Epidemiologic and Patient-Oriented Research Methods for Rheumatoid Arthritis Etiology and Outcomes

Presented by:
Jeffrey A. Sparks, MD, MMSc
Brigham and Women’s Hospital
Harvard Medical School
Disclosures/Funding

No personal financial disclosures

Funding

- NIAMS K23 AR069688 (Sparks)
- NIAMS R03 AR075886 (Sparks)
- NIAMS L30 AR066953 (Sparks)
- RRF K Supplement Award (Sparks)
- Brigham Research Institute Microgrant (Sparks)
- Joint Biology Consortium Microgrant (Sparks)

- NIAMS P30 AR070253 (JBC, Nigrovic)
- NIAMS P30 AR072577 (VERITY, Solomon)
- Autoimmune Centers of Excellence (StopRA, Deane/Holers)
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

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-DRB1, T and B cell activation, RF/ACPA production

Immune tolerance loss, joint specificity, arthralgias

Clinical RA

Clinical pulmonary diseases

Cigarette smoking (and other environmental factors)

Sparks JA, Karlson EW, Curr Rheumatol Rep, 2016
Prospective cohort studies for incident RA risk
Nurses’ Health Study (n=121,700; 30-55 years in 1976)

Baseline


Incident RA identified (n=1,100)

Smoking, BMI, physical activity, diet, medications, diseases, income, etc.

Blood banked

Nurses’ Health Study II (n=116,430; 25-42 years in 1989)

Baseline

1989  1991  1993  1995  1997  1999  2001  2003  2005  2007  2009  2011  2013  2015

Incident RA identified (n=600)

Smoking, BMI, physical activity, diet, medications, diseases, income, etc.

Blood banked
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

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

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

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

*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 **seropositive RA risk**

![Graph showing the relationship between years since smoking cessation and seropositive RA risk.](image)

*p = 0.002*

*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
Years since smoking cessation and seronegative RA risk

*p=0.78

*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

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

*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

Ford JA, ... , Sparks JA, Arthritis Rheumatol, 2020
### COPD and risk for incident RA in NHS/NHSII

Secondary analysis: Restricted to smokers aged >55 years

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

*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

Ford JA, ..., Sparks JA, *Arthritis Rheumatol*, 2020
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

Matching factors: age, menopausal status, PMH use

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

<table>
<thead>
<tr>
<th>Pre-RA ACPA Status</th>
<th>Multivariable**</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-RA ACPA+ RA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n=96$ outcomes from total $n=382$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No asthma</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td><strong>3.57 (1.58,8.04)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Pre-RA ACPA- RA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n=188$ outcomes from total $n=751$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No asthma</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>0.86 (0.46,1.60)</td>
<td></td>
</tr>
</tbody>
</table>

*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

Matched cohort studies for outcomes before/after RA diagnosis
Matched cohort study nested in the NHS for pre-RA biomarkers and outcomes

Blood draw date (index date; baseline for analyses)

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

Outcome: incident COPD

Covariates for adjustment

Exposure variables:
- All pre-RA vs. matched controls
- Pre-RA ACPA+ vs. matched controls
- Pre-RA ACPA- vs. matched controls

Questionnaires every 2 years
## Results: Pre-RA ACPA status and risk for incident COPD

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

*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)
- Baseline 1976
- Time in the Nurses’ Health Study
- RA diagnosis = Index date
- Follow-up for outcomes: Questionnaires every 2 years
- Time-varying covariates by IPW (confounders/mediators)
- End of f/u

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

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

## RA vs. comparators: Respiratory mortality risk

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

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

Up to 15 years of follow-up / recruitment ongoing

Outcome: RA-ILD

Predictor: DAS28

Follow-up for respiratory outcomes

Baseline

Time in BRASS

End of f/u

Measures every 6 months

Time-varying exposures/ covariates
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

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

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

CT chest scans

Clinical care

End of f/u
4/2016

<table>
<thead>
<tr>
<th>Time</th>
<th>Clinical Care</th>
<th>RA-ILD risk window</th>
<th>DAS28B, DAS28Y1, DAS28Y2, DAS28Y3</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

CT chest scans

Clinical care
DAS28 and RA-ILD risk

<table>
<thead>
<tr>
<th>RA-ILD risk</th>
<th>Remission/Low HR (95%CI)</th>
<th>Moderate/High HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases/person-years</td>
<td>26/5,459</td>
<td>35/2,509</td>
</tr>
<tr>
<td>Multivariable*</td>
<td>1.00 (Ref)</td>
<td>2.22 (1.28, 3.82)</td>
</tr>
</tbody>
</table>

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

### 4-level ordinal DAS28 and RA-ILD risk

<table>
<thead>
<tr>
<th>RA-ILD Risk</th>
<th>Remission HR (95%CI)</th>
<th>Low HR (95%CI)</th>
<th>Moderate HR (95%CI)</th>
<th>High HR (95%CI)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases/person-years</td>
<td>18/4,232</td>
<td>8/1,227</td>
<td>20/1,828</td>
<td>15/681</td>
<td></td>
</tr>
<tr>
<td>Multivariable*</td>
<td>1.00 (Ref)</td>
<td>1.41 (0.61,3.28)</td>
<td>2.08 (1.06,4.05)</td>
<td>3.48 (1.64,7.38)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RA-ILD Risk</th>
<th>HR (95%CI) per unit increase in DAS28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases/person-years</td>
<td>61/7,968</td>
</tr>
<tr>
<td>Multivariable*</td>
<td>1.35 (1.14,1.60)</td>
</tr>
</tbody>
</table>

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

Sparks JA, et al, Arthritis Rheumatol, 2019
Cohort analyses in BRASS (n = 1,600)

Predictors: DAS28, CCP, RF

Follow-up for respiratory outcomes

Time in BRASS

Baseline

Time-varying exposures/covariates

End of f/u

Outcomes: Dyspnea, RA-ILD, PFTs, chest CT

BRASS-ILD prospective substudy

PFTs, chest CT scan, 6MWT, blood, surveys

134 subjects enrolled

Measures at baseline and 2 years

Measures every 6 months
BRASS-ILD interim findings (n=106)

- 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
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%

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
Thanks

@jeffsparks
jsparks@bwh.harvard.edu

NHS
- Elizabeth Karlson
- Karen Costenbader
- Bing Lu
- Julia Ford
- Kazuki Yoshida
- Alessandra Zaccardelli
- Susan Malspeis
- Jing Cui
- Jiaqi Wang
- Lauren Prisco
- Lily Martin

BRASS
- Nancy Shadick
- Michael Weinblatt
- Christine Iannaccone
- Aliza Liebman
- Sicong Huang
- Weixing Huang
- Vivi Feathers
- Gabriela Maica
- Adel Andemeskel
- Joshua Colls

BRASS-ILD
- Tracy Doyle
- Wesley Xiong
- Lauren Prisco
- Lily Martin
- Allison Marshall
- Alessandra Zaccardelli
- Maura Friedlander
- Elizabeth Karlson
- Ivan Rosas
- Paul Dellaripa
- Anthony Esposito

Funders: NIH/NIAMS (K23, R03, Loan Repayment Program, JBC, VERITY), NIH/NIAID (StopRA), Rheumatology Research Foundation