

Myositis – Clues from the Environment

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Environmental Aspects of Myositis

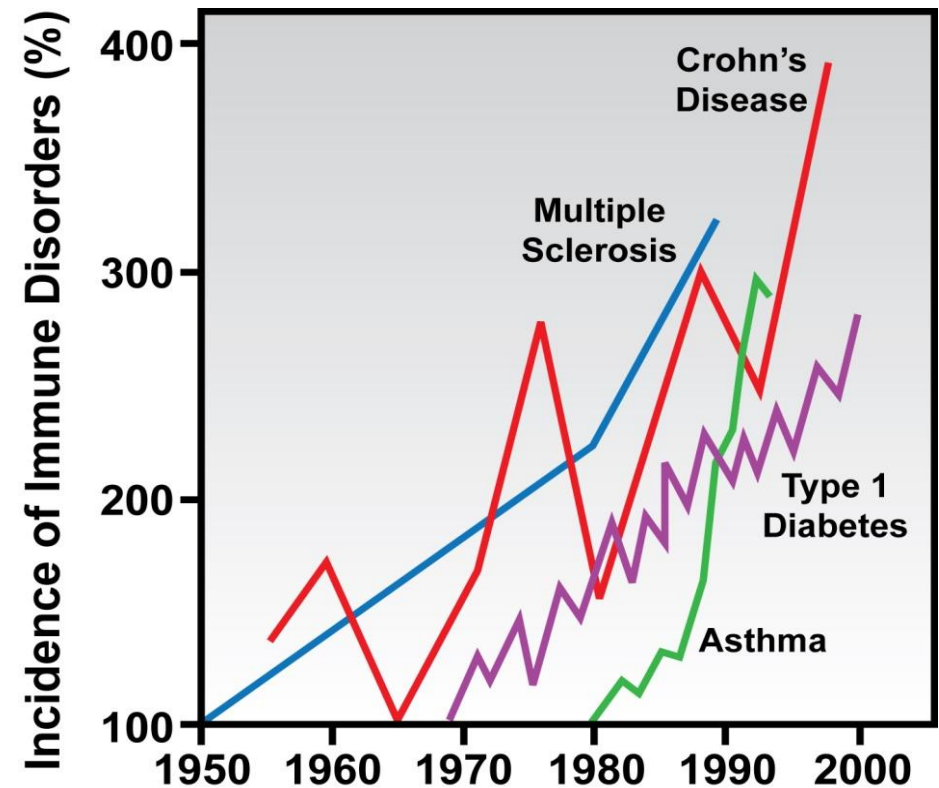
- Increasing evidence suggests that myositis results from environmental exposures in genetically susceptible persons
- New myositis genes and environmental risk factors are being identified and many studies are ongoing now that will likely identify more
- Given the many similarities between myositis and other autoimmune diseases it is useful to review what we know about environmental aspects of other autoimmune diseases

Autoimmune Diseases

- Encompass over 80 acquired disorders in which a person's immune system attacks his/her own tissues (auto = self) and results in illness (autoimmune disease)
- Together they affect 5-8% of the population and many are rapidly increasing in prevalence
- Are often incurable, are a leading cause of death and disability in young women, and result in great costs to society
- These diseases involve chronic immune activation likely as a result of environmental exposures in genetically susceptible individuals

Increasing Frequencies of Autoimmune Diseases

- Multiple sclerosis, Crohn's disease, Type I diabetes and asthma have been increasing in incidence over the past 2- 4 decades – also some evidence for increasing frequency of myositis
- Lupus, scleroderma, myasthenia gravis also appear to be increasing in prevalence
- These increases in the incidence and prevalence of autoimmune diseases could be due to changes in the environment

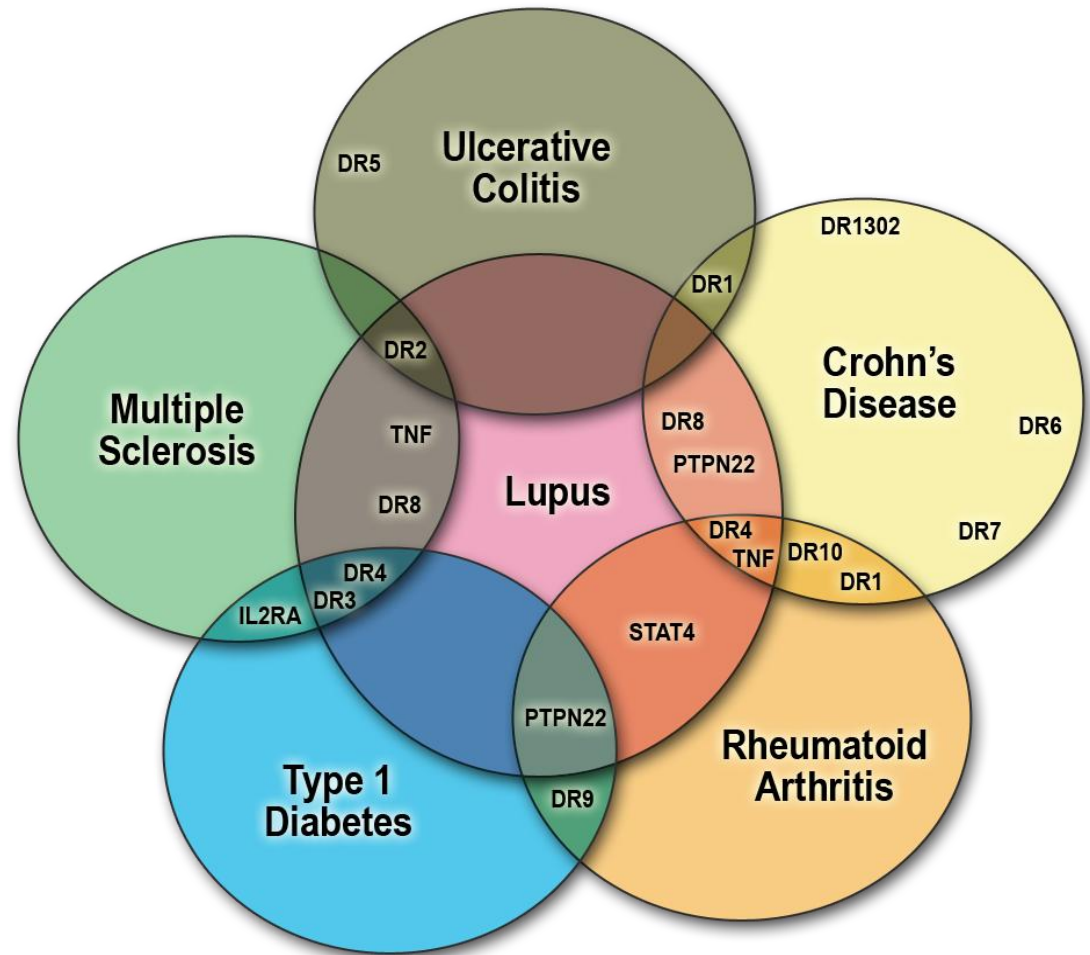


Types of Evidence Suggesting an Environmental Role in the Development of Autoimmune Diseases

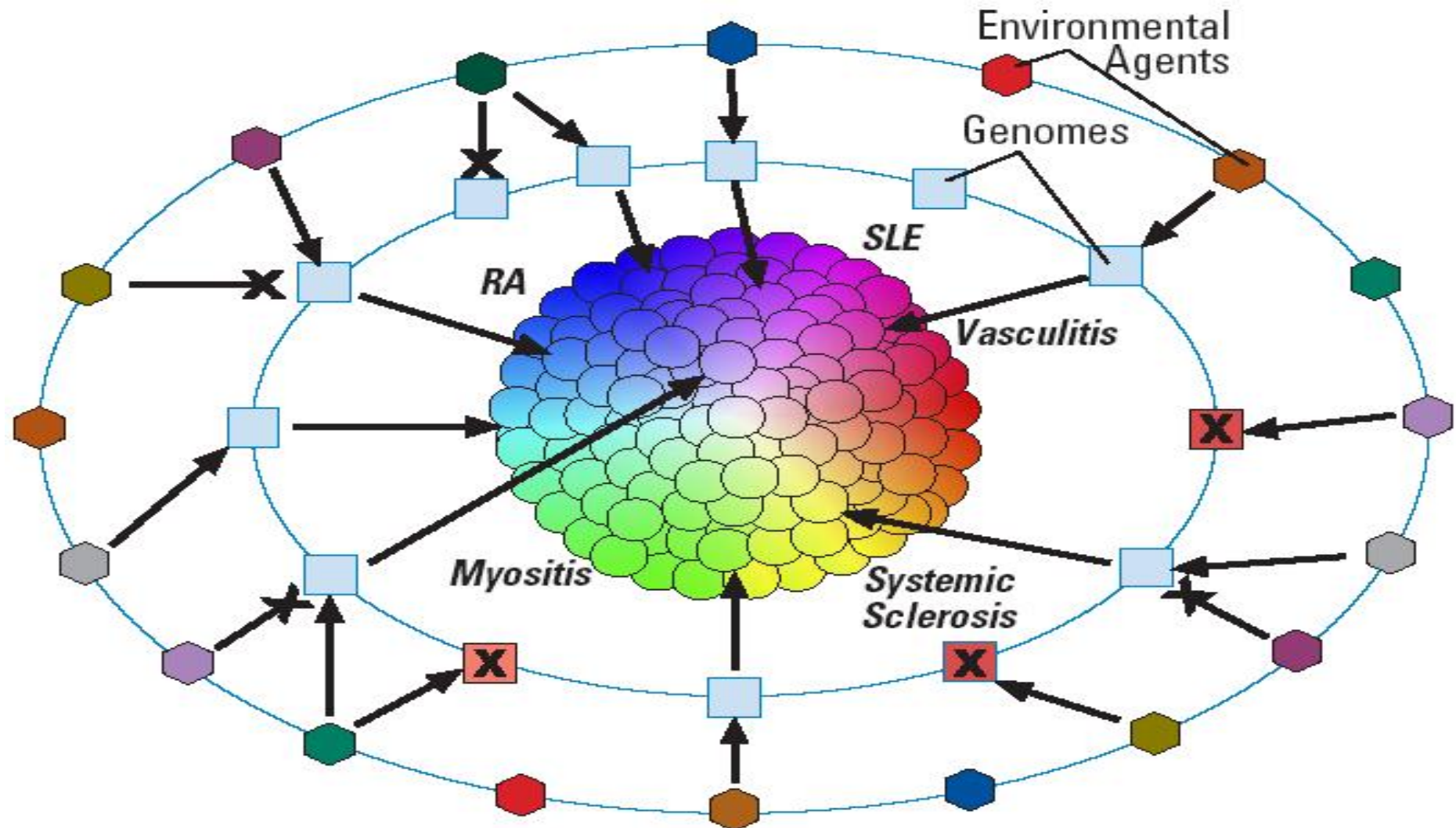
- Changes in disease incidence and prevalence over time
- Identical twins both develop disease less than 50% of the time
- Strong associations in time with some exposures and disease onset
- Epidemiologic studies show associations between exposures and diseases
- Certain seasons seem to predispose to disease onset and birth dates
- Disease improvement after agent removal (de-challenge), disease recurrence after agent re-exposure (re-challenge)
- Genes determining responses to exposures are major risk factors
- Studies in animals and cells provide biologic mechanisms

Evidence for a Genetic Role in the Etiology of Autoimmune Diseases

- Increased prevalence in certain families and ethnic groups
- Gradients of disease concordance in pedigrees: identical > fraternal twins > other relatives
- Associations with many genes – some are shared among multiple diseases



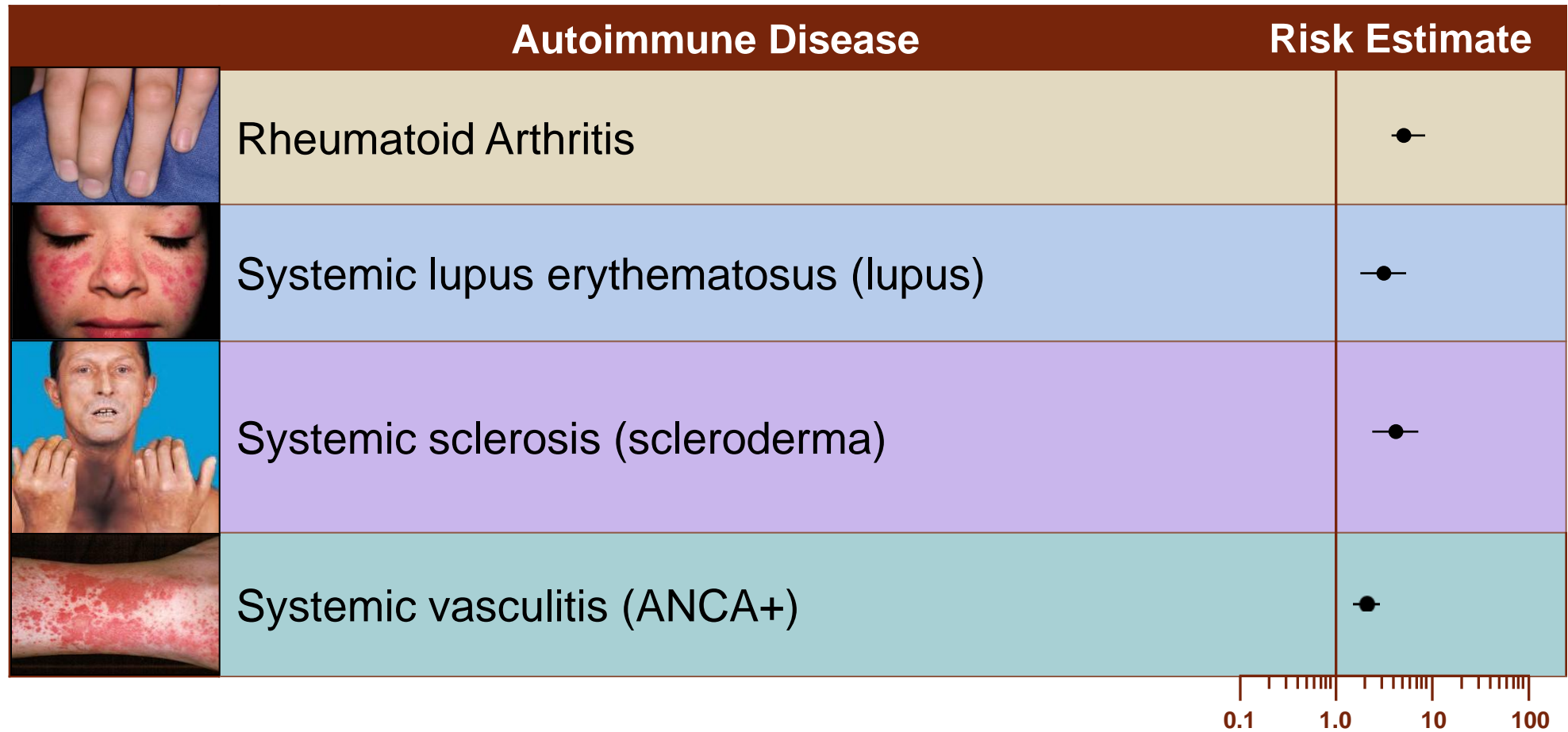
Possible Gene-Environment Interactions Resulting in Autoimmune Disorders



NIEHS Expert Panel On the Environment and Autoimmune Diseases – Epidemiology Consensus



Occupational Silica Exposure Contributes to Development Of Autoimmune Disease

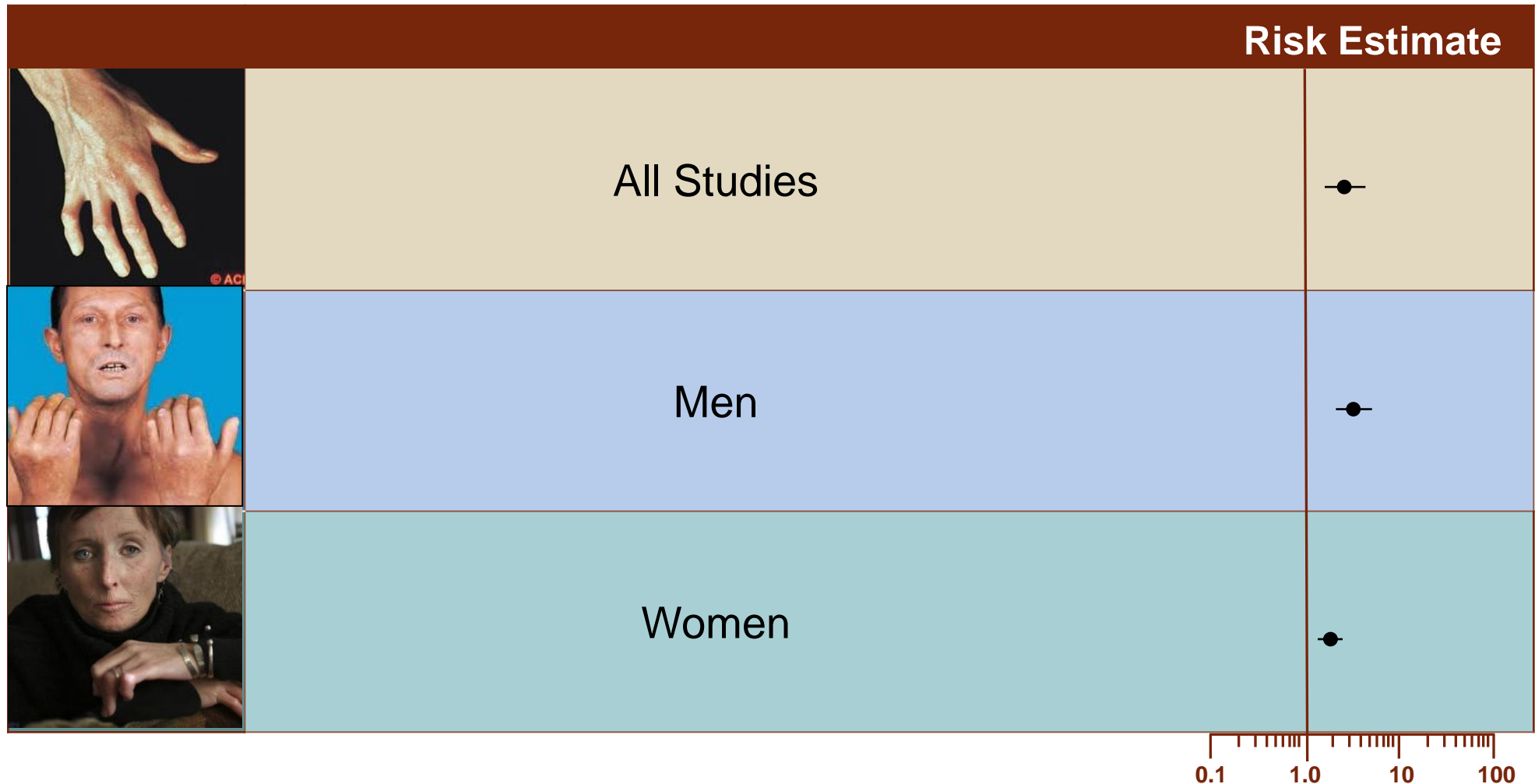


Typical occupational exposures include mining, heavy construction, masonry, farming, and manufacturing of tile, pottery, glass

NIEHS Expert Panel On the Environment and Autoimmune Diseases – Epidemiology Consensus



Occupational Solvent Exposure Contributes to Development of Scleroderma

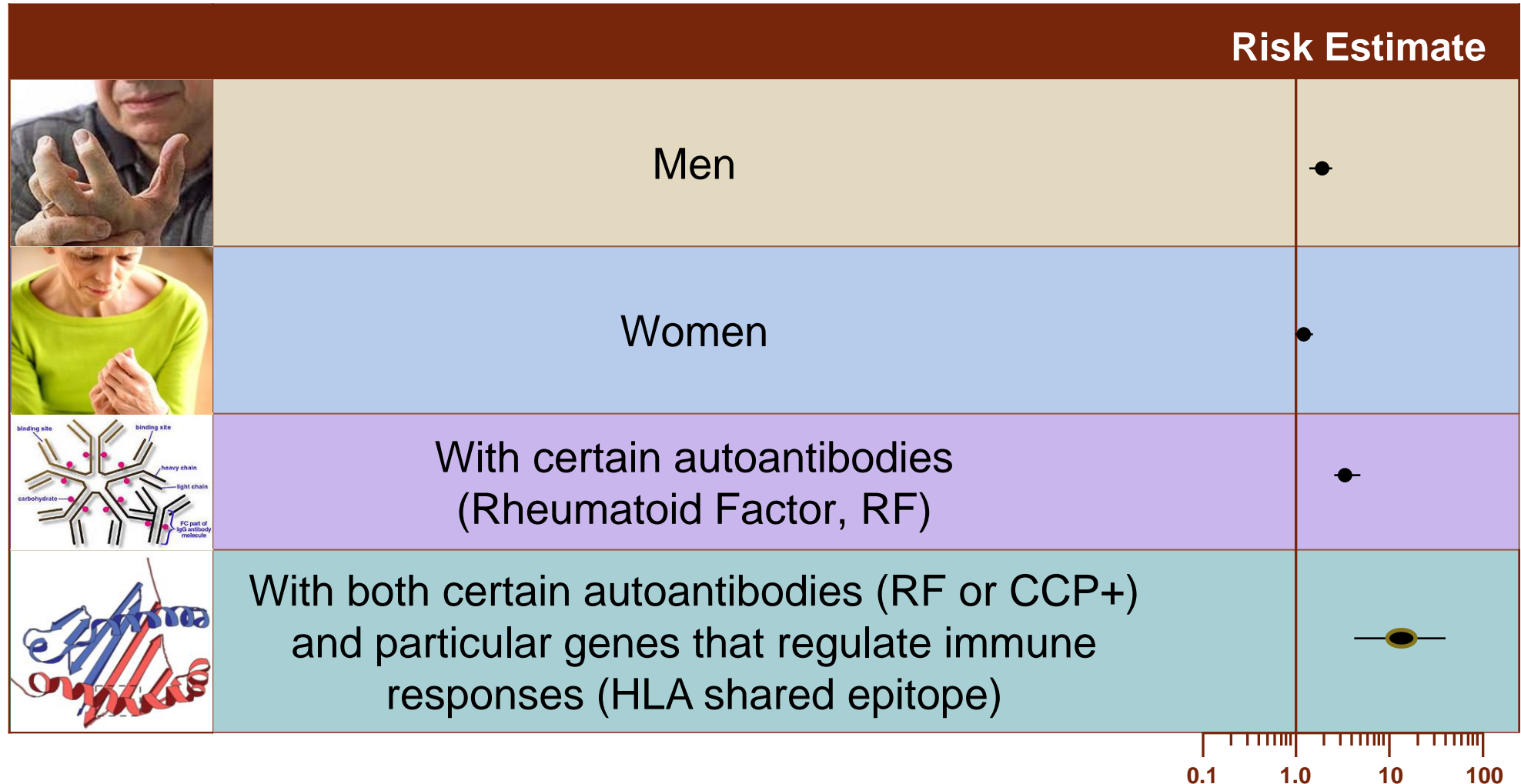


Typical occupational exposures include dry cleaning, metal working, painting

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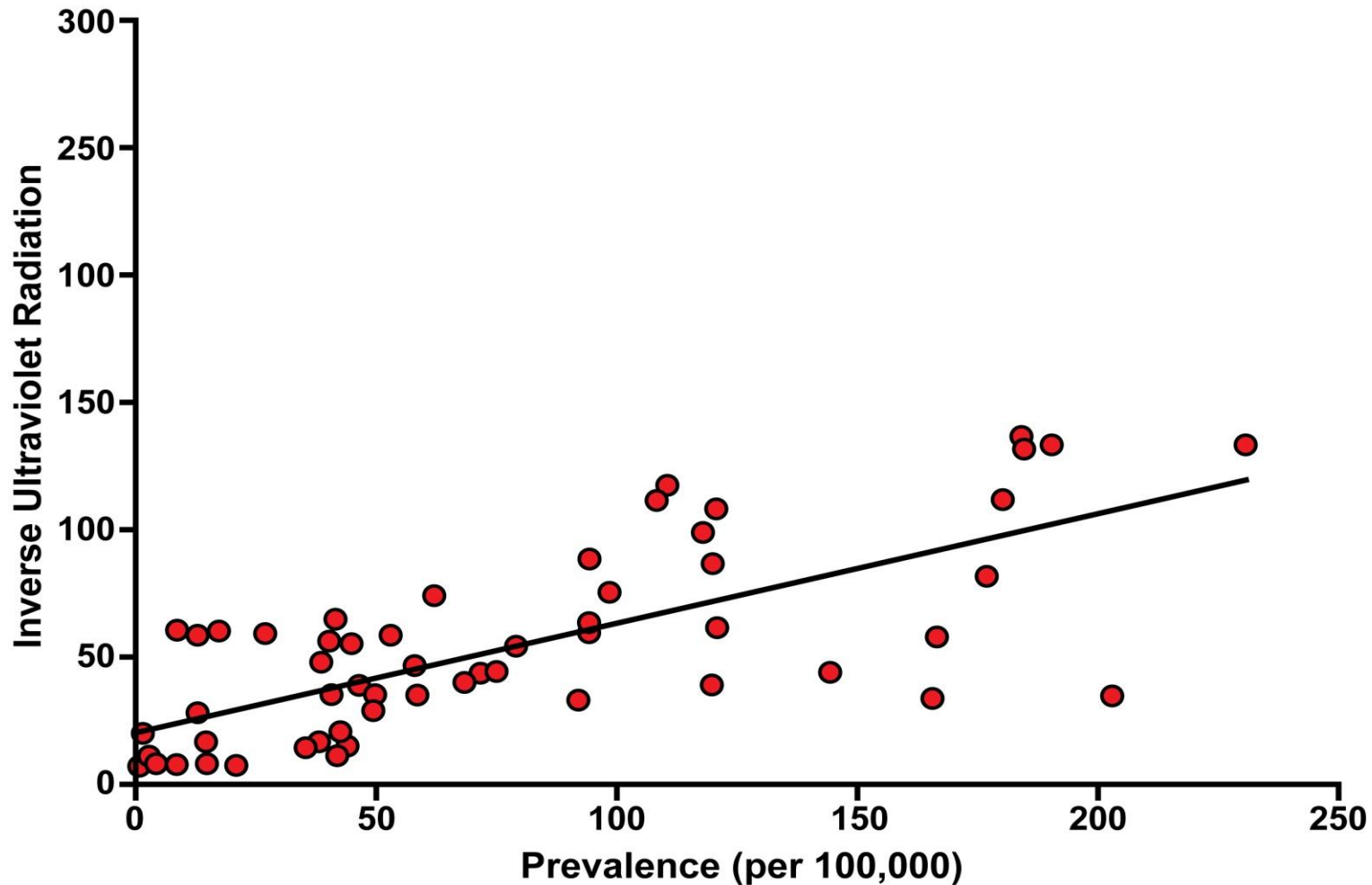
Smoking Contributes to the Development of Rheumatoid Arthritis



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Lower Exposure to Sunlight is Associated with an Increased Risk of Multiple Sclerosis





Dietary and Dietary Supplement Exposures Contribute to the Development of Certain Autoimmune Diseases

- Gluten (found in grains such as wheat, rye, barley) contributes to the development of Celiac Disease
- Certain batches of the dietary supplement L-tryptophan contribute to the development of Eosinophilia Myalgia Syndrome (elevations of a white blood cell, with skin rashes and muscle pain)



Conclusions

- Many specific exposures and other autoimmune diseases may be associated, but need additional study
 - Asbestos, heavy metals, pesticides, persistent organic pollutants, ultraviolet radiation, infections
- Epidemiology and other approaches will continue to contribute to our knowledge of environmental risk factors for autoimmune diseases
- More cost-effective, validated methods for assessing human exposures are needed
- More research is needed into autoimmune disease subsets, and how many exposures might interact with genetics

Summary

- Increasing incidence and other evidence suggest environmental factors play a role in the development of autoimmune diseases in genetically susceptible persons
- A number of environmental factors have been identified in several autoimmune diseases, based on epidemiologic studies
 - Occupational exposures: silica, solvents
 - Smoking
 - Ultraviolet radiation
 - Dietary factors
- However, many other diseases and exposures have not been adequately studied to reach conclusions

Difficulties in the Study of Environmental Disease

- Differentiating effects of the suspect triggering agent from effects of other exposures or from underlying conditions
- Incomplete knowledge of the suspect agent's mechanisms of action and pharmacodynamics
- Inadequate surveillance systems for accurate exposure estimates and for disease incidence/prevalence rates
- Varied individual risk factors (genetics, etc.)
- Few validated exposure assessment tools and bioassays
- No widely accepted standards for approaches to identify and define environmentally associated diseases

Proposed Stages in the Definition of an Environmental Disease

- **STAGE 1** - Case reports, defined by ascertainment criteria, propose a possible association of a specific clinical syndrome with a given exposure (*eosinophilia and myalgia following L-tryptophan ingestion*)
- **STAGE 2** – After such cases are reported, surveillance criteria are proposed and epidemiologic and laboratory studies test hypotheses (*eosinophilia-myalgia syndrome*)
- **STAGE 3** - If studies above are positive, specific classification and other criteria are defined for that specific environmental disease (*LT-associated EMS*)
- **STAGE 4** - Criteria are reassessed and refined as additional data are obtained about the disease

Possible Environmental Triggers of Myositis

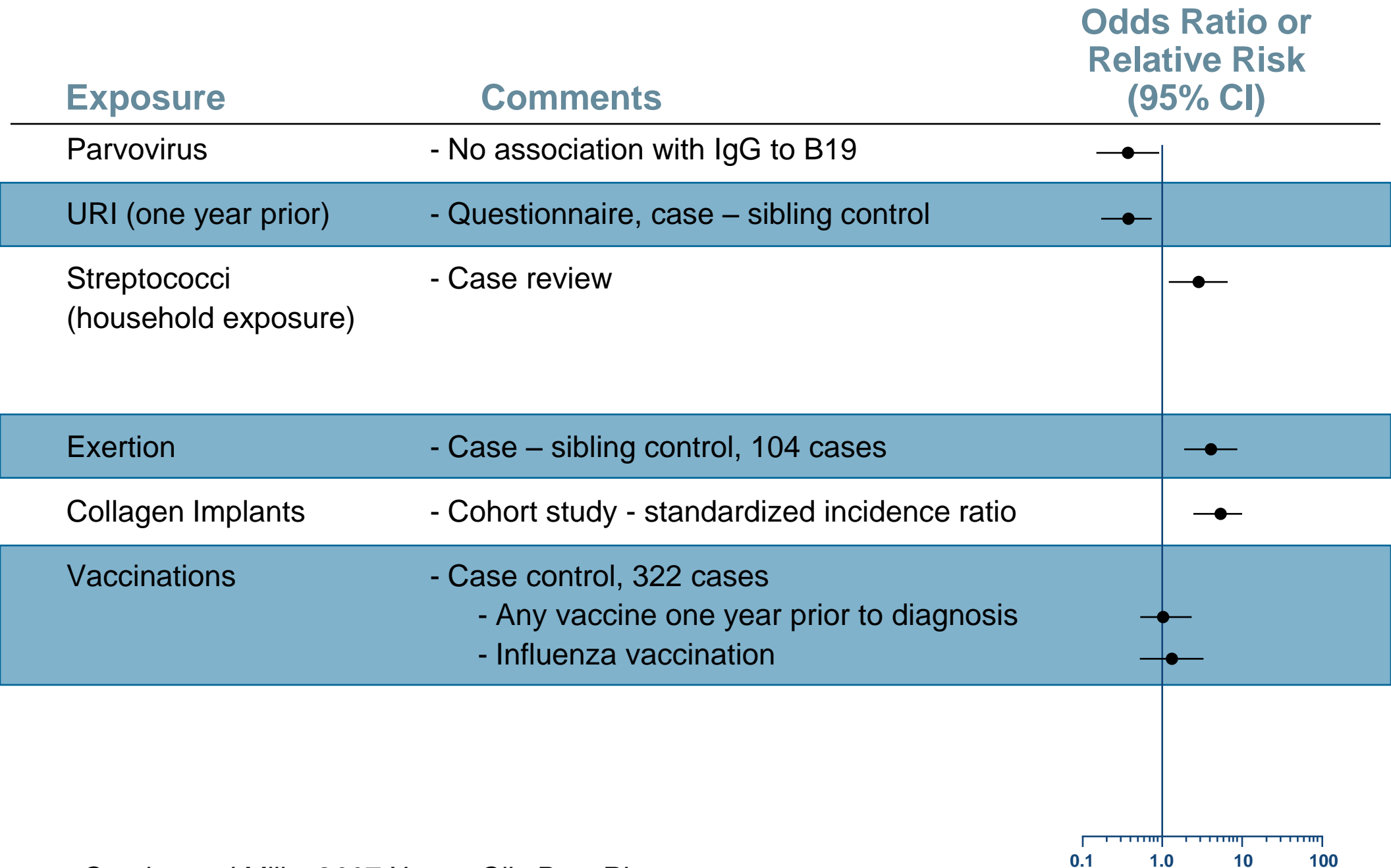
● *Infections*

- Viruses: **Echovirus**, HIV, Coxsackievirus, Hepatitis, others
- Bacteria: **Group A Streptococcus**, Lyme, others
- Parasites: Toxoplasma, others

● *Non-Infectious agents*

- Drugs: **D-penicillamine**, **growth hormone**, **cytokines**, cimetidine, estrogens, statins, others
- Foods: **L-tryptophan**, dietary supplements, ciguatera toxin, others
- Occupational exposure: Silica, super glues, others
- Other environmental exposures: **Collagen implants**, smoking, stress, **sunlight**, **exertion**, others

Epidemiology of Environmental Exposures and Myositis

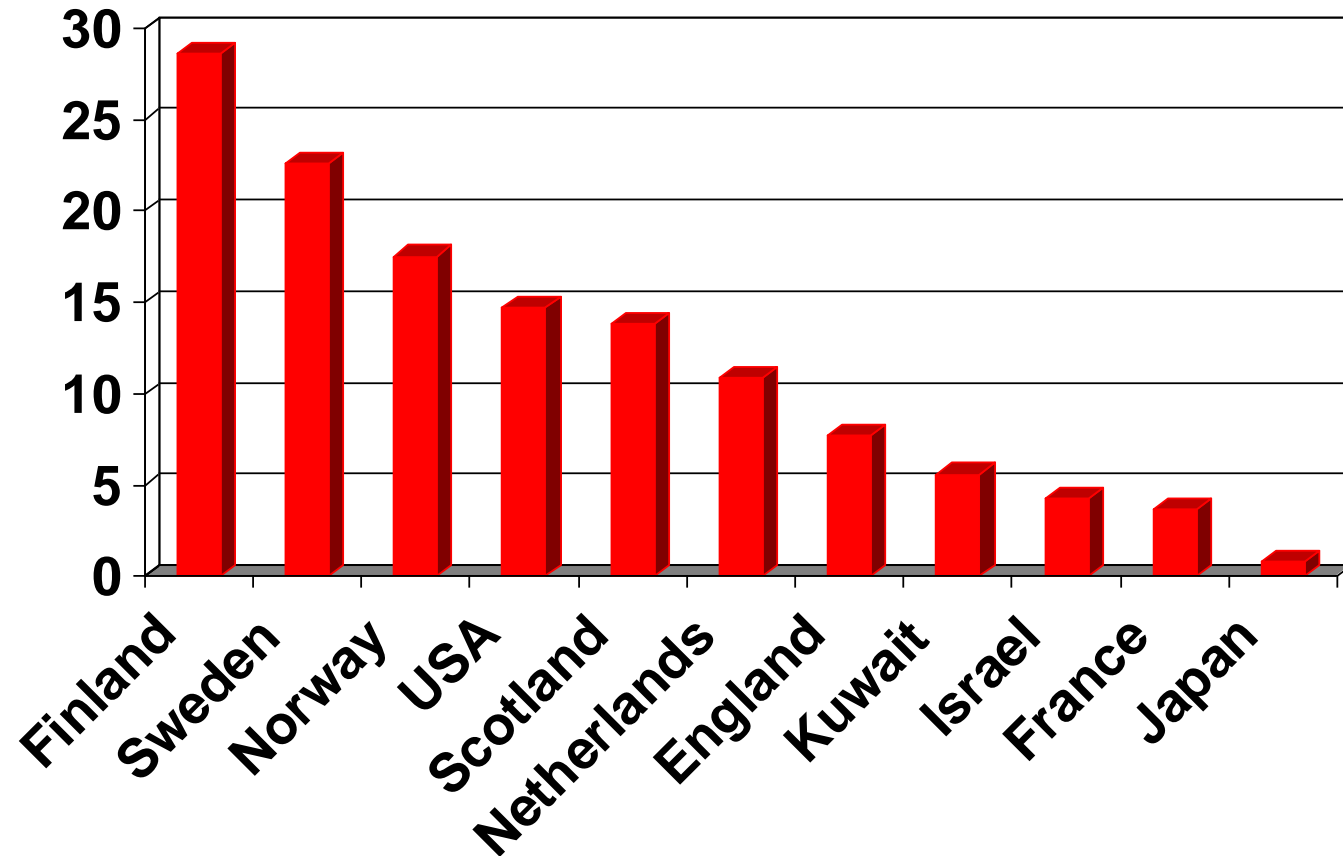


The Ethnogeography of Disease

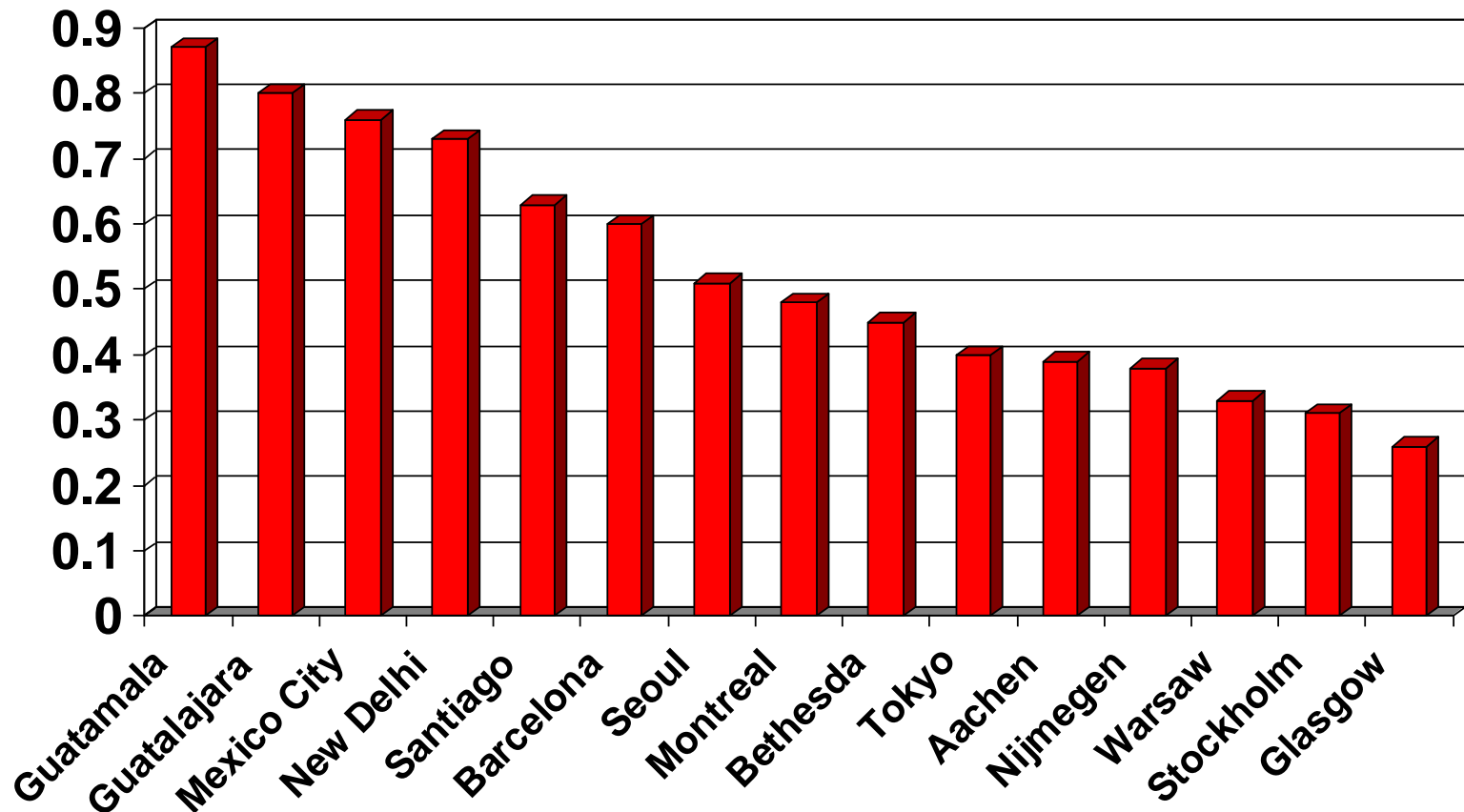
- Many diseases vary in prevalence and clinical expression in different areas around the world
- Reasons for these differences remain unknown but natural global variations in genetics and environments may play roles
- Understanding the causes of these differences may give insight into disease pathogenesis



Worldwide Annual Incidence per 100,000 Population of Type 1 Diabetes

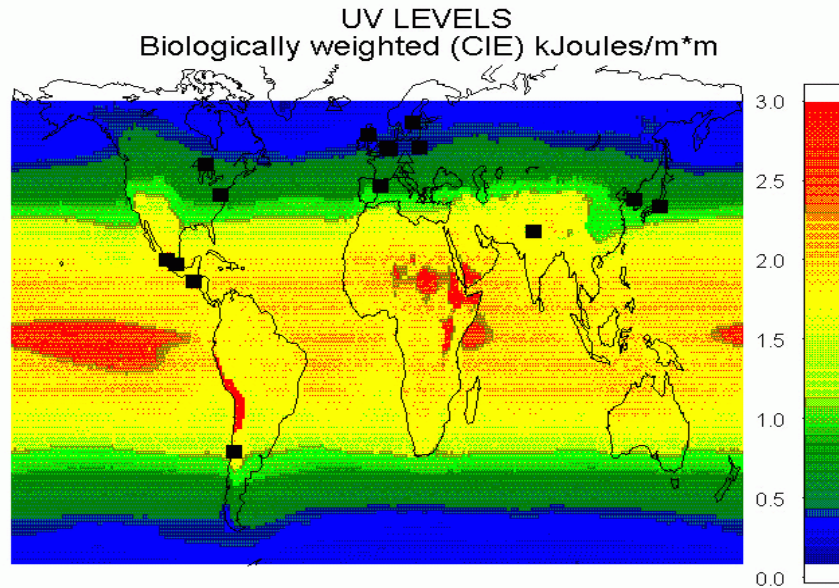


The Proportion of Dermatomyositis Patients in the Total Myositis Populations Varies at Referral Centers World-wide

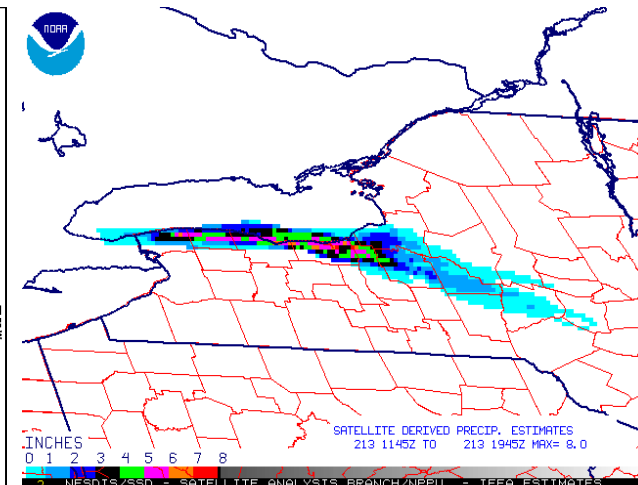
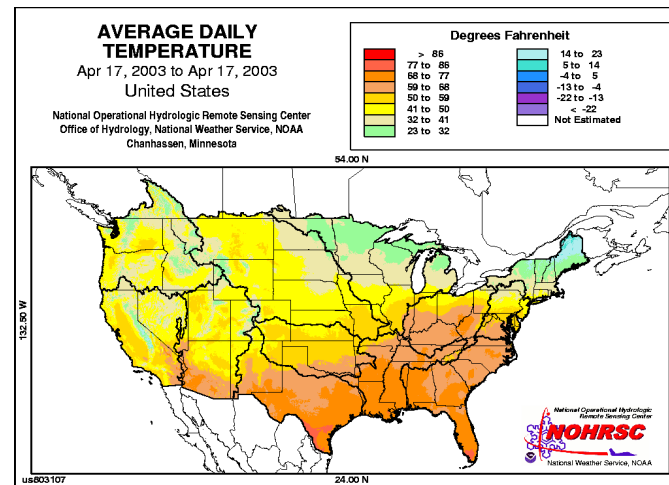
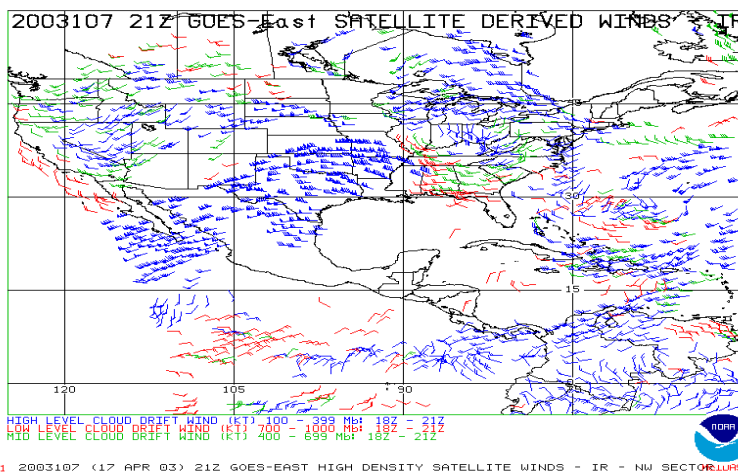
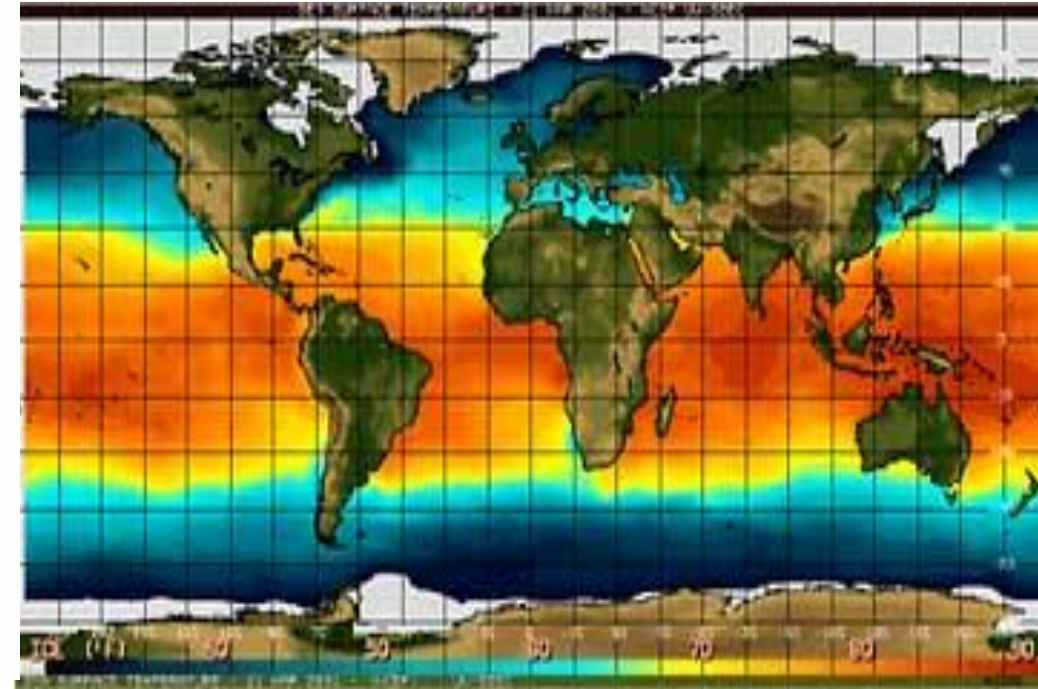


($N = 919$, Monte Carlo exact P value for equality of proportions $< 5 \times 10^{-7}$)

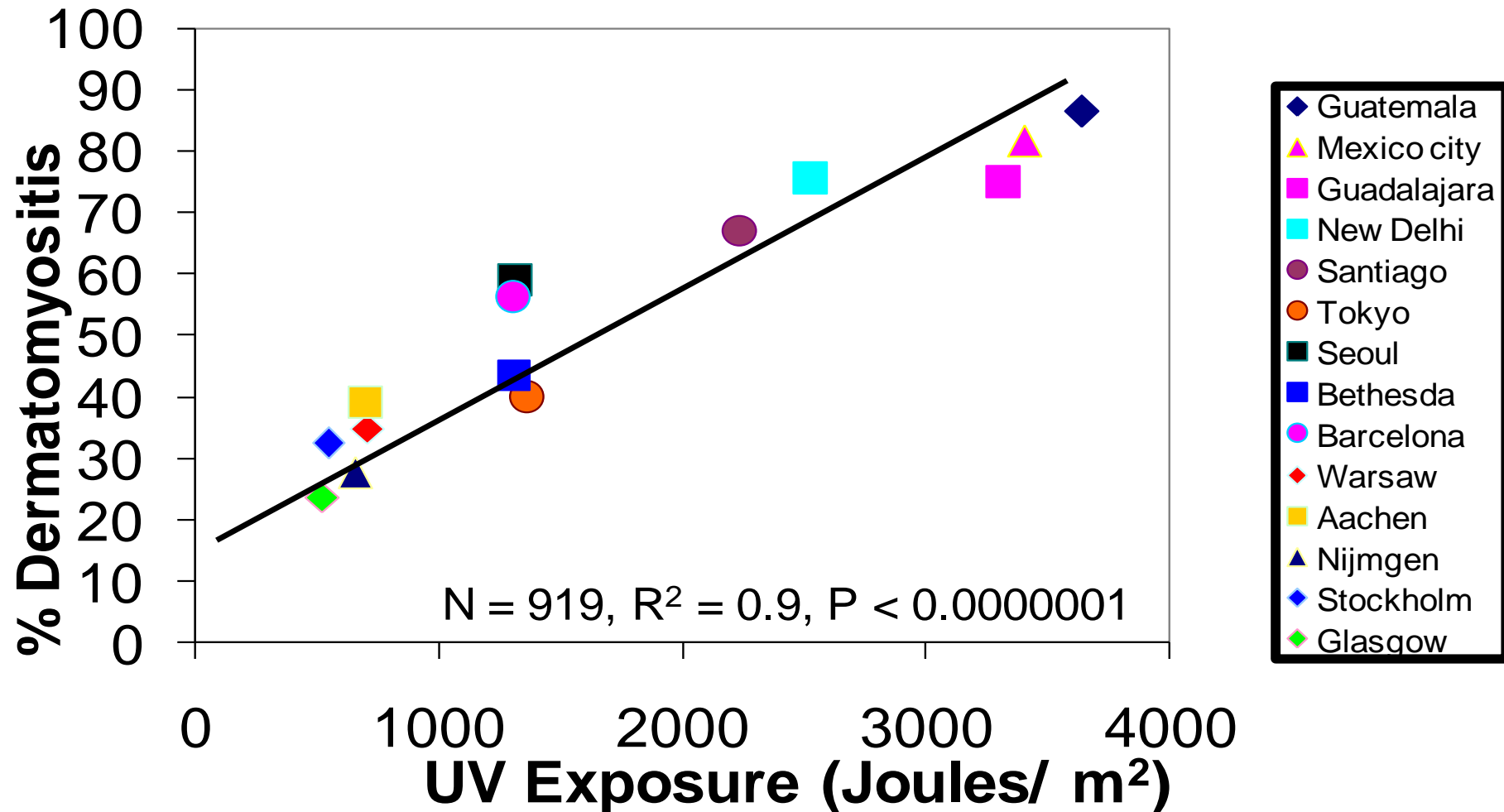
U.S. National Oceanic and Atmospheric Administration (NOAA)



Weatherhead Mon May 21 16:27:08 2001

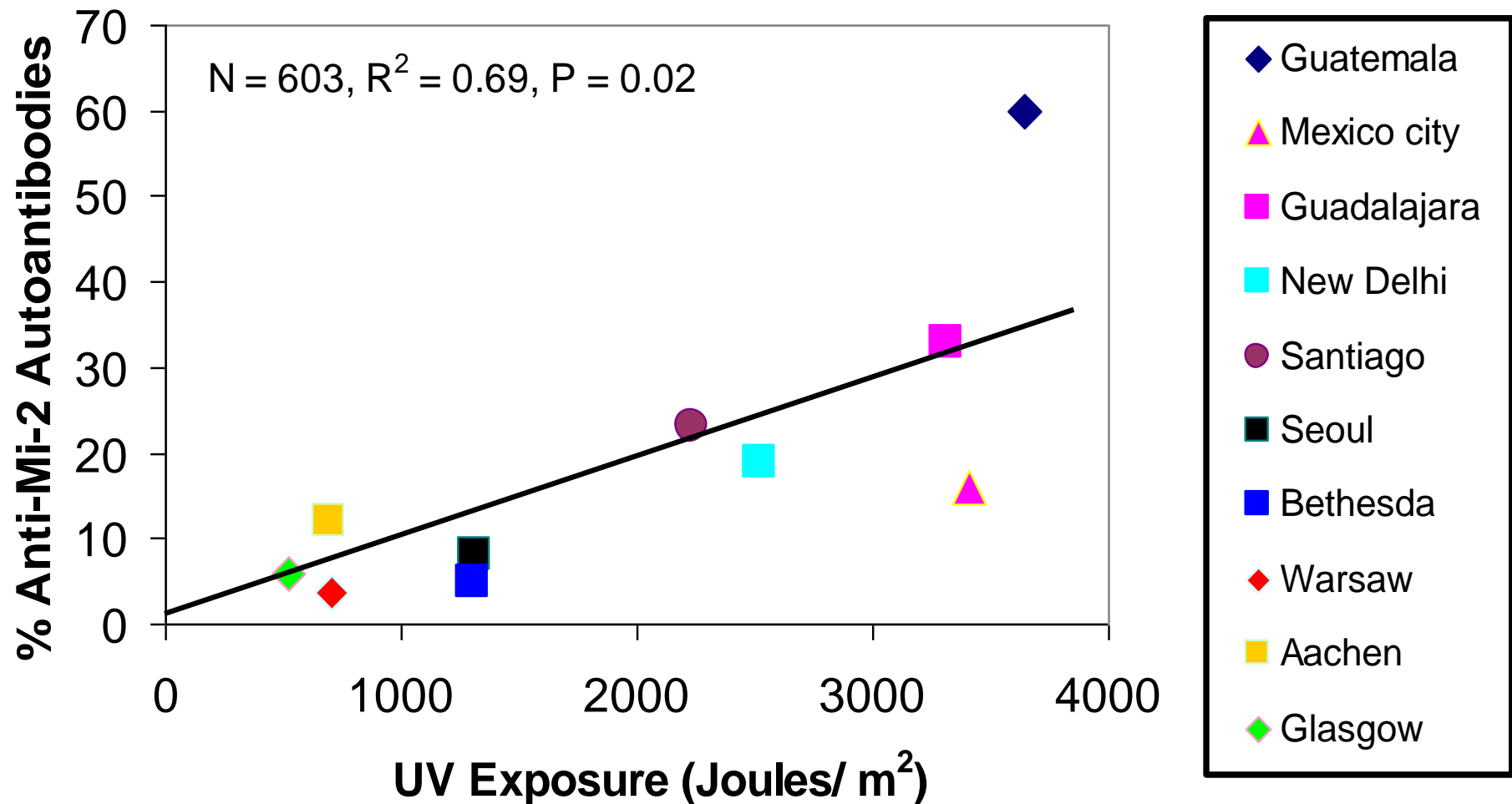


Global Sunlight Levels Best Predict the Proportion of Dermatomyositis World-wide



Okada et al. 2003 Arthritis & Rheum

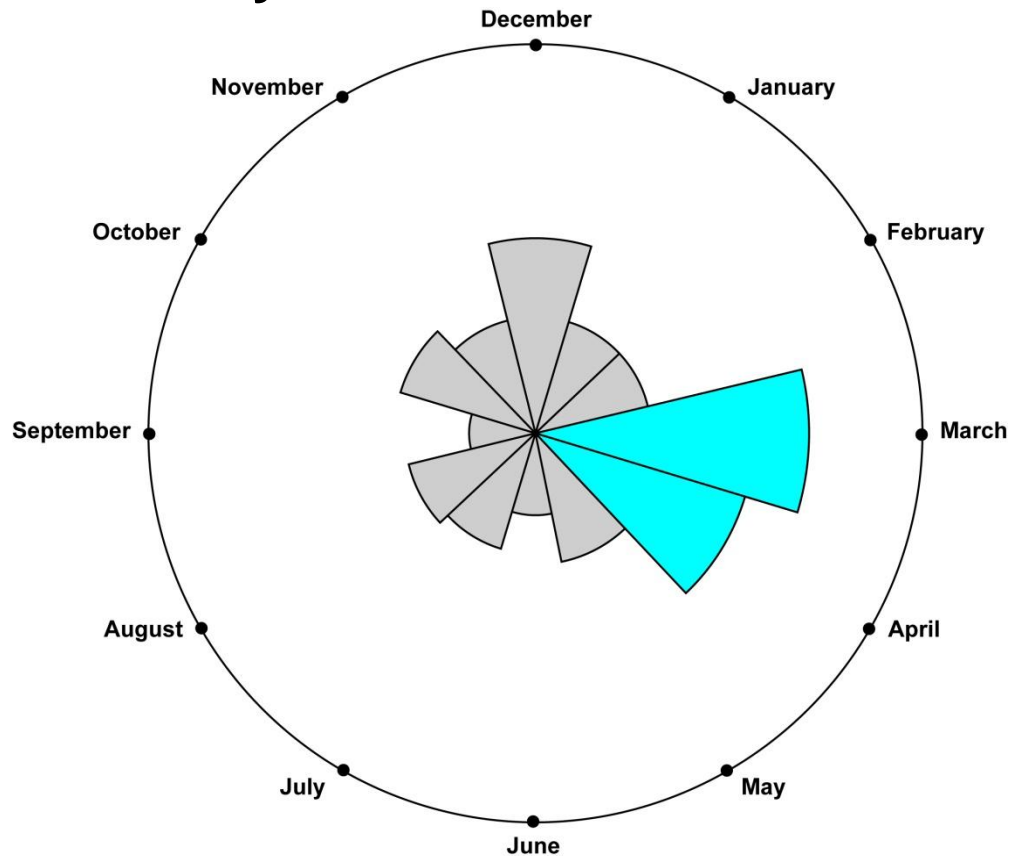
Global Sunlight Levels Best Predict the Proportion of Anti-Mi-2 World-wide



Okada et al. 2003 Arthritis & Rheum

Season of Disease Onset Varies Among Myositis Types

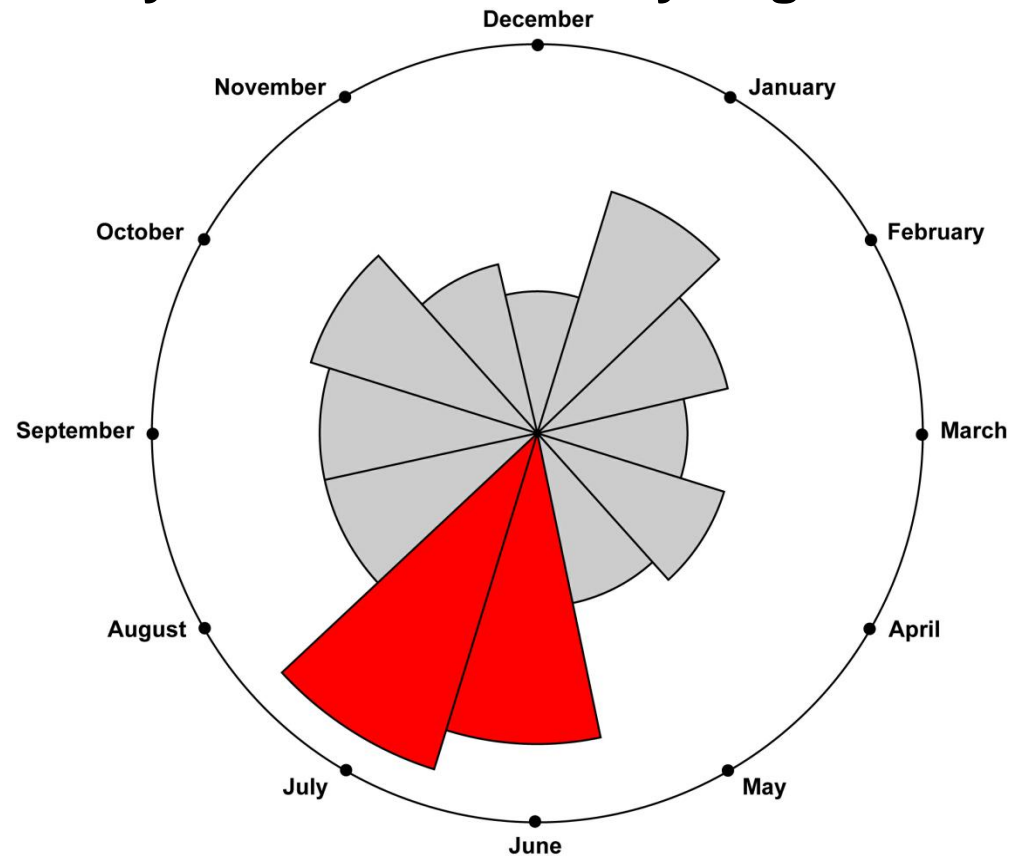
Anti-synthetase autoantibodies



**Onset peak in March-April, $n=173$, $p=0.03$;
Strongest associations in men with PM**

Sarkar et al. 2005 Arthritis Rheum

Myositis autoantibody negative



**Onset peak in June-July, $n=252$, $p=0.02$;
Strongest associations in women with DM**

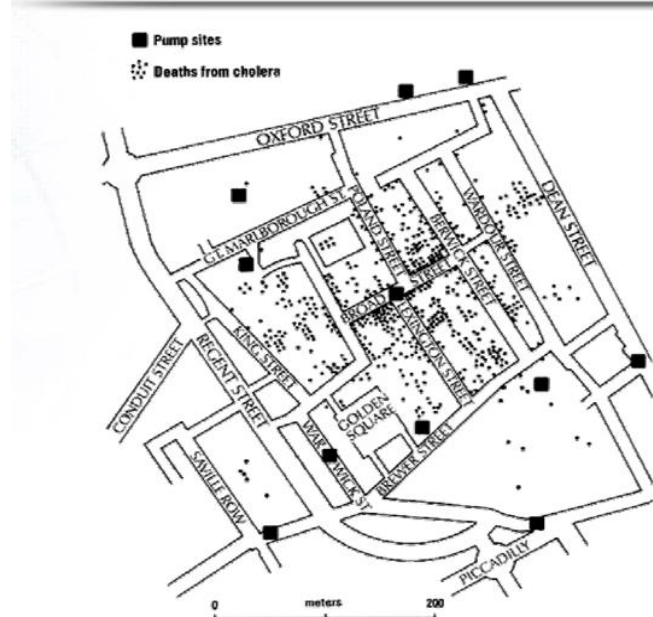
Approaches to Identify Environmental Risk Factors for Autoimmune Diseases

- Foster national / international consortia and coordination to integrate and optimally utilize existing and new clinical databases, registries, specimen repositories, animal models, other resources
- Develop and validate novel standardized environmental exposure assessment tools and biomarkers
 - Environmental sensors – geographically distributed in target areas
 - Geographic information systems - with new modeling and mapping tools
 - Wearable personal sensors – real time *in vitro* biologic response evaluation; body burden assays – to sum up a lifetime of exposures when possible
 - Environment-wide association studies (EWAS)
 - “Big data” initiatives
- Increased support for well-designed, population-based, case-controlled hypothesis-testing and hypothesis-generating studies for suspected environmental agents

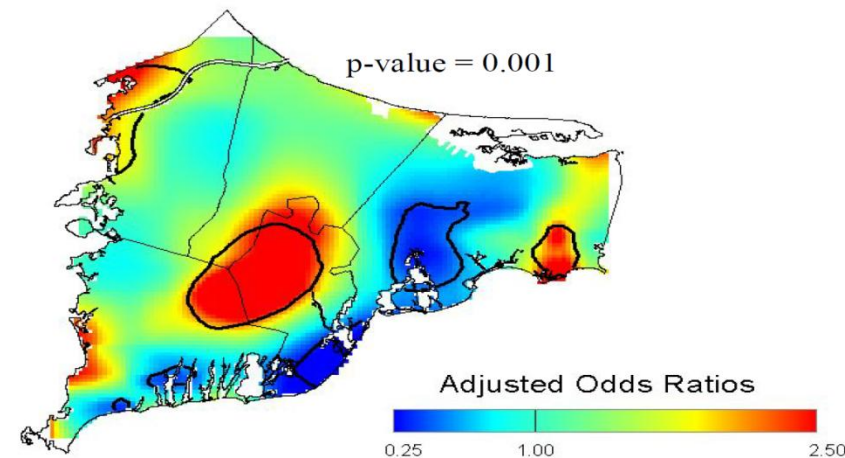
Geographic Information Systems (GIS)

- Computer mapping and analysis tools allowing environmental and epidemiologic data to be stored, viewed, edited and analyzed in a geographic context
- Can assess many environmental variables (air & water pollutants, UVR, geoclimatic information, fixed toxic waste sites, bodies of water, roadways, etc.) with diseases or outcomes over time
- Limited by the environmental and clinical databases available

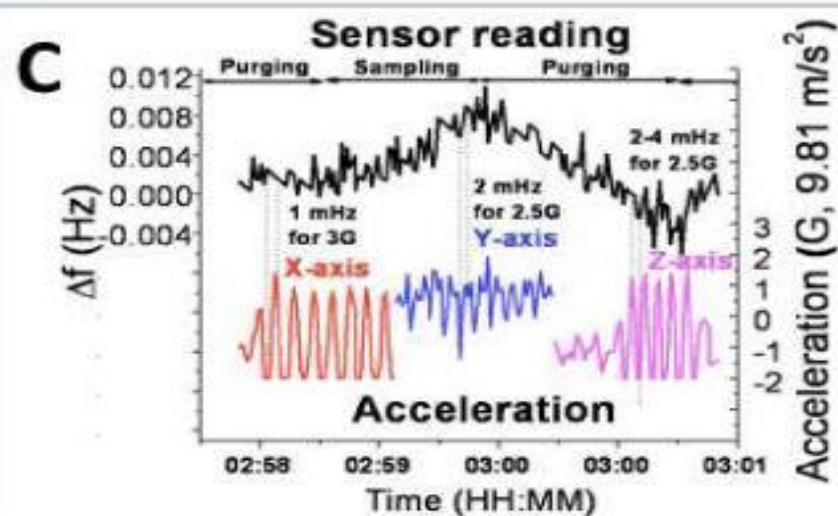
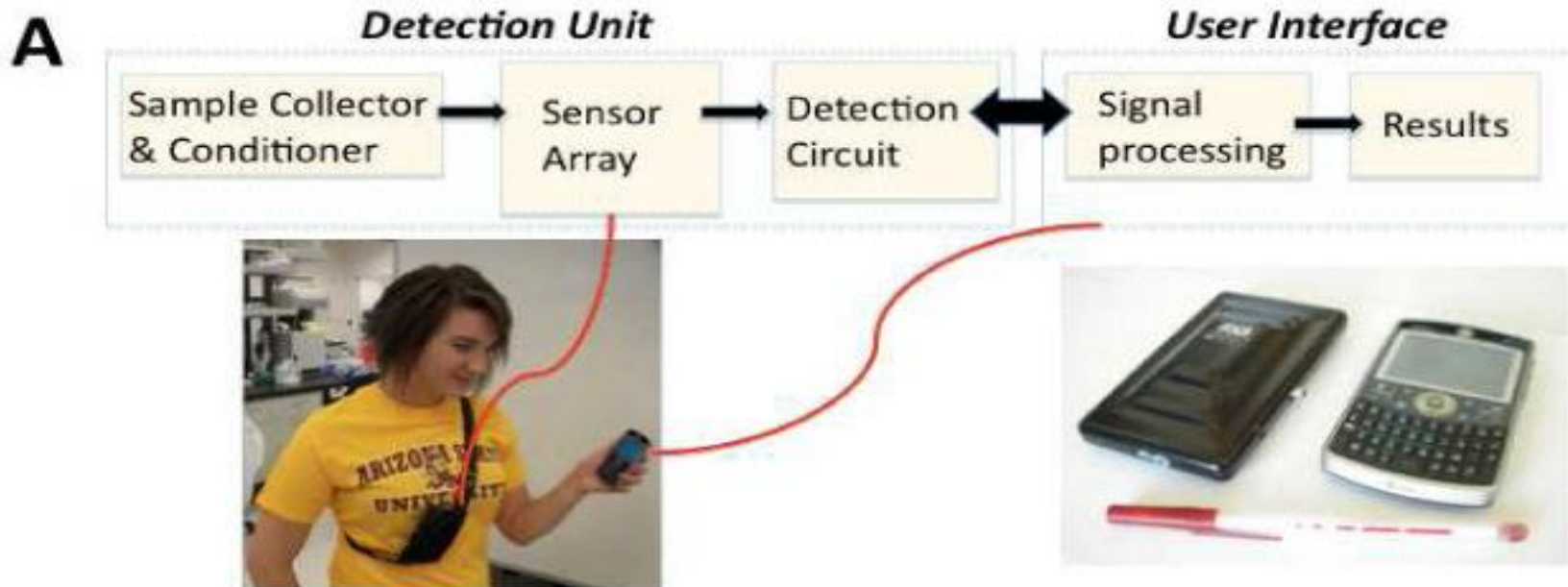
John Snow and Cholera Maps



Significant Risk Areas

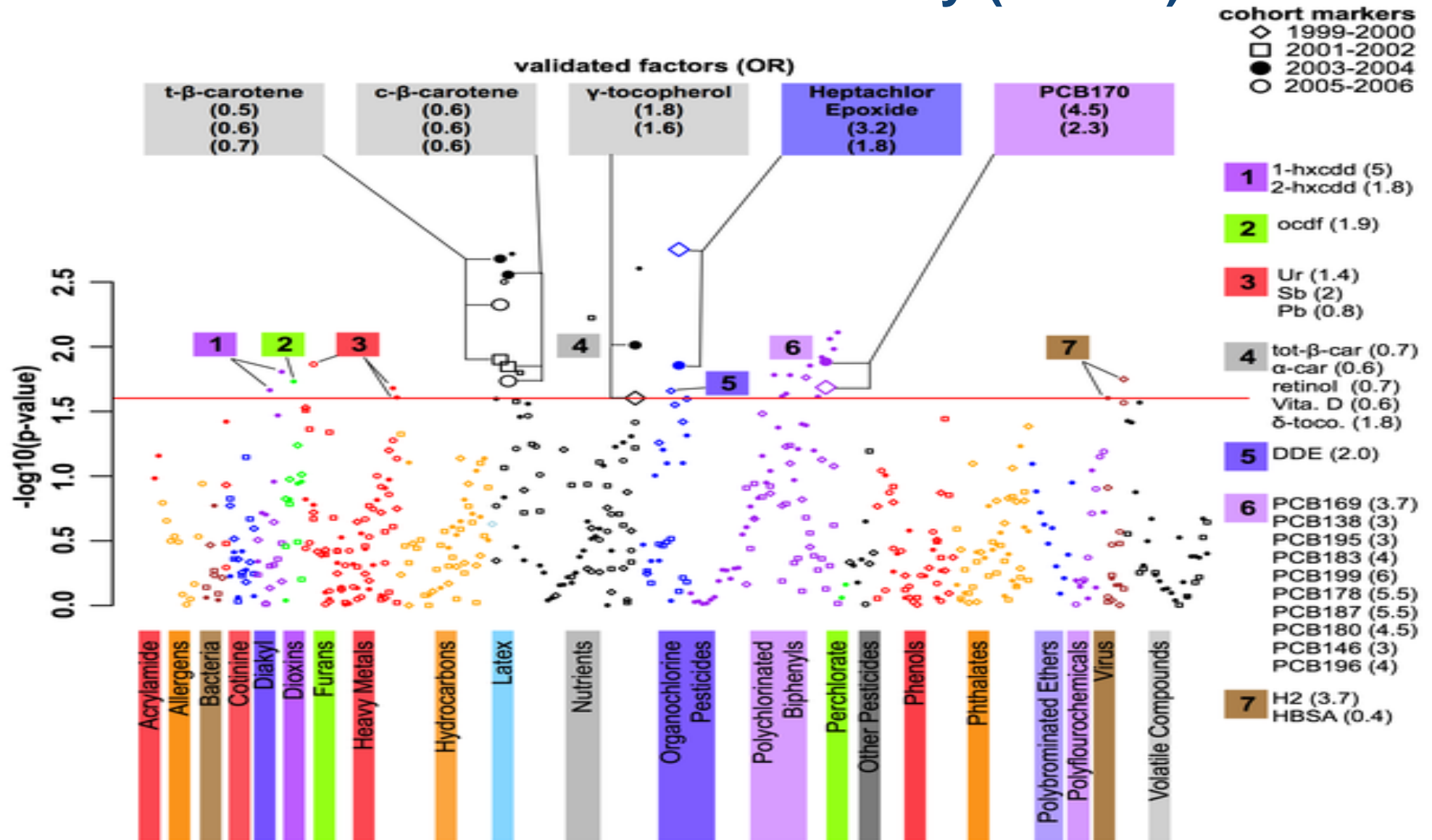


Wearable Real Time Environmental Sensors



Personal Exposure to Volatile Organic Compounds

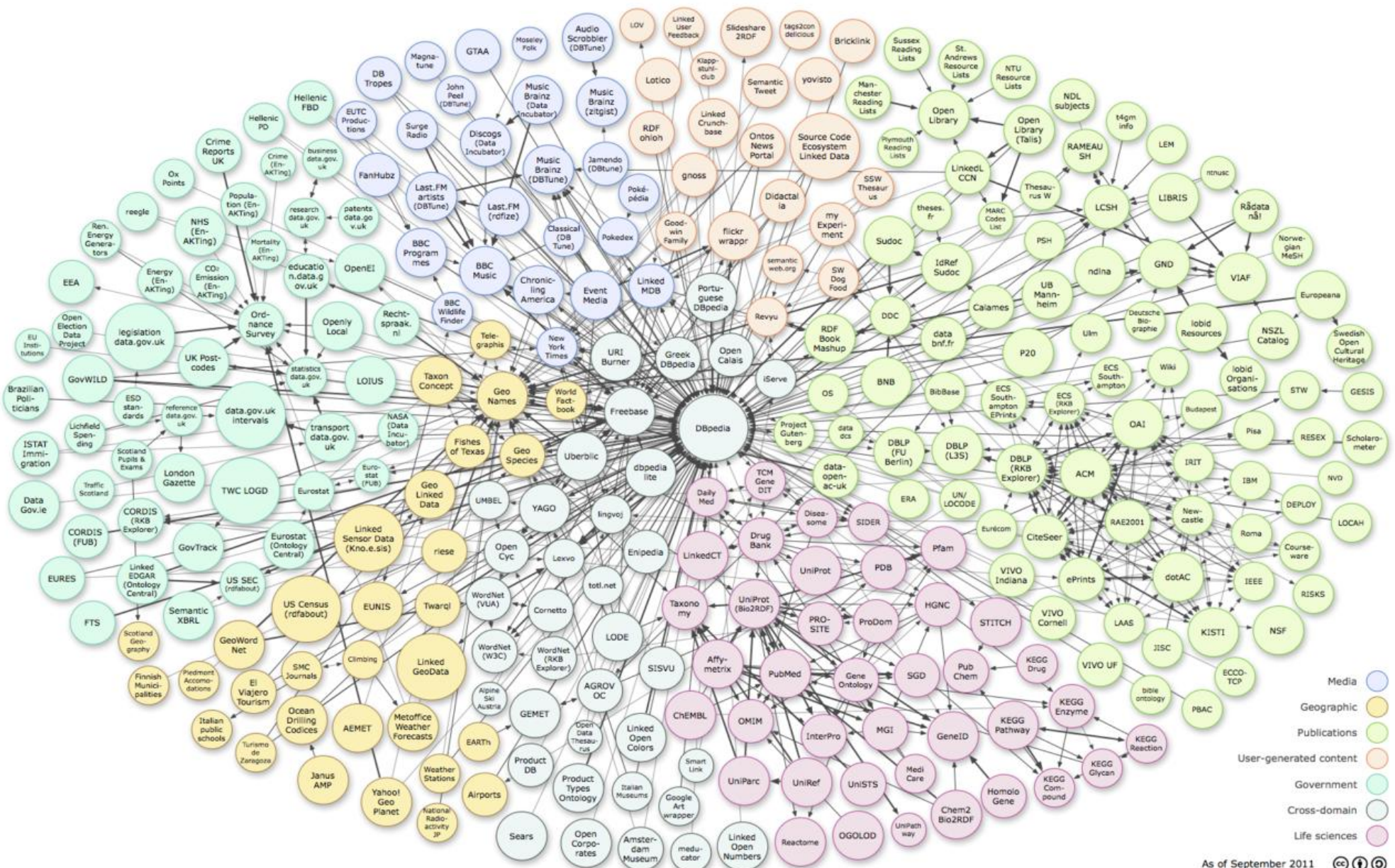
“Manhattan plot” style Graphic showing an NHANES Environment-wide Association Study (EWAS) with T2D



Patel CJ, Bhattacharya J, Butte AJ (2010) An Environment-Wide Association Study (EWAS) on Type 2 Diabetes Mellitus. PLoS ONE 5(5): e10746. doi:10.1371/journal.pone.0010746 – CDC NHANES, National Health and Nutrition Examination Survey

<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0010746>

BIG DATA INITIATIVES – Data Mining Linking Open Data Community Project Cloud Diagram



Expanded Environmental Scans?

- Just as whole genome scans have revolutionized our thinking of genetic risk factors for disease, the possibility of expanded environmental scans could revolutionize our capacity to define environmental risk factors in the future
- New exposure assessment technologies and validated biomarkers of exposure are needed
- Could begin by integrating data from environmental sensors, geographic information systems, biologic sensors, validated exposure questionnaires, systems biology biomarkers for exposures from RNA expression or epigenetic signatures, proteomic and metabolomic analyses, and antibody microarrays to capture the immune memory of a lifetime of exposures
- Use existing databases where multiple exposures have been assessed

NIEHS Twin-sib Study

- Adults and children diagnosed with rheumatoid arthritis, lupus, scleroderma or myositis within 4 years and who have a same sex sibling within 4 years of age and without autoimmune disease, and parents, are eligible
- The focus is on defining environmental risk factors and mechanisms of disease

Main Adult Subject Contact – Adam Schiffenbauer, M.D.
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Main Pediatric Subject Contact – Lisa Rider, M.D.
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Environmental Risk Factors for the Development of the Antisynthetase Syndrome

- Adults or children who were diagnosed with PM or DM within 2 years is eligible
- Antisynthetase cases will be compared to other myositis cases
- Myositis cases are matched to non-autoimmune cases

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Myositis in the Military Population

- Myositis appears to be increasing in the military and no study has assessed exposures that could explain this.
- Military personnel experience a number of intense, unique exposures, often over a relatively short interval, during deployment including: physical and emotional stresses; novel vaccines and medications; distinct occupational exposures; battlefield injuries; and unique chemicals
- A request to assess environmental aspects and mechanisms for the development of myositis in the military was advertised by the DoD, to be administered by The Myositis Association, and was awarded to Drs. Miller and Nagaraju in late 2011

Environmental Risk Factors for the Development of Myositis in the Military - Hypotheses

- Certain environmental exposures or geographic factors are associated with myositis that develops during military service, in that they will differ from those seen in matched military personnel without autoimmune or chronic muscle disease.
- Global DNA methylation epigenetic changes, microRNA and mRNA profiles in peripheral blood and muscle tissues from myositis patients will differ from those seen in controls and may provide insight into pathogenesis.

Environmental Risk Factors for the Development of Myositis in Military Personnel

- Any person who was diagnosed with any form of myositis during active U.S. military service is eligible
- Myositis cases are matched to non-autoimmune cases who served in the military during the same decade

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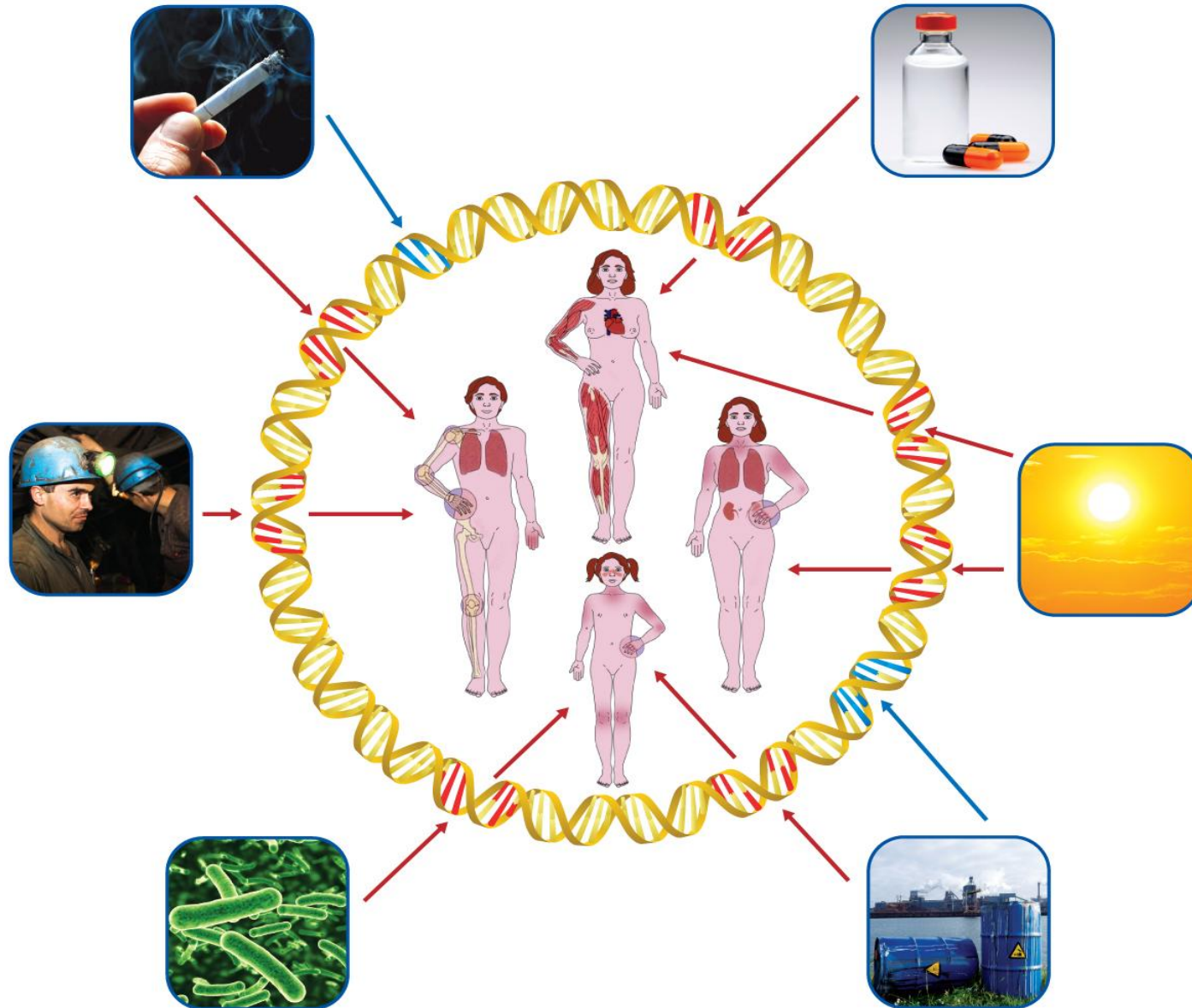
Summary – Environmental Aspects of Autoimmune Diseases

- Studies of environmental risk factors for autoimmunity are in their infancy
- Challenges include:
 - The rarity, heterogeneity and multifactorial nature of many diseases
 - Suboptimal coordination among nations, agencies and researchers
 - Inadequate validated exposure assessment tools and training
 - Limited population-based incidence, prevalence, demographic information and phenotype databases for most diseases
- The advances in novel technologies, statistical approaches and development of collaborating consortia and focused resources - which have resulted in the recent explosion of genetic information on many complex diseases - now need to be applied to environmental studies so that we can eventually interrupt pathogenesis before the onset of illness and transform the practice of medicine from curative to preemptive paradigms.

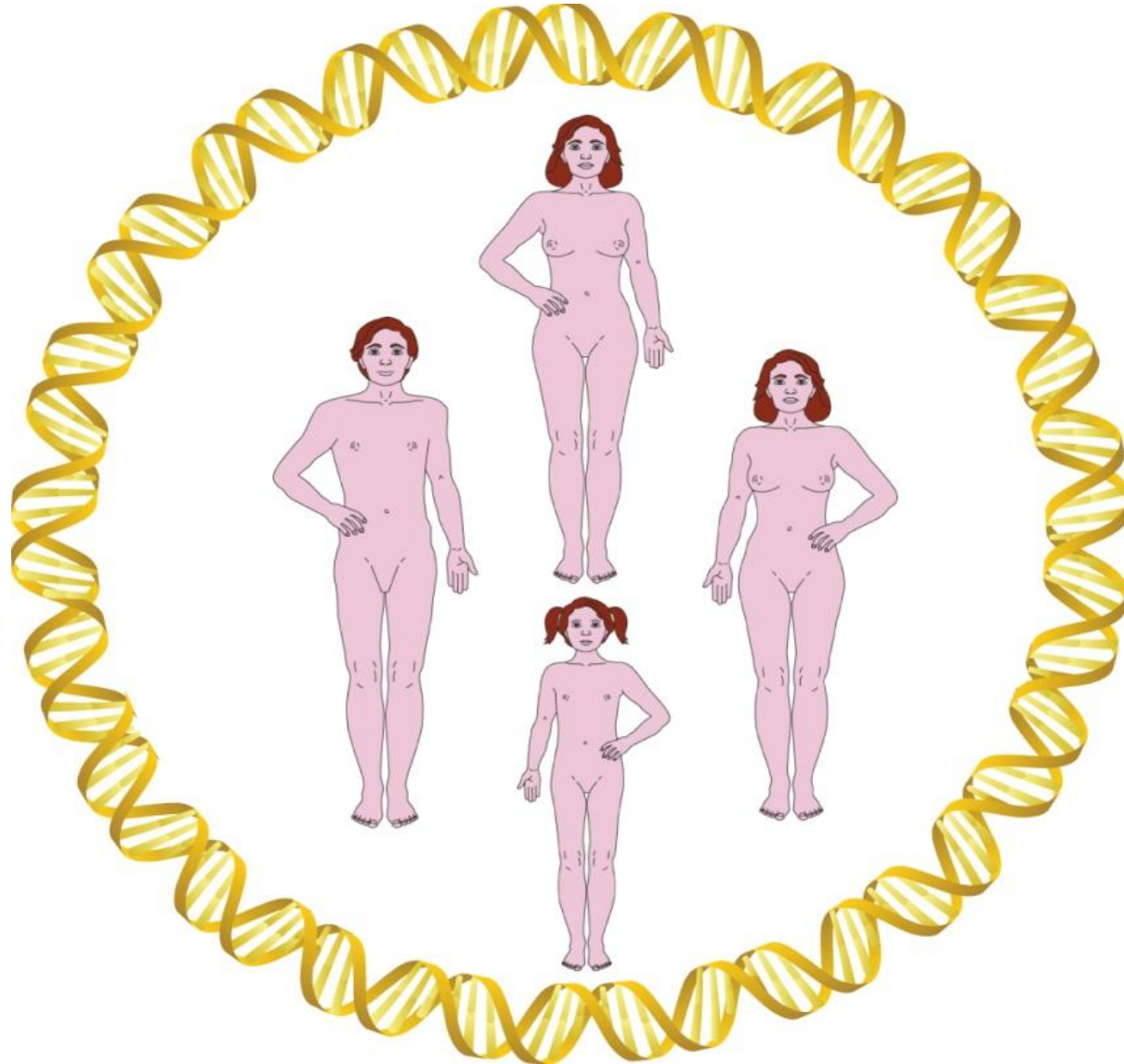
Myositis and the Environment – The Future

- Critical questions to tackle
 - How many mutually exclusive and stable types of myositis exist?
 - What are the necessary and sufficient genetic and environmental risk factors for each type?
 - By what mechanisms do the types develop?
 - Can we develop better therapies addressing these mechanisms?
 - Can we prevent myositis in the future?
- Critical needs
 - Increased national and international collaboration and coordination of studies to integrate and optimally utilize existing and new clinical databases, registries, specimen repositories and other resources
 - Clinically useful, standardized environmental exposure assessment tools and biomarkers for broad exposure scans
 - Increased support for well-designed, hypothesis-testing studies for defining genetics and environmental agents

Better Understanding of Environmental Factors



Better Understanding of Environmental Factors Could Enable Disease Prevention



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