An Introduction to Children's Environmental Health:

Why Kids? Why Environment?

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PEHSU Pediatric Environmental Health Specialty Units

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Pediatric Environmental Health Specialty Units

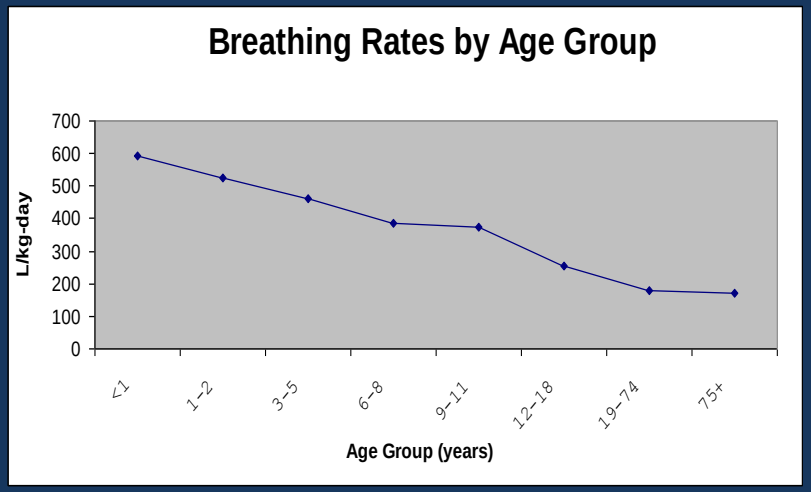
Western States PEHSU

http://coeh.berkeley.edu/ucpehsu/

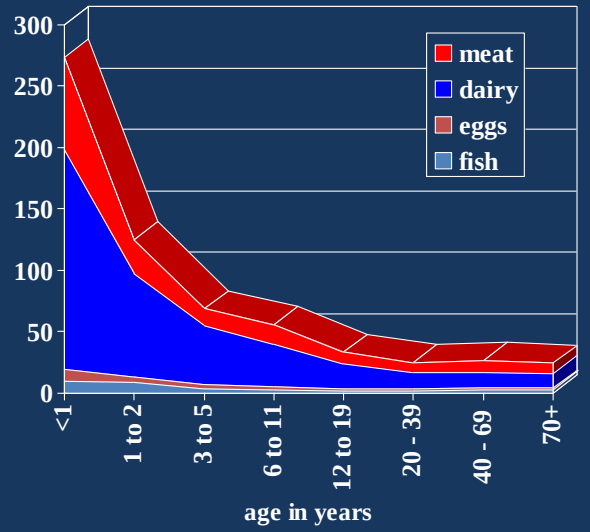
1-866-827-3478

National PEHSU System

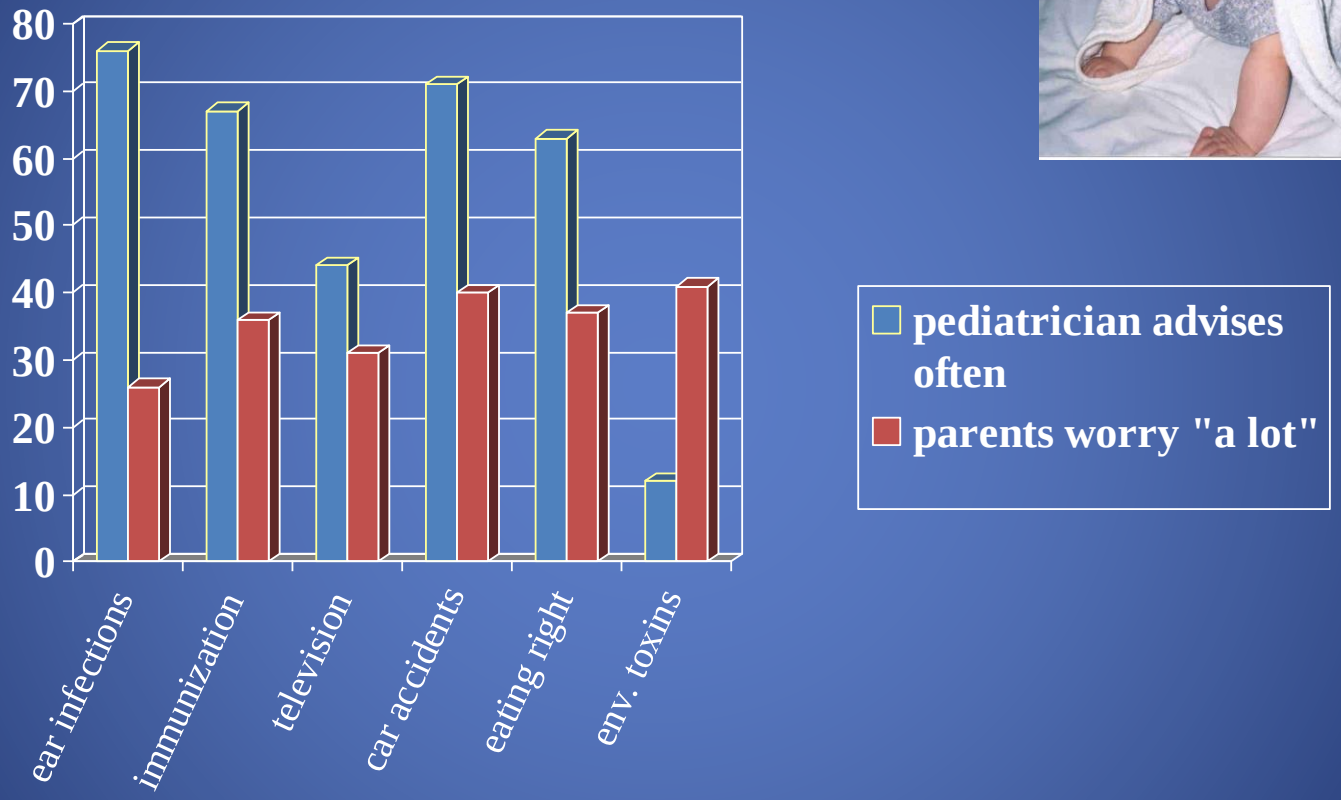
www.pehsu.net 888-347-2632



- Breathing rates calculated from inhalation rates (m^3/kg-day) and body weights reported in Layton (1993); original data from NFCS (1977-78).



Parental Concern vs. Pediatrician Advice



Stickler GB, Simmons PS., Clin Pediatr 1995

Case

- Female infant
- breastfed with formula supplement
- normal 1 month checkup (mother notes acrocyanosis at 2 weeks)
- At 2 months pharmacist comments on cyanotic color

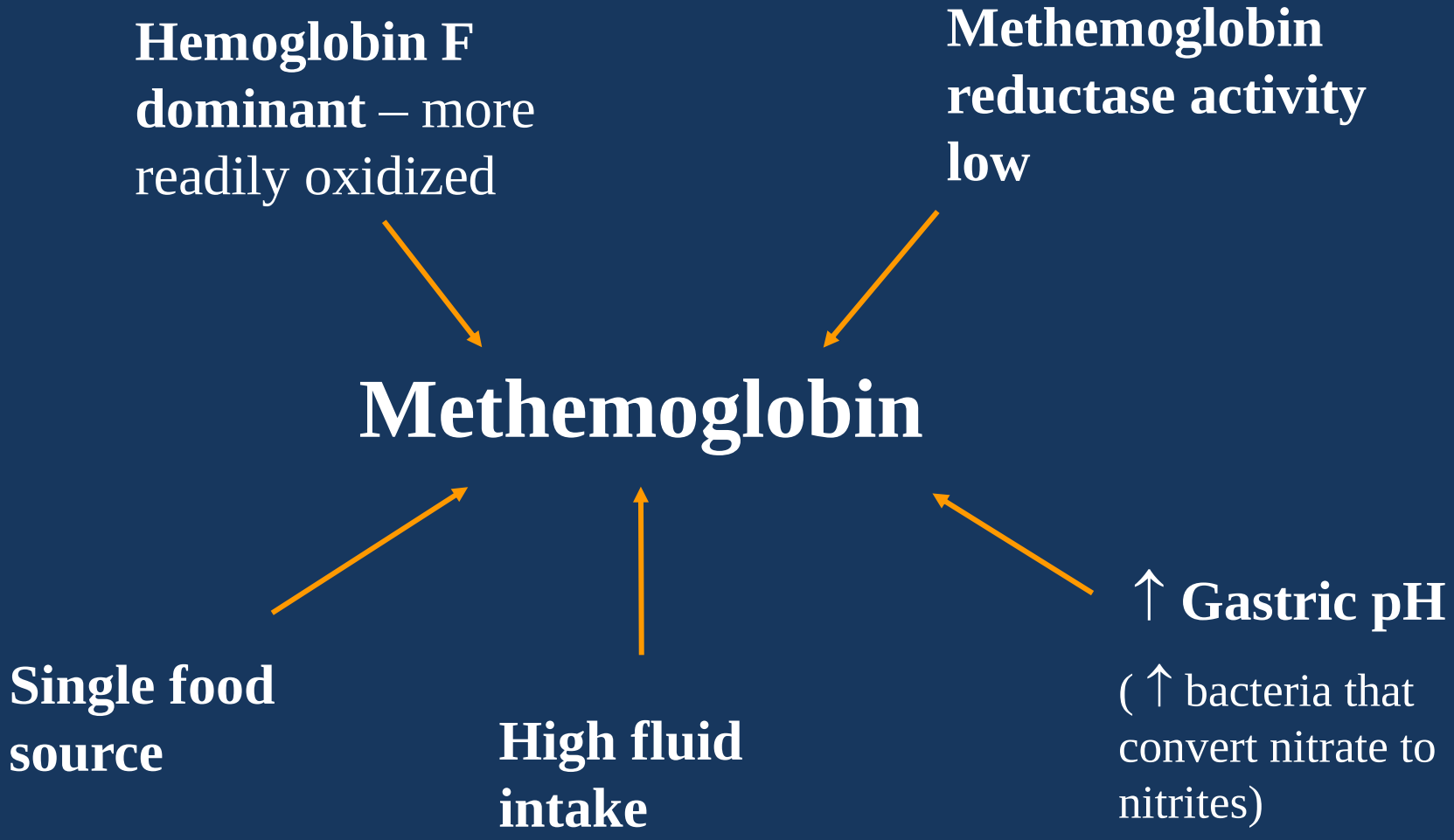
- Given progressively more formula made with well water
- At 2 months develops vomiting and severe diarrhea
- Rushed to physician - cyanosis doesn’t respond to oxygen / full arrest
- Chocolate-brown blood
- Well water 150mg/L nitrates

By Mike Blyth (Own work) [GFDL (http://www.gnu.org/copyleft/fdl.html). Commons

Nitrates

- Preventable cause of methemoglobinemia in infants
- Over 2,000 cases reported with case fatality rate of 10%
- EPA drinking water standards
  nitrates < 10mg/L (10ppm)
- 4.5 million people served > EPA standard
  - 65,000 infants
  - 117,000 children via public systems

Infant Under 4 Months



EXPOSURES DURING DEVELOPMENTAL PERIODS AND AT DOSES NOT ASSOCIATED WITH ADULT TOXICITY MAY RESULT IN IMPACTS UNEXPECTED BY ADULT EXPOSURE

Transient Hypertonia in an Infant

- ✓ 7lbs. 14 oz. term female, jaundice peak bili 12.6
- ✓ Nl. PE at 12 weeks except lower extremity hypertonicity
- ✓ Pediatric consult at 16 weeks - upper and lower extremity hypertonicity, ankle clonus with Dx of cerebral palsy
- ✓ Physical therapy begun
- ✓ No environmental hx was taken

Wagner SL, Orwick DL., Pediatrics 1994

Transient Hypertonia in an Infant

- Diazinon 1% sprayed by unlicensed pesticide applicator
- Levels still high six months after spraying
- Serum cholinesterase normal
- Urine metabolites high
  - similar to post-shift urine of applicators
- Six weeks after removal from house muscle tone returned to normal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Critical Windows of Development

Window of Vulnerability

A window of vulnerability is a time during which the fetus, infant, or child is especially susceptible to particular environmental chemical exposures, general environmental deprivation, suboptimal nutrition, or psychosocial stress.

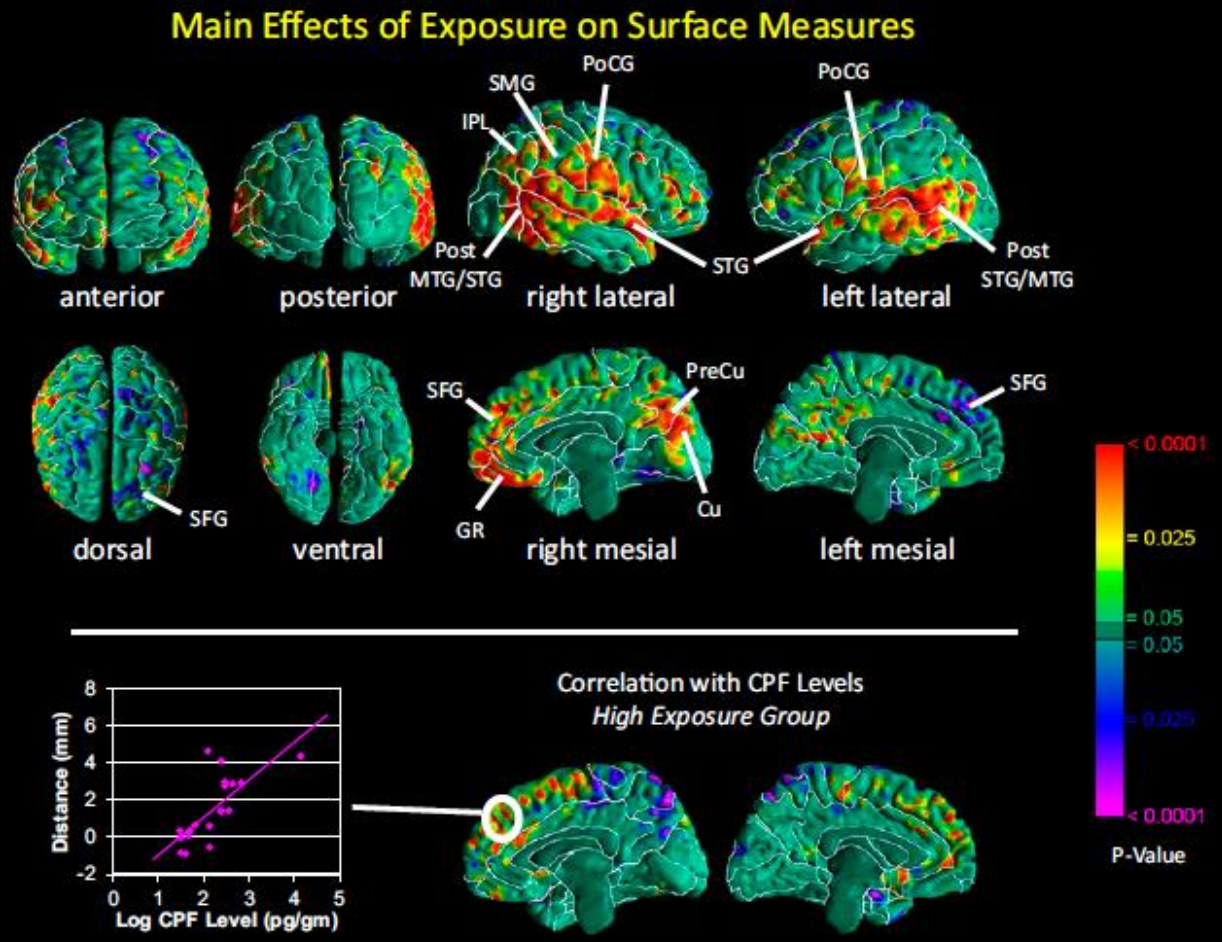
Chlorpyrifos Impacts Neurodevelopment

- Detected in >64% of maternal and newborn blood samples
  - Follow up at 3 yrs. for 189 children
- Highly exposed
  - Delays in psychomotor and mental developmental indexes (Bayley)
    - PDI delays 5 times as great (MDI 2.4 times)
- Symptoms ADHD and PDD significantly more likely (child behavior checklist)
- Declines in working memory and full scale IQ at age 7

Rauh et al. Pediatrics 20 06

Rauh et al., EHP 2011

Chlorpyrifos has Measurable Impact on Brain Structure (non-occupational)

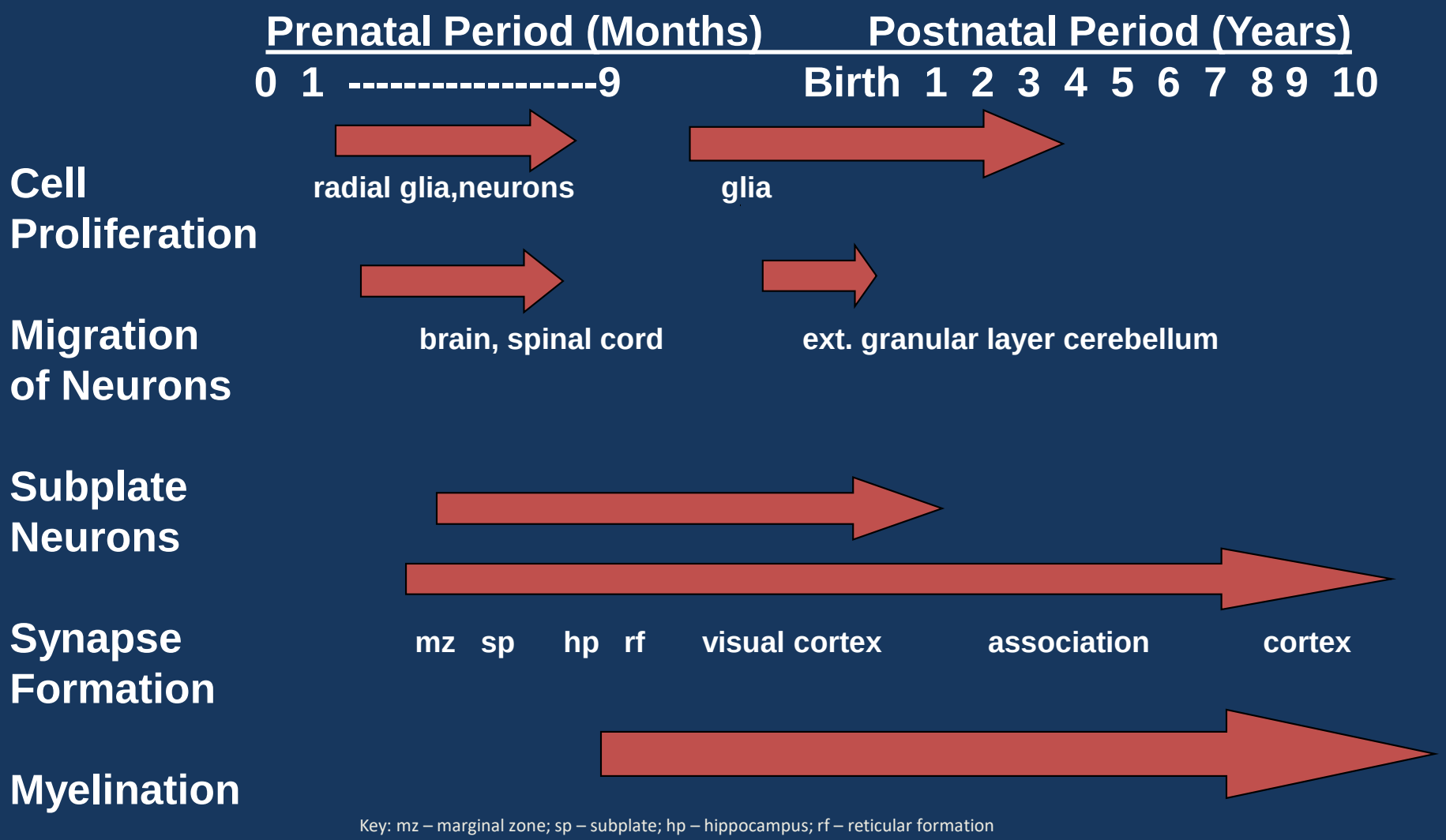


Brain anomalies in children exposed prenatally to a common organophosphate pesticide, Rauh et al., PNAS 2012 (copyrighted)

Regional enlargements of the cerebral surface (primarily underlying white matter)

- Posterior middle temporal, inferior postcentral gyri bilaterally
  - Attention and receptive language
- Superior frontal gyrus, superior temporal gyrus, cuneus, and precuneus
  - Social cognition
- Gyrus rectus (related orbitofrontal regions)
  - Reward, emotion, and inhibitory control
- L superior frontal gyrus (dorsal and mesial surfaces)
  - Executive function

Time Lines of Developmental Processes in Humans



Key: mz – marginal zone; sp – subplate; hp – hippocampus; rf – reticular formation

Specific processes disrupted by neurodevelopmental toxicants

proliferation	radiation, ethanol, mercury, cholinesterase inhibitors
migration	radiation, mercury, ethanol
differentiation	ethanol, nicotine, mercury, lead
synaptogenesis	radiation, ethanol, lead, triethyl tin, parathion, PCBs
gliogenesis & myelinization	thyroid, ethanol, lead
apoptosis	ethanol, lead, mercury
signaling	ethanol, cholinesterase inhibitors, mercury, lead, PCBs

What do parents do at work?

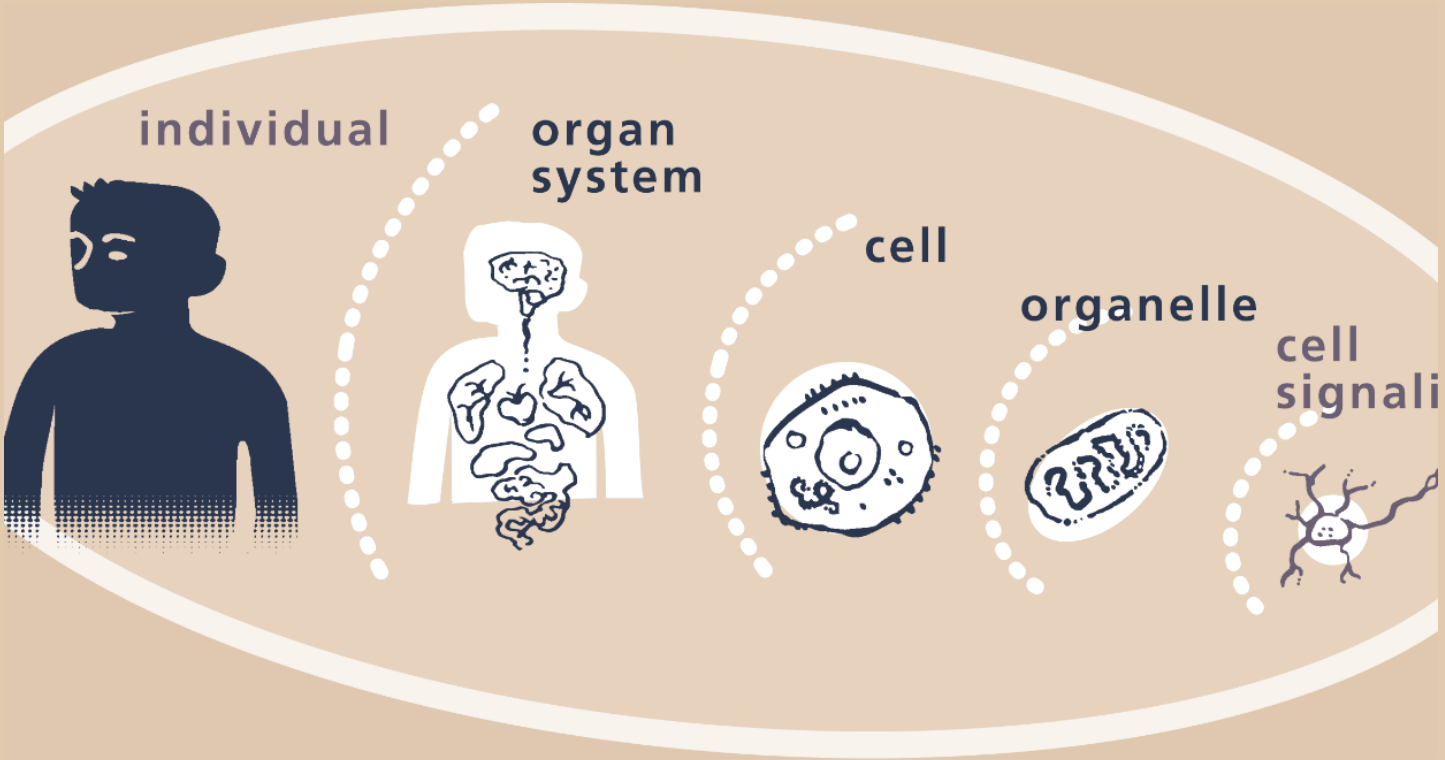
- ✓ A day laborer goes to the ER for a work related injury.
- ✓ Working on demolishing a firing range - lead level is 74 mcg/dl after 3 days on this job.
- ✓ Four other workers tested between 57 and 98 (all worked less than 2 ½ weeks).
- ✓ None had previously worked with lead.

Hipkins KL, Materna BL, Payne SF, Kirsch LC.,
Clin Pediatri 2004

Occupational/Take Home Exposures

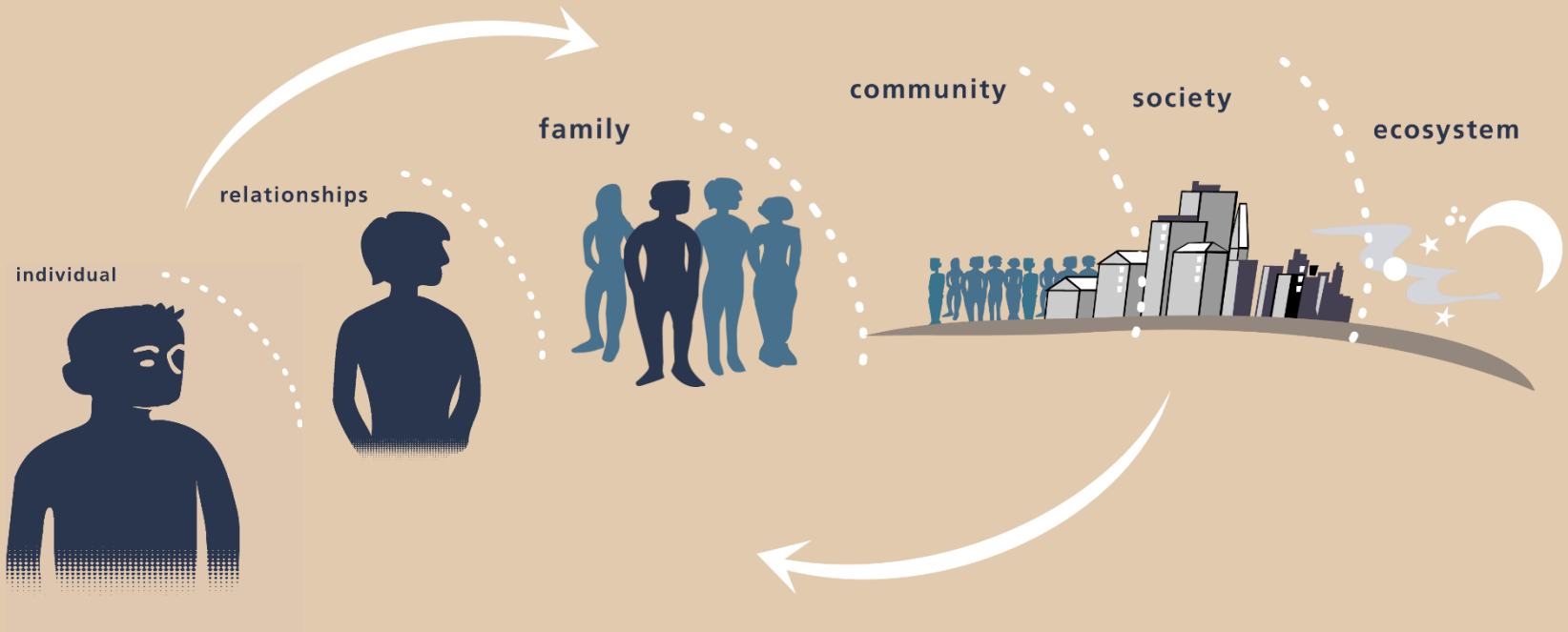
- ✓ 9 children of three workers tested between 13 and 34 mcg/dl. (highest 18 month old)
- ✓ Wife of one with symptoms and Pb level of 36 mcg/dl.
- ✓ Workers may bring home hazards on clothing, shoes, and body.
- ✓ In 2001-2002 year, 22% of California childhood lead poisoning cases had potential contribution from occupational sources.

Ecological Health Framework



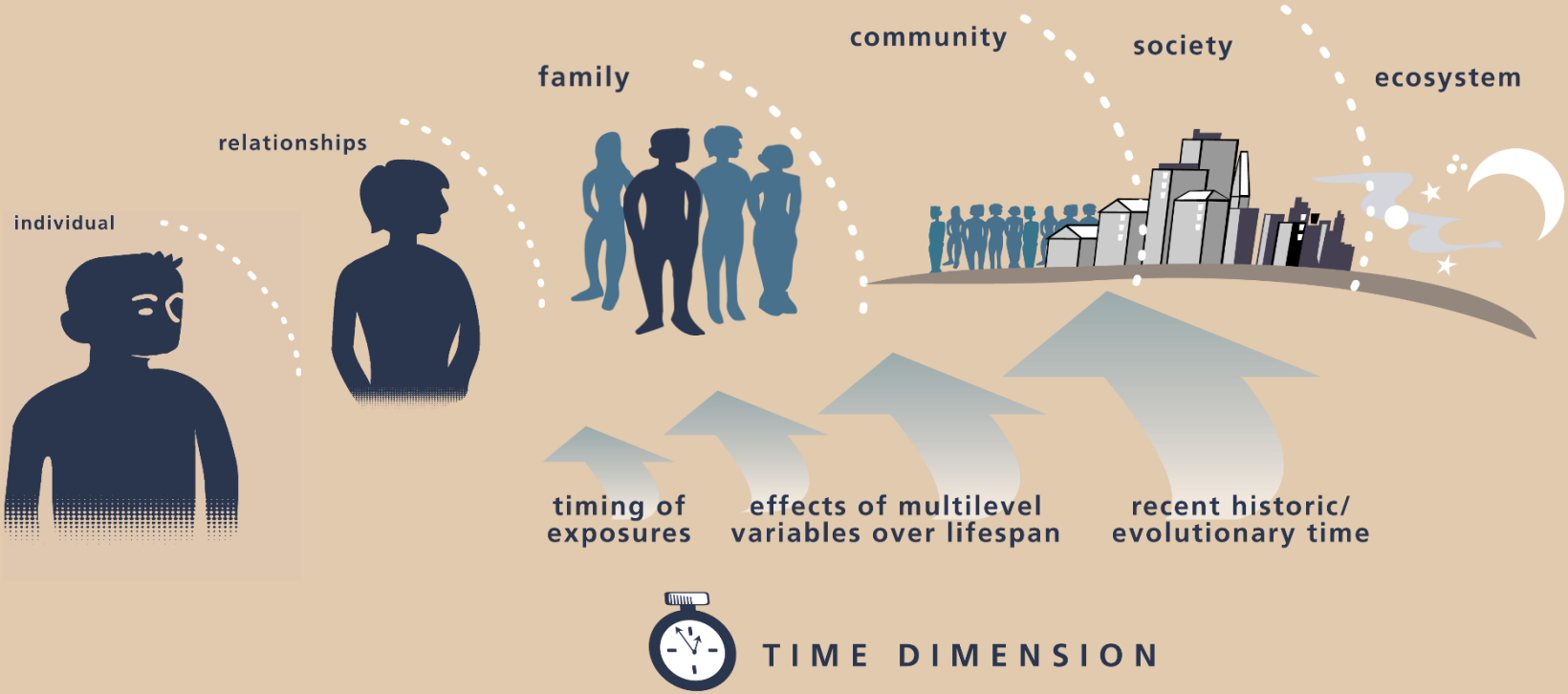
The ecological health framework extends to the sub-cellular level

Ecological Health Framework

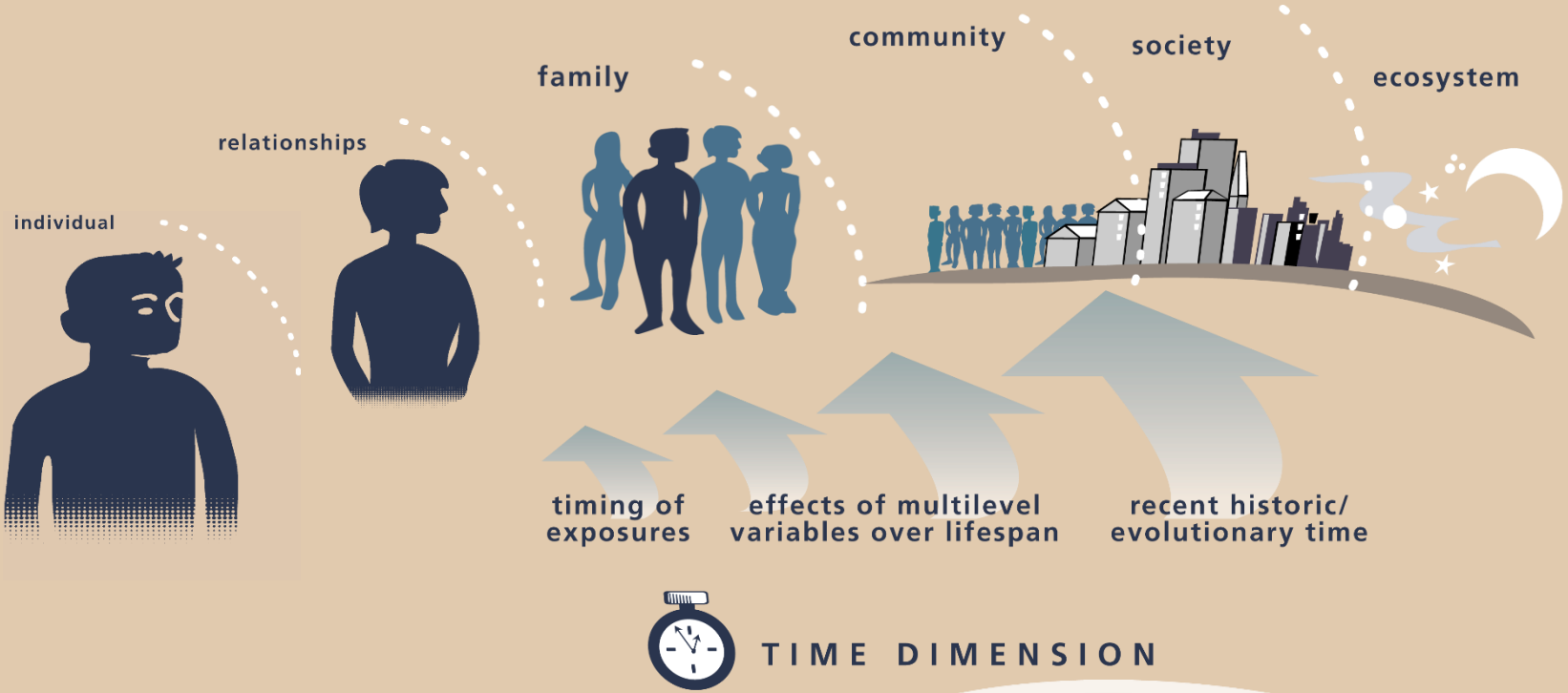


Not all of the factors that are important for health occur within the individual's genetic and biological makeup. Your interaction with your family, social support, and community can also impact your health.

Ecological Health Framework



Ecological Health Framework



Developmental origins of health and adult disease (DOHAD)

Life course approach

- Under-nutrition *in utero and infancy* resulted in changes in organ structure, function, and metabolism that were permanent
  - *adult lipid profiles linked to high cholesterol and hypertension*
  - *Impaired glucose regulation (insulin resistance)*
  - *Metabolic syndrome*

Wikipedia commons

Morris Water Maze

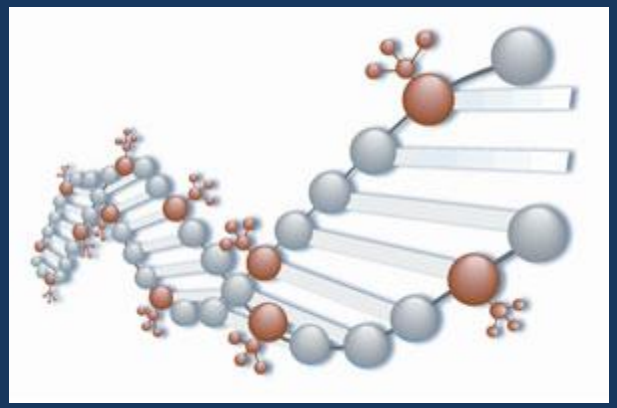
Wikipedia commons

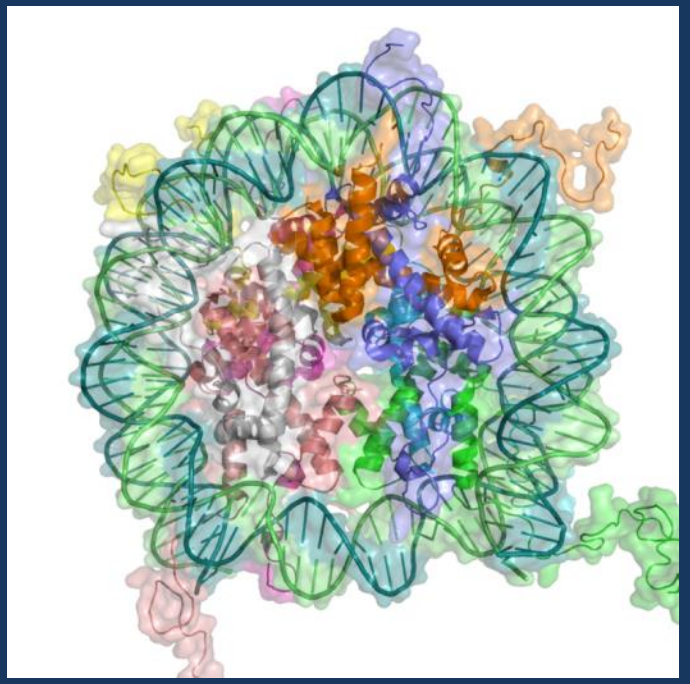
- Test of memory and spatial learning (adults)
- LG babies do better
  - Non-LG babies raised by LG mom's do better
- Adults born to mothers with prenatal stress but same post-natal environment do worse

It is a combination of genetics and pre / postnatal environment that determines function into adulthood

Genetics = Gene + Expression

Epigenetics

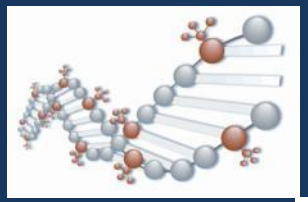




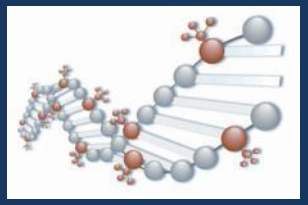
Wikipedia commons

Mother high licker groomer

pup



Increased Serotonin tone



less methylation GAD1

Demethylation of GR exon 1

Deacetylation of histones around GR

Increased NGF1-A activity hippocampus

Permanent increase in GR expression in hippocampus

exploratory, less fearful and stress reactive more cognitively intact in old age.

Adult

High hippocampal GR levels
High licker groomer behavior

Champagne and Meany, Behavioral Neuroscience 2007
Champagne et al., Journal Neuroscience 2008
Zhang et al, Journal Neuroscience Sept. 2010

Prenatal Stress – Effects in Adult Female Offspring

- Exposures
  - Relationship hardship (eg. Divorce)
  - Death/severe illness of someone close
  - Severe financial, car accident, refugee
- Impacts
  - Altered HPA axis response (Trier Social Stress and ACTH stimulation)
  - Bias to Th2, IL-4, IFN –gamma, IL6, IL10 production

Entringer et al Dev Psychobiol 2008
Entringer et al Hormones and Behavior, 2009

Allostasis – active process for adaptation (brain – body)

Limbic Plasticity effected by

- Parental resources
- Education
- Exposures/nurturance

Neuroendocrine
Immune
Autonomic
biomediators

Allostasis

Allostatic load

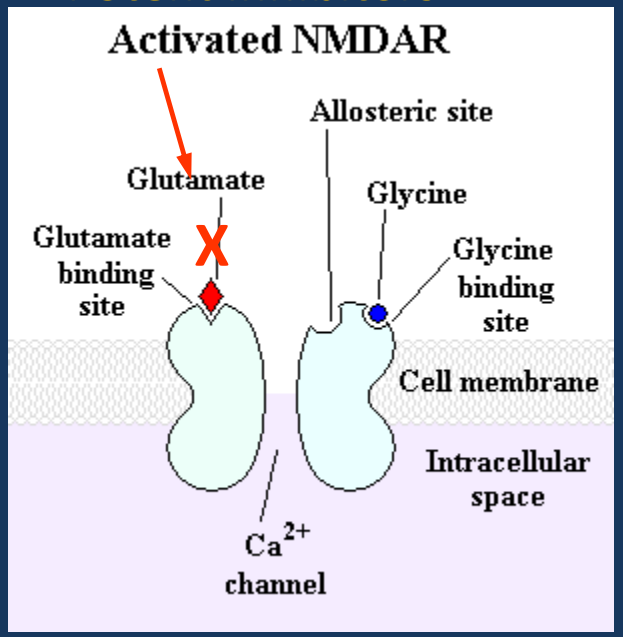
Adaptation

Costs: metabolic, cardiovascular, immune, behavioral dysregulation

Adapted from
McEwen and Gianaros, 2010

Lead/Stress Act by Similar Mechanisms
effects additive

Lead & Stress
Potent inhibitors



Wikipedia creative commons/public domain Delldot

- Learning and memory in hippocampus dependant on activation of NMDA glutamate receptors
- Stress or an environmental chemical (lead) impact same mechanism
- Both lead and stress impact HPA axis

Social Environment / chemical interaction

Guilarte Ann Neurology 2003
Neal Neurotoxicology 2011

Environmental enrichment enhances memory and learning /plasticity

Social environment

Social environment, exploration, play, spatial learning

Public domain wikipedia

- Early lead exposure results in decrease in learning, memory, NMDA r activity (BDNF)
- Enriched environment reduces leads cognitive impacts and normalizes NMDA r activity (BDNF)

Guilarte T, Ann Neurology, 2003

Environmental enrichment effective in ameliorating neuro-cognitive effects

Social environment

- Lead – association cognitive deficit <10mcg/dl only in "less advantaged", >10mcg/dl $\longrightarrow$ effect attenuated for "advantaged"*
- PCBs – (prenatal) negative effect only in "less optimal" parenting and home characteristics . Breastfeeding protective of attention at school age.
- ETS – greatest cognitive effect in those with "unmet basic needs in the areas of food, housing, and clothing"

Weiss and Bellinger, 2006
Rauh et al., Neurotox Teratol, 2004
Vreugdenhil et al. EHP 2002
Bellinger, Neurotox Teratol, 1988*, Miranda et al. 2008**
Jacobson and Jacobson, 2003

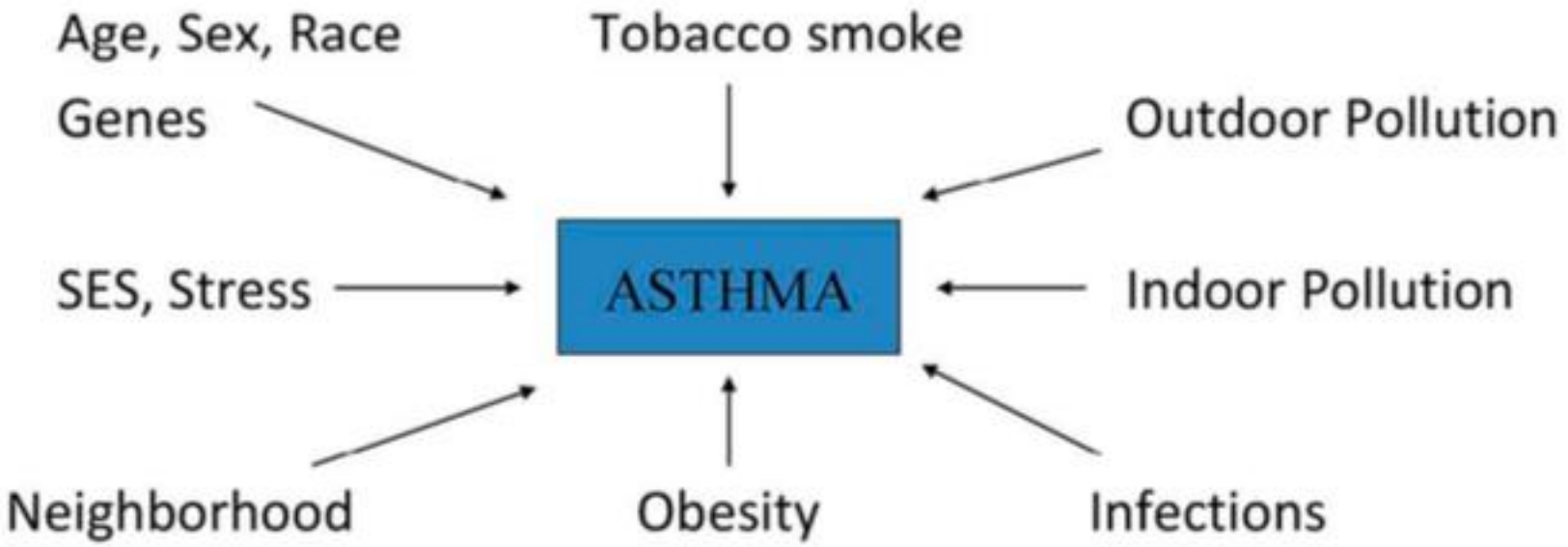
AAP Grand Rounds 6:16-17 (2001)

EPIDEMIOLOGY

Oral Succimer for Lead Chelation Does Not Lead to Better Neuropsychological Outcomes

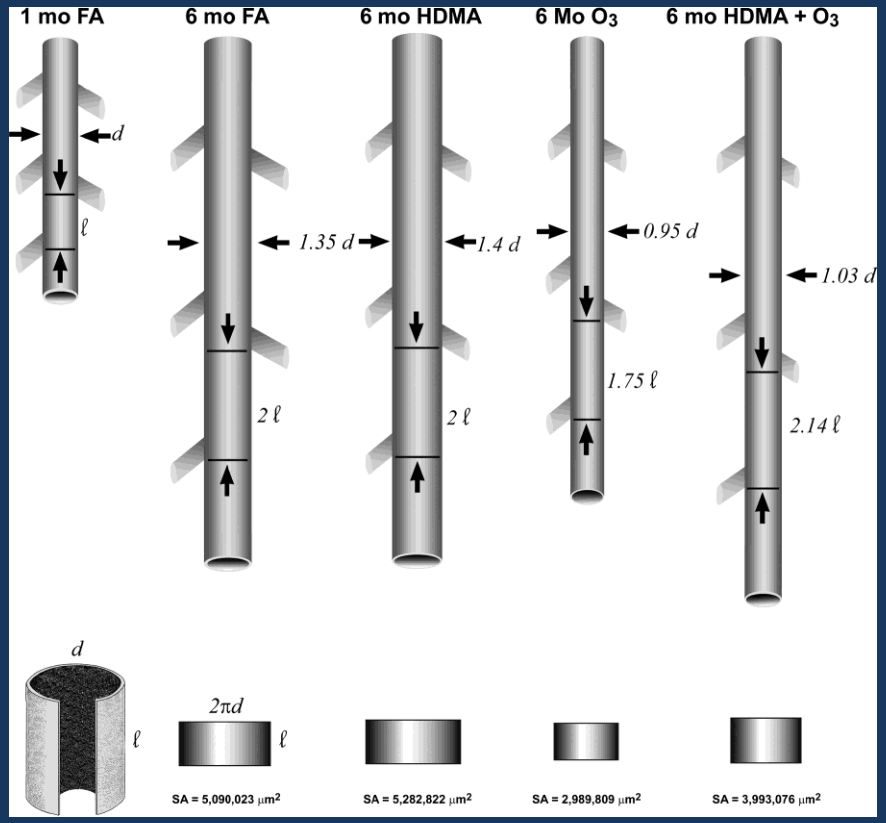
(children with 20 – 45 mcg/dl)

Risk Factors for Asthma



Ozone - postnatal exposure (+/-HDMA)

- Results permanently alters bronchioles (monkeys)
  - Fewer branches
  - Longer
  - Smaller diameter
  - Altered muscle bundle orientation
  - Change in innervation



Plopper et al. 2007

Community/Home Violence Link to Decrease in Lung Function

- Girls with home conflict

(highest tertile) had >5% decrease

in FEV_1 and FVC (smaller decrease in boys)

- Boys with exposure to community violence (highest tertile) had >5% decrease in FEV_1 and FVC
  - Independent of SES, SHS, birth wt., respiratory illness history

Suglia et al 2007 Psychosomatic Med

Asthma –
neurobiology underlying stress vulnerability

- Early life adversity (chronic stress) linked to:
  - Disturbed regulation of endocrine and autonomic processes
    - HPA axis; sympathetic adrenal medulllary system
      - May permanently program for exaggerated stress reponse
    - Alterations in Th1/Th2 balance
    - Alterations in inflammatory cytokines, IgE

Story of Health

RJ Wright Biological Psychology 2010

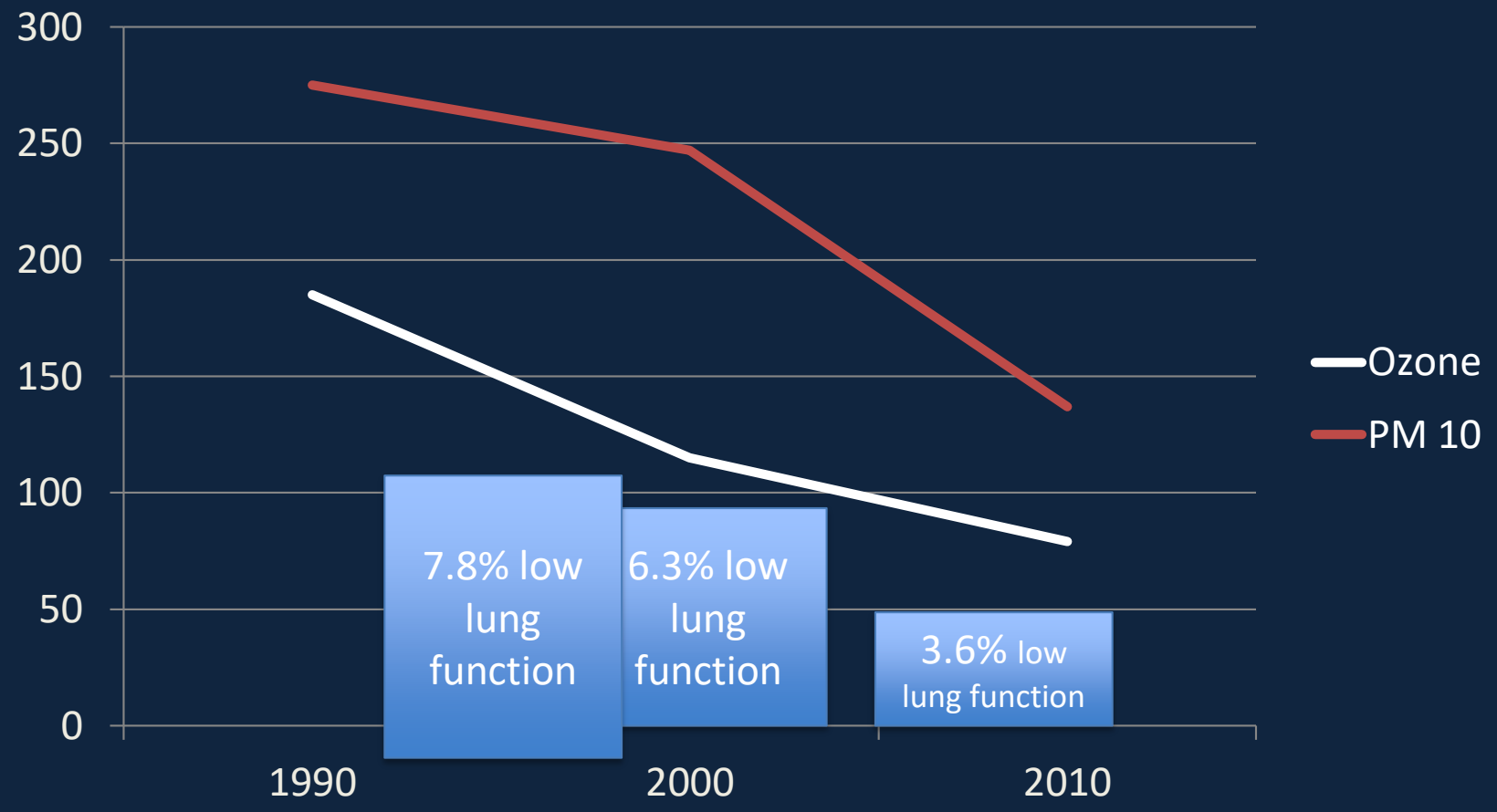
Air Pollution + Exposure to Violence (EOV) Synergistic Effects

- Birth cohort N=417
- $NO_{2\ measured}$
- Lifetime exposure to violence surveyed
  - Association between air pollution and asthma only in those with above median ETV
  - For lifetime residents (most accurate exposure)

    asthma OR 2.4 (1.48-3.88) for higher air pollution + ETV

Clougherty et al EHP 2007: Shankardas et al PNAS 2009
Shankardass, et.al. J Epidemiol Community Health 2011

Days exceeding CA standards for Ozone (1 hr) and PM10 (24 hr) (South Coast air basin Data California Air resources Board)



Gauderman WJ et al. N Engl J Med 2015;372:905-913 USC Children's Health Study

A portion of adult lung function is set by infancy

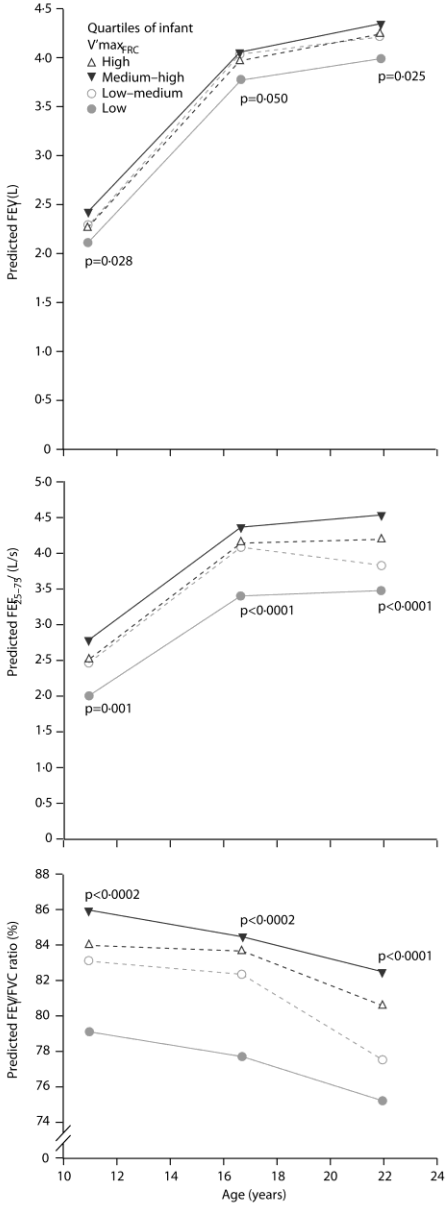
Up to 14% of adult lung function predicted by lung function at 2-3 mos
Stern 2007

FEV_1

FEF_{25-75}

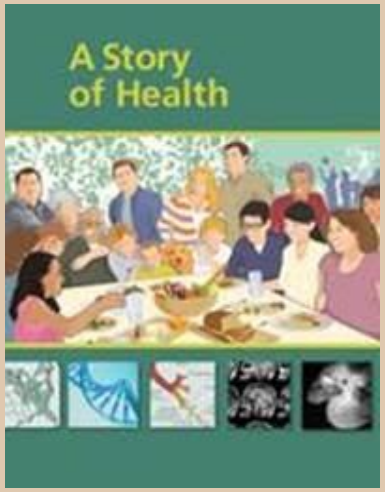
FEV_1/FVC ratio

Quartiles infant Vmax at functional residual capacity



Resources

- Western States PEHSU website (wspehsu.ucsf.edu)
  - Story of Health e-book (SOH).(https://wspehsu.ucsf.edu/for-clinical-professionals/training/a-story-of-health-a-multi-media-ebook/) Using the setting of a family reunion as a backdrop, SOH explores how various environments influence our health across the lifespan. Over 5,000 physicians, nurses, and health educators have already received CE credits from the CDC for completing chapters.



  - Pediatric Environmental HealthToolkit is a combination of easy-to-use reference guides for health providers and user friendly health education materials on preventing exposures to toxic chemicals and other substances that affect infant and child health. The new mobile device ready version to be posted soon. Online intro for CE at: https://www.atsdr.cdc.gov/emes/health_professionals/pediatrics.html

Coming soon!