Sex-specific associations between co-exposure to metals and learning in early adolescence

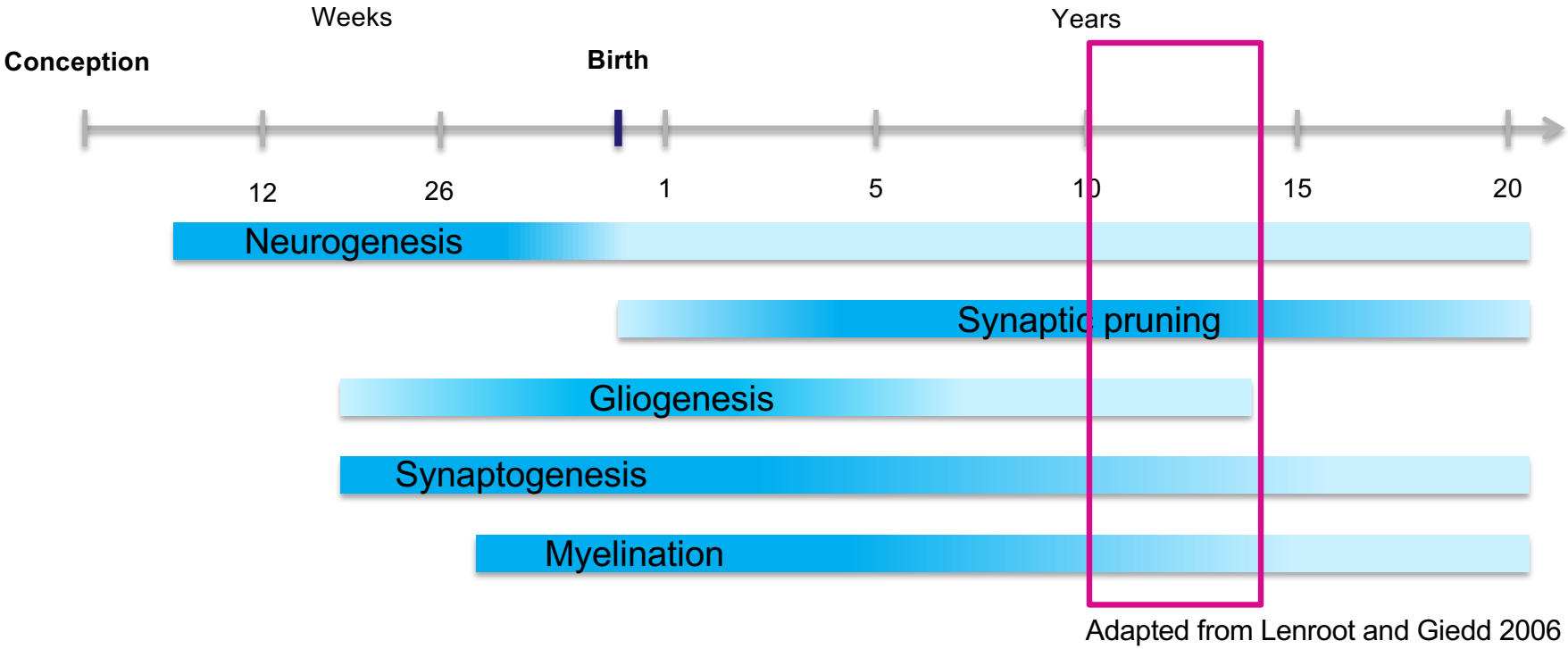
Elza Rechtman
Postdoctoral Fellow
Department of Environmental Medicine and Public Health
Icahn School of Medicine at Mount Sinai
elza.rechtman@mssm.edu

Mount Sinai

Background

Children and adolescents are uniquely vulnerable to metal exposure

- Brain development

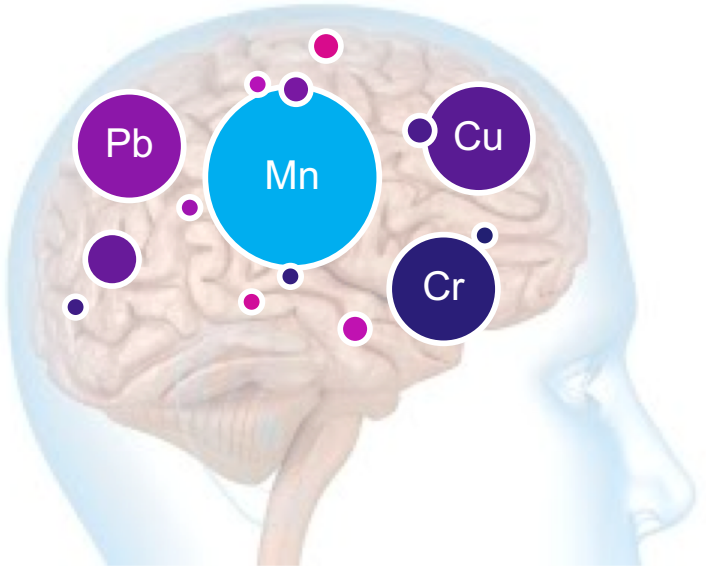


Adapted from Lenroot and Giedd 2006

- The Brain is a sexually dimorphic organ

Co-exposure to metals

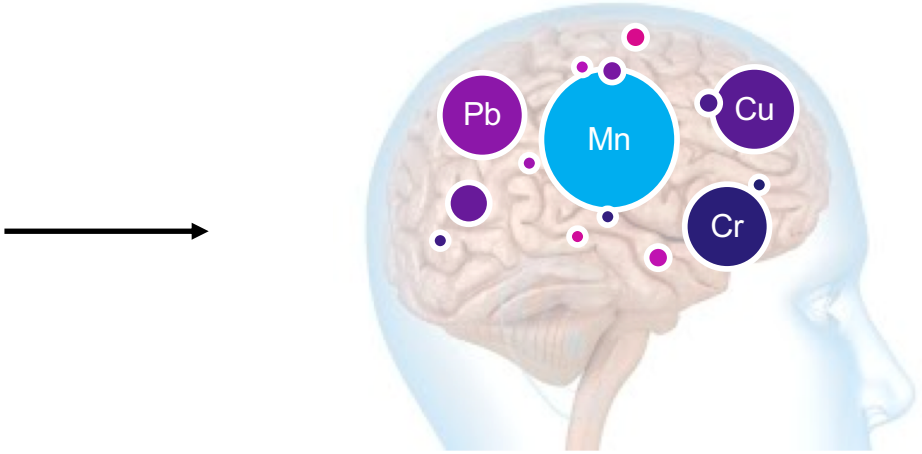
- Children and adolescents are exposed to low levels of several metals simultaneously throughout their childhood
- Interactions between metals may alter their toxicity
- Sex-dependent vulnerability



Cognition

Measuring the effect of exposure on the brain

- We don’t have access to the target tissue: the brain
- Lack of clear consensus regarding the best biomarker of exposure



Aims

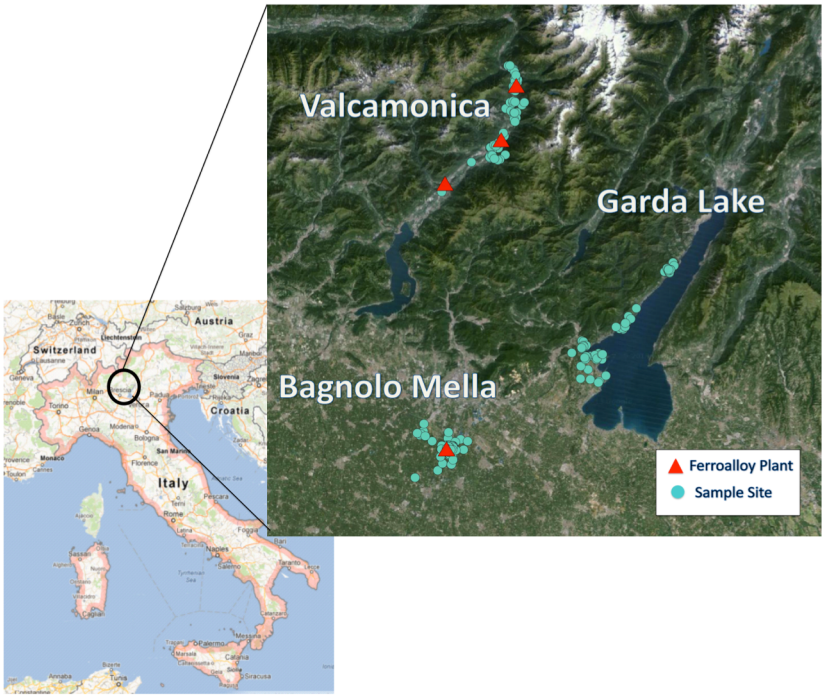
1. Is co-exposure to a mixture of metals associated with cognitive outcomes in adolescents? Is there a sex-dependent vulnerability?

2. What is the contribution of each metal to the overall mixture effect?

3. Which tissue best reflect the effect of exposure on the brain?

Methods

- The Public Health Impact of Metal Exposure in susceptible populations (PHIME) cohort



- Matrices: Blood, Urine, Hair, Nails, Saliva
- Metals: Mn, Pb, Cr, Cu

20 components

- Final sample: 188 participants (88 girls)

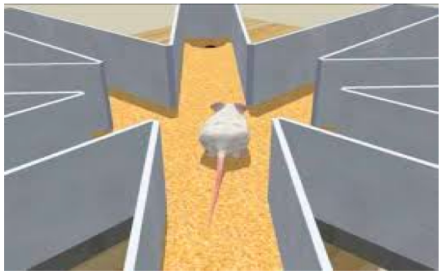
Sociodemographic characteristics

Characteristic	Girls (n=88) Mean ± SD or %	Boys (n=100) Mean ± SD or %	*p* *
Age (years)	12.1 ± 0.9	12.1 ± 0.8	0.51
SES			
Low	46.6 %	62 %	Ref
Medium	27.3 %	16 %	**0.02***
High	26.1 %	22 %	0.16
Daily frequency of playing video games			
Do not play	12.5 %	2 %	Ref
Rarely play	26.1 %	20 %	0.06
<1 hour/day	44.3 %	50 %	**0.01***
<2 hour/day	12.5 %	21 %	**0.01***
<3 hour/day	3.4 %	6 %	**0.03***
>3 hour/day	1.1 %	1 %	0.38
IQ	107.4 ± 13.6	107.1 ± 12.6	0.86

Outcome: The Virtual Radial Arm Maze (VRAM)

Humans

Rodents



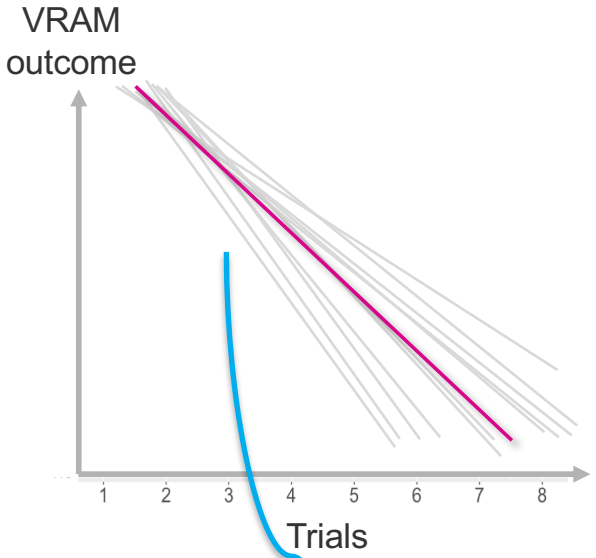
- In rodents, the RAM has been shown to be effective in detecting metal related visuospatial memory deficits
- Enables translational research

Statistical analyses

1. Generalized linear mixed models (GLMM) with random slopes

- Time to complete the maze
- Distance traveled
- Number of working memory errors
- Number of reference memory errors

Adjusted for age, SES, videos games



2. Weighted quantile sum (WQS) regression

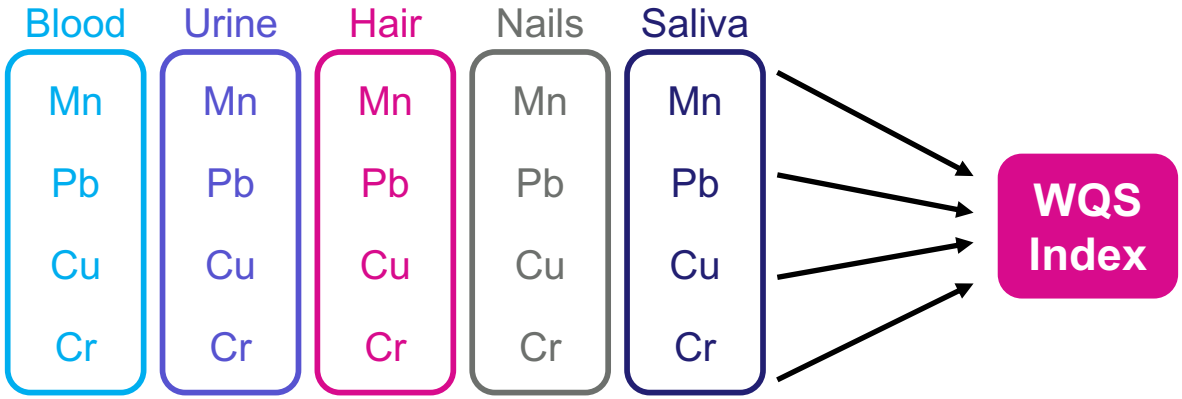


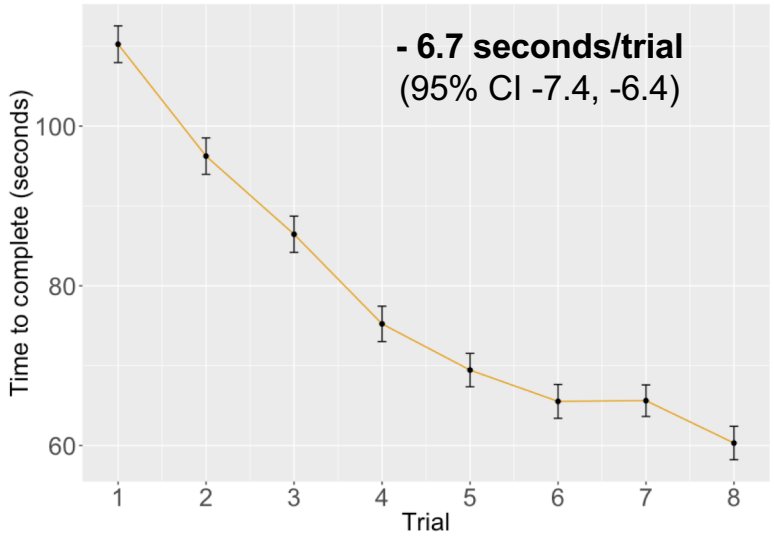
Figure: Eva Tanner

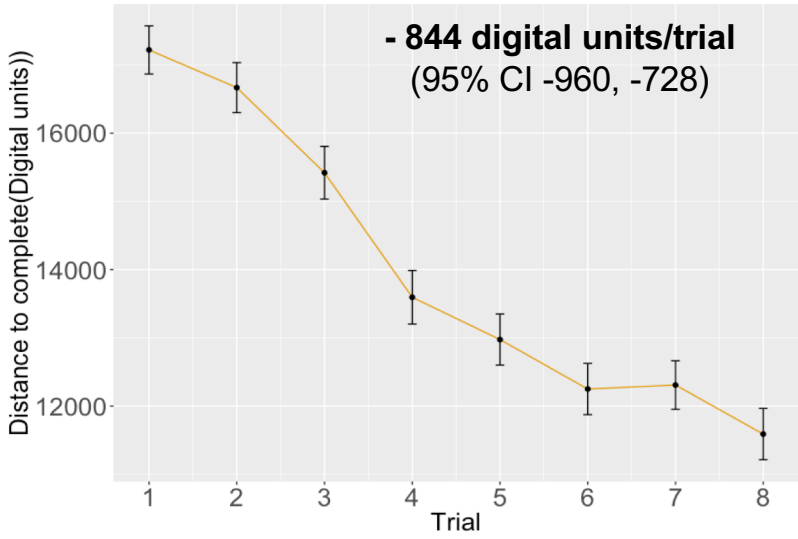
Learning curve

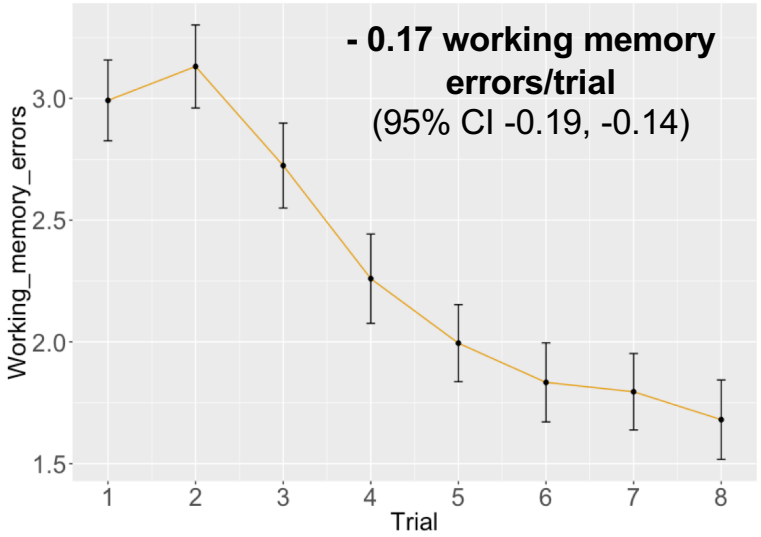
$$Learning\ curve = \beta_0 + \boldsymbol{\beta_1}\left(\sum_{i=1}^{c} \boldsymbol{w_i} q_i\right)$$

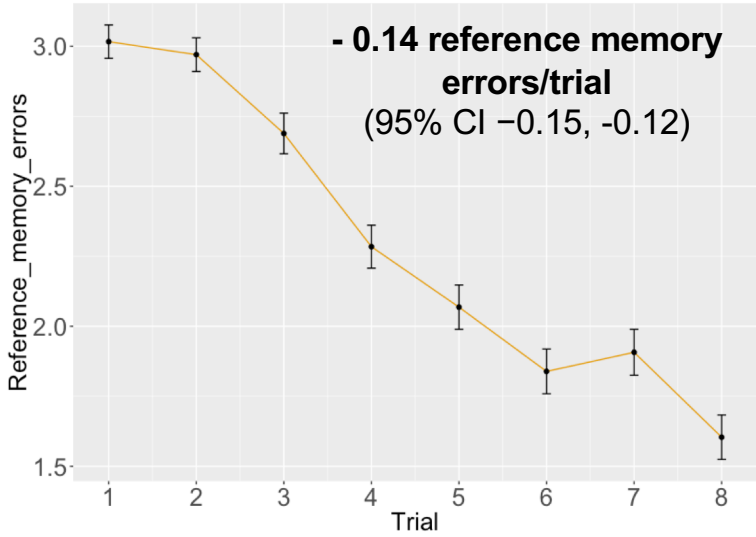
Results

GLMM: Estimated learning curve







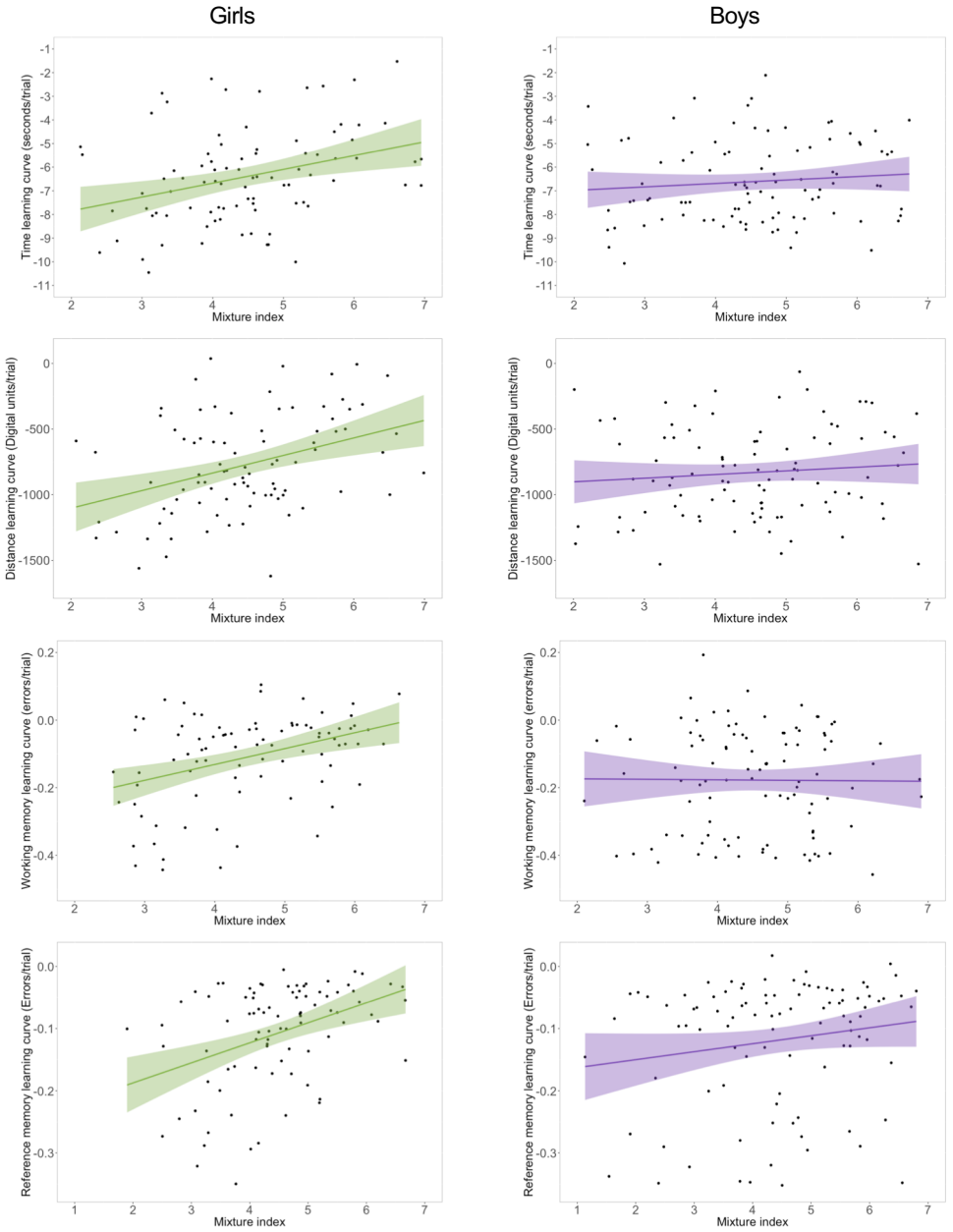


Weighted quartile sum (WQS) regression: the mixture effect

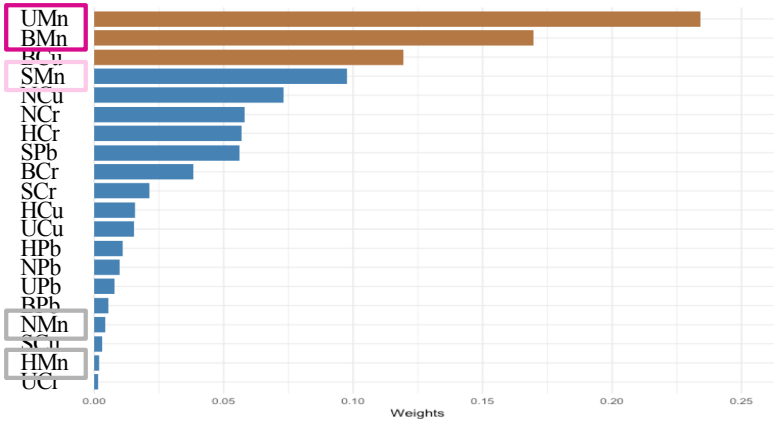
Learning curve	Girls (n=88)				
	WQS β	SE	t value	p value	p value (corrected)
Time to complete (seconds/trial)	0.56	0.18	3.18	0.002**	**0.030***
Distance to complete (digital units/trial)	130	34	3.8	0.0003***	**0.004****
Working memory (errors/trial)	0.04	0.01	3.26	0.0016**	**0.024***
Reference memory (errors/trial)	0.03	0.01	3.86	0.0002***	**0.006****

Learning curve	Boys (n=100)				
	WQS β	SE	t value	p value	p value (corrected)
Time to complete (seconds/trial)	0.18	0.13	1.38	0.171	0.5
Distance to complete (digital units/trial)	23	25	0.9	0.364	0.840
Working memory (errors/trial)	0.01	0.02	0.39	0.7	0.8
Reference memory (errors/trial)	0.01	0.01	1.69	0.094	0.5

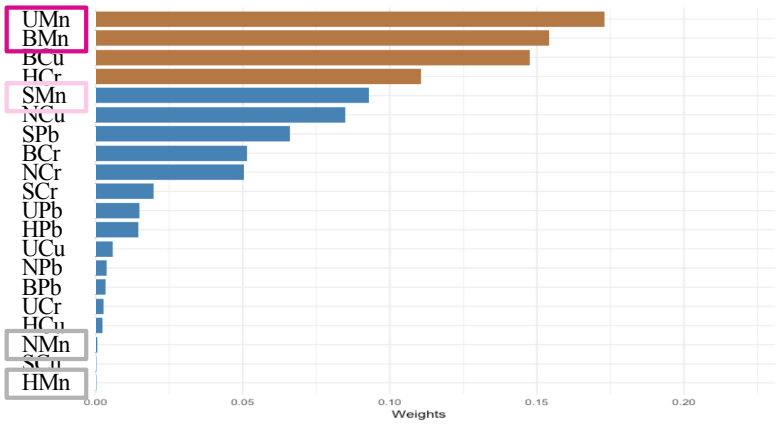
Weighted quartile sum (WQS) regression: the mixture effect



Weighted quartile sum (WQS) regression: Estimated weights



Time to complete
(seconds/trial)



Distance to complete
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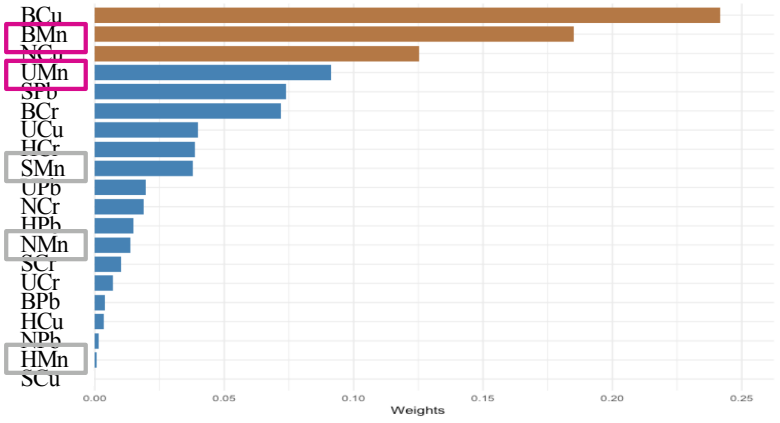
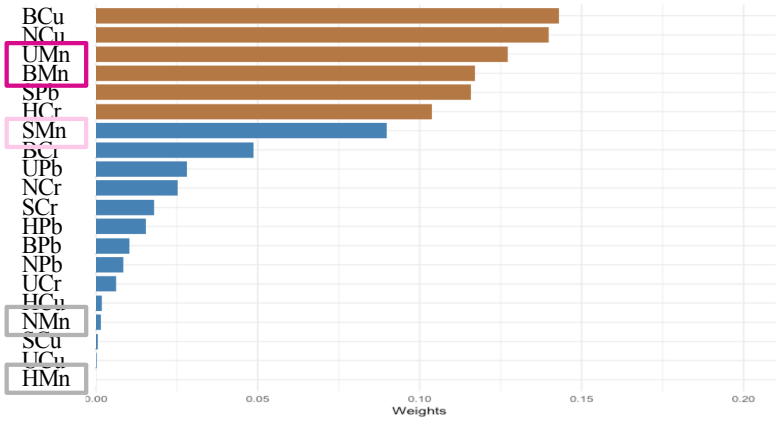
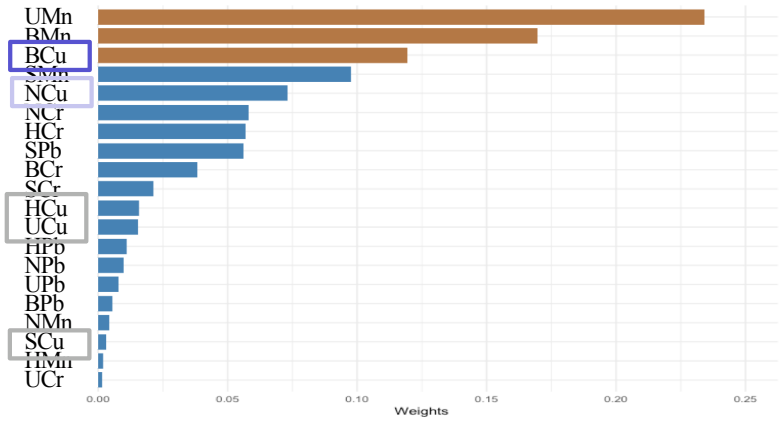


Working memory
(errors/trial)



Reference memory
(errors/trial)

Weighted quartile sum (WQS) regression: Estimated weights



Time to complete
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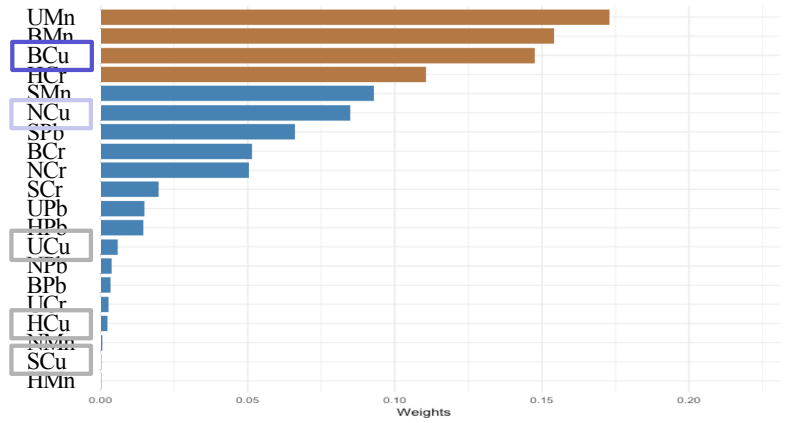

Distance to complete
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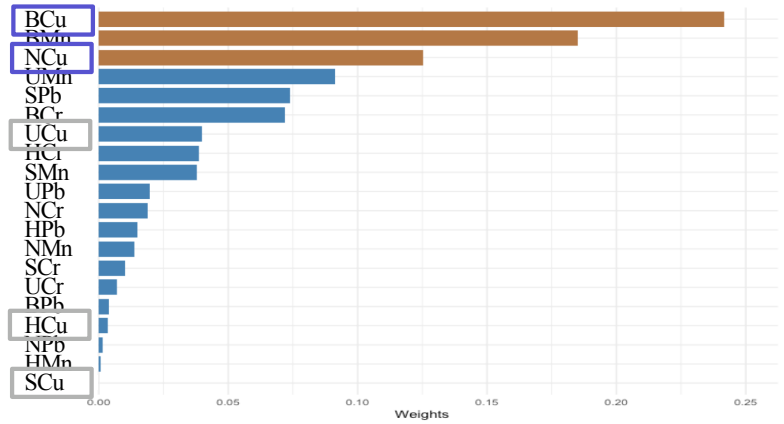

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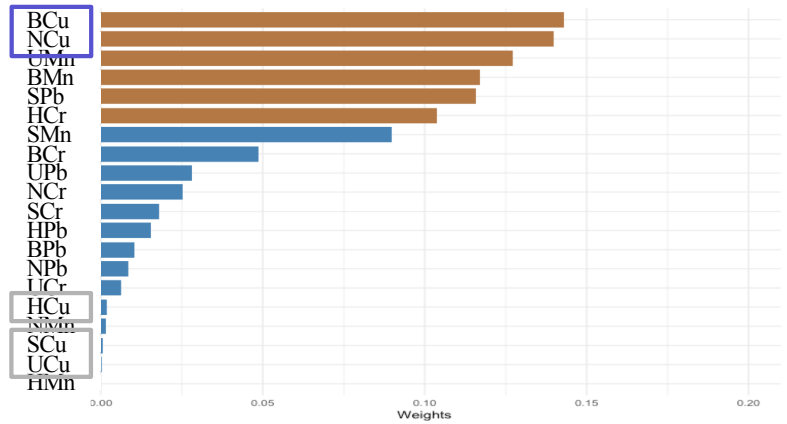

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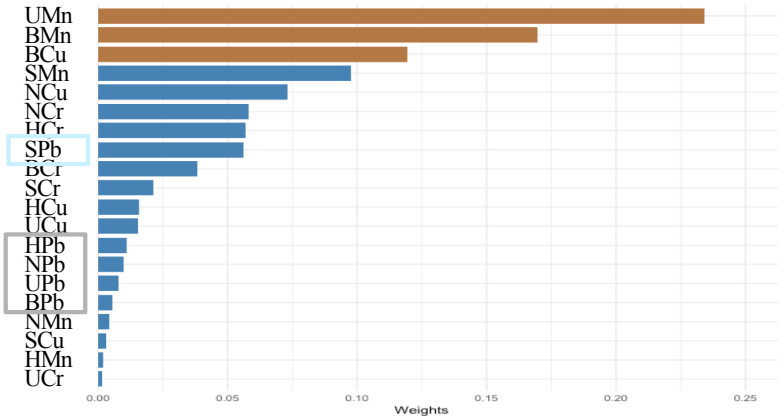
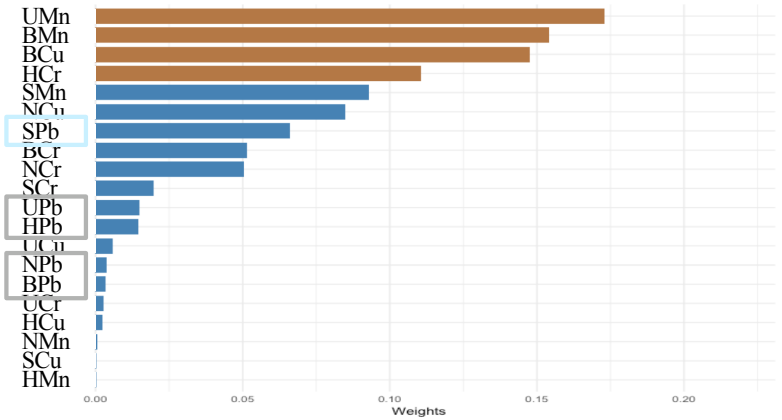


Time to complete
(seconds/trial)



Distance to complete
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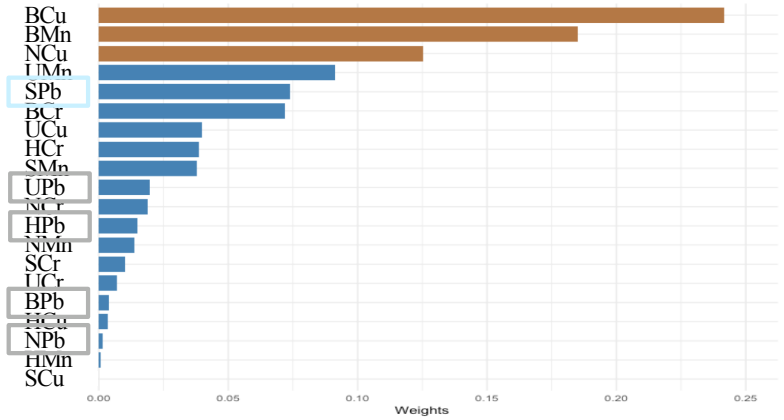

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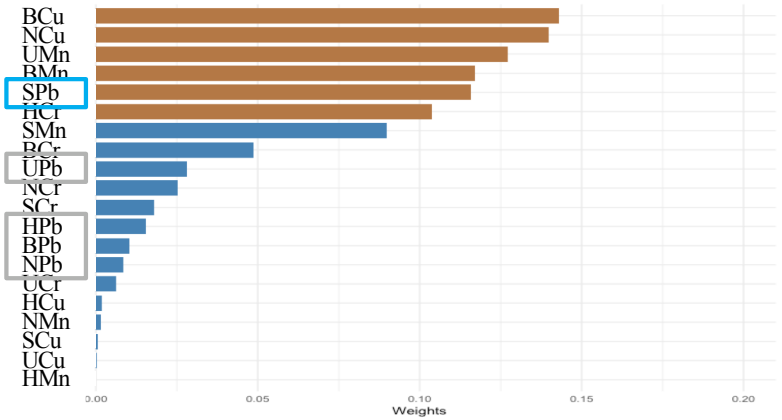

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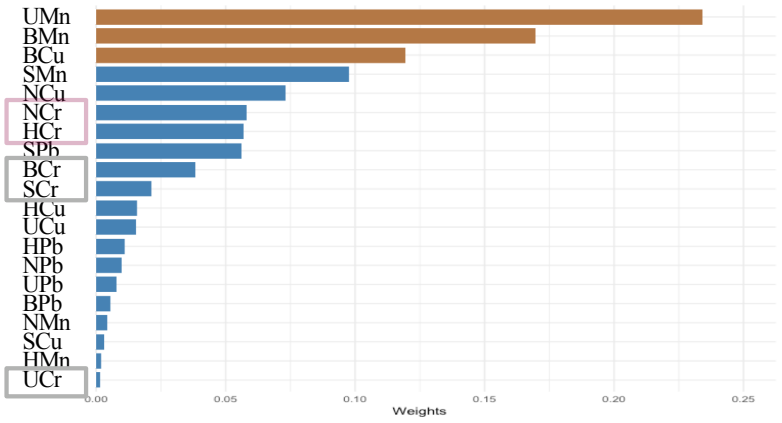

Time to complete
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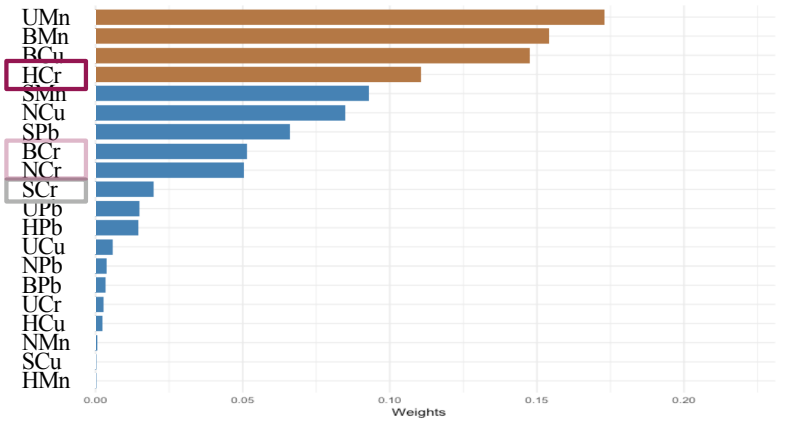

Distance to complete
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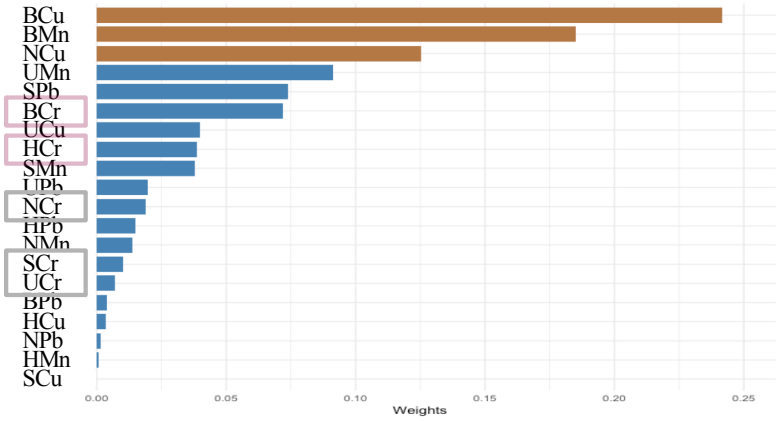

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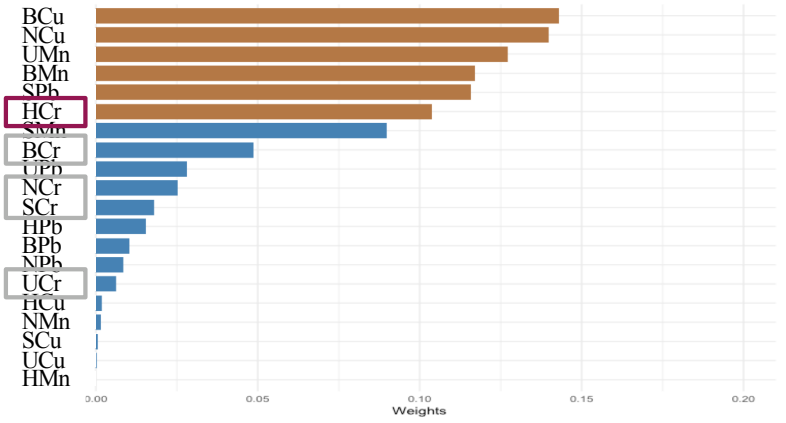


Reference memory
(errors/trial)

Discussion

1. **Is exposure to a mixture of metals associated with cognitive outcomes in adolescents?**

   - Yes, but only for girls

2. **What is the contribution of each metal to the overall mixture?**

3. **Which matrix best the effect of exposure on the brain?**

1. Is exposure to a mixture of metals associated with cognitive outcomes in adolescents?

2. **What is the contribution of each metal to the overall mixture?**

   - Mn and Cu are large contributors

3. Which matrix best reflect the effect of exposure on the brain?

1. Is exposure to a mixture of metals associated with cognitive outcomes in adolescents?

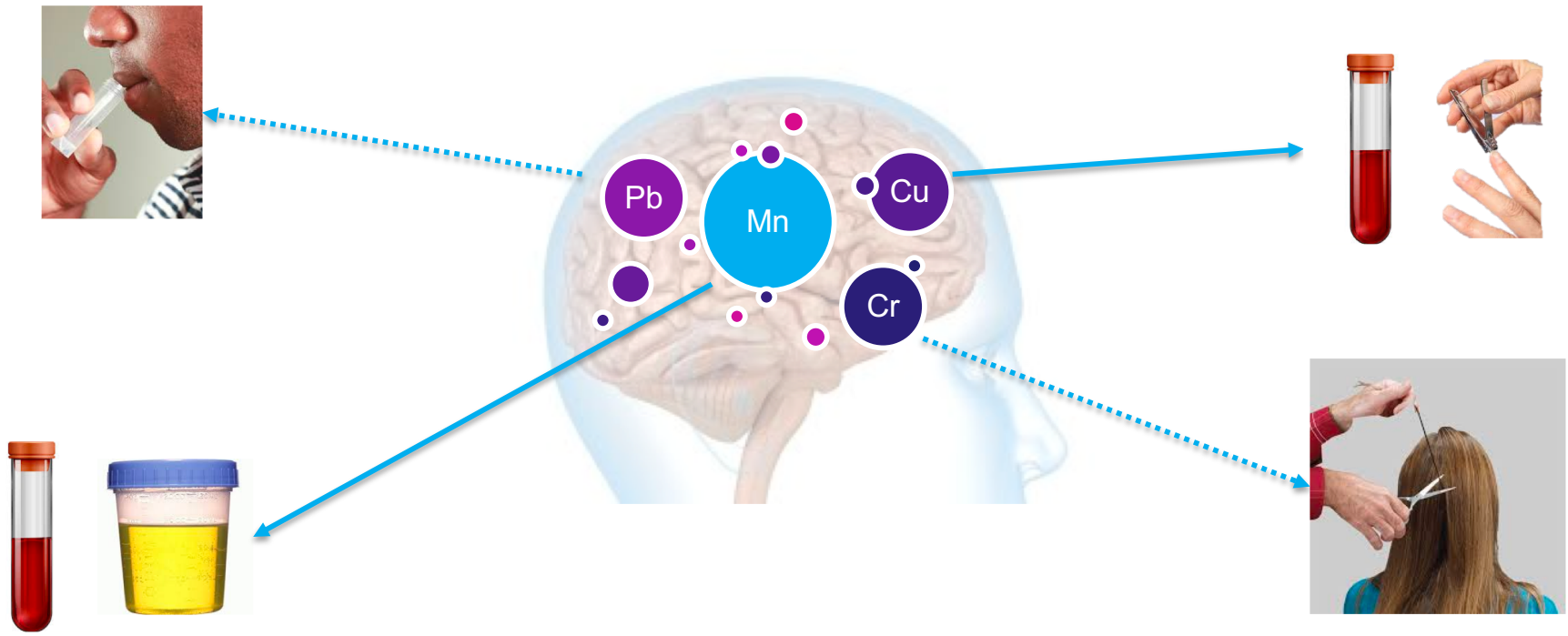
2. What is the contribution of each metal to the overall mixture?

3. **Which matrix best reflect the effect of exposure on the brain?**

- It's complicated…

Biomarkers of exposure: which reflect best the effect on the brain?

- Depending on the metal, different matrices represent the effect of exposure on the brain



Conclusion

- Exposure to this metal mixture during adolescence may disrupt learning in girls but not in boys
- Mn and Cu are large contributors
- Depending on the metal, different matrices represent the effect of exposure on the brain

- Translational research to address underlying neurotoxic mechanisms
- Mixtures analyses may not show the same results as single metal studies
- Future research should use the same approach to investigate other outcomes (motor, cognitive, behavioral, emotional)

Acknowledgments

Icahn School of Medicine at Mount Sinai, New York, USA

Megan K Horton

Roberto G Lucchini

Paul Curtin

Demetrios Papazaharias

Erik de Water

Elena Colicino

Robert O. Wright

University of Brescia, Brescia, Italy

Stefano Renzetti

Giuseppa Cagna

Marco Peli

Donatella Placidi

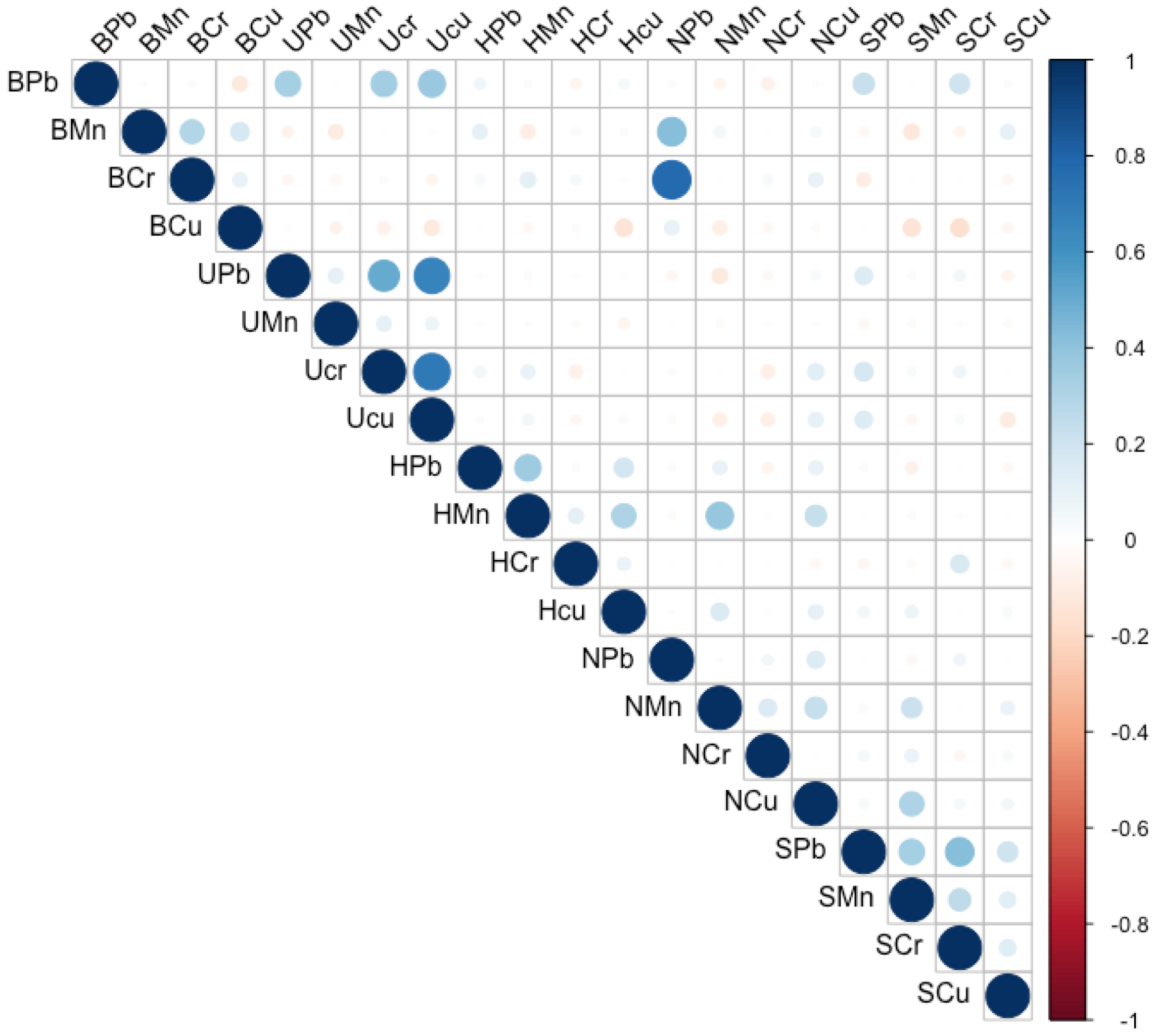
University of California, Santa Cruz, USA

Donald R Smith

Funding Sources:

- **NIEHS:**
  R01ES019222
- **The European Union Sixth Framework Program:**
  FOODCT-2006-016253
- **University of Brescia, Italy:**
  UNBSCLE 9015

Correlations of metals



Metal concentrations

Metal concentration	All participants GM ± GSD	Girls (n=88) GM ± GSD	Boys (n=100) GM ± GSD	p [a]
Blood (ug/L)				
Mn	10.92±1.36	10.98±1.39	10.87±1.34	0.58
Pb	14.48±1.80	12.53±1.71	16.45±1.82	**0.03***
Cr	0.74±2.04	0.69±2.01	0.78±2.06	0.72
Cu	845.17±1.16	827.88±1.16	860.68±1.15	0.07
Urine (ug/L)[b]				
Mn	0.23±3.26	0.25±3.25	0.20±3.26	0.68
Pb	0.69±1.81	0.67±1.82	0.72±1.80	0.71
Cr	0.19±1.86	0.18±1.77	0.19±1.93	0.21
Cu	8.46±1.68	8.28±1.61	8.63±1.75	0.34
Hair (ug/g)				
Mn	0.07±2.17	0.05±1.97	0.09±2.22	**0.001****
Pb	0.10±3.54	0.08±3.47	0.11±3.55	0.09
Cr	0.04±2.12	0.04±2.06	0.04±2.17	0.63
Cu	12.16±1.70	13.73±1.73	10.93±1.64	**0.008****
Nails (ug/g)				
Mn	0.27±3.81	0.26±3.74	0.27±3.91	0.73
Pb	0.24±4.54	0.22±4.89	0.25±4.26	0.33
Cr	0.17±2.33	0.19±2.29	0.15±2.35	0.24
Cu	2.51±1.73	2.45±1.84	2.56±1.63	0.74
Saliva (ug/L)				
Mn	3.26±2.95	2.97±2.98	3.54±2.92	0.43
Pb	0.32±3.84	0.30±3.44	0.35±4.22	0.10
Cr	0.30±2.60	0.29±2.33	0.30±2.85	0.19
Cu	16.63±2.90	18.91±2.76	14.85±2.99	0.66