Developmental exposures, kidney function, and biomarkers of cardiorenal signaling

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Mount Sinai

Washington, D.C.

- National Capitol
- Population: 6.2 million

Charlottesville, VA.

- Population: 48,000

BIOMEDICAL ENGINEERING

Madison, WI.

- Population: 260,000

COLLEGE OF ENGINEERING
UNIVERSITY OF WISCONSIN-MADISON

Chapel Hill, NC.

- Population: 65,000

UNC
GILLINGS SCHOOL OF
GLOBAL PUBLIC HEALTH

New York, NY.

- Population: 18.8 million

Mount Sinai School of Medicine

Lexington, KY.

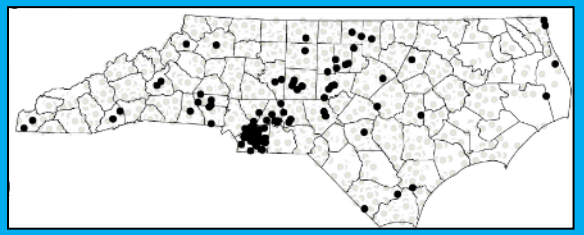
- Population: 320,000

Toxic metals and early life health effects

1. **Metals are widespread toxicants**

2. Early life exposures may program renal health

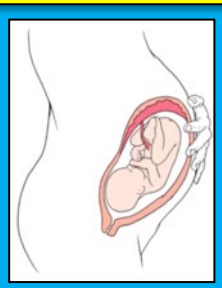
3. Novel kidney biomarkers

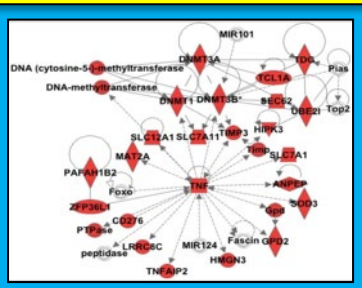


Exposure

Health Effects

Biomarkers

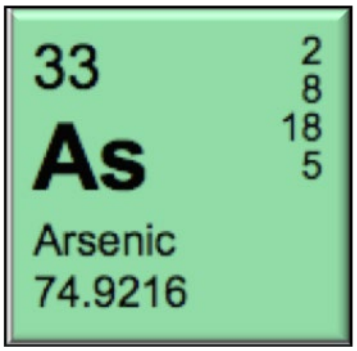


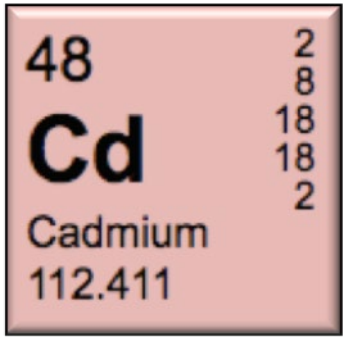


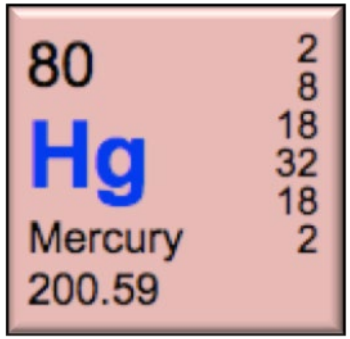
Toxic metals

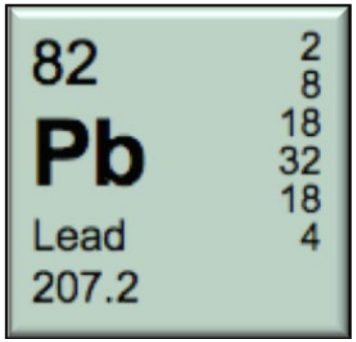
What are they? Are we exposed?

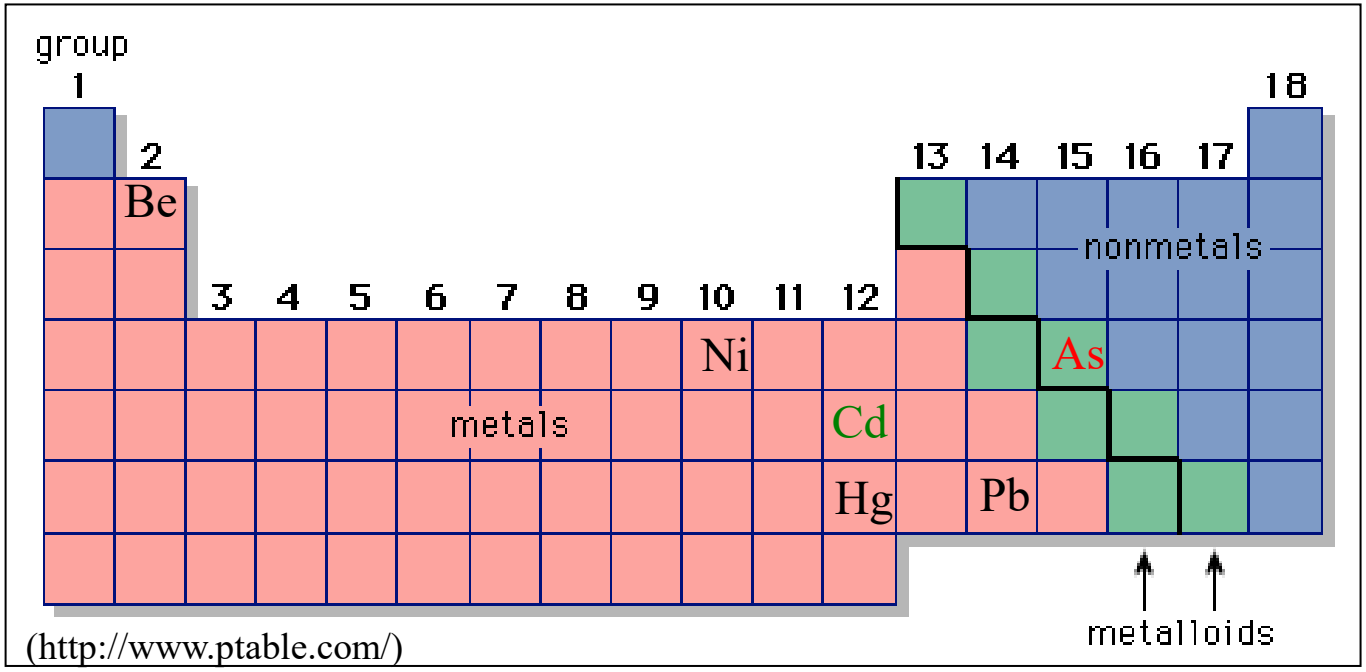
Toxic metals have no biological role



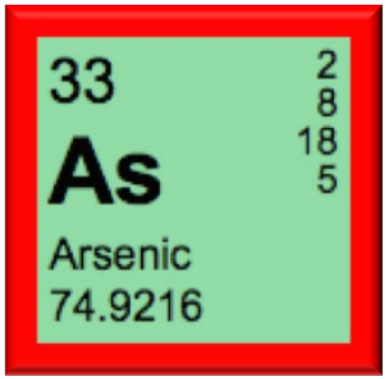


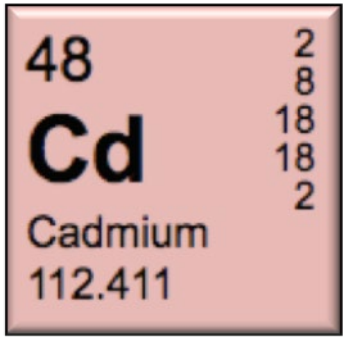


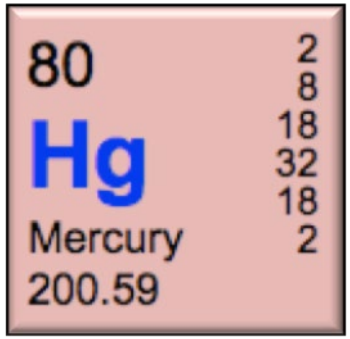


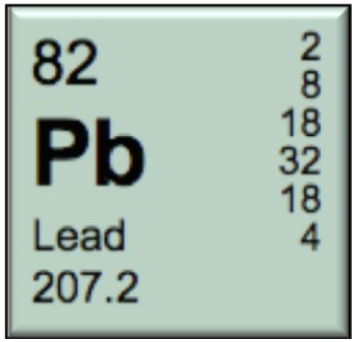


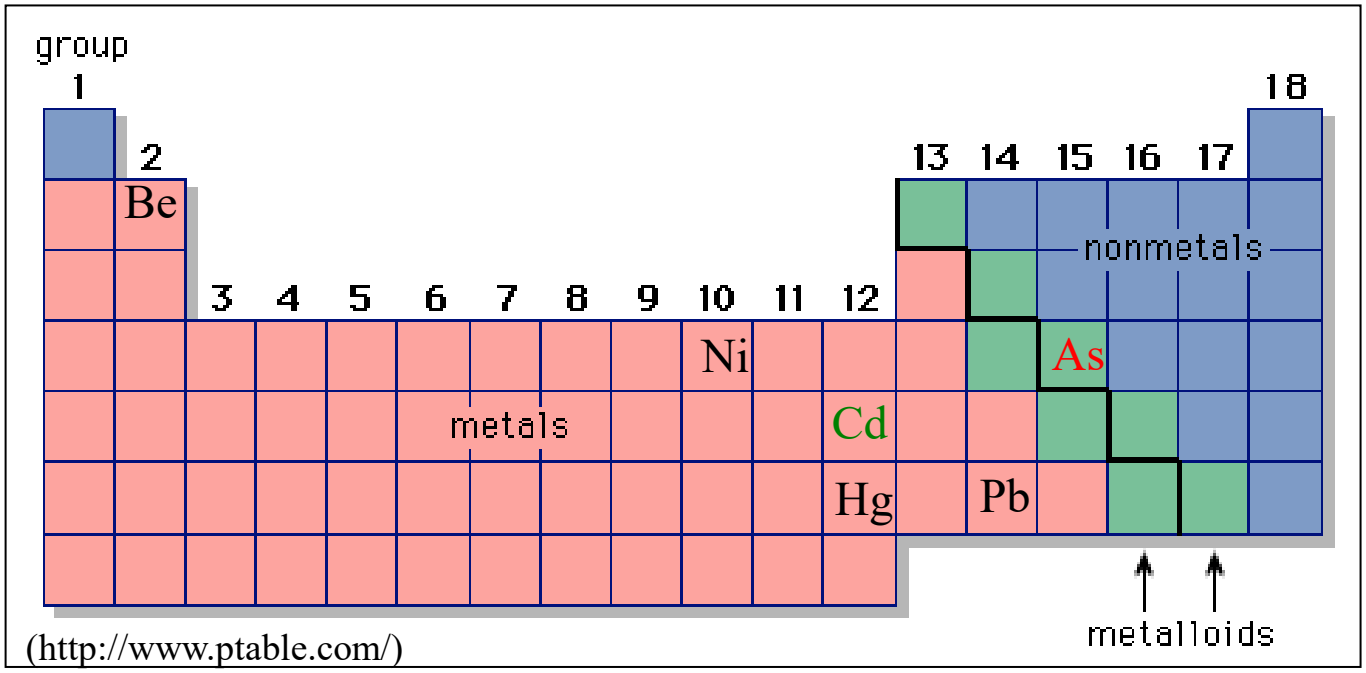
Toxic metals have no biological role







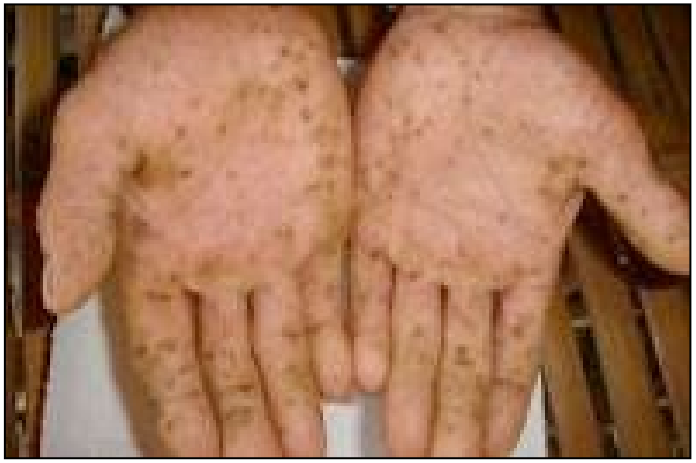




Arsenic

- 20th most abundant metal(oid) in the Earth's crust
- A known human carcinogen (bladder, lung, kidney, and skin)

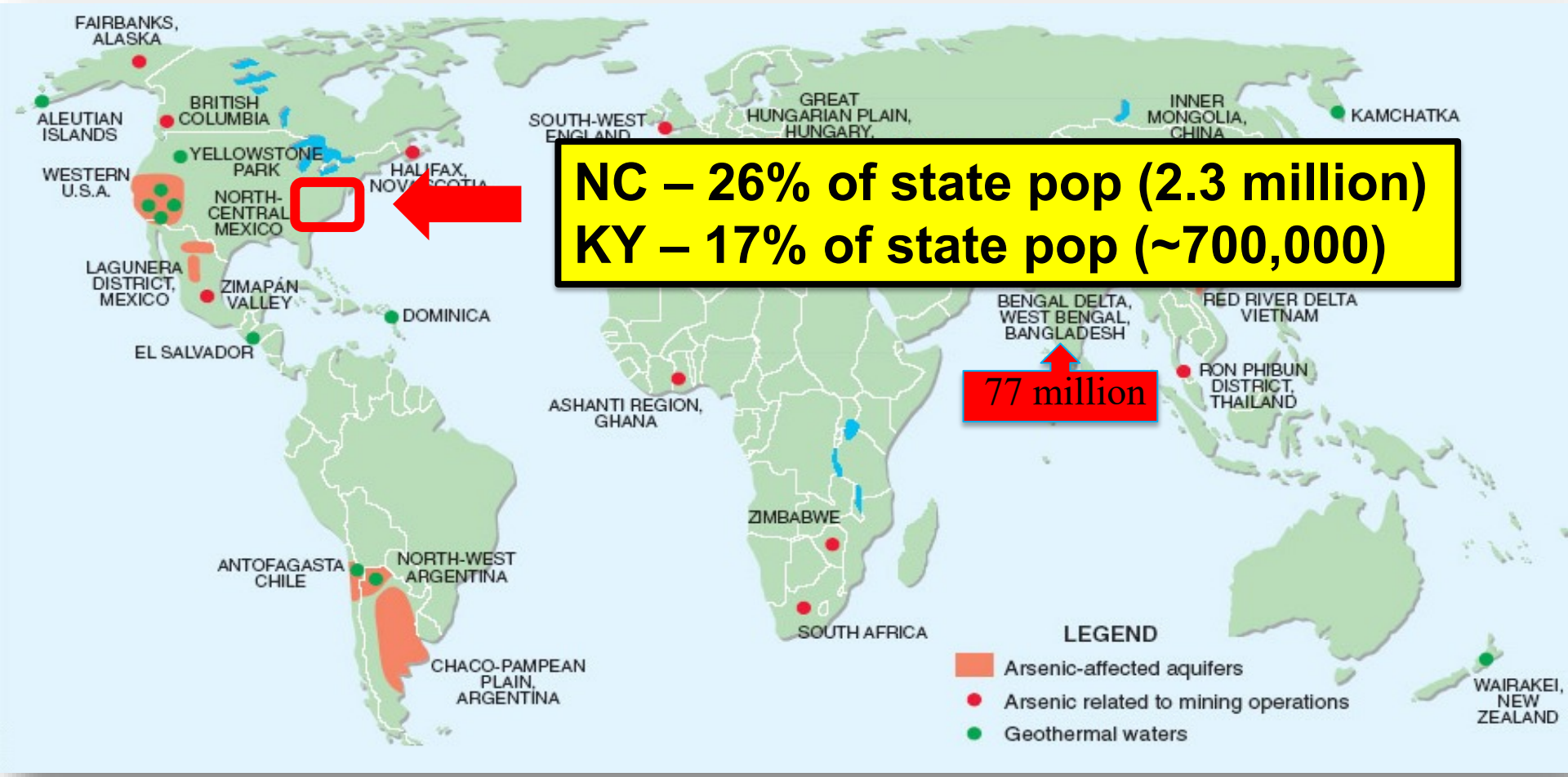
- Also non-cancer endpoints: cardiovascular disease, diabetes, neurological abnormalities, and skin hyperpigmentation (NRC, 2001)



- Sources: Pesticides, treated wood, coal emissions, diet, and drinking water.

Arsenic occurs in drinking water worldwide

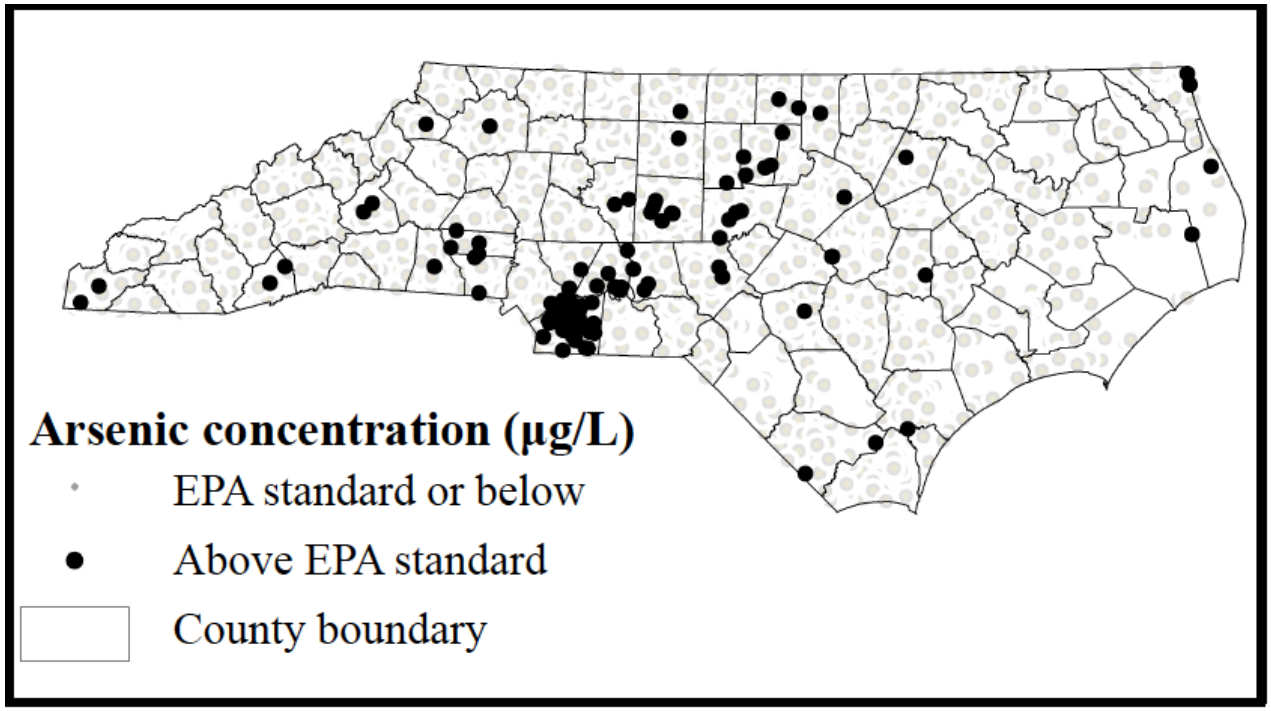
Arsenic occurs in drinking water worldwide



NC – 26% of state pop (2.3 million)
KY – 17% of state pop (~700,000)

Study goal: To comprehensively determine spatial trends of toxic metals in NC

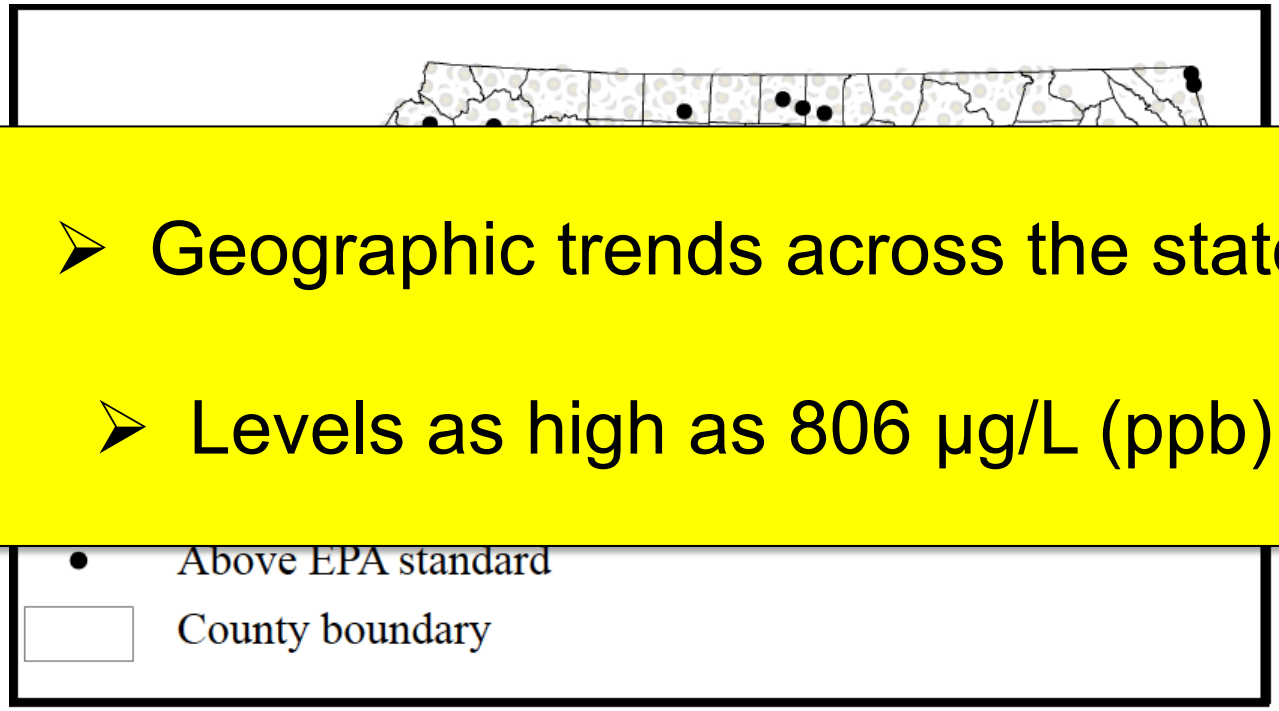
Largest study of metals in private wells in NC (60,000 wells)



- >7,700 had detectable arsenic (12%)
- Over 1,500 wells exceeded 10 µg/L (the EPA standard)

Sanders et al. *Env Int* 2012

Arsenic levels elevated in NC wells

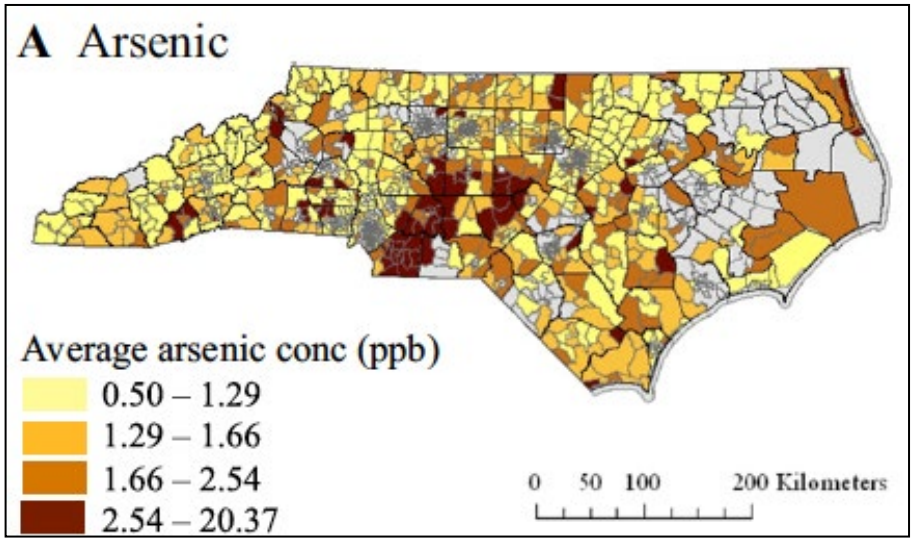


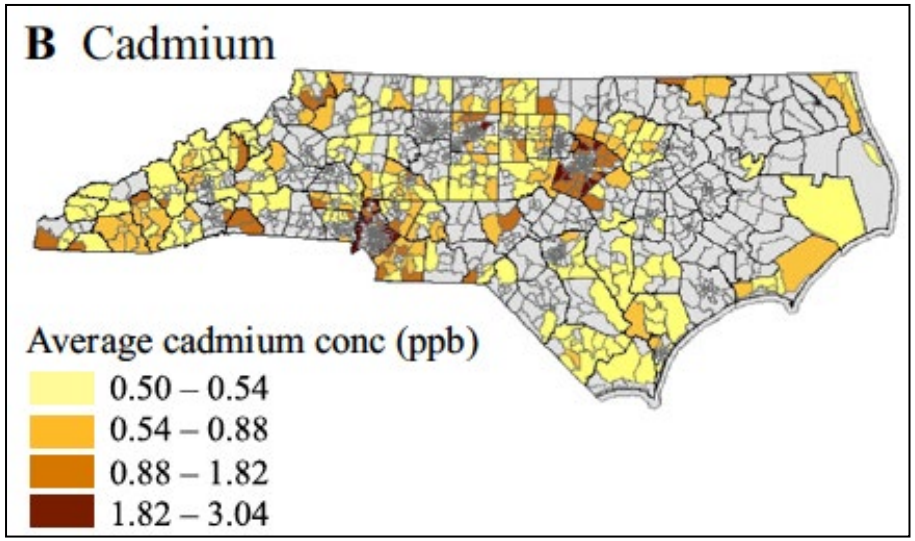
- Geographic trends across the state
- Levels as high as 806 µg/L (ppb)

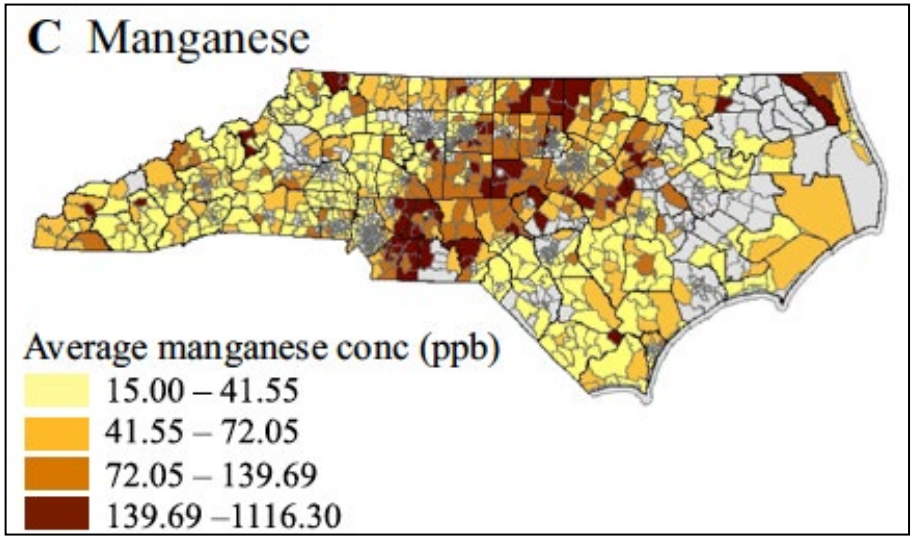
- >7,700 had detectable arsenic (12%)
- Over 1,500 wells exceeded 10 µg/L (the EPA standard)

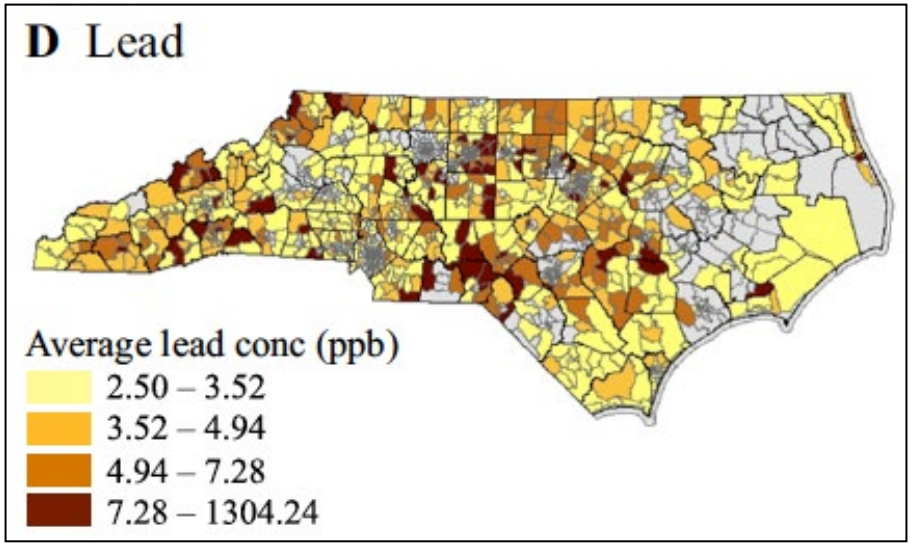
Sanders et al. *Env Int* 2012

Spatial patterns of metals in NC









Sanders et al. *BMC Pub Health* 2014

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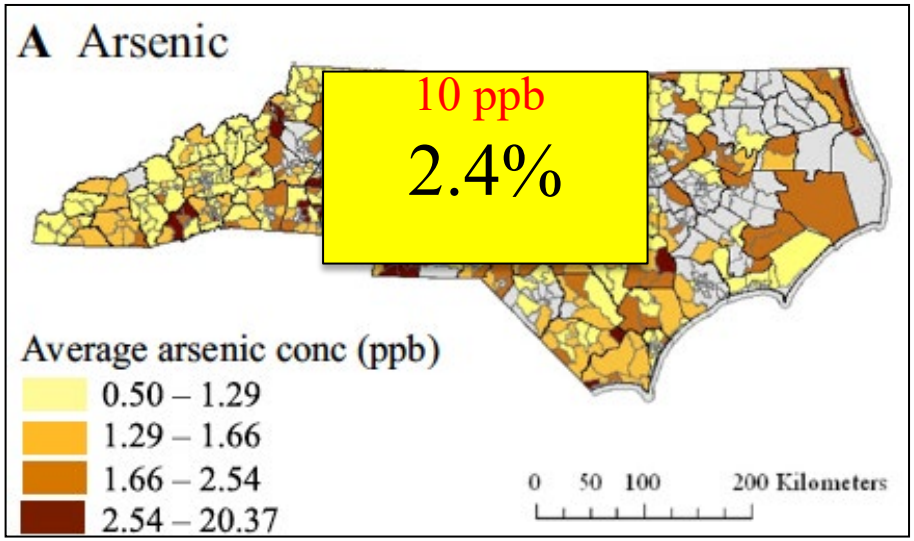
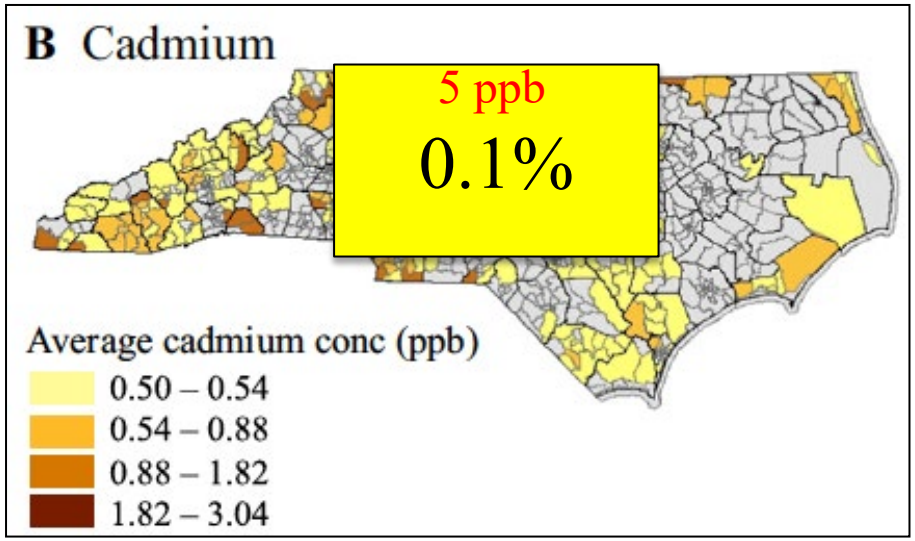
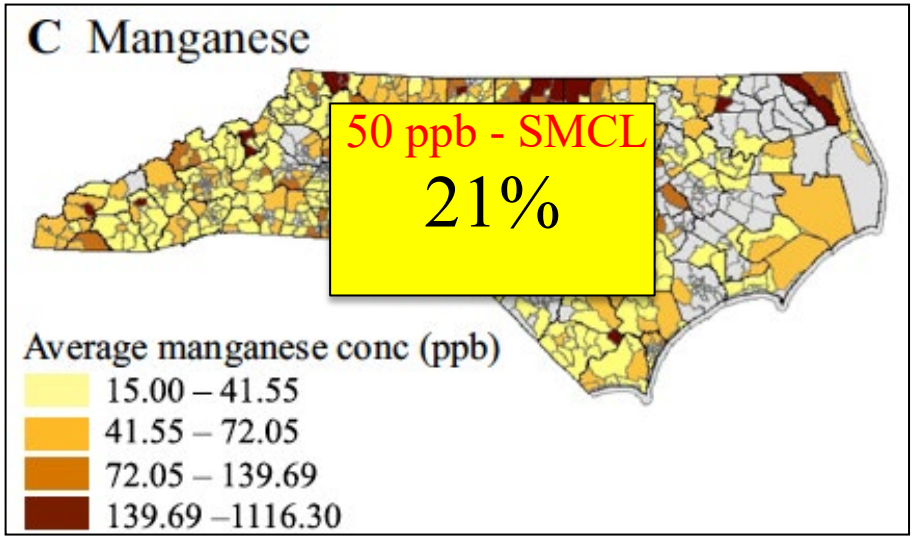
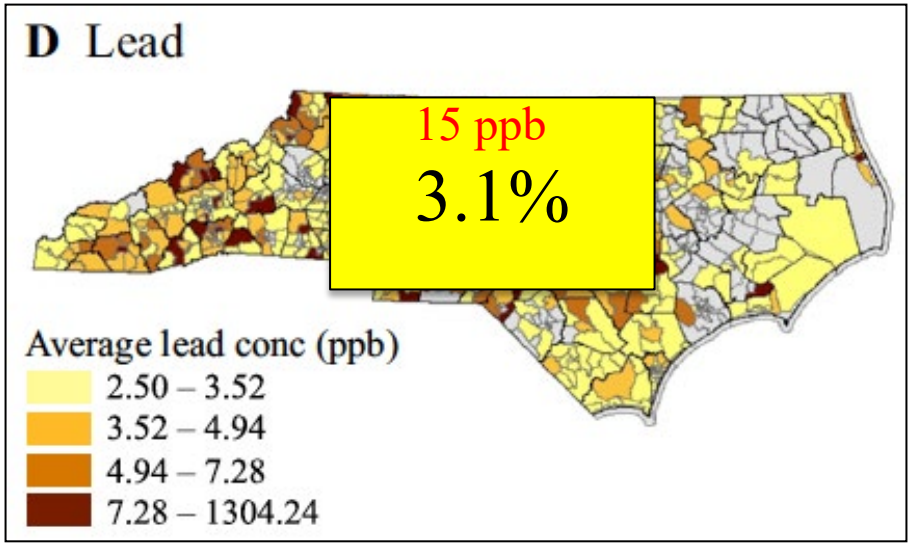


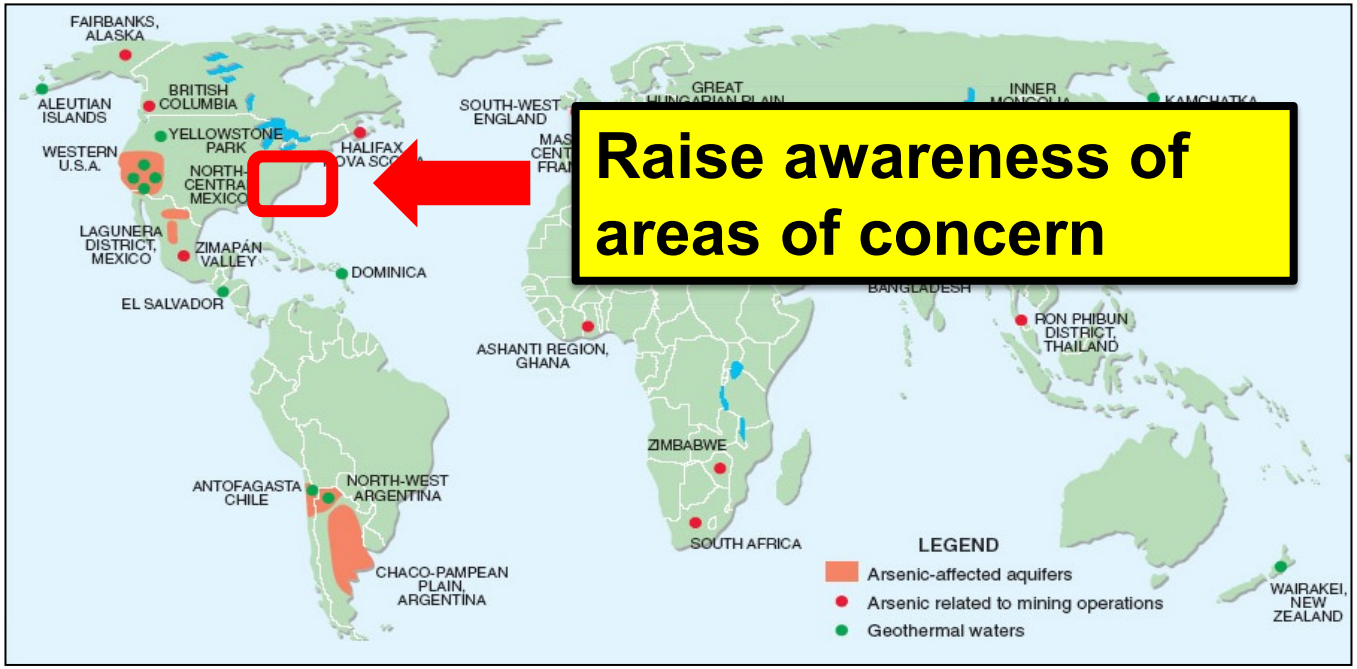






Sanders et al. *BMC Pub Health* 2014

Public health relevance



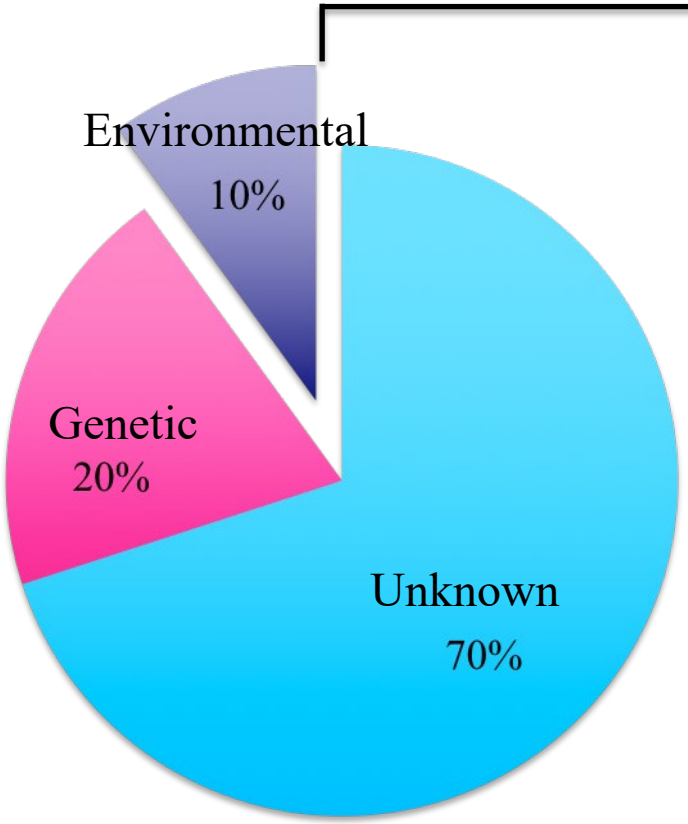
Raise awareness of areas of concern

Individuals relying on private wells for drinking water should have their well water tested.

Toxic metals

What are they? Are we exposed?

Metals are understudied environmental toxicants in human populations



Known causes of birth defects

Metals rank among the top 10 in the priority list of hazardous substances

2019 RANK	SUBSTANCE NAME
1	ARSENIC
2	LEAD
3	MERCURY
4	VINYL CHLORIDE
5	POLYCHLORINATED BIPHENYLS
6	BENZENE
7	CADMIUM

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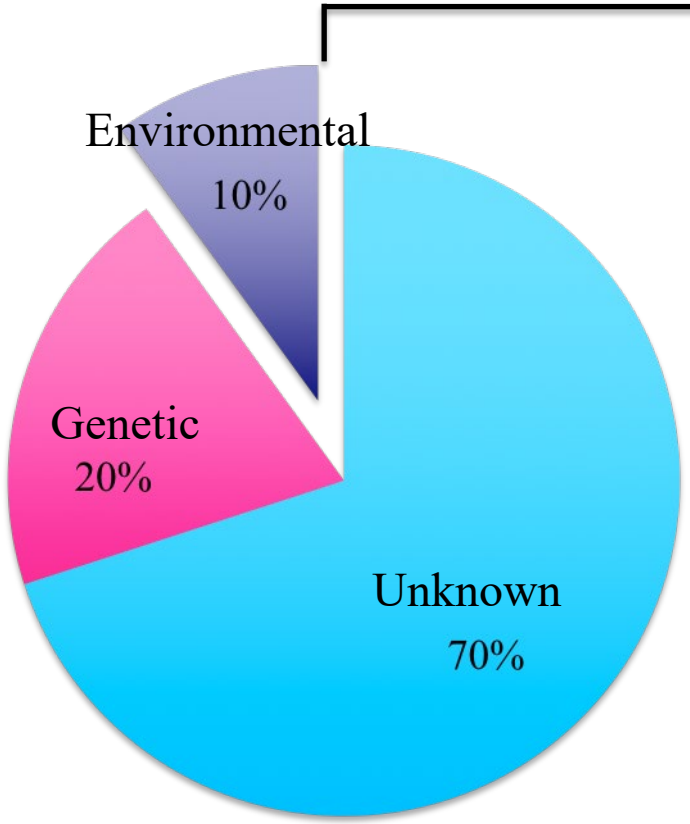


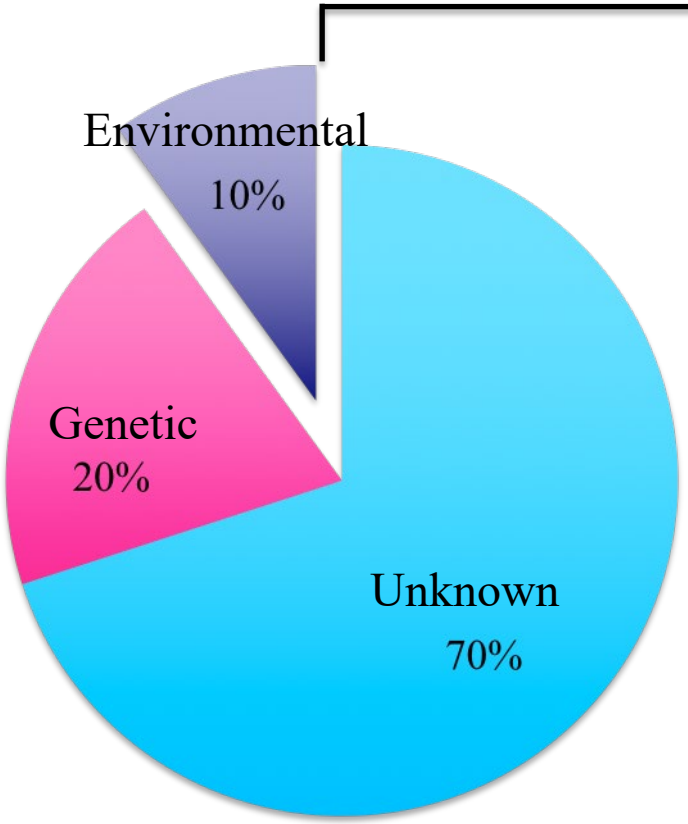
Known causes of birth defects

Evidence of metal exposure in NC pregnant women (n=211)

Metal	% detected
Arsenic	65.7
Cadmium	57.3
Mercury	63.8
Lead	100

Sanders et al. *PLoS ONE* 2012

Metals are understudied environmental toxicants in human populations



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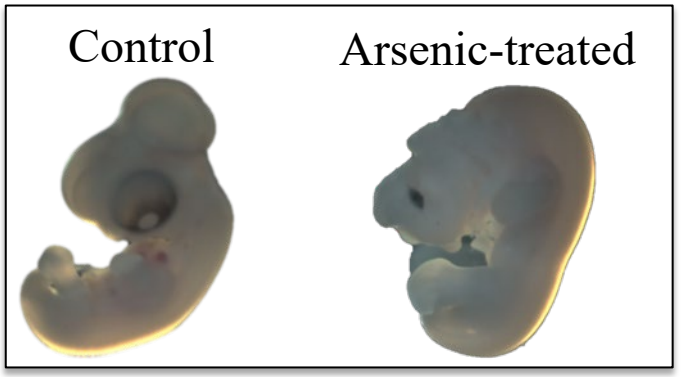
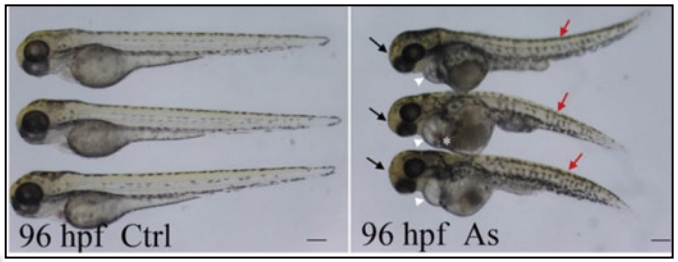
Evidence of metal-associated defects

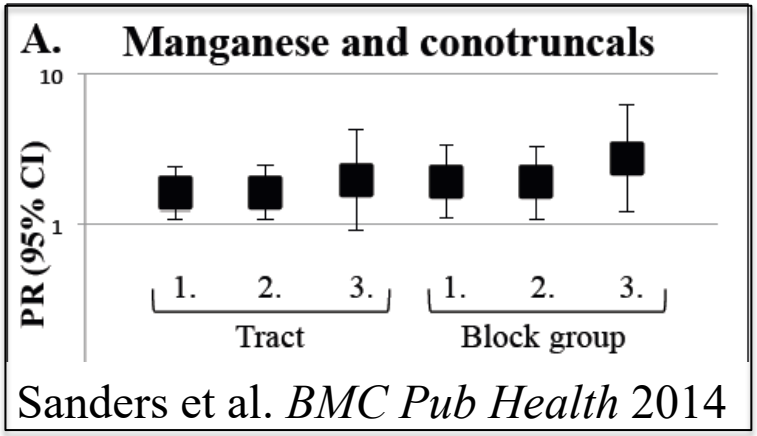
- Metals cause gross morphological defects
- Arsenic- and cadmium-induced heart defects
- Epidemiological links with metals in drinking water



Ahir, Sanders et al. *EHP* 2013



Li et al. 2009



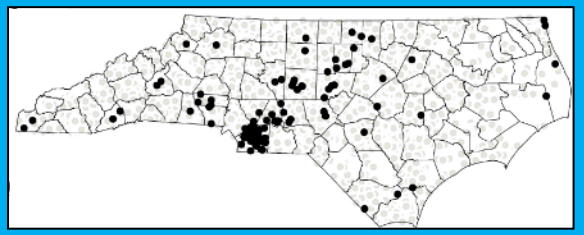
Sanders et al. *BMC Pub Health* 2014

Toxic metals and early life health effects

1. Metals are widespread toxicants

2. Early life exposures may program renal health

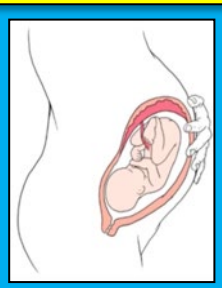
3. Novel kidney biomarkers

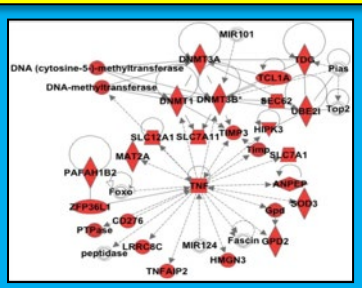


Exposure

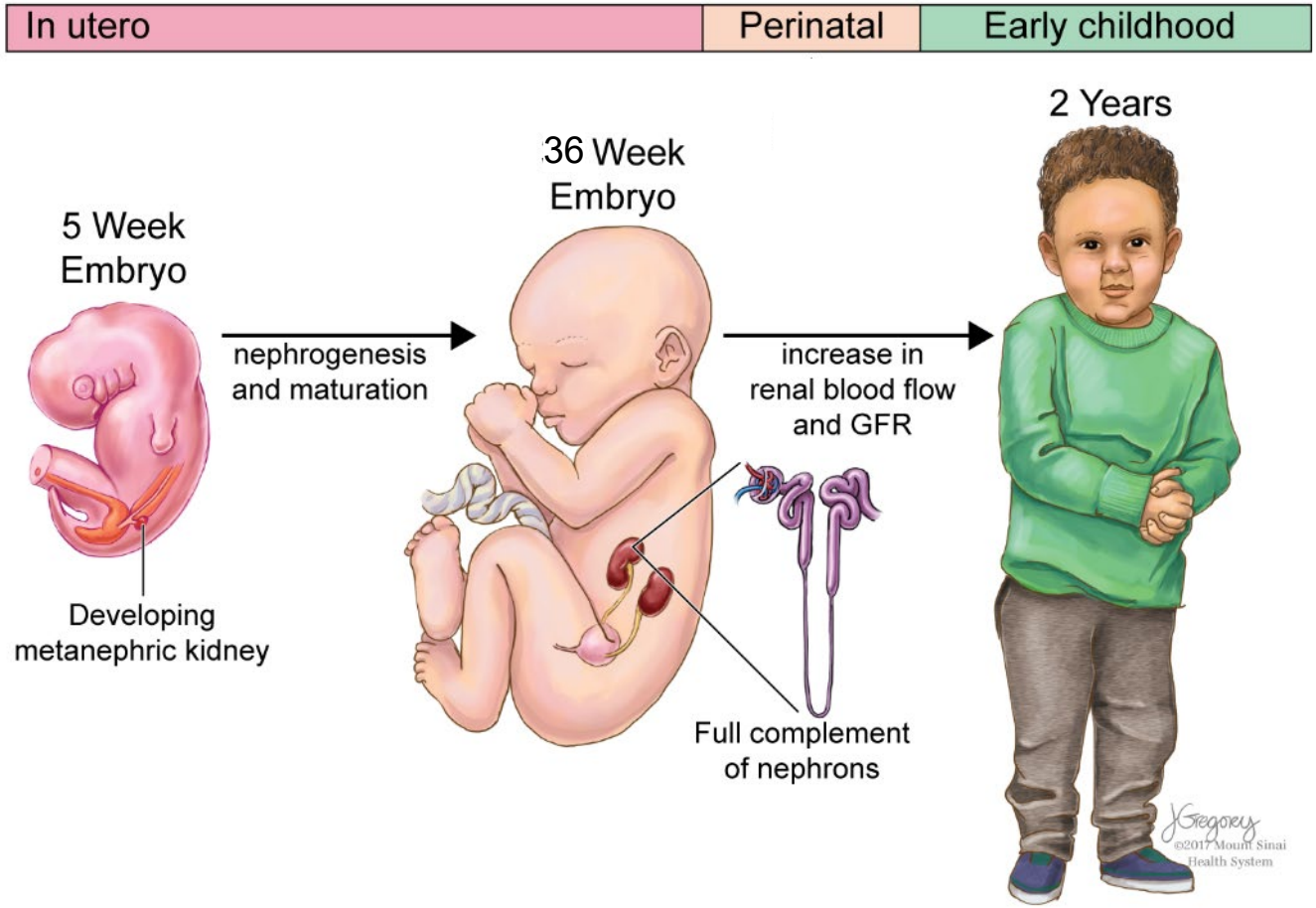
Health Effects

Biomarkers





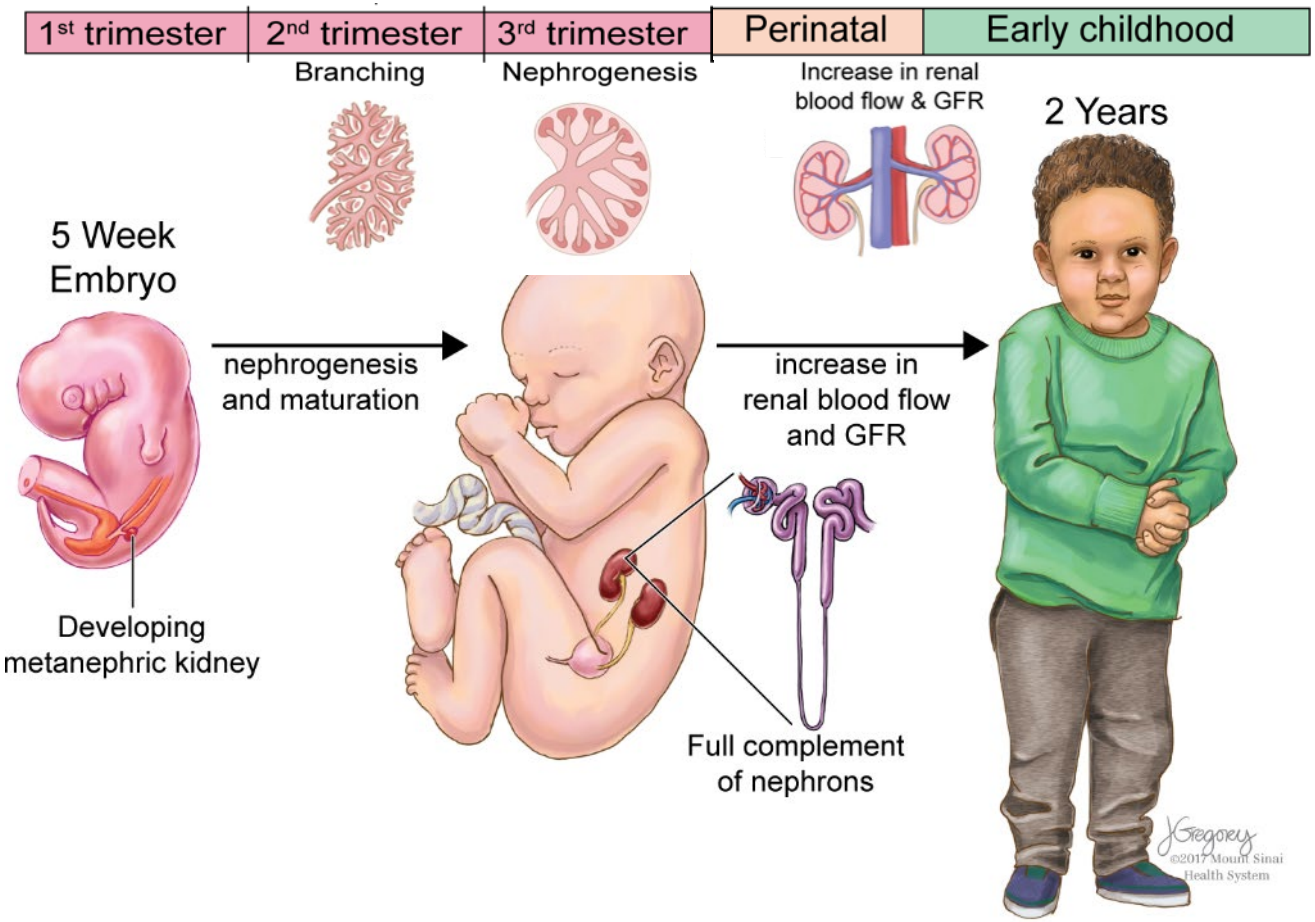
Critical windows of kidney development



- Environmental insults during susceptible periods of renal development may program later life kidney disease or hypertension

Sanders et al. *Ped Res* 2018

Critical windows of kidney development



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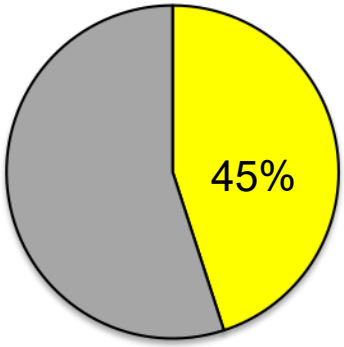
Sanders et al. *Ped Res* 2018

Public health need

- How the ~~fetal~~ **perinatal** kidney environment contributes to the origins of CKD and adult disease is a critical research need

- Identification of early life risk factors and intervention wield immense potential in clinical and public health practice.
  - Hypertension
  - Chronic kidney disease
  - End-stage renal disease



>100 million US adults

AHA 2018

Toxic metals are paradigm nephrotoxicants

- Nephrotoxic metals: As, Pb, Cd, Cr, and Li
  - Prevalent environmental exposures, occur concomitantly, mixed sources
  - Proximal and glomerular toxicants
  - Associated with adult chronic cardiorenal diseases

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Combined exposure to lead, cadmium, mercury, and arsenic and kidney health in adolescents age 12–19 in NHANES 2009–2014

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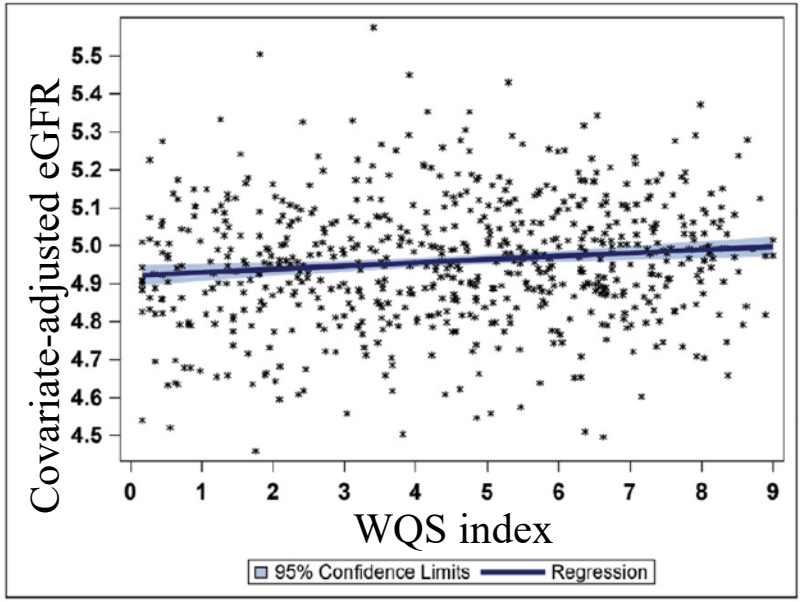
[a] Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[b] Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Metal mixtures and adolescent kidney parameters

- NHANES 2009-2014
- Metals assessed in **urine** and blood (n=2709)
- Average age: 15.4 years (n=2709)
- Outcomes: estimated glomerular filtration rate (eGFR), BUN, albumin

Metal Mixture	
Hg	61%
Cd	17%
As	13%
Pb	9%



Sanders et al. *Env Int* 2019

Toxic metals are paradigm nephrotoxicants

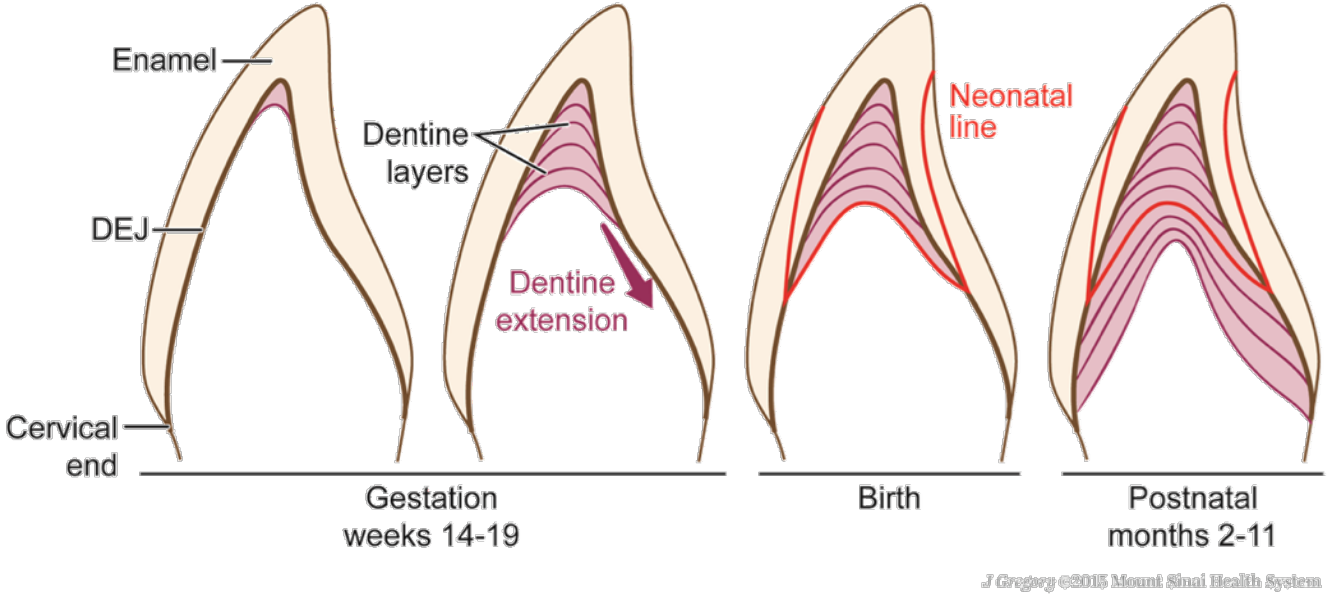
- Nephrotoxic metals: As, Pb, Cd, Cr, and Li
  - Prevalent environmental exposures, occur concomitantly, mixed sources
  - Proximal and glomerular toxicants
  - Associated with adult chronic cardiorenal diseases

- Toxic metals can disrupt:
  - nephrogenesis
  - primary developmental processes vital for maintaining nutrient and waste product homeostasis

- Research need: to fully account for nephrotoxic exposures that *predate* the onset of subclinical kidney disease.
  - How can we assess metal exposure longitudinally with **weekly** temporal resolution?
    - Tooth biomarker

Why Teeth?

- Commence development prenatally
- Grow incrementally (growth rings like a tree)
- Non-invasive collection from 6 to 13 years of age
- Hydroxyapatite incorporates many chemicals



[Slide from Dr. C. Austin]

Study Aim

To evaluate the relationship between perinatal toxic metals exposure assessed longitudinally in our tooth biomarker with children's kidney function at ages 8-10 years old.

a) Individual metals
b) Metal mixtures

PROGRESS birth cohort

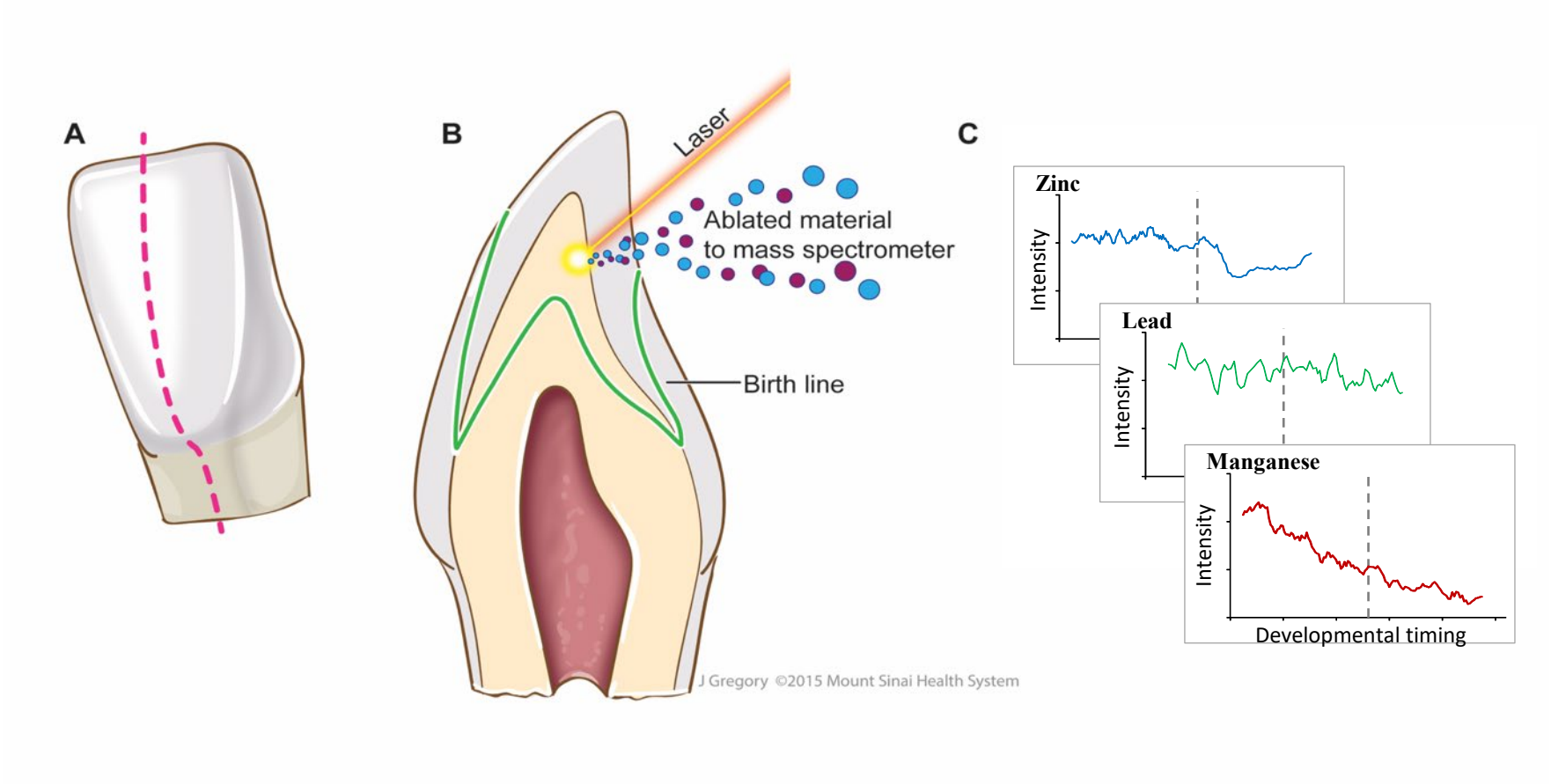
- Mexico City
- Enrolled pregnant women during the 2nd trimester (n=948)
- Infants followed into childhood (~10 yrs)
- ~700 active mother-child pairs
  - Preliminary subset: n = 253

Icahn School of Medicine at Mount Sinai

Instituto Nacional de Salud Pública

INPer

Methods



Arora et al. *Nat Comm* 2017

Methods

- Estimated glomerular filtration rate (eGFR) assessed by serum cystatin C:
  - $eGFR_{CKiD\ 2012}$: $70.69 * (Cystatin\ C)^{-0.931}$

- We used reverse distributed lag models (rDLMs) to examine time-varying associations between weekly perinatal metal concentrations and children's eGFR
  - adjusting for child's age, sex, BMI z-score, SES and prenatal exposure to tobacco smoke in the home.

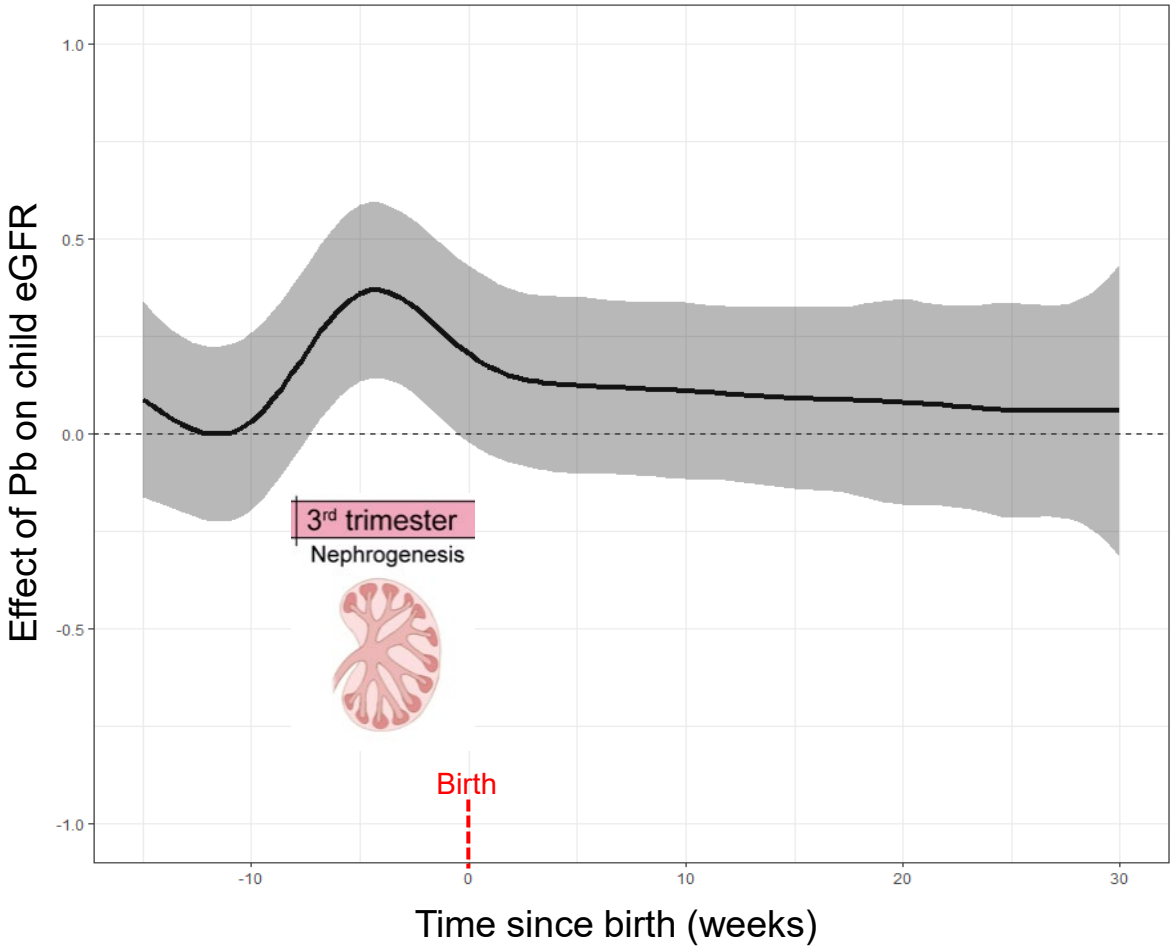
- To examine effects of time-varying metal mixtures, we then applied lagged Weighted Quantile Sum (WQS) regression.

Schwartz et al. *Kidney Int* 2012
Gennings et al. *Env Res* 2020

Demographics (n=253)

	Arithmetic mean (SD) or Percentage of Sample
Age, years	9.6 [9.1, 10.3]
Male sex, %	51%
Socioeconomic status	
Low	55%
Medium	36%
High	9%
Smoke exposure in the home (2T)	30%
Child BMI	
Normal Weight	53%
Overweight	24%
Obese	23%
$eGFR_{CysC2012}$ (mL/min/1.73m^2)	120.7 [92.2, 149.1]

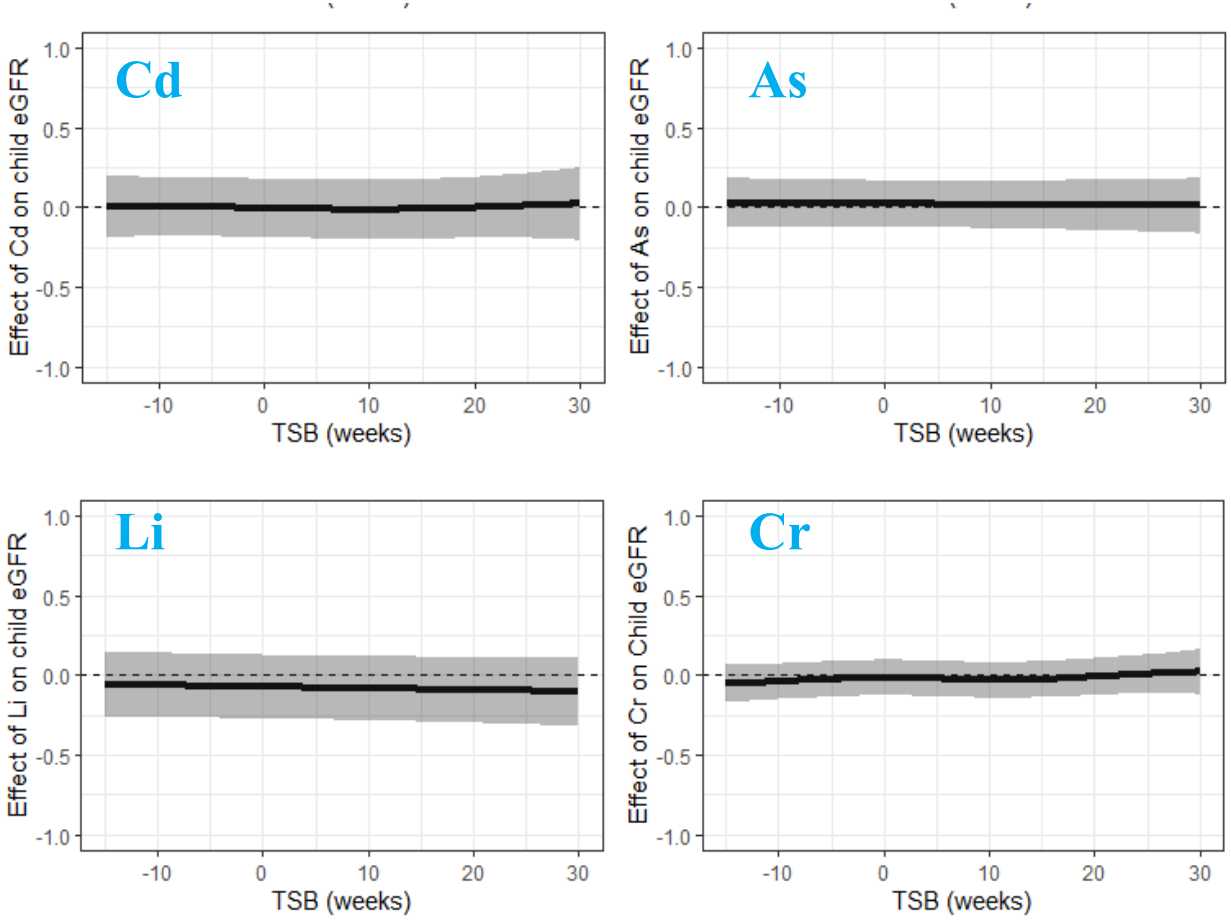
Results



Prenatal Pb exposure during the 7 weeks prior to birth was associated with increased eGFR at 8-10 years.

Unpublished data.

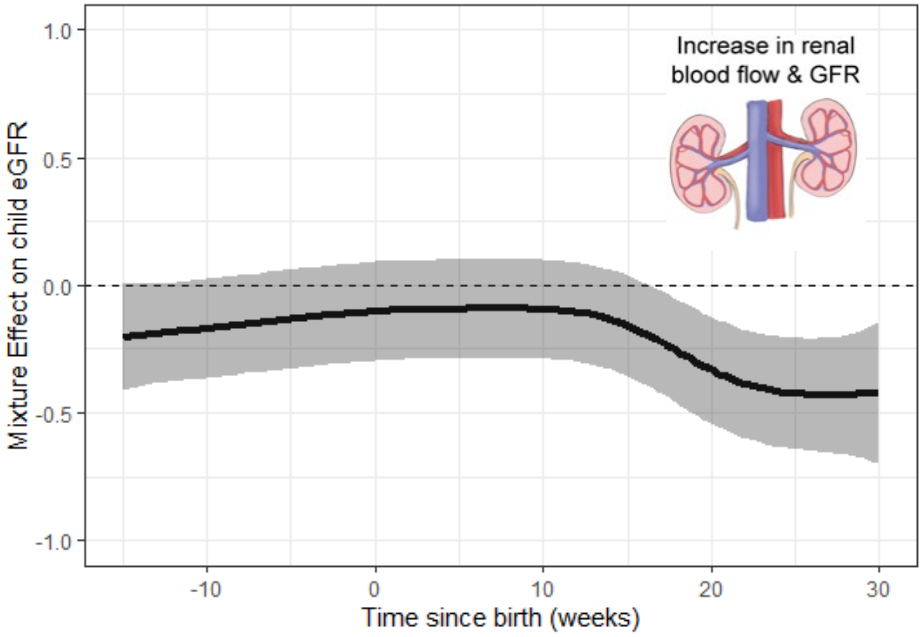
Results

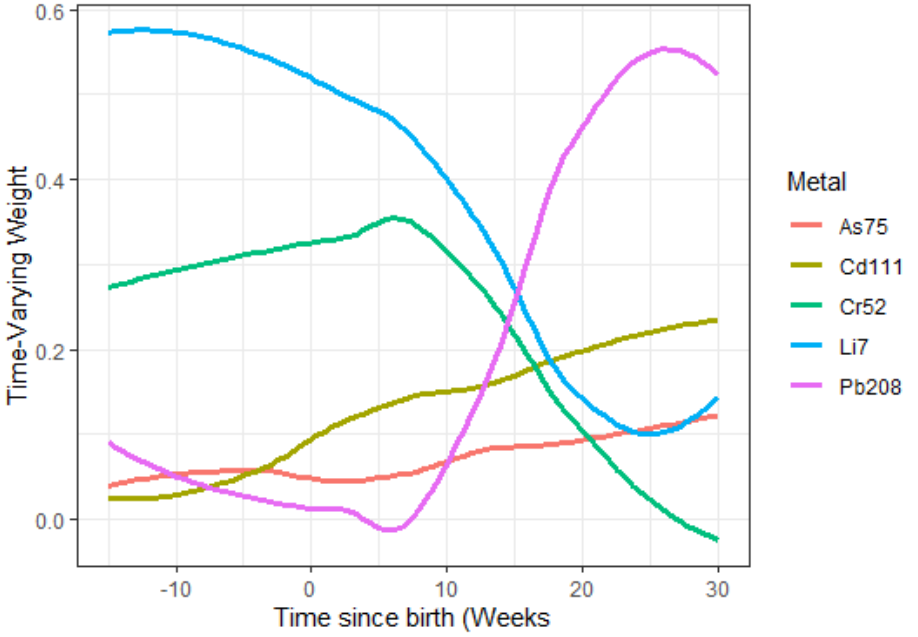


No significant associations were observed between single-metal Cd, As, Li, or Cr exposures and eGFR at age 8-10 years.

Unpublished data.

Results





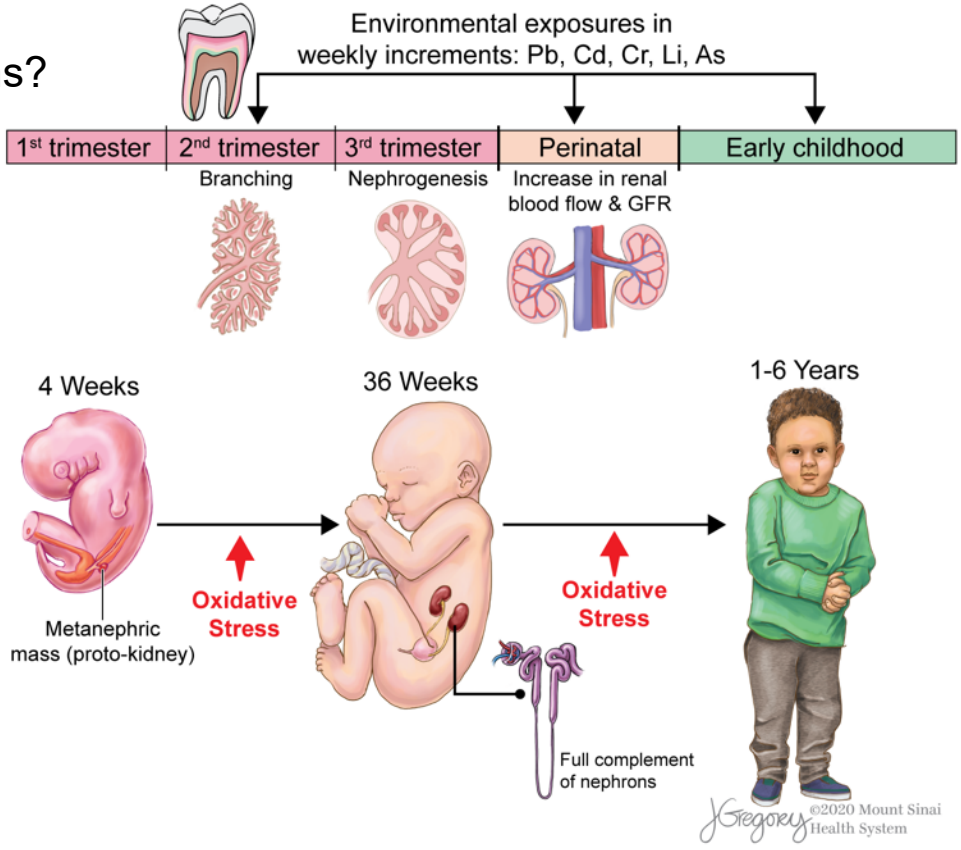
Postnatal metal mixture exposure 16-30 weeks after birth was associated with decreased eGFR at 8–10 years.

Highest weighted metals in this window: **Pb**, Li, Cd, Cr, As

Unpublished data.

Far-reaching implications of early life exposures

- Longitudinal follow-up will assess kidney function trajectories predictive of later life kidney disease
  - Will include glomerular, tubular and vascular kidney damage indicators
  - Potential unifying mechanisms?



What about other early life environmental exposures?

Fluoride exposure in the US

Environment International 132 (2019) 105012

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Fluoride exposure and kidney and liver function among adolescents in the United States: NHANES, 2013–2016

Dr. Ashley Malin

- NHANES 2013-2016
- Fluoride assessed in plasma (n=1983) and water (n=1742)
- Average age: 15.4 years

A 1 μmol/L increase in plasma fluoride was associated with a 10 mL/min/1.72m^2 lower eGFR

Malin et al. *Env Int* 2019

Early life fluoride and preadolescent kidney function

- PROGRESS birth cohort
- 438 children
- Urine fluoride assessed at age 4 yrs
- eGFR, BUN and BP at age 8-10 yrs

Charlie Saylor
3rd year med student

No significant association between urine fluoride and subsequent eGFR

-2.2 mL/min (-5.8, 1.4) p=0.2

Among children with obesity (n=103), we observed a marginally significant inverse relationship.

-4.8 mL/min (-10.2, 0.6) p=0.08

Saylor et al. in submission.

Perinatal air pollution and children's BP

Environmental Research 182 (2020) 109073

Contents lists available at ScienceDirect

Environmental Research

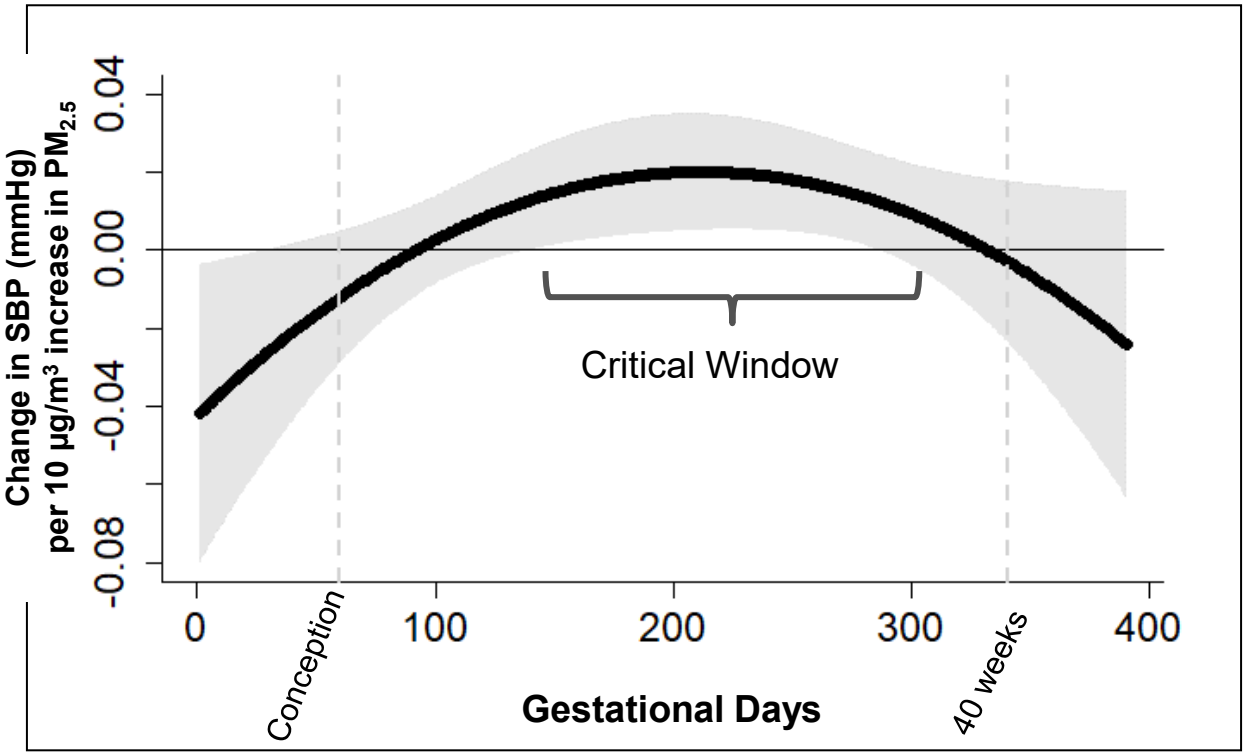
journal homepage: www.elsevier.com/locate/envres

Identifying critical windows of prenatal particulate matter ($PM_{2.5}$) exposure and early childhood blood pressure

Dr. Maria José Rosa

- PROGRESS dyads (n=537)
- Satellite-based spatio-temporal model (Just *et al*. 2015)
- Early childhood BP: age 4 to 6 years
- Examined windows of susceptibility using daily resolution.

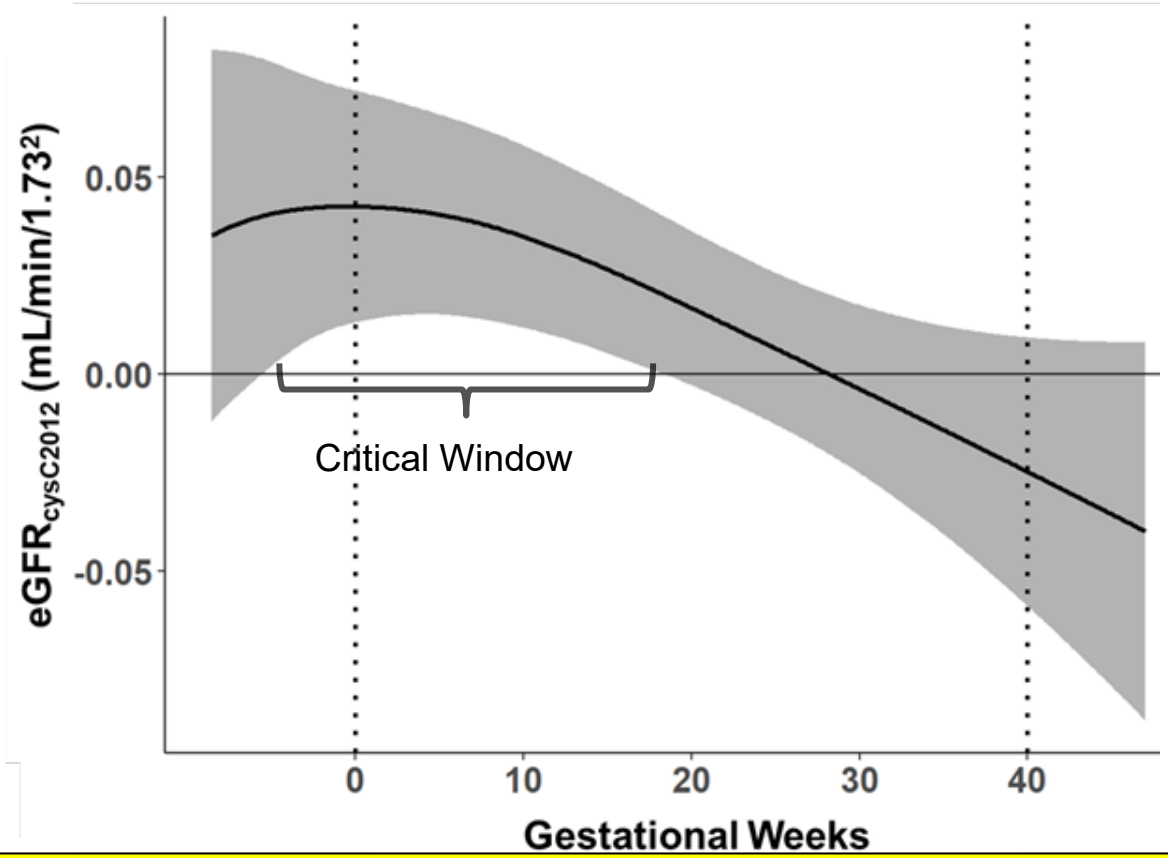
Prenatal $PM_{2.5}$ predicts early childhood BP



$PM_{2.5}$ exposure between weeks 11-32 of gestation was associated with increased BP at age 4-6 years.

Rosa et al. *Env Res* 2019

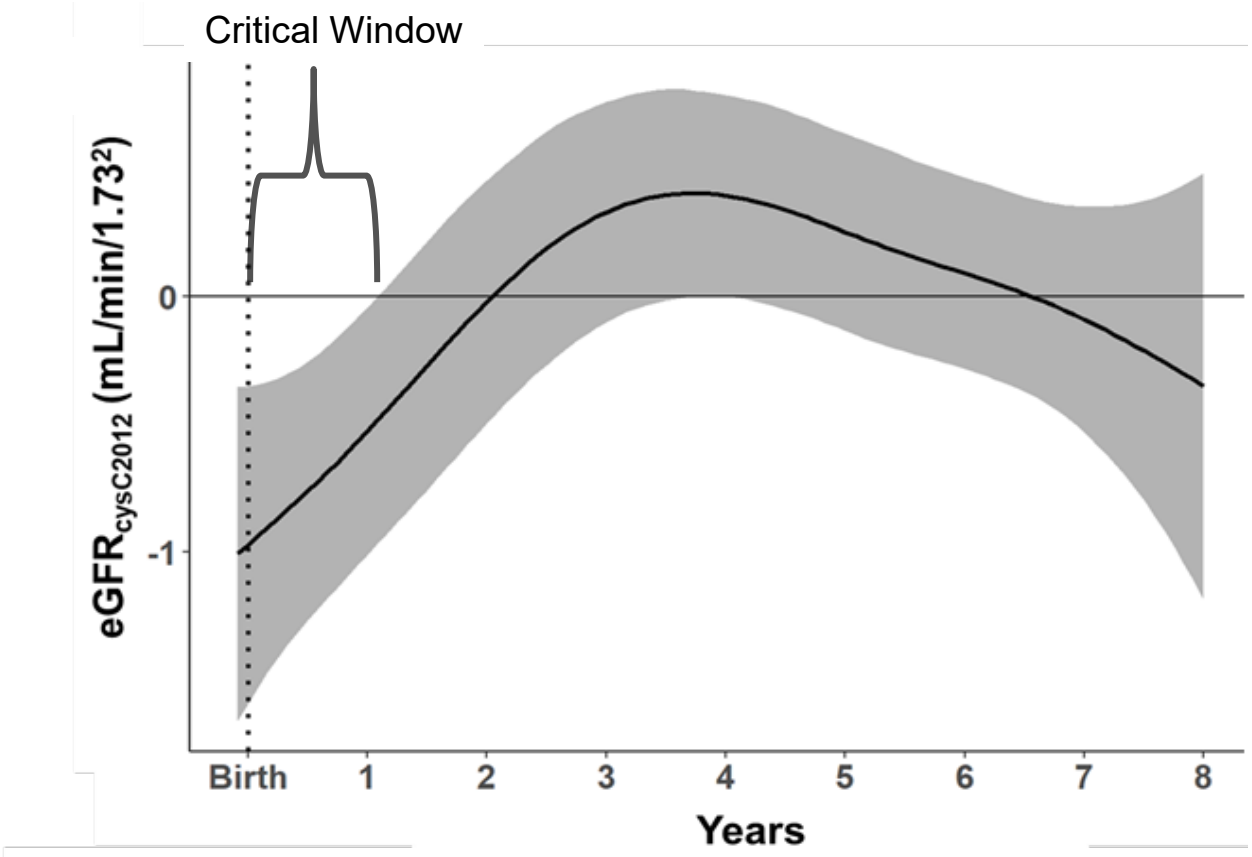
Prenatal $PM_{2.5}$ predicts preadolescent eGFR



$PM_{2.5}$ exposure between weeks 1-18 of gestation was associated with increased eGFR at age 8-10 years.

Rosa et al. *in submission*

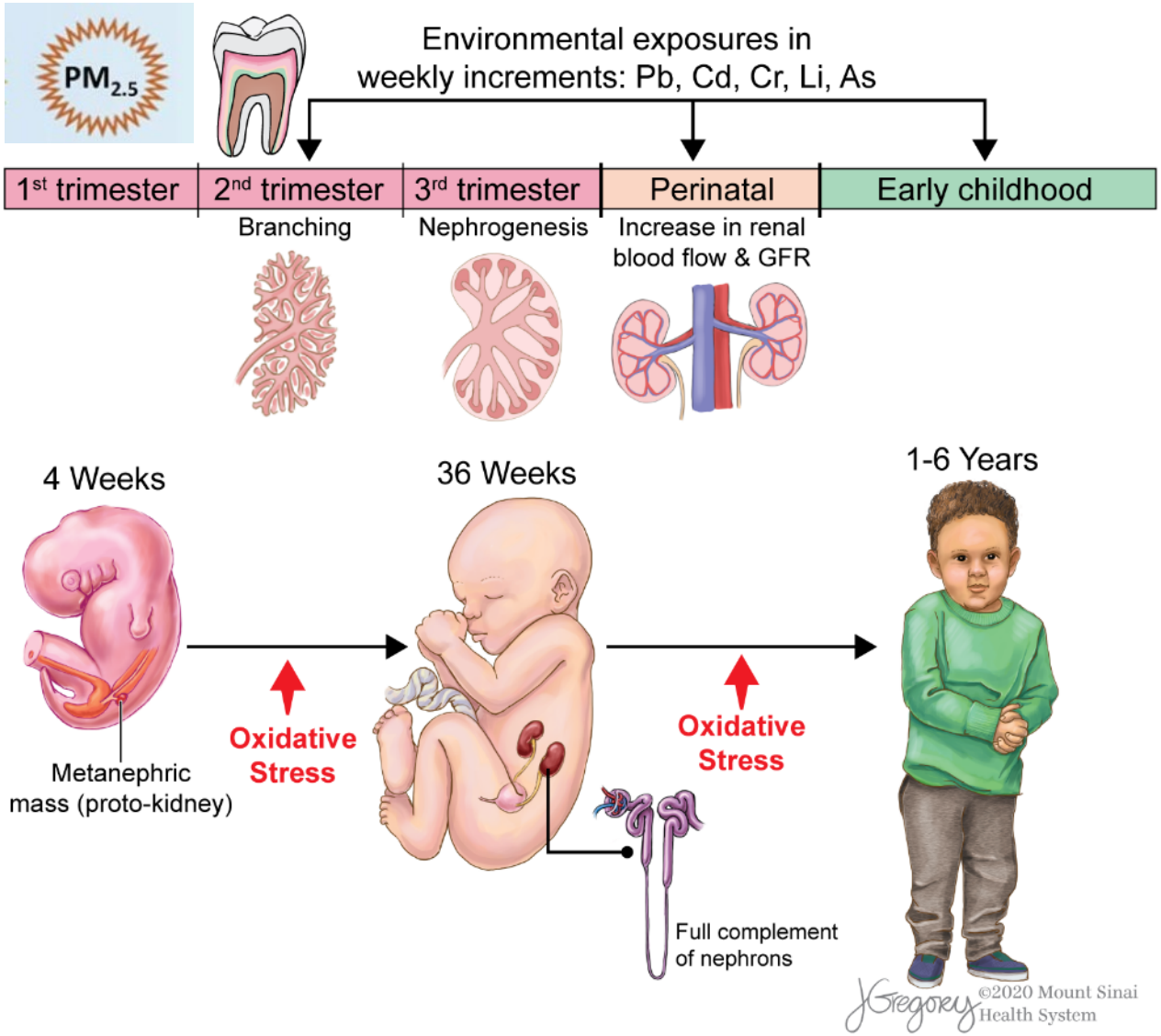
Prenatal $PM_{2.5}$ predicts preadolescent eGFR



$PM_{2.5}$ exposure in months 1-14 were associated with **reduced** eGFR at age 8-10 years.

Rosa et al. *in submission*

Potential unifying mechanisms?

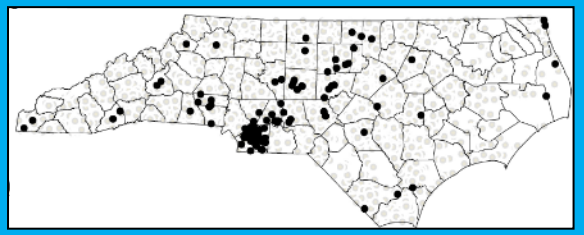


Toxic metals and early life health effects

1. Metals are widespread toxicants

2. Early life exposures may program renal health

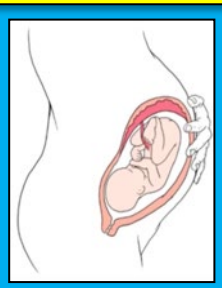
3. **Novel kidney biomarkers**

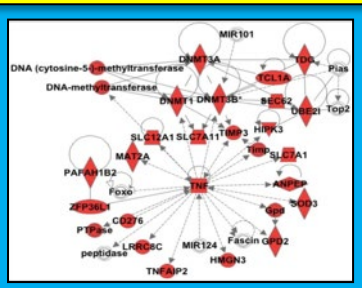


Exposure

Health Effects

Biomarkers

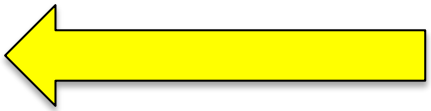




Towards better biomarkers of kidney health

- NIDDK: To discover new biomarkers or rigorously validate existing biomarkers of kidney disease

  - Cell-based/functional
  - Proteomic
  - Metabolomic
  - Epigenetic
  - RNA-based



- Extend this goal into children's environmental health.

Harrill & Sanders *Curr. Env Health Reports* 2020

Towards better biomarkers of renal health: microRNAs

Towards better biomarkers of renal health: microRNAs

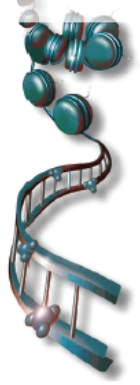
RESEARCH PAPER

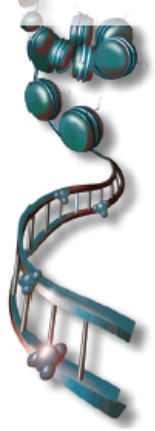
Epigenetics 10:3, 221–228; March 2015; © 2015 Taylor & Francis Group, LLC

microRNA expression in the cervix during pregnancy is associated with length of gestation

Alison P Sanders[1,#], Heather H Burris[2,#,*], Allan C Just[3], Valeria Motta[4,5], Katherine Svensson[1], Adriana Mercado-Garcia[6], Ivan Pantic[4,7], Joel Schwartz[3], Martha M Tellez-Rojo[6], Robert O Wright[1], and Andrea A Baccarelli[3,4]

Epigenomics





Bacterial and cytokine mixtures predict the length of gestation and are associated with miRNA expression in the cervix

Aim: Bacterial vaginosis may lead to preterm birth through epigenetic programming of the inflammatory response, specifically via miRNA expression. **Methods:** We quantified bacterial 16S rRNA, cytokine mRNA and 800 miRNA from cervical swabs obtained from 80 women at 16–19 weeks' gestation. We generated bacterial and cytokine indices using weighted quantile sum regression and examined associations with miRNA and gestational age at delivery. **Results & discussion:** Each decile of the bacterial and cytokine indices was negatively associated with [illegible] ($p_c < 0.005$) were associated with decreased expression of miR-575 and miR-4286. **Conclusion:** The

Alison P Sanders[1], Chris Gennings[1], Katherine Svensson[1], Valeria Motta[2,3], Adriana Mercado-Garcia[4], Maritsa Solano[4], Andrea A Baccarelli[2,6], Martha M Tellez-Rojo[4], Robert O Wright[1] & Heather H Burris[*,6,8,9]

Alison P Sanders[‡,1], Heather H Burris[*,‡,2], Allan C Just[3], Valeria Motta[4,5], Chitra Amarasiriwardena[1,4], Katherine Svensson[1], Emily Oken[6], Maritsa Solano-Gonzalez[7], Adriana Mercado-Garcia[7], Ivan Pantic[4,8], Joel Schwartz[3], Martha M Tellez-Rojo[7], Andrea A Baccarelli[3,4] & Robert O Wright[1]

Towards better biomarkers of renal health: microRNAs

RESEARCH PAPER

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Alison P Sanders[1,#], Heather H Burris[2,#,*], Allan C Just[3], Valeria Motta[4,5], Katherine Svensson[1], Adriana Mercado-Garcia[6], Ivan Pantic[4,7], Joel Schwartz[3], Martha M Tellez-Rojo[6], Robert O Wright[1], and Andrea A Baccarelli[3,4]

Epigenomics

Bacterial and cyto
the length of gest
with miRNA expre

Intracellular → Extracellular

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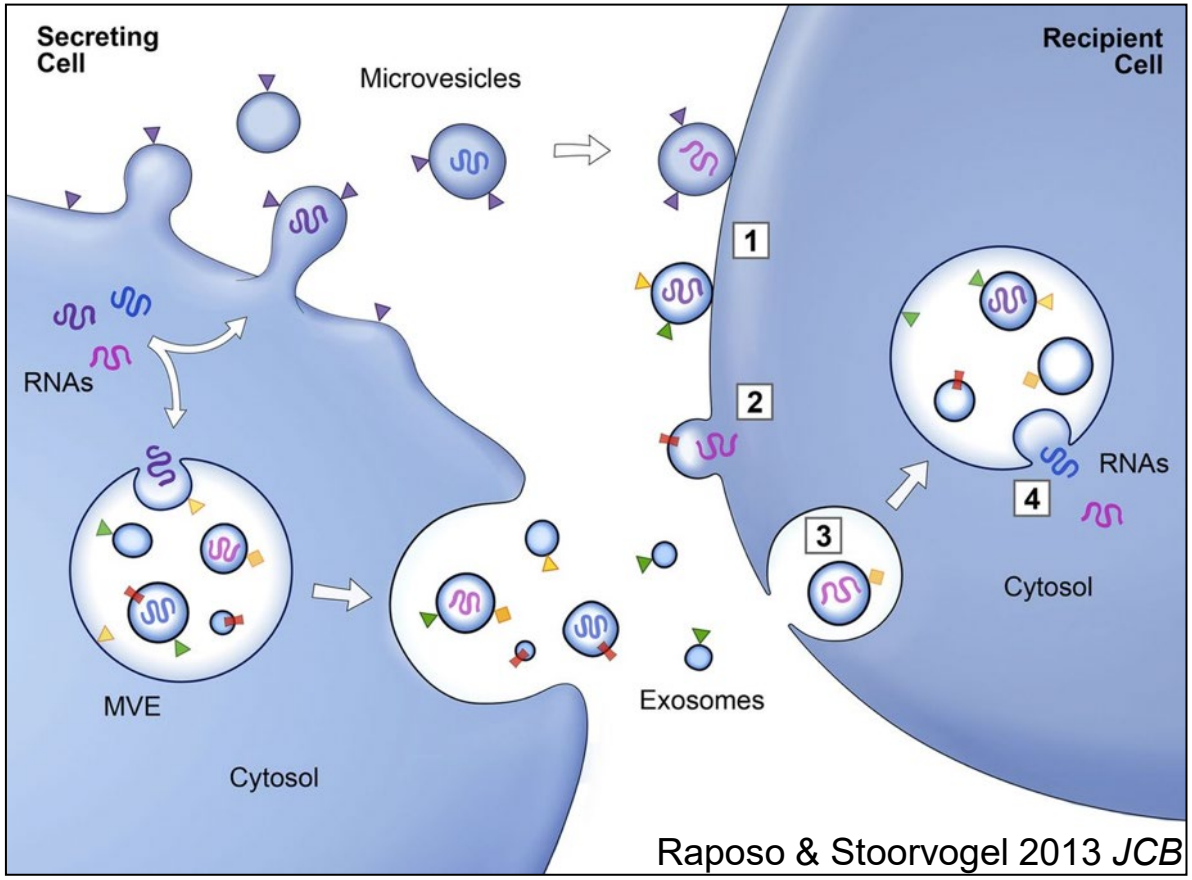
Towards better biomarkers of renal health: extracellular urinary microRNAs

microRNAs (miRNAs)

- 20-24 nucleotide, single-stranded RNA
- Post-transcriptional regulation that typically results in gene silencing
- Selectively bind and target hundreds of mRNA (~60% of genes)

Extracellular vesicles (EVs) transport cell-cell information

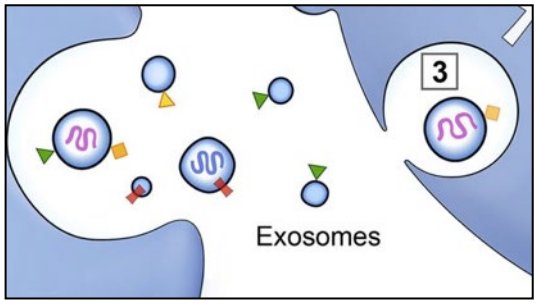


- **Microvesicles**: <1μm
- **Exosomes**: 30-150 nm
- Transfer mRNA, microRNA, lncRNA, proteins, etc.
-

- Travel in body fluids: blood, breast milk, urine

György *et al*. 2011 *Cell Mol Life Sci*

Why exosomes?



- Urinary exosomes reflect intrarenal signaling
- Contain miRNA from the glomerulus & all sections of the nephron.
- Can measure >750 miRNA in a single assay.

May serve as biomarkers of kidney dysfunction or nephrotoxicant exposure.

Harrill & Sanders *Curr. Env Health Reports* 2020

Study Aim

To evaluate relationships between urinary exosomal microRNA with cardiorenal parameters in early childhood.

PROGRESS birth cohort

- Mexico City
- Enrolled pregnant women during the 2nd trimester (n=948)
- Infants followed into childhood (~10 yrs)
- ~700 active mother-child pairs
  - P30 pilot subset: n = 105

Icahn School of Medicine at Mount Sinai

Instituto Nacional de Salud Pública

INPer

Methods

Dan Flores

Sample Preparation

10 mL urine sample thawed and gently vortexed

Exosome Isolation

Sample washed and centrifuged at three speeds to pellet exosomes

miRNA Isolation

- miRNeasy Kit
- MinElute cleanup
- Bioanalyzer picochip

Taqman OpenArray qPCR

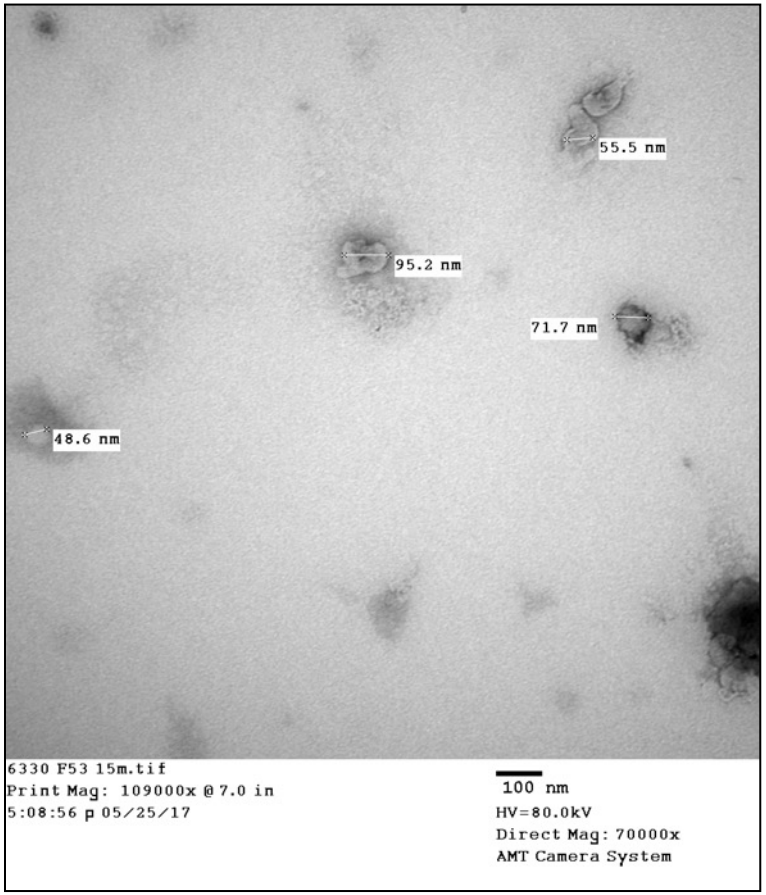
Exosome visualization

Sample added to paraformaldehyde-coated copper grid and stained

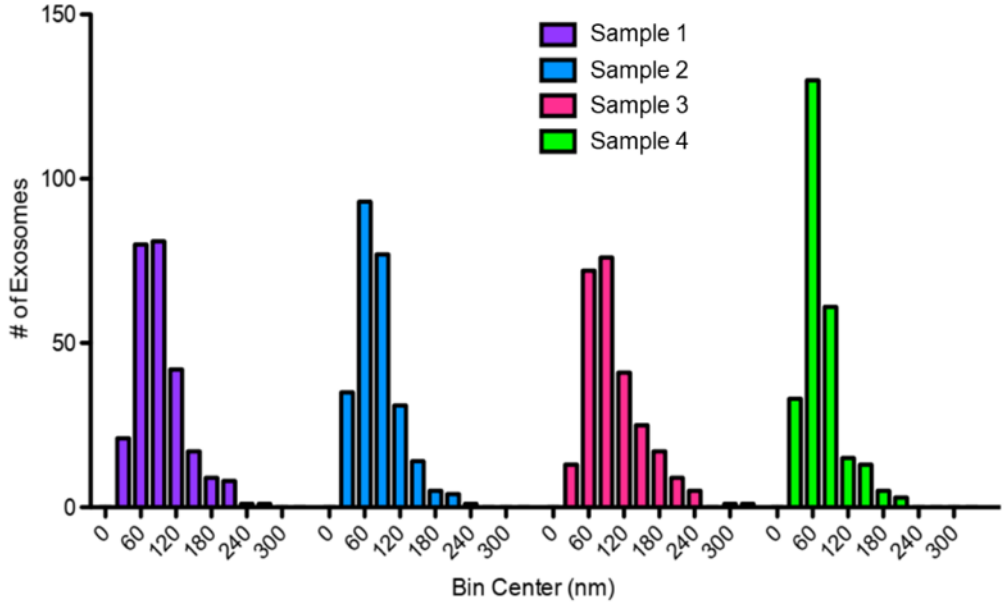
Transmission electron microscopy (TEM)

Exosome visualization

TEM: exosomes isolated from 4-year-old urine



Exosome size distribution



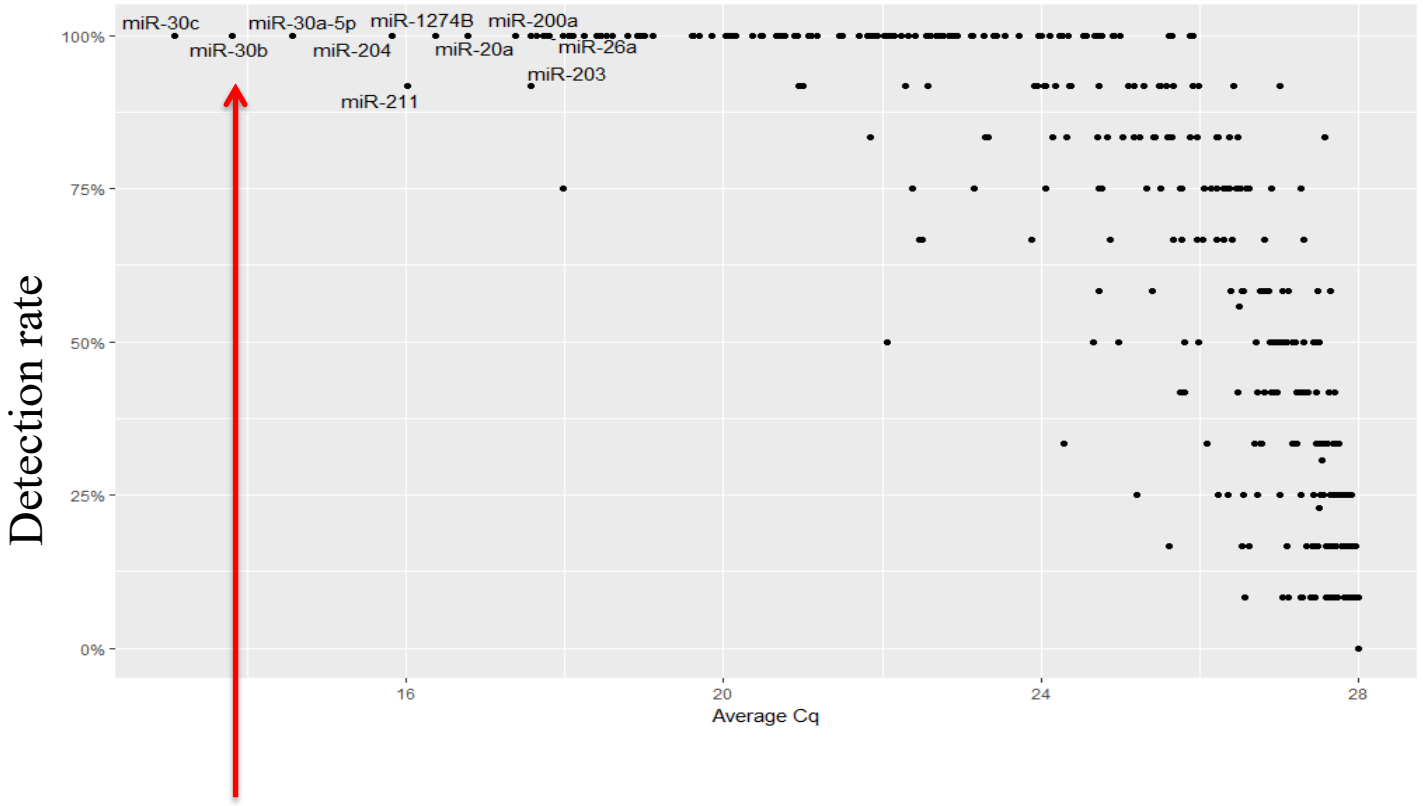
Levin-Schwartz et al. *Epigenomics* 2021

Methods

- Measured 754 miRNAs using OpenArray qPCR
- Relative quantification cycle (Cq) values were calculated by QuantStudio software.
- Signal ≥ 70% samples
- Normalized by using the deltaCq method of the NormqPCR R package, with U6 RNA selected as an appropriate normalization control

Exo-miR Identification

Detected over 150 extracellular microRNAs



Several members of miR-30 & miR-200 family were among the top hits.

Methods

- Measured spot urine sodium and potassium, calculated Na:K ratio
- BP assessed at age 4, using an automated SpaceLabs monitor
- Estimated glomerular filtration rate (eGFR) at age 8, assessed by serum cystatin C:

$$\text{eGFR}_{\text{CKiD 2012}}: \ 70.69 * (Cystatin\ C)^{-0.931}$$

Schwartz et al. *Kidney Int* 2012

- We used linear regression to examine associations between 193 exo-miRs and children's BP, urinary electrolytes, and eGFR
  - adjusting for child's age, sex, BMI z-score, urine specific gravity, SES and prenatal exposure to tobacco smoke in the home.
  - Applied a false-discovery rate (FDR) threshold of q<0.1
- We applied functional network and pathway analysis to identified miRNA and their target genes

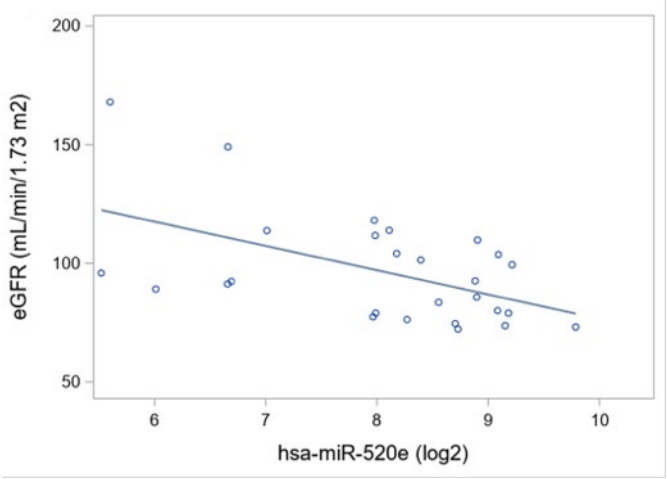
Demographics (n=88)

	Arithmetic mean (SD) or Percentage of Sample
Age, years	4.7 (0.5)
Male sex, %	47%
Socioeconomic status	
Low	52%
Medium	40%
High	8%
Smoke exposure in the home (2T)	32%
Child BMI	
Normal Weight	65%
Overweight	15%
Obese	8%
$eGFR_{CysC2012}$ (mL/min/1.73m^2)	99.3 (24.3)

Results

Dr. Yuri Levin-Schwartz

- Exo-miRs passing FDR correction
- Urine sodium (3): miR-1180, miR-34a, miR-32
  - A doubling of expression of each miRNA was associated with a 10-20 mmol/L unit increase in urine Na.
- Na:K ratio (17)
  - Indicator of risk for cardiovascular disease
- SBP or DBP (0)
  - Greater expression of miR-27a was associated with both lower SBP and DBP ($p<0.05$)
- eGFR at age 8-10 (4 years later): miR-520e
  - A doubling of miR-520e expression was associated with a 12 ml/min decrease in eGFR



Levin-Schwartz et al. *Epigenomics* 2021

Results - Biological functions of Na-associated exo-miRs and gene targets

- Exo-miRs involved in disrupted ion transport and endothelial injury/inflammation
- 343 mRNA targets identified

Top nephrotoxic pathways:

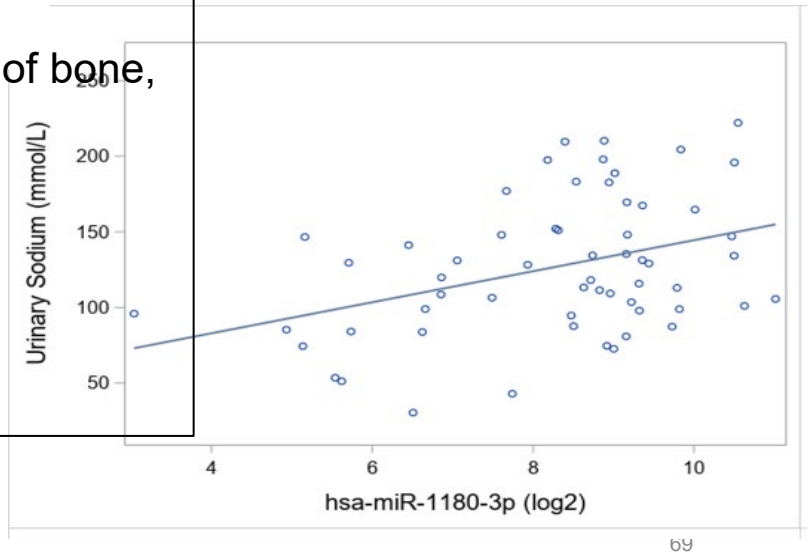
- renal necrosis/cell death, glomerular injury, renal proliferation, and renal hyperplasia/hyperproliferation.

The top identified regulator network enriched for diseases and functions:

- cell death of kidney cell lines, mineralization of bone, development of connective tissue

mRNA targets involved in:

- **insulin** and **aldosterone** receptor signaling pathways.



Discussion

- These exploratory findings highlight exosomal miRNAs as potential non-invasive biomarkers of early life cardiorenal parameters.
  - Findings in-line with prior studies

- To our knowledge, no previous studies have identified exo-miRs associated with BP, eGFR or urine biomarkers in healthy children.

- This was an observational study. Requires replication in other cohorts and clinically-relevant populations to assess reproducibility & generalizability of the findings.

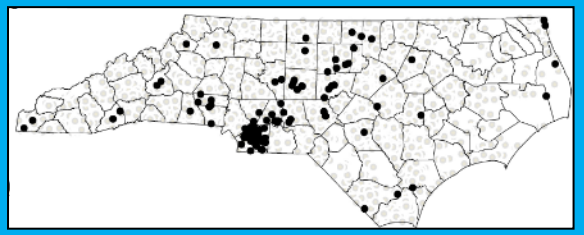
- Methodological considerations: flow cytometry/ immunolabeling of protein markers to distinguish cell type; RNAseq platform & pipeline; study design (case-control, older age, based on trajectory profiles)

Toxic metals and early life health effects

1. Metals are widespread toxicants

2. Early life exposures may program renal health

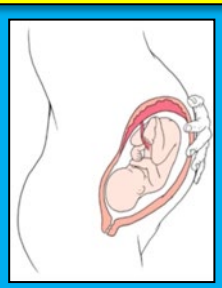
3. **Novel kidney biomarkers**

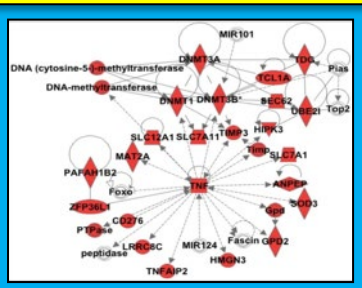


Exposure

Health Effects

Biomarkers





Acknowledgments

- Mount Sinai (New York, USA)
  - Christine Austin
  - Paul Curtin
  - Manish Arora
  - Chris Gennings
  - Lisa Satlin
  - Robert Wright (PROGRESS PI)
  - -Yuri Levin-Schwartz
  - -Katherine Svensson
  - -Ashley Malin
  - -Maria Jose Rosa
  - -Charlie Saylor
  - -Vasily Aushev
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  - Mara Tellez-Rojo (PROGRESS PI)
- National Council of Science and Technology (Mexico City, MX)
  - Marcela Tamayo-Ortiz
- National Institute of Perinatology (Mexico City, MX)
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  - Mari Cruz Tolentino
- Columbia University (New York, USA)
  - Andrea Baccarelli
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- Mount Sinai Children's Center Foundation

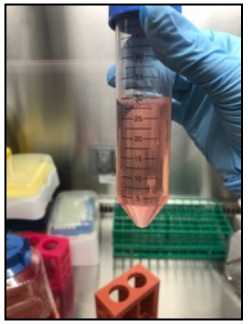
Questions?

Future Directions

- Child/maternal cardiorenal health
  - Nephrotoxic exposures: mixtures, fluoride, radon, PM, [bluespace/greenspace; nutrition]
    - Stress: heat, psychosocial, disordered sleep
    - Biomonitoring/Well water assessments
  - Longitudinal dyad cohorts recruited from EHR
    - Childhood lead levels; gestational age/BW; longitudinal BP; weight patterns
    - Tooth biomarker collection program
    - Banked serum samples for creatinine & cystatin C (eGFR)
    - Novel urinary biomarkers (EVmiRNA, metabolomics)
- Chronic disease comorbidities
  - Chronic kidney disease (pending R01, scored 11th percentile) APOL1 high risk variants
  - Obesity
  - Bladder cancer
  - Lung cancer/respiratory health
  - Agricultural workers with CKDu (Funded P30 pilot)
  - Appalachia (smokers, SES, racial disparities, proximity to coal mines/unconventional natural gas)

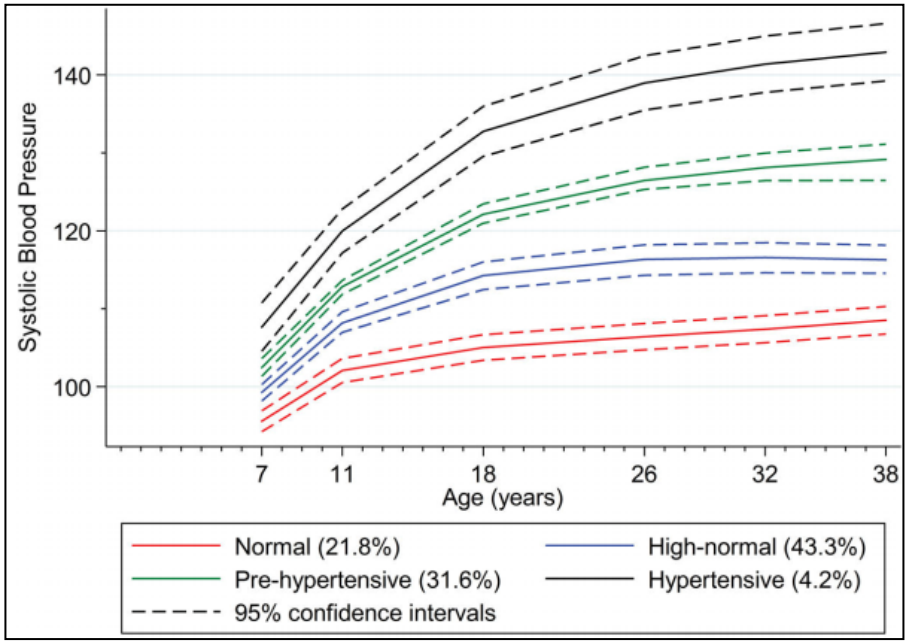
Future Directions

- In vitro / in vivo validation
  - Laboratory for Environmental Nephrotoxicology (Sanders Lab)
  - Mount Sinai zebrafish laboratory (Zhou lab) (Funded P30 pilot)
  - Renal Molecular Physiology Laboratory (Satlin Lab)
  - Pittsburgh Developmental Biology (Hukreide Lab)
  - UPMC Pediatric Nephrology (Kleyman Lab)



Does Pb exposure program hypertension or CKD?

- HTN prevalence: 45% US adults (~100 million)
  - 3.5% children
  - Rises to 3.8%–24.8% among overweight and obese adolescents
- Childhood BP predicts adult BP



Flynn *et al*. 2017

Theodore *et al*. 2015

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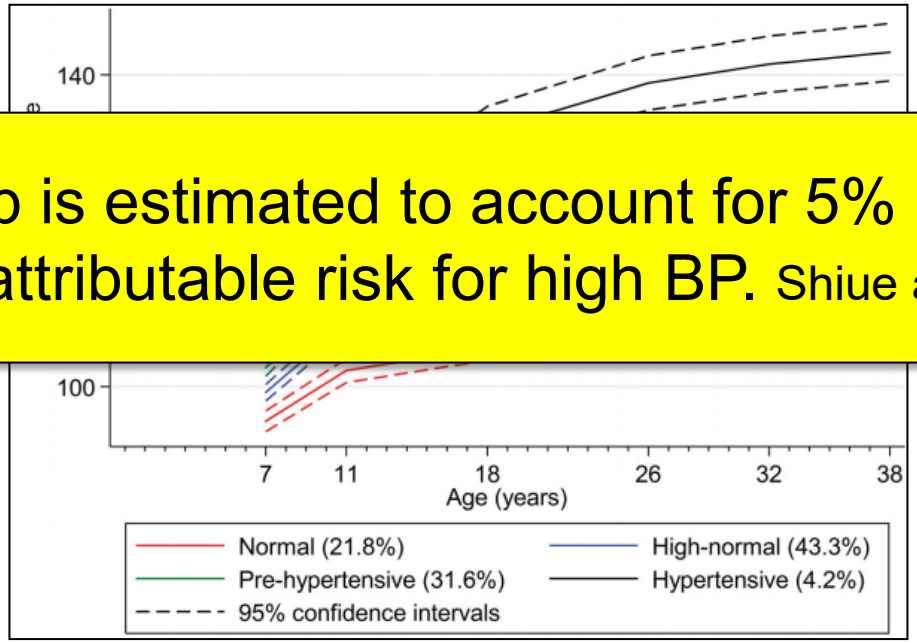
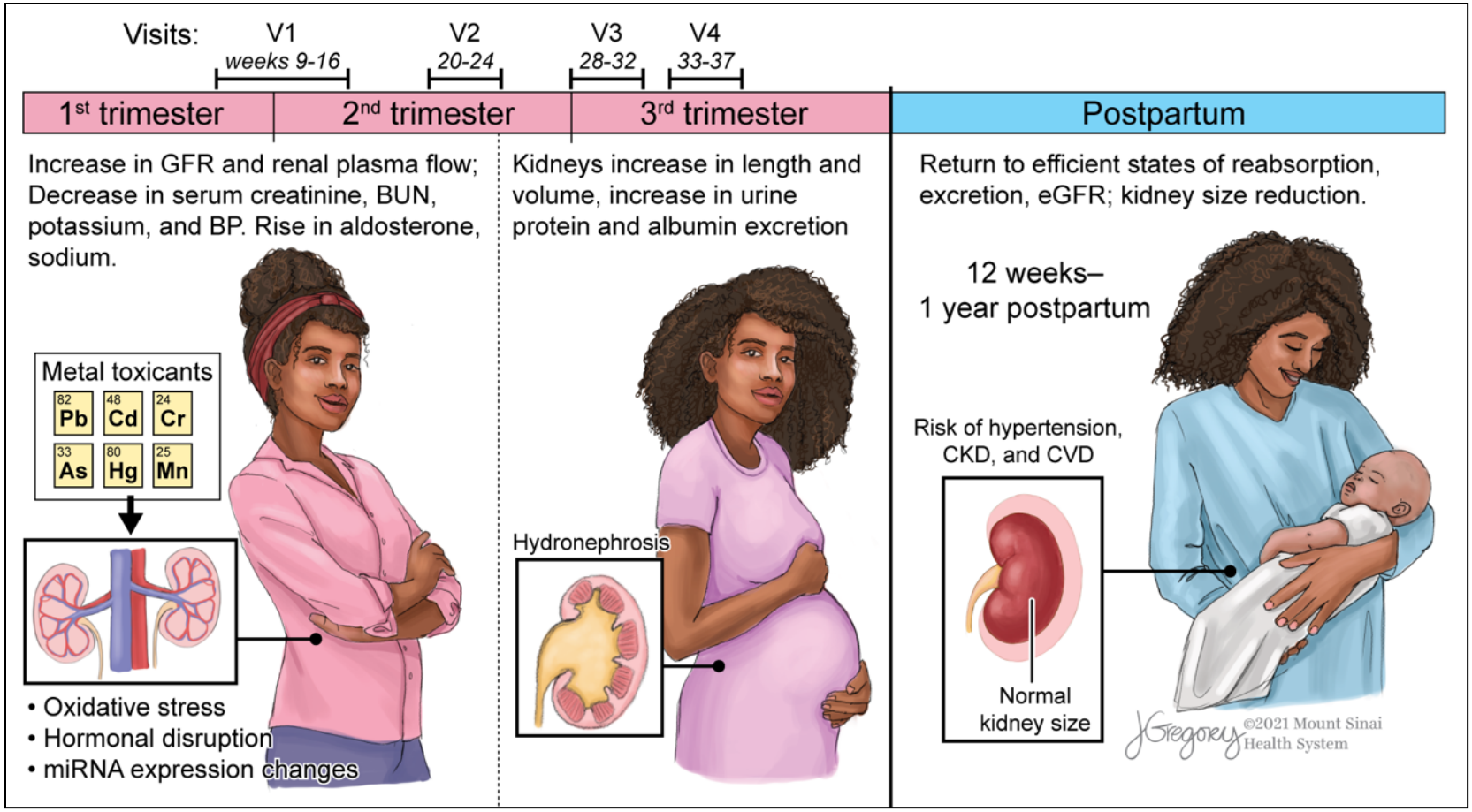


In adults, Pb is estimated to account for 5% of the US population attributable risk for high BP. Shiue and Hristova 2014

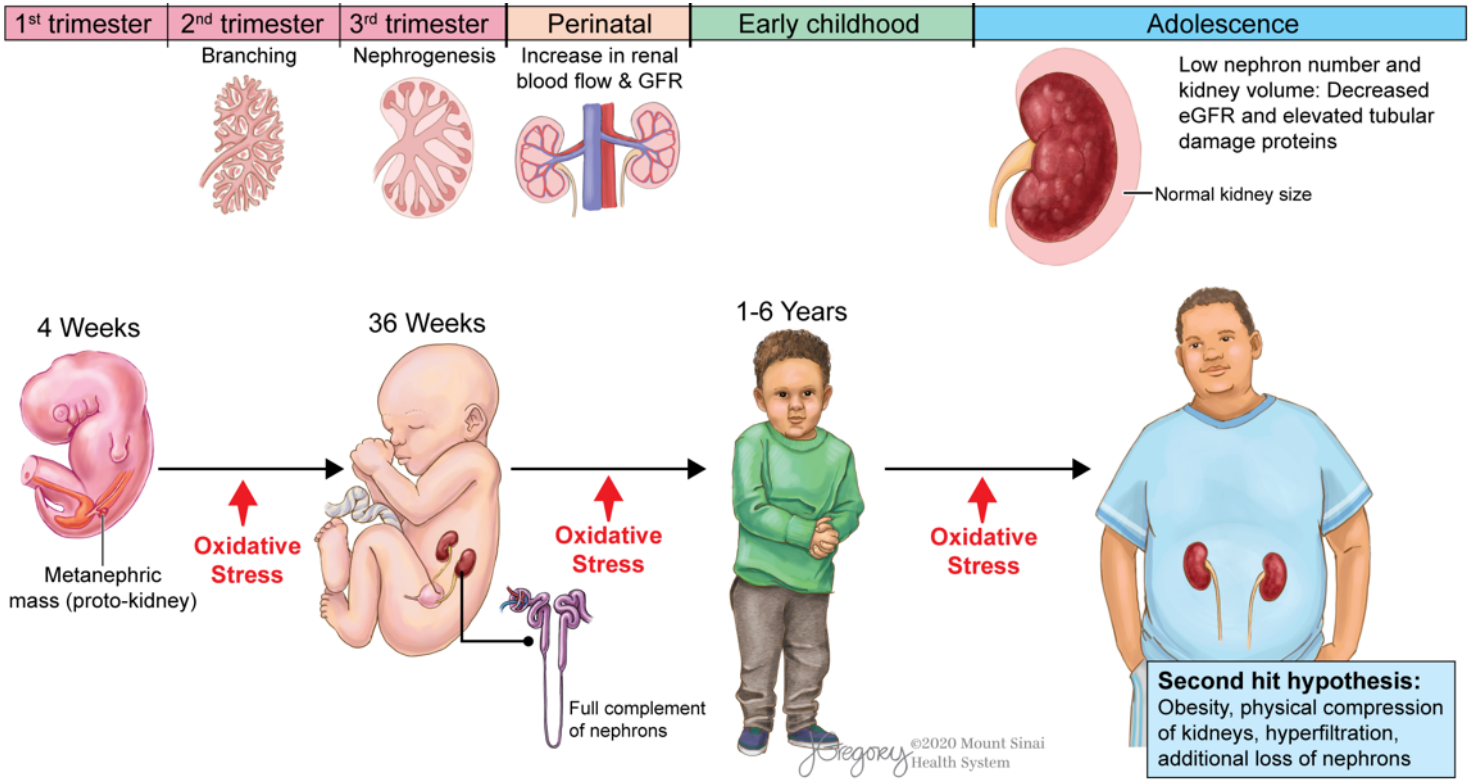
Flynn *et al*. 2017

Theodore *et al*. 2015

Maternal cardiorenal health equity



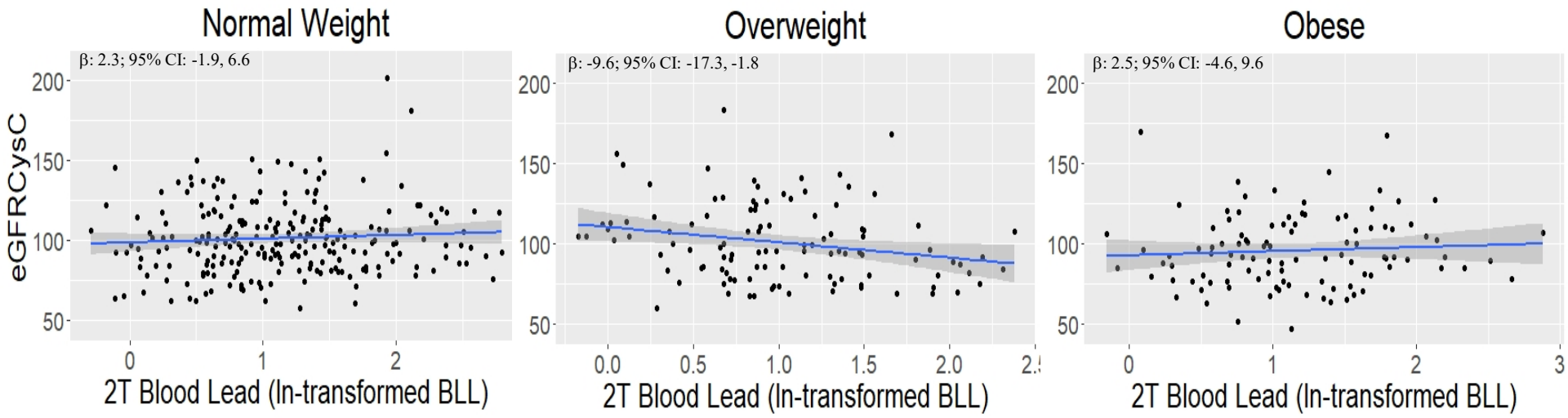
Effect modification by BMI



Effect modification by BMI?

- Observed null direct relationship between lead and eGFR

Charlie Saylor
3rd year med student



Among overweight children, a unit increase in 2nd trimester BLL was associated with a 10.5 unit decrease in eGFR at age 9 years.

Saylor et al. *Env Int* 2021

Are there susceptible subgroups?

- Prior studies of Pb exposure and childhood BP report mixed findings

- Our data show no direct association between prenatal BLL and altered:
  - BP
  - eGFR
  - urinary markers of tubular damage

Are there susceptible subgroups?

Low Birth Weight and Nephron Number working group (2017):

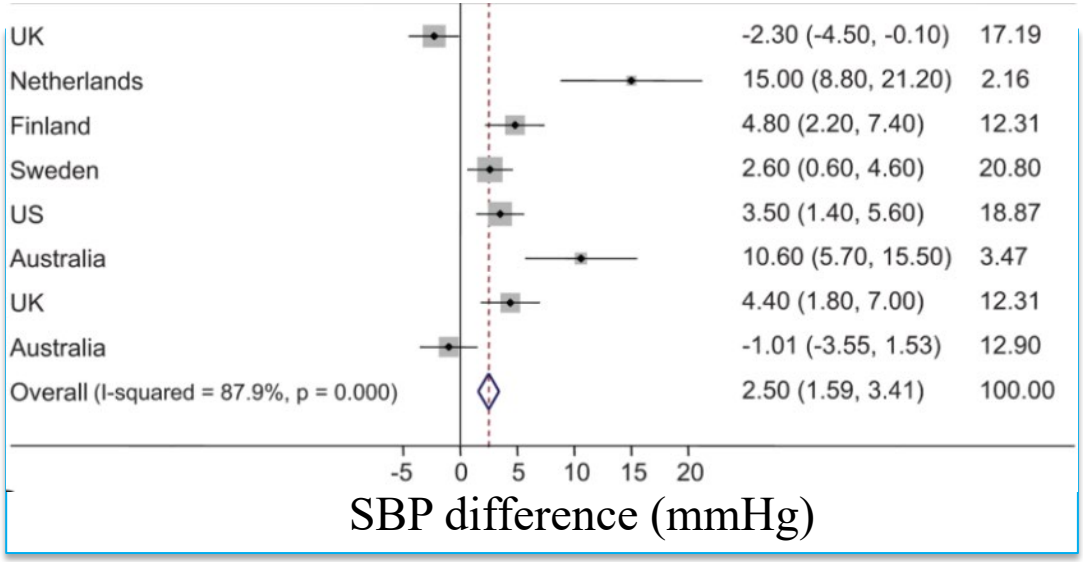
"the need to act early to prevent CKD and other related noncommunicable diseases later in life by reducing low birth weight, small for gestational age, prematurity, and low nephron numbers at birth through coordinated interventions"

American Academy of Pediatrics updated BP guidelines (Flynn et al. 2017):

the need to evaluate "children with a history of prematurity, an identified risk factor for HTN and CVD in adults".

Are there susceptible subgroups?

- Preterm infants have higher childhood BP

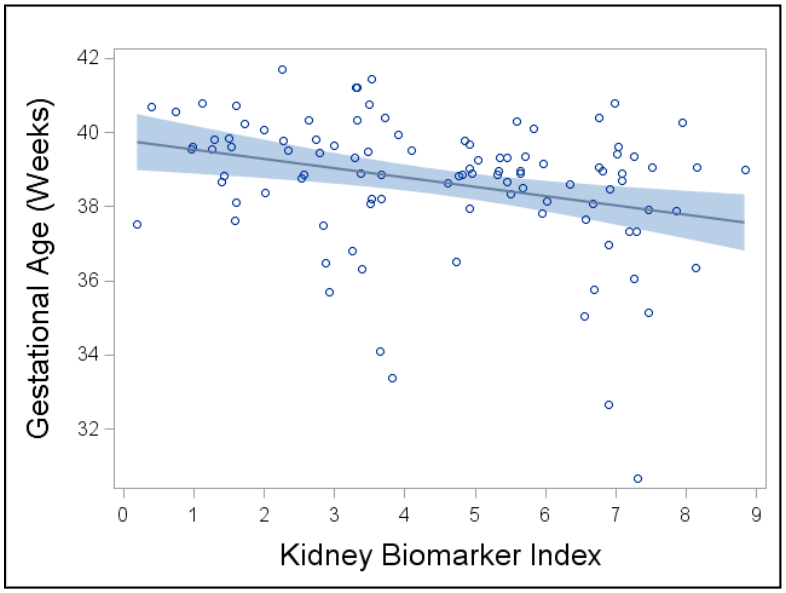


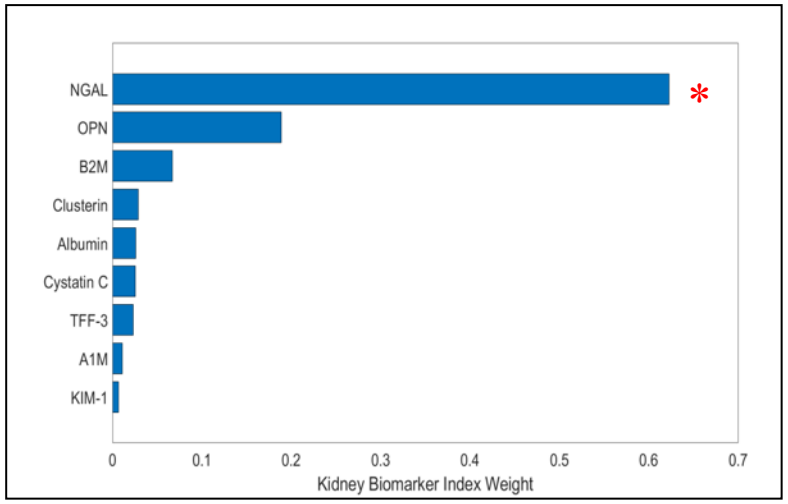
de Jong et al. 2012

Shorter gestations associated with higher protein levels

- PROGRESS (n=103)
- Average age: 4.7 years

Dr. Yuri Levin-Schwartz





Levin-Schwartz *et al.* PLoS ONE 2019

*All models adjusted for child's age, sex, BMI, and urinary creatinine

Shorter gestations associated with higher protein levels

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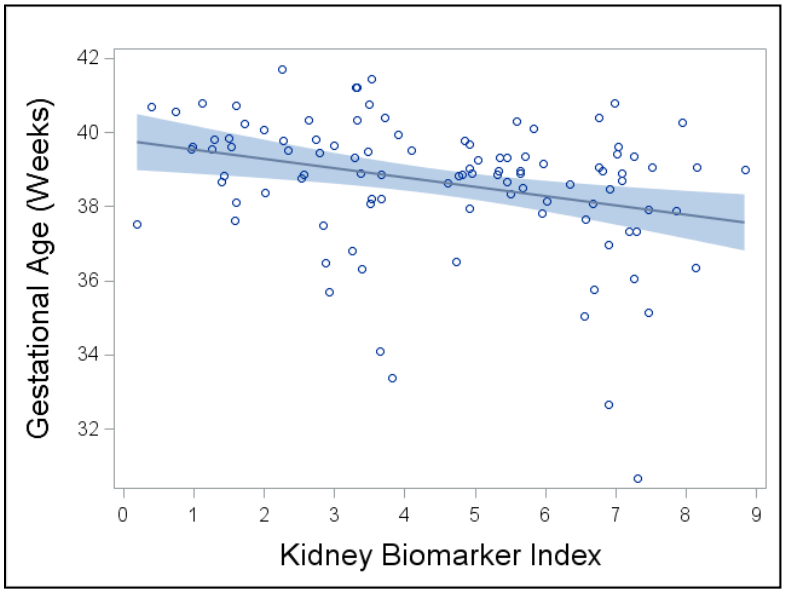
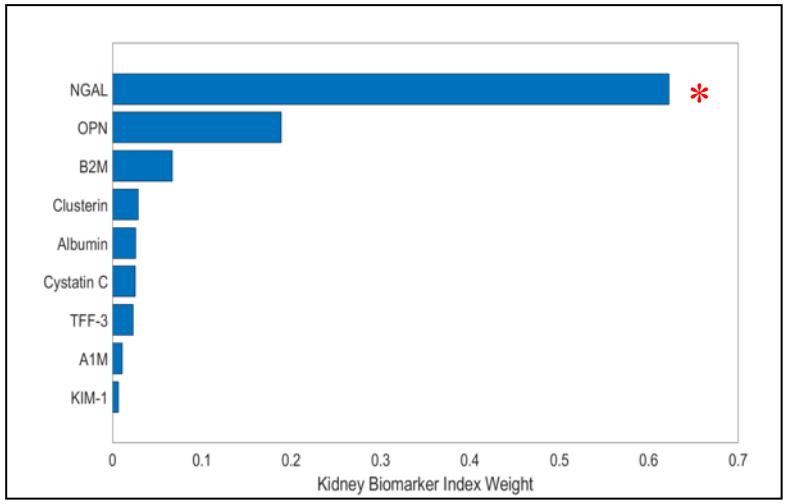


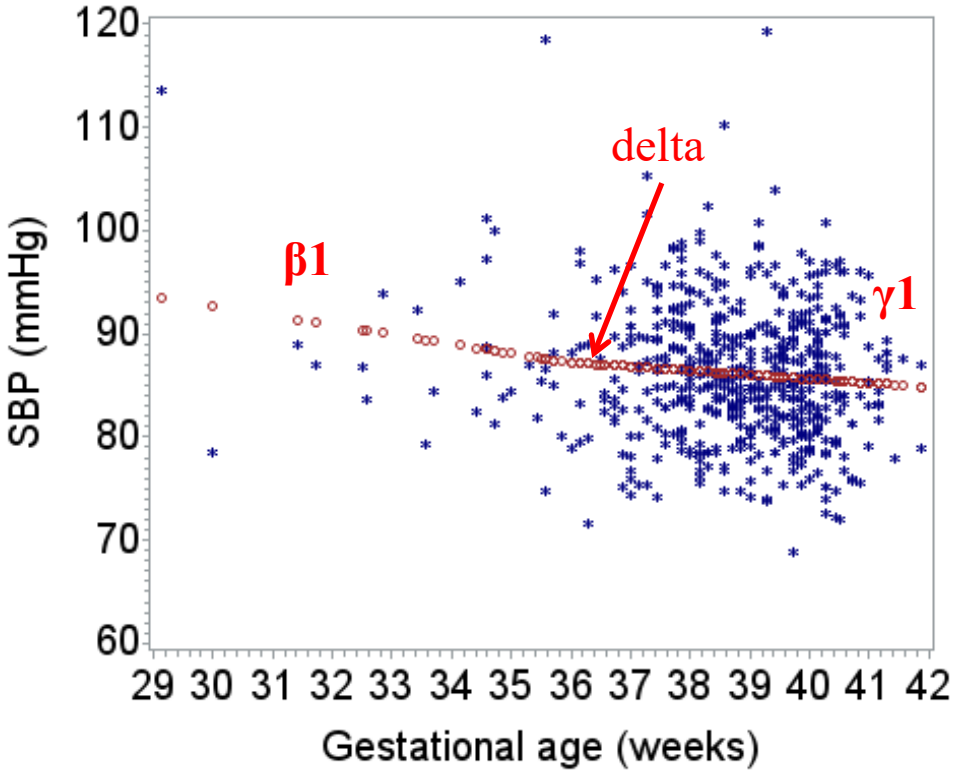


Levin-Schwartz *et al.* PLoS ONE 2019

Even children 4-6 years old, had elevated biomarkers of subclinical kidney damage.

Evidence of nonlinear relationships between shorter gestation and SBP

- PROGRESS (n=565)
- Average age: 4.8 years



β1 (95% CI): -0.9 (-2.3, 0.5)
γ1 (95% CI): -0.4 (-0.9, 0.06)
delta (95% CI): 35.9 (28.8, 43.0

Overall p-value: 0.02

Katherine Svensson
PhD Candidate

Sanders et al. *Env Int* 2018

Evidence of nonlinear relationships between shorter gestation and SBP

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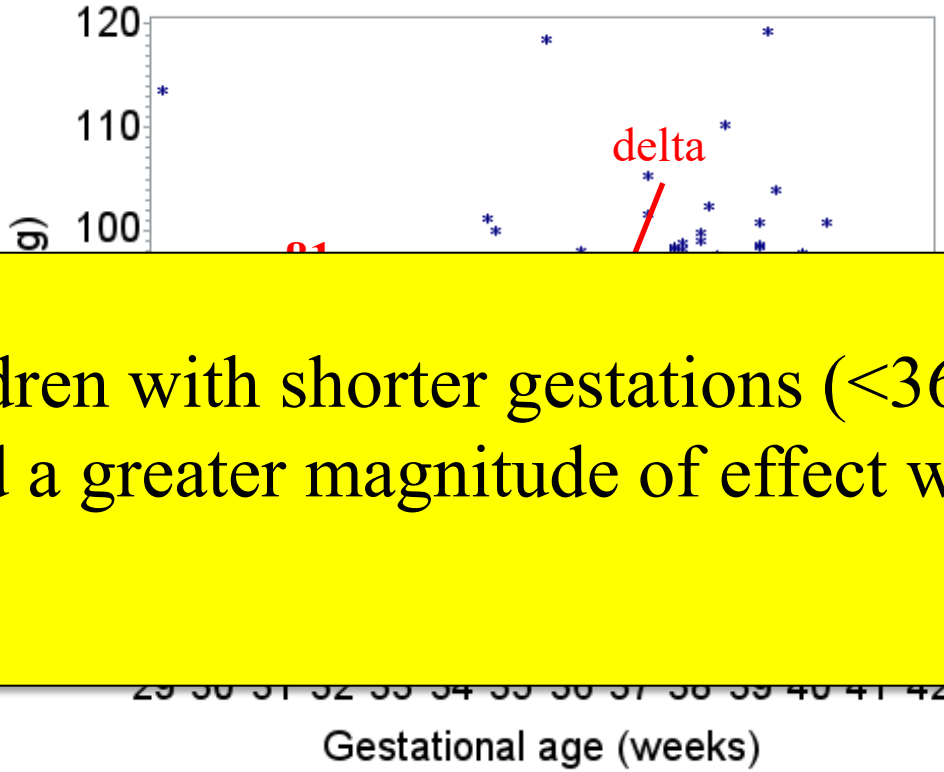
- Average age: 4.8 years



Among children with shorter gestations (<36 weeks), we observed a greater magnitude of effect with SBP.

β1 (95% CI): -0.9 (-2.3, 0.5)
γ1 (95% CI): -0.4 (-0.9, 0.06)
delta (95% CI): 35.9 (28.8, 43.0

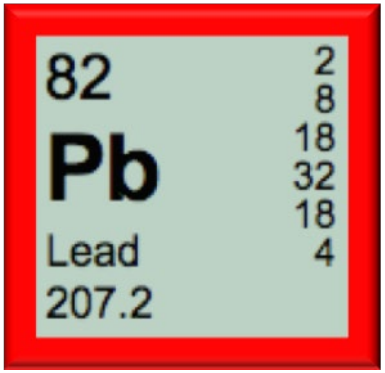
Overall p-value: 0.02

Sanders et al. *Env Int* 2018

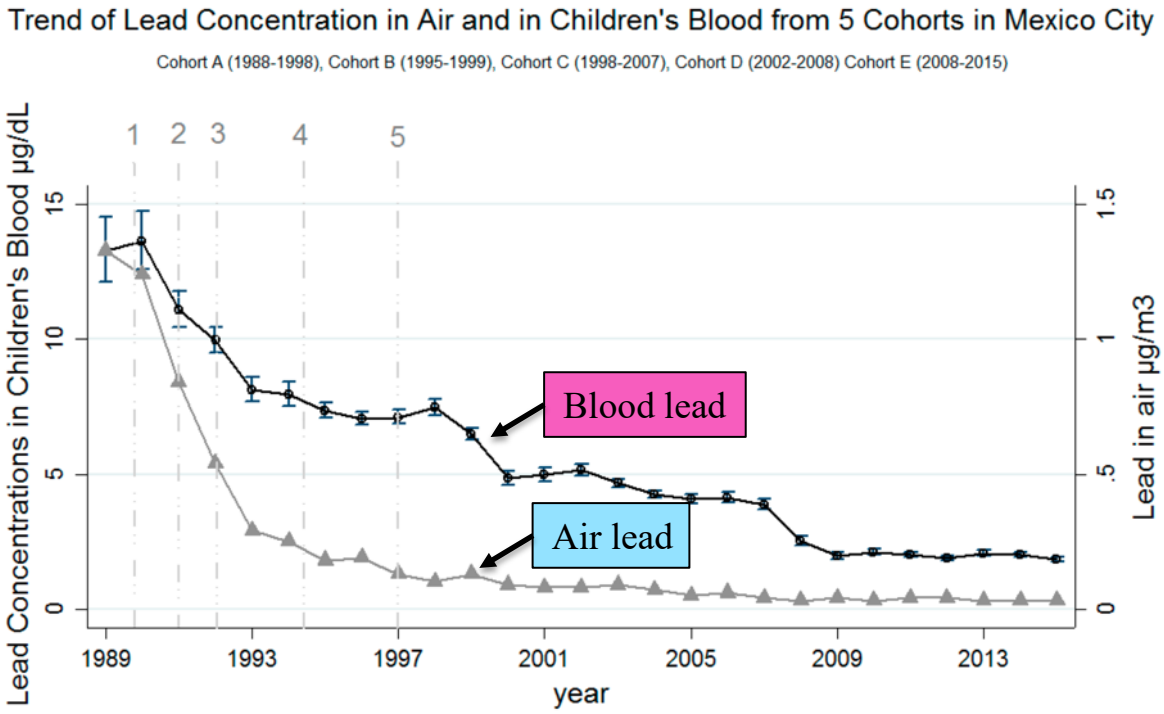
Environmental insults during susceptible periods of kidney development may program later life disease.

Lead (Pb) exposure occurs worldwide

- Pb is a developmental toxicant:
  - central nervous system & kidneys
- Ingestion or inhalation
  - Pb-based paint, gasoline
  - Leaded pipes for drinking water
  - Cosmetics, home remedies
  - Pb-glazed pottery
- CDC blood Pb reference level
  - 10 µg/dL in adults
  - 5 µg/dL in pregnant women & children
- There is no safe level of Pb exposure



Lead level decline in Mexico

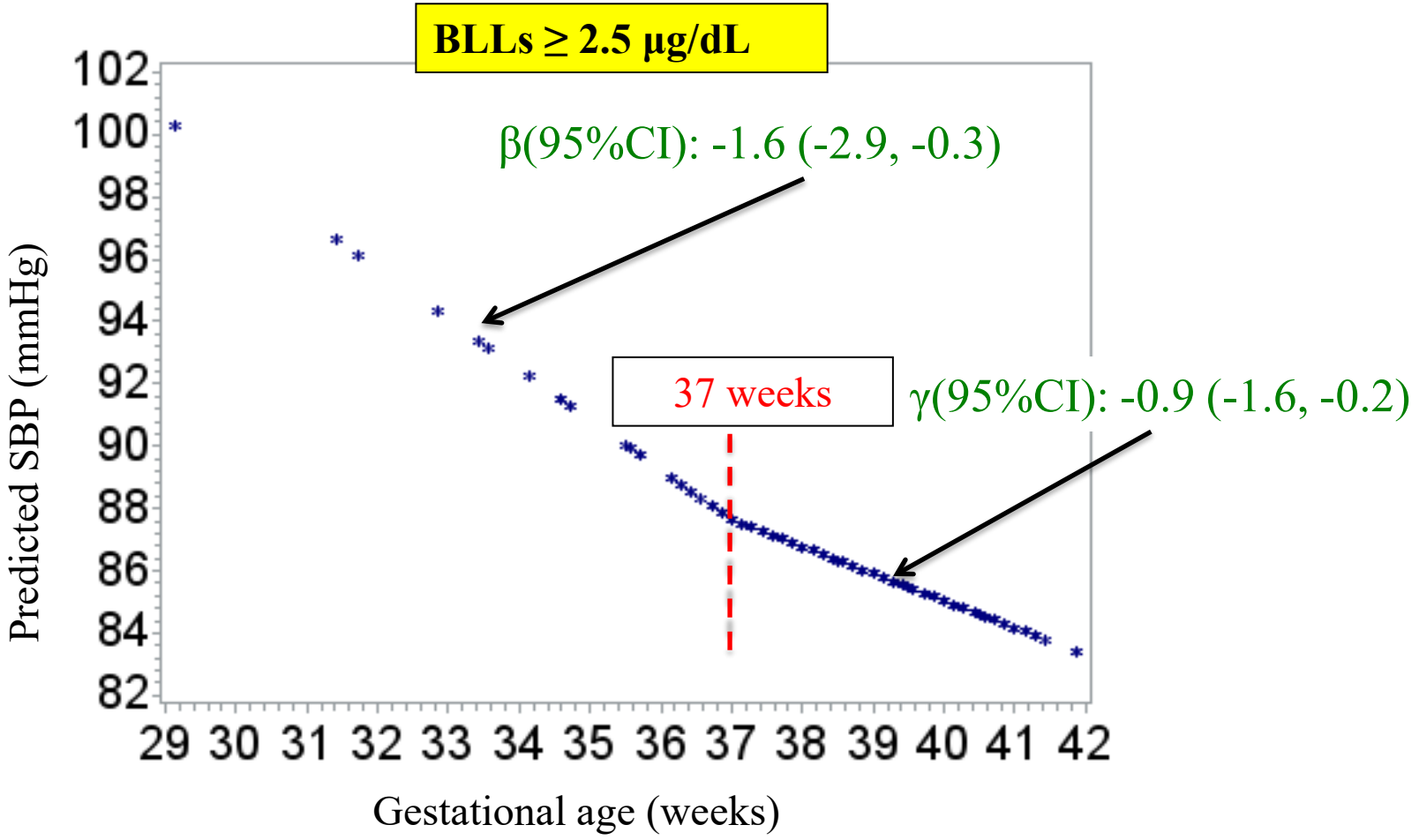


Pantic et al. 2018

Tamayo-Ortiz et al. 2016; 2018; 2020

Percentage of children with BLLs ≥ 5 µg/dL decreased from 92 to 8%.

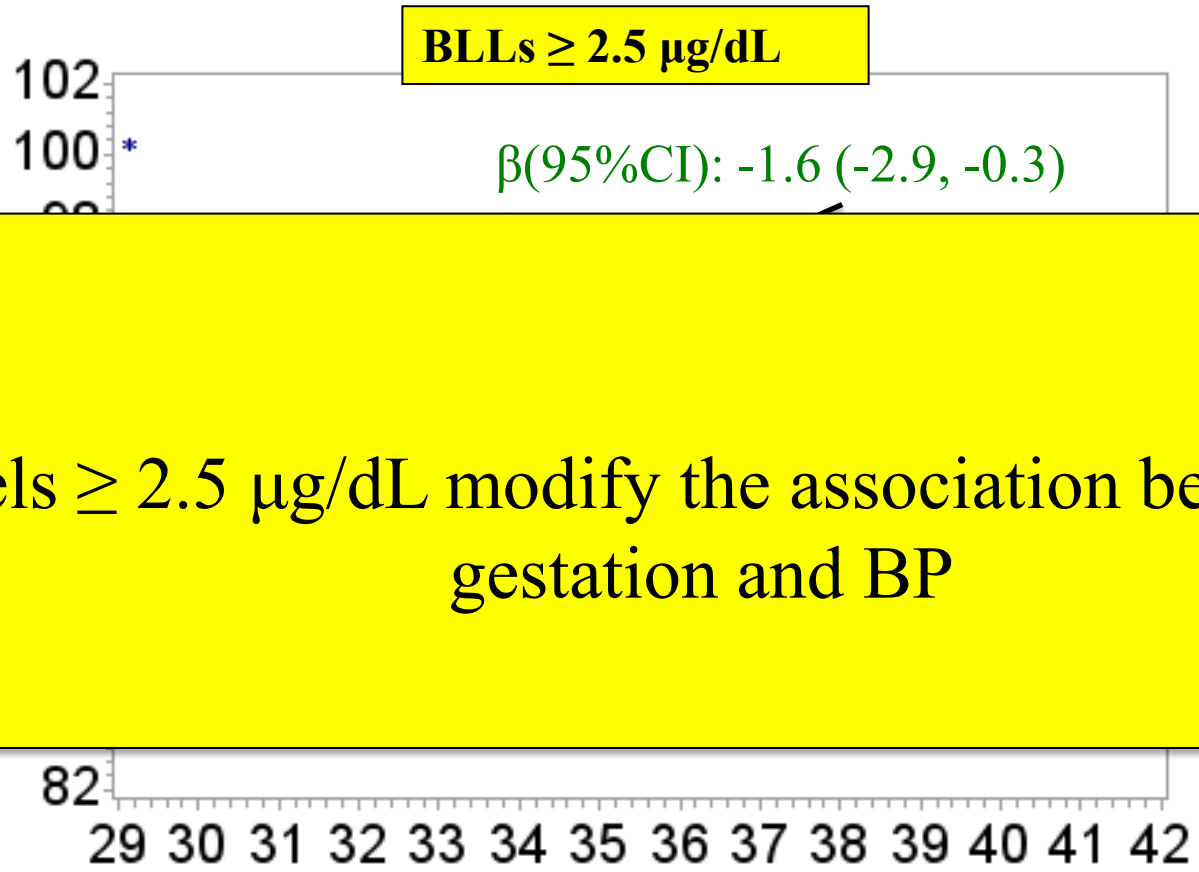
Prenatal lead exposure modifies the association between shorter gestation and SBP



Overall model p-value is p<0.0001

Sanders et al. *Env Int* 2018

Prenatal lead exposure modifies the association between shorter gestation and SBP



Pb levels ≥ 2.5 µg/dL modify the association between shorter gestation and BP

Overall model p-value is p<0.0001

Sanders et al. *Env Int* 2018