Bayesian Kernel Machine Regression Distributed Lag Models

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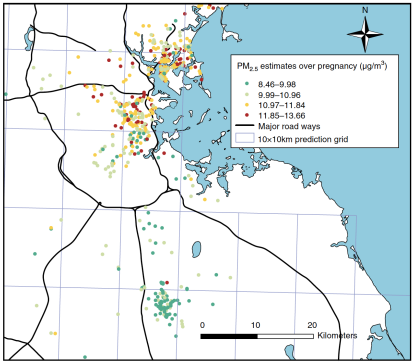
Overall Motivation

- Substantial research on mixture methods but mostly focused on exposure observed at a single time point
- Many methods to identify critical windows, mostly based on distributed lag models (DLMs), but generally for only a single exposure
- Our motivation is to identify critical windows and estimate the exposure-response relationship for mixtures that are assessed longitudinally

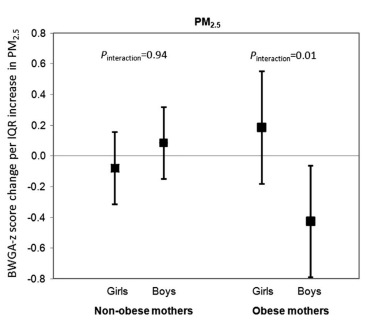
ACCESS Prospective Birth Cohort

- 997 Boston-area births between 8/2002 and 1/2007
- $PM_{2.5}$ and components at maternal residence for each week of pregnancy
- Primary outcome is birth weight for gestational age *z*-score (BWGAZ)
- Baseline covariates: maternal, age, education, race/ethnicity, pre-pregnancy BMI, atopy, self reported smoking during pregnancy, stress index, neighborhood disadvantage index, season of birth

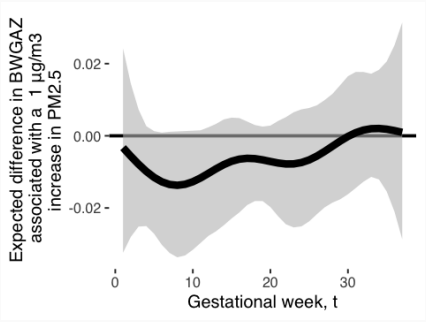


Source: Hsu et al. *Am J Respir Crit Care Med*.

Existing Evidence



Source: Lakshmanan et al. (2015) *Env. Res.*

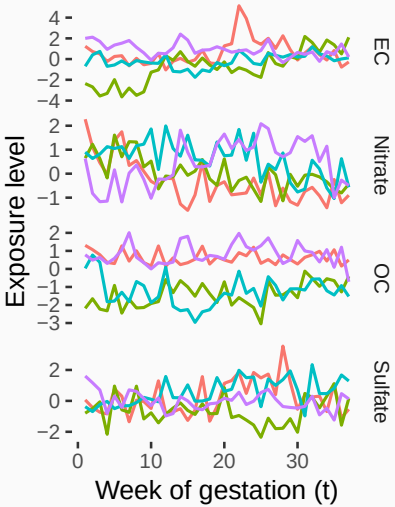


Source: Wilson et al. (2017) *Biostatistics*

- Evidence of an association between $PM_{2.5}$ exposure and BWGAZ for male babies with obese mothers ($n = 109$)
- What about nitrate, organic carbon (OC), elemental carbon (EC) and sulfate?

Data Setting and Objectives

- Resulting data structure is 4 exposures at 37 time points
  - High dimensional exposure data
  - Can be highly multicollinear
- Want a model that allows for:
  - Nonlinear associations
  - Interaction effects
  - Identification of critical windows



Bayesian Kernel Machine Regression (BKMR)

- BKMR estimates a high dimensional exposure-response function

$$Y_i = h(E_{i1}, \ldots, E_{iM}) + Z_i'\gamma + \epsilon_i$$

- For repeated measures of exposures we can:
  1. Reduce the dimension of the exposure by using pregnancy average exposure
     - Ignores variation in exposure and the magnitude of the effect over pregnancy
     - Cannot identify critical windows
     - May obscure effects that are limited to a small number of weeks
  2. Include all measures of exposures
     - May result in model instability
     - Fails to account for biological understand that exposure effect at proximal time points will likely be similar in sign and magnitude
     - Hard to interpret results

Distributed Lag Model (DLM)

- Our approach is to use the constrained DLM framework within BKMR
  - Reduces the dimension of the exposure data
  - Adds structure so that the exposure-effect varies smoothly across gestational weeks
  - Improves model stability
- The DLM model for a single exposure is

$$Y_i = \alpha + \sum_{t=1}^{T} X_{it}\delta_t + \mathbf{Z}_i'\boldsymbol{\gamma} + \epsilon_i$$

- Regression coefficient δ_t is constrained to vary smoothly over time
- Alternatively can be represented in a functional form using continuous time

$$\sum_{t=1}^{T} X_{it}\delta_t \quad \Longleftrightarrow \quad \int_{\mathcal{T}} x_i(t)\delta(t)dt$$

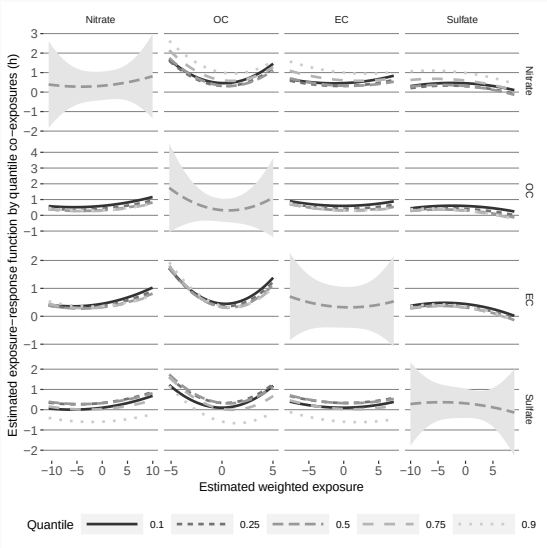
BKMR-DLM

- Represent each exposure as a weighted exposure
$$E_{im} = \int_{\mathcal{T}} w_m(t) x_{im}(t) dt$$
- Weight function $w_m(t)$ identifies critical windows similar to a constrained DLM
- The BKMR model estimates the exposure-response surface as a function of the weighted exposures
$$Y_i = h(E_{i1}, \ldots, E_{iM}) + \mathrm{Z}_i'\boldsymbol{\gamma} + \epsilon_i$$
- Bayesian model fitting estimates the weight functions $w_m(t)$ and the mixture effect $h()$ simultaneously.
- Weight functions are constrained to have norm one and positive integral for identifiability and parameterized with natural splines

BKMR-DLM Properties

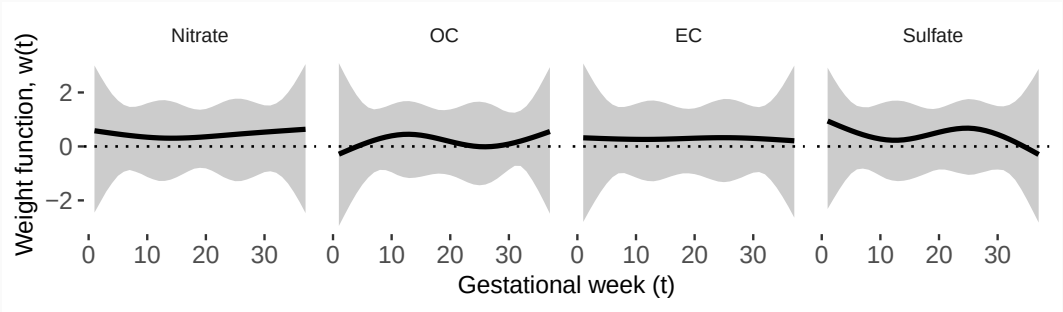
- Allows for nonlinear associations and higher order interactions
- Identifies critical windows through the weight function
- Exposures may have positive effect of some time periods and negative over other time periods
- Simulation results show
  - Ability to estimate nonlinear exposure-response functions and interactions
  - Low power to detect critical windows
  - Improved estimation of the exposure-response function even when a critical window cannot be identified
  - Very low frequency of identifying incorrect critical windows

Illustration on ACCESS Data



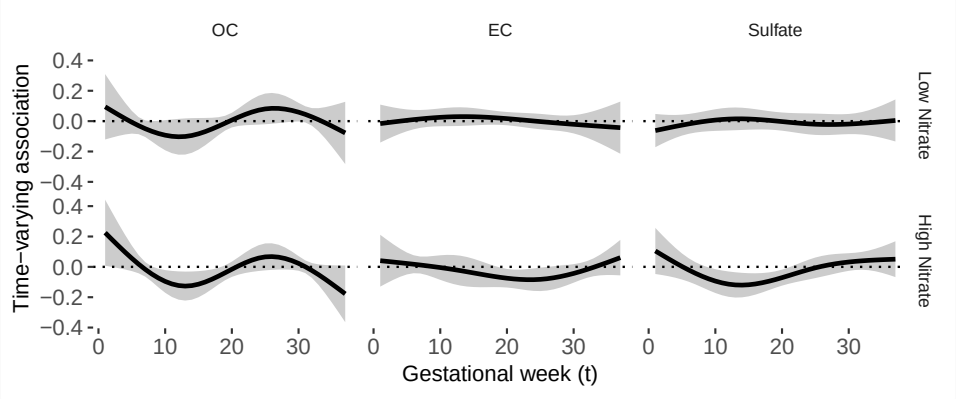
- Similar interpretation of exposure-response function to BKMR
- Key difference: x-axis is weighted exposure (estimated)

Illustration on ACCESS Data



- Areas of the weight function that deviate from zero identify critical windows
- The sign of the weight function does not determine the direction of the association

Illustration on ACCESS Data



- DLM for each exposure stratified by mean nitrate level over pregnancy
- BKMR-DLM is a potentially powerful exploratory tool to identify possible interactions to investigate with more parsimonious models

Summary

- BKMR-DLM allows for repeated measures of exposure to a mixture
- Improved estimation of exposure-response function compared to BKMR with pregnancy average exposures or an additive DLM or DLNM
- Allows for nonlinear associations and interactions
- Low power to identify critical windows but can in high-signal settings
- Software available: anderwilson.github.io/regimes

Thanks You!

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Thanks You!

anderwilson.github.io

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Wilson, A, Hsu, H-HL, Chiu, Y-HM, Wright, RO, Wright, RJ, Coull, BA (In press). Kernel Machine and Distributed Lag Models for Assessing Windows of Susceptibility to Environmental Mixtures in Children's Health Studies. *Annals of Applied Statistics*. ArXiv:1904.12417.

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