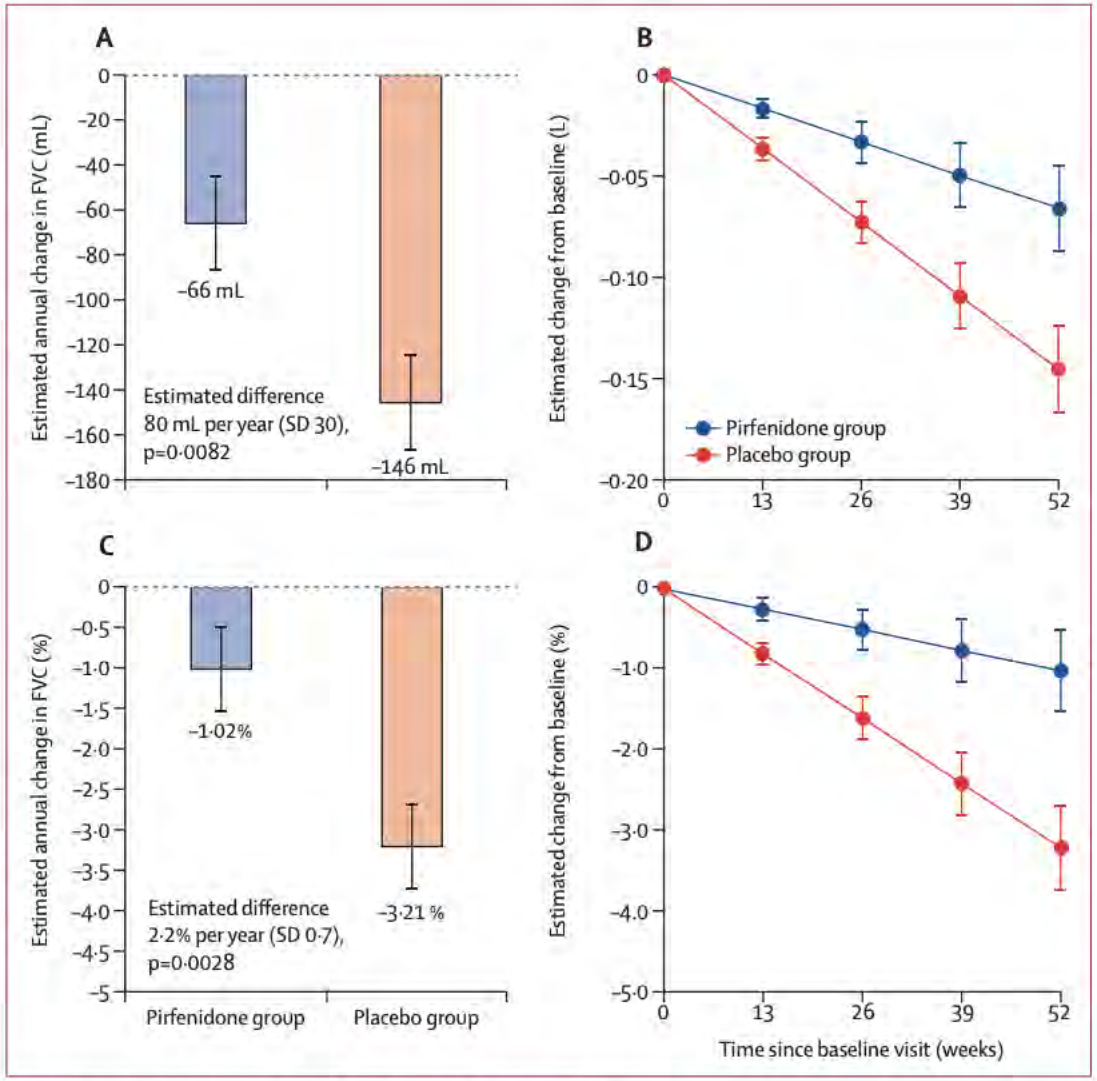


Figure 2: **Estimated change in FVC and percent predicted FVC**
(A) Estimated annual change in FVC (mL). (B) Estimated change in FVC (L) from baseline. (C) Estimated annual change in percent predicted FVC (%). (D) Estimated annual change in percent predicted FVC (%) from baseline. Error bars are SE. FVC=forced vital capacity.

Solomon JJ, *et al, Lancet Respir Med*, 2023

Pirfenidone by RA-UIP pattern

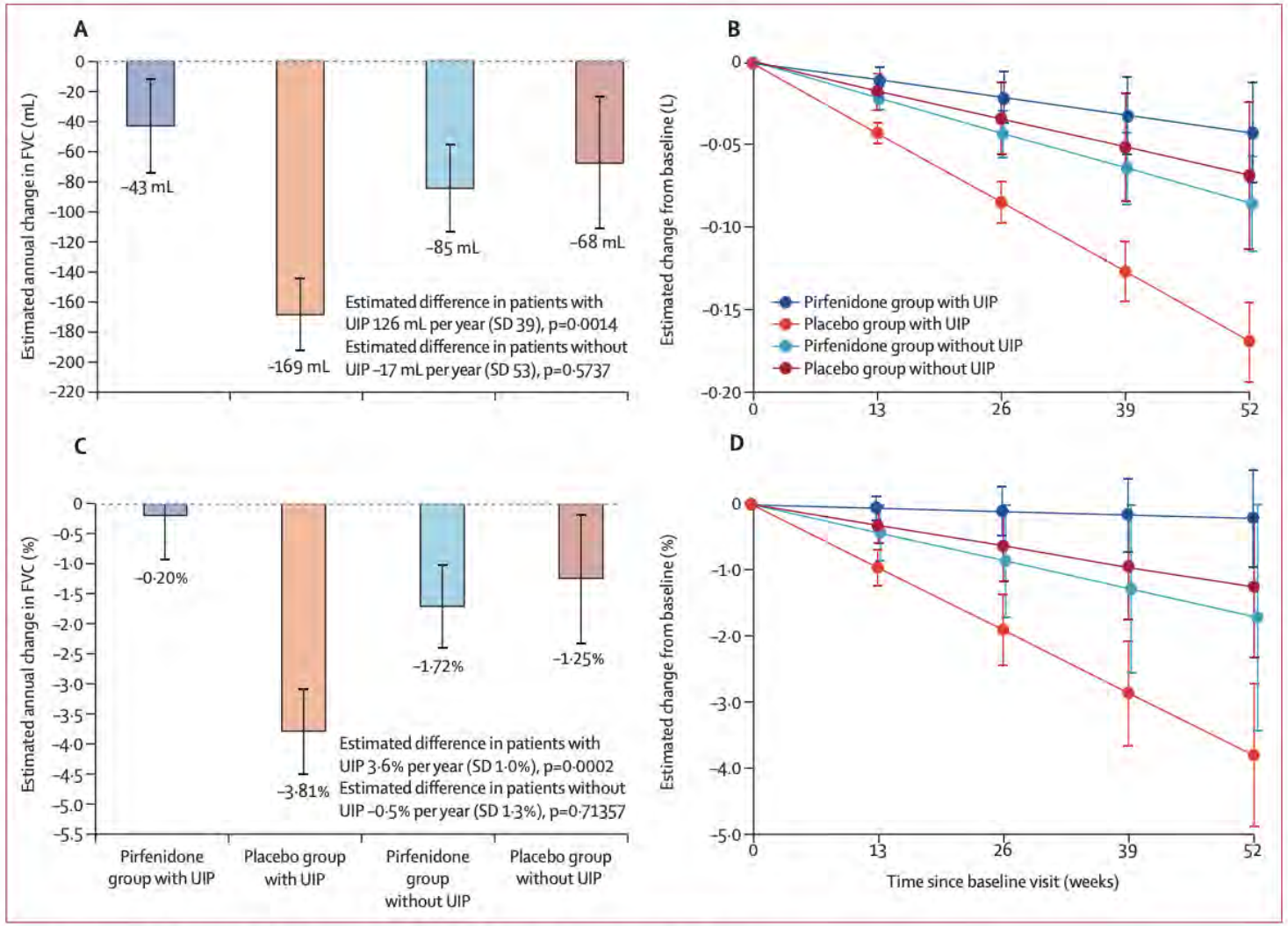


Figure 3: **Estimated change in FVC and percent predicted FVC by high-resolution CT pattern**
(A) Estimated annual change in FVC (mL). (B) Estimated change in FVC (L) from baseline. (C) Estimated annual change in percent predicted FVC (%). (D) Estimated annual change in percent predicted FVC (%) from baseline. Error bars are SE. FVC=forced vital capacity. UIP=usual interstitial pneumonia.

Solomon JJ, *et al, Lancet Respir Med*, 2023

“Inflammatory” RA-ILD

- “Holy grail”: single medication that treats both lungs and joints in RA
- Candidates
  - Glucocorticoids
  - Rituximab
  - Abatacept
  - Tocilizumab
  - Mycophenolate
  - Cyclophosphamide
- No controlled trial data
- TNF inhibitors
  - England BR, et al, ACR 2023 abstract: No difference in respiratory hospitalization or mortality compared to non-TNFi bDMARD
- JAK inhibitors: little data on treatment

Immunosuppression in RA-ILD

- Multi-center retrospective study of RA-ILD patients treated with immunosuppressants (n=227)

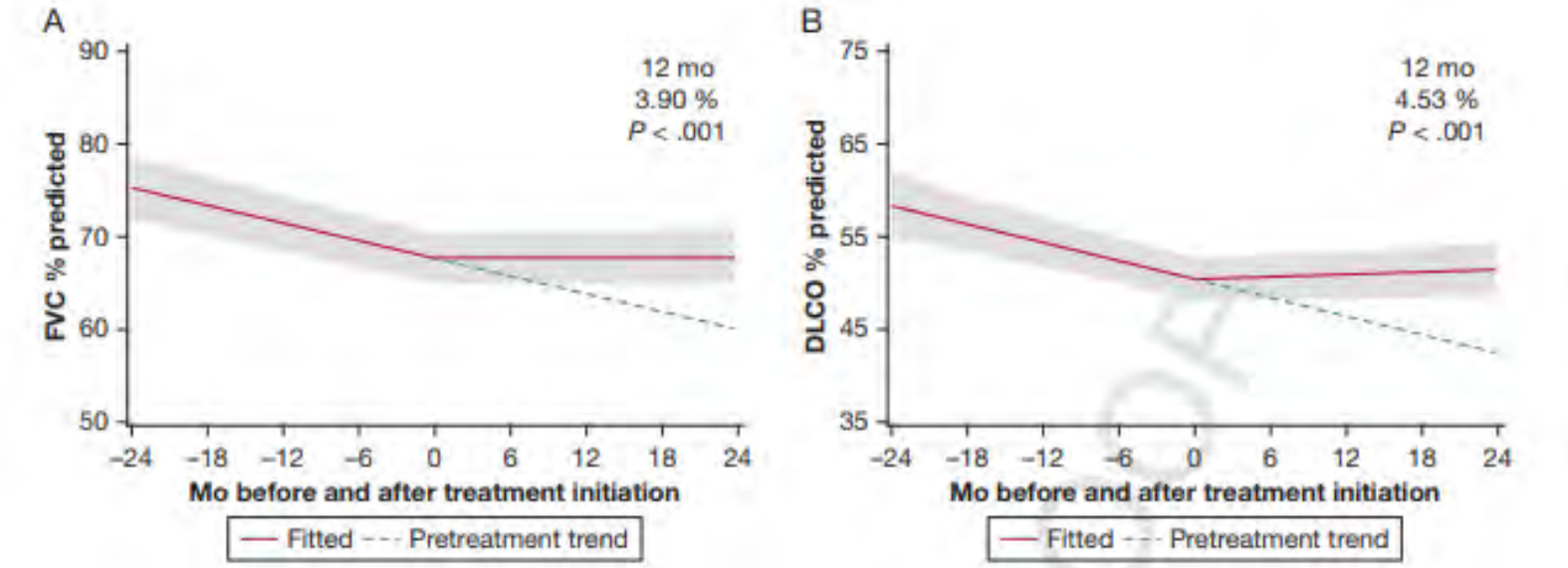


Figure 2 – *A, Line graph showing impact of immunosuppression on predicted trajectory of FVC % predicted. The pretreatment trend in FVC is shown from time –24 months to time 0, when RA-associated ILD-specific treatment was initiated. The pretreatment trend (blue dotted line) is projected forward from time 0 to +24 months and compared with the observed FVC trend after treatment initiation. After 12 months of treatment, significant increase in FVC % predicted was achieved compared with the projected trend without treatment (+3.90; P < .001; 95% CI, 1.95-5.84). Gray shading indicates 95% CIs. B, Line graph showing impact of immunosuppression on DLCO. A significant increase in DLCO % predicted after 12 months of treatment was found compared with the projected trend without treatment (+4.53%; P ≤ .001; 95% CI, 2.12-6.94). DLCO = diffusing capacity of the lungs for carbon monoxide.*

Matson S, *et al, Chest*, 2022

Glucocorticoids

- Avoid use in UIP
- Very commonly needed for exacerbations
- Pneumocystis prophylaxis until <15mg of prednisone
- Toxicity and side effects need close monitoring

Doyle TJ, et al. *Chest.* 2017

PANTHER-IPF Trial

- IPF patients
- Three-armed RCT
  - Combination therapy: prednisone, azathioprine, and N-acetyl-cysteine
  - N-acetyl-cysteine alone
  - Placebo
- Combination therapy had **increased** death and hospitalization compared to placebo

- Avoid prednisone and azathioprine in fibrotic ILDs

Ganesh R, et al. *N Engl J Med.* 2012

Mycophenolate mofetil

- Good evidence of efficacy in IPF
- Relatively poor efficacy for articular manifestations
  - May need other DMARDs in combination
- Use in patients with lung-predominant RA-ILD
- Consider mycophenolic acid for patients with GI issues or tolerability concerns
- May need to titrate up on the dose

Tzouvelekis A, et al. *Pulm Med.* 2012
Fischer A, et al. *J Rheumatol*. 2013
Tashkin DP, et al. *Lancet Respir Med*. 2016

Rituximab

- Observational studies suggest benefit in RA-ILD progression compared to other DMARDs
- Potential benefit in RA-bronchiectasis for prevention of exacerbations
- Anecdotal reports of benefits in pleural involvement

Md Yusof MY, *et al, Rheumatology,* 2017
Druce KL, *et al, RMD Open,* 2017

Cyclophosphamide

- Consider in severe forms of RA-ILD
- Safety concerns limit use

- Calcineurin inhibitors considered for refractory cases
  - Tacrolimus
  - Cyclosporine

Volkmann ER, et al. *Ann Rheum Dis.* 2019
Schupp JC, et al. *Respiration*. 2016

Tocilizumab

- FDA approval for SSc-related ILD
- Unclear if there may be similar efficacy in RA-ILD
- In RA-ILD, may be a reasonable option for joint predominant clinical course in patients with concurrent RA-ILD

Khanna D, et al. *Lancet.* 2016
Saper VE, et al. *Ann Rheum Dis*. 2019
Manfredi A, et al. *Intern Med J*. 2019

Abatacept

- Conflicting evidence, emerging as a potential therapy
  - More COPD exacerbations in RA clinical trials
  - Observational studies similar to other biologic DMARDs
- Single arm trial in RA-ILD suggests efficacy

Kang EH, *et al, Semin Arthritis Rheum,* 2020
Fernandez-Diaz C, et al, *Semin Arthritis Rheum*. 2018

Conclusions

- “Respiratory burden of RA”: high morbidity and mortality
- Heterogeneity of RA-ILD subtypes
  - UIP most common
  - NSIP common
- Many rheumatologic medications are important in management of these diseases
- Interdisciplinary approach is key to management
- Progress being made in identifying risk factors for RA-ILD

Thank you!

Brigham and Women's Hospital
Founding Member, Mass General Brigham

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