Developmental exposures, kidney function, and biomarkers of cardiorenal signaling

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Washington, D.C.

- National Capitol
- Population: 6.2 million
Charlottesville, VA.
• Population: 48,000
Madison, WI.

- Population: 260,000
Chapel Hill, NC.

- Population: 65,000
New York, NY.

- Population: 18.8 million
Lexington, KY.

- Population: 320,000
1. **Metals are widespread toxicants**

2. Early life exposures may program renal health

3. Novel kidney biomarkers
Toxic metals

What are they? Are we exposed?
Toxic metals have no biological role

(http://www.ptable.com/)
Toxic metals have no biological role

(http://www.ptable.com/)
Arsenic

- 20th most abundant metal(loid) 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.

77 million
Arsenic occurs in drinking water worldwide

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

77 million
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

A Arsenic

Average arsenic conc (ppb)
- 0.50 – 1.29
- 1.29 – 1.66
- 1.66 – 2.54
- 2.54 – 20.37

B Cadmium

Average cadmium conc (ppb)
- 0.50 – 0.54
- 0.54 – 0.88
- 0.88 – 1.82
- 1.82 – 3.04

C Manganese

Average manganese conc (ppb)
- 15.00 – 41.55
- 41.55 – 72.05
- 72.05 – 139.69
- 139.69 – 1116.30

D Lead

Average lead conc (ppb)
- 2.50 – 3.52
- 3.52 – 4.94
- 4.94 – 7.28
- 7.28 – 1304.24

Sanders et al. BMC Pub Health 2014
Spatial patterns of metals in NC

A. Arsenic
- 10 ppb: 2.4%
- Average arsenic conc (ppb): 0.50 – 1.29
- 0.50 – 1.66
- 1.66 – 2.54
- 2.54 – 20.37

B. Cadmium
- 5 ppb: 0.1%
- Average cadmium conc (ppb): 0.50 – 0.54
- 0.54 – 0.88
- 0.88 – 1.82
- 1.82 – 3.04

C. Manganese
- 50 ppb - SMCL: 21%
- Average manganese conc (ppb): 15.00 – 41.55
- 41.55 – 72.05
- 72.05 – 139.69
- 139.69 – 1116.30

D. Lead
- 15 ppb: 3.1%
- Average lead conc (ppb): 2.50 – 3.52
- 3.52 – 4.94
- 4.94 – 7.28
- 7.28 – 1304.24

Sanders et al. BMC Pub Health 2014
Public health relevance

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

Raise awareness of areas of concern
Toxic metals

What are they? Are we exposed?
Metals are understudied environmental toxicants in human populations.

Known causes of birth defects:

- Environmental (10%)
- Genetic (20%)
- Unknown (70%)

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

1. Arsenic
2. Lead
3. Mercury
4. Vinyl chloride
5. Polychlorinated biphenyls
6. Benzene
7. Cadmium

ATSDR 2019
Metals are understudied environmental toxicants in human populations

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

<table>
<thead>
<tr>
<th>Metal</th>
<th>% detected</th>
</tr>
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<tbody>
<tr>
<td>Arsenic</td>
<td>65.7</td>
</tr>
<tr>
<td>Cadmium</td>
<td>57.3</td>
</tr>
<tr>
<td>Mercury</td>
<td>63.8</td>
</tr>
<tr>
<td>Lead</td>
<td>100</td>
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</table>

Known causes of birth defects

Sanders et al. *PLoS ONE* 2012
Metals are understudied environmental toxicants in human populations

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

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**Known causes of birth defects**

- Genetic: 20%
- Environmental: 10%
- Unknown: 70%

Sanders et al. *PloS ONE* 2012
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
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

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

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
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 are paradigm nephrotoxicants

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Environment International 131 (2019) 104993

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

Alison P. Sanders\textsuperscript{a,b,*}, Matthew J. Mazzella\textsuperscript{a}, Ashley J. Malin\textsuperscript{a}, Gleicy M. Hair\textsuperscript{a}, Stefanie A. Busgang\textsuperscript{a}, Jeffrey M. Saland\textsuperscript{b}, Paul Curtin\textsuperscript{a}

\textsuperscript{a} Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA
\textsuperscript{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

<table>
<thead>
<tr>
<th>Metal</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Hg</td>
<td>61%</td>
</tr>
<tr>
<td>Cd</td>
<td>17%</td>
</tr>
<tr>
<td>As</td>
<td>13%</td>
</tr>
<tr>
<td>Pb</td>
<td>9%</td>
</tr>
</tbody>
</table>

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 *predict* 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
Methods

Arora et al. Nat Comm 2017
Methods

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

- 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)

<table>
<thead>
<tr>
<th></th>
<th>Arithmetic mean (SD) or Percentage of Sample</th>
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</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>9.6 [9.1, 10.3]</td>
</tr>
<tr>
<td><strong>Male sex, %</strong></td>
<td>51%</td>
</tr>
<tr>
<td><strong>Socioeconomic status</strong></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>55%</td>
</tr>
<tr>
<td>Medium</td>
<td>36%</td>
</tr>
<tr>
<td>High</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Smoke exposure in the home (2T)</strong></td>
<td>30%</td>
</tr>
<tr>
<td><strong>Child BMI</strong></td>
<td></td>
</tr>
<tr>
<td>Normal Weight</td>
<td>53%</td>
</tr>
<tr>
<td>Overweight</td>
<td>24%</td>
</tr>
<tr>
<td>Obese</td>
<td>23%</td>
</tr>
<tr>
<td><strong>eGFR$_{CysC2012}$ (mL/min/1.73m²)</strong></td>
<td>120.7 [92.2, 149.1]</td>
</tr>
</tbody>
</table>
Prenatal Pb exposure during the 7 weeks prior to birth was associated with increased eGFR at 8-10 years.

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

![Diagram showing developmental stages and environmental exposures in early life.](image-url)
What about other early life environmental exposures?
Fluoride exposure in the US


- 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/1.72m² 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

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

- 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.

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

Dr. Maria José Rosa
PM$_{2.5}$ exposure between weeks 11-32 of gestation was associated with increased BP at age 4-6 years.
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.
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?

Environmental exposures in weekly increments: Pb, Cd, Cr, Li, As

1st trimester | 2nd trimester | 3rd trimester | Perinatal | Early childhood

- Branching
- Nephrogenesis
- Increase in renal blood flow & GFR

4 Weeks

Metanephric mass (proto-kidney)

36 Weeks

Oxidative Stress

Full complement of nephrons

1-6 Years

Oxidative Stress

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Toxic metals and early life health effects

1. Metals are widespread toxicants

2. Early life exposures may program renal health

3. Novel kidney 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.
Towards better biomarkers of renal health: microRNAs
Towards better biomarkers of renal health: microRNAs

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

Alison P Sanders¹, Heather H Burris², All 2, Katherine Motta³, Valeria Svensson¹, Adriana Mercado-Garcia⁶, Ivan Pantic⁴, Joel Schwartz³, Martha M Tellez-Rojo⁶, Robert O Wright⁷, and Andrea A Baccarelli⁴,⁷

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 associated with gestational age at delivery (p < 0.05). miR-575 and miR-4286 were negatively associated with toenail mercury levels, and tibial bone lead levels were associated with decreased expression of miR-575 and miR-4286. Conclusion: The
Towards better biomarkers of renal health: microRNAs

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

Alison P Sanders¹, Heather H Burris²,*, Allan C Just³, Valeria Motta⁴,⁵, Katherine Svensson¹, Adriana Mercado-Garcia⁶, Ivan Pantic⁴,⁷, Joel Schwartz³, Martha M Tellez-Rojo⁶, Robert O Wright¹, and Andrea A Baccarelli³,⁴

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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
Methods

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

miRNA isolation

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
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:
  \[
  \text{eGFR}_{\text{CKiD} \ 2012} = 70.69 \times (\text{Cystatin C})^{-0.931}
  \]
  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)

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<td>Age, years</td>
<td>4.7 (0.5)</td>
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<td>Male sex, %</td>
<td>47%</td>
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<td>Socioeconomic status</td>
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<tr>
<td>Low</td>
<td>52%</td>
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<td>99.3 (24.3)</td>
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Results

- 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
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

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Acknowledgments

Mount Sinai (New York, USA)
- Christine Austin - Yuri Levin-Schwartz
- Paul Curtin - Katherine Svensson
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- Ivan Pantic
- Mari Cruz Tolentino

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- 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
Does Pb exposure program hypertension or CKD?

- HTN prevalence: 45% US adults (~100 million)
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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

<table>
<thead>
<tr>
<th>Visits:</th>
<th>1\textsuperscript{st} trimester</th>
<th>2\textsuperscript{nd} trimester</th>
<th>3\textsuperscript{rd} trimester</th>
<th>Postpartum</th>
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</thead>
<tbody>
<tr>
<td>V1 weeks 9-16</td>
<td>Increase in GFR and renal plasma flow; Decrease in serum creatinine, BUN, potassium, and BP. Rise in aldosterone, sodium.</td>
<td></td>
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<tr>
<td>V2 20-24</td>
<td>Kidneys increase in length and volume, increase in urine protein and albumin excretion</td>
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<tr>
<td>V3 28-32</td>
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<td>V4 33-37</td>
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<td>Return to efficient states of reabsorption, excretion, eGFR; kidney size reduction.</td>
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</table>

**Metal toxicants**

- Oxidative stress
- Hormonal disruption
- miRNA expression changes

**Hydronephrosis**

- Normal kidney size

12 weeks—1 year postpartum

Risk of hypertension, CKD, and CVD
Effect modification by BMI

<table>
<thead>
<tr>
<th>1st trimester</th>
<th>2nd trimester</th>
<th>3rd trimester</th>
<th>Perinatal</th>
<th>Early childhood</th>
<th>Adolescence</th>
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</thead>
<tbody>
<tr>
<td>Branching</td>
<td>Nephrogenesis</td>
<td>Increase in renal blood flow &amp; GFR</td>
<td></td>
<td></td>
<td>Low nephron number and kidney volume: Decreased eGFR and elevated tubular damage proteins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal kidney size</td>
</tr>
</tbody>
</table>

4 Weeks

Metanephric mass (proto-kidney)

36 Weeks

Oxidative Stress

1-6 Years

Oxidative Stress

Full complement of nephrons

Second hit hypothesis: Obesity, physical compression of kidneys, hyperfiltration, additional loss of nephrons

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Effect modification by BMI?

- Observed null direct relationship between lead and eGFR

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

![Graph showing SBP difference (mmHg) for different countries.](image)

de Jong et al. 2012
Shorter gestations associated with higher protein levels

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

*All models adjusted for child’s age, sex, BMI, and urinary creatinine
Shorter gestations associated with higher protein levels

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

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

\[ \beta_1 \ (95\% \ CI): -0.9 \ (-2.3, 0.5) \]
\[ \gamma_1 \ (95\% \ CI): -0.4 \ (-0.9, 0.06) \]
\[ \text{delta} \ (95\% \ CI): 35.9 \ (28.8, 43.0) \]

Overall p-value: 0.02

Sanders et al. *Env Int* 2018
Evidence of nonlinear relationships between shorter gestation and SBP

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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coefficient (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β1</td>
<td>-0.9 (-2.3, 0.5)</td>
</tr>
<tr>
<td>γ1</td>
<td>-0.4 (-0.9, 0.06)</td>
</tr>
<tr>
<td>delta</td>
<td>35.9 (28.8, 43.0)</td>
</tr>
</tbody>
</table>

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

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

Tamayo-Ortiz et al. 2016; 2018; 2020
Prenatal lead exposure modifies the association between shorter gestation and SBP

Predicted SBP (mmHg) vs Gestational age (weeks)

- BLLs ≥ 2.5 μg/dL
- β(95%CI): -1.6 (-2.9, -0.3)
- γ(95%CI): -0.9 (-1.6, -0.2)

37 weeks

Overall model p-value is p<0.0001
Prenatal lead exposure modifies the association between shorter gestation and SBP

\[ \beta(95\%CI): -1.6 (-2.9, -0.3) \]

\[ \beta(95\%CI): -0.9 (-1.6, -0.2) \]

Overall model p-value is \( p<0.0001 \)

BLLs ≥ 2.5 μg/dL

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

Gestational age (weeks)

Overall model p-value is \( p<0.0001 \)