National Institute of Environmental Health Sciences
Your Environment. Your Health.

NIEHS 50 YEARS 1966-2016

Our Environment, Our Health, Our Children's Future

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The National Institute of Environmental Health Sciences

- One of the 27 National Institutes of Health, but located in RTP, NC
- Wide variety of programs supporting our mission of environmental health:
  - Intramural laboratories
  - Extramural funding programs
  - Disease Prevention
  - Clinical research program
  - National Toxicology Program
  - Public Health Focus

NIEHS Strategic Plan

Mission

The mission of the National Institute of Environmental Health Sciences is to discover how the environment affects people in order to promote healthier lives.

Strategic Themes for Environmental Health Sciences

Vision

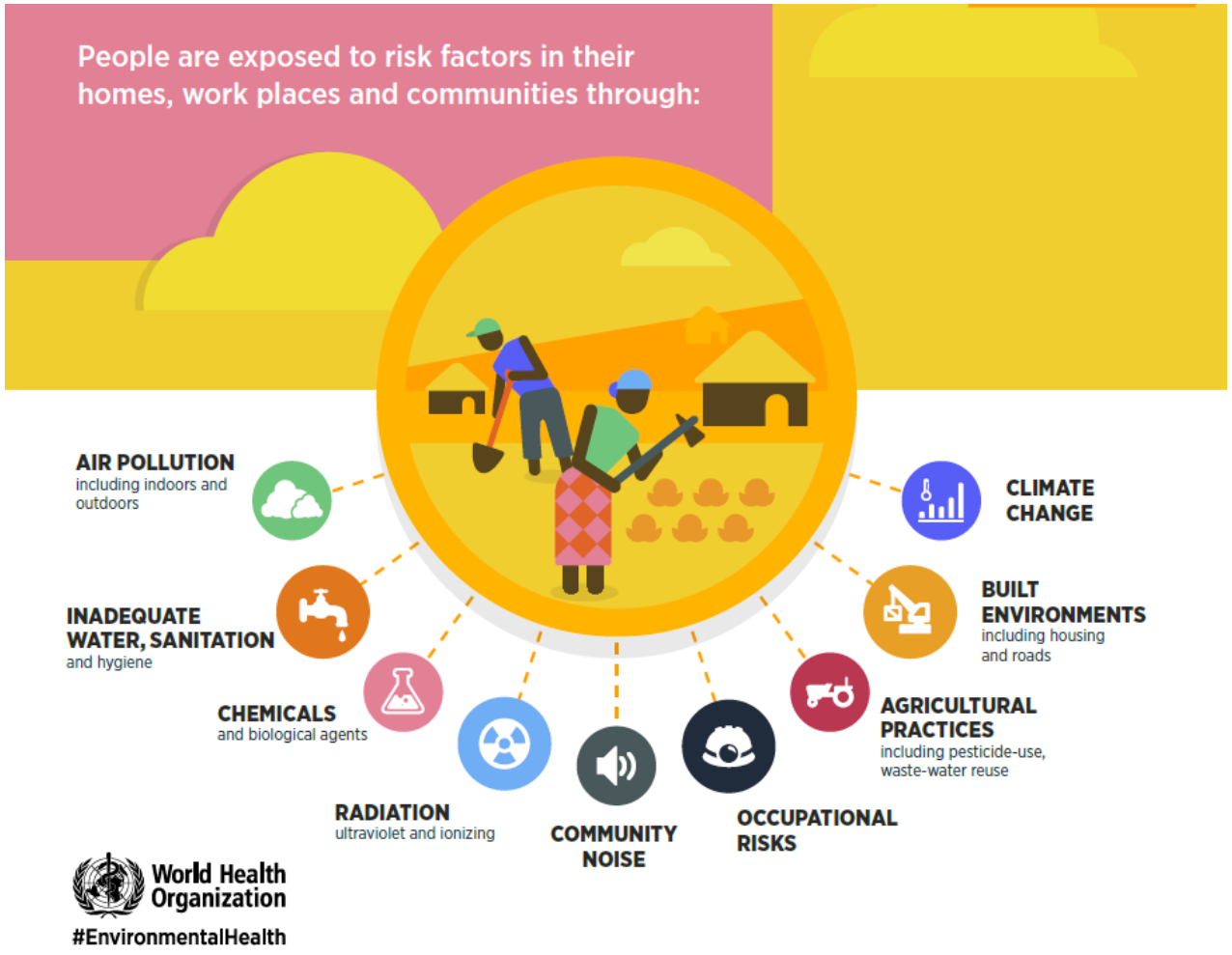
The vision of the National Institute of Environmental Health Sciences is to provide global leadership for innovative research that improves public health by preventing disease and disability.

Why Environmental Health Matters

Annual Deaths:

- Stroke – 2.5 million
- Ischaemic heart disease – 2.3 million
- Cancers – 1.7 million
- Chronic respiratory diseases – 1.4 million
- Respiratory infections – 567,000
- Neonatal conditions – 270,000

Why Environmental Health Matters



"There's an urgent need for investment in strategies to reduce environmental risks in our cities, homes and workplaces."

~Dr. Maria Neira

Diseases with a Known or Suspected Environmental Component Include:

- Cancers
- Birth defects (cleft palate, cardiac malformations)
- Reproductive dysfunction (infertility)
- Lung dysfunction (asthma, asbestosis)
- Neurodegenerative diseases (Parkinson's)
- Neurodevelopmental disorders (autism)
- Cardiovascular disease (air pollution, dioxins)
- Endocrine disorders (diabetes)

Ubiquitous Exposure

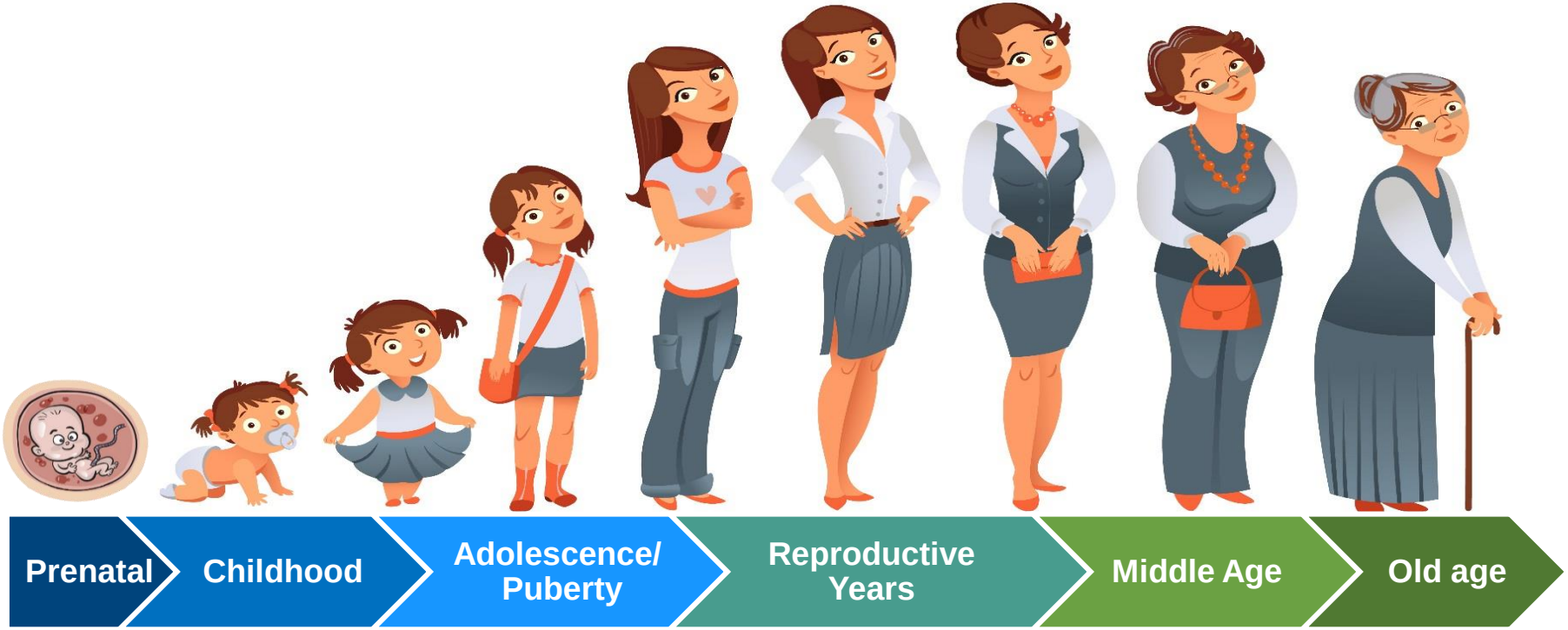
- Chemicals are ***widely dispersed in our environment***
- Chemicals are often dispersed at biologically effective levels, exposure to humans is common
- Exposures do not occur singly
- One exposure can alter body's response to other exposures
- Combinations must be studied
- "Exposome" is the totality of exposures for a person

NIEHS research is focused on understanding the interaction of our genetic susceptibilities and our environmental exposures.

Consideration of vulnerable populations

- Pregnant women
  - How do the complex series of immunological changes during pregnancy affect susceptibility to pollutant exposure and effects?
- In utero exposure of fetus to pollutants
  - Potential organizational effects from pollutants could lead to permanent changes
- Exposure of child during sensitive developmental windows
  - Susceptibility changes over time and could lead to different health outcomes from a single exposure

Exposures occur across the lifespan: Windows of Susceptibility



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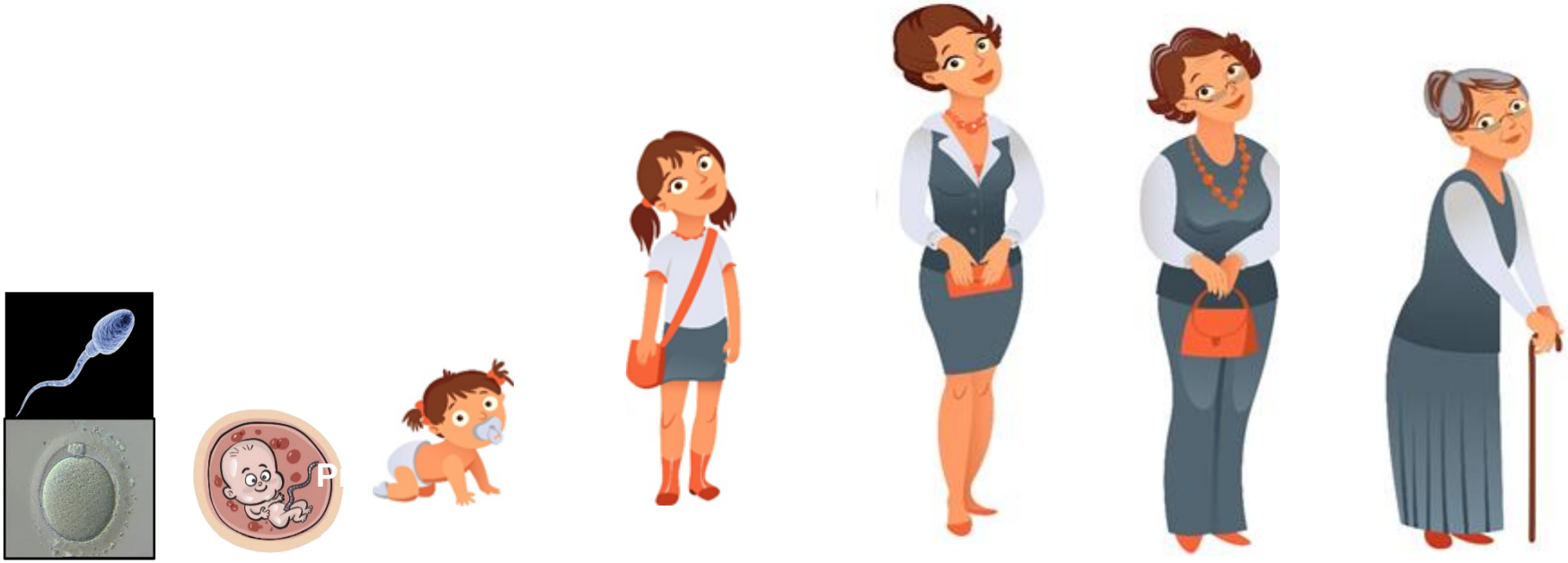
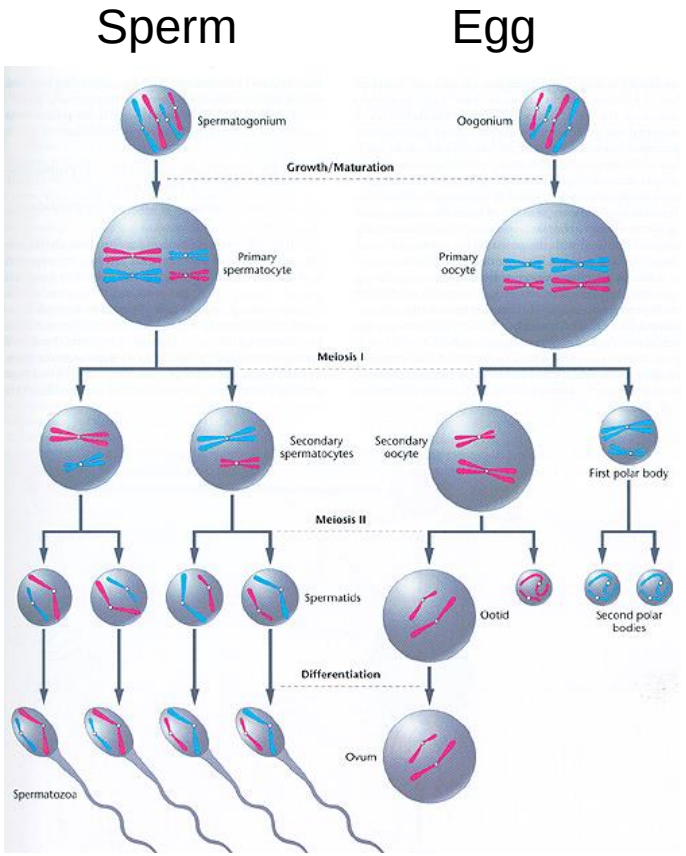


Can exposures during germ cell development effect the offspring?

The Preconception Window

- **Period of rapid changes**
  - Cell growth
  - Meiotic division
  - Hormonal changes
    - Estrogen, progesterone, GnRH,FSH, LH, androgen
  - Epigenetic changes



Gametogenesis

Exposures to Germ Cells and Supporting Tissues

- Teratogenic effects
- Alter germ cell quality, and fertility
- Cause DNA damage
- Disrupt mitochondrial integrity

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- Teratogenic effects
- Alter germ cell quality, and fertility
- Cause DNA damage
- Disrupt mitochondrial integrity
- DNA copy number variations
- Alter sex-specific gene expression
- Interfere with meiosis
- Alter Redox states, inflammation
- Alter the epigenome of germ cells

It is likely that some of these subtle effects carry on to the offspring

Examples of Paternal Exposures on Offspring

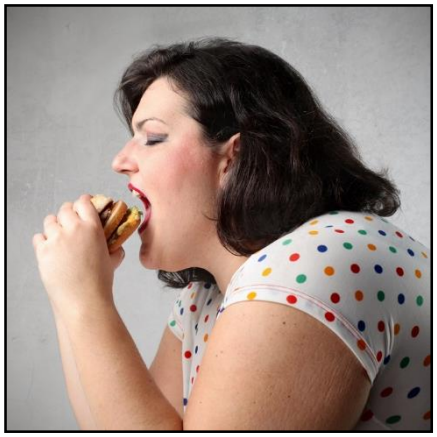
- **Drug use**
  - Cocaine exposure to adult males influences anxiety & other behaviors of offspring (Pierce, 2014; Killinger, 2012)
  - Similar developmental abnormalities seen in offspring of adult male use of alcohol, cannabis & tobacco

- **Social instability**
  - Dad's stress experience effects offspring stress response and metabolism (Bale, 2012, 2014)

- **Nutrition/ Obesity**
  - Offspring of adult males fed a Low Protein Diet show impaired liver function (Rando, 2010)
  - Offspring to dads fed a High Fat Diet have diabetes and poor semen quality (Ng, 2014)
  - Paternal obesity results in obese offspring (Freeman, 2011), increased rates of autism (Suren, 2013)

Examples of Maternal Preconceptional Exposures on Offspring

- **Obesity**
  - Maternal obesity alters oocyte maturation, embryo redox state, and offspring growth, and metabolism (Simmons, 2014)



- **Social behaviors**
  - Mom's anxiety effects offspring behavioral disorders (Saavedra-Rodríguez, 2013)
- **Smoking**
  - Preconceptional smoking associated with increased risk of congenital heart defects (Karatza, 2009)

- **Chemicals (POP's)**
  - Preconceptional paternal and maternal exposure to POP's associated with low birth weight (Buck Louis, 2014)

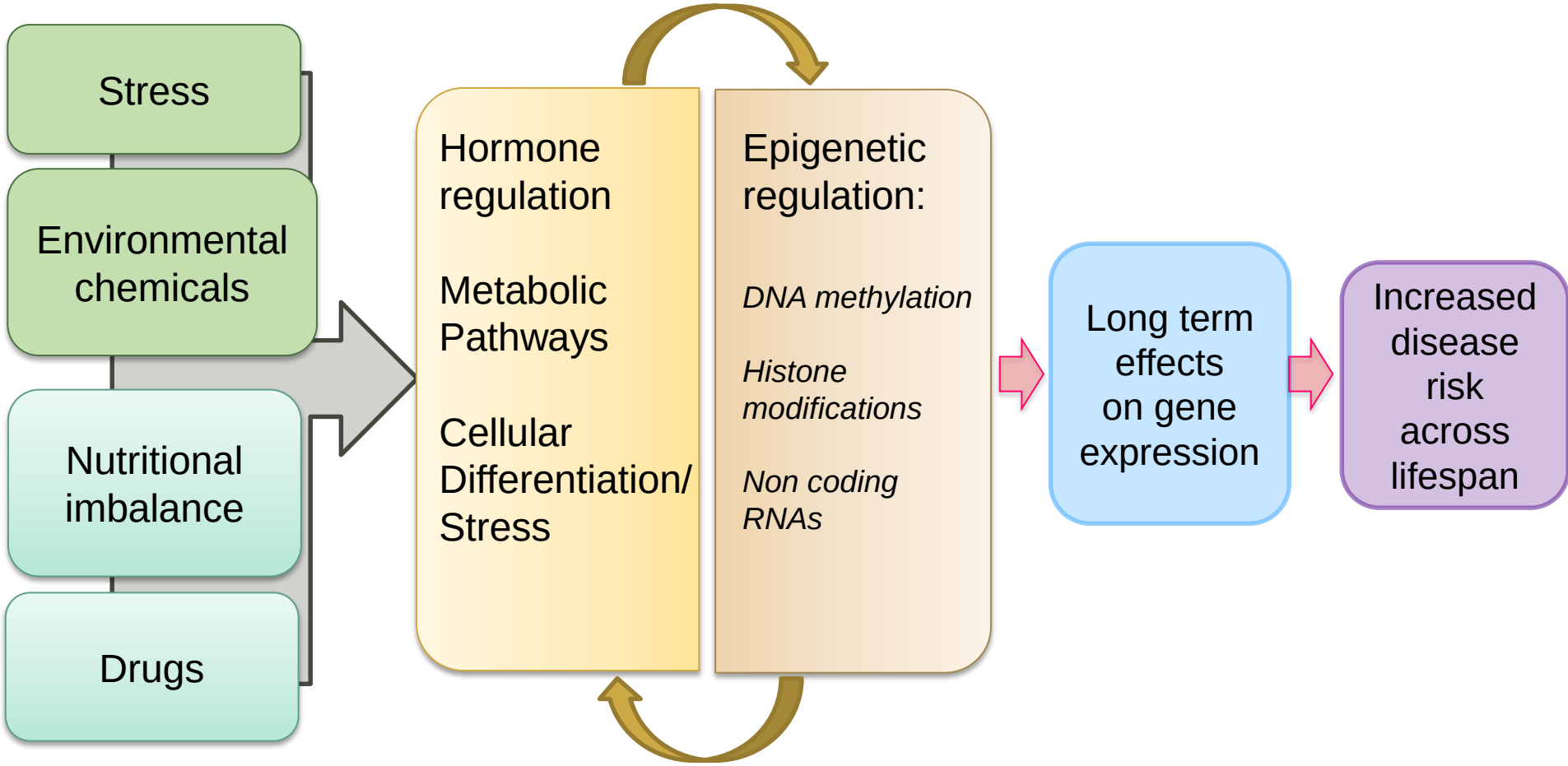
Exposures During Pregnancy

Early Life Exposures Have Lasting Effects

Developmental Origins of Health and Disease

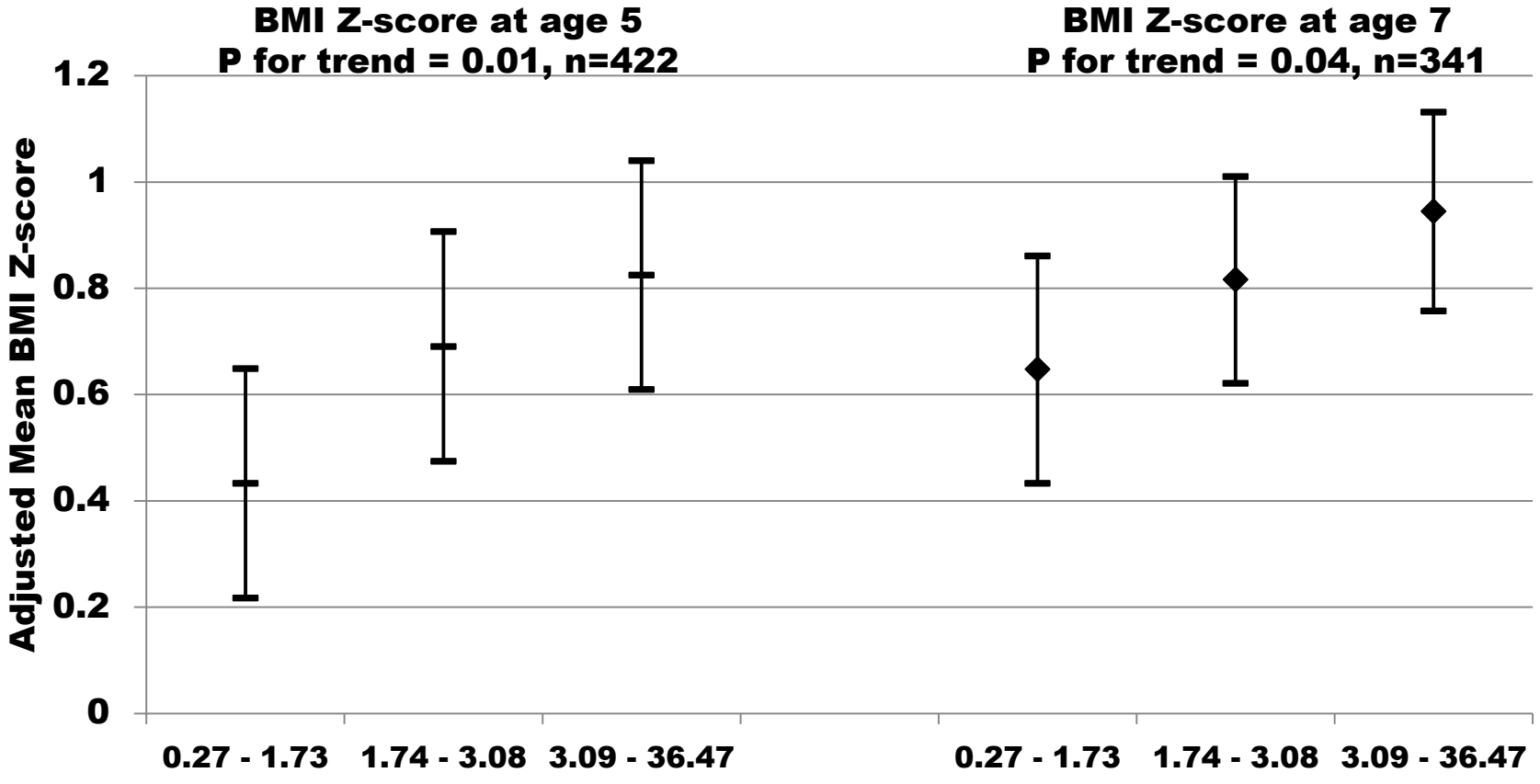
- Early life (in utero and early childhood) is a sensitive time for exposure:
  - Epigenetic programming set gene expression programs that lead to cell differentiation and tissue formation.
  - Chemical metabolism is immature
- Changes occurring during development permanently alter the potential of an organ… thereby increasing the sensitivity or set-point for disease across the lifespan and generations.

Developmental Origins of Health and Disease



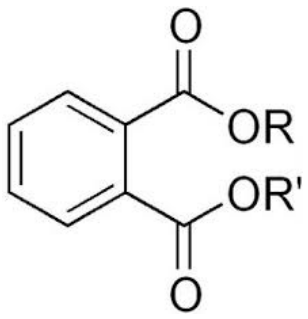
Barouki et al, Environ Health 2012

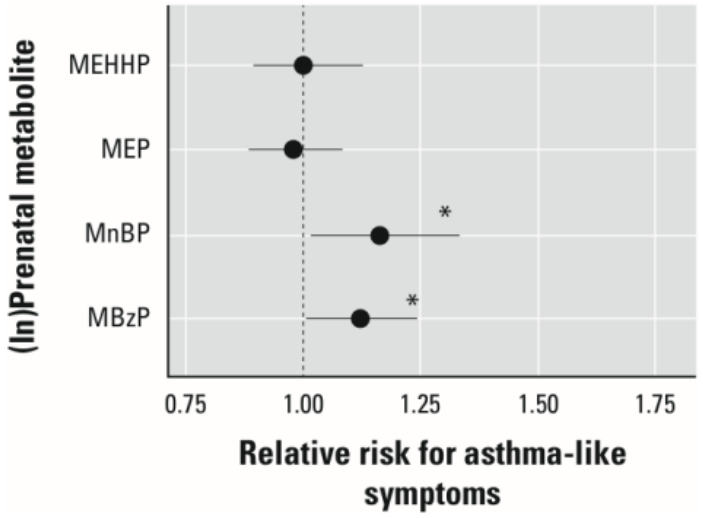
Prenatal PAH Exposure is Associated with BMI Z-score at Age 5 & 7

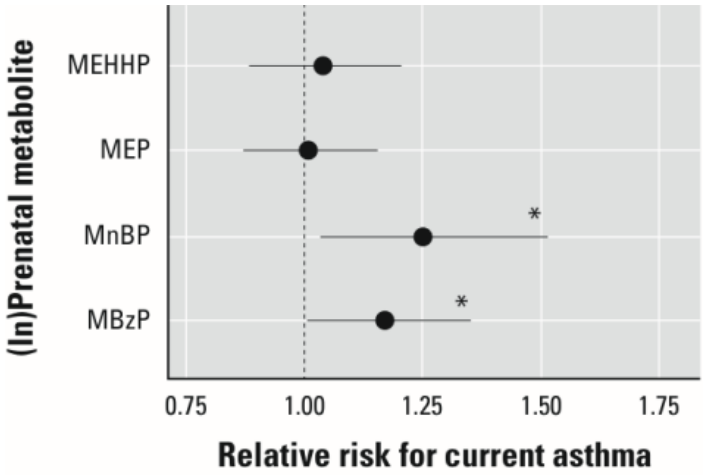


Adjusted for age, gender, ethnicity, birth weight, maternal obesity and maternal receipt of public assistance [Rundle et al., AJE, 2012]

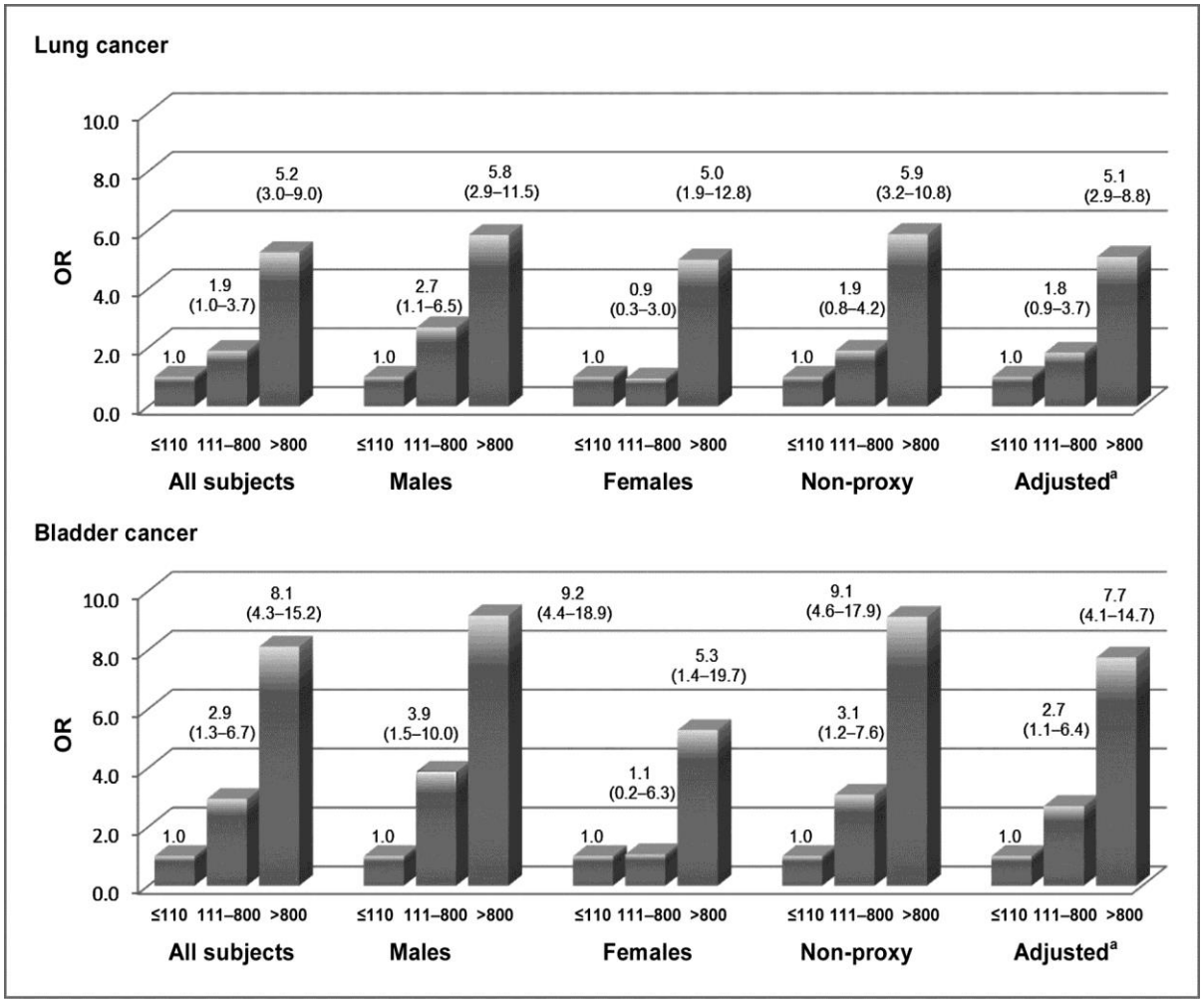
Childhood and prenatal exposures to phthalates and asthma







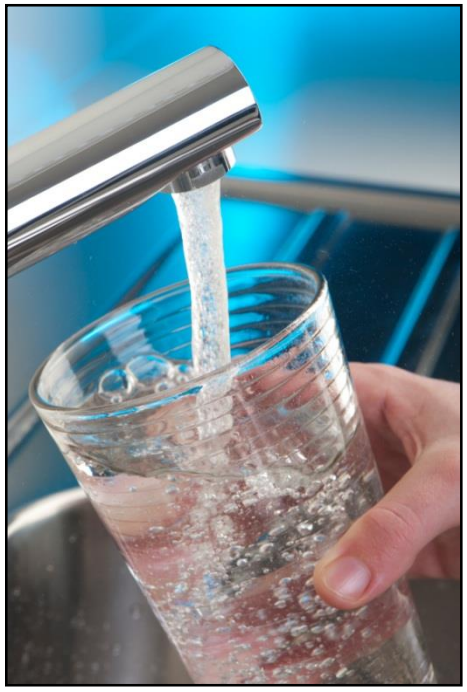
In Utero and Childhood Arsenic Exposure and Cancer
(Cancer diagnosis age >25yrs)



Steinmaus C et al. Cancer Epidemiol Biomarkers Prev 2014;23:1529-1538

Health Effects of Arsenic in Drinking Water

- Cancer – Lung, larynx, liver, kidney, bladder, skin
- Respiratory Effects – Bronchiectasis, COPD, Emphysema, Chronic Lung Infections
- Vascular and Cardiovascular Disease
- Reproductive and Developmental Problems
- Neurological Problems and Reduced Cognitive Function in Children
- Type 2 Diabetes
- Endocrine Disruptor – ER, PR, AR, GR, MR, RAR, TR, PPAR



ADHD and Pesticide Exposure Associated with lower IQ and increased ADHD, Autism

- In animal models, researchers are investigating pesticide exposure as a possible risk factor for ADHD
- In humans, researchers found that higher maternal urinary levels of organophosphate metabolites were associated with ADHD, decreased IQ, and behavioral issues in children

UC Berkeley; Marks *et al.*, 2010; Eskenazi *et al.*, 2013

Heavy Metal Exposure in Children

Real-world Exposures to Metals Often Consist of Low Doses

- Very low levels of Arsenic exposure (5-10ug/L) in drinking water are associated with lower IQ scores in 3-5 grade children
  Wasserman *et al.*, Environ Health (2014)

- Children exposed to Mercury show decreased visuospatial processing and memory.
  Grandjean *et al.*, Neurotoxicol Teratol (2014)

- Exposure to Manganese is associated with poorer memory and attention in children, even at low levels commonly encountered in North America Oulhote *et al.*, EHP (2014)

- Very low levels of lead exposure (below 10 µg/dL) are associated with lower IQ scores in children ages 3 and 5 years old Canfield *et al.*, NEJM (2003)

Children's Research on Air Pollution

- Living within 75m of a major roadway associated with increased risk of asthma
- Traffic-related air pollution during pregnancy and during first year of life is associated with autism.
- Autism risk in children was also elevated in association with prenatal exposure to several airborne toxics and solvents, including lead, formaldehyde, and 1,3-butadiene.
- Maternal exposure to urban air pollutants, known as PAHs, can adversely affect a child's IQ.
- Children in a high-pollution environment showed impaired function of regulatory T cells compared to children in low-pollution setting

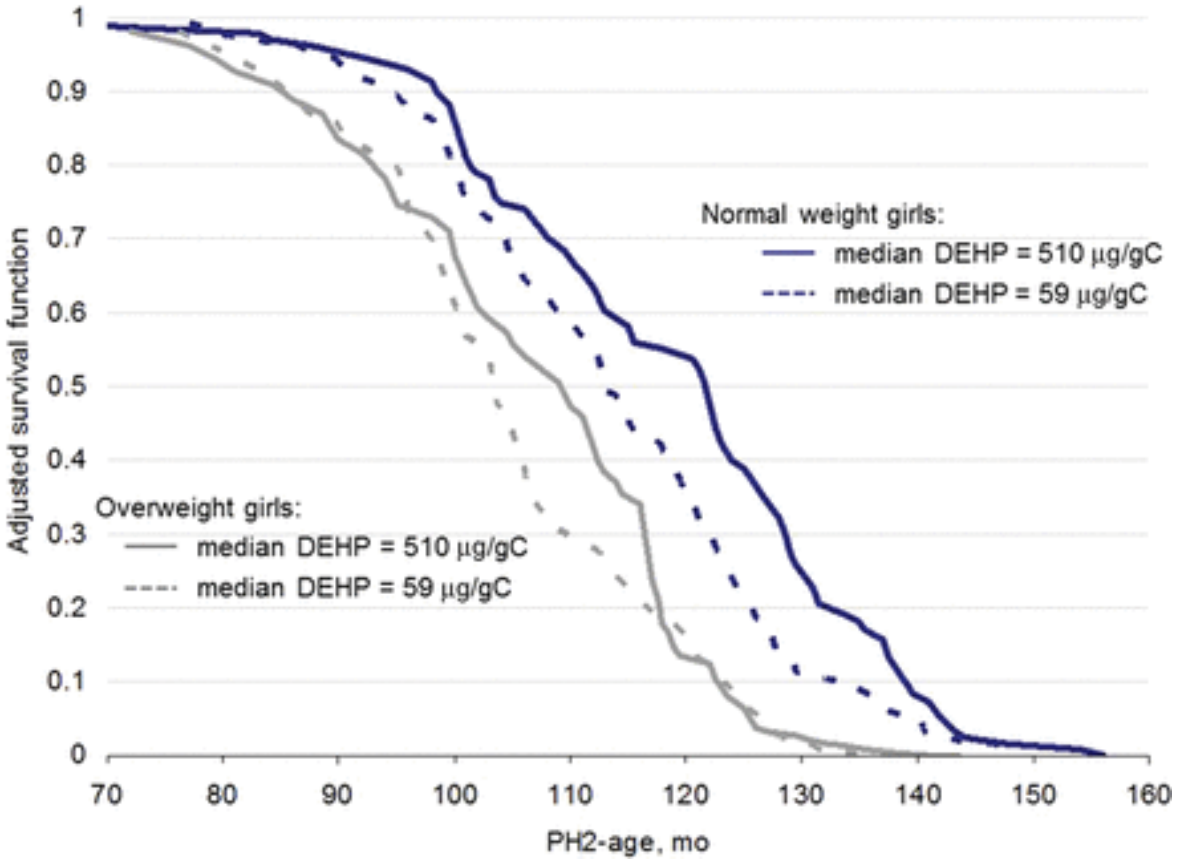
The air we breathe…indoors

- 3 billion exposed - Over 4 million deaths from cooking with solid fuels.
- More than 50% of premature deaths among children under 5 are due to pneumonia caused by particulate matter (soot) inhaled from household air pollution.

- Decreased Neurodevelopmental Performance Associated with Woodsmoke exposure. (Dix-Cooper et al. 2012)
- Indoor biomass fuel exposure is associated with increased risk of LBW (49%), respiratory illness (39%) and infant mortality (21%) (Tielsch et al. 2009)
- Asthma associated with open-fire cooking in Venezuela (Kraai et al. 2013)

Source: WHO http://www.who.int/mediacentre/factsheets/fs292/en/

High Molecular Weight Phthalates Linked to Later Puberty Onset



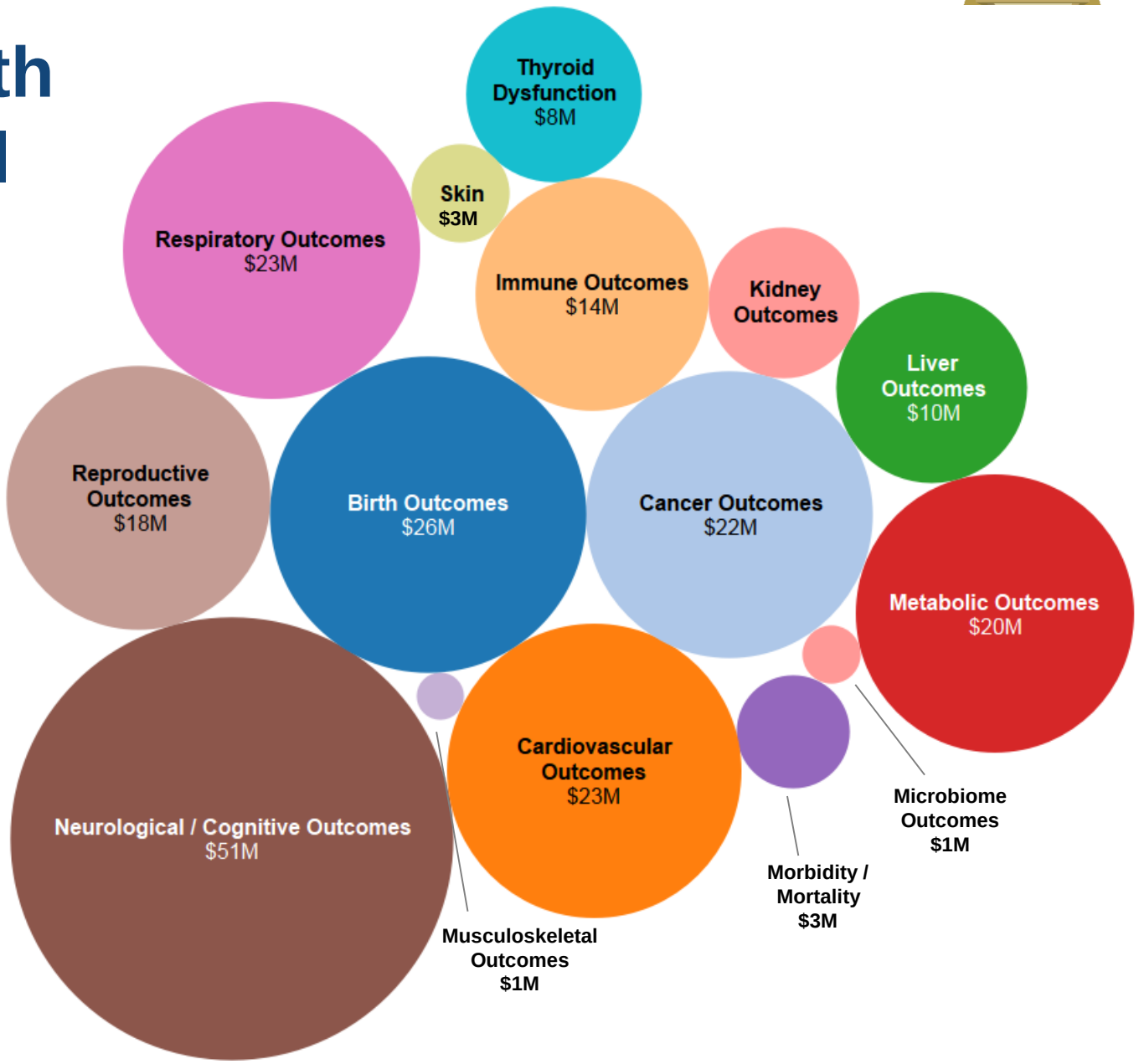
The association of ΣDEHP with adjusted age at PH2 was better in the normal-weight stratum than overweight.

EU environmentally attributable costs of childhood lead exposure, methylmercury exposure, developmental disabilities, asthma and cancer

- $70.9 billion in 2008 (range: $58.9-$90.6 billion).
- These costs amounted to ~0.480% of the gross domestic product of the EU.

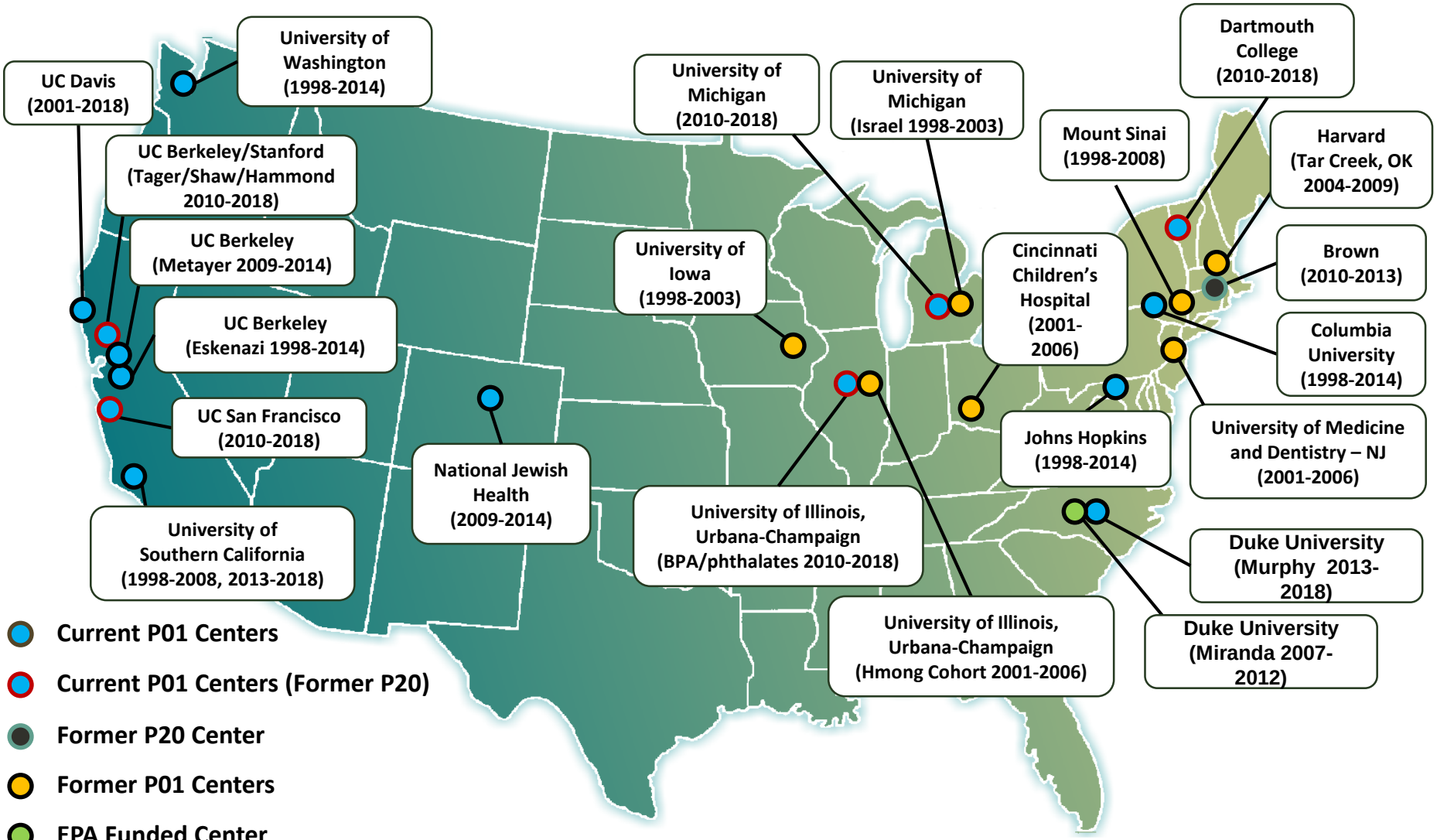
Bartlett and Trasande. 2014 Eur J Public Health.

Child Health Extramural Research Studies



2014 Data

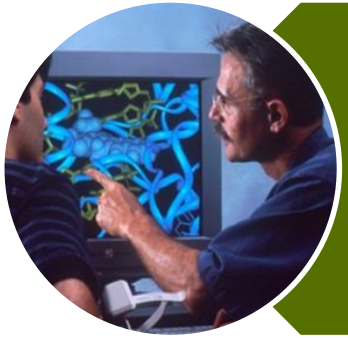
Current and Former NIEHS and EPA Children's Centers



Children's Health Exposure Analysis Resource (CHEAR)

Goal 1

Advance understanding of the impact of environmental exposures on children's health and development



Goal 2

Provide infrastructure for adding or expanding exposure analysis to studies involving research in children's health

Coordinating Center:

Administrative management and interface with the research community

National Exposure Assessment Laboratory Network:

Laboratory analysis of environmental exposures in existing biological samples

Data Repository, Analysis, and Science Center:

Data Repository and support for statistical analysis and interpretation

So Where are we…

- **Robust data** that Prenatal time period is a critical and likely most important window of susceptibility to environmental disruption.
  - Childhood is also a sensitive window… for some diseases/disorders.
- **Emerging data** indicate preconception is a sensitive window in males and females.
- **Preliminary data** indicates pregnancy is a sensitive window for the mother's susceptibility of the mother.
- **Some data** on multiple windows across the lifespan?
- Different things happen in different windows – and susceptibility varies

A Good Start Lasts a Lifetime!

Thank You

You can't change your Genes,
but you can Change your Environment!

National Institute of Environmental Health Sciences

National Toxicology Program
U.S. Department of Health and Human Services

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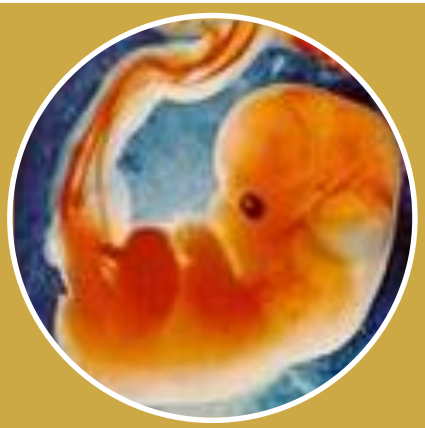
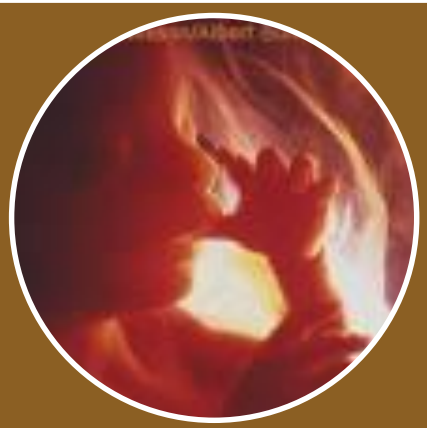
Stages of Prenatal and Postnatal Organ Development





Early Prenatal	Mid-Late Prenatal	Postnatal

Central nervous system (3wks - 20 years)

Ear (4-20 wks)

Kidneys (4-40 wks)

Heart (3-8)

Limbs (4-8wks)

Immune system (8-40 wks; competence & memory birth-10yrs)

Skeleton (1-12 wks)

Lungs (3-40 wks; alveoli birth-10yrs)

Reproductive system (7-40wks; maturation in puberty)

Week 1-16	Week 17-40	Birth – 25 years

Source: Altshuler, K; Berg, M et al. *Critical Periods in Development,* OCHP Paper Series on Children's Health and the Environment, February 2003.

Economic Costs of Autism Spectrum Disorders

- $17,000 more per year to care for a child with ASD compared to a child without ASD. For a child with more severe ASD, costs per year increase to over $21,000.
- Estimated that total societal costs of caring for children with ASD were over $9 billion in 2011.
- In addition to medical costs, intensive behavioral interventions for children with ASD can cost $40,000 to $60,000 per child per year.

Data: http://www.cdc.gov/ncbddd/autism/data.html

Studies on the Growing Brain

- Childhood Autism Risks from Genetics and the Environment (CHARGE)
- Markers of Autism Risk in Babies: Learning Early Signs (MARBLES)
- Early Autism Risk Longitudinal Investigation (EARLI)
- Environmental Epidemiology of Autism Research Network (EEARN)