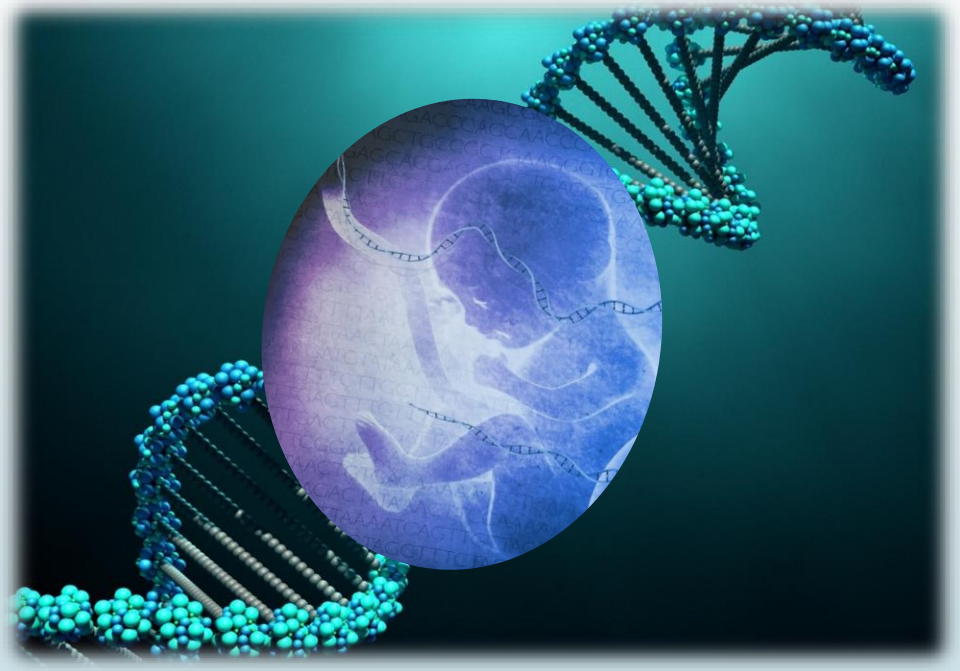
# Our Environment, Our Health: *Global is Local is Personal*

*Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.*
*Former Director*
*National Institute of Environmental Health Sciences*
*National Toxicology Program*

*University of Modena*
*Modena, Italy*

October 24, 2019

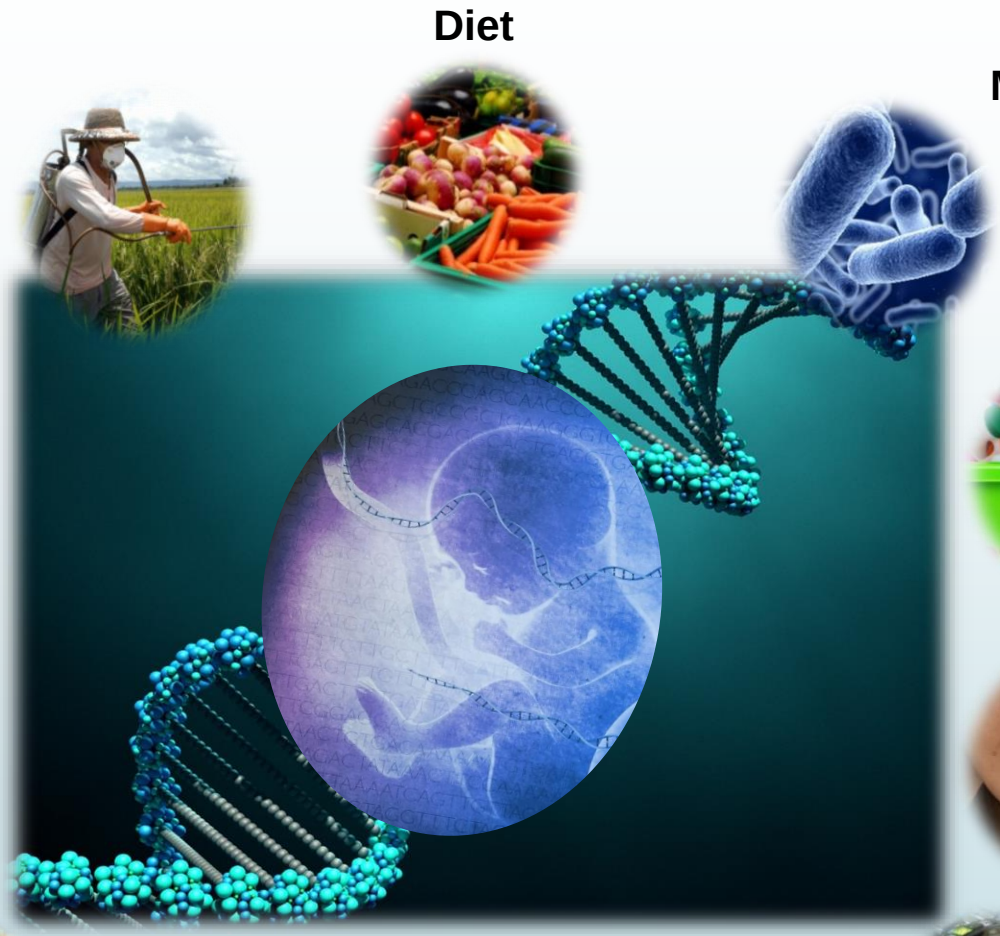
# Our Health



**Genetics**

Image adapted from: NHGRI

# Our Health



Diet

Microbiome

Pesticides

Medicines

Synthetic materials

Combustion by-products

Stress

Personal care products

Chemicals in electronics

**Genetics + Environment**

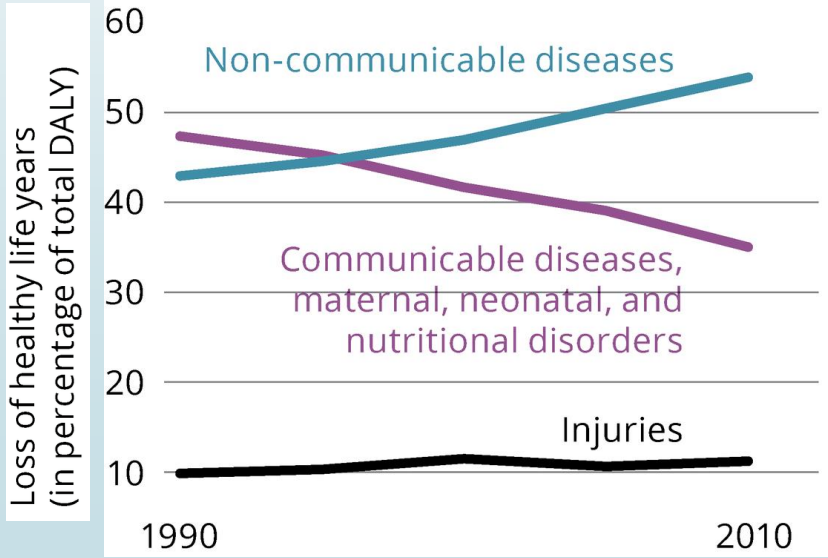
Image adapted from: NHGRI

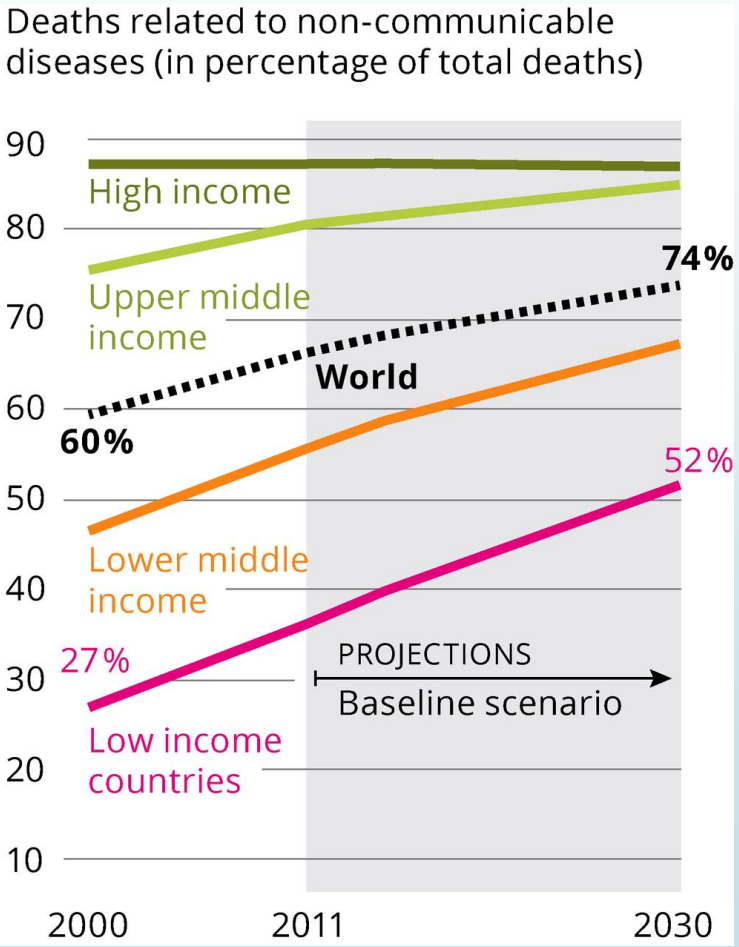
# Environmental Health

# Global Health Trend: Non-Communicable Disease "Epidemic"

**Examples:**

- Type II Diabetes
- Cardiovascular Disease
- Obesity
- Asthma
- Autism
- Cancer



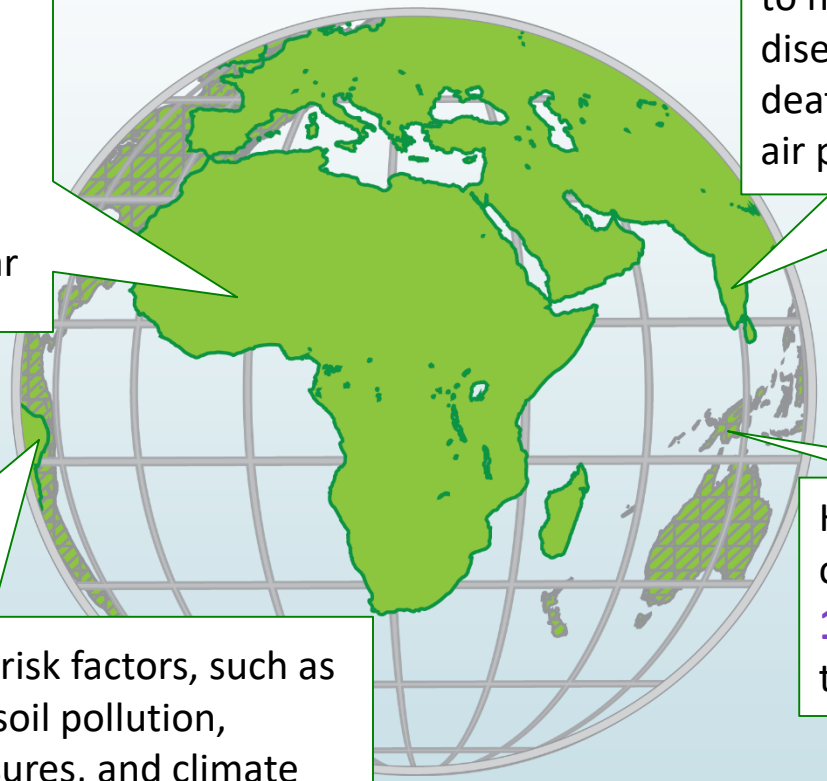




Source: European Environment Agency, 2015

# Environmental Burden of Disease

**23%** of all global deaths are linked to the environment — that's roughly **12.6 million** deaths a year

**8.2 million** deaths caused by the environment are due to non-communicable diseases. Most of these deaths are attributable to air pollution.



Environmental risk factors, such as air, water, and soil pollution, chemical exposures, and climate change contribute to more than **100 disease and injury types**

Healthier environments could prevent the deaths of **1.7 million children** under the age of 5 each year

Source: WHO, 2016

# Lancet Commission on Pollution and Health Report

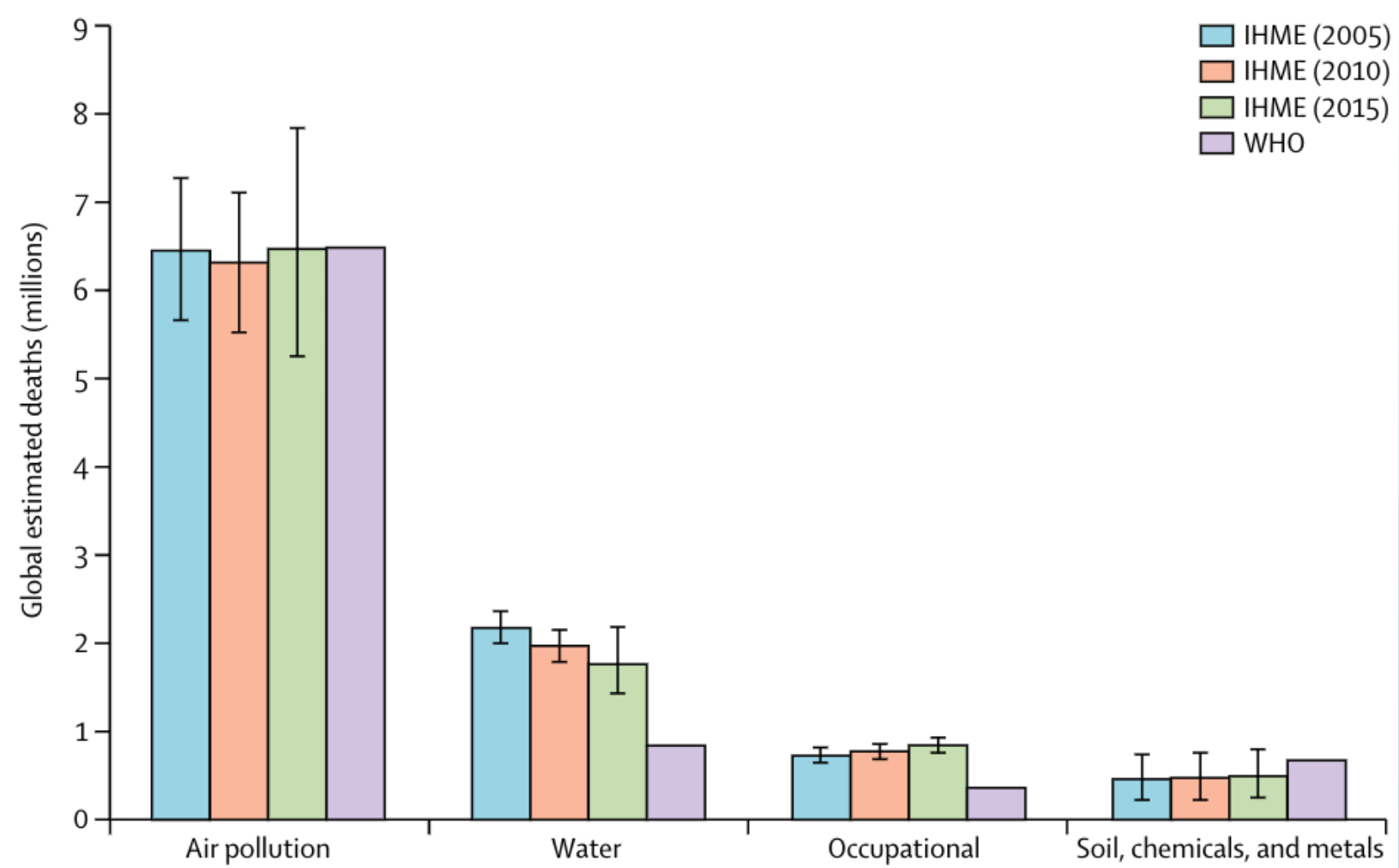
- Pollution Related Disease - 9 million deaths worldwide (16%)
- 92% of pollution-related deaths occur in low-income and middle-income countries
- Welfare losses due to pollution are estimated to amount to $4.6 trillion per year (6.2% global economic output)
- Good News: much pollution can be eliminated, and pollution prevention can be highly cost-effective

Landrigan et al., Lancet. 2018

- Environmental chemical exposures cost >10% of Global GDP
- Current estimated 5.18% DALYs from preventable environmental risk factors are Substantially Underestimated

Grandjean and Bellanger, Environmental Health. 2017

# Global estimated deaths (millions) by pollution risk factor




Landrigan et al., Lancet, 2018

# What's in your Water?

Global → Local → Personal

PETROLEUM PRODUCTS

icrobes

Perchlorate

PESTICIDES

PCBs

Algal Blooms

POPs

Mercury

Arsenic

Bacteria

Micro-Plastics

Disinfection Byproducts

PFAS (PFOS/PFOA)

LEAD

TRICHLOROETHYLENE

# Land, soil, and sediment…

ARSENIC

Chromium

Bioaccumulation

Metals

Mercury

DUST

Fertilizer

Bacteria

Polycyclic Aromatic Hydrocarbons

Copper

PESTICIDES

Dioxin

Polychlorinated biphenyls (PCB)




# Air pollution exposure contributes to:

Autoimmunity

OBESITY

Asthma

Behavioral effects

Autism

Diabetes

COPD

Alzheimer's

Developmental Disabilities

Pneumonia

Lower Respiratory Infections

Cancer

DECREASED IQ

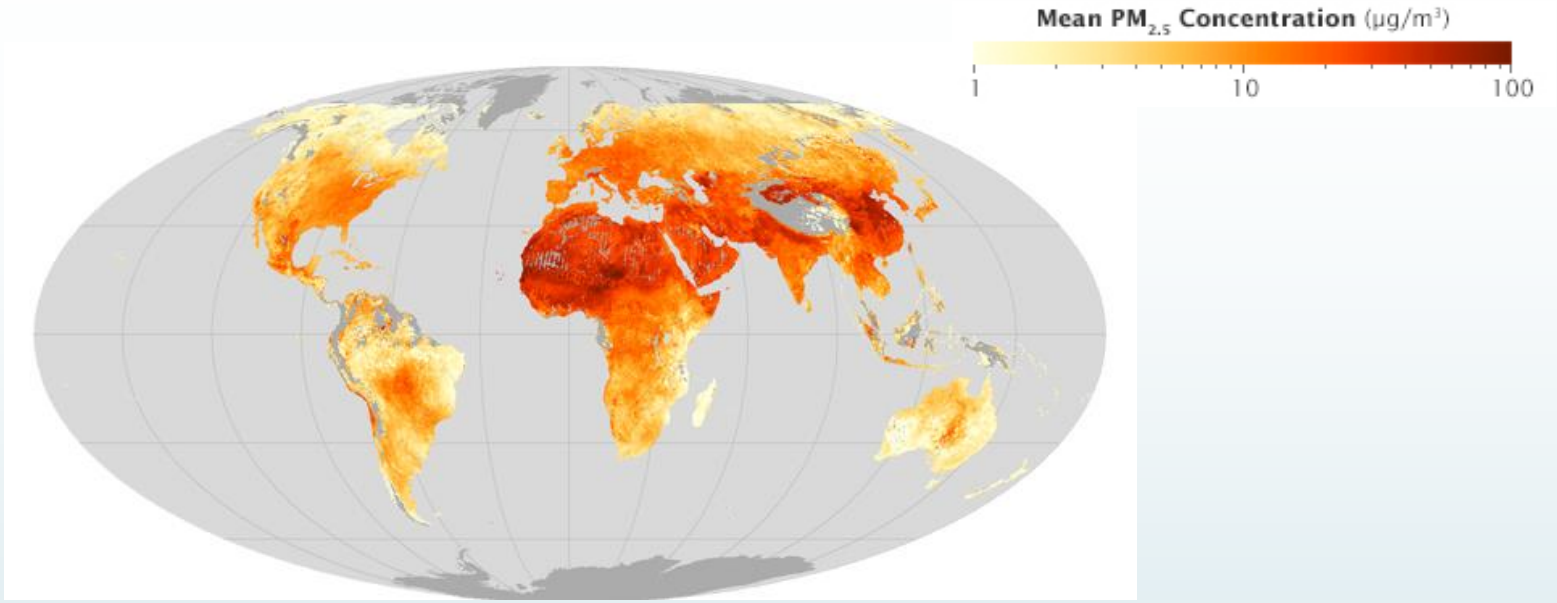
Pulmonary Disease

Cardiovascular Disease

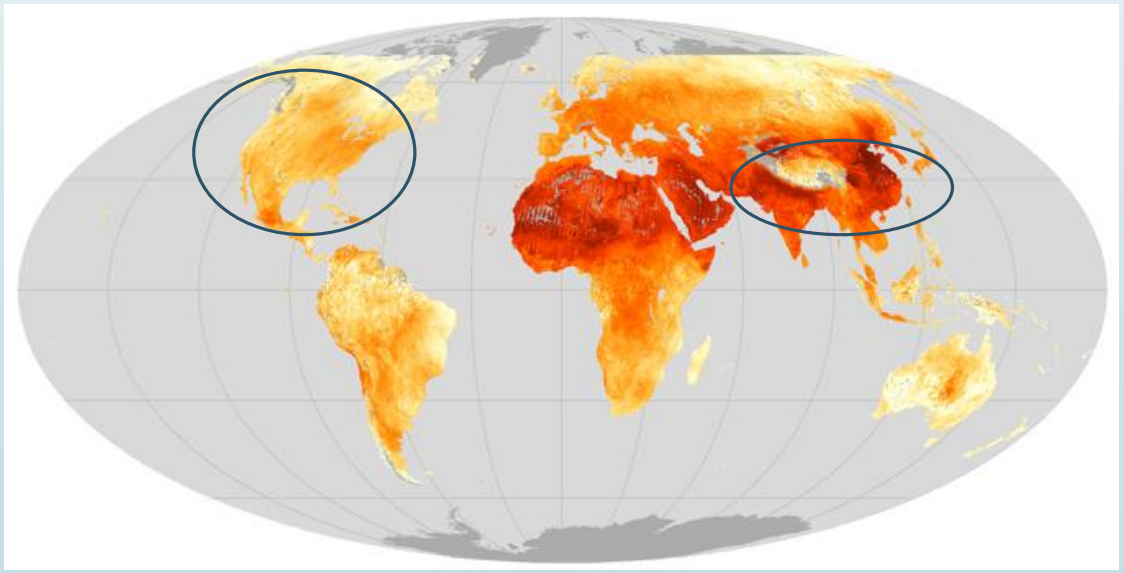



# Changing Views of PM2.5 Pollution Over Time

**1998 – 2000**




**2000 – 2012**

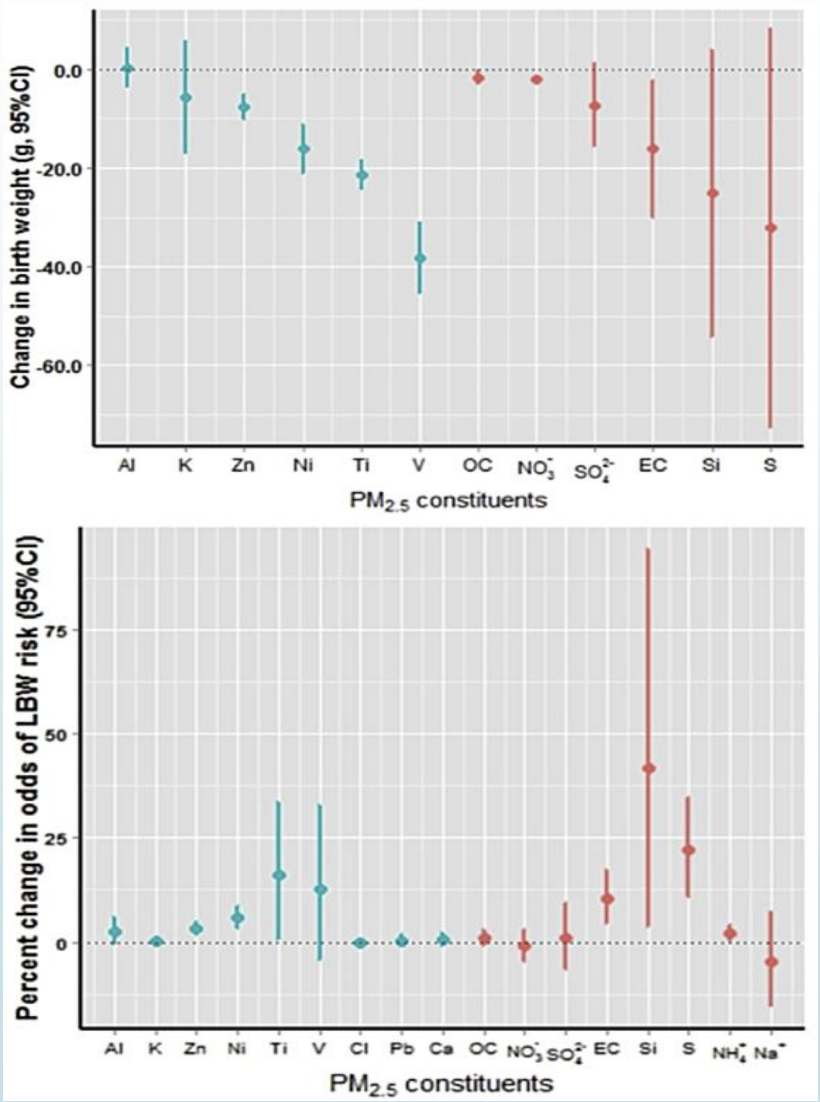


NASA Earth Observatory
Maps by Joshua Stevens
using global PM2.5 data
from Aaron van Donkelaar
(Dalhousie University)

NASA, 2010; 2015

# PM2.5 Air Pollution Associated with Low Birth Weight

- Clear association between $PM_{2.5}$ exposure during pregnancy and decreased birth weights
- Decreased birth weight more pronounced with 2nd and 3rd trimester exposure
- Some components of air pollution have greater effects on fetal birth weight than others

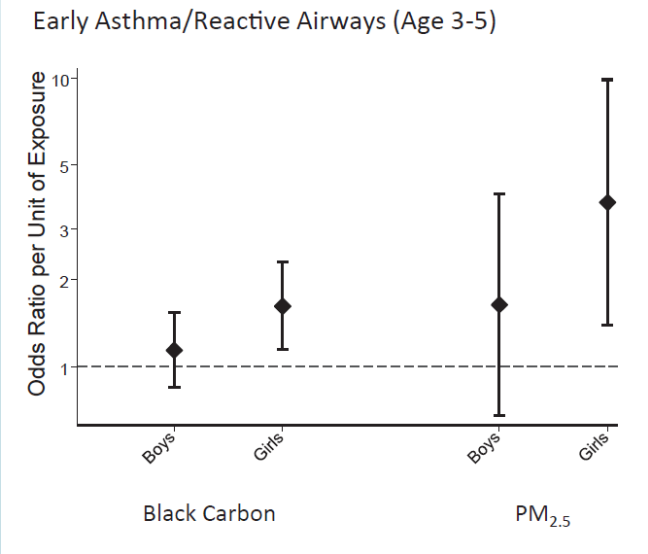


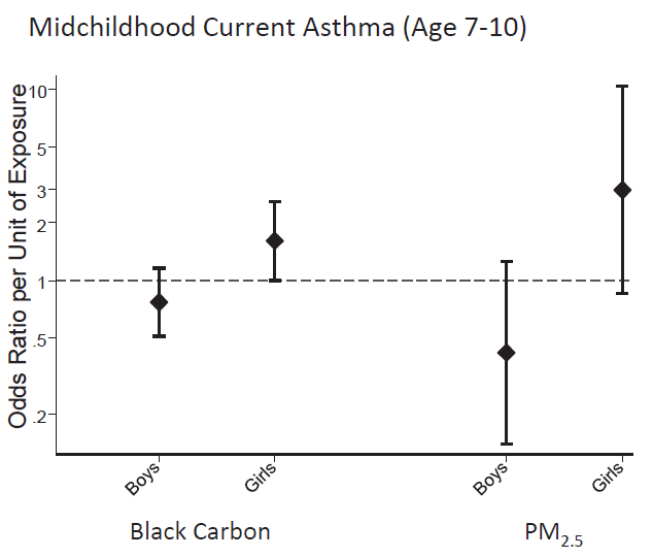

Sun et al., Environ Pollution, 2016

# Ambient Air Pollution and Asthma

- Living closer to major roads (<200m) associated with increased incidence and persistence of asthma
  (Bowatte et al., Environment International, 2018)
- Higher lifetime exposure to traffic-related pollution during childhood, not just early life exposure, increases risk of asthma
  (Brunst et al., Am J Respir Crit Care Med, 2015; Rice et al., J Allergy Clin Immunol, 2018)

**Sex-specific associations of lifetime pollution exposure and asthma**

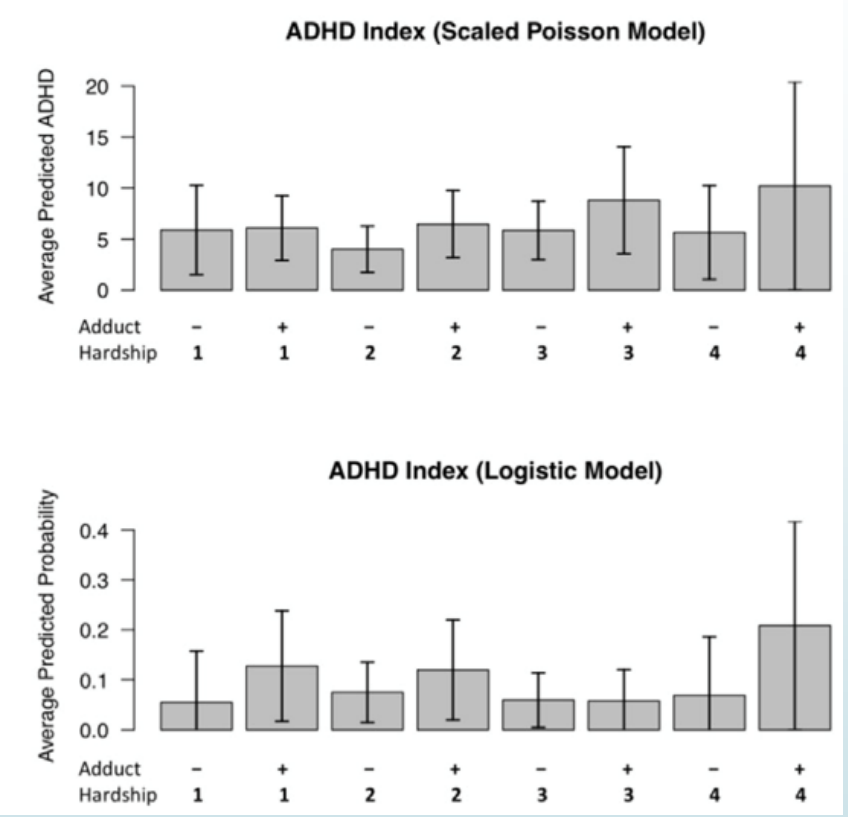



Sex modified several associations between pollution and asthma and early and midchildhood (Rice et al., J Allergy Clin Immunol, 2018)

# Air Pollution Impacts on the Brain, Cognition and Behavior in Children

- Children with high PAH exposure had increased risk for **ADHD**, especially in households with "material hardship" – co-exposures increase risk (Perera et al., Environ Res, 2018)
- Exposure to PM and NO2 impact **memory, verbal, and general cognition** – males are more susceptible (Lertxundi et al., Environ Res, 2019)
- Traffic-related air pollution (TRAP), from diesel exhaust is associated with increased **child-reported depression and anxiety** (Yolton et al., Environ Res, 2019)
- Living close to roadways might contribute to neurodevelopmental deficits in **memory/attention, response/motor coordination, information processing and working memory** (Khan et al., Neurotox, 2019)

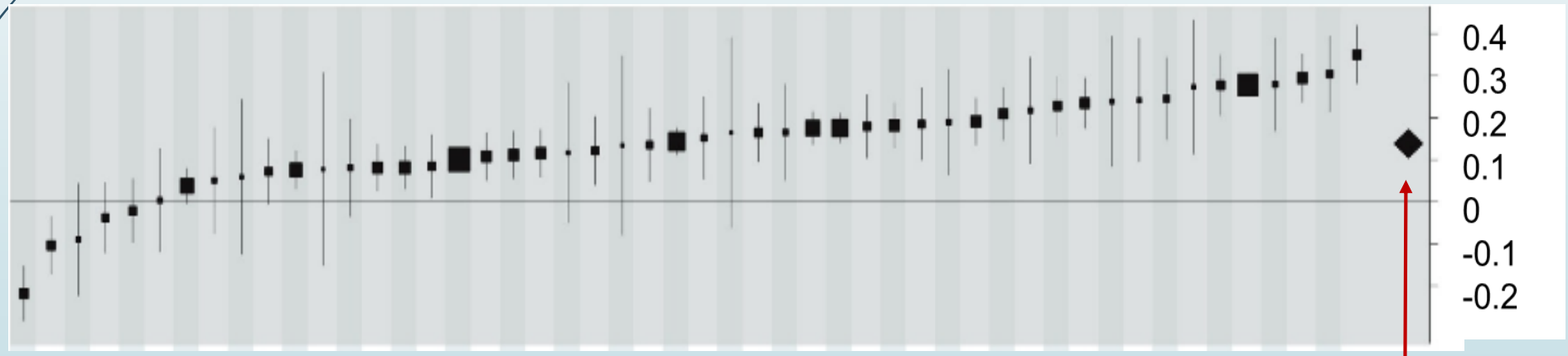



Figures show the effects of co-exposures – prenatal PAH and socioeconomic stress (material hardship) – on children's ADHD symptoms (Perera et al., Environ Res, 2018)

# $PM_{2.5}$ Exposure and Neurodegeneration

PM2.5 was significantly associated with hospital admissions for dementia, Alzheimer's, and Parkinson's disease in a pooled analysis of 9.8 million subjects from 50 U.S. cities

**Distribution of log(HR) Alzheimer's disease per 1 µg/m³ increase in PM2.5 in 50 U.S. Cities**




Kioumourtzoglou et al., Environ Health Perspect, 2016

# Improving Air Quality Improves Health

- Reductions in $PM_{2.5}$ **decreases mortality risk**, especially **cardiovascular and respiratory** mortality (Laden et al., Am J Respir Crit Care Med, 2006)
- Decreases in $NO_2$ and $PM_{2.5}$ led to **increases in lung function**, in children with and without asthma (Gauderman et al., N Engl J Med, 2015)
- In Southern California, reductions in $NO_2$ and $PM_{2.5}$ led to a **20% decrease** in asthma incidence after 4th grade. (Garcia et al., JAMA, 2019)
- In Atlanta, Georgia, reductions in air pollutants led **fewer asthma, respiratory, and cardiovascular ED visits.** (Abrams et al., Environ Int, 2019)

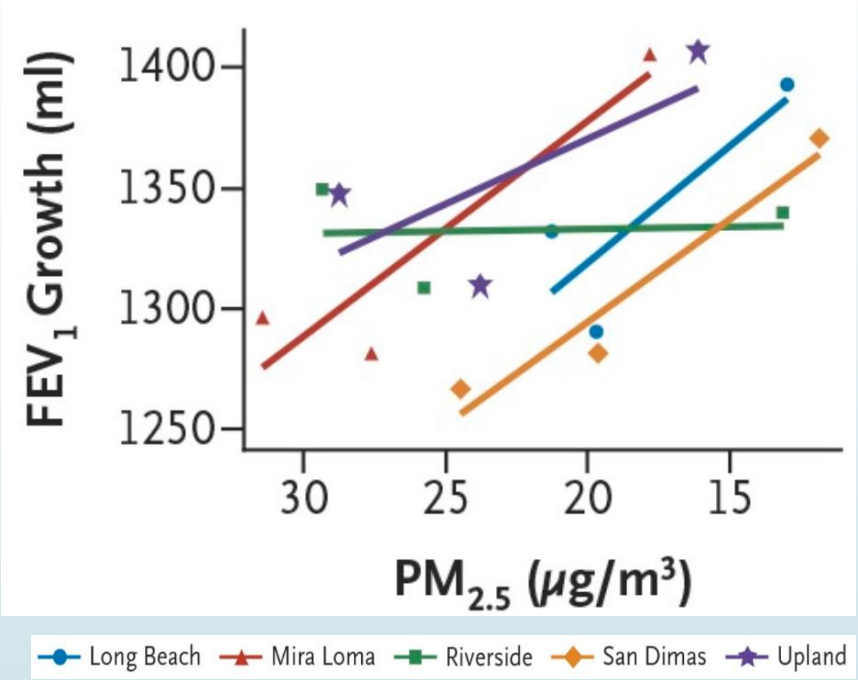
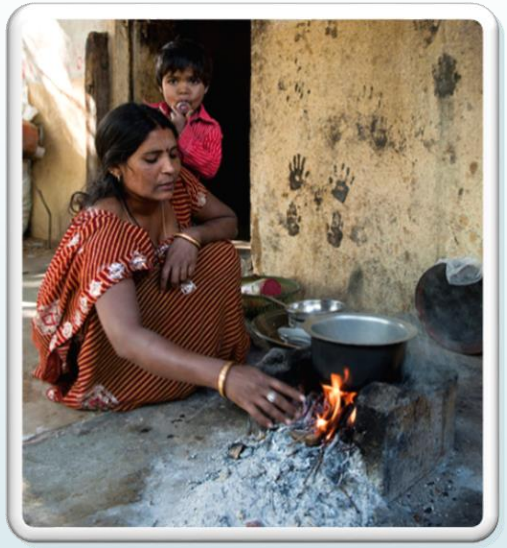



Figure shows mean 4-year growth of lung function, in terms of FEV1. Study found that long-term improvements in air quality were associated with positive effects on lung-function growth in children (Gauderman et al., N Engl J Med, 2015)

# Indoor Air Exposures – Household Air Pollution

- 3 billion people cook using open fires, kerosene stoves, biomass, and coal
  - 4.3 million deaths associated with household air pollution related to these practices (World Health Organization, Household Air Pollution and Health, 2018)
- Cookstove-related, CO exposure associated with **increased blood pressure** for pregnant women in Ghana (Quinn et al., Int J Hyg Environ Health, 2016; Quinn et al., Environ Health, 2017)
- Indoor wood-burning, even once a week, associated with a **higher risk of breast cancer** for women in U.S. (White and Sandler, Environ Health Perspect, 2017)



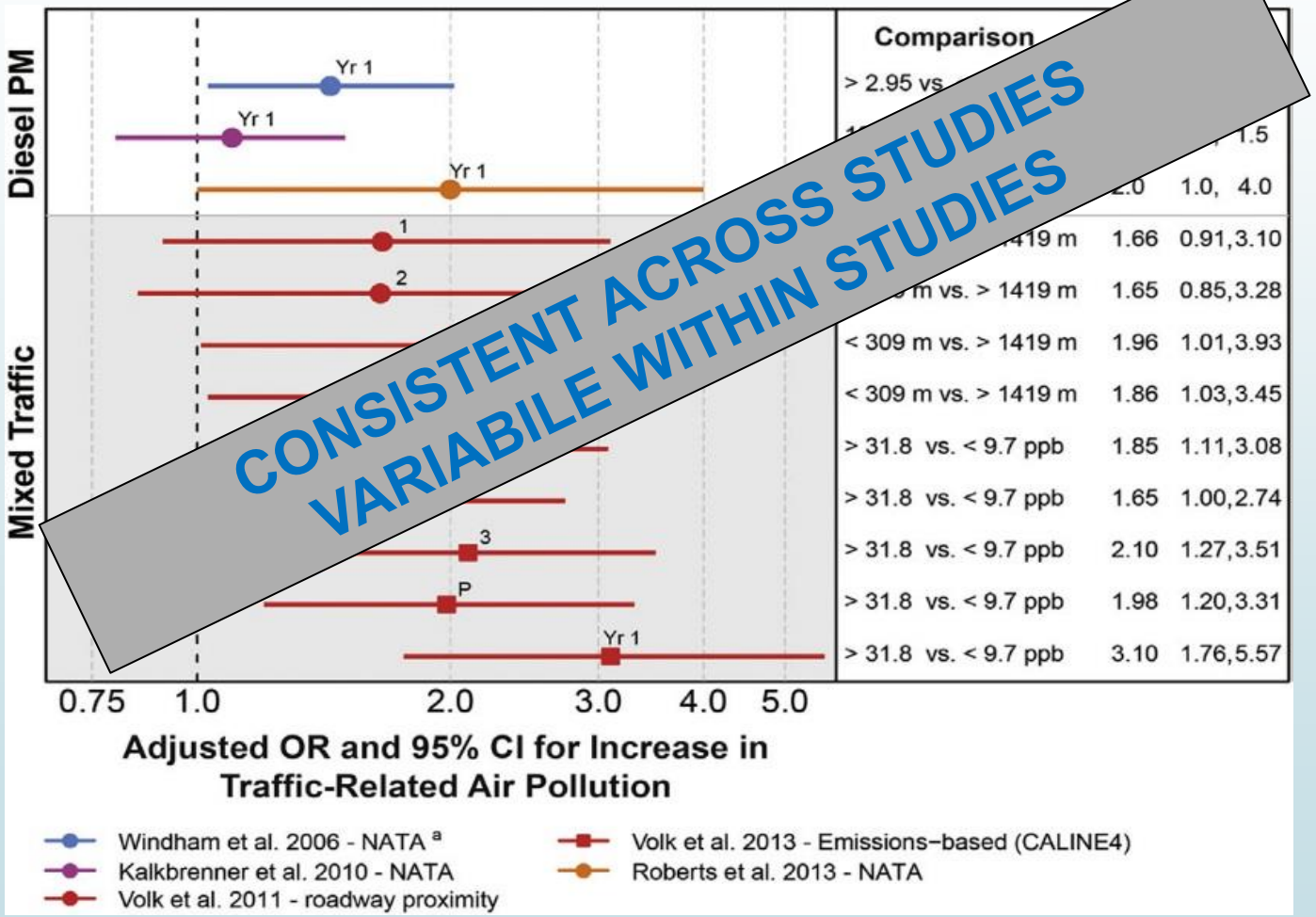
Women and children are disproportionately exposed due to daily cooking activities

Most deaths occur in low- and middle-income countries

# Cookstove Intervention Trials Improve Women and Children's Health

- **Randomized Exposure Study of Pollution Indoors and Respiratory Effects (RESPIRE) (Guatemala)**
  - Positive relationship between personal HAP exposure (CO ppm) and risk of respiratory symptoms and lung function in non-smoking women (Pope et al., Environ Health Perspect, 2015)
- **Chronic Respiratory Effects of Childhood Exposure to Respirable Particulate Matter (CRECER)**
  - Longer use of open fire associated with decrease in lung function in Guatemalan children (Heinzerling et al., Thorax, 2016)
- **NACER II: Reducing Prenatal Exposures to HAP in Rural Guatemala Through a Gas Stove/Behavior Intervention**
  - Developed a behavioral intervention to promote household use of cleaner gas stoves among young, pregnant women (Thompson et al., BMC Public Health, 2018)

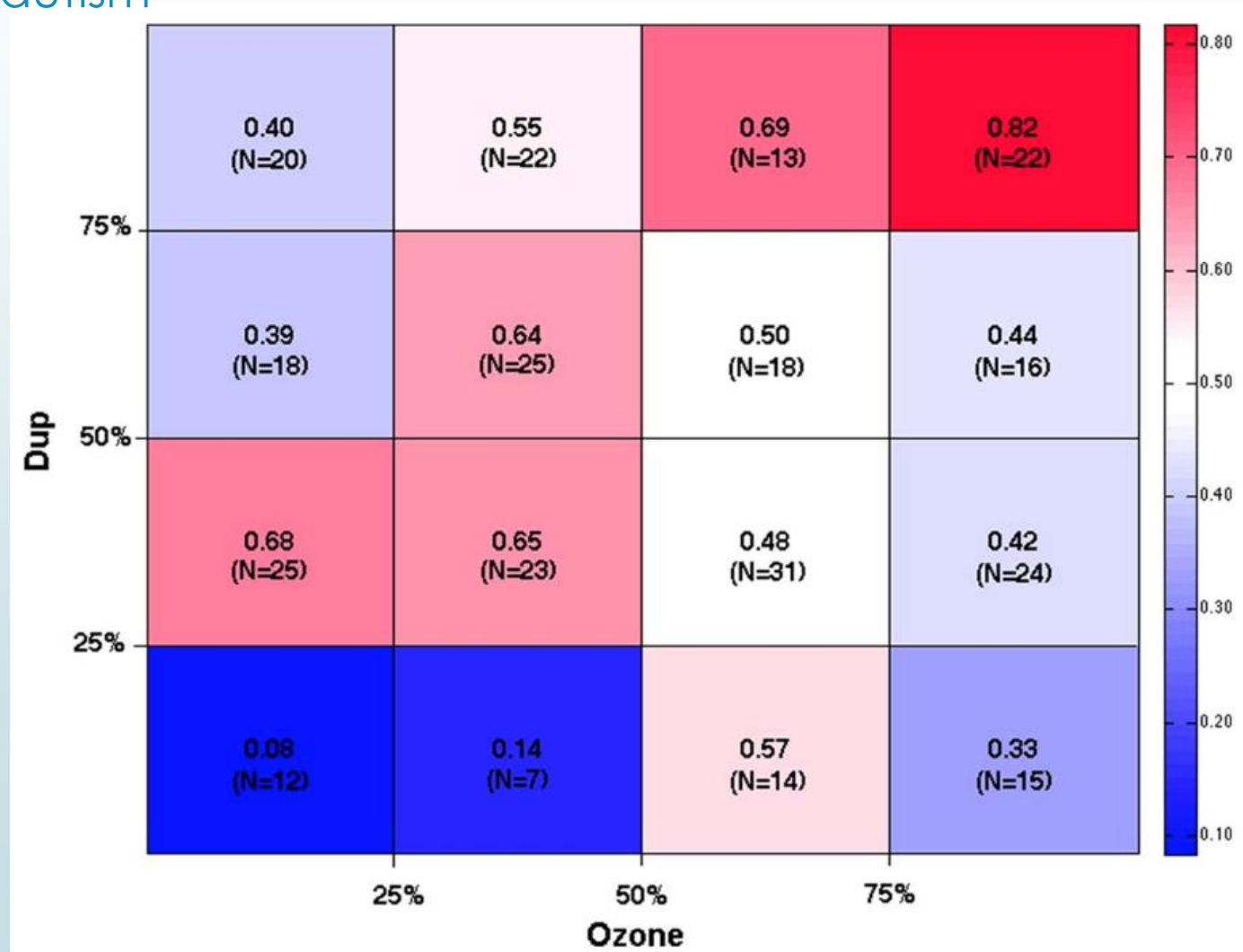
# Traffic Related Air Pollution and Autism




Kalkbrenner, Curren Probl Pediatr Adolesc Health Care, 2014

# Gene x Environment Interaction

## The joint effect of air pollution exposure and copy number variation on risk for autism



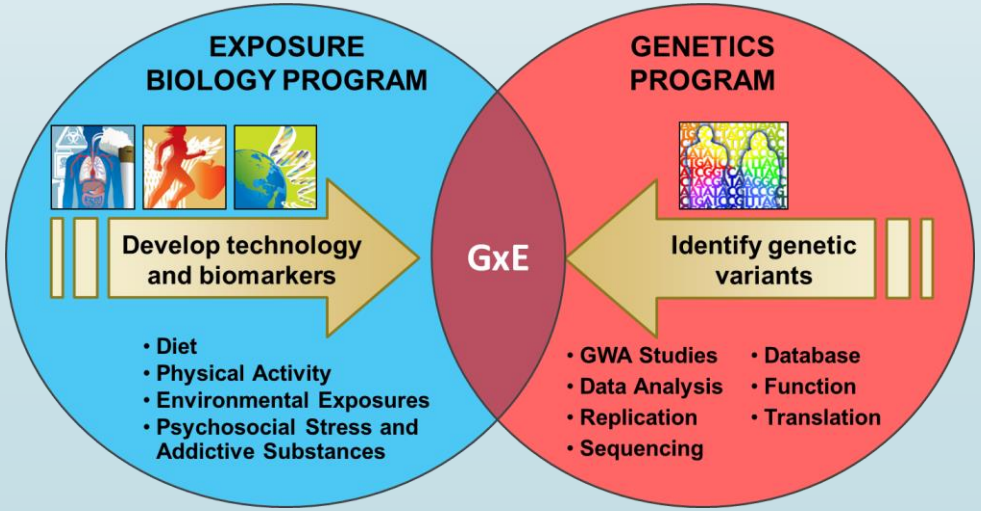

Kim et al., Autism Res, 2017

Global ⟶ Local ⟶ **Personal**

Global ⟶ Local ⟶ Personal

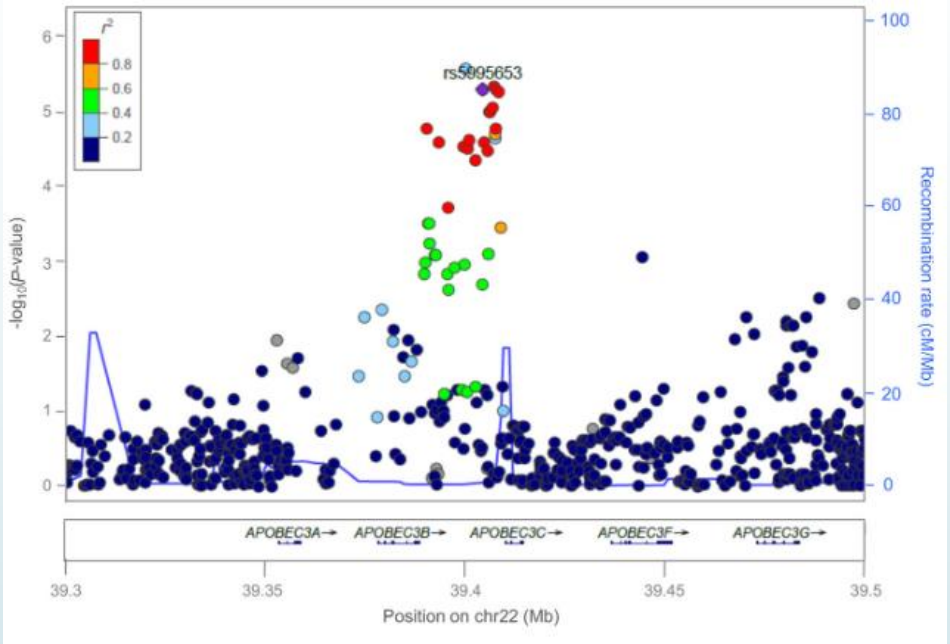
# Sources of Variability

- **Genetics**
  - Sex, epigenetics, tissue/cell type
- **Life Stage**
  - Preconception, fetal, childhood, adolescence, adulthood, pregnancy
- **Environment**
  - Chemicals, stress, nutrition, microbiome



# Interindividual Variability Leads to Health Disparities

- First GWAS of inhaled corticosteroid (ICS) response in Hispanic/Latino and African American children and young adults with asthma
- 15 independent variants were suggestively associated with asthma exacerbations, despite use of ICS
- Only 1 out of the 15 variants identified showed evidence of nominal replication in European populations
- Results revealed novel association of *APOBEC3B* and *ABOBEC3C* genes with ICS response




1 of the 15 SNPs (rs5995653), located within the intergenic region of APOBEC3B and APOBEC3C, showed evidence of nominal replication after combining European studies

Hernandez-Pacheco et al., Clin Exp Allergy, 2019

# Integrating Epidemiology and Toxicology

**Mechanistic Data**
**(*in vitro*, *in silico*)**

**Experimental**
**Animal Data**

**Human Data**
**(epidemiology)**

Interdisciplinary collaborations needed to better integrate epidemiological and toxicological data

# Using Mice as a "Model" for Human Exposures

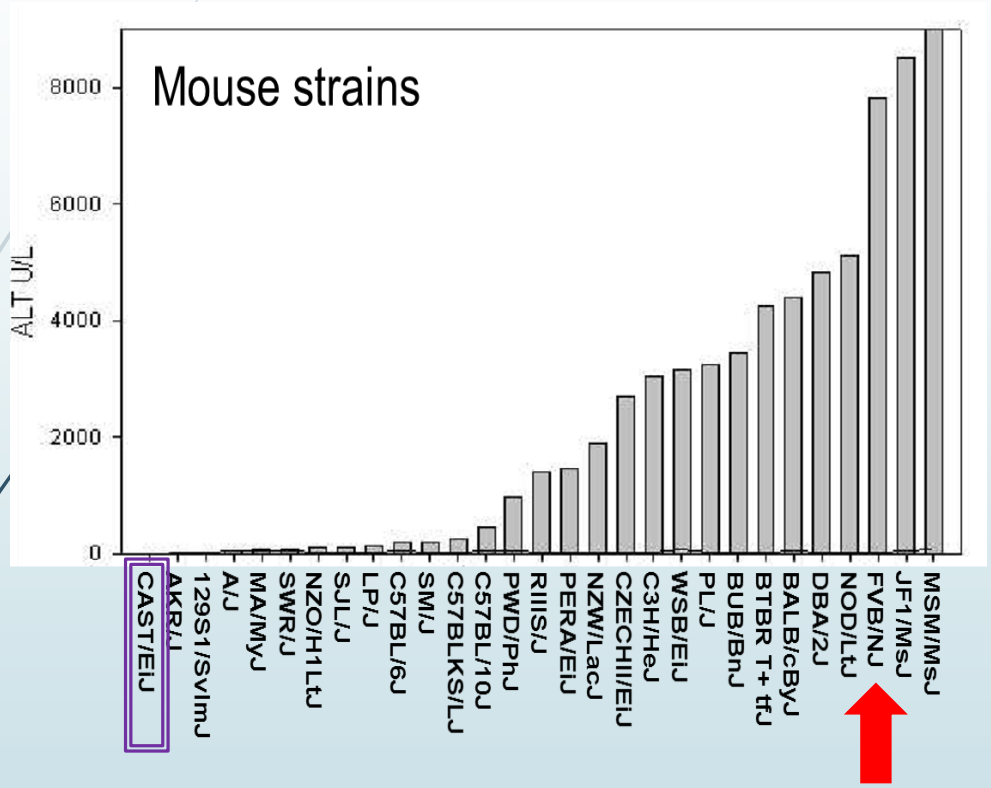
**Inbred Strain**
**(C57BL/6J)**
**(B6C3F1)**

≠

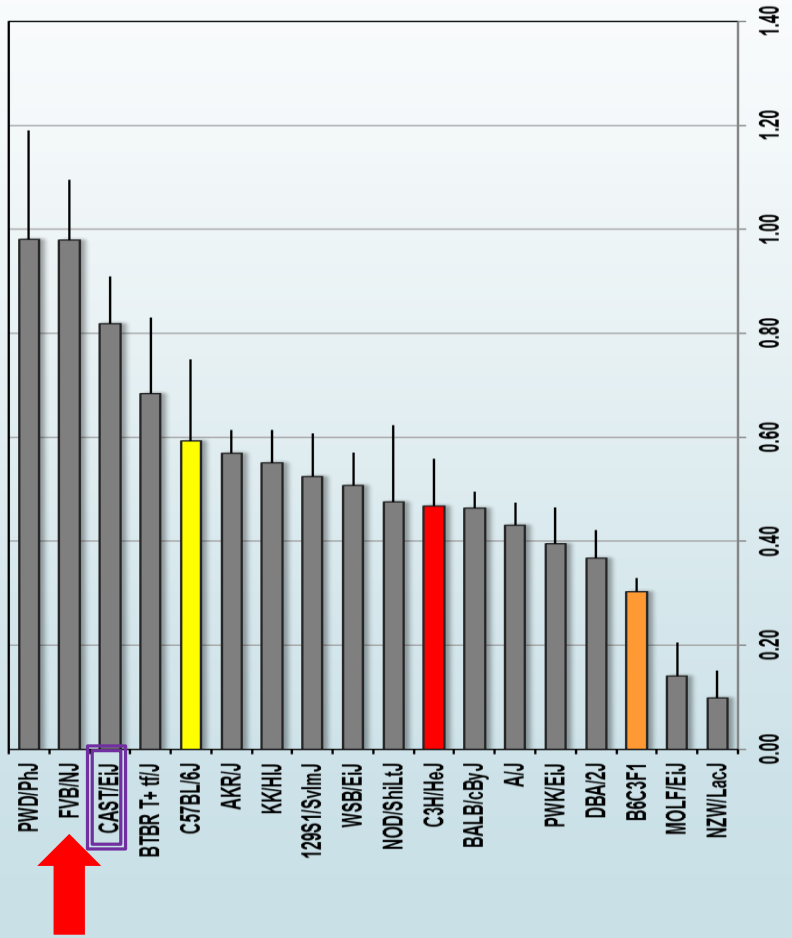
**Genetically Diverse Human Population**

# Variability Among Inbred Strains:

## Acetaminophen Toxicity




## Benzene Clearance




Threadgill and colleagues
UNC, JAX and NCSU

French et al., EHP, 2014

# "Modeling" Reference Human Populations with Reference Populations of Mice

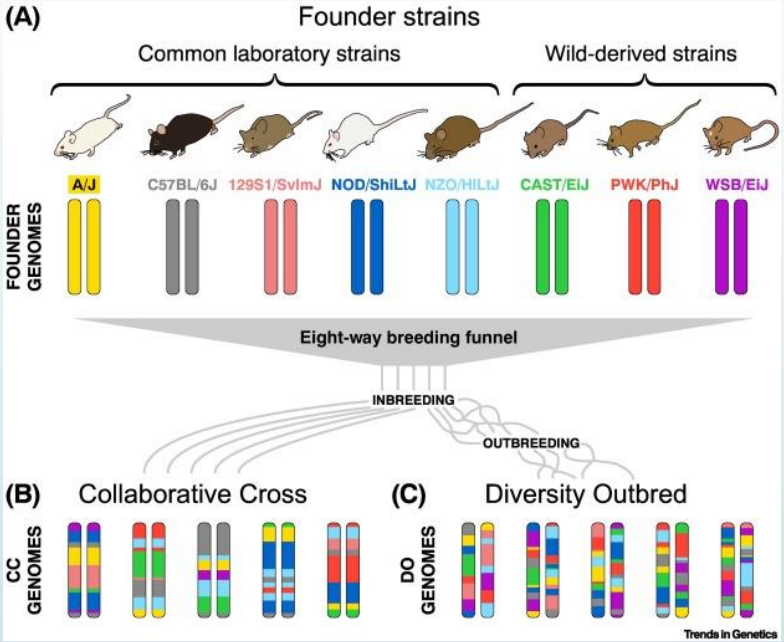
≈

**Genetically Diverse Mouse Population**

**Genetically Diverse Human Population**

# "Modeling" Reference Human Populations: The Collaborative Cross and Diversity Outbred Mice

- High-diversity mouse populations with known and reproducible genetic variation make complex trait genetics tractable in a mammalian system
- The Collaborative Cross (CC), founders, and the heterozygous CC-RIX are reproducible populations for genome-matched correlational and controlled studies
- The Diversity Outbred (DO) population displays high genetic and phenotypic variability and enables precise genetic mapping
- Ideal mouse population is dependent on the research question being asked



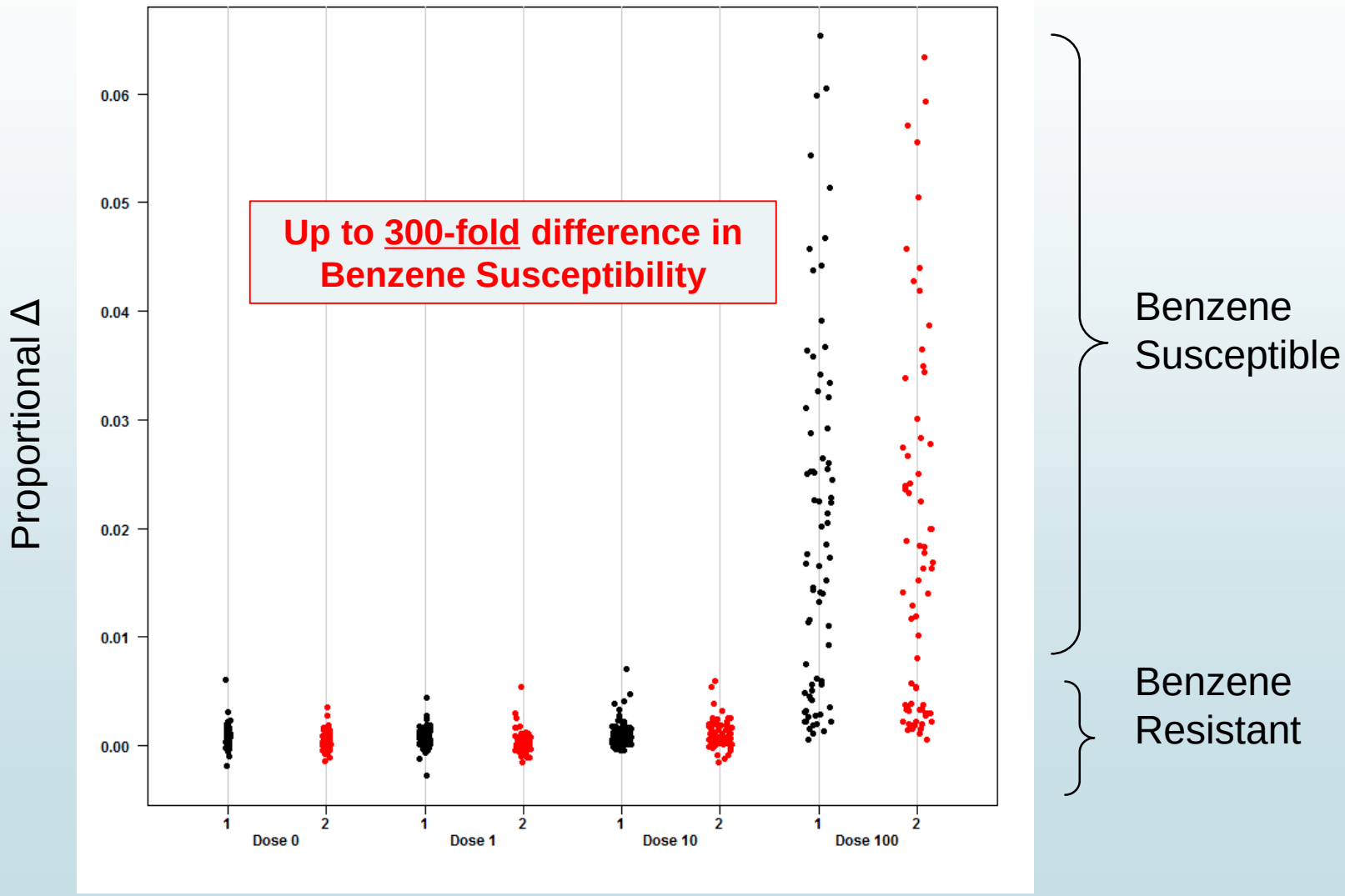

Saul et al., Trends Genet, 2019

# Proof of Concept of DO: Benzene 28 Day Inhalation Study

- Diversity outbred (J:DO) male mice: 7th and 8th randomly outbred generations; selected from 175 breeding pairs
- Due to broad phenotypic diversity, mice were randomly assigned to exposure group by weight
- **Dose levels: 0, 1, 10, 100 ppm benzene, 28 days, 6 hr** TWA
- 75 male mice per exposure group, 300 mice/study
- 600 mice total: 2 separate cohorts to assess reproducibility
- Endpoint for genetic damage assessment
  - **Micronuclei in bone marrow and blood reticulocytes and erythrocytes**
  - Mouse Universal Genotyping Array (9K SNPs; MUGA)
  - Mapping & Linkage analysis (QTLRel)

French et al., Environ Health Perspect, 2015

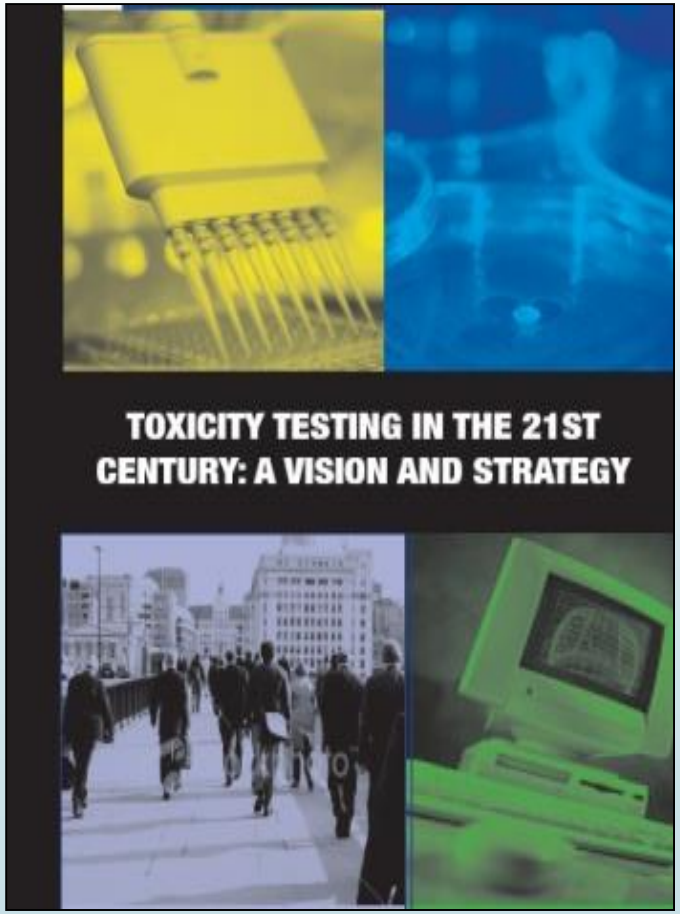
# Change in %MN-RET Before and After Exposure

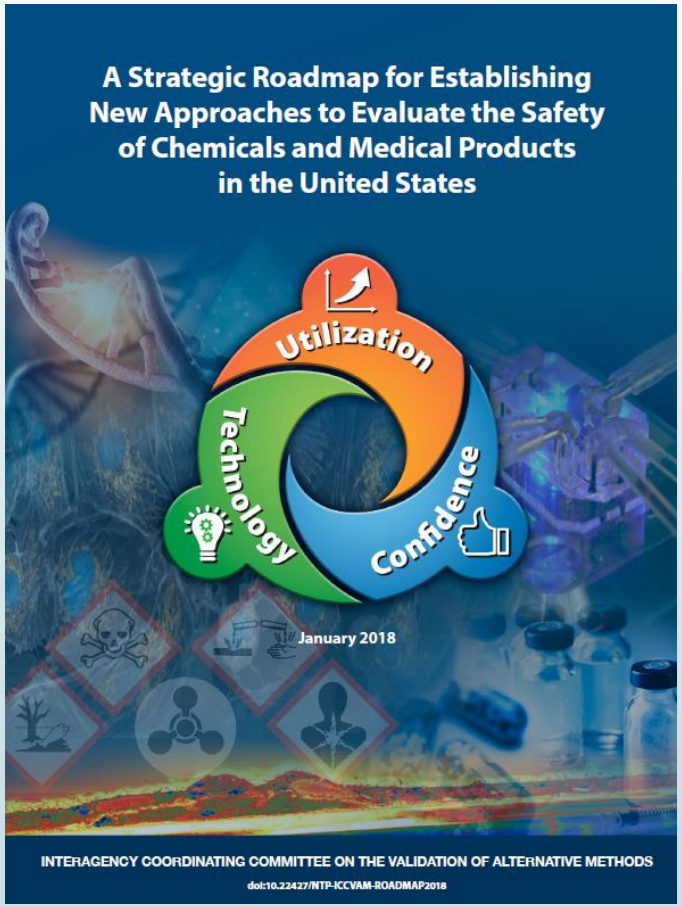



French et al., Environ Health Perspect, 2015

# Roadmaps for Future Research and Engagement

- Predictive Toxicology



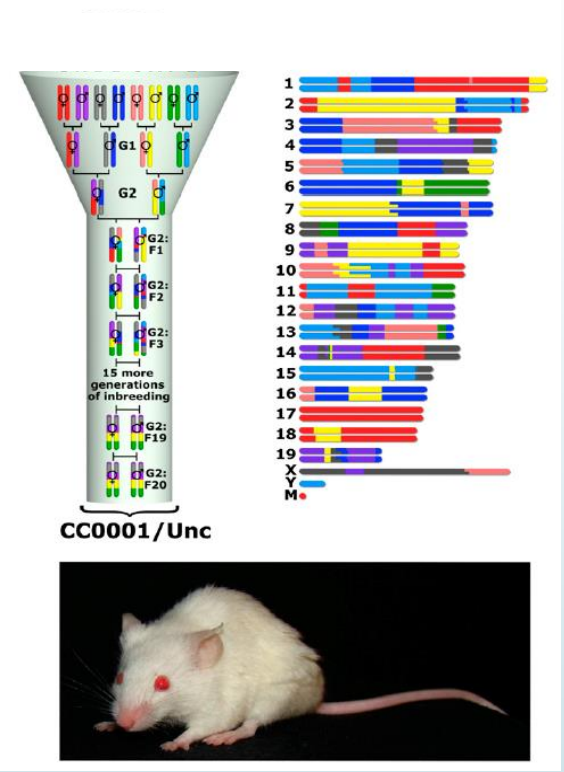



# Challenges Faced with *In Vitro* Screens


**How do we develop *in vitro* screens that capture interindividual variability?**

"Human-on-a-Chip" vs. "*Me*-on-a-Chip"

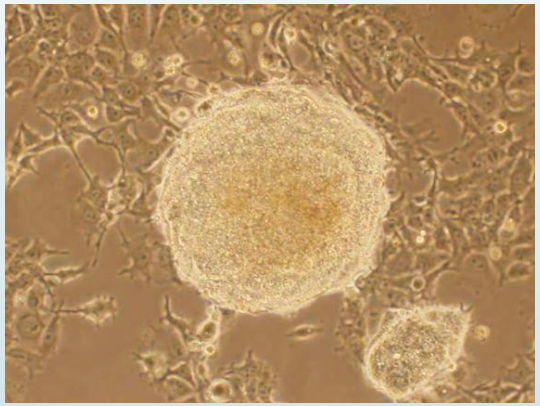
# Incorporating "In Vitro Genetic Studies" into Tox21




**Reference population of Mouse Lines (Human in the future)**

ES Derivation from Blastocysts

iPS reprogramming



**Reference population of ES/iPS Cell Lines**

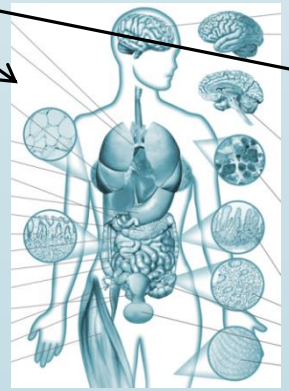
# Precision Medicine


Multifaceted environment


Multidisciplinary research

***Inter***individual variability

***Intra***individual variability



Precision Prevention

# Personalized Approach for Translational Research

## Example: Gene-Environment Interactions that Modulate Disease

- Question: Do SNPs in the TLR-4 pathway in combination with traffic-related air pollution exposure, predict asthma diagnosis and severity?
- Genotype: Toll-like Receptor 4 (TLR4) pathway **SNPs**
- Environment: Residential addresses + **Geospatial database**
  - Distance to major road (proxy for pollution exposure)
- Phenotype: **EPR Health and Exposure Survey**:
  - Asthma diagnosis/exacerbations
- Findings:
  - Asthma diagnosis rate was higher in genetically susceptible participants living close to a major road
  - Asthma severity was lower in genetically resistant participants living farther from a major road
- Personalized intervention: Avoidance of pollution based on genetic susceptibility may decrease asthmatic exacerbations

Schurman et al., Nature, 2018

Global ⟶ Local ⟶ Personal

# Data Integration

## *All of Us* (NIH)

- Develop ways to measure risk for a range of diseases based on environmental exposures, genetic factors, and interactions between the two
- Identify the causes of individual differences in response to commonly used drugs
- Discover biological markers that signal increased or decreased risk of developing common diseases
- Use mobile health technologies to correlate activity, physiological measures, and environmental exposures with health outcomes
- Develop new disease classifications and relationships
- Empower study participants with data and information to improve their own health
- Create a platform to enable trials of targeted therapies


The NIH *All of Us* Research Program seeks to extend precision medicine to all diseases by building a national research cohort of one million or more U.S. participants

# Individual Level

## Environment Correlated with Mental Health Effects

**Pesticides**

- Association of pyrethroid exposure and ADHD

**Air Pollution**

- Exacerbation of schizophrenia related to ultrafine air particle concentrations

**Metals**

- Young adult low level Pb exposure and increased risk of major depression/panic disorder

**Endocrine Disruptors**

- Prenatal BPA exposure and higher anxiety, hyperactivity and depression scores

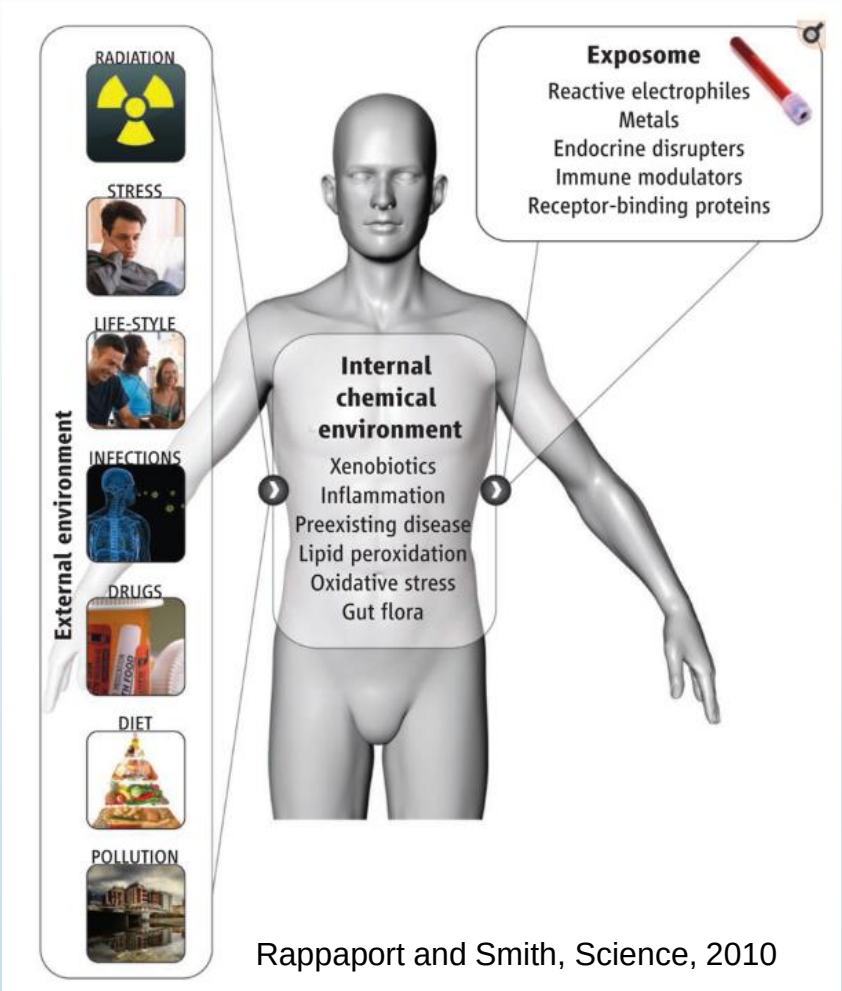
**BUT:**

**Nature**

- Green space may lead to less depressed teens; lower mortality among women

# Exposome

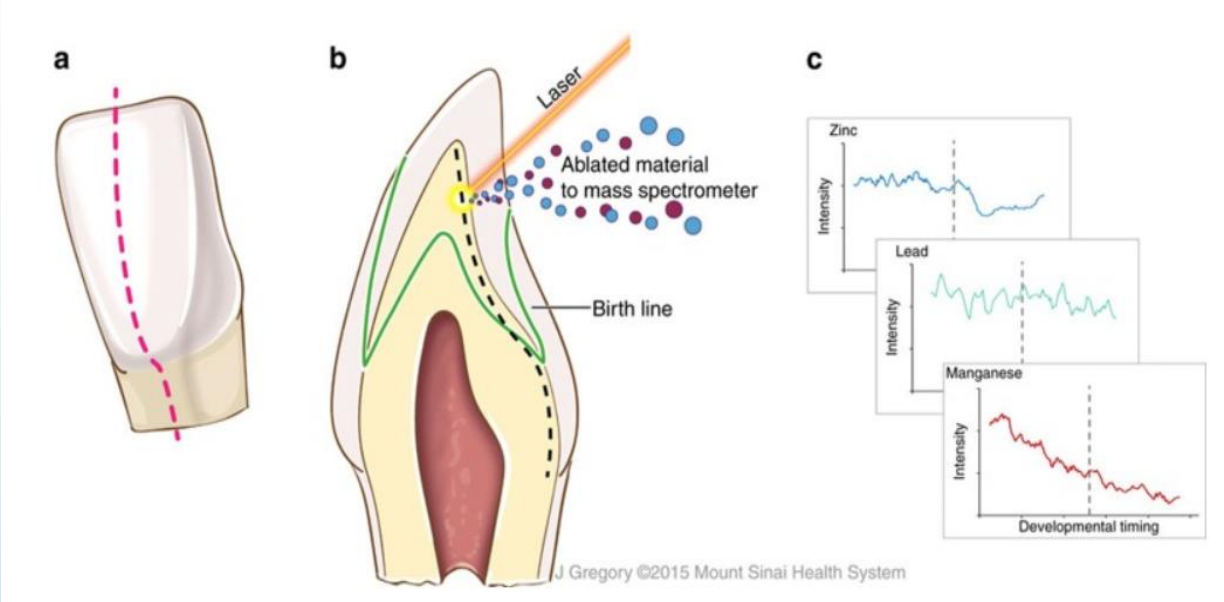
- **What is the exposome?**
  - An untargeted (hypothesis free) assessment of the totality of environmental exposures
  - External, internal, or both?
- **How to measure it?**
  - New tools necessary to monitor exposure
  - Can use biomonitoring or untargeted metabolomics to begin to do 'top-down' approach
- **What about mixtures?**
  - Chemical
  - Non-chemical (infectious agents, diet, psychosocial stress)




Rappaport and Smith, Science, 2010

# Individual Level
## Exposome

- Levels of essential and toxic metals in tooth-matrix were divergent in ASD cases and control siblings, but only during discrete developmental periods




- Epidemiologic associations were observed: Manganese and zinc levels were lower, and lead levels were elevated in cases compared to controls

Arora et al., Nat Commun, 2017

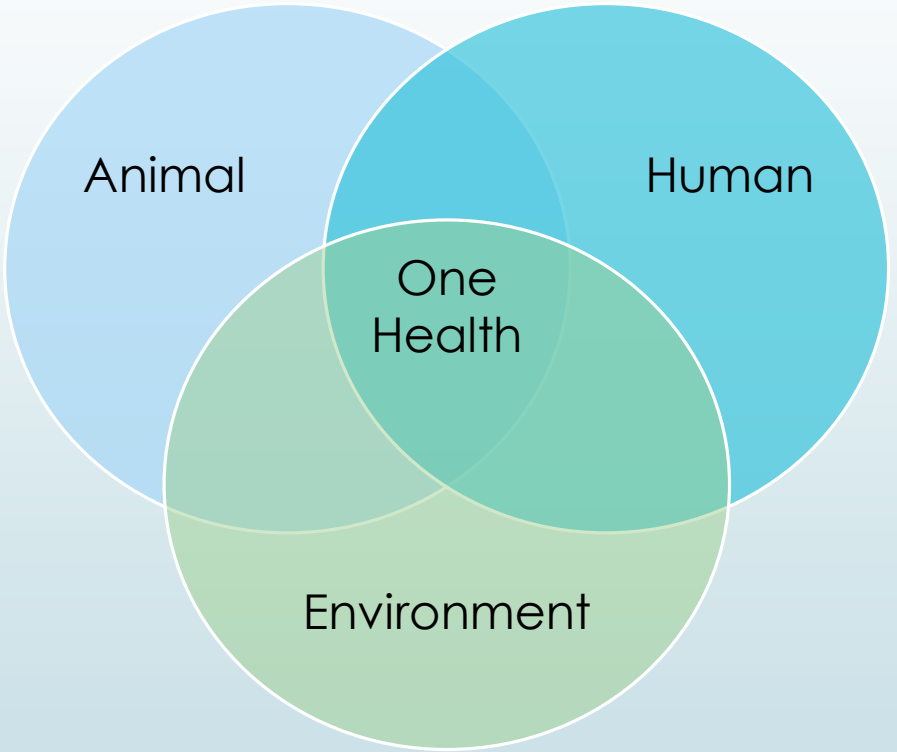
**Global ⟶ Local ⟶ Personal**

# One Health

*One Health aims to improve health and well-being through the prevention of risks and the mitigation of adverse effects that arise at the intersection of humans, animals, and their environment*

## Intersections

- **Planetary Level**
  - Climate and Health
- **Ecosystem/Community Level**
  - Sentinel Species
  - Infectious Disease and Chemicals
  - Ecological Restoration
  - Disaster Research Response
- **Individual Level**
  - Exposome
  - Microbiome
  - Environment and Mental Health
- **Research Tools, Translation, and Policy**



# Ecosystem/Community Level

## Infectious Diseases and Chemicals

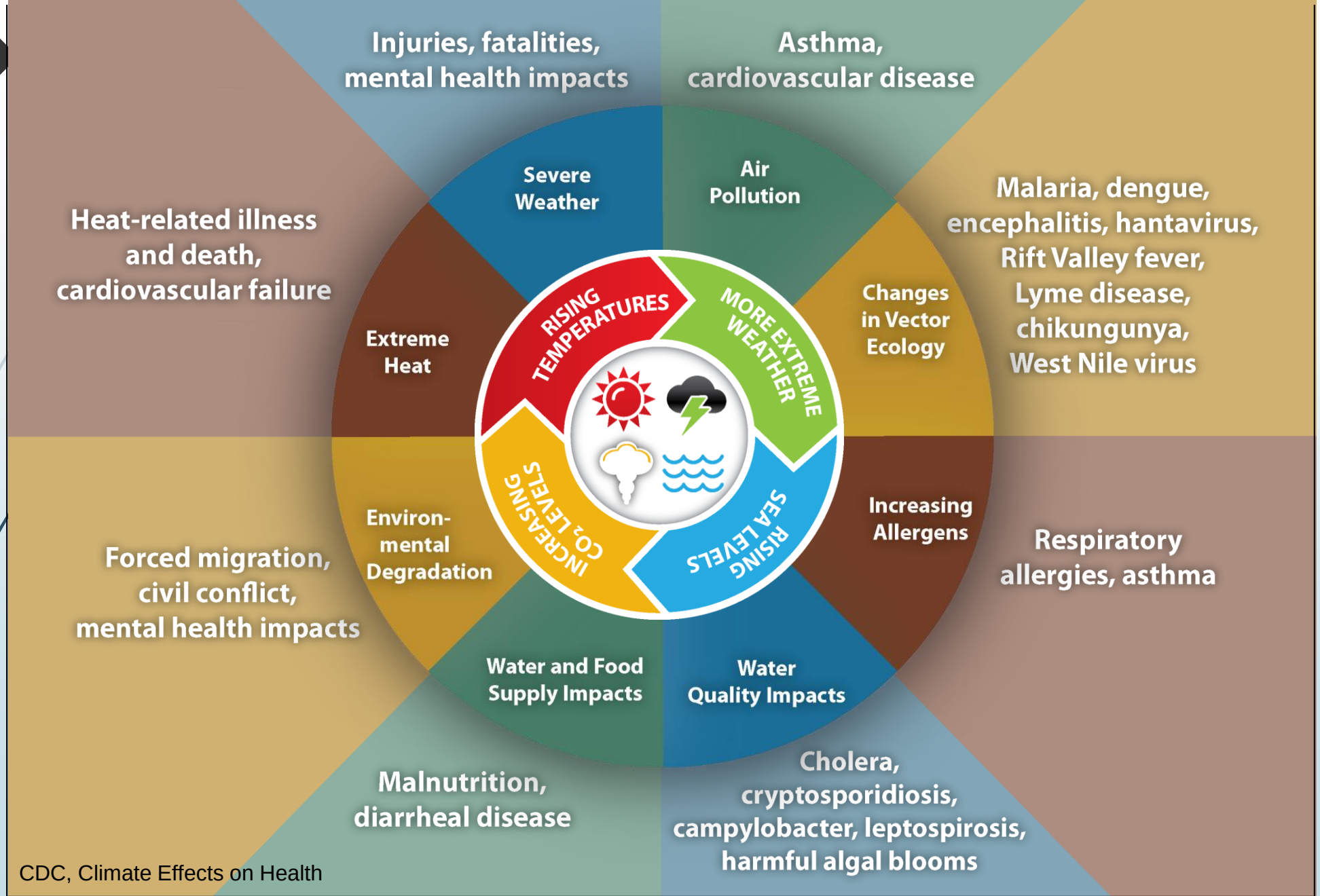
- PFAS and reduced immune response to vaccinations *(Philippe Grandjean, Harvard School of Public Health)*
- Arsenic and *Pseudomonas aeruginosa* infections in the lung *(Bruce Stanton, Dartmouth College)*
- Zika in Infants and Pregnancy (ZIP) study and impacts of neurotoxic pesticides *(Jose Cordero, U. of Georgia)*
- Pyriproxyfen (MPEP) testing in zebrafish for teratogenicity, pregnant rat/rabbit for TK fetal transfer, and rat for immunotox *(Barry McIntyre, NTP)*

# Ecosystem/Community Level

## Sentinel Species

- **Fish**
  - Legacy contaminants and emerging flame retardants (*Frank Von Hippel, Northern AZ U)*
  - Chronic kidney disease (CKD) (*Nishad Jayasundara, U of Maine)*
- **Whales, alligators, sea turtles**
  - Impacts of metals on lung cells *(John Wise, U. of Louisville)*
- **Sea lions**
  - Effects of exposure to domoic acid *(Paul Buckmaster, Stanford U)*
- **Horses**
  - Chemical exposure with neurological and reproductive effects *(Dorothy Ainsworth, Cornell U)*

# Planetary Level: Climate Change and Health




CDC, Climate Effects on Health

# Wrap-Up

- Environmental health research can inform strategies to reduce exposures and improve health
- Consider local context, but identify commonalities
- Scientific collaboration and building global research capacity are key to finding solutions

**Environmental factors are more readily identified and modified than genetic factors, and therefore, present a tremendous opportunity for Precision Health Approaches.**


**We can’t change our Genes,…**

**…but we can change our Environment.**

*Thank you!*