Understanding the connection between air pollution and rheumatic disease

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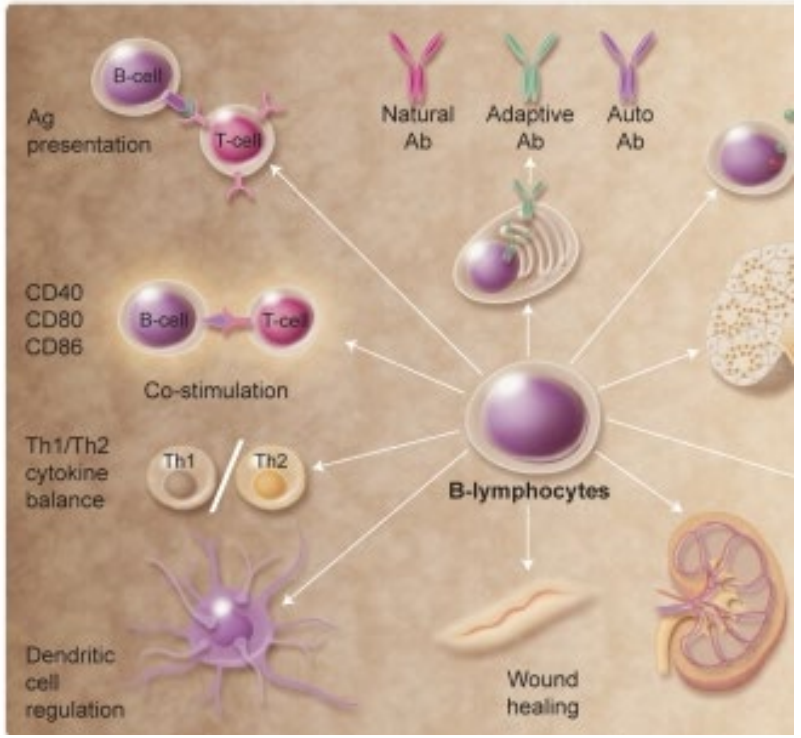
Autoimmunity (Autoimmune rheumatic disease)

- Antibodies are proteins our immune system (white cells) produces to fight infection. When our immune system detects infection, our body makes antibodies against the pathogen.
- Autoantibodies are proteins mistakenly produced that target a person's normal tissue instead of protecting against infection.
- Autoantibodies cause inflammation (and often damage) in normal organs.
- Rheumatoid arthritis (RA) and systemic autoimmune rheumatic diseases (SARDs) are chronic autoimmune disorders characterized by anti-citrullinated protein antibodies, ACPA, and antinuclear antibodies, ANA.

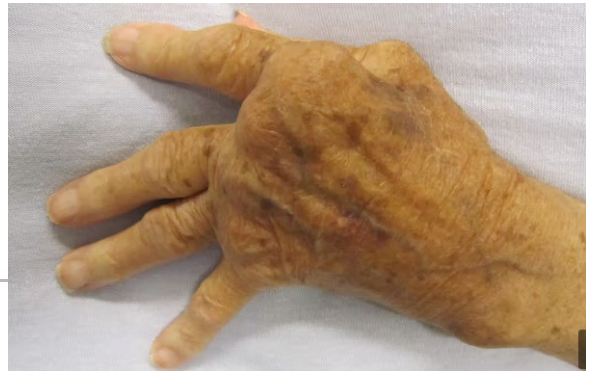


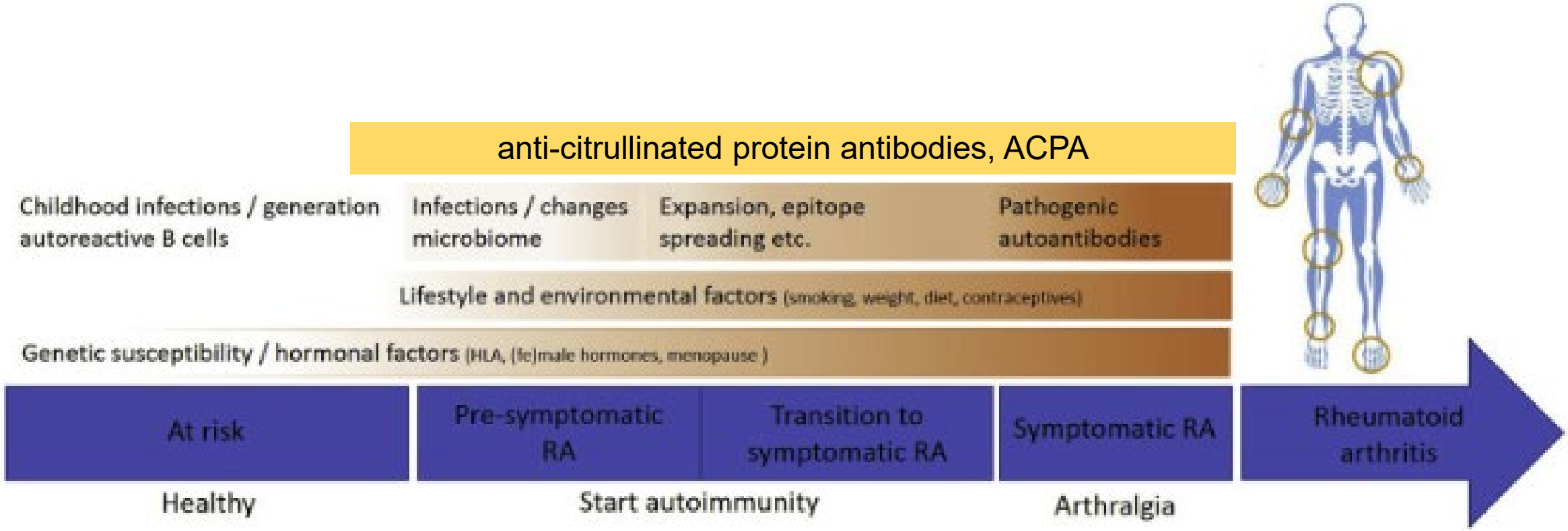
Blood. 2008 Sep 1;112(5):1570–1580. doi: 10.1182/blood-2008-02-078071

B lymphocytes: how they develop and function

Tucker W LeBien [1,*,✉], Thomas F Tedder [2,*,✉]

Overview of the development of RA





J. Autoimmunity 2020 Myrthe A.M. van Delft [a], Tom W.J. Huizinga [b]

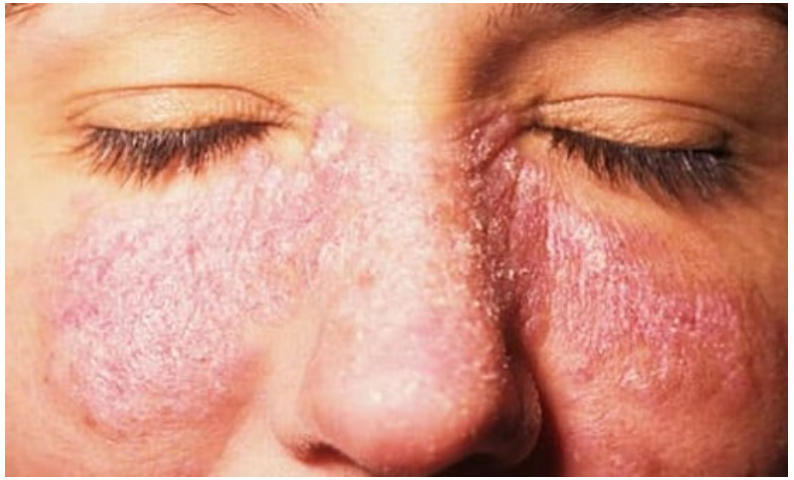
JIM Journal of Internal Medicine
Founded in 1863

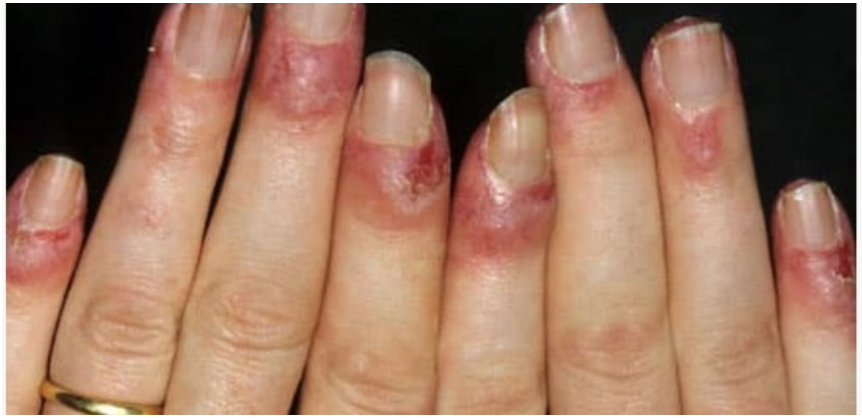
Review | Free Access

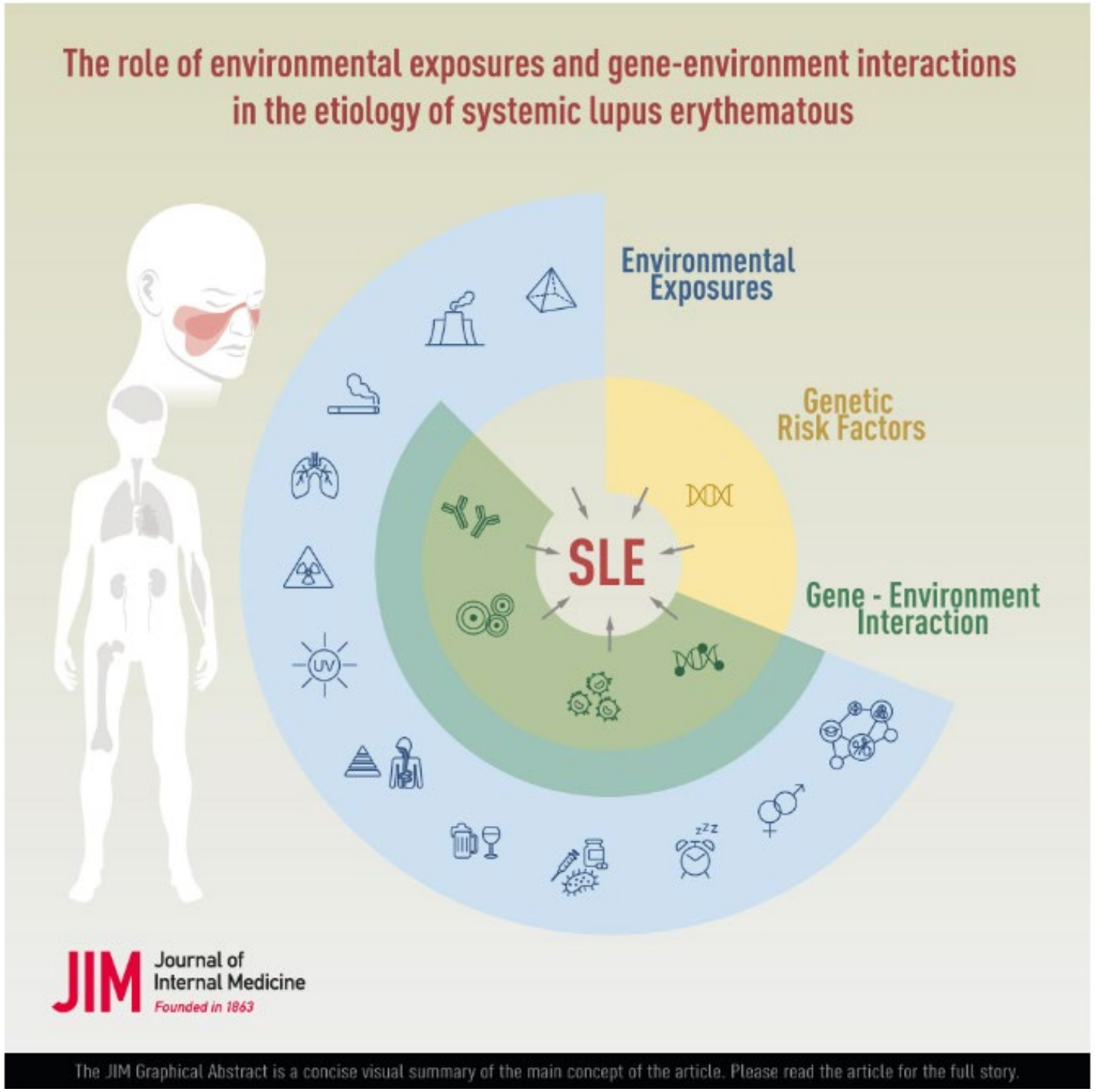
Antinuclear antibodies
ANA

The role of environmental exposures and gene–environment interactions in the etiology of systemic lupus erythematous

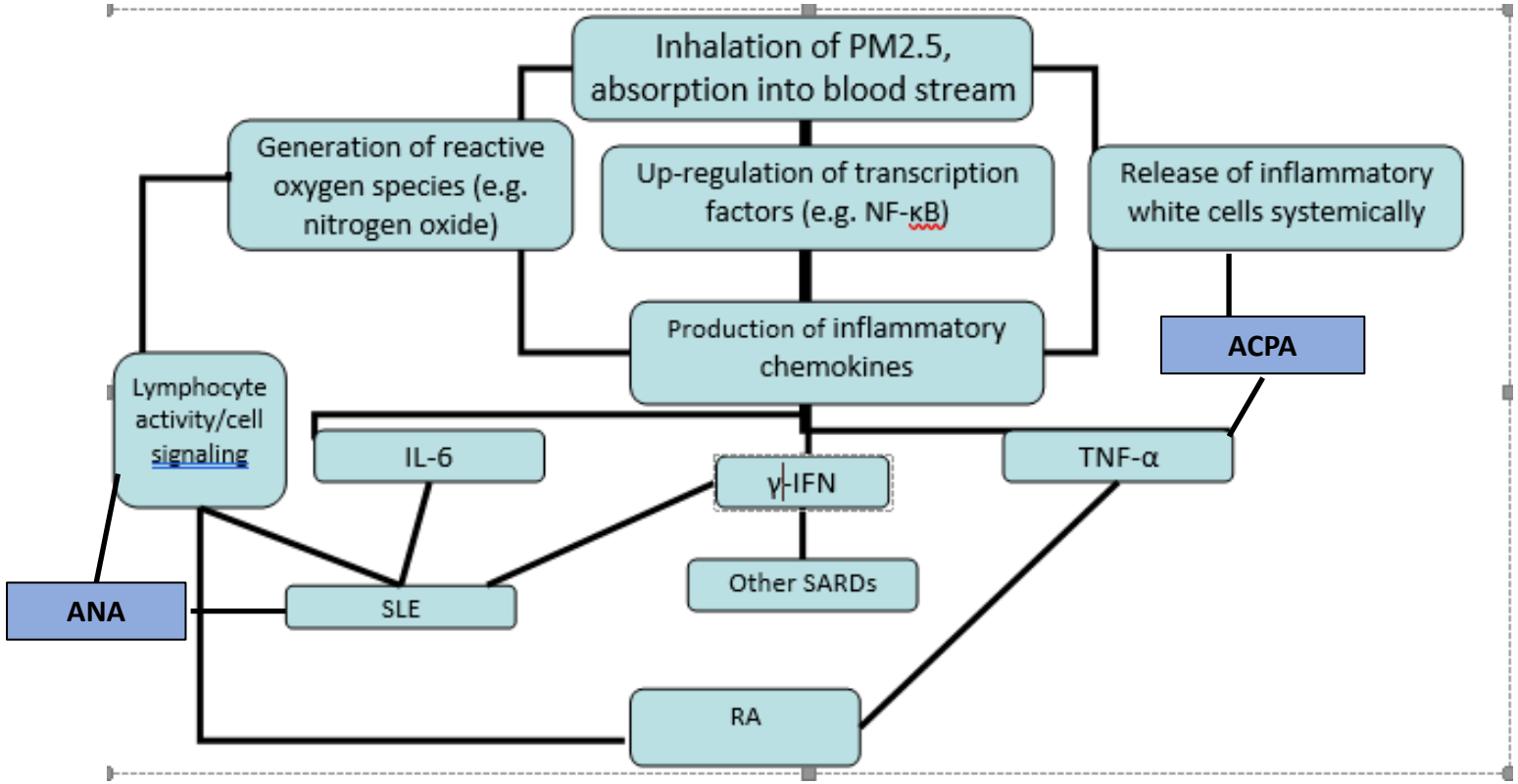
Jennifer M. P. Woo, Christine G. Parks, Søren Jacobsen, Karen H. Costenbader, Sasha Bernatsky







Inhaled elements of air pollution that may contribute to systemic inflammation and autoimmunity



CanPath: >300,000 Canadians

- Regional CanPath general population cohorts; baseline sera (at cohort entry) are stored with CARTaGENE (QC), the Ontario Health Study, OHS, BC Generations Project, and Alberta Tomorrow Project
- Participants in regional cohorts provide information on demographics, medical history, and residence
- We randomly chose 6,000 subjects with available baseline sera from CARTaGENE, and 4000 from OHS and assessed sera for ANA and ACPA.
- We will randomly select 4,000 sera from each of BCGP and ATP.
- We have worked closely with CanPath units and provincial data holders (e.g. ICES for OHS) to assign each subject values for environmental exposures over time, based on 6-digit postal code centroids

CanPath
Canadian Partnership for Tomorrow's Health

ANA and Ambient $PM_{2.5}$ in the general population

- We studied the Ontario Health Study (OHS) general population cohort (part of CanPath)
- Serum samples of 3,548 subjects (collected between 2010-2013) were randomly selected from OHS
- ANA titres (indirect immunofluorescence assay on Hep-2 cells).
- Annual average ambient $PM_{2.5}$ levels for the 5 years before sera collection were assigned based on six-digit residential postal codes.
- Ambient $PM_{2.5}$ estimates based on satellite images and chemical transport modeling, refined by ground-based observations and geographically weighted regression

Methods

- We used multivariable logistic regression to compute adjusted odds ratios (ORs) for ANA positivity, comparing the highest (fourth) quartile to the lowest (first) quartile of ambient $PM_{2.5}$
- Adjusted for
    - Basic socio-demographic factors (age, sex)
    - Smoking status at sera sample collection
    - Rurality Index of Ontario (characterizes urban/rural status).

Results

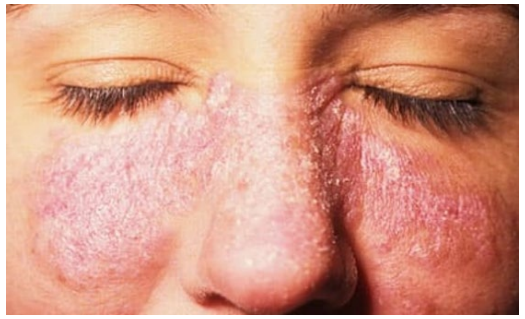
- Comparing the highest versus lowest quartile $PM_{2.5}$ exposure, the adjusted ORs
- For ANA titre ≥1:640 was 1.46 (95% CI 1.02-2.10).
- For ANA titre ≥1:1280 the OR was 1.54 (95% CI 1.06, 2.60).
- Lower titres were not clearly associated with PM2.5 exposures.
- $PM_{2.5}$ exposure was associated with ANA positivity at high titres.

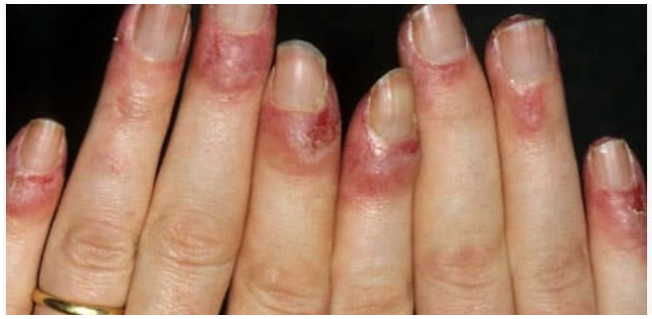
This strengthens the argument that air pollution could have systemic immune system effects, which could in turn lead to autoimmune disease.

Systemic autoimmune rheumatic diseases and industrial air pollutant emissions

Methods:

- Assembled an open cohort of over 12 million adults (without SARD diagnoses at cohort entry) based on Ontario health data (from 2007) and followed them until SARD onset, death, emigration, or end of study (December 2020).
- SARDs were identified using physician billing and hospitalization diagnostic codes for systemic lupus, scleroderma, myositis, undifferentiated connective tissue disease, and Sjogren's.





Methods (cont'd)

- Average $PM_{2.5}$, NO_2, and SO_2 industrial emissions from 2002 to one year before SARDs onset or end of study were assigned using residential postal codes.
- A quantile g-computation model for time to SARD onset was developed for the industrial emission mixture, adjusting for:
  - Sex, age, income, rurality index, calendar year
  - Chronic obstructive pulmonary disease (as a proxy for smoking)
  - Background (environmental overall) $PM_{2.5}$

Results

- We identified 43,931 new SARD diagnoses across 143,799,564 person-years.
- The adjusted HR for SARD onset related to an increase in all emissions by one decile was 1.018 (95% CI 1.013-1.022).
- $PM_{2.5}$ contributed more to SARD onset than NO_2 and SO_2 in the industrial mixture.

Thus we found positive associations between SARD onset and mixed industrial emissions, with $PM_{2.5}$ being the most important

Industrial air emissions and proximity to major industrial emitters are associated with ACPA

- Serum ACPA was determined for 7,600 randomly selected general population subjects
- Industrial SO_2, NO_2, and $PM_{2.5}$ concentrations, estimated by the California Puff atmospheric dispersion model, were assigned based on residential postal codes at the time of sera collection.
- Single-exposure logistic regressions were performed for ACPA positivity
- Associations between the combined 3 industrial exposures and the ACPA positivity also assessed by weighted quantile sum (WQS) regressions
- Defined by 20 U/ml, 40 U/ml, and 60 U/ml thresholds
- Adjusted for age, sex, smoking, and family income.
- Regional overall $PM_{2.5}$ exposure and ACPA positivity were also investigated.

Industrial air emissions and proximity to major industrial emitters are associated with ACPA

- With single-exposure logistic regression models, associations between ACPA positivity (at 20 U/ml threshold) were seen for industrial emissions of
  - $PM_{2.5}$ (OR = 1.19, 95% CI: 1.04-1.36)
  - SO_2 (OR = 1.03, 95% CI: 1.00-1.06)
- No clear associations for NO_2 (OR = 1.01, 95% CI: 0.86-1.17).
- WQS model showed a positive relationship between combined industrial exposures and ACPA positivity (OR = 1.36, 95% CI 1.10-1.69 at 20 U/ml) and suggested that industrial $PM_{2.5}$ may have a closer association with ACPA positivity than the other exposures.
- Similar findings were seen for the 40 U/ml threshold; at 60 U/ml, results were imprecise.
- No clear association between ACPA and regional overall $PM_{2.5}$ exposure.

Conclusions: Positive associations between ACPA and industrial emissions of $PM_{2.5}$ and SO_2. Industrial $PM_{2.5}$ exposure may play a particularly important role in this regard.

Fine Particulate Matter Components and Risk of RA in Ontario

- An open cohort of 11,696,930 Canadian adults was assembled using Ontario administrative health data from January 2007 onward.
- Individuals were followed until RA onset, death, emigration from Ontario, or the end of the study (December 2019).
- Incident RA cases were defined by physician billing and hospitalization discharge diagnostic codes.
- Average levels of $PM_{2.5}$ components (ammonium, black carbon, mineral dust, nitrate, organic matter, sea salt, and sulfate) for 5 years before cohort entry were assigned to participants based on residential postal codes.
- Cox hazard model for time to RA onset related to overall ambient $PM_{2.5}$
- Quantile g-computation model for mixture of $PM_{2.5}$ components

Results

- We identified 67,676 new RA cases across 130,934,256 person-years.
- Adjusted hazard ratios, HR for the time to RA onset:
  - 1.023 (95% CI 1.017-1.029) per 1 μg/m^3 increase in overall $PM_{2.5}$
  - 1.027 (95% confidence interval, CI 1.021-1.033) per every decile increase in exposures to all seven components
- Among the components, ammonium contributed the most to RA onset

Climate change and RA/SLE risk

- Climate change is greatly extending Canada's wildfire season.
  - 2023: 46 million acres burnt in Canada
    - 13 million acres in Quebec (ref. 5 million acres of farmland in Quebec)
- Wildfire smoke contains large amounts of air pollutants, severely degrading air quality for Canadians
- As other sources of air pollution are increasingly regulated, wildfire smoke will become an even more important source of ambient PM2.5
- Additionally, climate change leads to more extreme temperatures and consequently larger temperature variability.
- No one has studied the effects of PM2.5 from wildfire/biomass smoke in terms of autoimmune effects such as RA/SARDs or their autoantibodies.

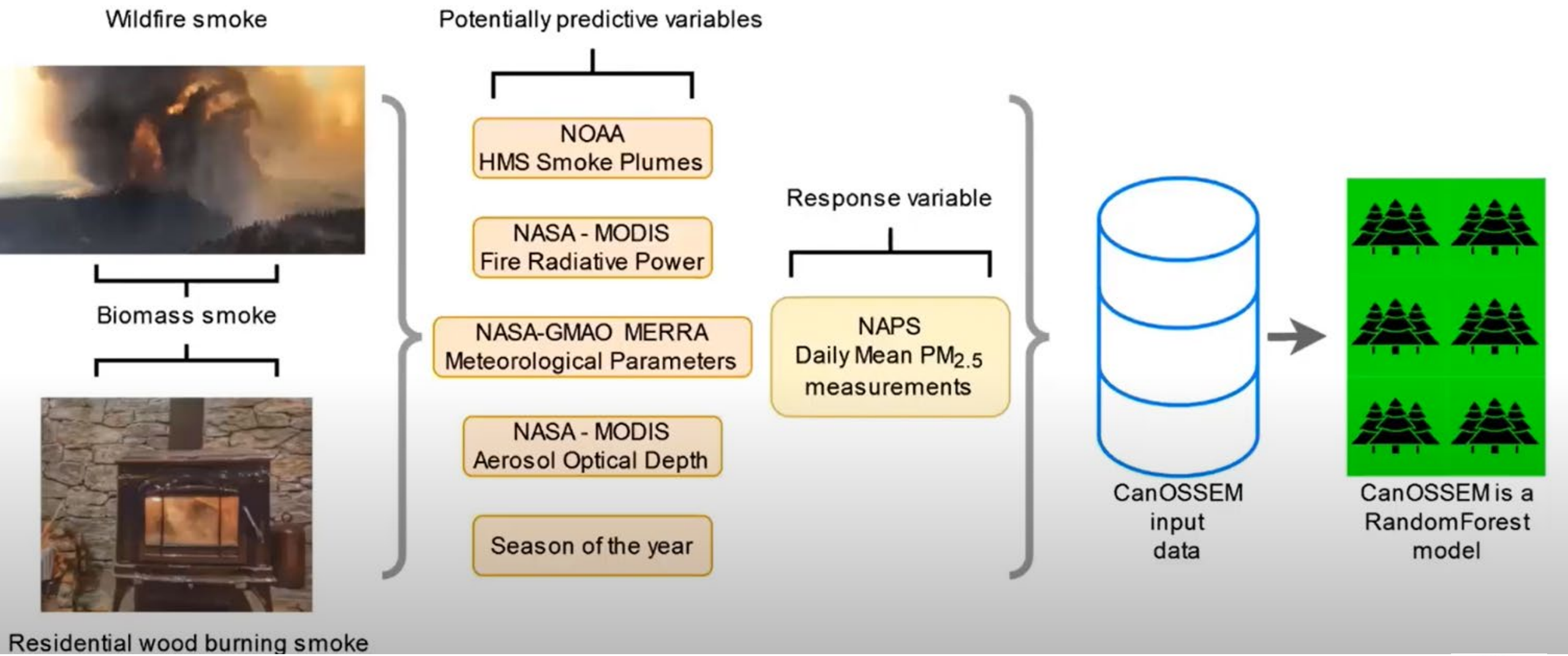
Newly funded objectives

Objective 1: determine if exposure to PM2.5 from wildfire smoke is associated with ACPA or ANA serology in a cross-sectional design, using bio-banked sera from CanPath

- Analyses will be adjusted for ambient temperature extremes and variability, sex, age, race, and other factors.
- Wildfire-PM2.5 concentrations (estimated from satellite image data/modelling).
- Daily mean temperatures (retrieved from updated weather forecast data) will be used to quantify temperature extremes and variability.
- Associations of wildfire-PM2.5 with ACPA or ANA positivity will be assessed by logistic regression and Bayesian machine learning regression models.

PM2.5 exposures related to wood/biomass burning

- Canadian Optimized Statistical Smoke Model (CanOSSEM) was developed by the Environmental Health Services of the BC Centre for Disease Control and is optimized to assess $PM_{2.5}$ related to wildfire smoke.
- Distributed by Canadian Urban Environmental Health Research Consortium
- Concentrations of $PM_{2.5}$ from wood/biomass burning have been estimated at 5×5 km spatial resolution by combining meteorological data with satellite-derived aerosol optical depth data and other data
- CanOSSEM $PM_{2.5}$ estimates for warm seasons (Mar.-Sept.) represent primarily wildfires, while estimates for winter represent woodstoves.
- Primary analyses will evaluate CanOSSEM $PM_{2.5}$ estimates across warm seasons (Mar.-Sept.) before each CanPath subject's biospecimen sample.
- Sensitivity analyses will assess year-round (and multi-year) exposures.



https://bclung.ca/lung-condition-video-resources/air-quality-health-webinars/

CANUE

Temperature extremes and variability

- Daily mean air temperatures (at spatial resolutions of 0.25 x 0.25^{o} latitude and longitude) will be obtained from the European Centre for Medium-Range Weather, which provides global daily atmospheric temperature estimates, including Canada.
- Our primary analyses will control for maximum warm-season temperatures and variability (quantified by the standard deviation of daily mean temperatures for warm seasons preceding CanPath cohort entry).
- Though the body is good at maintaining stable core temperature despite changes in ambient temperature, core temperature can still be affected, particularly for older/smaller individuals...

Other variables

- **Relative humidity** could itself be a potential confounder or effect modifier of our main exposures of interest (smoke-$PM_{2.5}$ and temperature variability). Humidity may be associated with symptoms in some rheumatic diseases, and if it correlates with $PM_{2.5}$ or temperature variability, it could be a confounder.
- **Other seasonal exposures**: Potentially relevant seasonal exposures in SARDs etiology are **ultraviolet (UV) light** and **viral infections**
- We have self-reported sun exposure for CanPath subjects.
- Regarding viral infections, our primary analyses are limited to warm seasons when most endemic respiratory viruses are in low circulation.
- We'll use calendar-month variables for analyses evaluating year-round outcomes (as opposed to warm seasons only).
- Our serology analyses will not use data after 2019, so COVID-19 not an issue

Newly funded objectives (cont'd)

Objective 2: investigate if same exposures correlate with RA or SARDs incidence, based on administrative provincial hospitalization and physician billing data from Jan. 2013 onward.

- Individuals reaching 18 years, living in BC, AB, ON, QC for 5+ years without RA/SARDs, followed until disease onset, death, emigration from province, or end of study.
  - One cohort for RA, one for SARDs (international classification diagnoses, ICD)
- Exposures assigned to subjects based on residential postal codes.
- Outcomes: Relevant ICD codes within physician billing data (≥2 claim codes, ≥8 weeks apart but within 2 years) or ≥1 relevant hospitalization diagnosis ICD code
- Hierarchical extended Cox multivariate models to estimate hazard ratios for RA and for SARDs related to wildfire-PM2.5, adjusting for ambient temperature extremes and variability, sex (stratifying also), age, and other factors (humidity, calendar year...)

Summary, future steps

- RA and SARDS are important autoimmune diseases; their unclear etiology remains a key barrier to effective prevention.
- Combine most up to date environmental exposure data with:
  - CanPath sera and samples
  - Population-wide administrative data

Future direction?

- CanPath bio-samples do include stored cells, from which DNA can be extracted.
- Possibly, genetic factors (e.g HLA-DR4 RA epitopes) can identify groups at highest risk

Canada Foundation for Innovation, CFI-Innovation Fund

March 13, 2024

CHRIM investigators, Dr. Andrew Halayko and Dr. Neeloffer Mookherjee of the Biology of Breathing Theme (BoB) have been awarded $2.4 million from Canada Foundation for Innovation (CFI) through the CFI-Innovation Fund. This will support a $4.8 million AirSAFE project, that is also receiving $2.4 million from the Research Manitoba CFI-Innovation Fund Matching Program.

AirSAFE will establish facilities for investigation of the effects of air pollutants on human health. The project involves a team of 10 members and will provide insight into how air pollution affects our health at all stages of life. The research will enable controlled exposures to different types of air pollutants and provide information about air quality in Manitoba with specific insight into how it directly affects our lungs.

This project and funding will enable the establishment of unique facilities to conduct controlled exposures of combinations of traffic pollution, biomass combustion (smoke from forest fires or stubble burning), tobacco and cannabis cigarette some, and e-cigarette vapours. The project will move forward to build labs with equipment for developing novel human lung cultures. The project includes partnership with SAFE Work Manitoba to monitor air quality at industrial sites and promote healthy environments.

McGill | School of Population and Global Health
Department of Equity, Ethics and Policy

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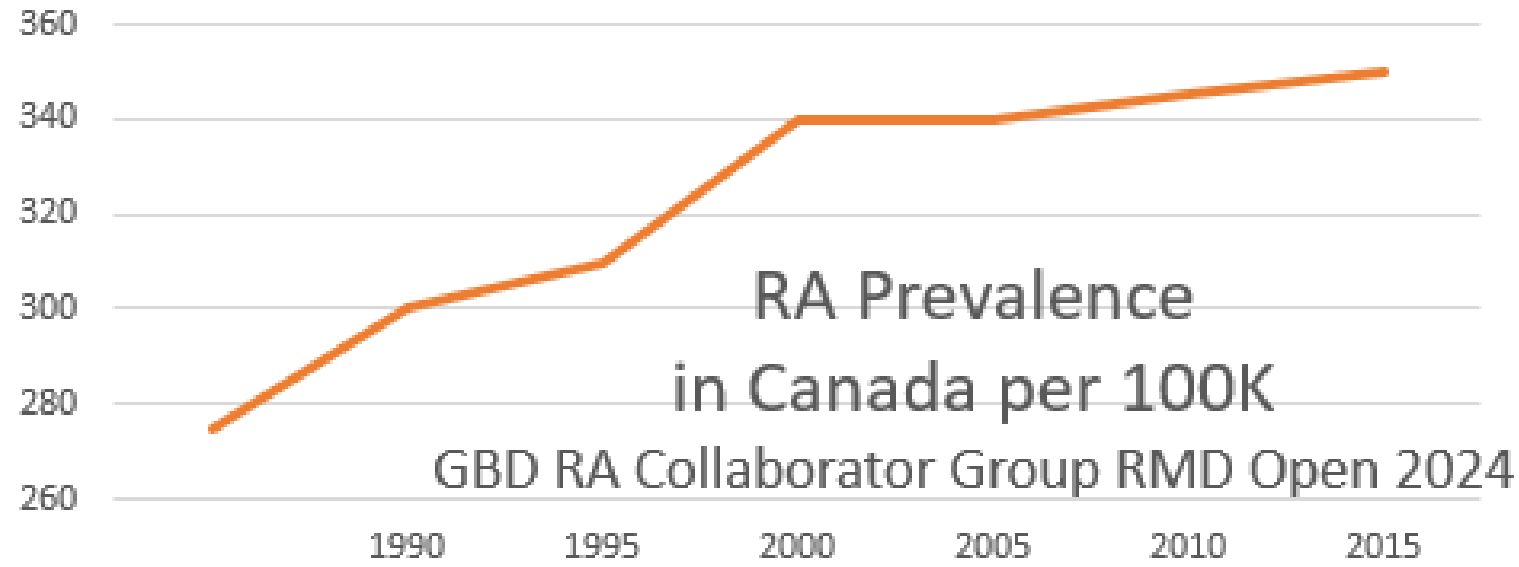
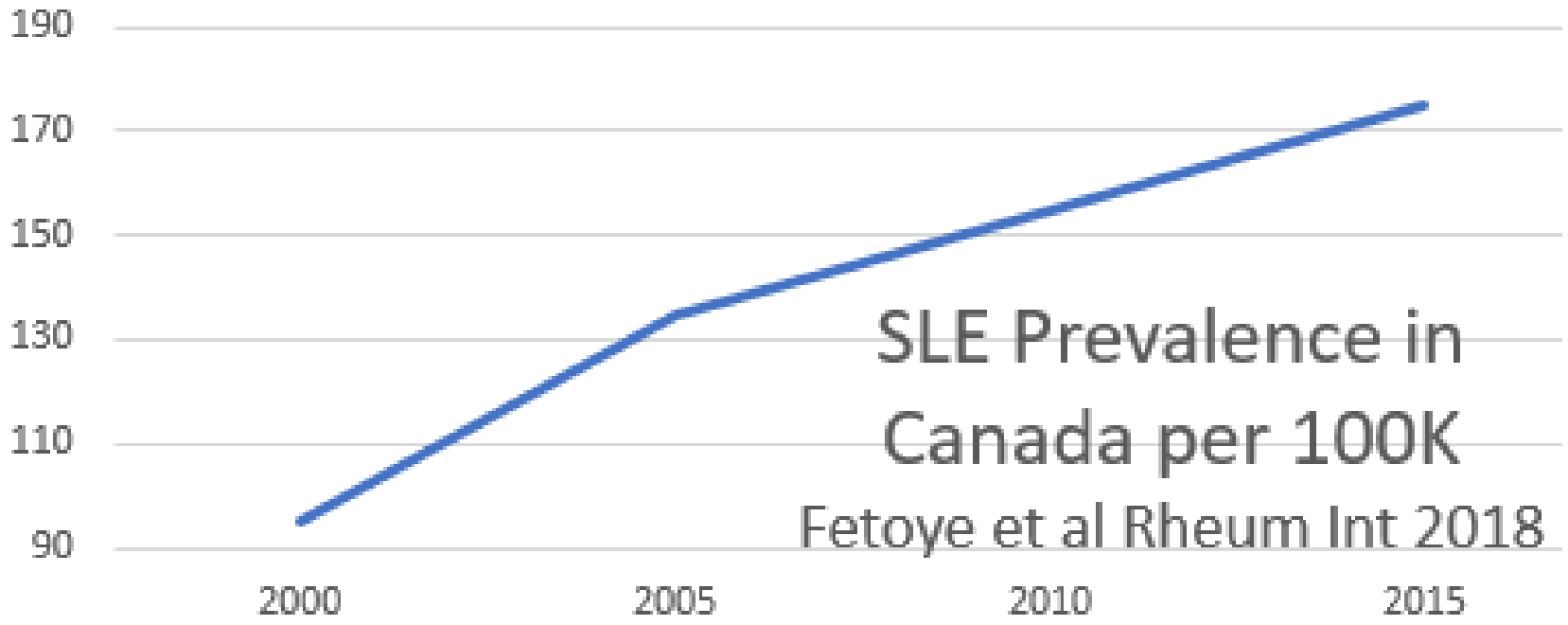
McGill Centre for Climate Change and Health

Co-Principal Investigators:

- A. Smargiassi, Université de Montréal
- J.A. Aviña-Zubieta, University of British Columbia
- H. Chen, Public Health Ontario

- Special thanks to Dr. Naizhuo Zhao, Dr. May Choi, Dr. Marvin Fritzler, Dr. Philip Awadalla, Autumn Neville, and Jennifer Lee


360
340
320
300
280
260
1990
1995
2000
2005
2010
2015
RA Prevalence
in Canada per 100K
GBD RA Collaborator Group RMD Open 2024


190
170
150
130
110
90
2000
2005
2010
2015
SLE Prevalence in
Canada per 100K
Fetoye et al Rheum Int 2018

CAN-AIM https://canaim.ca

The **CA**nadian **N**etwork for **A**dvanced **I**nterdisciplinary **M**ethods for comparative effectiveness research' was selected by Canada's Drug Agency (CDA) as a collaborator for their Post-Market Drug Evaluation Network (PMDE). CAN-AIM was previously funded by the Drug Safety and Effectiveness Network (DSEN) through a partnership between CIHR and Health Canada (2011-2022).

We aim to respond to key knowledge gaps regarding drug safety and effectiveness by answering queries from Health Canada and other regulatory parties using clinical and population-based cohorts and administrative data.

Mission: Enhance Canadian research on real-world drug effectiveness and safety (cohorts), develop novel statistical methods and build and enhance capacity (trainees and highly qualified personnel).

CANRAD Network https://canradnetwork.ca

The **CAN**adian **R**heumatology **A**dministrative **D**ata **Network** is a team of decision-makers, epidemiologists, clinicians and researchers funded by the Canadian Arthritis Network, the Canadian Institutes of Health Research, with the support of the Public Health Agency of Canada.

We are interested in administrative health data, including physician billing and hospitalization databases, for the research and surveillance of rheumatic disease, co-morbidity and adverse events. We support the exchange of best practice research and surveillance and the development of new methods to advance the efficiency of arthritis research and surveillance across Canada.

In 2011, we developed 13 best-practice consensus statements when using administrative data in rheumatic disease research and surveillance in Canada.