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Complex Chemical Mixtures in Environmental Epidemiology

Why care about mixtures?

- We are exposed to hundreds (thousands?) of chemicals at any single time point
- Traditionally, epi studies have focused on single-chemical analyses
  - This does not represent reality
- The combination of exposures likely induces different responses

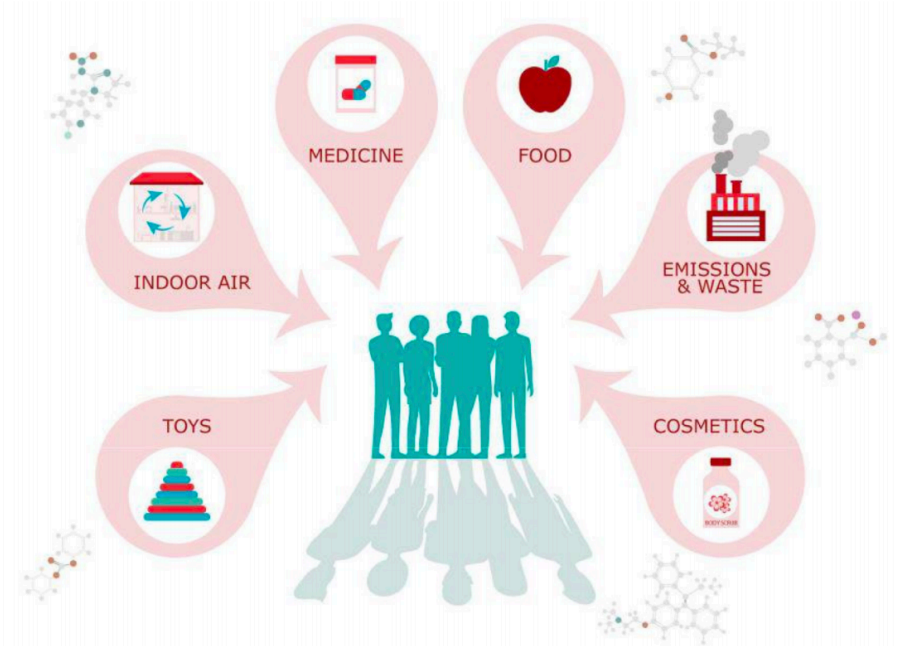

Image: ec.europa.eu via Yanelli Núñez

What is a mixture?

- Actually, there is no strict definition
- According to NIEHS "`a mixture must have at least three independent chemicals or chemical groups`"
- Generally, exposure to a mixture indicates exposure to multiple "stressors" simultaneously
  - Chemical
  - Non-chemical (SES, diet, etc)

Million dollar question

- The necessity to assess exposure to mixtures is now well-recognized
- US EPA, NRC, and NIEHS all agree

How can we represent the compexity of reality in a (single) statistical model?

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How can we represent the compexity of reality in a (single) statistical model?

How do we deal with exposure to mixtures?

- This is still a very open question
- Existing methods have limitations
- There have been several workshops held by EPA and NIEHS to address this issue
- The most recent NIEHS workshop (2015) concluded that
  1. Although some methods performed better than others, the presented estimated associations were still quite variable and not in agreement
  2. The choice of method should depend on the research question

Why do traditional methods fail?

- Chemicals are often highly-correlated
  - This means that they cannot go in the same regression model

  $\Rightarrow$ Large standard errors and unstable effect estimates
- Requires more flexible models
  - Group chemicals or assays
  - Drop some chemicals
  - Incorporate `machine learning techniques`

Some considerations

1. No single method outperforms all others for all potential questions
2. Interpretability
3. Robustness (stable solutions)
4. Computational scalability – as N and/or p increase, some methods begin to fail
5. Exploration vs. hypothesis testing
6. Not a good idea to "blindly" use methods from other fields – may need to adjust them first

Interpretability

Potential questions in mixtures analyses

For mixtures analyses the selected method depends on the primary research question

Bird's-eye (over)view of existing mixtures methods

Comparing results across methods

- Generally a good practice
  - Especially if complementary methods
  - Sensitivity analyses to assess robustness of results
- If different methods address different questions, consistency in findings is welcome, but not expected
- If/when differences across methods are detected $\rightarrow$ keep in mind what the aim of each method is!
- Trying different methods and choosing the answer we like the best should *always* be avoided
  - I.e., no cherry-picking!

Overall mixture effect

- We may want to estimate the overall mixture effect
- As chemical concentrations in the mixture increase, do we observe corresponding changes in the outcome?

Overall mixture effect example

A cross-sectional study of water arsenic exposure and intellectual function in adolescence in Araihazar, Bangladesh☆,☆☆

Gail A. Wasserman[a,b], Xinhua Liu[c], Faruque Parvez[c], Yu Chen[d], Pam Factor-Litvak[c], Nancy J. LoIacono[c], Diane Levy[c], Hasan Shahriar[e], Mohammed Nasir Uddin[f], Tariqul Islam[e], Angela Lomax[c], Roheeni Saxena[c], Elizabeth A. Gibson[c], Marianthi-Anna Kioumourtzoglou[c], Olgica Balac[c], Tiffany Sanchez[c], Jennie K. Kline[b,c], David Santiago[c], Tyler Ellis[g], Alexander van Geen[g], Joseph H. Graziano[c,*]

- Participants: 726 14–16 year olds whose mothers are participants in HEALS
- Exposure measurement: Blood As, Pb, Mn, Cd, and Se assessed at time of visit; maternal HEALS baseline creatinine-adjusted urinary As (mUAscr) used as indicator of *in utero* As exposure
- Outcome assessment: Culturally modified version of the WISC-IV, raw Full Scale scores

Overall mixture effect example (cont.)

Research question:

Is the metal mixture (As, Pb, Mn, Cd, Se, and maternal As) associated with intellectual function in adolescents?

Mixture method:

Bayesian Kernel Machine Regression (BKMR)

Overall mixture effect example (cont.)

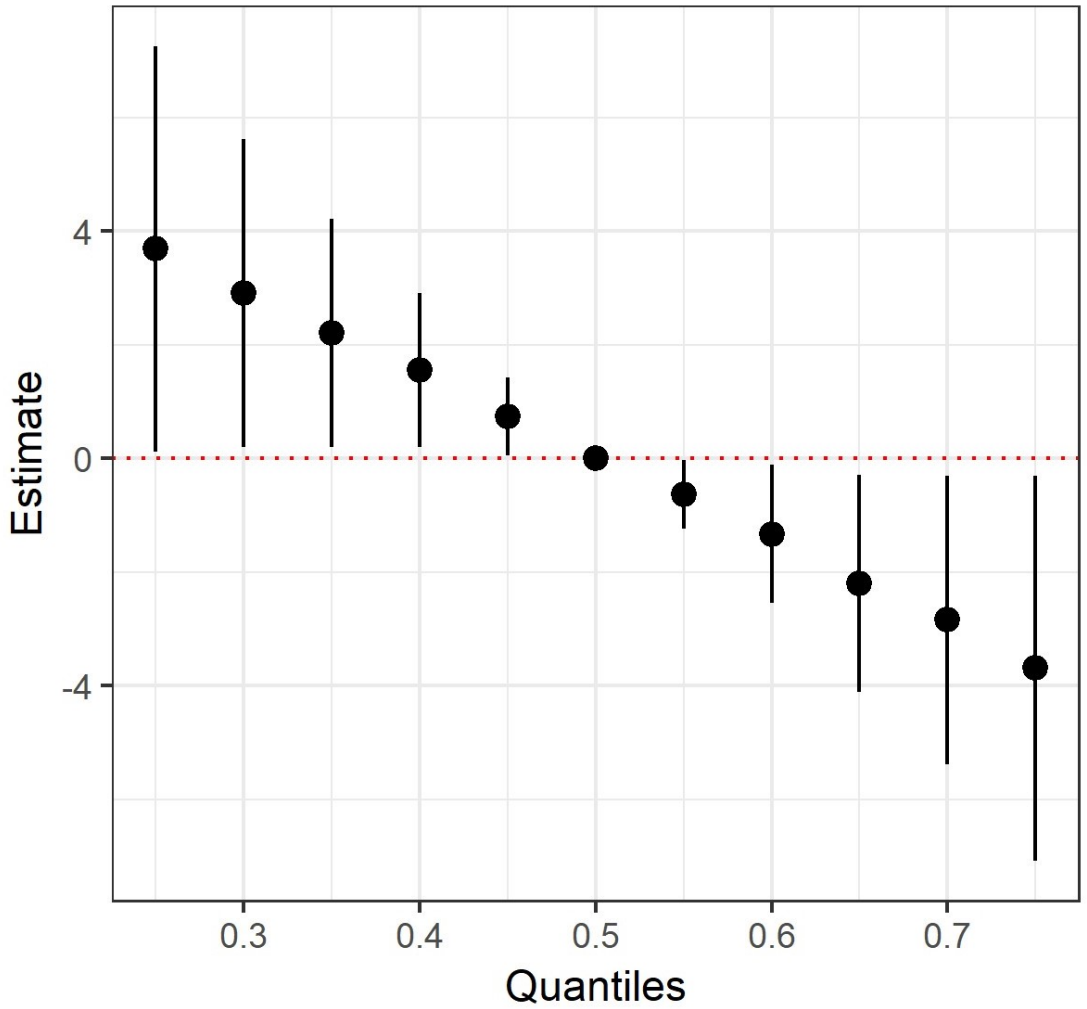
Bayesian Kernel Machine Regression (BKMR)

- Uses a flexible function of the exposures in the mixture
  - Specified by a Gaussian kernel

$$K\left(\mathbf{z}, \mathbf{z}'\right) = \exp\left\{-\sum_{m=1}^{M} r_m \left(z_m - z'_m\right)^2\right\}$$

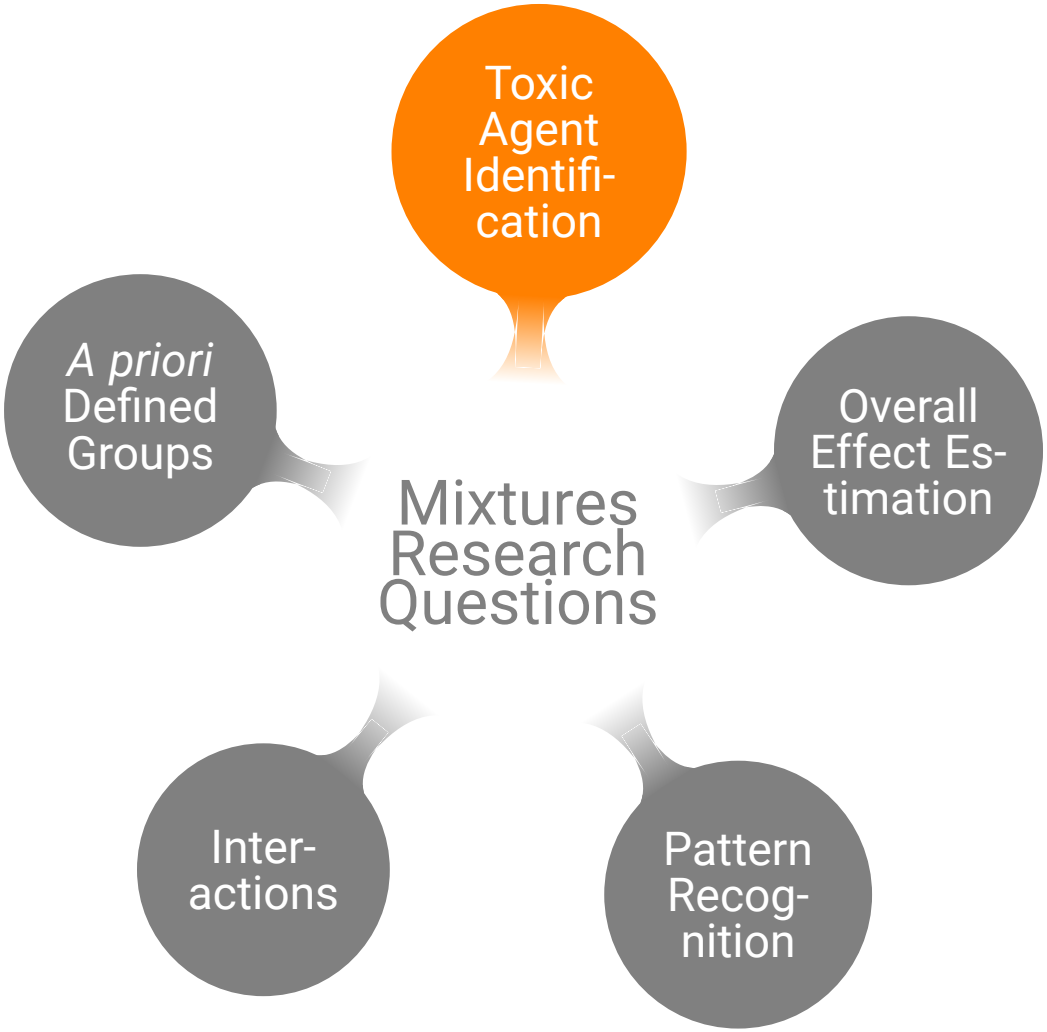
- Identifies important mixture members
  - Accounts for the correlated structure of the mixture
  - Incorporates a component-wise variable selection process
- Estimates potentially non-linear and non-additive exposure-response functions
- Evaluates high-order effects, i.e. interactions
- Bayesian framework allows overall effect estimation

Overall mixture effect example (cont.)



Identifying toxic agents

- *aka* “bad actors”
- Which chemical(s) in my mixture are related to the outcome?
- Estimate chemical-specific *independent* effects
- While accommodating the (potentially very) high correlations among mixture members



Toxic agent example

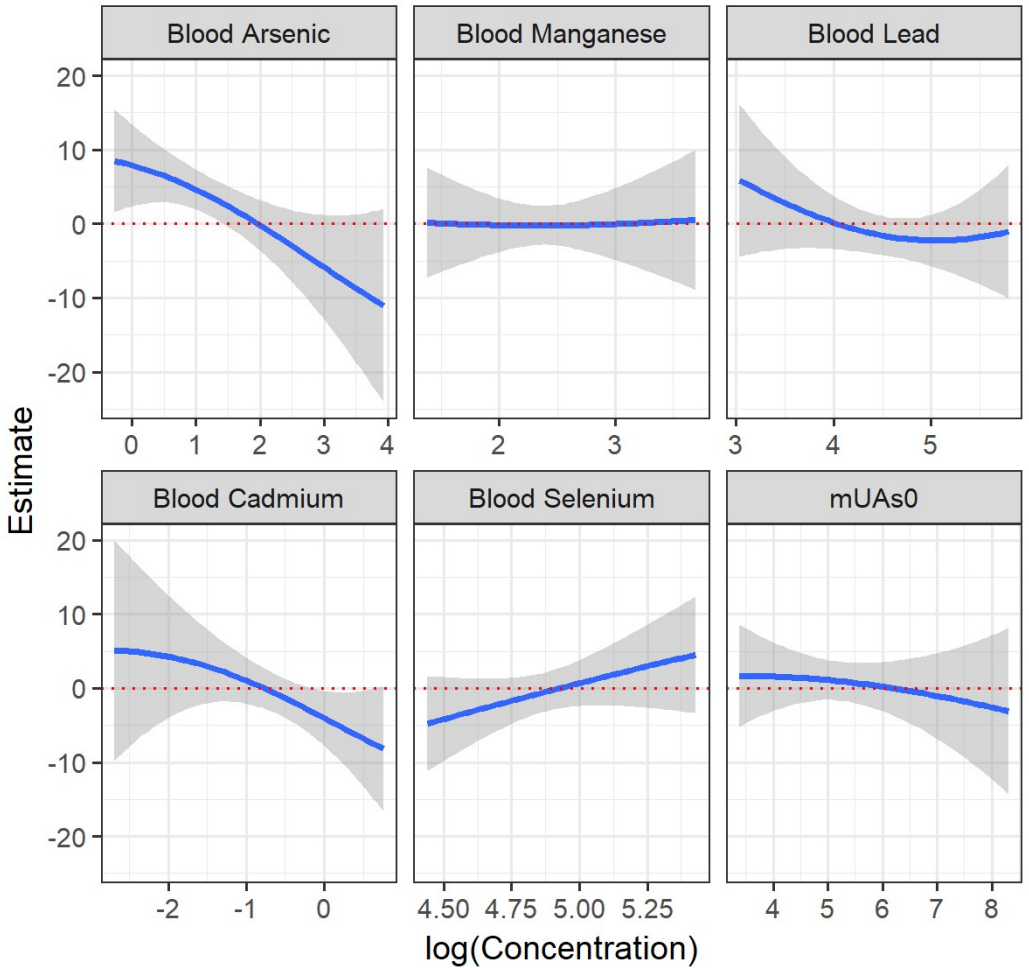
Research question:

Is adolescent As exposure associated with intellectual function while accounting for Pb, Mn, Cd, Se, and maternal As exposure during pregnancy?

Mixture method:

Bayesian Kernel Machine Regression (BKMR)

Toxic agent example (cont.)

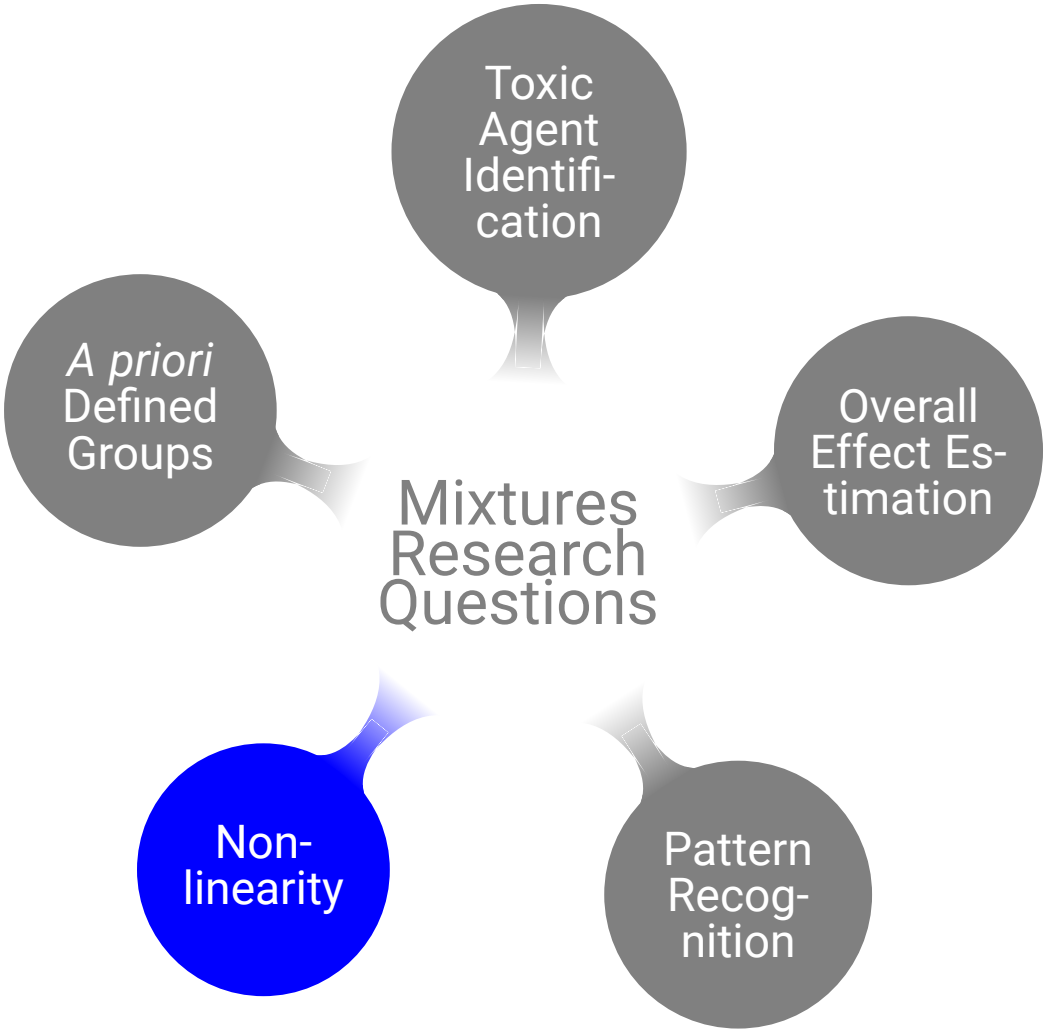


Interactions & non-linearity

- Actually, two different classifications of potential research questions
  1. Interactions among mixture members?
  2. Non-linear exposure – response curves?
- Methods tend to do both

Non-linearity

- Because linearity is just an assumption · · ·



Interactions among mixture members

- Combined health effects may be greater (or less) than the sum of independent effects
  - Potential synergism
- Most methods can accommodate *a priori* defined interactions
  - Need to hard code
  - Dimensionality · · ·

→ Semi- or non-parametric methods preferred

Interactions and non-linearity example

Early life and adolescent arsenic exposure from drinking water and blood pressure in adolescence

Yu Chen[a,b,*], Fen Wu[a,b], Xinhua Liu[c], Faruque Parvez[d], Nancy J. LoIacono[d], Elizabeth A. Gibson[d], Marianthi-Anna Kioumourtzoglou[d], Diane Levy[d], Hasan Shahriar[e], Mohammed Nasir Uddin[e], Taruqul Islam[e], Angela Lomax[d], Roheeni Saxena[d], Tiffany Sanchez[d], David Santiago[d], Tyler Ellis[f], Habibul Ahsan[g], Gail A. Wasserman[h], Joseph H. Graziano[d,**]

- Participants: 726 14–16 year olds whose mothers are participants in HEALS
- Exposure measurement: Creatinine-adjusted urinary As, blood Pb, Mn, Cd, and Se were assessed at time of recruitment
- Outcome assessment: Blood pressure measured at the time of recruitment

Interactions and non-linearity example (cont.)

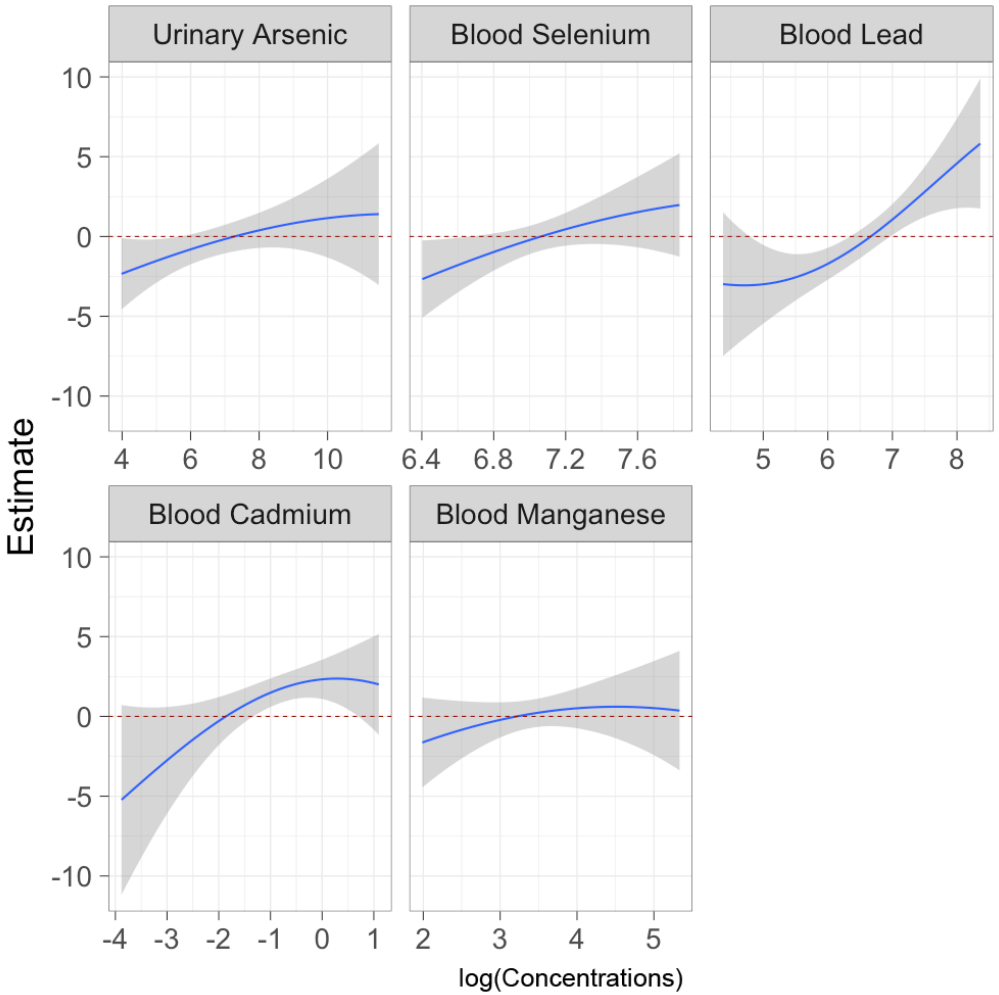
Research question:

Is the relationship between adolescent As exposure and blood pressure linear while accounting for Pb, Mn, Cd, and Se? Do these metals interact?

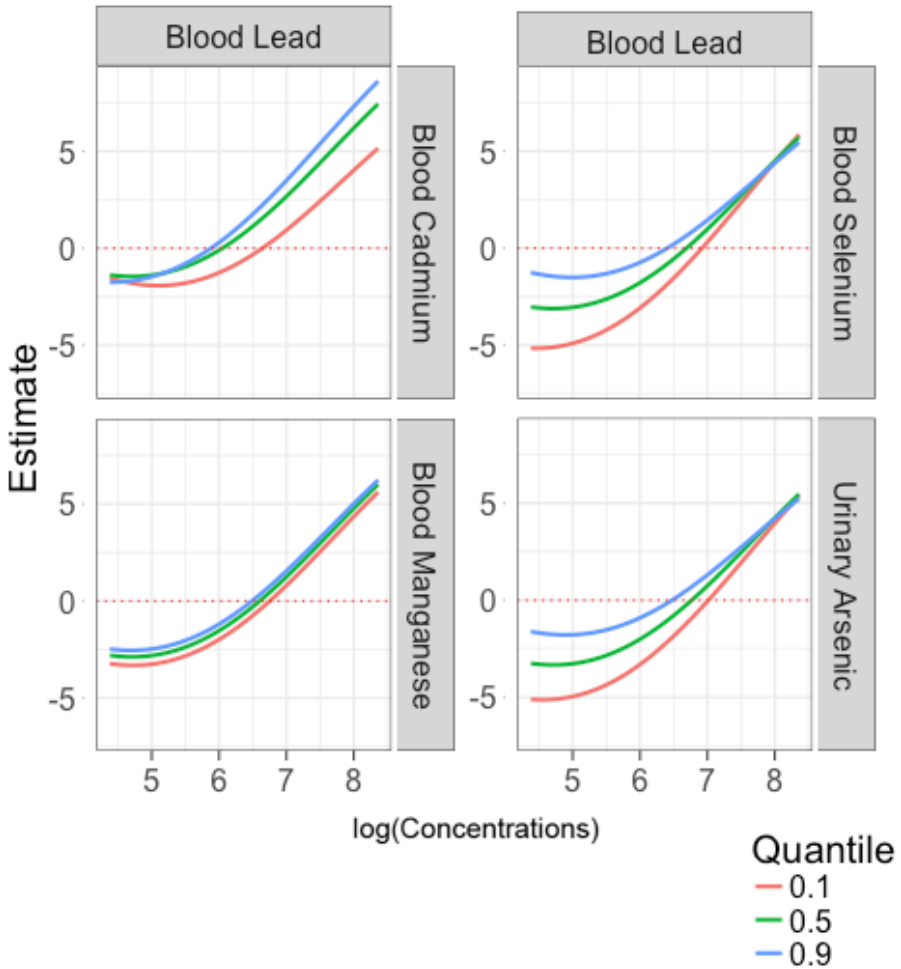
Mixture method:

Bayesian Kernel Machine Regression (BKMR)

Interactions and non-linearity example (cont.)

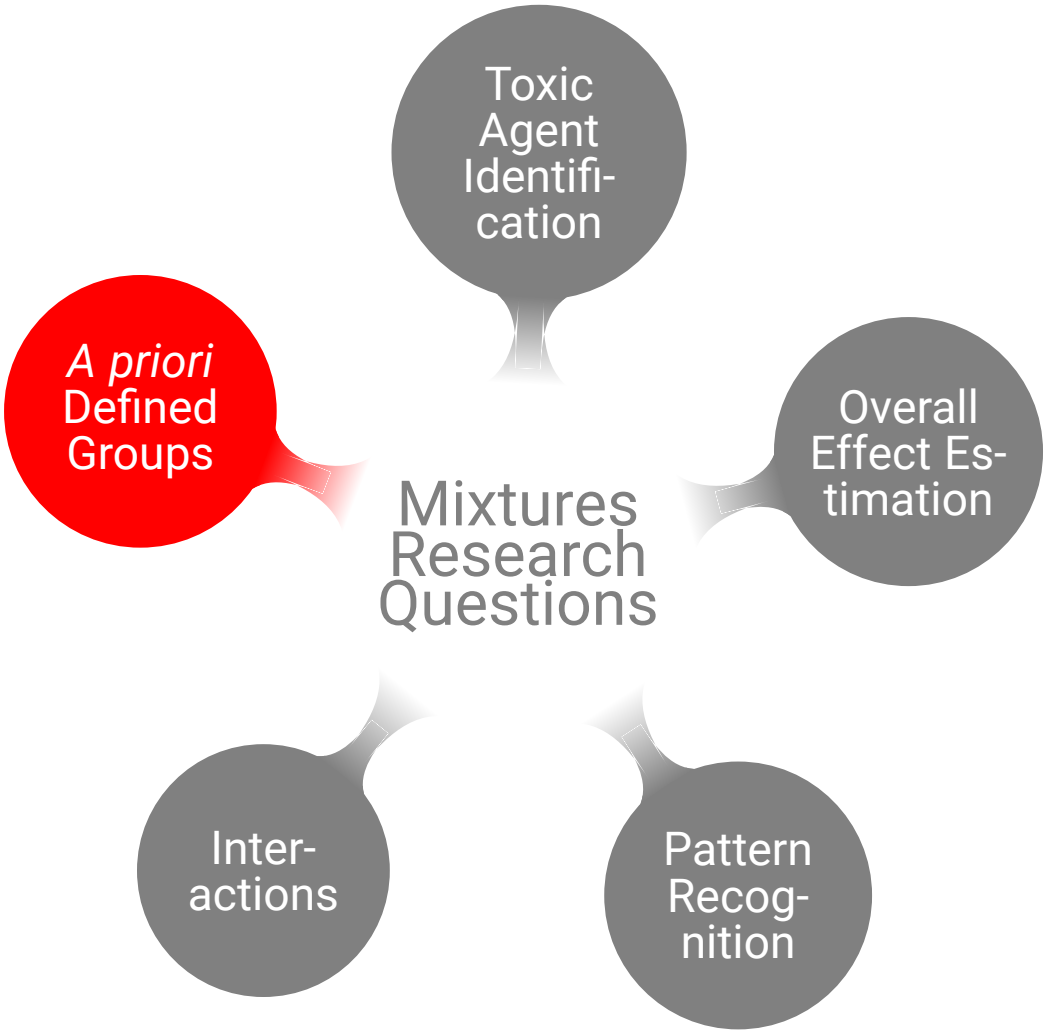


Interactions and non-linearity example (cont.)



A priori defined groups

- We might have some prior knowledge or hypothesis on how chemicals
  - Group naturally in the environment
  - Might share pathway to toxicity
- Methods exist to allow estimation both of group and within-group effects



A priori defined groups example

An overview of methods to address distinct research questions on environmental mixtures: an application to persistent organic pollutants and leukocyte telomere length

Elizabeth A. Gibson[1†], Yanelli Nunez[1†], Ahlam Abuawad[1], Ami R. Zota[2], Stefano Renzetti[3], Katrina L. Devick[4], Chris Gennings[5], Jeff Goldsmith[6], Brent A. Coull[4] and Marianthi-Anna Kioumourtzoglou[1*]

- Participants: 1,003 adults $\geq$ 20 years of age included in NHANES 2001–2002
- Exposure measurement: 18 PCBs, dioxins, and furans measured in blood serum and adjusted for serum lipids
- Outcome assessment: Leukocyte telomere length (LTL) relative to standard reference DNA (T/S ratio) was measured in whole blood DNA

A priori defined groups example (cont.)

- Toxic equivalency factor (TEF): a measure of relative potency compared with that of reference dioxin TCDD
- Original study used potency-weighted sums
- Created three groups with varying TEFs
  - Non–dioxin-like PCBs (no TEFs)
  - Non-ortho PCBs (high TEFs)
  - Mono-ortho PCB 118, furans, and dioxins (mid–high TEFs)

A priori defined groups example (cont.)

Research question:

Which defined congener groups are associated with changes in log-LTL and what are the magnitudes of individual congeners' associations within those groups?

Mixture method:

Group Lasso

A priori defined groups (cont.)

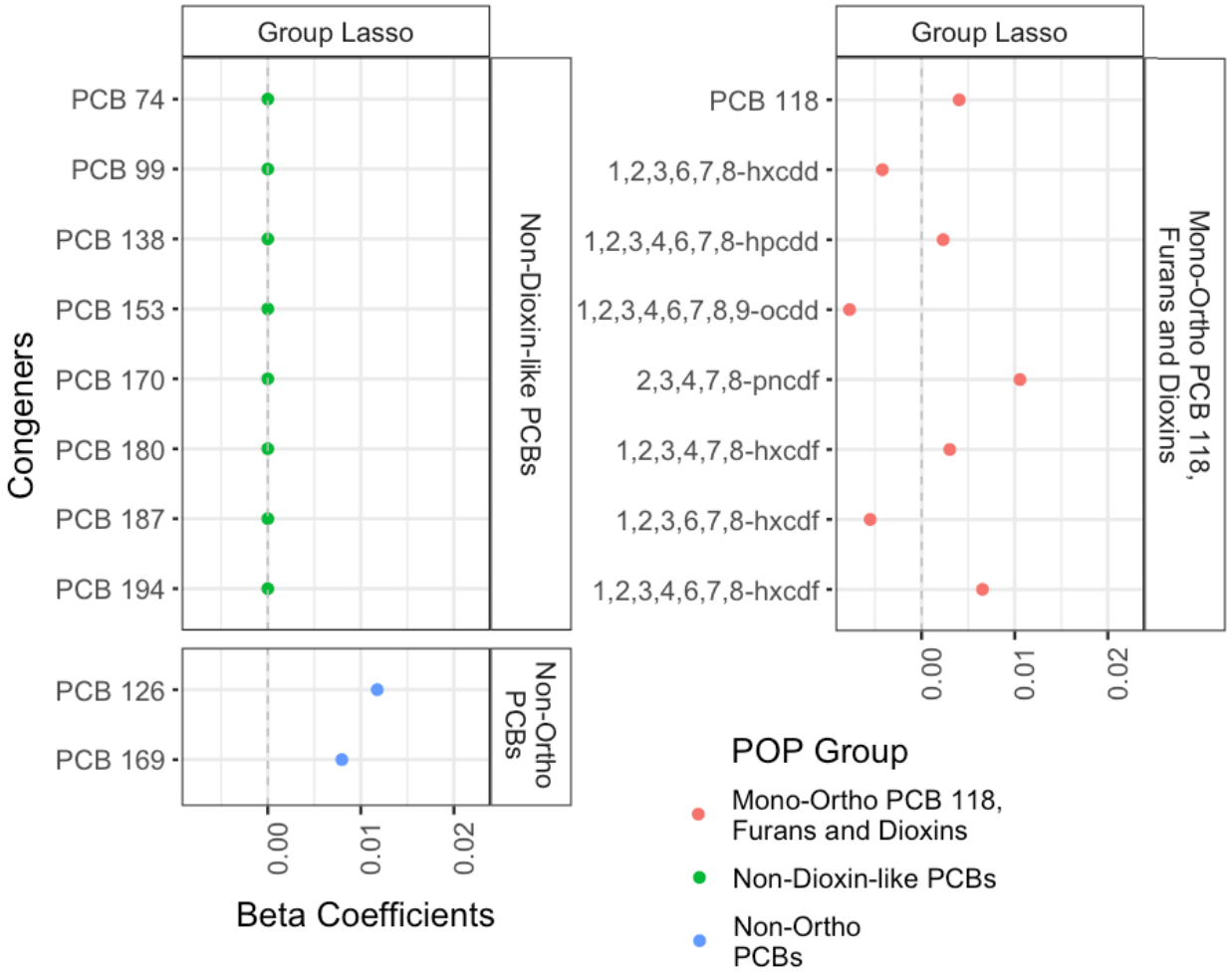
Group lasso

- Variable selection method:
  - Uses a penalty term to constrain the regression model
  - Minimizes the sum of the absolute values of the coefficients

$$\min_{\beta \in \mathbb{R}^p} \left(\left\| \mathbf{y} - \beta_0 \mathbf{1} - \sum_{\ell=1}^{L} \mathbf{X}_\ell \beta_\ell \right\|_2^2 + \lambda \sum_{\ell=1}^{L} \sqrt{p_\ell} \left\| \beta_\ell \right\|_2 \right)$$

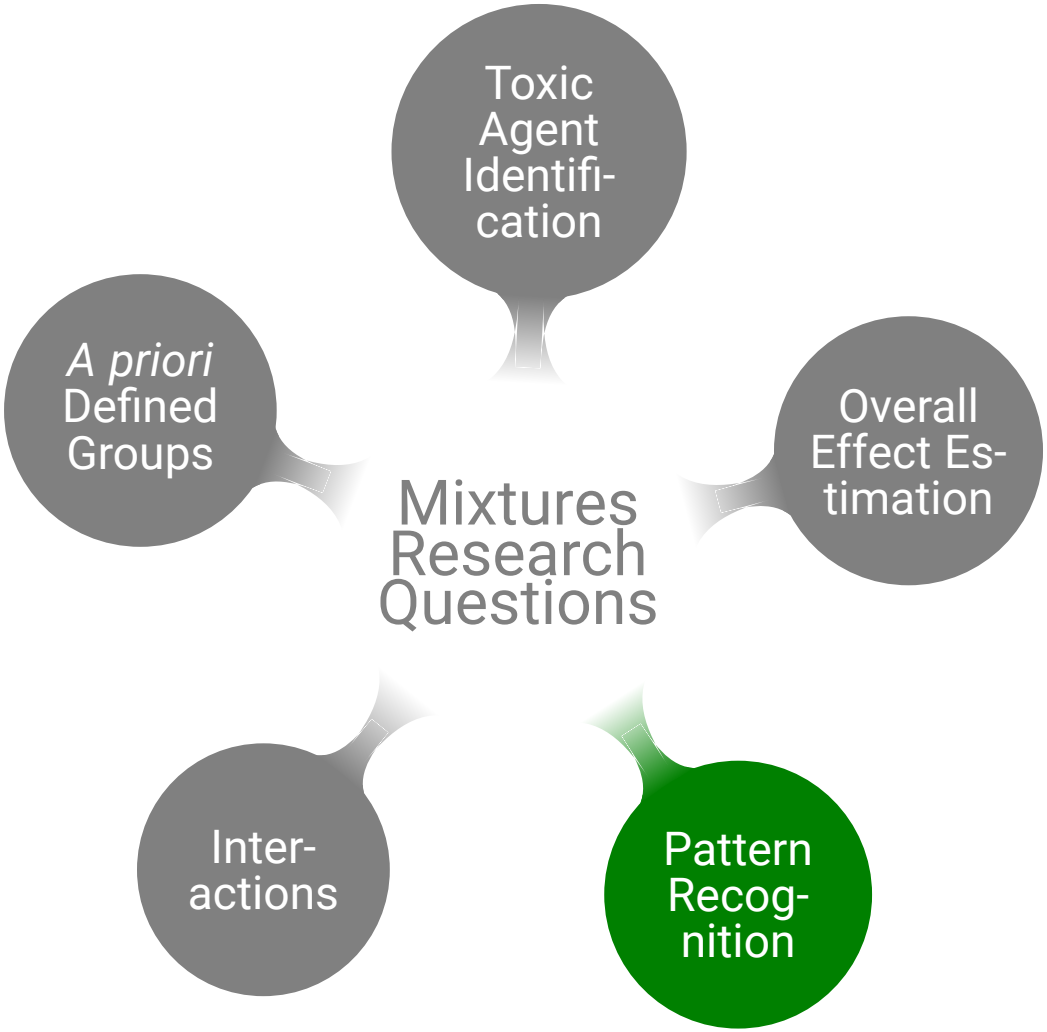
  - Keeps only those groups that are the most relevant to the outcome
  - Penalizes exposures within the same group equally

A priori defined groups example (cont.)

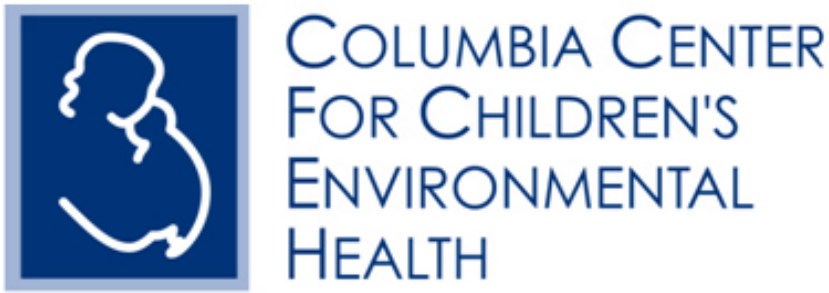


Exposure pattern recognition

- Why should we care about identifying exposure patterns to chemicals in a population?
  - Sources
  - Behaviors
- If we link these patterns to (multiple) adverse health outcomes
  - → Efficient regulations
  - → Targeted interventions



Exposure pattern recognition example



- Participants: 342 pregnant women aged 18–35 from Mothers & Newborns cohort
- Exposure measurement: 5 phenols, 3 parabens, and 9 phthalate metabolites from spot urine samples collected during the third trimester, adjusted for specific gravity
- Exposure sources: Personal care product use assessed via questionnaire

Exposure pattern recognition example (cont.)

Research question:

Are there patterns of phenol, paraben, and phthalate exposure in pregnant women, and are they associated with personal care product use?

Mixture method:

Principal Component Pursuit (PCP)

Exposure pattern recognition example (cont.)

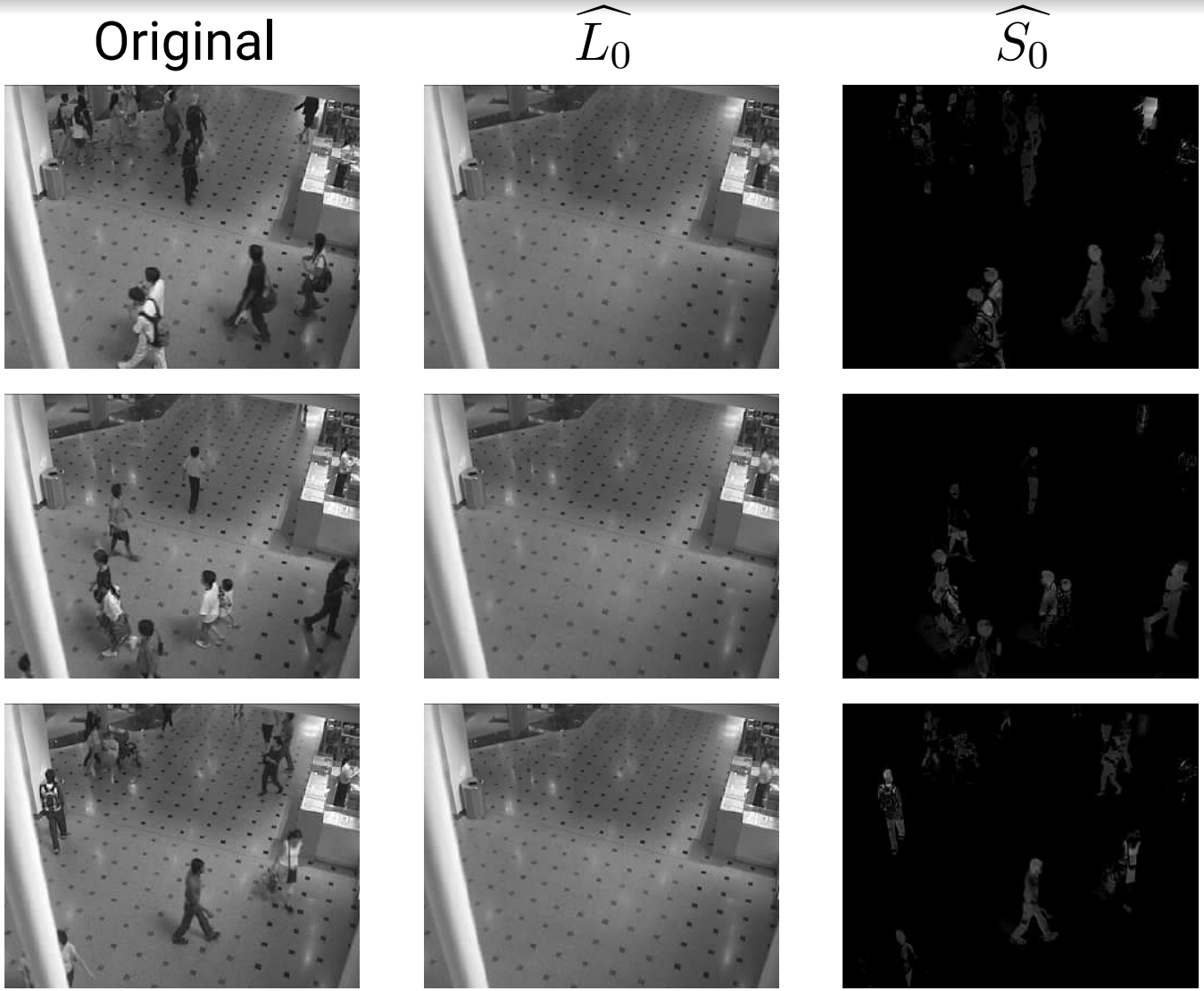
Principal Component Pursuit (PCP)

- Robust Principal Component Analysis (PCA)
- Data dimensionality reduction method adapted from computer vision
- Decomposes design matrix into low rank and sparse matrices
  - Low rank matrix estimates consistent exposure patterns
  - Sparse matrix identifies unique events

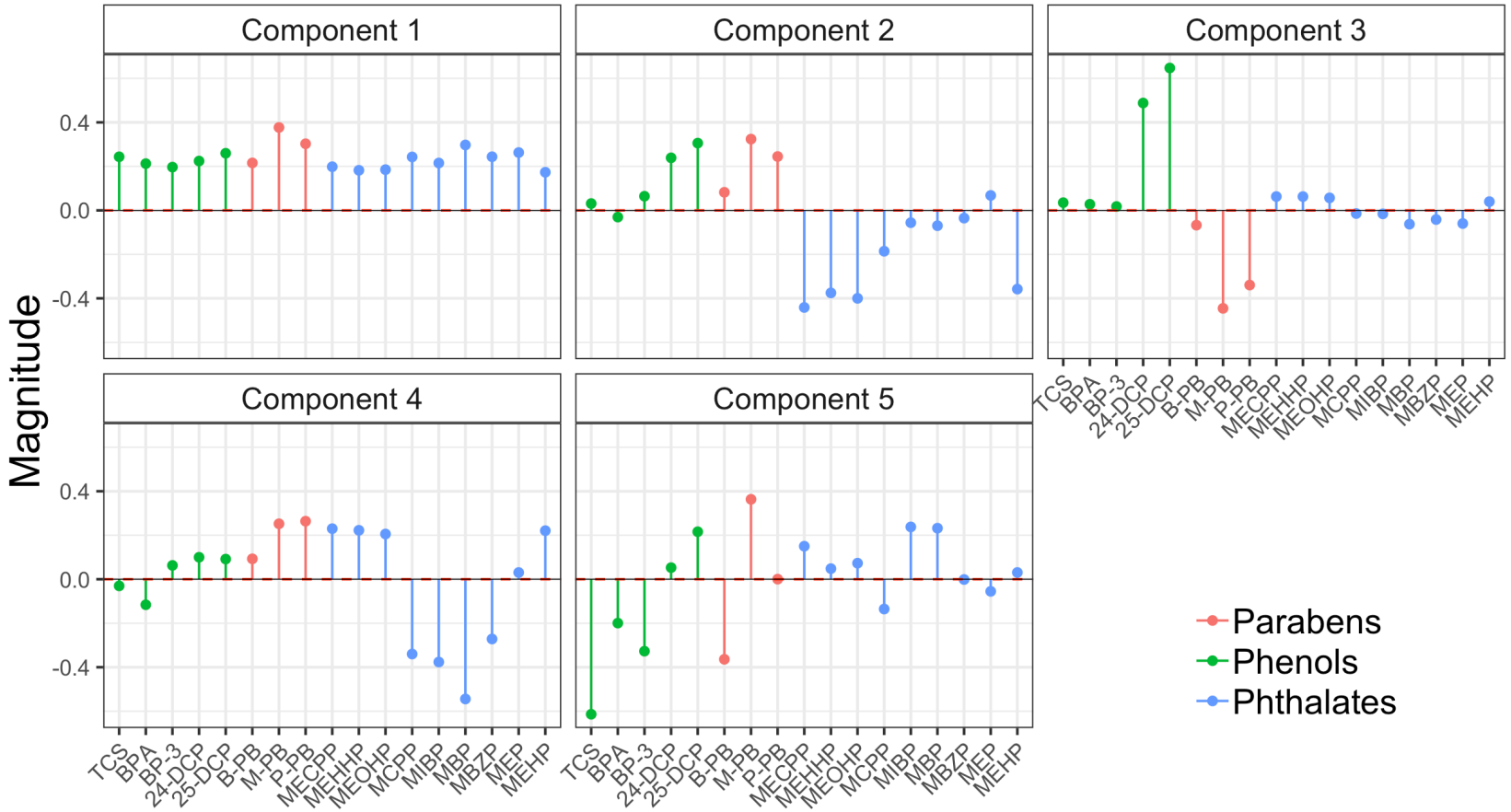
$$\min_{L,S} \|L\|_\star + \lambda \|S\|_1 + \frac{\mu}{2} \|L + S - X\|_F^2$$

- Robust to noisy/corupt data
  - Not influenced by outlying values

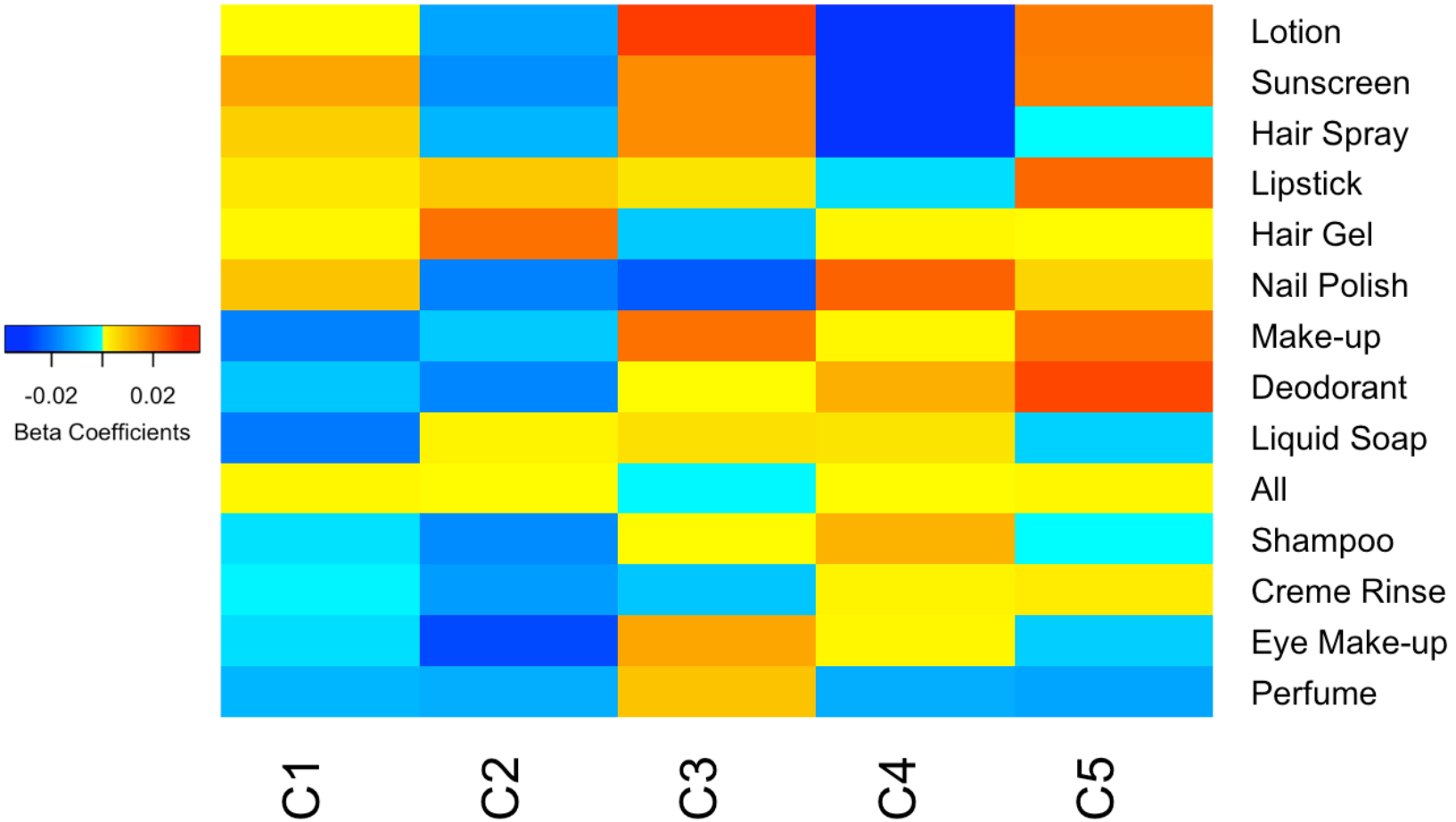
PCP image example



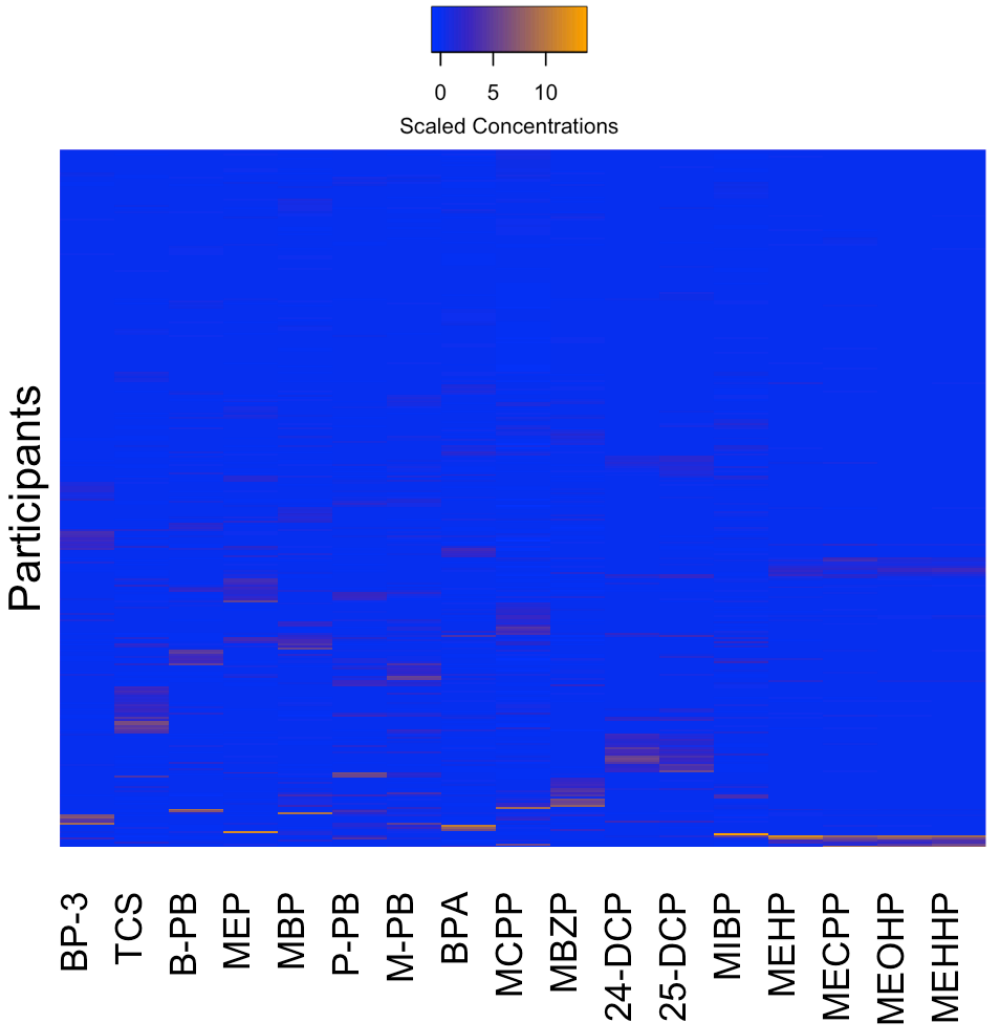
Exposure pattern recognition example (cont.)



Exposure pattern recognition example (cont.)



Exposure pattern recognition example (cont.)



Next steps

- PCP methods extension
  - Improve dependence on tuning parameters
  - Extend to allow for non-negative solutions
  - Implement novel penalty for values $\leq$LOD
  - Nest within supervised model
  - Assess performance and compare with existing methods
  - Publish user-friendly R package

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