Industrial Air Pollutants and Anti-Citrullinated Protein Antibodies

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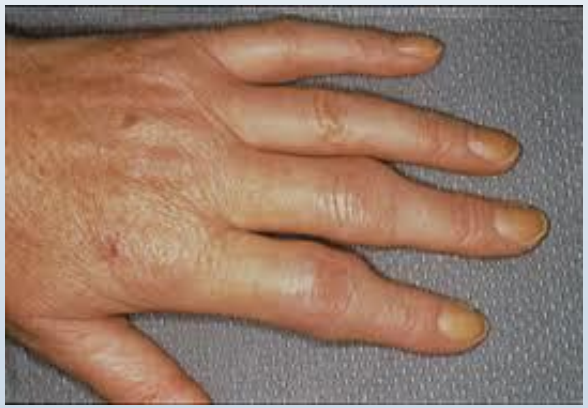
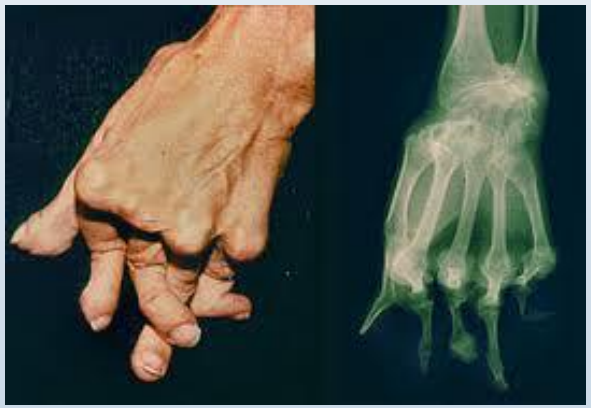
Rheumatoid arthritis

- Potentially devastating disease affecting almost 4 million North Americans (1%).
- May strike anyone, often affects people of work-force age.
- Associated with high economic burden
  - mean direct medical costs >$12,000 per patient per year
  - indirect costs averaging over $21,000 per patient per year
  - thus economic burden related to RA >$8 billion yearly
- Very poor understanding of RA pathogenesis – a key knowledge gap.

Rheumatoid arthritis

- The immune system in RA is auto-reactive, begins producing anti-bodies to self-proteins (auto-antibodies), triggering inflammation.
- Inflammation targets joint tissue, causing joint swelling and pain, damage, and impaired function.

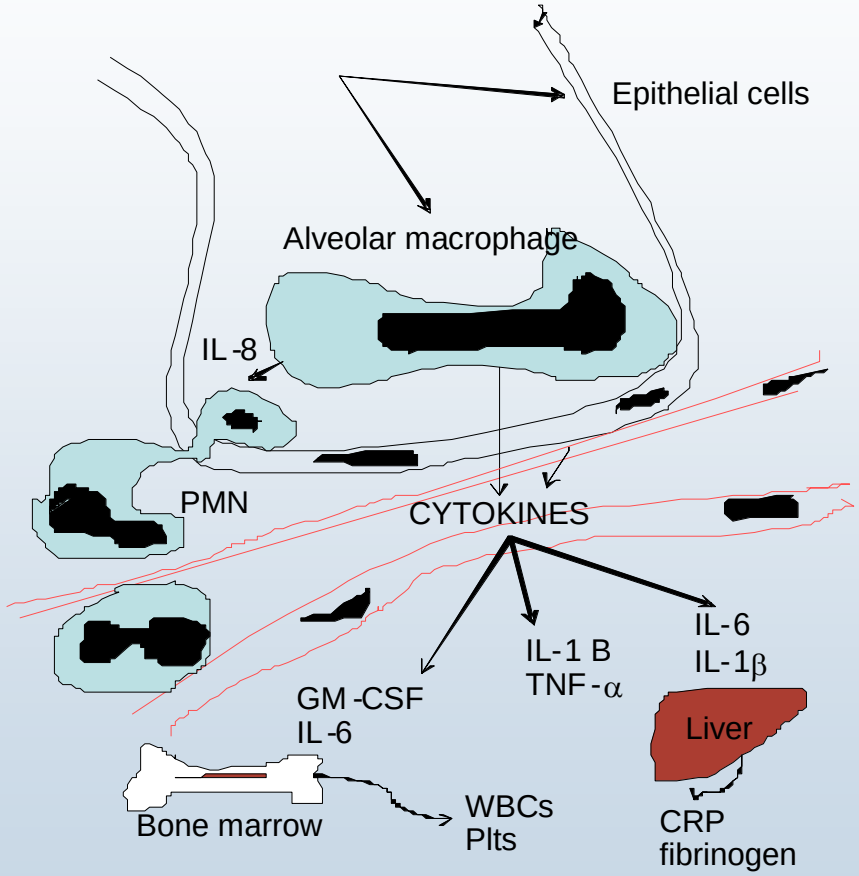




ACPA

- Anti-citrullinated protein antibodies (ACPA) are a characteristic finding in RA.
- These antibodies may occur in the absence of disease and may predate clinical manifestations of RA
- Lag time between antibody response and the first physical manifestations represents a possible 'window of opportunity' to intervene and induce remission (extremely difficult once symptoms become severe) or even prevent disease onset
- Identification of environmental triggers thus would have important public health implications

$PM_{2.5}$ can trigger systemic inflammatory responses and oxidative stress, both linked to ACPA and RA



Adapted from van Eeden, Proc Am Prorac Soc 2005[69].

- Up-regulation of transcription factors (e.g. nuclear factor-κB), pro-inflammatory genes, chemokines (e.g. interleukin, IL-6 and γ-interferon, IFN) and reactive oxygen species (e.g. nitric oxide), which amplify systemic inflammation.
- A type of PM, diesel exhaust nanoparticles, has pro-inflammatory effects in scleroderma cells.
- NO_2 (and ozone) may also have a direct effect on inflammation via oxidative damage.

Air pollution as a trigger for RA

- Particulate air pollution associated with increased risk of juvenile arthritis (Zeft et al 2009)
- In the Nurses' Health Study, RA risk was higher for those residing within 50 m of a major road (Hart et al 2009); De Roos et al (2013) similar findings
- Chang et al. (2016) found association between RA and ambient NO2
- Associations between ambient $PM_{2.5}$ and prevalence/ disease activity for systemic rheumatic diseases e.g. lupus (Bernatsky, 2011)

- No prior studies specifically of industrial emissions and rheumatic disease or antibodies

Methods

- CARTaGENE is part of the Canadian Partnership for Tomorrow Project, a population-health research platform to study genetics, behaviour, family health history, and environment in terms of health and disease.
- Subjects in the CARTaGENE cohort were randomly selected from the provincial health insurance database (if they had resided $\geq$ 5 years in Quebec), and invited to participate in the study.
  - Montreal, Quebec City, Sherbrooke, Saguenay–Lac- Saint-Jean
- Basic socio-demographic factors (e.g. age, sex, French Canadian ancestry, and family income) and medical data including smoking habits are included in the baseline CARTaGENE data.
- Serum ACPA was determined for 1,586 randomly selected subjects
- Biobanked serum samples assessed by immunoassay (Mitogen, Calgary)
  - Titer of 20 U/ml was the initial threshold of positive test; sensitivity analyses with higher thresholds

Methods

- Logistic regression; exposures based on subjects' baseline residential postal code
- Assessed distance to main industrial emitters of $PM_{2.5}$ and SO_2 (separate models) using data from NPRI
  - As per Brand et al. (2016) 'main' emitters defined as any industry emitting over 100 tons of $PM_{2.5}$ or SO_2 for at least 5 continuous years from 2002-2010
- Also assessed $PM_{2.5}$ and SO_2 annual industrial emissions in tons (separate models)
  - Industrial emissions of $PM_{2.5}$ and SO_2 in 2008 were summed for all industries (main emitters or not) within 2.5 km of each postal code.
- As per Leffondre et al. (2002) sensitivity analyses done to decompose exposure variables into two variables, one binary (1=exposed, 0=unexposed) and one continuous variable, centered to the mean exposure of those exposed.

Methods

- Also assessed regional $PM_{2.5}$ levels estimated from satellite imagery, produced with the Moderate Resolution Imaging Spectroradiometer and multi-angle imaging spectroradiometer systems.
  - Images interpreted using the chemical transport model of atmospheric compositions (Goddard Earth Observing System, GEOS-Chem) to estimate regional $PM_{2.5}$ levels with a geographic resolution of 10×10 km .
  - Estimates of long-term $PM_{2.5}$ averages (2001–2006) have been developed based on aerosol optical-depth data from satellite instruments. van Donkelaar et al. (2010)
- All six digit postal codes located within a 10×10 km cell were given the same regional $PM_{2.5}$ levels.
- Additional sensitivity analyses controlled for the four census metropolitan areas from which subjects had been recruited.

Results

- Adjusted analyses suggested a positive association between annual industrial $PM_{2.5}$ and SO_2 emissions and ACPA
- Data were also consistent with a negative association between the presence of ACPA, and distance to a major industrial emitter of both $PM_{2.5}$ and SO_2.
- No clear association of ACPA with regional ambient $PM_{2.5}$

$PM_{2.5}$ distance	**Adjusted OR (CI)**
$PM_{2.5}$ per km	0.42 (0.23 , 0.76)
$PM_{2.5}$ binary	0.51 (0.14 , 1.86)
Age (continuous)	1.00 (0.98 , 1.02)
Female	1.06 (0.78 , 1.45)
Smoker*	1.06 (0.71 , 1.59)
French Canadian	0.77 (0.56 , 1.07)
SO_2 distance	**OR (CI)**
SO_2 per km	0.86 (0.74 , 1.00)
SO_2 binary	1.06 (0.77 , 1.47)
Age (continuous)	1.00 (0.98 , 1.02)
Female	1.06 (0.78 , 1.44)
Smoker*	1.06 (0.71 , 1.58)

*Smoking defined as current (versus never or past) smoking

$PM_{2.5}$ Emissions	Adjusted OR (95% CI)
$PM_{2.5}$ per 10 ton increase	1.02 (1.01 , 1.04)
$PM_{2.5}$ binary	1.01 (0.73 , 1.41)
Age (continuous)	1.00 (0.98 , 1.02)
Female	1.07 (0.78 , 1.45)
Smoker**	1.05 (0.70 , 1.58)
French Canadian	0.76 (0.55 , 1.05)
SO_2 Emissions	Adjusted OR (CI)
SO_2 per 100 ton increase	1.02 (1.00 , 1.05)
SO_2 binary	1.08 (0.70 , 1.68)
Age (continuous)	1.00 (0.98 , 1.02)
Female	1.06 (0.78 , 1.45)
Smoker*	1.06 (0.71 , 1.58)
French Canadian	0.77 (0.56 , 1.06)

**Smoking defined as current (versus never or past) smoking

OR for ACPA, Regional Ambient $PM_{2.5}$

	Adjusted OR	95%	CI
Regional ambient $PM_{2.5}$ (µg/m3)	0.97	0.92	1.03
Age	1.00	0.98	1.02
Female	0.98	0.71	1.35
Current Smoker	1.07	0.70	1.61
French Canadian	0.76	0.54	1.07

Recent updates

- Repeated analyses with larger sample (N=7,600)
- Industrial $PM_{2.5,}$ SO_2, and NO_2 concentrations for 2005-2010, estimated by the California Puff (CALPUFF) atmospheric dispersion model, were assigned based on residential postal codes at the time of sera collection.
- Single-pollutant logistic regressions were performed for ACPA (20 U/ml, 40 U/ml, and 60 U/ml thresholds), adjusting for age, sex, French Canadian origin, smoking, and family income.
- Logistic regressions were also run for associations between ACPA and ambient $PM_{2.5}$
- Combined effects of all 3 industrial exposures were assessed by weighted quantile sum (WQS) regressions

Results

- Significant associations with ACPA positivity (at 20U/ml and 40U/ml thresholds) were seen in both single-exposure logistic and multi-exposure regression models, for industrial emissions of $PM_{2.5}$ and SO_2. No clear associations for NO_2.
- At the 60 U/m threshold, results for both the single-exposure logistic and multi-exposure regressions were very imprecise.
- In the multi-exposure regressions, industrial $PM_{2.5}$ was always most (and industrial NO_2 least) heavily weighted.
- No clear association between ACPA and ambient $PM_{2.5}$

Discussion

- Industrial $PM_{2.5}$ may be associated with ACPA.
- Does industrial emissions affect the immune system more than ambient $PM_{2.5}$?
  - Oxidative potential?
- Initial suggestion of industrial SO_2 in single-pollutant models not necessarily borne out in mulfi-pollutant models
- Mean industrial NO_2 levels in Quebec are relatively low, which may be why we failed to see associations between industrial NO_2 and ACPA?
- Cross sectional nature of our study was a limitation

Conclusions/Future directions

- We noted positive associations between ACPA and industrial emissions of $PM_{2.5}$ and SO_2, but industrial $PM_{2.5}$ exposure may play a more key role in this regard.
- No clear association for ACPA positivity and industrial NO_2 or ambient $PM_{2.5}$ detected
- Further studies will concurrently consider other environmental exposures (e.g. UV-B radiation, which is associated with lower RA risk).
- Correlations with epigenetic changes also planned

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