

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

Alfred Mahr, MD, MPH, PhD

Professor of Internal Medicine

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?

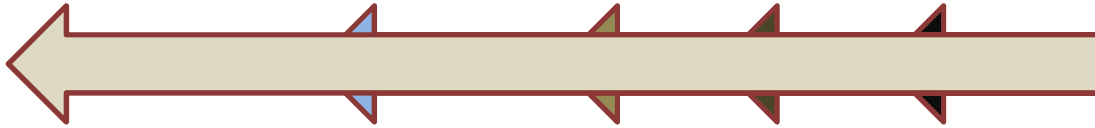
- There is much at stake
- Environmental risk factors:
 - Modifiable or treatable
- Extremely limited knowledge on the role on environmental factors
- Environment-disease relation is complex to study

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.

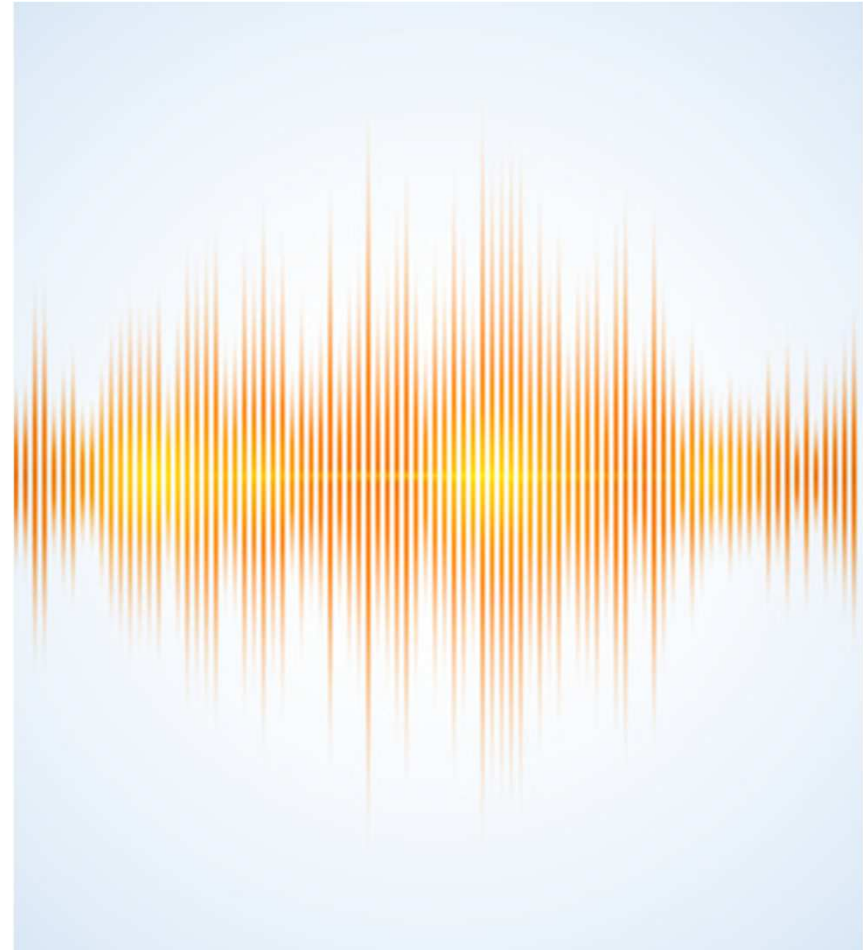
- No/few “natural” candidates
- No automated assessment
- No environment-WAS

Environmental Factors



Bias

- Selection bias
 - Cases
 - « Healthy worker bias »
- Recall bias
- Interviewer bias
- Confounding
- Publication bias

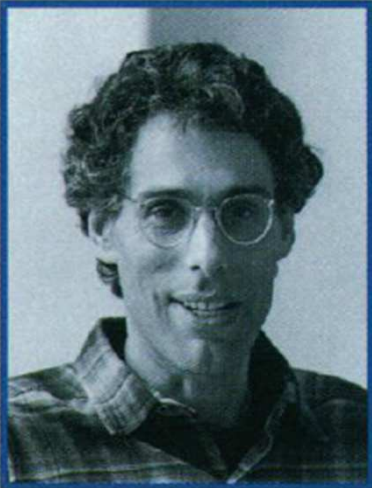


Environmental Epidemiology

- 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

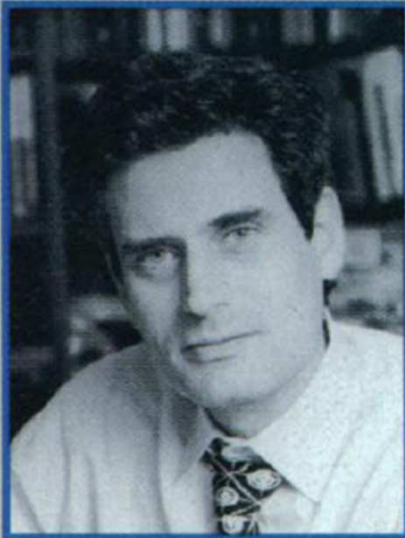
The search for subtle links between diet, lifestyle, or environmental factors and disease is an unending source of fear—but often yields little certainty



TERRY O'DONNELL

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


—Sander Greenland



MARNA KENNEDY

“We’re pushing the edge of what can be done with epidemiology.”

—Ken Rothman



KIMBERLY GRANT

“Authors and investigators are worried that there’s a bias against negative studies.”

—Marcia Angell

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

No single epidemiologic study is persuasive (...) unless the lower limit of its 95% confidence level falls above a 3-fold increased risk

Trichopoulos, Harvard

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

Review

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

Christine G. Parks^{1,*}, Frederick W. Miller², Kenneth Michael Pollard³, Carlo Selmi^{4,5},
Dori Germolec⁶, Kelly Joyce⁷, Noel R. Rose⁸ and Michael C. Humble⁹

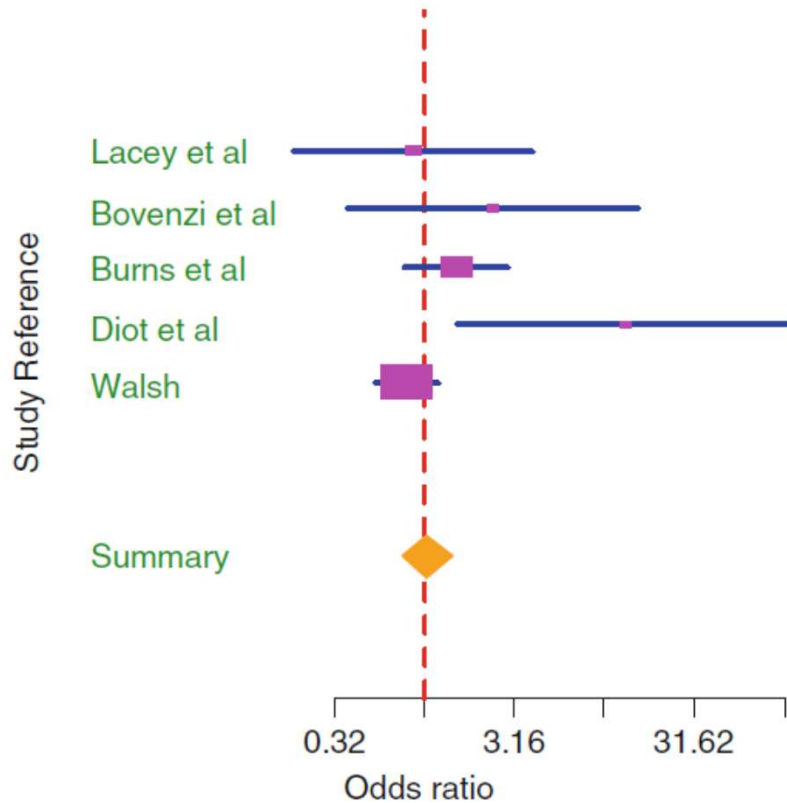
Expert Panel Workshop Consensus Statement

- 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

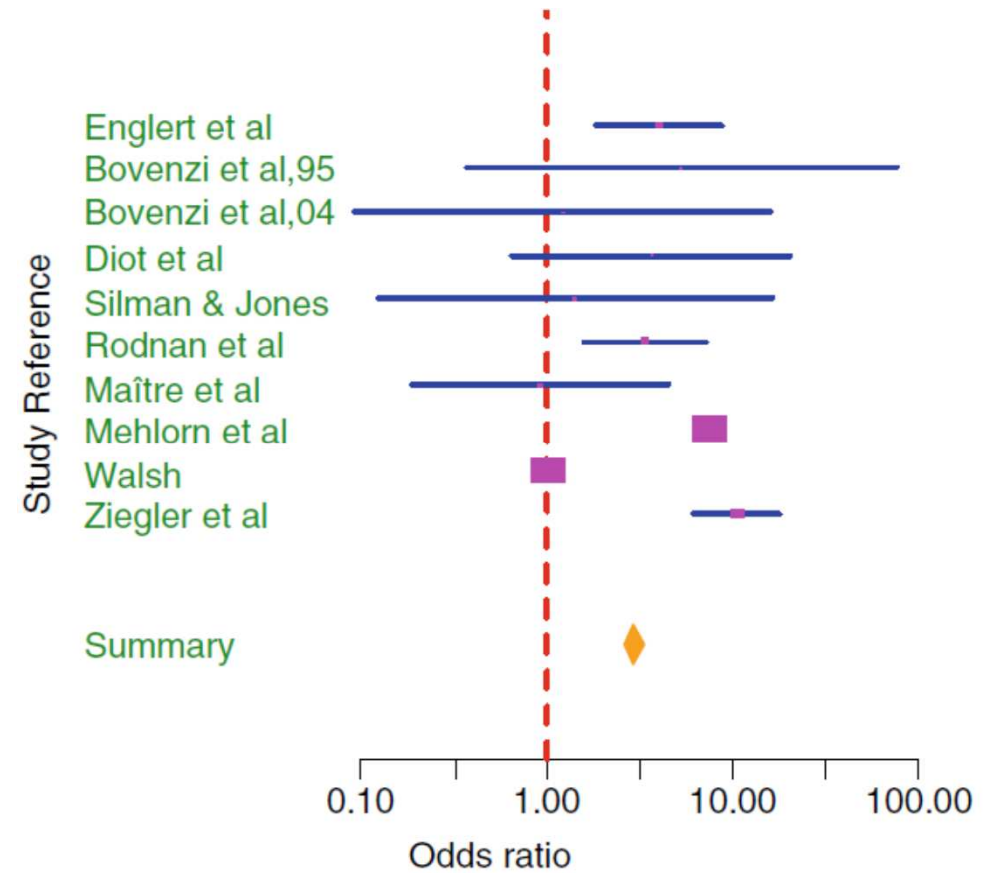
N.I. Environmental Health Sciences Expert Panel Workshop

- 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

Silica & Systemic sclerosis

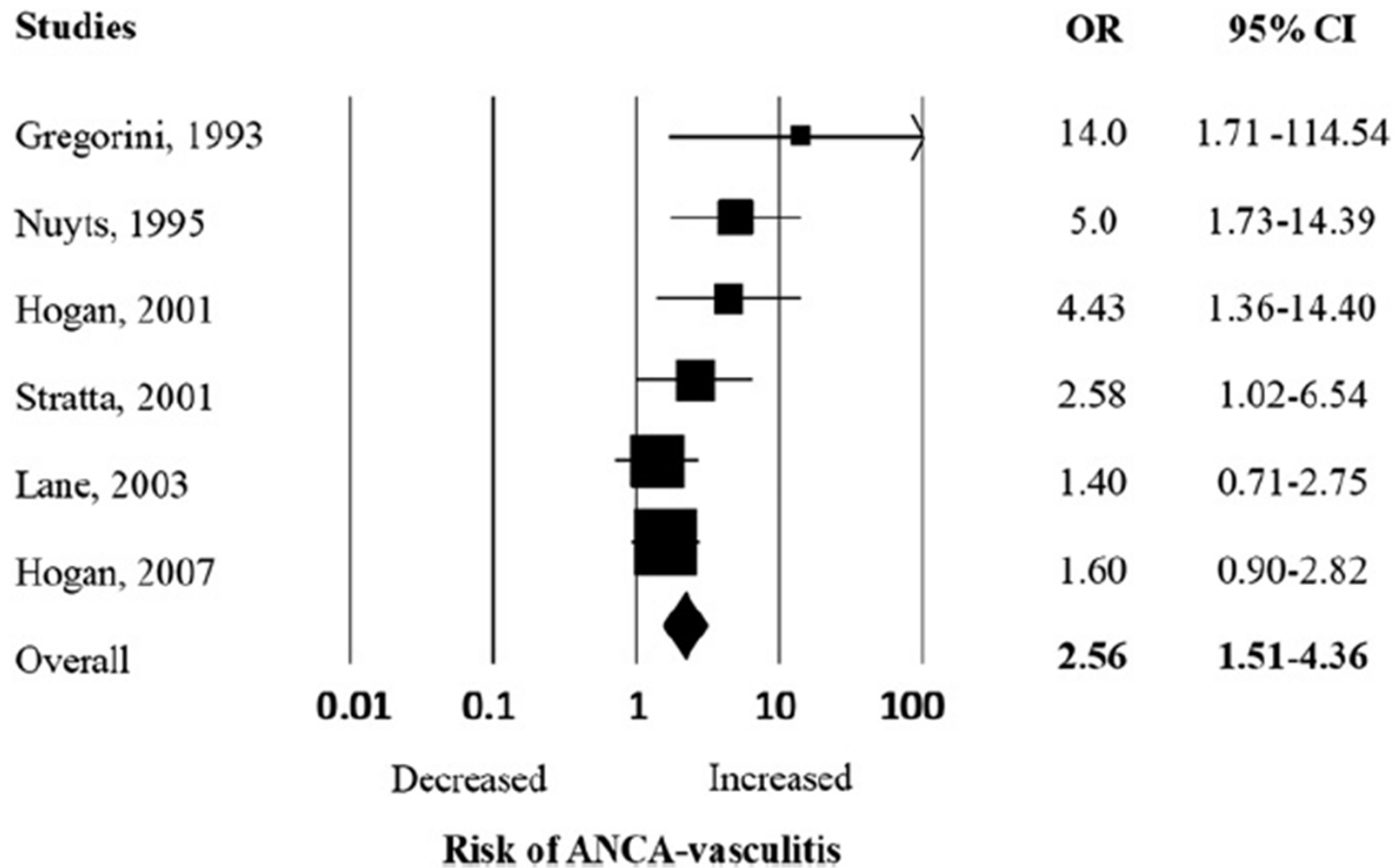


Women: 1.03 (95% CI, 0.74–1.44)



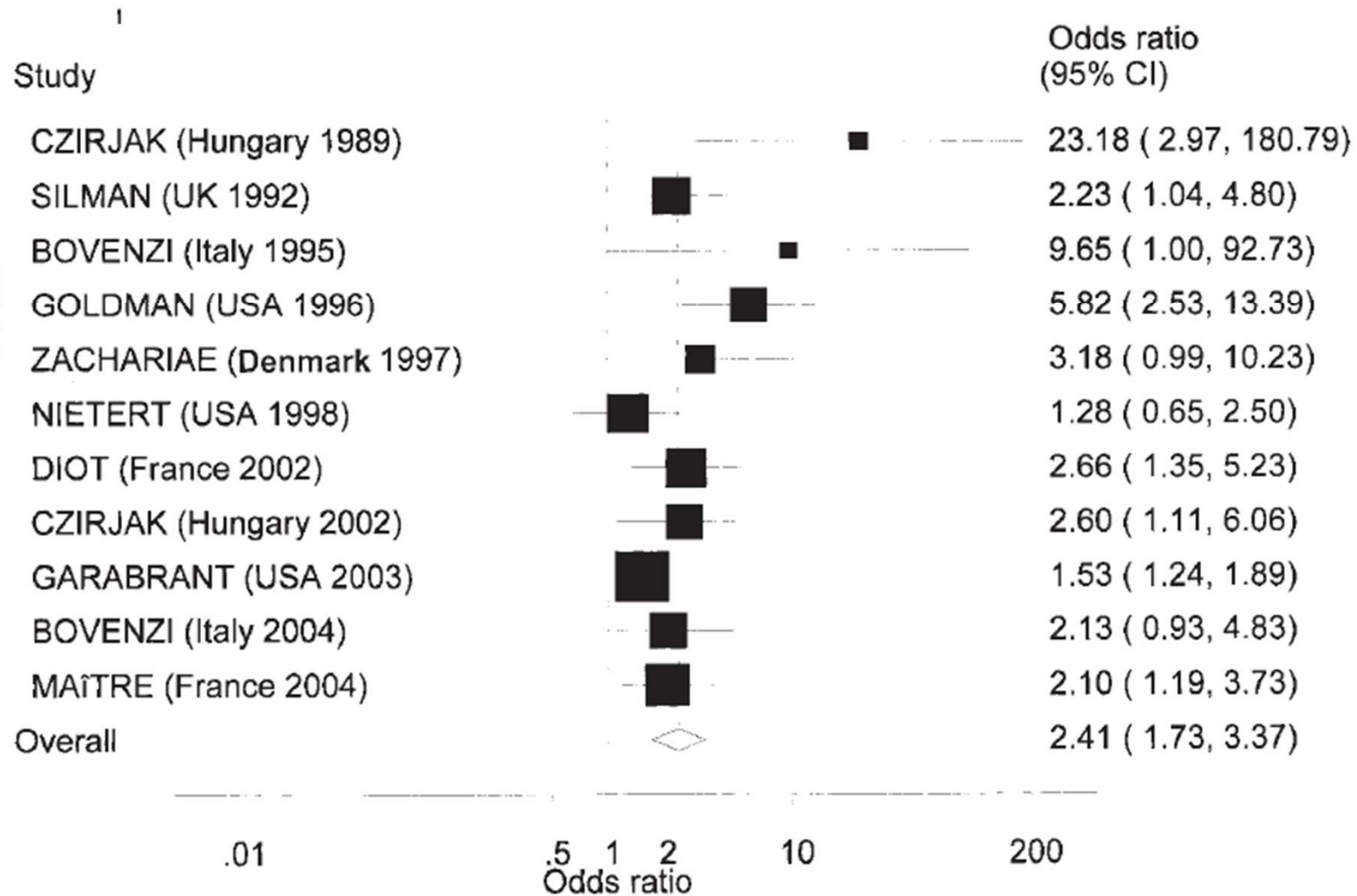
Males: 3.02 (95% CI, 1.24–7.35)

Silica & ANCA Vasculitis



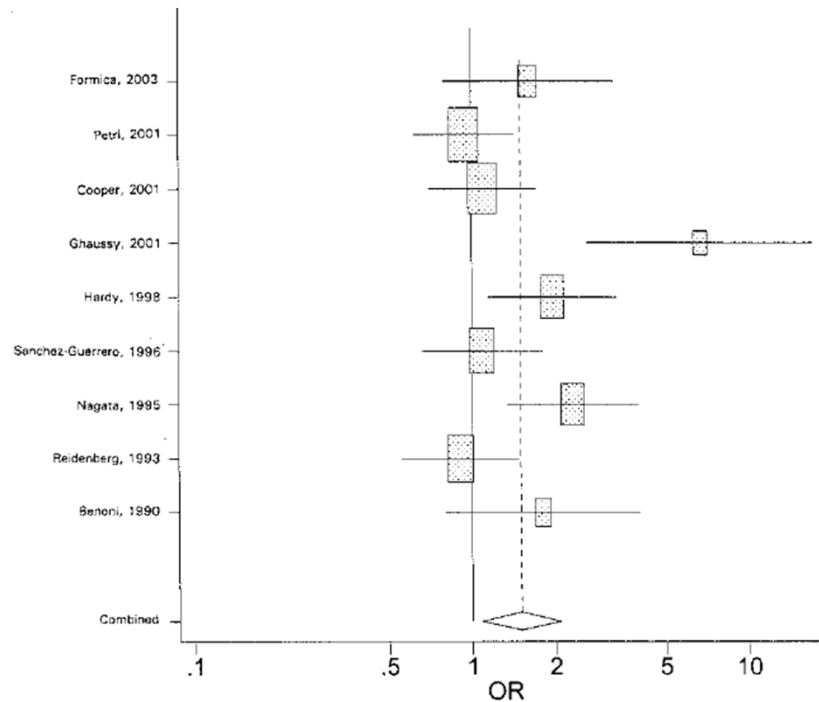
Gomez-Puerta et al (Autoimmunity Rev 2013)

Solvents & Systemic sclerosis



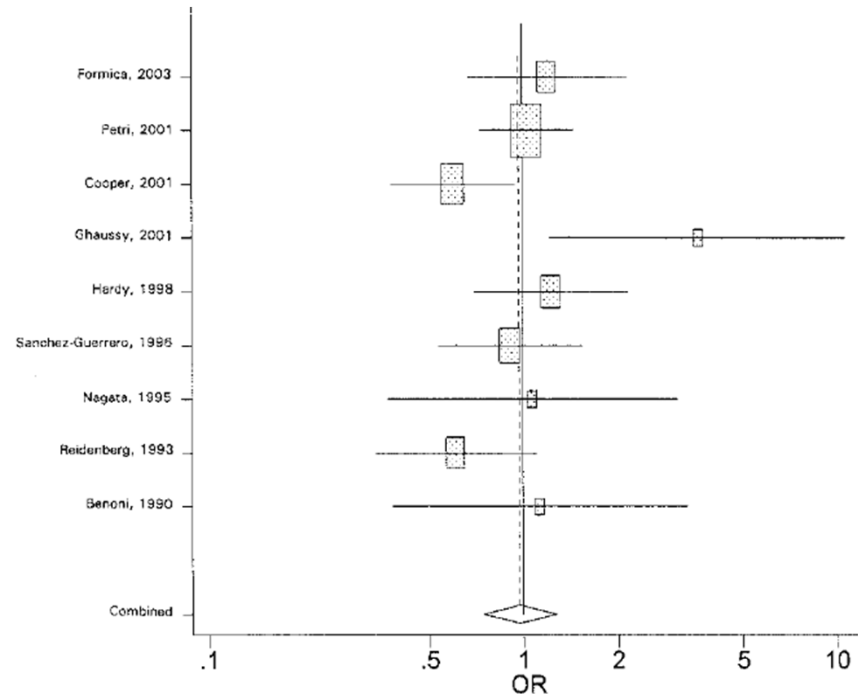
Smoking & Systemic lupus erythematosus

Current vs non-smokers



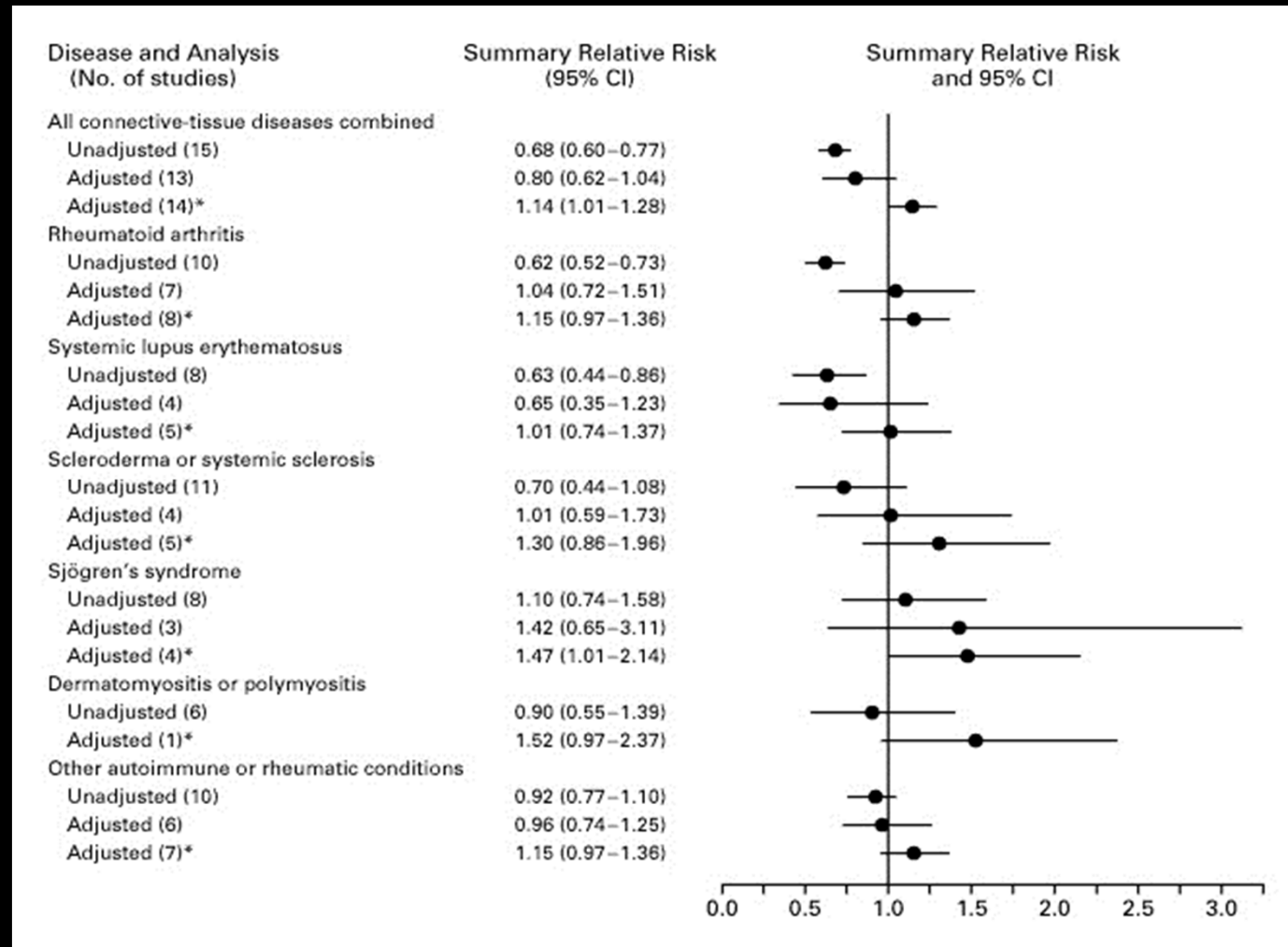
OR 1.50 (95% CI 1.09-2.08)

Ex- vs non-smokers



OR 0.98 (95% CI 0.75-1.27)

Breast implants & Connective tissue diseases



Vitamin D

Other outcomes

Autoimmune diseases

“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.”

Vit

review of
observat

related outcomes

disorders

2% Infectious
disorders

ses of

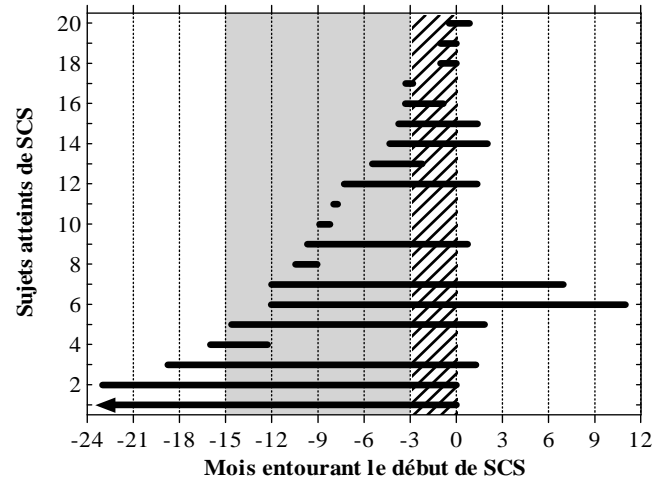
Vasculitis & Environment

Vasculitis entity	Risk factor	
	Infectious	Non-infectious
Giant cell arteritis	Various microorganisms (viruses, bacteria)	Tobacco use, preceding atherosclerotic disease, pregnancies (protective)
Takayasu arteritis Polyarteritis nodosa	Tuberculosis Hepatitis B , hepatitis C, human immunodeficiency virus	
Kawasaki disease	Various microorganisms (viruses, bacteria)	Carpet cleaning, residence near stagnant water
IgA vasculitis	Various microorganisms (viruses, bacteria)	Preceding or concomitant cancer (adults), vaccines (children)
Cryoglobulinemic vasculitis Behçet's disease	Hepatitis C Streptococci (oral flora)	Impaired oral health

Vasculitis & Environment

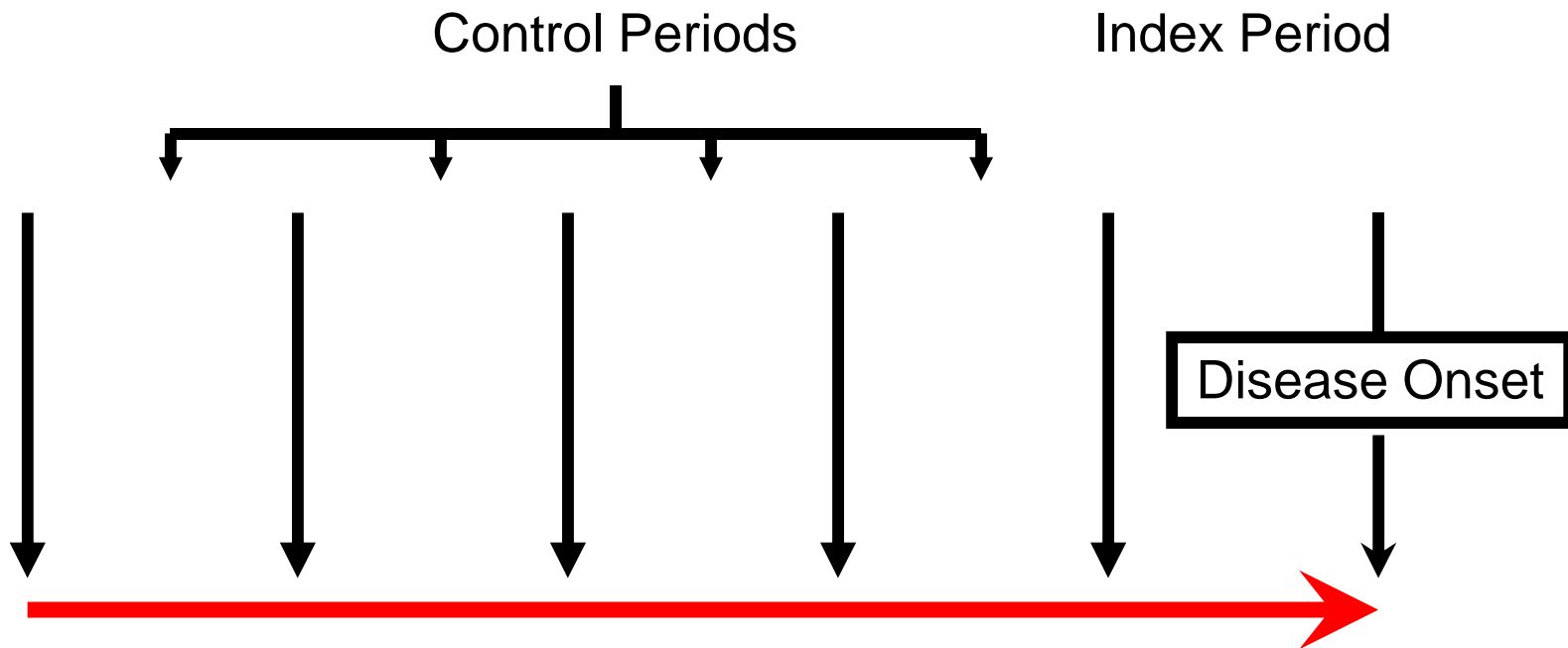
Vasculitis entity	Risk factor	
	Infectious	Non-infectious
Granulomatosis with polyangiitis	Staphylococcus aureus (nasal carriage)	Silica , organic solvents, industrial pollutants, inhalation of particulate material and fumes, farming (livestock), pesticides, allergy, cancer, tobacco use (protective)
Microscopic polyangiitis		Propylthiouracil, hydralazine and other drugs, silica
Eosinophilic granulomatosis with polyangiitis		Leukotriene receptor antagonists and other drugs, vaccines, desensitization, silica
Anti-glomerular basement membrane (anti-GBM) disease		Tobacco use

EGPA & Montelukast



Drug	3-Months Periods		OR (95% CI)	2-Months Periods		OR (95% CI)	4-Months Periods		OR (95% CI)
	Exposed, %	Control		Exposed, %	Control		Exposed, %	Control	
Montelukast	19%	11%	4.5 (1.5–13.9)	17%	11%	3.6 (1.2–10.5)	19%	13%	2.8 (0.9–8.7)
LABA	63%	57%	3.0 (0.8–10.5)	64%	58%	4.1 (1.0–16.6)	66%	62%	3.6 (0.7–19.0)
Inhaled corticoids	67%	64%	1.7 (0.5–5.4)	67%	64%	1.7 (0.5–5.7)	68%	67%	1.3 (0.4–4.9)
Oral corticoids	50%	42%	4.0 (1.3–12.5)	50%	42%	8.6 (2.2–33.3)	50%	43%	4.0 (1.0–15.6)

Case-Crossover Design



➔ 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

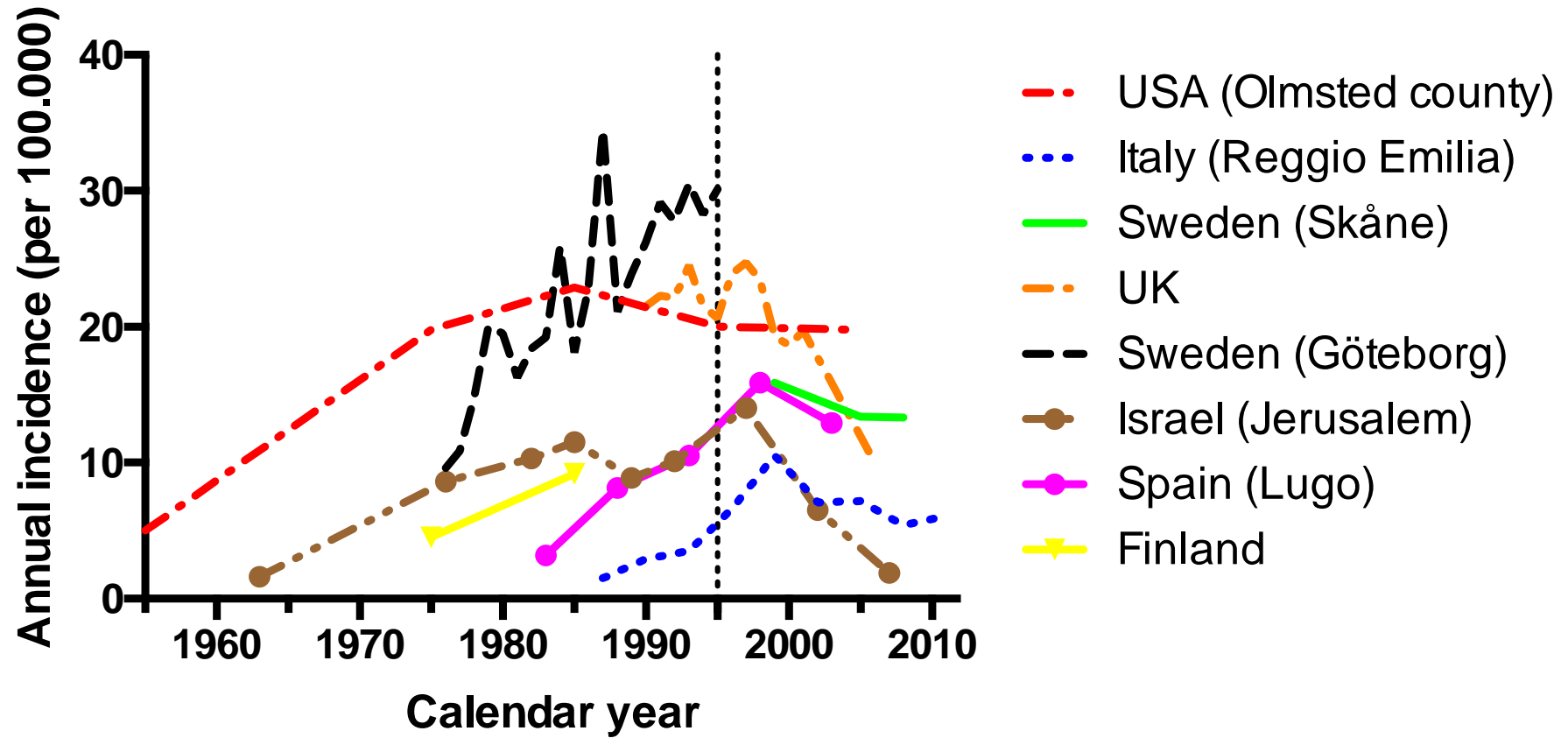
Isaac Newton

Build on descriptive data

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

Incidence of GCA

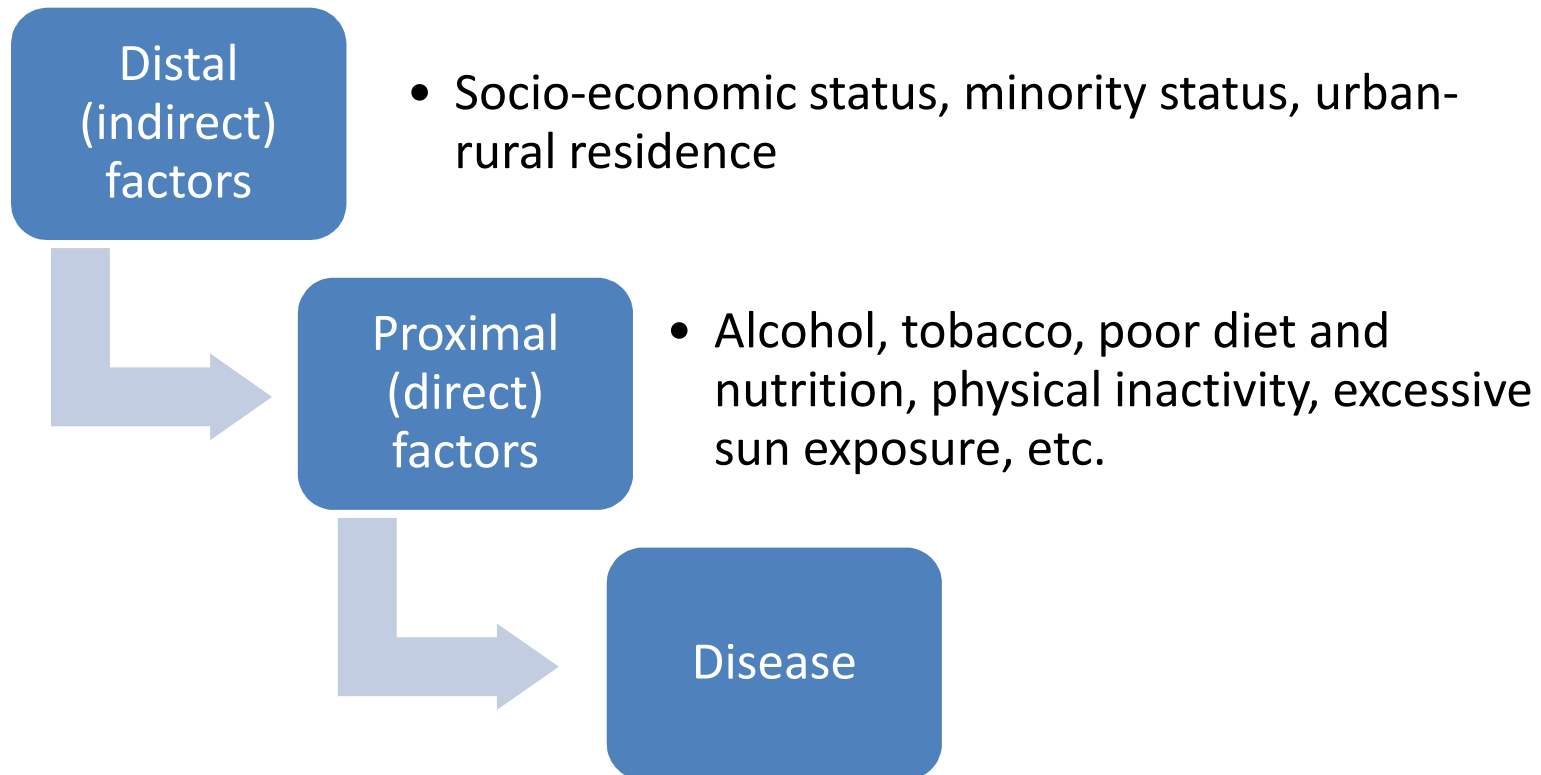
Giant Cell Arteritis



Identify good candidates (Vasculitis)

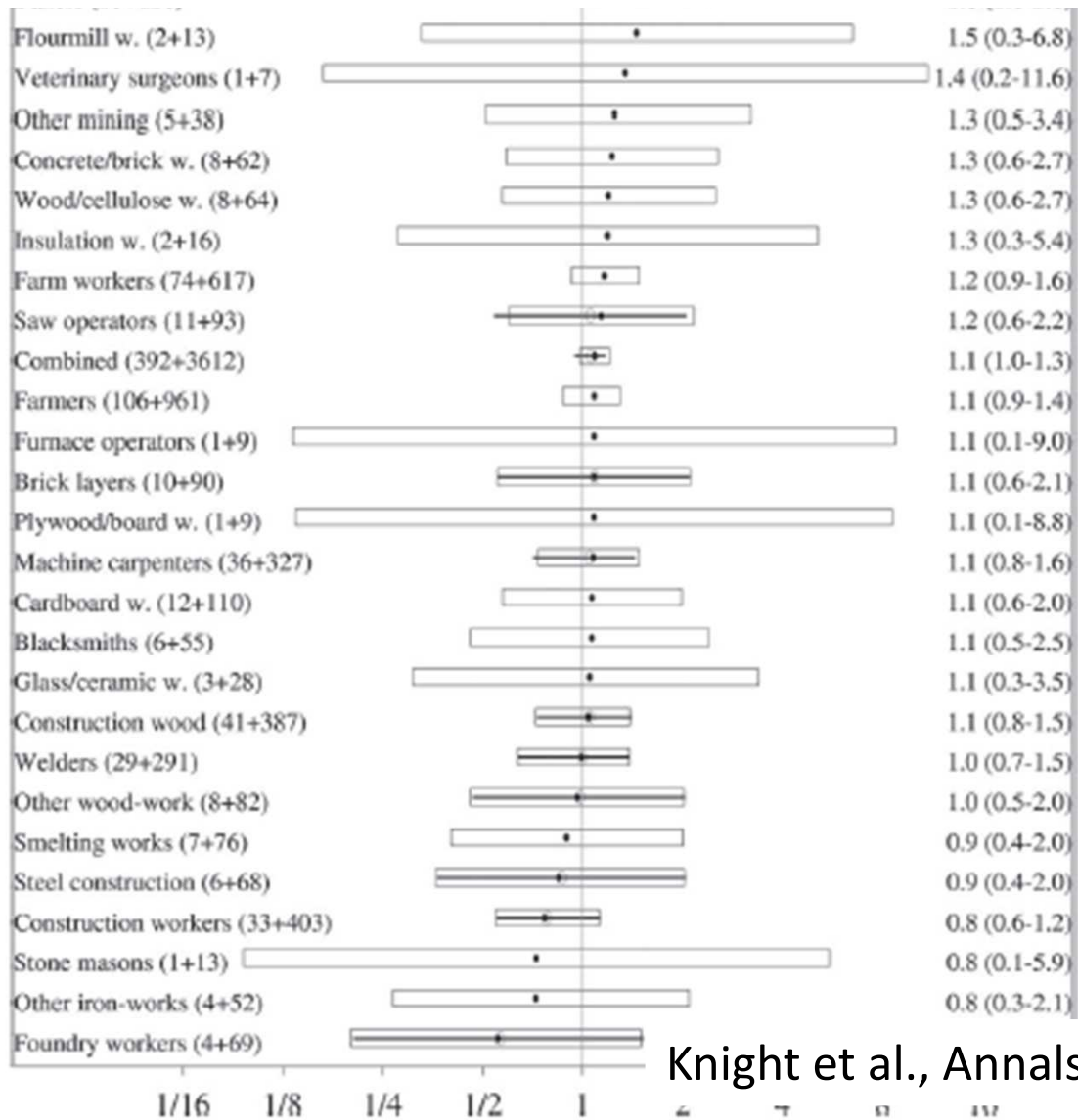
	Infection	Drugs	Hormonal factors	Behaviour, occupation, recreation	Cancer, Cardiovascular disease
GCA	Yellow		Yellow	Yellow	Yellow
TAK	Yellow		Yellow		
PAN	Green				
KD	Green				Red
GPA	Yellow			Yellow	Yellow
MPA	Yellow	Yellow		Yellow	Yellow
EGPA	Yellow	Yellow		Yellow	
IgAV	Green				Red with horizontal lines
Cryo	Green				Yellow
Behçet's	Yellow				

“Distal” risk factors





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