Metal mixtures and child neurodevelopment in Bangladesh

Investigating joint effects and windows of susceptibility using Bayesian Kernel Machine Machine Regression

Linda Valeri

Department of Biostatistics

Columbia University Mailman School of Public Health
Acknowledgments

- Bangladesh Reproductive Study Participants
- Dhaka Community Hospital
  Omar Ibne Hasan, Mustafa Golam, Sakila Afroz, Quazi Quamruzzaman
- Harvard T.H. Chan School of Public Health
  David Bellinger, Brent Coull, David Christiani, Maitreyi Mazumdar, Ema Rodriguez
- Mount Sinai
  Robert Wright
- Kaiser Permanente
  Jennifer Bobb
- Boston University
  Birgit Claus Henn
Background

Simultaneous exposure to a set of environmental toxicants ("environmental mixture") is a realistic scenario

Modern epidemiology has moved beyond the single exposure, single outcome paradigm

Epidemiologic investigations on mixtures’ effects can better inform decision making by

- Detection / estimation of an effect of the overall mixture.
- Identification of pollutant or group of pollutants responsible for observed mixture effects.
- Detection of interactions among individual pollutants.
- Assessing whether heterogeneities in exposure profiles explain inconsistencies in current findings
Background

- In Bangladesh metals mixture exposure is an important concern.

- Due to geological factors water is contaminated by arsenic (As) and manganese (Mn).

- Exposure to lead (Pb) is also high and source is still largely unknown.

- The developing brain of children can be affected by exposure to these metals in utero and in early childhood.

- Previous studies have focused on single metal exposure and are mostly based on developed countries.
Goals of the Study and Challenges

**GOAL:** Quantify the joint effect of exposure to a mixture of As, Mn and Pb on neurodevelopment in a cohort of Bangladeshi infants and identify windows of susceptibility (prenatal vs postnatal exposure)

**CHALLENGES:** complex mixture-outcome relationship, highly correlated exposures, potential unmeasured confounding, important study sites heterogeneities

**NEW APPROACH NEEDED:** Bayesian Kernel Machine Regression (BKMR, Bobb et al. 2015) allows estimation of non-linear and non-additive dose-response functions for a (potentially high-dimensional) set of correlated exposures accounting for uncertainty
Specific objectives

• VARIABLE SELECTION

• WINDOWS OF SUSCEPTIBILITY

• SHAPE OF THE DOSE-RESPONSE

• OVERALL/CUMULATIVE EFFECT OF MIXTURE

• INTERACTIONS
Kernel Machine Regression (KMR)

\[ Y_i = h(X_{1i},...,X_{Mi}) + \beta Z_i + \varepsilon_i \]

- \( Y_i \): continuous, normally distributed health endpoint.
- \( X_i \): M exposure measures
- \( Z_i \): potential confounders
- \( \varepsilon_i \): iid \( N(0, \sigma^2) \)
- \( h() \): is an unknown but smooth function
- \( \beta \): effects of potential confounders
KMR

Operationally we fit the model

\[ Y_i = h_i + \beta Z_i + \varepsilon_i \]

- We tie this to the multi-pollutant exposure by assuming a pair of random effects \((h_i; h_j)\) are correlated
- the strength of this correlation is determined by the “distance” between a pair in the multivariate exposure space.

- By clever selection of the distance metric (i.e. the “kernel” function), we can accommodate nonlinear and non-additive effects of the multivariate exposure.

- We use the so-called Gaussian kernel function.

Liu, Lin and Ghosh, Biometrics 2007
Bayesian Kernel Machine Regression (BKMR)

• If there are only a few components driving health effects, we can estimate the exposure-response function $h$ using variable selection:

$$Y_i = h(X_{1i}, X_{2i}, X_{3i}, \ldots, X_{Mi}) + \beta Z_i + \varepsilon_i$$

• Using a Bayesian approach to model fitting, we obtain:
  - $\hat{h}(X_{1i}, \ldots, X_{Mi})$ the exposure-response function
  - An estimate of the probability given the data that pollutant $m$ is important (PIP).

• Software: `bkmr` package in R.

*Bobb et al., Biostatistics, 2015; Environmental Health, 2018*
BKMR: Assumptions

• Used *Gaussian kernel function* with weight for each pollutant estimated from data
  – Allows for nonlinear and non-additive effects
  – Allows some pollutants to be more important than others

• For variable selection, assumed a *spike and slab prior* for pollutant weights
  – Allows some pollutant weights to be exactly 0 and therefore not included in model
BKMR: Assumptions

- Applied **diffuse (non-informative) prior distributions** on parameters

- \( \varepsilon_i \sim N (0, \sigma^2) \)

- **Confounders assumed to not interact with exposure variables** (although this could be relaxed)
BKMR

• **Advantages:**
  – Addresses issues of nonlinearity and non-additivity among high-dimensional set of exposures
  – Estimates importance of each variable while simultaneously estimating exposure-response relationships
  – Point estimation and uncertainty quantification for almost any summary measure of mixture effect

• **Potential limitations/pitfalls:**
  – Be wary of extrapolation when predicting h() where there is little data
  – Limited ability to identify important components among highly correlated exposures
BKMR: Hierarchical variable selection

1. Partition exposures into groups $S_g$
2. Estimate posterior inclusion probability for each group $S_g$
3. Estimate conditional posterior inclusion probability for each exposure within the group, given that group was selected into model

$$Y_i = h(x_{i1}, \ldots, x_{i4}, x_{i5}, x_{i6}, x_{i7}) + \beta Z_i + \varepsilon_i$$
Data

- Mother-infant pair were enrolled in DCH Community Clinics in Sirjaldikhan and Pabna
- Maternal and cord blood As, Pb and Mn collected at birth were available for 825 subjects
- 20-40 months blood Pb and water Mn and As were available
- Cognitive (CS), Linguistic and Motor Development Scores obtained at 20-40 months

Valeri et al., EHP, 2017
Heavy Metals: A Public Health Concern

Scale: μg/dL

US reference:
As: 0-5 μg/dL
Mn: 4-15 μg/dL
Pb: 0-5 μg/dL
Heterogeneity in Exposure Profiles

Cord Blood Levels (µg/dL)

Heavy Metals

Metal

ln(As)  ln(Mn)  ln(Pb)

Pabna

Sirajdikhan

Metal

ln(As)  ln(Mn)  ln(Pb)
Critical Windows
Residual unmeasured confounding

**PROS:** Adjustment for post-natal exposure to metals might help adjusting for confounding

**CONS:** Introduces in the model highly correlated variables.
BKMR applied to BGD data

\[ Y_i = h(As_{i\text{CB}}, Mn_{i\text{CB}}, Pb_{i\text{CB}}, As_{i\text{W}}, Mn_{i\text{W}}, Pb_{i\text{B}}) + \beta Z_i + \varepsilon_i \]

- **prenatal**
- **postnatal**

- **409 children** from Pabna clinic and **416 children** from Sirajdikhan clinic in Bangladesh

- **Outcome**: Bayley Cognitive Development Score (CS) at 20-40 months of age; z-scored

- **Exposure**: arsenic (As), manganese (Mn), and lead (Pb) measured in cord blood at birth and at 20-40 months in water or blood; log-transformed

- **Covariates**: infant sex, mother's IQ, homescore (SES proxy), and mother's education, maternal protein intake, smoking environment, age at testing, and maternal age at delivery
BKMR applied to BGD data

\[ Y_i = h(As_i^{CB}, Mn_i^{CB}, Pb_i^{CB}, As_i^{W}, Mn_i^{W}, Pb_i^{B}) + \beta Z_i + \varepsilon_i \]

- We can consider two windows of susceptibility. Maternal exposure measured with cord blood concentrations and child exposure at 2 years of age (water and blood)
- We can make probability statements about these two groups of exposures according to timing
- We obtain
  - an estimate of the probability each group of exposures is important
  - an estimate of the probability that, given a group is important, each exposure in that group is driving that group-outcome association.
Results
Change in CS SD for a change in log concentrations of each metal from 25\textsuperscript{th} to 75\textsuperscript{th} percentile when the other metals are at either 25\textsuperscript{th}, 50\textsuperscript{th}, or 75\textsuperscript{th} percentile
BKMR for prenatal exposures effect

\[ Y_i = h(As_{i}^{CB}, Mn_{i}^{CB}, Pb_{i}^{CB}) + \beta Z_i + \varepsilon_i \]

- To improve power we dropped post-natal measurements
- Results were robust to adjustment to post-natal measurements
Figure 2: Mixture-CS function

PABNA: Mn most neurotoxic

Higher levels indicate better CS

SIRAJDIKHAN Pb most neurotoxic
Figure 3: Overall Mixture-CS association
Figure 4: Summary of findings in Pabna
Summary

• Negative joint effect of the metal mixture on cognitive score when metal concentrations are all above the 60\textsuperscript{th} percentile in the Pabna clinic
• Negative and additive linear association of Pb with CS in the Sirajdikhan clinic
• Negative and non-linear association of manganese with CS within the overall mixture effect
• Suggestion of As-Mn interaction on CS (p-value=0.04, in models that \textit{adjust} for clinic)
• Results were reproduced in analyses using generalized additive models \textit{(gam)} models
Limitations

• Potential measurement error in confounders

• Potential residual unmeasured confounding

• Cord blood measurements at birth might not be optimal to capture exposure during pregnancy

• We adjusted for confounders in the main model assuming non-interactive effects with the mixture (potential model mis-specification)
Conclusion

• Using BKMR we evaluated the **joint effect** of prenatal As, Pb and Mn on cognitive development among 20-40 month old children in Bangladesh.

• The approach can **identify the most important windows of vulnerability** when exposures are correlated using hierarchical variable selection.

• Employing a Bayesian approach incorporates the uncertainty in the estimation of a high dimensional set of exposures, **accounting for multiple comparisons**.

• We identified a toxic effect of the mixture and prenatal exposure to **manganese** appeared the most neurotoxic component.

• Results of the analyses **differed by clinic** due to differences in exposure-profiles.
How to mitigate neurotoxicity?

- We have extend the analyses considering mixtures of nutritional factors are found to interact with the mixture.

- Arsenic exposure appears neurotoxic among malnourished mothers (Lee et al., under revision).

- We have extended BKMR to assess mediating mechanisms (Devick, manuscript in preparation).

- We have found evidence that birth outcomes (birth weight, birth length and head circumference) mediate and moderate prenatal exposures effects on neurodevelopment (Lee et al., IJE, 2018).
Work in progress

• Improve robustness and validity of epidemiological investigations on mixtures

• Account for measurement error in environmental exposure and confounders

• Allow for time-dependent confounding (weighted-BKMR)
Thank you!

lv2424@cumc.columbia.edu
References


