What can we learn on the occurrence of systemic rheumatic diseases from environmental studies?

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Hospital Saint-Louis
University Paris 7
Paris, France
Current paradigm

• Diseases involve genetic and environmental risk factors
• The genetic input seems relatively small for most diseases
• There are multiple pathways leading to disease
What can we learn?

• There is much at stake
• Environmental risk factors:
  – Modifiable or treatable
• Extremely limited knowledge on the role on environmental factors
• Environment-disease relation is complex to study
Environmental Factors

- Air pollutants, water contaminants, soil contaminants
- Alcohol consumption
- Chemical, physical and biological hazards
- Excessive sun exposure
- Hormonal factors
- Infection
- Medication
- Obesity
- Physical inactivity
- Poor diet and nutrition
- Pre-existing medical conditions
- Sexual activity
- Tobacco use
- Etc.

- No/few “natural” candidates
- No automated assessment
- No environment-WAS
Environmental Factors
Bias

• Selection bias
  – Cases
  – « Healthy worker bias »

• Recall bias

• Interviewer bias

• Confounding

• Publication bias
Environmental Epidemiology

• Complex research area
  – Resource-consuming
  – Results can be misleading

• Current knowledge
  – Scarce data
  – Many non-replicated studies
  – Risk factors with small effect sizes
Epidemiology Faces Its Limits

The search for subtle links between diet, lifestyle, or environmental factors and disease is an unending source of fear—but often yields little certainty

“The sin comes in believing a causal hypothesis is true because your study came up with a positive result.”
—Sander Greenland

“We're pushing the edge of what can be done with epidemiology.”
—Ken Rothman

“Authors and investigators are worried that there's a bias against negative studies.”
—Marcia Angell

Bias and confounders are the plague upon the house of epidemiology. Epidemiologists are quick to list risk factors for which accurate exposure measurements are virtually impossible. No single epidemiologic study is persuasive (...) unless the lower limit of its 95% confidence level falls above a 3-fold increased risk. Many respected epidemiologists (...) say it is so easy to be fooled that it is almost impossible to believe less-than-stunning results.

Bradford Hill Criteria

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSc FRCP(hon) FRS
(Professor Emeritus of Medical Statistics, University of London)
Principles of Risk-Factor Epidemiology

- Multiple concordant studies
- Strong effect size (high odds ratio)
- Risk factor specific for a given disease
- ... high percentage of cases exposed
  - High “population-attributable risk” (PAR)
Expert Consensus Statements

Review

Epidemiology of environmental exposures and human autoimmune diseases: Findings from a National Institute of Environmental Health Sciences Expert Panel Workshop

Frederick W. Miller\textsuperscript{a,*}, Lars Alfredsson\textsuperscript{b}, Karen H. Costenbader\textsuperscript{c}, Diane L. Kamen\textsuperscript{d}, Lorene M. Nelson\textsuperscript{e}, Jill M. Norris\textsuperscript{f}, Anneclaire J. De Roos\textsuperscript{g}

Review

Expert Panel Workshop Consensus Statement on the Role of the Environment in the Development of Autoimmune Disease

Christine G. Parks\textsuperscript{1,*}, Frederick W. Miller\textsuperscript{2}, Kenneth Michael Pollard\textsuperscript{3}, Carlo Selmi\textsuperscript{4,5}, Dori Germolec\textsuperscript{6}, Kelly Joyce\textsuperscript{7}, Noel R. Rose\textsuperscript{8} and Michael C. Humble\textsuperscript{9}
Expert Panel Workshop Consensus Statement

• Crystalline silica (quartz) contributes to development of
  – Systemic sclerosis
  – Systemic lupus erythematosus
  – ANCA-related vasculitis

• Solvents contribute to development of
  – Systemic sclerosis

• Smoking (likely) contributes to development of
  – Systemic lupus erythematosus

Parks et al (Int J Mol Sci 2014)
N.I. Environmental Health Sciences Expert Panel Workshop

• Agents we are confident contribute to
  – Systemic sclerosis: silica, solvents
  – Systemic lupus erythematosus: silica
  – AAV: silica

• Agents we believe likely contribute to
  – Systemic lupus erythematosus: current cigarette smoke

Miller et al (J Autoimmunity 2012)
Silica & Systemic sclerosis

Males: 3.02 (95% CI, 1.24–7.35)
Women: 1.03 (95% CI, 0.74–1.44)

McCormic et al., Int Arch Occup Environ Health (2010)
Silica & ANCA Vasculitis

Gomez-Puerta et al (Autoimmunity Rev 2013)
Solvents & Systemic sclerosis

Smoking & Systemic lupus erythematosus

Current vs non-smokers

Ex- vs non-smokers

OR 1.50 (95% CI 1.09–2.08)

OR 0.98 (95% CI 0.75–1.27)

Breast implants & Connective tissue diseases

<table>
<thead>
<tr>
<th>Disease and Analysis</th>
<th>Summary Relative Risk (95% CI)</th>
<th>Summary Relative Risk and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All connective-tissue diseases combined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted (15)</td>
<td>0.68 (0.60 – 0.77)</td>
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<tr>
<td>Adjusted (13)</td>
<td>0.80 (0.62 – 1.04)</td>
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<tr>
<td>Adjusted (14)*</td>
<td>1.14 (1.01 – 1.28)</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td></td>
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<tr>
<td>Unadjusted (10)</td>
<td>0.62 (0.52 – 0.73)</td>
<td></td>
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<tr>
<td>Adjusted (7)</td>
<td>1.04 (0.72 – 1.51)</td>
<td></td>
</tr>
<tr>
<td>Adjusted (8)*</td>
<td>1.15 (0.97 – 1.36)</td>
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<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted (8)</td>
<td>0.63 (0.44 – 0.86)</td>
<td></td>
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<tr>
<td>Adjusted (4)</td>
<td>0.65 (0.35 – 1.23)</td>
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<tr>
<td>Adjusted (5)*</td>
<td>1.01 (0.74 – 1.37)</td>
<td></td>
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<tr>
<td>Scleroderma or systemic sclerosis</td>
<td></td>
<td></td>
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<tr>
<td>Unadjusted (11)</td>
<td>0.70 (0.44 – 1.08)</td>
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<tr>
<td>Adjusted (4)</td>
<td>1.01 (0.59 – 1.73)</td>
<td></td>
</tr>
<tr>
<td>Adjusted (5)*</td>
<td>1.30 (0.86 – 1.96)</td>
<td></td>
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<tr>
<td>Sjögren’s syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted (8)</td>
<td>1.10 (0.74 – 1.58)</td>
<td></td>
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<tr>
<td>Adjusted (3)</td>
<td>1.42 (0.65 – 3.11)</td>
<td></td>
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<tr>
<td>Adjusted (4)*</td>
<td>1.47 (1.01 – 2.14)</td>
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<tr>
<td>Dermatomyositis or polymyositis</td>
<td></td>
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<tr>
<td>Unadjusted (6)</td>
<td>0.90 (0.55 – 1.39)</td>
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<tr>
<td>Adjusted (1)*</td>
<td>1.52 (0.97 – 2.37)</td>
<td></td>
</tr>
<tr>
<td>Other autoimmune or rheumatic conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted (10)</td>
<td>0.92 (0.77 – 1.10)</td>
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<tr>
<td>Adjusted (6)</td>
<td>0.96 (0.74 – 1.25)</td>
<td></td>
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<tr>
<td>Adjusted (7)*</td>
<td>1.16 (0.97 – 1.36)</td>
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</tbody>
</table>
“We identified a gap in the literature concerning autoimmune disease outcomes, as we found no formal meta-analyses of either observational studies or randomised controlled trials and these were examined only by systematic reviews.”
## Vasculitis & Environment

<table>
<thead>
<tr>
<th>Vasculitis entity</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infectious</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>Various microorganisms (viruses, bacteria)</td>
</tr>
<tr>
<td>Takayasu arteritis</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td><strong>Hepatitis B</strong>, hepatitis C, human immunodeficiency virus</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>Various microorganisms (viruses, bacteria)</td>
</tr>
<tr>
<td>IgA vasculitis</td>
<td>Various microorganisms (viruses, bacteria)</td>
</tr>
<tr>
<td>Cryoglobulinemic vasculitis</td>
<td><strong>Hepatitis C</strong></td>
</tr>
<tr>
<td>Behçet’s disease</td>
<td>Streptococci (oral flora)</td>
</tr>
</tbody>
</table>
# Vasculitis & Environment

<table>
<thead>
<tr>
<th>Vasculitis entity</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Granulomatosis with polyangiitis</strong></td>
<td>Infectious: Staphylococcus aureus (nasal carriage)</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>Propylthiouracile, hydralazine and other drugs, silica</td>
</tr>
<tr>
<td>Eosinophilic granulomatosis with polyangiitis</td>
<td>Leukotriene receptor antagonists and other drugs, vaccines, desensitization, silica</td>
</tr>
<tr>
<td>Anti-glomerular basement membrane (anti-GBM) disease</td>
<td>Tobacco use</td>
</tr>
</tbody>
</table>
### EGPA & Montelukast

<table>
<thead>
<tr>
<th>Drug</th>
<th>3-Months Periods</th>
<th>2-Months Periods</th>
<th>4-Months Periods</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed, %</td>
<td>OR (95% CI)</td>
<td>Exposed, %</td>
</tr>
<tr>
<td>Montelukast</td>
<td>Index</td>
<td>19%</td>
<td>4.5 (1.5–13.9)</td>
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<tr>
<td>LABA</td>
<td>Index</td>
<td>63%</td>
<td>3.0 (0.8–10.5)</td>
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<tr>
<td>Inhaled corticoids</td>
<td>Index</td>
<td>67%</td>
<td>1.7 (0.5–5.4)</td>
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<tr>
<td>Oral corticoids</td>
<td>Index</td>
<td>50%</td>
<td>4.0 (1.3–12.5)</td>
</tr>
</tbody>
</table>

Hauser et al. Thorax 2007
Case–Crossover Design

- Control Periods
- Index Period

→ Exposure to risk factor in index vs. control periods
Giant-Cell Arteritis & VZV infection

• VZV antigen
  – 61/82 (74%) GCA-positive TAs
  – 1/13 (8%) normal TAs
  – Relative risk 9.67 (95% CI 1.46, 63.69)

• VZV DNA (PCR)
  – 18/45 (40%) GCA-positive VZV Ag–positive TAs
  – 6/10 (60%) VZV Ag–positive skeletal muscles, and in one VZV Ag–positive normal TA

Prospects

• Identify good candidates
• Go for “big hits”
• Build on descriptive data
• Need more creativity

If I have ever made any valuable discoveries, it has been due more to patient attention, than to any other talent
Isaac Newton
Build on descriptive data

- Sex differences
- Incidence changes
- Ethnic/racial differences
- Migrant studies
- Prominent clinical characteristics (mechanistic pathways)
Incidence of GCA

Giant Cell Arteritis

Annual incidence (per 100,000)

Calendar year

USA (Olmsted county)
Italy (Reggio Emilia)
Sweden (Skåne)
UK
Sweden (Göteborg)
Israel (Jerusalem)
Spain (Lugo)
Finland
Identify good candidates (Vasculitis)

<table>
<thead>
<tr>
<th></th>
<th>Infection</th>
<th>Drugs</th>
<th>Hormonal factors</th>
<th>Behaviour, occupation, recreation</th>
<th>Cancer, Cardiovascular disease</th>
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</thead>
<tbody>
<tr>
<td>GCA</td>
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<td>TAK</td>
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<td>PAN</td>
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<tr>
<td>IgAV</td>
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<tr>
<td>Cryo</td>
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<tr>
<td>Behçet’s</td>
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</tbody>
</table>
“Distal” risk factors

- **Distal (indirect) factors**
  - Socio-economic status, minority status, urban-rural residence

- **Proximal (direct) factors**
  - Alcohol, tobacco, poor diet and nutrition, physical inactivity, excessive sun exposure, etc.

- **Disease**
Occupation & GPA

Knight et al., Annals Rheum Dis 2010
Summary: Environment and systemic rheumatic diseases

• Major challenge
  – We can “win it all”...
  – ... but also go through failures

• Many needs
  – Strong hypotheses to test
  – More (careful) studies
  – Cautious interpretation of the data