Disclosures/Funding

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Rheumatology Research Foundation
Advancing Treatment | Finding Cures

National Institutes of Health

NIAMS
National Institute of Arthritis and Musculoskeletal and Skin Diseases

BRIGHAM HEALTH
BWH BRIGHAM Research Institute

JBC JOINT BIOLOGY CONSORTIUM

VERITY

ACE Autoimmunity Centers of Excellence

Outline

1. Clinical background and development of rheumatoid arthritis (RA)

2. Prospective cohort studies for incident RA risk

3. Nested case-control studies for biomarkers and incident RA risk

4. Matched cohort studies for outcomes after RA diagnosis

5. Prospective RA registry studies for RA-associated interstitial lung disease (RA-ILD)

6. RA prevention randomized controlled trial design

Clinical background and development of RA
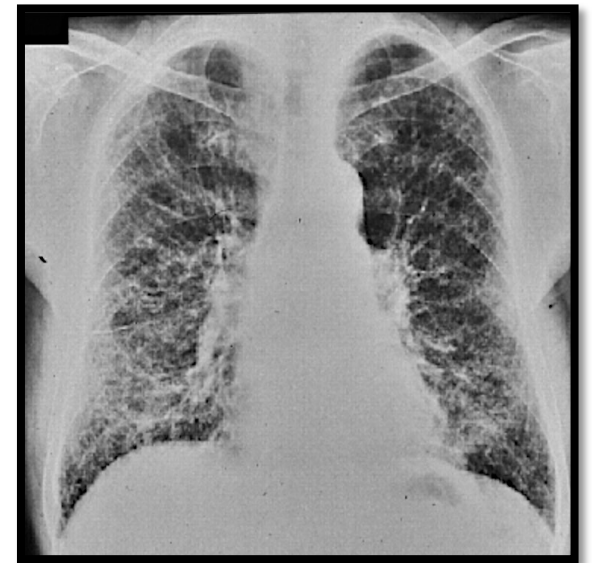
Background: Rheumatoid arthritis (RA)

- Chronic inflammatory autoimmune disease: **painful, swollen joints**

- Affects nearly 1% of adults (2.3 million in the US)

- 75% of patients with RA are **women**

- Median age at diagnosis: **55 years**

- Long-term consequences: **joint destruction, chronic pain, disability**

- **Autoantibodies**: rheumatoid factor (**RF**), anti-citrullinated protein antibodies (**ACPA**)
    - **Seropositive RA**: RF+ or ACPA+
        - 65% of patients
        - More severe clinical course
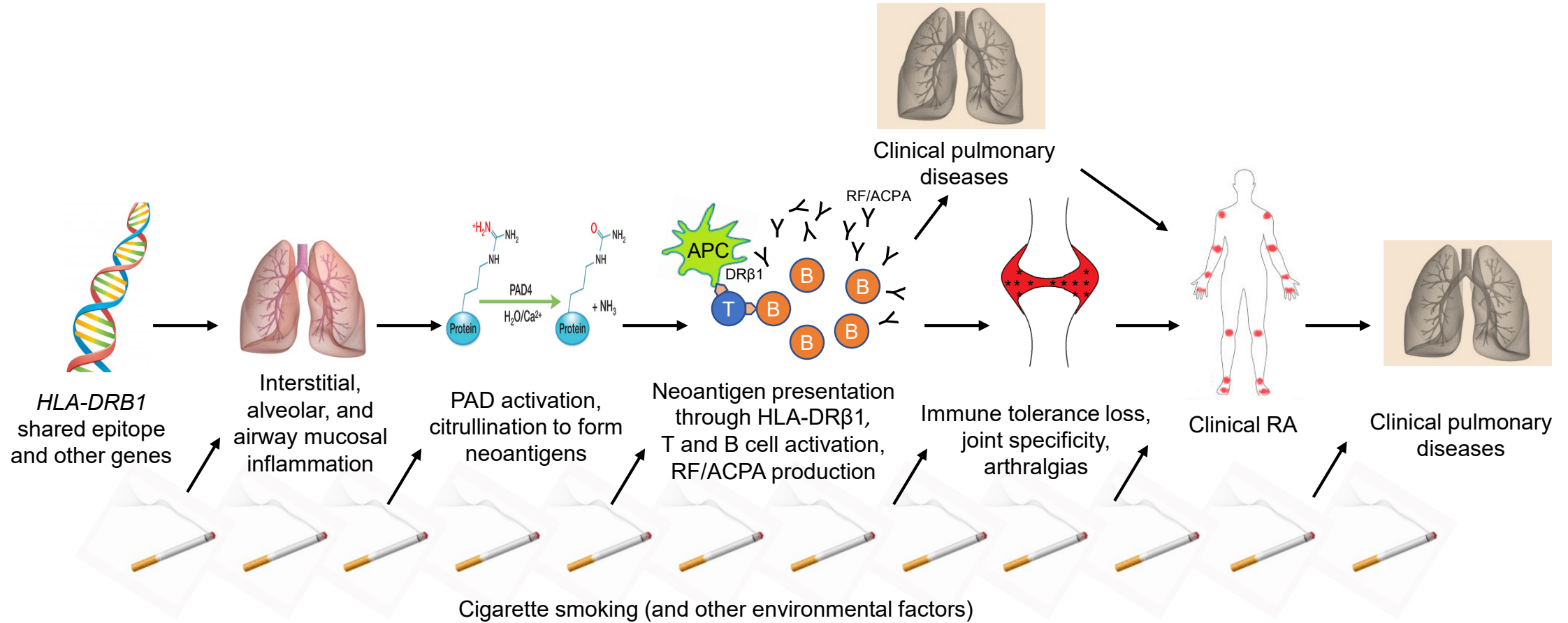   - **Seronegative RA**: RF- and ACPA-

- **Classification criteria** to define RA for research purposes

Sparks JA, *Ann Intern Med*, 2019

Background: RA and lung disease

- **RA-ILD**: Rheumatoid arthritis-associated interstitial lung disease
- Characterized by pulmonary **inflammation** and/or **fibrosis**
- Severe RA-ILD affects 2-10% of RA patients
  - Subclinical or mild RA-ILD in 25% of RA patients
- RA-ILD risk factors: male sex, older age, seropositivity
  - Can occur prior to articular involvement

- **Bronchiectasis**: damaged bronchi/airways
  - Shortness of breath and cough
  - Increases risk for pneumonia
  - Rare manifestation of longstanding, severe seropositive RA

6

Pipavath S, Godwin JD, *Clin Chest Med*, 2004

Background: Model of seropositive RA pathogenesis

HLA-DRB1 shared epitope and other genes

Interstitial, alveolar, and airway mucosal inflammation

PAD activation, citrullination to form neoantigens

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

Clinical pulmonary diseases

Immune tolerance loss, joint specificity, arthralgias

Clinical RA

Clinical pulmonary diseases

Cigarette smoking (and other environmental factors)

Prospective cohort studies for incident RA risk
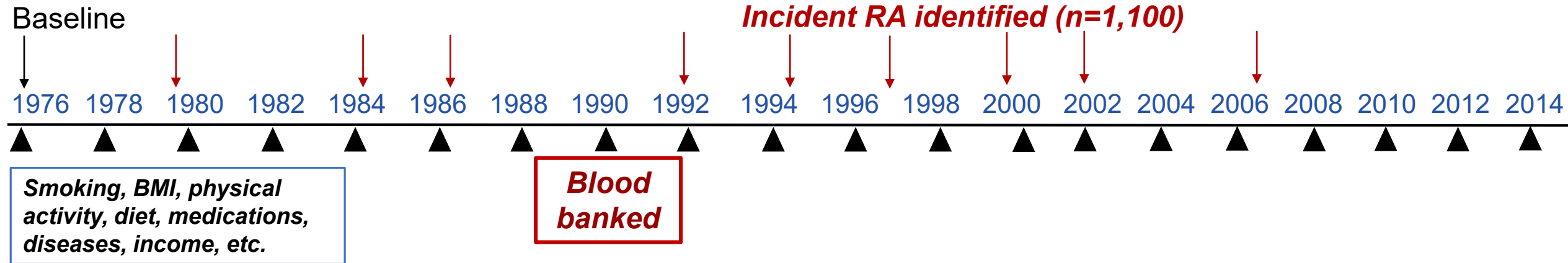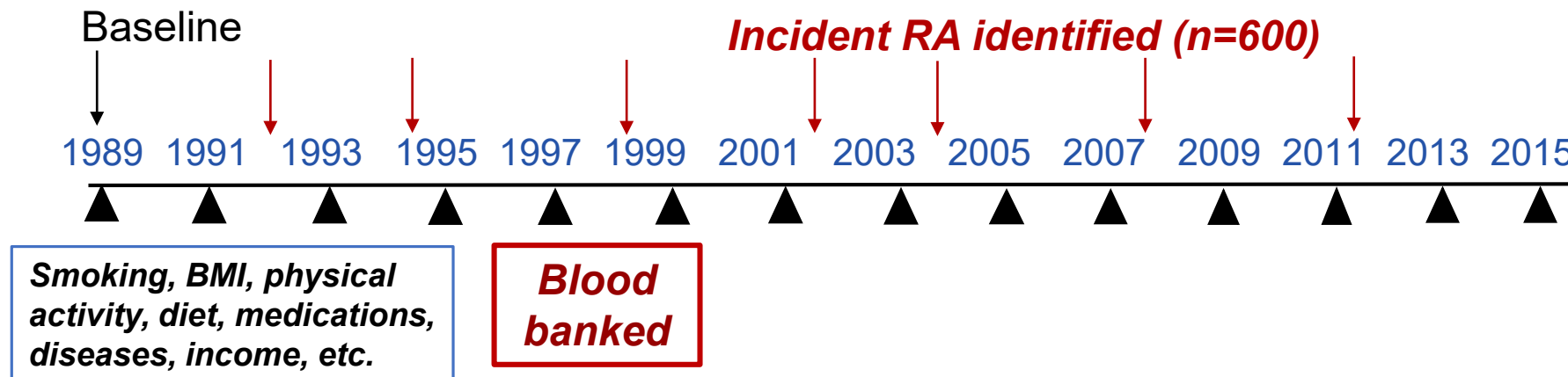
Identification of incident RA in the NHS and NHSII

Nurse self-reports new RA diagnosis

Screening Questionnaire mailed

Screen positive

Medical records requested/obtained

RA phenotyped from record review

RA cases meet ACR/EULAR criteria

Aletaha D, *et al, Arthritis Rheum*, 2010
Arnett FC, *et al, Arthritis Rheum,* 1988
Karlson EW, *et al, Ann Epidemiol,* 1995

Prospective cohort study design in the NHS for incident RA risk

Person-time by exposure status calculated for eligible **cases** and **non-cases**

RA diagnosed after start of NHS in 1976
Exposure measured at baseline

NHS starts 1976

Time in Nurses' Health Study
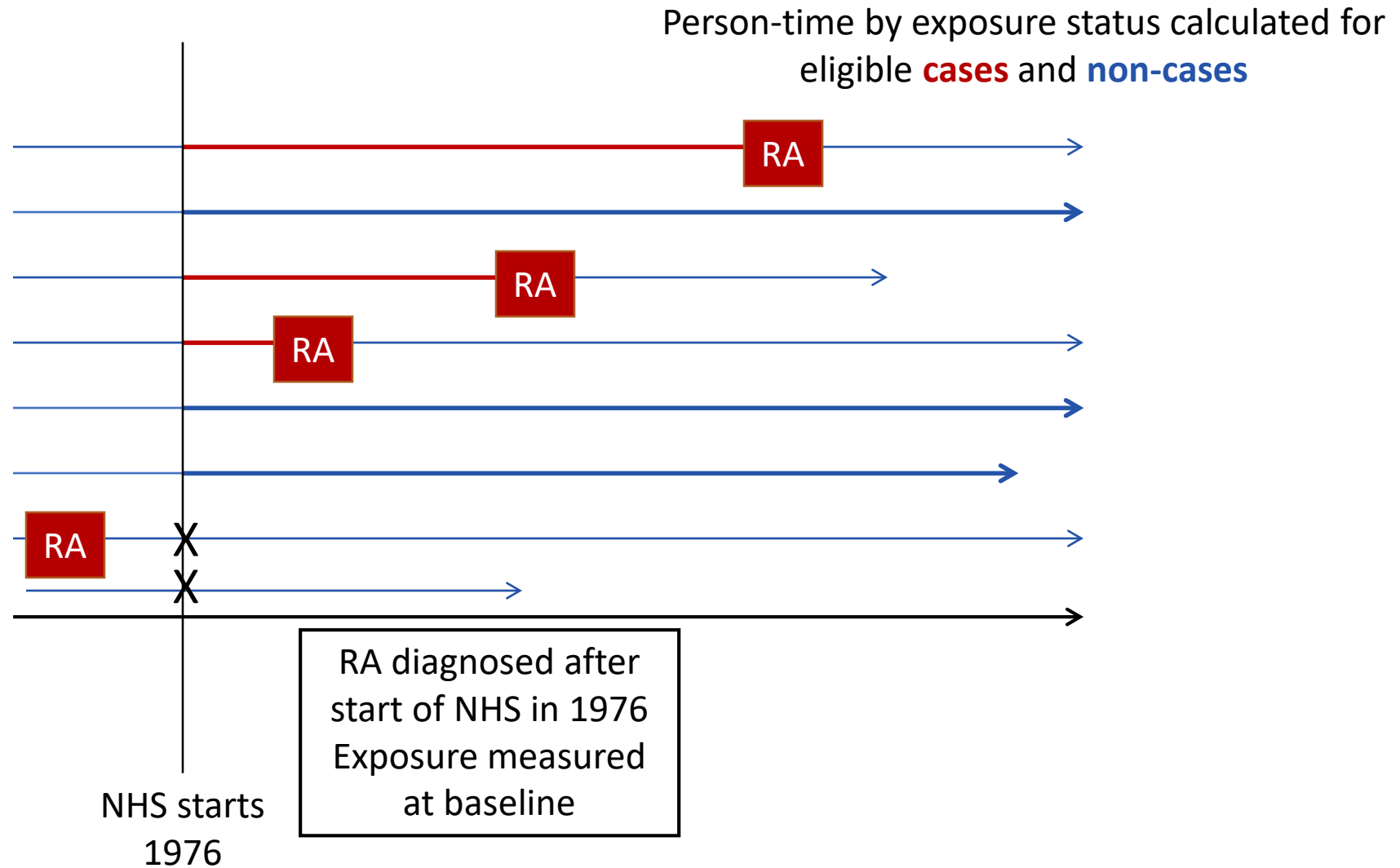
Follow-up and RA cases

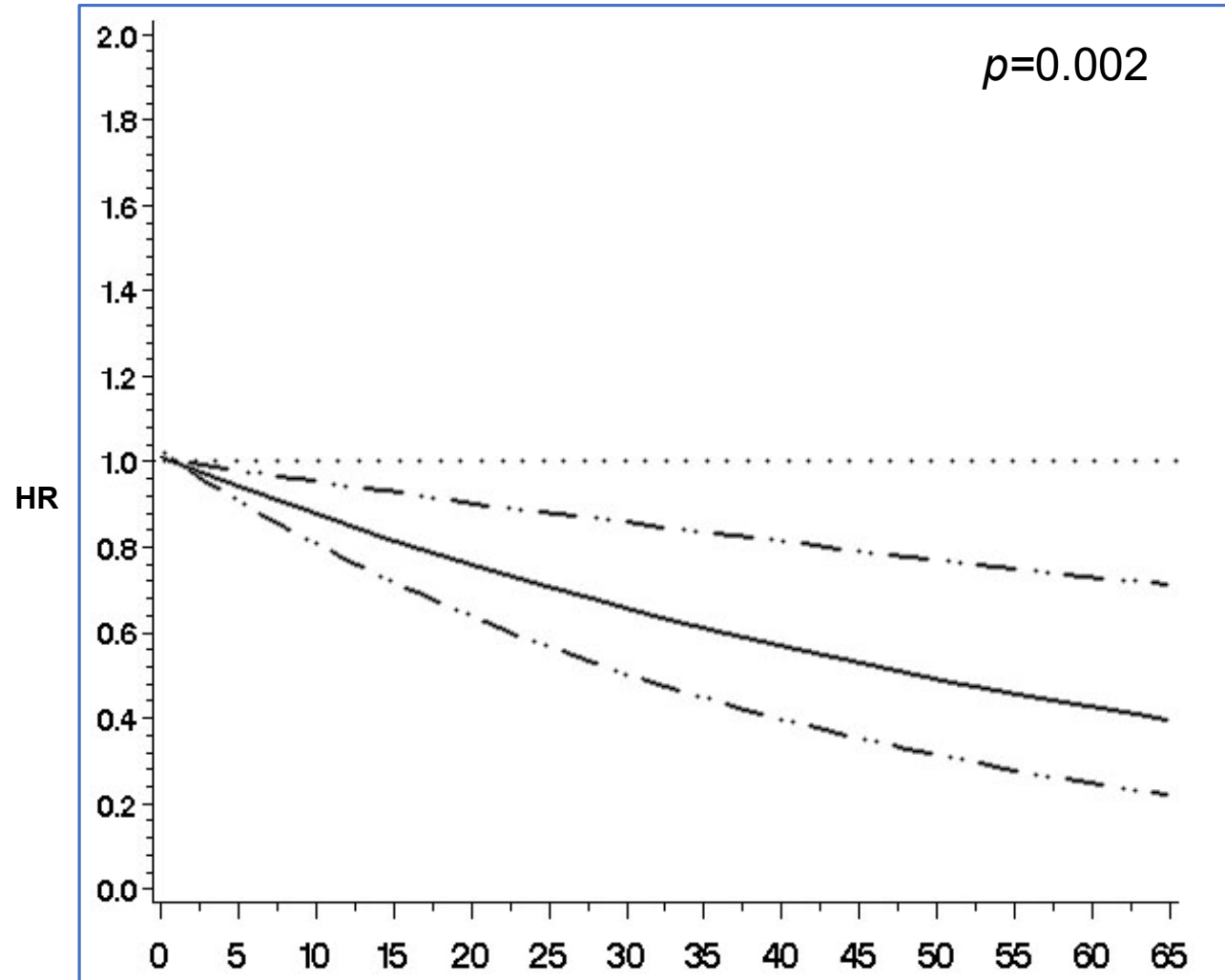- Total **n=230,732** women in the NHS/NHSII

- **1,528** incident RA cases during **6,037,151** person-years
  - Mean follow-up: 26.2 years/subject

  - 969 seropositive RA cases (63%)
  - 559 seronegative RA cases (37%)

Smoking status and RA risk

RA Type	Never HR (95%CI)	Past HR (95%CI)	Current HR (95%CI)
Seropositive RA			
Cases/person-yrs	415/3,254,327	385/1,932,207	169/832,888
Multivariable*	1.00 (Ref)	**1.48 (1.28,1.71)**	**1.65 (1.36,1.99)**
Seronegative RA			
Cases/person-yrs	260/3,254,901	211/1,932,090	88/832,099
Multivariable*	1.00 (Ref)	1.18 (0.98,1.43)	1.20 (0.93,1.55)

*Adjusted for age, calendar year, cohort, household income, body mass index, physical activity, alcohol intake, oral contraceptive use, parity/breastfeeding, and menopausal status/postmenopausal hormone use

Liu X, … , Sparks JA, *Arthritis Care Res*, 2019

Years since smoking cessation and <u>seropositive RA</u> risk

*Adjusted for age, questionnaire period, cohort, household income, body mass index, physical activity, alcohol intake, oral contraceptive use, parity/breastfeeding, and menopausal status/postmenopausal hormone use

Years since smoking cessation and <u>seronegative RA</u> risk

*Adjusted for age, questionnaire period, cohort, household income, body mass index, physical activity, alcohol intake, oral contraceptive use, parity/breastfeeding, and menopausal status/postmenopausal hormone use
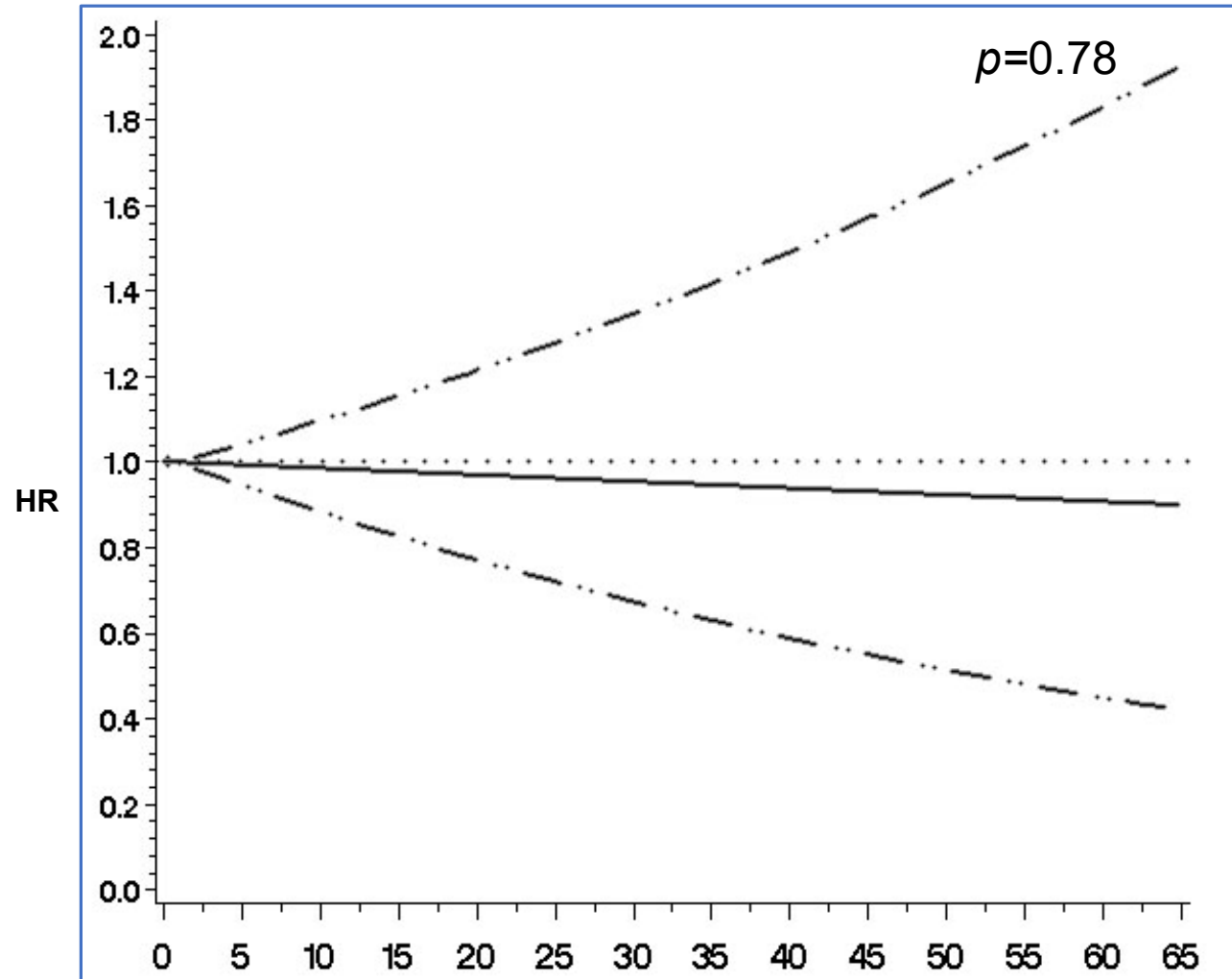
Liu X, ... , Sparks JA, *Arthritis Care Res*, 2019

COPD and risk for incident RA in NHS/NHSII
Primary analysis: Entire study sample

RA Type	No COPD or asthma HR (95%CI)	COPD HR (95%CI)
All RA		
Cases/person-years	1,029/4,337,186	31/47,285
Multivariable*	1.00 (Ref)	**1.80 (1.24,2.62)**
Seropositive RA		
Cases/person-years	642/4,328,257	21/47,134
Multivariable*	1.00 (Ref)	**1.97 (1.25,3.11)**
Seronegative RA		
Cases/person-years	387/4,327,740	10/47,121
Multivariable*	1.00 (Ref)	1.52 (0.79,2.91)

*Adjusted for age, questionnaire period, cohort, US geographic region, median household income, **smoking pack-years (continuous and quadratic), smoking status**, sedentary activity, parity/breastfeeding, menopausal status/postmenopausal hormone, dietary quality, body mass index, **passive smoking**
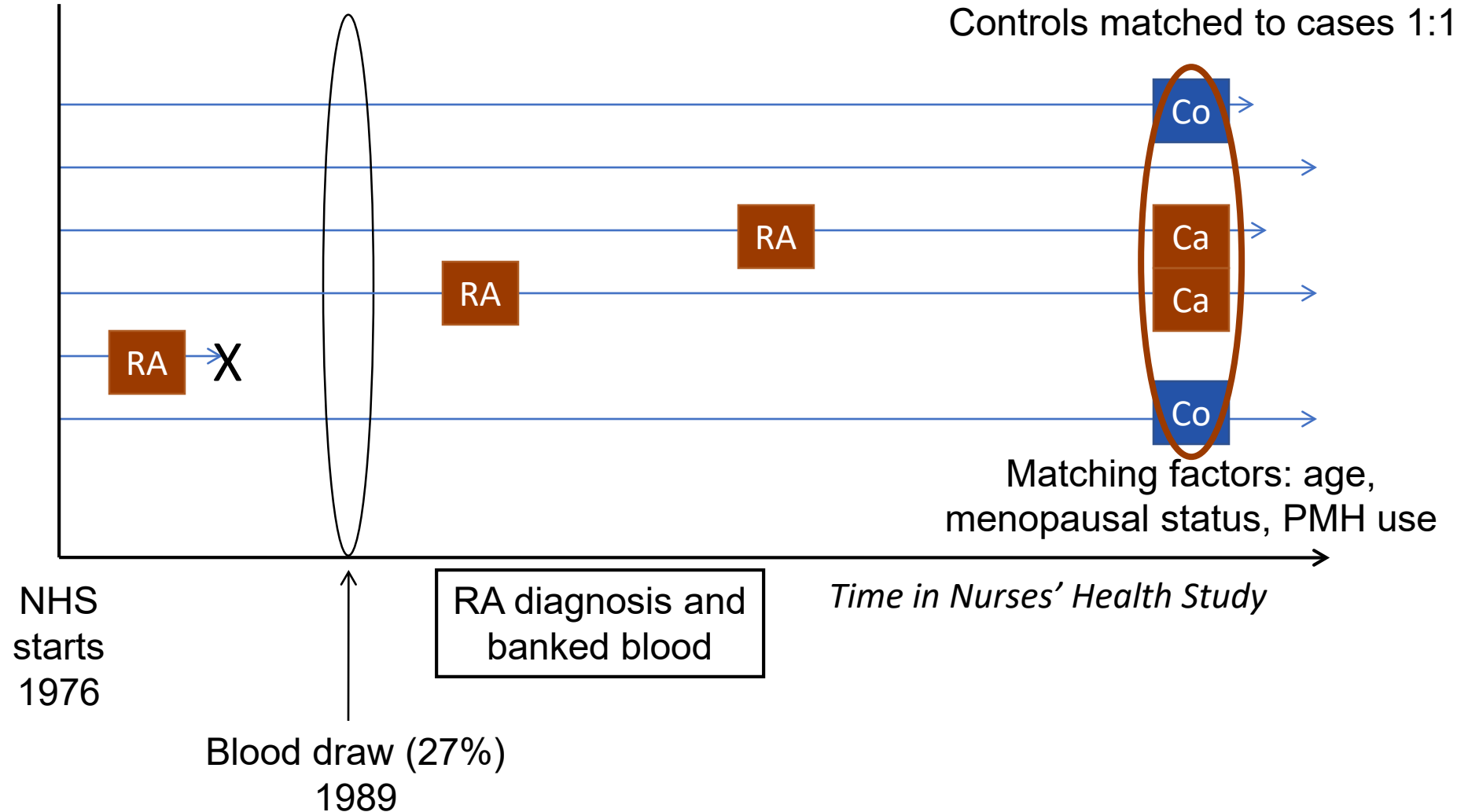
COPD and risk for incident RA in NHS/NHSII
Secondary analysis: Restricted to smokers aged >55 years

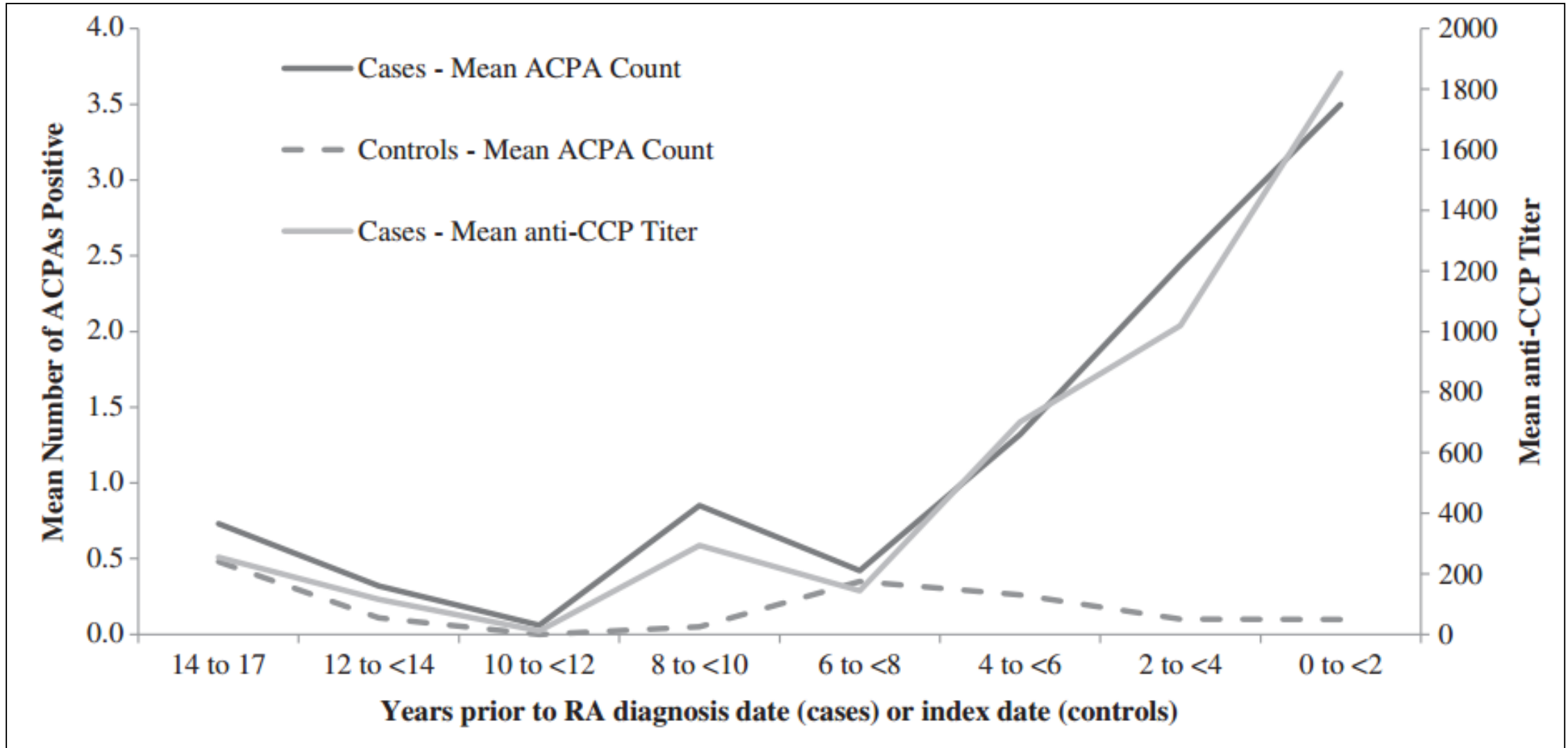| RA Type	No COPD or asthma HR (95%CI)	COPD HR (95%CI)
All RA		
Cases/person-years	295/928,014	21/29,365
Multivariable*	1.00 (Ref)	**2.20 (1.38,3.51)**
Seropositive RA		
Cases/person-years	176/926,338	15/29,271
Multivariable*	1.00 (Ref)	**2.85 (1.63,4.99)**
Seronegative RA		
Cases/person-years	119/926,271	6/29,279
Multivariable*	1.00 (Ref)	1.40 (0.59,3.29)

*Adjusted for age, questionnaire period, cohort, US geographic region, median household income, **smoking pack-years (continuous and quadratic), smoking status**, sedentary activity, parity/breastfeeding, menopausal status/postmenopausal hormone, dietary quality, body mass index, **passive smoking**

Nested case-control studies for biomarkers and incident RA risk

Nested case-control study design in the NHS for biomarkers and incident RA risk

Controls matched to cases 1:1

Co
Ca
Ca
Co

Matching factors: age, menopausal status, PMH use

RA
RA
RA X

NHS starts 1976

Blood draw (27%) 1989

RA diagnosis and banked blood

Time in Nurses' Health Study

Pre-diagnosis CCP/ACPA in RA cases/controls in the NHS

Asthma and RA risk by pre-RA ACPA status

Pre-RA ACPA Status	Multivariable** OR (95%CI)
Pre-RA ACPA+ RA	
n=96 outcomes from total n=382	
No asthma	1.00 (Ref)
Asthma	**3.57 (1.58,8.04)**
Pre-RA ACPA- RA	
n=188 outcomes from total n=751	
No asthma	1.00 (Ref)
Asthma	0.86 (0.46,1.60)

*Matching factors: age at index date, time from blood draw to index date, cohort, menopausal status, and postmenopausal hormone use

**Additionally adjusted for smoking pack-years, parental passive smoking, ever lived with smoker, and body mass index

Zaccardelli A & Liu X, ... , Sparks JA, *Arthritis Res Ther*, 2019

Matched cohort studies for outcomes before/after RA diagnosis

Matched cohort study nested in the NHS for pre-RA biomarkers and outcomes

Nurses' Health Study

Blood draw date (index date; baseline for analyses)

RA diagnosis date (or matched date for non-RA controls)

Outcome: incident COPD

End of f/u

Questionnaires every 2 years

Covariates for adjustment
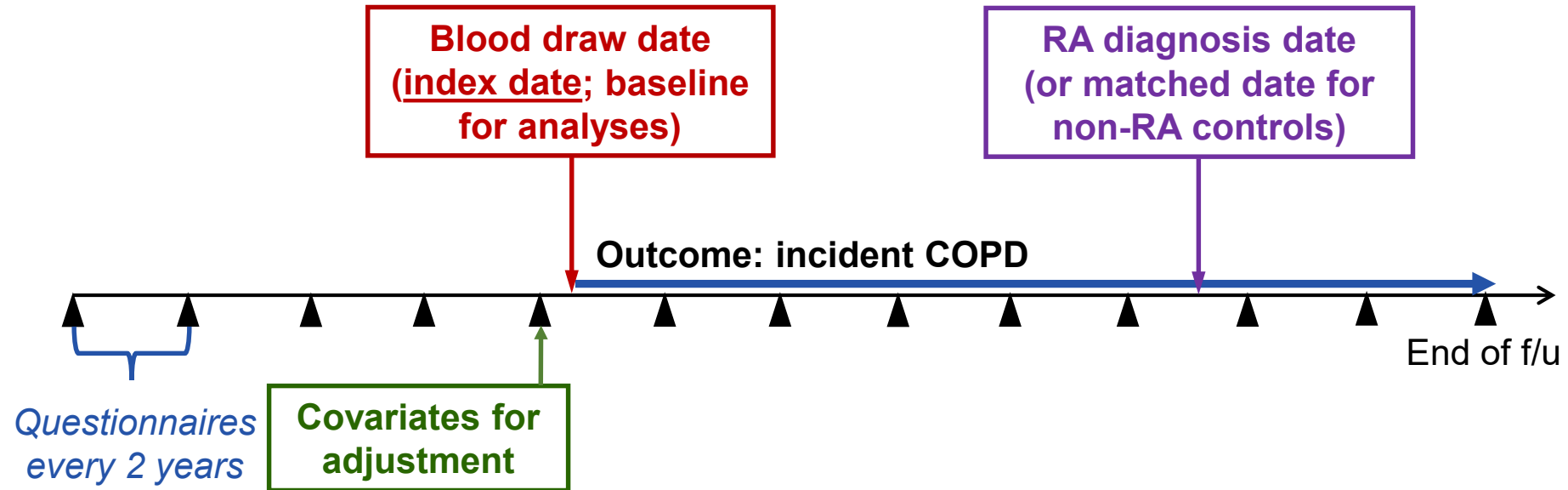
Exposure variables:
- **All pre-RA vs. matched controls**
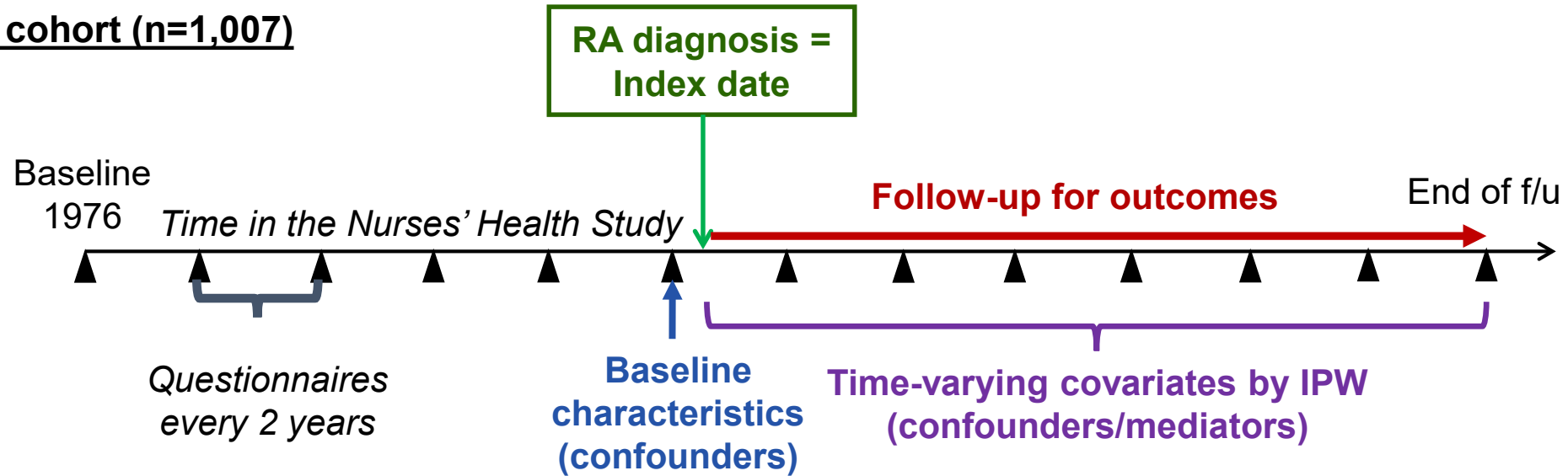- **Pre-RA ACPA+ vs. matched controls**
- **Pre-RA ACPA- vs. matched controls**

Results: Pre-RA ACPA status and risk for incident COPD

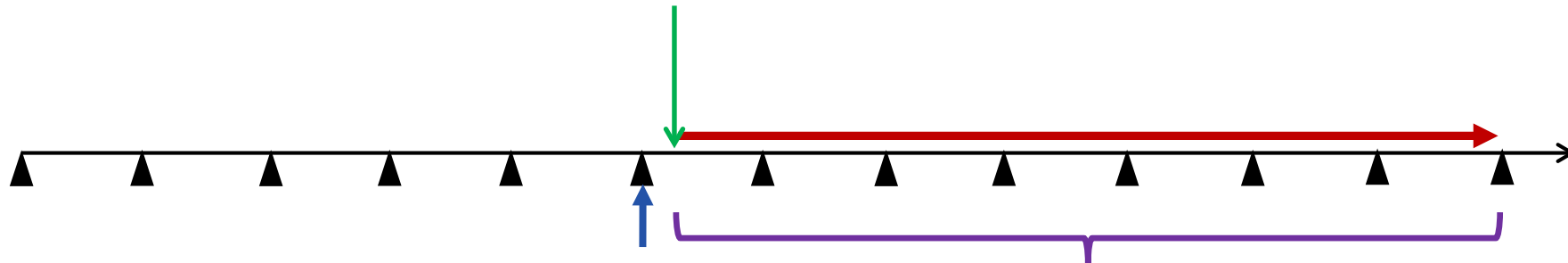| Pre-RA ACPA Status	COPD cases/ person-years	Multivariable* HR (95%CI)
Pre-RA ACPA+ (n=59)	13/1,030	**3.04 (1.33,7.00)**
Matched controls (n=176)	14/3,375	1.00 (Ref)
Pre-RA ACPA- (n=224)	23/4,117	1.07 (0.65,1.75)
Matched controls (n=666)	57/12,967	1.00 (Ref)

*Adjusted for matching factors (age, time to blood draw, cohort, menopause/hormone use), smoking pack-years, body mass index, and median household income

NHS: Matched prospective cohort study design for outcomes after RA diagnosis

Incident RA cohort (n=1,007)

RA diagnosis = Index date

Baseline
1976

Time in the Nurses' Health Study

Follow-up for outcomes

End of f/u

Questionnaires every 2 years

Baseline characteristics (confounders)

Time-varying covariates by IPW (confounders/mediators)

Comparator cohort (n=10,070): Each RA case matched to 10 non-RA comparators by age/year at index date

RA vs. comparators: Incident COPD risk

RA Type	COPD HR (95%CI)
All RA	
Age-adjusted	1.52 (1.17,1.97)
Smoking-adjusted	1.43 (1.09,1.87)
Multivariable adjusted	1.68 (1.36,2.07)
Seropositive RA	
Age-adjusted	1.60 (1.17,2.19)
Smoking-adjusted	1.44 (1.04,2.00)
Multivariable adjusted	1.74 (1.36,2.23)
Seronegative RA	
Age-adjusted	1.41 (0.89,2.23)
Smoking-adjusted	1.47 (0.91,2.39)
Multivariable adjusted	1.42 (0.91,2.40)

RA vs. comparators: Respiratory mortality risk

RA Type	HR (95%CI)
All RA	
1: Baseline confounders model	**2.57 (1.91,3.45)**
2: Model 1 + Time-updated lifestyle mediators	**2.23 (1.63,3.05)**
3: Model 2 + Multimorbidity mediators	**1.89 (1.39,2.57)**
Seropositive RA	
1: Baseline confounders model	**3.65 (2.59,5.14)**
2: Model 1 + Time-updated lifestyle mediators	**3.40 (2.38,4.86)**
3: Model 2 + Multimorbidity mediators	**2.91 (2.04,4.17)**
Seronegative RA	
1: Baseline confounders model	1.11 (0.59,2.08)
2: Model 1 + Time-updated lifestyle mediators	0.88 (0.44,1.76)
3: Model 2 + Multimorbidity mediators	0.80 (0.41,1.54)

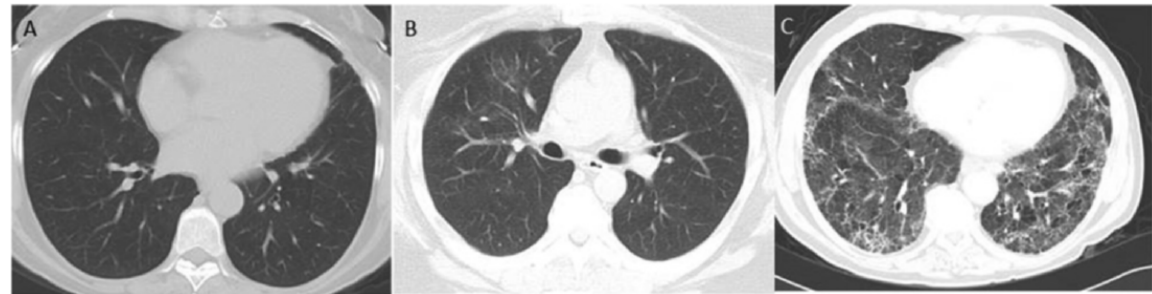# Prospective RA registry studies

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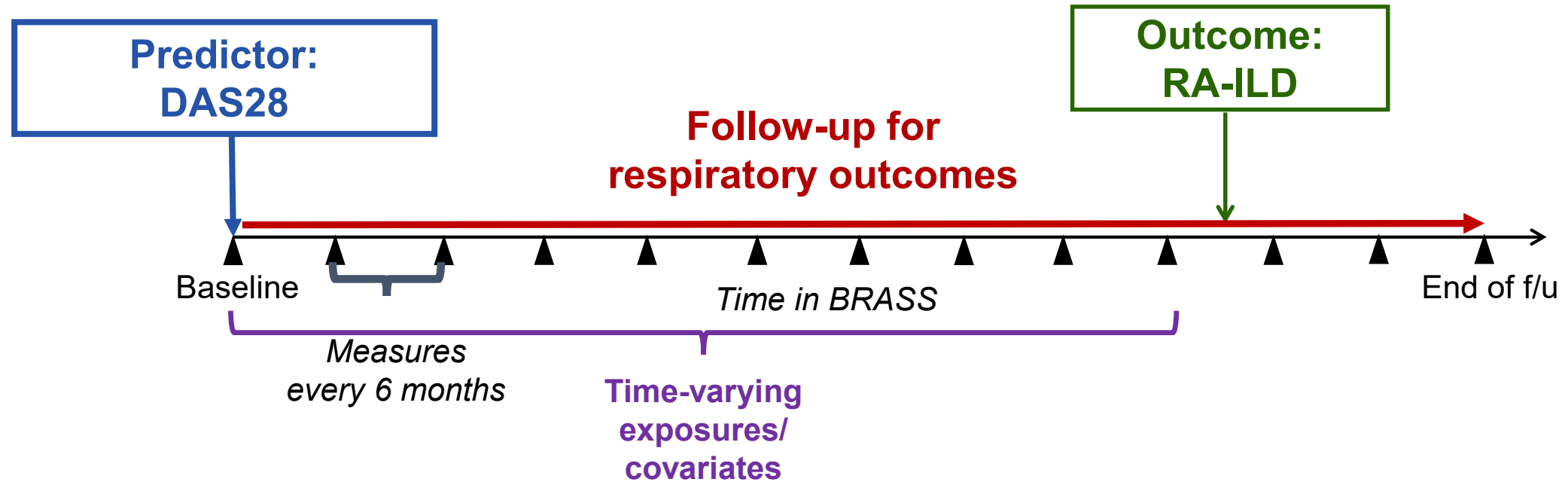
RA-ILD in BRASS

- Research review of images of clinically-indicated CT chest scans
  - 1 attending pulmonologist
  - 2 attending chest radiologists

- Each CT chest scan classified as:

Lung cancer
Pneumonia

Uninterpretable
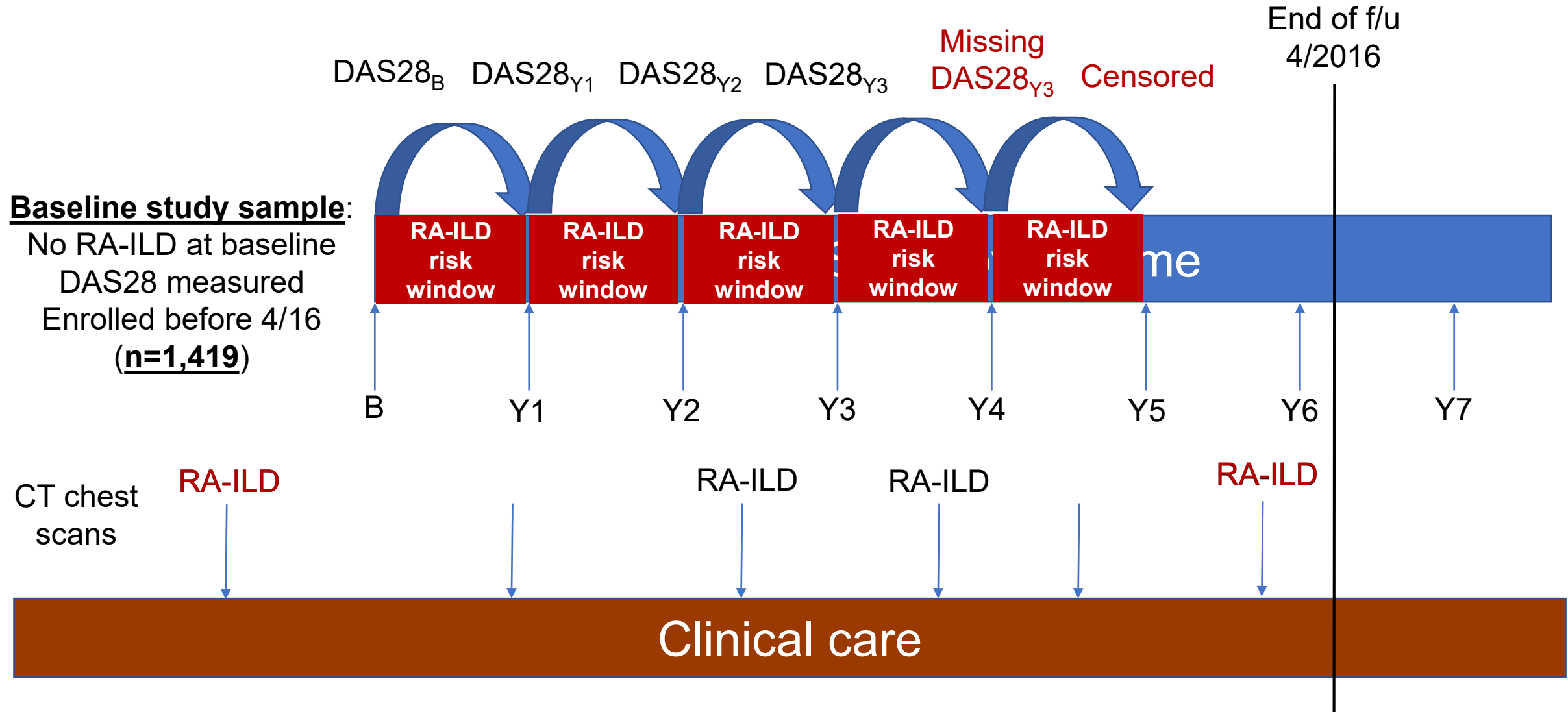

No RA-ILD   **Early RA-ILD**   **Clinically-significant ILD**

- ***Outcome definition***: early/clinically-significant RA-ILD (n=86)
  - Date of outcome: first CT chest scan performed satisfying criteria

Doyle TJ, *et al, Chest*, 2014

Study design: Prospective cohort
Primary analysis: Time-updated with censoring

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

End of f/u 4/2016

$DAS28_B$ $DAS28_{Y1}$ $DAS28_{Y2}$ $DAS28_{Y3}$ Missing $DAS28_{Y3}$ Censored

Baseline study sample: No RA-ILD at baseline DAS28 measured Enrolled before 4/16 (**n=1,419**)

| RA-ILD risk window | RA-ILD risk window | RA-ILD risk window | RA-ILD risk window | RA-ILD risk window |

B   Y1   Y2   Y3   Y4   Y5   Y6   Y7

CT chest scans

RA-ILD   RA-ILD   RA-ILD   RA-ILD

Clinical care

DAS28 and RA-ILD risk

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

4-level ordinal DAS28 and RA-ILD risk

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**

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

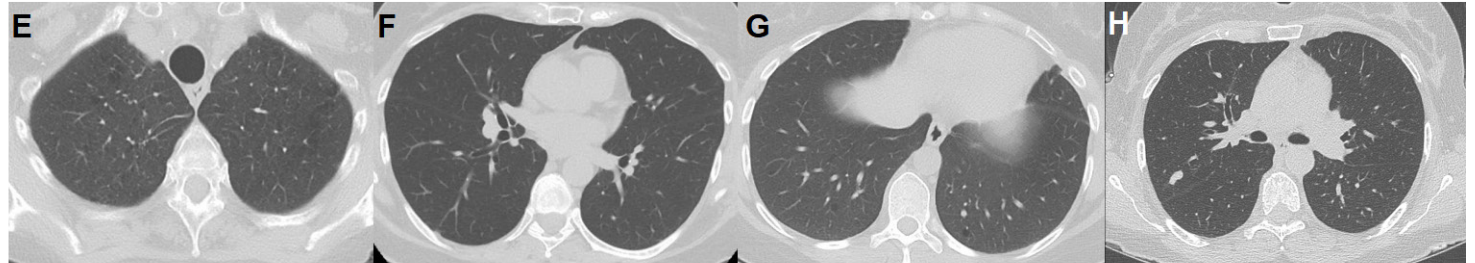*Adjusted for age, sex, smoking, RA duration, serostatus
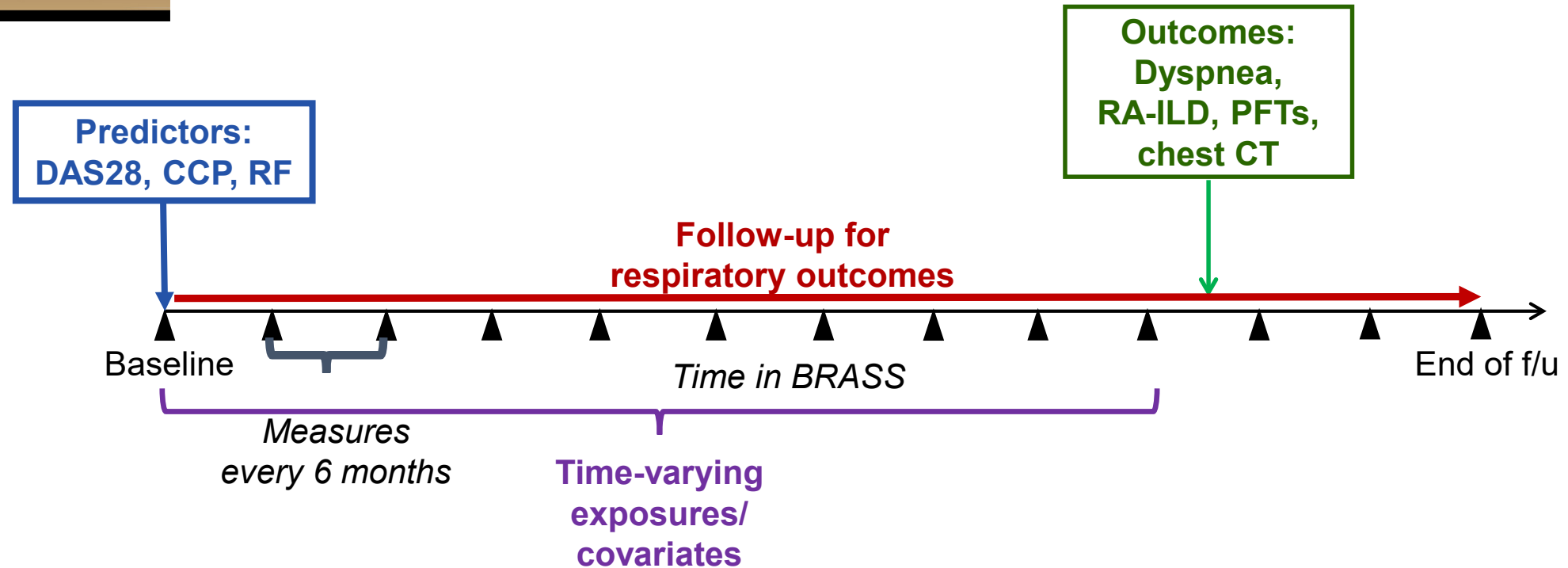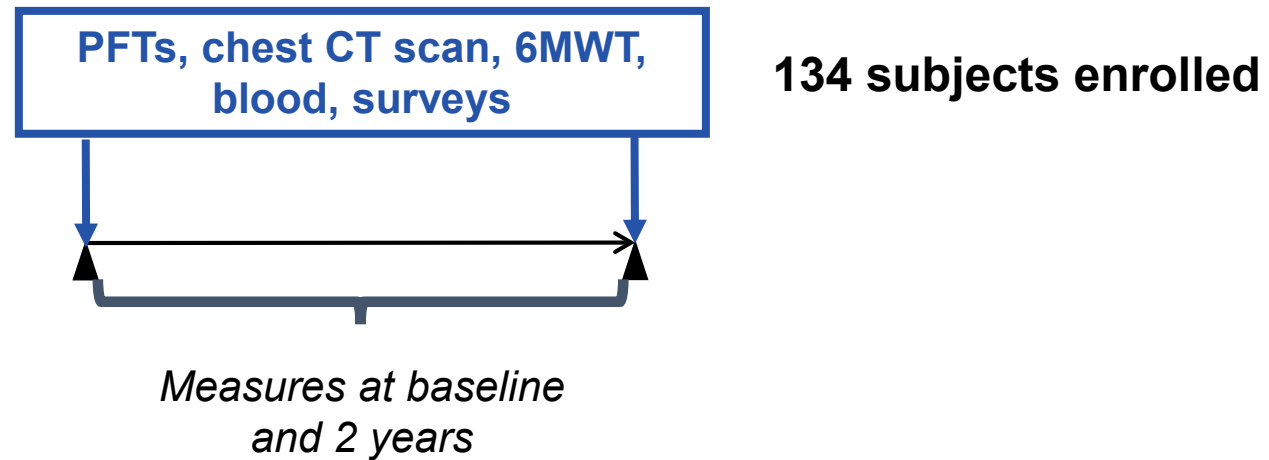
- Undiagnosed parenchymal lung disease: 44%
  - Associations: older age, white race, cough, lower D_{LCO}, diffusion defect, more dyspnea, higher RF titer, higher ACPA titer

- Emphysema: 37%
- Bronchiectasis: 28%
- Subclinical RA-ILD: 16%
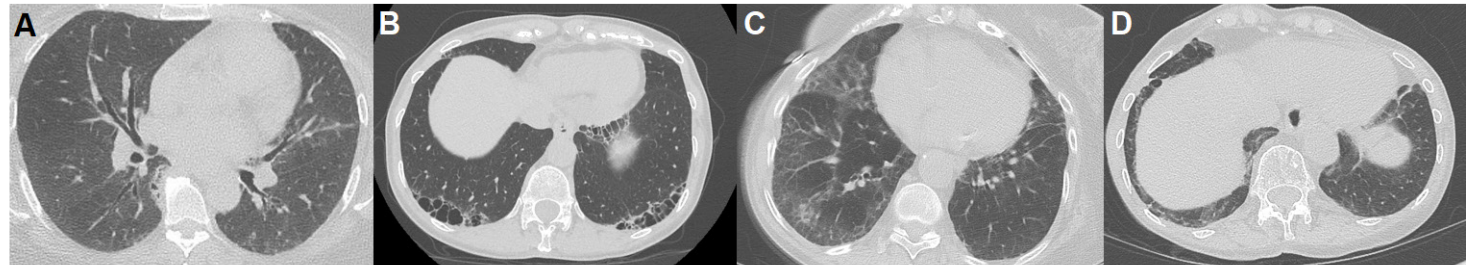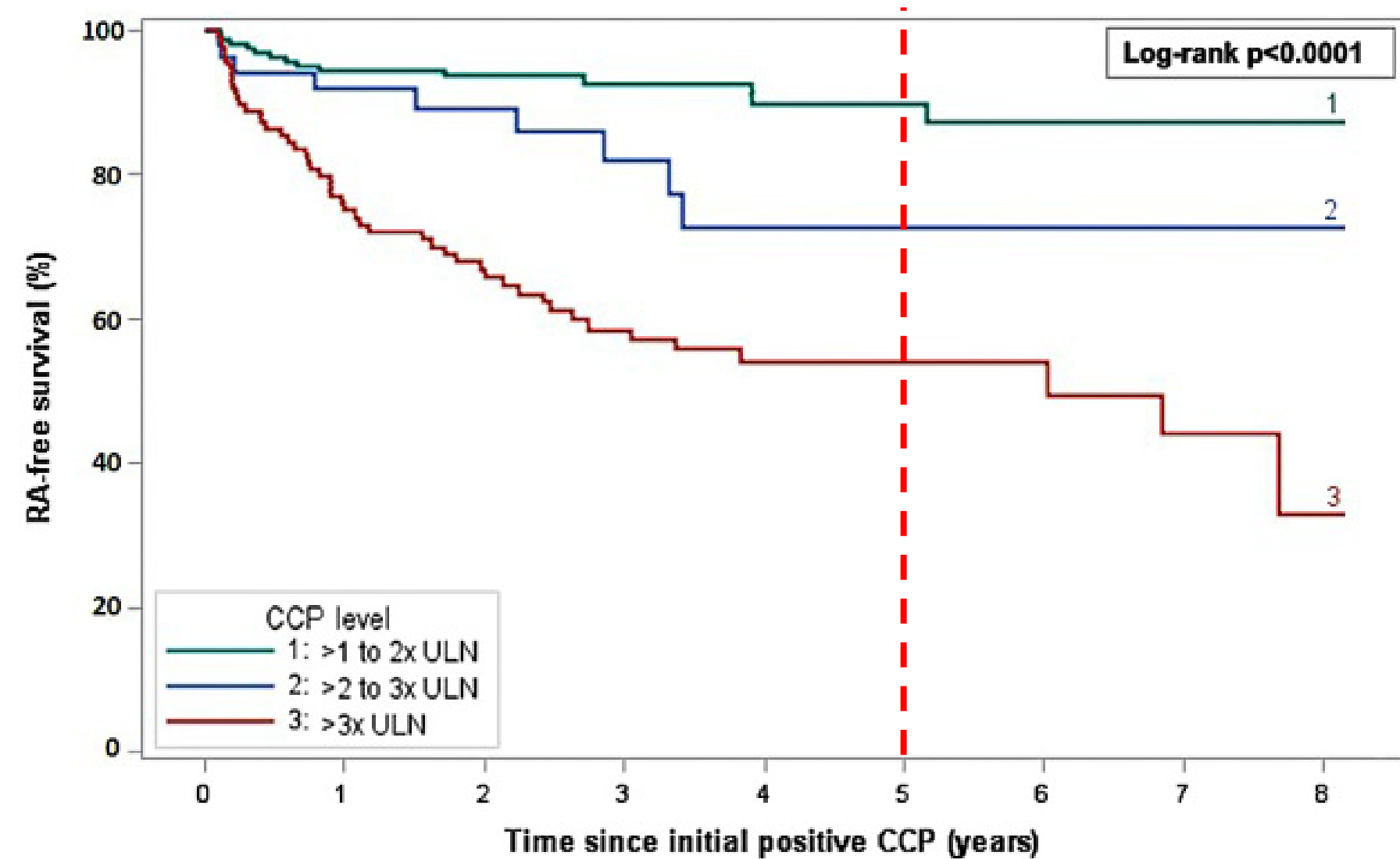

A-D. Interstitial Lung Abnormalities

E. Emphysema   F. Bronchiectasis   G. Cystic Lung Disease   H. Pulmonary Nodule

35

RA prevention randomized controlled trial design

RA-free survival according to ACPA level

5-year RA risk:

Low ACPA+: 10.2%

Medium ACPA+: 27.4%

High ACPA+: 46.0%

Log-rank p<0.0001

CCP level
1: >1 to 2x ULN
2: >2 to 3x ULN
3: >3x ULN

RA-free survival (%)

Time since initial positive CCP (years)

1	167	142	120	91	61	38	20	15	9
2	52	39	32	18	14	8	4	2	1
3	121	77	59	46	30	22	12	8	2

37

Ford JA, *et al, Arthritis Care Res*, 2019

StopRA: Strategy to Prevent Rheumatoid Arthritis

Clinical trial for RA prevention funded by the
Autoimmune Centers of Excellence (NIAID)

Eligibility:
ACPA+ >2x ULN
No RA or related diseases
No DMARD use
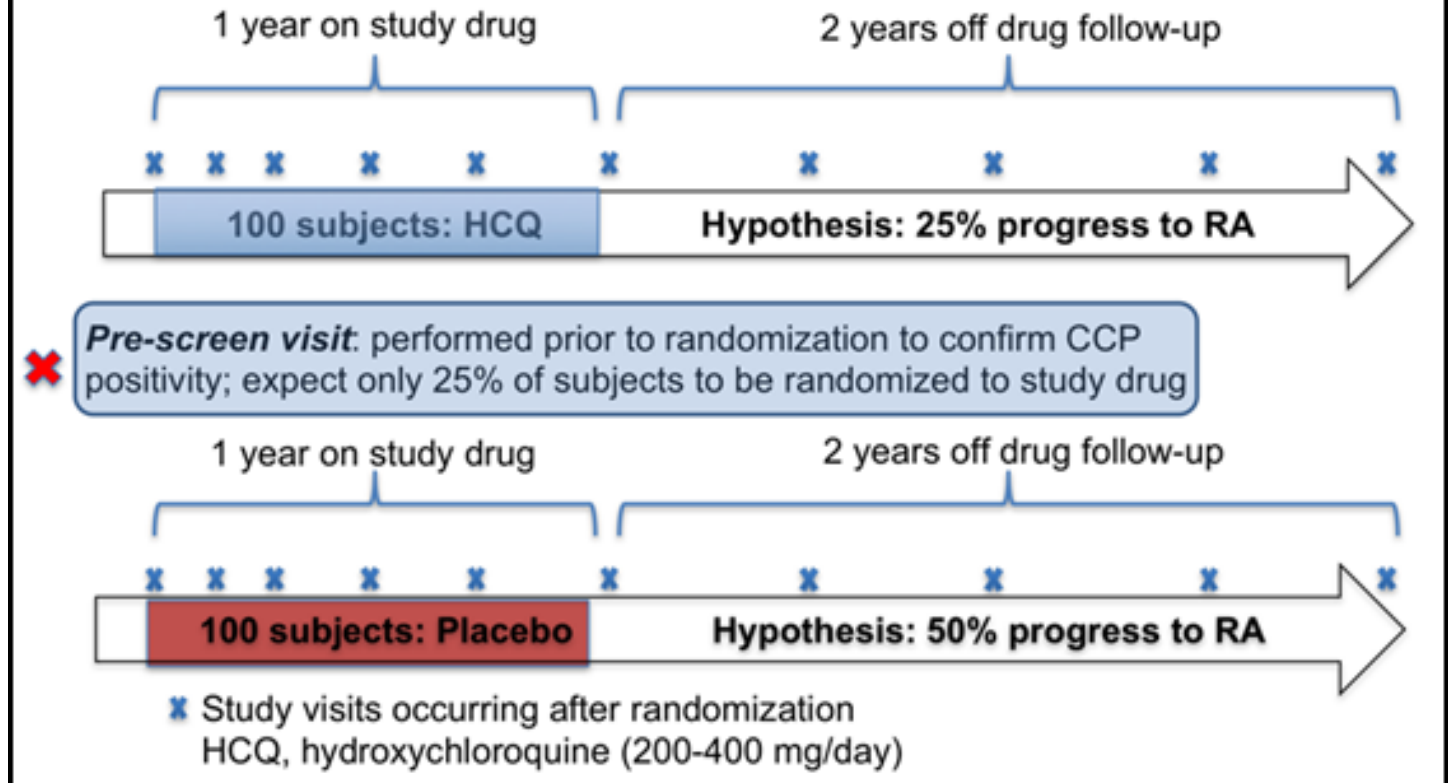
StopRA mechanistic studies

- Change in levels of RF, ACPA, and inflammatory markers

- Immunophenotyping of peripheral blood mononuclear cells

StopRA clinical/epidemiologic studies

- **Lung course/symptoms**

- Surveys
  - Lifestyle factors
  - Diet
  - Medications
  - Medical history
  - Family history
  - Symptoms

- Pain trajectory

- Transition to/after RA studies

Summary

- Illustrated different study designs to investigate respiratory burden of seropositive RA

- Prospective cohort studies
  - Associations of smoking and COPD with incident seropositive RA risk

- Biomarker studies in pre-RA
  - ACPA elevation 2-10 years prior to RA diagnosis
  - Pre-RA ACPA elevation strongly associated with asthma/COPD

- Excess COPD and respiratory mortality for seropositive RA not explained by smoking

- RA disease features and risk for respiratory outcomes
  - Increased articular disease activity and RA-ILD risk

- Recruitment ongoing for first RA prevention trial in the US

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